NCGC National Clinical Guideline Centre

Stakeholder consultation draft

Lower limb peripheral arterial disease

Diagnosis and management

NICE Clinical Guideline <…>

Appendices

08 March 2012

Draft for Consultation

Commissioned by the National Institute for Health and Clinical Excellence

Royal College of Physicians
Setting higher medical standards

Royal College of Nursing

RCS
ADVANCING SURGICAL STANDARDS

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Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published <Enter date>

Foreword

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Appendices

Appendix A: Scope

A.1 Guideline title:

Lower limb peripheral arterial disease: diagnosis and management

A.2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the diagnosis and management of lower limb peripheral arterial disease in adults'.

A.3 Clinical need for the guideline

A.3.1 Epidemiology

a. About 20% of people older than 60 have peripheral arterial disease, although only a quarter of these have symptoms. The incidence of peripheral arterial disease is high among people who smoke, people with diabetes, and people with coronary artery disease. Asymptomatic peripheral arterial disease is common in people with diabetes.
b. Even in the absence of symptoms, a reduced blood pressure at the ankle signifies an increased risk of cardiac and cerebrovascular morbidity and mortality.
c. Peripheral arterial disease causes pain in the leg on walking (claudication) and occurs in around 5% of people over 60. Symptoms become severe and progressive in approximately 20% of these people. Peripheral arterial disease may progress to critical limb ischaemia, with constant and intractable pain preventing sleep, often with ulceration or gangrene of the foot. People with critical limb ischaemia are at risk of losing their leg if they don't receive treatment, and a high proportion present for emergency care. Around 1–2% of people with claudication eventually undergo amputation, although the risk is higher (about 5%) in people with diabetes.

A.3.2 Current practice

a. The management of peripheral arterial disease remains controversial. Treatments include watchful waiting, medical management, exercise training, endovascular treatment and surgical reconstruction.
b. Mild symptoms are managed in primary care, but people experiencing more severe symptoms that decrease quality of life are referred to secondary care. Some people may require investigation and treatment for risk factors and associated diseases. A small number of people require invasive treatment.
c. Reduced Ankle Brachial Pressure Index (ABPI) is an independent predictor of cardiac and cerebrovascular morbidity and mortality and may help to identify people who would benefit from secondary prevention with aspirin, statins and angiotensin-converting enzyme (ACE) inhibitors. Treatments for secondary prevention are less commonly offered to people with peripheral arterial disease than to those with other cardiac and cerebrovascular risk factors.
d. People with intermittent claudication are often advised to exercise. Supervised exercise programmes are thought to improve walking distance and quality of life. However, access to supervised exercise classes is variable, and many are not funded by the NHS.
e. Drug treatments for claudication include those used for secondary prevention and those used specifically for the treatment of symptoms (including cilostazol, naftidrofuryl oxalate,

pentoxifylline and inositol nicotinate). Both ramipril and atorvastatin are believed to improve walking distances in people with claudication.

f. Other non-invasive treatments include the application of intermittent pneumatic compression to the calf and foot, and herbal remedies such as Ginkgo biloba.

g. People with severe symptoms that are inadequately controlled are often referred to secondary care for assessment for endovascular or surgical revascularisation. 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.

h. Endovascular treatments include balloon angioplasty, endovascular stents and a range of new adjunct or alternative treatments and techniques. The new treatments include drug-eluting stents, modified balloons, laser angioplasty, atherectomy, cryotherapy and brachytherapy.

i. Surgical reconstruction may be carried out to unblock or bypass occluded or narrowed arteries. Procedures include aorto-bifemoral, femoro-popliteal and femoro-distal bypass and common femoral endarterectomy. The risks and outcomes of these vary according to the nature of the procedure, the presenting symptoms, comorbidities, and the site and extent of the disease. The current trend is toward less invasive treatment.

j. There is a need for a guideline on lower limb peripheral arterial disease to resolve the considerable uncertainty and variations in practice resulting from rapid changes in diagnostic methods, the emergence of new endovascular treatments and organisational changes in the provision of vascular services associated with the emergence of new subspecialties in vascular surgery and interventional radiology.

A.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

A.4.1 Population

A.4.1.1 Groups that will be covered

a. Adults aged 18 and older.

b. People who present with symptoms of lower limb peripheral arterial disease, including intermittent claudication, ischaemic rest pain, and/or tissue loss.

c. People without symptoms of peripheral arterial disease (for example, those with venous ulceration) who have abnormal ankle/brachial pressure index (ABPI)

d. Subgroups based on ethnicity, socioeconomic factors, age or comorbidities (including people with diabetes), for which differences in management and outcome are identified.

A.4.1.2 Groups that will not be covered

a. Children and young people aged 17 and younger.

b. Adults who have acute ischaemia of the lower limb.

A.4.2 Healthcare setting

a. All NHS settings where people present with, or undergo treatment for, symptomatic or asymptomatic peripheral arterial disease.

A.4.3 Clinical management

A.4.3.1 Key clinical issues that will be covered

a. Diagnosis, for example using Ankle Brachial Pressure Index.
b. Drug treatments and other interventions, for managing symptoms and for secondary prevention (for example statins and antiplatelet therapy). Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
c. Assessment for intervention (for example, using duplex ultrasonography, magnetic resonance angiography or computed tomography angiography).
d. Supervised exercise programmes as an alternative or adjunct to medical management, endovascular or surgical treatment.
e. Endovascular treatments (for example, angioplasty and stents) compared with surgery.
f. Patient information.
g. The management of pain associated with critical ischaemia, including methods of pain relief and indications for amputation.

A.4.3.2 Clinical issues that will not be covered

a. Acute ischaemia of the lower limb.
b. Methods of amputation.
c. Rehabilitation after amputation.
d. Management of diabetic foot problems (see section 5).
e. Use of topical treatments and dressings.

A.4.4 Main outcomes

a. Mortality.
b. Health-related quality of life using measures such as EQ–5D, SF–36 and the Walking Impairment Questionnaire.
c. Walking distance.
d. Limb salvage rates.
e. Graft and vessel patency (primary and secondary).
f. Re-intervention rates.
g. Re-admission rates.
h. Adverse events.
i. Pain intensity scale.
j. Cardiovascular morbidity

A.4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be

conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

A.4.5 Status

A.4.6 Scope

This is the final scope.

A.4.6 Timing

The development of the guideline recommendations will begin in September 2010.

A.5 Related NICE guidance

A.5.1 Published guidance

- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal guidance 159 (2008). Available from www.nice.org.uk/guidance/TA159
- Preventing the uptake of smoking by children and young people. NICE public health guidance 14 (2008). Available from www.nice.org.uk/guidance/PH14
- Promoting physical activity in the workplace. NICE public health guidance 13 (2008). Available from www.nice.org.uk/guidance/PH13
- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10
- Physical activity and the environment. NICE public health guidance 8 (2008). Available from www.nice.org.uk/guidance/PH8
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from www.nice.org.uk/guidance/TA132
- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/guidance/TA123
- Obesity. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43
- Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006). Available from www.nice.org.uk/guidance/PH2
- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1
- Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org.uk/guidance/TA94
- Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. NICE technology appraisal guidance 90 (2005). Available from www.nice.org.uk/guidance/TA90
- Type 2 diabetes − footcare. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10
- Guidance on the use of patient-education models for diabetes. NICE technology appraisal guidance 60 (2003). Available from www.nice.org.uk/guidance/TA60

A.5.12 5. Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Percutaneous atherectomy of femoro-politeal arterial lesions with plaque excision devices. NICE interventional procedure guidance. Publication expected Autumn 2010.
- Diabetic foot problems. NICE clinical guideline. Publication expected March 2011.
- Endovascular repair for popliteal aneurysms. NICE interventional procedure guidance. Publication expected Spring 2011.
- Cilostazol, naftidrofyryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. NICE technology appraisal guidance. Publication expected June 2011.
- Type 2 diabetes: preventing pre-diabetes among adults in high-risk groups. NICE public health guidance. Publication expected June 2011.
- Hypertension. Update of NICE clinical guidelines 18 and 34. Publication expected August 2011.
- Type 2 diabetes: preventing the progression from pre-diabetes to type 2 diabetes among high-risk groups. NICE public health guidance. Publication expected May 2012.

A.6 Further information

Information on the guideline development process is provided in: 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS' 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of interest

B.1 Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required any actions.

B.2 Declarations of interest of the guideline development group

B.2.1 Jonathan Michaels (Chair)

GDG meeting	Declarations of interest
On application	JM declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests in the past 12 months or upcoming months. Declared two personal non-pecuniary interests Currently Vice-Chair of NICE appraisals committee. Acted as expert clinical advisor on the NICE TA "Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease", which was published in May 2011.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	Declared additional personal non-pecuniary interest We are just starting a research project that is a large multi-national study involving several European countries. This is being funded through the European community research funding through the FP7 funding stream and it is likely that a small proportion of my salary will be funded from my contribution to this research. The research is related to the development of computer models to predict the risk of stent fracture in the peripheral circulation. The project is with a number of academic partners from various University Departments around Europe, however there is one commercial partner which is Invatec. This is a Swiss stent manufacturer, who I understand has recently been taken over by Medtronic. As I understand it they are also a recipient of funding from the grant, so from my point of view there is no funding coming to me or the Sheffield from the commercial organisation and they have no input into the research that we are carrying out in Sheffield.
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No Interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.22 Barry Attwood

GDG meeting	Declarations of interest
On application	BA declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interestes to declare
GDG 13 – 15th May 2012	TBC

B.23 Andrew Beech

GDG meeting	Declarations of interest
On application	AB declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	Did not attend the 8th March meeting.
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.24 Andrew Bradbury

GDG meeting	Declarations of interest
On application	AB declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare

GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	Did not attend meeting
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.5 Duncan Ettles

GDG meeting	Declarations of interest
On application	DE declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	Did not attend this meeting.
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	Did not attend this meeting
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.6 Martin Fox

GDG meeting	Declarations of interest
On application	MF declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare

GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.217 Michael Flynn

GDG meeting	Declarations of interest
On application	MF declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	Did not attend this meeting.
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.228 Ammy Lam

GDG meeting	Declarations of interest
On application	AL declared she knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	Did not attend this meeting.
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	Did not attend this meeting
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.239 Peter Maufe

GDG meeting	Declarations of interest
On application	PM declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-

	pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	Did not attend this meeting.
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.10 Ricky Mullis

GDG meeting	Declarations of interest
On application	RM declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	Did not attend this meeting.
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	Did not attend this meeting
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.11 Anita Sharma

GDG meeting	Declarations of interest
On application	AS declared she knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	N/a
GDG 2 – 12th October 2010	N/a
GDG3 – 16th November 2010	N/a
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	Did not attend this meeting.

GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	Did not attend this meeting
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.12 Cliff Shearman

GDG meeting	Declarations of interest
On application	CS declared he knew of personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months. CS declared a personal pecuniary interest Invited speaker Diabetes footcare conference in Los Angeles - international meeting on diabetes foot care. Spoke on treatment of peripheral arterial disease in diabetes. No commercial link. Thard(?) paid a $1500 honerium - Mar 23-26 2011.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	Did not attend this meeting.
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.13 Hazel Trender

GDG meeting	Declarations of interest
On application	HT declared she knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare

GDG 9 – 13th September 2011	No interests to declare
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.2.14 Raman Uberoi

GDG meeting	Declarations of interest
On application	RU declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 1 – 7th September 2010	No interests to declare
GDG 2 – 12th October 2010	No interests to declare
GDG3 – 16th November 2010	No interests to declare
GDG4 – 01st February 2011	No interests to declare
GDG 5 – 8th and 9th March 2011	No interests to declare
GDG 6 – 12th April 2011	No interests to declare
GDG 7 – 17th May 2011	No interests to declare
GDG 8 – 28th June 2011	No interests to declare
GDG 9 – 13th September 2011	Did not attend this meeting
GDG 10 – 18th October 2011	No interests to declare
GDG 11 – 6th December 2011	No interests to declare
GDG 12 – 10th January 2012	No interests to declare
GDG 13 – 15th May 2012	TBC

B.3 Co-optee

B.3.1 Manohar Sharma

GDG meeting	Declarations of interest
On application	RM declared he knew of no personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.
GDG 7 – 17th May 2011	No interests to declare
GDG 12 – 10th January 2012	

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1 Appendix C: Review protocols

C.1 Information requirements

Component	Description
Review question	What are people's experiences of living with PAD and people's preferences for information requirements for PAD?
Objectives	To consider people's experience and people's preferences for information requirements for PAD.
Population	Adults (≥ 18 years old) with PAD both intermittent claudication or Fontaine stage II AND critical limb ischemia or Fontaine stage III, IV.
Subgroups	The following groups will be considered separately if data is present: • People with diabetes.
Intervention	Patients' experience and preferences for information requirements for PAD.
Outcomes	• The experiences of living with PAD. • The 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.
Study design	Qualitative studies.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care (excluding emergency care). • Community settings in which NHS care is received.
Search Strategy	See appendix D.3.1
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data • Qualitative analysis will be conducted.

C.2 Diagnosis of PAD

Component	Description
Review question	In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, better in determining the diagnosis and severity of PAD?
Objectives	To compare the diagnostic accuracy of ABPI as an adjunct to clinical assessment compared to clinical assessment alone, or ABPI alone in determining the diagnosis and severity of PAD.
Population	Adults (≥ 18 years old) with suspected PAD (symptoms of IC, leg ulcers, common foot problems or cardiovascular risk factors).
Subgroups	The following groups will be considered separately if data is present: • People with symptomatic PAD. • People with asymptomatic PAD. • People with diabetes. • People with renal failure/advanced renal disease.

Intervention	• ABPI as an adjunct to clinical assessment. • ABPI alone. • Clinical assessment alone (minimum within assessment to include assessing pulses, symptom history, validated claudication questionnaire for example Edinburgh claudication questionnaire, Charing questionnaire or Walking impairment questionnaire).
Comparison	All 3 diagnostic tools compared to reference standard: imaging.
Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio • Reproducibility.
Study design	Prospective diagnostic studies.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care (excluding emergency care).
Search Strategy	See appendix D.3.2
Review Strategy	Appraisal of methodological quality The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data Diagnostic meta-analysis where appropriate will be conducted.

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Component	Description
Review question	In people with suspected PAD undergoing ABPI, do different methods result in different diagnostic accuracy?
Objectives	To compare the clinical and cost effectiveness of different ABPI methods (how long patient is rested, higher or lower of two vessels) for diagnostic accuracy in people with suspected PAD.
Population	Adults (≥ 18 years old) with suspected PAD (symptoms if IC, leg ulcers, common foot problems or cardiovascular risk factors).
Subgroups	The following groups will be considered separately if data is present: • People with symptomatic PAD • People with asymptomatic PAD. • People with diabetes. • People with renal failure/advanced renal disease.
Intervention	• Different ABPI methods including: • Manual versus automatic ABPI measurements. • Duration of rest period prior to measurements. • Sitting versus lying down during measurement. • Location of the cuff. • Higher or lower vessel measurement.
Comparison	As above

Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio • Inter- and intra-operative reliability • Applicability.
Study design	Prospective diagnostic studies.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care (excluding emergency care).
Search Strategy	See appendix D.3.2
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data • Diagnostic meta-analysis where appropriate will be conducted.

C.3 Imaging for revascularisation

Component	Description
Review question	What is most clinical and cost-effective method of assessment of lower limb PAD (intermittent claudication and critical limb ischemia)?
Objectives	• To partially update 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" • Determine the diagnostic accuracy of DUS, MRA and CTA for the assessment of stenosis or occlusion in lower limb PAD. • To analyse the cost-effectiveness of these technologies.
Population	Adults (≥ 18 years old) with PAD including intermittent claudication or Fontaine stage II and critical limb ischemia or Fontaine stage III, IV.
Subgroups	None.
Intervention	• Duplex ultrasound (DUS). • Magnetic resonance angiography (MRA). • Computed tomography angiography (CTA).
Comparison	Reference standard: digital subtraction angiography / arteriography (DSA).
Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio.
Study design	Prospective diagnostic cohort or case control trials.
Population size and directness	• Studies with 20 or less patients will be excluded. • Studies with indirect populations will not be considered.

Setting	Secondary care (excluding emergency care).
Search Strategy	See appendix D.3.3
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data • Diagnostic meta-analysis where appropriate will be conducted.

C.4 Management of intermittent claudication

C.4.1 Supervised exercise compared to unsupervised exercise

Component	Description
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?
Objectives	To compare the clinical and cost effectiveness of supervised exercise therapy compared to unsupervised exercise therapy in the treatment of adults with intermittent claudication.
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage I or stage II.
Subgroups	The following groups will be considered separately if data is present: • People with IC due to aorto-iliac disease • People with IC due to femoro-popliteal disease.
Intervention	Supervised exercise therapy / programme.
Comparison	Unsupervised exercise therapy / programme (unsupervised programme or advice to exercise or increase usual exercise – exclude if clearly part of an education programme or lifestyle advice – intervention should be exercise only)
Outcomes	• Amputation free survival (report all) • CV events • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Exercise levels at follow up • Withdrawal rate from exercise programme and reason if stated • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use –what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi randomised trials.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.

Setting	• Primary care. • Secondary care (excluding emergency care). • Community settings in which NHS care is received.
Search Strategy	See Appendix D.3.4
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.412 Naftidrofuryl oxalate

Component	Description
Review question	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?
Objectives	To compare the clinical and cost effectiveness of naftidrofuryl oxalate compared to exercise therapy, angioplasty or stents in the treatment of adults with intermittent claudication PAD
Population	Adults (≥ 18 years old) with PAD Intermittent claudication or Fontaine stage I or stage II.
Subgroups	• People with IC due to aorto-iliac disease • People with IC due to femoro-popliteal disease • People with diabetes
Intervention	Naftidrofuryl oxalate
Comparison	• Exercise therapy • Angioplasty with or without stents
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Change in ABPI. Indicate if the following are reported in the study (do not need to extract actual results for these) • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi randomised trials
Population size and directness	• No limitations on sample size • Studies with indirect populations will not be considered
Setting	• Primary care (exercise therapy) • Secondary care (excluding emergency care) (angioplasty and exercise therapy)

	• Community settings in which NHS care is received (exercise therapy)
Search Strategy	See Appendix D.3.5
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data • Diagnostic meta-analysis where appropriate will be conducted.

C.413 Comparison of exercise, best medical treatment, angioplasty and bypass surgery

Component	Description
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 PAD in adults with intermittent claudication?
Objectives	To compare 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 PAD in adults with intermittent claudication.
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage I or stage II.
Subgroups	The following groups will be considered separately if data is present: • People with IC of the aorto-iliac artery • People with IC of the femoro-popliteal artery
Intervention	Supervised exercise therapy / programme or best medical treatment (defined as care which did not specifically exclude advice to exercise).
Comparison	• Angioplasty with or without stents • Bypass surgery.
Outcomes	• Amputation free survival (report all) • CV events • Quality of life (report all, including EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Exercise levels at follow up • Withdrawal rate from exercise programme and reason if stated • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use –what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs –any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi randomised trials.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care.

	• Secondary care (excluding emergency care). • Community settings in which NHS care is received.
Search Strategy	See appendix D.3.8
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.414 Angioplasty compared to bypass surgery

Component	Description
Review question	What is the clinical and cost effectiveness of angioplasty compared to bypass surgery for the treatment of PAD in adults with intermittent claudication?
Objectives	To compare the clinical and cost effectiveness of angioplasty with or without stents compared to bypass surgery in the treatment of PAD in adults with intermittent claudication.
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage or stage II.
Subgroups	The following groups will be considered separately if data is present: • People with IC due to aorto-iliac disease • People with IC due to femoro-popliteal disease • People with diabetes.
Intervention	Angioplasty with or without stents
Comparison	Bypass surgery
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, including EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use – what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs – any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi randomised trials.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care).
Search Strategy	See Appendix D.3.9
Review Strategy	Appraisal of methodological quality:

	• The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.415 Angioplasty with selective stent placement compared to primary stent placement

Component	Description
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?
Objectives	To compare the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement in the treatment of PAD in adults with intermittent claudication
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage I or II
Subgroups	The following groups will be considered separately if data is present: • People with IC due to aorto-iliac disease • People with IC due to femoro-popliteal disease • People with diabetes
Intervention	Angioplasty with selective stent placement (include all types of stents)
Comparison	Angioplasty with primary stent placement (include all types of stent)
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.6
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.416 Bare metal compared to drug eluting stents

Component	Description
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?
Objectives	To compare the clinical and cost effectiveness of bare metal stents compared to drug eluting stents in the treatment of PAD in adults with intermittent claudication.
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage I or II
Subgroups	The following groups will be considered separately if data is present: • People with IC due to aorto-iliac disease • People with IC due to femoro-poplitealdisease • People with diabetes
Intervention	Bare metal stents
Comparison	Drug eluting stents
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.7
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.427 Autologous vein compared to prosthetic bypass graft

Component	Description
Review question	What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in adults with intermittent claudication?
Objectives	To compare the clinical and cost effectiveness of autologous vein compared to

	prosthetic bypass for the treatment of PAD in adults with intermittent claudication.
Population	Adults (≥ 18 years old) with intermittent claudication or Fontaine stage I or II
Subgroups	The following groups will be considered separately if data is present: • People with IC due to aorto-iliac disease • People with IC due to femoro-poplitealdisease • People with diabetes
Intervention	Autologous vein
Comparison	Prosthetic bypass
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Walking distance (report all) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.9
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.5 Management of critical limb ischaemia

C.5.1 Angioplasty compared to bypass surgery

Component	Description
Review question	What is the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of PAD in adults with critical limb ischaemia?
Objectives	To compare the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation in the treatment of PAD in adults with critical limb ischaemia.
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV.
Subgroups	The following groups will be considered separately if data is present:

	• People with CLI due to aorto-iliac disease • People with CLI due to femoro-popliteal disease • People with diabetes • People with rest pain • People with tissue loss.
Intervention	• Angioplasty with or without stents • Bypass surgery • Amputation
Comparison	Interventions compared to each other
Outcomes	• Mortality • Amputation free survival • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Adverse events • Re-intervention rates • Change in ABPI. Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use – what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs – any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi randomised trials. For amputation compared to angioplasty, stents or bypass surgery where no RCT data is identified prospective observational studies will be included.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care).
Search Strategy	See Appendix D.3.9
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.512 Angioplasty with selective stent placement compared to primary stent placement

Component	Description
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 critical limb ischaemia?
Objectives	To compare the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement in the treatment of PAD in adults with critical limb ischaemia
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV

Subgroups	The following groups will be considered separately if data is present: • People with CLI due to aorto-iliac disease • People with CLI due to femoro-popliteal disease • People with diabetes • People with rest pain • People with tissue loss.
Intervention	Angioplasty with selective stent placement (include all types of stents)
Comparison	Angioplasty with primary stent placement (include all types of stent)
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.6
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.513 Bare metal compared to drug eluting stents

Component	Description
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 critical limb ischaemia?
Objectives	To compare the clinical and cost effectiveness of bare metal stents compared to drug eluting stents in the treatment of PAD in adults with critical limb ischaemia.
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV
Subgroups	The following groups will be considered separately if data is present: • People with CLI due to aorto-iliac disease • People with CLI due to femoro-poplitealdisease • People with diabetes • People with rest pain

	• People with tissue loss.
Intervention	Bare metal stents
Comparison	Drug eluting stents
Outcomes	• Mortality • Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.7
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.5.14 Autologous vein compared to prosthetic bypass

Component	Description
Review question	What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in adults with critical limb ischaemia?
Objectives	To compare the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in adults with critical limb ischaemia.
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV
Subgroups	The following groups will be considered separately if data is present: • People with CLI due to aorto-iliac disease • People with CLI due to femoro-poplitealdisease • People with diabetes • People with rest pain • People with tissue loss.
Intervention	Autologous vein
Comparison	Prosthetic bypass
Outcomes	• Mortality

	• Amputation free survival (report all) • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Adverse events • Re-intervention rates • Change in ABPI Indicate if the following are reported in the study (do not need to extract actual results for these): • Extra QOL information - HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life) • Resource Use -what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported, • Costs -any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT excluding quasi-randomised trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	Secondary care (excluding emergency care)
Search Strategy	See Appendix D.3.9
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.515 Management of ischaemic pain

Component	Description
Review question	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?
Objectives	To compare the clinical and cost effectiveness of chemical sympathectomy, opiates, gabapentin, pregabalin or tricyclic antidepressants (amitriptyline, nortiptyline and imipramine) compared to each other in any combination in the pain management of adults with critical limb ischemia.
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV.
Subgroups	The following groups will be considered separately if data is present: • People with diabetes • People with tissue loss.
Intervention	• Chemical sympathectomy • Opiates • Gabapentin • Pregabalin • Tricyclic anti-depressants (amitriptyline, nortiptyline or Imipramine)
Comparison	Interventions compared to each other or in combination with each other compared to combinations or single treatments.
Outcomes	• Mortality

	• Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), HUI (Health Utilities Index), QWB (Quality of Well Being), AQol (Assessment of Quality of Life), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) • Adverse events • Pain measures • Duration of pain control. • Patient satisfaction. Indicate if the following are reported in the study (do not need to extract actual results for these): • Resource Use – what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs – any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	RCT, if no RCTs identified prospective observational studies will be included.
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care • Secondary care (excluding emergency care) • Community settings in which NHS care is received
Search Strategy	See Appendix D.3.10
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

C.5.16 Major amputation for critical limb ischaemia

Component	Description
Review question	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?
Objectives	• To consider the clinical indications for major amputation for the management of pain in people with critical limb ischemia • To consider the change in quality of life before and after major amputation in people with critical limb ischemia
Population	Adults (≥ 18 years old) with critical limb ischemia or Fontaine stage III or IV.
Subgroups	The following groups will be considered separately if data is present: • People with diabetes • People with tissue loss.
Intervention	• Clinical indications for major amputation • Quality of life after major amputation
Comparison	• No comparison • Quality of life prior to major amputation
Outcomes	• Clinical indications for major amputation • Quality of life (report all, inc EQ-5D (EuroQol), SF-36 (Short Form 36), SF6D (Short Form 6-Dimensions), SF-12 (Short Form 12-Dimensions), HUI (Health Utilities Index),

	QWB (Quality of Well Being), AQol (Assessment of Quality of Life), RAND-36 (Research and Development Medical Outcomes Study Short Form-36)) Indicate if the following are reported in the study (do not need to extract actual results for these): • Resource Use – what exactly each exercise intervention involves, down-stream resource use associated with the adverse events or outcomes reported • Costs – any type of cost data or discussion of cost-effectiveness (often only a paragraph towards the end of the article).
Study design	Any
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care • Secondary care (excluding emergency care) • Community settings in which NHS care is received
Search Strategy	See Appendix D.3.11.
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Data synthesis of data: • Meta-analysis where appropriate will be conducted.

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Appendix D: Literature search strategies

Search strategies used for the lower limb peripheral arterial disease guideline were run in accordance with then NICE Guidelines Manual 2009:
http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

All searches were run up to 9th January 2012 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

Clinical searches

Searches for clinical reviews were run in Medline (OVID), Embase (OVID), the Cochrane Library (Wiley) and CINAHL (EBSCO). Typically, searches were constructed in the following way:

- A PICO format was used for intervention searches. Population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms (as indicated in the tables under each individual question in Section D.3). An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Study type filters were added where appropriate (see D.1).

In addition to the databases outlined above, search D.3.1 was run in PsycINFO (OVID).

Economic searches

Searches for economic evidence were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Centre for Reviews and Dissemination (CRD) interface. For Medline and Embase an economic filter was added to the same clinical search strategy (see D.1.4). All other searches were conducted using only population terms.

D.1 Study design search terms

D.1.1 Systematic review (SR)

Medline and Embase search terms	
1.	Review.pt. or review.ti. or "review"/
2.	(Systematic* or evidence*or methodol* or quantitativ* or analys* or assessment*).ti,sh,ab.
3.	1 and 2
4.	Meta-analysis.pt.
5.	Meta-analysis/
6.	Meta-analysis as topic/
7.	"Systematic review"/
8.	(Meta-analy* or metanaly* or metaanaly* or meta analy*).ti,ab.
9.	((Systematic* or evidence* or methodol* or quantitativ*) adj5 (review* or survey* or overview*)).ti,ab,sh.
10.	((Pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
11.	Or/3-10

D.1.2 Randomised controlled trials (RCTs)

Medline search terms

1.	Randomized controlled trial.pt.
2.	Controlled clinical trial.pt.
3.	Randomized.ab.
4.	Placebo.ab.
5.	Randomly.ab.
6.	Clinical Trials as topic.sh.
7.	Trial.ti.
8.	Or/1-7
1.	Random*.ti,ab.
2.	Factorial*.ti,ab.
3.	(Crossover* or cross over* or cross-over*).ti,ab.
4.	((Doubl* or singl*) adj blind*).ti,ab.
5.	(Assign* or allocat* or volunteer*).ti,ab.
6.	Crossover procedure/
7.	Double blind procedure/
8.	Single blind procedure/
9.	Randomized controlled trial/
10.	Or/1-9

1

Embase search terms	
1.	Random*.ti,ab.
2.	Factorial*.ti,ab.
3.	(Crossover* or cross over* or cross-over*).ti,ab.
4.	((Doubl* or singl*) adj blind*).ti,ab.
5.	(Assign* or allocat* or volunteer*).ti,ab.
6.	Crossover procedure/
7.	Double blind procedure/
8.	Single blind procedure/
9.	Randomized controlled trial/
10.	Or/1-9

D.123 Observational studies

Medline search terms	
1.	Randomized controlled trial.pt.
2.	Controlled clinical trial.pt.
3.	Double-blind method/ or random allocation/ or single-blind method/
4.	Exp clinical trial/
5	Exp clinical trials as topic/
6.	Clinical trial.pt.
7.	Random.ti,ab.
8.	(Clin* adj25 trial*).ti,ab.
9.	((Singl* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ti,ab.
10.	Placebos/ or placebo*.ti,ab.
11.	Research design/ or comparative study/

12.	Exp evaluation studies/ or follow-up studies/ or prospective studies/
13.	(Volunteer* or "control group" or controls or prospectiv*).ti,ab.
14.	Exp epidemiological studies/
15.	Cohort stud*.ti,ab.
16.	Case control stud*.ti,ab.
17.	((Crossover or cross-over or cross over) adj2 (design* or stud* or procedure* or trial*)).ti,ab.
18.	Or/1-17

1

Embase search terms	
1.	Controlled study/ or randomized controlled trial/
2.	Clinical trial/
3.	Clinical study/ or major clinical study/ or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/
4.	Placebo/
5.	"Double blind procedure"/
6.	Randomization/
7.	((Clinical* or control* or compar*) adj3 (trial* or study or studies)).mp.
8.	Or/1-7
9.	Compar*.tw.
10.	Control*.tw.
11.	9 and 10
12.	Placebo.tw.
13.	Randomi*.tw.
14.	(Blind* or mask*).tw.
15.	Crossover procedure/
16.	(Cross adj2 over adj2 (study or design)).ti,ab.
17.	Exp cohort analysis/
18.	Exp longitudinal study/
19.	Exp prospective study/
20.	Observational study/
21.	Exp follow up/
22.	Cohort studies.ti,ab.
23.	Exp case control study/
24.	Case control stud*.ti,ab.
25.	Or/8,11-24

D.124 Health economic and quality of life search terms

Medline search terms	
1.	exp “costs and cost analysis”?
2.	economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/
3.	exp "fees and charges"/ or exp budgets/
4.	budget$.tw.
5.	cost$.ti.

6.	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
7.	(economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
8.	(price$ or pricing$).tw.
9.	(financial or finance or finances or financed).tw.
10.	(fee or fees).tw.
11.	(value adj2 (money or monetary)).tw.
12.	value of life/ or quality adjusted life year/
13.	quality adjusted life.tw.
14.	(qaly$ or qald$ or qale$ or qtime$).tw.
15.	disability adjusted life.tw.
16.	daly$.tw.
17.	Health Status Indicators/
18.	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
20.	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
21.	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
22.	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
23.	(euroqol or euro qol or eq5d or eq 5d).tw.
24.	(hql or hqol or h qol or hrqol or hr qol).tw.
25.	(hye or hyes).tw.
26.	health$ year$ equivalent$.tw.
27.	health utilit$.tw.
28.	(hui or hui1 or hui2 or hui3).tw.
29.	disutilit$.tw.
30.	rosser.tw.
31.	(quality of wellbeing or quality of well being or qwb).tw.
32.	willingness to pay.tw.
33.	standard gamble$.tw.
34.	time trade off.tw.
35.	time tradeoff.tw.
36.	tto.tw.
37.	exp models, economic/ or *models, theoretical/ or *models, organizational/
38.	economic model$.tw.
39.	markov chains/
40.	markov$.tw.
41.	monte carlo method/
42.	monte carlo.tw.
43.	exp decision theory/
44.	(decision$ adj2 (tree$ or analy$ or model$)).tw.
45.	or/1-44

Embase search terms	
1.	Exp economic aspect/
2.	Cost*.ti.
3.	(Cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab.
4.	(Economic* or pharmacoeconomic* or pharmaco-economic*).ti.
5.	(Price* or pricing*).tw.
6.	(Financial or finance or finances or financed).tw.
7.	(Fee or fees).tw.
8.	(Value adj2 (money or monetary)).tw.
9.	Quality adjusted life year/
10.	Quality adjusted life.tw.
11.	(Qaly* or qald* or qale* or qtime*).tw.
12.	Disability adjusted life.tw.
13.	Daly*.tw.
14.	(Sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
15.	(Sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
16.	(Sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
17.	(Sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
18.	(Sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
19.	(Euroqol or euro qol or eq5d or eq 5d).tw.
20.	(Hql or hqol or h qol or hrqol or hr qol).tw.
21.	(Hye or hyes).tw.
22.	Health* year* equivalent*.tw.
23.	Health utilit*.tw.
24.	(Hui or hui1 or hui2 or hui3).tw.
25.	Disutilit*.tw.
26.	Rosser.tw.
27.	(Quality of wellbeing or quality of well being or qwb).tw.
28.	Willingness to pay.tw.
29.	Standard gamble*.tw.
30.	(Time trade off or time tradeoff or tto).tw.
31.	Exp mathematical model/
32.	Economic model*.tw.
33.	Markov*.tw.
34.	Monte carlo method/
35.	Monte carlo.tw.
36.	Decision theory/
37.	(Decision* adj2 (tree* or analy* or model*)).tw.
38.	Or/1-37

D.2 Standard population search strategies

Medline search terms	
1.[(a)]	Exp peripheral arterial disease/ or peripheral vascular diseases/
2.	Intermittent claudication/
3.	(Pvd or pvod or paod or poad).ti,ab,hw.
4.	(Claudication or claudicant*).ti,ab,hw.
5.	Peripheral vascular disease.ti,ab,hw.
6.	Peripheral arter* disease.ti,ab,hw.
7.	Peripheral arter* occlusive disease.ti,ab,hw.
8.	Critical limb isch?emia.ti,ab.
9.	Fontaine stage.ti,ab.
10.	Or/1-9
11.	Letter.pt.
12.	Letter/
13.	Letter*/
14.	Editorial.pt.
15.	Historical article.pt.
16.	Anecdote.pt.
17.	Commentary.pt.
18.	Note.pt.
19.	Case report/
20.	Case report*.pt.
21.	Case study/
22.	Case study.pt.
23.	Exp animal/ not human/
24.	Nonhuman/
25.	Exp animal studies/
26.	Animals, laboratory/
27.	Exp experimental animal/
28.	Exp animal experiment/
29.	Exp animal model/
30.	Exp rodentia/
31.	Exp rodents/
32.	Exp rodent/
33.	Or/11-32
34.	10 not 33
35.	Limit 34 to English language

(a) The term "peripheral vascular diseases/" was added to the searches from 2011 due to changes in MeSH at the end of 2010.

Embase search terms	
1.	*Peripheral vascular disease/
2.	*Artery disease/
3.	*Intermittent claudication/
4.	(Pvd or pvod or paod or poad).ti,ab.

5.	(Claudication or claudicant*).ti,ab.
6.	Peripheral vascular disease.ti,ab.
7.	Peripheral arter* disease.ti,ab.
8.	Peripheral arter* occlusive disease.ti,ab.
9.	Critical limb isch?emia.ti,ab.
10.	Fontaine stage.ti,ab.
11.	Or/1-10
12.	Letter.pt.
13.	Letter/
14.	Letter*/
15.	Editorial.pt.
16.	Historical article.pt.
17.	Anecdote.pt.
18.	Commentary.pt.
19.	Note.pt.
20.	Case report/
21.	Case report*.pt.
22.	Case study/
23.	Case study.pt.
24.	Exp animal/ not human/
25.	Nonhuman/
26.	Exp animal studies/
27.	Animals, laboratory/
28.	Exp experimental animal/
29.	Exp animal experiment/
30.	Exp animal model/
31.	Exp rodentia/
32.	Exp rodents/
33.	Exp rodent/
34.	Or/12-33
35.	11 not 34
36.	Limit 35 to English language

1

Cinahl search terms	
S1	(MH "peripheral vascular diseases+")
S2	(MH "intermittent claudication")
S3	Pvd or pvod or paod or poad
S4	Claudica*
S5	Peripheral vascular disease
S6	Peripheral arter* disease
S7	Peripheral arter* occlusive disease
S8	Critical limb ischemia
S9	Critical limb ischaemia
S10	Fontaine stage

S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10. Limiters - English Language; Exclude Medline Records

1

Cochrance search terms	
#1	MeSH descriptor peripheral vascular diseases explode all trees
#2	MeSH descriptor intermittent claudication explode all trees
#3	(Pvd or pvod or paod or poad or claudication or claudicant*):ti,ab,kw
#4	Peripheral next vascular next disease:ti,ab,kw
#5	Peripheral next arter* next disease:ti,ab,kw
#6	Peripheral next arter* next occlusive next disease:ti,ab,kw
#7	"Critical limb ischaemia":ti,ab,kw
#8	"Critical limb ischemia":ti,ab,kw
#9	Fontaine stage:ti,ab,kw
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)

2

PscyINFO search terms	
1.	atherosclerosis/
2.	"Arteries (Anatomy)"/
3.	intermittent claudication/
4.	(pvod or paod or poad).ti,ab,hw.
5.	(claudication or claudicant*).ti,ab,hw.
6.	peripheral vascular disease.ti,ab,hw.
7.	peripheral arter* disease.ti,ab,hw.
8.	peripheral arter* occlusive disease.ti,ab,hw.
9.	critical limb isch?emia.ti,ab.
10.	fontaine stage.ti,ab.
11.	or/1-10
12.	letter.pt.
13.	letter/
14.	letter$/
15.	editorial.pt.
16.	historical article.pt.
17.	anecdote.pt.
18.	commentary.pt.
19.	note.pt.
20.	case report/
21.	case report$.pt.
22.	case study/
23.	case study.pt.
24.	exp animal/ not human/
25.	nonhuman/
26.	exp animal studies/
27.	animals, laboratory/
28.	exp experimental animal/

29.	exp animal experiment/
30.	exp animal model/
31.	exp rodentia/
32.	exp rodents/
33.	exp rodent/
34.	or/12-33
35.	11 not 34
36.	limit 35 to english language

D.3 Searches by specific review questions

D.3.1 Information requirements

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

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Patientexperience or preference for information		Observational or SRs [Medline and Embase only]	All years – 09/01/12

Medline search terms	
1.	Exp consumer health information/ or patient education as topic/
2.	Access to information/
3.	Information centers/ or information services/
4.	Health knowledge, attitudes, practice/
5.	Computer-assisted instruction/
6.	Exp internet/
7.	Publications/ or pamphlets/ or electronic mail/ or telephone/ or answering services/ or television/
8.	*Communication/ or communication barriers/ or hotlines/ or information dissemination/ or information seeking behavior/ or persuasive communication/
9.	*Health education/
10.	(Helpline* or hotline* or advice-line* or website*).ti,ab.
11.	(Online adj2 (forum* or communit*)).ti,ab.
12.	((Education* or information) adj2 (provision or prescription* or requirement* or support or need* or pathway* or program* or resource* or material* or intervention*)).ti,ab.
13.	((Active or passive or supervised or interactive or individuali* or client* or patient* or consumer* or carer* or care-giver* or caregiver*) adj2 (information or leaflet* or pamphlet* or infopack* or training or education* or counsel* or advice or advise*)).ti,ab.
14.	("Patient story" or patient stories or access to information or workshop* or "face-to-face" or seminar* or "group setting").ti,ab.
15.	(Telephone adj2 (follow-up or follow up or support)).ti,ab.
16.	Or/1-15
17.	Patient participation/ or counseling/
18.	Social support/

19.	Patient compliance/
20.	Attitude to health/
21.	"Patient acceptance of health care"/ or exp patient satisfaction/
22.	Patient care management/ or comprehensive health care/ or patient-centered care/
23.	"Quality of health care"/
24.	((Client or patient) adj2 (satisfact* or perceive* or view* or buyin or buy-in or cooperation or co-operation or particip* or expectation* or choice* or attitud* or priorit* or perception* or particip* or belief* or preference* or expectation* or experience or opinion*)).ti,ab.
25.	(Patient adj2 (focus* or centered or centred)).ti,ab.
26.	Psychosocial.ti,ab.
27.	Or/17-26
28.	16 or 27

1

Embase search terms	
1.	Exp *patient information/
2.	Exp *patient advocacy/
3.	Exp *patient counseling/
4.	Exp *patient education/
5.	Exp *consumer health information/
6.	Exp *patient participation/
7.	Exp *social support/
8.	Exp *access to information/
9.	*Information center/ or *information dissemination/
10.	*Interpersonal communication/ or *communication skill/ or *persuasive communication/
11.	Exp *internet/
12.	Exp *information service/
13.	Exp *teaching/ or exp *learning/
14.	*E-mail/ or *telephone/ or *television/ or exp *publication/
15.	(Helpline* or hotline* or advice-line* or website*).ti,ab.
16.	(Online adj2 (forum* or communit*)).ti,ab.
17.	((Education* or information) adj2 (provision or prescription* or requirement* or support or need* or pathway* or program* or resource* or material* or intervention*)).ti,ab.
18.	((Active or passive or supervised or interactive or individuali* or client* or patient* or consumer* or carer* or care-giver* or caregiver*) adj2 (information or leaflet* or pamphlet* or infopack* or training or education* or counsel* or advice or advise*)).ti,ab.
19.	("Patient story" or patient stories or access to information or workshop* or "face-to-face" or seminar* or "group setting").ti,ab.
20.	(Telephone adj2 (follow-up or follow up or support)).ti,ab.
21.	*Patient compliance/
22.	*Attitude to health/
23.	*"Patient acceptance of health care"/ or exp *patient satisfaction/
24.	*Patient care management/ or *comprehensive health care/ or *patient-centered care/
25.	*"Quality of health care"/
26.	((Client or patient) adj2 (satisfact* or perceive* or view* or buyin or buy-in or cooperation or co-operation or particip* or expectation* or choice* or attitud* or priorit* or

	perception* or particip* or belief* or preference* or expectation* or experience or opinion*)).ti,ab.
27.	(Patient adj2 (focus* or centered or centred)).ti,ab.
28.	Psychosocial.ti,ab.
29.	Exp patient attitude/
30.	Or/1-29

1

PsycINFO search terms	
1.	(Helpline* or hotline* or advice-line* or website*).ti,ab.
2.	(Online adj2 (forum* or communit*)).ti,ab.
3.	((Education* or information) adj2 (provision or prescription* or requirement* or support or need* or pathway* or program* or resource* or material* or intervention*)).ti,ab.
4.	((Active or passive or supervised or interactive or individuali* or client* or patient* or consumer* or carer* or care-giver* or caregiver*) adj2 (information or leaflet* or pamphlet* or infopack* or training or education* or counsel* or advice or advise*)).ti,ab.
5.	("Patient story" or patient stories or access to information or workshop* or "face-to-face" or seminar* or "group setting").ti,ab.
6.	(Telephone adj2 (follow-up or follow up or support)).ti,ab.
7.	((Client or patient) adj2 (satisfact* or perceive* or view* or buyin or buy-in or cooperation or co-operation or particip* or expectation* or choice* or attitud* or priorit* or perception* or particip* or belief* or preference* or expectation* or experience or opinion*)).ti,ab.
8.	(Patient adj2 (focus* or centered or centred)).ti,ab.
9.	Psychosocial.ti,ab.
10.	Exp client education/ or health knowledge/ or health literacy/ or client participation/
11.	Information seeking/ or computer searching/ or information/ or information literacy/ or information services/
12.	Learning/ or computer assisted instruction/ or audiovisual communications media/ or exp communications media/ or internet/
13.	Exp social networks/ or exp social support/ or counseling/ or peer counseling/ or exp hot line services/
14.	Exp information dissemination/ or persuasive communication/ or interpersonal communiaction/ or group discussion/ or communication barriers/ or exp educational programs/
15.	Exp patient attitude/
16.	Exp client attitudes/ or exp consumer attitudes/ or exp health attitudes/ or patient satisfaction/ or patient care management/
17.	Client centered therapy/
18.	Treatment compliance/
19.	"Quality of care"/
20.	Or/1-19

2

Cinahl search terms	
S1	(MH "patient education") or (MH "consumer health information") or (MH "access to information+") or (MH "libraries+") or (MH "information centers") or (MH "information services") or (MH "library services") or (MH "telephone information services")
S2	(MH "information needs") or (MH "information literacy") or (MH "information resources+")

	or (MH "information seeking behavior") or (MH "communication barriers") or (MH "communications media") or (mm "communication") or (MH "mail+") or (MH "telecommunications+")
S3	(MH "computer assisted instruction") or (MH "electronic data interchange+") or (MH "computer communication networks+") or (mm "knowledge") or (MH "health knowledge") or (mm "learning") or (MH "support, psychosocial+") or (mm "counseling") or (MH "peer counseling") or (MH "consumer participation") or (MH "consumer attitudes")
S4	(MH "attitude to health") or (MH "consumer satisfaction") or (MH "patient satisfaction") or (MH "patient compliance")
S5	(MH "patient centered care") or (MH "quality of health care")
S6	Psychosocial or (patient n2 focus* or patient n2 centered or patient n2 centred) or (client n2 satisfact* or client n2 buyin or client n2 buy-in or client n2 cooperation or client n2 co-operation or client n2 particip* or client n2 expectation* or client n2 choice* or client n2 attitude* or client n2 priorit* or client n2 perception* or client n2 view* or client n2 perceive* or client n2 belief* or client n2 preferenc* or client n2 experience* or client n2 opinion*) or (patient n2 satisfact* or patient n2 buyin or patient n2 buy-in or patient n2 cooperation or patient n2 co-operation or patient n2 particip* or patient n2 expectation* or patient n2 choice* or patient n2 attitude* or patient n2 priorit* or patient n2 perception* or patient n2 view* or patient n2 perceive* or patient n2 belief* or patient n2 preferenc* or patient n2 experience* or patient n2 opinion*)
S7	(Helpline* or adviceline* or advice-line* or website* or hotline* or online n2 forum* or online n2 communit*) or ("patient story" or "patient stories" or "access to information" or workshop* or seminar* or "group setting" or "face-to-face") or (telephone n2 "follow up" or telephone n2 follow-up or telephone n2 support or telephone n2 followup)
S8	(Education* n2 provision or education* n2 prescription* or education* n2 requirement* or education* n2 support or education* n2 need* or education* n2 pathway* or education* n2 program* or education* n2 resource* or education* n2 material* or education* n2 intervention*) or (information n2 provision or information n2 prescription* or information n2 requirement* or information n2 support or information n2 need* or information n2 pathway* or information n2 program* or information n2 resource* or information* n2 material* or information n2 intervention*)
S9	(Active n2 learn* or active n2 education or active n2 information or passive n2 learn* or passive n2 information or interactive n2 education or interactive n2 learn* or interactive n2 information or individuali* n2 learn* or individuali* n2 training or individuali* n2 counsel* or individuali* n2 education or individuali* information or client* n2 information or client* n2 infopack* or client n2 training or client n2 education or client n2 counsel* or consumer n2 information or consumer n2 education or consumer n2 training) or (patient n2 education or patient n2 information or patient n2 leaflet* or patient n2 pamphlet* or patient n2 infopack* or patient n2 counsel*)
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

1

Cochrane search terms	
#1	MeSH descriptor health education explode all trees
#2	MeSH descriptor health education, this term only
#3	MeSH descriptor consumer health information explode all trees
#4	MeSH descriptor patient education as topic, this term only
#5	MeSH descriptor access to information, this term only
#6	MeSH descriptor information centers, this term only
#7	MeSH descriptor information services, this term only
#8	MeSH descriptor health knowledge, attitudes, practice, this term only
#9	MeSH descriptor computer-assisted instruction, this term only

#10	MeSH descriptor internet explode all trees
#11	MeSH descriptor search engine, this term only
#12	MeSH descriptor publications, this term only
#13	MeSH descriptor pamphlets, this term only
#14	MeSH descriptor hotlines, this term only
#15	MeSH descriptor information dissemination, this term only
#16	MeSH descriptor information seeking behavior, this term only
#17	MeSH descriptor communication barriers, this term only
#18	MeSH descriptor persuasive communication, this term only
#19	MeSH descriptor telephone explode all trees
#20	MeSH descriptor television, this term only
#21	MeSH descriptor electronic mail, this term only
#22	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)
#23	(Helpline* or adviceline* or advice-line* or website* or hotline*):ti,ab
#24	Online next (forum* or communit*):ti,ab
#25	((Education* or information) next (provision or prescription or requirement* or support or need* or pathway* or program* or resource* or material* or intervention*)):ti,ab
#26	((Active or passive or interactive or supervised or individuali* or client* or patient* or consumer* or carer* or care-giver* or caregiver*) next (information or leaflet* or pamphlet* or infopack* or training or advice or advise or education* or counsel*)):ti,ab
#27	("Patient story" or "face-to-face" or "patient stories" or "access to information" or workshop* or seminar* or "group setting"):ti,ab
#28	Telephone next ("follow up" or follow-up or support):ti,ab
#29	MeSH descriptor patient participation, this term only
#30	MeSH descriptor counseling, this term only
#31	MeSH descriptor social support, this term only
#32	(#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31)
#33	MeSH descriptor patient compliance explode all trees
#34	MeSH descriptor attitude to health, this term only
#35	MeSH descriptor patient acceptance of health care, this term only
#36	MeSH descriptor consumer satisfaction explode all trees
#37	MeSH descriptor patient care management, this term only
#38	MeSH descriptor comprehensive health care, this term only
#39	MeSH descriptor quality of health care, this term only
#40	MeSH descriptor patient-centered care explode all trees
#41	(#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#42	((Client or patient) next (satisfact* or buyin or buy-in or perceive* or view* or cooperation or co-operation or particip* or expectation* or choice* or attitud* or priorit* or perception* or particip* or belief* or preferenc* or "experience" or "experiences" or opinion*)):ti,ab
#43	(Patient next (focus* or centred or centered)):ti,ab
#44	Psychosocial:ti,ab
#45	(#42 or #43 or #44)
#46	(#22 or #32 or #41 or #45)

D.312 Diagnosis of PAD

The following two questions were searched using a single strategy:

- In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, better in determining the diagnosis and severity of PAD?
- In people undergoing ABPI, do different methods result in different diagnostic accuracy in people with PAD?

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	ABPI or clinical assessment	Diagnostic imaging		All years – 09/01/12

Medline search terms	
1.	Ankle/bs
2.	Leg/bs
3.	Blood pressure determination/
4.	Brachial artery/
5.	Ankle brachial index/
6.	Tibial arteries/
7.	(Abpi or abi or ((ankle or toe) adj2 brachial)).ti,ab.
8.	((Ankle or brachial or posterior or anterior or tibial) adj4 pressure*).ti,ab.
9.	Or/1-8
10.	Exp physical examination/
11.	Medical history taking/
12.	Questionnaires/
13.	(Questionnaire* or medical history).ti,ab.
14.	((Clinical or physical or clinician* or physician*) adj (exam* or assess*)).ti,ab.
15.	Patient history.ti,ab.
16.	Or/10-15
17.	Sensitiv*.ti,ab,hw.
18.	Diagnos*.ti,ab,hw.
19.	Mass screening/
20.	Screen*.ti,ab.
21.	Pc.fs.
22.	Di.fs.
23.	Exp diagnostic imaging/
24.	Or/17-23
25.	(9 or 16) and 24

Embase search terms	
1.	Ankle/
2.	Leg/
3.	Ankle brachial index/
4.	Blood pressure determination/

5.	Blood pressure monitoring/
6.	Brachial artery/
7.	Tibial artery/
8.	Blood pressure measurement/
9.	(ABPI or ABI or ((ankle or toe) adj2 brachial)).ti,ab.
10.	((Ankle or brachial or posterior or anterior or tibial) adj4 pressure*).ti,ab.
11.	Or/1-10
12.	Physical examination/
13.	Anamnesis/
14.	Questionnaires/
15.	(Questionnaire* or medical history).ti,ab.
16.	((Clinical or physical or clinician* or physician*) adj (exam* or assess*)).ti,ab.
17.	Patient history.ti,ab.
18.	Clinical assessment/ or clinical evaluation/
19.	Or/12-18
20.	Sensitiv*.ti,ab,hw.
21.	Diagnos*.ti,ab,hw.
22.	Mass screening/
23.	Screen*.ti,ab.
24.	Pc.fs.
25.	Di.fs.
26.	Exp diagnosis/
27.	Or/20-26
28.	(11 or 19) and 27

1

Cinahl search terms	
S1	MH "leg/bs"
S2	MH "ankle/bs"
S3	(MH "blood pressure determination+")
S4	(MH "brachial artery")
S5	(MH "tibial arteries")
S6	ABPI or ABI
S7	(Ankle or toe) and brachial
S8	(Ankle or brachial or posterior or anterior or tibial) and pressure*
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8
S10	(Clinical or physical or clinician* or physician*) and (exam* or assess*)
S11	Questionnaire* or medical history or patient history
S12	S10 or S11
S13	S9 or S12

2

Cochrane search terms	
#1	MeSH descriptor Ankle explode all trees with qualifier: BS
#2	MeSH descriptor Leg explode all trees with qualifier: BS

#3	MeSH descriptor Blood Pressure Determination, this term only
#4	MeSH descriptor Brachial Artery explode all trees
#5	MeSH descriptor Tibial Arteries explode all trees
#6	MeSH descriptor Ankle Brachial Index explode all trees
#7	(ABPI or ABI):ti,ab
#8	((ankle or toe) near/2 brachial):ti,ab
#9	((ankle or brachial or posterior or anterior or tibial) near/4 pressure*):ti,ab
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11	((clinical or physical or clinician* or physician*) near (exam* or assess*)):ti,ab,kw
#12	(questionnaire* or medical history):ti,ab,kw
#13	patient history:ti,ab
#14	(#11 or #12 or #13)
#15	(#10 or #14)

D.313 Imaging for revascularisation

What is the most clinical and cost effective method of assessment of lower limb PAD (intermittent claudication and critical limb ischaemia)?

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD[(a)]	Diagnostic imaging techniques			All years – 09/01/12

(a) Extra terms added to the standard population.

Medline extra population search terms	
1.	(Iliac adj (arter* or vein* or vessel*)).tw.
2.	(Femoral adj (arter* or vein* or vessel*)).tw.
3.	(Popliteal adj (arter* or vein* or vessel*)).tw.
4.	(Tibial adj (arter* or vein* or vessel*)).tw.
5.	(Peroneal adj (arter* or vein* or vessel*)).tw.
6.	(Genicular adj (arter* or vein* or vessel*)).tw.
7.	(Saphenous adj (vein* or vessel*)).tw.
8.	Femoropopliteal.tw.
9.	Iliofemoral.tw.
10.	Aortoiliac.tw.
11.	Infrapopliteal.tw.
12.	(tibial runoff adj (arter* or Vein* or vessel*)).tw.
13.	(Lower limb* adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
14.	(Lower extremit* adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
15.	(Leg adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
16.	Or/1-15

1

Medline intervention terms	
1.	Exp ultrasonography, doppler, duplex/
2.	Exp ultrasonography, doppler,color/
3.	Exp magnetic resonance angiography/
4.	Exp tomography, x-ray computed/
5.	Duplex ultrasound.tw.
6.	Echography.tw.
7.	Ct angiography.tw.
8.	MRA.ab,ti.
9.	(MR adj2 angiograph*).tw.
10.	(MRIadj2 angiograph*).tw.
11.	Cta.ti,ab.
12.	(Duplex adj2 ultrasound).tw.
13.	MR angiography.tw.
14.	Or/1-13
15.	Limit 14 to yr="2005 - 2011"

2

Embase extra population search terms	
1.	(Iliac adj (arter* or vein* or vessel*)).tw.
2.	(Femoral adj (arter* or vein* or vessel*)).tw.
3.	(Popliteal adj (arter* or vein* or vessel*)).tw.
4.	(Tibial adj (arter* or vein* or vessel*)).tw.
5.	(Peroneal adj (arter* or vein* or vessel*)).tw.
6.	(Genicular adj (arter* or vein* or vessel*)).tw.
7.	(Saphenous adj (vein* or vessel*)).tw.
8.	Femoropopliteal.tw.
9.	Iliofemoral.tw.
10.	Aortoiliac.tw,hw.
11.	Infrapopliteal.tw.
12.	(Tibial runoff adj (arter* or Vein* or vessel*)).tw.
13.	(Lower limb* adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
14.	(Lower extremit* adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
15.	(Leg adj2 (ischaemi* or ischemi* or arter* or vein* or vessel* or vascular or occlusive)).tw.
16.	Or/1-15

3

Embase intervention terms	
1.	Duplex ultrasound.tw.
2.	Echography.tw.
3.	Ct angiography.tw.
4.	Mr angiography.tw.
5.	MRA.ab,ti.

6.	(MR adj2 angiograph*).tw.
7.	(MRI adj2 angiograph*).tw.
8.	CTA.ti,ab.
9.	(Duplex adj2 ultrasound).tw.
10.	Exp computer assisted tomography/
11.	((Duplex or dopler) adj2 ultrasonograph*).tw.
12.	Exp echography/
13.	Or/1-12
14.	Limit 13 to yr="2005 -Current"

1

Cinahl extra population search terms	
S1	Iliac n1 arter* or iliac n1 vein* or iliac n1 vessel*
S2	Femoral n1 arter* or femoral n1 vein* or femoral n1 vessel*
S3	Popliteal n1 arter* or popliteal n1 vein* or popliteal n1 vessel*
S4	Tibial n1 arter* or tibial n1 vein* or tibial n1 vessel*
S5	Peroneal n1 arter* or peroneal n1 vein* or peroneal n1 vessel*
S6	Genicular n1 arter* or genicular n1 vein* or genicular n1 vessel*
S7	Saphenous n1 vein* or saphenous n1 vessel*
S8	Femoropopliteal or iliofemoral or aortoiliac or infrapopliteal
S9	Tibial runoff n1 arter* or tibial runoff n1 vein* or tibial runoff n1 vessel*
S10	Lower limb* n2 ischaem* or lower limb* n2 ischem* or lower limb* n2 arter* or lower limb* n2 vein* or lower limb* n2 vessel* or lower limb* n2 vascular or lower limb* n2 occlusive
S11	Lower extremit* n2 ischaem* or lower extremit* n2 ischem* or lower extremit* n2 arter* or lower extremit* n2 vein* or lower extremit* n2 vessel* or lower extremit* n2 vascular or lower extremit* n2 occlusive
S12	Leg n2 ischaem* or leg n2 ischem* or leg n2 arter* or leg n2 vein* or leg n2 vessel* or leg n2 vascular or leg n2 occlusive
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12

2

Cinahl intervention terms	
S1	(MH "ultrasonography, doppler, color+") or (MH "ultrasonography, doppler, duplex+")
S2	(MH "magnetic resonance angiography")
S3	(MH "tomography, x-ray computed+")
S4	Duplex ultrasound or echography or CT angiography or MT angiography or MRA or CTA
S5	MRI n2 angiograph* or mr n2 angiograph* or duplex n2 ultrasound
S6	S1 or S2 or S3 or S4 or S5

3

Cochrane extra population search terms	
#1	((Lower limb*) near/2 (ischaem* or ischem*)):ti,ab
#2	((Lower extremit*) near/2 (ischaem* or ischem*)):ti,ab
#3	(#1 or #2)

4

1

Cochrane intervention terms	
#1	MeSH descriptor ultrasonography, doppler explode all trees
#2	MeSH descriptor magnetic resonance angiography explode all trees
#3	MeSH descriptor tomography, x-ray computed explode all trees
#4	Duplex ultrasound:ti,ab
#5	Echography:ti,ab
#6	CT angiography:ti,ab
#7	MR angiography:ti,ab.
#8	(MR near/2 angiograph*):ti,ab
#9	(MRI near/2 angiograph*):ti,ab
#10	CTA:ti,ab
#11	(Duplex near/2 ultrasound):ti,ab
#12	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)

D.324 Supervised exercise compared to unsupervised exercise

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

5 Search constructed by combining the columns in the following table using the and Boolean operator:

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Exercise		RCTs or SRs [Medline and Embase only]	All years – 09/01/12

6

Medline search terms	
1.	Exercise/ or exercise therapy/ or physical exercise/ or walking/
2.	(Exercise* adj1 therap*).ti,ab.
3.	(Exercise* or training or program*).ti,ab.
4.	(Exercise adj1 class*).ti,ab.
5.	(Exercise adj3 advice).ti,ab.
6.	Or/1-5

7

Embase search terms	
1.	Exercise/ or kinesiotherapy/ or walking/
2.	(Exercise* adj1 therap*).ti,ab.
3.	(Exercise* or training or program*).ti,ab.
4.	(Exercise adj1 class*).ti,ab.
5.	(Exercise adj3 advice).ti,ab.
6.	Or/1-5

8

Cinahl search terms	
S1	(MH "exercise")
S2	(MH "therapeutic exercise+")
S3	(MH "physical activity")

S4	(MH "physical fitness")
S5	Exercise* n1 class*
S6	Exercise* n1 therap*
S7	Exercise* n3 advice
S8	Supervis* n1 exercise*
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

1

Cochrane search terms	
#1	MeSH descriptor exercise explode all trees
#2	MeSH descriptor exercise therapy explode all trees
#3	Mesh descriptor walking explode trees 1 and 2
#4	(Exercise* near class*):ti,ab
#5	(Exercise* near therap*):ti,ab
#6	(Supervis* near exercise*):ti,ab
#7	(Exercise* near3 advice):ti,ab
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)

D.325 Naftidrofuryl oxalate

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

5 Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Naftidrofuryl oxalate		RCTs [Medline and Embase only]	All years – 09/01/12

6

Medline search terms	
1.	(Cilostazol or opc 13013 or pletaal or pletal).ti
2.	(Inositol nicotinate or cyclohexanehexol hexanicotinate or esantene or hamovannat or hamovanned or hexanicit or hexanicotol or hexopal or inositol hexanicotinate or inositol niacinate or insitol niacinate or linodil or m inosite hexanicotinic acid ester or mesoinositol hexanicotinate or mesoinositol pentanicotinate or mesonex or nsc 49506 or palohexor or veno hexanicit or veno hexanicix).ti
3.	(Naftidrofuryl oxalate or dusodril or dusodril pi or eu 1806 or eu1806 or gevatran or gevatran 200 or iridus or ls 121 or ls121 or nafronyl oxalate or naftidrofuryl hydrogen oxalate or praxilene or sodipryl).ti
4.	(Pentoxifylline or agapurin or agapurin retard or azutrenat or bl 191 or bl191 or claudicat retard or "eht 0201" or eht0201 or elorgan or ikomio or oxpentifylline or oxpentiphylline or oxypentifylline or pentox or pentoxifyllin or pentoxiphylline or pentoxyfyllin or pentoxyfylline or pentoxyphylline or ralofect or ralofekt or relofekt or rentylin or thrental or torental or torestal or trental).ti
5.	Or/1-4

7

Embase search terms	
1.	Exp cilostazol/
2.	(Cilostazol or opc 13013 or pletaal or pletal).ti,ab.

3.	Exp Inositol Nicotinate/
4.	(Inositol nicotinate or cyclohexanehexol hexanicotinate or esantene or hamovannat or hamovanned or hexanicit or hexanicotol or hexopal or inositol hexanicotinate or inositol niacinate or insitol niacinate or linodil or m inosite hexanicotinic acid ester or mesoinositol hexanicotinate or mesoinositol pentanicotinate or mesonex or nsc 49506 or palohexor or veno hexanicit or veno hexanicix).ti,ab.
5.	Exp naftidrofuryl oxalate/
6.	(Naftidrofuryl oxalate or dusodril or dusodril pi or eu 1806 or eu1806 or gevatran or gevatran 200 or iridus or ls 121 or ls121 or nafronyl oxalate or naftidrofuryl hydrogen oxalate or praxilene or sodipryl).ti,ab.
7.	Exp pentoxifylline/
8.	(Pentoxifylline or agapurin or agapurin retard or azutrenat or bl 191 or bl191 or claudicat retard or "eht 0201" or eht0201 or elorgan or ikomio or oxpentifylline or oxpentiphylline or oxypentifylline or pentox or pentoxifyllin or pentoxiphylline or pentoxyfyllin or pentoxyfylline or pentoxyphylline or ralofect or ralofekt or relofekt or rentylin or thrental or torental or torestal or trental).ti,ab.
9.	Or/1-8

1

Cinahl search terms	
S1	Cilostazol or opc 13013 or pletaal or pletal
S2	Inositol nicotinate or cyclohexanehexol hexanicotinate or esantene or hamovannat or hamovanned or hexanicit or hexanicotol or hexopal or inositol hexanicotinate or inositol niacinate or insitol niacinate or linodil or m inosite hexanicotinic acid ester or mesoinositol hexanicotinate or mesoinositol pentanicotinate or mesonex or nsc 49506 or palohexor or veno hexanicit or veno hexanicix
S3	Naftidrofuryl oxalate or dusodril or dusodril pi or eu 1806 or eu1806 or gevatran or gevatran 200 or iridus or ls 121 or ls121 or nafronyl oxalate or naftidrofuryl hydrogen oxalate or praxilene or sodipryl
S4	Pentoxifylline or agapurin or agapurin retard or azutrenat or bl 191 or bl191 or claudicat retard or eht 0201 or eht0201 or elorgan or ikomio or oxpentifylline or oxpentiphylline or oxypentifylline or pentox or pentoxifyllin or pentoxiphylline or pentoxyfyllin or pentoxyfylline or pentoxyphylline or ralofect or ralofekt or relofekt or rentylin or thrental or torental or torestal or trental
S5	S1 or S2 or S3 or S4

2

Cochrane search terms	
#1	(Cilostazol or opc 13013 or pletaal or pletal):ti,ab
#2	(Inositol nicotinate or cyclohexanehexol hexanicotinate or esantene or hamovannat or hamovanned or hexanicit or hexanicotol or hexopal or inositol hexanicotinate or inositol niacinate or insitol niacinate or linodil or m inosite hexanicotinic acid ester or mesoinositol hexanicotinate or mesoinositol pentanicotinate or mesonex or nsc 49506 or palohexor or veno hexanicit or veno hexanicix):ti,ab
#3	(Naftidrofuryl oxalate or dusodril or dusodril pi or eu 1806 or eu1806 or gevatran or gevatran 200 or iridus or ls 121 or ls121 or nafronyl oxalate or naftidrofuryl hydrogen oxalate or praxilene or sodipryl):ti,ab
#4	(Pentoxifylline or agapurin or agapurin retard or azutrenat or bl 191 or bl191 or claudicat retard or eht 0201 or eht0201 or elorgan or ikomio or oxpentifylline or oxpentiphylline or oxypentifylline or pentox or pentoxifyllin or pentoxiphylline or pentoxyfyllin or pentoxyfylline or pentoxyphylline or ralofect or ralofekt or relofekt or rentylin or thrental or torental or torestal or trental):ti,ab

#5	(#1 or #2 or #3 or #4)

D.316 Angioplasty with selective stent placement compared to angioplasty with primary stent placement

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:

a. Intermittent claudication
b. Critical limb ischaemia

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Angioplasty		RCTs or SRs [Medline and Embase only]	All years – 09/01/12

Medline search terms	
1.	Exp angioplasty/ or exp angioplasty, balloon/ or exp angioplasty, laser/ or exp atherectomy/ or exp angioplasty, balloon, laser-assisted/ or exp catheterization, peripheral/
2.	(Angioplast* or atherectom*).ti,ab.
3.	(Endoluminal adj1 repair*).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
6.	(Catheter* adj2 peripheral).ti,ab.
7.	Or/1-6

Embase search terms	
1.	Exp percuteneous transluminal angioplasty/ or exp angioplasty/ or exp laser angioplasty/
2.	(Angioplast* or atherectom*).ti,ab.
3.	(Endoluminal adj1 repair).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Catheter* adj2 peripheral).ti,ab.
6.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
7.	Or/1-6

Cinahl search terms	
S1	MeSH descriptor angioplasty explode all trees
S2	(Angioplast* or atherectom*):ti,ab
S3	(Endoluminal near repair*):ti,ab
S4	(Balloon near (catheter* or dilatation*)):ti,ab
S5	(Dilatation* near2 (transluminal or arter*)):ti,ab
S6	(Catheter* near2 peripheral):ti,ab
S7	(S1 or S2 or S3 or S4 or S5 or S6)

1

Cochrane search terms	
#1	MeSH descriptor angioplasty explode all trees
#2	(Angioplast* or atherectom*):ti,ab
#3	(Endoluminal near repair*):ti,ab
#4	(Balloon near (catheter* or dilatation*)):ti,ab
#5	(Dilatation* near2 (transluminal or arter*)):ti,ab
#6	(Catheter* near2 peripheral):ti,ab
#7	(#1 or #2 or #3 or #4 or #5 or #6)

D.327 Bare metal compared to drug eluting stents

3 What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for
4 the treatment of PAD in adults with:

5 a. Intermittent claudication

6 b. Critical limb ischaemia

7 Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Stents		RCTs or SRs [Medline and Embase only]	All years – 09/01/12

8

Medline search terms	
1.	Stent*.ti,ab,hw.
2.	Restenosis.ti,ab.
3.	Stenos*.ti,ab.
4.	(Pathologic * adj constriction*).ti,ab.
5.	Stricture*.ti,ab.
6.	Pathologic constriction/
7.	Or/1-6

9

Embase search terms	
1.	Stent*.ti,ab,hw.
2.	Exp "Stenosis, Occlusion and obstruction"/ or exp stenosis/
3.	(Restenosis or stenos?s).ti,ab.
4.	(Pathologic * adj constriction*).ti,ab.
5.	Stricture*.ti,ab.
6.	Or/1-5

10

Cinahl search terms	
S1	(MH "stents+")
S2	(MH "graft occlusion, vascular")
S3	(MH "constriction, pathologic")
S4	Stenosis or stenoses or restenosis or stricture* or pathologic* n1 constriction*
S5	S1 or S2 or S3 or S4

1

Cochrane search terms	
#1	MeSH descriptor stents explode all trees
#2	MeSH descriptor constriction, pathologic explode all trees
#3	MeSH descriptor graft occlusion, vascular explode all trees
#4	Restenosis:ti,ab
#5	(Stenosis or stenoses):ti,ab
#6	Pathologic* near/1 constriction*:ti,ab
#7	Stricture*:ti,ab
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)

D.328 Comparison of exercise, best medical treatment angioplasty and bypass surgery

3 What is the clinical and cost effectiveness and safety of endovascular or surgical techniques
4 compared to or in combination with exercise or best medical treatment for the treatment of PAD in
5 adults with intermittent claudication?

6 Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Surgery	Exercise	RCTs or SRs [Medline and Embase only]	All years – 09/01/12

7

Medline search terms	
1.	Exp angioplasty/ or exp angioplasty, balloon/ or exp angioplasty, laser/ or exp atherectomy/ or exp angioplasty, balloon, laser-assisted/ or exp catheterization, peripheral/
2.	(Angioplast* or atherectom*).ti,ab.
3.	(Endoluminal adj1 repair*).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
6.	(Catheter* adj2 peripheral).ti,ab.
7.	Stent*.ti,ab,hw.
8.	Vascular surgical procedures/
9.	Exp surgical procedures, operative/
10.	Su.fs.
11.	Surg*.ti,ab,hw.
12.	Graft*.ti,ab,hw.
13.	Bypass*.ti,ab,hw.
14.	Or/1-13
15.	Exercise/ or exercise therapy/ or physical exercise/ or walking/
16.	(Exercise* adj1 therap*).ti,ab.
17.	(Exercise* or training or program*).ti,ab.
18.	(Exercise adj1 class*).ti,ab.
19.	(Exercise adj3 advice).ti,ab.
20.	Or/15-19
20.	14 and 20

1

Embase search terms	
1.	Exp Percutaneous transluminal angiolplasty/ or exp angioplasty/ or exp Laser angioplasty/
2.	(Angioplast* or atherectom*).ti,ab.
3.	(Endoluminal adj1 repair).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Catheter* adj2 peripheral).ti,ab.
6.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
7.	Stent*.ti,ab,hw.
8.	Exp vascular surgery/
9.	Su.fs.
10.	Exp surgery/
11.	Surg*.ti,ab,hw.
12.	Graft*.ti,ab,hw.
13.	Bypass*.ti,ab,hw.
14.	Or/1-13
15.	Exercise/ or kinesiotherapy/ or walking/
16.	(Exercise* adj1 therap*).ti,ab.
17.	(Exercise* or training or program*).ti,ab.
18.	(exercise adj1 class*).ti,ab.
19.	(exercise adj3 advice).ti,ab.
20.	or/15-19
21.	14 and 20

2

Cinahl search terms	
S1	(MH "angioplasty+") or (MH "angioplasty, balloon+") or (MH "angioplasty, balloon, laser-assisted") or (MH "angioplasty, laser+")
S2	Angioplast* or atherectom*
S3	Endoluminal n1 repair*
S4	Balloon n1 catheter* or balloon n1 dilatation*
S5	Catheter* n2 peripheral
S6	Stent*
S7	Surg* or graft* or bypass*
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7
S9	(MH "exercise")
S10	(MH "therapeutic exercise+")
S11	(MH "physical activity")
S12	(MH "physical fitness")
S13	Exercise* n1 class*
S14	Exercise* n1 therap*
S15	Exercise* n3 advice
S16	Supervis* n1 exercise*
S17	S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16
S18	S8 and S17

1

Cochrane search terms	
#1	MeSH descriptor angioplasty explode all trees
#2	(Angioplast* or atherectom*):ti,ab
#3	(Endoluminal near repair*):ti,ab
#4	(Balloon near (catheter* or dilatation*)):ti,ab
#5	(Dilatation* near2 (transluminal or arter*)):ti,ab
#6	(Catheter* near2 peripheral):ti,ab
#7	Stent*:ti,ab,kw
#8	Surg*:ti,ab,kw
#9	Graft*:ti,ab,kw
#10	Bypass*:ti,ab,kw
#11	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#12	MeSH descriptor Exercise explode all trees
#13	MeSH descriptor Exercise Therapy explode all trees
#14	MeSH descriptor Walking explode trees 1 and 2
#15	(exercise* near class*):ti,ab
#16	(exercise* near therap*):ti,ab
#17	(supervis* near exercise*):ti,ab
#18	(exercise* near3 advice):ti,ab
#19	(#12 or #13 or #14 or #15 or #16 or #17 or #18)
#20	#11 and #19

D.329 Angioplasty compared to bypass surgery compared to amputation and bypass types

3 The following three questions were searched using a single strategy:

4 • What is the clinical and cost effectiveness of angioplasty compared to bypass surgery for the
5 treatment of PAD in adults with intermittent claudication?

6 • What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for
7 treatment of PAD in adults with:

8 a. Intermittent claudication

9 b. Critical limb ischaemia

10 • What is the clinical and cost effectivess of angioplasty compared to surgery compared to
11 amputation for the treatment of PAD in adults with critical limb ischaemia?

12 Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Angioplasty or bypass surgery or amputation		RCTs or SRs [Medline and Embase only]	All years – 09/01/12

13

Medline search terms	
1.	Exp angioplasty/ or exp angioplasty, balloon/ or exp angioplasty, laser/ or exp atherectomy/ or exp angioplasty, balloon, laser-assisted/ or exp catheterization, peripheral/
2.	(Angioplast* or atherectom*).ti,ab.

3.	(Endoluminal adj1 repair*).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
6.	(Catheter* adj2 peripheral).ti,ab.
7.	Stent*.ti,ab,hw.
8.	Or/1-7
9.	Vascular surgical procedures/
10.	Exp surgical procedures, operative/
11.	Su.fs.
12.	Surg*.ti,ab,hw.
13.	Graft*.ti,ab,hw.
14.	Bypass*.ti,ab,hw.
15.	Or/9-14
16.	Exp amputation/
17.	Amput*.ti,ab.
18.	16 or 17
19.	Exp Amputation, Traumatic/
20.	(Trauma* adj amput*).ti,ab.
21.	(Disarticulation* or hemipelvectom*).ti,ab.
22.	(Leg* or lower limb*).ti,ab.
23.	18 or 21
24.	23 not (19 or 20)
25.	24 and 22
26.	8 or 15 or 25

1

Embase search terms	
1.	Exp percuteneous transluminal angioplasty/ or exp angioplasty/ or exp laser angioplasty/
2.	(Angioplast* or atherectom*).ti,ab.
3.	(Endoluminal adj1 repair).ti,ab.
4.	(Balloon adj1 (catheter* or dilatation*)).ti,ab.
5.	(Catheter* adj2 peripheral).ti,ab.
6.	(Dilatation* adj2 (transluminal or arter*)).ti,ab.
7.	Stent*.ti,ab,hw.
8.	Or/1-7
9.	Exp vascular surgery/
10.	Su.fs.
11.	Exp surgery/
12.	Surg*.ti,ab,hw.
13.	Graft*.ti,ab,hw.
14.	Bypass*.ti,ab,hw.
15.	Or/9-14
16.	Exp foot amputation/ or exp knee amputation/ or exp amputaton/ or exp below knee amputation/ or exp above knee amputation/ or exp leg amputation/ or exp limb amputation/

17.	(Amput* or disarticulation* or hemipelvectom*).ti,ab.
18.	16 or 17
19.	Traumatic amputation/
20.	(Trauma* adj amput*).ti,ab.
21.	19 or 20
22.	18 not 21
23.	(Leg* or lower limb*).ti,ab.
24.	22 and 23
25.	8 or 15 or 24

1

Cinahl search terms	
S1	(MH "angioplasty+") or (MH "angioplasty, balloon+") or (MH "angioplasty, balloon, laser-assisted") or (MH "angioplasty, laser+")
S2	Angioplast* or atherectom*
S3	Endoluminal n1 repair*
S4	Balloon n1 catheter* or balloon n1 dilatation*
S5	Catheter* n2 peripheral
S6	Stent*
S7	Surg* or graft* or bypass*
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7
S9	(MH "amputation+") or (MH "above-knee amputation") or (MH "below-knee amputation")
S10	Amput*
S11	Disarticulation* or hemipelvectom*
S12	S9 or S10 or S11
S13	(MH "amputation, traumatic")
S14	Trauma* n1 amput*
S15	S13 or S14
S16	S12 not S15
S17	Leg* or lower limb*
S18	S16 and S17
S19	S8 or S18

2

Cochrane search terms	
#1	MeSH descriptor angioplasty explode all trees
#2	(Angioplast* or atherectom*):ti,ab
#3	(Endoluminal near repair*):ti,ab
#4	(Balloon near (catheter* or dilatation*)):ti,ab
#5	(Dilatation* near2 (transluminal or arter*)):ti,ab
#6	(Catheter* near2 peripheral):ti,ab
#7	Stent*
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9	Surg*:ti,ab,kw
#10	Graft*:ti,ab,kw
#11	Bypass*:ti,ab,kw

#12	(#19 or #10 or #11)
#13	MeSH descriptor amputation explode all trees
#14	Amput*:ti,ab
#15	(Disarticulation* or hemipelvectom*):ti,ab
#16	(#13 or #14 or #15)
#17	(trauma* near amput*):ti,ab
#18	(#16 and not #17)
#19	(#8 or #12 or #18)

D.3.10 Management of ischaemic pain

What is the clinical and cost effectiveness of chemical sympathectomy, opiates, gabapentin, pregbalin or tricyclic antidepressants compared to each other in any combination for the management of pain in adults with critical limb ischaemia?

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Pain relieving agents			All years – 09/01/12

Medline search terms	
1.	Sympathectomy,chemical/
2.	Chemical sympathectom*.ti,ab.
3.	Chemosympathectom*.ti,ab.
4.	(Chemical adj2 sympathetic adj2 denervation).ti,ab.
5.	(Dopamine* or guanethidine* or hydroxydopamine*).ti,ab.
6.	*Analgesics, opioid/
7.	Buprenorphine/ or codeine/ or fentanyl/ or hydromorphone/ or methadone/ or morphine/ or oxycodone/ or pentazocine/ or tramadol/ or opium/
8.	(Buprenorphine or diamorphine or dihydrocodeine or dipipanone or codeine or fentanyl or hydromorphone or methadone or morphine or oxycodone or papaveretum or pentazocine or pethidine or tramadol).ti,ab.
9.	(Temgesic or butrans or transtec).ti,ab.
10.	("DF118 Forte" or "DHC Continus").ti,ab.
11.	(Diconal or abstral or effentora or instanyl or actiq or durogesic).ti,ab.
12.	(palladone or mepid or oramorph or sevredol or morphgesic or "MST continus" or zomorph or "MXL" or minijet or cyclimorph).ti,ab.
13.	(Oxynorm or oxycontin or targinact or hyoscine or pamergan).ti,ab.
14.	(Zamadol or zydol or larapam or mabron or maxitram or tramquel or zeridame or tradorec or tramacel).ti,ab.
15.	Exp nortriptyline/ or exp amitriptyline/ or exp imipramine/
16.	(Gabapentin or neurontin or pregabalin or lyrica or amitriptyline or triptafen or "triptafen-M" or nortriptyline or allegron or imipramine).ti,ab.
17.	Or/1-16

Embase search terms	
1.	Sympathectomy,chemical/

2.	(Chemical adj sympathectom*).ti,ab.
3.	(Chemical adj2 sympathetic adj2 denervation).ti,ab.
4.	Chemosympathectom*.ti,ab.
5.	(Dopamine* or guanethidine* or hydroxydopamine*).ti,ab.
6.	*Analgesics,opioid/
7.	Buprenorphine/ or diamorphine/ or dihydrocodeine/ or dipipanone/ or codeine/ or fentanyl/ or hydromorphone/ or methadone/ or morphine/ or oxycodone/ or papaveretum/ or pentazocine/ or pethidine/ or tramadol/ or opiate/ or opium/
8.	(Buprenorphine or diamorphine or dihydrocodeine or dipipanone or codeine or fentanyl or hydromorphone or methadone or morphine or oxycodone or papaveretum or pentazocine or pethidine or tramadol).ti,ab.
9.	(Temgesic or butrans or transtec).ti,ab.
10.	("DF118 Forte" or "DHC Continus").ti,ab.
11.	(Diconal or abstral or effentora or instanyl or actiq or durogesic).ti,ab.
12.	(palladone or mepid or oramorph or sevredol or morphgesic or "MST continus" or zomorph or "MXL" or minijet or cyclimorph).ti,ab.
13.	(Oxynorm or oxycontin or targinact or hyoscine or pamergan).ti,ab.
14.	(Zamadol or zydol or larapam or mabron or maxitram or tramquel or zeridame or tradorec or tramacel).ti,ab.
15.	Exp nortriptyline/ or exp amitriptyline/ or exp imipramine/ or exp gabapentin/
16.	(Gabapentin or neurontin or pregbalin or lyrica or amitriptyline or triptafen or "triptafen-M" or nortriptyline or allegron or imipramine).ti,ab.
17.	Or/1-16

1

Cinahl search terms	
S1	MH Sympathectomy or chemical sympathectom* or sympathetic n2 denervation or chemosympathect*
S2	MH Analgesics, opioid or buprenorphine or diamorphine or dihydrocodeine or dipipanone or codeine or fentanyl or hydromorphone or methadone or morphine or oxycodone or papaveretum or pentazocine or pethidine or tramadol or temgesic or butrans or transtec or "DF118 Forte" or "DHC Continus" or diconal or abstral or effentora or instanyl or actiq or durogesic or palladone or mepid or oramorph or sevredol or morphgesic or "MST continus" or zomorph or "MXL" or minijet or cyclimorph or oxynorm or oxycontin or targinact or hyoscine or pamergan or zamadol or zydol or larapam or mabron or maxitram or tramquel or zeridame or tradorec or tramacel
S3	Gabapentin or neurontin or pregbalin or lyrica or amuitriptyline or triptafen or "triptafen-M" or nortriptyline or allegron or imipramine
S4	S1 or S2 or S3

2

Cochrane search terms	
#1	MeSH descriptor sympathectomy, chemical, this term only
#2	Chemical sympathectom*:ti,ab,kw
#3	Chemosympathectom*:ti,ab,kw
#4	Sympathetic near denervation:ti,ab,kw
#5	Dopamine* or guanethidine* or hydroxydopamine*:ti,ab,kw
#6	Mesh descriptor analgesics, opioid explode all trees
#7	(Buprenorphine or diamorphine or dihydrocodeine or dipipanone or codeine or fentanyl or

	hydromorphone or methadone or morphine or oxycodone or papaveretum or pentazocine or pethidine or tramadol):ti,ab,kw
#8	(temgesic or butrans or transtec):ti,ab,kw or "DF118 Forte" or "DHC Continus" or diconal or abstral or effentora or instanyl or actiq or durogesic:ti,ab,kw or (palladone or mepid or oramorph or sevredol or morphgesic or "MST continus" or zomorph or "MXL" or minijet or cyclimorph):ti,ab,kw or (oxynorm or oxycontin or targinact or hyoscine or pamergan):ti,ab,kw or (zamadol or zydol or larapam or mabron or maxitram or tramquel or zeridame or tradorec or tramacel):ti,ab,kw
#9	MeSH descriptor nortriptyline explode all trees
#10	Mesh descriptor amitriptyline explode all trees
#11	Gabapentin or neurontin or pregbalin or lyrica or amitriplyline or triptafen or "triptafen-M" or nortriptyline or allegron or imipramine:ti,ab.
#12	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)

D.3.111 Major amputation for critical limb ischaemia

What are the clinical indications for major amputation for the management of pain in patients with critical limb ischaemia and does major amputation improve the quality of life in people with critical limb ischaemia?

Search constructed by combining the columns in the following table using the and Boolean operator

Population	Intervention	Comparison	Study filter used	Date parameters
PAD	Amputation			All years – 09/01/12

Medline search terms	
1.	exp amputation/
2.	amput*.ti,ab.
3.	1or 2
4.	exp Amputation, Traumatic/
5.	(trauma* adj amput*).ti,ab.
6.	(disarticulation* or hemipelvectom*).ti,ab.
7.	(leg* or lower limb*).ti,ab.
8.	3 or 6
9.	8 not (4 or 5)
10.	9 and 7

Embase search terms	
1.	Exp foot amputation/ or exp knee amputation/ or exp amputation/ or exp below knee amputation/ or exp above knee amputation/ or exp leg amputation/ or exp limb amputation/
2.	(amput* or disarticulation* or hemipelvectom*).ti,ab.
3.	1 or 2
4.	Traumatic amputation/
5.	(trauma* adj amput*).ti,ab.
6.	4 or 5
7.	3 not 6

8.	(leg* or lower limb*).ti,ab.
9.	7 and 8

1

Cinahl intervention terms	
S1	(MH "Amputation+") OR (MH "Above-Knee Amputation") OR (MH "Below-Knee Amputation")
S2	Amput*
S3	disarticulation* or hemipelvectom*
S4	S1 or S2 or S3
S5	(MH "Amputation, Traumatic")
S6	trauma* n1 amput*
S7	S5 or S6
S8	S4 NOT S7
S9	leg* or lower limb*
S10	S8 and S9

2

Cochrane intervention terms	
#1	MeSH descriptor Amputation explode all trees
#2	amput*.ti,ab.
#3	(disarticulation* or hemipelvectom*):ti,ab
#4	(#1 OR #2 OR #3)
#5	(trauma* NEAR amput*):ti,ab
#6	(#4 AND NOT #5)

D.4 Economic searches

D.4.1 Economic reviews

5 Economic searches were run in Medline and Embase by combining the standard population with the
6 economic filter and limiting by date range (see table below). Economic searches were executed in the
7 HEED and Centre for Reviews and Dissemination (CRD) (NHS EED and HTA) databases by simply
8 running a standard population without a date limitation. Search terms for the HEED and CRD
9 databases are given below.

10 Search constructed by combining the columns in the following table using the and Boolean operator

Population	Study filter used	Date parameters
PAD	Economic [only Embase and Medline]	• 2010- 09/01/12 (Medline and Embase) • All years – 09/01/12 (NHS EED, HTA and HEED)

11

HEED search terms	
1.	Ax= Peripheral and arterial and disease*
2.	AX= peripheral and vascular and disease*
3.	AX=pvd or pvod or paod or poad or pad
4.	AX=intermittent and claudication
5.	AX= claudication or claudicant*

HEED search terms	
6.	AX=peripheral and arter*and disease*
7.	AX='peripheral occlusive' within 2
8.	AX=peripheral and arter* and occlusive and disease*
9.	CS=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

1

CRD search terms	
1.	MeSH peripheral vascular diseases explode 1
2.	MeSH intermittent claudication explode 1 2
3.	Pvd or pvod or paod or poad or pad or claudication or claudicant*
4.	Peripheral and vascular and disease
5.	Peripheral and arter* and disease
6.	Peripheral and arter* and occlusive and disease
7.	#1 or #2 or #3 or #4 or #5 or #6

2

3

1 Appendix E: Exclusion lists – clinical evidence

E.1 Information requirements

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

5 Excluded n = 31

Study excluded	Reason
Aquarius AE, De VJ, Henegouwen DP, Hamming JF. Clinical Indicators and Psychosocial Aspects in Peripheral Arterial Disease. Archives of Surgery. 2006; 141(2):161-166. (Guideline Ref ID 16188)	Wrong study design (diagnostic study)
Berman JM. Patient Compliance to Written or Verbal Instructions on Taking Inositol Nicotinate (Hexopal) Suspension. A General Practice Study. Clinical Trials Journal. 1981; 18(1):1-8. (Guideline Ref ID 16217)	Wrong comparison (compliance to taking medication)
Bloom RJ, Stevick CA, Lennon S. Patient Perspectives on Smoking and Peripheral Vascular Disease. A Veteran Population Survey. American Surgeon. 1990; 56(9):535-539. (Guideline Ref ID 90)	Wrong comparison (views on smoking not on disease)
Clarke KE, Aish A. An Exploration of Health Beliefs and Attitudes of Smokers With Vascular Disease Who Participate in or Decline a Smoking Cessation Program. Journal of Vascular Nursing. 2002; 20(3):96-105. (Guideline Ref ID 154)	Wrong comparison (views on smoking not on disease)
Collins TC, Krueger PN, Kroll TL, Sharf BF. Face-to-Face Interaction Compared With Video Watching on Use of Physical Activity in Peripheral Arterial Disease: a Pilot Trial. Angiology. 2009; 60(1):21-30. (Guideline Ref ID 132)	Wrong comparison (treatment intervention)
Conn VS, Hafdahl AR, Brown SA, Brown LM. Meta-Analysis of Patient Education Interventions to Increase Physical Activity Among Chronically Ill Adults. Patient Education and Counseling. 2008; 70(2):157-172. (Guideline Ref ID 16267)	Wrong population (not only PAD patients)
Crosby FE, Ventura MR, Frainier MA, Wu YW. Well-Being and Concerns of Patients With Peripheral Arterial Occlusive Disease. Journal of Vascular Nursing. 1993; 11(1):5-11. (Guideline Ref ID 175)	Wrong study design (not a qualitative study)
Eigenbrodt ML, Fuchs FD, Couper DJ, Goff DC, Jr., Sanford CP, Hutchinson RG, Bursac Z. Changing Drinking Pattern Does Not Influence Health Perception: A Longitudinal Study of the Atherosclerosis Risk in Communities Study. Journal of Epidemiology and Community Health. 2006; 60(4):345-350. (Guideline Ref ID 16214)	Wrong population (not only PAD patients)
El-Awady S, Ali AM, Kumber O, El-Maksoud SA, Fareed M. Tibial Corticotomy and Periosteal Elevation Induce Angiogenesis in Chronic Critical Limb Ischaemia. Acta Orthopaedica Belgica. 2008; 74(6):823-830. (Guideline Ref ID 227)	Wrong comparison (surgical intervention)
Fujiwara Y, Takahashi M, Tanaka M, Hoshi T, Someya T, Shinkai S. Relationships Between Plasma Beta -Amyloid Peptide 1-42 and Atherosclerotic Risk Factors in Community-Based Older Populations. Gerontology. 2003; 49(6):374-379. (Guideline Ref ID 264)	Wrong comparison (treatment intervention)
Gorman C. An Educational Intervention for Reducing the Intake of Dietary Fats and Cholesterol Among Middle-Aged and Older Women. Educational Gerontology. 2001; 27(5):417-427. (Guideline Ref ID 16212)	Wrong population (not only PAD patients)
Grace ML, Crosby FE, Ventura MR. Nutritional Education for Patients With Peripheral Vascular Disease. Journal of Health Education. 1994; 25(3):142-146. (Guideline Ref ID 299)	Wrong comparison (treatment intervention)
Graham J, Hiremath S, Magner PO, Knoll GA, Burns KD. Factors Influencing the Prevalence of Central Venous Catheter Use in a Canadian Haemodialysis Centre. Nephrology Dialysis Transplantation. 2008; 23(11):3585-3591. (Guideline Ref ID 300)	Wrong comparison (treatment intervention)

Habib Sr GB. Prevention of Vascular Events in Patients With Cerebrovascular Disease: Efficacy and Appropriate Duration of Antiplatelet Therapy. Clinical Cardiology. 2006; 29(6):244-248. (Guideline Ref ID 16218)	Wrong comparison (preventative treatment)
Johnson M, Newton P, Jiwa M, Goyder E. Meeting the Educational Needs of People at Risk of Diabetes-Related Amputation: a Vignette Study With Patients and Professionals. Health Expectations. 2005; 8(4):324-333. (Guideline Ref ID 479)	Wrong population (not only PAD patients)
Kim YC, Park CI, Kim DY, Kim TS, Shin JC. Statistical Analysis of Amputations and Trends in Korea. Prosthetics & Orthotics International. 1996; 20(2):88-95. (Guideline Ref ID 417)	Wrong comparison
Kuusela J, Manninen HI, Karhapaa P. Infrapopliteal Balloon Angioplasty for Chronic Critical Limb Ischemia in Diabetic Patients With Uremia: When Is It Worth the Effort? Journal of Vascular & Interventional Radiology. 2009; 20(3):342-346. (Guideline Ref ID 437)	Wrong comparison (treatment intervention)
Luft FC. Renal Disease As a Risk Factor for Cardiovascular Disease. Basic Research in Cardiology, Supplement. 2000; 95(1):I/72-I/76. (Guideline Ref ID 468)	Wrong study design (risk factors study)
McDermott MM, Mazor KM, Reed G, Pagoto S, Graff R, Merriam P, Kibbe M, Greenland P, Ockene J, Olendzki B, Huimin T, Ockene I. Attitudes and Behavior of Peripheral Arterial Disease Patients Toward Influencing Their Physician's Prescription of Cholesterol-Lowering Medication. Vascular Medicine. 2010; 15(2):83-90. (Guideline Ref ID 501)	Wrong comparison (patient views on how they influence prescription choices)
Mortimer CM, MacDonald RJ, Martin DJ, McMillan IR, Ravey J, Steedman WM. A Focus Group Study of Health Professionals' Views on Phantom Sensation, Phantom Pain and the Need for Patient Information. Patient Education and Counseling. 2004; 54(2):221-226. (Guideline Ref ID 576)	Wrong population (post amputation)
Mortimer CM, Steedman WM, McMillan IR, Martin DJ, Ravey J. Patient Information on Phantom Limb Pain: a Focus Group Study of Patient Experiences, Perceptions and Opinions. Health Education Research. 2002; 17(3):291-304. (Guideline Ref ID 703)	Wrong population (post amputation)
Rafferty M, Walters MR, Dawson J. Anti-Platelet Therapy and Aspirin Resistance - Clinically and Chemically Relevant? Current Medicinal Chemistry. 2010; 17(36):4578-4586. (Guideline Ref ID 614)	Wrong comparison (treatment intervention)
Richter WO, Jahn P, Jung N, Nielebock E, Tachezy H. Fibrinogen Adsorption in the Diabetic Foot Syndrome and Peripheral Arterial Occlusive Disease: First Clinical Experience. Therapeutic Apheresis. 2001; 5(5):335-339. (Guideline Ref ID 630)	Wrong comparison (treatment intervention)
Sloan PJ. Survey of Patient Information Booklets. British Medical Journal. 1984; 288(6421):915-919. (Guideline Ref ID 1375)	Wrong population (not only PAD patients)
Soot LC, Moneta GL, Edwards JM. Vascular Surgery and the Internet: a Poor Source of Patient-Oriented Information. Journal of Vascular Surgery. 1999; 30(1):84-91. (Guideline Ref ID 854)	Wrong study objectives (states what information is available not patient views on information)
Ventura MR, Todd K, Burch K, Grace ML. Patient Newsletter: A Teaching Tool. Patient Education and Counseling. 1990; 15(3):269-274. (Guideline Ref ID 769)	Wrong study objectives (does not give results on what information is useful to patients)
Ventura MR, Young DE, Feldman MJ, Pastore P, Pikula S, Yates MA. Effectiveness of Health Promotion Interventions. Nursing Research. 1984; 33(3):162-167. (Guideline Ref ID 770)	Wrong intervention
Verhelle N, Vranckx J, Van den Hof B, Heymans O. Bone Exposure in the Leg: Is a Free Muscle Flap Mandatory? Plastic & Reconstructive Surgery. 2005; 116(1):170-177. (Guideline Ref ID 16213)	Wrong comparison (treatment intervention)
Yoshimasu K, Liu Y, Kodama H, Sasazuki S, Washio M, Tanaka K, Tokunaga S, Kono S, Arai H, Koyanagi S, Hiyamuta K, Doi Y, Kawano T, Nakagaki O, Takada K,	Wrong comparison (prevalence study)

Nii T, Shirai K, Ideishi M, Arakawa K, Mohri M, Takeshita A. Job Strain, Type A Behavior Pattern, and the Prevalence of Coronary Atherosclerosis in Japanese Working Men. Journal of Psychosomatic Research. 2000; 49(1):77-83. (Guideline Ref ID 825)	
Ziegler S, Mittermayer F, Plank C, Minar E, Wolzt M, Schernthaner GH. Homocyst(e)Ine-Lowering Therapy Does Not Affect Plasma Asymmetrical Dimethylarginine Concentrations in Patients With Peripheral Artery Disease. Journal of Clinical Endocrinology and Metabolism. 2005; 90(4):2175-2178. (Guideline Ref ID 834)	Wrong comparison (treatment intervention)
Zafar AM, Harris TJ, Murphy TP, Machan JT. Patients' Perspective About Risks and Benefits of Treatment for Peripheral Arterial Disease. Journal of Vascular and Interventional Radiology. 2011; 22(12):1657-1661. (Guideline Ref ID 16358)	Wrong population (did not have a diagnosis of PAD)

E.2 Diagnosis of PAD

The literature search covered the following two review questions:

- In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, better in determining the diagnosis and severity of PAD?
- In people with suspected PAD undergoing ABPI, do different methods result in different diagnostic accuracy?

Excluded n = 262

Study excluded	Reason
Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The Association Between Elevated Ankle Systolic Pressures and Peripheral Occlusive Arterial Disease in Diabetic and Nondiabetic Subjects. Journal of Vascular Surgery. 2008; 48(5):1197-1203. (Guideline Ref ID 16168)	Wrong study design (retrospective)
Aboyans V, Lacroix P, Doucet S, Preux P-M, Criqui MH, Laskar M. Diagnosis of Peripheral Arterial Disease in General Practice: Can the Ankle-Brachial Index Be Measured Either by Pulse Palpation or an Automatic Blood Pressure Device? International Journal of Clinical Practice. 2008; 62(7):1001-1007. (Guideline Ref ID 1740)	Wrong population (no suspected of having PAD as described in protocol)
Aboyans V, Lacroix P, Lebourdon A, Preux PM, Ferrieres J, Laskar M. The Intra- and Interobserver Variability of Ankle-Arm Blood Pressure Index According to Its Mode of Calculation. Journal of Clinical Epidemiology. 2003; 56(3):215-220. (Guideline Ref ID 16179)	Wrong comparison
AbuRahma AF, Diethrich EB. Doppler Ultrasound in Evaluating the Localization and Severity of Peripheral Vascular Occlusive Disease. Southern Medical Journal. 1979; 72(11):1425-1428. (Guideline Ref ID 2786)	Wrong study design (retrospective)
Aerden D, Massaad D, Von Kemp K, Van Tussenbroek F, Debing E, Keymeulen B, Van Den Brande P. The Ankle-Brachial Index and the Diabetic Foot: A Troublesome Marriage. Annals of Vascular Surgery. 2011; 25(6):770-777. (Guideline Ref ID 243)	Wrong population
Al Zahrani HA, Al Bar HM, Bahnassi A, Abdulaal AA. The Distribution of Peripheral Arterial Disease in a Defined Population of Elderly High-Risk Saudi Patients. International Angiology. 1997; 16(2):123-128. (Guideline Ref ID 2006)	No reference standard
Allard L, Cloutier G, Durand LG, Roederer GO, Langlois YE. Limitations of Ultrasonic Duplex Scanning for Diagnosing Lower Limb Arterial Stenoses in the Presence of Adjacent Segment Disease. Journal of Vascular Surgery. 1994; 19(4):650-657. (Guideline Ref ID 2265)	Wrong comparison
Allen J, Murray A. Comparison of Three Arterial Pulse Waveform Classification Techniques. Journal of Medical Engineering & Technology. 1996; 20(3):109-114. (Guideline Ref ID 2077)	Wrong population (not suspected of having PAD as described in protocol)

Allen J, Murray A. Development of a Neural Network Screening Aid for Diagnosing Lower Limb Peripheral Vascular Disease From Photoelectric Plethysmography Pulse Waveforms. Physiological Measurement. 1993; 14(1):13-22. (Guideline Ref ID 2335)	Wrong population (not suspected of having PAD as described in protocol)
Aly S, Sommerville K, Adiseshiah M, Raphael M, Coleridge Smith PD, Bishop CC. Comparison of Duplex Imaging and Arteriography in the Evaluation of Lower Limb Arteries. British Journal of Surgery. 1998; 85(8):1099-1102. (Guideline Ref ID 1916)	Wrong comparison
Anderstrom C, Hallbook T. Resting Blood Pressure Index in Arterial Occlusive Disease of the Lower Limbs. Scandinavian Journal of Thoracic and Cardiovascular Surgery. 1979; 13(2):143-146. (Guideline Ref ID 16191)	Wrong outcome
Aquarius AE, De VJ, Henegouwen DP, Hamming JF. Clinical Indicators and Psychosocial Aspects in Peripheral Arterial Disease. Archives of Surgery. 2006; 141(2):161-166. (Guideline Ref ID 16188)	Wrong study design (non comparative)
Arfvidsson B, Wennmalm A, Gelin J, Dahllof AG, Hallgren B, Lundholm K. Co-Variation Between Walking Ability and Circulatory Alterations in Patients With Intermittent Claudication. European Journal of Vascular Surgery. 1992; 6(6):642-646. (Guideline Ref ID 2185)	No reference standard
Armstrong DWJ, Tobin C, Matangi MF. The Accuracy of the Physical Examination for the Detection of Lower Extremity Peripheral Arterial Disease. Canadian Journal of Cardiology. 2010; 26(10):e346-e350. (Guideline Ref ID 5069)	Wrong comparison
Arveschoug AK, Revsbech P, Brochner-Mortensen J. Sources of Variation in the Determination of Distal Blood Pressure Measured Using the Strain Gauge Technique. Clinical Physiology. 1998; 18(4):361-368. (Guideline Ref ID 16183)	Wrong comparison
Augustine MJ, Eagleton KJ, Graham DH, Story SB, Sullivan WJ, Koontz C, Marchetti G, Tepper SH. Accuracy of the Ankle Brachial Pressure Measurement by Physical Therapists and Physical Therapy Students. Cardiopulmonary Physical Therapy Journal. 2000; 11(3):99-104. (Guideline Ref ID 2059)	Wrong comparison
Bagi P, Sillesen H, Hansen HJ. Quantitative Doppler Ultrasound Evaluation of Occlusive Arterial Disease in the Lower Limb. European Journal of Vascular Surgery. 1988; 2(6):409-415. (Guideline Ref ID 2552)	Wrong comparison
Baker WH, String ST, Hayes AC, Turner D. Diagnosis of Peripheral Occlusive Disease: Comparison of Clinical Evaluation and Noninvasive Laboratory. Archives of Surgery. 1978; 113(11):1308-1310. (Guideline Ref ID 2814)	Wrong population (not suspected of having PAD as described in protocol)
Balaceanu A, Diaconu C. Diagnostic Utility of Ankle-Brachial Index in the Detection and Quantification of Peripheral Arterial Disease of Lower Extremities. Archives of the Balkan Medical Union. 2010; 45(4):279-281. (Guideline Ref ID 1380)	Paper unavailable
Baum RA, Rutter CM, Sunshine JH, Blebea JS, John JP, Carpenter JP, Dickey KW, Quinn SF, Gomes AS, Grist TM, McNeil BJ. Multicenter Trial to Evaluate Vascular Magnetic Resonance Angiography of the Lower Extremity. JAMA. 1995; 274(11):875-880. (Guideline Ref ID 4273)	Wrong comparison
Becker F. Exploration of Arterial Function With Noninvasive Technics. Results in Chronic Arterial Occlusive Disease of the Lower Limbs According to Leriche and Fontaine Classification. International Angiology. 1985; 4(3):311-322. (Guideline Ref ID 2249)	Wrong study design (non comparative)
Beckman JA, Higgins CO, Gerhard-Herman M. Automated Oscillometric Determination of the Ankle-Brachial Index Provides Accuracy Necessary for Office Practice. Hypertension. 2006; 47(1):35-38. (Guideline Ref ID 514)	Wrong comparison
Belcaro G, Sager P, Borgwardt A, Holm A, Jelnes R, Rosenkvist L, Possati F. Arterial Pressure Measurements Correlated to Symptoms and Signs of Peripheral Arterial Disease. Acta Chirurgica Belgica. 1983; 83(5):320-326. (Guideline Ref ID 1201)	Wrong comparison

Benchimol D, Pillois X, Benchimol A, Houitte A, Sagardiluz P, Tortelier L, Bonnet J. Accuracy of Ankle-Brachial Index Using an Automatic Blood Pressure Device to Detect Peripheral Artery Disease in Preventive Medicine. Archives of Cardiovascular Diseases. 2009; 102(6-7):519-524. (Guideline Ref ID 16161)	Wrong population (no suspected of having PAD as described in protocol)
Benchimol A, Bernard V, Pillois X, Hong NT, Benchimol D, Bonnet J. Validation of a New Method of Detecting Peripheral Artery Disease by Determination of Ankle-Brachial Index Using an Automatic Blood Pressure Device. Angiology. 2004; 55(2):127-134. (Guideline Ref ID 626)	Wrong population (no suspected of having PAD as described in protocol)
Bendermacher BL, Teijink JA, Willigendael EM, Bartelink ML, Peters RJ, de Bie RA, Buller HR, Boiten J, Langenberg M, Prins MH. A Clinical Prediction Model for the Presence of Peripheral Arterial Disease--the Benefit of Screening Individuals Before Initiation of Measurement of the Ankle-Brachial Index: an Observational Study. Vascular Medicine. 2007; 12(1):5-11. (Guideline Ref ID 16172)	Wrong comparison
Bjellerup M. Does Dorsal Pedal Pulse Palpation Predict Hand-Held Doppler Measurement of Ankle-Brachial Index in Leg Ulcer Patients? Wounds. 2003; 15(7):237-240. (Guideline Ref ID 2061)	Wrong comparison
Bonham P, Cappuccio M, Hulsey T, Jenkins C, Kelechi T, Michel Y, Robison J. Determining the Validity of Using a Pocket Doppler to Measure Ankle Brachial Index (ABI) and Toe Brachial Index (TBI) for Noninvasive Assessment of Lower Extremity Arterial Disease (LEAD). Journal of Wound, Ostomy and Continence Nursing. 2006; 33(3S):S5. (Guideline Ref ID 2062)	Wrong comparison
Boyko EJ, Ahroni JH, Davignon D, Stensel V, Prigeon RL, Smith DG. Diagnostic Utility of the History and Physical Examination for Peripheral Vascular Disease Among Patients With Diabetes Mellitus. Journal of Clinical Epidemiology. 1997; 50(6):659-668. (Guideline Ref ID 1675)	Wrong study design (cross sectional); palpation of pulses defined as absent, diminished or normal (not continuous measures of ABPI)
Bozkurt AK, Tasci I, Tabak O, Gumus M, Kaplan Y. Peripheral Artery Disease Assessed by Ankle-Brachial Index in Patients With Established Cardiovascular Disease or at Least One Risk Factor for Atherothrombosis - CAREFUL Study: A National, Multi-Center, Cross-Sectional Observational Study. BMC Cardiovascular Disorders. 2011; 11(4) (Guideline Ref ID 5032)	Wrong comparison
Brantigan CO. Peripheral Vascular Disease. A Comparison Between the Vascular Laboratory and the Arteriogram in Diagnosis and Management. Colorado Medicine. 1980; 77(9):320-327. (Guideline Ref ID 2750)	Wrong comparison
Brothers TE, Esteban R, Robison JG, Elliott BM. Symptoms of Chronic Arterial Insufficiency Correlate With Absolute Ankle Pressure Better Than With Ankle: Brachial Index. Minerva Cardioangiologica. 2000; 48(4-5):103-109. (Guideline Ref ID 1732)	Wrong study design (retrospective)
Brouwer BG, Visseren FL, Algra A, Van Bockel JH, Bollen EL, Doevendans PA, Greving JP, Kappelle LJ, Moll FL, Pijl H, Romijn JA, van der Wall EE, van der Graaf Y. Effectiveness of a Hospital-Based Vascular Screening Programme (SMART) for Risk Factor Management in Patients With Established Vascular Disease or Type 2 Diabetes: a Parallel-Group Comparative Study. Journal of Internal Medicine. 2010; 268(1):83-93. (Guideline Ref ID 16242)	Wrong comparison
Bundo M, Munoz L, Perez C, Montero JJ, Montella N, Toran P, Pera G. Asymptomatic Peripheral Arterial Disease in Type 2 Diabetes Patients: a 10-Year Follow-Up Study of the Utility of the Ankle Brachial Index As a Prognostic Marker of Cardiovascular Disease. Annals of Vascular Surgery. 2010; 24(8):985-993. (Guideline Ref ID 16200)	Wrong outcome
Campbell NC, McNiff C, Sheran J, Brittenden J, Lee AJ, Ritchie LD. Targeted Screening for Peripheral Arterial Disease in General Practice: a Pilot Study in a High Risk Group. British Journal of General Practice. 2007; 57(537):311-315.	Wrong population (not suspected of having PAD as described in protocol)

(Guideline Ref ID 16246)	
Campbell WB, Fletcher EL, Hands LJ. Assessment of the Distal Lower Limb Arteries: a Comparison of Arteriography and Doppler Ultrasound. Annals of the Royal College of Surgeons of England. 1986; 68(1):37-39. (Guideline Ref ID 2639)	Wrong population already had diagnosis of PAD
Carbayo JA, Divison JA, Escribano J, Lopez-Abril J, Lopez de CE, Artigao LM, Martinez E, Sanchis C, Masso J, Carrion L, Grupo de Enfermedades Vasculares de Albacete (GEVA). Using Ankle-Brachial Index to Detect Peripheral Arterial Disease: Prevalence and Associated Risk Factors in a Random Population Sample. Nutrition Metabolism and Cardiovascular Diseases. 2007; 17(1):41-49. (Guideline Ref ID 421)	Wrong comparison
Cardia G, Cianci V, Iusco D, Nacchiero M. Ultrasound Duplex As a Sole Exam for Surgical Purposes in Lower Limb Arterial Obstructive Disease. [Review] [14 Refs]. Minerva Cardioangiologica. 2001; 49(5):349-355. (Guideline Ref ID 1622)	Wrong comparison
Carmo GA, Mandil A, Nascimento BR, Arantes BD, Bittencourt JC, Falqueto EB, Ribeiro AL. Can We Measure the Ankle-Brachial Index Using Only a Stethoscope? A Pilot Study. Family Practice. 2009; 26(1):22-26. (Guideline Ref ID 201)	Wrong comparison
Carser DG. Do We Need to Reappraise Our Method of Interpreting the Ankle Brachial Pressure Index? Journal of Wound Care. 2001; 10(3):59-62. (Guideline Ref ID 1582)	Wrong population (not suspected of having PAD as described in protocol)
Carter SA, Tate RB. Value of Toe Pulse Waves in Addition to Systolic Pressures in the Assessment of the Severity of Peripheral Arterial Disease and Critical Limb Ischemia. Journal of Vascular Surgery. 1996; 24(2):258-265. (Guideline Ref ID 2096)	Wrong comparison
Caruana MF, Bradbury AW, Adam DJ. The Validity, Reliability, Reproducibility and Extended Utility of Ankle to Brachial Pressure Index in Current Vascular Surgical Practice. [Review] [85 Refs]. European Journal of Vascular and Endovascular Surgery. 2005; 29(5):443-451. (Guideline Ref ID 562)	Wrong study design (review)
Christensen JH, Freundlich M, Jacobsen BA, Falstie-Jensen N. Clinical Relevance of Pedal Pulse Palpation in Patients Suspected of Peripheral Arterial Insufficiency. Journal of Internal Medicine. 1989; 226(2):95-99. (Guideline Ref ID 2184)	Wrong study design (non comparative)
Chung NS, Han SH, Lim SH, Hong YS, Won JH, Bae JI, Jo J. Factors Affecting the Validity of Ankle-Brachial Index in the Diagnosis of Peripheral Arterial Obstructive Disease. Angiology. 2010; 61(4):392-396. (Guideline Ref ID 5124)	Wrong study design (retrospective)
Clairotte C, Retout S, Potier L, Roussel R, Escoubet B. Automated Ankle-Brachial Pressure Index Measurement by Clinical Staff for Peripheral Arterial Disease Diagnosis in Nondiabetic and Diabetic Patients. Diabetes Care. 2009; 32(7):1231-1236. (Guideline Ref ID 16163)	Wrong reference standard
Collins TC, Suarez-Almazor M, Peterson NJ. An Absent Pulse Is Not Sensitive for the Early Detection of Peripheral Arterial Disease. Family Medicine. 2006; 38(1):38-42. (Guideline Ref ID 1037)	No reference standard
Coni NK. Peripheral Vascular Disease--the Geriatrician's Tale. Postgraduate Medical Journal. 1985; 61(722):1049-1053. (Guideline Ref ID 2644)	Wrong study design (retrospective)
Correa MC, Cullen SJ, Calderon-Ortiz M, Walburn FJ, Raines J. Identification of Peripheral Vascular Disease With Real-Time Ultrasonic Imaging. International Angiology. 1985; 4(2):255-261. (Guideline Ref ID 2642)	No reference standard
Cortez-Cooper MY, Supak JA, Tanaka H. A New Device for Automatic Measurements of Arterial Stiffness and Ankle-Brachial Index. American Journal of Cardiology. 2003; 91(12):1519-1522. (Guideline Ref ID 1587)	Wrong population (excluded those with cardiovascular risk factors)
Couch NP. How to Establish a Diagnosis in Peripheral Vascular Disease. Geriatrics. 1981; 36(2):44-52. (Guideline Ref ID 2744)	Wrong study design (narrative)
Cournot MB. Accuracy of the Screening Physical Examination to Identify	Wrong population (not

Subclinical Atherosclerosis and Peripheral Arterial Disease in Asymptomatic Subjects. Journal of Vascular Surgery. 2007; 46(6):1215-1221. (Guideline Ref ID 1805)	suspected of having PAD as described in protocol)
Creager MA. Clinical Assessment of the Patient With Claudication: The Role of the Vascular Laboratory. Vascular Medicine. 1997; 2(3):231-237. (Guideline Ref ID 1673)	Wrong study design (narrative)
Criqui MH, Coughlin SS, Fronek A. Noninvasively Diagnosed Peripheral Arterial Disease As a Predictor of Mortality: Results From a Prospective Study. Circulation. 1985; 72(4):768-773. (Guideline Ref ID 2655)	Wrong comparison
Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The Prevalence of Peripheral Arterial Disease in a Defined Population. Circulation. 1985; 71(3):510-515. (Guideline Ref ID 2667)	Wrong comparison
Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The Sensitivity, Specificity, and Predictive Value of Traditional Clinical Evaluation of Peripheral Arterial Disease: Results From Noninvasive Testing in a Defined Population. Circulation. 1985; 71(3):516-522. (Guideline Ref ID 2666)	Wrong comparison
Currie IC, Wilson YG, Baird RN, Lamont PM. Postocclusive Hyperaemic Duplex Scan: a New Method of Aortoiliac Assessment. British Journal of Surgery. 1995; 82(9):1226-1229. (Guideline Ref ID 2173)	Wrong comparison
Cushman M, Callas PW, Denenberg JO, Bovill EG, Criqui MH. Risk Factors for Peripheral Venous Disease Resemble Those for Venous Thrombosis: the San Diego Population Study. Journal of Thrombosis and Haemostasis. 2010; 8(8):1730-1735. (Guideline Ref ID 35)	Wrong population (DVT and pulmonary embolus patients)
Cutajar CL, Marston A, Newcombe JF. Value of Cuff Occlusion Pressures in Assessment of Peripheral Vascular Disease. BMJ. 1973; 2(5863):392-395. (Guideline Ref ID 1825)	Wrong comparison
Davies AH, Willcox JH, Magee TR, Currie I, Cole SE, Murphy P, Lamont PM, Baird RN. Colour Duplex in Assessing the Infrainguinal Arteries in Patients With Claudication. Cardiovascular Surgery. 1995; 3(2):211-212. (Guideline Ref ID 2204)	Wrong population (not suspected of having PAD as described in protocol)
de Graaff JC, Ubbink DT, Tijssen JG, Legemate DA. The Diagnostic Randomized Clinical Trial Is the Best Solution for Management Issues in Critical Limb Ischemia. Journal of Clinical Epidemiology. 2004; 57(11):1111-1118. (Guideline Ref ID 16194)	Wrong comparison
de Graaff JC, Ubbink DT, Legemate DA, Tijssen JG, Jacobs MJ. Evaluation of Toe Pressure and Transcutaneous Oxygen Measurements in Management of Chronic Critical Leg Ischemia: a Diagnostic Randomized Clinical Trial. Journal of Vascular Surgery. 2003; 38(3):528-534. (Guideline Ref ID 700)	Wrong comparison
de Graaff JC, Ubbink DT, Legemate DA, de Haan RJ, Jacobs MJ. Interobserver and Intraobserver Reproducibility of Peripheral Blood and Oxygen Pressure Measurements in the Assessment of Lower Extremity Arterial Disease. Journal of Vascular Surgery. 2001; 33(5):1033-1040. (Guideline Ref ID 16181)	Wrong outcomes
de Groote P, Millaire A, Deklunder G, Marache P, Decoulx E, Ducloux G. Comparative Diagnostic Value of Ankle-to-Brachial Index and Transcutaneous Oxygen Tension at Rest and After Exercise in Patients With Intermittent Claudication. Angiology. 1995; 46(2):115-122. (Guideline Ref ID 996)	Wrong comparison
de Virgilio C., Toosie K, Arnell T, Lewis RJ, Donayre CE, Baker JD, Melany M, White RA. Asymptomatic Carotid Artery Stenosis Screening in Patients With Lower Extremity Atherosclerosis: a Prospective Study. Annals of Vascular Surgery. 1997; 11(4):374-377. (Guideline Ref ID 2012)	Wrong comparison
Delius W, Erikson U. Correlation Between Angiographic and Hemodynamic Findings in Occlusions of Arteries of the Extremities. Vascular Surgery. 1969; 3(4):201-210. (Guideline Ref ID 2998)	Wrong comparison

Dewhurst G, Wood DA, Walker F, Lampe FC, Jeffreys M, Cooper M, Williams JD. A Population Survey of Cardiovascular Disease in Elderly People: Design, Methods and Prevalence Results. Age and Ageing. 1991; 20(5):353-360. (Guideline Ref ID 16231)	Wrong population (not suspected of having PAD as described in protocol)
Diehm C, Schuster A, Spengel FA, Trampisch HJ, Allenberg JR, Darius H, et al. GetABI: German Epidemiological Trial on Ankle Brachial Index for Elderly Patients in Family Practice to Dedect Peripheral Arterial Disease, Significant Marker for High Mortality. Vasa. 2002; 31(4):241-248. (Guideline Ref ID 1604)	Describes study protocol, results not available
Diehm N, Dick F, Czuprin C, Lawall H, Baumgartner I, Diehm C. Oscillometric Measurement of Ankle-Brachial Index in Patients With Suspected Peripheral Disease: Comparison With Doppler Method. Swiss Medical Weekly. 2009; 139(25-26):357-363. (Guideline Ref ID 16164)	Wrong outcome
Dormandy JA, Loh A. Differential Diagnosis of Intermittent Claudication and the Adequacy of Epidemiological Studies. Annales Chirurgiae Et Gynaecologiae. 1992; 81(2):112-114. (Guideline Ref ID 2388)	Wrong study design (narrative)
Dumville JC, Lee AJ, Smith FB, Fowkes FG. The Health-Related Quality of Life of People With Peripheral Arterial Disease in the Community: the Edinburgh Artery Study. British Journal of General Practice. 2004; 54(508):826-831. (Guideline Ref ID 600)	Describes patient characteristics
Dunican A, Patterson R, Scissons R, Gillis J, Weyman A, Hopkins R. The Use of Segmental Femoropopliteal Duplex Scanning for Initial Vascular Laboratory Testing of Patients With Peripheral Arterial Disease. Journal for Vascular Ultrasound. 2003; 27(3):157-160. (Guideline Ref ID 3908)	Wrong comparison
Duprez D, Missault L, Van WA, Clement DL. Comparison Between Ankle and Toe Index in Patients With Peripheral Arterial Disease. International Angiology. 1987; 6(3):295-297. (Guideline Ref ID 1157)	Wrong outcomes (no data for 2X2 table)
Edwards JM, Coldwell DM, Goldman ML, Strandness DE, Jr. The Role of Duplex Scanning in the Selection of Patients for Transluminal Angioplasty. Journal of Vascular Surgery. 1991; 13(1):69-74. (Guideline Ref ID 16233)	Wrong comparison
Eickhoff JH, Engell HC. Diagnostic Correctness of Distal Blood Pressure Measurements in Patients With Arterial Insufficiency. Scandinavian Journal of Clinical and Laboratory Investigation. 1980; 40(7):647-652. (Guideline Ref ID 2746)	Wrong comparison
Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JJF. Pilot Study of Prevalence of Asymptomatic Peripheral Arterial Occlusive Disease in Patients With Diabetes Attending a Hospital Clinic. Practical Diabetes International. 1999; 16(6):163-166. (Guideline Ref ID 3915)	No reference standard
Elsman BHP, Legemate DA, Van Der Heyden FWHM, de VH, Mali WPTM, Eikelboom BC. The Use of Color-Coded Duplex Scanning in the Selection of Patients With Lower Extremity Arterial Disease for Percutaneous Transluminal Angioplasty: A Prospective Study. Cardiovascular and Interventional Radiology. 1996; 19(5):313-316. (Guideline Ref ID 4235)	Wrong comparison
Endres HG, Hucke C, Holland-Letz T, Trampisch HJ. A New Efficient Trial Design for Assessing Reliability of Ankle-Brachial Index Measures by Three Different Observer Groups. BMC Cardiovascular Disorders. 2006; 6:33. (Guideline Ref ID 16175)	Wrong comparison
Erdoes LS, Hunter GC, Venerus BJ, Hall KA, Bull DA, Berman SS, Pallos LL, Copeland JC. Prospective Evaluation of Peripheral Vascular Disease in Heart Transplant Recipients. Journal of Vascular Surgery. 1995; 22(4):434-440. (Guideline Ref ID 2176)	Wrong population (heart transplant patients)
Ezio F, Giacomo C, Maurizio C, Antonella Q, Vincenzo C, Francesco S. Evaluation of Feasibility of Ankle Pressure and Foot Oximetry Values for the Detection of Critical Limb Ischemia in Diabetic Patients. Vascular and Endovascular Surgery. 2010; 44(3):184-189. (Guideline Ref ID 194)	Wrong outcomes

Faglia E, Caravaggi C, Marchetti R, Mingardi R, Morabito A, Piaggesi A, Uccioli L, Ceriello A, SCAR (SCreening for ARteriopathy) Study Group. Screening for Peripheral Arterial Disease by Means of the Ankle-Brachial Index in Newly Diagnosed Type 2 Diabetic Patients. Diabetic Medicine. 2005; 22(10):1310-1314. (Guideline Ref ID 534)	Wrong outcomes (prevalence of PAD in diabetic population)
Farkas K, Jarai Z, Kolossvary E, Ludanyi A, Kiss I. Screening for Asymptomatic Peripheral Artery Disease: First Results of the Evaluation of Ankle/BRachial Index in Hungarian HypertensiVes (ERV) Screening Program. European Heart Journal. 2009; 30(Suppl 1):509. (Guideline Ref ID 16352)	Wrong study design (abstract)
Feigelson HS, Criqui MH, Fronek A, Langer RD, Molgaard CA. Screening for Peripheral Arterial Disease: the Sensitivity, Specificity, and Predictive Value of Noninvasive Tests in a Defined Population. American Journal of Epidemiology. 1994; 140(6):526-534. (Guideline Ref ID 16225)	Wrong comparison
Fisher CM, Burnett A, Makeham V, Kidd J, Glasson M, Harris JP. Variation in Measurement of Ankle-Brachial Pressure Index in Routine Clinical Practice. Journal of Vascular Surgery. 1996; 24(5):871-875. (Guideline Ref ID 948)	Wrong comparison
FitzGerald DE, Carr J. Peripheral Arterial Disease: Assessment by Arteriography and Alternative Noninvasive Measurements. American Journal of Roentgenology. 1977; 128(3):385-388. (Guideline Ref ID 2844)	Wrong study design (retrospective)
Flanigan DP, Ballard JL, Robinson D, Galliano M, Blecker G, Harward TR. Duplex Ultrasound of the Superficial Femoral Artery Is a Better Screening Tool Than Ankle-Brachial Index to Identify at Risk Patients With Lower Extremity Atherosclerosis. Journal of Vascular Surgery. 2008; 47(4):789-792. (Guideline Ref ID 16127)	Regression analysis
Fowkes FG, Allan PL, Tsampoulas C, Smith FB, Donnan PT. Validity of Duplex Scanning in the Detection of Peripheral Arterial Disease in the General Population. European Journal of Vascular Surgery. 1992; 6(1):31-35. (Guideline Ref ID 16228)	Wrong comparison
Fowkes FG, Housley E, Macintyre CC, Prescott RJ, Ruckley CV. Variability of Ankle and Brachial Systolic Pressures in the Measurement of Atherosclerotic Peripheral Arterial Disease. Journal of Epidemiology and Community Health. 1988; 42(2):128-133. (Guideline Ref ID 16234)	Wrong comparison
Fozard JB, Wilkinson D, Parkin A, Kester RC. The Application of Isotope Limb Blood Flow Measurement to Diagnostic Problems in Vascular Surgery. Annals of the Royal College of Surgeons of England. 1990; 72(1):45-48. (Guideline Ref ID 2502)	Wrong comparison
Fronek A, Coel M, Bernstein EF. The Pulse-Reappearance Time: an Index of Over-All Blood Flow Impairment in the Ischemic Extremity. Surgery. 1977; 81(4):376-381. (Guideline Ref ID 2841)	Wrong population (not suspected of having PAD as described in protocol)
Fronek A, Johansen KH, Dilley RB, Bernstein EF. Noninvasive Physiologic Tests in the Diagnosis and Characterization of Peripheral Arterial Occlusive Disease. American Journal of Surgery. 1973; 126(2):205-214. (Guideline Ref ID 2931)	Wrong population (not suspected of having PAD as described in protocol)
Gaitini D, Torem S, Pery M, Kaftori JK. Image-Directed Doppler Ultrasound in the Diagnosis of Lower-Limb Venous Insufficiency. Journal of Clinical Ultrasound. 1994; 22(5):291-297. (Guideline Ref ID 16226)	Wrong population
Gale SS, Scissons RP, Salles-Cunha SX, Dosick SM, Whalen RC, Pigott JP, Beebe HG. Lower Extremity Arterial Evaluation: Are Segmental Arterial Blood Pressures Worthwhile? Journal of Vascular Surgery. 1998; 27(5):831-838. (Guideline Ref ID 896)	Wrong comparison
Gardner AW, Montgomery PS. Comparison of Three Blood Pressure Methods Used for Determining Ankle/Brachial Index in Patients With Intermittent Claudication. Angiology. 1998; 49(9):723-728. (Guideline Ref ID 890)	Wrong comparison and outcomes (compares 3 different types of measurements not to a reference standard, does

	not report sensitivity or specificity)
Giargiana FA, Jr., Siegel ME, James AE, Jr., Rhodes BA, Wagner HN, Jr., White RI, Jr. A Preliminary Report on the Complementary Roles of Arteriography and Perfusion Scanning in Assessment of Peripheral Vascular Disease. Radiology. 1973; 108(3):619-627. (Guideline Ref ID 2929)	Wrong comparison
Goodreau JJ, Creasy JK, Flanigan P, Burnham SJ, Kudrna JC, Schafer MF, Bergan JJ, Yao JS. Rational Approach to the Differentiation of Vascular and Neurogenic Claudication. Surgery. 1978; 84(6):749-757. (Guideline Ref ID 2812)	Wrong study design (retrospective)
Grondal N, Lindholt JS. Screening for Peripheral Arterial Disease. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):314-315. (Guideline Ref ID 1483)	Wrong study design (narrative)
Gruntzig A, Schlumpf M. The Validity and Reliability of Post-Stenotic Blood Pressure Measurement by Doppler Ultrasonic Sphygmomanometry. Vasa. 1974; 3(1):65-71. (Guideline Ref ID 1250)	Wrong comparison
Hallett JW, Jr., Greenwood LH, Robison JG. Lower Extremity Arterial Disease in Young Adults. A Systematic Approach to Early Diagnosis. Annals of Surgery. 1985; 202(5):647-652. (Guideline Ref ID 2650)	Wrong population (includes children)
Hamel J-F, Foucaud D, Fanello S. Comparison of the Automated Oscillometric Method With the Gold Standard Doppler Ultrasound Method to Access the Ankle-Brachial Pressure Index. Angiology. 2010; 61(5):487-491. (Guideline Ref ID 5113)	Wrong population (not suspected of having PAD as described in protocol)
Hardy DG, Eadie DG. The Use of Ultrasound in the Evaluation of Peripheral Vascular Disease. British Journal of Clinical Practice. 1972; 26(1):3-8. (Guideline Ref ID 2952)	Wrong comparison
Harrison ML, Lin HF, Blakely DW, Tanaka H. Preliminary Assessment of an Automatic Screening Device for Peripheral Arterial Disease Using Ankle-Brachial and Toe-Brachial Indices. Blood Pressure Monitoring. 2011; 16(3):138-141. (Guideline Ref ID 16297)	Wrong population
Hayko DM. Clinical Practice. Peripheral Vascular Assessment of the Lower Extremities. Home Health Focus. 1998; 5(1):1. (Guideline Ref ID 3940)	Wrong study design (classification)
Hayko DM. Peripheral Vascular Assessment. Is It Venous or Arterial Insufficiency? Home Health Focus. 1998; 5(2):13. (Guideline Ref ID 3941)	Wrong study design (case report)
Hembling BP, Hubler KC, Richard PM, O'Keefe WA, Husfloen C, Wicks R, Dressor H. The Limitations of Ankle Brachial Index When Used Alone for the Detection/Screening of Peripheral Arterial Disease in a Population With an Increased Prevalence of Diabetes. Journal for Vascular Ultrasound. 2007; 31(3):149-151. (Guideline Ref ID 1440)	Wrong study design (retrospective)
Hiatt WR. Sounding the PAD Alarm. GPs Can Diagnose Peripheral Artery Disease With a Simple Ankle-and-Arm Blood Pressure Test. Health News. 2004; 10(4):7. (Guideline Ref ID 16192)	Wrong study design (commentary)
Hiatt WR, Hoag S, Hamman RF. Effect of Diagnostic Criteria on the Prevalence of Peripheral Arterial Disease. The San Luis Valley Diabetes Study. Circulation. 1995; 91(5):1472-1479. (Guideline Ref ID 998)	Wrong outcomes (looked at prevalence of PAD in diabetic population)
Hiatt WR, Marshall JA, Baxter J, Sandoval R, Hildebrandt W, Kahn LR, Hamman RF. Diagnostic Methods for Peripheral Arterial Disease in the San Luis Valley Diabetes Study. Journal of Clinical Epidemiology. 1990; 43(6):597-606. (Guideline Ref ID 2488)	Wrong comparison
Hirai T, Ohishi H, Kichikawa K, Yoshimura H, Uchida H. Ultrasonographic Screening for Arterial Occlusive Disease in the Pelvis and Lower Extremities. Radiation Medicine. 1998; 16(6):411-416. (Guideline Ref ID 1881)	Wrong population (not suspected of having PAD as described in protocol)
Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW,	Wrong population (not

Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care. JAMA. 2001; 286(11):1317-1324. (Guideline Ref ID 16209)	suspected of having PAD as described in protocol)
Hirsch AT, Halverson SL, Treat-Jacobson D, Hotvedt PS, Lunzer MM, Krook S, Rajala S, Hunninghake DB. The Minnesota Regional Peripheral Arterial Disease Screening Program: Toward a Definition of Community Standards of Care. Vascular Medicine. 2001; 6(2):87-96. (Guideline Ref ID 16195)	Wrong study design (non comparative)
Hoffmann MJ, Knudson PE, Silver-Thorn MB. A Device for Noninvasive Assessment of Vascular Impairment Risk in the Lower Extremity. IEEE Transactions on Biomedical Engineering. 2008; 55(12):2786-2791. (Guideline Ref ID 214)	Wrong comparison
Holland-Letz T, Endres HG, Biedermann S, Mahn M, Kunert J, Groh S, Pittrow D, von BP, Sternitzky R, Diehm C. Reproducibility and Reliability of the Ankle-Brachial Index As Assessed by Vascular Experts, Family Physicians and Nurses. Vascular Medicine. 2007; 12(2):105-112. (Guideline Ref ID 374)	Wrong comparison (skill level)
Hooi JD, Stoffers HE, Kester AD, van RJ, Knottnerus JA. Peripheral Arterial Occlusive Disease: Prognostic Value of Signs, Symptoms, and the Ankle-Brachial Pressure Index. Medical Decision Making. 2002; 22(2):99-107. (Guideline Ref ID 16210)	Wrong population (not suspected of having PAD as described in protocol)
Hurlow RA, Chandler ST, Hardman J, Strachan CJ. The Noninvasive Assessment of Aortoiliac Disease: a Comparison of Dynamic Isotope Angiology With Thigh Brachial Pressure Index. Surgery. 1978; 84(2):278-282. (Guideline Ref ID 16236)	Wrong population (not suspected of having PAD as described in protocol)
Hutchison KJ, Oberle K, Scott JA, French AS. A Comparison of Doppler Ultrasonic Waveforms Processed by Zero Crossing and Spectrographic Techniques in the Diagnosis of Peripheral Arterial Disease. Angiology. 1981; 32(4):277-289. (Guideline Ref ID 2737)	Wrong comparison
Imagama S, Matsuyama Y, Sakai Y, Ito Z, Wakao N, Deguchi M, Hachiya Y, Osawa Y, Yoshihara H, Kamiya M, Kanemura T, Kato F, Yukawa Y, Yoshida T, Harada A, Kawakami N, Suzuki K, Matsubara Y, Goto M, Sato K, Ito S, Maruyama K, Yanase M, Ishida Y, Kuno N, Hasegawa T, Ishiguro N. An Arterial Pulse Examination Is Not Sufficient for Diagnosis of Peripheral Arterial Disease in Lumbar Spinal Canal Stenosis: A Prospective Multicenter Study. Spine. 2011; 36(15):1204-1210. (Guideline Ref ID 16298)	No reference standard
Izquierdo-Porrera AM, Gardner AW, Bradham DD, Montgomery PS, Sorkin JD, Powell CC, Katzel LI. Relationship Between Objective Measures of Peripheral Arterial Disease Severity to Self-Reported Quality of Life in Older Adults With Intermittent Claudication. Journal of Vascular Surgery. 2005; 41(4):625-630. (Guideline Ref ID 331)	Wrong comparison
Jarrett F, Detmer DE. The Use of Noninvasive Vascular Studies in the Diagnosis of Peripheral Vascular Disease. Wisconsin Medical Journal. 1977; 76(1):S8-10. (Guideline Ref ID 2846)	Wrong study design (narrative)
Jeelani NU, Braithwaite BD, Tomlin C, MacSweeney ST. Variation of Method for Measurement of Brachial Artery Pressure Significantly Affects Ankle-Brachial Pressure Index Values. European Journal of Vascular and Endovascular Surgery. 2000; 20(1):25-28. (Guideline Ref ID 16182)	Wrong study design (survey)
Jelinek HF, Austin M. The Ankle-Brachial Index in Clinical Decision Making. Foot. 2006; 16(3):153-157. (Guideline Ref ID 1480)	Wrong outcome
Johansson K, Behre CJ, Bergstrom G, Schmidt C. Ankle-Brachial Index Should Be Measured in Both the Posterior and the Anterior Tibial Arteries in Studies of Peripheral Arterial Disease. Angiology. 2010; 61(8):780-783. (Guideline Ref ID 42)	Wrong outcomes
Johansson KE, Marklund BR, Fowelin JH. Evaluation of a New Screening Method for Detecting Peripheral Arterial Disease in a Primary Health Care Population of Patients With Diabetes Mellitus. Diabetic Medicine. 2002; 19(4):307-310. (Guideline Ref ID 16180)	Wrong comparison

Johnston KW, Hosang MY, Andrews DF. Reproducibility of Noninvasive Vascular Laboratory Measurements of the Peripheral Circulation. Journal of Vascular Surgery. 1987; 6(2):147-151. (Guideline Ref ID 1162)	Wrong comparison
Johnston KW, Kakkar VV. Noninvasive Measurement of Systolic Pressure Slope: a Reliable Index of the Presence of Peripheral Arterial Occlusive Disease. Archives of Surgery. 1974; 108(1):52-56. (Guideline Ref ID 2904)	Wrong population (not suspected of having PAD as described in protocol)
Jonsson B, Laurent C, Eneling M, Skau T, Lindberg LG. Automatic Ankle Pressure Measurements Using PPG in Ankle-Brachial Pressure Index Determination. European Journal of Vascular and Endovascular Surgery. 2005; 30(4):395-401. (Guideline Ref ID 537)	Wrong population (no suspected of having PAD as described in protocol)
Jonsson B, Lindberg LG, Skau T, Thulesius O. Is Oscillometric Ankle Pressure Reliable in Leg Vascular Disease? Clinical Physiology. 2001; 21(2):155-163. (Guideline Ref ID 2292)	Wrong population (no suspected of having PAD as described in protocol)
Jorgensen HS, Nakayama H, Raaschou HO, Gam J, Olsen TS. Silent Infarction in Acute Stroke Patients. Prevalence, Localization, Risk Factors, and Clinical Significance: the Copenhagen Stroke Study. Stroke. 1994; 25(1):97-104. (Guideline Ref ID 2273)	Wrong comparison
Jude EB, Eleftheriadou I, Tentolouris N. Peripheral Arterial Disease in Diabetes-a Review. [Review]. Diabetic Medicine. 2010; 27(1):4-14. (Guideline Ref ID 16154)	Wrong study design (review)
Kaiser V, Kester AD, Stoffers HE, Kitslaar PJ, Knottnerus JA. The Influence of Experience on the Reproducibility of the Ankle-Brachial Systolic Pressure Ratio in Peripheral Arterial Occlusive Disease. European Journal of Vascular and Endovascular Surgery. 1999; 18(1):25-29. (Guideline Ref ID 839)	Wrong comparison
Kallero KS, Ericsson BF, Bergentz SE. The Diagnosis Intermittent Claudication. The Value of Walking Test, Ankle Pressure Index and Calf Plethysmography in Relation to the Clinical Findings. Acta Chirurgica Scandinavica. 1983; 149(4):377-382. (Guideline Ref ID 16193)	No reference standard
Karacagil S, Lofberg AM, Granbo A, Lorelius LE, Bergqvist D. Value of Duplex Scanning in Evaluation of Crural and Foot Arteries in Limbs With Severe Lower Limb Ischaemia--a Prospective Comparison With Angiography. European Journal of Vascular and Endovascular Surgery. 1996; 12(3):300-303. (Guideline Ref ID 2074)	Wrong comparison
Katsamouris AN, Giannoukas AD, Tsetis D, Kostas T, Petinarakis I, Gourtsoyiannis N. Can Ultrasound Replace Arteriography in the Management of Chronic Arterial Occlusive Disease of the Lower Limb? European Journal of Vascular and Endovascular Surgery. 2001; 21(2):155-159. (Guideline Ref ID 1670)	Wrong comparison
Kawamura T. Assessing Ankle-Brachial Index (ABI) by Using Automated Oscillometric Devices. Arquivos Brasileiros De Cardiologia. 2008; 90(5):294-298. (Guideline Ref ID 270)	Wrong outcome
Kazmers A, Koski ME, Groehn H, Oust G, Meeker C, Bickford-Laub T, Abson K, Bass N. Assessment of Noninvasive Lower Extremity Arterial Testing Versus Pulse Exam. American Surgeon. 1996; 62(4):315-319. (Guideline Ref ID 2151)	Wrong population (no suspected of having PAD as described in protocol)
Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the Clinical Examination Predict Lower Extremity Peripheral Arterial Disease?. [Review] [65 Refs]. JAMA. 2006; 295(5):536-546. (Guideline Ref ID 16177)	Wrong study design (review – cross checked for studies which match review protocol)
Khan TH, Farooqui FA, Niazi K. Critical Review of the Ankle Brachial Index. Current Cardiology Reviews. 2008; 4(2):101-106. (Guideline Ref ID 1413)	Wrong study design (narrative)
Kiekara O, Riekkinen H, Soimakallio S, Lansimies E. Correlation of Angiographically Determined Reduction of Vascular Lumen With Lower-Limb Systolic Pressures. Acta Chirurgica Scandinavica. 1985; 151(5):437-440. (Guideline Ref ID 2651)	Wrong outcome
Kitaura K, Kida M, Harima K. Assessment of Peripheral Arterial Disease of Lower	Wrong population (not

Limbs With Ultrasonography and Ankle Brachial Index at the Initiation of Hemodialysis. Renal Failure. 2009; 31(9):785-790. (Guideline Ref ID 268)	suspected of having PAD as described in protocol)
Koelemay MJ, Legemate DA, de VH, van Gurp AJ, Balm R, Reekers JA, Jacobs MJ. Duplex Scanning Allows Selective Use of Arteriography in the Management of Patients With Severe Lower Leg Arterial Disease. Journal of Vascular Surgery. 2001; 34(4):661-667. (Guideline Ref ID 1611)	Wrong comparison
Koelemay MJ, den HD, Prins MH, Kromhout JG, Legemate DA, Jacobs MJ. Diagnosis of Arterial Disease of the Lower Extremities With Duplex Ultrasonography. [Review] [48 Refs]. British Journal of Surgery. 1996; 83(3):404-409. (Guideline Ref ID 2119)	Wrong comparison
Komiyama T, Shigematsu H, Yasuhara H, Muto T. Near-Infrared Spectroscopy Grades the Severity of Intermittent Claudication in Diabetics More Accurately Than Ankle Pressure Measurement. British Journal of Surgery. 2000; 87(4):459-466. (Guideline Ref ID 1766)	Wrong comparison
Komiyama T, Shigematsu H, Yasuhara H, Muto T. An Objective Assessment of Intermittent Claudication by Near-Infrared Spectroscopy. European Journal of Vascular Surgery. 1994; 8(3):294-296. (Guideline Ref ID 16227)	Wrong comparison
Korno M, Eldrup N, Sillesen H. Comparison of Ankle-Brachial Index Measured by an Automated Oscillometric Apparatus With That by Standard Doppler Technique in Vascular Patients. European Journal of Vascular and Endovascular Surgery. 2009; 38(5):610-615. (Guideline Ref ID 2163)	Wrong population (no suspected of having PAD as described in protocol)
Kravos A, Bubnic-Sotosek K. Ankle-Brachial Index Screening for Peripheral Artery Disease in Asymptomatic Patients Between 50 and 70 Years of Age. Journal of International Medical Research. 2009; 37(5):1611-1619. (Guideline Ref ID 16157)	Wrong comparison
Kroger K, Bock E, Hohenberger T, Moysidis TH, Santosa F, Pfeifer M. ABI Derived From the Highest and Lowest Ankle Pressure. What Is the Difference? International Angiology. 2010; 29(6):482-488. (Guideline Ref ID 1385)	Wrong population (includes children)
Kroger K, Stewen C, Santosa F, Rudofsky G. Toe Pressure Measurements Compared to Ankle Artery Pressure Measurements. Angiology. 2003; 54(1):39-44. (Guideline Ref ID 685)	Wrong comparison (compares toe and ankle measurements)
Kurtoglu M, Dolay K, Karamustafaoglu B, Yanar H, Kuzkaya M. The Role of the Ankle Brachial Pressure Index in the Diagnosis of Peripheral Arterial Injury. Ulusal Travma Ve Acil Cerrahi Dergisi = Turkish Journal of Trauma & Emergency Surgery: TJTES. 2009; 15(5):448-452. (Guideline Ref ID 16159)	Wrong comparison
Laing S, Greenhalgh RM. The Detection and Progression of Asymptomatic Peripheral Arterial Disease. British Journal of Surgery. 1983; 70(10):628-630. (Guideline Ref ID 2699)	Wrong outcome
Lansing AM. Clinical Evaluation of the Ischemic Leg. Journal of the Kentucky Medical Association. 1971; 69(10):771-776. (Guideline Ref ID 2969)	Wrong study design (narrative)
Larch E, Minar E, Ahmadi R, Schnurer G, Schneider B, Stumpflen A, Ehringer H. Value of Color Duplex Sonography for Evaluation of Tibioperoneal Arteries in Patients With Femoropopliteal Obstruction: a Prospective Comparison With Anterograde Intraarterial Digital Subtraction Angiography. Journal of Vascular Surgery. 1997; 25(4):629-636. (Guideline Ref ID 2026)	Wrong comparison
Lee MY, Lin KD, Chang YH, Hsiao PJ, Shin SJ. Albuminuria Is the Stronger Risk Factor for Peripheral Arterial Disease Than EGFR Decline in a Type 2 Diabetic Taiwanese Population. Kidney and Blood Pressure Research. 2010; 33(5):352-359. (Guideline Ref ID 16153)	Wrong comparison
Lennihan R, Jr., Mackereth M. What Constitutes Proper Evaluation for the Patient With Intermittent Claudication? Vascular Surgery. 1977; 11(5):278-290. (Guideline Ref ID 2824)	Wrong study design (narrative)
Lennihan R, Jr., Mackereth M. Ankle Blood Pressures in Vascular Insufficiency Involving the Legs. Journal of Clinical Ultrasound. 1973; 1(2):120-124. (Guideline	Wrong outcome

Ref ID 2908)	
Lennihan R, Jr., Mackereth M. Ultrasound As an Aid in the Diagnosis and Treatment of Intermittent Claudication. Delaware Medical Journal. 1971; 43(6):157-159. (Guideline Ref ID 2972)	Wrong comparison
Lezack JD, Carter SA. The Relationship of Distal Systolic Pressures to the Clinical and Angiographic Findings in Limbs With Arterial Occlusive Disease. Scandinavian Journal of Clinical and Laboratory Investigation - Supplement. 1973; 128:97-101. (Guideline Ref ID 2911)	Wrong population (not suspected of having PAD as described in protocol)
London NJ, Nydahl S, Hartshorne T, Fishwick G. Use of Colour Duplex Imaging to Diagnose and Guide Angioplasty of Lower Limb Arterial Lesions. British Journal of Surgery. 1999; 86(7):911-915. (Guideline Ref ID 1803)	Wrong comparison
Lundgren F, Schoon IM, Suurkula M. Assessment of Aorto-Iliac Disease by Intraarterial Pressure Measurement. Vasa. 1985; 14(2):139-143. (Guideline Ref ID 1798)	Paper unavailable
Mackaay AJ, Beks PJ, Dur AH, Bischoff M, Scholma J, Heine RJ, Rauwerda JA. The Distribution of Peripheral Vascular Disease in a Dutch Caucasian Population: Comparison of Type II Diabetic and Non-Diabetic Subjects. European Journal of Vascular and Endovascular Surgery. 1995; 9(2):170-175. (Guideline Ref ID 2197)	Wrong comparison
Mackaay AJC, Beks PJ, Dur AHM, Bischoff M, Scholma J, Heine RJ, Rauwerda JA. Is Toe Pressure a Better Parameter of Peripheral Vascular Integrity Than Ankle Pressure? Comparison of Diabetic With Nondiabetic Subjects in Dutch Epidemiological Study. Journal of Vascular Technology. 1995; 19(1):5-9. (Guideline Ref ID 1704)	Wrong comparison
Manzano L, Mostaza JM, Suarez C, Del Valle FJ, Ortiz JA, Sampedro JL, Pose A, Roman P, Vieitez P, Sanchez-Zamorano MA, Merito II Study Group. Prognostic Value of the Ankle-Brachial Index in Elderly Patients With a Stable Chronic Cardiovascular Event. Journal of Thrombosis and Haemostasis. 2010; 8(6):1176-1184. (Guideline Ref ID 76)	No reference standard
Marcon G, Barbato O, Scevola M, Bettin MG, Zolli M. Unnecessary Arterial Doppler Examination of the Legs. Clinical Decision Rules May Help? Quality Assurance in Health Care. 1991; 3(2):115-122. (Guideline Ref ID 16230)	Wrong study design (retrospective)
Marinelli MR, Beach KW, Glass MJ, Primozich JF, Strandness DE, Jr. Noninvasive Testing Vs Clinical Evaluation of Arterial Disease. A Prospective Study. JAMA. 1979; 241(19):2031-2034. (Guideline Ref ID 2800)	No reference standard
Marshall C. The Ankle: Brachial Pressure Index. A Critical Appraisal. British Journal of Podiatry. 2004; 7(4):93-95. (Guideline Ref ID 2090)	Wrong study design (narrative review)
Matesanz JM, Patwardhan N, Herrmann JB. A Simplified Method for Evaluating Peripheral Arterial Occlusive Disease in a Clinical Vascular Laboratory. Angiology. 1978; 29(11):791-799. (Guideline Ref ID 2126)	Wrong study design (retrospective)
Mazzariol F, Ascher E, Salles-Cunha SX, Gade P, Hingorani A. Values and Limitations of Duplex Ultrasonography As the Sole Imaging Method of Preoperative Evaluation for Popliteal and Infrapopliteal Bypasses. Annals of Vascular Surgery. 1999; 13(1):1-10. (Guideline Ref ID 1842)	Wrong comparison
McCully KK, Landsberg L, Suarez M, Hofmann M, Posner JD. Identification of Peripheral Vascular Disease in Elderly Subjects Using Optical Spectroscopy. Journals of Gerontology Series A: Biological Sciences & Medical Sciences. 1997; 52(3):B159-B165. (Guideline Ref ID 2021)	Wrong population (not suspected of having PAD as described in protocol)
McGee SR, Boyko EJ. Physical Examination and Chronic Lower-Extremity Ischemia: a Critical Review. Archives of Internal Medicine. 1998; 158(12):1357-1364. (Guideline Ref ID 1936)	Wrong study design (review)
McPhail I, Spittell PC, Weston SA, Bailey KR. Intermittent Claudication: An Objective Office-Based Assessment. Journal of the American College of Cardiology. 2001; 37(5):1381-1385. (Guideline Ref ID 1630)	Wrong comparison

McWhirt L. Screening Patients for PAD: Early Detection = Treatment & Intervention. Oklahoma Nurse. 2011; 56(2):10. (Guideline Ref ID 16299)	Wrong study design (narrative)
Mehlsen J, Wiinberg N, Joergensen BS, Schultz-Larsen P. High Prevalence of Peripheral Arterial Disease in Patients With Previous Cerebrovascular or Coronary Event. Blood Pressure. 2010; 19(5):308-312. (Guideline Ref ID 16240)	No reference standard
Mehlsen J, Wiinberg N, Bruce C. Oscillometric Blood Pressure Measurement: a Simple Method in Screening for Peripheral Arterial Disease. Clinical Physiology and Functional Imaging. 2008; 28(6):426-429. (Guideline Ref ID 16166)	Wrong reference standard
Migliacci R, Nasorri R, Ricciarini P, Gresele P. Ankle-Brachial Index Measured by Palpation for the Diagnosis of Peripheral Arterial Disease. Family Practice. 2008; 25(4):228-232. (Guideline Ref ID 252)	Wrong comparison
Moffatt CJ, Oldroyd MI, Greenhalgh RM, Franks PJ. Palpating Ankle Pulses Is Insufficient in Detecting Arterial Insufficiency in Patients With Leg Ulceration. Phlebology. 1994; 9(4):170-172. (Guideline Ref ID 4286)	Wrong comparison
Mourad JJ, Cacoub P, Collet JP, Becker F, Pinel JF, Huet D, Sevestre-Pietri MA, Priollet P, ELLIPSE scientific committee and study investigators. Screening of Unrecognized Peripheral Arterial Disease (PAD) Using Ankle-Brachial Index in High Cardiovascular Risk Patients Free From Symptomatic PAD. Journal of Vascular Surgery. 2009; 50(3):572-580. (Guideline Ref ID 16160)	Wrong comparison
Myers KA. Clinical Assessment of Peripheral Arterial Disease. Australian Family Physician. 1980; 9(10):696-706. (Guideline Ref ID 2752)	Wrong study design (narrative)
Nam SC, Han SH, Lim SH, Hong YS, Won JH, Bae JI, Jo J. Factors Affecting the Validity of Ankle-Brachial Index in the Diagnosis of Peripheral Arterial Obstructive Disease. Angiology. 2010; 61(4):392-396. (Guideline Ref ID 16202)	Wrong study design (retrospective)
Nelson JP. The Vascular History and Physical Examination 2413. Clinics in Podiatric Medicine and Surgery. 1992; 9(1):1-17. (Guideline Ref ID 16235)	Wrong study design (narrative)
Niazi K, Khan TH, Easley KA. Diagnostic Utility of the Two Methods of Ankle Brachial Index in the Detection of Peripheral Arterial Disease of Lower Extremities. Catheterization and Cardiovascular Interventions. 2006; 68(5):788-792. (Guideline Ref ID 16173)	Wrong study design (retrospective)
Nicholson ML, Byrne RL, Steele GA, Callum KG. Predictive Value of Bruits and Doppler Pressure Measurements in Detecting Lower Limb Arterial Stenosis. European Journal of Vascular Surgery. 1993; 7(1):59-62. (Guideline Ref ID 16211)	No reference standard
Nicolai SP, Kruidenier LM, Rouwet EV, Bartelink ML, Prins MH, Teijink JA. Ankle Brachial Index Measurement in Primary Care: Are We Doing It Right? British Journal of General Practice. 2009; 59(563):422-427. (Guideline Ref ID 16165)	Wrong comparison (GP V hospital)
Nyamekye I, Sommerville K, Raphael M, Adiseshiah M, Bishop C. Non-Invasive Assessment of Arterial Stenoses in Angioplasty Surveillance: a Comparison With Angiography. European Journal of Vascular and Endovascular Surgery. 1996; 12(4):471-481. (Guideline Ref ID 2063)	Wrong comparison
Nzeh DA, Allan PL, McBride K, Gillespie I, Ruckley CV. Comparison of Colour Doppler Ultrasound and Digital Subtraction Angiography in the Diagnosis of Lower Limb Arterial Disease. African Journal of Medicine and Medical Sciences. 1998; 27(3-4):177-180. (Guideline Ref ID 1876)	Wrong study design (retrospective)
O'Donnell JA, Hobson RW, Lynch TG, Jamil Z, Hart L. Impedance Plethysmography. Noninvasive Diagnosis of Deep Venous Thrombosis and Arterial Insufficiency. American Surgeon. 1983; 49(1):26-30. (Guideline Ref ID 2714)	Wrong outcome
Oksala NK, Viljamaa J, Saimanen E, Venermo M, ATTAC Study Group. Modified Ankle-Brachial Index Detects More Patients at Risk in a Finnish Primary Health Care. European Journal of Vascular and Endovascular Surgery. 2010; 39(2):227-233. (Guideline Ref ID 84)	Wrong comparison
Osmundson PJ. Noninvasive Tests in the Diagnosis of Peripheral Vascular	Wrong study design

Disease. Cardiovascular Clinics. 1980; 10(3):271-277. (Guideline Ref ID 2768)	(narrative)
Pahlsson HI, Laskar C, Stark K, Andersson A, Jogestrand T, Wahlberg E. The Optimal Cuff Width for Measuring Toe Blood Pressure. Angiology. 2007; 58(4):472-476. (Guideline Ref ID 16171)	Wrong comparison
Papanas N, Kakagia D, Papatheodorou K, Papazoglou D, Alexandridou M, Pagkalos A, Karadimas EJ, Maltezos E. Lanarkshire Oximetry Index As a Diagnostic Tool for Peripheral Arterial Disease in Type 2 Diabetes: a Pilot Study. Angiology. 2010; 61(4):388-391. (Guideline Ref ID 16243)	No reference standard
Parkin A, Robinson PJ, Martinez D, Wilkinson D, Kester RC. Radionuclide Limb Blood Flow in Peripheral Vascular Disease: a Review of 1100 Measurements. Nuclear Medicine Communications. 1991; 12(10):835-851. (Guideline Ref ID 16229)	Wrong outcome
Pearson T, Kukulka G, Ur RZ. Ankle Brachial Index Measurement in Primary Care Setting: How Long Does It Take? Southern Medical Journal. 2009; 102(11):1106-1110. (Guideline Ref ID 16158)	Wrong outcomes (assessing the length of time to measure ABPI)
Pearson TL. Peripheral Arterial Disease. Simple Screening Tool Could Diagnose More Cases. [Review] [22 Refs]. Advance for Nurse Practitioners. 2006; 14(7):47-48. (Guideline Ref ID 16174)	Wrong study design (commentary)
Perrodin JP. Non Invasive Assessment of the Peripheral Vascular System: Hand-Held Doppler, Oscillometry, and Air Plethysmography. Acute Care Perspectives. 2001; 10(3):13-15. (Guideline Ref ID 4034)	Paper unavailable
Piecuch T, Jaworski R. Resting Ankle-Arm Pressure Index in Vascular Diseases of the Lower Extremities. Angiology. 1989; 40(3):181-185. (Guideline Ref ID 1134)	Wrong comparison
Postiglione A, Cicerano U, Gallotta G, Gnasso A, Lamenza F, Rubba P, Mancini M. Prevalence of Peripheral Arterial Disease and Related Risk Factors in Elderly Institutionalized Subjects. Gerontology. 1992; 38(6):330-337. (Guideline Ref ID 2384)	Wrong population (no suspected of having PAD as described in protocol)
Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and Utility of Ankle Brachial Index in Patients With Diabetes. [Review]. European Journal of Vascular and Endovascular Surgery. 2011; 41(1):110-116. (Guideline Ref ID 16155)	Wrong study design (review)
Quin RO, Evans DH, Fyee T, Bell PR. Evaluation of Indirect Blood Pressure Measurement As a Method of Assessment of Peripheral Vascular Disease. Journal of Cardiovascular Surgery. 1977; 18(2):109-116. (Guideline Ref ID 1236)	Wrong outcomes (not enough data to construct 2X2 table)
Raines J, Traad E. Noninvasive Evaluation of Peripheral Vascular Disease. Medical Clinics of North America. 1980; 64(2):283-304. (Guideline Ref ID 2766)	Wrong study design (retrospective)
Raines JK, Farrar J, Noicely K, Pena J, Davis WW, Willens HJ, Wallace DD. Ankle/Brachial Index in the Primary Care Setting. Vascular and Endovascular Surgery. 2004; 38(2):131-136. (Guideline Ref ID 1307)	Wrong study design
Ramaswami G, Al-Kutoubi A, Nicolaides AN, Dhanjil S, Coen LD, Belcaro G. The Role of Duplex Scanning in Decision Making for Patients With Claudication. Annals of Vascular Surgery. 1999; 13(6):606-612. (Guideline Ref ID 16222)	Wrong comparison
Ramos R, Baena-Diez JM, Quesada M, Solanas P, Subirana I, Sala J, Alzamora M, Fores R, Masia R, Elosua R, Grau M, Cordon F, Pera G, Rigo F, Marti R, Ponjoan A, Cerezo C, Brugada R, Marrugat J. Derivation and Validation of REASON: A Risk Score Identifying Candidates to Screen for Peripheral Arterial Disease Using Ankle Brachial Index. Atherosclerosis. 2011; 214(2):474-479. (Guideline Ref ID 5038)	Regression model
Ramos R, Quesada M, Solanas P, Subirana I, Sala J, Vila J, Masia R, Cerezo C, Elosua R, Grau M, Cordon F, Juvinya D, Fito M, Isabel CM, Clara A, Angel Munoz M, Marrugat J, REGICOR I. Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-Brachial Index to Stratify Cardiovascular Risk. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):305-311. (Guideline Ref ID 16244)	Wrong population (not suspected of having PAD as described in protocol)

Ramsey DE, Manke DA, Sumner DS. Toe Blood Pressure. A Valuable Adjunct to Ankle Pressure Measurement for Assessing Peripheral Arterial Disease. Journal of Cardiovascular Surgery. 1983; 24(1):43-48. (Guideline Ref ID 2711)	Wrong comparison
Remes L, Isoaho R, Vahlberg T, Viitanen M, Rautava P. Quality of Life Among Lower Extremity Peripheral Arterial Disease Patients Who Have Undergone Endovascular or Surgical Revascularization: a Case-Control Study. European Journal of Vascular and Endovascular Surgery. 2010; 40(5):618-625. (Guideline Ref ID 16156)	Wrong outcomes
Richart T, Kuznetsova T, Wizner B, Struijker-Boudier HA, Staessen JA. Validation of Automated Oscillometric Versus Manual Measurement of the Ankle-Brachial Index. Hypertension Research. 2009; 32(10):884-888. (Guideline Ref ID 131)	Wrong population (no suspected of having PAD as described in protocol)
Sadr SM, Namayandeh SM, Rafiei M, Poor SMB, Aflatoonian M, Mosadegh MM, Foroozannia SK. Agreement Between ABI (Ankle Brachial Index) and USD (Ultrasound Duplex Scanning) in Symptomatic Peripheral Arterial Disease Patients. Journal of Tehran University Heart Center. 2008; 3(1):35-38. (Guideline Ref ID 5350)	No reference standard
Sahli D, Eliasson B, Svensson M, Blohme G, Eliasson M, Samuelsson P, Ojbrandt K, Eriksson JW. Assessment of Toe Blood Pressure Is an Effective Screening Method to Identify Diabetes Patients With Lower Extremity Arterial Disease. Angiology. 2004; 55(6):641-651. (Guideline Ref ID 1544)	Wrong comparison
Sahli D, Svensson M, Lidgren J, Ojbrandt K, Eriksson JW. Evaluation of Simple Non-Invasive Techniques for Assessment of Lower Extremity Arterial Disease. Clinical Physiology and Functional Imaging. 2005; 25(3):129-134. (Guideline Ref ID 4697)	Wrong population (not suspected of having PAD as described in protocol)
Santilli JD, Santilli SM. Chronic Critical Limb Ischemia: Diagnosis, Treatment and Prognosis. [Review] [21 Refs]. American Family Physician. 1999; 59(7):1899-1908. (Guideline Ref ID 2172)	Wrong study design (narrative)
Santilli JD, Rodnick JE, Santilli SM. Claudication: Diagnosis and Treatment. [Review] [35 Refs]. American Family Physician. 1996; 53(4):1245-1253. (Guideline Ref ID 2177)	Wrong study design (retrospective)
Santo SS, Anzaldi M, Fiore V, Catanzaro S, Simili M, Torrisi B, Neri S. Study on Unrecognized Peripheral Arterial Disease (PAD) by Ankle/Brachial Index and Arterial Comorbidity in Catania, Sicily, Italy. Angiology. 2010; 61(6):524-529. (Guideline Ref ID 16201)	Wrong reference standard
Savader SJ, Ehrman KO, Porter DJ, Wilson LD, Oteham AC. The Legs For Life Screening for Peripheral Vascular Disease: Results of a Prospective Study Designed to Improve Patient Compliance With Physician Recommendations. Journal of Vascular and Interventional Radiology. 2001; 12(10):1149-1155. (Guideline Ref ID 1614)	Wrong population (not suspected of having PAD as described in protocol)
Saxon RR, Coffman JM, Gooding JM, Natuzzi E, Ponec DJ. Long-Term Results of EPTFE Stent-Graft Versus Angioplasty in the Femoropopliteal Artery: Single Center Experience From a Prospective, Randomized Trial. Journal of Vascular and Interventional Radiology. 2003; 14(3):303-311. (Guideline Ref ID 441)	Wrong comparison
Schatz IJ. Clinical Assessment of Chronic Occlusive Peripheral Arterial Disease. Hawaii Medical Journal. 1977; 36(5):138-142. (Guideline Ref ID 2837)	Wrong study design (narrative)
Schroll M, Munck O. Estimation of Peripheral Arteriosclerotic Disease by Ankle Blood Pressure Measurements in a Population Study of 60-Year-Old Men and Women. Journal of Chronic Diseases. 1981; 34(6):261-269. (Guideline Ref ID 2736)	Wrong population (not suspected of having PAD as described by protocol)
Sensier Y, Hartshorne T, Thrush A, Handford H, Nydahl S, London NJ. The Effect of Adjacent Segment Disease on the Accuracy of Colour Duplex Scanning for the Diagnosis of Lower Limb Arterial Disease. European Journal of Vascular and Endovascular Surgery. 1996; 12(2):238-242. (Guideline Ref ID 2098)	Wrong comparison

Shafer R, Shafer N, Positano RG. The Early Diagnosis of Peripheral Vascular Disease 2596. Clinics in Podiatric Medicine and Surgery. 1987; 4(3):729-742. (Guideline Ref ID 2596)	Wrong study design (narrative)
Shaheen R, Sohail S. A Doppler-Based Evaluation of Peripheral Lower Limb Arterial Insufficiency in Diabetes Mellitus. Journal of the College of Physicians & Surgeons - Pakistan:JCPSP. 2010; 20(1):22-25. (Guideline Ref ID 16203)	Wrong outcomes
Siegel ME, Giargiana FA, Jr., White RI, Jr., Friedman BH, Wagner HN, Jr. Peripheral Vascular Perfusion Scanning. Correlation With the Arteriogram and Clinical Assessment in the Patient With Peripheral Vascular Disease. American Journal of Roentgenology. 1975; 125(3):628-633. (Guideline Ref ID 2864)	Wrong comparison
Siitonen O, Uusitupa M, Pyorala K, Voutilainen E, Lansimies E. Peripheral Arterial Disease and Its Relationship to Cardiovascular Risk Factors and Coronary Heart Disease in Newly Diagnosed Non-Insulin-Dependent Diabetics. Acta Medica Scandinavica. 1986; 220(3):205-212. (Guideline Ref ID 2348)	Wrong population (not suspected of having PAD as described in protocol)
Sodhi HS, Shrestha SK, Rauniyar R, Rawat B. Prevalence of Peripheral Arterial Disease by Ankle-Brachial Index and Its Correlation With Carotid Intimal Thickness and Coronary Risk Factors in Nepalese Population Over the Age of Forty Years. Kathmandu University Medical Journal. 2007; 5(1):12-15. (Guideline Ref ID 16170)	Wrong comparison
Soulen RL, Lapayowker MS, Tyson RR, Korangy AA. Angiography, Ultrasound, and Thermography in the Study of Peripheral Vascular Disease. Radiology. 1972; 105(1):115-119. (Guideline Ref ID 2945)	Wrong comparison
Spittell JA, Jr. Occlusive Arterial Disease: Recognition and Management. Cardiovascular Clinics. 1980; 10(3):289-300. (Guideline Ref ID 2767)	Wrong study design (narrative)
Sprengers RW, Janssen KJ, Moll FL, Verhaar MC, van der Graaf Y, SMART Study Group. Prediction Rule for Cardiovascular Events and Mortality in Peripheral Arterial Disease Patients: Data From the Prospective Second Manifestations of ARTerial Disease (SMART) Cohort Study. Journal of Vascular Surgery. 2009; 50(6):1369-1376. (Guideline Ref ID 112)	Wrong comparison and outcomes (prevalence study)
Steer HW, Fletcher EW, Morris PJ. A Comparison Between the Ankle Systolic Pressure and Mercury Strain Gauge Plethysmography in the Assessment of Patients With Arterial Disease of the Lower Limbs. Surgery. 1980; 88(5):636-641. (Guideline Ref ID 2749)	Wrong comparison
Stein R, Hriljac I, Halperin JL, Gustavson SM, Teodorescu V, Olin JW. Limitation of the Resting Ankle-Brachial Index in Symptomatic Patients With Peripheral Arterial Disease. Vascular Medicine. 2006; 11(1):29-33. (Guideline Ref ID 16176)	Wrong study design (retrospective)
Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Kitslaar PJ, Knottnerus JA. The Diagnostic Value of the Measurement of the Ankle-Brachial Systolic Pressure Index in Primary Health Care. Journal of Clinical Epidemiology. 1996; 49(12):1401-1405. (Guideline Ref ID 945)	Wrong comparison (reference standard was consensus of two operators)
Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Knottnerus JA. Diagnostic Value of Signs and Symptoms Associated With Peripheral Arterial Occlusive Disease Seen in General Practice: a Multivariable Approach. Medical Decision Making. 1997; 17(1):61-70. (Guideline Ref ID 2209)	No reference standard
Stoffers J, Kaiser V, Kester A, Schouten H, Knottnerus A. Peripheral Arterial Occlusive Disease in General Practice: the Reproducibility of the Ankle-Arm Systolic Pressure Ratio. Scandinavian Journal of Primary Health Care. 1991; 9(2):109-114. (Guideline Ref ID 16232)	Wrong population (not suspected of having PAD as described in protocol)
Suzuki E, Kashiwagi A, Nishio Y, Egawa K, Shimizu S, Maegawa H, Haneda M, Yasuda H, Morikawa S, Inubushi T, Kikkawa R. Increased Arterial Wall Stiffness Limits Flow Volume in the Lower Extremities in Type 2 Diabetic Patients. Diabetes Care. 2001; 24(12):2107-2114. (Guideline Ref ID 1600)	Wrong comparison
Svensson P, de F, Niklasson U, Ostergren J. Office Blood Pressure	Wrong comparison

Underestimates Ambulatory Blood Pressure in Peripheral Arterial Disease in Comparison to Healthy Controls. Journal of Human Hypertension. 2004; 18(3):193-200. (Guideline Ref ID 1557)	
Symes JF, Graham AM, Mousseau M. Doppler Waveform Analysis Versus Segmental Pressure and Pulse-Volume Recording: Assessment of Occlusive Disease in the Lower Extremity. Canadian Journal of Surgery. 1984; 27(4):345-347. (Guideline Ref ID 2679)	Wrong comparison
Takahashi O, Shimbo T, Rahman M, Musa R, Kurokawa W, Yoshinaka T, Fukui T. Validation of the Auscultatory Method for Diagnosing Peripheral Arterial Disease. Family Practice. 2006; 23(1):10-14. (Guideline Ref ID 16178)	Wrong comparison
Taniwaki H, Shoji T, Emoto M, Kawagishi T, Ishimura E, Inaba M, Okuno Y, Nishizawa Y. Femoral Artery Wall Thickness and Stiffness in Evaluation of Peripheral Vascular Disease in Type 2 Diabetes Mellitus. Atherosclerosis. 2001; 158(1):207-214. (Guideline Ref ID 2252)	Wrong study design (retrospective)
Taylor AJ, George KP. Ankle to Brachial Pressure Index in Normal Subjects and Trained Cyclists With Exercise-Induced Leg Pain. Medicine & Science in Sports & Exercise. 2001; 33(11):1862-1867. (Guideline Ref ID 1607)	Wrong population (not suspected of having PAD as described in protocol)
Taylor-Piliae RE, Fair JM, Varady AN, Hlatky MA, Norton LC, Iribarren C, Go AS, Fortmann SP. Ankle Brachial Index Screening in Asymptomatic Older Adults. American Heart Journal. 2011; 161(5):979-985. (Guideline Ref ID 33)	Wrong study objective
Tellier P, Aquilanti S, Lecouffe P, Vasseur C. Comparison Between Exercise Whole Body Thallium Imaging and Ankle-Brachial Index in the Detection of Peripheral Arterial Disease. International Angiology. 2000; 19(3):212-219. (Guideline Ref ID 761)	Wrong reference standard
Terenzi TJ, Beadle E, Muller D, DeMeersman R. Doppler Ultrasound Diastolic Flow Analysis for the Early Identification of Peripheral Arterial Disease. Journal of Manipulative and Physiological Therapeutics. 1992; 15(5):286-292. (Guideline Ref ID 2394)	Wrong population (not suspected of having PAD as described in protocol)
Ubbink DT, Tulevski II, de Graaff JC, Legemate DA, Jacobs MJ. Optimisation of the Non-Invasive Assessment of Critical Limb Ischaemia Requiring Invasive Treatment. European Journal of Vascular and Endovascular Surgery. 2000; 19(2):131-137. (Guideline Ref ID 821)	Wrong comparison
Ubbink DT, Tulevski II, den HD, Koelemay MJ, Legemate DA, Jacobs MJ. The Value of Non-Invasive Techniques for the Assessment of Critical Limb Ischaemia. European Journal of Vascular and Endovascular Surgery. 1997; 13(3):296-300. (Guideline Ref ID 2028)	No reference standard
van Kuijk JP, Flu WJ, Bax JJ, Poldermans D. Prevalence of (a)Symptomatic Peripheral Arterial Disease; the Additional Value of Ankle-Brachial Index on Cardiovascular Risk Stratification. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):312-313. (Guideline Ref ID 333)	Wrong outcomes
van Langen H, van GJ, Rubbens L. Interobserver Variability of Ankle-Brachial Index Measurements at Rest and Post Exercise in Patients With Intermittent Claudication. Vascular Medicine. 2009; 14(3):221-226. (Guideline Ref ID 16162)	Wrong comparison and outcomes
Van Tongeren RB, Bastiaansen AJNM, Van W, Le C, Hamming JF, Van B. A Comparison of the Doppler-Derived Maximal Systolic Acceleration Versus the Ankle-Brachial Pressure Index or Detecting and Quantifying Peripheral Arterial Occlusive Disease in Diabetic Patients. Journal of Cardiovascular Surgery. 2010; 51(3):391-398. (Guideline Ref ID 1341)	Wrong study design (retrospective)
Vasli LR, Larsen S. The Predictive Value of Noninvasive Testing in Intermittent Claudication. Vascular Surgery. 1991; 25(5):396-404. (Guideline Ref ID 4377)	Wrong outcome (disease progression)
Vigilance JE, Reid HL, Richards-George P. Peripheral Occlusive Arterial Disease in Diabetic Clinic Attendees. West Indian Medical Journal. 1999; 48(3):143-146. (Guideline Ref ID 2351)	Wrong outcomes

Vogelberg KH, Sauerzweig A. Measurement of Doppler Velocity in Diagnosis of Peripheral Vascular Disease in Diabetics With Peripheral Pulse Deficit. Diabetes Research. 1989; 11(1):33-37. (Guideline Ref ID 2510)	Wrong comparison
Vogelberg KH, Helbig G, Stork W. Doppler Sonographic Examination of Reactive Hyperemia in the Diagnosis of Peripheral Vascular Disease. Klinische Wochenschrift. 1988; 66(19):970-975. (Guideline Ref ID 2560)	Wrong population (not suspected of having PAD as described in protocol)
Vorwerk D, Guenther RW, Schurmann K, Wendt G, Peters I. Primary Stent Placement for Chronic Iliac Artery Occlusions: Follow-Up Results in 103 Patients. Radiology. 1995; 194(3):745-749. (Guideline Ref ID 2214)	Wrong comparison
Vowden K, Vowden P. Doppler and ABPI or LOI in Screening for Arterial Disease. Wounds UK. 2006; 2(1):13-16. (Guideline Ref ID 4615)	Wrong study design (narrative)
Vowden KR, Goulding V, Vowden P. Hand-Held Doppler Assessment for Peripheral Arterial Disease. Journal of Wound Care. 1996; 5(3):125-128. (Guideline Ref ID 4225)	Wrong study design (educational article)
Walsh JJ, Jr., Cofelice M, Lumpkin D, Kerstein MD. Is Screening for Vascular Disease a Valuable Proposition? Journal of Cardiovascular Surgery. 1988; 29(3):306-309. (Guideline Ref ID 2577)	Wrong population (not suspected of having PAD as described in protocol)
Ward AS, Martin TP. Some Aspects of Ultrasound in the Diagnosis and Assessment of Aortoiliac Disease. American Journal of Surgery. 1980; 140(2):260-265. (Guideline Ref ID 2757)	Wrong population (not suspected of having PAD as described in protocol)
Weatherley BD, Chambless LE, Heiss G, Catellier DJ, Ellison CR. The Reliability of the Ankle-Brachial Index in the Atherosclerosis Risk in Communities (ARIC) Study and the NHLBI Family Heart Study (FHS). BMC Cardiovascular Disorders. 2006; 6:7. (Guideline Ref ID 490)	Wrong population (no suspected of having PAD as described in protocol)
Wikstrom J, Hansen T, Johansson L, Lind L, Ahlstrom H. Ankle Brachial Index <0.9 Underestimates the Prevalence of Peripheral Artery Occlusive Disease Assessed With Whole-Body Magnetic Resonance Angiography in the Elderly. Acta Radiologica. 2008; 49(2):143-149. (Guideline Ref ID 16128)	Wrong population (not suspected of having PAD as described in protocol)
Wilkinson D, Vowden P, Parkin A, Wiggins PA, Robinson PJ, Kester RC. A Reliable and Readily Available Method of Measuring Limb Blood Flow in Intermittent Claudication. British Journal of Surgery. 1987; 74(6):516-519. (Guideline Ref ID 2597)	Wrong comparison
Williams DT, Harding KG, Price P. An Evaluation of the Efficacy of Methods Used in Screening for Lower-Limb Arterial Disease in Diabetes. Diabetes Care. 2005; 28(9):2206-2210. (Guideline Ref ID 16208)	Wrong population (not suspected of having PAD as described in protocol)
Wilson YG, Davies AH, Currie IC, McGrath C, Morgan M, Baird RN, Lamont PM. Angioscopically-Assisted in Situ Saphenous Vein Bypass for Infrainguinal Revascularisation. European Journal of Vascular and Endovascular Surgery. 1996; 12(2):223-229. (Guideline Ref ID 2099)	Wrong comparison
Wolosker N, Rosoky RA, Nakano L, Basyches M, Puech-Leao P. Predictive Value of the Ankle-Brachial Index in the Evaluation of Intermittent Claudication. Revista Do Hospital Das Clinicas; Faculdade De Medicina Da Universidade De Sao Paulo. 2000; 55(2):61-64. (Guideline Ref ID 800)	Wrong outcomes
Wyatt MF, Stickrath C, Shah A, Smart A, Hunt J, Casserly IP. Ankle-Brachial Index Performance Among Internal Medicine Residents. Vascular Medicine. 2010; 15(2):99-105. (Guideline Ref ID 28)	Wrong comparison (study about educating interns)
Xu D, Li J, Zou L, Xu Y, Hu D, Pagoto SL, Ma Y. Sensitivity and Specificity of the Ankle--Brachial Index to Diagnose Peripheral Artery Disease: a Structured Review. [Review]. Vascular Medicine. 2010; 15(5):361-369. (Guideline Ref ID 21)	Wrong study design (review)
Xu Y, Wu Y, Li J, Ma W, Guo X, Luo Y, Hu D. The Predictive Value of Brachial-Ankle Pulse Wave Velocity in Coronary Atherosclerosis and Peripheral Artery Diseases in Urban Chinese Patients. Hypertension Research. 2008; 31(6):1079-1085. (Guideline Ref ID 16169)	Wrong population (coronary atherosclerosis)

Zamorski M. Diagnosing Peripheral Arterial Occlusive Disease. Journal of Family Practice. 1997; 44(4):340-341. (Guideline Ref ID 2032)	Wrong outcomes
Zetterquist S, Bergvall U, Linde B, Pernow B. The Validity of Some Conventional Methods for the Diagnosis of Obliterative Arterial Disease in the Lower Limb As Evaluated by Arteriography. Scandinavian Journal of Clinical and Laboratory Investigation. 1971; 28(4):409-421. (Guideline Ref ID 2962)	Wrong study design (retrospective)

E.3 Imaging for revascularisation

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

4 Excluded n = 134

Study excluded	Reason
Adriaensen ME, Kock MC, Stijnen T, Van Sambeek MR, van UH, Pattynama PM, Myriam Hunink MG. Peripheral Arterial Disease: Therapeutic Confidence of CT Versus Digital Subtraction Angiography and Effects on Additional Imaging Recommendations. Radiology. 2004; 233(2):385-391. (Guideline Ref ID 4249)	Wrong outcomes
Albrecht T, Foert E, Holtkamp R, Kirchin MA, Ribbe C, Wacker FK, Kruschewski M, Meyer BC. 16-MDCT Angiography of Aortoiliac and Lower Extremity Arteries: Comparison With Digital Subtraction Angiography. American Journal of Roentgenology. 2007; American Journal of Roentgenology. 189(3):702-711. (Guideline Ref ID 228)	Wrong population (patient population includes acute ischaemia)
Arthurs ZMB, Bishop PD, Feiten LE, Eagleton MJ, Clair D, Kashyap VS. Evaluation of Peripheral Atherosclerosis: A Comparative Analysis of Angiography and Intravascular Ultrasound Imaging. Journal of Vascular Surgery. 2010; 51(4):933-939. (Guideline Ref ID 1410)	Does not report required outcomes
Atanasova IP, Kim D, Lim RP, Storey P, Kim S, Guo H, Lee VS. Noncontrast MR Angiography for Comprehensive Assessment of Abdominopelvic Arteries Using Quadruple Inversion-Recovery Preconditioning and 3D Balanced Steady-State Free Precession Imaging. Journal of Magnetic Resonance Imaging. 2011; 33(6):1430-1439. (Guideline Ref ID 396)	Wrong reference standard
Azam SM, Carman TL. Diagnostic Approach to Peripheral Arterial Disease. Cardiology Clinics. 2011; 29(3):319-329. (Guideline Ref ID 16300)	Wrong study design (narrative)
Berg F, Bangard C, Bovenschulte H, Nijenhuis M, Hellmich M, Lackner K, Gossmann A. Hybrid Contrast-Enhanced MR Angiography of Pelvic and Lower Extremity Vasculature at 3.0 T: Initial Experience. European Journal of Radiology. 2009; 70(1):170-176. (Guideline Ref ID 16118)	Not all patients had reference standard
Berg F, Bangard C, Bovenschulte H, Hellmich M, Nijenhuis M, Lackner K, Gossmann A. Feasibility of Peripheral Contrast-Enhanced Magnetic Resonance Angiography at 3.0 Tesla With a Hybrid Technique: Comparison With Digital Subtraction Angiography. Investigative Radiology. 2008; 43(9):642-649. (Guideline Ref ID 16125)	Wrong outcomes (intraobserver)
Bierig SMJ. Accuracy and Cost Comparison of Ultrasound Versus Alternative Imaging Modalities, Including CT, MR, PET, and Angiography. Journal of Diagnostic Medical Sonography. 2009; 25(3):138-144. (Guideline Ref ID 2210)	Wrong study design (review)
Bilecen D, Schulte AC, Heidecker HG, Aschwanden M, Huegli R, Jaeger KA, Ostheim-Dzerowycz W, Bongartz G. Lower Extremity: Low-Dose Contrast Agent Intraarterial MR Angiography in Patients--Initial Results. Radiology. 2005; 234(1):250-255. (Guideline Ref ID 401)	Sample size < 20
Bodikova S., Flak L. Ischemic Disease of Lower Extremities--Risk Factors and Ultrasound Diagnostic. Bratislavske Lekarske Listy. 2007; 108(2):89-92. (Guideline Ref ID 16150)	Wrong study design (retrospective)

Bogot NR, Fingerle A, Shaham D, Nissenbaum I, Sosna J. Image Quality of Low-Energy Pulmonary CT Angiography: Comparison With Standard CT. American Journal of Roentgenology. 2011; 197(2):W273-W278. (Guideline Ref ID 375)	Wrong population
Bonel HM, Saar B, Hoppe H, Keo HH, Husmann M, Nikolaou K, Ludwig K, Szucs-Farkas Z, Srivastav S, Kickuth R. MR Angiography of Infrapopliteal Arteries in Patients With Peripheral Arterial Occlusive Disease by Using Gadofosveset at 3.0 T: Diagnostic Accuracy Compared With Selective DSA. Radiology. 2009; 253(3):879-890. (Guideline Ref ID 89)	Wrong outcomes
Bosch E, Kreitner KF, Peirano MF, Thurnher S, Thurner S, Shamsi K, Parsons EC. Safety and Efficacy of Gadofosveset-Enhanced MR Angiography for Evaluation of Pedal Arterial Disease: Multicenter Comparative Phase 3 Study. American Journal of Roentgenology. 2008; 190(1):179-186. (Guideline Ref ID 4223)	Wrong comparison (looking at different dosages of contrast agent)
Brockmann C, Jochum S, Hesser J, Maksimov D, Schnitzer A, Weiss C, Diezler P, Schoenberg SO, Diehl S. Graph-Matching-Based Computed Tomography Angiography in Peripheral Arterial Occlusive Disease. Clinical Imaging. 2010; 34(5):367-374. (Guideline Ref ID 16104)	Wrong comparison
Brockmann C, Jochum S, Sadick M, Huck K, Ziegler P, Fink C, Schoenberg SO, Diehl SJ. Dual-Energy CT Angiography in Peripheral Arterial Occlusive Disease. Cardiovascular and Interventional Radiology. 2009; 32(4):630-637. (Guideline Ref ID 117)	Wrong comparison
Budovec JJ, Pollema M, Grogan M. Update on Multidetector Computed Tomography Angiography of the Abdominal Aorta. Radiologic Clinics of North America. 2010; 48(2):283-309. (Guideline Ref ID 16301)	Wrong study design (narrative)
Bui TD, Gelfand D, Whipple S, Wilson SE, Fujitani RM, Conroy R, Pham H, Gordon IL. Comparison of CT and Catheter Arteriography for Evaluation of Peripheral Arterial Disease. Vascular and Endovascular Surgery. 2005; 39(6):481-490. (Guideline Ref ID 16139)	Wrong study design (retrospective)
Bui BT, Miller S, Mildenberger P, Sam A, Sheng R, Omniscan MRA, I. Comparison of Contrast-Enhanced MR Angiography to Intraarterial Digital Subtraction Angiography for Evaluation of Peripheral Arterial Occlusive Disease: Results of a Phase III Multicenter Trial. Journal of Magnetic Resonance Imaging. 2010; 31(6):1402-1410. (Guideline Ref ID 16109)	Wrong study design (phase 3 clinical trial)
Cernic S, Pozzi Mucelli F, Pellegrin A, Pizzolato R, Cova MA. Comparison Between 64-Row CT Angiography and Digital Subtraction Angiography in the Study of Lower Extremities: Personal Experience. Radiologia Medica. 2009; 114(7):1115-1129. (Guideline Ref ID 16114)	Wrong study design (retrospective)
Chang CY, Cheng CY, Shih WJ, Peng GS, Tzeng TW, Chen ES, Huang WS, Wong CYO. Applications of FDG PET/CT in Atherosclerosis and Its Potential for Monitoring Therapeutic Responses. Journal of Medical Sciences. 2009; 29(3):107-117. (Guideline Ref ID 2199)	Wrong study design (review)
Cournot MB. Accuracy of the Screening Physical Examination to Identify Subclinical Atherosclerosis and Peripheral Arterial Disease in Asymptomatic Subjects. Journal of Vascular Surgery. 2007; 46(6):1215-1221. (Guideline Ref ID 1805)	Healthy patient population
Deutschmann HA, Schoellnast H, Portugaller HR, Preidler KW, Reittner P, Tillich M, Pilger E, Szolar DH. Routine Use of Three-Dimensional Contrast-Enhanced Moving-Table MR Angiography in Patients With Peripheral Arterial Occlusive Disease: Comparison With Selective Digital Subtraction Angiography. Cardiovascular and Interventional Radiology. 2006; 29(5):762-770. (Guideline Ref ID 16134)	Wrong study design (retrospective)
Diehm N, Kickuth R, Baumgartner I, Srivastav SK, Gretener S, Husmann MJ, Jaccard Y, Do dD, Triller J, Bonel HM. Magnetic Resonance Angiography in Infrapopliteal Arterial Disease: Prospective Comparison of 1.5 and 3 Tesla Magnetic Resonance Imaging. Investigative Radiology. 2007; 42(6):467-476.	Sample size < 20

(Guideline Ref ID 250)	
D'Othee BJ, Langdon DR, Bell GK, Bettmann MA. Operating Expenses for the Diagnosis and Treatment of Peripheral Vascular Disease in an Academic Interventional Radiology Department: Cost Calculations According to a Microeconomic Method. Journal of Vascular and Interventional Radiology. 2006; 17(1):85-94. (Guideline Ref ID 312)	Health economics study
Du J, Thornton F, Mistretta C, Grist T. Dynamic MR Venography: An Intrinsic Benefit of Time-Resolved MR Angiography. Journal of Magnetic Resonance Imaging. 2006; 24(4):922-927. (Guideline Ref ID 16145)	Not PAD population
Edelman RR, Sheehan JJ, Dunkle E, Schindler N, Carr J, Koktzoglou I. Quiescent-Interval Single-Shot Unenhanced Magnetic Resonance Angiography of Peripheral Vascular Disease: Technical Considerations and Clinical Feasibility. Magnetic Resonance in Medicine. 2010; 63(4):951-958. (Guideline Ref ID 16110)	Wrong reference standard
Edwards AJ, Wells IP, Roobottom CA. Multidetector Row CT Angiography of the Lower Limb Arteries: a Prospective Comparison of Volume-Rendered Techniques and Intra-Arterial Digital Subtraction Angiography. Clinical Radiology. 2005; 60(1):85-95. (Guideline Ref ID 400)	Data split by observers
Elgzyri T, Ekberg G, Peterson K, Lundell A, Apelqvist J. Can Duplex Arterial Ultrasonography Reduce Unnecessary Angiography? Journal of Wound Care. 2008; 17(11):497-500. (Guideline Ref ID 111)	Wrong outcomes and non comparative study
Farha FS, Ammar AD. Duplex Ultrasonography Rarely Changes Management Decisions in Chronic Lower Extremity Ischemia. Annals of Vascular Surgery. 2007; 21(4):438-442. (Guideline Ref ID 233)	Wrong outcomes
Favaretto E, Pili C, Amato A, Conti E, Losinno F, Rossi C, Faccioli L, Palareti G. Analysis of Agreement Between Duplex Ultrasound Scanning and Arteriography in Patients With Lower Limb Artery Disease. Journal of Cardiovascular Medicine. 2007; 8(5):337-341. (Guideline Ref ID 16130)	Not enough data for 2x2 table
Flanigan DP, Ballard JL, Robinson D, Galliano M, Blecker G, Harward TR. Duplex Ultrasound of the Superficial Femoral Artery Is a Better Screening Tool Than Ankle-Brachial Index to Identify at Risk Patients With Lower Extremity Atherosclerosis. Journal of Vascular Surgery. 2008; 47(4):789-792. (Guideline Ref ID 16127)	Wrong comparison
Foley WD, Stonely T. CT Angiography of the Lower Extremities. Radiologic Clinics of North America. 2010; 48(2):367-396. (Guideline Ref ID 801)	Wrong study design (narrative)
Fontcuberta J, Flores A, Orgaz A, Doblas M, Gil J, Leal I, Rodriguez R, Benito JM, Bermudez MD. Reliability of Preoperative Duplex Scanning in Designing a Therapeutic Strategy for Chronic Lower Limb Ischemia. Annals of Vascular Surgery. 2009; 23(5):577-582. (Guideline Ref ID 103)	Wrong reference standard
Gerretsen SC, le Maire TF, Miller S, Thurnher SA, Herborn CU, Michaely HJ, Kramer H, Vanzulli A, Vymazal J, Wasser MN, Ballarati CE, Kirchin MA, Pirovano G, Leiner T. Multicenter, Double-Blind, Randomized, Intraindividual Crossover Comparison of Gadobenate Dimeglumine and Gadopentetate Dimeglumine for MR Angiography of Peripheral Arteries 48. Radiology. 2010; 255(3):988-1000. (Guideline Ref ID 16151)	Wrong comparison (contrast agents)
Goyen M, Edelman M, Perreault P, O'Riordan E, Bertoni H, Taylor J, Siragusa D, Sharafuddin M, Mohler ER, III, Breger R, Yucel EK, Shamsi K, Weisskoff RM. MR Angiography of Aortoiliac Occlusive Disease: a Phase III Study of the Safety and Effectiveness of the Blood-Pool Contrast Agent MS-325. Radiology. 2005; 236(3):825-833. (Guideline Ref ID 370)	Wrong study design (phase 3 clinical trial)
Goyen M, Herborn CU, Kroger K, Ruehm SG, Debatin JF. Total-Body 3D Magnetic Resonance Angiography Influences the Management of Patients With Peripheral Arterial Occlusive Disease. European Radiology. 2006; 16(3):685-691. (Guideline Ref ID 334)	Not sensitivity/specificity of MRA compared with gold standard for diagnosing PAD but use of whole body MRA to

	diagnose disease apart from PAD (e.g. carotid stenosis)
Gozzi M, Amorico MG, Colopi S, Favali M, Gallo E, Torricelli P, Polverini I, Gargiulo M. Peripheral Arterial Occlusive Disease: Role of MR Angiography. Radiologia Medica. 2006; 111(2):225-237. (Guideline Ref ID 16137)	Wrong population (not exclusively PAD population)
Grijalba FU, Esandi MC. Comparison of Gadofosveset-Enhanced Three-Dimensional Magnetic Resonance Angiography With Digital Subtraction Angiography for Lower-Extremity Peripheral Arterial Occlusive Disease. Acta Radiologica. 2010; 51(3):284-289. (Guideline Ref ID 67)	Wrong comparison
Grondal N, Lindholt JS. Screening for Peripheral Arterial Disease. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):314-315. (Guideline Ref ID 1483)	Wrong study design (review)
Habibi RK. High-Spatial-Resolution Lower Extremity MR Angiography at 3.0 T: Contrast Agent Dose Comparison Study. Radiology. 2008; 248(2):680-692. (Guideline Ref ID 2290)	Wrong population and study design
Hadizadeh DR, Gieseke J, Lohmaier SH, Wilhelm K, Boschewitz J, Verrel F, Schild HH, Willinek WA. Peripheral MR Angiography With Blood Pool Contrast Agent: Prospective Intraindividual Comparative Study of High-Spatial-Resolution Steady-State MR Angiography Versus Standard-Resolution First-Pass MR Angiography and DSA. Radiology. 2008; 249(2):701-711. (Guideline Ref ID 16123)	Wrong population (not exclusively PAD population)
Hagspiel KD, Yao L, Shih MC, Burkholder B, Bissonette E, Harthun NL. Comparison of Multistation MR Angiography With Integrated Parallel Acquisition Technique Versus Conventional Technique With a Dedicated Phased-Array Coil System in Peripheral Vascular Disease. Journal of Vascular and Interventional Radiology. 2006; 17(2 Pt 1):263-269. (Guideline Ref ID 330)	Wrong population (not exclusively PAD population)
Hahn WY, Hecht EM, Friedman B, Babb JS, Jacobowitz GR, Lee VS. Distal Lower Extremity Imaging: Prospective Comparison of 2-Dimensional Time of Flight, 3-Dimensional Time-Resolved Contrast-Enhanced Magnetic Resonance Angiography, and 3-Dimensional Bolus Chase Contrast-Enhanced Magnetic Resonance Angiography. Journal of Computer Assisted Tomography. 2007; 31(1):29-36. (Guideline Ref ID 16133)	Not all patients received reference standard
Hiatt MD, Fleischmann D, Hellinger JC, Rubin GD. Angiographic Imaging of the Lower Extremities With Multidetector CT. Radiologic Clinics of North America. 2005; 43(6):1119-1127. (Guideline Ref ID 2531)	Wrong study design (review)
Hingorani AP, Ascher E, Marks N. Duplex Arteriography for Lower Extremity Revascularization. Perspectives in Vascular Surgery and Endovascular Therapy. 2007; 19(1):6-20. (Guideline Ref ID 1085)	Wrong study design (review)
Holden A, Merrilees S, Mitchell N, Hill A. Magnetic Resonance Imaging of Popliteal Artery Pathologies. European Journal of Radiology. 2008; 67(1):159-168. (Guideline Ref ID 1734)	Wrong study design (review)
Huegli RW, Aschwanden M, Bongartz G, Jaeger K, Heidecker HG, Thalhammer C, Schulte AC, Hashagen C, Jacob AL, Bilecen D. Intraarterial MR Angiography and DSA in Patients With Peripheral Arterial Occlusive Disease: Prospective Comparison. Radiology. 2006; 239(3):901-908. (Guideline Ref ID 321)	Comparison performed post angioplasty
Humphries MD, Pevec WC, Laird JR, Yeo KK, Hedayati N, Dawson DL. Early Duplex Scanning After Infrainguinal Endovascular Therapy. Journal of Vascular Surgery. 2011; 53(2):353-358. (Guideline Ref ID 2284)	Wrong study design (retrospective)
Iezzi R, Cotroneo AR, Filippone A, Giancristofaro D, Storto ML. Four-Detector Row Computed Tomographic Angiography in the Evaluation of Infrarenal Aorta and Peripheral Arterial Occlusive Disease: Influence of Contrast Medium Concentration. Journal of Computer Assisted Tomography. 2008; 32(5):690-696. (Guideline Ref ID 16124)	Not enough data for 2x2 table
Janka R, Wenkel E, Fellner C, Lang W, Bautz W, Uder M. Magnetic Resonance	Wrong outcomes as per

Angiography of the Peripheral Vessels in Patients With Peripheral Arterial Occlusive Disease: When Is an Additional Conventional Angiography Required? Cardiovascular and Interventional Radiology. 2006; 29(2):220-229. (Guideline Ref ID 335)	protocol. Not all patients received reference standard
Janka R, Fellner C, Wenkel E, Lang W, Bautz W, Fellner FA. Contrast-Enhanced MR Angiography of Peripheral Arteries Including Pedal Vessels at 1.0 T: Feasibility Study With Dedicated Peripheral Angiography Coil. Radiology. 2005; 235(1):319-326. (Guideline Ref ID 16144)	Not all patients received DSA as reference standard
Jones L, Pressdee DJ, Lamont PM, Baird RN, Murphy KP. A Phase Contrast (PC) Rephase/Dephase Sequence of Magnetic Resonance Angiography (MRA): a New Technique for Imaging Distal Run-Off in the Pre-Operative Evaluation of Peripheral Vascular Disease. Clinical Radiology. 1998; 53(5):333-337. (Guideline Ref ID 4280)	Sample size <20
Kakkos SK, Tsolakis IA. Is Duplex Ultrasound Scanning for Peripheral Arterial Disease of the Lower Limb a Non-Invasive Alternative or an Adjunct to Angiography? European Journal of Vascular and Endovascular Surgery. 2010; 40(4):513-514. (Guideline Ref ID 407)	Wrong study design (commentary)
Kang JW, Lim TH, Choi CG, Ko GY, Kim JK, Kwon TW. Evaluation of Contrast-Enhanced Magnetic Resonance Angiography (MRA) Using Gd-DOTA Compared With Time-of-Flight MRA in the Diagnosis of Clinically Significant Non-Coronary Arterial Disease. European Radiology. 2010; 20(8):1934-1944. (Guideline Ref ID 410)	Health economics study and not PAD population
Karnon J, Brennan A, Pandor A, Fowkes G, Lee A, Gray D, Coshall C, Nicholls C, Akehurst R. Modelling the Long Term Cost Effectiveness of Clopidogrel for the Secondary Prevention of Occlusive Vascular Events in the UK. Current Medical Research and Opinion. 2005; 21(1):101-112. (Guideline Ref ID 369)	Health economics study
Katsanos KN, Siablis D, Zeller T, Lammer J, Bosiers M, Commeau P, Krankenberg H, Baumgartner I, Rubino P, Brechtel K, Geist V, Huppert PE, Peregrin JH, Lansink W, Sidhu P, Magnan P, Van RM, Stoll H-P, Scheinert D. The ACHILLES Study, a Prospective, Randomized, Multicenter Comparison of Balloon Angioplasty and CYPHER SELECT Plus Stent Implantation in the Treatment of Patients With Ischemic Infrapopliteal Arterial Disease. Cardiovascular and Interventional Radiology. 2011; 34:505. (Guideline Ref ID 1287)	Wrong study design (abstract)
Kau T, Eicher W, Reiterer C, Niedermayer M, Rabitsch E, Senft B, Hausegger KA. Dual-Energy CT Angiography in Peripheral Arterial Occlusive Disease-Accuracy of Maximum Intensity Projections in Clinical Routine and Subgroup Analysis. European Radiology. 2011; 21(8):1677-1686. (Guideline Ref ID 16302)	Not all patients received reference standard
Kawarada O, Yokoi Y, Morioka N, Takemoto K. Renal Artery Stenosis in Cardio- and Cerebrovascular Disease: Renal Duplex Ultrasonography As an Initial Screening Examination. Circulation Journal. 2007; 71(12):1942-1947. (Guideline Ref ID 213)	Wrong population (not a study of PAD patients)
Klingebiel RK. Comparative Evaluation of 64-Slice CT Angiography and Digital Subtraction Angiography in Assessing the Cervicocranial Vasculature. Vascular Health and Risk Management. 2008; 4(4):901-907. (Guideline Ref ID 2320)	Wrong population and study design
Kock MC, Adriaensen ME, Pattynama PM, Van Sambeek MR, van UH, Stijnen T, Hunink MG. DSA Versus Multi-Detector Row CT Angiography in Peripheral Arterial Disease: Randomized Controlled Trial. Radiology. 2005; 237(2):727-737. (Guideline Ref ID 358)	Wrong outcomes
Kramer H, Nikolaou K, Reiser MF. Cardiovascular Whole-Body MRI. European Journal of Radiology. 2009; 70(3):418-423. (Guideline Ref ID 2212)	Wrong study design (review)
Kramer H, Zenge M, Schmitt P, Glaser C, Reiser MF, Herrmann KA. Peripheral Magnetic Resonance Angiography (MRA) With Continuous Table Movement at 3.0 T: Initial Experience Compared With Step-by-Step MRA. Investigative Radiology. 2008; 43(9):627-634. (Guideline Ref ID 169)	Sample size <20

Kramer H, Michaely HJ, Reiser MF, Schoenberg SO. Peripheral Magnetic Resonance Angiography at 3.0 T. [Review] [19 Refs]. Topics in Magnetic Resonance Imaging. 2007; 18(2):135-138. (Guideline Ref ID 16146)	Wrong study design (review)
Krause U, Kroencke T, Spielhaupter E, Taupitz M, Kenn W, Hamm B, Hahn D. Contrast-Enhanced Magnetic Resonance Angiography of the Lower Extremities: Standard-Dose Vs. High-Dose Gadodiamide Injection. Journal of Magnetic Resonance Imaging. 2005; 21(4):449-454. (Guideline Ref ID 393)	Wrong comparison (comparing doses of contrast agent)
Krnic A, Vucic N, Sucic Z. Duplex Scanning Compared With Intra-Arterial Angiography in Diagnosing Peripheral Arterial Disease: Three Analytical Approaches. Vasa. 2006; 35(2):86-91. (Guideline Ref ID 16136)	Wrong outcomes
Kumamaru KK, Hoppel B, Mather RT, Rybicki FJ. CT Angiography: Current Technology and Clinical Use. Radiologic Clinics of North America. 2010; 48(2):213-235. (Guideline Ref ID 2235)	Wrong study design (review)
Kurcz JN. The Usefulness of CT-Angiography in Detecting Anatomical Variants of Arteries Arising From the Abdominal Aorta and Aortic Arch. Advances in Clinical and Experimental Medicine. 2007; 16(6):751-760. (Guideline Ref ID 2367)	Wrong population (not exclusively PAD)
Lanzman RS, Blondin D, Schmitt P, Orzechowski D, Godehardt E, Scherer A, Modder U, Kropil P. Non-Enhanced 3D MR Angiography of the Lower Extremity Using ECG-Gated TSE Imaging With Non-Selective Refocusing Pulses--Initial Experience. Rofo: Fortschritte Auf Dem Gebiete Der Rontgenstrahlen Und Der Nuklearmedizin. 2010; 182(10):861-867. (Guideline Ref ID 16107)	Sample size <20
Lapeyre M, Kobeiter H, Desgranges P, Rahmouni A, Becquemin JP, Luciani A. Assessment of Critical Limb Ischemia in Patients With Diabetes: Comparison of MR Angiography and Digital Subtraction Angiography. American Journal of Roentgenology. 2005; American Journal of Roentgenology. 185(6):1641-1650. (Guideline Ref ID 16140)	Wrong population (diabetic population with suspected limb ischaemia)
Laswed T, Rizzo E, Guntern D, Doenz F, Denys A, Schnyder P, Qanadli SD. Assessment of Occlusive Arterial Disease of Abdominal Aorta and Lower Extremities Arteries: Value of Multidetector CT Angiography Using an Adaptive Acquisition Method. European Radiology. 2008; 18(2):263-272. (Guideline Ref ID 203)	Wrong comparison
Lee HM, Wang Y, Sostman HD, Schwartz LH, Khilnani NM, Trost DW, Ramirez de AE, Teeger S, Bush HL. Distal Lower Extremity Arteries: Evaluation With Two-Dimensional MR Digital Subtraction Angiography. Radiology. 1998; 207(2):505-512. (Guideline Ref ID 4283)	Mixed patient population
Leiner T, Kessels AG, Nelemans PJ, Vasbinder GB, De Haan MW, Kitslaar PE, Ho KY, Tordoir JH, van Engelshoven JM. Peripheral Arterial Disease: Comparison of Color Duplex US and Contrast-Enhanced MR Angiography for Diagnosis. Radiology. 2005; 235(2):699-708. (Guideline Ref ID 16143)	Not all patients received reference standard
Lohr HA, Froehlich JM, Pfyffer M, Bader CW, Zollikofer CL, Wentz KU. Comparison of Gd-BOPTA and Gd-DOTA for Peripheral CE-MRA: a Double-Blind Clinical Study. Academic Radiology. 2002; 9 Suppl 2:S421-S424. (Guideline Ref ID 4263)	Does not have enough data for 2x2 table
MacDonald E.Froggatt. Are Automated Blood Pressure Monitors Accurate Enough to Calculate the Ankle Brachial Pressure Index? Journal of Clinical Monitoring and Computing. 2008; 22(5):381-384. (Guideline Ref ID 2310)	Wrong population
Mandolfino T, Canciglia A, D'Alfonso M, Carmignani A. Infrainguinal Revascularization Based on Duplex Ultrasound Arterial Mapping 310. International Angiology. 2006; 25(3):256-260. (Guideline Ref ID 310)	Not all patients received reference standard
Meissner OA, Rieger J, Weber C, Siebert U, Steckmeier B, Reiser MF, Schoenberg SO. Critical Limb Ischemia: Hybrid MR Angiography Compared With DSA. Radiology. 2005; 235(1):308-318. (Guideline Ref ID 16147)	Sample size <20
Menke J. Improving the Image Quality of Contrast-Enhanced MR Angiography by	Wrong comparison

Automated Image Registration: a Prospective Study in Peripheral Arterial Disease of the Lower Extremities. European Journal of Radiology. 2010; 75(3):e1-e8. (Guideline Ref ID 16101)	
Menke J, Larsen J. Meta-Analysis: Accuracy of Contrast-Enhanced Magnetic Resonance Angiography for Assessing Steno-Occlusions in Peripheral Arterial Disease. [Review] [96 Refs]. Annals of Internal Medicine. 2010; 153(5):325-334. (Guideline Ref ID 16108)	Wrong study design (review)
Mestre XM, Castellote MA, Coll RV, Villegas AR. Arterial Mapping With Duplex Ultrasound: Diagnostic-Therapeutic Strategy in Patients With Critical Lower-Limb Ischemia. International Angiology. 2009; 28(3):209-214. (Guideline Ref ID 4207)	Wrong outcomes as per protocol, unable to extract data required
Meyer BC, Werncke T, Foert E, Kruschewski M, Hopfenmuller W, Ribbe C, Wolf KJ, Albrecht T. Do the Cardiovascular Risk Profile and the Degree of Arterial Wall Calcification Influence the Performance of MDCT Angiography of Lower Extremity Arteries? European Radiology. 2010; 20(2):497-505. (Guideline Ref ID 16111)	Wrong study design (retrospective)
Meyer BC, Oldenburg A, Frericks BB, Ribbe C, Hopfenmuller W, Wolf KJ, Albrecht T. Quantitative and Qualitative Evaluation of the Influence of Different Table Feeds on Visualization of Peripheral Arteries in CT Angiography of Aortoiliac and Lower Extremity Arteries. European Radiology. 2008; 18(8):1546-1555. (Guideline Ref ID 16126)	Wrong study design (retrospective)
Mihai G, Chung YC, Kariisa M, Raman SV, Simonetti OP, Rajagopalan S. Initial Feasibility of a Multi-Station High Resolution Three-Dimensional Dark Blood Angiography Protocol for the Assessment of Peripheral Arterial Disease. Journal of Magnetic Resonance Imaging. 2009; 30(4):785-793. (Guideline Ref ID 99)	Sample size <20
Mishra A, Bhaktarahalli JN, Ehtuish EF. Imaging of Peripheral Arteries by 16-Row Multidetector Computed Tomography Angiography: a Feasible Tool? European Journal of Radiology. 2007; 61(3):528-533. (Guideline Ref ID 16132)	Wrong comparison
Mishra A, Ehtuish EF. Imaging of Peripheral Arteries by 16-Slice Computed Tomography Angiography. A Valuable Tool? Saudi Medical Journal. 2007; 28(7):1091-1095. (Guideline Ref ID 16129)	Wrong study design (retrospective)
Mulligan SA, Matsuda T, Lanzer P, Gross GM, Routh WD, Keller FS, Koslin DB, Berland LL, Fields MD, Doyle M. Peripheral Arterial Occlusive Disease: Prospective Comparison of MR Angiography and Color Duplex US With Conventional Angiography. Radiology. 1991; 178(3):695-700. (Guideline Ref ID 4306)	Sample size <20
Nael K, Krishnam M, Nael A, Ton A, Ruehm SG, Finn JP. Peripheral Contrast-Enhanced MR Angiography at 3.0T, Improved Spatial Resolution and Low Dose Contrast: Initial Clinical Experience. European Radiology. 2008; 18(12):2893-2900. (Guideline Ref ID 16121)	Not all patients had reference standard
Nael K, Ruehm SG, Michaely HJ, Saleh R, Lee M, Laub G, Finn JP. Multistation Whole-Body High-Spatial-Resolution MR Angiography Using a 32-Channel MR System. American Journal of Roentgenology. 2007; American Journal of Roentgenology. 188(2):529-539. (Guideline Ref ID 273)	Not all patients had DSA as reference standard
Nielsen YW, Eiberg JP, Logager VB, Just S, Schroeder TV, Thomsen HS. Whole-Body Magnetic Resonance Angiography With Additional Steady-State Acquisition of the Infragenicular Arteries in Patients With Peripheral Arterial Disease. Cardiovascular and Interventional Radiology. 2010; 33(3):484-491. (Guideline Ref ID 50)	Not all patients had reference standard
Nielsen YJW. Whole-Body MR Angiography in Patients With Peripheral Arterial Disease. Danish Medical Bulletin. 2010; 57(12) (Guideline Ref ID 1648)	Wrong study design (PHD thesis)
Nielsen YW, Eiberg JP, Logager VB, Schroeder TV, Just S, Thomsen HS. Whole-Body Magnetic Resonance Angiography at 3 Tesla Using a Hybrid Protocol in Patients With Peripheral Arterial Disease. Cardiovascular and Interventional Radiology. 2009; 32(5):877-886. (Guideline Ref ID 106)	Some patients received IV DSA

Nielsen YW, Eiberg JP, Logager VB, Hansen MA, Schroeder TV, Thomsen HS. Whole-Body MR Angiography With Body Coil Acquisition at 3 T in Patients With Peripheral Arterial Disease Using the Contrast Agent Gadofosveset Trisodium. Academic Radiology. 2009; 16(6):654-661. (Guideline Ref ID 128)	Sample size <20
Nikolaou KK. High-Spatial-Resolution Multistation MR Angiography With Parallel Imaging and Blood Pool Contrast Agent: Initial Experience. Radiology. 2006; 241(3):861-872. (Guideline Ref ID 1932)	Wrong population (compares to healthy population)
Ouwendijk R, de Vries M, Stijnen T, Pattynama PM, Van Sambeek MR, Buth J, Tielbeek A, Van D, V, Schutzekool LJ, Kitslaar PJ, De Haan MW, van Engelshoven JM, Hunink MG. Multicenter Randomized Controlled Trial of the Costs and Effects of Noninvasive Diagnostic Imaging in Patients With Peripheral Arterial Disease: the DIPAD Trial (Provisional Abstract). American Journal of Roentgenology. 2008; 190(5):1349-1357. (Guideline Ref ID 2399)	Wrong reference standard
Ouwendijk R, Kock MC, van Dijk LC, Van Sambeek MR, Stijnen T, Hunink MG. Vessel Wall Calcifications at Multi-Detector Row CT Angiography in Patients With Peripheral Arterial Disease: Effect on Clinical Utility and Clinical Predictors. Radiology. 2006; 241(2):603-608. (Guideline Ref ID 295)	Wrong study design (retrospective)
Ouwendijk R, Kock MC, Visser K, Pattynama PM, De Haan MW, Hunink MG. Interobserver Agreement for the Interpretation of Contrast-Enhanced 3D MR Angiography and MDCT Angiography in Peripheral Arterial Disease. American Journal of Roentgenology. 2005; American Journal of Roentgenology. 185(5):1261-1267. (Guideline Ref ID 357)	Not all patients received DSA as reference standard
Pardo M, Alcaraz M, Ramon BF, Bernal FL, Felices JM, Canteras M. Increased Transcutaneous Oxygen Pressure Is an Indicator of Revascularization After Peripheral Transluminal Angioplasty. Acta Radiologica. 2010; 51(9):990-993. (Guideline Ref ID 409)	Wrong comparison
Pavlovic C, Futamatsu H, Angiolillo DJ, Guzman LA, Wilke N, Siragusa D, Wludyka P, Percy R, Northrup M, Bass TA, Costa MA. Quantitative Contrast Enhanced Magnetic Resonance Imaging for the Evaluation of Peripheral Arterial Disease: a Comparative Study Versus Standard Digital Angiography. International Journal of Cardiovascular Imaging. 2007; 23(2):225-232. (Guideline Ref ID 16131)	Sample size <20
Perreault P, Edelman MA, Baum RA, Yucel EK, Weisskoff RM, Shamsi K, Mohler ER. MR Angiography With Gadofosveset Trisodium for Peripheral Vascular Disease: Phase II Trial. Radiology. 2003; 229(3):811-820. (Guideline Ref ID 4254)	Wrong study design (RCT) and wrong comparison
Pirro F, Iezzi R, Nestola M, Latorre M, Santoro M, Bonomo L. Diagnostic Accuracy of CT Angiography in the Evaluation of Lower Limbs Stenosis: Comparison Between Visual Score and Quantitative Analysis Using a Semi-Automated 3D Software. Cardiovascular and Interventional Radiology. 2011; 34:587. (Guideline Ref ID 1276)	Wrong study design (abstract)
Poschenrieder F, Hamer OW, Herold T, Schleicher T, Borisch I, Feuerbach S, Zorger N. Diagnostic Accuracy of Intraarterial and I.v. MR Angiography for the Detection of Stenoses of the Infrainguinal Arteries. American Journal of Roentgenology. 2009; American Journal of Roentgenology. 192(1):117-121. (Guideline Ref ID 16120)	Wrong comparison (comparing observers)
Pregowski J, Kepka C, Kalinczuk L, Kruk M, Mintz GS, Ciszewski A, Chmielak Z, Ciszewski M, Wolny R, Szubielski M, Tyczynski P, Witkowski A. Comparison of Intravascular Ultrasound, Quantitative Coronary Angiography, and Dual-Source 64-Slice Computed Tomography in the Preprocedural Assessment of Significant Saphenous Vein Graft Lesions. American Journal of Cardiology. 2011; 107(10):1453-1459. (Guideline Ref ID 16303)	Wrong outcome
Rapp JH, Wolff SD, Quinn SF, Soto JA, Meranze SG, Muluk S, Blebea JS, Johnson SP, Rofsky NM, Duerinckx A, Foster GS, Kent KC, Moneta G, Middlebrook MR, Narra VR, Toombs BD, Pollak J, Yucel EK, Shamsi K, Weisskoff RM. Aortoiliac Occlusive Disease in Patients With Known or Suspected Peripheral Vascular	Wrong study design (phase 3 clinical trial)

Disease: Safety and Efficacy of Gadofosveset-Enhanced MR Angiography--Multicenter Comparative Phase III Study. Radiology. 2005; 236(1):71-78. (Guideline Ref ID 16142)	
Reid AWR. Imaging in Endovascular Therapy: Our Future. Journal of Endovascular Therapy. 2009; 16 Suppl 1(pp I22-41):Feb. (Guideline Ref ID 2165)	Wrong population
Rohrl BK. Gadofosveset-Enhanced MR Angiography of the Pedal Arteries in Patients With Diabetes Mellitus and Comparison With Selective Intraarterial DSA. European Radiology. 2009; 19(12):2993-3001. (Guideline Ref ID 2160)	Sample size <20
Ruhl KM, Katoh M, Langer S, Mommertz G, Guenther RW, Niendorf T, Spuentrup E. Time-Resolved 3D MR Angiography of the Foot at 3 T in Patients With Peripheral Arterial Disease. American Journal of Roentgenology. 2008; American Journal of Roentgenology. 190(6):W360-W364. (Guideline Ref ID 184)	Wrong comparison and outcomes
Schaefer FKW. A Multicenter, Site-Independent, Blinded Study to Compare the Diagnostic Accuracy of Contrast-Enhanced Magnetic Resonance Angiography Using 1.0 M Gadobutrol (Gadovist) to Intraarterial Digital Subtraction Angiography in Body Arteries. European Journal of Radiology. 2007; 61(2):315-323. (Guideline Ref ID 15975)	Wrong population (not exclusively PAD population)
Schernthaner R, Fleischmann D, Stadler A, Schernthaner M, Lammer J, Loewe C. Value of MDCT Angiography in Developing Treatment Strategies for Critical Limb Ischemia. American Journal of Roentgenology. 2009; American Journal of Roentgenology. 192(5):1416-1424. (Guideline Ref ID 16117)	Wrong study design (retrospective)
Schernthaner R, Fleischmann D, Lomoschitz F, Stadler A, Lammer J, Loewe C. Effect of MDCT Angiographic Findings on the Management of Intermittent Claudication. American Journal of Roentgenology. 2007; American Journal of Roentgenology. 189(5):1215-1222. (Guideline Ref ID 219)	Wrong study design (retrospective)
Schlager O, Francesconi M, Haumer M, Dick P, Sabeti S, Amighi J, Mlekusch W, Koppensteiner R, Minar E, Schillinger M. Duplex Sonography Versus Angiography for Assessment of Femoropopliteal Arterial Disease in a "Real-World" Setting. Journal of Endovascular Therapy. 2007; 14(4):452-459. (Guideline Ref ID 229)	Wrong study design (retrospective)
Schmitt R, Coblenz G, Cherevatyy O, Brunner H, Frohner S, Wedell E, Karg G, Christopoulos G. Comprehensive MR Angiography of the Lower Limbs: a Hybrid Dual-Bolus Approach Including the Pedal Arteries. European Radiology. 2005; 15(12):2513-2524. (Guideline Ref ID 355)	Wrong study design (retrospective)
Schulte AC, Bongartz G, Huegli R, Aschwanden M, Jaeger KA, Ostheim-Dzerowycz W, Jacob AL, Bilecen D. Intraarterial Versus IV Gadolinium Injections for MR Angiography: Quantitative and Qualitative Assessment of the Infrainguinal Arteries. American Journal of Roentgenology. 2005; American Journal of Roentgenology. 185(3):735-740. (Guideline Ref ID 367)	Sample size <20
Shareghi S, Gopal A, Gul K, Matchinson JC, Wong CB, Weinberg N, Lensky M, Budoff MJ, Shavelle DM. Diagnostic Accuracy of 64 Multidetector Computed Tomographic Angiography in Peripheral Vascular Disease. Catheterization and Cardiovascular Interventions. 2010; 75(1):23-31. (Guideline Ref ID 77)	Not enough data for 2x2 table
Shrikhande GV, Graham AR, Aparajita R, Gallagher KA, Morrissey NJ, McKinsey JF, Dayal R. Determining Criteria for Predicting Stenosis With Ultrasound Duplex After Endovascular Intervention in Infrainguinal Lesions. Annals of Vascular Surgery. 2011; 25(4):454-460. (Guideline Ref ID 16305)	Wrong population
Sottiurai V, White JV. Extensive Revascularization or Primary Amputation: Which Patients With Critical Limb Ischemia Should Not Be Revascularized?. [Review] [44 Refs]. Seminars in Vascular Surgery. 2007; 20(1):68-72. (Guideline Ref ID 458)	Wrong study design (review)
Spronk S, den Hoed PT, de Jonge LC, van Dijk LC, Pattynama PM. Value of the Duplex Waveform at the Common Femoral Artery for Diagnosing Obstructive Aortoiliac Disease. Journal of Vascular Surgery. 2005; 42(2):236-242. (Guideline Ref ID 373)	Wrong reference standard (MRA used as reference standard)
Tato FH. Comparison of Angiography, Duplex Sonography and Intravascular	Wrong outcomes

Ultrasound for the Graduation of Femoropopliteal Stenoses Before and After Balloon Angioplasty. Ultrasound in Medicine and Biology. 2006; 32(12):1837-1843. (Guideline Ref ID 1945)	
Tawfick W, Sultan S. Five-Year Prospective Study of Duplex Ultrasound Arterial Mapping (DUAM) As a Primary Modality in Management of Critical Lower Limb Ischemia (CLI): Technical and Clinical Outcome After Bypass Surgery (BS) and Endovascular Revascularization (EVR). Vascular. 2010; 18(Suppl 2):S44-S45. (Guideline Ref ID 16357)	Wrong study design (abstract)
Thornton FJ, Du J, Suleiman SA, Dieter R, Tefera G, Pillai KR, Korosec FR, Mistretta CA, Grist TM. High-Resolution, Time-Resolved MRA Provides Superior Definition of Lower-Extremity Arterial Segments Compared to 2D Time-of-Flight Imaging. Journal of Magnetic Resonance Imaging. 2006; 24(2):362-370. (Guideline Ref ID 16152)	Wrong comparison
Thurnher S, Miller S, Schneider G, Ballarati C, Bongartz G, Herborn CU, Schoenberg S, Cova MA, Morana G, Niazi K, Iezzi R, Taupitz M, Bluemke DA, Kreitner KF, Kirchin MA, Pirovano G. Diagnostic Performance of Gadobenate Dimeglumine Enhanced MR Angiography of the Iliofemoral and Calf Arteries: a Large-Scale Multicenter Trial. American Journal of Roentgenology. 2007; American Journal of Roentgenology. 189(5):1223-1237. (Guideline Ref ID 218)	Compares observers
Tongdee RN, V. Hybrid Peripheral 3D Contrast-Enhanced MR Angiography of Calf and Foot Vasculature. American Journal of Roentgenology. 2006; 186(6):1746-1753. (Guideline Ref ID 16148)	Wrong reference standard
Turkvatan AB. Multidetector Computed Tomographic Angiography of Aberrant Subclavian Arteries. Vascular Medicine. 2009; 14(1):5-11. (Guideline Ref ID 2226)	Wrong population
Utsunomiya D, Oda S, Funama Y, Awai K, Nakaura T, Yanaga Y, Hirai T, Yamashita Y. Comparison of Standard- and Low-Tube Voltage MDCT Angiography in Patients With Peripheral Arterial Disease. European Radiology. 2010; 20(11):2758-2765. (Guideline Ref ID 16103)	Wrong reference standard
Vahl AC, Geselschap J, Montauban van Swijndregt AD, Smit J, Sala J, Turkcan K, Dijksman LM, Visser MJ. Contrast Enhanced Magnetic Resonance Angiography Versus Intra-Arterial Digital Subtraction Angiography for Treatment Planning in Patients With Peripheral Arterial Disease: a Randomised Controlled Diagnostic Trial. European Journal of Vascular and Endovascular Surgery. 2008; 35(5):514-521. (Guideline Ref ID 290)	Health economics study
Valecchi D, Bacci D, Gulisano M, Conti AA, Sibilio M, Lipoma M, Sgambati E, Macchi C. Evaluation of the Pattern of Proximal and Distal Occlusion and Collateral Circulation of Lower Limb Arteries Using Combined Contrast Arteriography and Color Doppler Ecography. Italian Journal of Anatomy and Embryology. 2009; 114(2-3):121-127. (Guideline Ref ID 16113)	Not comparison of diagnostic tests accuracy between new test and reference standard
Vogt FM, Zenge MO, Ladd ME, Herborn CU, Brauck K, Luboldt W, Barkhausen J, Quick HH. Peripheral Vascular Disease: Comparison of Continuous MR Angiography and Conventional MR Angiography--Pilot Study. Radiology. 2007; 243(1):229-238. (Guideline Ref ID 260)	Sample size <20
Voth M, Haneder S, Huck K, Gutfleisch A, Schonberg SO, Michaely HJ. Peripheral Magnetic Resonance Angiography With Continuous Table Movement in Combination With High Spatial and Temporal Resolution Time-Resolved MRA With a Total Single Dose (0.1 Mmol/Kg) of Gadobutrol at 3.0 T. Investigative Radiology. 2009; 44(9):627-633. (Guideline Ref ID 16116)	Wrong reference standard
Walker TG. Acute Limb Ischemia. Techniques in Vascular and Interventional Radiology. 2009; 12(2):117-129. (Guideline Ref ID 2169)	Wrong study design (review)
Wang CC, Liang HL, Hsiao CC, Chen MC, Wu TH, Wu CJ, Huang JS, Lin YH, Pan HB. Single-Dose Time-Resolved Contrast Enhanced Hybrid MR Angiography in Diagnosis of Peripheral Arterial Disease: Compared With Digital Subtraction Angiography. Journal of Magnetic Resonance Imaging. 2010; 32(4):935-942.	Compares observer readings

(Guideline Ref ID 16102)	
Wann S.Rao. Cardiac Computed Tomographic Angiography: Evaluation of Non-Cardiac Structures. Journal of Nuclear Cardiology. 2009; 16(1):139-150. (Guideline Ref ID 2183)	Wrong population
Wikstrom J, Hansen T, Johansson L, Lind L, Ahlstrom H. Ankle Brachial Index <0.9 Underestimates the Prevalence of Peripheral Artery Occlusive Disease Assessed With Whole-Body Magnetic Resonance Angiography in the Elderly. Acta Radiologica. 2008; 49(2):143-149. (Guideline Ref ID 16128)	Wrong comparison (ABPI)
Willmann JK, Baumert B, Schertler T, Wildermuth S, Pfammatter T, Verdun FR, Seifert B, Marincek B, Bohm T. Aortoiliac and Lower Extremity Arteries Assessed With 16-Detector Row CT Angiography: Prospective Comparison With Digital Subtraction Angiography. Radiology. 2005; 236(3):1083-1093. (Guideline Ref ID 368)	Wrong comparison (comparing observers)
Wyttenbach R, Gianella S, Alerci M, Braghetti A, Cozzi L, Gallino A. Prospective Blinded Evaluation of Gd-DOTA- Versus Gd-BOPTA-Enhanced Peripheral MR Angiography, As Compared With Digital Subtraction Angiography. Radiology. 2003; 227(1):261-269. (Guideline Ref ID 4257)	Wrong study design (RCT) and comparison (doses of contrast agent)
Yucel EK. Magnetic Resonance Angiography and the Peripheral Vasculature: How Useful Is It? Nature Clinical Practice Cardiovascular Medicine. 2005; 2(3):136-137. (Guideline Ref ID 2559)	Wrong study design (review)
Zhang Z, Fan Z, Carroll TJ, Chung Y, Weale P, Jerecic R, Li D. Three-Dimensional T2-Weighted MRI of the Human Femoral Arterial Vessel Wall at 3.0 Tesla. Investigative Radiology. 2009; 44(9):619-626. (Guideline Ref ID 16115)	Sample size <20

E.4 Management of intermittent claudication

E.4.1 Comparisons of supervised vs unsupervised exercise and exercise, best medical treatment, angioplasty and bypass surgery

The search and exclusion list included the following review questions:

- 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?
- 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 PAD in adults with intermittent claudication?

Excluded n = 283

Study excluded	Reason
Abahji TN, Tato F, Rieger J, Offner A, Will S, Hoelscher G, Weiss N, Hoffman U. Stenting of the Superficial Femoral Artery After Suboptimal Balloon Angioplasty: One-Year Results. International Angiology. 2006; 25(2):184-189. (Guideline Ref ID 1214)	Wrong study design (observational)
Abbassian A, Khan AZ, Poulter E, Ransome R, Thomas PR. Treating Lower Limb Vascular Claudication Using Community-Based Exercise Rehabilitation. International Journal of Therapy and Rehabilitation. 2006; 13(5):216-222. (Guideline Ref ID 24)	Wrong study design (observational)
Abdelsalam H, Markose G, Bolia A. Revascularization Strategies in Below the Knee Interventions. Journal of Cardiovascular Surgery. 2008; 49(2):185-189. (Guideline Ref ID 1218)	Wrong study design (review)
Abdul Raouf A, Rouleau Y, Clement A, Le Roux P, Genay P, Ricco JB. Endoluminal Angioplasty of the Popliteal Artery. Review of 54 Consecutive Patients. European Journal of Vascular and Endovascular Surgery. 2005; 30(6):610-613. (Guideline Ref	Wrong study design (observational)

ID 3055)	
Agnoletti G, Marini D, Ou P, Vandrell MC, Boudjemline Y, Bonnet D. Cheatham Platinum (CP) and Palmaz Stents for Cardiac and Vascular Lesions Treatment in Patients With Congenital Heart Disease. EuroIntervention. 2009; 4(5):620-625. (Guideline Ref ID 1225)	Wrong study design (observational)
Ah Chong AK, Tan CB, Wong MW, Cheng FS. Bypass Surgery or Percutaneous Transluminal Angioplasty to Treat Critical Lower Limb Ischaemia Due to Infrainguinal Arterial Occlusive Disease? Hong Kong Medical Journal. 2009; 15(4):249-254. (Guideline Ref ID 62)	Wrong study design (observational)
Ahn S, Rutherford RB. A Multicenter Prospective Randomized Trial to Determine the Optimal Treatment of Patients With Claudication and Isolated Superficial Femoral Artery Occlusive Disease: Conservative Versus Endovascular Versus Surgical Therapy. Journal of Vascular Surgery. 1992; 15(5):889-891. (Guideline Ref ID 794)	Description of study only – not results
Allie DE. Creative Limb-Salvage Surgical and Endovascular Revascularization Strategies in Treating Critical Limb Ischemia. Surgical Technology International. 2008; 17:97-104. (Guideline Ref ID 1244)	Wrong study design (review)
Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of Revascularization Procedures for Peripheral Arterial Occlusive Disease in Ontario Between 1991 and 1998: a Population-Based Study. Journal of Vascular Surgery. 2003; 38(2):279-288. (Guideline Ref ID 1235)	Wrong study design (observational)
Amighi J, Schillinger M, Dick P, Schlager O, Sabeti S, Mlekusch W, Haumer M, Mathies R, Heinzle G, Schuster A, Loewe C, Koppensteiner R, Lammer J, Minar E, Cejna M. De Novo Superficial Femoropopliteal Artery Lesions: Peripheral Cutting Balloon Angioplasty and Restenosis Rates--Randomized Controlled Trial. Radiology. 2008; 247(1):267-272. (Guideline Ref ID 157)	Wrong comparison (compares types of angioplasty)
Andreozzi GM, Leone A, Martini R, Laudani R, Salimistraro G, Deinite G. Effectiveness and Costs of a Short-Course Supervised Training Program in Claudicants: Proposal for a Shared Protocol With Aerobic Working Load (Provisional Abstract). International Angiology. 2008; 27:401-407. (Guideline Ref ID 2439)	Wrong study design (observational)
Antoniucci D, Valenti R, Moschi G, Santoro GM, Bolognese L, Trapani M, Fazzini PF. Cost-Effective Analysis of Primary Infarct-Artery Stenting Versus Optimal Primary Angioplasty (the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) Trial) (Structured Abstract). American Journal of Cardiology. 2000; 85(10):1247-1249. (Guideline Ref ID 1185)	Health economic study
Arain SA, White CJ. Endovascular Therapy for Critical Limb Ischemia. Vascular Medicine. 2008; 13(3):267-279. (Guideline Ref ID 1259)	Wrong study design (review)
Arfvidsson B, Karlsson J, Dahllof AG, Lundholm K, Sullivan M. The Impact of Intermittent Claudication on Quality of Life Evaluated by the Sickness Impact Profile Technique. European Journal of Clinical Investigation. 1993; 23(11):741-745. (Guideline Ref ID 15937)	Wrong study objective
Arosio E, Minuz P, Prior M, Zuliani V, Gaino S, De Marchi S, Fontana L, Andrioli G, Lechi C, Lechi A. Vascular Adhesion Molecule-1 and Markers of Platelet Function Before and After a Treatment With Iloprost or a Supervised Physical Exercise Program in Patients With Peripheral Arterial Disease. Life Sciences. 2001; 69(4):421-433. (Guideline Ref ID 734)	Wrong comparison (control group received iloprost treatment)
Arosio E, Cuzzolin L, De Marchi S, Minuz P, Degan M, Crivellente F, Zannoni M, Benoni G. Increased Endogenous Nitric Oxide Production Induced by Physical Exercise in Peripheral Arterial Occlusive Disease Patients. Life Sciences. 1999; 65(26):2815-2822. (Guideline Ref ID 843)	Wrong comparison (control group received iloprost treatment)
Bali HK, Bhargava M, Jain AK, Sharma BK. De Novo Stenting of Descending Thoracic Aorta in Takayasu Arteritis: Intermediate-Term Follow-Up Results. Journal of Invasive Cardiology. 2000; 12(12):612-617. (Guideline Ref ID 1290)	Wrong study design (observational)

Balzer JO, Thalhammer A, Khan V, Zangos S, Vogl TJ, Lehnert T. Angioplasty of the Pelvic and Femoral Arteries in PAOD: Results and Review of the Literature. European Journal of Radiology. 2010; 75(1):48-56. (Guideline Ref ID 1295)	Wrong study design (observational)
Balzer JO, Zeller T, Rastan A, Sixt S, Vogl TJ, Lehnert T, Khan V. Percutaneous Interventions Below the Knee in Patients With Critical Limb Ischemia Using Drug Eluting Stents. Journal of Cardiovascular Surgery. 2010; 51(2):183-191. (Guideline Ref ID 1293)	Wrong study design (observational)
Barbeau GR, Seeger JM, Jablonski S, Kaelin LD, Friedl SE, Abela GS. Peripheral Artery Recanalization in Humans Using Balloon and Laser Angioplasty. Clinical Cardiology. 1996; 19(3):232-238. (Guideline Ref ID 1299)	Wrong study design (observational)
Barbosa Nunes APDO, Dos Santos Rios AC, Da Cunha GA, Pereira Barretto AC, Negrao CE. The Effects of Nonsupervised Exercise Program, Via Internet, on Blood Pressure and Body Composition in Normotensive and Pre-Hipertensive Individuals. Arquivos Brasileiros De Cardiologia. 2006; 86(4):288-295. (Guideline Ref ID 1775)	Wrong population (study does not consider patients with PAD)
Becker GJ, Ferguson JG, Bakal CW, Kinnison ML, McLean GK, Pentecost M, Perler BA, van BA, Veith FJ. Angioplasty, Bypass Surgery, and Amputation for Lower Extremity Peripheral Arterial Disease in Maryland: a Closer Look. Radiology. 1993; 186(3):635-638. (Guideline Ref ID 774)	Wrong study design (observational)
Becquemin JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic Versus Selective Stent Placement After Superficial Femoral Artery Balloon Angioplasty: a Multicenter Prospective Randomized Study. Journal of Vascular Surgery. 2003; 37(3):487-494. (Guideline Ref ID 442)	Wrong comparison
Becquemin JP, Allaire E, Cavillon A, Desgranges P, Melliere D. Conventional Versus Endovascular Surgical Procedures: a No Choice Option. European Journal of Vascular and Endovascular Surgery. 1995; 10(1):1-3. (Guideline Ref ID 719)	Wrong study design (review)
Becquemin JP, Cavillon A, Allaire E, Haiduc F, Desgranges P. Iliac and Femoropopliteal Lesions: Evaluation of Balloon Angioplasty and Classical Surgery. Journal of Endovascular Surgery. 1995; 2(1):42-50. (Guideline Ref ID 1315)	Wrong study design (observational)
Belli AM, Cumberland DC, Procter AE, Welsh CL. Total Peripheral Artery Occlusions: Conventional Versus Laser Thermal Recanalization With a Hybrid Probe in Percutaneous Angioplasty--Results of a Randomized Trial. Radiology. 1991; 181(1):57-60. (Guideline Ref ID 3063)	Wrong comparison (recanalization)
Bendermacher BL, Willigendael EM, Nicolai SP, Kruidenier LM, Welten RJ, Hendriks E, Prins MH, Teijink JA, de Bie RA. Supervised Exercise Therapy for Intermittent Claudication in a Community-Based Setting Is As Effective As Clinic-Based. Journal of Vascular Surgery. 2007; 45(6):1192-1196. (Guideline Ref ID 276)	Wrong study design (observational)
Bendermacher BL, Willigendael EM, Teijink JA, Prins MH. Supervised Exercise Therapy Versus Non-Supervised Exercise Therapy for Intermittent Claudication. Cochrane Database of Systematic Reviews. 2006; Issue 2:CD005263. (Guideline Ref ID 2413)	Cochrane review – cross checked for studies which match review protocol
Berceli SA, Hevelone ND, Lipsitz SR, Bandyk DF, Clowes AW, Moneta GL, Conte MS. Surgical and Endovascular Revision of Infrainguinal Vein Bypass Grafts: Analysis of Midterm Outcomes From the PREVENT III Trial. Journal of Vascular Surgery. 2007; 46(6):1173-1179. (Guideline Ref ID 171)	Wrong study design (observational)
Birkenstock WE, Louw JH, Terblanche J, Immelman EJ, Dent DM, Baker PM. Smoking and Other Factors Affecting the Conservative Management of Peripheral Vascular Disease. South African Medical Journal. 1975; Suid-Afrikaanse Tydskrif Vir Geneeskunde. 49(28):1129-1132. (Guideline Ref ID 1301)	Wrong comparison (not BMT as described in protocol)
Black JH, III, LaMuraglia GM, Kwolek CJ, Brewster DC, Watkins MT, Cambria RP. Contemporary Results of Angioplasty-Based Infrainguinal Percutaneous Interventions. Journal of Vascular Surgery. 2005; 42(5):932-939. (Guideline Ref ID 1335)	Wrong study design (observational)
Boccalandro F, Muench A, Sdringola S, Rosales O. Wireless Laser-Assisted	Wrong study design

Angioplasty of the Superficial Femoral Artery in Patients With Critical Limb Ischemia Who Have Failed Conventional Percutaneous Revascularization. Catheterization and Cardiovascular Interventions. 2004; 63(1):7-12. (Guideline Ref ID 1337)	(observational)
Bosch JL, Tetteroo E, Mali WP, Hunink MG. Iliac Arterial Occlusive Disease: Cost-Effectiveness Analysis of Stent Placement Versus Percutaneous Transluminal Angioplasty. Dutch Iliac Stent Trial Study Group. Radiology. 1998; 208(3):641-648. (Guideline Ref ID 2459)	Health economic study
Bosch JL, Hunink MG. Meta-Analysis of the Results of Percutaneous Transluminal Angioplasty and Stent Placement for Aortoiliac Occlusive Disease. Radiology. 1997; 204(1):87-96. (Guideline Ref ID 2458)	Wrong study design (meta-analysis)
Bosiers M, Peeters P, D'Archambeau O, Hendriks J, Pilger E, Duber C, Zeller T, Gussmann A, Lohle PN, Minar E, Scheinert D, Hausegger K, Schulte KL, Verbist J, Deloose K, Lammer J, AMS INSIGHT Investigators. AMS INSIGHT--Absorbable Metal Stent Implantation for Treatment of Below-the-Knee Critical Limb Ischemia: 6-Month Analysis. Cardiovascular and Interventional Radiology. 2009; 32(3):424-435. (Guideline Ref ID 78)	Wrong study design (observational)
Bosiers M, Cagiannos C, Deloose K, Verbist J, Peeters P. Drug-Eluting Stents in the Management of Peripheral Arterial Disease. Vascular Health and Risk Management. 2008; 4(3):553-559. (Guideline Ref ID 1349)	Wrong study design (review)
Bosiers M, Deloose K, Moreialvar R, Verbist J, Peeters P. Current Status of Infrapopliteal Artery Stenting in Patients With Critical Limb Ischemia. Jornal Vascular Brasileiro. 2008; 7(3):248-255. (Guideline Ref ID 1348)	Wrong study design (review)
Bosiers M, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular Therapy As the Primary Approach for Limb Salvage in Patients With Critical Limb Ischemia: Experience With 443 Infrapopliteal Procedures. Vascular. 2006; 14(2):63-69. (Guideline Ref ID 3065)	Wrong study design (observational)
Bosiers M, Peeters P, Elst FV, Vermassen F, Maleux G, Fourneau I, Massin H. Excimer Laser Assisted Angioplasty for Critical Limb Ischemia: Results of the LACI Belgium Study. European Journal of Vascular and Endovascular Surgery. 2005; 29(6):613-619. (Guideline Ref ID 345)	Wrong study design (observational)
Bown MJ, Bolia A, Sutton AJ. Subintimal Angioplasty: Meta-Analytical Evidence of Clinical Utility. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):323-337. (Guideline Ref ID 60)	Wrong study design (meta-analysis)
Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, Raab G, Ruckley CV. Multicentre Randomised Controlled Trial of the Clinical and Cost-Effectiveness of a Bypass-Surgery-First Versus a Balloon-Angioplasty-First Revascularisation Strategy for Severe Limb Ischaemia Due to Infrainguinal Disease. The Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial. Health Technology Assessment. 2010; 14(14):1-236. (Guideline Ref ID 1356)	Included in angioplasty compared to bypass
Brandsma JW, Robeer BG, van den Heuvel S, Smit B, Wittens CH, Oostendorp RA. The Effect of Exercises on Walking Distance of Patients With Intermittent Claudication: a Study of Randomized Clinical Trials. Physical Therapy. 1998; 78(3):278-286. (Guideline Ref ID 2483)	Wrong study design (systematic review)
Breek JC, de Vries J, Hamming JF. The Oslo Balloon Angioplasty Versus Conservative Treatment Study (OBACT) - The 2-Years Results of a Single Centre, Prospective, Randomised Study in Patients With Intermittent Claudication. European Journal of Vascular and Endovascular Surgery. 2007; 34(3):378. (Guideline Ref ID 2761)	Wrong study design (letter)
Brewster DC, Cambria RP, Darling RC, Athanasoulis CA, Waltman AC, Geller SC, Moncure AC, LaMuraglia GM, Freehan M, Abbott WM. Long-Term Results of Combined Iliac Balloon Angioplasty and Distal Surgical Revascularization. Annals of Surgery. 1989; 210(3):324-330. (Guideline Ref ID 3051)	Wrong study design (observational)
Bronas UG, Treat-Jacobson D, Leon AS. Comparison of the Effect of Upper Body-	Wrong comparison

Ergometry Aerobic Training Vs Treadmill Training on Central Cardiorespiratory Improvement and Walking Distance in Patients With Claudication. Journal of Vascular Surgery. 2011; 53(6):1557-1564. (Guideline Ref ID 16285)	(non exercise control)
Bronas UG, Hirsch AT, Murphy T, Badenhop D, Collins TC, Ehrman JK, Ershow AG, Lewis B, Treat-Jacobson D, Walsh ME, Oldenburg N, Regensteiner JG, CLEVER Research Group. Design of the Multicenter Standardized Supervised Exercise Training Intervention for the Claudication: Exercise Vs Endoluminal Revascularization (CLEVER) Study. Vascular Medicine. 2009; 14(4):313-321. (Guideline Ref ID 22)	Description of study not yet completed. CLEVER study due to be published in June 2012
Bronas UG. Comparison of the Effect of Upper Body Ergometer Aerobic Training Vs. Treadmill Training on Walking Distance in Patients With Claudication: Influence of Central Cardiorespiratory Improvement: a Randomized Controlled Study. -136. 2007. University of Minnesota. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2009982240&site=ehost-live. (Guideline Ref ID 3)	Wrong study design (PHD thesis)
Brunkwall J, Weibull H, Bergqvist D, Takolander R, Bergentz SE. Arterial Surgery and Angioplasty in Patients Under 40 Years of Age: A Retrospective Study. Medical Principles and Practice. 1989; 1(1):37-43. (Guideline Ref ID 1369)	Wrong study design (observational)
Bucek RA, Hudak P, Schnurer G, Ahmadi R, Wolfram RM, Minar E. Clinical Long-Term Results of Percutaneous Transluminal Angioplasty in Patients With Peripheral Arterial Occlusive Disease. Vasa. 2002; 31(1):36-42. (Guideline Ref ID 1370)	Wrong study design (observational)
Burns P, Gough S, Bradbury AW. Management of Peripheral Arterial Disease in Primary Care. BMJ. 2003; 326(7389):584-588. (Guideline Ref ID 15924)	Wrong study design (review)
Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and Outcome of Patients Hospitalised for Lower Extremity Peripheral Artery Disease in France: the COPART Registry. European Journal of Vascular and Endovascular Surgery. 2010; 39(5):577-585. (Guideline Ref ID 16)	Wrong study design (observational)
Canaud L, Alric P, Berthet JP, Marty-Ane C, Mercier G, Branchereau P. Infrainguinal Cutting Balloon Angioplasty in De Novo Arterial Lesions. Journal of Vascular Surgery. 2008; 48(5):1182-1188. (Guideline Ref ID 113)	Wrong study design (observational)
Cao P, De Rango P, Verzini F, Maselli A, Norgiolini L, Giordano G. Outcome of Carotid Stenting Versus Endarterectomy: A Case-Control Study. Stroke. 2006; 37(5):1221-1226. (Guideline Ref ID 1386)	Wrong study design (observational)
Cejna M, Schoder M, Lammer J. PTA Versus Stenting in Femoropopliteal Obstructive Disease. Radiologe. 1999; 39(2):144-150. (Guideline Ref ID 1054)	Paper not in English
Cheng SWK, Ting ACW, Ho P. Angioplasty and Primary Stenting of High-Grade, Long-Segment Superficial Femoral Artery Disease: Is It Worthwhile? Annals of Vascular Surgery. 2003; 17(4):430-437. (Guideline Ref ID 1407)	Wrong study design (observational)
Chetter IC, Spark JI, Scott DJ, Kester RC. Does Angioplasty Improve the Quality of Life for Claudicants?: A Prospective Study. Annals of Vascular Surgery. 1999; 13(1):93-103. (Guideline Ref ID 602)	Wrong study design (observational)
Chiriano J, Bianchi C, Teruya TH, Mills B, Bishop V, Abou-Zamzam Jr AM. Management of Lower Extremity Wounds in Patients With Peripheral Arterial Disease: A Stratified Conservative Approach. Annals of Vascular Surgery. 2010; 24(8):1110-1116. (Guideline Ref ID 16291)	Wrong study design (observational)
Chong PF, Golledge J, Greenhalgh RM, Davies AH. Exercise Therapy or Angioplasty? A Summation Analysis. European Journal of Vascular and Endovascular Surgery. 2000; 20(1):4-12. (Guideline Ref ID 565)	Wrong study design (review)
Christman SK. Intervention to Slow Progression of Peripheral Arterial Disease. -123. 2003. Ohio State University. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2005064115&site=ehost-live. (Guideline Ref ID 13)	Wrong study design (PHD thesis)

Ciuffetti G, Paltriccia R, Lombardini R, Lupattelli G, Pasqualini L, Mannarino E. Treating Peripheral Arterial Occlusive Disease: Pentoxifylline Vs Exercise. International Angiology. 1994; 13(1):33-39. (Guideline Ref ID 3044)	Wrong comparison (BMT not as described in protocol)
Cleveland T, Gaines P, Beard J, Chan P. Aortoiliac Stenting, Determinants of Clinical Outcome. European Journal of Vascular and Endovascular Surgery. 1999; 17(4):351-359. (Guideline Ref ID 1417)	Wrong study design (observational)
Collins T, Lunos S. Home-Based Walking Therapy Improves Walking Ability and Quality of Life in Persons With Diabetes Mellitus and Peripheral Arterial Disease. Vascular Medicine. 2010; 15 (2):155. (Guideline Ref ID 16292)	Wrong outcomes
Collins TC, Johnson SL, Souchek J. Unsupervised Walking Therapy and Atherosclerotic Risk-Factor Management for Patients With Peripheral Arterial Disease: a Pilot Trial. Annals of Behavioral Medicine. 2007; 33(3):318-324. (Guideline Ref ID 265)	Wrong comparison (comparison group told not to increase exercise)
Collins EG, Langbein WE, Orebaugh C, Bammert C, Hanson K, Reda D, Edwards LC, Littooy F. Cardiovascular Training Effect Associated With Polestriding Exercise in Patients With Peripheral Arterial Disease. Journal of Cardiovascular Nursing. 2005; 20(3):177-185. (Guideline Ref ID 474)	Wrong comparison (comparison group told not to exercise)
Collins EG, Edwin Langbein W, Orebaugh C, Bammert C, Hanson K, Reda D, Edwards LC, Littooy F. PoleStriding Exercise and Vitamin E for Management of Peripheral Vascular Disease. Medicine & Science in Sports & Exercise. 2003; 35(3):384-393. (Guideline Ref ID 601)	Wrong comparison (comparison to vitamins E)
Cordero-Yordan H, Lopez A, Heuser RR. Carotid Artery Percutaneous Transluminal Angioplasty and Stenting: Indications, Technical Approach, and Complications. Journal of Interventional Cardiology. 1999; 12(6):499-504. (Guideline Ref ID 1425)	Wrong study design (review)
Cotton LT, Roberts VC. Extended Deep Femoral Angioplasty: an Alternative to Femoropopliteal Bypass. British Journal of Surgery. 1975; 62(5):340-343. (Guideline Ref ID 1428)	Wrong study design (observational)
Creasy TS, Fletcher EW. Prospective Randomized Trial of PTA Versus Supervised Exercise Therapy for Intermittent Claudication. British Journal of Radiology. 1992; 65(Suppl):108. (Guideline Ref ID 2985)	Wrong study design (abstract)
Creasy TS, McMillan PJ, Walton J, Fletcher EW, Collin J, Morris PJ. A Prospective Randomised Trial of Percutaneous Transluminal Angioplasty (PTA) Versus Exercise Therapy for Lower Limb Claudication. Clinical Radiology. 1989; 40(6):638. (Guideline Ref ID 1153)	Wrong study design (abstract)
Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. The Influence of a Long Term Exercise Program on Lower Limb Movement Variability and Walking Performance in Patients With Peripheral Arterial Disease. Human Movement Science. 2009; 28(4):494-503. (Guideline Ref ID 56)	Wrong comparison (comparison group told not to exercise)
Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a Long-Term Exercise Program on Lower Limb Mobility, Physiological Responses, Walking Performance, and Physical Activity Levels in Patients With Peripheral Arterial Disease. Journal of Vascular Surgery. 2008; 47(2):303-309. (Guideline Ref ID 216)	Wrong outcomes
Cunningham MA, Swanson V, O'Carroll RE, Holdsworth RJ. Increasing Walking in Patients With Intermittent Claudication: Protocol for a Randomised Controlled Trial. BMC Cardiovascular Disorders. 2010; 10(49) (Guideline Ref ID 16286)	Wrong comparison (non exercise control)
Dahllof AG, Holm J, Schersten T, Sivertsson R. Peripheral Arterial Insufficiency, Effect of Physical Training on Walking Tolerance, Calf Blood Flow, and Blood Flow Resistance. Scandinavian Journal of Rehabilitation Medicine. 1976; 8(1): UNKNOWN. (Guideline Ref ID 1300)	Wrong comparison (comparison group told not to exercise)
Dahllof AG, Bjorntorp P, Holm J, Schersten T. Metabolic Activity of Skeletal Muscle in Patients With Peripheral Arterial Insufficiency. European Journal of Clinical Investigation. 1974; 4(1):9-15. (Guideline Ref ID 3045)	Wrong comparison (comparison group told not to exercise)

Dave RM, Patlola R, Kollmeyer K, Bunch F, Weinstock BS, Dippel E, Jaff MR, Popma J, Weissman N, CELLO Investigators. Excimer Laser Recanalization of Femoropopliteal Lesions and 1-Year Patency: Results of the CELLO Registry. Journal of Endovascular Therapy. 2009; 16(6):665-675. (Guideline Ref ID 34)	Wrong study design (observational)
de Belder AJ, Smith RE, Wainwright RJ, Thomas MR. Transradial Artery Coronary Angiography and Intervention in Patients With Severe Peripheral Vascular Disease. Clinical Radiology. 1997; 52(2):115-118. (Guideline Ref ID 672)	Wrong study design (observational)
de Vries SO, Visser K, de Vries JA, Wong JB, Donaldson MC, Hunink MG. Intermittent Claudication: Cost-Effectiveness of Revascularization Versus Exercise Therapy. Radiology. 2002; 222(1):25-36. (Guideline Ref ID 2460)	Health economic study
Degischer S, Labs KH, Hochstrasser J, Aschwanden M, Tschoepl M, Jaeger KA. Physical Training for Intermittent Claudication: a Comparison of Structured Rehabilitation Versus Home-Based Training. Vascular Medicine. 2002; 7(2):109-115. (Guideline Ref ID 638)	Wrong study design (observational)
Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or Endovascular Revascularization in Patients With Critical Limb Ischemia: Influence of Diabetes Mellitus on Clinical Outcome. Journal of Vascular Surgery. 2007; 45(4):751-761. (Guideline Ref ID 220)	Wrong study design (observational)
Diehm N, Savolainen H, Mahler F, Schmidli J, Do DD, Baumgartner I. Does Deep Femoral Artery Revascularization As an Isolated Procedure Play a Role in Chronic Critical Limb Ischemia? Journal of Endovascular Therapy. 2004; 11(2):119-124. (Guideline Ref ID 408)	Wrong study design (observational)
Donaghue CC, Bohannon RW, Maljanian R, Frigon L, Horowitz S, McGovern A. Improved Health-Related Quality of Life 12 Months After Bypass or Angioplasty for Peripheral Arterial Disease. Journal of Vascular Nursing. 2000; 18(3):75-82. (Guideline Ref ID 885)	Wrong study design (observational)
Donas KP, Schwindt A, Pitoulias GA, Schonefeld T, Basner C, Torsello G. Endovascular Treatment of Internal Iliac Artery Obstructive Disease. Journal of Vascular Surgery. 2009; 49(6):1447-1451. (Guideline Ref ID 1474)	Wrong study design (observational)
Dorigo W, Pulli R, Marek J, Troisi N, Fargion A, Giacomelli E, Spina I, Bellandi S, Pratesi G, Pratesi C. A Comparison Between Open and Endovascular Repair in the Treatment of Critical Limb Ischemia. Italian Journal of Vascular and Endovascular Surgery. 2009; 16(1):17-22. (Guideline Ref ID 1478)	Wrong study design (observational)
Dosluoglu HH, Cherr GS, Lall P, Harris LM, Dryjski ML. Stenting Vs Above Knee Polytetrafluoroethylene Bypass for TransAtlantic Inter-Society Consensus-II C and D Superficial Femoral Artery Disease. Journal of Vascular Surgery. 2008; 48(5):1166-1174. (Guideline Ref ID 1486)	Wrong study design (observational)
Dosluoglu HH, Cherr GS, Harris LM, Dryjski ML. Rheolytic Thrombectomy, Angioplasty, and Selective Stenting for Subacute Isolated Popliteal Artery Occlusions. Journal of Vascular Surgery. 2007; 46(4):717-723. (Guideline Ref ID 186)	Wrong study design (observational)
D'Othee BJ, Morris MF, Powell RJ, Bettmann MA. Cost Determinants of Percutaneous and Surgical Interventions for Treatment of Intermittent Claudication From the Perspective of the Hospital (Brief Record). Cardiovascular and Interventional Radiology. 2008; 31:56-65. (Guideline Ref ID 2404)	Health economic study
Drescher P, McGuckin J, Rilling WS, Crain MR. Catheter-Directed Thrombolytic Therapy in Peripheral Artery Occlusions: Combining Reteplase and Abciximab. American Journal of Roentgenology. 2003; 180(5):1385-1391. (Guideline Ref ID 1492)	Wrong comparison (compares types of drugs)
Drozdz W, Lejman W. Response to Exercise Training in Patients With Intermittent Claudication. Polski Przeglad Chirurgiczny. 2006; 78(1) (pp 85-105), 2006. Date of Publication: 2006.):-105. (Guideline Ref ID 1792)	Paper not in English
Dryjski ML. Comments Regarding 'Walking Performance and Health-Related	Wrong study design

Quality of Life After Surgical or Endovascular Invasive Versus Non-Invasive Treatment for Intermittent Claudication--a Prospective Randomised Trial'. European Journal of Vascular and Endovascular Surgery. 2011; 42(2):228-229. (Guideline Ref ID 16293)	(commentary)
Duda SH, Bosiers M, Pusich B, Huttl K, Oliva V, Muller-Hulsbeck S, Bray A, Luz O, Remy C, Hak JB, Beregi JP. Endovascular Treatment of Peripheral Artery Disease With Expanded PTFE-Covered Nitinol Stents: Interim Analysis From a Prospective Controlled Study. Cardiovascular and Interventional Radiology. 2002; 25(5):413-418. (Guideline Ref ID 457)	Wrong study design (observational)
Eiberg JP, Hansen MA, Jorgensen LG, Rasmussen JBG, Jensen F, Schroeder TV. In-Situ Bypass Surgery on Arteriographically Invisible Vessels Detected by Doppler-Ultrasound for Limb Salvage. Journal of Cardiovascular Surgery. 2004; 45(4) (pp 375-379), 2004. Date of Publication: Aug 2004.):-379. (Guideline Ref ID 561)	Wrong study design (observational)
Elgzyri T, Ekberg G, Peterson K, Lundell A, Apelqvist J. Can Duplex Arterial Ultrasonography Reduce Unnecessary Angiography? Journal of Wound Care. 2008; 17(11):497-500. (Guideline Ref ID 111)	Wrong objective (study considered assessment not intervention)
Elliott JM, Berdan LG, Holmes DR, Isner JM, King SB, Keeler GP, Kearney M, Califf RM, Topol EJ. One-Year Follow-Up in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I). Circulation. 1995; 91(8):2158-2166. (Guideline Ref ID 1103)	Wrong comparison (excisional atherectomy)
Ellozy SH, Carroccio A. Drug-Eluting Stents in Peripheral Vascular Disease: Eliminating Restenosis. Mount Sinai Journal of Medicine. 2003; 70(6):417-419. (Guideline Ref ID 1508)	Wrong study design (review)
Ernst E, Fialka V. A Review of the Clinical Effectiveness of Exercise Therapy for Intermittent Claudication. Archives of Internal Medicine. 1993; 153(20):2357-2360. (Guideline Ref ID 1074)	Wrong study design (review)
Evans C, Peter N, Gibson M, Torrie EP, Galland RB, Magee TR. Five-Year Retrograde Transpopliteal Angioplasty Results Compared With Antegrade Angioplasty. Annals of the Royal College of Surgeons of England. 2010; 92(4):347-352. (Guideline Ref ID 1516)	Wrong study design (observational)
Faglia E, Clerici G, Clerissi J, Caminiti M, Quarantiello A, Curci V, Losa S, Vitiello R, Lupattelli T, Somalvico F. Angioplasty for Diabetic Patients With Failing Bypass Graft or Residual Critical Ischemia After Bypass Graft. European Journal of Vascular and Endovascular Surgery. 2008; 36(3):331-338. (Guideline Ref ID 1522)	Wrong study design (observational)
Feinglass J, McCarthy WJ, Slavensky R, Manheim LM, Martin GJ. Functional Status and Walking Ability After Lower Extremity Bypass Grafting or Angioplasty for Intermittent Claudication: Results From a Prospective Outcomes Study. Journal of Vascular Surgery. 2000; 31(1 Pt 1):93-103. (Guideline Ref ID 806)	Wrong study design (observational)
Feiring AJ, Krahn M, Nelson L, Wesolowski A, Eastwood D, Szabo A. Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents: the PaRADISE (PReventing Amputations Using Drug Eluting StEnts) Trial. Journal of the American College of Cardiology. 2010; 55(15):1580-1589. (Guideline Ref ID 5)	Wrong study design (observational)
Flu HC, Tamsma JT, Lindeman JH, Hamming JF, Lardenoye JH. A Systematic Review of Implementation of Established Recommended Secondary Prevention Measures in Patients With PAOD. European Journal of Vascular and Endovascular Surgery. 2010; 39(1):70-86. (Guideline Ref ID 61)	Wrong study design (review)
Fowkes FG, Gillespie IN. Angioplasty (Versus Non Surgical Management) for Intermittent Claudication. Cochrane Database of Systematic Reviews. 2000;(2):CD000017. (Guideline Ref ID 2407)	Cochrane review - cross checked for studies which match review protocol
Garasic JM, Creager MA. Percutaneous Interventions for Lower-Extremity Peripheral Atherosclerotic Disease. Reviews in Cardiovascular Medicine. 2001; 2(3):120-125. (Guideline Ref ID 1562)	Wrong study design (review)
Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, Goldberg	Wrong comparison

AP. Exercise Rehabilitation Improves Functional Outcomes and Peripheral Circulation in Patients With Intermittent Claudication: a Randomized Controlled Trial. Journal of the American Geriatrics Society. 2001; 49(6):755-762. (Guideline Ref ID 735)	(comparison group told not to exercise)
Gardner AW, Katzel LI, Sorkin JD, Goldberg AP. Effects of Long-Term Exercise Rehabilitation on Claudication Distances in Patients With Peripheral Arterial Disease: a Randomized Controlled Trial. Journal of Cardiopulmonary Rehabilitation. 2002; 22(3):192-198. (Guideline Ref ID 661)	Wrong comparison (comparison group told not to exercise)
Gardner AW, Katzel LI, Sorkin JD, Killewich LA, Ryan A, Flinn WR, Goldberg AP. Improved Functional Outcomes Following Exercise Rehabilitation in Patients With Intermittent Claudication. Journals of Gerontology Series A: Biological Sciences & Medical Sciences. 2000; 55A(10):M570-M577. (Guideline Ref ID 12)	Wrong study design (observational)
Gardner AW, Poehlman ET. Exercise Rehabilitation Programs for the Treatment of Claudication Pain. A Meta-Analysis. JAMA. 1995; 274(12):975-980. (Guideline Ref ID 404)	Wrong study design (meta-analysis)
Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG, Sandstrom R, Arfvidsson B, Lundholm K. Treatment Efficacy of Intermittent Claudication by Surgical Intervention, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients I: One Year Results of Functional and Physiological Improvements. European Journal of Vascular and Endovascular Surgery. 2001; 22(2):107-113. (Guideline Ref ID 3046)	Patients had either angioplasty or bypass, GDG agreed this was a flawed study and should be excluded
Gibellini R, Fanello M, Bardile AF, Salerno M, Aloi T. Exercise Training in Intermittent Claudication. International Angiology. 2000; 19(1):8-13. (Guideline Ref ID 789)	Wrong comparison (comparison group told not to exercise)
Girolami B, Bernardi E, Prins MH, ten Cate JW, Hettiarachchi R, Prandoni P, Girolami A, Buller HR. Treatment of Intermittent Claudication With Physical Training, Smoking Cessation, Pentoxifylline, or Nafronyl: a Meta-Analysis. Archives of Internal Medicine. 1999; 159(4):337-345. (Guideline Ref ID 832)	Wrong study design (meta-analysis)
Grant AG, White CJ, Collins TJ, Jenkins JS, Reilly JP, Ramee SR. Infrapopliteal Drug-Eluting Stents for Chronic Limb Ischemia. Catheterization and Cardiovascular Interventions. 2008; 71(1):108-111. (Guideline Ref ID 166)	Wrong study design (observational)
Gray BH, Laird JR, Ansel GM, Shuck JW. Complex Endovascular Treatment for Critical Limb Ischemia in Poor Surgical Candidates: a Pilot Study. Journal of Endovascular Therapy. 2002; 9(5):599-604. (Guideline Ref ID 464)	Wrong study design (observational)
Gray BH. Endovascular Treatment of Peripheral Arterial Disease. Journal of the American Osteopathic Association. 2000; 100(10 Su Pt 2):S15-S20. (Guideline Ref ID 1586)	Wrong study design (observational)
Gray BH, Olin JW. Limitations of Percutaneous Transluminal Angioplasty With Stenting for Femoropopliteal Arterial Occlusive Disease. Seminars in Vascular Surgery. 1997; 10(1):8-16. (Guideline Ref ID 1585)	Wrong study design (observational)
Greenhalgh RM. MIMIC Trials: Angioplasty effective in randomised controlled trials for peripheral arterial disease. Available from: http://www.cxvascular.com/in-latest-news?ccs=485&cs=4222 Last accessed on: 2 February 2009. (Guideline Ref ID 924)	Wrong study design (commentary)
Grizzo Cucato G, de Moraes Forjaz CL, Kanegusuku H, da Rocha Chehuen M, Riani Costa LA, Wolosker N, Kalil Filho R, de Fatima Nunes Marucci M, Mendes Ritti-Dias R. Effects of Walking and Strength Training on Resting and Exercise Cardiovascular Responses in Patients With Intermittent Claudication. Vasa. 2011; 40(5):390-397. (Guideline Ref ID 16353)	Wrong comparison
He EY, He N, Wang Y, Fan H. Percutaneous Transluminal Angioplasty (PTA) Alone Versus PTA With Balloon-Expandable Stent Placement for Short-Segment Femoropopliteal Artery Disease: A Metaanalysis of Randomized Trials. Journal of Vascular and Interventional Radiology. 2008; 19(4):499-503. (Guideline Ref ID 1502)	Wrong study design (meta-analysis)

Helgerud J, Wang E, Mosti MP, Wiggen ON, Hoff J. Plantar Flexion Training Primes Peripheral Arterial Disease Patients for Improvements in Cardiac Function. European Journal of Applied Physiology. 2009; 106(2):207-215. (Guideline Ref ID 108)	Wrong outcomes
Henry M, Henry I, Klonaris C, Hugel M. Clinical Experience With the OptiMed Sinus Stent in the Peripheral Arteries. Journal of Endovascular Therapy. 2003; 10(4):772-779. (Guideline Ref ID 1616)	Wrong study design (observational)
Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of Treadmill Walking Exercise Versus Strength Training for Patients With Peripheral Arterial Disease. Implications for the Mechanism of the Training Response. Circulation. 1994; 90(4):1866-1874. (Guideline Ref ID 1044)	Wrong comparison (control group was a non treatment group)
Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of Exercise Conditioning for Patients With Peripheral Arterial Disease. Circulation. 1990; 81(2):602-609. (Guideline Ref ID 1169)	Wrong comparison (comparison group told not to exercise)
Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The Effect of Supervised Exercise and Cilostazol on Coagulation and Fibrinolysis in Intermittent Claudication: a Randomized Controlled Trial. Journal of Vascular Surgery. 2007; 45(1):65-70. (Guideline Ref ID 309)	Results presented in paper are inaccurate therefore not possible to interpret evidence
Hobbs SD, Bradbury AW. The EXercise Versus Angioplasty in Claudication Trial (EXACT): Reasons for Recruitment Failure and the Implications for Research into and Treatment of Intermittent Claudication. Journal of Vascular Surgery. 2006; 44(2):432-433. (Guideline Ref ID 3047)	Wrong study design (letter)
Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The Constitutive Procoagulant and Hypofibrinolytic State in Patients With Intermittent Claudication Due to Infrainguinal Disease Significantly Improves With Percutaneous Transluminal Balloon Angioplasty. Journal of Vascular Surgery. 2006; 43(1):40-46. (Guideline Ref ID 16368)	Wrong comparison (BMT not as described in protocol)
Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized Controlled Trial of Supervised Exercise to Evaluate Changes in Cardiac Function in Patients With Peripheral Atherosclerotic Disease. Clinical Physiology and Functional Imaging. 2008; 28(1):32-37. (Guideline Ref ID 224)	Wrong outcomes
Hoeks SE, Smolderen KG, Scholte op Reimer WJM, Verhagen HJM, Spertus JA, Poldermans D. Clinical Validity of a Disease-Specific Health Status Questionnaire: The Peripheral Artery Questionnaire. Journal of Vascular Surgery. 2009; 49(2):371-377. (Guideline Ref ID 3070)	Wrong study design (observational)
Hoffer EK, Sultan S, Herskowitz MM, Daniels ID, Sclafani SJ. Prospective Randomized Trial of a Metallic Intravascular Stent in Hemodialysis Graft Maintenance. Journal of Vascular and Interventional Radiology. 1997; 8(6):965-973. (Guideline Ref ID 1073)	Wrong population
Hynes N, Akhtar Y, Manning B, Aremu M, Oiakhinan K, Courtney D, Sultan S. Subintimal Angioplasty As a Primary Modality in the Management of Critical Limb Ischemia: Comparison to Bypass Grafting for Aortoiliac and Femoropopliteal Occlusive Disease. Journal of Endovascular Therapy. 2004; 11(4):460-471. (Guideline Ref ID 15935)	Wrong study design (observational)
Iannone L, Rough R, Ghali M, Rayl KL, Phillips S. Angioplasty Treatment for Peripheral Vascular Disease. Iowa Medicine. 1996; 86(7):281-283. (Guideline Ref ID 1653)	Wrong study design (observational)
Ihnat DM, Duong ST, Taylor ZC, Leon LR, Mills JL, Sr., Goshima KR, Echeverri JA, Arslan B. Contemporary Outcomes After Superficial Femoral Artery Angioplasty and Stenting: the Influence of TASC Classification and Runoff Score. Journal of Vascular Surgery. 2008; 47(5):967-974. (Guideline Ref ID 147)	Wrong study design (observational)
Is an Exercise Program Helpful for Patients With Symptomatic Stable Intermittent Claudication? Evidence-Based Practice. 1998; 1(5):-10, insert. (Guideline Ref ID 14)	Wrong study design (review)

Jaff MR, Cahill KE, Yu AP, Birnbaum HG, Engelhart LM. Clinical Outcomes and Medical Care Costs Among Medicare Beneficiaries Receiving Therapy for Peripheral Arterial Disease. Annals of Vascular Surgery. 2010; 24(5):577-587. (Guideline Ref ID 1662)	Wrong study design (observational)
Jahnke T, Voshage G, Muller-Hulsbeck S, Grimm J, Heller M, Brossmann J. Endovascular Placement of Self-Expanding Nitinol Coil Stents for the Treatment of Femoropopliteal Obstructive Disease. Journal of Vascular and Interventional Radiology. 2002; 13(3):257-266. (Guideline Ref ID 3059)	Wrong study design (observational)
Jamsen TS, Manninen HI, Tulla HE, Jaakkola PA, Matsi PJ. Infrainguinal Revascularization Because of Claudication: Total Long-Term Outcome of Endovascular and Surgical Treatment. Journal of Vascular Surgery. 2003; 37(4):808-815. (Guideline Ref ID 1667)	Wrong study design (observational)
Johnston KW, Rae M, Hogg-Johnston SA, Colapinto RF, Walker PM, Baird RJ, Sniderman KW, Kalman P. 5-Year Results of a Prospective Study of Percutaneous Transluminal Angioplasty. Annals of Surgery. 1987; 206(4):403-413. (Guideline Ref ID 858)	Wrong study design (observational)
Kasapis C, Henke PK, Chetcuti SJ, Koenig GC, Rectenwald JE, Krishnamurthy VN, Grossman PM, Gurm HS. Routine Stent Implantation Vs. Percutaneous Transluminal Angioplasty in Femoropopliteal Artery Disease: a Meta-Analysis of Randomized Controlled Trials. European Heart Journal. 2009; 30(1):44-55. (Guideline Ref ID 98)	Wrong study design (meta-analysis)
Keeling AN, Naughton PA, O'Connell A, Lee MJ. Does Percutaneous Transluminal Angioplasty Improve Quality of Life? Journal of Vascular and Interventional Radiology. 2008; 19(2 Pt 1):169-176. (Guideline Ref ID 159)	Wrong study design (observational)
Keo H, Grob E, Guggisberg F, Widmer J, Baumgartner I, Schmid JP, Kalka C, Saner H. Long-Term Effects of Supervised Exercise Training on Walking Capacity and Quality of Life in Patients With Intermittent Claudication. Vasa. 2008; 37(3):250-256. (Guideline Ref ID 177)	Wrong study design (observational)
Kickuth R, Keo HH, Triller J, Ludwig K, Do DD. Initial Clinical Experience With the 4-F Self-Expanding XPERT Stent System for Infrapopliteal Treatment of Patients With Severe Claudication and Critical Limb Ischemia. Journal of Vascular and Interventional Radiology. 2007; 18(6):703-708. (Guideline Ref ID 1705)	Wrong study design (observational)
Kidney D, Murphy J, Malloy M. Balloon-Expandable Intravascular Stents in Atherosclerotic Iliac Artery Stenosis: Preliminary Experience. Clinical Radiology. 1993; 47(3):189-192. (Guideline Ref ID 1706)	Wrong study design (observational)
Killewich LA, Macko RF, Montgomery PS, Wiley LA, Gardner AW. Exercise Training Enhances Endogenous Fibrinolysis in Peripheral Arterial Disease. Journal of Vascular Surgery. 2004; 40(4):741-745. (Guideline Ref ID 505)	Wrong comparison (comparison group told not to exercise)
Kim J-S, Kang TS, Ahn CM, Ko YG, Choi D, Jang Y, Chung N, Shim W-H, Cho S-Y. Efficacy of Subintimal Angioplasty/Stent Implantation for Long, Multisegmental Lower Limb Occlusive Lesions in Patients Unsuitable for Surgery. Journal of Endovascular Therapy. 2006; 13(4):514-521. (Guideline Ref ID 1707)	Wrong study design (observational)
Klein WM, van der Graaf Y, Seegers J, Spithoven JH, Buskens E, Van Baal JG, Buth J, Moll FL, Overtoom TT, Van Sambeek MRHM, Mali WP. Dutch Iliac Stent Trial: Long-Term Results in Patients Randomized for Primary or Selective Stent Placement. Radiology. 2006; 238(2):734-744. (Guideline Ref ID 1715)	Wrong comparison
Klevsgard R, Risberg BO, Thomsen MB, Hallberg IR. A 1-Year Follow-Up Quality of Life Study After Hemodynamically Successful or Unsuccessful Surgical Revascularization of Lower Limb Ischemia. Journal of Vascular Surgery. 2001; 33(1):114-122. (Guideline Ref ID 1716)	Wrong study objectives (considers impact of successful or unsuccessful treatment)
Koerkamp BG, Spronk S, Stijnen T, Hunink MGM. Value of Information Analyses of Economic Randomized Controlled Trials: The Treatment of Intermittent Claudication. Value in Health. 2010; 13(2):242-250. (Guideline Ref ID 36)	Health economic study

Kovalik EC, Newman GE, Suhocki P, Knelson M, Schwab SJ. Correction of Central Venous Stenoses: Use of Angioplasty and Vascular Wallstents. Kidney International. 1994; 45(4):1177-1181. (Guideline Ref ID 749)	Wrong study design (observational)
Krause D, Dittmar K. Combination of Physiotherapeutic Exercise Therapy With Bencyclane in Intermittent Claudication. Munchener Medizinische Wochenschrift. 1976; 118(40):1281-1284. (Guideline Ref ID 3034)	Paper not in English
Kruidenier LM, Nicolai SP, Hendriks EJ, Bollen EC, Prins MH, Teijink JA. Supervised Exercise Therapy for Intermittent Claudication in Daily Practice. Journal of Vascular Surgery. 2009; 49(2):363-370. (Guideline Ref ID 1449)	Wrong study design (observational)
Kudo T, Chandra FA, Ahn SS. Long-Term Outcomes and Predictors of Iliac Angioplasty With Selective Stenting. Journal of Vascular Surgery. 2005; 42(3):466. (Guideline Ref ID 1738)	Wrong study design (observational)
Kujala UM. Evidence for Exercise Therapy in the Treatment of Chronic Disease Based on at Least Three Randomized Controlled Trials - Summary of Published Systematic Reviews. Scandinavian Journal of Medicine and Science in Sports. 2004; 14(6):339-345. (Guideline Ref ID 1903)	Wrong study design (review)
Lai DTM, Huber D, Glasson R, Grayndler V, Evans J, Hogg J, Etheredge S. Colour-Coded Duplex Ultrasonography in Selection of Patients for Transluminal Angioplasty. Australasian Radiology. 1995; 39(3):243-245. (Guideline Ref ID 1094)	Wrong objective (study considered assessment not intervention)
Lammer J, Dake MD, Bleyn J, Katzen BT, Cejna M, Piquet P, Becker GJ, Settlage RA. Peripheral Arterial Obstruction: Prospective Study of Treatment With a Transluminally Placed Self-Expanding Stent-Graft. Radiology. 2000; 217(1):95-104. (Guideline Ref ID 1753)	Wrong study design (observational)
Langbein WE, Collins EG, Orebaugh C, Maloney C, Williams KJ, Littooy F, Edwards LC. Increasing Exercise Tolerance of Persons Limited by Claudication Pain Using Polestriding. Journal of Vascular Surgery. 2002; 35(5):887-893. (Guideline Ref ID 666)	Wrong comparison (comparison group told not to exercise)
Lantis J, Jensen M, Benvenisty A, Mendes D, Gendics C, Todd G. Outcomes of Combined Superficial Femoral Endovascular Revascularization and Popliteal to Distal Bypass for Patients With Tissue Loss. Annals of Vascular Surgery. 2008; 22(3):366-371. (Guideline Ref ID 145)	Wrong study design (observational)
Larsen OA, Lassen NA. Effect of Daily Muscular Exercise in Patients With Intermittent Claudication. Scandinavian Journal of Clinical and Laboratory Investigation. 1967; 99:168-171. (Guideline Ref ID 3048)	Wrong study design (observational)
Larsen OA, Lassen NA. Effect of Daily Muscular Exercise in Patients With Intermittent Claudication. Lancet. 1966; 288(7473):1093-1096. (Guideline Ref ID 1312)	Wrong comparison (comparison group told not to exercise)
Lee HL, Mehta T, Ray B, Heng TS, McCollum P, Chetter IC. A Trial of the Clinical and Cost-Effectiveness of a Supervised Exercise Programme for Claudication. British Journal of Surgery. 2005; 92(Suppl 1):11. (Guideline Ref ID 2782)	Wrong study design (abstract)
Litvack F, Grundfest WS, Adler L, Hickey AE, Segalowitz J, Hestrin LB, Mohr FW, Goldenberg T, Laudenslager JS, Forrester JS. Percutaneous Excimer-Laser and Excimer-Laser-Assisted Angioplasty of the Lower Extremities: Results of Initial Clinical Trial. Radiology. 1989; 172(2):331-335. (Guideline Ref ID 3062)	Wrong study design (observational)
Liu C, Guan H, Li Y, Zheng Y, Liu W. Combined Intraoperative Iliac Artery Stents and Femoro-Popliteal Bypass for Multilevel Atherosclerotic Occlusive Disease. Chinese Medical Sciences Journal. 2001; 16(3):165-168. (Guideline Ref ID 1777)	Wrong study design (observational)
Lopez-Galarza LA, Ray LI, Rodriguez-Lopez J, Diethrich EB. Combined Percutaneous Transluminal Angioplasty, Iliac Stent Deployment, and Femorofemoral Bypass for Bilateral Aortoiliac Occlusive Disease. Journal of the American College of Surgeons. 1997; 184(3):249-258. (Guideline Ref ID 1786)	Wrong study design (observational)
Lorenzi G, Domanin M, Costantini A, Rolli A, Agrifoglio G. Role of Bypass, Endarterectomy, Extra-Anatomic Bypass and Endovascular Surgery in Unilateral	Wrong study design (observational)

Iliac Occlusive Disease: a Review of 1257 Cases. Cardiovascular Surgery. 1994; 2(3):370-373. (Guideline Ref ID 746)	
Lundgren F, Dahllof AG, Schersten T, Bylund-Fellenius AC. Muscle Enzyme Adaptation in Patients With Peripheral Arterial Insufficiency: Spontaneous Adaptation, Effect of Different Treatments and Consequences on Walking Performance. Clinical Science. 1989; 77(5):485-493. (Guideline Ref ID 1178)	Wrong population (patients did not have PAD)
Mahler F, Do DD, Triller J. Interventional Angiology. European Journal of Medicine. 1992; 1(5):295-301. (Guideline Ref ID 1793)	Wrong study design (review)
Mannarino E, Pasqualini L, Innocente S, Scricciolo V, Rignanese A, Ciuffetti G. Physical Training and Antiplatelet Treatment in Stage II Peripheral Arterial Occlusive Disease: Alone or Combined? Angiology. 1991; 42(7):513-521. (Guideline Ref ID 1131)	Wrong comparison (no BMT group)
Martens JM, Knippenberg B, Vos JA, de Vries JP, Hansen BE, van OH, PADI Trial Group. Update on PADI Trial: Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. Journal of Vascular Surgery. 2009; 50(3):687-689. (Guideline Ref ID 57)	Study protocol
Martinez CA, Carmeli E, Barak S, Stopka CB. Changes in Pain-Free Walking Based on Time in Accommodating Pain-Free Exercise Therapy for Peripheral Arterial Disease. Journal of Vascular Nursing. 2009; 27(1):2-7. (Guideline Ref ID 130)	Wrong comparison
Matsi PJ, Manninen HI. Complications of Lower-Limb Percutaneous Transluminal Angioplasty: a Prospective Analysis of 410 Procedures on 295 Consecutive Patients. Cardiovascular and Interventional Radiology. 1998; 21(5):361-366. (Guideline Ref ID 3054)	Wrong study design (observational)
McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, Nelson M, Lloyd-Jones D, Van HL, Garside D, Kibbe M, Domanchuk K, Stein JH, Liao Y, Tao H, Green D, Pearce WH, Schneider JR, McPherson D, Laing ST, McCarthy WJ, Shroff A, Criqui MH. Treadmill Exercise and Resistance Training in Patients With Peripheral Arterial Disease With and Without Intermittent Claudication: a Randomized Controlled Trial. JAMA. 2009; 301(2):165-174. (Guideline Ref ID 139)	Wrong comparison (comparison group only received nutritional advice)
McDermott MM, Liu K, Ferrucci L, Criqui MH, Greenland P, Guralnik JM, Tian L, Schneider JR, Pearce WH, Tan J, Martin GJ. Physical Performance in Peripheral Arterial Disease: a Slower Rate of Decline in Patients Who Walk More. Annals of Internal Medicine. 2006; 144(1):10-20. (Guideline Ref ID 392)	Wrong study design (observational)
McGuigan MRM, Newton RU, Bronks R. Resistance Training for Patients With Peripheral Arterial Disease: a Model of Exercise Rehabilitation. Strength and Conditioning Journal. 2001; 23(3):26-32. (Guideline Ref ID 20)	Wrong study design (observational)
McLean L, Jeans WD, Horrocks M, Baird RN. The Place of Percutaneous Transluminal Angioplasty in the Treatment of Patients Having Angiography for Ischaemic Disease of the Lower Limb. Clinical Radiology. 1987; 38(2):157-160. (Guideline Ref ID 861)	Wrong study design (observational)
Menêses AL, de Lima GH, Forjaz CL, Lima AH, Silva GQ, Cucato GG, Rodrigues SL, Wolosker N, Marucci MF, Dias RM. Impact of a Supervised Strength Training or Walking Training Over a Subsequent Unsupervised Therapy Period on Walking Capacity in Patients With Claudication. Journal of Vascular Nursing. 2011; 29(2):81-86. (Guideline Ref ID 972)	Wrong comparison
Meneses AL, de Lima GHC, Forjaz CLdM, Lima AHRdA, Silva GQdM, Cucato GG, Rodrigues SLC, Wolosker N, Marucci MdFN, Dias RMR. Impact of a Supervised Strength Training or Walking Training Over a Subsequent Unsupervised Therapy Period on Walking Capacity in Patients With Claudication. Journal of Vascular Nursing. 2011; 29(2):81-86. (Guideline Ref ID 16282)	Wrong comparison (compares types of supervised exercise)
Michaels J, Galland RB. Case Mix and Outcome of Patients Referred to the Vascular Service at a District General Hospital. Annals of the Royal College of Surgeons of England. 1993; 75(5):358-361. (Guideline Ref ID 762)	Wrong study design (observational)
Mika P, Spodaryk K, Cencora A, Mika A. Red Blood Cell Deformability in Patients	Wrong comparison

With Claudication After Pain-Free Treadmill Training. Clinical Journal of Sport Medicine. 2006; 16(4):335-340. (Guideline Ref ID 351)	(comparison group told not to exercise)
Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental Model of Pain-Free Treadmill Training in Patients With Claudication. American Journal of Physical Medicine and Rehabilitation. 2005; 84(10):756-762. (Guideline Ref ID 433)	Wrong comparison (comparison group told not to exercise)
Minar E, Schillinger M. New Stents for SFA. Journal of Cardiovascular Surgery. 2009; 50(5):635-645. (Guideline Ref ID 1847)	Wrong study design (review)
Muller-Buhl U, Strecker EP, Gottmann D, Vetter S, Boos IBL. Improvement in Claudication After Angioplasty of Distal Ostial Collateral Stenosis in Patients With Long-Segment Occlusion of the Femoral Artery. Cardiovascular and Interventional Radiology. 2000; 23(6):447-451. (Guideline Ref ID 1868)	Wrong study design (observational)
Muradin GSR, Bosch JL, Stijnen T, Hunink MGM. Balloon Dilation and Stent Implantation for Treatment of Femoropopliteal Arterial Disease: Meta-Analysis. Radiology. 2001; 221(1):137-145. (Guideline Ref ID 1871)	Wrong study design (meta-analysis)
Muradin GSR, Hunink MGM. Cost and Patency Rate Targets for the Development of Endovascular Devices to Treat Femoropopliteal Arterial Disease. Radiology. 2001; 218(2):464-469. (Guideline Ref ID 863)	Health economic study
Murphy TP, Hirsch AT, Cutlip DE, Regensteiner JG, Comerota AJ, Mohler E, Cohen DJ, Massaro J, CLEVER Investigators. Claudication: Exercise Vs Endoluminal Revascularization (CLEVER) Study Update. Journal of Vascular Surgery. 2009; 50(4):942-945. (Guideline Ref ID 52)	Description of study not yet completed. CLEVER study due to be published in June 2012
Murphy TP, Webb MS, Lambiase RE, Haas RA, Dorfman GS, Carney J, Morin CJ. Percutaneous Revascularization of Complex Iliac Artery Stenoses and Occlusions With Use of Wallstents: Three-Year Experience. Journal of Vascular and Interventional Radiology. 1996; 7(1):21-27. (Guideline Ref ID 1874)	Wrong study design (observational)
Nawaz S, Walker RD, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. The Inflammatory Response to Upper and Lower Limb Exercise and the Effects of Exercise Training in Patients With Claudication. Journal of Vascular Surgery. 2001; 33(2):392-399. (Guideline Ref ID 756)	Wrong study design (observational)
Nelson PR, Powell RJ, Schermerhorn ML, Fillinger MF, Zwolak RM, Walsh DB, Cronenwett JL. Early Results of External Iliac Artery Stenting Combined With Common Femoral Artery Endarterectomy. Journal of Vascular Surgery. 2002; 35(6):1107-1113. (Guideline Ref ID 1888)	Wrong study design (observational)
Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, Whittemore AD, Belkin M. Infrainguinal Vein Bypass Graft Revision: Factors Affecting Long-Term Outcome. Journal of Vascular Surgery. 2004; 40(5):916-923. (Guideline Ref ID 1892)	Wrong study design (observational)
Nordanstig J, Gelin J, Hensater M, Taft C, Osterberg K, Jivegrd L. Walking Performance and Health-Related Quality of Life After Surgical or Endovascular Invasive Versus Non-Invasive Treatment for Intermittent Claudication - A Prospective Randomised Trial. European Journal of Vascular and Endovascular Surgery. 2011; 42(2):220-227. (Guideline Ref ID 16283)	Patients had either angioplasty or bypass – GDG agreed this was a flawed study design and should be excluded
Oka RK, Altman M, Giacomini JC, Szuba A, Cooke JP. Exercise Patterns and Cardiovascular Fitness of Patients With Peripheral Arterial Disease. Journal of Vascular Nursing. 2004; 22(4) (pp 109-114), 2004. Date of Publication: December 2004.):-114. (Guideline Ref ID 1905)	Wrong comparison (comparison group told not to exercise)
Okada M, Yoshida M, Tsuji Y. Clinical Experience of Laser Angioplasty for the Cardiovascular Disease. Diagnostic and Therapeutic Endoscopy. 1995; 2(1):11-18. (Guideline Ref ID 1904)	Wrong study design (observational)
Osborn JJ, Pfeiffer RB, Jr., String ST. Directional Atherectomy and Balloon Angioplasty for Lower Extremity Arterial Disease. Annals of Vascular Surgery. 1997; 11(3):278-283. (Guideline Ref ID 663)	Wrong study design (observational)

Ouriel K. Comparison of Surgical and Thrombolytic Treatment of Peripheral Arterial Disease. Reviews in Cardiovascular Medicine. 2002; 3 Suppl 2:S7-16. (Guideline Ref ID 3064)	Wrong study design (review)
Overdevest GM, Luijsterburg PA, Brand R, Koes BW, Bierma-Zeinstra SM, Eekhof JA, Vleggeert-Lankamp CL, Peul WC. Design of the Verbiest Trial: Cost-Effectiveness of Surgery Versus Prolonged Conservative Treatment in Patients With Lumbar Stenosis. BMC Musculoskeletal Disorders. 2011; 12:57. (Guideline Ref ID 16294)	Wrong comparison
Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison Between Coronary Angioplasty and Coronary Artery Bypass Surgery for the Treatment of Unprotected Left Main Coronary Artery Stenosis (the Bologna Registry). American Journal of Cardiology. 2006; 98(1):54-59. (Guideline Ref ID 1910)	Wrong study design (observational)
Parmenter BJ, Raymond J, Fiatarone Singh MA. The Effect of Exercise on Haemodynamics in Intermittent Claudication: a Systematic Review of Randomized Controlled Trials. Sports Medicine. 2010; 40(5):433-447. (Guideline Ref ID 31)	Wrong study design (observational)
Parr BM, Noakes TD, Derman EW. Peripheral Arterial Disease and Intermittent Claudication: Efficacy of Short-Term Upper Body Strength Training, Dynamic Exercise Training, and Advice to Exercise at Home. South African Medical Journal. 2009; 99(11):800-804. (Guideline Ref ID 49)	Wrong outcomes
Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a Supervised Exercise Program for the Therapy of Arterial Claudication. Journal of Vascular Surgery. 1997; 25(2):312-318. (Guideline Ref ID 940)	Wrong comparison (compares level of supervision in exercise programmes)
Pozzi Mucelli F, Fisicaro M, Calderan L, Malacrea M, Mazzone C, Cattin L, Scardi S, Pozzi Mucelli R. Percutaneous Revascularization of Femoropopliteal Artery Disease: PTA and PTA Plus Stent. Results After Six Years' Follow-Up. Radiologia Medica. 2003; 105(4):339-349. (Guideline Ref ID 436)	Wrong study design (observational)
Price JF, Leng GC, Fowkes FG. Should Claudicants Receive Angioplasty or Exercise Training?. Cardiovascular Surgery. 1997; 5(5):463-470. (Guideline Ref ID 202)	Wrong study design (review)
Puma JA, Banko LT, Pieper K, Sacchi TJ, O'Shea JC, Dery JP, Tcheng JE. Clinical Characteristics Predict Benefits From Eptifibatide Therapy During Coronary Stenting: Insights From the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) Trial. Journal of the American College of Cardiology. 2006; 47(4):715-718. (Guideline Ref ID 294)	Wrong comparison (compares populations)
Quinn SF, Schuman ES, Demlow TA, Standage BA, Ragsdale JW, Green GS, Sheley RC. Percutaneous Transluminal Angioplasty Versus Endovascular Stent Placement in the Treatment of Venous Stenoses in Patients Undergoing Hemodialysis: Intermediate Results. Journal of Vascular and Interventional Radiology. 1995; 6(6):851-855. (Guideline Ref ID 1104)	Wrong study design (observational)
Reekers JA, Vorwerk D, Rousseau H, Sapoval MR, Gaines PA, Stockx L, Delcour CP, Raat H, Voshage G, Biamino G, Hoogeveen YL. Results of a European Multicentre Iliac Stent Trial With a Flexible Balloon Expandable Stent. European Journal of Vascular and Endovascular Surgery. 2002; 24(6):511-515. (Guideline Ref ID 460)	Wrong study design (observational)
Regensteiner JG. Exercise Rehabilitation for the Patient With Intermittent Claudication: a Highly Effective Yet Underutilized Treatment. Current Drug Targets - Cardiovascular and Haematological Disorders. 2004; 4(3):233-239. (Guideline Ref ID 507)	Wrong study design (observational)
Regensteiner JG, Steiner JF, Hiatt WR. Exercise Training Improves Functional Status in Patients With Peripheral Arterial Disease. Journal of Vascular Surgery. 1996; 23(1):104-115. (Guideline Ref ID 991)	Wrong comparison (control group was a non treatment group)
Regensteiner JG, Steiner JF, Panzer RJ, Hiatt W. Evaluation of Walking Impairment by Questionnaire in Patients With Peripheral Arterial Disease. Journal of Vascular	Not a randomised to surgery, only part of

Medicine and Biology. 1990; 2:142-152. (Guideline Ref ID 3050)	study was randomised
Reifler DR, Feinglass J, Slavensky R, Martin GJ, Manheim L, McCarthy WJ. Functional Outcomes Far Patients With Intermittent Claudication: Bypass Surgery Versus Angioplasty Versus Noninvasive Management. Journal of Vascular Medicine and Biology. 1994; 5(5-6):203-211. (Guideline Ref ID 1954)	Wrong study design (observational)
Ricco JB, Probst H, French University Surgeons Association. Long-Term Results of a Multicenter Randomized Study on Direct Versus Crossover Bypass for Unilateral Iliac Artery Occlusive Disease. Journal of Vascular Surgery. 2008; 47(1):45-53. (Guideline Ref ID 165)	Wrong comparison (compares types of bypass)
Robeer GG, Brandsma JW, van den Heuvel SP, Smit B, Oostendorp RA, Wittens CH. Exercise Therapy for Intermittent Claudication: a Review of the Quality of Randomised Clinical Trials and Evaluation of Predictive Factors. European Journal of Vascular and Endovascular Surgery. 1998; 15(1):36-43. (Guideline Ref ID 877)	Wrong study design (review)
Roberts AJ, Roberts EB, Sykes K, De Cossart L, Edwards P, Cotterrell D. Physiological and Functional Impact of an Unsupervised but Supported Exercise Programme for Claudicants. European Journal of Vascular and Endovascular Surgery. 2008; 36(3):319-324. (Guideline Ref ID 174)	Wrong study design (observational)
Rodriguez A, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, Vogel D, Grinfeld R, Delacasa A, Garrido M, Oliveri R, Mele E, Palacios I, O'Neill W. Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II): 30-Day and One-Year Follow-Up Results. ERACI II Investigators. Journal of the American College of Cardiology. 2001; 37(1):51-58. (Guideline Ref ID 540)	Wrong population (patients had coronary artery disease)
Roine E, Roine RP, Rasanen P, Vuori I, Sintonen H, Saarto T. Cost-Effectiveness of Interventions Based on Physical Exercise in the Treatment of Various Diseases: a Systematic Literature Review. International Journal of Technology Assessment in Health Care. 2009; 25(4):427-454. (Guideline Ref ID 2443)	Health economics review
Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-Analysis of Infrapopliteal Angioplasty for Chronic Critical Limb Ischemia. Journal of Vascular Surgery. 2008; 47(5):975-981. (Guideline Ref ID 146)	Wrong study design (meta-analysis)
Rosales O, Mathewkutty S, Gnaim C. Drug Eluting Stents for Below the Knee Lesions in Patients With Critical Limb Ischemia: Long-Term Follow-Up. Catheterization and Cardiovascular Interventions. 2008; 72(1):112-115. (Guideline Ref ID 1966)	Wrong study design (observational)
Rosenthal D, Dickson C, Rodriguez FJ, Blackshear WM, Jr., Clark MD, Lamis PA, Pallos LL. Infrainguinal Endovascular in Situ Saphenous Vein Bypass: Ongoing Results. Journal of Vascular Surgery. 1994; 20(3):389-394. (Guideline Ref ID 744)	Wrong study design (observational)
Rybicki FJ, Nallamshetty L, Yucel EK, Holtzman SR, Baum RA, Foley WD, Ho VB, Mammen L, Narra VR, Stein B, Moneta GL. ACR Appropriateness Criteria on Recurrent Symptoms Following Lower-Extremity Angioplasty. Journal of the American College of Radiology. 2008; 5(12):1176-1180. (Guideline Ref ID 1979)	Wrong study design (review)
Sadek M, Ellozy SH, Turnbull IC, Lookstein RA, Marin ML, Faries PL. Improved Outcomes Are Associated With Multilevel Endovascular Intervention Involving the Tibial Vessels Compared With Isolated Tibial Intervention. Journal of Vascular Surgery. 2009; 49(3):638-643. (Guideline Ref ID 87)	Wrong study design (observational)
Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients With Peripheral Artery Disease Who Complete 12-Week Supervised Exercise Training Program Show Reduced Cardiovascular Mortality and Morbidity. Circulation Journal. 2009; 73(1):167-173. (Guideline Ref ID 1453)	Wrong study design (observational)
Sanborn TA, Gibbs HH, Brinker JA, Knopf WD, Kosinski EJ, Roubin GS. A Multicenter Randomized Trial Comparing a Percutaneous Collagen Hemostasis Device With Conventional Manual Compression After Diagnostic Angiography and Angioplasty. Journal of the American College of Cardiology. 1993; 22(5):1273-1279. (Guideline Ref ID 313)	Wrong comparison (compression)

Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-Term Effects of Cycle and Treadmill Training on Exercise Tolerance in Peripheral Arterial Disease. Journal of Vascular Surgery. 2006; 44(1):119-127. (Guideline Ref ID 354)	Wrong comparison (comparison group told not to exercise)
Sandri M, Adams V, Gielen S, Linke A, Lenk K, Krankel N, Lenz D, Erbs S, Scheinert D, Mohr FW, Schuler G, Hambrecht R. Effects of Exercise and Ischemia on Mobilization and Functional Activation of Blood-Derived Progenitor Cells in Patients With Ischemic Syndromes: Results of 3 Randomized Studies. Circulation. 2005; 111(25):3391-3399. (Guideline Ref ID 455)	Wrong comparison (comparison group told not to increase exercise)
Satiani B, Mohan Das B, Vaccaro PS, Gawron D. Angiographic Follow-Up After Laser-Assisted Balloon Angioplasty. Journal of Vascular Surgery. 1993; 17(5):960-965. (Guideline Ref ID 772)	Wrong study design (observational)
Saxon RR, Coffman JM, Gooding JM, Natuzzi E, Ponec DJ. Long-Term Results of EPTFE Stent-Graft Versus Angioplasty in the Femoropopliteal Artery: Single Center Experience From a Prospective, Randomized Trial. Journal of Vascular and Interventional Radiology. 2003; 14(3):303-311. (Guideline Ref ID 441)	Same patients as study ID 142
Saxton JM, Zwierska I, Blagojevic M, Choksy SA, Nawaz S, Pockley AG. Upper- Versus Lower-Limb Aerobic Exercise Training on Health-Related Quality of Life in Patients With Symptomatic Peripheral Arterial Disease. Journal of Vascular Surgery. 2011; 53(5):1265-1273. (Guideline Ref ID 16284)	Wrong comparison (non exercise control)
Saxton JM, Zwierska I, Hopkinson K, Espigares E, Choksy S, Nawaz S, Walker R, Pockley AG. Effect of Upper- and Lower-Limb Exercise Training on Circulating Soluble Adhesion Molecules, Hs-CRP and Stress Proteins in Patients With Intermittent Claudication. European Journal of Vascular and Endovascular Surgery. 2008; 35(5):607-613. (Guideline Ref ID 199)	Subset of patients from Zwierska 2005 (ID 420), data extraction would lead to double counting
Schillinger M, Exner M, Mlekusch W, Haumer M, Ahmadi R, Rumpold H, Wagner O, Minar E. Balloon Angioplasty and Stent Implantation Induce a Vascular Inflammatory Reaction. Journal of Endovascular Therapy. 2002; 9(1):59-66. (Guideline Ref ID 482)	Wrong study design (observational)
Schmieder GC, Richardson AI, Scott EC, Stokes GK, Meier GH, III, Panneton JM. Selective Stenting in Subintimal Angioplasty: Analysis of Primary Stent Outcomes. Journal of Vascular Surgery. 2008; 48(5):1175-1181. (Guideline Ref ID 2018)	Wrong study design (observational)
Schneider PA, Caps MT, Nelken N. Infrainguinal Vein Graft Stenosis: Cutting Balloon Angioplasty As the First-Line Treatment of Choice. Journal of Vascular Surgery. 2008; 47(5):960-966. (Guideline Ref ID 2020)	Wrong study design (observational)
Schwarten DE. Balloon Angioplasty Still Tops in Peripheral Vessels. Diagnostic Imaging. 1990; 12(9):88-93. (Guideline Ref ID 2025)	Wrong study design (review)
Sculpher M, Michaels J, McKenna M, Minor J. A Cost-Utility Analysis of Laser-Assisted Angioplasty for Peripheral Arterial Occlusions. International Journal of Technology Assessment in Health Care. 1996; 12:104-125. (Guideline Ref ID 2442)	Health economic study
Semaan E, Hamburg N, Nasr W, Shaw P, Eberhardt R, Woodson J, Doros G, Rybin D, Farber A. Endovascular Management of the Popliteal Artery: Comparison of Atherectomy and Angioplasty. Vascular and Endovascular Surgery. 2010; 44(1):25-31. (Guideline Ref ID 2034)	Wrong study design (observational)
Serracino-Inglott F, Owen G, Carter A, Dix F, Smyth JV, Mohan IV. All Patients Benefit Equally From a Supervised Exercise Program for Claudication. Vascular and Endovascular Surgery. 2007; 41(3):212-216. (Guideline Ref ID 267)	Wrong study design (observational)
Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P. A Comparison of Balloon-Expandable-Stent Implantation With Balloon Angioplasty in Patients With Coronary Artery Disease. Benestent Study Group. New England Journal of Medicine. 1994; 331(8):489-495. (Guideline Ref ID 1108)	Wrong population
Shafique S, Murphy MP, Dalsing MC. Is Cryoplasty the Best Treatment for Peripheral Arterial Disease? Italian Journal of Vascular and Endovascular Surgery.	Wrong comparison (cryoplasty)

2008; 15(3):207-211. (Guideline Ref ID 2037)	
Shalhoub J, Qureshi M, Davies A. Supervised Exercise in Intermittent Claudication: a Sedentary Notion?. Vascular. 2009; 17(2):66-73. (Guideline Ref ID 105)	Wrong study design (review)
Shindelman LE, Ninnul GB, Curtiss SI, Konigsberg SF. Ambulatory Endovascular Surgery: Cost Advantage and Factors Influencing Its Safe Performance. Journal of Endovascular Surgery. 1999; 6(2):160-167. (Guideline Ref ID 581)	Health economic study
Siablis D, Kraniotis P, Karnabatidis D, Kagadis GC, Katsanos K, Tsolakis J. Sirolimus-Eluting Versus Bare Stents for Bailout After Suboptimal Infrapopliteal Angioplasty for Critical Limb Ischemia: 6-Month Angiographic Results From a Nonrandomized Prospective Single-Center Study. Journal of Endovascular Therapy. 2005; 12(6):685-695. (Guideline Ref ID 327)	Wrong study design (observational)
Sise MJ, Shackford SR, Rowley WR, Pistone FJ. Claudication in Young Adults: A Frequently Delayed Diagnosis. Journal of Vascular Surgery. 1989; 10(1):68-74. (Guideline Ref ID 2065)	Study considered diagnosis not intervention
Sixt S, Alawied AK, Rastan A, Schwarzwalder U, Kleim M, Noory E, Schwarz T, Frank U, Muller C, Hauk M, Beschorner U, Nazary T, Burgelin K, Hauswald K, Leppanen O, Neumann FJ, Zeller T. Acute and Long-Term Outcome of Endovascular Therapy for Aortoiliac Occlusive Lesions Stratified According to the TASC Classification: a Single-Center Experience. Journal of Endovascular Therapy. 2008; 15(4):408-416. (Guideline Ref ID 126)	Wrong study design (observational)
Smeets L, Ho GH, Tangelder MJ, Algra A, Lawson JA, Eikelboom BC, Moll FL, Dutch BOA Study Group. Outcome After Occlusion of Infrainguinal Bypasses in the Dutch BOA Study: Comparison of Amputation Rate in Venous and Prosthetic Grafts. European Journal of Vascular and Endovascular Surgery. 2005; 30(6):604-609. (Guideline Ref ID 1355)	Wrong study design (observational)
Sorace P, Ronai P, Churilla JR. Peripheral Arterial Disease: EXERCISE IS MEDICINE. ACSMS Health and Fitness Journal. 2010; 14(1):23-29. (Guideline Ref ID 18)	Wrong study design (observational)
Spaargaren GJ, Lee MJ, Reekers JA, van OH, Schultze Kool LJ, Hoogeveen YL. Evaluation of a New Balloon Catheter for Difficult Calcified Lesions in Infrainguinal Arterial Disease: Outcome of a Multicenter Registry. Cardiovascular and Interventional Radiology. 2009; 32(1):132-135. (Guideline Ref ID 92)	Wrong study design (observational)
Spies JB, LeQuire MH, Brantley SD, Williams JE, Beckett WC, Mills JL. Comparison of Balloon Angioplasty and Laser Thermal Angioplasty in the Treatment of Femoropopliteal Atherosclerotic Disease: Initial Results of a Prospective Randomized Trial. Work in Progress. Journal of Vascular and Interventional Radiology. 1990; 1(1):39-42. (Guideline Ref ID 820)	Wrong comparison (compares types of angioplasty)
Spitzer S, Bach R, Schieffer H. Walk Training and Drug Treatment in Patients With Peripheral Arterial Occlusive Disease Stage II. A Review. International Angiology. 1992; 11(3):204-210. (Guideline Ref ID 2497)	Wrong study design (review)
Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-Effectiveness of Endovascular Revascularization Compared to Supervised Hospital-Based Exercise Training in Patients With Intermittent Claudication: a Randomized Controlled Trial. Journal of Vascular Surgery. 2008; 48(6):1472-1480. (Guideline Ref ID 2451)	Health economic study
Steinberg EP, Bass EB, Tunis SR. Interventional Management of Peripheral Vascular Disease: What Did We Learn in Maryland and Where Do We Go From Here? Radiology. 1993; 186(3):639-642. (Guideline Ref ID 773)	Wrong study design (review)
Steinmetz OK, McPhail NV, Hajjar GE, Barber GG, Cole CW. Endarterectomy Versus Angioplasty in the Treatment of Localized Stenosis of the Abdominal Aorta. Canadian Journal of Surgery. 1994; 37(5):385-390. (Guideline Ref ID 3053)	Wrong study design (observational)
Stewart AH, Lamont PM. Exercise Training for Claudication. Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland. 2007; 5(5):291-299. (Guideline Ref ID 3037)	Wrong study design (review)

Suding PN, McMaster W, Hansen E, Hatfield AW, Gordon IL, Wilson SE. Increased Endovascular Interventions Decrease the Rate of Lower Limb Artery Bypass Operations Without an Increase in Major Amputation Rate. Annals of Vascular Surgery. 2008; 22(2):195-199. (Guideline Ref ID 2092)	Wrong study design (observational)
Taft C, Sullivan M, Lundholm K, Karlsson J, Gelin J, Jivegard L. Predictors of Treatment Outcome in Intermittent Claudication. European Journal of Vascular and Endovascular Surgery. 2004; 27(1):24-32. (Guideline Ref ID 16069)	Wrong study design (observational)
Taft C, Karlsson J, Gelin J, Jivegard L, Sandstrom R, Arfvidsson B, Dahllof AG, Lundholm K, Sullivan M. Treatment Efficacy of Intermittent Claudication by Invasive Therapy, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients II: One-Year Results of Health-Related Quality of Life. European Journal of Vascular and Endovascular Surgery. 2001; 22(2):114-123. (Guideline Ref ID 732)	Study same as ID 3046
Taylor SM, Kalbaugh CA, Healy MG, Cass AL, Gray BH, Langan EM, III, Cull DL, Carsten CG, III, York JW, Snyder BA, Youkey JR. Do Current Outcomes Justify More Liberal Use of Revascularization for Vasculogenic Claudication? A Single Center Experience of 1,000 Consecutively Treated Limbs. Journal of the American College of Surgeons. 2008; 206(5):1053-1062. (Guideline Ref ID 144)	Wrong study design (observational)
Tellier P, Aquilanti S, Lecouffe P, Vasseur C. Comparison Between Exercise Whole Body Thallium Imaging and Ankle-Brachial Index in the Detection of Peripheral Arterial Disease. International Angiology. 2000; 19(3):212-219. (Guideline Ref ID 761)	Wrong study design (observational)
Tetteroo E, van der Graaf Y, van Engelen AD, Hunink MGM, Eikelboom BC, Mali WP. No Difference in Effect on Intermittent Claudication Between Primary Stent Placement and Primary Percutaneous Transluminal Angio Plasty Followed by Selective Stent Placement: A Prospective Randomized Trial. Nederlands Tijdschrift Voor Geneeskunde. 2000; 144(4):167-171. (Guideline Ref ID 1040)	Paper not in English
Tetteroo E, van Engelen AD, Spithoven JH, Tielbeek A, van der Graaf Y, Mali WP. Stent Placement After Iliac Angioplasty: Comparison of Hemodynamic and Angiographic Criteria. Dutch Iliac Stent Trial Study Group. Radiology. 1996; 201(1):155-159. (Guideline Ref ID 305)	Wrong study design (observational)
The Netherlands Organisation for Health Research and Development (ZonMw). Exercise Therapy in Patients With Peripheral Arterial Disease: the Costs and Effectiveness of Physiotherapeutic Supervision With or Without Therapy Feedback Versus a 'Go Home and Walk' Advice (Project Record). 2005. (Guideline Ref ID 3041)	Not a published paper
Thel MC, Califf RM, Tcheng JE, Sigmon KN, Lincoff AM, Topol EJ, Ellis SG. Clinical Risk Factors for Ischemic Complications After Percutaneous Coronary Interventions: Results From the EPIC Trial. The EPIC Investigators. American Heart Journal. 1999; 137(2):264-273. (Guideline Ref ID 1045)	Wrong study objectives (considers risk factors)
Thomson IA, van Rij AM, Morrison ND, Packer SGK, Christie R. A Ten Year Randomised Controlled Trial of Percutaneous Femoropopliteal Angioplasty for Claudication. Australian and New Zealand Journal of Medicine. 1999; 69(Suppl):98. (Guideline Ref ID 3052)	Wrong study design (abstract)
Tiefenbacher C. Abdominal Aortic Aneurysm Repair in Cardiac High Risk Patients--Medication, Surgery or Stent? Clinical Research in Cardiology. 2008; 97(4):215-221. (Guideline Ref ID 156)	Wrong study design (review)
Tielbeek A, Vroegindeweij D, Buth J, Landman GH. Comparison of Balloon Angioplasty and Simpson Atherectomy for Lesions in the Femoropopliteal Artery: Angiographic and Clinical Results of a Prospective Randomized Trial. Journal of Vascular and Interventional Radiology. 1996; 7(6):837-844. (Guideline Ref ID 678)	Wrong comparison (atherectomy)
Timaran CH, Ohki T, Gargiulo NJ, III, Veith FJ, Stevens SL, Freeman MB, Goldman MH. Iliac Artery Stenting in Patients With Poor Distal Runoff: Influence of Concomitant Infrainguinal Arterial Reconstruction. Journal of Vascular Surgery.	Wrong study design (observational)

2003; 38(3):479-484. (Guideline Ref ID 2117)	
Timaran CH, Prault TL, Stevens SL, Freeman MB, Goldman MH. Iliac Artery Stenting Versus Surgical Reconstruction for TASC (TransAtlantic Inter-Society Consensus) Type B and Type C Iliac Lesions. Journal of Vascular Surgery. 2003; 38(2):272-278. (Guideline Ref ID 2118)	Wrong study design (observational)
Tisi PV, Shearman CP. The Impact of Treatment of Intermittent Claudication on Subjective Health of the Patient. Health Trends. 1998; 30:109-114. (Guideline Ref ID 3049)	Wrong objective (study did not consider which treatment was effective)
Tran T, Brown M, Lasala J. An Evidence-Based Approach to the Use of Rotational and Directional Coronary Atherectomy in the Era of Drug-Eluting Stents: When Does It Make Sense? Catheterization and Cardiovascular Interventions. 2008; 72(5):650-662. (Guideline Ref ID 115)	Wrong study design (observational)
Treesak C, Kasemsup V, Treat-Jacobson D, Nyman JA, Hirsch AT. Cost-Effectiveness of Exercise Training to Improve Claudication Symptoms in Patients With Peripheral Arterial Disease. Vascular Medicine. 2004; 9(4):279-285. (Guideline Ref ID 493)	Health economics study
Trocciola SM, Chaer R, Dayal R, Lin SC, Kumar N, Rhee J, Pierce M, Ryer EJ, McKinsey J, Morrissey NJ, Bush HL, Kent KC, Faries PL, Woody JD. Comparison of Results in Endovascular Interventions for Infrainguinal Lesions: Claudication Versus Critical Limb Ischemia. American Surgeon. 2005; 71(6):474-480. (Guideline Ref ID 2131)	Wrong study design (observational)
Troeng T, Bergqvist D, Janzon L, Jendteg S, Lindgren B. The Choice of Strategy in the Treatment of Intermittent Claudication - A Decision Tree Approach. European Journal of Vascular Surgery. 1993; 7(4):438-443. (Guideline Ref ID 2132)	Wrong study design (observational)
Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, Chen YJ, Liu JC. The Effects of Exercise Training on Walking Function and Perception of Health Status in Elderly Patients With Peripheral Arterial Occlusive Disease. Journal of Internal Medicine. 2002; 252(5):448-455. (Guideline Ref ID 613)	Wrong comparison (comparison group told not to exercise)
Ubels FL, Links TP, Sluiter WJ, Reitsma WD, Smit AJ. Walking Training for Intermittent Claudication in Diabetes. Diabetes Care. 1999; 22(2):198-201. (Guideline Ref ID 3043)	Wrong objective (study comparing populations)
van Rij AM, Packer SGK, Morrison N. A Randomized Controlled Study of Percutaneous Angioplasty for Claudicants With Femoro-Popliteal Disease. Journal of Cardiovascular Surgery. 1991; 32:34. (Guideline Ref ID 1141)	Wrong study design (commentary)
Walker RD, Nawaz S, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. Influence of Upper- and Lower-Limb Exercise Training on Cardiovascular Function and Walking Distances in Patients With Intermittent Claudication. Journal of Vascular Surgery. 2000; 31(4):662-669. (Guideline Ref ID 799)	Wrong study design (control group not randomised)
Wang E, Hoff J, Loe H, Kaehler N, Helgerud J. Plantar Flexion: an Effective Training for Peripheral Arterial Disease. European Journal of Applied Physiology. 2008; 104(4):749-756. (Guideline Ref ID 164)	Outcomes don't match protocol
Watson L, Ellis B, Leng GC. Exercise for Intermittent Claudication. Cochrane Database of Systematic Reviews. 2008; Issue 4:CD000990. (Guideline Ref ID 2472)	Cochrane review – cross checked for studies which match review protocol
Weichert W, Meents H, Abt K, Lieb H, Hach W, Krzywanek HJ, Breddin HK. Acetylsalicylic Acid-Reocclusion-Prophylaxis After Angioplasty (ARPA-Study). A Randomized Double-Blind Trial of Two Different Dosages of ASA in Patients With Peripheral Occlusive Arterial Disease. Vasa. 1994; 23(1):57-65. (Guideline Ref ID 1109)	Wrong comparison (compares drug doses)
Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial. Circulation. 2008; 118(13):1358-1365. (Guideline Ref ID 120)	Wrong comparison (compares types of angioplasty)

Whyman MR, Ruckley CV. Should Claudicants Receive Angioplasty or Just Exercise Training? Cardiovascular Surgery. 1998; 6(3):226-231. (Guideline Ref ID 623)	Wrong study design (review)
Whyman MR, Fowkes FGR, Kerracher EMG, Gillespie IN, Lee A, Housley E et al. Intermittent Claudication Is Not Improved by Percutaneous Transluminal Angioplasty - A Randomised Controlled Trial. 1996. (Guideline Ref ID 1082)	Paper not available
Willenberg T, Baumgartner I, Silvestro A, Do DD, Zwahlen M, Diehm N. An Angiographic Analysis of Atherosclerosis Progression in Below-the-Knee Arteries After Femoropopliteal Angioplasty in Claudicants. Journal of Endovascular Therapy. 2010; 17(1):39-45. (Guideline Ref ID 3057)	Wrong study objective (study considered assessment not intervention)
Wilson S, Gelfand D, Jimenez J, Gordon I. Comparison of the Results of Percutaneous Transluminal Angioplasty and Stenting With Medical Treatment for Claudicants Who Have Superficial Femoral Artery Occlusive Disease. Vascular. 2006; 14(2):81-87. (Guideline Ref ID 266)	Wrong study design (review)
Wilson SE, White GH, Wolf G, Cross AP. Proximal Percutaneous Balloon Angioplasty and Distal Bypass for Multilevel Arterial Occlusion. Veterans Administration Cooperative Study No. 199. Annals of Vascular Surgery. 1990; 4(4):351-355. (Guideline Ref ID 828)	Wrong study design (observational)
Wind J, Koelemay MJ. Exercise Therapy and the Additional Effect of Supervision on Exercise Therapy in Patients With Intermittent Claudication. Systematic Review of Randomised Controlled Trials. European Journal of Vascular and Endovascular Surgery. 2007; 34(1):1-9. (Guideline Ref ID 275)	Wrong study design (review)
Wolosker N, Nakano L, Morales Anacleto MM, Puech-Leao P. Primary Utilization of Stents in Angioplasty of Superficial Femoral Artery. Vascular and Endovascular Surgery. 2003; 37(4):271-277. (Guideline Ref ID 2219)	Wrong study design (observational)
Woo EY, Fairman RM, Velazquez OC, Golden MA, Karmacharya J, Carpenter JP. Endovascular Therapy of Symptomatic Innominate-Subclavian Arterial Occlusive Lesions. Vascular and Endovascular Surgery. 2006; 40(1):27-33. (Guideline Ref ID 2224)	Wrong study design (observational)
Wood RE, Sanderson B, Askew CD, Walker PJ, Green S, Stewart IB. Effect of Training on the Response of Plasma Vascular Endothelial Growth Factor to Exercise in Patients With Peripheral Arterial Disease. Clinical Science. 2006; 111(6):401-409. (Guideline Ref ID 326)	Wrong comparison (comparison group told not to exercise)
Wyttenbach R, Gallino A, Alerci M, Mahler F, Cozzi L, Di Valentino M, Badimon JJ, Fuster V, Corti R. Effects of Percutaneous Transluminal Angioplasty and Endovascular Brachytherapy on Vascular Remodeling of Human Femoropopliteal Artery by Noninvasive Magnetic Resonance Imaging. Circulation. 2004; 110(9):1156-1161. (Guideline Ref ID 386)	Wrong comparison (byachtherapy)
Zeller T. Current State of Endovascular Treatment of Femoro-Popliteal Artery Disease. Vascular Medicine. 2007; 12(3):223-234. (Guideline Ref ID 2247)	Wrong study design (review)
Zorger N, Manke C, Lenhart M, Finkenzeller T, Djavidani B, Feuerbach S, Link J. Peripheral Arterial Balloon Angioplasty: Effect of Short Versus Long Balloon Inflation Times on the Morphologic Results. Journal of Vascular and Interventional Radiology. 2002; 13(4):355-359. (Guideline Ref ID 487)	Wrong comparison (compares types of angioplasty)

E.4.12 Naftidrofuryl oxalate

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?

Excluded n = 26

Study excluded	Reason
Belcaro G, Nicolaides AN, Griffin M, De Sanctis MT, Cesarone MR, Incandela L, Ippolito E, Pomante P, Geroulakos G, Ramaswami G. Intermittent Claudication in	Wrong comparison (Pentoxifylline not

Diabetics: Treatment With Exercise and Pentoxifylline--a 6-Month, Controlled, Randomized Trial. Angiology. 2002; 53 Suppl 1:S39-S43. (Guideline Ref ID 16058)	recommended in NICE TA 223)
Bergqvist, D., Rolandsson, O., and Sawe, J. Cilostazol for Treatment of Intermittent Claudication (Structured Abstract). 2010. (Guideline Ref ID 548)	Paper in Swedish
Ciuffetti G, Paltriccia R, Lombardini R, Lupattelli G, Pasqualini L, Mannarino E. Treating Peripheral Arterial Occlusive Disease: Pentoxifylline Vs Exercise. International Angiology. 1994; 13(1):33-39. (Guideline Ref ID 3044)	Wrong comparison (Pentoxifylline not recommended in NICE TA 223)
Clyne CA, Galland RB, Fox MJ, Gustave R, Jantet GH, Jamieson CW. A Controlled Trial of Naftidrofuryl (Praxilene) in the Treatment of Intermittent Claudication. British Journal of Surgery. 1980; 67(5):347-348. (Guideline Ref ID 155)	Wrong comparison
Ernst E, Koll, RL, Resch KL. Does Pentoxifylline Prolong the Walking Distance in Exercised Claudicants? A Placebo-Controlled Double-Blind Trial. Angiology. 1992; 43(2):121-125. (Guideline Ref ID 110)	Wrong comparison
Ernst E, Kollar L, Resch KL, Bergmann H. Arterial Occlusive Disease. Comparison Between Pentoxifylline and Exercise Vs. Exercise Alone in Patients With Stage II of Disease. Munchener Medizinische Wochenschrift. 1990; 132(28-29):456-458. (Guideline Ref ID 16065)	Wrong comparison (Pentoxifylline not recommended in NICE TA 223)
Farkas K, Horvath P, Farsang C. Pentoxifyllin Treatment of Patients With Peripheral Obstructive Vascular Disease. International Angiology. 1993; 12:64. (Guideline Ref ID 443)	Wrong study design (abstract)
Heather AJ. The Use of Hexanicotol (Inositol Niacinate) in Peripheral Vascular Disease. Delaware Medical Journal. 1967; 39(2):33-38. (Guideline Ref ID 158)	Wrong study design (narrative)
Hepp W, Von BS, Corovic D, Diehm C, Muhe E, Rudofsky G, Scheffler P, Trubestein G, Vogelpohl M. Intravenous Prostaglandin E1 Versus Pentoxifylline: a Randomized Controlled Study in Patients With Intermittent Claudication. International Angiology. 1995; 14(Suppl 1):280. (Guideline Ref ID 431)	Wrong study design (abstract)
Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of Treadmill Walking Exercise Versus Strength Training for Patients With Peripheral Arterial Disease. Implications for the Mechanism of the Training Response. Circulation. 1994; 90(4):1866-1874. (Guideline Ref ID 1044)	Wrong intervention
Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The Effect of Supervised Exercise and Cilostazol on Coagulation and Fibrinolysis in Intermittent Claudication: a Randomized Controlled Trial. Journal of Vascular Surgery. 2007; 45(1):65-70. (Guideline Ref ID 309)	Wrong comparison (Cilosatazol not recommended in NICE TA 223)
Kester RC, European Study Group. Intravenous Pentoxifylline Treatment for Chronic Critical Limb Ischaemia (CLI). International Angiology. 1995; 14(Suppl 1):316. (Guideline Ref ID 16063)	Wrong study design (abstract)
Kester RC. Intravenous Pentoxifylline Treatment of Rest Pain From Chronic Critical Limb Ischaemia in a Double-Blind Trial. Cardiovascular Surgery. 1995; 22N:118. (Guideline Ref ID 430)	Wrong study design (abstract)
Kiesewetter H, Blume J, Jung F, Waldhausen P, Gerhards M. Intermittent Claudication. Increase in Walking Distance and Improvement of Hemorheologic Parameters by Pentoxifylline (Trental 400). Munchener Medizinische Wochenschrift. 1988; 130:357-360. (Guideline Ref ID 472)	Wrong comparison (Pentoxifylline not recommended in NICE TA 223)
Kiff RS, Quick CR. Does Inositol Nicotinate (Hexopal) Influence Intermittent Claudication? A Controlled Trial. British Journal of Clinical Practice. 1988; 42(4):141-145. (Guideline Ref ID 125)	Wrong comparison
Neumann AJ. Presentation and Medical Management of Peripheral Arterial Disease in General Practice: Rationale, Aims, Design and Baseline Results of the PACE-PAD Study. Journal of Public Health. 2009; 17(2):127-135. (Guideline Ref ID 178)	Wrong study design (observational study)
O'Hara J. A Double-Blind Placebo-Controlled Study of Hexopal in the Treatment	Wrong comparison

of Intermittent Claudication. Journal of International Medical Research. 1985; 13(6):322-327. (Guideline Ref ID 138)	
Pohle W, Hirche H, Barmeyer J, Schumichen C, Hoffman G. A Double-Blind Trial of Naftidrofuryl Hydrogen Oxalate in Patients Suffering From Occlusive Peripheral Arterial Disease. Die Medizinische Welt. 1979; 30(7):269-272. (Guideline Ref ID 518)	Paper in German
Reilly DT. Pentoxifylline and Intermittent Claudication. New Zealand Medical Journal. 1987; 100(833):640. (Guideline Ref ID 484)	Wrong study design (letter)
Rudofsky G, van Laak HH. Treatment Costs of Peripheral Arterial Occlusive Disease in Germany: a Comparison of Costs and Efficacy. Journal of Cardiovascular Pharmacology. 1994; 23(Suppl):S22-S25. (Guideline Ref ID 725)	Health Economics paper
Rudofsky G, Haussler KF, Künkel HP, Schneider-May H, Spengel F, Symann O, Werner H-J. On Intravenous Pentoxifyllin-Treatment of Chronic Peripheral Arterial Occlusive Disease. Die Medizinische Welt. 1988; 39:1136-1140. (Guideline Ref ID 466)	Paper in German
Rudofsky G, Haussler KF, Kunkel HP, Schneider-May H, Spengel F, Symann O, Werner H-J. Intravenous Pentoxifylline Treatment in Chronic Peripheral Arterial Disease. Die Medizinische Welt. 1988; 39(39):1136-1140. (Guideline Ref ID 467)	Paper in German
Shalhoub J, Davies AH. Adjunctive Pharmacotherapies for Intermittent Claudication. NICE Guidance. Heart. 2012; 98(3):244-245. (Guideline Ref ID 16356)	Wrong study design (narrative)
Simpson LO. Pentoxifylline and Intermittent Claudication. New Zealand Medical Journal. 1987; 100(835):693. (Guideline Ref ID 483)	Wrong study design (letter)
Spincemaille GH, Klomp HM, Steyerberg EW, Habbema JD. Pain and Quality of Life in Patients With Critical Limb Ischaemia: Results of a Randomized Controlled Multicentre Study on the Effect of Spinal Cord Stimulation. ESES Study Group. European Journal of Pain. 2000; 4(2):173-184. (Guideline Ref ID 879)	Wrong intervention (to be considered for pain question)
Spitzer S, Bach R, Schieffer H. Walk Training and Drug Treatment in Patients With Peripheral Arterial Occlusive Disease Stage II. A Review. International Angiology. 1992; 11(3):204-210. (Guideline Ref ID 2497)	Wrong study design (review)

E.5 Angioplasty compared to bypass surgery and graft types

The search and exclusion list covers the following review questions:

- What is the clinical and cost effectiveness of angioplasty compared to bypass surgery for the treatment of PAD in adults with intermittent claudication?
- What is the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of PAD in adults with critical limb ischemia?
- What is the clinical effectiveness autologous vein compared to prosthetic bypass for the treatment of PAD in adults with:
  a. Intermittent claudication
  b. Critical limb ischamia

Excluded N=127

Study excluded	Reason
Aalders GJ, van Vroonhoven TJ. Polytetrafluoroethylene Versus Human Umbilical Vein in Above-Knee Femoropopliteal Bypass: Six-Year Results of a Randomized Clinical Trial. Journal of Vascular Surgery. 1992; 16(6):816-823. (Guideline Ref ID 1362)	Wrong comparison
Abbott WM, Green RM, Matsumoto T, Wheeler JR, Miller N, Veith FJ, Suggs WD, Hollier L, Money S, Garrett HE. Prosthetic Above-Knee Femoropopliteal Bypass	Wrong comparison

Grafting: Results of a Multicenter Randomized Prospective Trial. Above-Knee Femoropopliteal Study Group. Journal of Vascular Surgery. 1997; 25(1):19-28. (Guideline Ref ID 16307)	
Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL): Multicentre, Randomised Controlled Trial. Lancet. 2005; 366(9501):1925-1934. (Guideline Ref ID 16067)	Reports same data to 1356 and 3061
Ah Chong K, Chiu KM, Lo SF, Iu PP, Yip AW. Arterial Lesions in Severe Lower Limb Ischaemia: a Prospective Study of 100 Consecutive Ischaemic Limbs in a Hong Kong Chinese Population. Australian and New Zealand Journal of Surgery. 1999; 69(1):48-51. (Guideline Ref ID 16269)	Wrong comparison
Ahn S, Rutherford RB. A Multicenter Prospective Randomized Trial to Determine the Optimal Treatment of Patients With Claudication and Isolated Superficial Femoral Artery Occlusive Disease: Conservative Versus Endovascular Versus Surgical Therapy. Journal of Vascular Surgery. 1992; 15(5):889-891. (Guideline Ref ID 794)	Study plan, does not include results
Amighi J, Schillinger M, Dick P, Schlager O, Sabeti S, Mlekusch W, Haumer M, Mathies R, Heinzle G, Schuster A, Loewe C, Koppensteiner R, Lammer J, Minar E, Cejna M. De Novo Superficial Femoropopliteal Artery Lesions: Peripheral Cutting Balloon Angioplasty and Restenosis Rates--Randomized Controlled Trial. Radiology. 2008; 247(1):267-272. (Guideline Ref ID 157)	Wrong comparison
Antoniucci D, Valenti R, Moschi G, Santoro GM, Bolognese L, Trapani M, Fazzini PF. Cost-Effective Analysis of Primary Infarct-Artery Stenting Versus Optimal Primary Angioplasty (the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) Trial) (Structured Abstract). American Journal of Cardiology. 2000; 85(10):1247-1249. (Guideline Ref ID 1185)	Health economics study
Baumgartner I. ReoPro and Peripheral Arterial Intervention to Improve Clinical Outcome in Patients With Peripheral Arterial Disease (RIO-Trial). ACC Cardiosource Review Journal. 2007; 16(10):15-19. (Guideline Ref ID 16051)	Wrong comparison
Bax LW. Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function: A Randomized Trial. Annals of Internal Medicine. 2009; 150(12):840-848. (Guideline Ref ID 16048)	Wrong population
Belcaro G, Nicolaides AN, Errichi BM, Cesarone MR, De Sanctis MT, Incandela L, Venniker R. Superficial Thrombophlebitis of the Legs: a Randomized, Controlled, Follow-Up Study. Angiology. 1999; 50(7):523-529. (Guideline Ref ID 16026)	Wrong comparison
Biancari F, Kangasniemi OP, Mahar MA, Ylonen K. Need for Late Lower Limb Revascularization and Major Amputation After Coronary Artery Bypass Surgery. European Journal of Vascular & Endovascular Surgery. 2008; 35(5):596-602. (Guideline Ref ID 100)	Wrong comparison
Bosch JL, van der Graaf Y, Hunink MG. Health-Related Quality of Life After Angioplasty and Stent Placement in Patients With Iliac Artery Occlusive Disease: Results of a Randomized Controlled Clinical Trial. The Dutch Iliac Stent Trial Study Group. Circulation. 1999; 99(24):3155-3160. (Guideline Ref ID 588)	Wrong comparison (study included in angioplasty v stents)
Bosch JL, Tetteroo E, Mali WP, Hunink MG. Iliac Arterial Occlusive Disease: Cost-Effectiveness Analysis of Stent Placement Versus Percutaneous Transluminal Angioplasty. Dutch Iliac Stent Trial Study Group. Radiology. 1998; 208(3):641-648. (Guideline Ref ID 2459)	Health economics study
Bosiers M, Peeters P, D'Archambeau O, Hendriks J, Pilger E, Duber C, Zeller T, Gussmann A, Lohle PN, Minar E, Scheinert D, Hausegger K, Schulte KL, Verbist J, Deloose K, Lammer J, AMS INSIGHT Investigators. AMS INSIGHT--Absorbable Metal Stent Implantation for Treatment of Below-the-Knee Critical Limb Ischemia: 6-Month Analysis. Cardiovascular and Interventional Radiology. 2009; 32(3):424-435. (Guideline Ref ID 78)	Wrong study design (observational study – does not consider amputation)
Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab	Does not answer

GM, BASIL Trial Participants. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial: A Survival Prediction Model to Facilitate Clinical Decision Making. Journal of Vascular Surgery. 2010; 51(5 Suppl):52S-68S. (Guideline Ref ID 8)	question
Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM, BASIL Trial Participants. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial: A Description of the Severity and Extent of Disease Using the Bollinger Angiogram Scoring Method and the TransAtlantic Inter-Society Consensus II Classification. Journal of Vascular Surgery. 2010; 51(5 Suppl):32S-42S. (Guideline Ref ID 10)	Does not answer question
Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM, BASIL Trial Participants. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial: Analysis of Amputation Free and Overall Survival by Treatment Received. Journal of Vascular Surgery. 2010; 51(5 Suppl):18S-31S. (Guideline Ref ID 11)	Same patients as other BASIL trials
Breek JC, de Vries J, Hamming JF. The Oslo Balloon Angioplasty Versus Conservative Treatment Study (OBACT) - The 2-Years Results of a Single Centre, Prospective, Randomised Study in Patients With Intermittent Claudication. European Journal of Vascular and Endovascular Surgery: the Official Journal of the European Society for Vascular Surgery. 2007; 34(3):378. (Guideline Ref ID 2761)	Wrong study design (letter)
Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity Analysis of Long-Term Survival After Surgical or Percutaneous Revascularization in Patients With Multivessel Coronary Artery Disease and High-Risk Features. Circulation. 2004; 109(19):2290-2295. (Guideline Ref ID 659)	Wrong study design (observational study – does not consider amputation)
Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K, Lammer J. PTA Versus Palmaz Stent Placement in Femoropopliteal Artery Obstructions: a Multicenter Prospective Randomized Study. Journal of Vascular & Interventional Radiology. 2001; 12(1):23-31. (Guideline Ref ID 539)	Wrong comparison (study included in angioplasty v stents)
Chikiar DS, Grandjean M, Abelleyra J. Femoropopliteal Bypass Grafting for Arterial Occlusive Disease. Patency and Complications. Randomized Retrospective Study. Prensa Medica Argentina. 2003; 90(4):338-344. (Guideline Ref ID 4353)	Not in English
Cikrit DF, Fiore NF, Dalsing MC, Lalka SG, Sawchuk AP, Ladd AP, Dodson S. A Comparison of Endovascular Assisted and Conventional in Situ Bypass Grafts. Annals of Vascular Surgery. 1995; 9(1):37-43. (Guideline Ref ID 1470)	Wrong study design (observational study – does not consider amputation)
Conte MS. Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (Hoped for) Dawn of Evidence-Based Treatment for Advanced Limb Ischemia. [Review] [21 Refs]. Journal of Vascular Surgery. 2010; 51(5 Suppl):69S-75S. (Guideline Ref ID 40)	Wrong study design (review)
Conte MS, Bandyk DF, Clowes AW, Moneta GL, Seely L, Lorenz TJ, Namini H, Hamdan AD, Roddy SP, Belkin M, Berceli SA, DeMasi RJ, Samson RH, Berman SS, PREVENT III Investigators. Results of PREVENT III: a Multicenter, Randomized Trial of Edifoligide for the Prevention of Vein Graft Failure in Lower Extremity Bypass Surgery. Journal of Vascular Surgery. 2006; 43(4):742-751. (Guideline Ref ID 440)	Wrong comparison
Conte MS, Lorenz TJ, Bandyk DF, Clowes AW, Moneta GL, Seely BL. Design and Rationale of the PREVENT III Clinical Trial: Edifoligide for the Prevention of Infrainguinal Vein Graft Failure. Vascular and Endovascular Surgery. 2005; 39(1):15-23. (Guideline Ref ID 585)	Wrong comparison
Creasy TS, McMillan PJ, Walton J, Fletcher EW, Collin J, Morris PJ. A Prospective Randomised Trial of Percutaneous Transluminal Angioplasty (PTA) Versus Exercise Therapy for Lower Limb Claudication. Clinical Radiology. 1989;	Wrong study design (abstract)

40(6):638. (Guideline Ref ID 1153)	
de Donato G, Weber G, de Donato G. Minimally Invasive or Conventional Aorto-Bifemoral by-Pass. A Randomised Study. European Journal of Vascular & Endovascular Surgery. 2002; 24(6):485-491. (Guideline Ref ID 754)	Wrong comparison
De Popa IP, Pacescu M, Patrut M, Filipescu D, Ototu M, Baila S. 'In Situ' Saphenous by-Pass or Amputation? Annals of Fundeni Hospital. 1997; 2(1):5-10. (Guideline Ref ID 733)	Wrong study design (not comparative)
de Vos AMR. Non-Invasive Cardiac Assessment in High Risk Patients (The GROUND Study): Rationale, Objectives and Design of a Multi-Center Randomized Controlled Clinical Trial. Trials. 2008; 9:49. (Guideline Ref ID 2299)	Wrong comparison
de Vries SO, Visser K, de Vries JA, Wong JB, Donaldson MC, Hunink MG. Intermittent Claudication: Cost-Effectiveness of Revascularization Versus Exercise Therapy. Radiology. 2002; 222(1):25-36. (Guideline Ref ID 2460)	Health economics study
Desai ND, Naylor CD, Kiss A, Cohen EA, Feder-Elituv R, Miwa S, Radhakrishnan S, Dubbin J, Schwartz L, Fremes SE, Radial Artery Patency Study Investigators. Impact of Patient and Target-Vessel Characteristics on Arterial and Venous Bypass Graft Patency: Insight From a Randomized Trial. Circulation. 2007; 115(6):684-691. (Guideline Ref ID 359)	Wrong population
Dereume JP, van RA, Vincent G, Engelmann E. Femoropopliteal Bypass With a Compliant, Composite Polyurethane/Dacron Graft: Short-Term Results of a Multicentre Trial. Cardiovascular Surgery. 1993; 1(5):499-503. (Guideline Ref ID 1306)	Wrong study design (observational study – does not consider amputation)
Dodds TM, Fillinger MP, Walsh DB, Surgenor SD, Mandel D, Yeager MP. Clinical Outcomes After Lower Extremity Revascularization: a Comparison of Epidural and General Anesthesia. Journal of Applied Research. 2007; 7(3):238-249. (Guideline Ref ID 3847)	Wrong comparison
Donaghue CC, Bohannon RW, Maljanian R, Frigon L, Horowitz S, McGovern A. Improved Health-Related Quality of Life 12 Months After Bypass or Angioplasty for Peripheral Arterial Disease. Journal of Vascular Nursing. 2000; 18(3):75-82. (Guideline Ref ID 885)	Wrong study design (observational study – does not consider amputation)
Dorigo W, Pulli R, Castelli P, Dorrucci V, Ferilli F, De Blasis G, Monaca V, Vecchiati E, Pratesi C, Propaten Italian Registry Group. A Multicenter Comparison Between Autologous Saphenous Vein and Heparin-Bonded Expanded Polytetrafluoroethylene (EPTFE) Graft in the Treatment of Critical Limb Ischemia in Diabetics. Journal of Vascular Surgery. 2011; 54(5):1332-1338. (Guideline Ref ID 16351)	Wrong study design (observational study)
Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Oliva V, Tielbeek A, Anderson J, Wiesinger B, Tepe G, Lansky A, Jaff MR, Mudde C, Tielemans H, Beregi JP. Drug-Eluting and Bare Nitinol Stents for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery: Long-Term Results From the SIROCCO Trial. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 2006; 13(6):701-710. (Guideline Ref ID 248)	Included in bare metal stents v drug eluting stents
Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Tielbeek A, Anderson J, Wiesinger B, Tepe G, Lansky A, Mudde C, Tielemans H, Beregi JP. Sirolimus-Eluting Versus Bare Nitinol Stent for Obstructive Superficial Femoral Artery Disease: the SIROCCO II Trial. Journal of Vascular & Interventional Radiology. 2005; 16(3):331-338. (Guideline Ref ID 15987)	Included in bare metal stent v drug eluting stent
Duda SH, Poerner TC, Wiesinger B, Rundback JH, Tepe G, Wiskirchen J, Haase KK. Drug-Eluting Stents: Potential Applications for Peripheral Arterial Occlusive Disease. [Review] [87 Refs]. Journal of Vascular & Interventional Radiology. 2003; 14(3):291-301. (Guideline Ref ID 728)	Wrong study design (review)
Dumas BE, Spronk S, Boelhouwer RU, den Hoed PT. Subfascial Ligation at Three Different Levels Versus Partial Exeresis of the Incompetent Short Saphenous	Wrong population

Vein: a Randomized Clinical Trial. Journal of Vascular Nursing: Official Publication of the Society for Peripheral Vascular Nursing. 2007; 25(1):12-18. (Guideline Ref ID 4131)	
Eiberg JP, Roder O, Stahl-Madsen M, Eldrup N, Qvarfordt P, Laursen A, Greve M, Florenes T, Nielsen OM, Seidelin C, Vestergaard-Andersen T, Schroeder TV. Fluoropolymer-Coated Dacron Versus PTFE Grafts for Femorofemoral Crossover Bypass: Randomised Trial. European Journal of Vascular & Endovascular Surgery. 2006; 32(4):431-438. (Guideline Ref ID 398)	Wrong comparison (Dacron v prosthetic)
Eickhoff JH, Broome A, Ericsson BF, Buchardt Hansen HJ, Kordt KF, Mouritzen C, Kvernebo K, Norgren L, Rostad H, Trippestad A. Four Years' Results of a Prospective, Randomized Clinical Trial Comparing Polytetrafluoroethylene and Modified Human Umbilical Vein for Below-Knee Femoropopliteal Bypass. Journal of Vascular Surgery. 1987; 6(5):506-511. (Guideline Ref ID 16308)	Wrong outcomes
Eickhoff JH, Buchardt Hansen HJ, Bromme A, Ericsson BF, Kordt KF, Mouritzen C, Myhre HO, Norgren L, Rostad H, Trippestad A. A Randomized Clinical Trial of PTFE Versus Human Umbilical Vein for Femoropopliteal Bypass Surgery. Preliminary Results. British Journal of Surgery. 1983; 70(2):85-88. (Guideline Ref ID 1692)	Outcome data not reported by group but for whole trial – unable to distinguish data
Fiorani PT. Surgical Treatment of Intermittent Claudication. International Angiology. 1993; 12(3 SUPPL. 1):40-44. (Guideline Ref ID 3621)	Wrong study design (observational study – does not consider amputation)
Foley WJD. Crossover Femoro-Femoral Bypass Grafts. Archives of Surgery (Chicago, Ill. 1969;(1):83-87. (Guideline Ref ID 3819)	Wrong study design (observational study – does not consider amputation)
Forbes C, Leng GC. Peripheral Vascular Diseases and the Cochrane Collaboration. Gefasschirurgie. 1999; 4(2):81-84. (Guideline Ref ID 3366)	Wrong study design (review of Cochrane's)
Fowkes F, Leng GC. Bypass Surgery for Chronic Lower Limb Ischaemia. Cochrane Database of Systematic Reviews. 2008;(2):CD002000. (Guideline Ref ID 2419)	Cochrane review – cross checked for studies which match review protocol
Gelin J, Jivegard L, Taft C, Karlsson J, Sullivan M, Dahllof AG, Sandstrom R, Arfvidsson B, Lundholm K. Treatment Efficacy of Intermittent Claudication by Surgical Intervention, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients I: One Year Results of Functional and Physiological Improvements. European Journal of Vascular and Endovascular Surgery. 2001; 22(2):107-113. (Guideline Ref ID 3046)	Wrong comparison (exercise v angioplasty)
Gisbertz SS, Ramzan M, Tutein Nolthenius RP, van der Laan L, Overtoom TT, Moll FL, de Vries JP. Short-Term Results of a Randomized Trial Comparing Remote Endarterectomy and Supragenicular Bypass Surgery for Long Occlusions of the Superficial Femoral Artery [the REVAS Trial]. European Journal of Vascular & Endovascular Surgery. 2009; 37(1):68-76. (Guideline Ref ID 16033)	Wrong comparison
Green RM, Abbott WM, Matsumoto T, Wheeler JR, Miller N, Veith FJ, Money S, Garrett HE. Prosthetic Above-Knee Femoropopliteal Bypass Grafting: Five-Year Results of a Randomized Trial. Journal of Vascular Surgery. 2000; 31(3):417-425. (Guideline Ref ID 16309)	Wrong comparison
Greenhalgh RM. MIMIC Trials: Angioplasty Effective in Randomised Controlled Trials for Peripheral Arterial Disease. Http://Www Cxvascular Com/Interventionalnews/Latestnews Cfm?Ccs=485&Cs=4222 (Accessed 2 February 2009). 2009; (Guideline Ref ID 924)	Wrong study design (commentary)
Hamsho A, Nott D, Harris PL. Prospective Randomised Trial of Distal Arteriovenous Fistula As an Adjunct to Femoro-Infrapopliteal PTFE Bypass. European Journal of Vascular & Endovascular Surgery. 1999; 17(3):197-201.	Wrong comparison

(Guideline Ref ID 943)	
Hankey GJN. Medical Treatment of Peripheral Arterial Disease. Journal of the American Medical Association. 2006; 295(5):547-553. (Guideline Ref ID 2682)	Wrong study design (review)
He EY, He N, Wang Y, Fan H. Percutaneous Transluminal Angioplasty (PTA) Alone Versus PTA With Balloon-Expandable Stent Placement for Short-Segment Femoropopliteal Artery Disease: A Metaanalysis of Randomized Trials. Journal of Vascular and Interventional Radiology. 2008; 19(4):499-503. (Guideline Ref ID 1502)	Wrong study design (meta-analysis)
Hiatt WR. Medical Treatment of the Patient With Intermittent Claudication. Journal of Vascular Technology. 1994; 18(5):311-315. (Guideline Ref ID 3581)	Wrong study design (narrative review)
Hobbs SD, Bradbury AW. The EXercise Versus Angioplasty in Claudication Trial (EXACT): Reasons for Recruitment Failure and the Implications for Research into and Treatment of Intermittent Claudication. Journal of Vascular Surgery. 2006; 44(2):432-433. (Guideline Ref ID 3047)	Wrong study design (letter)
Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized Controlled Trial of Supervised Exercise to Evaluate Changes in Cardiac Function in Patients With Peripheral Atherosclerotic Disease. Clinical Physiology and Functional Imaging. 2008; 28(1):32-37. (Guideline Ref ID 224)	Wrong comparison (study included in supervised exercise v unsupervised exercise)
Ihnat DM, Duong ST, Taylor ZC, Leon LR, Mills JL, Sr., Goshima KR, Echeverri JA, Arslan B. Contemporary Outcomes After Superficial Femoral Artery Angioplasty and Stenting: the Influence of TASC Classification and Runoff Score. Journal of Vascular Surgery. 2008; 47(5):967-974. (Guideline Ref ID 147)	Wrong study design (observational study – does not consider amputation)
Jalan R, Harrison DJ, Redhead DN, Hayes PC. Transjugular Intrahepatic Portosystemic Stent-Shunt (TIPSS) Occlusion and the Role of Biliary Venous Fistulae. Journal of Hepatology. 1996; 24(2):169-176. (Guideline Ref ID 1132)	Wrong study design (observational study – does not consider amputation)
Jensen LP, Lepantalo M, Fossdal JE, Roder O, Jensen BS, Madsen MS, Grenager O, Fasting H, Myhre HO, Baekgaard N, Nielsen OM, Helgstrand U, Schroeder TV. Dacron or PTFE for Above-Knee Femoropopliteal Bypass. a Multicenter Randomised Study. European Journal of Vascular & Endovascular Surgery. 2007; 34(1):44-49. (Guideline Ref ID 324)	Wrong comparison (Dacron v prosthetic)
Jepson RPH. Femoro-Femoral Cross-Over Grafts. Australia and New Zealand Journal of Surgery. 1970; 39(4):345-348. (Guideline Ref ID 3818)	Wrong study design (observational study – does not consider amputation)
Kapfer X, Meichelboeck W, Groegler FM. Comparison of Carbon-Impregnated and Standard EPTFE Prostheses in Extra-Anatomical Anterior Tibial Artery Bypass: a Prospective Randomized Multicenter Study. European Journal of Vascular and Endovascular Surgery : the Official Journal of the European Society for Vascular Surgery. 2006; 32(2):155-168. (Guideline Ref ID 4162)	Wrong comparison (Prosthetic v carbon prosthetic)
Khan UAK. A Comparative Analysis of Saphenous Vein Conduit Harvesting Techniques for Coronary Artery Bypass Grafting - Standard Bridging Versus the Open Technique. Interactive Cardiovascular and Thoracic Surgery. 2010; 10(1):27-31. (Guideline Ref ID 16049)	Wrong population
Klein WM, van der Graaf Y, Seegers J, Spithoven JH, Buskens E, Van Baal JG, Buth J, Moll FL, Overtoom TT, Van Sambeek MRHM, Mali WP. Dutch Iliac Stent Trial: Long-Term Results in Patients Randomized for Primary or Selective Stent Placement. Radiology. 2006; 238(2):734-744. (Guideline Ref ID 1715)	Wrong comparison (compares primary or selective stenting)
Krajcer Z, Sioco G, Reynolds T. Comparison of Wallgraft and Wallstent for Treatment of Complex Iliac Artery Stenosis and Occlusion. Preliminary Results of a Prospective Randomized Study. Texas Heart Institute Journal. 1997; 24(3):193-199. (Guideline Ref ID 641)	Wrong comparison
Krankenberg H, Schluter M, Steinkamp HJ, Burgelin K, Scheinert D, Schulte KL, Minar E, Peeters P, Bosiers M, Tepe G, Reimers B, Mahler F, Tubler T, Zeller T.	Included in angioplasty v stents

Nitinol Stent Implantation Versus Percutaneous Transluminal Angioplasty in Superficial Femoral Artery Lesions Up to 10 Cm in Length: the Femoral Artery Stenting Trial (FAST). Circulation. 2007; 116(3):285-292. (Guideline Ref ID 200)	
Krankenberg HS, I. Percutaneous Transluminal Angioplasty of Infrapopliteal Arteries in Patients With Intermittent Claudication: Acute and One-Year Results. Catheterization and Cardiovascular Interventions. 2005; 64(1):12-17. (Guideline Ref ID 2834)	Wrong study design (observational study – does not consider amputation)
Loosemore TM, Chalmers TC, Dormandy JA. A Meta-Analysis of Randomized Placebo Control Trials in Fontaine Stages III and IV Peripheral Occlusive Arterial Disease. International Angiology. 1994; 13(2):133-142. (Guideline Ref ID 1264)	Wrong study design (meta-analysis)
Lumsden ABR. Medical Management of Peripheral Arterial Disease: A Therapeutic Algorithm. Journal of Endovascular Therapy. 2006; 13(SUPPL. 2):II19-II29. (Guideline Ref ID 2676)	Wrong study design (review)
Lundgren F, Dahllof AG, Lundholm K, Schersten T, Volkmann R. Intermittent Claudication. Surgical Reconstruction or Physical Training? A Prospective Randomized Trial of Treatment Efficiency. Annals of Surgery. 1989; 209(3) (pp 346-355), 1989. Date of Publication: 1989.):-355. (Guideline Ref ID 2558)	Included in exercise compared to angioplasty
Manzi M, Fusaro M, Ceccacci T, Erente G, Dalla PL, Brocco E. Clinical Results of Below-the Knee Intervention Using Pedal-Plantar Loop Technique for the Revascularization of Foot Arteries. Journal of Cardiovascular Surgery. 2009; 50(3):331-337. (Guideline Ref ID 127)	Wrong study design (observational study – does not consider amputation)
Martens JM, Knippenberg B, Vos JA, de Vries JP, Hansen BE, van OH, PADI Trial Group. Update on PADI Trial: Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. Journal of Vascular Surgery. 2009; 50(3):687-689. (Guideline Ref ID 57)	Study protocol
Matsagas MI, Rivera MA, Tran T, Mitchell A, Robless P, Davies AH, Geroulakos G. Clinical Outcome Following Infra-Inguinal Percutaneous Transluminal Angioplasty for Critical Limb Ischemia. Cardiovascular and Interventional Radiology. 2003; 26(3):251-255. (Guideline Ref ID 694)	Wrong study design (observational study – does not consider amputation)
Matyas L, Berry M, Menyhei G, Tamas L, Acsady G, Cuypers P, Halmos F, de Vries AC, Forgacs V, Ingenito G, Avelar R. The Safety and Efficacy of a Paclitaxel-Eluting Wrap for Preventing Peripheral Bypass Graft Stenosis: a 2-Year Controlled Randomized Prospective Clinical Study. European Journal of Vascular & Endovascular Surgery. 2008; 35(6):715-722. (Guideline Ref ID 15985)	Wrong comparison (Prosthetic + wrap v prosthetic)
Mazari FA, Gulati S, Rahman MN, Lee HL, Mehta TA, McCollum P, Chetter IC. Early Outcomes From a Randomized, Controlled Trial of Supervised Exercise, Angioplasty, and Combined Therapy in Intermittent Claudication. Annals of Vascular Surgery. 2010; 24(1):69-79. (Guideline Ref ID 39)	Included in exercise compared to angioplasty
Mazari F, Khan J, Abdul Rahman MNA, Mehta T, Gulati S, McCollum P. Cost Utility Analysis of a Randomised Control Trial of Percutaneous Transluminal Angioplasty (PTA), Supervised Exercise Programme (SEP) and Combined Treatment (PTA+SEP) for Patients With Intermittent Claudication (IC) Due to Femoropopliteal Disease. The Vascular Society of Great Britain & Ireland Yearbook 2009. 2009;44. (Guideline Ref ID 3966)	Wrong study design (abstract)
Mazari FAK, Mehta T, Rahman MN, McCollum P, Chetter IC. A RCT of Non-Surgical Treatment for Intermittent Claudication in Femoro-Popliteal Disease: 12-Month Results. The Vascular Society of Great Britain & Ireland Yearbook 2008. 2008;75. (Guideline Ref ID 4013)	Wrong study design (abstract)
Mingoli AS. Femorofemoral Bypass Grafts: Factors Influencing Long-Term Patency Rate and Outcome. Surgery. 2001; 129(4):451-458. (Guideline Ref ID 3249)	Wrong study design (observational study – does not consider amputation)
Moody APE. In Situ Versus Reversed Femoropopliteal Vein Grafts: Long-Term Follow-Up of a Prospective, Randomized Trial. British Journal of Surgery. 1992;	Wrong comparison (study considers

79(8):750-752. (Guideline Ref ID 3662)	reversed v in situ procedures)
Moore WS, Brewster DC, Bernhard VM. Aorto-Uni-Iliac Endograft for Complex Aortoiliac Aneurysms Compared With Tube/Bifurcation Endografts: Results of the EVT/Guidant Trials. Journal of Vascular Surgery: Official Publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2001; 33(2 Suppl):S11-S20. (Guideline Ref ID 4430)	Wrong study design (observational study – does not consider amputation)
Moore WS, Quinones-Baldrich WJ. An Argument Against All-Autogenous Tissue for Vascular Bypasses Below the Inguinal Ligament. Advances in Surgery. 1991; 24:91-101. (Guideline Ref ID 1458)	Wrong study design (review)
Myhre HF. Cost-Effectiveness of Therapeutic Options for Critical Limb Ischaemia. Critical Ischaemia. 1996; 6(2):36-41. (Guideline Ref ID 3502)	Health economics study
Okadome K, Funahashi S, Odashiro T, Komori K, Akazawa K, Sugimachi K. Do Patients With Intermittent Claudication Need Surgical Treatment? International Angiology. 1994; 13(2):103-108. (Guideline Ref ID 1265)	Wrong study design (observational study – does not consider amputation)
Panneton JM, Hollier LH, Hofer JM. Multicenter Randomized Prospective Trial Comparing a Pre-Cuffed Polytetrafluoroethylene Graft to a Vein Cuffed Polytetrafluoroethylene Graft for Infragenicular Arterial Bypass. Annals of Vascular Surgery. 2004; 18(2):199-206. (Guideline Ref ID 1371)	Wrong comparison (Pre-cuff prosthetic v prosthetic)
Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise Training Versus Angioplasty for Stable Claudication. Long and Medium Term Results of a Prospective, Randomised Trial. European Journal of Vascular & Endovascular Surgery. 1996; 11(4):409-413. (Guideline Ref ID 984)	Included in exercise compared to angioplasty
Pinzur MSB. Amputation Surgery in Peripheral Vascular Disease. Instructional Course Lectures. 1999; 48(pp 687-691):1999. (Guideline Ref ID 3335)	Wrong study design (narrative review)
Powell TW, Burnham SJ, Johnson G, Jr. Second Leg Ischemia. Lower Extremity Bypass Versus Amputation in Patients With Contralateral Lower Extremity Amputation. American Surgeon. 1984; 50(11):577-580. (Guideline Ref ID 16270)	Wrong study design (retrospective study)
Puskas JD, Wright CE, Miller PK, Anderson TE, Gott JP, Brown WM, III, Guyton RA. A Randomized Trial of Endoscopic Versus Open Saphenous Vein Harvest in Coronary Bypass Surgery. Annals of Thoracic Surgery. 1999; 68(4):1509-1512. (Guideline Ref ID 16027)	Wrong population
Raghunathan A, Rapp JH, Littooy F, Santilli S, Krupski WC, Ward HB, Thottapurathu L, Moritz T, McFalls EO, Investigators C.A.R.P. Postoperative Outcomes for Patients Undergoing Elective Revascularization for Critical Limb Ischemia and Intermittent Claudication: a Subanalysis of the Coronary Artery Revascularization Prophylaxis (CARP) Trial. Journal of Vascular Surgery. 2006; 43(6):1175-1182. (Guideline Ref ID 15982)	Wrong study design (observational study – does not consider amputation)
Reed AB, Delvecchio C, Giglia JS. Major Lower Extremity Amputation After Multiple Revascularizations: Was It Worth It? Annals of Vascular Surgery. 2008; 22(3):335-340. (Guideline Ref ID 16271)	Wrong study design (not comparative)
Reyes RC. Long-Term Follow-Up of Iliac Wallstents. Cardiovascular and Interventional Radiology. 2004; 27(6):624-631. (Guideline Ref ID 2863)	Wrong study design (observational study – does not consider amputation)
Robinson BI, Fletcher JP, Australian and New Zealand Femoropopliteal Graft Trial Participants. Fluoropolymer Coated Dacron or Polytetrafluoroethylene for Femoropopliteal Bypass Grafting: a Multicentre Trial. Australian and New Zealand Journal of Surgery. 2003; 73(3):95-99. (Guideline Ref ID 16029)	Wrong comparison (Dacron v prosthetic)
Robinson BI, Fletcher JP, Tomlinson P, Allen RD, Hazelton SJ, Richardson AJ, Stuchbery K. A Prospective Randomized Multicentre Comparison of Expanded Polytetrafluoroethylene and Gelatin-Sealed Knitted Dacron Grafts for	Wrong comparison (Dacron v prosthetic)

Femoropopliteal Bypass. Cardiovascular Surgery. 1999; 7(2):214-218. (Guideline Ref ID 934)	
Rodriguez A, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, Vogel D, Grinfeld R, Delacasa A, Garrido M, Oliveri R, Mele E, Palacios I, O'Neill W. Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II): 30-Day and One-Year Follow-Up Results. ERACI II Investigators. Journal of the American College of Cardiology. 2001; 37(1):51-58. (Guideline Ref ID 540)	Wrong population
Sabeti S, Schillinger M, Amighi J, Sherif C, Mlekusch W, Ahmadi R, Minar E. Primary Patency of Femoropopliteal Arteries Treated With Nitinol Versus Stainless Steel Self-Expanding Stents: Propensity Score-Adjusted Analysis. Radiology. 2004; 232(2):516-521. (Guideline Ref ID 258)	Wrong study design (observational study – does not consider amputation)
Santilli S. The Coronary Artery Revascularization Prophylaxis (CARP) Trial: Results and Remaining Controversies. Perspectives in Vascular Surgery and Endovascular Therapy. 2006; 18(4):282-285. (Guideline Ref ID 16047)	Wrong comparison
Saxon RR, Dake MD, Volgelzang RL, Katzen BT, Becker GJ. Randomized, Multicenter Study Comparing Expanded Polytetrafluoroethylene-Covered Endoprosthesis Placement With Percutaneous Transluminal Angioplasty in the Treatment of Superficial Femoral Artery Occlusive Disease. Journal of Vascular & Interventional Radiology. 2008; 19(6):823-832. (Guideline Ref ID 142)	Wrong comparison (angioplasty v stents)
Saxon RR, Coffman JM, Gooding JM, Natuzzi E, Ponec DJ. Long-Term Results of EPTFE Stent-Graft Versus Angioplasty in the Femoropopliteal Artery: Single Center Experience From a Prospective, Randomized Trial. Journal of Vascular & Interventional Radiology. 2003; 14(3):303-311. (Guideline Ref ID 441)	Same population as ID 142, ID 142 included in angioplasty v stents
Scharn DM, Dirven M, Barendregt WB, Boll AP, Roelofs D, Van Der Vliet JA. Human Umbilical Vein Versus Heparin-Bonded Polyester for Femoro-Popliteal Bypass: 5-Year Results of a Prospective Randomized Multicentre Trial. European Journal of Vascular and Endovascular Surgery. 2008; 35(1):61-67. (Guideline Ref ID 272)	Wrong comparison
Schillinger M, Sabeti S, Dick P, Amighi J, Mlekusch W, Schlager O, Loewe C, Cejna M, Lammer J, Minar E. Sustained Benefit at 2 Years of Primary Femoropopliteal Stenting Compared With Balloon Angioplasty With Optional Stenting. Circulation. 2007; 115(21):2745-2749. (Guideline Ref ID 209)	Included in angioplasty compared to stents
Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, Schlager O, Cejna M, Lammer J, Minar E. Balloon Angioplasty Versus Implantation of Nitinol Stents in the Superficial Femoral Artery. New England Journal of Medicine. 2006; 354(18):1879-1888. (Guideline Ref ID 288)	Wrong comparison (study included in angioplasty v stents)
Schulman ML, Badhey MR, Yatco R. Superficial Femoral-Popliteal Veins and Reversed Saphenous Veins As Primary Femoropopliteal Bypass Grafts: a Randomized Comparative Study. Journal of Vascular Surgery. 1987; 6(1):1-10. (Guideline Ref ID 1588)	Wrong study design (quasi randomised trial)
Siablis D, Karnabatidis D, Katsanos K, Diamantopoulos A, Spiliopoulos S, Kagadis GC, Tsolakis J. Infrapopliteal Application of Sirolimus-Eluting Versus Bare Metal Stents for Critical Limb Ischemia: Analysis of Long-Term Angiographic and Clinical Outcome. Journal of Vascular & Interventional Radiology. 2009; 20(9):1141-1150. (Guideline Ref ID 47)	Wrong study design (observational study – does not consider amputation)
Siablis D, Karnabatidis D, Katsanos K, Kagadis GC, Kraniotis P, Diamantopoulos A, Tsolakis J. Sirolimus-Eluting Versus Bare Stents After Suboptimal Infrapopliteal Angioplasty for Critical Limb Ischemia: Enduring 1-Year Angiographic and Clinical Benefit. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 2007; 14(2):241-250. (Guideline Ref ID 211)	Wrong study design (observational study – does not consider amputation)
Smeets L, Ho GH, Tangelder MJ, Algra A, Lawson JA, Eikelboom BC, Moll FL, Dutch BOA Study Group. Outcome After Occlusion of Infrainguinal Bypasses in the Dutch BOA Study: Comparison of Amputation Rate in Venous and Prosthetic	Wrong study design (observational study – does not consider

Grafts. European Journal of Vascular and Endovascular Surgery : the Official Journal of the European Society for Vascular Surgery. 2005; 30(6):604-609. (Guideline Ref ID 1355)	amputation)
Surowiec SMD. Percutaneous Angioplasty and Stenting of the Superficial Femoral Artery. Journal of Vascular Surgery. 2005; 41(2):269-278. (Guideline Ref ID 2817)	Wrong study design (review)
Taft C, Karlsson J, Gelin J, Jivegard L, Sandstrom R, Arfvidsson B, Dahllof AG, Lundholm K, Sullivan M. Treatment Efficacy of Intermittent Claudication by Invasive Therapy, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients II: One-Year Results of Health-Related Quality of Life. European Journal of Vascular & Endovascular Surgery. 2001; 22(2):114-123. (Guideline Ref ID 732)	Wrong outcomes
Tangelder MJ, McDonnel J, Van Busschbach JJ, Buskens E, Algra A, Lawson JA, Eikelboom BC. Quality of Life After Infrainguinal Bypass Grafting Surgery. Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group. Journal of Vascular Surgery. 1999; 29(5):913-919. (Guideline Ref ID 937)	Wrong comparison
Tetteroo E, Haaring C, van der Graaf Y, van Schaik JP, van Engelen AD, Mali WP. Intraarterial Pressure Gradients After Randomized Angioplasty or Stenting of Iliac Artery Lesions. Dutch Iliac Stent Trial Study Group. Cardiovascular and Interventional Radiology. 1996; 19(6):411-417. (Guideline Ref ID 1124)	Wrong outcomes
Thompson MM, Sayers RD, Reid A, Underwood MJ, Bell PR. Quality of Life Following Infragenicular Bypass and Lower Limb Amputation. European Journal of Vascular & Endovascular Surgery. 1995; 9(3):310-313. (Guideline Ref ID 16272)	Wrong outcome (QoL measure can not be mapped)
Thomson IA, van Rij AM, Morrison ND, Packer SGK, Christie R. A Ten Year Randomised Controlled Trial of Percutaneous Femoropopliteal Angioplasty for Claudication. Australian and New Zealand Journal of Medicine. 1999; 69(Suppl):98. (Guideline Ref ID 3052)	Wrong study design (abstract)
Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of Arm-Ergometry Versus Treadmill Exercise Training to Improve Walking Distance in Patients With Claudication. Vascular Medicine. 2009; 14(3):203-213. (Guideline Ref ID 91)	Included in supervised v unsupervised exercise
Twine CP, McLain A. Graft Type for Femoro-Popliteal Bypass Surgery. Cochrane Database of Systematic Reviews. 2010; Issue 5:CD001487. (Guideline Ref ID 2476)	Cochrane review – cross checked for studies which match review protocol
van Det RJ, Vriens BH, van der Palen J, Geelkerken RH. Dacron or EPTFE for Femoro-Popliteal Above-Knee Bypass Grafting: Short- and Long-Term Results of a Multicentre Randomised Trial. European Journal of Vascular & Endovascular Surgery. 2009; 37(4):457-463. (Guideline Ref ID 16034)	Wrong comparison (Dacron V prosthetic)
van Hattum ES, Tangelder MJD, Lawson JA, Moll FL, Algra A. The Quality of Life in Patients After Peripheral Bypass Surgery Deteriorates at Long-Term Follow-Up. Journal of Vascular Surgery. 2011; 53(3):643-650. (Guideline Ref ID 16296)	Wrong comparison
van Rij AM, Packer SGK, Morrison N. A Randomized Controlled Study of Percutaneous Angioplasty for Claudicants With Femoro-Popliteal Disease. Journal of Cardiovascular Surgery. 1991; 32:34. (Guideline Ref ID 1141)	Wrong study design (commentary)
van Royen N, Piek JJ, Legemate DA, Schaper W, Oskam J, Atasever B, Voskuil M, Ubbink D, Schirmer SH, Buschmann I, Bode C, Buschmann EE. Design of the START-Trial: STimulation of ARTeriogenesis Using Subcutaneous Application of GM-CSF As a New Treatment for Peripheral Vascular Disease. A Randomized, Double-Blind, Placebo-Controlled Trial. Vascular Medicine. 2003; 8(3):191-196. (Guideline Ref ID 680)	Wrong comparison
Varnauskas E. Twelve-Year Follow-Up of Survival in the Randomized European Coronary Surgery Study. New England Journal of Medicine. 1988; 319(6):332-337. (Guideline Ref ID 1568)	Wrong population

Veasey RAL. A Randomised Controlled Trial Comparing StarClose and AngioSeal Vascular Closure Devices in a District General Hospital - The SCOAST Study. International Journal of Clinical Practice. 2008; 62(6):912-918. (Guideline Ref ID 2328)	Wrong comparison
Veith FJ, Gupta SK, Ascer E, White-Flores S, Samson RH, Scher LA, Towne JB, Bernhard VM, Bonier P, Flinn WR. Six-Year Prospective Multicenter Randomized Comparison of Autologous Saphenous Vein and Expanded Polytetrafluoroethylene Grafts in Infrainguinal Arterial Reconstructions. Journal of Vascular Surgery : Official Publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 1986; 3(1):104-114. (Guideline Ref ID 15984)	Wrong study design (quasi randomised trial)
Wang FW, Uretsky BF, Freeman JL, Zhang D, Giordano SH, Goodwin JS. Survival Advantage in Medicare Patients Receiving Drug-Eluting Stents Compared With Bare Metal Stents: Real or Artefactual? Catheterization and Cardiovascular Interventions. 2008; 71(5):636-643. (Guideline Ref ID 116)	Wrong study design (observational study – does not consider amputation)
Wang J, Zhou S, Bronks R, Graham J, Myers S. Effects of Supervised Treadmill Walking Training on Calf Muscle Capillarization in Patients With Intermittent Claudication. Angiology. 2009; 60(1):36-41. (Guideline Ref ID 153)	Wrong outcomes
Ward RPM. High Prevalence of Important Cardiac Findings in Patients With Peripheral Arterial Disease Referred for Echocardiography. Journal of the American Society of Echocardiography. 2005; 18(8):844-849. (Guideline Ref ID 15981)	Wrong outcomes
Watelet J, Soury P, Menard JF, Plissonnier D, Peillon C, Lestrat JP, Testart J. Femoropopliteal Bypass: in Situ or Reversed Vein Grafts? Ten-Year Results of a Randomized Prospective Study. Annals of Vascular Surgery. 1997; 11(5):510-519. (Guideline Ref ID 4651)	Wrong comparison (study considers reversed v in situ procedures)
Wengerter KR, Veith FJ, Gupta SK, Goldsmith J, Farrell E, Harris PL, Moore D, Shanik G. Prospective Randomized Multicenter Comparison of in Situ and Reversed Vein Infrapopliteal Bypasses. Journal of Vascular Surgery : Official Publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 1991; 13(2):189-197. (Guideline Ref ID 1511)	Wrong comparison (study considers reversed v in situ procedures)
Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial. Circulation. 2008; 118(13):1358-1365. (Guideline Ref ID 120)	Wrong comparison (compares types of angioplasty)
Whittaker L, Wijesinghe LD, Berridge DC, Scott DJ. Do Patients With Critical Limb Ischaemia Undergo Multiple Amputations After Infrainguinal Bypass Surgery? European Journal of Vascular & Endovascular Surgery. 2001; 21(5):427-431. (Guideline Ref ID 16273)	Wrong study design (not comparative)
Zdanowski Z, Albrechtsson U, Lundin A, Jonung T, Ribbe E, Thorne J, Norgren L. Percutaneous Transluminal Angioplasty With or Without Stenting for Femoropopliteal Occlusions? A Randomized Controlled Study. International Angiology. 1999; 18(4):251-255. (Guideline Ref ID 3056)	Included in angioplasty compared to stents)

E.6 Angioplasty (selective and primary stent placement) and stent type

The search and exclusion list included the following review questions:

- 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:
  a. Intermittent claudication
  b. Critical limb ischaemia

- What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with:
  a. Intermittent claudication
  b. Critical limb ischemia

Excluded n = 199

Study excluded	Reason
Abahji TN, Tato F, Rieger J, Offner A, Will S, Hoelscher G, Weiss N, Hoffman U. Stenting of the Superficial Femoral Artery After Suboptimal Balloon Angioplasty: One-Year Results. International Angiology. 2006; 25(2):184-189. (Guideline Ref ID 1214)	Wrong study design (observational)
Abdelsalam H, Markose G, Bolia A. Revascularization Strategies in Below the Knee Interventions. Journal of Cardiovascular Surgery. 2008; 49(2):185-189. (Guideline Ref ID 1218)	Wrong study design (review)
Abdul Raouf A, Rouleau Y, Clement A, Le Roux P, Genay P, Ricco JB. Endoluminal Angioplasty of the Popliteal Artery. Review of 54 Consecutive Patients. European Journal of Vascular and Endovascular Surgery. 2005; 30(6):610-613. (Guideline Ref ID 3055)	Wrong study design (observational)
Agnoletti G, Marini D, Ou P, Vandrell MC, Boudjemline Y, Bonnet D. Cheatham Platinum (CP) and Palmaz Stents for Cardiac and Vascular Lesions Treatment in Patients With Congenital Heart Disease. EuroIntervention. 2009; 4(5):620-625. (Guideline Ref ID 1225)	Wrong study design (observational)
Ah Chong AK, Tan CB, Wong MW, Cheng FS. Bypass Surgery or Percutaneous Transluminal Angioplasty to Treat Critical Lower Limb Ischaemia Due to Infrainguinal Arterial Occlusive Disease? Hong Kong Medical Journal. 2009; 15(4):249-254. (Guideline Ref ID 62)	Wrong study design (observational)
Ahn S, Rutherford RB. A Multicenter Prospective Randomized Trial to Determine the Optimal Treatment of Patients With Claudication and Isolated Superficial Femoral Artery Occlusive Disease: Conservative Versus Endovascular Versus Surgical Therapy. Journal of Vascular Surgery. 1992; 15(5):889-891. (Guideline Ref ID 794)	Paper describes study plan
Allie DE. Creative Limb-Salvage Surgical and Endovascular Revascularization Strategies in Treating Critical Limb Ischemia. Surgical Technology International. 2008; 17:97-104. (Guideline Ref ID 1244)	Wrong study design (review)
Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of Revascularization Procedures for Peripheral Arterial Occlusive Disease in Ontario Between 1991 and 1998: a Population-Based Study. Journal of Vascular Surgery. 2003; 38(2):279-288. (Guideline Ref ID 1235)	Wrong study design (observational)
Amighi J, Schillinger M, Dick P, Schlager O, Sabeti S, Mlekusch W, Haumer M, Mathies R, Heinzle G, Schuster A, Loewe C, Koppensteiner R, Lammer J, Minar E, Cejna M. De Novo Superficial Femoropopliteal Artery Lesions: Peripheral Cutting Balloon Angioplasty and Restenosis Rates--Randomized Controlled Trial. Radiology. 2008; 247(1):267-272. (Guideline Ref ID 157)	Wrong comparison (compares types of angioplasty)
Ansel GM, Silver MJ, Botti CF, Jr., Rocha-Singh K, Bates MC, Rosenfield K, Schainfeld RM, Laster SB, Zander C. Functional and Clinical Outcomes of Nitinol Stenting With and Without Abciximab for Complex Superficial Femoral Artery Disease: a Randomized Trial. Catheterization and Cardiovascular Interventions. 2006; 67(2):288-297. (Guideline Ref ID 189)	Wrong comparison (compared abciximab after stenting)
Antoniucci D, Valenti R, Moschi G, Santoro GM, Bolognese L, Trapani M, Fazzini PF. Cost-Effective Analysis of Primary Infarct-Artery Stenting Versus Optimal Primary Angioplasty (the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) Trial) (Structured Abstract). American Journal of Cardiology. 2000; 85(10):1247-1249. (Guideline Ref ID 1185)	Health economics study

Arain SA, White CJ. Endovascular Therapy for Critical Limb Ischemia. Vascular Medicine. 2008; 13(3):267-279. (Guideline Ref ID 1259)	Wrong study design (review)
Arfvidsson B, Karlsson J, Dahllof AG, Lundholm K, Sullivan M. The Impact of Intermittent Claudication on Quality of Life Evaluated by the Sickness Impact Profile Technique. European Journal of Clinical Investigation. 1993; 23(11):741-745. (Guideline Ref ID 15937)	Wrong objective
Bachoo P, Thorpe PA, Maxwell H, Welch K. Endovascular Stents for Intermittent Claudication. Cochrane Database of Systematic Reviews. 2010; Issue 1:CD003228. (Guideline Ref ID 2423)	Cochrane review – cross checked for studies which match review protocol
Bali HK, Bhargava M, Jain AK, Sharma BK. De Novo Stenting of Descending Thoracic Aorta in Takayasu Arteritis: Intermediate-Term Follow-Up Results. Journal of Invasive Cardiology. 2000; 12(12):612-617. (Guideline Ref ID 1290)	Wrong study design (observational)
Balzer JO, Thalhammer A, Khan V, Zangos S, Vogl TJ, Lehnert T. Angioplasty of the Pelvic and Femoral Arteries in PAOD: Results and Review of the Literature. European Journal of Radiology. 2010; 75(1):48-56. (Guideline Ref ID 1295)	Wrong study design (observational)
Balzer JO, Zeller T, Rastan A, Sixt S, Vogl TJ, Lehnert T, Khan V. Percutaneous Interventions Below the Knee in Patients With Critical Limb Ischemia Using Drug Eluting Stents. Journal of Cardiovascular Surgery. 2010; 51(2):183-191. (Guideline Ref ID 1293)	Wrong study design (observational)
Barbeau GR, Seeger JM, Jablonski S, Kaelin LD, Friedl SE, Abela GS. Peripheral Artery Recanalization in Humans Using Balloon and Laser Angioplasty. Clinical Cardiology. 1996; 19(3):232-238. (Guideline Ref ID 1299)	Wrong study design (observational)
Becker GJ, Ferguson JG, Bakal CW, Kinnison ML, McLean GK, Pentecost M, Perler BA, van BA, Veith FJ. Angioplasty, Bypass Surgery, and Amputation for Lower Extremity Peripheral Arterial Disease in Maryland: a Closer Look. Radiology. 1993; 186(3):635-638. (Guideline Ref ID 774)	Wrong study design (observational)
Becquemin JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic Versus Selective Stent Placement After Superficial Femoral Artery Balloon Angioplasty: a Multicenter Prospective Randomized Study. Journal of Vascular Surgery. 2003; 37(3):487-494. (Guideline Ref ID 442)	Wrong population (compares treatment after failed angioplasty)
Becquemin JP, Allaire E, Cavillon A, Desgranges P, Melliere D. Conventional Versus Endovascular Surgical Procedures: a No Choice Option. European Journal of Vascular and Endovascular Surgery. 1995; 10(1):1-3. (Guideline Ref ID 719)	Wrong study design (review)
Becquemin JP, Cavillon A, Allaire E, Haiduc F, Desgranges P. Iliac and Femoropopliteal Lesions: Evaluation of Balloon Angioplasty and Classical Surgery. Journal of Endovascular Surgery. 1995; 2(1):42-50. (Guideline Ref ID 1315)	Wrong study design (observational)
Belli AM, Cumberland DC, Procter AE, Welsh CL. Total Peripheral Artery Occlusions: Conventional Versus Laser Thermal Recanalization With a Hybrid Probe in Percutaneous Angioplasty--Results of a Randomized Trial. Radiology. 1991; 181(1):57-60. (Guideline Ref ID 3063)	Wrong comparison (recanalization)
Berceli SA, Hevelone ND, Lipsitz SR, Bandyk DF, Clowes AW, Moneta GL, Conte MS. Surgical and Endovascular Revision of Infrainguinal Vein Bypass Grafts: Analysis of Midterm Outcomes From the PREVENT III Trial. Journal of Vascular Surgery. 2007; 46(6):1173-1179. (Guideline Ref ID 171)	Wrong study design (observational)
Black JH, III, LaMuraglia GM, Kwolek CJ, Brewster DC, Watkins MT, Cambria RP. Contemporary Results of Angioplasty-Based Infrainguinal Percutaneous Interventions. Journal of Vascular Surgery. 2005; 42(5):932-939. (Guideline Ref ID 1335)	Wrong study design (observational)
Boccalandro F, Muench A, Sdringola S, Rosales O. Wireless Laser-Assisted Angioplasty of the Superficial Femoral Artery in Patients With Critical Limb Ischemia Who Have Failed Conventional Percutaneous Revascularization.	Wrong study design (observational)

Catheterization and Cardiovascular Interventions. 2004; 63(1):7-12. (Guideline Ref ID 1337)	
Bosch JL, Tetteroo E, Mali WP, Hunink MG. Iliac Arterial Occlusive Disease: Cost-Effectiveness Analysis of Stent Placement Versus Percutaneous Transluminal Angioplasty. Dutch Iliac Stent Trial Study Group. Radiology. 1998; 208(3):641-648. (Guideline Ref ID 2459)	Health economics study
Bosch JL, Hunink MG. Meta-Analysis of the Results of Percutaneous Transluminal Angioplasty and Stent Placement for Aortoiliac Occlusive Disease. Radiology. 1997; 204(1):87-96. (Guideline Ref ID 2458)	Wrong study design (meta-analysis)
Bosiers M, Deloose K, Callaert J, Keirse K, Verbist J, Peeters P. Drug-Eluting Stents Below the Knee. Journal of Cardiovascular Surgery. 2011; 52(2):231-234. (Guideline Ref ID 16279)	Wrong study design (narrative)
Bosiers M, Peeters P, D'Archambeau O, Hendriks J, Pilger E, Duber C, Zeller T, Gussmann A, Lohle PN, Minar E, Scheinert D, Hausegger K, Schulte KL, Verbist J, Deloose K, Lammer J, AMS INSIGHT Investigators. AMS INSIGHT--Absorbable Metal Stent Implantation for Treatment of Below-the-Knee Critical Limb Ischemia: 6-Month Analysis. Cardiovascular and Interventional Radiology. 2009; 32(3):424-435. (Guideline Ref ID 78)	Wrong study design (observational)
Bosiers M, Cagiannos C, Deloose K, Verbist J, Peeters P. Drug-Eluting Stents in the Management of Peripheral Arterial Disease. Vascular Health and Risk Management. 2008; 4(3):553-559. (Guideline Ref ID 1349)	Wrong study design (review)
Bosiers M, Deloose K, Moreialvar R, Verbist J, Peeters P. Current Status of Infrapopliteal Artery Stenting in Patients With Critical Limb Ischemia. Jornal Vascular Brasileiro. 2008; 7(3):248-255. (Guideline Ref ID 1348)	Wrong study design (review)
Bosiers M, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular Therapy As the Primary Approach for Limb Salvage in Patients With Critical Limb Ischemia: Experience With 443 Infrapopliteal Procedures. Vascular. 2006; 14(2):63-69. (Guideline Ref ID 3065)	Wrong study design (observational)
Bosiers M, Peeters P, Elst FV, Vermassen F, Maleux G, Fourneau I, Massin H. Excimer Laser Assisted Angioplasty for Critical Limb Ischemia: Results of the LACI Belgium Study. European Journal of Vascular and Endovascular Surgery. 2005; 29(6):613-619. (Guideline Ref ID 345)	Wrong study design (observational)
Bown MJ, Bolia A, Sutton AJ. Subintimal Angioplasty: Meta-Analytical Evidence of Clinical Utility. European Journal of Vascular and Endovascular Surgery. 2009; 38(3):323-337. (Guideline Ref ID 60)	Wrong study design (meta-analysis)
Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, Raab G, Ruckley CV. Multicentre Randomised Controlled Trial of the Clinical and Cost-Effectiveness of a Bypass-Surgery-First Versus a Balloon-Angioplasty-First Revascularisation Strategy for Severe Limb Ischaemia Due to Infrainguinal Disease. The Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial. Health Technology Assessment. 2010; 14(14):1-236. (Guideline Ref ID 1356)	Included in angioplasty compared to bypass
Brewster DC, Cambria RP, Darling RC, Athanasoulis CA, Waltman AC, Geller SC, Moncure AC, LaMuraglia GM, Freehan M, Abbott WM. Long-Term Results of Combined Iliac Balloon Angioplasty and Distal Surgical Revascularization. Annals of Surgery. 1989; 210(3):324-330. (Guideline Ref ID 3051)	Wrong study design (observational)
Bronas UG, Hirsch AT, Murphy T, Badenhop D, Collins TC, Ehrman JK, Ershow AG, Lewis B, Treat-Jacobson D, Walsh ME, Oldenburg N, Regensteiner JG, CLEVER Research Group. Design of the Multicenter Standardized Supervised Exercise Training Intervention for the Claudication: Exercise Vs Endoluminal Revascularization (CLEVER) Study. Vascular Medicine. 2009; 14(4):313-321. (Guideline Ref ID 22)	Description of study not yet completed. CLEVER study due to be published in June 2012
Brunkwall J, Weibull H, Bergqvist D, Takolander R, Bergentz SE. Arterial Surgery and Angioplasty in Patients Under 40 Years of Age: A Retrospective Study.	Wrong study design (observational)

Medical Principles and Practice. 1989; 1(1):37-43. (Guideline Ref ID 1369)	
Bucek RA, Hudak P, Schnurer G, Ahmadi R, Wolfram RM, Minar E. Clinical Long-Term Results of Percutaneous Transluminal Angioplasty in Patients With Peripheral Arterial Occlusive Disease. Vasa. 2002; 31(1):36-42. (Guideline Ref ID 1370)	Wrong study design (observational)
Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and Outcome of Patients Hospitalised for Lower Extremity Peripheral Artery Disease in France: the COPART Registry. European Journal of Vascular and Endovascular Surgery. 2010; 39(5):577-585. (Guideline Ref ID 16)	Wrong study design (observational)
Canaud L, Alric P, Berthet JP, Marty-Ane C, Mercier G, Branchereau P. Infrainguinal Cutting Balloon Angioplasty in De Novo Arterial Lesions. Journal of Vascular Surgery. 2008; 48(5):1182-1188. (Guideline Ref ID 113)	Wrong study design (observational)
Cao P, De Rango P, Verzini F, Maselli A, Norgiolini L, Giordano G. Outcome of Carotid Stenting Versus Endarterectomy: A Case-Control Study. Stroke. 2006; 37(5):1221-1226. (Guideline Ref ID 1386)	Wrong study design (observational)
Cejna M, Schoder M, Lammer J. PTA Versus Stenting in Femoropopliteal Obstructive Disease. Radiologe. 1999; 39(2):144-150. (Guideline Ref ID 1054)	Paper not in English
Cheng SWK, Ting ACW, Ho P. Angioplasty and Primary Stenting of High-Grade, Long-Segment Superficial Femoral Artery Disease: Is It Worthwhile? Annals of Vascular Surgery. 2003; 17(4):430-437. (Guideline Ref ID 1407)	Wrong study design (observational)
Chetter IC, Spark JI, Scott DJ, Kester RC. Does Angioplasty Improve the Quality of Life for Claudicants?: A Prospective Study. Annals of Vascular Surgery. 1999; 13(1):93-103. (Guideline Ref ID 602)	Wrong study design (observational)
Chong PF, Golledge J, Greenhalgh RM, Davies AH. Exercise Therapy or Angioplasty? A Summation Analysis. European Journal of Vascular and Endovascular Surgery. 2000; 20(1):4-12. (Guideline Ref ID 565)	Wrong study design (review)
Cleveland T, Gaines P, Beard J, Chan P. Aortoiliac Stenting, Determinants of Clinical Outcome. European Journal of Vascular and Endovascular Surgery. 1999; 17(4):351-359. (Guideline Ref ID 1417)	Wrong study design (observational)
Cordero-Yordan H, Lopez A, Heuser RR. Carotid Artery Percutaneous Transluminal Angioplasty and Stenting: Indications, Technical Approach, and Complications. Journal of Interventional Cardiology. 1999; 12(6):499-504. (Guideline Ref ID 1425)	Wrong study design (review)
Cotton LT, Roberts VC. Extended Deep Femoral Angioplasty: an Alternative to Femoropopliteal Bypass. British Journal of Surgery. 1975; 62(5):340-343. (Guideline Ref ID 1428)	Wrong study design (observational)
Creasy TS, McMillan PJ, Walton J, Fletcher EW, Collin J, Morris PJ. A Prospective Randomised Trial of Percutaneous Transluminal Angioplasty (PTA) Versus Exercise Therapy for Lower Limb Claudication. Clinical Radiology. 1989; 40(6):638. (Guideline Ref ID 1153)	Wrong study design (abstract)
Dake MD. Zilver PTX Randomized Trial of Paclitaxel-Eluting Stents for Femoropopliteal Artery Disease: 24-Month Update. Journal of Vascular and Interventional Radiology. 2011; 22(3 SUPPL. 1):S7-S8. (Guideline Ref ID 16350)	Wrong study design (abstract)
Dave RM, Patlola R, Kollmeyer K, Bunch F, Weinstock BS, Dippel E, Jaff MR, Popma J, Weissman N, CELLO Investigators. Excimer Laser Recanalization of Femoropopliteal Lesions and 1-Year Patency: Results of the CELLO Registry. Journal of Endovascular Therapy. 2009; 16(6):665-675. (Guideline Ref ID 34)	Wrong study design (observational)
de Belder AJ, Smith RE, Wainwright RJ, Thomas MR. Transradial Artery Coronary Angiography and Intervention in Patients With Severe Peripheral Vascular Disease. Clinical Radiology. 1997; 52(2):115-118. (Guideline Ref ID 672)	Wrong study design (observational)
de Vries SO, Visser K, de Vries JA, Wong JB, Donaldson MC, Hunink MG. Intermittent Claudication: Cost-Effectiveness of Revascularization Versus Exercise Therapy. Radiology. 2002; 222(1):25-36. (Guideline Ref ID 2460)	Health economics study

Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or Endovascular Revascularization in Patients With Critical Limb Ischemia: Influence of Diabetes Mellitus on Clinical Outcome. Journal of Vascular Surgery. 2007; 45(4):751-761. (Guideline Ref ID 220)	Wrong study design (observational)
Diehm N, Savolainen H, Mahler F, Schmidli J, Do DD, Baumgartner I. Does Deep Femoral Artery Revascularization As an Isolated Procedure Play a Role in Chronic Critical Limb Ischemia? Journal of Endovascular Therapy. 2004; 11(2):119-124. (Guideline Ref ID 408)	Wrong study design (observational)
Donaghue CC, Bohannon RW, Maljanian R, Frigon L, Horowitz S, McGovern A. Improved Health-Related Quality of Life 12 Months After Bypass or Angioplasty for Peripheral Arterial Disease. Journal of Vascular Nursing. 2000; 18(3):75-82. (Guideline Ref ID 885)	Wrong study design (observational)
Donas KP, Schwindt A, Pitoulias GA, Schonefeld T, Basner C, Torsello G. Endovascular Treatment of Internal Iliac Artery Obstructive Disease. Journal of Vascular Surgery. 2009; 49(6):1447-1451. (Guideline Ref ID 1474)	Wrong study design (observational)
Dorigo W, Pulli R, Marek J, Troisi N, Fargion A, Giacomelli E, Spina I, Bellandi S, Pratesi G, Pratesi C. A Comparison Between Open and Endovascular Repair in the Treatment of Critical Limb Ischemia. Italian Journal of Vascular and Endovascular Surgery. 2009; 16(1):17-22. (Guideline Ref ID 1478)	Wrong study design (observational)
Dosluoglu HH, Cherr GS, Lall P, Harris LM, Dryjski ML. Stenting Vs Above Knee Polytetrafluoroethylene Bypass for TransAtlantic Inter-Society Consensus-II C and D Superficial Femoral Artery Disease. Journal of Vascular Surgery. 2008; 48(5):1166-1174. (Guideline Ref ID 1486)	Wrong study design (observational)
Dosluoglu HH, Cherr GS, Harris LM, Dryjski ML. Rheolytic Thrombectomy, Angioplasty, and Selective Stenting for Subacute Isolated Popliteal Artery Occlusions. Journal of Vascular Surgery. 2007; 46(4):717-723. (Guideline Ref ID 186)	Wrong study design (observational)
D'Othee BJ, Morris MF, Powell RJ, Bettmann MA. Cost Determinants of Percutaneous and Surgical Interventions for Treatment of Intermittent Claudication From the Perspective of the Hospital (Brief Record). Cardiovascular and Interventional Radiology. 2008; 31:56-65. (Guideline Ref ID 2404)	Health economics study
Drescher P, McGuckin J, Rilling WS, Crain MR. Catheter-Directed Thrombolytic Therapy in Peripheral Artery Occlusions: Combining Reteplase and Abciximab. American Journal of Roentgenology. 2003; 180(5):1385-1391. (Guideline Ref ID 1492)	Wrong comparison (compares types of drugs)
Duda SH, Bosiers M, Pusich B, Huttl K, Oliva V, Muller-Hulsbeck S, Bray A, Luz O, Remy C, Hak JB, Beregi JP. Endovascular Treatment of Peripheral Artery Disease With Expanded PTFE-Covered Nitinol Stents: Interim Analysis From a Prospective Controlled Study. Cardiovascular and Interventional Radiology. 2002; 25(5):413-418. (Guideline Ref ID 457)	Wrong study design (observational)
Eiberg JP, Hansen MA, Jorgensen LG, Rasmussen JBG, Jensen F, Schroeder TV. In-Situ Bypass Surgery on Arteriographically Invisible Vessels Detected by Doppler-Ultrasound for Limb Salvage. Journal of Cardiovascular Surgery. 2004; 45(4) (pp 375-379), 2004. Date of Publication: Aug 2004.):-379. (Guideline Ref ID 561)	Wrong study design (observational)
Elgzyri T, Ekberg G, Peterson K, Lundell A, Apelqvist J. Can Duplex Arterial Ultrasonography Reduce Unnecessary Angiography? Journal of Wound Care. 2008; 17(11):497-500. (Guideline Ref ID 111)	Wrong comparison (assessment)
Elliott JM, Berdan LG, Holmes DR, Isner JM, King SB, Keeler GP, Kearney M, Califf RM, Topol EJ. One-Year Follow-Up in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I). Circulation. 1995; 91(8):2158-2166. (Guideline Ref ID 1103)	Wrong comparison (excisional atherectomy)
Ellozy SH, Carroccio A. Drug-Eluting Stents in Peripheral Vascular Disease: Eliminating Restenosis. Mount Sinai Journal of Medicine. 2003; 70(6):417-419. (Guideline Ref ID 1508)	Wrong study design (review)

Evans C, Peter N, Gibson M, Torrie EP, Galland RB, Magee TR. Five-Year Retrograde Transpopliteal Angioplasty Results Compared With Antegrade Angioplasty. Annals of the Royal College of Surgeons of England. 2010; 92(4):347-352. (Guideline Ref ID 1516)	Wrong study design (observational)
Faglia E, Clerici G, Clerissi J, Caminiti M, Quarantiello A, Curci V, Losa S, Vitiello R, Lupattelli T, Somalvico F. Angioplasty for Diabetic Patients With Failing Bypass Graft or Residual Critical Ischemia After Bypass Graft. European Journal of Vascular and Endovascular Surgery. 2008; 36(3):331-338. (Guideline Ref ID 1522)	Wrong study design (observational)
Feiring AJ, Krahn M, Nelson L, Wesolowski A, Eastwood D, Szabo A. Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents: the PaRADISE (PReventing Amputations Using Drug Eluting StEnts) Trial. Journal of the American College of Cardiology. 2010; 55(15):1580-1589. (Guideline Ref ID 5)	Wrong study design (observational)
Garasic JM, Creager MA. Percutaneous Interventions for Lower-Extremity Peripheral Atherosclerotic Disease. Reviews in Cardiovascular Medicine. 2001; 2(3):120-125. (Guideline Ref ID 1562)	Wrong study design (review)
Grant AG, White CJ, Collins TJ, Jenkins JS, Reilly JP, Ramee SR. Infrapopliteal Drug-Eluting Stents for Chronic Limb Ischemia. Catheterization and Cardiovascular Interventions. 2008; 71(1):108-111. (Guideline Ref ID 166)	Wrong study design (observational)
Gray BH, Laird JR, Ansel GM, Shuck JW. Complex Endovascular Treatment for Critical Limb Ischemia in Poor Surgical Candidates: a Pilot Study. Journal of Endovascular Therapy. 2002; 9(5):599-604. (Guideline Ref ID 464)	Wrong study design (observational)
Gray BH, Olin JW. Limitations of Percutaneous Transluminal Angioplasty With Stenting for Femoropopliteal Arterial Occlusive Disease. Seminars in Vascular Surgery. 1997; 10(1):8-16. (Guideline Ref ID 1585)	Wrong study design (observational)
Gray BH. Endovascular Treatment of Peripheral Arterial Disease. Journal of the American Osteopathic Association. 2000; 100(10 Su Pt 2):S15-S20. (Guideline Ref ID 1586)	Wrong study design (observational)
Greenhalgh RM. MIMIC Trials: Angioplasty effective in randomised controlled trials for peripheral arterial disease. Available from: http://www.cxvascular.com/in-latest-news?ccs=485&cs=4222 Last accessed on: 2 February 2009. (Guideline Ref ID 924)	Wrong study design (commentary)
He EY, He N, Wang Y, Fan H. Percutaneous Transluminal Angioplasty (PTA) Alone Versus PTA With Balloon-Expandable Stent Placement for Short-Segment Femoropopliteal Artery Disease: A Metaanalysis of Randomized Trials. Journal of Vascular and Interventional Radiology. 2008; 19(4):499-503. (Guideline Ref ID 1502)	Wrong study design (meta-analysis)
Henry M, Henry I, Klonaris C, Hugel M. Clinical Experience With the OptiMed Sinus Stent in the Peripheral Arteries. Journal of Endovascular Therapy. 2003; 10(4):772-779. (Guideline Ref ID 1616)	Wrong study design (observational)
Hoeks SE, Smolderen KG, Scholte op Reimer WJM, Verhagen HJM, Spertus JA, Poldermans D. Clinical Validity of a Disease-Specific Health Status Questionnaire: The Peripheral Artery Questionnaire. Journal of Vascular Surgery. 2009; 49(2):371-377. (Guideline Ref ID 3070)	Wrong study design (observational)
Hoffer EK, Sultan S, Herskowitz MM, Daniels ID, Sclafani SJ. Prospective Randomized Trial of a Metallic Intravascular Stent in Hemodialysis Graft Maintenance. Journal of Vascular and Interventional Radiology. 1997; 8(6):965-973. (Guideline Ref ID 1073)	Wrong population
Hynes N, Akhtar Y, Manning B, Aremu M, Oiakhinan K, Courtney D, Sultan S. Subintimal Angioplasty As a Primary Modality in the Management of Critical Limb Ischemia: Comparison to Bypass Grafting for Aortoiliac and Femoropopliteal Occlusive Disease. Journal of Endovascular Therapy. 2004; 11(4):460-471. (Guideline Ref ID 15935)	Wrong study design (observational)

Iannone L, Rough R, Ghali M, Rayl KL, Phillips S. Angioplasty Treatment for Peripheral Vascular Disease. Iowa Medicine. 1996; 86(7):281-283. (Guideline Ref ID 1653)	Wrong study design (observational)
Ihnat DM, Duong ST, Taylor ZC, Leon LR, Mills JL, Sr., Goshima KR, Echeverri JA, Arslan B. Contemporary Outcomes After Superficial Femoral Artery Angioplasty and Stenting: the Influence of TASC Classification and Runoff Score. Journal of Vascular Surgery. 2008; 47(5):967-974. (Guideline Ref ID 147)	Wrong study design (observational)
Jaff MR, Cahill KE, Yu AP, Birnbaum HG, Engelhart LM. Clinical Outcomes and Medical Care Costs Among Medicare Beneficiaries Receiving Therapy for Peripheral Arterial Disease. Annals of Vascular Surgery. 2010; 24(5):577-587. (Guideline Ref ID 1662)	Wrong study design (observational)
Jahnke T, Voshage G, Muller-Hulsbeck S, Grimm J, Heller M, Brossmann J. Endovascular Placement of Self-Expanding Nitinol Coil Stents for the Treatment of Femoropopliteal Obstructive Disease. Journal of Vascular and Interventional Radiology. 2002; 13(3):257-266. (Guideline Ref ID 3059)	Wrong study design (observational)
Jamsen TS, Manninen HI, Tulla HE, Jaakkola PA, Matsi PJ. Infrainguinal Revascularization Because of Claudication: Total Long-Term Outcome of Endovascular and Surgical Treatment. Journal of Vascular Surgery. 2003; 37(4):808-815. (Guideline Ref ID 1667)	Wrong study design (observational)
Johnston KW, Rae M, Hogg-Johnston SA, Colapinto RF, Walker PM, Baird RJ, Sniderman KW, Kalman P. 5-Year Results of a Prospective Study of Percutaneous Transluminal Angioplasty. Annals of Surgery. 1987; 206(4):403-413. (Guideline Ref ID 858)	Wrong study design (observational)
Karnabatidis D, Spiliopoulos S, Katsanos K, Siablis D. Below-the-Knee Drug-Eluting Stents and Drug-Coated Balloons. Expert Review of Medical Devices. 2012; 9(1):85-94. (Guideline Ref ID 16354)	Wrong study design (narrative)
Karnabatidis D, Spiliopoulos S, Diamantopoulos A, Katsanos K, Kagadis GC, Kakkos S, Siablis D. Primary Everolimus-Eluting Stenting Versus Balloon Angioplasty With Bailout Bare Metal Stenting of Long Infrapopliteal Lesions for Treatment of Critical Limb Ischemia. Journal of Endovascular Therapy. 2011; 18(1):1-12. (Guideline Ref ID 16287)	Wrong study design (observational)
Kasapis C, Henke PK, Chetcuti SJ, Koenig GC, Rectenwald JE, Krishnamurthy VN, Grossman PM, Gurm HS. Routine Stent Implantation Vs. Percutaneous Transluminal Angioplasty in Femoropopliteal Artery Disease: a Meta-Analysis of Randomized Controlled Trials. European Heart Journal. 2009; 30(1):44-55. (Guideline Ref ID 98)	Wrong study design (meta-analysis)
Keeling AN, Naughton PA, O'Connell A, Lee MJ. Does Percutaneous Transluminal Angioplasty Improve Quality of Life? Journal of Vascular and Interventional Radiology. 2008; 19(2 Pt 1):169-176. (Guideline Ref ID 159)	Wrong study design (observational)
Kickuth R, Keo HH, Triller J, Ludwig K, Do DD. Initial Clinical Experience With the 4-F Self-Expanding XPERT Stent System for Infrapopliteal Treatment of Patients With Severe Claudication and Critical Limb Ischemia. Journal of Vascular and Interventional Radiology. 2007; 18(6):703-708. (Guideline Ref ID 1705)	Wrong study design (observational)
Kidney D, Murphy J, Malloy M. Balloon-Expandable Intravascular Stents in Atherosclerotic Iliac Artery Stenosis: Preliminary Experience. Clinical Radiology. 1993; 47(3):189-192. (Guideline Ref ID 1706)	Wrong study design (observational)
Kim J-S, Kang TS, Ahn CM, Ko YG, Choi D, Jang Y, Chung N, Shim W-H, Cho S-Y. Efficacy of Subintimal Angioplasty/Stent Implantation for Long, Multisegmental Lower Limb Occlusive Lesions in Patients Unsuitable for Surgery. Journal of Endovascular Therapy. 2006; 13(4):514-521. (Guideline Ref ID 1707)	Wrong study design (observational)
Klevsgard R, Risberg BO, Thomsen MB, Hallberg IR. A 1-Year Follow-Up Quality of Life Study After Hemodynamically Successful or Unsuccessful Surgical Revascularization of Lower Limb Ischemia. Journal of Vascular Surgery. 2001; 33(1):114-122. (Guideline Ref ID 1716)	Wrong objective (considers the impact of successful or unsuccessful procedure)

Koerkamp BG, Spronk S, Stijnen T, Hunink MGM. Value of Information Analyses of Economic Randomized Controlled Trials: The Treatment of Intermittent Claudication. Value in Health. 2010; 13(2):242-250. (Guideline Ref ID 36)	Health economic study
Kovalik EC, Newman GE, Suhocki P, Knelson M, Schwab SJ. Correction of Central Venous Stenoses: Use of Angioplasty and Vascular Wallstents. Kidney International. 1994; 45(4):1177-1181. (Guideline Ref ID 749)	Wrong study design (observational)
Krajcer Z, Sioco G, Reynolds T. Comparison of Wallgraft and Wallstent for Treatment of Complex Iliac Artery Stenosis and Occlusion. Preliminary Results of a Prospective Randomized Study. Texas Heart Institute Journal. 1997; 24(3):193-199. (Guideline Ref ID 641)	Wrong comparison (compares two types of bare metal stents)
Kudo T, Chandra FA, Ahn SS. Long-Term Outcomes and Predictors of Iliac Angioplasty With Selective Stenting. Journal of Vascular Surgery. 2005; 42(3):466. (Guideline Ref ID 1738)	Wrong study design (observational)
Lai DTM, Huber D, Glasson R, Grayndler V, Evans J, Hogg J, Etheredge S. Colour-Coded Duplex Ultrasonography in Selection of Patients for Transluminal Angioplasty. Australasian Radiology. 1995; 39(3):243-245. (Guideline Ref ID 1094)	Wrong comparison (assessment)
Lammer J, Dake MD, Bleyn J, Katzen BT, Cejna M, Piquet P, Becker GJ, Settlage RA. Peripheral Arterial Obstruction: Prospective Study of Treatment With a Transluminally Placed Self-Expanding Stent-Graft. Radiology. 2000; 217(1):95-104. (Guideline Ref ID 1753)	Wrong study design (observational)
Lantis J, Jensen M, Benvenisty A, Mendes D, Gendics C, Todd G. Outcomes of Combined Superficial Femoral Endovascular Revascularization and Popliteal to Distal Bypass for Patients With Tissue Loss. Annals of Vascular Surgery. 2008; 22(3):366-371. (Guideline Ref ID 145)	Wrong study design (observational)
Litvack F, Grundfest WS, Adler L, Hickey AE, Segalowitz J, Hestrin LB, Mohr FW, Goldenberg T, Laudenslager JS, Forrester JS. Percutaneous Excimer-Laser and Excimer-Laser-Assisted Angioplasty of the Lower Extremities: Results of Initial Clinical Trial. Radiology. 1989; 172(2):331-335. (Guideline Ref ID 3062)	Wrong study design (observational)
Liu C, Guan H, Li Y, Zheng Y, Liu W. Combined Intraoperative Iliac Artery Stents and Femoro-Popliteal Bypass for Multilevel Atherosclerotic Occlusive Disease. Chinese Medical Sciences Journal. 2001; 16(3):165-168. (Guideline Ref ID 1777)	Wrong study design (observational)
Lopez-Galarza LA, Ray LI, Rodriguez-Lopez J, Diethrich EB. Combined Percutaneous Transluminal Angioplasty, Iliac Stent Deployment, and Femorofemoral Bypass for Bilateral Aortoiliac Occlusive Disease. Journal of the American College of Surgeons. 1997; 184(3):249-258. (Guideline Ref ID 1786)	Wrong study design (observational)
Lorenzi G, Domanin M, Costantini A, Rolli A, Agrifoglio G. Role of Bypass, Endarterectomy, Extra-Anatomic Bypass and Endovascular Surgery in Unilateral Iliac Occlusive Disease: a Review of 1257 Cases. Cardiovascular Surgery. 1994; 2(3):370-373. (Guideline Ref ID 746)	Wrong study design (observational)
Mahler F, Do DD, Triller J. Interventional Angiology. European Journal of Medicine. 1992; 1(5):295-301. (Guideline Ref ID 1793)	Wrong study design (review)
Martens JM, Knippenberg B, Vos JA, de Vries JP, Hansen BE, van OH, PADI Trial Group. Update on PADI Trial: Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. Journal of Vascular Surgery. 2009; 50(3):687-689. (Guideline Ref ID 57)	Wrong study design (study protocol)
Matsi PJ, Manninen HI. Complications of Lower-Limb Percutaneous Transluminal Angioplasty: a Prospective Analysis of 410 Procedures on 295 Consecutive Patients. Cardiovascular and Interventional Radiology. 1998; 21(5):361-366. (Guideline Ref ID 3054)	Wrong study design (observational)
McLean L, Jeans WD, Horrocks M, Baird RN. The Place of Percutaneous Transluminal Angioplasty in the Treatment of Patients Having Angiography for Ischaemic Disease of the Lower Limb. Clinical Radiology. 1987; 38(2):157-160.	Wrong study design (observational)

(Guideline Ref ID 861)	
Michaels J, Galland RB. Case Mix and Outcome of Patients Referred to the Vascular Service at a District General Hospital. Annals of the Royal College of Surgeons of England. 1993; 75(5):358-361. (Guideline Ref ID 762)	Wrong study design (observational)
Minar E. Drug-Eluting Stents Above the Knee. Journal of Cardiovascular Surgery. 2011; 52(2):225-229. (Guideline Ref ID 16280)	Wrong study design (narrative)
Minar E, Schillinger M. New Stents for SFA. Journal of Cardiovascular Surgery. 2009; 50(5):635-645. (Guideline Ref ID 1847)	Wrong study design (review)
Muller-Buhl U, Strecker EP, Gottmann D, Vetter S, Boos IBL. Improvement in Claudication After Angioplasty of Distal Ostial Collateral Stenosis in Patients With Long-Segment Occlusion of the Femoral Artery. Cardiovascular and Interventional Radiology. 2000; 23(6):447-451. (Guideline Ref ID 1868)	Wrong study design (observational)
Muradin GSR, Bosch JL, Stijnen T, Hunink MGM. Balloon Dilation and Stent Implantation for Treatment of Femoropopliteal Arterial Disease: Meta-Analysis. Radiology. 2001; 221(1):137-145. (Guideline Ref ID 1871)	Wrong study design (meta-analysis)
Muradin GSR, Hunink MGM. Cost and Patency Rate Targets for the Development of Endovascular Devices to Treat Femoropopliteal Arterial Disease. Radiology. 2001; 218(2):464-469. (Guideline Ref ID 863)	Health economics study
Murphy TP, Hirsch AT, Cutlip DE, Regensteiner JG, Comerota AJ, Mohler E, Cohen DJ, Massaro J, CLEVER Investigators. Claudication: Exercise Vs Endoluminal Revascularization (CLEVER) Study Update. Journal of Vascular Surgery. 2009; 50(4):942-945. (Guideline Ref ID 52)	Description of study not yet completed. CLEVER study due to be published in June 2012
Murphy TP, Webb MS, Lambiase RE, Haas RA, Dorfman GS, Carney J, Morin CJ. Percutaneous Revascularization of Complex Iliac Artery Stenoses and Occlusions With Use of Wallstents: Three-Year Experience. Journal of Vascular and Interventional Radiology. 1996; 7(1):21-27. (Guideline Ref ID 1874)	Wrong study design (observational)
Nakagawa Y, Yajima J, Oikawa Y, Ogasawara K, Kirigaya H, Nagashima K, Funada R, Matsuno S, Inaba T, Nakamura M, Sawada H, Aizawa T. Clinical Outcomes After Percutaneous Peripheral Intervention for Chronic Total Occlusion of Superficial Femoral Arteries: Comparison Between Self-Expandable Nitinol Stent and Stainless Steel Stent. Journal of Cardiology. 2009; 53(3):417-421. (Guideline Ref ID 1268)	Wrong study design (observational)
Nelson PR, Powell RJ, Schermerhorn ML, Fillinger MF, Zwolak RM, Walsh DB, Cronenwett JL. Early Results of External Iliac Artery Stenting Combined With Common Femoral Artery Endarterectomy. Journal of Vascular Surgery. 2002; 35(6):1107-1113. (Guideline Ref ID 1888)	Wrong study design (observational)
Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, Whittemore AD, Belkin M. Infrainguinal Vein Bypass Graft Revision: Factors Affecting Long-Term Outcome. Journal of Vascular Surgery. 2004; 40(5):916-923. (Guideline Ref ID 1892)	Wrong study design (observational)
Okada M, Yoshida M, Tsuji Y. Clinical Experience of Laser Angioplasty for the Cardiovascular Disease. Diagnostic and Therapeutic Endoscopy. 1995; 2(1):11-18. (Guideline Ref ID 1904)	Wrong study design (observational)
Osborn JJ, Pfeiffer RB, Jr., String ST. Directional Atherectomy and Balloon Angioplasty for Lower Extremity Arterial Disease. Annals of Vascular Surgery. 1997; 11(3):278-283. (Guideline Ref ID 663)	Wrong study design (observational)
Ouriel K. Comparison of Surgical and Thrombolytic Treatment of Peripheral Arterial Disease. Reviews in Cardiovascular Medicine. 2002; 3 Suppl 2:S7-16. (Guideline Ref ID 3064)	Wrong study design (review)
Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison Between Coronary Angioplasty and Coronary Artery Bypass Surgery for the Treatment of Unprotected Left Main	Wrong study design (observational)

Coronary Artery Stenosis (the Bologna Registry). American Journal of Cardiology. 2006; 98(1):54-59. (Guideline Ref ID 1910)	
Pozzi Mucelli F, Fisicaro M, Calderan L, Malacrea M, Mazzone C, Cattin L, Scardi S, Pozzi Mucelli R. Percutaneous Revascularization of Femoropopliteal Artery Disease: PTA and PTA Plus Stent. Results After Six Years' Follow-Up. Radiologia Medica. 2003; 105(4):339-349. (Guideline Ref ID 436)	Wrong study design (observational)
Price JF, Leng GC, Fowkes FG. Should Claudicants Receive Angioplasty or Exercise Training?. Cardiovascular Surgery. 1997; 5(5):463-470. (Guideline Ref ID 202)	Wrong study design (review)
Puma JA, Banko LT, Pieper K, Sacchi TJ, O'Shea JC, Dery JP, Tcheng JE. Clinical Characteristics Predict Benefits From Eptifibatide Therapy During Coronary Stenting: Insights From the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) Trial. Journal of the American College of Cardiology. 2006; 47(4):715-718. (Guideline Ref ID 294)	Wrong comparison (compares populations)
Quinn SF, Schuman ES, Demlow TA, Standage BA, Ragsdale JW, Green GS, Sheley RC. Percutaneous Transluminal Angioplasty Versus Endovascular Stent Placement in the Treatment of Venous Stenoses in Patients Undergoing Hemodialysis: Intermediate Results. Journal of Vascular and Interventional Radiology. 1995; 6(6):851-855. (Guideline Ref ID 1104)	Wrong study design (observational)
Raghunathan A, Rapp JH, Littooy F, Santilli S, Krupski WC, Ward HB, Thottapurathu L, Moritz T, McFalls EO, Investigators C.A.R.P. Postoperative Outcomes for Patients Undergoing Elective Revascularization for Critical Limb Ischemia and Intermittent Claudication: a Subanalysis of the Coronary Artery Revascularization Prophylaxis (CARP) Trial. Journal of Vascular Surgery. 2006; 43(6):1175-1182. (Guideline Ref ID 15982)	Wrong study design (observational)
Reekers JA, Vorwerk D, Rousseau H, Sapoval MR, Gaines PA, Stockx L, Delcour CP, Raat H, Voshage G, Biamino G, Hoogeveen YL. Results of a European Multicentre Iliac Stent Trial With a Flexible Balloon Expandable Stent. European Journal of Vascular and Endovascular Surgery. 2002; 24(6):511-515. (Guideline Ref ID 460)	Wrong study design (observational)
Regensteiner JG, Steiner JF, Panzer RJ, Hiatt W. Evaluation of Walking Impairment by Questionnaire in Patients With Peripheral Arterial Disease. Journal of Vascular Medicine and Biology. 1990; 2:142-152. (Guideline Ref ID 3050)	Wrong study design (only part of the study was randomised)
Reifler DR, Feinglass J, Slavensky R, Martin GJ, Manheim L, McCarthy WJ. Functional Outcomes Far Patients With Intermittent Claudication: Bypass Surgery Versus Angioplasty Versus Noninvasive Management. Journal of Vascular Medicine and Biology. 1994; 5(5-6):203-211. (Guideline Ref ID 1954)	Wrong study design (observational)
Ricco JB, Probst H, French University Surgeons Association. Long-Term Results of a Multicenter Randomized Study on Direct Versus Crossover Bypass for Unilateral Iliac Artery Occlusive Disease. Journal of Vascular Surgery. 2008; 47(1):45-53. (Guideline Ref ID 165)	Wrong comparison (considers types of bypass)
Rodriguez A, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, Vogel D, Grinfeld R, Delacasa A, Garrido M, Oliveri R, Mele E, Palacios I, O'Neill W. Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II): 30-Day and One-Year Follow-Up Results. ERACI II Investigators. Journal of the American College of Cardiology. 2001; 37(1):51-58. (Guideline Ref ID 540)	Wrong population (patients had coronary artery disease)
Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-Analysis of Infrapopliteal Angioplasty for Chronic Critical Limb Ischemia. Journal of Vascular Surgery. 2008; 47(5):975-981. (Guideline Ref ID 146)	Wrong study design (meta-analysis)
Rosales O, Mathewkutty S, Gnaim C. Drug Eluting Stents for Below the Knee Lesions in Patients With Critical Limb Ischemia: Long-Term Follow-Up. Catheterization and Cardiovascular Interventions. 2008; 72(1):112-115. (Guideline Ref ID 1966)	Wrong study design (observational)

Rosenthal D, Dickson C, Rodriguez FJ, Blackshear WM, Jr., Clark MD, Lamis PA, Pallos LL. Infrainguinal Endovascular in Situ Saphenous Vein Bypass: Ongoing Results. Journal of Vascular Surgery. 1994; 20(3):389-394. (Guideline Ref ID 744)	Wrong study design (observational)
Rybicki FJ, Nallamshetty L, Yucel EK, Holtzman SR, Baum RA, Foley WD, Ho VB, Mammen L, Narra VR, Stein B, Moneta GL. ACR Appropriateness Criteria on Recurrent Symptoms Following Lower-Extremity Angioplasty. Journal of the American College of Radiology. 2008; 5(12):1176-1180. (Guideline Ref ID 1979)	Wrong study design (review)
Sabeti S, Schillinger M, Amighi J, Sherif C, Mlekusch W, Ahmadi R, Minar E. Primary Patency of Femoropopliteal Arteries Treated With Nitinol Versus Stainless Steel Self-Expanding Stents: Propensity Score-Adjusted Analysis. Radiology. 2004; 232(2):516-521. (Guideline Ref ID 258)	Wrong study design (observational)
Sadek M, Ellozy SH, Turnbull IC, Lookstein RA, Marin ML, Faries PL. Improved Outcomes Are Associated With Multilevel Endovascular Intervention Involving the Tibial Vessels Compared With Isolated Tibial Intervention. Journal of Vascular Surgery. 2009; 49(3):638-643. (Guideline Ref ID 87)	Wrong study design (observational)
Sanborn TA, Gibbs HH, Brinker JA, Knopf WD, Kosinski EJ, Roubin GS. A Multicenter Randomized Trial Comparing a Percutaneous Collagen Hemostasis Device With Conventional Manual Compression After Diagnostic Angiography and Angioplasty. Journal of the American College of Cardiology. 1993; 22(5):1273-1279. (Guideline Ref ID 313)	Wrong comparison (compression)
Satiani B, Mohan Das B, Vaccaro PS, Gawron D. Angiographic Follow-Up After Laser-Assisted Balloon Angioplasty. Journal of Vascular Surgery. 1993; 17(5):960-965. (Guideline Ref ID 772)	Wrong study design (observational)
Saxon RR, Dake MD, Volgelzang RL, Katzen BT, Becker GJ. Randomized, Multicenter Study Comparing Expanded Polytetrafluoroethylene-Covered Endoprosthesis Placement With Percutaneous Transluminal Angioplasty in the Treatment of Superficial Femoral Artery Occlusive Disease. Journal of Vascular and Interventional Radiology. 2008; 19(6):823-832. (Guideline Ref ID 142)	GDG agreed the study had a high drop out rate and should be excluded from the review
Saxon RR, Coffman JM, Gooding JM, Natuzzi E, Ponec DJ. Long-Term Results of EPTFE Stent-Graft Versus Angioplasty in the Femoropopliteal Artery: Single Center Experience From a Prospective, Randomized Trial. Journal of Vascular and Interventional Radiology. 2003; 14(3):303-311. (Guideline Ref ID 441)	GDG excluded ref ID 142 due to high drop out rate, study ID 441 had same patient population as ID 142
Schillinger M, Exner M, Mlekusch W, Haumer M, Ahmadi R, Rumpold H, Wagner O, Minar E. Balloon Angioplasty and Stent Implantation Induce a Vascular Inflammatory Reaction. Journal of Endovascular Therapy. 2002; 9(1):59-66. (Guideline Ref ID 482)	Wrong study design (observational)
Schmieder GC, Richardson AI, Scott EC, Stokes GK, Meier GH, III, Panneton JM. Selective Stenting in Subintimal Angioplasty: Analysis of Primary Stent Outcomes. Journal of Vascular Surgery. 2008; 48(5):1175-1181. (Guideline Ref ID 2018)	Wrong study design (observational)
Schneider PA, Caps MT, Nelken N. Infrainguinal Vein Graft Stenosis: Cutting Balloon Angioplasty As the First-Line Treatment of Choice. Journal of Vascular Surgery. 2008; 47(5):960-966. (Guideline Ref ID 2020)	Wrong study design (observational)
Schwarten DE. Balloon Angioplasty Still Tops in Peripheral Vessels. Diagnostic Imaging. 1990; 12(9):88-93. (Guideline Ref ID 2025)	Wrong study design (review)
Sculpher M, Michaels J, McKenna M, Minor J. A Cost-Utility Analysis of Laser-Assisted Angioplasty for Peripheral Arterial Occlusions. International Journal of Technology Assessment in Health Care. 1996; 12:104-125. (Guideline Ref ID 2442)	Health economic study
Semaan E, Hamburg N, Nasr W, Shaw P, Eberhardt R, Woodson J, Doros G, Rybin D, Farber A. Endovascular Management of the Popliteal Artery: Comparison of Atherectomy and Angioplasty. Vascular and Endovascular Surgery. 2010; 44(1):25-31. (Guideline Ref ID 2034)	Wrong study design (observational)

Serracino-Inglott F, Owen G, Carter A, Dix F, Smyth JV, Mohan IV. All Patients Benefit Equally From a Supervised Exercise Program for Claudication. Vascular and Endovascular Surgery. 2007; 41(3):212-216. (Guideline Ref ID 267)	Wrong study design (observational)
Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P. A Comparison of Balloon-Expandable-Stent Implantation With Balloon Angioplasty in Patients With Coronary Artery Disease. Benestent Study Group. New England Journal of Medicine. 1994; 331(8):489-495. (Guideline Ref ID 1108)	Wrong population
Shafique S, Murphy MP, Dalsing MC. Is Cryoplasty the Best Treatment for Peripheral Arterial Disease? Italian Journal of Vascular and Endovascular Surgery. 2008; 15(3):207-211. (Guideline Ref ID 2037)	Wrong comparison (cryoplasty)
Shindelman LE, Ninnul GB, Curtiss SI, Konigsberg SF. Ambulatory Endovascular Surgery: Cost Advantage and Factors Influencing Its Safe Performance. Journal of Endovascular Surgery. 1999; 6(2):160-167. (Guideline Ref ID 581)	Health economics study
Siablis D, Karnabatidis D, Katsanos K, Diamantopoulos A, Spiliopoulos S, Kagadis GC, Tsolakis J. Infrapopliteal Application of Sirolimus-Eluting Versus Bare Metal Stents for Critical Limb Ischemia: Analysis of Long-Term Angiographic and Clinical Outcome. Journal of Vascular and Interventional Radiology. 2009; 20(9):1141-1150. (Guideline Ref ID 47)	Wrong study design (observational)
Siablis D, Karnabatidis D, Katsanos K, Kagadis GC, Kraniotis P, Diamantopoulos A, Tsolakis J. Sirolimus-Eluting Versus Bare Stents After Suboptimal Infrapopliteal Angioplasty for Critical Limb Ischemia: Enduring 1-Year Angiographic and Clinical Benefit. Journal of Endovascular Therapy. 2007; 14(2):241-250. (Guideline Ref ID 211)	Wrong study design (observational)
Siablis D, Kraniotis P, Karnabatidis D, Kagadis GC, Katsanos K, Tsolakis J. Sirolimus-Eluting Versus Bare Stents for Bailout After Suboptimal Infrapopliteal Angioplasty for Critical Limb Ischemia: 6-Month Angiographic Results From a Nonrandomized Prospective Single-Center Study. Journal of Endovascular Therapy. 2005; 12(6):685-695. (Guideline Ref ID 327)	Wrong study design (observational)
Sise MJ, Shackford SR, Rowley WR, Pistone FJ. Claudication in Young Adults: A Frequently Delayed Diagnosis. Journal of Vascular Surgery. 1989; 10(1):68-74. (Guideline Ref ID 2065)	Wrong comparison (diagnosis)
Sixt S, Alawied AK, Rastan A, Schwarzwalder U, Kleim M, Noory E, Schwarz T, Frank U, Muller C, Hauk M, Beschorner U, Nazary T, Burgelin K, Hauswald K, Leppanen O, Neumann FJ, Zeller T. Acute and Long-Term Outcome of Endovascular Therapy for Aortoiliac Occlusive Lesions Stratified According to the TASC Classification: a Single-Center Experience. Journal of Endovascular Therapy. 2008; 15(4):408-416. (Guideline Ref ID 126)	Wrong study design (observational)
Smeets L, Ho GH, Tangelder MJ, Algra A, Lawson JA, Eikelboom BC, Moll FL, Dutch BOA Study Group. Outcome After Occlusion of Infrainguinal Bypasses in the Dutch BOA Study: Comparison of Amputation Rate in Venous and Prosthetic Grafts. European Journal of Vascular and Endovascular Surgery. 2005; 30(6):604-609. (Guideline Ref ID 1355)	Wrong study design (observational)
Spaargaren GJ, Lee MJ, Reekers JA, van OH, Schultze Kool LJ, Hoogeveen YL. Evaluation of a New Balloon Catheter for Difficult Calcified Lesions in Infrainguinal Arterial Disease: Outcome of a Multicenter Registry. Cardiovascular and Interventional Radiology. 2009; 32(1):132-135. (Guideline Ref ID 92)	Wrong study design (observational)
Spies JB, LeQuire MH, Brantley SD, Williams JE, Beckett WC, Mills JL. Comparison of Balloon Angioplasty and Laser Thermal Angioplasty in the Treatment of Femoropopliteal Atherosclerotic Disease: Initial Results of a Prospective Randomized Trial. Work in Progress. Journal of Vascular and Interventional Radiology. 1990; 1(1):39-42. (Guideline Ref ID 820)	Wrong comparison (compares types of angioplasty)
Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-Effectiveness of Endovascular Revascularization Compared to Supervised	Health economic study

Hospital-Based Exercise Training in Patients With Intermittent Claudication: a Randomized Controlled Trial. Journal of Vascular Surgery. 2008; 48(6):1472-1480. (Guideline Ref ID 2451)	
Steinberg EP, Bass EB, Tunis SR. Interventional Management of Peripheral Vascular Disease: What Did We Learn in Maryland and Where Do We Go From Here? Radiology. 1993; 186(3):639-642. (Guideline Ref ID 773)	Wrong study design (review)
Steinmetz OK, McPhail NV, Hajjar GE, Barber GG, Cole CW. Endarterectomy Versus Angioplasty in the Treatment of Localized Stenosis of the Abdominal Aorta. Canadian Journal of Surgery. 1994; 37(5):385-390. (Guideline Ref ID 3053)	Wrong study design (observational)
Suding PN, McMaster W, Hansen E, Hatfield AW, Gordon IL, Wilson SE. Increased Endovascular Interventions Decrease the Rate of Lower Limb Artery Bypass Operations Without an Increase in Major Amputation Rate. Annals of Vascular Surgery. 2008; 22(2):195-199. (Guideline Ref ID 2092)	Wrong study design (observational)
Taft C, Karlsson J, Gelin J, Jivegard L, Sandstrom R, Arfvidsson B, Dahllof AG, Lundholm K, Sullivan M. Treatment Efficacy of Intermittent Claudication by Invasive Therapy, Supervised Physical Exercise Training Compared to No Treatment in Unselected Randomised Patients II: One-Year Results of Health-Related Quality of Life. European Journal of Vascular and Endovascular Surgery. 2001; 22(2):114-123. (Guideline Ref ID 732)	Wrong outcomes (outcomes do not match protocol)
Taylor SM, Kalbaugh CA, Healy MG, Cass AL, Gray BH, Langan EM, III, Cull DL, Carsten CG, III, York JW, Snyder BA, Youkey JR. Do Current Outcomes Justify More Liberal Use of Revascularization for Vasculogenic Claudication? A Single Center Experience of 1,000 Consecutively Treated Limbs. Journal of the American College of Surgeons. 2008; 206(5):1053-1062. (Guideline Ref ID 144)	Wrong study design (observational)
Tetteroo E, van der Graaf Y, van Engelen AD, Hunink MGM, Eikelboom BC, Mali WP. No Difference in Effect on Intermittent Claudication Between Primary Stent Placement and Primary Percutaneous Transluminal Angio Plasty Followed by Selective Stent Placement: A Prospective Randomized Trial. Nederlands Tijdschrift Voor Geneeskunde. 2000; 144(4):167-171. (Guideline Ref ID 1040)	Paper not in English
Tetteroo E, van Engelen AD, Spithoven JH, Tielbeek A, van der Graaf Y, Mali WP. Stent Placement After Iliac Angioplasty: Comparison of Hemodynamic and Angiographic Criteria. Dutch Iliac Stent Trial Study Group. Radiology. 1996; 201(1):155-159. (Guideline Ref ID 305)	Wrong study design (observational)
Thel MC, Califf RM, Tcheng JE, Sigmon KN, Lincoff AM, Topol EJ, Ellis SG. Clinical Risk Factors for Ischemic Complications After Percutaneous Coronary Interventions: Results From the EPIC Trial. The EPIC Investigators. American Heart Journal. 1999; 137(2):264-273. (Guideline Ref ID 1045)	Wrong objective (considers risk factors)
Thomson IA, van Rij AM, Morrison ND, Packer SGK, Christie R. A Ten Year Randomised Controlled Trial of Percutaneous Femoropopliteal Angioplasty for Claudication. Australian and New Zealand Journal of Medicine. 1999; 69(Suppl):98. (Guideline Ref ID 3052)	Wrong study design (abstract)
Tiefenbacher C. Abdominal Aortic Aneurysm Repair in Cardiac High Risk Patients--Medication, Surgery or Stent?. Clinical Research in Cardiology. 2008; 97(4):215-221. (Guideline Ref ID 156)	Wrong study design (review)
Tielbeek A, Vroegindeweij D, Buth J, Landman GH. Comparison of Balloon Angioplasty and Simpson Atherectomy for Lesions in the Femoropopliteal Artery: Angiographic and Clinical Results of a Prospective Randomized Trial. Journal of Vascular and Interventional Radiology. 1996; 7(6):837-844. (Guideline Ref ID 678)	Wrong comparison (atherectomy)
Timaran CH, Ohki T, Gargiulo NJ, III, Veith FJ, Stevens SL, Freeman MB, Goldman MH. Iliac Artery Stenting in Patients With Poor Distal Runoff: Influence of Concomitant Infrainguinal Arterial Reconstruction. Journal of Vascular Surgery. 2003; 38(3):479-484. (Guideline Ref ID 2117)	Wrong study design (observational)
Timaran CH, Prault TL, Stevens SL, Freeman MB, Goldman MH. Iliac Artery	Wrong study design

Stenting Versus Surgical Reconstruction for TASC (TransAtlantic Inter-Society Consensus) Type B and Type C Iliac Lesions. Journal of Vascular Surgery. 2003; 38(2):272-278. (Guideline Ref ID 2118)	(observational)
Tran T, Brown M, Lasala J. An Evidence-Based Approach to the Use of Rotational and Directional Coronary Atherectomy in the Era of Drug-Eluting Stents: When Does It Make Sense?. Catheterization and Cardiovascular Interventions. 2008; 72(5):650-662. (Guideline Ref ID 115)	Wrong study design (observational)
Trocciola SM, Chaer R, Dayal R, Lin SC, Kumar N, Rhee J, Pierce M, Ryer EJ, McKinsey J, Morrissey NJ, Bush HL, Kent KC, Faries PL, Woody JD. Comparison of Results in Endovascular Interventions for Infrainguinal Lesions: Claudication Versus Critical Limb Ischemia. American Surgeon. 2005; 71(6):474-480. (Guideline Ref ID 2131)	Wrong study design (observational)
Troeng T, Bergqvist D, Janzon L, Jendteg S, Lindgren B. The Choice of Strategy in the Treatment of Intermittent Claudication - A Decision Tree Approach. European Journal of Vascular Surgery. 1993; 7(4):438-443. (Guideline Ref ID 2132)	Wrong study design (observational)
Twine CP, Coulston J, Shandall A, McLain AD. Angioplasty Versus Stenting for Superficial Femoral Artery Lesions. Cochrane Database of Systematic Reviews. 2009; Issue 2:CD006767. (Guideline Ref ID 16317)	Cochrane review – cross checked for studies which match review protocol
van Rij AM, Packer SGK, Morrison N. A Randomized Controlled Study of Percutaneous Angioplasty for Claudicants With Femoro-Popliteal Disease. Journal of Cardiovascular Surgery. 1991; 32:34. (Guideline Ref ID 1141)	Wrong study design (commentary)
Wang FW, Uretsky BF, Freeman JL, Zhang D, Giordano SH, Goodwin JS. Survival Advantage in Medicare Patients Receiving Drug-Eluting Stents Compared With Bare Metal Stents: Real or Artefactual? Catheterization and Cardiovascular Interventions. 2008; 71(5):636-643. (Guideline Ref ID 116)	Wrong study design (observational)
Weichert W, Meents H, Abt K, Lieb H, Hach W, Krzywanek HJ, Breddin HK. Acetylsalicylic Acid--Reocclusion--Prophylaxis After Angioplasty (ARPA-Study). A Randomized Double-Blind Trial of Two Different Dosages of ASA in Patients With Peripheral Occlusive Arterial Disease. Vasa. 1994; 23(1):57-65. (Guideline Ref ID 1109)	Wrong comparison (compares drug doses)
Werk M, Langner S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U, Hosten N, Hamm B, Speck U, Ricke J. Inhibition of Restenosis in Femoropopliteal Arteries: Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial. Circulation. 2008; 118(13):1358-1365. (Guideline Ref ID 120)	Wrong comparison (compares types of angioplasty)
Whyman MR, Ruckley CV. Should Claudicants Receive Angioplasty or Just Exercise Training? Cardiovascular Surgery. 1998; 6(3):226-231. (Guideline Ref ID 623)	Wrong study design (review)
Whyman MR, Fowkes FGR, Kerracher EMG, Gillespie IN, Lee A, Housley E et al. Intermittent Claudication Is Not Improved by Percutaneous Transluminal Angioplasty - A Randomised Controlled Trial. 1996. (Guideline Ref ID 1082)	Paper not available
Willenberg T, Baumgartner I, Silvestro A, Do DD, Zwahlen M, Diehm N. An Angiographic Analysis of Atherosclerosis Progression in Below-the-Knee Arteries After Femoropopliteal Angioplasty in Claudicants. Journal of Endovascular Therapy. 2010; 17(1):39-45. (Guideline Ref ID 3057)	Wrong comparison (assessment)
Wilson S, Gelfand D, Jimenez J, Gordon I. Comparison of the Results of Percutaneous Transluminal Angioplasty and Stenting With Medical Treatment for Claudicants Who Have Superficial Femoral Artery Occlusive Disease. Vascular. 2006; 14(2):81-87. (Guideline Ref ID 266)	Wrong study design (observational)
Wilson SE, White GH, Wolf G, Cross AP. Proximal Percutaneous Balloon Angioplasty and Distal Bypass for Multilevel Arterial Occlusion. Veterans Administration Cooperative Study No. 199. Annals of Vascular Surgery. 1990; 4(4):351-355. (Guideline Ref ID 828)	Wrong study design (observational)

Wolosker N, Nakano L, Morales Anacleto MM, Puech-Leao P. Primary Utilization of Stents in Angioplasty of Superficial Femoral Artery. Vascular and Endovascular Surgery. 2003; 37(4):271-277. (Guideline Ref ID 2219)	Wrong study design (observational)
Woo EY, Fairman RM, Velazquez OC, Golden MA, Karmacharya J, Carpenter JP. Endovascular Therapy of Symptomatic Innominate-Subclavian Arterial Occlusive Lesions. Vascular and Endovascular Surgery. 2006; 40(1):27-33. (Guideline Ref ID 2224)	Wrong study design (observational)
Wyttenbach R, Gallino A, Alerci M, Mahler F, Cozzi L, Di Valentino M, Badimon JJ, Fuster V, Corti R. Effects of Percutaneous Transluminal Angioplasty and Endovascular Brachytherapy on Vascular Remodeling of Human Femoropopliteal Artery by Noninvasive Magnetic Resonance Imaging. Circulation. 2004; 110(9):1156-1161. (Guideline Ref ID 386)	Wrong comparison (brachytherapy)
Yip VSK. An Analysis of Risk Factors Associated With Failure of Below Knee Amputations. World Journal of Surgery. 2006; 30(6):1081-1087. (Guideline Ref ID 15976)	Wrong study design (observational)
Zeller T, Tiefenbacher C, Steinkamp HJ, Langhoff R, Wittenberg G, Schluter M, Buergelin K, Rastan A, Krumsdorf U, Sixt S, Schulte CL, Tubler T, Krankenberg H. Nitinol Stent Implantation in TASC A and B Superficial Femoral Artery Lesions: the Femoral Artery Conformexx Trial (FACT). Journal of Endovascular Therapy. 2008; 15(4):390-398. (Guideline Ref ID 101)	Wrong study design (observational)
Zeller T. Current State of Endovascular Treatment of Femoro-Popliteal Artery Disease. Vascular Medicine. 2007; 12(3):223-234. (Guideline Ref ID 2247)	Wrong study design (review)
Zorger N, Manke C, Lenhart M, Finkenzeller T, Djavidani B, Feuerbach S, Link J. Peripheral Arterial Balloon Angioplasty: Effect of Short Versus Long Balloon Inflation Times on the Morphologic Results. Journal of Vascular and Interventional Radiology. 2002; 13(4):355-359. (Guideline Ref ID 487)	Wrong comparison (compares types of angioplasty)

E.7 Management of ischaemic pain in critical limb ischaemia

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?

Excluded n = 18

Study excluded	Reason
Aurilio B, Pace MC, and Passavanti MB. Transdermal buprenorphine combined with spinal morphine and naropine for pain relief in chronic peripheral vasculopathy. Minerva Anestesiologica. 2005, 71: 445-9. (Guideline Ref ID 16077)	Wrong comparator (local anaesthetic)
Aurilio C, Pace MC, Passavanti MB, Paladini A, Maisto M, Iannotti M, Pota V, D'amora E, Sansone P, Barbarisi M. Treatment of ischemic pain in patients suffering from peripheral vasculopathy with transdermal buprenorphine plus epidural morphine with ropivacaine vs. epidural morphine with ropivacaine. Pain Pract. 2009;9(2):105-14. (Guideline Ref ID 16078)	Wrong comparator (local anaesthetic)
Bapat AR, Kshirsagar NA, Padmashree RB, Bhagtand KC, Bapat RD, Parulkar GB. Improvement in peripheral perfusion in peripheral vascular disease cases with epidural morphine. J Postgrad Med 1980;26:246. (Guideline Ref ID 48)	Wrong comparators (epidural morphine versus epidural placebo or intravenous morphine)
Belch JJ, McKay A, McArdle B, Leiberman P, Pollock JG, Lowe GD, Forbes CD, Prentice CR. Epoprostenol (prostacyclin) and severe arterial disease. A double-blind trial. Lancet. 1983;1(8320):315-7. (Guideline Ref ID 162)	Wrong comparators (epoprostenol, placebo)
Caputi CA, De Carolis G, Fogliardi A, Busca G. Clinical and instrumental evaluation	Wrong comparators

Study excluded	Reason
of IV regional treatment with sympatholytic drugs (guanethidine; labetalol) in peripheral vascular disease. A preliminary study. Clinical Trials Journal. 1985, 122(3):257-62. (Guideline Ref ID 160)	(guanethidine, labetalol)
Cross FW, Cotton LT. Chemical lumbar sympathectomy for ischemic rest pain. A randomized, prospective controlled clinical trial. Am J Surg. 1985;150(3):341-5. (Guideline Ref ID 1636)	Wrong comparator (bupivacaine only) and no control data after 7 days
Dorresteijn JA, Kriegsman DM, Valk GD. Complex interventions for preventing diabetic foot ulceration. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007610. (Guideline Ref ID 16079)	Wrong population
Haeger K, Lundskog O. Lumbar chemical sympathectomy in the treatment of peripheral arterial disease of the legs. Vasc Surg. 1967;1(3):162-70. (Guideline Ref ID 54)	No comparator
Holiday FA, Barendregt WB, Slappendel R, Crul BJ, Buskens FG, van der Vliet JA. Lumbar sympathectomy in critical limb ischaemia: surgical, chemical or not at all? Cardiovasc Surg. 1999;7(2):200-2. (Guideline Ref ID 16080)	Wrong comparator (surgical sympathectomy)
Huber KH, Rexroth W, Werle E, Koeth T, Weicker H, Hild R. Sympathetic neuronal activity in diabetic and non-diabetic subjects with peripheral arterial occlusive disease. Klin Wochenschr. 1991;69(6):233-8. (Guideline Ref ID 16081)	No comparator
Keskinbora K, Aydinli I. Perineural morphine in patients with chronic ischemic lower extremity pain: efficacy and long-term results. J Anesth. 2009;23(1):11-8. (Guideline Ref ID 16082)	Wrong follow up (follow-up intervals <7 days for relevant outcomes)
Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. Pain. 2002;97(3):275-81. (Guideline Ref ID 124)	Wrong comparator (ketamine)
Persson J, Hasselström J, Wiklund B, Heller A, Svensson JO, Gustafsson LL. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Acta Anaesthesiol Scand. 1998;42(7):750-8. (Guideline Ref ID 16083)	Wrong comparator (ketamine)
Samolsky Dekel BG, Melotti RM, Gargiulo M, Freyrie A, Stella A, Di Nino G. Pain management in peripheral arterial obstructive disease: oral slow-release oxycodone versus epidural l-bupivacaine. Eur J Vasc Endovasc Surg. 2010;39(6):774-8. (Guideline Ref ID 16085)	Wrong study design (retrospective study)
Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. Health Technol Assess. 2009;13(17):iii, ix-x, 1-154. (Guideline Ref ID 68)	Wrong comparator (spinal cord stimulation)
Spincemaille GH, Klomp HM, Steyerberg EW, Habbema JD. Pain and quality of life in patients with critical limb ischaemia: results of a randomized controlled multicentre study on the effect of spinal cord stimulation. ESES study group. Eur J Pain. 2000;4(2):173-84. (Guideline Ref ID 879)	Wrong comparator (spinal cord stimulation)
Vulpio C, Borzone A, Iannace C, Agnes S, Mascaro A, De Santis M, Mingrone G, Flore R, Pola P, Castagneto M, Salgarello G. Lumbar chemical sympathectomy in end stage of arterial disease: early and late results. Angiology. 1989;40(11):948-52. (Guideline Ref ID 151)	No comparator
Walsh JA, Glynn CJ, Cousins MJ, Basedow RW. Blood flow, sympathetic activity and pain relief following lumbar sympathetic blockade or surgical sympathectomy. Anaesth Intensive Care. 1985;13(1):18-24. (Guideline Ref ID 16086)	Wrong comparator (surgical sympathectomy)

E.8 Major amputation for critical limb ischaemia

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?

Excluded n = 12

Study excluded	Reason
Buzato MA, Tribulatto EC, Costa SM, Zorn WG, van BB. Major Amputations of the Lower Leg. The Patients Two Years Later. Acta Chirurgica Belgica. 2002; 102(4):248-252. (Guideline Ref ID 15963)	Wrong outcomes
Collin C, Wade DT, Cochrane GM. Functional Outcome of Lowe Limb Amputees With Peripheral Vascular Disease. Clinical Rehabilitation. 1992; 6(1):13-21. (Guideline Ref ID 16315)	Wrong objective (evaluating rehabilitation)
De Godoy JMP. Quality of Life After Amputation. Psychology, Health and Medicine. 2002; 7(4):397-400. (Guideline Ref ID 16099)	Wrong outcomes (does not give before and after QoL scores)
Dillingham TR, Pezzin LE, Shore AD. Reamputation, Mortality, and Health Care Costs Among Persons With Dysvascular Lower-Limb Amputations. Archives of Physical Medicine and Rehabilitation. 2005; 86(3):480-486. (Guideline Ref ID 16314)	Wrong outcomes
Pell JP, Donnan PT, Fowkes FG, Ruckley CV. Quality of Life Following Lower Limb Amputation for Peripheral Arterial Disease. European Journal of Vascular Surgery. 1993; 7(4):448-451. (Guideline Ref ID 16312)	Wrong comparison (compares to healthy controls not before and after QoL scores)
Powell TW, Burnham SJ, Johnson G, Jr. Second Leg Ischemia. Lower Extremity Bypass Versus Amputation in Patients With Contralateral Lower Extremity Amputation. American Surgeon. 1984; 50(11):577-580. (Guideline Ref ID 16270)	Wrong comparison (compares bypass in patients who had prior amputation and those who had no amputation)
Reed AB, Delvecchio C, Giglia JS. Major Lower Extremity Amputation After Multiple Revascularizations: Was It Worth It? Annals of Vascular Surgery. 2008; 22(3):335-340. (Guideline Ref ID 16271)	Wrong outcomes
Remes L, Isoaho R, Vahlberg T, Viitanen M, Koskenvuo M, Rautava P. Quality of Life Three Years After Major Lower Extremity Amputation Due to Peripheral Arterial Disease. Aging Clinical and Experimental Research. 2010; 22(5-6):395-405. (Guideline Ref ID 16310)	Wrong outcomes (does not give before and after QoL scores)
Schoppen T, Boonstra A, Groothoff JW, de Vries J, Goeken LN, Eisma WH. Physical, Mental, and Social Predictors of Functional Outcome in Unilateral Lower-Limb Amputees. Archives of Physical Medicine and Rehabilitation. 2003; 84(6):803-811. (Guideline Ref ID 254)	Wrong outcomes
Sprengers RW, Teraa M, Moll FL, de Wit GA, van der Graaf Y, Verhaar MC, JUVENTAS Study Group, SMART Study Group. Quality of Life in Patients With No-Option Critical Limb Ischemia Underlines the Need for New Effective Treatment. Journal of Vascular Surgery. 2010; 52(4):843-849. (Guideline Ref ID 16095)	Wrong intervention
Thompson DM, Haran D. Living With an Amputation: What It Means for Patients and Their Helpers. International Journal of Rehabilitation Research Internationale Zeitschrift Fur Rehabilitationsforschung Revue Internationale De Recherches De Readaptation. 1984; 7(3):283-292. (Guideline Ref ID 522)	Wrong outcomes
Thompson MM, Sayers RD, Reid A, Underwood MJ, Bell PR. Quality of Life Following Infragenicular Bypass and Lower Limb Amputation. European Journal of Vascular & Endovascular Surgery. 1995; 9(3):310-313. (Guideline Ref ID 16272)	Wrong outcomes (does not give before and after QoL scores)

F Appendix F: Exclusion lists – economic evidence

F.1 Information requirements

No cost-effectiveness evidence was identified for this question.

F.2 Diagnosis of peripheral arterial disease

No cost-effectiveness evidence was identified for this question.

F.3 Imaging for revascularisation

Study	Reason
Berry 2002. The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review. Health Technology Assessment. 6(7).	This HTA has been replaced by the updated Collins 2007
Coffi 2008. Cost-effectiveness of identifying aortoiliac and femoropopliteal arterial disease with angiography and duplex scanning. European Journal of Radiology. 66; 142-148.	Does not include QALYs as a measure of effectiveness.
Hay 2009. Cost impact of diagnostic imaging for lower extremity peripheral vascular occlusive disease. Value in Health 12(2); 262 - 266	Retrospective cost analysis rather than cost-effectiveness analysis.
Ouwendijk 2008. Multicentre randomised controlled trial of the cost and effects of noninvasive diagnostic imaging in patients with peripheral arterial disease: the DIPAD trail. American Journal of Roenterology 190(5); 1349 - 1357	Results not presented in such a way as to allow calculation of incremental cost and effects.
Schwartz 2009. Arterial duplex ultrasound is the most cost-effective, non-invasive diagnostic imaging modality before treatment of lower extremity arterial occlusive disease. Journal for Vascular Ultrasound. 33(2); 75-79	Retrospective cost analysis rather than cost-effectiveness analysis.
Vahl 2008. Contrast enhanced magnetic resonance angiography versus digital subtraction angiography for treatment planning in patients with peripheral arterial disease: A randomised controlled diagnostic trial. European Journal of Endovascular Surgery 35 (5);514 - 521	Includes costs but no health-related quality of life outcomes.

F.4 Management of intermittent claudication

F.4.1 Supervised exercise compared to unsupervised exercise

Study	Reason
Ambrosetti 2004. Economic evaluation of a short-course intensive rehabilitation program in patients with intermittent claudication. International Angiology. 23(2); 108-113	Wrong intervention/comparison.
Kakkos 2005. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomised controlled trial. European Journal of Vascular and Endovascular Surgery. 30(2)164-175.	Brief narrative about cost-effectiveness, but no costs or QALYs provided.
Roine 2009. Cost-effectiveness of interventions based on physical exercise in the treatment of various diseases: a systematic literature review. International Journal of Technology Assessment in Health Care. 25(4); 427-454.	No IC/PAD population.
Spronk 2008. Cost-effectiveness of new cardiac and vascular rehabilitation strategies for patients with coronary artery disease. PLoS ONE. 3(12).	Wrong intervention/comparison

F.412 Naftidrofuryl oxalate

2 No cost-effectiveness evidence was identified for this question.

F.433 Comparisons of exercise, best medical treatment, angioplasty and bypass surgery

Study	Reason
Chong 2000. Exercise therapy or angioplasty? A summation analysis. European Journal of Vascular and Endovascular Surgery. 20(1); 4-12	Review
Fry 2011. Comparative effectiveness and efficiency in peripheral vascular surgery. The American Journal of Surgery 201; 363-368.	Retrospective cost analysis. No utility data.
Koerkamp 2010. Value of information analyses of economic randomized controlled trials: The treatment of intermittent claudication. Value in Health. 13(2); 242-250	Value of information analysis of included study (Spronk 2008)
Medical Advisory Secretariat 2010. Stenting for peripheral arterial disease of the lower extremities. Ontario Health Technology Assessment Series. 10(18)	Review of economic analyses comparing angioplasty and angioplasty with selective stenting.
Mittmann 2005. Economic evaluation of drug eluting stents. Canadian Coordinating Office for Health Technology Assessment	Coronary stents.
O'Brien-Irr 2008. Lower extremity endovascular interventions: can we improve cost-efficiency? Journal of Vascular Surgery 47; 982-7	Retrospective cost analysis. No utility or comparative evaluation.
Stoner 2008. Cost per day of patency: Understanding the impact of patency and reintervention in a sustainable model of healthcare. Journal of Vascular Surgery 41; 1489-96	Not a comparative evaluation.
Treesak 2004. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. Vascular Medicine. 9(4); 279-285	No QALYs; cost per metre.
Whyman 1998. Should claudicants receive angioplasty or just exercise training? Cardiovascular Surgery. 6(3); 226-231	Review

F.444 Bare metal compared to drug eluting stents

5 No cost-effectiveness evidence was identified for this question.

F.455 Autologous vein compared to prosthetic bypass

7 No cost-effectiveness evidence was identified for this question.

F.5 Management of critical limb ischaemia

Study	Reason
Allie 2009. 24-carat gold, 14-carat gold, or platinum standards in the treatment of CLI: Bypass surgery or endovascular intervention? Journal of Endovascular Therapy 16(Suppl I):I134-I146	Review. No cost or quality of life data.
Balland 1998. Aortoiliac stent deployment versus surgical reconstruction: analysis of outcome and cost. Journal of Vascular Surgery 28; 94-103	Based on a non-randomised study. No QALYs. Mean total hospital costs per limb (rather than per patient) were reported
Brothers 2007. Prospective decision analysis for peripheral vascular disease	This study was designed

predicts future quality of life. Journal of Vascular Surgery 46; 701-8	to measure the relationship between patient's measured utilities following intervention and model predictions. Although the model reported contains all of our interventions of interest, the model inputs and results are not reported.
Brothers 2004. Prospective decision analysis modelling indicates that clinical decisions in vascular surgery often fail to maximize patient expected utility. Journal of Surgical Research 120; 278-87	This study was designed to measure the relationship between surgeon's decisions and model predictions. Although the model reported contains all of our interventions of interest, the model inputs and results are not reported.
Ebaugh 2008. Comparison of costs of staged versus simultaneous lower extremity arterial hybrid procedures. The American Journal of Surgery 196; 634-40	Wrong comparison (staged vs. simultaneous bypass).
Haustein 1997. State of the art – treatment fo peripheral occlusive arterial disease (POAD) with drugs vs. vascular reconstruction or amputation. International Journal of Clinical Pharmacology and Therapeutics 35(7);266-274	Non-systematic review; no costs.
Muradin 2001. Cost and patency rate targets for the development of endovascular devices to treat femoropopliteal arterial disease. Radiology 218;264-9	This a threshold analysis of the cost-effectiveness of a hypothetical endovascular device based on the model by Hunick et al (1995) and not a comparative evaluation of our interventions of interest.
Nelson 2001. Impact of endovascular-assisted in situ staphenous vein bypass technique on hospital costs. Annals of Vascular Surgery 15; 653-60	Wrong comparison (in situ vs. conventional bypass)
Nolan 2007. The treatment of disabling intermittent claudication in patients with superficial femoral artery occlusive disease – Decision analysis. Journal of Vascular Surgery 45; 1179-84	This model included QALYs but not costs. QALYs determined using Nottingham Health Profile.
O'Brien-Irr 2008. Lower extremity endovascular interventions: can we improve cost-efficiency? Journal of Vascular Surgery 47; 982-7	This study did not compare the interventions of interest and was not relevant to the UK setting.
Piano 1998. Assessing outcomes, costs, and benefits of emerging technology for minimally invasive staphenous vein in situ distal arterial bypasses. Archives of Surgery 133; 613-8	Wong comparison (in situ vs conventional bypass)
Sultan 2009. Five year Irish trial of CLI patient with TASC II Type C/D lesions undergoing subintimal angioplasty or bypass surgery based on plaque	Based on observational data, QALYs evaluated

echolucency. Journal of Endovascular Therapy 16(3); 270 -283	using Time Spent Without Symptoms of Disease and Toxicity of Treatment (TWiST).
Werneck 2009. Tibial angioplasty for limb salvage in high risk patients and cost analysis .Annals of Vascular Surgery 23; 554-9	Population subgroup of patients with end-stage renal disease. Very short time horizon (mean 7.7 months), based on a retrospective analysis.

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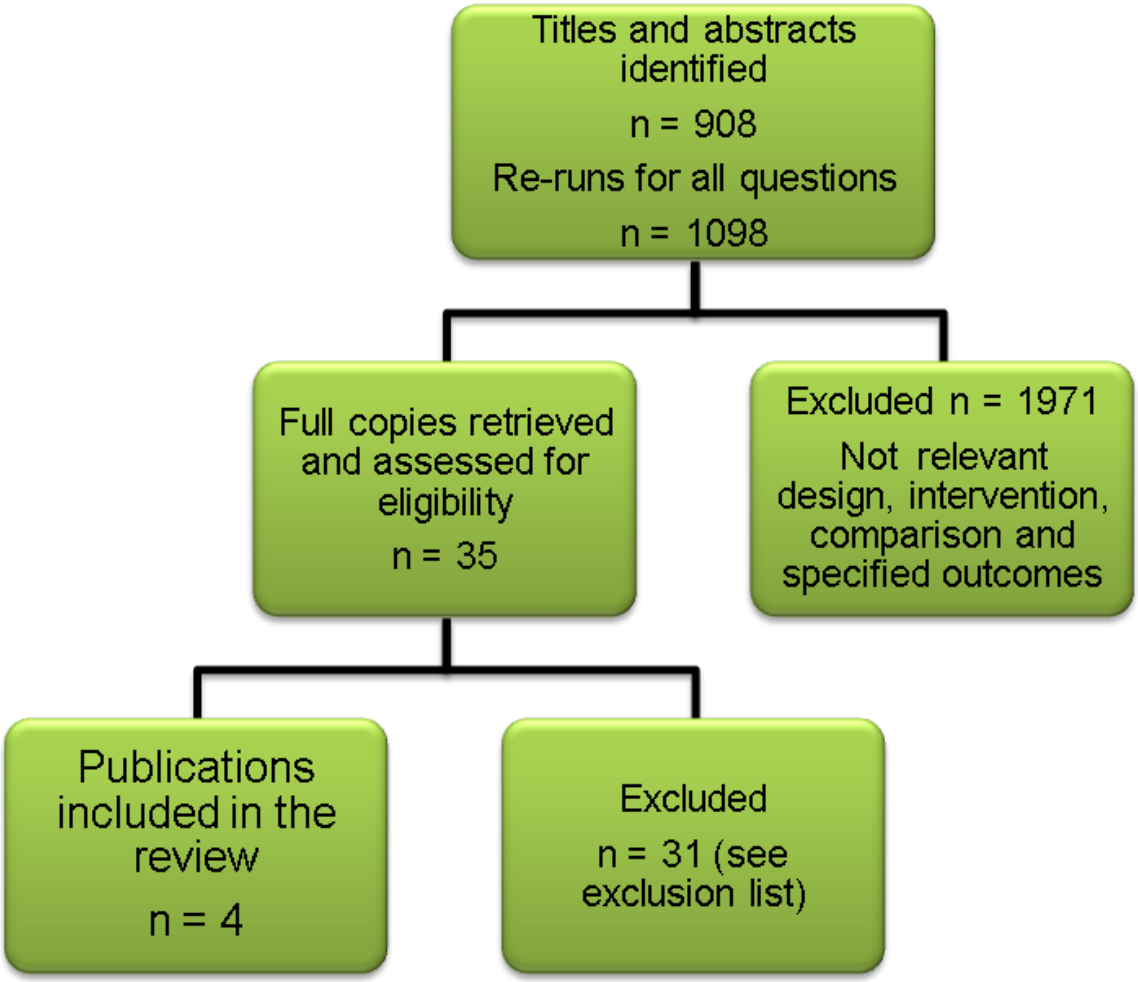
Appendix G: Clinical evidence - study selection flowcharts

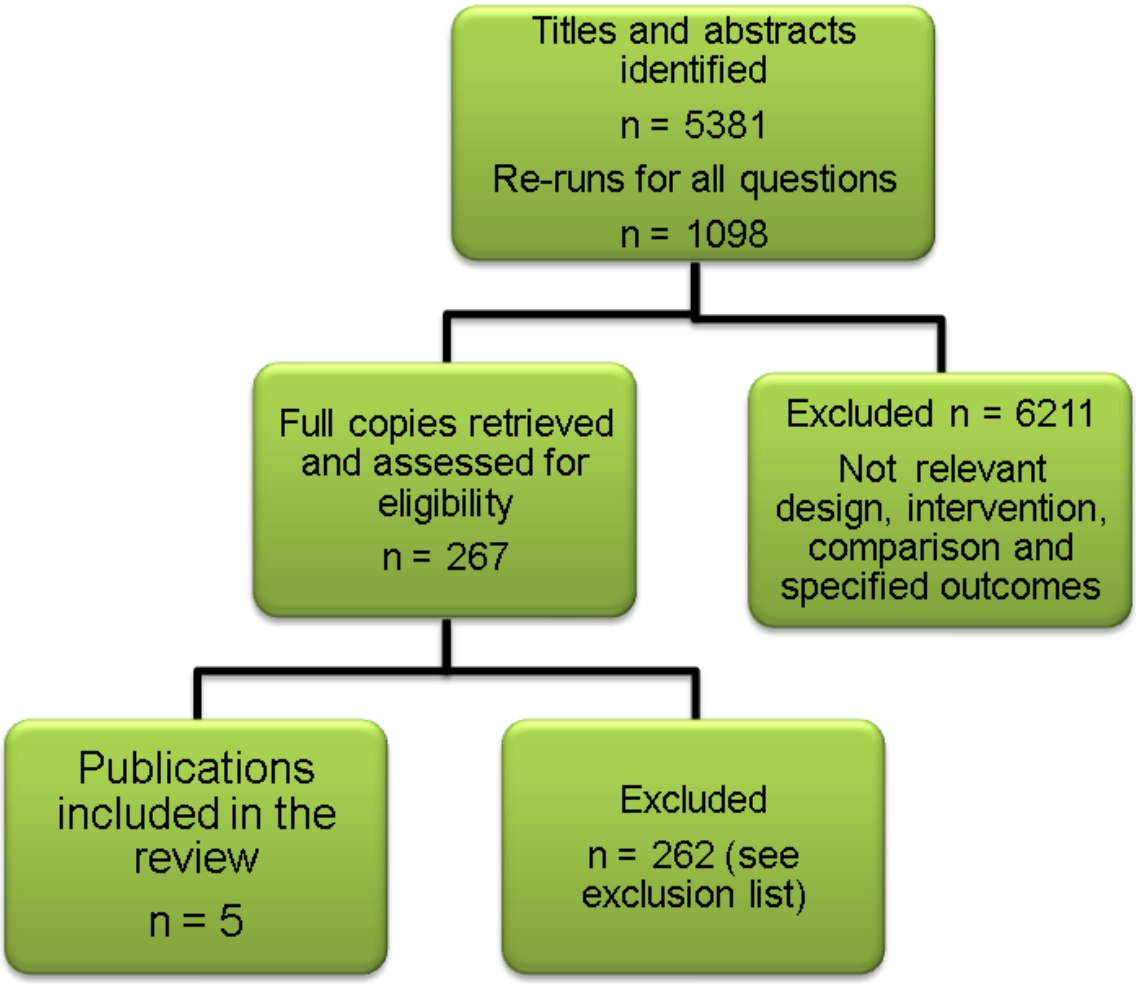
G.1 Information requirements

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

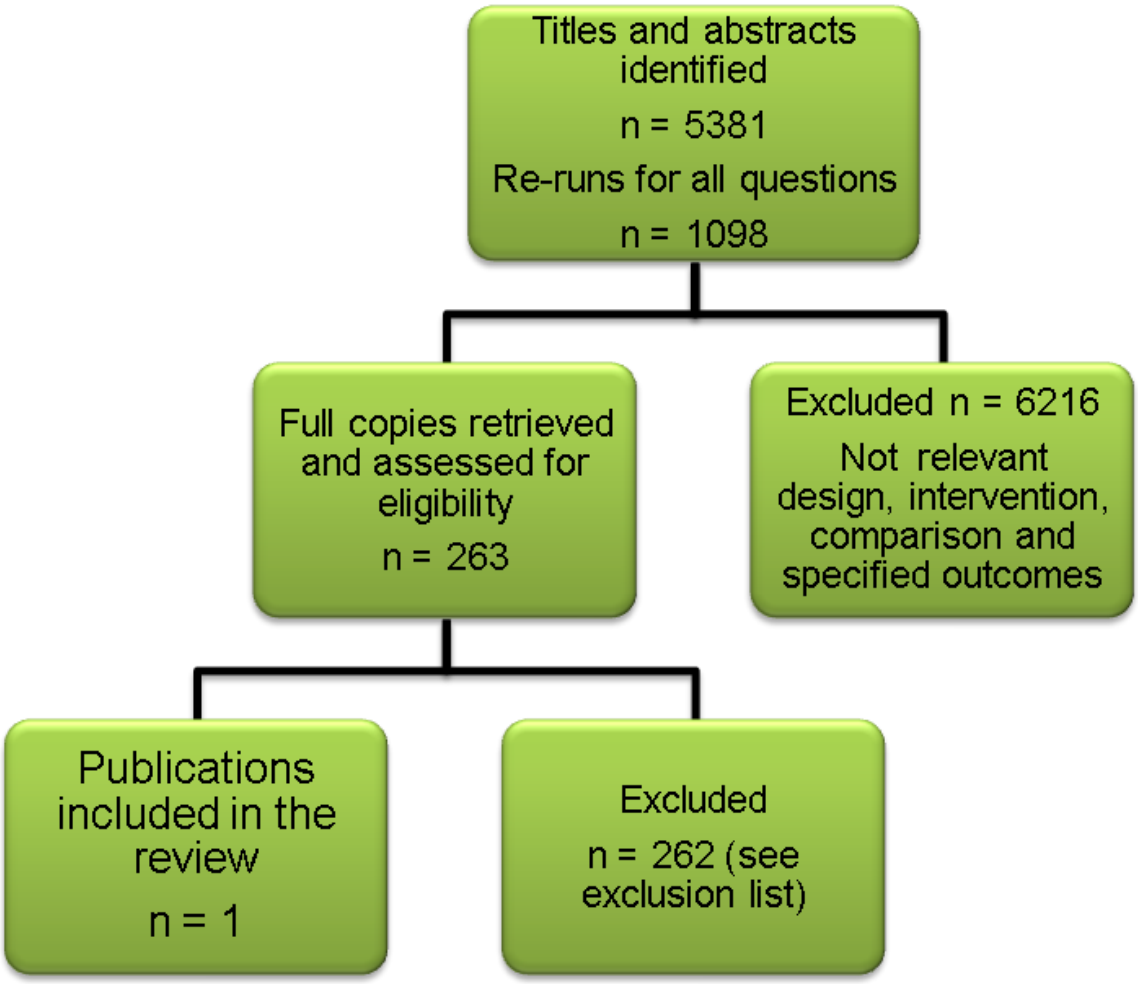


G.2 Diagnosis of PAD

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

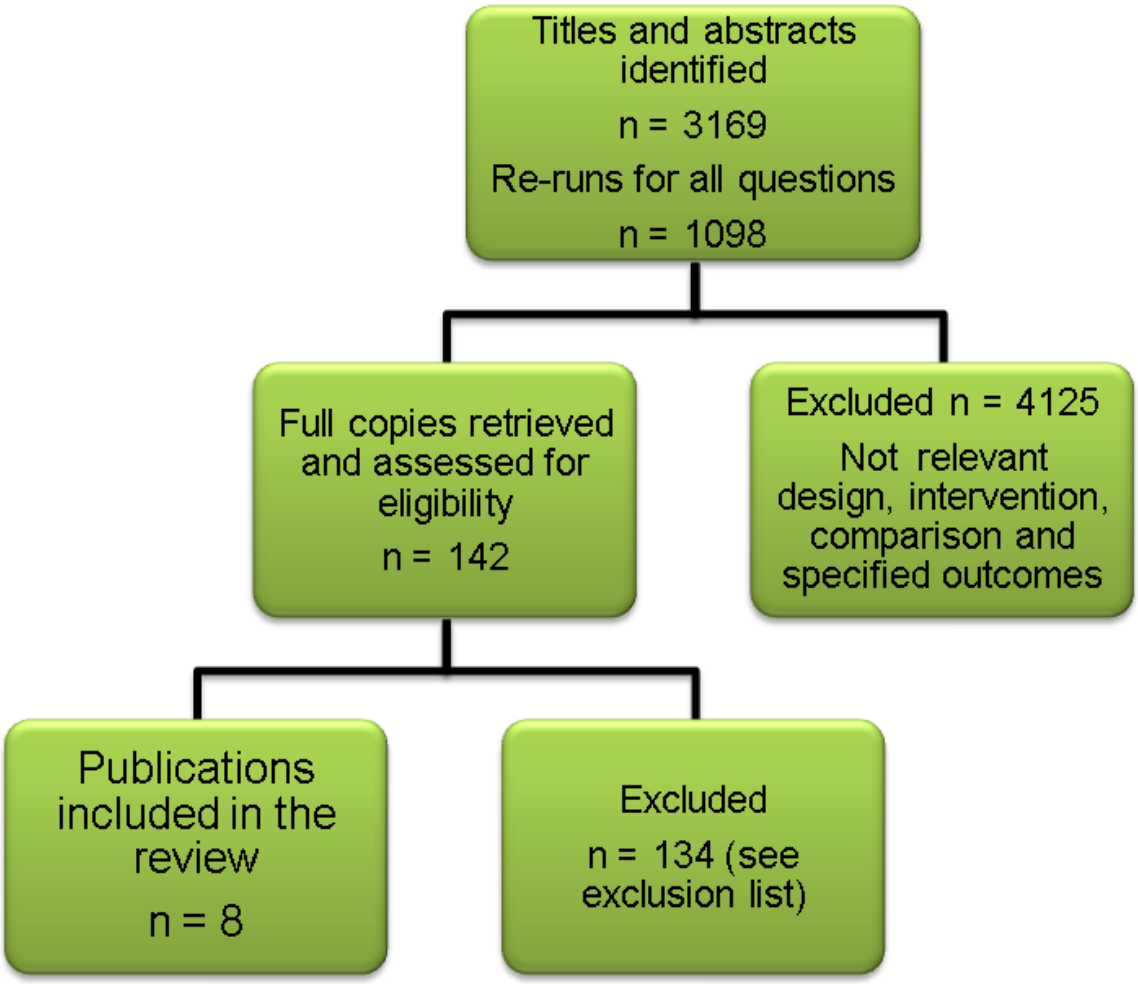


In people with suspected PAD undergoing ABPI, do different methods result in different diagnostic accuracy?



G.3 Imaging for revascularisation

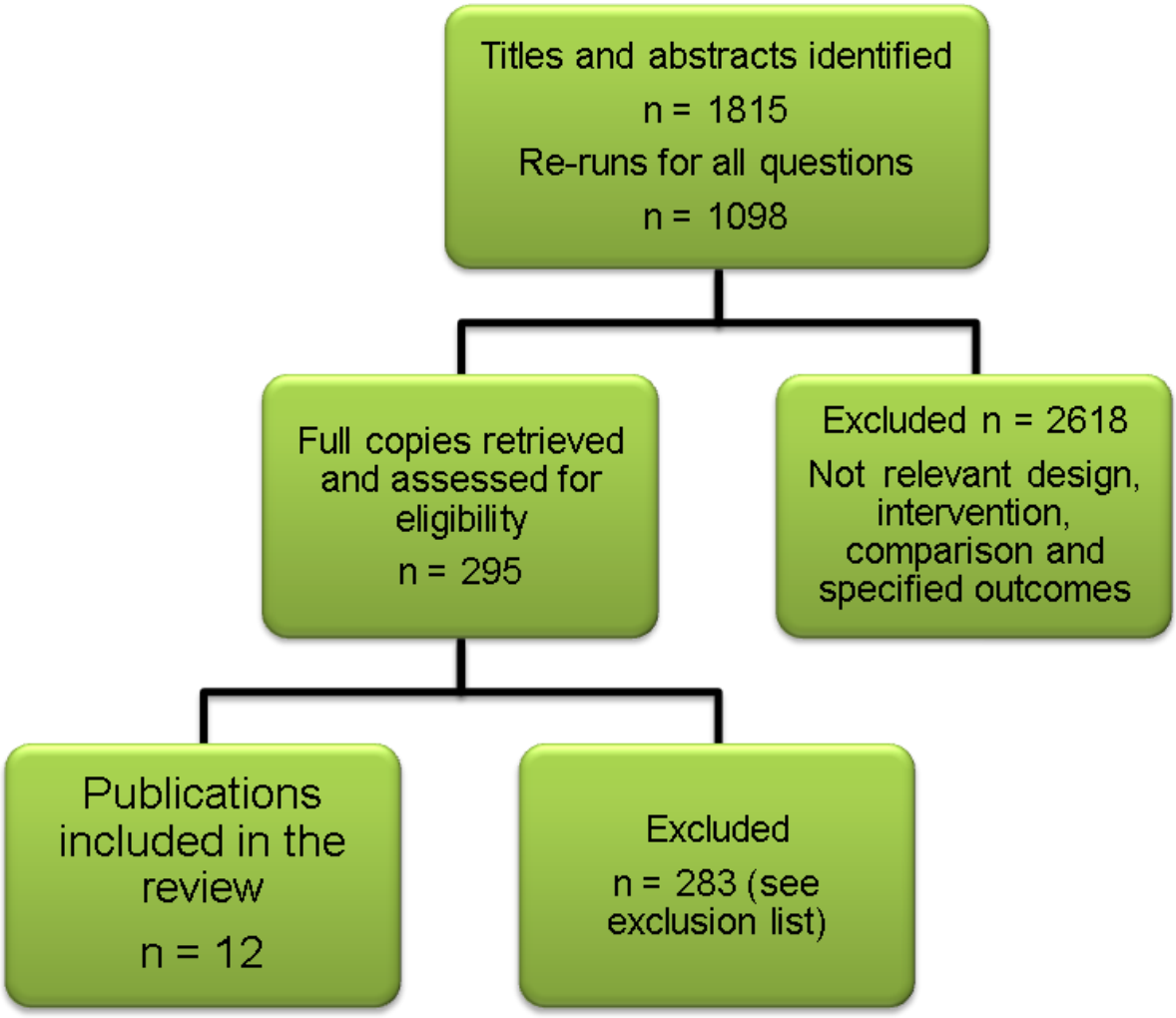
What is the most clinical and cost effective method of assessment of PAD (intermittent claudication and critical limb ischemia)?



G.4 Intermittent claudication

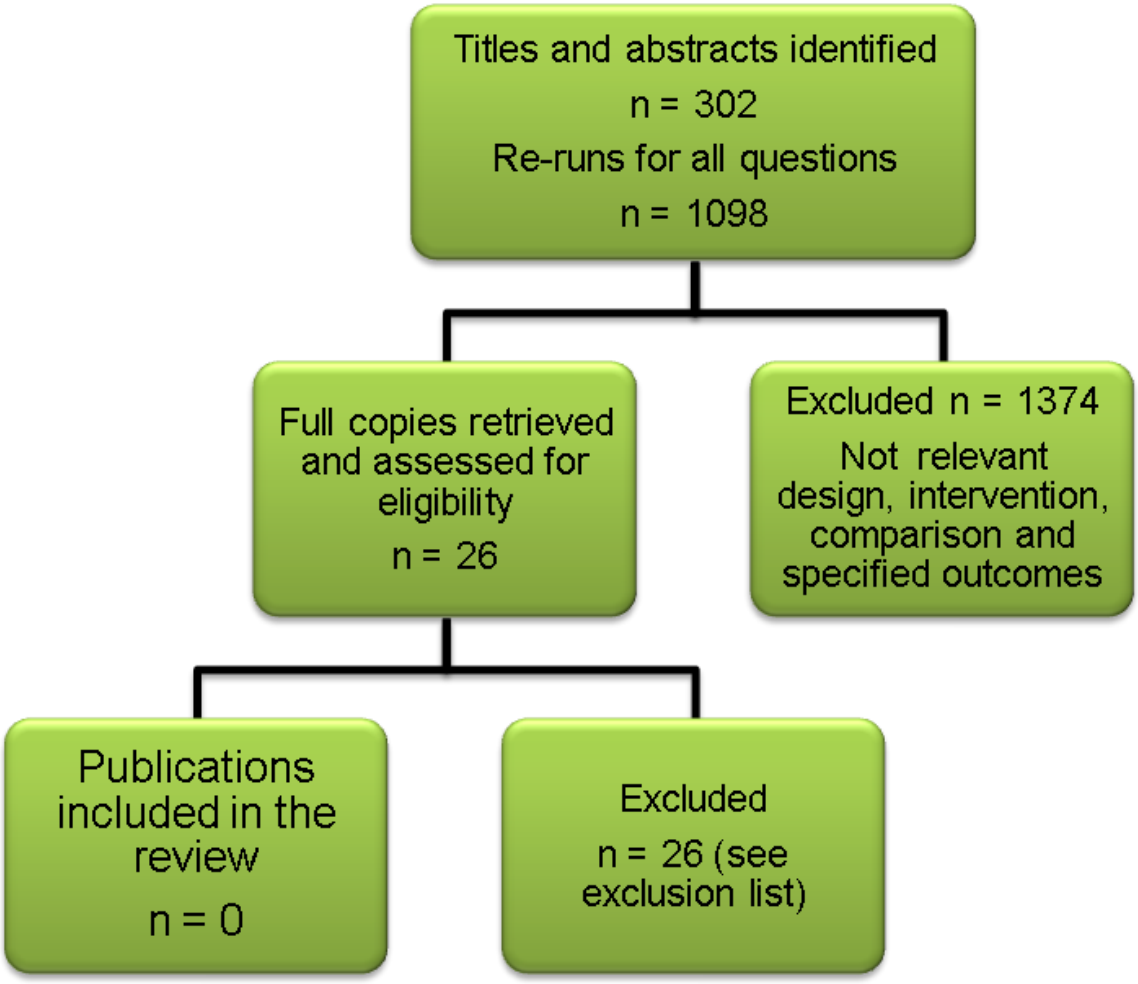
G.4.1 Supervised exercise compared to unsupervised exercise

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



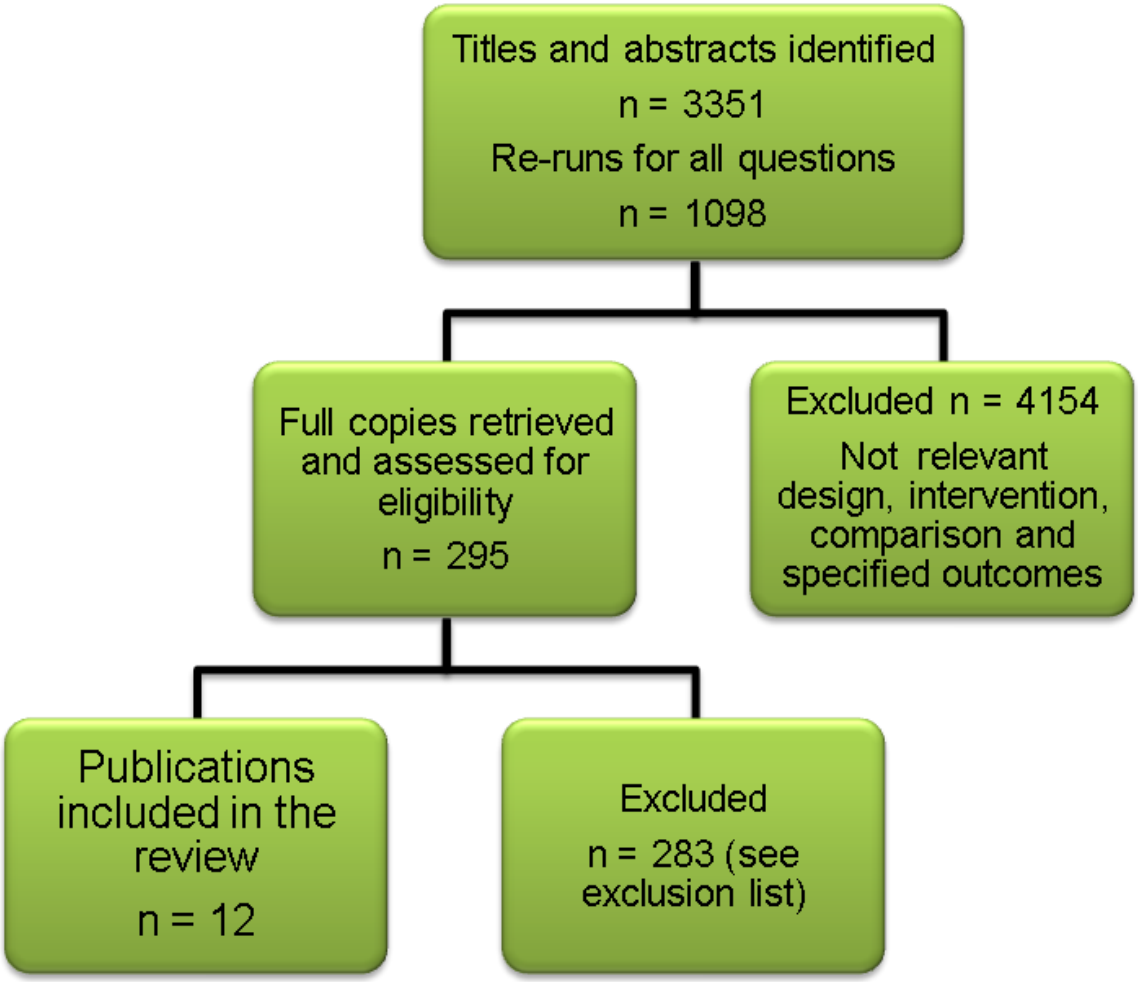
G.412 Naftidrofuryl oxalate

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?



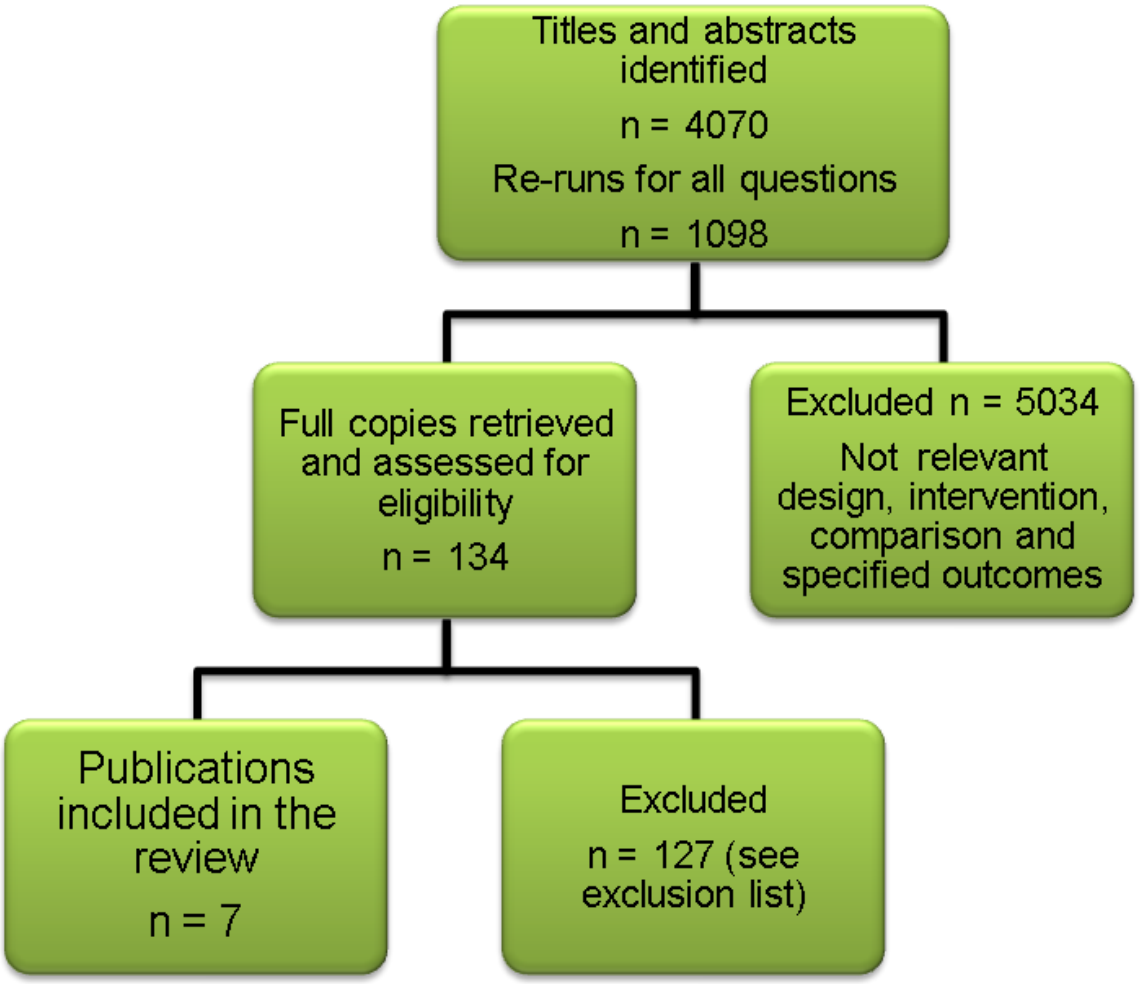
G.413 Comparisons of exercise, best medical treatment, angioplasty and bypass surgery

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 PAD in adults with intermittent claudication?



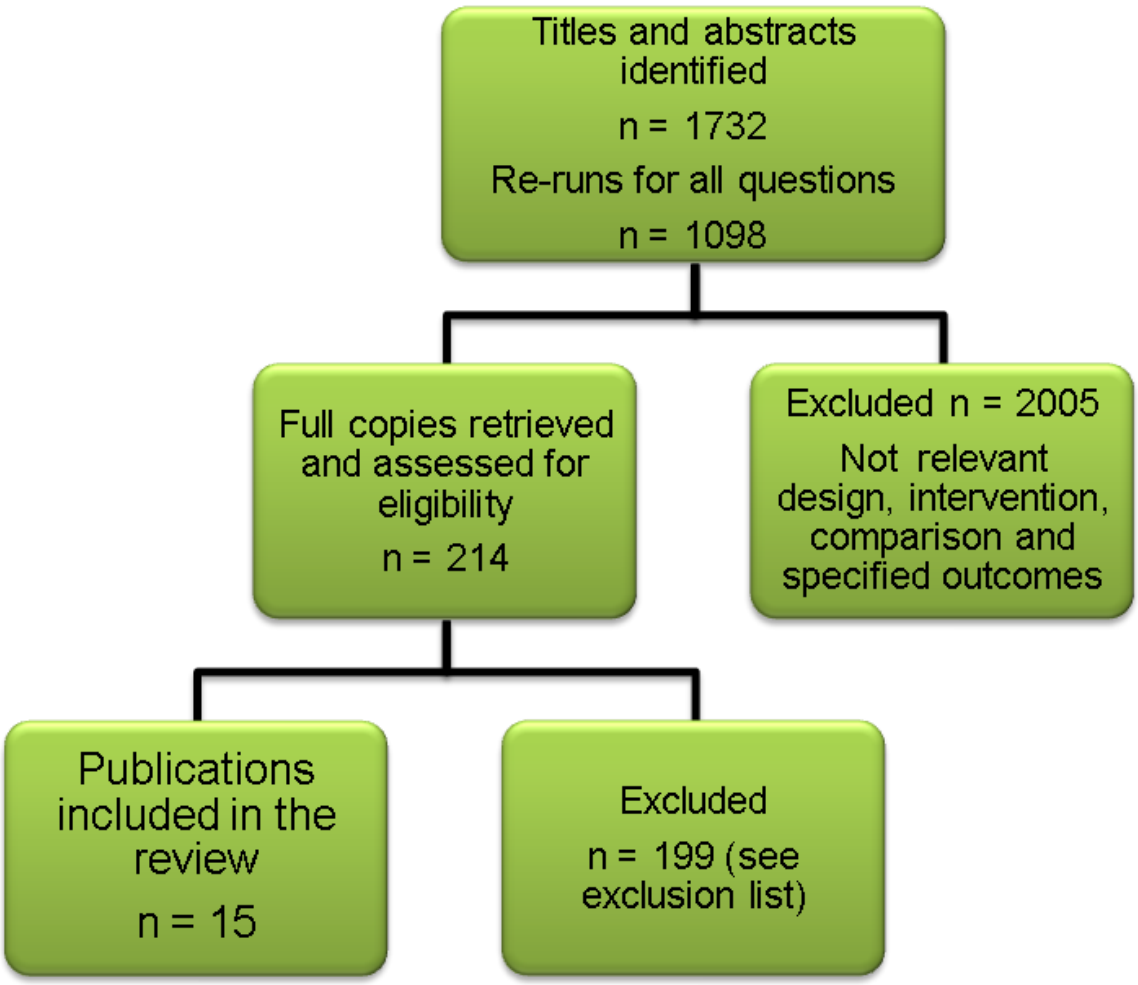
G.414 Angioplasty compared to bypass surgery

What is the clinical and cost effectiveness of angioplasty compared to bypass surgery for the treatment of PAD in adults with intermittent claudication?



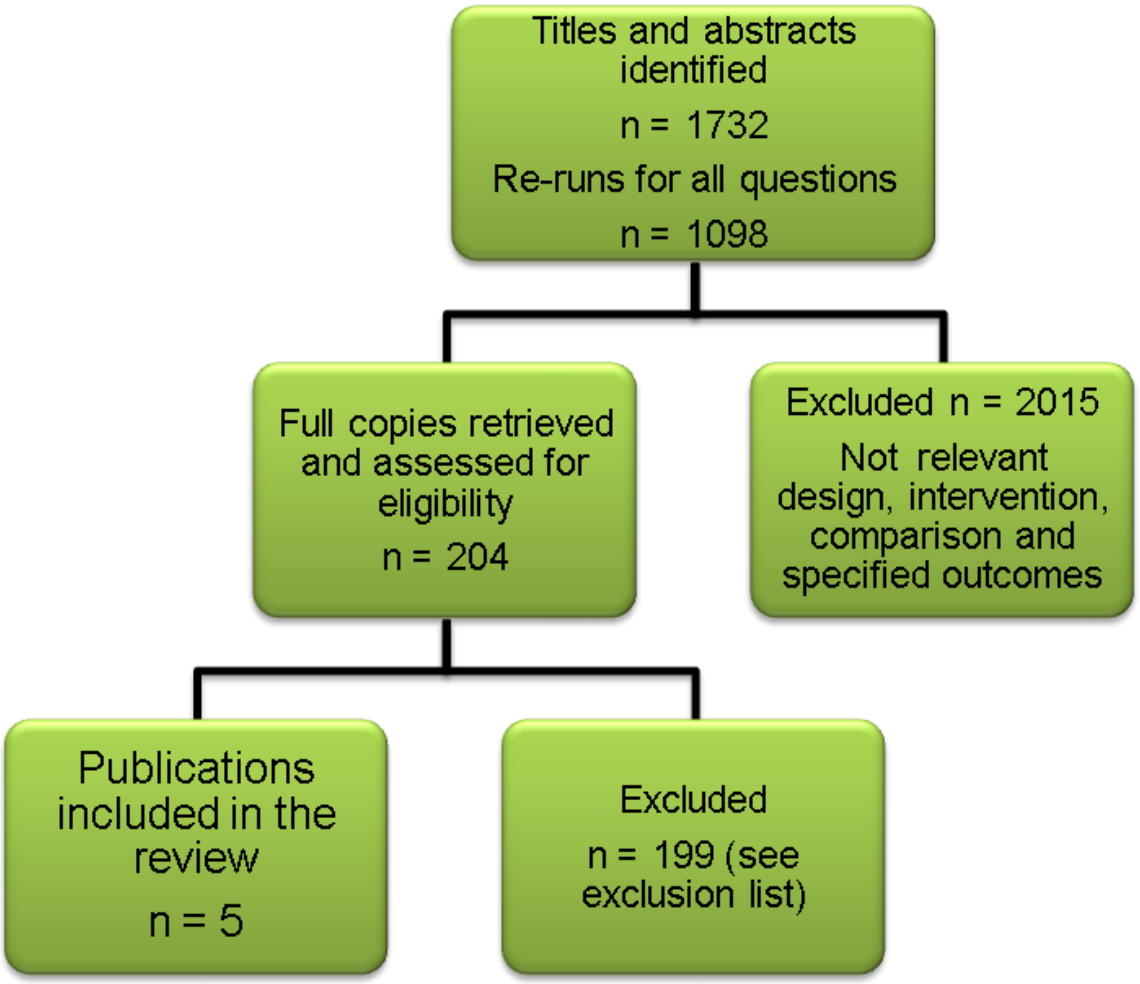
G.415 Angioplasty with selective stent placement compared primary stent placement

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?



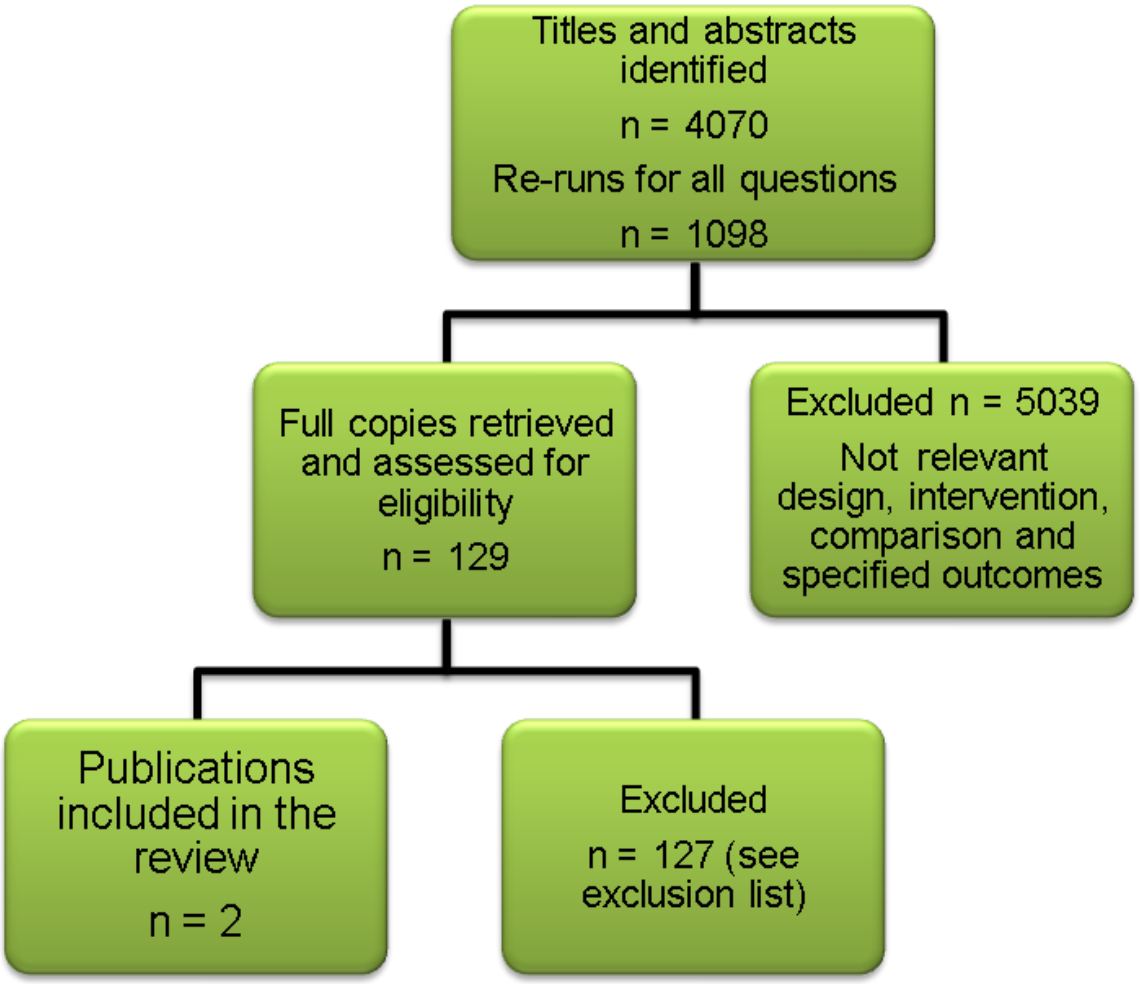
G.416 Bare metal compared to drug eluting stents

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?



G.417 Autologous vein compared prosthetic bypass

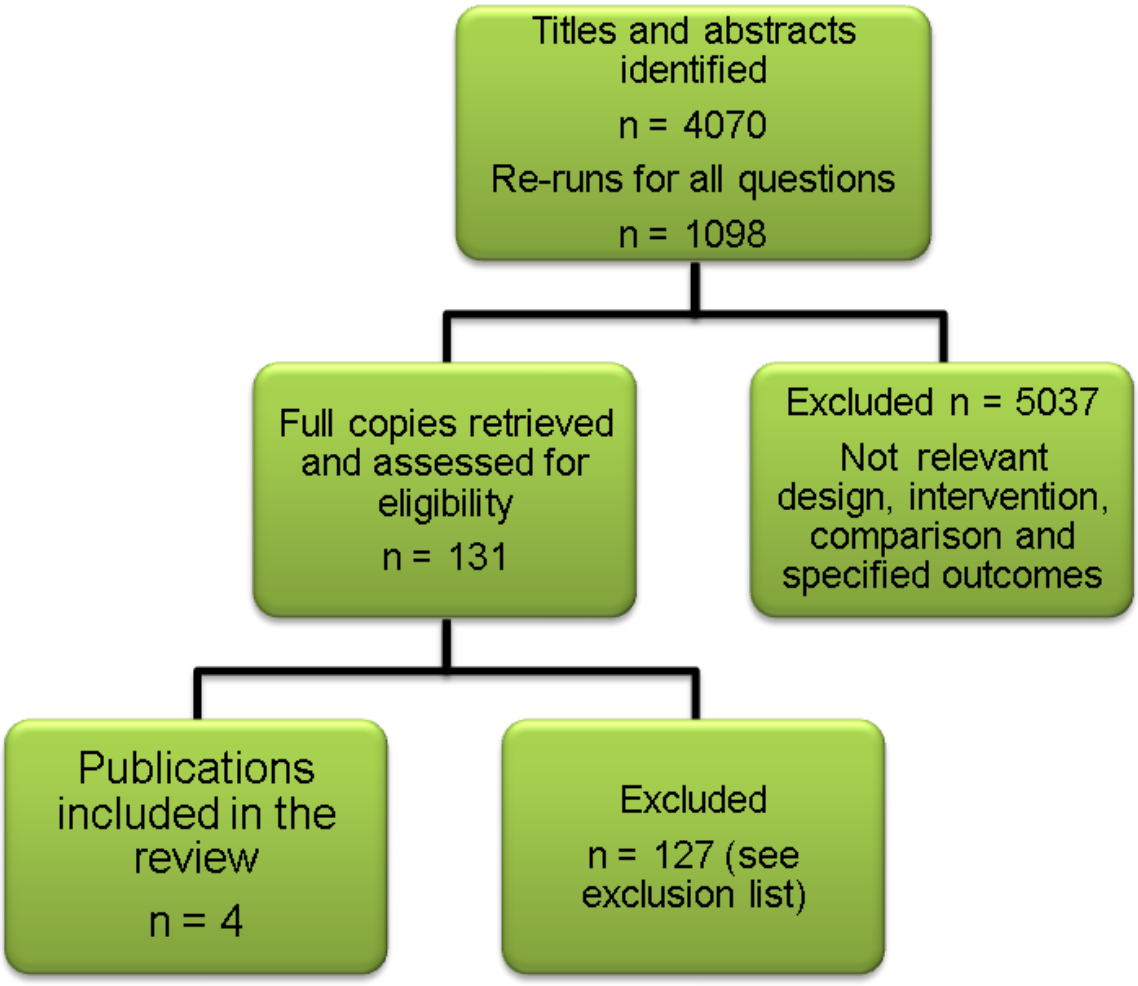
What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass for the treatment of PAD in adults with intermittent claudication?



G.5 Management of critical limb ischaemia

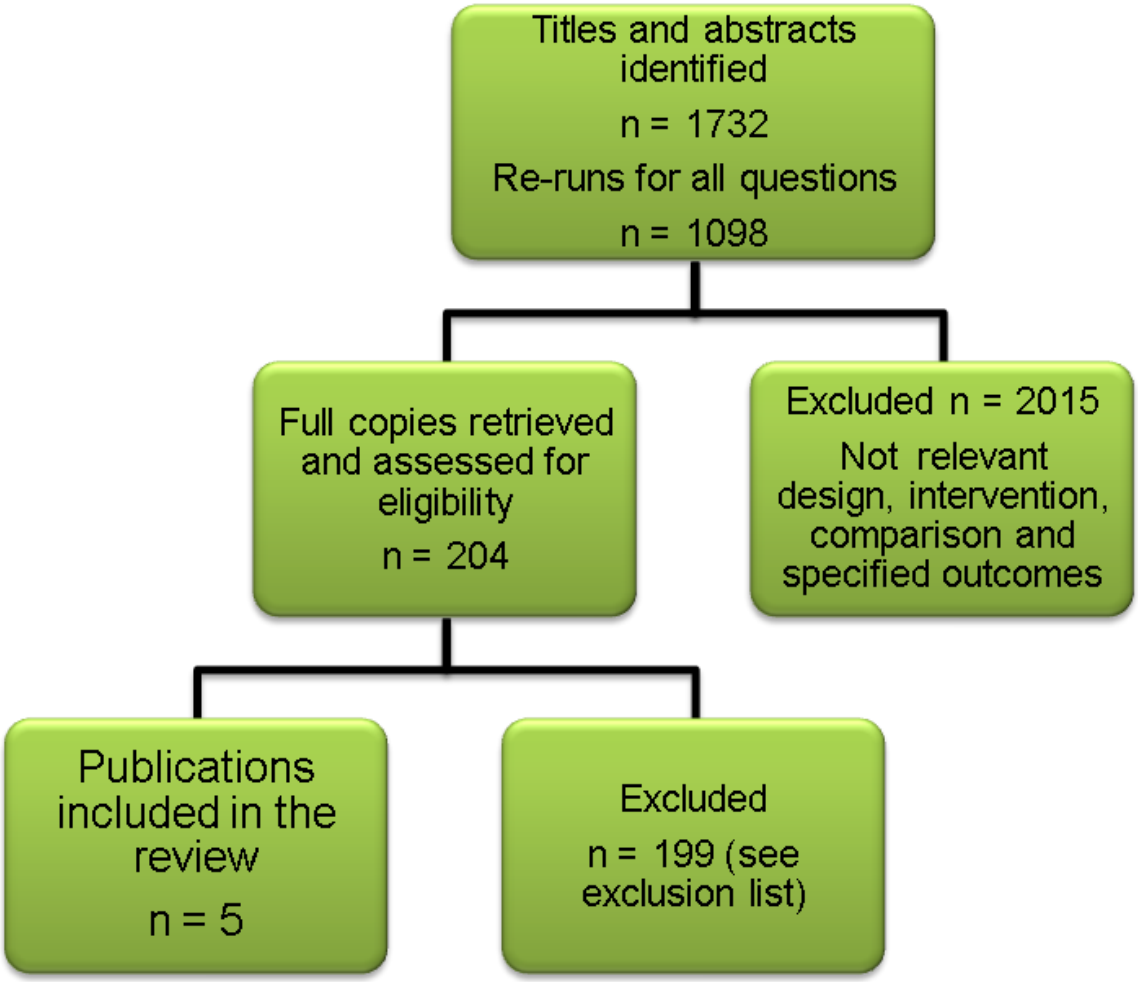
G.5.1 Angioplasty compared to bypass surgery

What is the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of PAD in adults with critical limb ischaemia?



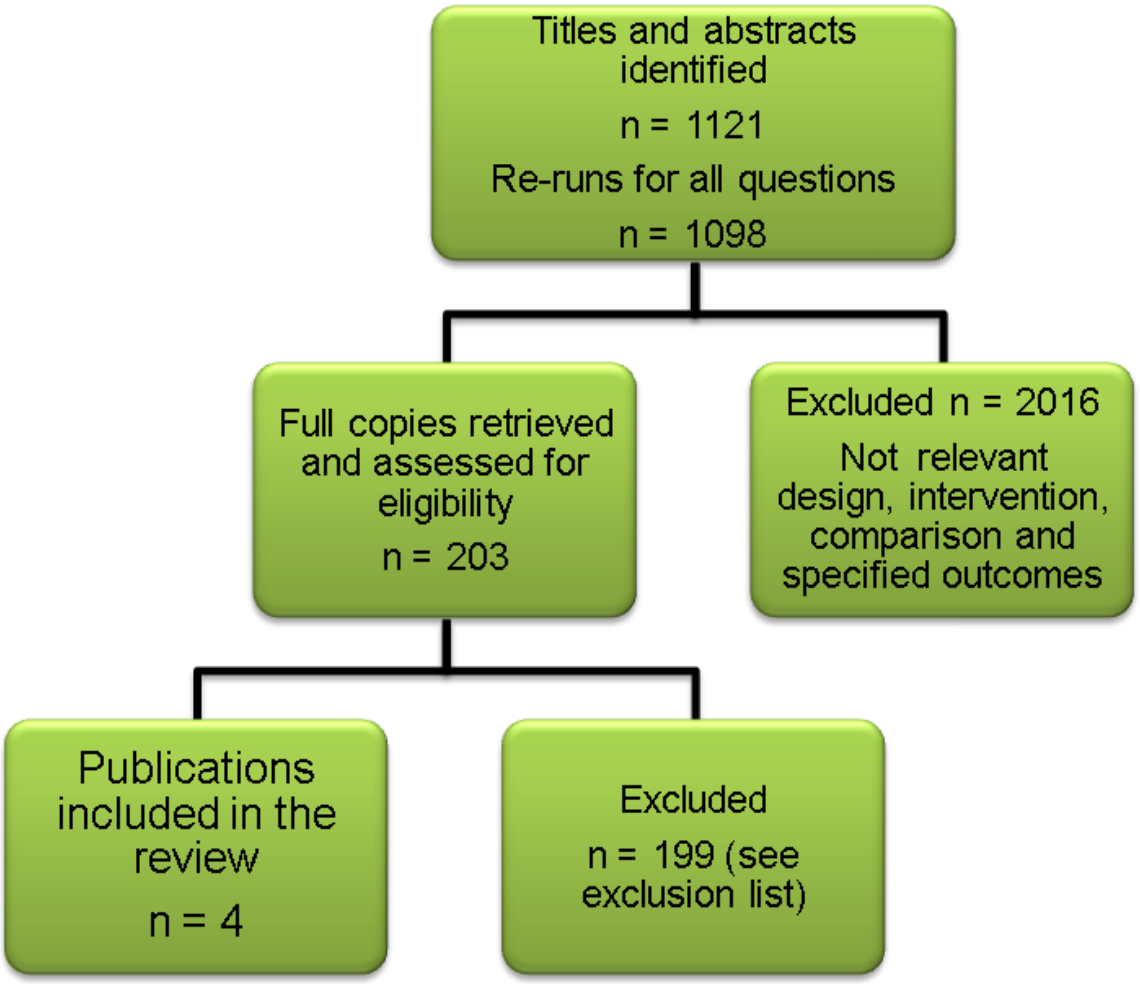
G.512 Angioplasty with selective stent placement compared to angioplasty with primary stent placement

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?



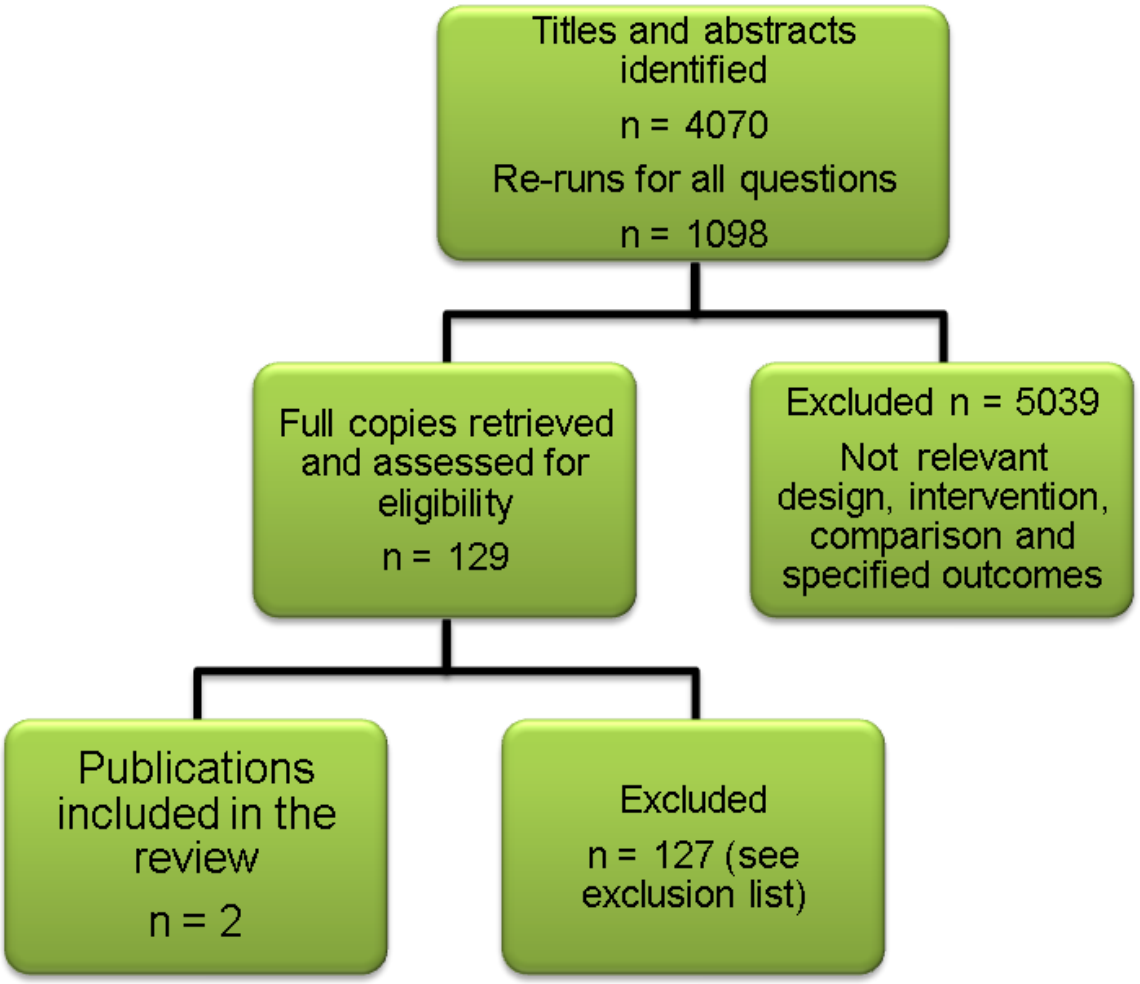
G.513 Bare metal compared to drug eluting stents

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?



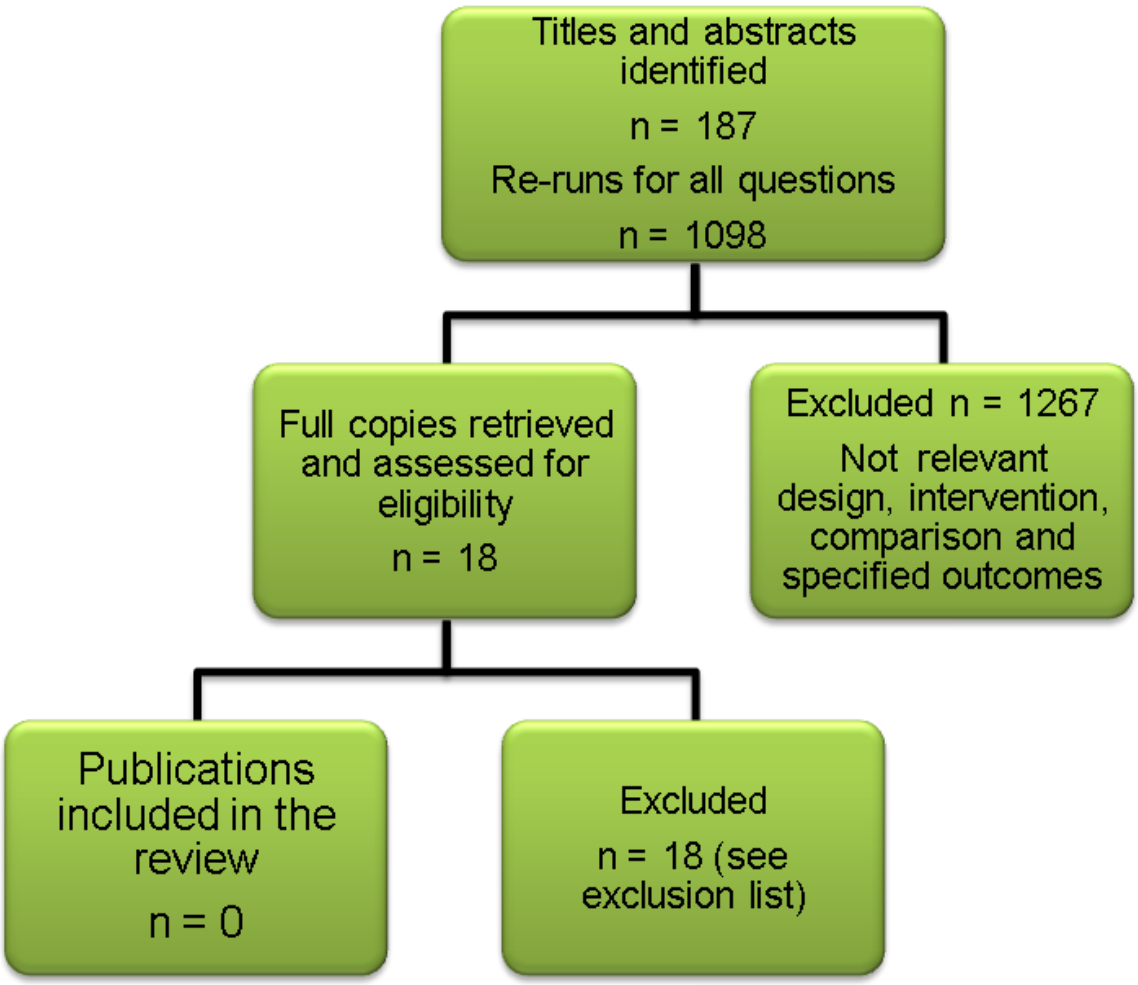
G.514 Autologous vein compared to prosthetic bypass

What is the clinical and cost effectiveness of autologous vein compared to prosthetic bypass grafting for the treatment of PAD in adults with critical limb ischaemia?



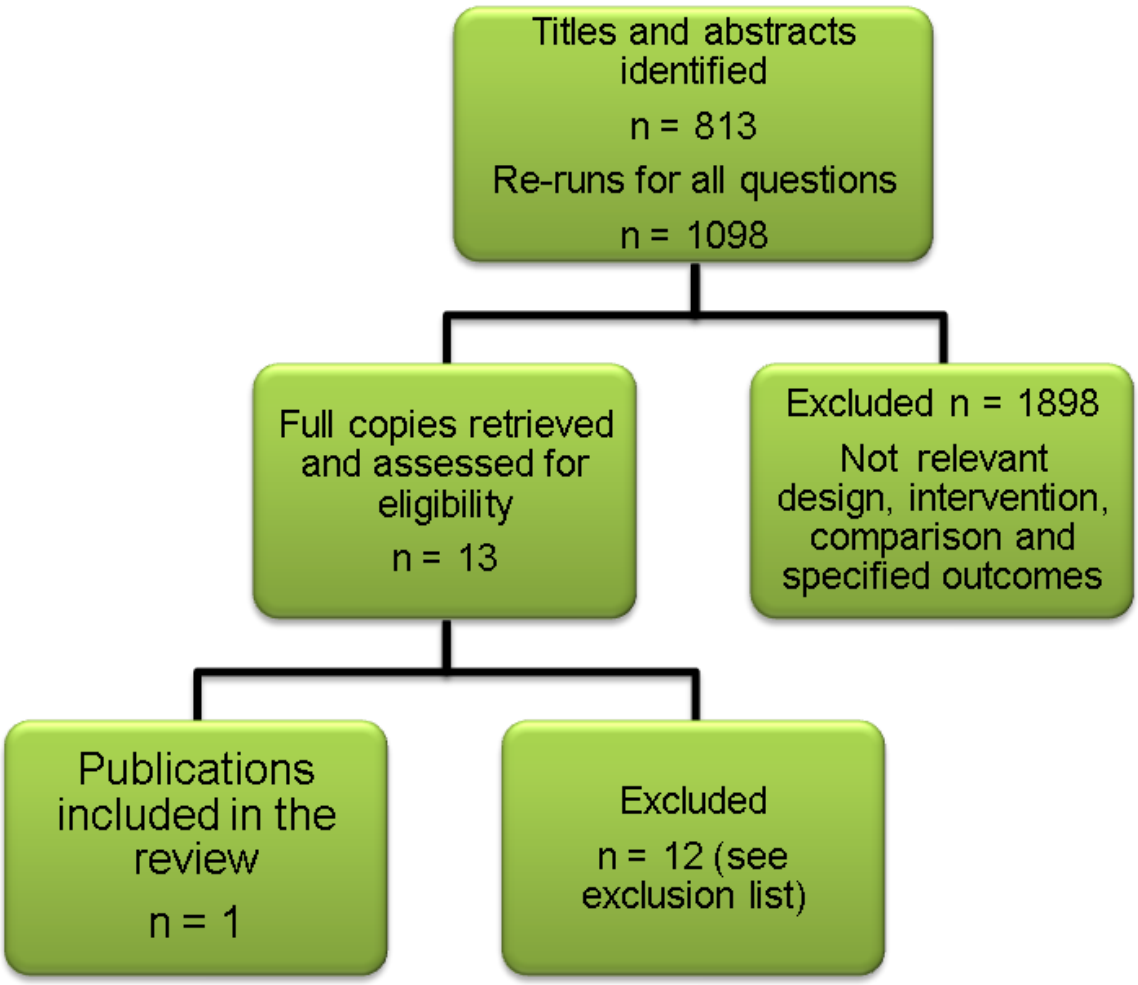
G.515 Management of ischaemic pain

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?



G.5.16 Major amputation

What are the clinical indications for major amputation for the management of pain in people with critical limb ischemia and does amputation improve the quality of list in people with critical limb ischaemia?



Appendix H: Clinical evidence tables

H.1 Information requirements

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Gibson JM. 1998; (Guideline Ref ID 16220)	Qualitative study to explore the experience of living with PVD and how treatment of the condition affects individuals' coping strategies	Phenomenological grounded theory approach with constant comparative method of data collection and analysis and member checking	Audio taped one-to-one interviews (in patient's home) and researcher's field notes, validated with a group of experienced vascular nurses. Transcripts analysed using open and axial coding techniques; major and minor categories identified and related to other data collected.	**Inclusion:** • Patients attending a specialist vascular outpatients clinic who had had vascular bypass surgery within last 3-18 months. **Exclusion:** • any psychiatric dysfunction • unable to communicate verbally in English Baseline characteristics: n=9 (convenience sample) 6 men + 3 women; age range 62-75 years; time since initial diagnosis of PVD 18months-10 years; age at diagnosis 54-72 years. All had had vascular bypass surgery for PVD; none had diabetes.	not stated	Small convenience sample; all had had prior surgery	Patients with PAD without prior surgery

Key themes:

Pain:

- All patients had experienced pain (mainly pre-operative; had a major impact on quality of life) and altered sensation (e.g. coldness/deadness of limb). Fear of recurrence of pain. Strategies to deal with pain pre-operatively included medication and alteration of activity (but had little effect). Sleep disturbance due to pain. Participants expected pain to be considerable in the early post-operative period but then to reduce rapidly and not recur; they were concerned and disappointed when pain persisted after they expected to have recovered (may be related to unrealistic hope int eh power of medicine to alleviate symptoms and focus on surgery as a cure).

Someone else's problem – patienthood:

- 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).

Someone else's problem – expectations:

- Prior to surgery, expectations were unrealistic and positive (e.g. belief operation would get things "back to normal" and "that would be it"); afterwards, when it became apparent that surgery had not restored their function as much as they hoped, expectations were tempered by 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"). Role of chance in getting illness in the first place, getting access to treatment, whether treatment successful. Mostly external factors identified as causes of patients' health problems (although 1 participant identified responsibility for his condition due to smoking and that giving up was his best chance of cure). Patients perceived a lack of control over course of illness; treatment not guaranteed to work.

Someone else's problem – playing by the rules:

- Participants 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); others 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).

Shrinking horizons:

- Physical and mental horizons limited by illness (e.g. limited to walking slowly for short distances but also couldn't be bothered going anywhere because could not do it as well as used to be able to). Adapted to physical limitations over time (learned by trial and error; allowed for day-to-day variations in ability; prioritising activities and carrying them out efficiently with suitable resting places). Loss of mobility compromised independence, made it difficult to accomplish goals, changed interaction with environment and other people, had major impact on quality of life, and contributed to powerlessness. Acceptance (being realistic, facing up to problems, lowering expectations); trying to create sense of normality, modifying routines, adjusting to changed social relationships, dealing with role changes. Loss of sense of self (having to give up activities and independence).

Control, choice and changing outlook:

- Some patients had internal locus of control, which was threatened by PVD and resulting dependence. Tried to maintain control of factors within their remit; maintaining independence (e.g. shopping). Changes in lifestyle and health status affected thoughts; depression; fear (e.g. waiting for treatment, fear of hospitalisation and surgery, fear of operation failing) which tended to be concealed from themselves (putting it to the back of one's mind) and from others (not discussing it).
- Vascular patients experience pain and also powerlessness in relation to the direct effects of their condition and in relation to its treatment modalities. The "acute" style of management of PVD led to unrealistic expectations on the patient's part, which gave rise to the experience powerlessness.

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Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Leech JE. 1982; (Guideline Ref ID 16219)	4 questions: 1) What physiological, psychological, and sociocultural needs (need defined as a state or condition, either identified by the investigator or expressed by the patient, to which nursing knowledge or skill could be applied to promote a favourable change in the condition or situation of the patient) do patients with chronic AOD experience during the preoperative period? 2) What similarities and differences exist between male and female patients' body cathexis (defined as the degree of feeling of satisfaction/ dissatisfaction with various parts and	not stated	Three sources of information: an interview schedule - mainly closed questions (48 items exploring 10 areas of potential need imbalance within physiological, psychological, and sociocultural categories, plus patient's level of adaptation to disease and perceived severity of illness; primarily closed questions with precoded nominal or ordinal scales), the Secord and Jourard body cathexis questionnaire (referenced Secord and Jourard 1953; 40 parts and functions of the body listed; each rated on 5-point scale of satisfaction/	**Inclusion:** Patients admitted to the hospital for reconstructive vascular surgery (excluding aneurysm repair); aware of scheduled date for surgery; sufficiently free of discomfort to participate fully; understood, spoke and read English. **Exclusion:** had been living in an institution (extended care facility, psychiatric hospital) prior to hospitalisation	not stated	Convenience sample; interview schedule reliability and validity not measured, although authors state that no major revisions were thought necessary following pretest on 10 subjects.	Higher socioeconomic bracket; recent onset of symptoms; mild disease; those not scheduled for surgery

	processes of the body)? 3) What similarities and differences in expressed/identified needs exist between a) male and female and b) older (≥65 years) and younger (≤64 years) patients? 4) To what extent are needs associated with a) body cathexis, b) perceived severity of illness, c) level of adaptation to disease, d) previous vascular surgery, e) physiological severity of disease and f) type of surgical procedure?		dissatisfaction; patients given 2 scores, one based on the total scale and one on teh 12 items relating directly to PAOD; mean score derived from each raw score and classified as negative (1.00-2.99), neutral (3.00-3.99) or positive (4.00-5.00)) and patient's hospital chart (demographic data, medical history, physiological severity of disease by arteriogram, type of surgical procedure).	Baseline characteristics: n= 60 (convenience sample): 40 men and 20 women; mean age 61.5 years; lower socioeconomic bracket; mean of 2.2 concurrent diseases; not working at hospitalisation due to AOD; vascular symptoms (primarily intermittent claudication) for >1 year; difficulty bending and climbing stairs; walking tolerance <1 block; moderately severe disease; around half had had previous vascular surgery and scheduled for aortic procedure. All had PAD; diabetes not stated			
Key themes:							
All 10 potential need areas explored in interview schedule were of concern to patients. • Physiological needs: All had history of smoking. 85% considered decreasing or quitting to be important but this was related to fear of lung cancer rather than vascular							

disease; only 26% had actually stopped. >80% did not related perceived benefits of dietary management and regular foot care to vascular disease and were not following these practices. 28% taking large amounts of analgesics without knowledge of side effects. Patient felt they had not been adequately prepared for aortographic procedures under local anaesthetic and they experienced discomfort.

- Psychosocial needs: Difficulties in coping with alterations in self-concept and role function were closely related: 83% of patients were unhappy with changes that had occurred with the progression of their disease: felt uselessness, frustration and depression with situation and with their perceived inability to cope with it. Only 42% felt themselves to be in control during hospitalisation. Patients perceived a need to have a sense of control over the future. They experienced anxiety about the effect of surgery on disease progression (more than about hospitalisation itself). 70% indicated preoperative information would be helpful to decrease anxiety, but many patients stated they did not wish to know "too much" and 27% desired no information at all. 83% considered preoperative passive support measures to be helpful; they wanted a friendly, positive atmosphere and emphasised the importance of considering patients as people, not just individuals with a particular disease condition. 28% expressed loneliness and separation from families.

- Patients expressed need for support regarding difficulties coping with negatively perceived changes in self-concept and alterations in role relationships, anxiety about the effect of surgery on disease progression and general operative support measures.

- Investigator identified a need for information on preventive health behaviours (diet, smoking, foot care, use of analgesics) and need for support (active emotional support by nurses; fostering sense of control; reducing anxiety; enhancing family support).

- Male and female patients differed significantly in body cathexis scores in 4/10 areas. Women had lower scores indicating greater dissatisfaction with body structure and function. Males perceived emotional support to be the most beneficial intervention in preoperative period; women identified both physical and emotional support to be helpful. Twice as many women as men perceived themselves to be in control int eh hospital while twice as many men as women felt lonely and cut off from normal family support. Men three times more likely to have financial worries due to reduction in income.

- Compared to the younger (≤64 years) group, older patients perceived less need to follow a special diet; demonstrated less awareness of the negative relationship between smoking and circulatory pathology; perceived general nursing support as more helpful; and desired less preoperative information.

Associations (Kendall's tau)

	Total body cathexis score	**AOD body cathexis score**	**Level of adaptation to disease**	**Perception of illness as severe**	**Extent of previous surgery**	**Physiological severity of disease**
Changes in self-concept	-0.42	-0.48	-0.39	0.62	-	0.58
Role relationships	-	0.34	-	0.51	-	0.48
Understanding of	-	-	-	-	0.47	-

coming events						
Belief in the need for a special diet	-	-	-	0.42	-	-
Financial insecurity	-	-	-	0.40	-	-

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Reference	**Research Parameters**			**Population**	**Funding**	**Additional comments**	
	Research question	**Theoretical approach**	**Data collection**	**Population and sample collection**	**Source of funding**	**Limitations**	**Evidence gap**
Treat-Jacobson D, 2002; (Guideline Ref ID 748)	to evaluate the effects of peripheral arterial disease (PAD) on health-related quality of life (HRQoL) from the patient's perspective	grounded theory methodology	Open-ended, tape-recorded unstructured interviews (in medical centre in private quiet rooms away from clinical environment); general opening questions were "Tell me about your life with PAD" and "How has this disease affected your life?" Tapes transcribed, coded and analysed to identify themes and subthemes, and conceptual domains (descriptions, patterns of phenomena and relationships); field notes to add contextual information. Multiple reviews for completeness and accuracy.	Inclusion: PAD; range of ages, geographical location, genders and disease severity (claudication to ischaemic pain and non-healing wounds) Exclusion: not stated Baseline characteristics: n=38 (sample size determined by rule of redundancy, i.e. the point at which interviewers heard no new information): 24 men + 14 women; mean	Grant-in-aid from the University of Minnesota Graduate School, and Otsuka America Pharmaceutical Incorporated, and by a Vascualr Diseases Academic Award from the National heart, Lung, and Blood Institute.	Lack of people with asymptomatic PAD for comparison; lack of ethnic diversity in the sample.	People from ethnic minorities

				age 65 years (range 44-83 years). All had PAD; diabetes not stated			

Key themes:

1) delay in diagnosis and frustration with management of disease (patient 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]; lack of control; lack of knowledge of disease and importance of risk factor management; smoking 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)

2) pain (cramping, aching, burning, fatigue)

3) limitation in physical functioning (walking impairment and limitation in activities [physical tasks at home or work and recreational activities; "becoming an invalid"])

4) limitation in social and role functioning (social isolation or inadequacy [slowing down friends or family]; being a burden to family [other people having to bear responsibility for supporting the family]; role and employment limitations [threat of job loss; need to change jobs; loss of opportunity for promotion; homemakers expressed inability to fulfil role including parenting)

5) compromise of self (compromising sense of wholeness; premature aging; feeling abnormal [sense of shame]; unfulfilled desire; loss of self ["who they are"; loss of the person they used to be])

6) uncertainty and fear (fragile or obscured anticipation of a future; fear of loss of function or independence; fear of amputation; fear of death)

7) adaptation to the effects of the disease and demonstration of resiliency (adjustment, flexibility)

Generally participants with more severe disease expressed more negative feelings; many people expressed both positive and negative feelings.

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Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Wann-Hansson C, 2005; (Guideline Ref ID 1088)	To investigate patients' experiences of living with peripheral arterial disease and the	manifest and latent content analysis	Interviews (tape recorded in respondent's home); respondents invited to talk openly about their experiences and how the circulation problems in their leg affected their daily life. The opening question was "I am interested in what it is like to live with circulation problems in the legs. Could you please tell me about your experience?" Respondents were also asked to talk about the strategies	Inclusion: Patients with varying degrees of PAD admitted for planned active treatment; able to participate in interviews Exclusion: serious mental and/or linguistic disorder); other serious disorders that might overshadow the experience of PAD	Lori Lindahls Foundation and Department of Nursing Science, Lund University,	Only aged 60 or more; symptoms severe	Mild/moderate symptoms; younger patients

	influence on activities of daily living.		they had used to handle the disease. The interview schedule included areas such as pain, sleep, mobility, emotions, energy and social life. Transcribed texts were analysed using manifest (surface structure of text of patient's descriptions) and latent (interpretation of symbolism underlying data) content analysis: identification of patterns (referenced). First reading of text to understand the interview as a whole and identify words and phrases carrying important meaning for people living with PAD, organised into sub-themes and themes.	Baseline characteristics: n=24 (purposive sampling; limited by rule of redundancy, i.e. stopping when no new information collected): 12 women + 12 men; 4 with severe intermittent claudication and 20 with critical ischaemia; mean age 77 years (range 60-92 years). All had PAD; diabetes not stated	the Vardal Institute, the Swedish Institute for Health Sciences, Lund and Departme nt of Vascular Disease, Malmo University Hospital		
Key themes:							
Living with PAD meant carrying a hard-to-bear physical, social and emotional burden and struggling for relief. **Burden:** 1) being limited by burden: restricted mobility (compromising independence and activities [physical and social]); fatigue and powerlessness (sleep disturbance, lack of energy, feeling useless); isolation (restricting freedom, loneliness, missing previous activities, loss of interest); emotional changes (e.g. depression, mood and temper influenced by pain, having to ask for help, despair, and impact on relationships and friends; fear of amputation) 2) striving to relieve the burden: relieving pain and promoting circulation (pain unpredictable; analgesics used but fear of taking pills and unwanted effects; changing position of leg; distracting activities e.g. TV); managing non-healing wounds (looking after wounds, trying different bandages, letting professionals take care of wounds); struggling against loss of independence (modifying routines to maintain some control [e.g. walking where they could rest]; struggling to not accept limitations but live as normally as possible [e.g. exercises and keeping in good shape]) 3) accepting and adapting to the feeling of burden: reorientation (adjusting activities, taking on new interests [e.g. reading] to compensate for loss of old ones, positive thinking [e.g. others worse off]); resignation (being realistic, facing up to problems, lowering expectations, giving responsibility to healthcare professionals).							

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H.2 Diagnosis of PAD

H.2.1 ABPI compared to clinical assessment

Reference	Study type and comments on quality	No. of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sens and spec	PPV and NPV	Source of funding
Baxter GM, 1993; (Guideline Ref ID 4342)	• Cross sectional study • High quality	20	Arteriography diagnosed 13 femoro-popliteal occlusions; 11 femoro-popliteal stenoses; 11 iliac disease (7 occlusions and 4 stenoses) and 5 patients with all normal vessels (i.e. total 15/20 with disease). Five cases had both an iliac lesion and femoral stenosis	Inclusion: patients under assessment with symptoms of lower limb claudication, rest pain or cellulitis. Exclusion: not stated Baseline: 12 male + 8 female patients; age range 21 to 86 years (mean 62 years).	Ankle:brachial pressure monitoring (within 48 hours of arteriography): brachial systolic pressures measured in both arms; higher value used. segmental pressure readings at upper thigh, lower thigh, upper calf, lower calf where possible and posterior tibial or dosalis pedis arteries as reference vessels. Thigh and calf pressure ratios used to determine segmental disease (a drop in this ratio of 0.15 [30mmHg] or more regarded as	Lower limb arteriography used as gold standard (evaluated blindly by consensus of two angiographers). Each femoral and popliteal segment was graded as insignificant narrowing (0-49%), significant narrowing (50-99%) or occluded. Significant iliac disease was present if either a stenosis of >50% or an occluded segment was seen.	see below	not stated	not stated

					significant and reflective of segmental disease). With regard to localisation of iliac disease, thigh/brachial ratio <0.9 regarded as significant. Colour Doppler ultrasound also measured.				

Effect Size

Outcome	ABPI ratio <1.0	Colour Doppler
Sensitivity	100%	92%
Specificity	40%	80%
Overall accuracy	92.5%	90%

- A thigh:brachial index could localise disease to the iliac vessels with an accuracy of 70% while a segmental pressure drop was only 55% accurate in disease localisation below the inguinal ligament, this dropping further in the presence of iliac disease.
- Thigh and calf pressure ratios localised disease correctly in 12 of 13 femoro-popliteal occlusions but in only one of 11 femoro-popliteal stenoses.
- Mean ABPI measurements showed no significant difference between those patients who had normal arteriograms (0.92 [SD 0.12]) and those with femoral stenosis (0.86 [0.12]), although those with iliac disease had a mean ABPI of 0.59 (0.12) and femoro-popliteal occlusion 0.51 (0.2).

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sens and spec	+ve and -ve predictive values	Source of funding
Guo X, Li J, 2008; (Guideline	Cross sectional study	298	7.09% PAD according to	Inclusion: Cardiology inpatients with ABI	Oscillometric method was used to obtain	Conventional digital subtraction angiography (DSA).	see below	see below	Omron (China) Co Ltd

Ref ID 619)	High quality		angiography	performed within 30 days prior to angiography; Han ethnicity; older than 35 years; living in the community; unrelated to other participants. Exclusion: multiple organ dysfunction syndrome; pregnancy or lactation; mental disorder; serious diabetes mellitus or hypertension and their complications; secondary hypertension, type 1 diabetes; non-compressible vessels (ABI >1.40). Baseline characteristics and medications		BP in all 4 extremities; lowest ABI of both legs was index leg used	Images were reviewed by two experienced angiographers PAD defined as ≥50% stenosis of any lower extremity artery from aorto-iliac bifurcation to ankle arteries. Occlusion <50%, mild atherosclerosis and luminal irregularities not considered PAD. Stenosis graded: 1=normal vessel; 2=mild vessel irregularities (<30% narrowing); 3=moderate arterial (30-49%) stenosis; 4=severe arterial (50-69%) stenosis; 5=severe areterial (70-89%) stenosis; 6=≥90% or occlusion. Grades 4, 5 and 6 considered haemodynamically significant.			and Beijing Century Trade Corp
				Sex	199 male/ 99 femal e				
				Mean age	64.93 (±11. 32)				

					years					
				SBP (mm Hg)	126.13±19.84					
				DBP (mm Hg)	71.68±11.71					
				Total cholesterol (mmol/L)	4.78±2.50					
				Triglycerides (mmol/L)	1.75±1.27					
				LDL (mmol/L)	2.88±0.93					
				HDL (mmol/L)	1.10±0.26					
				Fasting plasma glucose (mmol/L)	6.23±2.11					
				Ever smoked	45.0 %					
				CAD	53.0 %					
				Cerebral infarction	13.4 %					
				2-DM	22.8 %					
				Dyslipidemia	33.9 %					
				Statins	90.3 %					

				ACEI	71.1 %					
				ARB	12.8 %					
				Antiplatelet	96.3 %					
				ß – receptor blockers	66.1 %					
				CCB	36.2 %					
				Diuretics	11.4 %					
				Oral hypoglycaemic agents	16.8 %					
				Nitrates	77.5 %					
				Digitalis	5.7%					

Effect Size

ABPI cut-off point	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
1.12	100.0%	40.0%	1.67	0
0.95	91.0%	86.0%	6.5	0.10
0.90	76.0%	90.0%	7.6	0.27
0.53	14.3%	100.0%	0.14	0.86

- Area under the ROC curves using angiography as the gold standard in defining ≥30%, ≥50% ≥70% were 0.786 (95% CI 0.712 to 0.860), 0.927 (0.869 to 0.984) and 0.963 (0.927 to 0.999).
- The greater the area under the curve, the more accurate the test, but there was only 1 patient in the ≥70% category. So ≥50% (n = 21) was used as the gold standard in this study.

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics		Index test	Reference standard	Sens and spec	PPV and NPV	Source of funding
Janssen A. 2005; (Guideline Ref ID 1060)	Cross sectional study High quality	106 patients; 140 feet with parallel investigations available for analysis	61 feet with and 79 feet without critical limb ischaemia (CLI).	Patients with diabetes hospitalised because of painless skin lesions of the feet. All patients had peripheral polyneuropathy Exclusion: not stated Patient demographics		Doppler ABI with 8Mhz Doppler probe. A 12 cm sphygmomanometer cuff was placed just above the elbow and the ankle respectively	CLI was diagnosed according to the need for revascularisation to heal the foot wound. This need was determined by a physician of internal medicine together with an interventional radiologist and/or vascular surgeon on the basis of clinical and arteriographic findings. Clinical assessment (Wagner classification: 0=no skin lesion; 1=superficial ulcer; 2=full	see below	see below	not stated
				Number of patients (males/females)	106 (72/34)					
				Median age, years (males/females)	71.6 (69.6/75.8)					
				Diabetes type I	6					
				Diabetes type II	100					
				Diabetes duration (median), years	20.3					
				Insulin therapy	82					
				Neuropathy	106					
				Nephropathy	74					
				Renal insufficiency	38; dialysis 8; previous transplant 1					
				Retinopathy	33; previous laser therapy 11					
				Medial arterial calcification	76					

				Foot skin lesions	Toe 77; midfoot 34; heel 17; dorsal 3		thickness ulcer; 3=abscess, osteitis, arthritis; 4=necrosis of forefoot; 5=necrosis involving whole foot) and radiological criteria (digital subtraction arteriography; Bollinger score: plaque ≤25%, stenosis ≤50%, stenosis >50%, occlusion)			
				Duration of the lesion (median)	8.9 months					
				Charcot foot	1					
				Previous revascularisations	PTA 22 (2 iliacal, 17 femoro-popliteal; 3 others); bypasses 18 (5 iliacal, 14 femoro-popliteal)					
				Previous amputations ipsilateral	18; toe 11; toe and metatarsals 5; midfoot 2					
				Previous amputations contralateral	23; toe 8; toe and metatarsals 1; midfoot 4; calf 6; thigh 5					
				Hypertension	88					
				Hyperlipoproteinaemia	52					
				Ischemic heart disease	49; previous ACVB 24; PTCA 5, MI 28					
				Congestive heart disease	31; previous decompensation 12					
				Atrial fibrillation	26					
				Cardiac pacemaker	7					
				Previous reanimation	2					

				Aortic valvular disease	7					
				Mitral valvular disease	6					
				Tricuspidal valvular disease	2					
				Previous heart valve replacement	5					
				Previous cerebral ischaemia	18; completed strokes with permanent neurological deficit 6					
				Dementia	10					
				Venous insufficiency	12					
				Malignancy	9					
				Liver cirrhosis	1					
				Coagulopathy	1					

Effect size

- In 76 of 140 feet medial arterial calcification was present on plain X-ray (in 70 legs ≥1 calf arteries proved to be incompressible); In the CLI group 30/61 feet displayed evidence of medial arterial calcification.
- In the non-CLI group 46/79 feet displayed evidence of medial arterial calcification; these findings implied that the results of any sphygmomanometry would be unreliable in 54% of the total population.

	ABPI <0.5	**ABPI <0.7**	**ABPI <0.9**
Sensitivity	0.36	0.59	0.71
Specificity	0.86	0.67	0.42
Positive predictive power	0.67	0.58	0.48
Negative predictive power	0.64	0.68	0.65

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sens and spec	PPV and NPV	Source of funding
Premalatha G, 2002;(Guideline Ref ID 1461)	Cross sectional study High quality	100 patients; 6 excluded in calculations of sensitivity/specificity of ABI due to calcification of peripheral vessels	68/94 abnormal on colour duplex ultrasound	Patients with type 2 diabetes with severe foot infections necessitating admission to hospital. Exclusion: not stated **Patient demographics** N: 100 Age, years: 59.5±10.1 BMI (kg/m2): 24.2±3.5 SBP (mm Hg): 136±19 DBP (mm Hg): 86±11 Duration, years: 11.7±8.1 Fasting plasma glucose (mg/dl): 186±76 Glycosylated haemoglobin (%): 9.5±2.0 Smoking n (%): 24 (24%) Treatment OHA alone: 19 (19%) Insulin alone: 16 (16%) OHA and insulin: 60 (60%) Diet: 5 (5%)	Doppler brachial pulses in the upper limb; mean of dorsalis pedis and posterior tibial pulses; ABI <0.9 in either foot defined as peripheral vascular disease: grade 1=ABI ≥0.9; grade 2=0.7 to 0.9; grade 3=0.5 to 0.7;grade 4 ≤0.5	High-resolution colour duplex ultrasound of common iliac, external iliac and common femoral arteries. The SFA was traced up to the popliteal fossa and the profunda was evaluated in its proximal segment. The infrapopliteal vessels, anterior tibial, peroneal, posterior tibial and dorsalis pedis were also evaluated. PVD was diagnosed if arterial stenosis was ≥50% or had occlusion	see below	see below	not stated

Effect Size			
ABPI <0.9 was the cut-off used for PAD diagnosis			
	ABPI Normal	**ABPI abnormal**	**Total**
CDU normal	23	3	26
CDU abnormal	20	48	68
Total	43	51	94
Sensitivity: 70.6% Specificity: 88.5% Positive predictive value: 94.1% Negative predictive value: 53.4% Overall agreement poor (42.6%)			

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Reference	Study type and comments on quality	No. of pts	Prevalence	Patient characteristics	Index test	Reference standard	Sens and spec	PPV and NPV	Source of funding
Schroder F, 2006; (Guideline Ref ID 16207)	Cross sectional study High quality	216	According to ultrasound, 52% of patients had PAD.	Patients aged >40 years suspected of having vascular disease who presented at outpatient clinic. Exclusion: not consenting; limb amputations proximal to the heads of the metatarsals of one or both lower limbs and amputations proximal to the wrists of one or both arms; limb wounds or ulcerations proximal to the metatarsal heads in the lower limbs; prior bypass surgery to the lower limb arteries or prosthetic vascular reconstructions of the abdominal aorta and subclavian/ axillary arteries or angioplasty; marked oedema of one or both feet as well as oedema of both arms; acute limb ischaemia; body mass index >40; atrial fibrillation; ABPI >1.3 in both lower limbs; poor sonographic window	ABI: a sphygmomanometer with a cuff width of 29-40cm and Doppler device with an 8.2 MHz continuous wave probe was used. It was performed by two experienced examiners blinded to all assessed baseline parameters. Two methods used: Higher ankle pressure (HAP)	Colour coded duplex ultrasound (CCDU). By two experienced sonographers blinded to all assessed baseline parameters. A sector array probe of 2 to 4 MHz was used to scan the abdominal aorta and iliac arteries. A linear array probe of 4 to 7 MHz was used to scan the femoral, popliteal, and proximal segments of the infrageniculate arteries. The mid and distal segments of the infrageniculate arteries were scanned by a 7- to 10-MHz linear array probe.	see below	see below	not stated

				of abdomen or lower limb arteries. Participants with a unilaterally elevated ABPI were included and the limb with normal or diminished ABPI was evaluated Baseline: 139 men and 77 women; mean age 64.4 years (median 65 years). 81 had intermediate claudication (44 at Fontaine stage IIa and 35 at Fontaine stage IIb) 74 had diabetes mellitus, 65 were current smokers, 47 were previous smokers, 165 had hypertension and 143 had dyslipidemia	method and lower ankle pressure (LAP) method				

Effect Size

Group	ABPI by HAP method	ABPI by LAP method	PAD on ultrasound	Description	No of patients (n=216)
IA	Normal	Normal	Absent	True negative for PAD	96 (44%)
IB	Normal	Normal	Present	False negative for PAD	13 (6%)
IIA	Diminished	Diminished	Present	True positive for PAD by both methods	77 (36%)
IIB	Diminished	Diminished	Absent	False positive for PAD by both methods	1 (0.5%)
IIIA	Normal	Diminished	Present	True positive by LAP and false negative by HAP	23 (11%)
IIIB	Normal	Diminished	Absent	False positive by LAP and true negative by HAP	6 (3%)

Group I: Subjects had an ABI ≥0.9 as assessed by HAP and LAP methods
Group II: Subjects had an ABI <0.9 as assessed by HAP and LAP methods

Group III: Subjects had an ABI <0.9 as assessed by the LAP method but not the HAP method
A: No haemodynamically relevant flow-limiting stenosis according to CCDU
B: Haemodynamically relevant flow-limiting stenosis (70-99%) defined as increase in peak velocity ratio of >2 according to CCDU

	HAP method	LAP method
True negative for PAD	102 (47%)	96 (44%)
False negative for PAD	36 (17%)	13 (6%)
True positive for PAD	77 (36%)	100 (46%)
False positive for PAD	1 (0.5%)	7 (3%)
Sensitivity	0.68	0.89
Specificity	0.99	0.93
Positive predictive power	0.99	0.93
Negative predictive power	0.74	0.88

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H.22 Methods of ABPI

Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sens and spec	PPV and NPV	Source of funding
Gornik HL, , 2008; (Guideline Ref ID 16167)	Cross sectional study High quality	106 recruited; 2 did not complete full protocol; data from 4 patients excluded due to bilateral non-compressible vessels	31% of patients had ABI ≤0.9	Inclusion: Patients aged ≥60 years presenting to a single non-invasive vascular laboratory for evaluation of suspected arterial disease and scheduled for ABI or segmental leg pressure study with pulse volume recordings, carotid duplex ultrasound scan, arterial duplex ultrasound scan of lower extremities or abdominal aorta, renal or	In the seated position after supine measurements taken and additional rest period of 5 minutes. Doppler SBP measurements in arms and ankles (same	After 10 minutes of rest in the supine position: Doppler SBP measurements in arms and ankles (right brachial, right posterior tibial [PT], right dorsalis pedis	NA	NA	Summit Doppler Systems, Inc, Golden, Colo, and William F. Keating Career Developme nt Award of the American

				mesenteric arterial duplex scan. Exclusion: unable to give informed consent, unable to lie supine for 15 minutes, unable to speak English. **Patient demographics** Mean age: 71.7 ± 7.4 (range 60-90 years) Male: 82% Cardiovascular risk factors Mean BMI: 29.4±4.4 kg/m2 Diabetes*: 24% Hypertension*: 93% Hyperlipidaemia*: 79% History of tobacco use Current smoker: 4% Former smoker: 66% Life-time non-smoker: 22% Not obtainable: 8% Established cardiovascular disease Prior diagnosis of PAD: 35.4% Coronary artery disease: 62% History of stroke or	sequence as for supine measurements) — corrected for hydrostatic pressure using formula taking into account specific gravity of blood and mercury and the vertical distance between arm and ankle cuffs. Higher of 2 brachial pressures for both legs, and higher of DP or PT used for each leg; lower ABI of each of the two limbs in the supine position was used as overall ABI. ABI ≤0.9 was considered diagnostic; 0.9-1.29 normal; >1.30 considered non-diagnostic due to (partially) non-compressible vessels.	[DP], left brachial, left PT and left DP arteries using a portable ABI measurement unit with a continuous-wave 8 MHz Doppler scan transducer			College of Cardiology

				TIA						
				Carotid artery disease	39%					
				*Defined as a documented history of the risk factor or the prescription of pharmacologic therapy **Defined as stenosis of ≥1 internal carotid arteries of ≥40% on duplex ultrasound scan or prior cartotid endarterectomy or stenting procedure						

Effect Size

Correlation between seated and supine measurements evaluated, not sensitivity/specificity. Correlation coefficient for supine and seated ABI measures was 0.936 (p<0.001).

H.3 Imaging for revascularisation

Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Bueno A, 2010; (Guideline Ref ID 16105)	Prospective study High quality	40 patients (43 segments per patient for a total of 1720 segments; grouped as aorto-iliac,	clinical situation: Fontaine stage III 15% and IV 50%	Inclusion: Scheduled for DSA because of lower extremity arterial disease Exclusion: Patients with metal implants Baseline characteristics: 90% men; 60% smokers; 62.5%	Duplex ultrasound (abdominal aorta and pelvic iliac arteries scanned and lower limbs to	Digital subtraction angiography from abdominal aorta to pedal	see below	see below	no financial support

		femoro-popliteal and infra-popliteal)		hypertension; 57.5% diabetes; 15% hyperlipidaemia; 25% ischaemic cardiopathy; 15% renal insufficiency	pedal vessels; significant lesions: PSV ratio 2.5 or more, stenosis >50% or no Doppler signal=occlusion) and hybrid contrast-enhanced magnetic resonance angiography. Assessed unaware of patients' identity and clinical situation or other tests.	vessels; angiographers unaware of patients' identity and clinical situation. Maximum time between investigations 15 days.			

Effect Size

Stenosis graded for each segment: normal; stenosis <50%; stenosis >50% or occlusion

Duplex ultrasound vs. DSA as gold standard (95% CI)					
	Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**	**% missing segments**
Aorto-iliac: >50% stenosis **Occlusion**	100% (67.8-100) 100% (56-100)	99.5% (97-99) 100% (67-100)	91.6% (59-99) 100% (56-100)	100% (97-100) 100% (67-100)	10.7%
Femoro-popliteal: >50% stenosis **Occlusion**	87% (78-92) 93.6% (83-98)	98% (96-99) 100% (94-100)	95.2% (87-98) 100% (92-100)	96% (93-97) 95.2% (87-98)	4.58%
Infra-popliteal: >50% stenosis **Occlusion**	77% (70-83) 88% (83-92)	99% (97-99) 96.4% (91-98)	97% (92-99) 97.6% (94-99)	91.5% (88-93) 84% (77-89)	9.79%
Total: >50% stenosis **Occlusion**	81.4% (76-85) 90% (85-93)	99% (98-99.5) 97% (94-99)	96.2% (92-98) 98.1% (95-99)	94.8% (93-96) 88.4% (83-91)	8.5%
Contrast-enhanced MRA vs. DSA as gold standard (95% CI)					
	Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**	**% missing segments**

Aorto-iliac: >50% stenosis **Occlusion**	100% (69-100) 100% (56-100)	99% (96-99) 100% (69-100)	85% (56-97) 100% (56-100)	100% (98-100) 100% (69-100)	5.7%
Femoro-popliteal: >50% stenosis **Occlusion**	97.8% (91-99) 97% (88-99)	98.3% (96-99) 100% (95-100)	95% (87-98) 100% (93-100)	99% (97-99) 97.8% (91-99)	1.45%
Infra-popliteal: >50% stenosis **Occlusion**	88% (82-92) 94.8% (91-97)	99% (98-99) 97% (93-98)	98.8% (95-99) 97.9% (95-99)	95.3% (92-97) 92.7% (87-95)	4.8%
Total: >50% stenosis **Occlusion**	91% (87-94) 95.4% (92-97)	99% (98-99) 98% (95-99)	96.7% (93-98) 98.4% (96-99)	97.6% (96-98) 94.7% (91-96)	4.01%
Kappa value for interobserver agreement 0.93 (0.91-0.95) for MRA (0.95 [0.93-0.97] aorto-iliac; 0.97 [0.95-0.99] femoro-popliteal; 0.91 [0.88-0.93] infra-popliteal) and 0.72(0.68-0.74) for DSA (0.78 [0.66-0.90] aorto-iliac; 0.69 [0.62-0.75] femoro-popliteal; 0.66 [0.62-0.70] infra-popliteal). Complete agreement between MRA, DSA and DU in 83.6% of segments; 7.8% different categories in 1 of the 3 tests, and 8.5% missing data.					

	Aorto-iliac	**Femoro-popliteal**	**Infra-popliteal**	**Total**
Same results	247	425	766	1438
Different results	2	33	100	135
Missing	31	22	94	147
Total	280	480	960	1720

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Reference	**Study type**	**Number of studies/ patients**	**Study/patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Collins R, 2007; (Guideline Ref ID 2434)	Systematic review: to assess stenosis/occlusion. Studies were identified through searches of MEDLINE, EMBASE, BIOSIS Previews, Science Citation Index, LILACS and	A total of 58 studies provided diagnostic accuracy results: Aly, 1998 Ashleigh, 1993 Baum, 1995 Baxter, 1993 Bergamini, 1995	RCTs comparing diagnostic accuracy of different tests to evaluate stenosis and occlusion in patients with peripheral	Angiography (with DSA in most studies)	2D PC MRA 2D TOF MRA CE MRA CTA	Dependant on each study	Diagnostic accuracy of tests to diagnose stenosis/occlusion	HTA programme

	Pascal from 1996 to April 2004, with update searches in May 2005, handsearching of journals, scanning reference lists of included studies and consultation with experts in the field	Bostrom, 2001 Catalano, 2004 Cortell, 1996 Cronberg, 2003 Currie, 1995 Davies, 1992 Eiberg, 2001 Eklof, 1998 El-Kayali, 2004 Fletcher, 1990 Grassbaugh,2003 Hany, 1997 Hatsukami, 1992 Heuschmid, 2003 Hirai, 1998 Hoch, 1996 Hoch, 1999 Hofmann, 2004 Karacagil, 1996 Koelemay, 1997 Koelemay, 1998 Kreitner, 2000 Lai, 1995 Lai, 1996 Laissy, 1998 Legemate, 1991 Lenhart, 2000 Linke, 1994 Lundin, 2000 Martin, 2003 McDermott, 1995 Meaney, 1999	arterial disease		DUS			

		Mergelsberg,1986 Portugaller, 2004 Puls, 2002 Rieker, 1996 Rieker, 1997 Schafer, 2003 Sensier, 1996 Shaalan, 2003 Snidow, 1995 Snidow, 1996 Steffens, 1997 Steffens, 2003 Sueyoshi, 1999 Timonina, 1999 Vavrik, 2004 Whyman, 1992 Wilson, 1997 Winterer, 1999 Yucel, 1993 Zeuchner, 1994 Zhang, 2005						
Effect size								
2D PC or 2d TOF MRA								
Study	**Stenosis threshold**	**Results reported by**	**TP**		**FP**	**FN**	**TN**	
2D PC MRA; whole leg								
Steffens 1997	50-100%	area of stenosis / occlusion	229		5	5	14	
2D TOF MRA; whole leg ≥50% stenosis								
Baum, 1995	50-100%	Segment	527		101	100	460	
Houch 1999	50-100%	Segment	161		37	44	302	
Houch 1996	50-100%	Segment	172		13	12	155	
Snidow 1995	50-100%	Segment	80		76	7	215	
Yucel 1993	50-100%	Segment	65		16	6	119	
2D TOF MRA: whole leg, ≥70% stenosis								
Yucel 1993	70-100%	Segment	53		5	6	142	

2D TOF MRA; whole leg, occlusion						
Baum, 1995	100%	Segment	322	118	76	672
Hoch 1999	100%	Segment	103	17	31	393
Hoch 1996	100%	Segment	101	4	11	236
Yucel 1993	100%	Segment	40	4	0	162
2D TOF MRA; above knee						
Lundin 2000	50-100%	Segment	35	20	8	197
	100%	Segment	13	7	2	238
Currie, 1995	50-99%	Segment	25	7	10	38
Timonina 1999	100%	Artery	36	0	1	163
2D TOF MRA: below the knee						
Cortell 1996	50-100%	Segment	172	10	3	208
	75-100%	Segment	155	10	3	225
	100%	Segment	125	7	3	258
McDermott 1995	100%	Segment	95	1	21	99
	diseased or occluded	Segment	124	7	15	70
Eklof 1998	50-100%	Artery	59	2	14	31
	100%	Artery	40	10	7	49
2D TOF MRA: foot						
Eklof 1998	100%	Artery	19	8	3	3
CE MRA						
Study	**Stenosis threshold**	**Results reported by**	**TP**	**FP**	**FN**	**TN**
Whole leg, ≥50% stenosis						
Cronberg, 2003	50-100%	Segment	227	62	20	109
Laissy 1998	50-100%	Segment	104	14	9	393
Lenhart 2000	50-100%	Segment	79	8	4	129
Schafer 2003	50-100%	Segment	138	13	9	416
Steffens, 2003	51-100%	Segment	185	8	1	706

Sueyoshi 1999	50-100%	Segment	67	3	2	351
Winterer, 1999	51-100%	Segment	362	43	14	1361
Whole leg, ≥70% stenosis						
Schafer 2003	76-100%	Segment	110	3	4	459
Steffens, 2003	76-100%	Segment	147	11	4	738
Sueyoshi 1999	75-100%	Segment	53	4	0	366
Vavrik 2004	70-100%	Segment	170	26	17	661
Whole leg; occlusion						
Lenhart 2000	100%	Segment	54	2	4	160
Meaney 1999	100%	Segment	83	16	15	526
Schafer 2003	100%	Segment	72	1	5	498
Steffens, 2003	100%	Segment	85	7	4	804
Sueyoshi 1999	100%	Segment	39	1	0	383
Winterer, 1999	100%	Segment	255	11	13	1502
Above knee, ≥50% stenosis						
Lenhart 2000	50-100%	Segment	24	6	2	83
Lundin 2000	50-100%	Segment	35	18	8	204
Hany 1997	50-100%	Artery	62	7	2	163
Snidow 1996	50-100%	Artery	26	6	0	96
Above knee, ≥70% stenosis						
Vavrik 2004	70-100%	Segment	86	13	9	468
Above knee, occlusion						
Lenhart 2000	100%	Segment	14	0	2	99
Lundin 2000	100%	Segment	13	0	2	250
Hany 1997	100%	Segment	19	1	0	214
Snidow 1996	100%	Segment	18	0	0	110
Below knee ≥50% stenosis						
Kreitner 2000	50-100%	Segment	27	3	11	33
Lenhart 2000	50-100%	Segment	55	2	2	46

Zhang, 2005	51-100%	Segment	252	31	52	207
Below knee ≥70% stenosis						
Vavrik 2004	70-100%	Segment	84	13	8	193
Below knee; occlusion						
Lenhart 2000	100%	Segment	40	2	2	61
Zhang, 2005	100%	Segment	200	22	32	288
Foot						
Zhang, 2005	51-100%	Segment	59	20	16	48
	100%	Segment	50	11	13	69
CTA						
Study	**Stenosis threshold**	**Results reported by**	**TP**	**FP**	**FN**	**TN**
Whole leg; ≥50% stenosis						
Heuschmid 2003	51-100%	Segment	133	40	16	379
Martin 2003	50-100%	Segment	327	61	38	886
Puls 1996	51-100%	Segment	56	17	7	106
Rieker, 1996	50-100%	Segment	111	20	3	193
Catalano, 2004	51-100%	Segment	251	23	3	860
Portugaller, 2004	50-100%	Segment	240	80	21	399
Whole leg; ≥70% stenosis						
Heuschmid 2003	76-100%	Segment	88	7	12	461
Martin 2003	75-100%	Segment	236	20	34	1022
Rieker, 1996	75-100%	Segment	91	6	6	224
Whole leg, occlusion						
Heuschmid 2003	100%	Segment	49	6	5	508
Martin 2003	100%	Segment	202	2	26	1082
Puls 1996	100%	Segment	13	0	0	173
Rieker, 1996	100%	Segment	61	1	1	264
Catalano, 2004	100%	Segment	170	5	5	957

Above knee; ≥50% stenosis						
Rieker 1997	50-100%	Segment	49	2	3	101
Rieker 1997	50-100%	Segment	63	4	2	114
Portugaller, 2004	50-100%	Segment	86	23	3	238
Above knee ≥70% stenosis						
Rieker 1997	75-100%	Segment	28	0	0	127
Rieker 1997	75-100%	Segment	30	0	0	153
Above knee, occlusion						
Rieker 1997	100%	Segment	39	0	2	114
Rieker 1997	100%	Segment	48	1	2	132
Below knee; ≥50% stenosis						
Portugaller, 2004	50-100%	Segment	154	57	18	161
DUS						
Study	**Stenosis threshold**	**Results reported by**	**TP**	**FP**	**FN**	**TN**
Whole leg; ≥50% stenosis						
Aly, 1998	50-100%	Segment	404	27	34	2643
Beramini 1995	50-100%	Segment	94	13	24	273
Hatsukami 1992	50-100%	Segment	73	6	12	152
Linke 1994	50-100%	Segment	41	4	2	87
Sensier, 1996	50-100%	Segment	214	26	28	201
El-Kayali 2004	50-100%	Segment	123	15	3	216
Legemate, 1991	50-100%	Segment	179	30	33	676
Ashleigh, 1993	50-100%	Limb	69	2	0	5
Baxter 1993	50-100%	Limb	32	1	3	5
Whole leg; occlusion						
Aly, 1998	100%	Segment	272	18	25	2793
Beramini 1995	100%	Segment	76	10	13	305
Hatsukami 1992	100%	Segment	51	3	6	173

Linke 1994	100%	Segment	14	0	5	115
Sensier, 1996	100%	Segment	166	11	21	271
Zeuchner, 1994	100%	Segment	50	3	3	266
Legemate, 1991	100%	Segment	103	6	9	800
Ashleigh, 1993	100%	Limb	36	7	6	27
Whole leg; other stenosis thresholds						
Zeuchner, 1994	50-99%	Segment	12	1	4	305
Ashleigh, 1993	Suitability for angioplasty	Limb	25	7	4	42
Lai, 1995	Selection for angioplasty	Limb	14	9	9	54
Above knee; ≥50% stenosis						
Bergamini 1995	50-100%	Segment	83	12	8	194
Fletcher 1990	50-100%	Segment	59	12	8	89
Hatsukami 1992	50-100%	Segment	34	2	6	73
Lai, 1996	50-100%	Segment	124	12	42	354
Lundin 2000	50-100%	Segment	27	7	11	207
El-Kayali 2004	50-100%	Segment	74	9	1	171
Whyman 1992	51-100%	Segment	41	1	0	1
Eiberg, 2001	50-100%	Limb	50	8	1	35
Shaalan, 2003	50-100%	Limb	97	12	5	100
Above knee; ≥70% stenosis						
Fletcher 1990	75-100%	Segment	14	2	0	40
Lai, 1996	76-100%	Segment	83	8	44	397
Above knee; occlusion						
Currie, 1995	100%	Segment	25	4	5	146
Fletcher 1990	100%	Segment	45	7	5	111
Hatcukami 1992	100%	Segment	29	0	1	85
Hirai, 1998	100%	Segment	64	0	1	454

Lai, 1996	100%	Segment	50	0	12	470
Lundin 2000	100%	Segment	13	1	1	237
Whyman 1992	100%	Segment	26	1	0	16
Davies 1992	100%	Limb	27	1	1	36
Mergelsberg	100%	Limb	25	6	1	17
Above knee; other stenosis thresholds						
Bostrom, 2001	Suitabel for endovascular intervention	Segment	93	11	6	53
Hirai, 1998	50-99%	Segment	43	3	9	399
Davies 1992	50-99%	Limb	16	1	1	47
Below knee, ≥50% stenosis						
Bergamini 1995	50-100%	Segment	11	1	16	79
Hatsukami 1992	50-100%	Segment	27	1	6	44
Karacagil 1996	51-100%	Segment	211	47	36	186
El-Kayali 2004	50-100%	Segment	49	6	2	45
Below knee; occlusion						
Hatsukami 1992	100%	Segment	25	0	5	48
Karacagil 1996	100%	Segment	199	44	34	203
Koelemay, 1998	100%	Segment	457	77	324	655
Koelemay, 1997	100%	Segment	84	21	33	121
Wilson 1997	100%	Segment	80	1	5	36
Grassbaugh 2003	100%	Artery	36	6	12	56
Below knee; other stenosis thresholds						
Koelemay, 1998	Severe stenosis	Segment	813	99	257	344
Koelemay, 1997	Severe and occluded	Segment	136	23	52	48
Foot						
Hofmann 2004	Target vessels suitable for surgery	Segment	54	11	30	45

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Eiberg JP, 2010; Guideline Ref ID 16106)	Prospective study Moderate (sample may not be representative)	169 patients (15 segments per patient; grouped as supragenicular and infragenicular total 2535 segments). Only 169/530 eligible (32%) enrolled, limited by availability of DUS equipment and examiners, and patient consent	Intermittent claudication 25%; critical limb ischaemia 75%	Inclusion: Patients admitted with lower limb ischaemia scheduled for arteriography as part of treatment Exclusion: Patients with previous infra-inguinal reconstructions Baseline characteristics: median age 71 (interquartile range 62-77) years; 63% male; ankle BP 60 (IQ range 44-80)mmHg; ankle-brachial index 0.38 (IQ range 0.30-0.53); symptoms: claudication <300m: 25%, rest pain 31%, tissue loss	Duplex ultrasound (the day before DSA) from common femoral artery to pedal arteries after 15 minutes rest (femoral and anterior tibial, patient supine; popliteal, peroneal and posterior tibial patients in lateral decubitus position); <50% stenosis if peak systolic velocity	Digital subtraction angiography from distal aorta to pedal arteries; classified as <50% stenosis or ≥50% stenosis (including occlusions), or non-diagnostic if neither genuine vessel nor unnamed collaterals could be visualised due to inadequate amount of contrast.	see below	see below	Danish Medical Research Council, Frode V. Nyegaardand Wife's Foundation and the Kathrine and Vigo Skovgaards Foundation

				44%; type I or type II diabetes 31%; renal insufficiency (creatinine >150mmol/L) 6%.	<2; ≥50% stenosis if PSV ≥2.				

Effect Size

Overall agreement "good": kappa 0.67 (0.64-0.70)

Agreement according to level or severity of disease (1st p value compares supra- and infra-genicular segments; 2nd p value compares intermittent claudication and critical limb ischaemia)

	Supragenicular segments (n=845)	Infragenicular segments (n=1690)	Intermittent claudication (n=615)	Critical limb ischaemia (n=1860)	All segments (n=2535)
Kappa	0.75 (0.70-0.80)	0.63 (0.59-0.67) p<0.0001	0.63 (0.56-0.70)	0.70 (0.66-0.73) NS	0.67 (0.64-0.70)
Sensitivity	0.88 (0.85-0.91)	0.88 (0.85-0.90) NS	0.88 (0.85-0.91)	0.87 (0.85-0.89) NS	0.88 (0.86-0.89)
Specificity	0.88 (0.84-0.91)	0.75 (0.71-0.78) p<0.0001	0.75 (0.68-0.80)	0.82 (0.79-0.85) p<0.01	0.79 (0.77-0.82)
PPV	0.93 (0.90-0.95)	0.83 (0.81-0.86) p<0.01	0.87 (0.83-0.90)	0.86 (0.84-0.88) NS	0.87 (0.85-0.88)
NPV	0.81 (0.77-0.85)	0.81 (0.77-0.84) NS	0.77 (0.70-0.82)	0.84 (0.81-0.86) p<0.01	0.81 (0.78-0.84)
Technical success rate:					
DUS	100% (844)	93% (1569) p<0.001	96% (589)	95% (1765) NS	95% (2413)
DSA	99% (839)	93% (1573) p<0.001	91% (562)	96% (1790) p<0.001	95% (2412)

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Gjonnaess E, 2006; (Guideline Ref ID 16138)	Prospective Moderate quality (time between investigations not stated)	58 patients (15 segments each for total of 870	Significant stenoses: ≥50% 61/870 and	Inclusion: Patients with intermittent claudication (Fontaine stage IIa/IIb) referred for angiography of the	Gadolinium-enhanced magnetic resonance angiograph	Digital subtraction angiography	see below	see below	Pfizer AS, Norway

		segments; segments pooled into supra-inguinal [Aorta+ Common iliac artery+ External iliac artery]; thigh [Common femoral artery + Deep femoral artery + Superficial femoral artery] and knee regions [Popliteal artery+ Tibio-peroneal trunk artery])	occlusions 61/870 segments	lower extremities Exclusion: previous vascular or endovascular treatment Baseline characteristics: 36 men and 22 women; median age 66.5 years (range 47-80); previous cardiac infarction 4 patients; angina 5; heart failure 0; hypertension 24; hypercholesterolaemia 19; chronic obstructive pulmonary disease 5;diabetes 7; renal failure 0	y and colour duplex ultrasound (stenosis defined as significant [>50%] when 100% rise in Doppler peak velocity compared to velocities in normal adjacent [proximal or distal] segment; occluded if Doppler signals absent)				

Stenosis >50% or occlusion combined to "positive" category.

Segments	Stenosis ≥50%	Occlusion
Aorta	4	0
Common iliac artery	10	5
External iliac artery	4	3
Common femoral artery	3	5
Deep femoral artery	5	1
Superficial femoral artery	18	34
Popliteal artery	9	4

Tibio-peroneal trunk artery		8		9	
Total		61		61	
Effect Size					
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Kappa**
Magnetic resonance angiography	94% (89-98)	95% (93-97)	76% (69-83)	99% (98-100)	0.81 (0.74-0.87)
Duplex ultrasound	70% (61-78)	98% (96-99)	82% (74-90)	95% (94-97)	0.72 (0.65-0.79)
Suprainguinal region:					
MRA	96% (90-100)	94% (91-97)	64% (50-79)	100% (99-100)	0.74 (0.63-0.85)
DU	91% (79-100)	96% (93-98)	67% (50-83)	99% (98-100)	0.74 (0.62-0.86)
Thigh region:					
MRA	92% (86-99)	95% (92-97)	80% (71-89)	98% (97-100)	0.82 (0.72-0.93)
DU	76% (66-87)	99% (98-100)	94% (88-100)	95% (92-97)	0.81 (0.71-0.92)
Knee region:					
MRA	93% (84-100)	96% (94-99)	80% (67-93)	99% (97-100)	0.84 (0.71-0.97)
DU	33% (14-52)	98% (96-100)	67% (40-93)	91% (87-95)	0.40 (0.27-0.52)
Both duplex ultrasound and magnetic resonance angiography had a tendency to overestimate the length of the lesion.					
	Too short	**Correct (within 2cm of DSA measurement)**	**Too long**		
Magnetic resonance angiography	9%	70%	21%		
Duplex ultrasound	7%	65%	28%		
All 870 segments were successfully visualised with magnetic resonance angiography, but duplex ultrasound failed to visualise 10% segments in the suprainguinal region; 2% in the thigh region and 13% in the knee region.					

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Kos S, 2009; (Guideline Ref ID 16119)	Prospective High quality	20 patients (14 segments per foot [60% of	All patients had peripheral arterial occlusive disease	Inclusion: Patients with confirmed PAOD referred for percutaneous transluminal angiography	Contrast-enhanced magnetic resonance angiography (mean of 1.5	Digital subtraction angiography with selective imaging of	see below	see below	none stated

		patients had left foot measured and 40% right foot] for a total of 280 segments)	diagnosed by an experienced angiologist; Fontaine stage I (complicated by e.g. acral lesions) 5 patients (25%); stage II with claudication limiting quality of life 13 patients (65%); stage III 1 patient (5%); stage IV 1 patient (5%)	Exclusion: contraindications to MRI; estimated glomerular filtration rate <30mL/min/1.73m 2 body surface area Baseline characteristics: 9 women and 11 men; mean age 71.8 (range 58-83) years; smoker 60%; diabetes 40%; arterial hypertension 80%; dyslipidaemia 50%; mean ankle-brachial index 0.91 (range 0.59-1.26)	days [range 1-7 days] after DSA); 2 readers performed consensus reading in random manner; readers blinded to patient name, clinical history and results of other examination .	pedal vessels; 2 readers performed consensus readings			

Stenosis graded for each segment: grade 0 = no stenosis; grade 1 = 1-49% stenosis; grade 2 = 51-99% stenosis; grade 3 = occlusion <50% of segment; grade 4 = occlusion >50% of segment; arterial visualisation grade 1=excellent; 2=good; 3=moderate; 4=poor; 5=none. Mean score for arterial visibility DSA 2.89 (SEM 0.11) and MRA 2.70 (0.10), NS.

235/280 (83.9%) segments usable; 39 (13.9%) suboptimal and 6 (2.2%) unusable

Effect Size

156/280 segments had any grade of stenosis or occlusion on DSA (128 [82%] rated as clinically significant i.e. ≥50% stenosis or occlusion).

MRA overestimated lesions in 26/280 (9.3%) segments and underestimated 21/280 (7.5%, including 17 [13.3%] with clinically significant stenosis or occlusion).

	MRA				
DSA:	**Normal**	**Stenosis <50%**	**Stenosis ≥50%**	**Occlusion <50% of segment**	**Occlusion ≥50% of segment**
Normal	104	18	2	0	0
Stenosis <50%	4	20	4	0	0
Stenosis ≥50%	0	4	7	2	0

Occlusion <50% of segment	2	0	0	12	0
Occlusion ≥50% of segment	3	2	2	4	90

MRA vs. DSA in detecting clinically significant lesions i.e. ≥50% stenosis or occlusion

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
All segments	91.4%	96.1%	95.1%	93.0%	93.9%

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Kreitner KF, 2008; (Guideline Ref ID 206)	Prospective High quality	22 patients (7 vascular segments per patient: distal anterior tibial; distal posterior tibial; distal peroneal; dorsalis pedis; lateral plantar; medial plantar; pedal arch; total 154 segments)	10 moderate and 10 severe claudication; 1 ischaemic gangrene and 1 minor tissue loss with non-healing ulcer	Inclusion: patients with peripheral arterial occlusive disease Exclusion: Baseline characteristics: 14 men and 8 women; mean age 64 years (range 43-83 years); ankle-brachial index ranged from 0.2 to 1.64 (mean 0.71)	Contrast-enhanced magnetic resonance angiography; image analysis performed by 2 readers in random order after interval of 6 weeks, blinded to result of DSA, patient identity and clinical history	Digital subtraction angiography within 7 days of MRA; read after 4-week interval by 2 readers	not stated and insufficient data to calculate	not stated and insufficient data to calculate	not stated
Segments classified as patent or occluded; patent divided into stenosis ≤50% (including no stenosis) or >50%. Image quality scored 1=excellent; 2=good; 3=moderate; 4=non-diagnostic. Motion artefacts scored 1=none, 2=slight, 3=moderate, 4=severe. Higher image quality and fewer motion artefacts for MRA (1.32 [0.84] for MRA vs. 1.77 [0.61] for DSA, p=0.021 and 1.32 [0.84] vs. 1.95 [0.72], p=0.008 respectively). Intraobserver agreement good (kappa = 0.78) for image quality and moderate (kappa = 0.46) for motion artefacts.									
Effect Size									
	No. of arterial segments seen								

	MRA and DSA	Neither	MRA only	DSA only	Total	Kappa	95% CI	p value
Anterior tibial	18	3	1	0	22	0.83	0.68-1.32	1.00
Posterior tibial	22	0	0	0	22	1.00	1.00-1.00	1.00
Peroneal	17	4	1	0	22	0.86	0.60-1.12	1.00
Dorsalis pedis	20	2	0	0	22	1.00	1.00-1.00	1.00
Lateral plantar	21	1	0	0	22	1.00	1.00-1.00	1.00
Medial plantar	18	3	1	0	22	0.83	0.51-1.15	1.00
Pedal arch	21	1	0	0	22	1.00	1.00-1.00	1.00
Overall	137	14	3	0	154	0.89	0.77-1.00	0.25

Overall agreement “very good”; but on DSA, significantly more patent vessel segments assessed as partially occluded than on MRA (p=0.004)
Of the 137 patent vessels visualised by both techniques:

Characterised by MRA:

Characterised by DSA:	With segmental occlusion	Without segmental occlusion	Total
With segmental occlusion	23	20	43
Without segmental occlusion	5	89	94
Total	28	109	137

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Napoli A, 2011; (Guideline Ref ID 16355)	Prospective study High quality	212 patients; 7392 segments; 1060 regions Pelvic and leg arteries were imaged	By DSA: atherosclerotic lesions detected in 6126 / 7420 (82.6%) arterial segments; 657 (62%) vascular regions; 210 (99.1%	Patients with symptomatic PAD (Fontaine stage IIa-IV), positive ABI index test results, and referred for imaging of the abdominal aorta and in-	Multidetector CT angiography using 64 section scanner and Visual Station for visualisation (MD- CTA blinded to	Digital subtraction angiography (DSA blinded to CTA)	see below	see below	None mentioned

			patients). Atherosclerotic lesions classified as: grade 1 – 1961 (32%) segments; grade 2 – 1041 (17%) segments; grade 3 – 2994 (48.9% segments) and grade 4 occlusion in 130 (2.1%) segments.	flow and run-off arteries after duplex US. Baseline characteristics: 168 men + 44 women; mean age 62 years (men), 68 years (women) – range 41-88; current smokers 123 (SD 58), previous smokers 34 (SD 16); diabetes 176 (83); BMI 28 (5.0); Fontaine IIa – 97 (45.8); Fontaine IIb – 55 (25.9); Fontaine III – 34 (16); Fontaine IV – 26 (12).	DSA)				
Stenosis graded visually for each segment: grade 1 = no / mild stenosis (≤49% luminal narrowing); grade 2 = moderate stenosis (50-69% luminal narrowing); grade 3 severe stenosis (70-99% luminal narrowing); grade 4 = occlusion (100% luminal blockage)									
Effect Size Segments									
		DSA (negative)			**DSA (positive)**			**Total**	

CT (negative)	4141 (TN)	39 (FN)	4180
CT (positive)	115 (FP)	3072 (TP)	3187
Total	4256	3111	7367

Diagnostic accuracy of CTA vs DSA fro detecting clinically relevant steno-occlusive disease at segmental level.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Whole leg + 70% stenosis	99% (3072/3113)	97% (4141/4279)	96% (3072/3187)	99% (4141/4180)

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Reference	Study type and comments on quality	Number of patients	Prevalence	Patient characteristics	Index test	Reference standard	Sensitivity and specificity	PPV and NPV	Source of funding
Schernthaner R, 2008; (Guideline Ref ID 197)	Prospective study Moderate quality (not all vessel segments visualised during DSA due to ethical considerations concerning exposure of patient to more radiation than required for clinical purposes.)	50 patients; 1351 vessels	358/1351 significant stenoses by DSA; 247 occluded by DSA	Patients referred for DSA of the lower legs due to known or suspected peripheral arterial occlusive disease. 27 men + 23 women; mean age 68 years (range 43-90 years)	Multidetector CT angiography using 16-row scanner and MulitPathCPR for visualisation (MD-CTA blinded to DSA) of aorta and run-off vessels at least 1 day prior to DSA (mean 12 days, range 1-30 days)	Digital subtraction angiography (DSA blinded to CTA); not all vessel segments visualised during DSA due to ethical considerations concerning exposure of patient to more radiation than required for clinical purposes.	see below	see below	Fonds zur Förderung der wissen-schaftlichen Forschung (FWF Austria)

- Stenosis graded visually for each segment: grade 0 = healthy; grade 1 = 1-49% stenosis (i.e. patent); grade 2 = 51-69% stenosis (no haemodynamic significance); grade 3 = 70-99% stenosis (haemodynamically significant); grade 4 = 100% stenosis (occlusion); grades 3 and 4 combined to “positive” category.
- Stenosis length graded as: short (<1cm); 1-3cm; 3-5cm; 5-10cm; entire segment.

• Number of lesions within each segment graded as: single or multiple lesions per segment.			
Effect Size **Segments (same table as above but divided as above and below knee)**			
	DSA <70% stenosis (negative)	**DSA >70% stenosis (positive)**	**Total**
Iliac and FP: **CT <70% stenosis (negative)** **CT >70% stenosis (positive)**	 614 (TN) 4 (FP)	 2 (FN) 192 (TP)	812
Infrapopliteal: **CT <70% stenosis (negative)** **CT >70% stenosis (positive)**	 374 (TN) 1 (FP)	 3 (FN) 161 (TP)	539
Total	993	358	1351
Above knee ≥ 70% stenosis: sensitivity = 99%; specificity = 99.4% Below knee ≥ 70% stenosis: sensitivity = 98.2; specificity = 99.7%			

H.4 Management of intermittent claudication

H.4.1 Supervised exercise compared to unsupervised exercise

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Cheetham 2004; (Guideline Ref ID 549) RCT **Randomisation:** Computer generated **Allocation concealment:** unclear **Blinding:** Patients not blinded but outcome assessors blinded to allocation.	Total N = 59 **Inclusion criteria:** • Resting ABPI<0.9 or a positive response to a validated stress test (a drop in ankle pressure of .30 mmHg following 1 min of treadmill walking at 10% slope and 4 km/h measured 40 s post exercise). • PAD confirmed by duplex scans of the affected leg(s). • Positive response to the Edinburgh Claudication Questionnaire. • Minimum of 6-month period of stable mild –	Supervised exercise (N=29) Advice as per non-supervised group and in addition weekly 45 min supervised exercise (under medical and physiotherapy supervision) and motivation class for 6 months based in a hospital gym.	Unsupervised exercise (N = 30) All patients in both groups received both written and verbal exercise advice. A walking programme of at least 3 times per week to near maximal pain, for at least half an hour per session.	SF 36	Funding source: No details

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Sample size calculation: Based on CCCQ. **Drop outs:** 6 months - 56/59 were assessed. One was abroad, one died, one left the area 12 months – 55/59 were assessed (2 deaths and 2 moved out of area). No deaths were attributed to a vascular event during the year period. **Follow-up duration:** 3 and 6 months at study end and 12 months.	moderate IC symptoms (able to walk 300 m on the flat in 6 min). **Exclusion criteria:** • Severe IC requiring radiological or surgical intervention. • CLI • Significant co-morbidity preventing participation • Vascular or endovascular intervention within the last 2 years. • Received drugs within previous 6months to improve symptoms. **Baseline characteristics:** Mean age: 70yrs (exercise) and 65 years (unsupervised) Mean age 67 years (range 45 – 86 years), (supervised) 73% male, 100% current or ex smokers and 19% were diabetics. No further details provided, but no differences between groups at baseline with the exception of age which was adjusted for in the analysis of the results.	Exercise was self determined in a walking circuit with seven 2 minute exercise stations aimed at lower limb strength. All patients were given BMT - appropriate initiation of anti-platelet therapy, anti-hypertensive therapy, cholesterol-lowering agents and diabetic control	Additional leg exercises to be performed at home, such as stair climbing and tiptoe walking, were also advised. Reviewed 3 monthly.		

Effect Size			
Outcome	Supervised exercise (N=29)	Unsupervised exercise (N=30)	P value
SF-36 physical functioning score (median)			
3 months	64	55	P>0.7
6 months	70	55	P<0.05
9 months	70	55	P=0.09
12 months	69	55	P=0.02

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Gardner 2011 (Guideline Ref ID 16281)
RCT

Randomisation: No details

Allocation concealment: No details

ITT analysis: None

Follow up duration
No follow up beyond three month intervention period</td>
<td>Total N = 119

Inclusion criteria:
• History of any type of exertional leg pain.
• Ambulation during a graded treadmill test limited by leg pain consistent with IC and ABPI ≤0.90 at rest or ≤0.73 after exercise.

Exclusion criteria: none reported

Baseline clinical characteristics
<table>
<tr><th>Variables</th><th>Supervised exercise (n=40)</th><th>Home-based exercise (n=40)</th></tr>
<tr><td>Age, y</td><td>66 (12)</td><td>65 (11)</td></tr>
<tr><td>Weight, kg</td><td>82.2 (21.5)</td><td>85.2 (17.6)</td></tr>
<tr><td>Body mass index, kg/m2</td><td>29.2 (7.1)</td><td>29.9 (5.6)</td></tr>
<tr><td>ABPI</td><td>0.71 (0.25)</td><td>0.72 (0.23)</td></tr>
<tr><td>White, %</td><td>45</td><td>65</td></tr>
<tr><td>Currently smoking, %</td><td>10</td><td>10</td></tr>
<tr><td>Male, %</td><td>45</td><td>45</td></tr>
<tr><td>Diabetes mellitus, %</td><td>43</td><td>43</td></tr>
<tr><td>Hypertension %</td><td>88</td><td>88</td></tr>
<tr><td>Dislipidemia %</td><td>88</td><td>90</td></tr>
<tr><td>Abdominal</td><td>45</td><td>55</td></tr>
</table>
</td>
<td>Supervised exercise (n=40)
3 months of supervised, intermittent treadmill walking for 3 days/week at a speed of 2 mph. Walking began at 15 minutes for the first two weeks and increased by 5 minutes biweekly until a total of 40 minutes of walking during final 2 weeks of programme.</td>
<td>Home-based exercise (n=40) rehabilitation programme - 12 weeks of intermittent walking to near-maximal claudication pain 3 days/week at self-selected pace.</td>
<td>Sessions attended

Dropouts

Adverse events</td>
<td>Funding source: CMRI diabetes and metaboloic research programme</td>
</tr>
</table>

Study details	Patients			Intervention	Comparison	Outcome measures	Other comments
	obesity, %						
	Metabolic syndrome components, n	3.4 (1.4)	3.5 (1.1)				
	Metabolic syndrome, %	73	83				
	Obesity, %	43	48				
	Values are means (SD) when appropriate						
Effect size:							
Drop outs: 27 out of 92 people did not complete the study. No significant difference among groups was found for total number of dropouts (P=0.56), dropouts owing to disinterest (P=0.845), and drop outs resulting from adverse events (P=0.592). Adverse events: 3 in supervised group, and 4 in the home-based exercise group.							
Exercise intervention measures							
Variables	Supervised Exercise Group (n=33)		Home-based Exercise Group (n=29)		P		
Exercise sessions completed, %	84.8 (20.9)		82.5 (27.7)		0.712		
Values are means (SD)							

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Kakkos. 2005; Guideline Ref ID 453) RCT **Randomisation**: Blind block	Total N = 34 **Inclusion criteria:** • Stable IC >6 months due to SFA occlusion ≥6 cm in length on ultrasound and/or angiogram.	Supervised exercise (n=12) Daily exercise by walking as much as possible to near maximal pain and attend 6 month, 3 x per week supervised	N = 9 Unsupervised group Advised to exercise daily by walking as much as possible to near maximal pain, for a period of at least 45	Compliance Withdrawal MOS SF36	Funding source: No details

telephone randomisation generated by computer (Stratified by age and ACD).

Allocation concealment: Central allocation

Blinding: None

ITT analysis: No

Sample size calculation: Based on ICD

Drop out:

Treatment end:

Supervised - 6 patients discontinued and 8 available for analysis;

Unsupervised – 0 dropout and 9 available for analysis

Follow-up duration:

1 year - 2 allocated to supervised exercise withdrew consent; 1 in the supervised exercise group withdrew

Exclusion criteria:

- Symptom duration <6 months,
- Angioplasty or arterial surgery to the symptomatic leg, myocardial infarction within the previous 6 months
- Unable to undertake treadmill examination or training
- Psychiatric illness or other reason making follow up difficult
- Ischaemic rest pain, gangrene or ischaemic ulceration
- Unable to attend exercise programme
- Severe peripheral neuropathy (diabetes, etc.)
- Enrolment ABPI >0.9 or non-compressible calf arteries (diabetes, chronic renal failure, etc.) precluding ABPI measurement.
- Iliac occlusions or stenoses amenable to surgery or angioplasty, femoral artery occlusion <6cm on duplex
- Suitable for angioplasty
- Limited exercise capacity due to angina, CHF, COPD, spinal column disease, venous disease, neurological disease or arthritis.
- Maximum claudication distance >300m or <50m on treadmill test.
- Baseline tests differed by >25% for ACD.

Baseline characteristics:

Baseline	Supervised exercise n = 12	Unsupervised exercise N = 9
Age (years)	69 (11.8)	66 (10.5)
Male (n)	11 (92%)	8 (89%)

exercise programme.

Attended physiotherapy department. Supervision provided on individual or group basis. Sessions lasted approx. 60min.

Consisted of 5 min warm up, 50 min intermittent exercise and ended with 5 min cool-down using a graded exercise protocol.

N = 13

Intermittent pneumatic compression- not discussed further

Patients in both interventions:

Advice to cease smoking

Commence antiplatlet therapy – preferably 75mg aspirin od.

Lipid lowering statins prescribed and titrated to reduce LDL serum levels <2.5 – 3 mmol/l if necessary.

Patients followed the same advice for the 6

min.

.

	Smoking history (n)			month post treatment follow up as the unsupervised group had received.			
	Current	2	3				
	Previous	8	6				
	CHD (n)	2	1				
	CABG (n)	0	1				
	Diabetes (n)	3	1				
	Hypertension (n)	4	2				
	Hypercholesterolaemia (n)	5	5				
	BMI (Kg/m2)	24.9 (5.3)	24.7 (10.9)				

Effect size:

Compliance in supervised group ranged from 12.8 to 100% median 60.3% of the expected attendance (72 days)

Withdrawal/complications/reinterventions

	At 6 weeks	**At 6 months**	**At 12 months**
Supervised exercise	2 patients withdrew consent	4 patients stopped physiotherapy due to fatigue, GI bleeding Minor domestic leg injury, Bladder cancer (subsequently died) Latter two did not have their walking distance assessed at 6 months	2 patients withdrew consent
Available for analysis	10	8	Unclear
Unsupervised exercise		1 patient developed rest pain and subsequently had a femoro-popliteal bypass surgery	1 patient moved and withdrew consent
Available for analysis	9	9	8

QoL: SF-36 – median (IQR) scores given

SF-36 Median (IQR)		**Supervised**	**Unsupervised**
Physical functioning	Baseline	65 (56-70)	50 (35-65)
	6 months	65 (50 – 73)	60 (46 - 69)
	12 months	50 (35 – 65)	45 (35 - 60)
Role physical	Baseline	50 (50-94)	100 (50-100)
	6 months	50 (38 – 50)	75 (56 – 94)
	12 months	0 (0 – 100)	50 (25 – 100)

Bodily pain	Baseline	60 (51-78)	60 (32-77)
	6 months	70 (48 – 90)	62 (43 – 70)
	12 months	62 (41 – 84)	51 (31 – 74)
General Health	Baseline	35 (26-45)	35 (28-59)
	6 months	35 (30 – 43)	40 (35 – 49)
	12 months	50 (42 – 72)	40 (35 – 45)
Physical composite score	Baseline	49 (41-61)	52 (45-62)
	6 months	52 (35 -61)	53 (50 – 55)
	12 months	48 (40 -54)	47 (43 -57)
Vitality	Baseline	70 (60-70)	60 (65-43)
	6 months	60 (50 – 75)	65 (46 – 70)
	12 months	50 (45 – 60)	50 (45 – 60)
Social functioning	Baseline	78 (69-89)	78 (67-78)
	6 months	78 (72 – 83)	72 (58 – 78)
	12 months	89 (78 – 100)	89 (22 - 100)
Role emotional	Baseline	0 (0-25)	33 (0-33)
	6 months	0 (0 – 33)	33 (33 - 33)
	12 months	0 (0 – 33)	67 (0 – 100)
Mental health	Baseline	44 (32-52)	52 (38-66)
	6 months	56 (40 – 60)	44 (37 – 64)
	12 months	76 (60 – 80)	88 (64 – 100)
Mental composite score	Baseline	54 (47-62)5	51 (38-62)
	6 months	51 (41 – 63)	58 (47 – 66)
	12 months	53 (49 – 62)	63 (49 – 79)

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comment
Nicolai 2010; (Guideline Ref ID 15927)	Total N = 304 No study data: 1 patient control group.	N = 109 (analysed n = 93) Supervised exercise	N = 102 (analysed n = 83)	Withdrawal rate	Funding source: Netherlan

RCT - Multicentre (11 sites, Netherlands)

Randomised: Central randomisation by telephone. Numbers generated by computer-generated block randomisation list (block size 9, first block opened at random) stratified by center.

Allocation concealment: Centralised

Blinding:
Therapists, vascular surgeons and subjects not blinded but outcome assessors were.

Sample size calculation: Based on primary outcome

ITT analysis: Modified ITT using data from patients who had treadmill data after 12 months of treatment. Excluded patients who dropped out with <12 months follow-up. Patients who crossed over or stopped treatment but performed assessment were analysed in their original group

Drop outs:
Control group - 1 did not start

Inclusion criteria:
- Fontaine stage II PAD who were considered for conservative treatment.
- ABPI<0.9 and ACD <500m assessed with a standardised treadmill test.

Exclusion criteria:
- Prior supervised exercise programme for IC
- Previous peripheral vascular intervention
- Insufficient command of the Dutch language,
- Serious cardiopulmonary limitations (New York Heart Association functional class III or IV),
- Previous lower limb amputation, psychiatric instability, and other serious comorbidity that might hinder physical training.
- COPD and CHD defined as angina pectoris or myocardial infarction, were recorded by medical history.

Baseline	Supervised N=109	Unsupervised N = 102
Age (years) SD	66.1±9.0	66.9±8.6
Male (%)	72.5	55.9
BMI (mean, SD)	27.4±4.2	28.2±4.7
ABI (mean, SD)	0.67±0.19	0.65±0.17
Smoking history (%)	88	88.3

therapy (SET) provided by local community based physical therapists

Or SET plus personal activity monitor accelerometer for feedback (assesses physical activity during normal life). N = 93 (analysed n = 76)

Local therapist and SET administered according to the guidelines of the Royal Dutch Society for Physical Therapy.

The programme aim was to increase walking distance through interval training and also consisted of walking pattern improvement and enhancement of endurance and strength. Patients generally started with a frequency of two to three sessions of 30 minutes weekly. This was tailored to the individual need of the patient during the treatment year. In conformity with the control group, all SET patients were

Walking advice only.
Verbal walking advice and a brochure distributed by the Patients Association of Vascular Diseases explaining exercise therapy. Patients were instructed by their clinicians to complete three training sessions per day. During each session, maximum pain level should be reached three times. Hence, patients were advised to walk until maximum pain level nine times a day, divided in three sessions.

Reintervention

MOS SF36

EQ-5D

ds Organisation for Health Research and Development

the study after randomisation. 5 received intervention during the study (analysed in control group). 15 lost to follow-up and 3 died (83/102, 81% analysed). Supervised group - 12 lost to follow-up, 4 died and 11 others stopped the intervention for other reasons than satisfaction with improved walking distance but were eligible for analysis (93/109, 85% analysed). Supervised with feedback - 3 did not start the study and 27 stopped programme, of whom 14 were lost to follow-up and 13 patients discontinued but were available for analysis **Follow-up duration:** 1 year				encouraged to perform at least three walking sessions every day. All patients received cardiovascular risk management, cholesterol-lowering medication, antiplatelet therapy, the advice to stop smoking and modification of other atherosclerotic risk factors that were present			

Effect size:

- Supervised exercise groups were analysed together since 28.9% of the 'supervised exercise with feedback group' reported not using the PAM accelerometer (feedback device) at all or for only part of the study year.
- During the study 9 patients of unsupervised group and 13 of both supervised groups together underwent a peripheral vascular intervention due to worsening of complaints or dissatisfaction with the results of the exercise programme.

Withdrawal rate

	Randomisation (did not receive intervention – not analysed)	Follow-up (not analysed)
Unsupervised	1 (no details)	18 15 lost to follow-up; lack of motivation (7), CHD (1), CVA (1), orthopedic disease (2), other concomitant disease (4)

		3 died; CHD (2), RCC (renal cell carcinoma) (1) 10 patients discontinued but were eligible for analysis
Supervised exercise	0	16 12 lost to follow-up; lack of motivation (3), PAD progression (2), CHD (1), orthopedic disease (2), diabetic foot (1), other concomitant disease (3) 4 died; complication lower extremity bypass surgery (1), lung carcinoma (1), ruptured abdominal aortic aneurysm (1), pancreatic cancer (1) 13 patients discontinued but were eligible for analysis
Supervised exercise with feedback	3 (no details)	14 lost to follow-up; lack of motivation (5), amputation (1), CHD (2), orthopedic disease (3), other concomitant disease (3)

Relevant domains of the SF-36 (physical function, pain) improved statistically significantly in the superviseed groups compared with the unsupervised group

	Unsupervised				**Supervised**				
	Baseline	12 months*	P value**	Change	Baseline	12 months*	P value**	Change	P value***
SF-36									
Physical function	52.4±15.0	59.0±19.0	<.001	6.6±18.5	52.8±14.3	65.1±16.8	<.001	12.3±18.3	.004
Physical role	51.0±40.8	55.8±39.8	.71	4.8±49.4	45.8±39.1	65.3±36.2	<.001	16.6±45.2	.19
Pain	52.0±18.0	55.8±22.7	.36	3.9±26.6	51.1±16.6	64.8±22.5	<.001	13.4±24.5	.002
General health	54.9±13.0	54.2±12.8	.53	-0.7±14.0	53.7±12.6	53.6±14.3	.10	0.7±13.5	.82
Physical summary score	35.2±8.1	37.7±8.8	.01	2.5±10.3	34.6±7.1	40.4±8.4	<.001	5.8±8.6	.02
Social function	79.9±19.6	75.4±25.3	.06	-4.5±27.4	77.1±22.8	81.7±22.8	.04	4.3±26.6	.09
Emotional role	85.1±29.0	82.4±34.9	.81	-2.7±41.5	85.2±32.6	86.1±29.1	.8	0.3±38.7	.31
Mental health	76.4±17.2	74.6±19.1	.25	-1.8±15.6	75.5±17.8	74.9±20.3	.42	0.3±16.8	.15

Vitality	63.0±20.3	59.2±19.8	.05	-3.9±18.7	61.6±18.7	62.0±18.9	.46	-0.6±17.5	.17
Mental summary score	55.9±9.9	53.0±11.4	.006	-2.8±10.1	55.3±10.5	53.5±10.4	.009	-1.8±10.4	.38

*Data at 3, 6, 9 months were not detailed
**Repeated measurements analysis of variance
*** Repeated measurements analysis of covariance with baseline measurement as covariant

	Unsupervised (mean ± SD)	**Supervised (mean ± SD)**	**P-value (Mann-Whitney)**
Baseline	0.62 ± 0.23	0.66 ± 0.2	0.51
3 months	0.68 ± 0.23	0.69 ± 0.21	0.5
6 months	0.69 ± 0.19	0.72 ± 0.17	0.4
9 months	0.68 ± 0.23	0.73 ± 0.21	0.03
12 months	0.66 ± 0.26	0.74 ± 0.2	0.03
QALY	0.67	0.71	Difference (boot strapped 2.5th – 97.5th perc) 0.038 (0.0003-0.0796

1

Study details	**Patients**	**Intervention**	**Comparison**	**Outcome measures**	**Other comments**
Pinto 1997; (Guideline Ref ID 17) RCT **Randomisation:** Based on median split of maximum walking time on the treadmill test for each cohort. **Allocation concealment:** None reported	Total N = 60 **Inclusion criteria:** • Diagnosis of arterial claudication ABPI <0.9 • Decrease in ankle pressure by 15mmHg or more following standard exercise protocol. **Exclusion criteria:** • Not meeting inclusion criteria • Ischaemic rest pain, tissue loss, arthritis and/or obstructive pulmonary disease.	N = 30 Onsite supervised exercise lasting 12 weeks. Sessions 3 times a week lasting 60 minutes and included incremental stationary bicycling or arm cycling and treadmill exercise. Also attended a weekly health education lecture	N = 30 Home based exercise, attended 12 weekly 1 hr educations sessions. Also asked to walk at home to tolerance for 20-40 minutes at least 3 times a week. To pause at onset of pain and then continue. Log their walk- pauses in a home log.	Withdrawals Compliance MOS SF36	Funding source: American Heart Association, National Institutes of Health

Blinding: None **Sample size calculation:** Based on differences in MWD. **ITT analysis:** None **Drop outs:** 5 dropped out before start of programme (3 supervised, 2 unsupervised) 8 dropped out during treatment programme – 3 supervised, 5 unsupervised (no details) 8 additional dropouts between end of treatment and 6 month follow-up – 5 supervised, 3 unsupervised (no details) **Follow up duration:** 12 week (intervention end) and 6 month follow up.	**Baseline characteristics**			programme (1 hrduration), although patients not required to make lifestyle changes recommended. Compliance 88%	Vascular nurses provided feedback and problem solving prior to the weekly lecture.		
	Baseline	Supervised N= 27	Unsupervised N= 28				
	Mean age (years) SD	67.9 (7.5)	70.3 (8.6)				
	BMI	28.8 (3.9)	27.7 (4.9)				
	Resting ABPI	0.57 (0.12)	0.59 (0.15)				
	Mean time to claudication (min)	3.8 (2.7)	3.6 (2.7)				
	Maximal walking time (min)	5.5 (3.2)	5.3 (2.8)				
	Male (%)	59.3	46.4				
	Caucasian (%)	88.9	82.1				
	Smoking history (%)	25.9	21.4				
	Chronic illnesses						
	Myocardial infarction	9 (33.3%)	8 (28.6%)				
	Hypertension	19 (70.4%)	15 (53.6%)				
	Diabetes	8 (29.6%)	11 (39.3%)				
	Back injury	8 (29.6%)	5 (17.9%)				
	Numbers in parentheses denote standard deviations unless otherwise noted.						

Effect size:			
Withdrawal rate			
	Prior to programme start	**3 months**	**6 months**
Supervised exercise	3	3; 23 questionnaires and walking test; 1 questionnaires only	5; 15 questionnaires and walking test; 3 questionnaires only; 1 walking test only
Unsupervised exercise	2	5; 23 questionnaires and walking test	3; 19 questionnaires and walking test; 1 questionnaires only
Mean (SD) quality of life (SF-36) scores at baseline, post-treatment (3 months) and follow-up (6 months)			

	Baseline	3 months	6 months
Physical functioning			
SE	46.9±18.4	53.2±23.1	56.1±14.4
UE	43.5±21.4	53.7±25.3	54.2±23.4
Bodily pain			
SE	55.0±20.4	64.0±20.3	61.5±20.5
UE	54.1±22.1	63.7±20.9	63.6±19.3
Vitality			
SE	56.4±16.0	52.0±16.2	53.8±17.9
UE	50.0±17.4	57.5±15.6	54.5±19.4
Physical component score			
SE	36.7±7.5	38.1±8.5	39.3±8.5
UE	34.1±10.0	38.7±12.2	37.7±11.1
Mental health component score			
SE	55.1±6.7	53.3±7.7	51.3±10.2
UE	54.3±8.4	53.8±8.1	54.9±7.3

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Regensteiner 1997; (Guideline Ref ID 931) RCT Single centre trial. **Randomisation:** Unclear **Allocation concealment:** Unclear	Total N = 20 **Inclusion criteria:** • Disabling intermittent claudication (impacting on ability to perform social, recreational, or vocational activities) • stable claudication symptoms over previous 3 months • Resting ABPI<0.94 decreasing to <0.73 after exercise. • No leg pain at rest, ischemic ulceration, or gangrene.	N = 10 Supervised exercise 3 x weekly hospital based supervised treadmill walking sessions for 12 weeks. All patients taking chronic medications continued their drugs, with the dosage	N= 10 Unsupervised exercise 3 x weekly home based walking programme for 12 weeks.	ABPI Compliance Withdrawals Medical Outcomes Study SF-20	Funding source: The Denver Veterans Administration Hospital

Blinding: none

Sample size calculation: None

ITT analysis: Yes

Drop outs: None reported

Follow-up duration: 12 weeks at study end.

Exclusion criteria:

- Unable to walk on the treadmill at a speed of at least 2 mph
- Or whose exercise capacity was limited by symptoms of angina, congestive heart failure, COPD or arthritis, diabetes,
- Had undergone vascular surgery or angioplasty within the previous year.

No differences in risk factors and comorbid conditions or medications.

Baseline characteristics

	Supervised exercise N = 10	Unsupervised exercise N = 10
Mean age	65 ± 7	64 ± 7
Risk factors and comorbid conditions		
Vascular surgery/angioplasty	2	1
Coronary artery disease	3	3
Cerebrovascular disease	3	2
Hypertension	5	5
Hyperlipidemia	4	3
Current smoker	6	5
Pack years	47±31	45±29
Medications		
Pentoxifylline	1	1
Aspirin	5	4

unchanged during the study

	Other antiplatelet	2	0				
	ß-adrenergic-blocker	3	2				
	Calcium channel blocker	0	1				
	ACE inhibitor	1	0				
	Other antihypertensive	4	5				

Effect Size:

Compliance:

- All patients in both groups completed 36 sessions of exercise training. Subjects in the hospital-based programme completed 36 sessions within 13.5±1.4 weeks. Subjects in the home-based programme completed 36 sessions within 14.1±1.7 weeks

Outcome at 3 months (Mean ± SD)	**Supervised exercise**	**Unsupervised exercise**	**Outcome at 3 months (Mean ± SD)**	**Supervised exercise**
	Baseline	12 weeks		Baseline
Resting ABPI	0.64±0.19	0.63±0.19	Resting ABPI	0.64±0.19
MOS SF-20 (%)			MOS SF20 (%)	
Physical function	52±19	72±18	Physical function	52±19
Social function	58±14	60±16	Social function	58±14
Role function	65±20	63±18	Role function	65±20
Well-being	67±13	65±22	Well-being	67±13
Overall health	45±18	56±19	Overall health	45±18

1

Study details	**Patients**	**Intervention**	**Comparison**	**Outcome measures**	**Other comments**
Savage 2001; (Guideline Ref ID 3035) RCT	Total N = 21 **Inclusion criteria:** • >50 years with clinical diagnosis of IC (Grade I or	N = 11 Supervised exercise 3 x per week for 12	N = 10 Home based exercise.	Absolute claudication distance, initial	Funding source: Supported in part by

Randomisation: Unclear

Allocation concealment: Unclear

ITT: Unclear

Sample size calculation: Unclear

Dropouts: Unclear

Follow up duration:
12 weeks to end of study and then a further 12 weeks. Total 24 weeks

Category 1, 2, or 3 according to the Society for Vascular Surgery/International Society for Cardiovascular Surgery's standardized reporting system).

Exclusion criteria:

- Unstable cardiopulmonary disease, severe lower extremity arthritis, tobacco use, weight greater than 40 kg above ideal, renal insufficiency,
- use of beta-blocking drugs, use of pentoxifylline or cilostazol within 8 weeks of entry to the study
- functioning lower-extremity bypass, or severe cognitive impairment.

Baseline characteristics

Baseline mean	Supervised exercise n = 11	Home based exercise n = 10
Age (years) SD	66.4 ± 9.1	66.1 ± 8.9
Gender M/F	8/3	7/3
ACD (meters)	521.5±263.4	532.2±263.5
ICD (meters)	241.2±188.2	182.8±150.5
ABPI	0.71±0.1	0.75±0.13

weeks (exclusively treadmill walking). Instructed to walk to point of intense pain during each session, at which time they rested by standing on the treadmill. Exercise resumed when claudication pain dissipated, continuing this process until 15 minutes of total walking time was accumulated. The 15 minute walking period was extended 5 minutes every 2 weeks until patient was walking for a total of 40 minutes.

Note: At the end of 12 weeks, the on-site patients transitioned to the same home exercise programme used by the home group for an additional 12 weeks.

Exercise at least 3 times weekly, walking to the point of intense pain, resting, then continuing for 15 minutes of walking. Instructed to gradually increase duration to total of 40 minutes of walking.
Contacted by telephone monthly to discuss programme.

claudication distance, ABPI

MOS SF36

the General Clinical Research Center, University of Vermont College of Medicine and by the Medical Research Council of Canada (Dr. Brochu), and American Heart Association (Vermont affiliate).

Effect Size							
Outcome	**Supervised exercise**				**Unsupervised exercise**		
Absolute claudication distance (m)							
3 months	833.3 ± 376.3				736.5 ±290.3		
6 months	741.9 ± 365.6				715.0 ± 394.4		
Initial claudication distance (m)							
3 months	456.9 ±317.2				225.8 ±150.5		
6 months	483.8 ±317.2				263.4 ±155.9		
ABPI							
3 months	0.71 ± 0.1				0.76 ± 0.08		
6 months	0.81 ± 0.22				0.71 ± 0.15		
MOS SF-36							
Physical function							
Baseline	54 ± 14				45 ± 17		
3 months	60 ± 16				61 ± 10		
6 months	56 ± 14				54 ± 27		

Role-physical		
Baseline	84 ± 30	47 ± 47
3 months	77 ± 34	68 ± 43
6 months	84 ± 19	47 ± 46
Bodily pain		
Baseline	59 ± 20	50 ± 13
3 months	70 ± 18	72 ± 23
6 months	65 ± 19	64 ± 14
General health		
Baseline	71 ± 17	67 ± 9
3 months	64 ± 14	65 ± 17
6 months	66 ± 18	65 ± 19
Vitality		
Baseline	66 ± 17	49 ± 22
3 months	68 ± 17	47 ± 6
6 months	63 ± 16	52 ± 19
Social function		
Baseline	91 ± 11	85 ± 19
3 months	92 ± 10	90 ± 15
6 months	91 ± 10	85 ± 20
Role-emotional		
Baseline	97 ± 10	75 ± 46
3 months	82 ± 35	81 ± 38
6 months	71 ± 45	74 ± 43
Mental health		
Baseline	79 ± 16	83 ± 13
3 months	82 ± 12	74 ± 17
6 months	73 ± 17	65 ± 31

1

<table>
<tr><th>Study design</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Stewart 2008; (Guideline Ref ID 167)

RCT - Single centre in England

Randomisation: No details

Allocation concealment: by independent investigator

Blinding: Double Investigators blinded to randomisation and participants blinded to outcome for treadmill test results

Sample size calculation: Based on primary outcome measures

Drop outs:
At 3 months: 4 (2 from each group)
At 6 months: Additional 5 (1 from intervention, 4 from control group).

ITT analysis: No

Follow up duration:
3 months end of treatment and 3 months further follow-up</td>
<td>Total N = 60

Inclusion criteria:
Symptoms of calf or buttock claudication limiting exercise and APBI <0.90 in affected leg.

Exclusion criteria:
• Comorbidity that limited exercise,
• Symptoms of recent onset (within previous 3 months) or recent revascularization (within previous 3 months).
• Patients reporting wide variations in symptom severity on different days or recent periods of symptom improvement (or deterioration,
• History of recent myocardial infarction (within 3 months).

Baseline characteristics
<table>
<tr><th>Baseline</th><th>Supervised exercise
N = 30</th><th>Unsupervised exercise
N = 30</th></tr>
<tr><td>Mean age (years) mean±SD</td><td>68 ± 7.73</td><td>68 ± 8.87</td></tr>
<tr><td>M/F</td><td>20/10</td><td>22/8</td></tr>
<tr><td>Diabetes</td><td>8</td><td>5</td></tr>
<tr><td>Current smoker</td><td>7</td><td>9</td></tr>
<tr><td>Past smoker</td><td>19</td><td>18</td></tr>
<tr><td>Hypertension</td><td>19</td><td>16</td></tr>
<tr><td>Hypercholesterolemia</td><td>12</td><td>14</td></tr>
</table>
</td>
<td>N = 30
Circuit based (5 exercises) supervised exercise twice weekly for 3 months in the hospital physiotherapy gym. Advised to rest if pain developed then recommence when subsided. Each part of the circuit took 8 minutes. Classes lasted 40 minutes plus warm up and down time. Exercises were mainly based on calf muscle and could be continued at home. No treadmill exercises.
Compliance was 79%</td>
<td>N = 30 Unsupervised exercise advice only.

After 3 month intervention both groups continued for a further 3 months with exercise advice.

No change in medications during the trial</td>
<td>Withdrawal

Compliance</td>
<td>Funding source: No details</td>
</tr>
</table>

	BMI mean±SD	25.5±4.27	26.5±4.49				
	Iliac artery stenosis/occlusion	1	2				
	Femoral artery stenosis/occlusion	21	17				
	Iliac and femoral artery disease	3	5				
	Distal disease	0	2				
	Site unknown	5	4				
	PFWD (m) median (IQR)	56 (34.0-84.5)	47.5 (25.8-68.5)				
	MWD (m) median (IQR)	108.5 (68.3-184.3)	72.5 (54.8-113.8)				
Effect Size:							
Withdrawal rate							
		3 months			**6 months**		
Supervised		2 patients 1 fatal stroke 1 aggravated back injury			1 patient 1 developed arterial ulcer and underwent revascularisation		
Unsupervised		2 patients 1 without giving a reason 1 aggravated back injury			4 patients 3 without giving a reason 1 nonfatal stroke and unable to attend follow-up		
Compliance with supervised exercise programme Mean attendance: 19 of 24 classes (range 11 – 24)							

1

Study details	Patient	Intervention	Comparison	Outcome measures	Other comments
Tew 2009 (Guideline Ref ID 81) RCT - Single centre, England.	Total N = 57 **Inclusion criteria:**	N = 29 Supervised arm crank exercise sessions twice	N = 28 Unsupervised. Subjects informed of	MWD PFWD	Funding source: No specific

Randomisation: Computer generated

Allocation concealment: None

Blinding: None

Sample size calculation: No details

ITT analysis: No only data for patients completing the study were included in the analyses

Dropouts:
Two from supervised and four from unsupervised.

Follow-up duration: 12 weeks at end of study

- Fontaine stage II PAD, stable IC
- ambulation during incremental treadmill test limited by IC
- ABPI at rest ≤0.9 in their most symptomatic leg
- 7 patients meeting clinical criteria who had an ABPI >0.9 and clinically important decrease of ≥0.15 after maximal walking exercise were also included.

Exclusion criteria:
- Absence of PAD
- Inability to obtain ABPI due to non-compressible vessels,
- Asymptomatic PAD (Fontaine stage I)
- Rest pain due to PAD (Fontaine stage III)
- exercise tolerance limited by factors other than claudication (e.g. dyspnoea, angina and arthritic pain)
- History of IC<12 month
- Re-vascularisation or other major surgery within previous 12 months.

No patients were receiving specific medication for IC and medication throughout the study did not change.

Baseline characteristics:

	Supervised N = 27	Unsupervised N = 24
Age (years)	69±9	70±8
BMI	26.8±3.5	25.9±3.7
Resting ABPI	0.68±0.13	0.69±0.12
Duration of	76±92	44±40

weekly for 12 weeks. During each session, patients trained in cycles of 2-min exercise at a crank rate of 50 rev./min, followed by 2 min of rest, for a total exercise time of 20 min in a 40-min session.

- - - - - - - -

the benefits of an active lifestyle, but did not undertake any supervised exercise.

- - - - - - - - - - - -

Physical activity levels were assessed using standardised questionnaire at baseline and 12 weeks in both groups.

ABI

Complications

Adverse events

Withdrawals

Compliance

funding

	claudication (months)						
	Previous MI (%)	19	21				
	Previous stroke (%)	11	17				
	Diabetes (%)	30	8				
	Smoking status (%)						
	Current	26	33				
	Previous	56	58				
	Never	18	9				
	Medication (%)						
	ß-blockers	15	17				
	ACEIs	33	21				
	Calcium blockers	19	25				
	Diuretics	19	33				
	Nitrates	26	25				
	Antiplatelet agents	96	96				
	Statins	100	92				

Effect Size

There were no injuries or adverse events resulting from exercise training:

Outcome	**Supervised arm cranking** **N = 27**	**Unsupervised group** **N = 24**
	Baseline	12 weeks
Resting ABPI at 12 weeks	0.68±0.13	0.71±0.13
PFWD (metres)	147±125	225±167
MWD (metres)	496±250	661±324

Withdrawals:

- 2 from the exercise group; 4 from the control group
- 1 died of a heart attack; 1 developed a lower-limb ulcer that required revascularisation surgery; 1 was identified as having a popliteal artery aneurysm; 1 returned to full-time employment; 2 due to lack of time
- Compliance to the supervised exercise programme was 97%

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Tisi 1997 (Guideline Ref ID 3042) **Randomisation:** No details **Allocation concealment:** No details **Blinding:** No details **ITT analysis**: No details **Sample size calculation:** No details **Drop outs:** No details **Follow-up duration:** 3, 6 and 12 months	Total N = 67 **Inclusion criteria:** • Exercise-limiting calf pain on walking of at least 6 months' duration. • positive Edinburgh Claudication Questionnaire • ABPI <0.8 and at least 30 mmHg drop in ankle systolic pressure following a 1 min treadmill test. • Pain free (PFWD) and maximum walking distances (MWD) measured by constant-load treadmill testing (3 km/h on a 10% gradient) and patients recruited IF walking distance was between 50 and 250 m. **Exclusion criteria:** • Significant improvement/deterioration in claudication symptoms within previous 6 months • therapeutic intervention for PAD within previous 6 months • Exercise limited by symptoms other than claudication • Any concurrent inflammatory disease e.g. rheumatoid arthritis or inflammatory bowel disease • Treatment with steroids or an inability to complete the assessment visits or comply with the allocated treatment. **Baseline characteristics:** | | Claudicants | | Male | 46 |	Exercise training programme (n=22) Group classes weekly for 4 weeks, lasting for 1 h. The programme consisted of a series of active and passive leg exercises performed to the limit of claudication pain. The sessions were supervised by a single physiotherapist and designed to teach the exercises and tailor them to the individual patient. Patients were encouraged to exercise for at least 45 min every day at home, in addition to daily walks of at least 1 mile. ---------- All patients received a standard leaflet advising on weight loss, smoking and exercise, and were prescribed aspirin 75 mg daily unless contraindicated.	Observation (n=17) Angioplasty (n=28) - these results were not reported in this paper and are not discussed further	ABPI Exercise levels at follow-up	Funding source: Not stated

	Female	21				
	Age Mean	69.3				
	CV events					
	Current angina	13				
	Previous MI	11				
	Coronary artery bypass	8				
	TIA	6				
	Stroke	2				
	Carotid endarterectomy	3				
	Diabetes	7				
	Hypertension	51				
	Hyperlipidaemia	6				
	Smoking					
	Current	20				
	Ex	41				
	Non	6				
	Low dose aspirin	39				
	No difference between the exercise and observation groups on baseline characteristics.					
Effect size						
1 patient missed 2/4 physiotherapy sessions due to an exercise induced achilles tendon injury. Good compliance with the exercise programme was achieved at all follow-up times. The mean number of weekly exercise sessions self-reported was 6.3 at 3 months, 5.6 at 6 months and 4.9 at 12 months.						
		Baseline	3 months	6 months	12 months	
Mean ABPI (SE) [SD]	Supervised exercise	0.66 (0.02)	0.64 (0.03)[0.14]	0.65 (0.03)[0.14]	0.64 (0.05)[0.23]	
	Observation	0.70 (0.03)	0.69 (0.03)[0.12]	0.72 (0.05)[0.2]	0.74 (0.07)[0.29]	

1

2

Study details	Patient characteristics	Intervention	Comparison	Outcome measures	Other comments
Treat-Jacobson 2009; (Guideline Ref ID 91) RCT - single centre, USA **Randomisation:** Unclear **Allocation concealment:** Unclear **ITT analysis:** No **Sample size calculation:** Based on primary endpoint (maximum walking distance) **Drop outs:** At 12 weeks: 4 2 from arms 2 from treadmill At 24 weeks: Additional 10 2 from arms 2 from treadmill 4 from combination 2 from control group **Follow up duration:** 12 week trial, follow-up at 1 week after study end and then after a further 12 weeks (24 weeks total).	Total N = 45 **Inclusion criteria:** • ≥18 years with lifestyle-limiting claudication • ABPI ≤ 0.90 and/or decrement in ABPI≥10% following symptom-limited treadmill exercise test • Able to walk at rate of 2.0 mph on a treadmill and able and willing to participate in a 12-week supervised exercise programme. • Diabetics included if their fasting blood glucose within normal limits. **Exclusion criteria:** • Uncontrolled hypertension (> 200 systolic blood pressure and/ or diastolic blood pressure>100) • Ischemic rest leg pain and/or leg/foot ulceration, or impending gangrene • Exercise capacity limited by health problems other than claudication such as angina pectoris, severe arthritis, marked dyspnoea on exertion • Recent myocardial infarction or unstable CHD • Coronary or lower extremity revascularisation procedure within the past 3 months. • Inconsistent baseline measurements varying more than 15% on multiple occaisions. Patients already taking pentoxyphlline or cilostazol were included if medication had been initiated at least 3 months prior to study entry and initiation or discontinuation of this medication was not recommended unless prescribed by a primary physician.	N = 13 Treadmill exercise Sessions three times a week for 12 weeks.(total 36 sessions). Sessions were 60 minutes in length plus warm up and warm down time. The protocol consisted of walking on the treadmill at a speed of 2 mph starting at a 0% grade (flat). The treadmill grade was increased 3.5% every 3 minutes until a 10.5% grade was obtained, at which time the speed was increased by 0.5 mph every 3 minutes, while maintaining the grade at 10.5%. This approximates an increase in exercise intensity of 1 metabolic equivalent (MET) per test stage. Participants were only permitted to hold the handrail lightly in order to maintain balance. N = 12	N =8 Unsupervised exercise group Provided with standardised written walking instructions for claudication patients and exercise log. Participants were instructed to record the mode, intensity, and time spent in unsupervised exercise. Participants were considered to have performed unsupervised exercise if their exercise log listed moderate-intensity exercise (usually walking), for a minimum of 30 minutes a session, at least three times per week for the control group participants and at least twice per week for exercise group participants. - - - - - - - -	Maximum walking distance Pain free walking distance Withdrawal Compliance ---------- Graded treadmill exercise test.	Funding source: American Heart Association Northland Affiliate, Fesler Lampert Chair of Aging Studies Award, University of Minniesota Scholar Award.

	Baseline characteristics – baseline mean (SD) or n (%)					Arm ergometry sessions lasted a total of 60 minutes. Following a 2- minute warm-up against no resistance, participants maintained a constant rate of 60 revolutions/ minute, starting at a workload of 10 watts. The intensity was manually increased by 10 watts at 3-minute intervals, until the participant was unable to continue. The maximal power achieved was recorded as the power at which the patient stopped exercising. N= 12 Combination arm ergometry and treadmill exercise 45% of subjects in the treadmill group, 25% of those in the combination group, and 20% in the arm ergometry group reported participating in outside exercise at least 3 days a week.	75% of the unsupervised group reported participating in outside exercise at least 3 days a week - - - - - - - - - All participants (including those in the control group) were asked to maintain a record of any exercise performed beyond the supervised exercise training.		
		Arm ergometry (n = 10)	Treadmill (n = 11)	Combination (n = 12)	Unsupervised (n = 8)				
	Age (years)	64 (8.6)	64 (11.7)	71.9 (11.3)	70 (7.8)				
	Male	8 (80)	7 (64)	7 (58)	7 (88)				
	Caucasian	9 (90)	11 (100)	9 (75)	6 (75)				
	Diabetes	6 (60)	1 (9)	5 (42)	3 (37.5)				
	Smoking (current/past)	10 (100)	11 (100)	10 (83)	7 (88)				
	Pack years	45.7 (24.8)	46.6 (35.3)	35.4 (19.5)	36.4 (21.6)				
	Dyslipidemia	10 (100)	9 (81.8)	10 (100)	6 (75)				
	Hypertension	7 (70)	9 (82)	10 (83)	7 (88)				
	Lowest resting ABI	0.66 (0.15)	0.68 (0.11)	0.65 (0.1)	0.69 (0.15)				
	Prior leg revascularization	2 (20)	4 (36.4)	3 (25)	3 (37.5)				
	CHD	7 (70)	7 (63.6)	7 (58.3)	4 (50)				
	BMI	29.9 (8.8)	26.4 (3.1)	28.3 (3.8)	29.1 (5.4)				
	Current medications:								

	Cilostazol	2 (20)	3 (27.3)	2 (16.7)	0	All participants were instructed to maintain their current dietary habits and prescribed medications throughout the study			
	Antiplatelet agent	10 (100)	8 (72.7)	9 (75)	6 (75)				
	Warfarin	0	3 (27.3)	1 (8.3)	0				
	Lipid-lowering agent	9 (90)	8 (72.7)	11 (91.7)	4 (50)				
	Beta-blocking agent	5 (50)	4 (36.4)	6 (50)	4 (50)				
	ACE inhibitor	8 (80)	4 (36.4)	7 (58.3)	2 (25)				

Effect size		
Withdrawal rate		
	12 weeks	24 weeks
Arm-ergometry	2 patients	2 patients

	1 family crisis 1 unrelated injury	1 lost to follow-up 1 study-unrelated health problem
Treadmill	2 patients 2 family crisis	2 patients 2 study-unrelated health problem
Combination	0 patients	4 patients 1 lost to follow-up 3 study-unrelated health problem
Control	0 patients	2 patients 1 lost to follow-up 1 study-unrelated health problem

Compliance

- Twenty (61%) participants from the supervised exercise groups completed all 36 sessions within 14 weeks; 12 completed all 36 sessions but took longer than 14 weeks; and 97% of participants completed at least 75% of the prescribed training sessions
- Reasons for non-attendance included illness, vacations, scheduling conflicts or transportation difficulties
- Based on patient exercise records, 45% (treadmill), 25% (combination), 20% (arm-ergometry) participated in unsupervised exercise (≥2 additional days per week). 75% of control group participated in unsupervised exercise (≥3 days per week)

Primary outcome – Change in MWD

- At 12 weeks, improvements in MWD were significantly greater in all of the supervised exercise groups compared with usual care – there were no significant differences between the three exercise groups.
- Compared with usual care, this improvement remained statistically significant at 24 weeks for the treadmill and arm-ergometry groups but not for the combination group.

Group	Baseline MWD (m) Mean (SD)	Change in MWD (m). Baseline to 12 weeks Mean (SD)	Change in MWD log transformation. Baseline to 12 weeks Adj. mean (SE)*	ANCOVA** F = 10.3 P < 0.001	Change in MWD (m). Baseline to 24 weeks Mean (SD)	Change in MWD log transformation. Baseline to 24 weeks Adj. mean (SE)*	ANCOVA** F = 5.7 P = 0.004
Arm-ergometry	421.6 (188.7)	182.1 (126.7)	0.18 (0.03)	P = 0.002 vs control	240.3 (164.1)	0.23 (0.04)	P = 0.01 vs control
Treadmill	483.3 (290.9)	294.7 (163.5)	0.23 (0.03)	P < 0.001 vs control	294.4 (162.2)	0.20 (0.03)	P = 0.02 vs control
Combination	441.3 (184.1)	217.2 (72.7)	0.22 (0.03)	P < 0.001 vs control	109.7 (159.6)	0.12 (0.03)	P = 0.73 vs control

3 exercise groups combined		232.4 (133.6)			218 (179.6)		
Control	360.8 (185.2)	45.3 (92.7)	-0.02 (0.04)		73.3 (65.6)	0.03 (0.04)	
2° outcome – Change in PFWD At 12 and 24 weeks, improvements in PFWD were significantly greater in the arm-ergometry group compared with usual care. A positive trend toward improvement was observed in the other supervised exercise groups at 12 and 24 weeks compared with usual care but this did not reach statistical significance							
Group	Baseline PFWD (m) Mean (SD)	Change in PFWD (m). Baseline to 12 weeks Mean (SD)	Change in MWD log transformation. Baseline to 12 weeks Adj. mean (SE)*	ANCOVA** F = 3.3 P = 0.032	Change in PFWD (m). Baseline to 24 weeks Mean (SD)	Change in MWD log transformation. Baseline to 24 weeks Adj. mean (SE)*	ANCOVA** F = 5.29 P = 0.006
Arm-ergometry	133.1 (64.1)	89.6 (74.0)	0.24 (0.07)	P = 0.03 vs control	39.7 (97.2)	0.34 (0.08)	P = 0.01 vs control
Treadmill	200.4 (151.4)	91.6 (148.4)	0.14 (0.06)	P = 0.20 vs control	155.1 (180.7)	0.22 (0.07)	P = 0.11 vs control
Combination	173.6 (100.4)	61.94 (109.94)	0.17 (0.06)	P = 0.11 vs control	21.6 (81.3)	0.04 (0.07)	P = 1.00 vs control
3 exercise groups combined		80.21 (116.6)			75.45 (143.2)		
Control	119.2 (62.2)	4.0 (45.4)	-0.10 (0.08)		10.9 (27.4)	-0.07 (0.09)	

**Values for PFWD were log transformed to normalise the distribution due to large positively skewed standard deviations*
***Differences between groups in PFWD at 12 and 24 weeks were assessed using analysis of covariance (ANCOVA) with unsupervised exercise and baseline values for each of these variables entered as covariants*

Study details	Patients	Intervention	Comparison	Outcome measures	Other Comments
Zwierska 2005; (Guideline Ref ID 420) RCT - UK **Randomisation:** not stated **Allocation concealment:**	Total N = 104 **Inclusion criteria:** Stable intermittent claudication (in two-thirds of the patients, claudication was due to superficial femoral artery disease) **Exclusion criteria:** • Significant upper-extremity arterial disease	BMT (n=33) Lifestyle advice including encouragement to undertake regular exercise (but no supervised exercise training)	Upper limb aerobic exercise (n=34) Lower limb aerobic exercise (n=37) Both twice a week for 24	ABPI Withdrawal	Funding source: British Heart Foundation

not stated

Blinding: no

Sample size calculation: not stated

ITT analysis: yes

Drop outs: 4 from upper limb group; 5 from lower limb group; 1 from medical therapy group, primarily for medical reasons

Follow-up duration:
3, 6 months

- Symptoms for <12 months
- Unstable disease (significant change in walking ability within 12 months)
- Critical ischaemia
- Revascularisation in last 12 months
- Severe arthritis (unable to walk unaided or perform upper- or lower-limb cranking exercise due to joint pain)
- Severe lumbar spine disease or unstable cardiorespiratory conditions

Baseline characteristics:

	Lower-limb exercise (n=37)	Upper-limb exercise (n=34)	BMT (n=33)
Median age (range)	69 (50-85)	66 (54-84)	72 (56-84)
Mean (SE) BMI	26.6 (0.6)	28.6 (0.6)	27.8 (1.0)
Male (%)	81	79	73
Resting ABPI	0.64±0.03	0.65±0.03	0.69±0.03
Disease duration (months)	59	50	55
Angina (%)	14	18	24
Previous MI (%)	3	9	12
Previous stroke (%)	19	18	15
Diabetes mellitus (%)	8	18	27
Current smoker (%)	38	24	33

Most patients were on aspirin and statins. Some also taking ß-blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers, nitrates, diuretics or warfarin

weeks for a total exercise time of 20 minutes in 40 minute session (2 mins exercise + 2 mins rest)

	Former smoker (%)	54	73	61				
Effect size:								
Withdrawal								
First 6 weeks			Weeks 6-12			Weeks 12-18		
3 Bowel cancer Became full-time carer for his wife Assessments too stressful			5 Gout Heart attack Pneumonia (resulted in death) Other medical conditions			2 Broken bone in foot Lower-limb ulcers		
• In the 94 patients who completed the 24-week intervention (30 arm; 32 leg; 32 control), compliance with the twice weekly training schedule was 99% • Self-reported physical activity level did not differ from baseline in any group for work or household activities; leisure activities increased in the training groups due to participation in the training sessions themselves.								
Resting ABPI								
Resting ABPI, Mean (SE) [SD]			Baseline			24 weeks		
Leg-training group, m (n = 37)			0.64 (0.03) [0.18]			0.66 (0.03) [0.18]		
Arm-training group, m (n = 34)			0.65 (0.03) [0.17]			0.68 (0.04) [0.23]		
BMT, m (n = 33)			0.69 (0.03) [0.17]			0.68 (0.03) [0.17]		

H.4.2 Comparison of exercise, best medical treatment, angioplasty and bypass surgery

H.4.2.1 Best medical treatment compared to best medical treatment with angioplasty

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
1 year results: 2007; (Guideline Ref ID 59) 2 year results: Nylaende 2007; (Guideline Ref ID 311)	Total N = 56 **Inclusion criteria:** • Mild to moderate symptomatic IC for minimum 3 months • <80 years	Optimal medical treatment (OMT) n=28: Smokers offered nicotine plasters and	OMT + angioplasty n=28: As OMT group plus angioplasty	ABPI Pain-free walking distance (PFWD)	Funding source: Unrestricted grants from Pfizer AS, Norway

RCT - Norway

Randomisation: Computerised randomisation list

Allocation concealment: Consecutively numbered sealed envelopes

Blinding: Not stated

Sample size calculation: Based on a 20% difference in change of QoL (the primary outcome measure) between the two arms at 2 years which would require 200 patients; recruitment stopped after 2 years when only 56 patients recruited (i.e. underpowered)

ITT analysis: Yes

Drop outs: 12 months -

4 patients lost (2 moved away, 2 declined further participation), 1 died and 1 crossed over from OMT to OMT + angioplasty group

24 months - 5 patients lost to follow-up (4 OMT; 1 OMT + angioplasty) 1 dead (1 OMT + angioplasty), 2 crossed over from OMT to OMT + angioplasty

- ABPI<0.9 without pain at rest and/or ulcers
- Subjective pain-free walking distance <400m
- Able to exercise on treadmill
- Lesion feasible for angioplasty (i.e. >50% stenotic or occluded over a length of <8cm)

Exclusion criteria:

- Previous vascular or endovascular surgery
- Diabetic ulceration
- Renal insufficiency (s-creatinine >150 µmol/l)
- Oral anticoagulant treatment
- Physical or mental disorder expected to impede compliance

Baseline characteristics:

Baseline median	OMT N=28	OMT + angioplasty N=28
Age (years)*	69 (61,75)	68 (56,72)
Male	54%	57%
Duration IC, months*	12 (5, 48)	17 (6, 36)
ABPI, symptomatic leg*	0.65 (0.52, 0.74)	0.63 (0.56, 0.71)
Antiplatelets (aspirin/ clopidogrel)**	46%	18%
Treated hypercholesterolemia	21%	29%
Untreated hypercholesterolemia	71%	57%
Diabetes (types I and II)	21%	14%

buproprion hydrochloride if not contraindicated.

Advised about home-based exercise programme

Nutritional advice and individualised optimal Mediterranean-type diet

Aspirin 160 mg daily prescribed to all patients not already on it; those with history of peptic ulcer prescribed clopidogrel 75 mg daily

Patients with untreated hypercholesterolaemia prescribed statins

High blood pressure treated in cooperation with patients GP in accordance with recommended guidelines

Iliac occlusions treated with primary stenting

Iliac stenoses were selectively stented

Stents were not used infrainguinally

Maximum walking distance (MWD)

Complications

Reinterventions

ABPI determined after 5 minute rest in supine position

Standard treadmill test at 3 km/h and a fixed grade of 10º up to maximum of 600m (12 min).

Follow up duration: 3, 12, 24 months	CHD	18%	7%				
	Current smoking	68%	71%				
	Former smoking	29%	21%				
	BMI, kg/m2*	25 (23, 26)	26 (23, 28)				
	*median (25, 75 percentiles) ** p=0.022 between groups						

Effect size		
Angiographical peripheral arterial obstruction. Location and limb involvement (n = 56).		
	Total population	
	Unilateral	Bilateral
Aorto-iliac n (%)	1 (1.8)	9 (16.1)
Femoro-popliteal n (%)	0	1 (1.8)
Combined n (%)	0	45 (80.4)
Total n (%)	1 (1.8)	55 (98.2)
• The angioplasty was technically successful in all 28 cases. At 12 months none of the patients was in need of surgical revision • No significant complications were encountered, such as bleeding, local thrombosis, emboli, local arterial dissection or perforation • A few patients had a small haematoma in the groin, but none was in need of surgical revision		

Clinical results								
	OMT n=28	OMT + angioplasty n=28		OMT n=28	OMT + angioplasty n=28		OMT n=28	OMT + angioplasty n=28
	Baseline	3 months		Baseline	3 months		Baseline	3 months

ABI (mean, SD)	0.65 (0.01)	0.68 (0.01)	ABI (mean, SD)	0.65 (0.01)	0.68 (0.01)	ABI (mean, SD)	0.65 (0.01)	0.68 (0.01)
Treadmill PFWD (m) Mean (SD)	69.6 (54.2)	96.6 (99.1)	Treadmill PFWD (m) Mean (SD)	69.6 (54.2)	96.6 (99.1)	Treadmill PFWD (m) Mean (SD)	69.6 (54.2)	96.6 (99.1)
Treadmill MWD (m) Mean (SD)	265.4 (173.5)	303.4 (202)	Treadmill MWD (m) Mean (SD)	265.4 (173.5)	303.4 (202)	Treadmill MWD (m) Mean (SD)	265.4 (173.5)	303.4 (202)

Results of the SF-36 questionnaire

SF-36	Baseline	3 months	12 months	24 months
Physical functioning	NS	OMT: 0.33 (0.12); OMT + angioplasty: 0.16 (0.02)	NS	OMT: 0.11 (0.32); OMT + angioplasty: -0.06 (0.26)
Physical role	NS	NS	NS	NS
Bodily pain	NS	OMT: 0.03 (0.25) OMT + angioplasty: -0.07 (0.20)	NS	NS
General health	NS	NS	NS	NS
Vitality	NS	NS	NS	NS
Social functioning	NS	NS	NS	NS
Role emotional	NS	NS	NS	OMT: -0.15 (0.33) OMT + angioplasty: 0.02 (0.34)
Mental health	NS	NS	NS	NS
Reported health transition	NS	OMT: -0.16 (0.50) OMT + angioplasty: -0.60 (0.26)	NS	NS

NS: Not significant. Mean and standard deviation is calculated as difference of score between actual month and start of study

CLAU-S	Baseline	3 months	12 months	24 months
Every day life	NS	NS	OMT: -0.01 (0.25) OMT + angioplasty: -0.12 (0.17)	NS
Pain during activity	NS	OMT: -0.04 (0.17) OMT + angioplasty: -0.20 (0.19)	OMT: -0.06 (0.28) OMT + angioplasty: -0.19 (0.21)	NS
Severity of pain	NS	OMT: -0.03 (0.09) OMT + angioplasty: -0.10 (0.08)	OMT: 0.16 (0.24) OMT + angioplasty: -0.02 (0.22)	NS

Pain related to sleep	NS	NS	NS	NS
Social life	NS	NS	NS	NS
Specific fears related to illness	NS	NS	NS	NS
Psychological wellbeing	NS	NS	NS	NS
NS: Not significant. Mean and standard deviation is calculated as difference of score between actual month and baseline				

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Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Whyman 1996; (Guideline Ref ID 688) Whyman 1997; (Guideline Ref ID 640) **Randomisation and allocation concealment:** telephone link to external computerised random allocation sequence. **Blinding:** No details **ITT analysis:** No **Sample size calculation:** Based on PFWD **Drop outs:** 6 months - 0 2 years - Unclear	Total N= 62 **Inclusion criteria:** • Predominantly unilateral IC. • Lesions suitable for angioplasty – discrete femoral or iliac stenoses or femoro-popliteal occlusions ≤10cm long. **Exclusion criteria:** • Previous angioplasty or arterial surgery in symptomatic leg • MI within last 6months • patients taking oral coagulants • symptom duration <1month • Inability to manage treadmill test • Psychiatric illness or other reason making follow-up difficult. • Iliac occlusion, >10 cm length femoropopliteal occlusion, multiple stenosis, diffuse disease with long stenoses. **Baseline characteristics:**	Angioplasty by balloon dilation and conventional medical treatment (usually carried out at same session as arteriography). N=30 Arterial stenting was not routinely used in the department at the time of this study	Conventional medical treatment (low dose aspirin, smoking advice, exercise advice – continue to walk as far and frequently as possible within limits imposed by pain) N= 32	ABPI Complications Reinterventions	Funding source: Chief Scientists Office, Scottish Office Home and Health Dept.

	Angioplasty	CMT

Follow-up duration: 6 months, 2 years	Number of patients	30	32				
	Age and sex	60.6 (44-73)	62.6(45-78)				
	Males (n)	23	28				
	CV risk factors						
	Current smokers – n	15	16				
	Serum cholesterol – mean (s.e.)mmol/l	6.69 (0.26)	6.44 (0.33)				
	Systolic BP – Mean (s.e.) mmHg	157.9 (4.1)	155.4 (3.5)				
	BMI – mean (s.e.) kg/m2	25.78 (0.50)	26.20 (0.70)				
	Diabetes – n	4	1				
	Severity of disease						
	ABPI mean (s.e.)	0.74 (0.03)	0.71 (0.02)				
	MWD meters – median (IQR)	228 (77-442)	183 (117-519)				
	PFWD meters – median (IQR)	56 (33-133)	78 (56-100)				
	Site and type of lesion						
	Number of femoral occlusions	7	9				
	Number of femoral stenoses	16	15				
	Number of iliac stenoses	7	8				
	Length of femoral occlusions (median)	3 cm (1-10)	4 cm (2-8)				

Effect size:

6 months follow up:

- No surgery for CLI or symptom deterioration in either group.
- No major complications were reported (defined as needing surgery to correct, or prolongation of length of admission)

• 3 angioplasty patients had further angioplasty on other leg within six months.		
	Angioplasty	Conventional medical treatment
ABPI – mean (SE) [SD]	0.88 (0.03) [0.16] n = 29	0.74 (0.03) [0.16] n = 30
2 yrs follow up:		
	Angioplasty	Conventional medical treatment
Repeat angioplasty on same lesion (n)	1	-
Surgery for symptom deterioration (n)	0	1
Angioplasty (n)	1 (return of claudication to previous level)	2 (1 for deterioration and 1 for no symptom improvement)
Mortality (unrelated to procedure(n))	0	2 (1 MI; 1CRC)
ABPI mean (SE)	0.81(0.03)	0.75 (0.04)

1 **angioplasty in other leg*

H.4.222 Supervised exercise with best medical treatment compared to supervised exercise, best medical treatment and angioplasty

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Greenhalgh 2008; (Guideline Ref ID 107) RCT - Two separate trials for: Aorto-iliac disease Femoro-popliteal disease **Randomisation:** Randomly permuted blocks generated by computer **Allocation concealment:** not stated **Blinding:** no	Total N = 34 in aorto-iliac trial Total N= 93 in femoro-popliteal trial Entry criteria were the same for both trials **Inclusion criteria:** • Stable IC (3-month history of pain despite optimisation of best medical therapy and smoking cessation) • Positive Edinburgh Claudication Questionnaire • ABPI <0.9 or >0.9 with positive stress test • Aortoiliac or femoropopliteal target lesion amenable to angioplasty **Exclusion criteria:** • Symptoms too mild to consider angioplasty or so severe	BMT plus supervised exercise Aorto-iliac – n=15 Femoro-popliteal – n=45 **Best medical therapy** Aspirin 75mg or clopidogrel (if aspirin intolerant) Blood pressure, total and high-density lipoprotein serum cholesterol and serum glucose were	BMT plus supervised exercise plus angioplasty Aorto-iliac – n=19 Femoro-popliteal – n= 48 Best medical therapy and supervisede exercise - as described in previous column	**Primary:** Absolute walking distance (AWD) in metres at 24 months Measured on a treadmill machine set at a 10° incline running at 4 km h-1 up to	Funding source: Camelia Botnar Arterial Research Foundation; independent educational grants from Bard Lyd, Boston Scientific Ltd and

Sample size calculation:
Intended recruitment 170 patients in each trial based on 90% power to detect an improvement of 60 m in AWD at 24 months (p=0.05). Recruitment slower than expected and stopped early in order to complete 24 month follow up of those already recruited with available funding; 127 consented (34 in aorto-iliac and 93 in femoro-popliteal trial), i.e. underpowered

ITT analysis: No

Drop outs: Overall 83% attended at 24 months of whom 89% treadmill tested for outcome measure:

Attendance:
Aorto-iliac trial
12/15 (80%) BMT
14/19 (74%) angioplasty

Femoro-popliteal trial
37/45 (82%) BMT
43/48 (90%) angioplasty

Outcome available:
Aorto-iliac trial

that intervention mandatory
- Critical limb ischaemia
- Concomitant disease prohibiting exercise

Baseline characteristics:

Femoro-popliteal trial

	BMT + exercise (n = 45)	BMT + exercise + angioplasty (n = 48)
Age (yr)	68.5 (9.4)*	63.9 (9.0)*
BMI (kg m-2)	26.9 (4.5)	27.0 (5.1)
AWD (m)a	126 (62)	133 (77)
ICD (m) a	63 (30)	71 (41)
ABPI	0.69 (0.12)	0.66 (0.14)
SF36 physical health score	39.7 (7.4)	38.9 (8.5)
SF36 mental health score	47.6 (12.5)	50.4 (11.2)
Male n (%)	26 (58%)	33 (69%)
Ever smoked n (%)	38 (84%)	38 (79%)
Hypertension n (%)	34 (76%)	35 (73%)
Ischaemic heart disease n (%)	10 (22%)*	21 (44%)*
Using statins n (%)	30 (67%)*	40 (83%)*
Using antiplatelets n (%)	40 (89%)	44 (92%)

assessed and drug therapy commenced where necessary
Smoking cessation (advice + nicotine replacement where necessary).

Supervised exercise
30 minutes continuous exercise to maximum pain threshold (walking circuit + 7 lower limb training stations) 1 or more per week for 6 months and encouraged to increase daily exercise).

Angioplasty - balloon catheter. For unsatisfactory results a stent is sometimes used

a maximum of 15 m (i.e. 1000 m)

Secondary:
initial claudication distance (ICD)

Reintervention

Complications

Compliance

Cook.

12/15 (80%) BMT 11/19 (58%) angioplasty Femoro-popliteal trial 34/45 (76%) BMT 37/48 (77%) angioplasty **Follow-up duration:** 6, 12, 24 months	Aorto-iliac trial					
		BMT + exercise (n = 15)	BMT + exercise + angioplasty (n = 19)			
	Age (yr)	62.5 (9.8)	63.9 (8.6)			
	BMI (kg m-2)	25.2 (3.8)	27.2 (3.6)			
	AWD (m)a	126 (53)	114 (87)			
	ICD (m) a	64 (20)	49 (38)			
	ABPI	0.66 (0.11)	0.68 (0.19)			
	SF-36 physical health score	37.7 (8.2)	38.3 (9.0)			
	SF-36 mental health score	44.0 (11.4)	43.1 (12.2)			
	Male n (%)	10 (67%)	12 (62%)			
	Ever smoked n (%)	15 (100%)	17 (89%)			
	Hypertension n (%)	8 (53%)	11 (58%)			
	Ischaemic heart disease n (%)	6 (40%)	5 (26%)			
	Using statins n (%)	12 (80%)	11 (58%)			
	Using antiplatelets n (%)	11 (73%)	16(84%)			
	Geometric mean (approximate SD)					
Effect size						
Femoro-popliteal trial						
	BMT + exercise	BMT + exercise + angioplasty		Outcome	Ratio adjusted for baseline measures, age, gender, smoking and	

				ABPI; 95% CI; p value
AWD (geometric mean, metres) 24 months (n = 71)	155	245	Ratio angioplasty: BMT 1.58	 1.38 (1.01-1.90), p=0.04
ICD (% attaining 200 m without claudication pain): 24 months (n = 71)	22% (7/34)*	63% (23/37)*	Hazard Ratio angioplasty: BMT 2.83	 3.11 (1.42-6.81), p=0.004
Mean SF-36 physical score (n = 79)	39.2	40.9	1.7	-0.4 (-4.2 to +3.4), p=0.82
Mean SF-36 mental score (n = 79)	47.6	51.5	3.9	2.4 (-1.7 to +6.5), p=0.25

Reintervention:

- Among the 48 patients randomised to angioplasty, angioplasty was carried out in 44 patients. In 11 patients, the angioplasty was recorded as 'failed' by the local radiologist. Of the 33 successful angioplasty, 21 were of the target lesion alone, seven were of a target and of a non-target lesion (mostly other femoropopliteal lesions), and five were of a non-target lesion alone (all aortoiliac lesions). No stents were used for any femoropopliteal angioplasties but for two patients who also underwent an additional aortoiliac angioplasty, a stent was placed in this segment
- Four patients of the 44 randomised to the control group went on to receive angioplasty (all of the target lesion) during the follow-up period

Complications:

- Following angioplasty procedures: five minor haematomas and one dissected artery. Similarly, there were few adverse events in either group with no myocardial infarctions: two strokes and two distal bypass graft operations during the course of 24 months follow-up

Compliance:

- Both randomised groups attended a similar proportion of the available weekly supervised exercise classes (means: 62% angioplasty and 61% control)

Aorto-iliac trial

	BMT + exercise	BMT + exercise + angioplasty	Outcome	Ratio adjusted for baseline measures, age, gender and ABPI; 95% CI; p value
AWD (geometric mean after log transformation) metres 24 months (n = 23)	168	354	Ratio angioplasty: BMT 2.11	 1.78 (1.00-3.16), p=0.05

ICD (% attaining 200m without claudication pain): 24 months (n = 23)	25% (3/12)*	61% (7/11)*	Hazard Ratio angioplasty: BMT 3.1	3.6 (1.0-12.8), p=0.05
Mean SF-36 physical score (n = 25)	38.6	46.4	7.8	7.8 (1.5-14.1), p=0.02
Mean SF-36 mental score (n = 25)	46.0	50.3	4.3	4.9 (-1.3 to +11.1), p=0.12

Reintervention:

- For the 19 patients in the aortoiliac trial randomised to receive angioplasty, 17 had successful angioplasty of the target lesion. Amongst the 15 patients in the control group, four went onto receive angioplasty later during the follow-up period. A total of five stents were used across all the aortoiliac angioplasties (four in the target lesion and one in a non-target aortoiliac lesion).

Complications:

- Following the angioplasty procedures: three minor haematomas and one sensory deficit. Similarly, there were few adverse events in either group with no myocardial infarctions, two strokes and no distal bypass graft operations during the course of the 24 months follow-up.

Compliance:

- Both groups attended a similar proportion of the available weekly exercise classes (means: 53% angioplasty, 48% control).

**Derived from % and known number of participants in each group*

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Mazari 2010; (Guideline Ref ID 39) RCT - Single centre, UK **Randomised:** Not described **Allocation concealment:** Sealed envelopes **Blinding:** Not reported	Total N = 178 **Inclusion criteria:** • Symptomatic unilateral IC • Angioplastiable lesion, femoropopliteal lesion • >3 months on best medical treatment. **Exclusion criteria:** • CLI • Severe limitation of physical activity due to systemic	N = 60 3 supervised sessions a week for 12 weeks. Session consisted of: warm up exercises, circuit of exercise stations (walking up and down a 6 inch step, double heel raise, single leg press, exercise bike, knee	N = 60 Angioplasty contralateral up and over access was used in all cases followed by angiogram and balloon angiography. Primary stenting	Complications Withdrawal	Funding source: BJS Bursary 2002, ESVS Research Grant 2005

Sample size calculation: calculated for walking distance, ABPI, SF-36, VacuQoL

ITT analysis: Not reported

Drop outs: Angioplasty group - 3 withdrew.

Exercise group – 8 withdrew.

Combination group - 10 withdrew

Follow-up duration: 3 months

disease

- inability to tolerate treadmill testing (unrelated to limb ischemia);
- Significant ischemic ECG during treadmill testing; ipsilateral surgery or angioplasty in previous 6 months.

Baseline characteristics:

Baseline	Exercise N = 60	Exercise plus angioplasty N = 58
Male (n)	37	33
Median age (IQR)	69 (63-76)	69.5 (64-79)
Diabetic (n)	9	8
Hypertensive (n)	40	34
Hypercholesterolerolemia (n)	47	43
Smoking (n)	18	19
PRWD (m)*	100 (50-200)	150 (69-300)
ABIRe*	0.65 (0.53-0.8)	0.65 (0.53-0.86)
ICD (m)*	33.5 (18.7-62.1)	40 (20.7-67.6)
MWD (m)*	46.2 (32-85.4)	63.1 (40.2-98.0)
ABIPE*	0.31 (0.25-0.56)	0.44 (0.22-0.59)
SF-36 PF*	30 (20-55)	40 (20-50)

extension, elbow flexion), and cool down with stretching.

For the first 6 weeks patients completed 1 complete circuit after that it was increased by 1 station each week. Patients spent 2 minutes at each station and performed a 2 minute walking circuit between station.

All groups prescribed antiplatelet therapy (aspirin and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation programme) and risk factor modification (target orientated management of hypertension, hypercholesterolemi a and diabetes). Advice leaflet

or adjunctive procedures were not performed.

Angioplasty only arm not reported here.

Combination (angioplasty plus supervised exercise) n = 58

Patients received angioplasty as described and then were enrolled into an supervised exercise the following week

	SF-36 RP*	20 (20-50)	25 (0-75)	regarding exercise.			
	SF-36 BP*	41 (22-64)	41 (31-62)				
	SF-36 GH*	55 (35-72)	55 (42-67)				
	SF-36 V*	45 (35-55)	45 (35-56)				
	SF-36 SF*	62 (37-87)	62 (52-87)				
	SF-36 ER*	33 (0-100)	66 (33-100)				
	SF-36 MH*	68 (56-84)	70 (59-84)				
	SF-36 index*	0.57 (0.53-0.62)	0.63 (0.52-0.69)				
	VascuQoL*	3.7 (2.7-5)	4.2 (2.9-5.2)				
	*Median (range)						

Effect size		
	Exercise N = 60	Combination N = 58
Withdrawals over the course of the study (n)	8	10
Complications: There were no complications associated with either supervised exercise or angioplasty in any of the three groups. The drop-out rate arose from distance between their homes and unavailability of transportation.		

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<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Mazari 2012 (Guideline Ref ID 104)

RCT - UK

Randomisation: Not reported

Allocation concealment: Not reported

Blinding: Not reported

Sample size calculation:
Calculated for all outcomes

ITT analysis:
ITT

Drop outs:
Supvervised exercise group: 5
Angio group: 8
Angio +Supervised group:

Follow-up duration: 1, 3, 6 and 12 months (only 12 month data reported)</td>
<td>Total N = 118

Inclusion criteria:
• symptomatic unilateral IC
• femoro-popliteal lesion amenable to angioplasty
• symptoms stable after 3 months of BMT

Exclusion criteria:
• critical ischaemia
• incapacitating systemic disease
• inability to tolerate treadmill testing (unrelated to limb ischaemia)
• significant ischemic changes on ECG during treadmill testing
• ipsilateral vascular surgery or angioplasty within previous 6 months

Baseline characteristics:
<table>
<tr><th>Baseline</th><th>Angio</th><th>SE</th><th>Angio + SE</th></tr>
<tr><td>Age (years) median, 95% CI</td><td>70 (63, 75)</td><td>69 (63, 76)</td><td>69.5 (64, 79)</td></tr>
<tr><td>Sex ratio M:F</td><td>37:23</td><td>37:23</td><td>33:25</td></tr>
<tr><td>Side (number)
Right
Left</td><td>
29
31</td><td>
24
36</td><td>
34
24</td></tr>
<tr><td>Risk factors (number)
Diabetes
Hypertension
Hypercholesterolaemia</td><td>
8
40
45</td><td>
9
40
47</td><td>
8
34
43</td></tr>
</table>
</td>
<td>Supervised exercise n = 60
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.

All patients received BMT:
Antiplatelet therapy (aspirin and/or clopidogrel)
Smoking cessation advice and support
Risk factor management
Advice leaflets of physical activity and</td>
<td>Angioplasty n = 60
Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure

Angioplasty +SE n = 58
Combined treatment with exercise staring a week after angioplasty</td>
<td>Maximum walking distance

Claudication distance

QoL

Re-intervention

ABPI</td>
<td>Funding source: BJS research bursary and European society of Vascular Surgery research grant and support from the Academic Vascular Surgical Unit, University of Hull</td>
</tr>
</table>

	Current smoker	18	18	19	exercise			

Effect size			
	Angio	SE	Angio + SE
Re-intervention at 12 months	9 out of 60	6 out of 60	0 out of 58
Study reported there was no statistically significant difference between the 3 groups for resting ABPI, intermittent claudication walking distance and maximum walking distance. The study reported a statistically significant difference for ABPI after exercise. The study did not report individual group results, therefore no meta-analysis was possible.			

SF36 results at 12 months – individual domain scores not reports P values reported for intergroup analysis and graph reported	
Physical function	P value = 0.758
Role limitation physical	P value = 0.865
Bodily pain	P value = 0.284
General health	P value = 0.839
Vitality	P value = 0.800
Social function	P value = 0.701

Role limitation emotional	P value = 0.988
Mental health	P value = 0.906

H.4.213 Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Kruidenier2011; (Guideline Ref ID 16326)

RCT - The Netherlands

Randomisation: Computerised block randomisation list (blocks of 5)

Allocation concealment: Consecutively numbered sealed envelopes
Blinding: Not blinded

Sample size calculation: Not reported

ITT analysis: Available case analysis

Drop outs:
Angioplasty group:
1 crossed over at patient request
8 withdrew from follow-up (3 refused treadmill testing; 1 moved away from area; 1 lost to follow-up; 1 malignacy; 1</td>
<td>Total N=70

Inclusion criteria:
• PAD Rutherford stage 1-4
• Scheduled for angioplasty
• Maximum walking distance after a angioplasty< 1600m as measured by a standardized treadmill test

Exclusion criteria:

• History of or current participation in supervised exercise programme
• Serious cardiopulmonary co morbidity (New York Heart Association stage II-IV)
• Other serious co morbidity preventing physical activity
• Insufficient knowledge of the Dutch language
• No insurance for supervised exercise therapy.
• Major amputation or tissue loss

Baseline characteristics:
<table>
<tr><th>Baseline median</th><th>Angio N=35</th><th>Angio + exercise N=35</th></tr>
<tr><td>Age (years)</td><td>60.2 ± 10</td><td>64.5 ± 9.3</td></tr>
<tr><td>Male</td><td>21 out of 35</td><td>22 out of 35</td></tr>
<tr><td>BMI</td><td>27.5 ± 4.9</td><td>26.6 ± 3.4</td></tr>
</table>
</td>
<td>Angioplasty - n=35:
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

All patients received
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
life style changes</td>
<td>Angio + supervised exercise - n=35:
Angio as described in angio group

Supervised exercise started with 3 weeks of angioplasty.
Community based setting, trained by 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</td>
<td>Maximum walking distance

Pain free walking distance

Withdrawal from treatment

Complications

SF-36</td>
<td>Funding source: Not reported</td>
</tr>
</table>

increase in complaints PAD; 1 withdrew consent) **Follow-up duration:** 3, 6 months PVI +SET group 7 crossed over (1 not motivated for SET; 2 too busy with working / social life; 1 insurance related; 1 orthopedic co-morbidity; 2 unknown) 1 withdrew from follow-up (knee problems)	ABPI, before PVI	0.741 ± 0.18	0.69 ± 0.21	(e.g. physical activity, weight, diet)	sessions		
	ABPI after PVI	0.91 ± 0.22	0.87 ± 0.22				
	Current smokers	21	18				
	Previous vascular intervention	7	9				
	Hypertension	24	25				
	Hypercholesterolemia	31	30				
	CVA or TIA	2	4				
	COPD	5	3				
	Diabetes	5	9				
	Orthopedic disease	4	8				
	CHD	7	13				
	Walking distance						
	PFWD pre angio	282.2 ± 292.8	186.1 ± 116.2				
	PFWD post angio	562.5 ± 356.8	484.6 ± 285.5				
	MWD pre angio	343.3 ± 247.9	293.4 ± 189.6				
	MWD post angio	650.8 ± 327.5	550.2 ± 289				
	SF-36						
	Phy func	41.6 ± 17.5	43.6 ± 19.4				
	Phy role	39.1 ± 43.5	33.3 ± 39.9				
	Pain	43 ± 16.4	41.4 ± 19.9				
	Gen.health	52.2 ± 13.2	51.5 ± 11.3				
	Phy score	31 ± 9.1	30.5 ± 7.7				
	Social func	69.1 ± 28	64 ± 22.8				
	Emot role	83.9 ± 35.4	80.8 ± 38.2				
	Mental heal	72.8 ± 18.3	72.2 ± 20.8				
	Vitality	51.2 ± 18.8	57.4 ± 20.2				
	Metal score	53.8 ± 11.6	53.8 ± 11.7				
	Rutherford stage						
	1	0	1				
	2	20	15				

	3 4	12 0	13 1				
	Angioplasty Recanalisation Both	29 3 3	25 7 3				
	Stent placement	12	16				
Effect size							
		Angio			Angio + supervised exercise		
Maximum walking distance at 3 months		782.9 ± 384.9 (n = 29)			974 ± 512.6 (n = 32)		
Maximum walking distance at 6 months		685 ± 313.5 (n = 27)			956.3 ± 490.4 (n = 34)		
Pain free walking distance at 3 months		660.4 ± 399 (n = 28)			896 ± 520.8 (n = 32)		
Pain free walking distance at 6 months		547.2 ± 263.5 (n = 27)			842.4 ± 478.3 (n = 34)		
Withdrawal from treatment		1 out of 35 (patient requested supervised)			7 out of 35 (1 not motivated for exercise; 2 too busy with working / social life; 1 insurance related; 1 orthopedic co-morbidity; 2 unknown)		
Bleeding after angio		0 out of 35			1 out of 35		
Embolism after angio		0 out of 35			1 out of 35		
Aortic rupture after angio		0 out of 35			1 out of 35		
Total major adverse events at 6 months		0 out of 35			3 out of 35		
SF-36 at 6 months							
Physical functioning		72.2 ± 18 (n = 29)			72.7 ± 22.3 (n = 33)		
Physical role		71.6 ± 37 (n = 29)			56.3 ± 40.2 (n = 32)		
Pain		64.7 ± 26 (n = 29)			70 ± 22.8 (n = 33)		
General health		53.7 ± 12.5 (n = 28)			56.9 ± 12.6 (n = 33)		
Physical summary score		44.1 ± 7.8 (n = 28)			41.9 ± 9.5 (n = 31)		
Social functioning		77.2 ± 31 (n = 29)			80.7 ± 19.8 (n = 33)		
Emotional role		77 ± 40.9 (n = 29)			82.3 ± 35.9 (n = 32)		
Mental health		68 ± 19.5 (n = 29)			79.4 ± 17.5 (n = 32)		
Vitality		57.1 ± 20 (n = 29)			67.3 ± 17.7 (n = 32)		

Mental summary score	49 ± 11.7 (n = 28)	53.7 ± 9.2 (n = 31)

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Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Mazari 2012 (Guideline Ref ID 104) RCT - UK **Randomisation:** Not reported **Allocation concealment:** Not reported **Blinding:** Not reported Sample size calculation: Calculated for all outcomes **ITT analysis**: ITT **Drop outs:** Supvervised exercise group: 5 Angio group: 8 Angio +Supervised group: **Follow-up duration:** 1, 3, 6 and 12 months (only 12 month data reported)	Total N = 118 **Inclusion criteria:** • symptomatic unilateral IC • femoro-popliteal lesion amenable to angioplasty • symptoms stable after 3 months of BMT **Exclusion criteria:** • critical ischaemia • incapacitating systemic disease • inability to tolerate treadmill testing (unrelated to limb ischaemia) • significant ischemic changes on ECG during treadmill testing • ipsilateral vascular surgery or angioplasty within previous 6 months **Baseline characteristics:**	Supervised exercise n = 60 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. All patients received BMT: Antiplatelet therapy (aspirin and/or clopidogrel) Smoking cessation advice and support Risk factor	Angioplasty n = 60 Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure Angioplasty +SE n = 58 Combined treatment with exercise staring a week after angioplasty	Maximum walking distance Claudication distance QoL Re-intervention ABPI	Funding source: BJS research bursary and European society of Vascular Surgery research grant and support from the Academic Vascular Surgical Unit, University of Hull

Baseline	Angio	SE	Angio + SE
Age (years) median, 95% CI	70 (63, 75)	69 (63, 76)	69.5 (64, 79)
Sex ratio M:F	37:23	37:23	33:25
Side (number)			
Right	29	24	34
Left	31	36	24
Risk factors (number)			

	Diabetes Hypertension Hypercholesterolaemia Current smoker	8 40 45 18	9 40 47 18	8 34 43 19	management Advice leaflets of physical activity and exercise			
Effect size								
		Angio			SE		Angio + SE	
Re-intervention at 12 months		9 out of 60			6 out of 60		0 out of 58	
Study reported there was no statistically significant difference between the 3 groups for resting ABPI, intermittent claudication walking distance and maximum walking distance. The study reported a statistically significant difference for ABPI after exercise. The study did not report individual group results, therefore no meta-analysis was possible.								
SF-36 results at 12 months – individual domain scores not reports P values reported for intergroup analysis and graph reported								
Physical function	P value = 0.758							
Role limitation physical	P value = 0.865							
Bodily pain	P value = 0.284							
General health	P value = 0.839							
Vitality	P value = 0.800							
Social function	P value = 0.701							
Role limitation emotional	P value = 0.988							
Mental health	P value = 0.906							

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H.4.224 Angioplasty compared to supervised exercise

Study type	Patients	Intervention	Comparison	Outcome measures	Other comments
Creasy 1990; (Guideline Ref ID 1160) RCT - Single centre (Oxford regional vascular service, UK) **Randomisation:** no description	Total N=36 **Inclusion criteria:** • stable unilateral claudication with failure of conservative treatment for at least 3 months • A treadmill claudicating distance of less than 375 m • Angiographically significant lesion(s) suitable for	N = 20 Angioplasty using conventional guide-wire and balloon catheter technique aiming to overdilate the lumen by about	N = 16 Twice weekly sessions for 6 months and on a regular basis according to progress	Maximum walking distance Complications	Oxford District Research Committee

Allocation concealment: not reported

Blinding: not reported

Sample size calculation: not reported

ITT analysis: not reported

Drop outs: Not reported

Follow-up duration: 1 year

treatment by angioplasty.

Exclusion criteria: not reported.

Baseline characteristics:

Baseline	Angioplasty N=20	Exercise N = 16
Mean age (years) SD	63.6 ± 8.9	62.2 ± 8.6
Male (%)	75	75
Past smoker	18 (90%)	16 (100%)
Current smoker	12 (60%)	11 (69%)
Hypertension	8 (40%)	5 (31%)
Diabetes mellitus	0 (0%)	2 (12%)
Arteriography		
Grade A	5 (25%)	1 (6%)
Grade B	3 (15%)	7 (44%)
Grade C	12 (60%)	8 (50%)
Mean number of distal vessels	2.7	2.7
Mean ABPI (±SE)	0.63 ± 0.03	0.66 ± 0.04
Mean claudicating distance (± SE)	91 ±37	77 ± 20
Mean maximum walking distance m (± SE)	127 ± 37	120 ± 28

10% above normal. Balloons were inflated at least twice for 45 seconds at the sight of the lesion.

thereafter. 30 minute sessions supervised by a physiotherapist (group or individual) intensity of treatment was increased as exercise tolerance was improved. Exercise included walking, walking on tip toe, walking and running on the spot, static bicycling, step-ups, going up and down on tiptoes while on and incline and dribbling a football.

Patients were also encouraged to perform exercise daily at home.

Reinterventi on

Compliance

Treadmill set at 3 km/h up a 10° incline (measured up to a maximum of 750 m, equivalent to 15 min)

Effect size:

Additional data presented in graphs

- 21 attempted angioplasties were performed on the 20 patients in the angioplasty group, one patient requiring a repeat angioplasty of a recurrent common iliac stenosis
- Of the 21 attempted angioplasties, 8 were in the common iliac artery, 4 in the external iliac artery and 9 in the femero-popliteal artery
- Two angioplasties were unsuccessful
- There were four complications; three groin haematomas, all of which were treated conservatively, and a rupture of an external iliac artery requiring an emergency ilio-femoral graft, which was uncomplicated. One other patient had surgical intervention; an elective aortobifemoral graft for deterioration in symptoms 6 months following angioplasty. The remaining 16 patients in the angioplasty group received no other treatment
- One patient in the exercise group requested angioplasty having increased their maximal walking distance only marginally at three months. No cardiac complications were reported in the exercise group

Outcome	Angioplasty	Exercise
Number of patients with doubling of mean maximum walking distance		
3 months	4 (n = 16)	7 (n = 15)
6 months	5 (n = 14)	9 (n = 12)
9 months	4 (n = 11)	9 (n = 12)
12 months	2 (n = 5)	6 (n = 7)
Exercise levels at follow-up		
Mean attendance over 6 months (sessions per week)	-	0.89
'Good attenders' (on average >1 session per week)	-	8
'Poor attenders' (on average <1 session per week)	-	8

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<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Mazari 2010; (Guideline Ref ID 39)

RCT - Single centre, UK

Randomised: Not described

Allocation concealment: Sealed envelopes

Blinding: Not reported

Sample size calculation: calculated for walking distance, ABPI, SF-36, VacuQoL

ITT analysis: Not reported

Drop outs: Angioplasty group - 3 withdrew.
Exercise group – 8 withdrew.
Combination group - 10 withdrew

Follow-up duration: 3 months</td>
<td>Total N = 178

Inclusion criteria:
• Symptomatic unilateral IC
• Angioplastiable lesion, femoropopliteal lesion
• >3 months on best medical treatment.

Exclusion criteria:
• CLI
• Severe limitation of physical activity due to systemic disease
• inability to tolerate treadmill testing (unrelated to limb ischemia);
• Significant ischemic ECG during treadmill testing; ipsilateral surgery or angioplasty in previous 6 months.

Baseline characteristics:
<table>
<tr><th>Baseline</th><th>Exercise N = 60</th><th>Exercise plus angioplasty N = 58</th></tr>
<tr><td>Male (n)</td><td>37</td><td>33</td></tr>
<tr><td>Median age (IQR)</td><td>69 (63-76)</td><td>69.5 (64-79)</td></tr>
<tr><td>Diabetic (n)</td><td>9</td><td>8</td></tr>
<tr><td>Hypertensive (n)</td><td>40</td><td>34</td></tr>
<tr><td>Hypercholesterolerolemia (n)</td><td>47</td><td>43</td></tr>
<tr><td>Smoking (n)</td><td>18</td><td>19</td></tr>
<tr><td>PRWD (m)*</td><td>100 (50-</td><td>150 (69-300)</td></tr>
</table>
</td>
<td>N = 60
3 supervised sessions a week for 12 weeks. Session consisted of: warm up exercises, circuit of exercise stations (walking up and down a 6 inch step, double heel raise, single leg press, exercise bike, knee extension, elbow flexion), and cool down with stretching.

For the first 6 weeks patients completed 1 complete circuit after that it was increased by 1 station each week. Patients spent 2 minutes at each station and performed a 2 minute walking circuit between station.

All groups prescribed antiplatelet therapy (aspirin and/or clopidogrel), received</td>
<td>N = 60

Angioplasty contralateral up and over access was used in all cases followed by angiogram and balloon angiography.
Primary stenting or adjunctive procedures were not performed.
Angioplasty only arm not reported here.

Combination (angioplasty plus supervised exercise) n = 58
Patients received angioplasty as described and then were enrolled into an supervised exercise the following week</td>
<td>Complications

Withdrawal</td>
<td>Funding source: BJS Bursary 2002, ESVS Research Grant 2005</td>
</tr>
</table>

		200)		smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation programme) and risk factor modification (target orientated management of hypertension, hypercholesterolemia and diabetes). Advice leaflet regarding exercise.			
	ABIRe*	0.65 (0.53-0.8)	0.65 (0.53-0.86)				
	ICD (m)*	33.5 (18.7-62.1)	40 (20.7-67.6)				
	MWD (m)*	46.2 (32-85.4)	63.1 (40.2-98.0)				
	ABIPE*	0.31 (0.25-0.56)	0.44 (0.22-0.59)				
	SF-36 PF*	30 (20-55)	40 (20-50)				
	SF-36 RP*	20 (20-50)	25 (0-75)				
	SF-36 BP*	41 (22-64)	41 (31-62)				
	SF-36 GH*	55 (35-72)	55 (42-67)				
	SF-36 V*	45 (35-55)	45 (35-56)				
	SF-36 SF*	62 (37-87)	62 (52-87)				
	SF-36 ER*	33 (0-100)	66 (33-100)				
	SF-36 MH*	68 (56-84)	70 (59-84)				
	SF-36 index*	0.57 (0.53-0.62)	0.63 (0.52-0.69)				
	VascuQoL*	3.7 (2.7-5)	4.2 (2.9-5.2)				

	*Median (range)				

Effect size		
	Exercise N = 60	Combination N = 58
Withdrawals over the course of the study (n)	8	10
Complications: There were no complications associated with either supervised exercise or angioplasty in any of the three groups. The drop-out rate arose from distance between their homes and unavailability of transportation.		

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Study details	**Patients**	**Intervention**	**Comparison**	**Outcome measures**	**Other comments**
Mazari 2012 (Guideline Ref ID 104) RCT - UK **Randomisation:** Not reported **Allocation concealment:** Not reported **Blinding:** Not reported **Sample size calculation:** Calculated for all outcomes **ITT analysis:** ITT	Total N = 118 **Inclusion criteria:** • symptomatic unilateral IC • femoro-popliteal lesion amenable to angioplasty • symptoms stable after 3 months of BMT **Exclusion criteria:** • critical ischaemia • incapacitating systemic disease • inability to tolerate treadmill testing (unrelated to limb ischaemia) • significant ischemic changes on ECG during treadmill testing • ipsilateral vascular surgery or angioplasty within previous 6 months	Supervised exercise n = 60 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	Angioplasty n = 60 Angioplasty was performed by a consultant vascular radiologist in accordance with the units standard procedure Angioplasty +SE n = 58 Combined treatment with exercise staring a week after	Maximum walking distance Claudication distance QoL Re-intervention ABPI	Funding source: BJS research bursary and European society of Vascular Surgery research grant and support from the Academic Vascular Surgical Unit, University

Drop outs: Supvervised exercise group: 5 Angio group: 8 Angio +Supervised group: **Follow-up duration:** 1, 3, 6 and 12 months (only 12 month data reported)	Baseline characteristics:				ending with completing 2 full circuits. All patients received BMT: Antiplatelet therapy (aspirin and/or clopidogrel) Smoking cessation advice and support Risk factor management Advice leaflets of physical activity and exercise	angioplasty		of Hull
	Baseline	Angio	SE	Angio + SE				
	Age (years) median, 95% CI	70 (63, 75)	69 (63, 76)	69.5 (64, 79)				
	Sex ratio M:F	37:23	37:23	33:25				
	Side (number) Right Left	 29 31	 24 36	 34 24				
	Risk factors (number) Diabetes Hypertension Hypercholesterolaemia Current smoker	 8 40 45 18	 9 40 47 18	 8 34 43 19				

Effect size			
	Angio	SE	Angio + SE
Re-intervention at 12 months	9 out of 60	6 out of 60	0 out of 58

Study reported there was no statistically significant difference between the 3 groups for resting ABPI, intermittent claudication walking distance and maximum walking distance. The study reported a statistically significant difference for ABPI after exercise. The study did not report individual group results, therefore no meta-analysis was possible.

SF-36 results at 12 months – individual domain scores not reports P values reported for intergroup analysis and graph reported	
Physical function	P value = 0.758
Role limitation physical	P value = 0.865
Bodily pain	P value = 0.284
General health	P value = 0.839
Vitality	P value = 0.800
Social function	P value = 0.701
Role limitation emotional	P value = 0.988
Mental health	P value = 0.906

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<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comment</th></tr>
<tr>
<td>Perkins 1996; (Guideline Ref ID 984)

RCT - Single centre (UK)

Randomised: Not described

Allocation concealment: Not reported

Blinding: Not reported

Sample size calculation: Not reported

ITT analysis: Not reported

Drop outs: No details on 0-15 months

At long-term follow-up: 22 angioplasty and 15 exercise were re-tested; 10 had died (4 angioplasty; 6 exercise) and the remaining patients were either uncontactable, too ill for review or had undergone amputation

Follow up duration: 3,6,9,15 months then:</td>
<td>Total N=56

Inclusion criteria:
• Stable unilateral claudication with a failure of conservative management for 3 months prior to randomisation;
• Lesion(s) on angiography suitable for angioplasty
• Maximum walking distance of less than 375 m.

Exclusion criteria:
Not reported

The study reported there were no significant differences between the groups for age, gender, ABPI, claudication distance, maximum walking distance and % fall in ankle pressure.

Baseline characteristics
<table>
<tr><td>Baseline</td><td>Angioplasty N=30</td><td>Exercise N = 26</td></tr>
<tr><td>Site of lesion</td><td></td><td></td></tr>
<tr><td>Superficial femoral artery</td><td>15</td><td>13</td></tr>
<tr><td>Iliac artery / iliac and superficial femoral artery</td><td>15</td><td>13</td></tr>
</table>
</td>
<td>N = 30
angioplasty performed using conventional guide-wire and balloon catheter technique. The lumen was overdilated by 10% above normal, the balloon was inflated for two periods of 45 seconds.</td>
<td>N = 26
Supervised exercise classes twice a week for 6 months, classes were for 30 minutes and consisted of dynamic leg exercises with the intensity of exercise increasing as the patients tolerance increased. Patients were also encouraged to perform the same exercises at home.</td>
<td>Long-term adherence to exercise

Reintervention

Treadmill set at 3 km/h up a 10° incline (measured up to a maximum of 750 m, equivalent to 15 min)</td>
<td>Funding source: Not reported</td>
</tr>
</table>

Exercise: median 70 months (range: 45 to 83) Angioplasty: median 74 (range 48-83)							

Effect size:

- Additional data presented in graph format for ABPI, MWD and claudication distance
- Claudication distance was significantly greater than pre-treatment values in the exercise group at 6 months (p = 0.005), 9 months (p = 0.001), 12 months (p = 0.001) and 15 months (p = 0.0001). In contrast the angioplasty group showed no significant improvement at any of these time intervals
- Significant differences in ABPI were seen only in the group receiving angioplasty, regardless of the site of disease
- The most significant increases in MWD were seen in the exercise group
- Since randomisation, 4 patients in the angioplasty group and 4 patients in the exercise group had undergone angioplasty of the ipsilateral leg. Of the angioplasty patients undergoing repeat ipsilateral angioplasty, 3 had the original disease site re-angioplastied, and one patient had a further angioplasty in a different arterial segment. In the contralateral leg, three angioplasty patients and three exercise patients had received further angioplasty. Two patients had undergone reconstructive surgery; one in the angioplasty group had an aortobifemoral graft, and one in the exercise group had a femero-femerol cross-over graft donating to the ipsilateral leg
- There were no complications of exercise training
- Overall in the entire randomised group of 56 patients, only two had undergone amputation.

Outcome	Angioplasty	Exercise
Exercise levels at long-term follow-up (n)		
Exercising daily	-	2
Exercising more than twice a week	-	3

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Study details	Patient characteristics	Intervention	Comparison	Outcome measures	Other comments
Spronk 2009; (Guideline Ref ID 134) RCT - Single centre (Ikazia Hospital, Rotterdam, the Netherlands)	Total N = 151 No study data: 1 patient angioplasty group as patient refused to continue participation prior to baseline data and intervention. **Inclusion criteria:**	N = 75 Angioplasty using 10% oversized balloon For Illiac revascularisation the	N = 76 Hospital based exercise. Twice a week 30 minute sessions walking on a treadmill for 24 weeks	ABP Maximum pain-free walking distance	Funding source: The authors disclosed no financial

Randomisation: generated block randomisation list (block size 16) prepared by independent statistician.

Allocation concealment: not reported

Blinding: Not reported

Sample size calculation: Not reported

ITT analysis: ITT.
Excluded – 1 patient excluded from analysis who refused to continue in the trial before baseline characteristics recorded or intervention.

Drop outs:
Exercise group - 3 died (1 - CVA and 2 - lung cancer).

Angioplasty group - 2 lost to follow up, 5 died (1 - CVA, 2 due to colon cancer, 1 - lung cancer, 1 - MI).

Death not related to either PAD or the intervention. No patients discontinued intervention

Follow-up duration: 6, 12 months

- Rutherford category 1, 2 or 3 claudication with a duration of ≥ 3 months
- maximum pain-free walking distance of less than 350 m
- ABPI <0.9 at rest or an ABPI that decreased by more than 0.15 after treadmill test
- One or more vascular stenoses >50% diameter reduction at the iliac or femo-popliteral level at magnetic resonance angiography; informed consent.

Exclusion criteria:
- abdominal aortic aneurysm
- Life-incapacitating cardiac disease (New York Heart Association class III and higher)
- multilevel disease; isolated tibial artery disease; lesions deemed unsuitable for revascularisation; prior treatment for the lesions (including exercise therapy).

Baseline characteristics:

Baseline	Angioplasty N=75	Exercise N = 75
Age (years)	65 ± 11.4	66 ± 9.1
Men (n)	44	39
Arterial hypertension (n)¥	32	28
Diabetes mellitus (n)	11	15
Hyperlipidemia (n) †	40	38
History or ischemic heart disease (n)	14	21
Pulmonary disease (n)	7	9
Osteoarthritis of lower limb (n)	7	5
Renal insufficiency (n)	1	3
History of cerebrovascular	8	4

procedure was considered successful if the mean residual pressure gradient across the treated artery segment was less than 10 mm Hg at rest. If it had failed a self expanding nitinol stent was placed.

Femoral revascularisation was considered successful if after angioplasty the residual lumen diameter was >50% according to angiography. If the procedure was unsuccessful an additional self expanding nitinol stent was placed.

Patients in the revascularization group did not perform a similar exercise programme but were given general recommendations concerning lifestyle changes according to

supervised by a vascular technologist. Treadmill exercise was started at 3.5 km/hour with no graded incline, this was decreased to 1 km/hour when maximum claudication pain occurred (as assessed by the patient) this was increased once the pain subsided. If a patient 's maximum pain-free walking distance increased the workload was increased by speed or graded incline to ensure stimulation of claudication pain during the exercise. Patients were also instructed to walk for 30 minutes 3 times a week outside the hospital setting.

Maximum walking distance

Re-intervention; complications

Long-term adherence to exercise

Treadmill set at 3.5 km/h and no graded incline)

relationships

	disease (n)			the guidelines for cardiovascular disease prevention All patients received atherosclerotic risk factor treatment that included hypertension, serum glucose, cholesterol, lipid profile, and homocysteinemia (in patients <50 years of age) management, and 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			
	Smoking (n) Current Ever Never	 12 40 23	 17 32 25				
	BMI kg/m2	26 ± 4.3	25 ± 4.9				
	ABPIΔ At rest After exercise	 0.62 ± 0.18 0.41 ± 0.22	 0.63 ± 0.17 0.42 ± 0.21				
	Maximal pain-free walking distance (m)	82 ± 48	104 ± 65				
	Maximum walking distance (m)	174 ± 76	186 ± 97				
	Rutherford (n) § 1 or 2 3	 57 18	 57 18				
	SF-36 Physical funct. Physical role Pain General health	 42 ± 26 37 ± 52 50 ± 21 53 ± 23	 49 ± 20 49 ± 45 55 ± 23 54 ± 20				
	Total Vascular Quality of Life Questionnaire score	4.2 ± 1.1	4.3 ± 1.1				
	Unless otherwise indicated data are means ±SD						

Baseline lesion characteristics			
Variable	Endovascular revascularisation (n = 75)	Hospital based exercise (n = 75)	P value
Iliac disease	55	51	.47
Bilateral	13	12	.88

Unilateral in both common and external iliac arteries	3	5	.77
Total no. of iliac lesions	71	68	
Stenosis*	62	61	.90
Occlusion	9	7	.96
Femoral disease	20	24	.47
Bilateral	8	12	.32
Unilateral with multiple (>1) femoral arteries	5	6	.17
Total no. of femoral lesions	40	45	
Stenosis*	23	29	.18
Occlusion	17	16	.67
Unless otherwise specified, data are numbers of patients *diameter reduction of 51%-99%			

Effect size:

Additional treatment	Endovascular revascularisation (n = 75)		Supervised hospital based exercise (n = 75)	
	0-6 months	6-12 months	0-6 months	6-12 months
Endovascular revascularisation with or without stent placement				
Common iliac artery	0	1	2	3
Femoral artery	0	1	2	1
Surgical intervention				
Aortic bifurcation graft	2	0	1	0
Femoral-femoral cross-over graft	1	0	0	0
Femoro-popliteal bypass	0	0	2	0
Patch plasty of common femoral artery	2	0	0	0

- Data are numbers of patients
- Stents were used in 46 of 71 iliac lesions (34 patients) and in 20 of 40 femoral lesions (16 patients)
- Additional treatment of patients who underwent revascularization was indicated by (a) technical failure (n = 4 [one iliac occlusion, two femoral occlusions, and one instance of multiple femoral stenoses]) and (b) symptomatic and hemodynamic failure (n = 6 [two iliac occlusions and four femoral occlusions]).

- Additional treatment of patients in the exercise programme was related to symptomatic failures (three patients with iliac occlusions, five patients with bilateral iliac lesions, and three patients with multiple femoral lesions).
- Seven patients in the revascularization group experienced minor complications: six hematomas and one small dissection, for which a second stent placement was needed.
- The patients in the exercise group had no complications.
- The mean number of sessions in the supervised exercise programme was 33 ± 10 (standard deviation) (median, 32). The mean time spent on home-based walking exercise was 4.2 hours per week ± 4.7 (median, 3.5 hours per week) during the first 6 months and 3.4 hours per week ± 3.5 (median, 3.5 hours per week) during the second 6 months.

Outcome	Angioplasty N=75	Exercise N = 75	Adjusted mean difference∞
ABPI at rest (mean score improvement compared with baseline [99% CI])Δ			
6 months	0.14 (0.08, 0.19) (calculated sd 0.18)	0.03 (-0.01, 0.07) (calculated sd 0.13)	0.00 (-0.05, 0.05)
12 months	0.16 (0.10, 0.21) (calculated sd 0.18)	0.04 (0.00, 0.07) (calculated sd 0.11)	0.00 (-0.04, 0.04)
ABPI after exercise (mean score improvement compared with baseline [99% CI])Δ			
6 months	0.27 (0.20, 0.34) (calculated sd 0.24)	0.14 (0.08, 0.20) (calculated sd 0.20)	0.01 (-0.06, 0.08)
12 months	0.27 (0.24, 0.30) (calculated sd0.1)	0.20 (0.15, 0.26) (calculated sd 0.18)	0.01 (-0.04, 0.06)
Maximum pain-free walking distance (m) (mean score improvement compared with baseline [99% CI])			
6 months	679 (519, 837) (calculated sd 534.5)	899 (743, 1054) (calculated sd 537.9)	-16 (-32, 2)
12 months	806 (646, 960) (calculated sd 527.8)	943 (786, 1099) (calculated sd 526.1)	24 (-42, 91)
Maximum walking distance (m) (mean score improvement compared with baseline [99% CI])			
6 months	755 (600, 909) (calculated sd 519.4)	1138 (1006, 1270) (calculated sd 443.8)	16 (-60, 93)
12 months	826 (680, 970) (calculated sd 487.5)	1034 (896, 1170) (calculated sd 460.6)	24 (-42, 91)
SF-36 QoL score (mean score improvement compared with baseline [99% CI])	Angioplasty N=75	Exercise N = 75	Adjusted mean difference∞
Physical functioning			
6 months	19 (14, 25)	12 (7, 18)	2 (-3, 8)
12 months	17 (12, 22)	13 (8, 18)	2 (-1, 6)
Physical-role functioning			
6 months	25 (14, 36)	14 (4, 24)	7 (-5, 19)

12 months	21 (10, 32)	6 (-4, 16)	7 (-5, 19)
Bodily pain			
6 months	14 (7, 21)	7 (2, 13)	4 (-4, 10)
12 months	11 (5, 17)	10 (4, 16)	3 (-3, 8)
General health			
6 months	1 (-4, 6)	5 (1, 9)	-1 (-6, 5)
12 months	2 (-3, 7)	5 (1, 9)	-1 (-4, 4)
Vascular Quality of Life Questionnaire score≠ (mean score improvement compared with baseline [99% CI])			
6 months	0.6 (0.1, 1.1) (sd 2.61)	0.7 (0.4, 1.0) (sd 1.3)	0.1 (-0.3, 0.4)
12 months	0.7 (0.3, 1.1) (sd 1.74)	0.6 (0.3, 0.9) (sd 1.3)	0.1 (-0.2, 0.3)

¥Diastolic pressure of more than 95 mm Hg
†Cholesterol level of ≥5.0 mmol/L
ΔMinimum value of those for right and left leg
§Most severe classification per person
∞Adjusted for baseline quality of life scores, age, sex, severity of disease (mild or moderate vs severe) smoking, hypertension, hyperlipidemia and diabetes mellitus. Positive differences indicate endovascular treatment has a better outcome
≠The Vascular Quality of Life Questionnaire score is a PAD-specific assessment and is responsive to subtle treatment effects. It contains 35 questions subdivided into 5 domains (activity, symptom, pain, emotion and social functioning). Each question has a seven-point response option.

H.4.295 Bypass surgery compared to supervised exercise

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Lundgren 1989; (Guideline Ref ID 2558) RCT - Single centre (Sweden) **Randomisation:** Central randomisation to 3 treatment groups according to an algorithm which accounted for the distribution of sex, age and	Total N=75 **Inclusion criteria:** • Intermittent claudicants who professional or social life hampered **Exclusion criteria:** • maximal walking distance of >600 m • Rest pain, ischemic ulcers • blood pressure of the first toe below 30 mmHg	Surgery; n = 25 Operation to eliminate hemodynamically important arterial obstructions above the knee. Thrombendarterectomy, synthetic Y-graft, bypass with saphenous vein or	Exercise; n = 25 3 sessions per week lasting 30 minutes with a physiotherapist. And consisted of dynamic leg exercise beyond the appearance of pain due to arterial	Change in symptom free walking distance Change in maximum walking distance	Funding source: Not reported

diabetes. **Allocation concealment:** Not reported **Blinding:** Not reported **Sample size calculation:** Not reported **ITT analysis:** Not reported **Drop outs:** Complete follow-up data is lacking for 4 surgery patients; 2 exercise patients and 4 combination patients **Follow-up durations:** Mean length of follow up for surgery was 12.6 ± 0.9 months, for the exercise group was 11.2 ± 0.6 months and 15.2 ± 0.8 months for the combined group	• aged <40 and >80 years old. Baseline Mean ± SE / Surgery n=25 / Exercise n = 25 Age (years): 64 ± 2 / 64 ± 1 Duration (months): 28 ± 6 / 26 ± 6 Ankle index: 0.55 ± 0.03 / 0.59 ± 0.03 BPFT (mmHg): 58 ± 4 / 55 ± 3 PMBF (ml/110 ml/min): 14.8 ± 1.5 / 16.7 ± 1.7 SFWD (m): 85 ± 6 / 67 ± 7 MWD (m): 209 ± 20 / 183 ± 22 • 47% of patients had the lesion of the most symptomatic leg below the inguinal ligament, 41% above the ligament and 12% had combined lesions • 21% of patients were female • 93% were smokers • 8% had a history of diabetes; 25% angina pectoris; 19% MI; 31% hypertension; 7% cardiac insufficiency; 3% transient ischaemic attacks There were no statistically significant differences between the treatment groups in the location of the lesion, diabetes, angina pectoris, MI, hypertension, cardiac insufficiency and transient ischaemic attacks	expanded polytetrafluoroethylene graft.	insufficiency. Patients were also encouraged to exercise at home. The minimum training period was 6 months Combination; n = 25 Started exercise 6 weeks after the last operation. Not reported here	Withdrawals	

Effect size:

- 58 operations were performed in 48 patients (the two patients in the group treated with physical training who underwent operations for limb-threatening ischaemia and the patient who underwent emergency operation for aortic dissection are included); 26 on the aorta and iliac arteries; 32 on the femoro-popliteal level. Of the 48 patients 26 underwent reconstructive surgery on the aorto-illiac level, 25 on the femoro-popliteal level, 3 on both levels and 23 bilaterally
- Additional data presented in graphs

Outcome	Surgery N=25	Exercise N = 25

Change in symptom free walking distance (±SE)	320 ± 78 (standard deviation = 390)	120 ± 47 (standard deviation = 235)
Change in maximum walking distance (±SE)	361 ± 73 (standard deviation = 365)	276 ± 66 (standard deviation = 330)

- In pooled observations of the three groups, age, symptom duration, and a history of myocardial ischemic disease correlated negatively with walking performance after treatment
- Complications and reinterventions within 30 days of surgery: 3 evacuate haematomas; 3 reconstructive surgery; 2 MI (the emergency case of aortic dissection already had an infarction when the operation was performed); 1 pulmonary emboli; 1 death (MI patient with emergency case of aortic dissection). Later two patients had re-operations and two died before follow-up
- There were no observed complications caused directly by the physical training; two patients developed limb-threatening ischaemia and underwent operations; two others developed severe cardiac insufficiency and were unable to receive training

H.413 Angioplasty compared to bypass

Study details	Patients	Intervention	Comparison	Outcome measures	Other comment
McQuade 2010; (Guideline Ref ID 15980) Study methods and 12 months follow-up published in: Kedora 2007; (Guideline Ref ID 3060) 24 months follow-up data published in: McQuade 2009; (Guideline Ref ID 94) RCT - Single-centre prospective, USA **Randomisation:** By limb. Method not stated **Allocation concealment:** Not stated	Total N = 86 patients, 100 limbs Pts initially assessed by clinical exam, ABPI and Duplex US to confirm infrainguinal disease. Those considered for treatment then had angiograpy or computed tomography angiography for location and extent of disease. **Inclusion criteria:** • Atherosclerotic stenotic or occlusive lesions of the superficial femoral artery with no significant aorto-iliac disease. Patent infra-popliteal segment with at least single vessel run-off to the ankle. Patients had to be 'acceptable surgical candidates' **Exclusion criteria:** Not stated Four patients with bilateral disease and one limb randomised to each group **Baseline Characteristics:**	Stent N = 50 limbs (40 patients) Percutaneous stent graft (expanded polytetrafluoroethylene/nitrol self-expanding stent Stent graft placement technically successful in 100% of limbs in stent graft group 114 stents placed in 50 limbs, mean 2.3 per limb	Bypass N = 50 limbs (46 patients) Femoral to above-knee popliteal artery bypass with synthetic graft: Dacron/ePTFE Femoral-popliteal artery bypass successfully performed in 100% of limbs in surgical group Additional therapy: Post	ABPI Complications Re-intervention rates Limb salvage rates All-cause mortality Costs Amputation	W.L Gore & Associates, Flagstaff Arizona

Blinding: Open **Sample size calculation:** Mentioned but no details **ITT Analysis:** Yes **Drop outs:** 6 patients (7 limbs) lost to follow-up (stent), 15 patients lost to follow-up (bypass) = 24% of total patients Follow up at 12mnths: Bypass grp: 4 died and 5 lost to follow up **Follow-up duration:** Follow-up at 3,6,9,12,18,24,36 & 48 months Follow-up rates (at 48 months): Stent: 32/50 limbs (64%) Bypass: 26/50 limbs (52%)		Stent (n=40 pts, 50 limbs)	Bypass (n=46pts, 50 limbs)	P val.	Additional therapy: Post procedure aspirin and clopidorgel for minimum 3 months (in 93% of patients)	procedure aspirin and clopidorgel for minimum 3 months (in 52% of patients), remainder on aspirin monotherapy or warfarin		
	Mean age	72 (40-84)	67 (40-86)	0.033				
	Male (no. Of limbs)	32	36	1.00				
	Smoking hx (n pts)	22	27	0.828				
	Diabetes (n pts)	14	20	0.509				
	Significant difference in patient age (p=0.033), no sig diff in other comorbidities Four patients with bilateral disease and one limb randomised to each group							

Effect size

- The initial study design was only intended to be powered for a follow up of 24 months.
- Length of hospital stay: The mean was 0.9 ± 0.8days for the stent group and 3.1 ± 1.8 for the surgical group (this was significant at p<0.001)

ABPI mean improvement

Length of follow-up (cumulative)	Stent (N = 50 limbs)	Bypass (N = 50 limbs)	P value
Baseline	0.57 ±0.19	0.46 ± 0.22	-
12 months	0.23	0.37	0.11

24 months	0.23	0.38	0.14
48 months	N/A	N/A	N/A
All-cause mortality (unrelated to Infrainguinal disease) – cumulative			
Length of follow-up (cumulative)	Stent (N = 50 limbs)	Bypass (N = 50 limbs)	
12 months	4	4	
24 months	6	5	
48 months	9	8	
Re-intervention rate			
Length of follow-up (cumulative)	Stent (N = 50 limbs)	Bypass (N = 50 limbs)	
12 months	13/50 stents	12/50 grafts	
24 months	17/50 stents	17/50 grafts	
48 months	18/50 stents	15/50 grafts	
Immediate procedure-related and early postoperative nonthrombotic complications			
	Stent (N = 50 limbs)	Bypass (N = 50 limbs)	
Complications	4/50 limbs (40 patients)*	3/50 (46 patients)≠	
2 perioperative graft thromobses. Further 16 graft (per stent not patient) thromboses within 12 months. 1 further graft thrombosis between 24-48 month follow up. 13 stent grafts failed secondary to thrombosis (1 in post operative period), others unsure of timepoint but reported in 12month Kedora paper.			
Limb salvage / amputation			
Length of follow-up (cumulative)	Stent (N = 50 limbs)	Bypass (N = 50 limbs)	
12 months	49/50 limbs	45/50 limbs	
24 months	49/50 limbs	45/50 limbs	
48 months	39/40 patients	40/46 patients	
There was 1 amputation in stent group and 6 amputations in surgical group at 4 yrs			

** SFA dissection, transient mild leg oedema in treated limb, severe thigh pain, small groin haematoma*
≠ groin lymphocele (requiring washout and reclosure), groin seroma, small superficial groin wound dehiscence

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Wilson 1989 (Guideline Ref ID 847)	Total N = 263	N =130 pts	N =133 N=126 (no. of	Wolf et al: Repeat	Funding source:

Wolf 1993; (Guideline Ref ID 3058) RCT - Multicentre (9 sites, USA). 2 sites dropped because of low accrual and 1 added to make up final numbers. **Randomisation:** List of randomisation numbers prepared by coordinating centre. Randomisation via telephone. Stratified by centre and by each of the following disease categories: • Iliac disease with claudication • Iliac disease with rest pain • Femoro-popliteal disease with claudication • Femoro-popliteal disease with rest pain Note: Because eligibility criteria required that all lesions randomised for treatment be suitable for angioplasty, the severity of disease was less than that of the general population. **Allocation concealment:** Yes, centralised	Mean age ±SE 61.5±0.44 Pts considered for the study on basis of arteriogram and review by radiologist and vascular surgeon. **Inclusion criteria:** • Angiography showing presence of significant stenosis (>80) or occlusion <10 cm in length of the iliac, superficial femoral, or popliteal arteries. • Resting ABPI in the affected leg ≤0.9 • The patient exhibited at least one of the following symptoms in the affected leg severely limiting activity: (a) claudication that restricted walking to less than two blocksand prevented performance of daily activities judged important by the patient and the physician, (b) rest pain by ischemia and (c) impending gangrene presumed caused by the arterial lesion to be treated **Exclusion criteria:** • Patients in whom a short-term course of heparin would be contraindicated • Patients with a life expectancy of less than 3 years • patients unlikely to be available for follow up evaluation • Patients not candidates for major surgery because of medical contraindications ABPI at randomisation by location of study lesion: IC / IRP / FC / FRP Angioplasty 59 / 22 / 38 / 11	Angioplasty Technical details of interventions were left to the discretion of individual physicians at each site although standard guidelines were provided	limbs = 133) Bypass Technical details of interventions were left to the discretion of individual physicians at each site although standard guidelines were provided	intervention at site Amputation Mortality Wilson et al, Limb survival 2o Outcome Wilson et al, Sickness Impact Profile (SIP)	Veterans Administration Cooperative Studies Program

Blinding: Not reported **Sample size calculation:** Yes, based on an initial survey of 6 Veterans Administration Centres. This showed that 1320 angiograms were obtained annually for claudication and rest pain or necrosis. Approximately, 26% of these patients would have been candidates for angioplasty of the iliac arteries and 23% for angioplasty of the femoral or popliteal arteries. The authors estimated that they would need to recruit 8 centres which would provide a minimum of 300 patients. Sample size gave a 90% power to detect an odds ratio of 2.3 between bypass and angioplasty with a significance of 0.05 **ITT analysis:** Yes Drop outs: 8 patients withdrew, 20 were lost to follow up, 73 deaths. Follow up scheduled at 1 and 3 months and at 3 month intervals thereafter for 3 years. In Wolf et al, the follow up is stated up to 6 yrs Follow up included: clinical exam,	(n)							
	Angioplasty Mean ABPI±SE	0.56 ±0.02	0.32 ±0.02	0.52 ±0.02	0.44 ±0.07			
	Bypass (n)	59	23	35	16			
	Bypass Mean ABPI±SE	0.6 ±0.03	0.36 ±0.02	0.53 ±0.02	0.45 ±0.04			
	IC= iliac claudication; IRP= iliac rest pain; FC=femorpopliteal claudication; FRP=femorpopliteal rest pain							
	Baseline characteristics:							
		Bypass (n=133)	Angioplasty (n=130)	Overall (ie. Where intervention not stated)				
	Age, yrs, mean (S.E.)	62.0 (0.64)	60.9 (0.59)					
	Smoking history							
	Never	3	0					
	Currently	105	102					
	Previous	25	28					
	CV history							
	Angina	22	31					
	MI	25	28					
	CHF	8	6					
	Stroke	20	16					
	TIA	17	8					
	Diabetes	-	-	26%				
	Iliac lesions (n)							
	Claudicants	-	-	118/163				
	Rest pain	-	-	45/163				

pulses, Doppler derived ABPIs of calf, thigh and ankle. SIP administered at randomisation, 1 month, 1 and 2 yrs	Femoropopliteal disease							
	Claudicants	-	-	73/100				
	Rest pain	-	-	27/100				

Effect Size			
		Angioplasty (n=130)	Bypass (n=126)
Total mortality at 2yrs		20/112	26/126
Perioperative mortality		0	1
Mortality at 3mnths		0	2
Moratlity at 12 months		0	3
Amputation	Total at 2 y	8	13
	Perioperative	2	2
Perioperative Complications	Graft thrombosis	-	9
	Infection		1
	Acute thrombosis	5	
	Puncture site bleeding	12	-
	Contrast extravasion	8	0
	Minor peripheral embolism	2	-
	Total	27	10
Re-intervention at 2 yrs		26/112	20/126
Three deaths are described as study related (all from bypass group)			
ABPI:			
	Baseline	Change after treatment (no timepoint specified)	Change at 3 years
Bypass	0.50 ± 0.01	0.32 ± 0.02	0.28 ± 0.04
Angioplasty	0.50 ± 0.02	0.28 ± 0.02	0.3 ± 0.05
Limb survival by assigned intervention, study lesion location and pre-operative symptom category after median follow up of 4 years (Wolf et al 1993)			
Outcome	Angioplasty (N=130)	Bypass (N =133)	

	n	n	
Limb survival			
Iliac			
Rest pain	16 out of 22	17 out of 23	
Femoro-popliteal			
Claudication	35 out of 38	30 out of 35	
Overall	114 out of 130	113 out of 133	
Note: n= patients at risk by intention to treat			

SIP scores during 2 years follow up (Wolf et al 1993)

Follow up interval	Angioplasty (N=130)			Bypass (N =133)		
	N	Mean (SD)	Median	N	Mean (SD)	Median
Baseline	130	15.6±11.3	12	128	15.8±11.2	13
1 month	120	11.3±9.4	9	115	12.2±8.8	11
1 year	98	10.8±10.2	8	95	10.6±10.2	7
2 years	75	11.2±10.2	8	76	9.6±8.1	7.5
Total score*	75	-4.7±12.8	4	74	-5.7±9.4	5
*change after 2 years of follow up in patients with complete data						

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Holm J, Arfvidsson B, Jivegard L, Lundgren F, Lundholm K, Schersten T, Stenberg B, Tylen U, Zachrisson BF, Lindberg H.	RCT Multicentre (2 centres in Sweden) Randomised: A sequential	Total N = 102 Mean age 70 (range: 37-87) No	Inclusion criteria: Patients with or without diabetes with either severe limb ischemia, i.e. rest pain or ischemic ulcerations as well as patients with severe claudication who had not benefited from exercise training, in whom cardiac, pulmonary, renal other contraindications for vascular surgery were not found. Only occlusions or significant stenoses 6	N = 53 Angioplasty Technique not described Concomitant treatment:	N =49 Bypass In lesions situated above the inguinal ligament, synthetic grafts	Patients were followed up at 1, 3, 6 and 12 months after discharge. Follow up	1o Outcome Ankle-arm index Ankle pressure Amputation Complications Mortality Reintervention	The study was supported by grants from the Swedish Medical Research Council

Chronic Lower Limb Ischaemia. A Prospective Randomised Controlled Study Comparing the 1-Year Results of Vascular Surgery and Percutaneous Transluminal Angioplasty (PTA). European Journal of Vascular Surgery. 1991; 5(5):517-522. (Guideline Ref ID 803)	treatment assignment with balancing for prognostic factors according to Pocock and Simon 1975 (Biometrics 1975; 31: 103-115). This was performed to ensure that the two treatment groups should be comparable. This stratification included symptoms (claudication vs severe limb ischemia), diabetes vs non diabetes, age (< vs ≥ 62 years), occlusion vs stenosis and planned treatment level (above vs below the	study data: 0	cm or shorter in the common iliac, external iliac, femoral or popliteal artery were accepted for treatment. A stenosis was considered significant if the cross sectional area according to the angiogram was reduced by 75% or more. Thus patients who were included were those who according to both surgical and radiographic consensus could be treated by either vascular surgery or angioplasty. Exclusion criteria: Patients with concomitant disease contraindicating surgery. Patients with mental disorders indicating that the treatment or the follow up could not be performed properly. Patients not willing to give their informed consent. **Baseline** / **Angioplasty N=53** / **Bypass N= 49** Age* (years) SD: 70±NR / 69±NR Male (%): NR / NR ABI (mean, SD): NR / NR Smoking history (%): NR / NR Claudication * (%): 43 / 37	Patients were given 5000 IE heparin intra-arterially immediately before the dilatation. Dextran 40 (500ml) was given on the day of treatment and for the following 1 to 3 days	or endarterectomy were used equally. Synthetic grafts were used only when other techniques were not feasible. Concomitant treatment: Patients were given 2500-5000 IE heparin intravenously during the operation followed by Dextran 40 (500 ml) or heparin infusions post-operatively (15000-20000 IE per day) during their hospital stay. No long-term antocoagulant or anti-platelet treatment was given post operatively.	included: Arm and ankle systolic pressures and clinical exam. Angiography carried out at study selection and at 1 yr follow up.		

	inguinal ligament) Allocation concealment: Unclear Blinding: Unclear. Sample size calculation: None ITT analysis: Yes However, the authors state that the 5 patients who were randomised to surgery but did not end up having surgery may influence the results in a negative way. It was apparently not stated in the protocol that venous		Rest pain/ gangrene* (%)	57	63					
			Diabetics* (%)	26	27					
			Occlusion* (%)	47	33					
			Above inguinal ligament* (%)	38	38					
			Duration (?) (months)	17.5±2.7	18.8±3.3					
			Ankle pressure (mmHg)	68±5.2	69.5±6.1					
			Ankle-Arm index	0.43±0.04	0.44±0.04					
			*Results of stratification							
			There were no significant differences at admission between the 2 groups.							

	by-pass should be performed whenever possible in the distal regions. This resulted in a variety of procedures being performed with less than satisfactory results (please see discussion for more details) Drop outs: 0							

Effect Size

ABPI on admission and at discharge from hospital

	Before treatment	At discharge	P value
Angioplasty (n=53)	68.0 ± 5.2	102.8 ± 7.5	P<0.01
Bypass (n=49)	69.5± 6.1	104.4 ± 9.6	P<0.01
	n.s.	n.s	

Outcome	Angioplasty, N=53	Bypass, N= 49
	claudication	claudication
Ankle-arm index (mean ± SEM)	Before: 0.49±0.04 At 1 year: 0.81±0.04	Before: 0.51±0.04 At 1 year: 0.69±0.10

AT 12 month follow – up:		
Amputation at 12mnths above knee (n)	0	0
Amputation at 12 months below knee (n)	1	0
Complications(n) (assume peri-operative – 30 days)		
Bleeding	2	0
Occlusion	1	1
Infection	0	0
Embolisation	0	0
Mortality (n) at 12mnths	1	0
Perioperative mortality (within 30 days)	0	0

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or Bypass for Superficial Femoral Artery Disease? A Randomised Controlled Trial. European	RCT BASIC trial Multicentre (13 centres, Netherlands and UK) Randomisation: Computer randomisation, stratified by each centre Allocation concealment: Not	Total N = 56 National Health Council decided inclusion of patients to beterminated before the required 200 patients was realised (as only 56 patients had enrolled at a	Inclusion criteria: Intermittent claudication not responding to conservative therapy for at least 3 months and a stenois or occlusion of the SFA with a length between 5 and 15 cm. Exclusion criteria: haemodynamically significant stenosis of the aorto-iliac tract as detected by duplex scanning, absence of patent crural arteries, previous Tx of the femoropoplieal segment, life expectancy less than	N= 31 Angioplasty Conventional balloon dilatation of the lesion. A stent could be placed according to the decision of the interventional radiologist. If angioplasty technically failed, the patient	N =25 Bypass surgery Using standard vascular techniques, using an in situ or reversed autogeneous vein graft.	12 months (1, 6, and 12 months)	Mortality Adverse events Re-intervention Major amputation	Not reported

Journal of Vascular and Endovascular Surgery. 2004; 28(2):132-137. (Guideline Ref ID 16306)	mentioned Blinding: Not mentioned. Sample size calculation: Yes based on primary patency (but sample size not met). ITT analysis: Yes (says that 30 patients were analysed though in the angioplasty group) but the last objective evaluation was used to determine study endpoints. Dropouts: Angioplasty: N=1 person in the angioplasty group was not randomised as remained on the waiting list for the procedure. Otherwise no drop-outs. N=30	particular time point)	1 year due to concomitant diseases and contra-indication for angioplasty or surgery, such as severe cardiopulmonary diseases.. Baseline: PTA N = 31; bypass N = 25 Age (median years), range: 68 (45-84); 66 (42-83) Male %: 68; 64 Medical history Hypertension %: 55; 32 Hyperlipidaemia %: 26; 24 Previous surgery: 39; 36 Myocardial infarct %: 23; 16 Stroke %: 10; 16 Diabetes %: 16; 12 Smoking: 39; 60 Clinical stage of PAD (Rutherford classification) Category 1 %: 13; 28 Category 2 %: 45; 40 Category 3 %: 32; 32 Category 4 %: 10; 0 Lesion % Stenosis: 10; 8	received a bypass graft. - - - - - - - - - - - - All patients in both groups received aspirin 100 mg/day after treatment for at least 3 months. For both groups / procedures, haemodynamic significant re-stenosis or occlusion were treated either by angio or bypass according to the deciiosn of the responsible surgeon. Follow-up continued after a redo-procedure. All patients in both group s were followed in a thorough non-invasive surveillance programme consisting of QoL questionnaire,				

	were analysed in the angioplasty group. 2 patients lost to follow-up after 2 and 3 years respectively. The last objectiv evalusation was used to determine study endpoints. Bypass: N=2 refused surgery, of whom n=1 underwent angioplasty after all. Other patient refused participation. N=24 were analysed in the bypass group. N=23 received the allocated bypass procedure (1 patient lost to follow-up after 3 years due to life-threatening concomitant disease)		Occlusion Length cm (range)	90 9 (5-15)	92 9 (5-15)	physical examination, blodd SBP measurements, treadmill test and duplex scan of the target limb. These visits were proformed at 1, 6 and 12 months after the procedure and every following year if symptoms reoccurred.				
			Number of patent crural arteries, % 1 2 3	 35 35 29	 32 36 28					
			ABPI (ankle brachial index), % and range	55 (15-84)	58 (22-92)					
Effect Size										

Baseline characteristics were similar for each group Median follow-up for all patients was 703 days (range 39-1430 days). Stent placed in N=7 patients.		
Outcome	Angioplasty N = 30	Bypass N = 25
Re-intervention at 12 months	1	1
Mortality (30 days)	0%	0%
Major amputation of target limb at 12 months	N=1	N=0
AEs at 12 months	n=0	N=4 (n=1 stroke, n=1 serious wound infection in groin, n=2 haematoma)
Minor adverse events (as defined by GDG)	n=0	N=4 (n=2 haematoma)
Major adverse events (as defined by GDG)	n=0	N=2 (n=1 stroke, n=1 serious wound infection in groin)

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H.424 Angioplasty with selective stent placement compared to angioplasty with primary stent placement

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Krankenberg H, Schluter M, Steinkamp HJ, Burgelin	RCT Multicentre (n=11 sites,Germany)	Total N = 244	Inclusion criteria: ≥ 21 years of age and had a de novo SFA lesion located at least 1 cm from the	N = 123 Self expanding open-cell nitinol stent (BARD Luminex)	N= 121 Balloon angioplasty +/- stent if required	Evaluated at baseline, before discharge and 1, 6 and 12 months.	1o outcome: Target lesion	C.R. Bard Inc, Murray Hill, NJ.

K, Scheinert D, Schulte KL, Minar E, Peeters P, Bosiers M, Tepe G, Reimers B, Mahler F, Tubler T, Zeller T. Nitinol Stent Implantation Versus Percutaneous Transluminal Angioplasty in Superficial Femoral Artery Lesions Up to 10 Cm in Length: the Femoral Artery Stenting Trial (FAST). Circulation. 2007; 116(3):285-292. (Guideline Ref ID 200)	FAST trial Randomisation: 4 block randomisation Allocation concealment: Envelopes provided by independent management organisation Blinding: Outcome assessors were blinded Sample size calculation: Yes based on 12 month binary		SFA origin with a length between 1 and 10 cm. Target lesion diameter stenosis had to be ≥ 70% by visual estimate. The popliteal artery as well as 1 of the infrapopliteal (below-the-knee) vessels had to be continuously patent for sustained distal runoff. Clinically, the patients had to suffer from chronic limb ischemia of at least Rutherford category 2 (moderate claudication). Exclusion criteria: A target lesion that required pretreatment with adjunctive devices such as lasers or debulking catheters; a target lesion that extended into the popliteal artery; previous stent implantation in the targeted SFA; multiple lesions exceeding a total length of 10 cm; acute or subacute (≤4 weeks) thrombotic		13 patients required a stent insertion Patients who had received a stent were given 300 mg of clopidogrel within 1 hour of the final digital subtraction angiography	Follow up consisted of ABPI at rest, treadmill test if possible, duplex ultrasound, and biplane xray for stents at 12mnths.	revascularization ABPI Absolute walking distance Rutherford category of peripheral arterial disease. Major adverse events Mortality	

	stenosis ITT analysis: Yes Drop outs: 9 in the stent group and 6 in the PTA group dropped out of clinical follow- up at 12 months		occlusion; an untreated ipsilateral iliac artery stenosis; ongoing dialysis treatment; and treatment with oral anticoagulants other than antiplatelet agents.					
			Baseline	Stent N=123	PTA N = 121	All patients had to be premedicated with acetylsalicylic acid (aspirin, 100 mg/d) for at least 10 days. Patients not on this regimen were given an intravenous bolus of 500 mg of aspirin immediately before the intervention NOTE: All patients were discharged the day after the intervention on a regimen of aspirin (100 mg/d indefinitely). Patients who had undergone stent implantation were additionally prescribed clopidogrel (75		
			Mean age (years) SD	67±9	66±10			
			Male (%)	62.6	75.2			
			BMI SD	26.6±4.3	27.3±4.5			
			Smoking history (%)	68.3	72.7			
			Diabetes Mellitus (%)	35.8	30.6			
			Hypertension (%)	82.9	82.6			
			Stroke (%)	10.6	5.8			
			Hyperlipidaemia (%)	60.2	61.2			
			History of CAD	42.3	31.4			
			Clinical grade Rutherford category %					
			0 asymptomatic	1/119 (0.8)	1/114 (0.9)			
			2 mild/moderate claudication	35/119 (29.4)	26/114 (31.6)			
			3 Severe claudication	80/119 (67.2)	73/114 (64)			
			4 Ischaemic pain at rest	1/119 (0.8)	3/114 (2.6)			
			5 Minor tissue loss	2/119 (1.7)	1/114 (0.9)			
			ABPI rest	0.68±0.16 n=105	0.72±0.15 n = 102			

			Median (IQR) Walking distance (m)	110 (68-163) n = 97	100(60-150) n = 99	mg/d) for at least 4 weeks.		

Baseline characteristics
Patients well matched expect for a lower baseline line ABPI in the stent group (unknown if statistically significant).

Effect Size
Reintervention: A second stent was required in 4 patients. 13 PTA pts crossed over to receive a stent, therefore on treatment cohort of 108 (PTA) and 136 for stenting.

There was no statistical difference in the improvement in clinical category or change in ABPI between groups

OR of 12 months stenosis in diabetic patients was 0.48 (95%CI 0.17-1.34) and for non diabetics was OR 0.94 (0.46- 1.90). There was no significant effect.

Outcome	Stent N=123	PTA N = 121
Procedural complications (<30days)	8/123 (7%)	5/121 (4%)
Overall mortality 12 months	4	1
Lower limb amputations due to pre-existing gangrene	2	0
Cumulative reintervention (TLR) at 12 months	17	21
Median change in ABPI at rest 12 months (subset of pts)	0.21	0.15
Procedural complications		
Total, n (%)	8 (7%)	5 (4%)
False aneurysm	2	2
Hematoma	3	0
Dissection	1	1
Distal embolisation	0	0
Reaction to contrast agent	1	0
Contract nephropathy	0	0
Residual thrombus	0	1
Arteriovenous fistula	0	1

Closure device failure	1	0

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Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bosch JL, 1999; (Guideline Ref ID 588) Tetteroo E, 1998;. (Guideline Ref ID 627) Klein WM, 2006; (Guideline Ref ID 1715) Klein WM, 2004; (Guideline Ref ID 16347)	RCT Multicentre (6 sites Netherlands) DIST trial Randomisation: Computer generated randomisation table Allocation concealment: Randomisation table kept at the trial office and unavailable to the treating physicians Blinding: Open study but outcome assessors	Total N = 279 patients	Inclusion criteria: Intermittent claudication consisting of pain localised in the buttock, upper leg, or calf; reduced pulsation of the femoral artery and reduced ankle-brachial index (ABI); reduction, evident by angiography, in arterial diameter greater than 50%; and stenosis ≤ 10 cm in length in the common or external iliac artery or occlusion of 5 cm or less that allowed passage with a guide wire. Exclusion criteria: Stenosis > 10 cm in length; arterial occlusion > 5 cm in length, or of ≤5 cm not allowing the passage of a guide wire; stenosis involving the distal aorta; severe comorbidity (eg, severe cardiac or cerebrovascular abnormality, malignant disease); and non-medical factors such as inability to understand Dutch, or expected poor compliance. The majority of patients had intermittent claudication			N = 143 patients (187 lesions) Palmaz Stent Stent placement was not possible in 1 patient - - - - - - - - All patients received anticoagulant medication (aspirin or oral anticoagulants) in accordance with local guidelines or the individual preference of the physician who initially referred the	N = 136 patients (169 lesions) Primary balloon angioplasty + selective stent placement if required Nine patients were not treated according to protocol - - - - - - - - 59 patients (43%) had selective stent placement	1, 3, 12, 24 months. Mean follow-up was 14.7 months (range 3 – 24 months). Also long-term follow-up of 6-8 years (mean 6.3 years, SD 1.8, range 0.7 to 8.6 years).	1o outcome: Quality of life: RAND 36 Time tradeoff Health Utilities Index EuroQol-5D Standard gamble 2 o outcomes: ABPI Walking distance	This study was supported by grant (OG-93/001) from the Commission of Investigative Medicine of the Dutch National Health Insurance Council and a Pionier award from the Netherlands Organisation for Scientific Research.
			Baseline	Stent N=143	Primary angioplasty N = 136					
			Mean age (years) SD	59±11	60±10					
			M/F	102/41	99/37					
			Tobacco use (%)	87%	94%					

	were blinded Sample size calculation: Yes based on 12 month patency ITT analysis: Yes		Diabetes Mellitus (%)	9%	11%	patient for treatment. Medication was independent of the type of intervention.				
			Hypertension (%)	28%	27%					
			Stroke (%)	14%	7%					
			Hyperlipidaemia (%)	24%	26%					
			Clinical grade (SVS/ISCVS) %							
			1	24%	27%					
			2	54%	51%					
			3	16%	13%					
			4	5%	8%					
	Drop outs: 25 due to the time between enrollment in the study and the procedure being too short to perform the interview or patients could not be reached by telephone). 2 year follow-up was available in 101 of the 108 eligible patients At 6-8 year follow-up: (Numerators indicate		5	1%	1%					
			ABPI rest	0.74±0.20	0.73±0.20					
			Walking distance (m)	190±109	204±106					

	number of pts attending follow-up session. Denominators decreased from number at inclusion because some patients died) Symptom assessment results – 95/118 (81%), ABI mmts – 101/118 (86%) Duplex US results for iliac arteries 109/118 (92%)									

Effect Size

Results from Tettroo, 1998

Overall there were no differences identified between the two groups

No difference in clinical success at 2 years between groups for improvement in clinical category (SVS/ISCVS).

No difference in quality of life between groups although there was an improvement within groups compared with baseline

No between group differences at 2 years in cumulative patency or reintervention.

Primary angioplasty followed by selective stent placement seems to be the strategy of choice for treatment of lifestyle-limiting intermittent claudication-particularly since the strategy also seems the most cost-effective, requiring only a fraction of the stents needed in a strategy of primary stent placement (65 [38%] of 169 in this

study).

Outcome	Stent N=143	Primary angioplasty N = 136
Complication rates (% patients)*	6 (4%)	10 (7%)
Reintervention at treated site 3 months	2	2
Reintervention at treated site 1 year	4	2
Reintervention at treated site 2 years	4	2
Cumulative reintervention at treated site rate after 2 years	10/143 (7%)	6/136 (4%)
Mortality at 3 months	0	0
Mortality at 1 year	1	2
Mortality at 2 years	0	0
Cumulative mortality rate after 2 years	1	2

*puncture site haematoma, arterial-wall perforation, acute occlusion of treated arterial segment, embolism, vasovagal collapse

Results from Bosch, 1999
Quality of Life results
91% (254 patients) undertook QoL assessment. This was assessed at baseline, 1, 3, 12, and 24 months after treatment. 1 year follow up
Both groups showed significant improvements in the RAND 36 after treatment but there were no significant differences between groups.
Values for the Health Utilities Index and the EuroQol 5D did not differ between groups.

Outcome	Stent N=143	Primary angioplasty N = 136
ABPI (mean±SD)		
ABPI rest before treatment	0.74±0.20	0.73±0.21
ABPI rest 3 months	0.92±0.25	0.93±0.22
ABPI rest 12 months	0.92±0.22	0.94±0.19
ABPI rest 24 months	0.88 ±0.24	0.96±0.20
Walking distance, m (mean±SD)		

Walking distance before treatment	190±109	204±106
Walking distance 3 months	263±57	255±64
Walking distance 12 months	261±58	263±65
Walking distance 24 months	258±68	255±68
Immediate post-procedure complications (% patients)	6 (4%)	10 (7%)
RAND 36 Median (95%CI)		
Physical functioning before treatment	40 (5-79)	45 (10-85)
Physical functioning 1 month	85 (10-100)	80 (15-100)
Physical functioning 3 months	85 (10-100)	85 (10-100)
Physical functioning 1 year	70 (7-100)	85 (20-100)
Physical functioning 2 years	75 (5-100)	85 (5-100)
Physical role functioning before treatment	0 (0-100)	0 (0-100)
Physical role functioning 1 month	0 (0-100)	0 (0-100)
Physical role functioning 3 months	100 (0-100)	100 (0-100)
Physical role functioning 1 year	100 (0-100)	100 (0-100)
Physical role functioning 2 years	75 (0-100)	100 (0-100)
Bodily pain before treatment	45 (3-100)	45 (0-99)
Bodily pain 1 month	80 (4-100)	67 (0-100)
Bodily pain 3 months	90 (20-100)	78 (10-100)
Bodily pain 1 year	78 (4-100)	80 (22-100)
Bodily pain 2 years	78 (2-100)	90 (20-98)
General health perception before treatment	55 (15-94)	55 (10-90)
General health perception 1 month	65 (16-100)	60 (15-95)
General health perception 3 months	65 (15-100)	60 (10-95)
General health perception 1 year	63 (15-100)	65 (15-95)
General health perception 2 years	55 (2-99)	60 (15-100)
Vitality before treatment	50 (6-95)	50 (5-90)
Vitality 1 month	65 (15-100)	65 (10-100)
Vitality 3 months	70 (15-100)	70 (20-100)

Vitality 1 year	65 (12-100)	65 (16-100)
Vitality 2 years	70 (15-100)	60 (15-100)
Social functioning before treatment	60 (0-100)	75 (13-100)
Social functioning 1 month	88 (13-100)	88 (13-100)
Social functioning 3 months	100 (14-100)	88 (13-100)
Social functioning 1 year	100 (0-100)	88 (25-100)
Social functioning 2 years	88 (0-100)	94 (0-100)
Emotional role functioning before treatment	100 (0-100)	67 (0-100)
Emotional role functioning 1 month	100 (0-100)	100 (0-100)
Emotional role functioning 3 months	100 (0-100)	100 (0-100)
Emotional role functioning 1 year	100 (0-100)	100 (0-100)
Emotional role functioning 2 years	100 (0-100)	100 (0-100)
Mental health before treatment	76 (13-100)	74 (20-100)
Mental health 1 month	80 (28-100)	80 (24-100)
Mental health 3 months	84 (28-100)	80 (28-100)
Mental health 1 year	80 (6-100)	76 (30-100)
Mental health 2 years	80 (30-100)	80 (24-100)
Health utilities index, Median (95% CI)		
Health utilities index before treatment	0.68 (0.35-0.87)	0.69 (0.28-0.80)
Health utilities index 1 month	0.70 (0.37-1.00)	0.70 (0.24-1.00)
Health utilities index 3 months	0.76 (0.04-1.00)	0.77 (0.28-1.00)
Health utilities index Median	0.70 (0.28-1.0)	0.77 (0.28-1.0)
Health utilities index Median	0.70 (0.22-1.0)	0.70 (0.16-1.0)
EuroQoL-5D, Median (95% CI)		
EuroQoL-5D before treatment	0.46 (0.20-0.75)	0.46 (0.15-0.75)
EuroQoL-5D 1 month	0.70 (0.15-1.00)	0.70 (0.20-1.00)
EuroQoL-5D 3 months	0.75 (0.15-1.00)	0.70 (0.20-1.00)
EuroQol-5D Median (95%CI) 1 year	0.59 (0.19-1.0)	0.70 (0.15-1.0)
EuroQol-5D Median (95%CI) 2 years	0.70 (0.09 -1.0)	0.66 (0.15-1.0)

Results from Klein 2004			
	Stent	Angioplasty	Log rank p value
Mortality at 5 years	21 out of 143 people	22 out of 136 people	
Re-intervention at 5 years	33 out of 187 limbs	33 out of 169 people	0.7
Amputation at 5 years	3 out of 143 people	8 out of 136 people	
Results from Klein, 2005			
6-8 years (RESULTS PER LESION)	Stent N=????	Primary angioplasty N = ????	
ABI measurement, mean (SD)	0.90 (0.20)	0.96 (0.22)	
Reinterventions, n (%)	12/118 (10)	21/110 (19)	
RAND-36 Scores, Mean (SD) at baseline	Stent N=????	Primary angioplasty N = ????	
Physical functioning	39.6 (18.9)	42.1 (20.4)	
Physical role functioning	27.1 (36.1)	32.0 (40.5)	
Emotional role functioning	59.9 (44.5)	54.8 (44.7)	
Social functioning	63.8 (27.0)	68.5 (28.2)	
Bodily pain	50.3 (22.2)	49.3 (24.6)	
General health perception	56.7 (21.0)	53.5 (22.8)	
Mental health	70.4 (21.4)	69.1 (21.9)	
Vitality	50.9 (23.3)	52.6 (21.5)	
Health change	30.9 (22.5)	31.2 (21.0)	
RAND-36 Scores, Mean (SD) at 1 month	Stent N=????	Primary angioplasty N = ????	
Physical functioning	73.0 (25.2)	72.9 (25.4)	
Physical role functioning	58.5 (44.3)	55.9 (45.2)	

Emotional role functioning	72.2 (40.6)	66.4 (41.3)
Social functioning	77.8 (25.9)	76.4 (26.0)
Bodily pain	75.8 (24.6)	67.5 (27.8)
General health perception	63.2 (22.4)	57.2 (21.5)
Mental health	75.3 (20.2)	74.2 (19.2)
Vitality	62.2 (23.5)	61.3 (21.9)
Health change	71.2 (27.4)	62.4 (30.0)
RAND-36 Scores, Mean (SD) at 5 years	Stent N=????	Primary angioplasty N = ????
Physical functioning	61.0 (27.3)	71.2 (26.1)
Physical role functioning	61.2 (41.2)	70.0 (39.2)
Emotional role functioning	80.7 (35.3)	86.4 (28.2)
Social functioning	80.4 (25.1)	80.2 (23.6)
Bodily pain	67.8 (25.8)	77.5 (24.2)
General health perception	53.7 (21.1)	59.7 (24.4)
Mental health	75.2 (17.9)	76.7 (17.3)
Vitality	61.1 (20.6)	64.3 (20.6)
Health change	47.9 (22.1)	47.5 (18.9)

1

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Zeller T, Roubin GS, Burket MW, Khatib Y, Snyder SA, Ragheb AO, White JK, Machan LS,	RCT Multinational Randomisation: Block randomisation by interactive voice response system	479	Inclusion criteria: Rutherford category ≥2 and resting ankle brachial index (ABI) <0.9, lesion length ≤14 cm, ≥50% DS, reference vessel diameter 4-9 mm, and at least one patent runoff vessel (<50% DS throughout its course). Exclusion criteria: criteria	Angioplasty n = 238 Performed according to institutional standard procedure	Angioplasty with primary self expanding nitinol stent n = 241	6 and 12 months (only 12 months reported)	All cause mortality Procedure or device related mortality Amputation TLR	Cook Medical

Zilver PTX Investigators. Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease: Twelve-Month Zilver PTX Randomized Study Results. Circulation: Cardiovascular Interventions. 2011; (Guideline Ref ID 16288)	Allocation concealment: Not reported Blinding: Not reported Sample size calculation: Calculated for primary outcome ITT analysis: ITT Drop outs: Angio group: 0 dropped out Stents group: 10 dropped out (5 withdrew and 5 loss to follow up		included: untreated >50% diameter stenosis (DS) of the inflow tract, lesion pre-treatment with adjunctive devices, and previous target vessel stenting Baseline / Angio / Stent Mean age: 67.7 ± 10.6 / 67.9 ± 9.6 Male sex: 152 / 155 BMI: 28.2 ± 5.6 / 28.4 ± 5.3 Claudication: 90.7% / 90.2% CLI: 8.5% / 8.9% Diabetes: 100 / 116 Type 1: 13 / 19 Type 2: 87 / 97 Hypertension: 194 / 210 Hypercholesterolemia: 166 / 180 History of smoking: 200 / 204 Renal disease: 25 / 34 Pulmonary disease: 38 / 45 History of MI: 41 / 50 SFA: 232 / 229 SFA/poplite: 6 / 9				ABPI	

			al							
			Popliteal	13	9					
			Previous interventio n prior to study	14	13					
			ABPI	0.68 ± 0.2	0.67 ± 0.2					

Effect size		
	PTA (n = 238)	Stents (n = 241)
All cause mortality at 12 months	4	9
Procedure or device related mortality at 12 months	0	0
Amputation (toe at 12 months)	0	1
TLR at 12 months	39	21
ABPI	0.89 ± 0.2	0.91 ± 0.23

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dick P, Wallner H, Sabeti S, Loewe C, Mlekusch W, Lammer J, Koppensteiner R, Minar E, Schillinger M. Balloon Angioplasty Versus Stenting With Nitinol Stents in	RCT ASTRON trial Multicentre (3 sites, Austria) Randomisation: Random number generator. Stratified by claudication versus critical	Total N = 73	Inclusion criteria: Symptomatic peripheral artery disease (PAD) with either severe intermittent claudication (Rutherford class 3) or chronic critical limb ischemia with rest pain (Rutherford class 4) or ischemic ulcers (Rutherford class 5). >50% stenosis or occlusion of the SFA with a target lesion length between 30 mm and 200 mm, and at least one patent (<50% stenosis) tibioperoneal run-off vessel.	N= 34 Primary stent implantation. Predilation with undersized balloons was performed restrictively in patients with very tight stenosis or heavily calcified	N =39 PTA with optional secondary stenting. Minimal time for each balloon inflation was 2 minutes at 10–12 atm.	12 months (3, 6, and 12 months)	Complications Maximum walking distance ABPI Mortality	No details

Intermediate Length Superficial Femoral Artery Lesions. Catheterization and Cardiovascular Interventions. 2009; 74(7):1090-1095. (Guideline Ref ID 32)	limb ischemia, and length of the target lesion (≤ vs. >60 mm) Allocation concealment: Sealed envelopes Blinding: Not for primary researcher or patient but outcome assessors were blinded. Sample size calculation: Yes based on restenosis rate. ITT analysis: Yes Dropouts: Complete follow-up data could be obtained 97% at 3 months, and in 93% at 6 and 12 months, Follow-up data		Exclusion criteria: Acute critical limb ischemia, previous bypass surgery or stenting of the SFA, untreated inflow disease of the ipsilateral pelvic arteries (>50% stenosis or occlusion), and known intolerance of study medications or contrast agent. 95% of patients had intermittent claudication			lesions that did not allow primary passage with the stent introducer device. Stents were implanted to extend 10 mm proximal and distal to the margins of the target lesion. Multiple stents were overlapped for 10 mm. Postdilation after stenting was performed strictly within the stented segment with up to 10% oversizing of the postdilation balloon. - - - - - - - - - All interventions performed percutaneously - - - - - - - - - - - - All patients received aspirin 100 mg/day indefinitely	After dilation control angiograms were obtained. In cases with a suboptimal primary result, a second prolonged balloon dilation (>2 minutes) of was performed. In patients with a persistent suboptimal result after the second balloon dilation, secondary stenting was performed. - - - - - - - - - For stent implantation in both groups, self-expandable nitinol stents			

Baseline	Stent N = 34	PTA N = 39
Age (years) SD	69±9	69±10
Male %	74	64
BMI (SD)	27.9±3.6	27.7±3.8
Co-morbidity		
Hypertension %	79	85
Hyperlipidaemia %	91	92
Symptomatic coronary artery Disease %	35	31
History of myocardial infarction %	15	15
History of stroke %	6	5

	were not available in two patients at 3 months (one died and one refused reevaluation) and in five patients at 6 and 12 months (three died, two refused reevaluation).		Diabetes mellitus %	29	31	and clopidogrel 75 mg/day for 3 months postintervention. Aspirin and clopidogrel were initiated at least 2 days before the intervention in most patients; otherwise a loading dose of 300 mg clopidogrel was given during the intervention. Additionally patients received statins, antihypertensive medication, and oral antidiabetic therapy according to their cardiovascular risk profile.	with a nominal diameter of 6 mm were used.			
			Current smoker	35	44					
			Clinical stage of PAD (Rutherford)							
			Class 3 (intermittent claudication) %	91	97					
			Class 4 (ischemic rest pain) %	3	0					
			Class 5 (ischemic ulcers) %	6	3					
			Maximum walking distance (m)	131±188	103±92					
			ABPI	0.64±0.	0.63±0.					
Effect Size In the PTA group, 10 of 39 patients (26%) underwent secondary stenting after two attempts of balloon dilation, due to a flow limiting dissection in six cases and a residual stenosis >30% in four cases. Significantly higher rates of restenosis in angioplasty group. Significanlty higher mean walking capacity in stent group compared with angioplasty group at 6 months and 12 months. No significant differences between groups in ABPI										

Outcome	Stent N = 34	PTA N = 39	P Value
Complications	0	1 (pseudoaneurysm)	
Baseline maximum walking capacity, m (mean ± SD)	131 ±188	103 ± 92	0.86
Maximum walking capacity, m at 6 months (mean)	800	600	0.002
Maximum walking capacity, m at (12 months (mean)	800	550	0.042
ABPI baseline (mean ± SD)	0.64 ± 0.33	0.63 ± 0.24	0.70
ABPI 6 months (mean)	1.20	1.06	0.84
ABPI 12 months (mean)	0.93	0.89	0.40
1 death at 3 months, 3 deaths at 12 months (group unkown) No ABPI/walking capacity data at 1 or 3 months			

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Laird JR. Nitinol Stent Implantation Versus Balloon Angioplasty for Lesions in the Superficial Femoral Artery and Proximal Popliteal Artery: Twelve-Month Results From the RESILIENT Randomized Trial. Circulation: Cardiovascular Interventions. 2010; 3(3):267-276. (Guideline Ref ID 590)	RCT RESILIENT: Randomized Study C omparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone in LEsions INvolving The SFA and/or Proximal Popliteal Artery 24 centres in Europe and US Dec 2004 – Aug 2006 Randomised: Computer-generated randomisation (by patient)	Total N = 206	Inclusion criteria: Patients aged ≥18 years with symptoms of intermittent claudication (Rutherford 1 – 3) who were candidates for angioplasty or stenting, had de novo stenotic, occlusive or restenotic lesions in SFA, proximal popliteal art or both and had at least 1 patent infrapopliteal run-off vessel to the foot. Stenosis/restenosis of ≥50% and total lesion length of ≤150 mm.	Angio N = 72 Percutaneous transluminal angioplasty Provisional (bailout) stent used if after multiple balloon inflations suboptimal angioplasty	Stent N = 134 Self-expanding nitinol stent with predilatation and optional postdilatation	12 months	Mortality Amputation Target lesion revascularisation QoL	Not reported

	in blocks of 6 on 2:1 (2 stent : 1 angio) ratio Allocation concealment: Not mentioned Blinding: Open Sample size calculation: Yes, for primary outcome ITT Analysis: Yes, all endpoints Drop outs: 12 (6%)		Exclusion criteria: Patients with critical limb ischaemia (Rutherford 4 – 6), sensitivity to contrast media that was not amenable to pretreatment with steroids, antihistamines, or both known allergies to study medications or materials, renal failure (Cr > 2.0 mg/dL) or hepatic insufficiency, previous bypass surgery of the target limb, extensive peripheral vascular disease that precluded safe insertion of introducer sheath, aneurysmal disease in the vessel segment to be treated, thrombus in the area to be treated that could not be resolved, angiographic evidence of poor inflow that was inadequate to support vascular bypass patients who were receiving dialysis or immunosuppressive therapy	with flow-limiting dissection or residual stenosis >30% 40% (n=29) underwent bailout stenting				

			Baseline characteristics of randomised patients: Age, sex, race and pre-procedure classification of symptoms not significantly different between treatment groups (p>0.05). CV risk factors not significantly different between groups (p≥0.09) except slightly higher reported prevalence of hypertension in angio group compared with stent group (p=0.03)					

Effect size

Outcome

	Angio n=72	Stent n=134	P-value
Freedom from target lesion revascularisation (6 months)	52.6%	98.5%	P<0.0001
Freedom from target lesion revascularisation (12 months)	45.1%	87.3%	P<0.0001
Death within 30 days of procedure	0	0	
Amputations at 12 months	2†	0	
Quality of Life			
SF-8 baseline	41.0±10.5	41.4±9.2	
Change in SF-8 at 12 months	5.9±11.2	5.7±11.2	P<0.0001 versus baseline
Change at 12 months in walking distance score from baseline	29.4±37.4	25.6±34.6	P<0.0001 versus baseline

†Single toe amputations

Patients in the angioplasty group reported more claudication pain at 12 months than patients in the stent group (Walking Improvement Questionnaire evaluation, P=0.009); no further details given

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Greenberg D, Rosenfield K, Garcia LA, Berezin RH, Lavelle T, Fogleman S, Cohen DJ. In-Hospital Costs of Self-Expanding Nitinol Stent Implantation Versus Balloon Angioplasty in the Femoropopliteal Artery (The VascuCoil Trial). Journal of Vascular and Interventional Radiology. 2004; 15:1065-1069. (Guideline Ref ID 2447) US Food and Drug Administration. IntraCoil® Self-Expanding Peripheral Stent: Summary of Safety and	RCT Multicenter prospective randomised trial (20 sites) – USA May 1997-Dec 1999 Randomised: Patients randomised – method not stated Allocation concealment: Not stated Blinding: Open Sample size calculation:	Total N = 266	Inclusion criteria: Candidates for angioplasty with symptomatic leg ischaemia requiring treatment of the superficial femoral/popliteal vessel with an occluded lesion length ≤12 cm or a stenotic lesion length ≤15 cm and located proximal to the bifurcation of the tibial artery Exclusion criteria: Baseline characteristics of randomised patients: P-value non-significant for all comparisons: Baseline characteristics: Stent: Age 66.8±10.6; Male % 67.4 Angioplasty: Age 68.1±0.2; Male % 63.4	Angio N=131 patients, 177 lesions Percutaneous transluminal angioplasty (angio) Pts in angio arm allowed to crossover to Stent if i) actue results indicated abrupt closure or impending closure due to severe recoil or extensive dissection, not correctable despite repeated balloon	Stent N=135, 175 lesions Intracoil fermoropoplitea l stent	Clinical follow- up visits were conducte d at 6 months, 9 months and 1 year, with continuin g annual follow- up for safety.	Mortality Amputatio n Adverse events ABPI	Supported in part by a grant from IntraTherapeutics .

Effectiveness Data. Silver Spring, MD: US Food and Drug Administration, 2002. (Guideline Ref ID 16318)	Not stated, however study originally designed to enroll 500 patients, but was stopped early due to slow patient enrollment. ITT Analysis: Yes Drop outs: not stated		DM %	38.0	37.4	inflation or larger balloon size (if appropriate) or ii) during follow-up there was angiographically defined restenosis or dissection that was limb threatening				
			Smoking hx %	81.9	80.0					
			Prior MI %	37.2	29.1					
			Ref vessel diameter (mm)	4.2±0.96	4.2±1.0					
			Lesion length (cm)	3.6±3.0	3.3±3.0					
			Total occlusion	22.7%	16.8%					

Effect size Outcome		
	Angioplasty (n=131 patients)	Stent (n=135 patients)
All-Cause Mortality	13	5
Amputation	1	0
Change in ABI (from baseline to 9 months) range (min, max)	0.08 ± 0.19 (n=64) (-0.25,0.52)	0.19 ± 0.20 (n=83) (-0.43,0.56)
Distal embolisation (major)	1	0
Major bleeding complications (major)	1	1
Major vascular complications (major)	6	5
Renal failure (major)	3	0
Total major adverse events (as defined by GDG)	11	6

1

2

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Vroegindeweij 1997; (Guideline Ref ID 2255)	RCT Single centre (Netherlands) Randomisation: Method unclear Allocation concealment: Numbered envelopes Blinding: None Sample size calculation: No details ITT analysis: Yes Drop outs: No details	Total N = 51	Inclusion criteria: Lesions confined to the femoropopliteal artery, excluding below-knee lesions; eligibility of lesions for balloon angioplasty alone (BA) and balloon angioplasty combined with stenting (ST), which excluded all patients with multisegmental disease and with no runoff; and) maximal length of the lesion 5 cm. No patients had undergone any previous endovascular or operative interventions in the ipsilateral femoral artery. Only patients who would be able to comply with the frequent follow-up study visits required by the color-flow duplex surveillance protocol were selected. Exclusion criteria: No details. 82% of patients had intermittent claudication			N = 24 Stenting using Palmaz stents - - - - - - - - After the procedure all patients started on oral coumadin. Anticoagulation treatment was continued during the first 3 months, whereafter the treatment was changed to aspirin 80 mg/day indefinitely. 4 patients randomised to stent were treated with	N = 27 Balloon angioplasty	2 years The median duration of followup, until reintervention, restenosis, or occlusion, as indicated by color-flow duplex US or the last visit to the outpatient clinic, was 14.1 months (range 0–31 months) in patients with BA and 13.4 months (range 0–27 months) in patients with ST.	ABPI Complications	No details
			Baseline	Stent N = 24	Angioplasty N =27					
			Mild to moderate intermittent claudication (Class I1-2)	20	22					

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Severe claudication (Class I3)	4	5	angioplasty				
			Age (years) Mean (range)	65 (46–78)	64 (41–82)					
			M/F	17/7	19/8					
			Comorbidiities (n)							
			Coronary heart disease	6	9					
			Diabetes mellitus	3	3					
			Smoking	14	18					
			Hypertension	3	6					
			Hypercholesterolemia	9	7					

Effect Size

Outcome	Stent N = 24	Angioplasty N =27
Minor complications within 30 days	1	1
ABPI at 1 year	0.78 ± 0.18	0.81 ± 0.18

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Grimm J,. 2001; (Guideline Ref	RCT	Total N	Inclusion criteria: Occlusion or severe stenosis of the superficial femoral artery	N = 30	N = 23 Angioplasty	3, 6, 12 months	Mortality	No

<table>
<tr>
<td>ID 2254)</td>
<td>Single centre in Germany

Randomisation: Method unclear

Allocation concealment: Sealed envelopes

Blinding: none

Sample size calculation: No details

ITT analysis: Yes

Drop outs: Six died and 6 lost to follow-up (Groups unknown)</td>
<td>= 53</td>
<td>including the P1 segment of the popliteal artery.
The lesion had to be situated at least 1 cm distal from the femoral bifurcation in the superficial femoral artery and could include the P1 segment of the popliteal artery. The P2 segment had to be free of disease at the time of the study. Length of the stenosis ≤ 5 cm; the percentage of stenosis > 70%. At least two patent vessels in the lower limb had to provide sufficient run-off. To ensure proper placement of the stent, the vessel diameter had to be between 4 and 8 mm. Significant stenoses in the iliac or popliteal vessels had to be treated before stent placement.

Exclusion criteria: Lesions exceeding 5 cm in length requiring more than two stents, multifocal disease or complete of the superficial femoral artery, hemodynamically relevant stenoses in the lower limb previously untreated, occlusion of more than two arteries in the lower limb, lesions distal to the P1 segment or including the femoral bifurcation, thrombus within the superficial femoral artery, and existing contraindications for vascular surgery or anticoagulation.

The majority of patients had intermittent claudication
<table>
<tr><td>Baseline</td><td>Angioplasty +Stent
N = 30</td><td>Angioplasty
N = 23</td></tr>
<tr><td>Age (years) SD</td><td>70.5±9.8</td><td>68.1±8.4</td></tr>
<tr><td>Sex (M/F)</td><td>22/8</td><td>10/13</td></tr>
<tr><td>Ankle-brachial</td><td>0.47 ± 0.36</td><td>0.62 ± 0.3</td></tr>
</table>
</td>
<td>Angioplasty + Palmaz Stent

Palmaz stent is made of stainless steel and balloon expandable.</td>
<td>alone (PTA)

- - - - - - - - - -
All patients received intravenous heparin for 24 hours after the procedure and thereafter received aspirin (100 mg/d) for the remainder of their lives.</td>
<td>and annually thereafter for a max. of 39 months in both groups (Mean follow-up was 29.1 months ± 13.4 in the PTA group and 20.9 months ± 14 in the Palmaz group.</td>
<td>Claudication distance

ABPI

Complications

Re-intervention</td>
<td>details</td>
</tr>
</table>

			index							
			Preoperative claudication distance (m)	166.4 ± 140.1	150.3 ±160.5					

Effect Size

Stent placement and PTA were technically successful in all cases, there were no side effects or deaths related to the procedure, and there was no mortality within the first month.

No differences between groups for primary or secondary patency rates

Outcome	Angioplasty +Stent N = 30	Angioplasty N = 23	P value
Pre operative claudication distance, m (mean ± SD)	166.4 ± 140.1	150.3 ± 160.5	0.32
Postoperative claudication distance, m (mean ± SD)	383.5 ± 237.5	466.7 ± 461.9	0.71
Pre operative ABPI (mean ± SD)	0.47 ± 0.36	0.62 ± 0.3	0.12
Post operative ABPI (mean ± SD) time point not given	0.91 ± 0.19	0.85 ± 0.2	
Reintervention (n)- angioplasty	8 (after mean 7 months)	7 (after mean 11 months)	0.3
Post operative mortality (1 month)	0	0	
Complications: 7 groin haematomas (group unknown)			

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K, Lammer J. PTA Versus Palmaz	RCT Multicentre (n = 4 sites Austria) Randomisation: Randomised by	Total N = One hundred fifty-four limbs in 141 patients	Inclusion criteria: up to three lesions (stenosis and/or occlusions), up to 5 cm in length, located in the superficial femoral artery or in the aboveknee segment of the popliteal artery. At least one run-off vessel had to be patent at angiography.	N = 77 limbs PTA alone	N = 77 limbs' PTA + stent	3, 6, 12 months after intervention. Mean 352 days (range 1-1,252 days) for PTA and 353 days	Mortality ABPI Amputation Re-	

Stent Placement in Femoropopliteal Artery Obstructions: a Multicenter Prospective Randomized Study. Journal of Vascular and Interventional Radiology. 2001; 12(1):23-31. (Guideline Ref ID 539)	limb. Unclear method Allocation concealment: Closed envelopes Blinding: Open labelled Sample size calculation: Yes based on patency in lesions ITT analysis: Yes Drop outs: Angiographic follow-up within 12 months was available in 45 limbs in the PTA group and 46 limbs in the Stent group). No angiographic follow-up was available in 33 limbs (13 PTA, 20 stent) No clinical follow up was available for 20 limbs (6		Exclusion criteria: Pregnant women, or patients with an acute onset of symptoms (with an angiographic appearance resembling an acute thromboembolism). Patients who had previous vascular surgery in the treated segments, with an untreated obstruction of the inflow vessels (eg, iliac and common femoral arteries), or patients who were unable or unwilling to participate in follow-up examinations and drug therapy Inadvertently, two patients (39 and 87 years old, respectively) were randomized and included in the study. Six patients who had mild (walking distances between 250 and 500 m) but severely life-style inhibiting claudication were included (PTA, n = 4 versus stent, n= 2), as well as a patient who was 87 years old (stent, n = 1)	- - - - - - - - All patients received acetylsalicylic acid (100 mg/d) orally beginning the day before treatment. After successful PTA or stent placement, patients received intravenous heparin at 750–1000 units per hour for 2 days. Acetylsalicylic acid (100 mg/d) was prescribed as a continuous life-long medication.	- - - - - - - - - - Two patients underwent bilateral PTA, one patient underwent bilateral stent placement. Randomised groups not clear	(range 1-1,215 days for stent group)	intervention Complications	
			Baseline	PTA N = 77 limbs	PTA +stent N = 77 limbs				

	PTA, 14 stent)		Age (years) Range	65.5 (39.2 -83)	68.6 (39.2-87)					
			Male %	59.8	63.6					
			Co-morbidities							
			Hyperlipidemia (%)	46.8	35.0					
			Diabetes mellitus (%)	40.2	39.0					
			Smoking history (%)	61	62.4					
			SVS-ISCVS categories							
			Mild and moderate(%)	16.9	14.3					
			Severe claudication(%)	58.4	50.6					
			Ischaemic rest pain (%)	9.0	14.2					
			Minor tissue loss	15.6	20.8					
			Location on lesion							
			Proximal SFA	14.2	22.0					
			Distal SFA and hiatus adductoris	75.4	72.8					
			Above knee popliteal artery	10.4	5.2					
Effect Size ABPI significantly increased following each procedure but there were no between group differences. IN the stent group initial technical success was significantly greater than PTA alone (P=0.009) There was no significant difference between groups for major or minor complications. There were no differences between groups in primary or secondary patency rates There were no significant differences between groups in clinical stage of disease.										

Outcome	PTA N = 77 limbs	PTA +stent N = 77 limbs
Mortality		
Mortality <30 d (n) patients	2 (MI; Sepsis)	0
Mortality >30 d (n)	5	12
Total mortality (n)	7	12
Outcome	PTA N = 77 limbs	PTA +stent N = 77 limbs
Reintervention at 12 months follow-up (n)	12	21
Bypass at 12 monthsfollow-up (n)	4	7
Total reintervention at 12 months follow-up	16	28
Complications		
Major complication Large groin haematoma (n)	2	0
Early thrombosis <30d (n)	1	3
Peripheral embolisation (treated) (n)	3	4
Amputations <30d (n)	4 (digits)	2 (crural)
ABPI		
ABPI pre-treatment (mean±SD)	0.62±0.22	0.63±0.20
ABPI post-treatment at unspecified timepoint (mean±SD)	0.97±0.20	0.99±0.18

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Schillinger M, 2006; (Guideline Ref	RCT Austria	Total N = 104	Patients referred for endovascular treatment of the superficial femoral artery owing to intermittent	N = 51 Self-	N = 53 Angioplasty	24 hours, 3, 6	Complications	Medical University of Vienna and the

ID 288) Schillinger M, 2007; (Guideline Ref ID 209) Sabeti S, 2007; (Guideline Ref ID 1983)	Randomisation: Blocks of four with the use of computer-generated random digits. Patients were stratified according to the reason for revascularization (claudication vs. critical limb ischemia) and the length of the target lesion (≤60 mm vs. >60 mm). Allocation concealment: Sealed envelopes Blinding: Not for patient or investigator but outcome assessors were blinded Sample size calculation: Yes based on		claudication or chronic critical limb ischemia. Inclusion criteria: Symptomatic peripheral-artery disease with severe intermittent claudication (Rutherford stage 3), chronic critical limb ischemia with pain while at rest (Rutherford stage 4), or chronic critical limb ischemia with ischemic ulcers (Rutherford stage 5). Stenosis of more than 50 percent or occlusion of the ipsilateral superficial femoral artery, a target-lesion length of more than 30 mm, and at least one patent (less than 50 percent stenosed) tibioperoneal runoff vessel. Exclusion criteria: Acute critical limb ischemia, previous bypass surgery or stenting of the superficial femoral artery, untreated inflow disease of the ipsilateral pelvic arteries (more than 50 percent stenosis or occlusion), and known intolerance to study medications or contrast agents. 88% of patients had intermittent claudication Baseline | Stent N = 51 | Angioplasty +/- stent N = 53	expanding nitinol stent. Percutaneous approach See Dick 2009 Ref ID 32 for details - - - - - - - - - All patients received aspirin (100 mg daily) indefinitely and clopidogrel (75 mg daily) for three months after the intervention. Most patients started taking clopidogrel at least two days before the intervention; for those who did not,	with optional secondary stenting. Percutaneous approach See Dick 2009 Ref ID 32 for details - - - - - - - - - 17 (32 %) underwent secondary stenting	and 12 months	Maximum walking distance ABPI Moratliy Reintervention Amputation SF-36	Vienna General Hospital.

	restenosis rate ITT analysis: Yes Drop outs: Data were not available for three patients at 12 months 2 from stent group and 1 from angioplasty group(one died and two declined to be reevaluated). Groups not reported.		Age (years) SD	65±10	68±10	a loading dose of 300 mg of clopidogrel was given during the intervention.				
			Male %	59	47					
			BMI (SD)	27.5±3.8	27.4±4.0					
			Co-morbidities							
			Hypertension (%)	94	89					
			Hyperlipidemia (%)	92	87					
			Diabetes mellitus (%)	43	32					
			Smoking at baseline (%)	53	36					
			Coronary artery disease (%)	67	75					
			History of myocardial infarction (%)	20	8					
			History of stroke (%)	4	9					
			Rutherford stage of peripheral-artery disease							
			3 (%)	88	87					
			4 (%)	2	4					
			5 (%)	10	9					
			Maximal distance walked on a treadmill (median, IQR)	92 (45–113)	87 (44–118)					
			ABPI (SD)	0.57±0.19	0.54±0.20					
Effect Size										

Results from Schillinger, 2006		
Outcome	Stent N = 51	Angioplasty +/- stent N = 53
Complications during operation		
Major complication	0	0
Minor complications	1	1
Maximal walking distance, m (median, 95% CI)		
Maximal walking distance (Metres) 6 months	363 (260, 450)	270 (180, 340)
Maximal walking distance (Metres) 12 months	387 (310, 480)	267(170, 340)
ABPI (mean, 95% CI)		
ABPI 6 months	0.81 (0.75, 0.9)	0.73 (0.71, 0.80)
ABPI 12 months	0.87 (0.82, 0.91)	0.75 (0.7, 0.81)
Ipsilateral re-intervention within 12 months		
Balloon angioplasty	10/49	15/52
Stent implantation	1/49	1/52
Bypass surgery (supragenicular)	3/49	0/52
Total ipsilateral re-intervention rate within 12 months	14/49	16/52
Amputation		
Within 6 mo	0/51	0/53
Within 12 mo	0/51	0/53
Death		
Within 6 mo	0/51	0/53
Within 12 mo	1/51	0/53
Results from Schillinger, 2007 There had been no major complications at baseline.		
Outcome	Stent N = 46	Angioplasty +/- stent N = 52

Walking capacity treadmill Median (IQR) at 2 years	302 (99-700)	196 (77 – 355)
ABPI mean SD at 2 years	0.88 ± 0.18	0.78±0.17
Reinterventions at 2 years	17	28
Minor amputation at 2 years	0	1
Results from Sabeti, 1983 Up to 12 months follow-up all parameters of QoL significantly improved in the entire population (P<0.01) except for social functioning and role emotional perception. Patients without stenosis at 6 (physical and mental component score) and 12 months (physical component score) had significantly better quality of life compared with patients with restenosis There were no significant difference for any parameter of QoL at any time interval between stent and balloon angioplasty groups.		

Outcome	Stent N = 51	Angioplasty +/- stent N = 53	
SF-36 Median (IQR)			
Physical functioning baseline	50 (32-60)	45 (30-55)	NS
Physical functioning 6 months	60 (35-85)	62 (35-85)	NS
Physical functioning 12 months	65 (45-82)	67 (38-45)	NS
Role physical functioning baseline	0 (0-75)	0 (0-50)	NS
Role physical functioning 6 months	0 (0-100)	0 (0-100)	NS
Role physical functioning 12 months	25 (0-100)	0 (0-100)	NS
Bodily pain baseline	30 (12-41)	22 (10-40)	NS
Bodily pain 6 months	51 (22-100)	52 (30-74)	NS
Bodily pain 12 months	52 (22-100)	46 (22-76)	NS
General health baseline	52 (35-62)	45 (35-63)	NS
General health 6 months	47 (35-67)	47 (32-70)	NS
General health 12 months	52 (35-64)	50 (30-71)	NS
Vitality baseline	45 (30-55)	40 (27-50)	NS
Vitality 6 months	50 (36-60)	47 (33-66)	NS
Vitality 12 months	50 (37-67)	45 (30-66)	NS

Social functioning baseline	88 (50-100)	75 (50-100)	NS
Social functioning 6 months	88 (63-100)	88 (59-100)	NS
Social functioning 12 months	100 (75-100)	88 (59-100)	NS
Role emotional baseline	67 (0-100)	100 (0-100)	NS
Role emotional 6 months	100 (33-100)	100 (0-100)	NS
Role emotional 12 months	100 (67-100)	67 (0-100)	0.04
Mental health baseline	64 (46-80)	64 (52-78)	NS
Mental health 6 months	72 (48-84)	66 (48-80)	NS
Mental health 12 months	72 (58-84)	60 (48-84)	NS
Physical component summary baseline	31 (26-37)	27 (22-35)	0.07
Physical component summary 6 months	33 (29-49)	37 (30-47)	NS
Physical component summary 12 months	35 (30-48)	37 (27-49)	NS
Mental component summary baseline	48 (41-59)	49 (38-60)	NS
Mental component summary 6 months	53 (42-58)	50 (35-58)	NS
Mental component summary 12 months	54 (45-49)	51 (35-58)	NS
QoL outcome data not reported at 3 months			

1

H.425 Bare metal compared to drug eluting stents

Study details	Patients	Intervention	Comparison	Outcomes	Other comments
Dake 2011; (Guideline Ref ID 16288) RCT Multicentre RCT **Randomised:** block randomised in blocks of 4 or 6	Total N = 120 The inclusion / exclusion criterion below is for the study as a whole which first randomisation for PTA to DES. This data extraction is for the secondary randomisation for patients who failed PTA and were therefore randomised to DES or BMS. Patients who failed PTA were those who had ≥ 30% DS noted on arteriography after 1 repeat 2-3 minute balloon	N = 61 Drug eluting stent – self expanding nitinol drug eluting stent	N = 59 Bare metal stent – 3µg/mm2 polymer-free paclitaxel coating	Procedure / device related deaths All cause morality	Funding source: Cook Medical

using interactive voice response system **Allocation concealment:** not reported **Blinding:** not reported **Sample size calculation**: not reported **ITT analysis:** ITT performed. **Drop outs:** 7 in total, 4 withdrew and 1 was lost from the BMS group, 2 withdrew from the DES group. **Follow-up duration**: 2 years	inflation **Inclusion criteria:** • Rutherford category ≥2 and ABP <0.9, • lesion length ≤14 cm, ≥50% DS, • reference vessel diameter 4-9 mm, and at least one patent runoff vessel (<50% DS throughout its course). **Exclusion criteria:** • untreated >50% diameter stenosis (DS) of the inflow tract, • lesion pre-treatment with adjunctive devices, • previous target vessel stenting The study did not report baseline characteristics for those who failed PTA and went on to have DES or BMS Baseline characteristics for all patients randomised to PTA (including those who had successful PTA) Mean age, years - 67.7 ± 10.6 Male sex, n 152 (63.9%) Claudication (Rutherford class 2-4) - 95.4% Critical Limb Ischemia - (Rutherford class 2-4) - 3.8% Diabetes, n - 100 (42.0%) Type I diabetes, n - 13 (13.0%) Type II diabetes, n - 87 (87.0%) Hypertension, n - 194 (81.5%) Hypercholesterolemia, n - 166 (69.7%) History of smoking, n - 200 (84.0%) Renal disease, n - 25 (10.5%) Pulmonary disease, n - 38 (16.0%)				

	History of myocardial infarction, n - 41 (17.2%) Lesion Characteristics Lesions, n - 251 247 Lesion location: SFA - 232 (92.4%) SFA/Popliteal - 6 (2.4%) Popliteal - 13 (5.2%)				

Effect size		
Outcome	BMS N = 59	DES N = 61
12 month results		
Procedure / device related deaths	0	0
All cause mortality	1	0

1

Study details	**Patient characteristics**				**Intervention**	**Comparison**	**Outcome measures**	**Other comments**
Rastan, 2011; (Guideline Ref ID 16034) RCT - Multi-centre (4) **Randomisation:** Double-blind (physicians and patient), Computer generated random sequence, set in blocks. **Intention to treat analysis** **Follow up duration:** 6 and 12 month including	N=161 Recruited between April 2006 and April 2008 N=82 polymer-free SES; N=79 received BMS				Polymer free SES (Yukon, Translumina, Hecklingen, Germany), coated in 2% sirolimus-containing solution All patients received oral aspirin (100mg daily) and oral clopidogrel (a loading does of 600mg 24 hr before the procedure follower by 75mg daily for 6 months)	Bare metal stent coated with ethanol	Mortality ABPI Adverse events Amputation Limb salvage Target limb re-intervention Target lesion revascularisation	Funding source: Not reported
		All patients (n=161)	Sirolimus stent	Bare-metal stent (n=79)				

clinical examination, ABPI, and DI (3-9 MHz linear transducer, IU 22 Philips, Bothell, WA, USA). Angiography performed in case of any conditioning limiting DU.			(n=82)					
	Age (years)	72.9 ± 9	73.4 ± 8	72.3 ± 9				
	Male sex (%)	66.5	67.9	64.9				
	Body mass index	27 ± 4	28 ± 5	27 ± 4				
	Diabetes mellitus (%)	53.8	56.8	50.6				
	Dyslipidaemia %	76.6	76.5	76.6				
	Hypertension (%)	89.9	91.4	88.3				
	Current smoker (%)	28.5	28.4	28.6				
	Renal insufficiency*	35.4	35.8	35.1				
	Critical limb ischaemia %	46.6	51.2	41.8				
	Target lesion Anterior tibial artery (%)	27	22	31				
	Tibioperoneal trunk	37	42	33				
	Peroneal artery	21	19	23				
	Posterior tibial	15	17	13				

	artery							
	ABI pre-intervention	0.48 ± 0.16	0.47 ± 0.18	0.49 ± 0.14				
	ABI post-intervention	0.84 ± 0.17	0.86 ± 0.`5	0.83 ± 0.19				
	* defined by creatinine ≥ 1.5mg/dL							

Effect size:(Results reported for 12 months only)		
Both CLI and IC	Sirolimus stent (n=82)	Bare-metal stent (n=79)
Mean change in ABPI		
Baseline	0.49 ± 0.15	0.51 ± 0.15 (P=0.72)
After 12 months	0.72 ± (0.16	0.65 ± 0.13 (P=0.14)
Adverse events		
Total	22 (27.1%)	29 (36.7%)
Death (major cardiac event – 8 [5%]; gastrointestinal and pulmonary infections – 5 [3.1%]; lung cancer – 1 [0.6%]; uncertain – 11 [6.8%])	14 (17.1%)	11 (13.9%, P=0.66)
TLR during follow-up	6 (9.7%)	11 (17.5%, P=0.29)
Target limb reintervention (inflow lesion)	8 (12.9%)	7 (11.1, P=0.84)
Amputation due to insufficiently controlled wound infection despite adequate antiobiotic treatment	Lower leg major amputation – 1 Minor toe amputation of target limb - 1	Lower-leg major amputation – 2 Minor toe amputation – 2
Limb salvage rates after 12 months	98.4%	96.8% (P=0.61)
Results at 12 months in patients with IC at baseline		
	Sirolimus stent (n=40)	Bare-metal stent (n=46)
Mean change in ABPI		
Baseline	0.54 ± 0.09	0.53 ± 0.15 (P=0.79)
After 12 months	0.73 ± 0.17	0.66 ± 0.12 (P=0.23)
Major adverse events		
Death	5 (12.5%)	3 (6.5%)
Target lesion revascularisation	2 (5.9%)	8 (20%)

H.416 Autologous vein compared to prosthetic bypass

<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr>
<td>Burger DH, et al.
2000; (Guideline Ref ID 16040)

Klinkert P, et al. 2003; (Guideline Ref ID 739)
Prospective randomised trial

Randomisation: decided on operating table. If vein deemed suitable (ie diameter >4mm proximally and 3mm distally) then randomised. Closed envelope following surgeons inspection on popliteal artery and saphenous vein.

Allocation concealment: Not stated

Blinding: Not stated

ITT: Not stated

Drop out:
11 lost to follow up at 5yrs

Follow-up duration:</td>
<td>N= 151 operations in 136 patients.

Inclusion criteria:
patients with severe claudication, rest pain, or tissue loss undergoing femoropopliteal reconstruction with site of distal anastomosis above the knee joint.

Exclusion criteria:
• previous arterial bypass graft on same leg or if greater saphenous vein had been removed.
• Patients where vein unsuitable for use as graft.
_____
Pts could be included in study twice for primary operation on left or right limb.
_____
New operations not considered in cases of mild claudication. Where there was necrosis or pain, redo bypass grafts were performed.

Baseline characteristics (table taken from Klinkert paper):
<table>
<tr><td></td><td>Total (n)</td><td>Human vein (n)</td><td>PTFE (n)</td><td>p-value</td></tr>
<tr><td>Reconstructions (n)</td><td>151</td><td>75</td><td>76</td><td>-</td></tr>
<tr><td>Median age</td><td>69</td><td>70</td><td>68</td><td>0.10</td></tr>
<tr><td>Male Gender (n)</td><td>88</td><td>42</td><td>46</td><td>0.28</td></tr>
<tr><td colspan="5">Indication for surgery (n)</td></tr>
</table>
</td>
<td>Autologous saphenous vein graft.</td>
<td>6mm Polytetrafluoroethylene (PTFE) bypass graft

If PTFE graft occluded and occlusion detected within 7 days, pt underwent thrombectomy.</td>
<td>Mortality
Complications
Reintervention
Amputation</td>
<td>Funding source: Not stated</td>
</tr>
</table>

5years, this study reports 2 year data. Pts examined 6wks, 3mnths, 6mnths and every year thereafter.	Claudication	120	62	58	-				
	Rest pain	20	9	11	-				
	Necrosis	11	4	7	-				
	Risk factors (n)								
	Smoking	105	48	57	0.07				
	Diabetes	33	12	21	0.04				
	Cardiac history	31	15	16	0.44				
	Cerebrovascular accident	7	5	2	0.12				

Effect size

Overall data (data same in both Burger and Klinkert papers):

- No died in hospital or within 30 days of operation
- Superficial wound infection seen in 3 PTFE grafts and 4 venous grafts. None resulted in reoperation or bypass graft loss.

Data at 2yrs (reported in Burger study)

- Amputation – 1 case after 2 years. Does not state which intervention.
- Reintervention - 4 below knee graft (3 x PTFE and 1 with human umbilical vein graft) and 1 above knee PTFE

Data at 5yrs (reported in Klinkert paper)

		Vein (n)	PFTE (n)	P value
Re-intervention		5	16	0.011
Amputation	Above knee	1	1	-
	Below knee	1	1	-
Death		24	18	-

1

H.5 Management of critical limb ischemia

H.5.1 Angioplasty compared to bypass surgery

Study details	Patients			Intervention	Comparison	Outcome measures	Other comments
Bradbury 2010; (Guideline Ref ID 1356) N.B. Final ITT analysis of main outcomes (AFS and OS) also reported in: Bradbury 2010; (Guideline Ref ID 3061) RCT - Stratified multicentre (27 sites, United Kingdom) **Randomisation:** Randomisation by trial manager in one-to-one ratio using randomly sized permutated blocks using computerised random-number generator. Stratified by centre and then four clinical groups: AP≥50 mmHg Grp 1: Rest/night pain only – 93 Tissue loss ±rest/night pain – 222 AP<50mmHg Rest/night pain only –23 Tissue loss ±rest/night pain -	Total N = 452 Inclusion criteria: Hospital inpatients with severe limb ischaemia (ischaemic rest and/or night pain requiring opiate analgesia and/or tissue loss (ulcer or gangrene) as the result of Infrainguinal atherosclerosis eligible for immediate or early revascularisation in the opinion of the responsible vascular surgeon/interventional radiologist. Need adequate suprainguinal 'inflow' Exclusion criteria: Unable to give fully informed written consent Have a degree of limb ischaemia, or a co-existing medical or surgical condition that makes revascularisation inappropriate Baseline characteristics reported as similar Baseline characteristics of randomised patients:			N = 228 Bypass surgery Centres were encouraged to undertake the allocated procedure as soon as possible after randomisation. The responsible consultant vascular surgeons and interventionalists were permitted to use their normal practice for preintervention assessment, the procedure itself and aftercare. Of the 228 patients randomised to bypass surgery, 195 underwent attempted bypass surgery.	N = 224 Balloon angioplasty Of the 224 patients randomised to balloon angioplasty, 216 underwent attempted balloon angioplasty.	1º Outcome Amputation free survival – pt alive without amputation of trial leg at transtibial level or above (AFS) 2º Outcomes Overall survival - death from any cause (OS) Post-procedural morbidity & mortality Re-intervention Health-related quality of life (HRQoL) – VascuQoL, EuroQoL 5D, SF-36, SF-6D Use of hospital	Funding source: UK NIHR HTA Program
		Angioplasty	Bypass				
	Male	57%	62%				

114 **Allocation concealment:** Randomisation results supplied to co-ordinating centre in sealed envelopes **Blinding:** no mention of blinding **Sample size calculation:** Yes, based on 1º outcome **ITT Analysis**: Yes. On-treatment analysis also reported. **Drop outs:** During follow-up: Bypass: 3 Angioplasty: 1 Follow-up duration: 100% patients followed for 3 years. 54% for 5 years. At least 3 years, 54% followed-up for >5 years. Longest follow-up 7 years Interim (2005) and final (2008) analyses reported	<70 years	30%	35%			resources Study also reports costs of procedure and hospital stay costs, hospital admissions and LoS, cost-effectiveness analysis	
	70-79 years	46%	39%				
	≥80 years	24%	26%				
	Trial leg = right	46%	43%				
	Never smoked	21%	21%				
	Current smoker	32%	32%				
	Ex-smoker >1 year	46%	46%				
	Not known diabetic	58%	58%				
	IDDM	17%	17%				
	NIDDM	25%	25%				
	Angina	19%	18%				
	Prior MI	20%	15%				
	Prior stroke/TIA	18%	25%				
	Previous intervention in trial leg	18%	12%				
	Previous intervention in other leg	16%	21%				
	No symptomatic arterial disease in other leg	67%	64%				
	IC in other leg	9%	11%				
	Severe limb ischaemia in other leg	23%	26%				
	Rest/night pain but no tissue loss in trial leg	24%	27%				

	Tissue loss in trial leg	75%	73%				
	On statin	34%	33%				
	On antihypertensive	63%	59%				
	On antiplatelet	54%	62%				
	Mean creatinine (SD) (µmol/l)	113 (62)	116 (95)				

Effect size				
Outcome at final follow-up				
	Angioplasty (n =224)		Bypass (n = 228)	
Lost to follow-up	1		3	
Dead	131 (59%)		119 (53%)	
Alive with amputation	10 (4%)		20 (9%)	
Alive no amputation	82 (37%)		86 (38%)	
Cox proportional hazard ratios, by time from randomisation				
End point	Time from randomisation		Hazard ratio (95% CI)	
Amputation free survival	Before 2 years		1.03 (0.76, 1.39)	
	After 2 years		0.85 (0.5, 1.07)	
Overall survival	Before 2 years		1.19 (0.84, 1.68)	
	After 2 years		0.61 (0.50, 0.75)	
Re-interventions within 30 days of first intervention whether or not that was the treatment allocated at randomisation				
	During same admission		Following discharge	
	Angioplasty	Bypass	Angioplasty	Bypass
Balloon angioplasty	3	1	1	0
Bypass surgery	21	2	13	0
Above-knee amputation	4	3	0	0
Below-knee amputation	5	3	1	0
Minor amputation	11	11	2	2

Graft exploration	0	5	0	0
Embolectomy	1	2	1	0
Thrombectomy	0	3	0	1
Wound debridement	3	6	1	1
Other (non-vascular)	0	0	0	1
Total	48	36	19	5
Adverse events within 30 days of first intervention whether or not that was the treatment allocated at randomisation				
	During same admission		Following discharge	
	Angioplasty	Bypass	Angioplasty	Bypass
Mortality	7	11	0	0
Angina	4	4	1	2
Myocardial infarction	6	13	2	2
Stroke	1	3	2	0
Haematoma	14	10	1	5
Haematoma requiring surgical drainage	2	9	0	0
Wound infection	18	45	25	29
Chest infection	4	10	3	2
Urine infection	8	7	2	6
False aneurysm	0	1	0	0
False aneurysm requiring surgical repair	0	1	0	0
VTE	1	0	2	0
Other cardiovascular	0	0	3	2
Gastrointestinal	0	1	2	2
Other	2	1	3	5
Total major events (as defined by GDG)	23	37	13	14
Total minor events (as defined by GDG)	37	68	33	41
Quality of Life				
	Angioplasty (n = 224) Mean score (SD, number of patients)	Bypass (n = 228) Mean score (SD, number of patients)	Adjusted difference for baseline score, mean (SE, number of patients)	p-value

VascuQoL				
Baseline	2.78 (1.01, 215)	2.91 (1.10, 207)	1	
0-3 months	4.32 (1.39 – 162)	4.55 (1.30, 153)	0.17 (0.14, 306)	0.22
3-6 months	4.28 (1.38, 143)	4.54 (1.34, 131)	0.19 (0.15, 268)	0.20
6-12 months	4.53 (1.42, 133)	4.67 (1.37, 121)	0.02 (0.17, 248)	0.91
12-24 months	4.58 (1.53, 62)	4.72 (1.50, 78)	0.14 (0.28, 134)	0.63
24-36 months	4.61 (1.41, 46)	4.44 (1.55, 49)	-0.39 (0.30, 92)	0.20
EQ-5D weighted index score				
Baseline	0.26 (0.32, 215)	0.29 (0.34, 206)	1	
0-3 months	0.53 (0.31, 164)	0.57 (0.28, 152)	0.01 (0.03, 305)	0.87
3-6 months	0.52 (0.34, 144)	0.56 (0.31, 131)	0.04 (0.04, 267)	0.35
6-12 months	0.55 (0.31, 133)	0.62 (0.29, 119)	0.05 (0.04, 244)	0.19
12-24 months	0.56 (0.32, 63)	0.59 (0.34, 76)	0.08 (0.06, 132)	0.16
24-36 months	0.61 (0.25, 48)	0.54 (0.35, 49)	-0.06 (0.05, 93)	0.29
SF-6D weighted index score				
Baseline	0.53 (0.10, 213)	0.54 (0.11, 207)	1	
0-3 months	0.60 (0.13, 163)	0.61 (0.13, 152)	0.01 (0.01, 304)	0.68
3-6 months	0.61 (0.13, 144)	0.61 (0.13, 131)	0.00 (0.02, 267)	0.92
6-12 months	0.62 (0.13, 133)	0.63 (0.12, 119)	0.00 (0.02, 245)	0.86
12-24 months	0.62 (0.15, 63)	0.64 (0.14, 76)	0.01 (0.03, 133)	0.61
24-36 months	0.64 (0.14, 48)	0.60 (0.15, 49)	-0.05 (0.03, 94)	0.08
SF-36 physical component summary				
Baseline	17.50 (7.97, 213)	17.80 (9.06, 207)	1	
0-3 months	23.80 (11.68, 163)	24.37 (12.45, 152)	-0.41 (1.25, 304)	0.74
3-6 months	24.62 (11.58, 144)	24.88 (13.51, 131)	-0.47 (1.35, 267)	0.73
6-12 months	24.58 (11.70, 133)	26.13 (13.54, 119)	0.08 (1.57, 245)	0.96
SF-36 mental component summary				
Baseline	43.47 (11.64, 213)	45.17 (11.96, 207)	1	
0-3 months	47.69 (11.28, 163)	48.68 (11.13, 152)	0.12 (1.22, 304)	0.92

3-6 months	46.67 (12.19, 144)	48.60 (10.75, 131)	1.72 (1.38, 267)	0.21
6-12 months	48.26 (11.76, 133)	50.16 (10.60, 119)	1.67 (1.33, 245)	0.21

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Holm J, 1991; (Guideline Ref ID 803) RCT - Multicentre (2 centres in Sweden) **Randomised:** A sequential treatment assignment with balancing for prognostic factors according to Pocock and Simon 1975 (Biometrics 1975; 31: 103-115). This was performed to ensure that the two treatment groups should be comparable. This stratification included symptoms (claudication vs severe limb ischemia), diabetes vs non diabetes, age (< vs ≥ 62 years), occlusion vs stenosis and planned treatment level (above vs below the inguinal ligament) **Allocation concealment**: Unclear	Total N = 102 Mean age 70 (range: 37-87) No study data: 0 **Inclusion criteria:** • Patients with or without diabetes with either severe limb ischemia, i.e. rest pain or ischemic ulcerations as well as patients with severe claudication who had not benefited from exercise training, in whom cardiac, pulmonary, renal other contraindications for vascular surgery were not found. • Only occlusions or significant stenoses 6 cm or shorter in the common iliac, external iliac, femoral or popliteal artery were accepted for treatment. • A stenosis was considered significant if the cross sectional area according to the angiogram was reduced by 75% or more. • Thus patients who were included were those who according to both surgical and radiographic consensus could be treated by either vascular surgery or angioplasty. **Exclusion criteria:** • Patients with concomitant disease contraindicating surgery.	N = 53 Angioplasty Technique not described Concomitant treatment: Patients were given 5000 IE heparin intra-arterially immediately before the dilatation. Dextran 40 (500ml) was given on the day of treatment and for the following 1 to 3 days	N =49 Bypass In lesions situated above the inguinal ligament, synthetic grafts or endarterectomy were used equally. Synthetic grafts were used only when other techniques were not feasible. Concomitant treatment: Patients were given 2500-5000 IE heparin intravenously during the operation	1o Outcome Ankle-arm index Ankle pressure Amputation Complications Mortality Reintervention	Funding source: Swedish Medical Research Council grants

Blinding:
Unclear.

Sample size calculation:
None

ITT analysis: Yes
However, the authors state that the 5 patients who were randomised to surgery but did not end up having surgery may influence the results in a negative way. It was apparently not stated in the protocol that venous by-pass should be performed whenever possible in the distal regions. This resulted in a variety of procedures being performed with less than satisfactory results (please see discussion for more details)

Drop outs: 0

Follow-up duration:
Patients were followed up at 1, 3, 6 and 12 months after discharge.

Follow up included:
Arm and ankle systolic pressures and clinical exam.

- Patients with mental disorders indicating that the treatment or the follow up could not be performed properly.
- Patients not willing to give their informed consent.

Baseline characteristics:

Baseline	Angioplasty N=53	Bypass N= 49
Age* (years) SD	70±NR	69±NR
Male (%)	NR	NR
ABI (mean, SD)	NR	NR
Smoking history (%)	NR	NR
Claudication* (%)	43	37
Rest pain/ gangrene* (%)	57	63
Diabetics* (%)	26	27
Occlusion* (%)	47	33
Above inguinal ligament* (%)	38	38
Duration (?) (months)	17.5±2.7	18.8±3.3
Ankle pressure (mmHg)	68±5.2	69.5±6.1
*Results of stratification		

There were no significant differences at admission between the 2 groups.

followed by Dextran 40 (500 ml) or heparin infusions post-operatively (15000-20000 IE per day) during their hospital stay. No long-term antocoagulant or anti-platelet treatment was given post operatively.

Angiography carried out at study selection and at 1 yr follow up.					
Effect Size					
ABPI on admission and at discharge from hospital					
	Before treatment	At discharge	P value		
Angioplasty (n=53)	68.0 ± 5.2	102.8 ± 7.5	P<0.01		
Bypass (n=49)	69.5± 6.1	104.4 ± 9.6	P<0.01		
	n.s.	n.s			
• There were no significant differences between the angioplasty and bypass groups for any of the outcomes. • Authors state that 'the ankle-arm index had increased significantly and was similar in the two groups in the 1 year survivors even when divided into central (iliac) and peripheral (femoral) lesions'. No p values provided.					
Outcome	Angioplasty, N=53	Bypass, N= 49			
	Rest pain/ gangrene	Rest pain/ gangrene			
Ankle-arm index (mean ± SEM)	Before: 0.39±0.05 At 1 year: 0.67±0.07	Before: 0.32±0.05 At 1 year: 0.66±0.08			
AT 12 month follow – up:					
Amputation at 12mnths above knee (n)	0 out of 30	1 out of 31			
Amputation at 12 months below knee (n)	2 out of 30	7 out of 31			
Complications(n) (assume peri-operative – 30 days)					
Bleeding	2 out of 30	2 out of 31			
Occlusion	1 out of 30	2 out of 31			
Infection	0 out of 30	4 out of 31			
Embolisation	0 out of 30	4 out of 31			
Mortality (n) at 12mnths	5 out of 30	4 out of 31			
Perioperative mortality (within 30 days)	0 out of 30	0 out of 31			
Re-intervention at 12mnths (n)	10	4			
Ankle-arm index before and after 1 year in relation to the location of the treated lesion					

Outcome	Before treatment		One year after		P value
	Iliac	Femoral	Iliac	Femoral	
Angioplasty (N=53)	0.45±0.05	0.42±0.05	0.77±0.05	0.71±0.07	P<0.01
Bypass (N=49)	0.46±0.07	0.43±0.05	0.67±0.1	0.72±0.07	P<0.01
	Not significant		Not significant		
Complications: • In angioplasty group, 2 instances of thrombosis and limb threatening ischaemia occurred immediately after angioplasty.					

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Wilson et al 1989 (Guideline Ref ID 847) Wolf et al 1993 (Guideline Ref ID 3058) RCT - Multicentre (9 sites, USA). 2 sites dropped because of low accrual and 1 added to make up final numbers. **Randomised:** A list of randomisation numbers were prepared by a Program coordinating centre. A physician or study coordinator telephoned a biostatistician at the coordinating centre for treatment randomisation.	Total N = 263 Mean age ±SE 61.5±0.44 Pts considered for the study on basis of arteriogram and review by radiologist and vascular surgeon. **Inclusion criteria:** • Angiography showing the presence a significant stenosis (>80) or an occlusion < 10 cm in length of the iliac, superficial femoral, or popliteal arteries. • ABPI in the affected leg was 0.9 or less at rest • The patient exhibited at least one of the following symptoms in the affected leg severely limiting activity: (a) claudication that restricted walking to less than two blocksand prevented performance of daily activities judged important by the patient and the physician (b) rest pain by ischemia (c) impending gangrene presumed caused by the arterial lesion to be treated	N =130 pts Angioplasty Technical details of interventions were left to the discretion of individual physicians at each site although standard guidelines were provided	N =133 N=126 (no. of limbs = 133) Bypass Technical details of interventions were left to the discretion of individual physicians at each site although standard guidelines were provided	Wolf et al, Repeat intervention at site Amputation Mortality Wilson et al, Limb survival 2o Outcome Wilson et al, Sickness Impact Profile (SIP)	Veterans Administration Cooperative Studies Programme

Randomisation was stratified by centre and by each of the following disease categories:

- Iliac disease with claudication
- Iliac disease with rest pain
- Femoropopliteal disease with claudication
- Femoropopliteal disease with rest pain

Note:
Because eligibility criteria required that all lesions randomised for treatment be suitable for angioplasty, the severity of disease was less than that of the general population.

Allocation concealment:
Yes, centralised

Blinding: Not reported

Sample size calculation: Yes, based on an initial survey of 6 Veterans Administration Centres. This showed that 1320 angiograms were obtained annually for claudication and rest pain or necrosis. Approximately, 26% of these patients would have

Exclusion criteria:

- Patients in whom a short-term course of heparin would be contraindicated
- Patients with a life expectancy of less than 3 years
- patients unlikely to be available for follow up evaluation
- Patients not candidates for major surgery because of medical contraindications

ABI at randomisation by location of study lesion:

	IC	IRP	FC	FRP
Angioplasty No. patients	59	22	38	11
Angioplasty Mean ABI±SE	0.56 ±0.02	0.32 ±0.02	0.52 ±0.02	0.44 ±0.07
Bypass No. patients	59	23	35	16
Bypass Mean ABI±SE	0.6 ±0.03	0.36 ±0.02	0.53 ±0.02	0.45 ±0.04

IC= iliac claudication; IRP= iliac rest pain; FC=femorpopliteal claudication; FRP=femorpopliteal rest pain

Baseline characteristics:

	Bypass (n=133)	Angioplasty (n=130)	Overall (ie. Where intervention not stated)

been candidates for angioplasty of the iliac arteries and 23% for angioplasty of the femoral or popliteal arteries. The authors estimated that they would need to recruit 8 centres which would provide a minimum of 300 patients. Sample size gave a 90% power to detect an odds ratio of 2.3 between bypass and angioplasty with a significance of 0.05 ITT analysis: Yes Drop outs: Really not sure about this. Please check, if you consider patients who were censored as drop out this adds up to 101 (maybe double counting?)! (8 patients withdrew, 20 were lost to follow up, 73 deaths. Follow up duration: scheduled at 1 and 3 months and at 3 month intervals thereafter for 3 years. In Wolf et al, the follow up is stated up to 6 yrs Follow up included: clinical	Age, yrs, mean (S.e.)	62.0 (0.64)	60.9 (0.59)					
	Smoking history (n)							
	Never	3	0					
	Currently	105	102					
	Previous	25	28					
	CV history (n)							
	Angina	22	31					
	MI	25	28					
	CHF	8	6					
	Stroke	20	16					
	TIA	17	8					
	Diabetes	-	-	26%				
	Iliac lesions (n)							
	Claudicants	-	-	118/163				
	Rest pain	-	-	45/163				
	Femoropopliteal disease							
	Claudicants	-	-	73/100				
	Rest pain	-	-	27/100				

exam, pulses, Doppler derived ABPIs of calf, thigh and ankle. SIP administered at randomisation, 1 month, 1 and 2 yrs								
Effect Size								
Limb survival by assigned intervention, study lesion location and pre-operative symptom category after median follow up of 4 years (Wolf et al 1993)								
Outcome	Angioplasty (N=130)				Bypass (N =133)			
	n				n			
Limb survival								
Iliac								
Rest pain	16 out of 22				17 out of 23			
Femoropopliteal								
Rest pain	10 out of 11				10 out of 16			
Note: n= patients at risk by intention to treat								

1

H.522 Angioplasty with selective stent placement compared to angioplasty with primary stent placement

Study details	Patient	Intervention	Comparison	Outcome measures	Other comments
Brodmann2011; 40(6):482-490. (Guideline Ref ID 16349) RCT - Austria **Randomisation:** Computer generated block randomisation	Total N=54 **Inclusion criteria:** • CLI • Femoropopliteal • Lesion characterized by either isolated stenoses greater than 70%; sequential stenoses up to cumulative length of 12 cm or total occusion of the curual arteries with a maximum length of 12 cm	Angioplasty n = 33 Performed with Amphirion Deep catheter	Stent n = 21 Balloon expandable stent with a silicon carbide coating the Motion Explorer Stent	Complications	Funding source: Not reported

Allocation concealment: Sealed envelopes

Blinding: Not reported

Sample size calculation: Not reported

ITT analysis: ITT

Drop outs: not reported

Follow-up duration: 12 months

- the target vessel must be a distal run-off vessel
- written informed consent
- life expectancy of at least 12 months

Exclusion criteria:

- endovascular procedure in last 3 months
- refused informed consent
- known allergy to clopidogrel or aspirin,
- indication for oral anticoagulation
- concomitant participation in another clinical trial

Baseline	Angio	Stent
Age	74.9 ± 1.3	68.9 ± 2.9
Weight (kg)	72.3 ± 13.2	76.5 ± 15.2
BMI	25.9 ± 3.7	26.9 ± 3.2
Female	60.6%	42.9%
Hypertension	27	19
Hyperlipidaemia	6	14
Diabetes mellitus Insulin dependat	24 36.4%	16 47.6%
Smoking	8	7
CVD	29	18
CAD	29	18

Effect size

	PTA (n = 33)	Stent (n = 21)
Complications at 12 months Acute re-obstruction	 0	 0

Peripheral embolisation	1	0
Local haematoma	3	0
Haemodynamically instability	0	0
Need of blood transfusion	0	0
Total minor complications at 12 months (as defined by GDG)	4	0

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Rand 2006; (Guideline Ref ID 302) RCT - Single centre - Austria **Randomisation:** one to one and performed per patient. Unclear method Randomisation performed after target lesion was passed by guidewire. **Allocation concealment:** Numbered envelopes **Blinding:** Outcome assessors blinded **Sample size calculation:** No details **ITT analysis:** No **Drop outs:** 14 patients (20 angioplasty and 17 stents) in	Total N = 51 (95 lesions) **Inclusion criteria:** • chronic critical limb ischemia stages III and IV of the Fontaine classification • Isolated stenosis >70% or occlusion of the tibial arteries • patients with up to three lesions; and lesions up to 3 cm with a cumulative lesion length of ≤9 cm, including the tibiofibular trunk, anterior and posterior tibial arteries, and peroneal artery. There was no further limitation regarding lesion position. **Exclusion criteria:** Patients with: • a significant inflow obstruction at the pelvic or superficial femoral artery level; • evidence of a systemic coagulopathy in whom anticoagulant and antiplatelet treatment was contraindicated, • previously implanted stents in the target lesion, patients with total occlusion in the target vessel following the target lesion, • patients without distal runoff, • inflammatory vascular disease, • peptic ulcer or gastric/intestinal bleeding in the	N=27 patients (53 infra-popliteal lesions) PTA Balloon angioplasty Postinterventional anticoagulation therapy for the angioplasty group consisted of low molecular- weight heparin (Enoxaparin 2 · 40mg) for 3 days and acetylsalicylic acid (ASA; ThromboAss, 100 mg per day permanently). 1 failure resulted in secondary stenting	N=24 patients (42 infrapopliteal lesions) Stent (Carbostent) Adjunct therapy for the stent group consisted of clopidrogel (Plavix), administered as a bolus of 300 mg on the day of the procedure and 75 mg per day orally for 4 weeks, and ASA medication permanently. 1 failure	Minor and major amputations Complications Re-intervention Mortality	Funding source: Ludwig Boltzmann Institute for Radiologic Tumor Diagnosis and the Ludwig Boltzmann Institute of Interdisciplinary Vascular Research.

total. By lesion, 21 lesions from angioplasty group and 17 lesions from stents **Follow up duration:** 6 months angioplasty (mean 5.6±1.97) Stent (mean 6.0±3.21). Consisted of clinical investigation and Doppler US within 2 days of procedure. At 6 mnths – digital subtraction angiography or spiral CT angiography was performed.	previous 6 months, and patients with clinically assessed intolerance to contrast medium. Total occlusion through which the guidewire could not be passed. Claudication only. Mean age 72 (range 47 -80) years					
	Baseline (n)	Angioplasty N = 27	Stent N = 24			
	Lesions	53	42			
	Fontaine III	8	4			
	Fontaine IV	19	20			
	Diabetes	19	16			
	Smoking	17	14			
	Cardiac disease	11	9			

Effect Size

Outcome	Angioplasty N = 27	Stent N = 24
Amputation total – no time point given (assume 6 months) Major Minor	1 0 1	2 1 1
Re-intervention (6 months)	0	1

- Reintervention: 1 stent patient underwent bypass procedure, which later failed and resulted in minor amputation. No further data presented on reintervention
- Mortality: 2 deaths (of 51 patients) within 30days and 1 death at >30 days from sepsis (groups unknown).
- Complications: rate of major complications within 30 days was 3.9% (2/51 patients). 1 major complication (haematoma) group unknown

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Rand. 2011;. (Guideline Ref ID 277)	Total N = 88	Angioplasty n = 44	Stent n= 44	Mortality	Funding source: Sorin

RCT - Multicente, Europe **Randomisation:** Not reported **Allocation concealment:** Not reported **Blinding:** Not reported **Sample size calculation:** Not reported **ITT analysis:** Available case analysis **Drop outs:** Angio group: 24 dropped out Stents group: 19 dropped out **Follow-up duration:** 3 and 9 months	**Inclusion criteria:** • Symptomatic PAD due to de novo lesion of an infrapopliteral artery • Stenosis of at least 50% • Substantial inflow stenosis if stenosis had been successfully treated without complication • In-line circulation to the foot distal to the lesion present **Exclusion criteria:** • Previous treatment • Total occlusion located in the target vessel • No distal run off • Underlying disease				Amputation TLR ABPI	Biomedica Cardio supplied devices for the trial

Baseline	Angio (n = 44)	Stent (n = 44)
Number of limbs	45	44
Male sex	28/45	30/44
Age	72.1 ± 9.5	71.4 ± 8
Diabetes	34/45	35/44
Rest pain	10/45	1/44
Ulcer and or gangrene	35/45	43/44
Number of lesions	69/45	62
De nono	69/69	61/62
Concentric	32/69	28/62
Calcification	54/69	49/62
Total occlusion	19/69	12/62

Effect size		
	Angio	Stent

Mortality at 3 months	3 out of 32	5 out of 33
Mortality at 9 months	5 out of 24	5 out of 19
Amputation at 3 months	4 out of 32	6 out of 33
Amputation at 9 months	7 out of 24	10 out of 19
TLR at 3 months	0 out of 32	1 out of 33
TLR at 9 months	6 out of 24	7 out of 19
ABPI at 3 months	0.7 ± 0.3 (n = 32)	0.9 ± 0.1 (n = 33)
ABPI at 9 months	0.8 ± 0.3 (n = 24)	0.8 ± 0.1 (n = 19)

1

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Randon 2010; (Guideline Ref ID 1) RCT - Single centre pilot study for multicentre study (Belgium) **Randomisation:** By limb, computer generated **Allocation concealment:** Sealed, consecutively numbered envelopes. **Blinding:** None **Sample size calculation:** Yes based on patency and limb salvage **ITT analysis:** Yes **Drop outs:** 1 limb allocated to angioplasty did not receive the	Total N= 35 (38 limbs) Chronic leg ischaemia as defined as rest pain for more than 2 weeks or a nonhealing ulcer/gangrene (Rutherford 4–6, Fontaine 3 and 4) **Inclusion criteria:** Patients with stenosis of >70% or occlusions of the infrapopliteal arteries **Exclusion criteria:** • Patients who needed bypass surgery for popliteal or superficial femoral occlusions, • patients who needed simultaneous angioplasty of the infrapopliteal and more then one proximal vessel. • acute limb ischemia, • multisegmental inflow lesions (longer than infarction during the previous 14 days, • blue toe syndrome (microembolisation), • and inability to ambulate.	N = 16 limbs Primary stenting with bare metal stents.	N = 22 limbs Balloon Angioplasty	Limb salvage (freedom from amputation above the ankle) Mortality Re-intervention Complications	Funding source: No details

intervention ≥70% stenosis. Trial closed early due to modifications in the delivery system. The multicenter study has not yet been published. **Followup duration:** Every 3-6 months for 2 years or to major amputation or death						
	Baseline	Angioplasty N = 22	Stent N = 16			
	Age (Years) SD	72 (10)	72 (9)			
	M/F	14/8	6/10			
	Rutherford IV/V	1/21	4/12			
	Diabetes	12	10			
	Renal failure (creatinine C 1.5 mg%)	8	2			
	Previous vascular reconstructions in this or other leg	13	3			
	Smoking history	4	1			
	Hypertension	22	16			
	Dyslipemia	9	7			
	Coronary artery disease	18	12			
	Stroke	1	4			

Effect Size

- No differences in mortality or limb salvage between groups.
- In multivariate analysis on renal insufficiency was identified as a negative predicting factor for limb salvage in both groups.

Baseline	Angioplasty N = 22	Stent N = 16
Major amputation at 2 years	2	3
Minor amputation at 2 years	1	1
Re-intervention at 2 years	5	2
Persistent ulcer at 2 years (major adverse event as defined by the GDG)	2	2
Minor complications (30 day)	2	4
Major complications (30 day)	1	1

Post-operative mortality (30 day)	1	1
All cause mortality (2 years)	7	3

1

Study details	Patients			Intervention	Comparison	Outcome measures	Other comments
Zdanowski Z, 1999; (Guideline Ref ID 3056) RCT - Single centre (Sweden) **Randomisation:** Computer generated list **Allocation concealment:** No details **Blinding:** No details **Sample size calculation**: None **ITT analysis**: No **Drop outs:** 1 patient- group unknown. 7 patients in the angioplasty and 2 in the angioplasty+ stent group refused follow-up angiography. **Followup duration:** 12 months	Total N = 32 • Patients with chronic leg ischaemia, femoral or popliteal • No other details of inclusion or exclusion criteria			N = 15 Angioplasty + Strecker stent For all patients Aspirin 160mg daily was administered post-operatively but no anticoagulation was used.	N = 17 Angioplasty alone	Mortality Re-intervention Amputation Complications	Funding source: No details
	Baseline	Angioplasty + Stent (n = 15)	Angioplasty alone (n = 17)				
	Median age (years)	72 (62-80)	71 (41-86)				
	M/F	10/5	4/13				
	Smoking	5	6				
	Diabetes	5	5				
	Hypertension	4	4				
	ABPI (Median)	0.48 (0.13-0.79)	0.42 (0.19 – 0.65)				

Effect Size		
No significant differences between groups in clinical improvement, angiographic re-occlusion/restensosis and ABPI increase >0.10.		
Outcome	Angioplasty + Stent (n = 15)	Angioplasty alone (n = 17)
Reintervention (1 year)	2	2
Post operative mortality (30 day)	0	0

Amputations (1 year)	0	0
Major complication (1 year)	1	4
Overall mortality 2 (Group unknown)		

H.513 Bare metal compared to drug eluting stents

Study details	Patients	Intervention	Comparison	Outcome measures	Other comments
Duda 2006;(Guideline Ref ID 248) Duda 2002; (Guideline Ref ID 15986) Duda 2005 (Guideline Ref ID 15987) RCT- Multicentre (Europe and Canada) Trial conducted in two phases **Randomised:** yes but method not stated **Allocation concealment:** not reported **Blinding:** double blinded **Sample size calculation:** not reported **ITT analysis:** ITT performed. Drop outs: In the sirolimus stent group 7 patients died (1 due to stroke, 1 due to lung emboli, 1 due to cancer, 2 due to cardiac disease and 2 due to natural causes). In the bare stent group 2 patients died (1 due to complications of coronary bypass surgery and 1 due	Total N = 93 **Inclusion criteria:** • aged over 30 years old, symptomatic PAD (Rutherford scale 1 to 4) • obstructive (≥70 %) de novo or restenotic lesions in the native SFA. • The reference vessel diameter was 4 to 6 mm, stenotic lesions varied in length from 7 cm to 20 cm in the first phase of the study and 7 to 14.5 cm in the second phase of the study. The occlusions varied from 4 to 20 cm in the first phase of the study and 4 to 14.5 in the second phase. • All lesions were classified as TASC type C **Exclusion criteria:** • poor aorto-iliac or common femoral inflow, • uremia, • aneurism in target vessels, tandem lesions, previously stented lesions, • ischemic tissue loss, • deep venous thrombosis, pregnancy, hepatic insufficiency, end stage renal failure requiring dialysis, immunosuppressant therapy, • recent hemorrhagic stroke within past 3 months, • severe calcification that was deemed resistant to stenting, vessel tortuosity, revascularisation	N = 47 Sirolimus-eluting SMART stent For both types of sent: SIROCCO I: a maximum of 3 stents implanted SIROCCO II: maximum of 2 stents implanted Patients not already on aspirin received a loading dose of 300 mg 1 day before the procedure; all received intra-arterial heparin boluses (3000-5000 units) at the time of the procedure,	N = 46 Bare SMART nitinol stent	Restenosis ABPI Adverse events Amputation	Funding source: Cordis Corporation, a Johnson and Johnson company, Miami lakes, Florida, USA

to progressive cardiac failure). In addition to those lost from the study due to death, at 24 months there are no outcome data for an extra 5 in the sirolimus stent group and 6 (for restenosis)/7 (for ABI) in the bare stent group. **Follow-up duration:** 2 years	involving the same limb within 30 days, total occlusions of the iliac artery on the same side, requirement for stent in the popliteal artery, • allergies to aspirin, heparin, sirolimus, nitinol, anticoagulants, antiplatelet therapy or contrast media, known or suspected active infection, presence of a aortic, iliac or femoral vascular prosthesis, • life expectancy < 2 years, • female patients of child bearing potential had a documented negative pregnancy test within 3 days prior to randomisation			followed by a 750-1000-U/h infusion as necessary. After the procedure either ticlopidine or clopidogrel was recommended for 4 weeks in addition to aspirin for 12 months.			
	Baseline	DES N=47	BMS N = 46				
	Age (years) SD	66.3 ±9.1	65.9 ± 10.8				
	Men %	66	78				
	Rutherford (n) 1+2 3+4	 20 27	 26 20				
	ASA 1 2 3	 15 24 8	 17 22 7				
	Cardiomyopathy (n)	23	18				
	Diabetes (n)	20	16				
	Hyperlipidemia (n)	30	29				
	Hypertension (n)	32	32				
	Current smoker (n)	22	14				
	Reference vessel diameter, mm	4.9 ± 0.7	4.7 ± 0.6				
	Lesion length mm	85 ± 44	81 52				

	Calcification (n) (moderate and severe)	27	16				
	Types of lesion De novo (n) Restenotic (n)	 42 5	 44 2				
	Total occlusion (n)	31	26				
	Total stents (n) 1 2 3 4	 15 25 6 1	 10 28 8 0				

Effect size				
At 24 months the cumulative in-stent restenosis rates did not differ significantly between the treatment groups; following the procedure the ABI increased in both groups and remained elevated 24 months after stent implantation and there was no significant difference between the treatment groups at 24 months.				
Outcome	Sirolimus stent N = 47	Bare stent N = 46	p-value	P value from kaplin meier
ABPI at 24 months (mean±SD/median)	0.90±0.17/0.96 (n = 35)	0.84±0.20/0.87 (n = 37)	0.127*	
Adverse event rates at 24 months				
Target vessel revascularisation	6 (13%)	10 (22%)		0.33 Calculated variance 3.75; OE 1.89)
Target lesion revascularisation	3 (6%)	6 (13%)		0.3 Calculated variance 2.00; OE 1.47)
Total occlusion (minor adverse event)	0 (0%)	3 (6%)		
Amputation as a complication of the stent procedure	0 (0%)	0 (0%)		
Death	7 (15%)	2 (4%)		

Data extracted from Duda, 2002 (ref ID 15986) SIROCCO I			
Outcome	Sirolimus stent	Bare stent	p-value

	N = 18	N = 18	
Adverse events at 6 months			
Suspected cellulites (minor adverse event)	1	0	
Occlusion (minor adverse event)	0	1	
Data extracted from Duda, 2005 (ref ID 15987) SIROCCO II			
Outcome	Sirolimus stent N = 29	Bare stent N = 28	p-value
ABPI			
ABPI before procedure (mean±SD)	0.67 ± 0.2 n=23	0.61 ± 0.16 n=27	0.227
ABPI after procedure (mean±SD)	0.87 ± 0.11 n=26	0.86 ± 0.15 n=26	0.940
ABPI at 1 month (mean±SD)	0.96 ± 0.13 n=27	095 ± 0.16 n=23	0.935
ABPI at 6 months (mean±SD)	0.92 ± 0.15 n=23	0.88 ± 0.15 n=24	0.356
Adverse events at 6 months			
During procedure – stent thrombosis (minor adverse event)	1*	1*	
During procedure – pseudoaneurysm (minor adverse event)	1*	0	
During procedure – bleeding (minor adverse event)	0	1*	
Before discharge – revascularisation procedure on contralateral leg	2	2	
Out of hospital events			
Death	2	1	
Target lesion revascularization	0	0	
Target vessel revascularization	1	3	
Atypical chest pain (minor adverse event)	1	0	
Hematoma at puncture site (minor adverse event)	0	1*	
Severe internal bleeding (major	1	0	

adverse event)			
Revascularisation procedure on contralateral leg	3	2	
Total number (%)	13 (44.8)	13 (46.4)	
* Highly probably related to study procedure			

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Study details	Patients				Intervention	Comparison	Outcome measures	Other comments
Rastan 2011; (Guideline Ref ID 16034) RCT - Multi-centre (4) **Randomisation:** Double-blind (physicians and patient), Computer generated random sequence, set in blocks **Intention to treat analysis** **Follow-up duration:** 6 and 12 month including clinical examination, calculation of the ankle brachial index (ABI), and DI (3-9 MHz linear transducer, IU 22 Philips, Bothell, WA, USA). Angiography performed in case of any conditioning limiting DU	Total N=161 Recruited between April 2006 and April 2008 N=82 polymer-free SES; N=79 received BMS				Polymer free SES (Yukon, Translumina, Hecklingen, Germany), coated in 2% sirolimus-containing solution All patients received oral aspirin (100mg daily) and oral clopidogrel (a loading does of 600mg 24 hr before the procedure follower by 75mg daily for 6 months)	Bare metal stent coated with ethanol	.Mortality Target lesion revascularisation Amputation ABI	Funding source: Not reported
		All patients (n=161)	Sirolimus stent (n=82)	Bare-metal stent (n=79)				
	Age (years)	72.9 ± 9	73.4 ± 8	72.3 ± 9				
	Male sex (%)	66.5	67.9	64.9				
	Body mass index	27 ± 4	28 ± 5	27 ± 4				
	Diabetes mellitus (%)	53.8	56.8	50.6				
	Dyslipidaemia %	76.6	76.5	76.6				
	Hypertension (%)	89.9	91.4	88.3				
	Current smoker (%)	28.5	28.4	28.6				
	Renal insufficiency*	35.4	35.8	35.1				
	Critical limb ischaemia %	46.6	51.2	41.8				
	Target lesion Anterior tibial artery (%)	27	22	31				
	Tibioperoneal trunk	37	42	33				
	Peroneal artery	21	19	23				
	Posterior tibial artery	15	17	13				

	ABI pre-intervention	0.48 ± 0.16	0.47 ± 0.18	0.49 ± 0.14				
	ABI post-intervention	0.84 ± 0.17	0.86 ± 0.`5	0.83 ± 0.19				
	* defined by creatinine ≥ 1.5mg/dL							
Effect size:								
Results at 6 and 12 months								
Both CLI and IC	Sirolimus stent				Bare-metal stent			
Mean change in ABPI								
Baseline	0.49 ± 0.15				0.51 ± 0.15 (P=0.72)			
After 12 months	0.72 ± (0.16				0.65 ± 0.13 (P=0.14)			
Adverse events								
Total	22 (27.1%)				29 (36.7%)			
Death (major cardiac event – 8 [5%]; gastrointestinal and pulmonary infections – 5 [3.1%]; lung cancer – 1 [0.6%]; uncertain – 11 [6.8%])	14 (17.1%)				11 (13.9%, P=0.66)			
TLR during follow-up	6 (9.7%)				11 (17.5%, P=0.29)			
Target limb reintervention (inflow lesion)	8 (12.9%)				7 (11.1, P=0.84)			
Amputation due to insufficiently controlled wound infection despite adequate antiobiotic treatment	Lower leg major amputation – 1 Minor toe amputation of target limb - 1				Lower-leg major amputation – 2 Minor toe amputation – 2			
Limb salvage rates after 12 months	98.4%				96.8% (P=0.61)			
Results at 12 months in patients with CLI at baseline								
	Sirolimus stent (n=42)				Bare-metal stent (n=33)			
Mean change in ABPI								
Baseline	0.35 ± 0.18				0.45 ± 0.15 (P=0.33)			
After 12 months	0.71 ± 0.13				0.64 ± 0.14 (P=0.23)			
Major adverse events								
Death	9 (21.4%)				8 (24.3%)			
Minor amputation	1 (3.4%)				1 (4.3%)			
Major amputation	1 (3.4%)				1 (4.3%)			

Target Lesion Revascularisation	4 (13.8%)	3 (13%)

H.514 Autologous vein compared to prosthetic bypass

Study details	Patients			Intervention	Comparison	Outcome measures	Other comments
Ballotta 2003; (Guideline Ref ID 944) RCT- Single centre (Italy) **Randomisation:** Computer generated randomisation schedule **Allocation concealment:** Sealed envelopes **Blinding:** No details **Sample size calculation:** No details **ITT analysis:** No details **Drop outs:** Unclear **Follow up duration:** 59 months mean follow-up (range: 1-108 months) (1,3,6,12 months and every 6 months thereafter)	51 patients (102 limbs) **Inclusion criteria:** • Disabling claudication after failure of a nonsurgical protocol (i.e. earlier risk modification and gradual exercise with or without pharmacologic therapy) • Angiographic evidence of a long superficial femoral artery occlusion and above-knee rehabilitation of the popliteal artery with 1-3 runoff vessels • Adequate segments of SV available for revascularisation on the basis of duplex scan venous mapping (compliant vein with diameter of ≥4 mm proximally and 3 mm distally) Exclusion criteria: Patients with uncompressible vessels ABI >0.9 SV already removed, or previously placed ipsilateral prosthetic or SV femoropopliteal above-knee or below-knee bypass graft Short life expectancy (<1 year) Popliteal aneurysm disease Serum creatinine >2.0 mg/dL Polycythemia (red blood cell count >7.5 x 106/mm3) Platelet count >106/mm2			Treatment consisted of reversed SV graft in one limb and PTFE graft in the contralateral limb for above-knee femoropopliteal revasculaisation All bilateral procedures were generally performed 6-8 weeks apart All anastomoses were made end-to-side with continous 5/0 polypropylene suture, proximal to the ipsilateral common femoral artery and distal to the above-knee popliteal artery Intravenous heparin (5000 IU) was administered before clamping Blood pressure was maintained at average preoperative level or slightly higher Heparinisation was not reversed with protamine Oral warfarin therapy was started the day before the operation and was continued for 6 months, aiming for a normalised ration between 2 and 4. After 6 months, 325 mg of aspirin was taken daily		Reintervention rates Amputation rates Mortality Perioperative complication rates	Funding source: Not detailed
	Baseline	n	%				

	Patients	51				
	Procedures	102				
	Age (years)					
	Median	62				
	Range	47-82				
	Male gender	33	65			
	Critical ischemia		87			
	Hypertension*	31	61			
	Coronary artery disease	13	25			
	Smoking	44	86			
	Diabetes mellitus	27	53			
	Hyperlipidemia	22	43			
	History of stroke	12	23.5			
	Previous ipsilateral inflow procedure	8	16			
	*Defined as elevated blood pressure treated with medication					
	Mean preoperative ABI					
	SV	0.53 ± 0.07				
	PTFE	0.54 ± 0.07				

Effect size	
Perioperative complication rates	
SV	PTFE
14%	12%
	1 patient; perioperative pneumonia
3 patients; deep vein thrombosis	2 patients; deep vein thrombosis
2 patients; significant bleeding requiring surgical exploration	2 patients; significant bleeding requiring surgical exploration

2 patients; non-infectious wound complications	1 patient; non-infectious wound complications

- No perioperative (30 day) limb loss or death
- 5 late deaths (3 due to myocardial infarction; 2 due to cancer) – late survival rate 90%. Median observation time before death was 637 days. Unknown which interventions.
- Reintervention rates: PTFE: 5 patients (1, disabling claudication; 4, rest pain. All five required new bypass grafts); SV: 1 patient (onset of rest pain prompted creation of a new bypass graft)
- No major amputation was necessary during follow-up in the two groups

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<table>
<tr><th>Study details</th><th>Patients</th><th>Intervention</th><th>Comparison</th><th>Outcome measures</th><th>Other comments</th></tr>
<tr><td rowspan="2">Tilanus. 1985; (Guideline Ref ID 1631)

RCT

Randomised: A card was drawn that randomised between PTFE and saphenous vein

Allocation concealment: Not detailed

Blinding: Not detailed

Sample size calculation: Not detailed

ITT analysis: Not detailed

Drop outs: Not detailed

Follow-up duration: 3–5 years (every 3 months for the first year then every 6 months)</td><td colspan="3">Total N = 49

Inclusion criteria:
• Patients with peripheral ischemia due to an occlusion of the superficial femoral artery
• The ipsilateral saphenous vein had a diameter of ≥4 mm and the vein was thought to be usable as a femoropopliteal bypass
• Before surgery, all patients had an angiography and the quality of the outflow tract was qualified according to Morton et al (Arch Surg 1967;94:592-9) as good, moderate, or bad in a progressive obstruction.

Baseline characteristics</td><td>Femoro-popliteal bypass using PTFE grafts
N = 24</td><td>Femoro-popliteal bypass using autologous saphenous vein

N = 25</td><td rowspan="2">Mortality

Adverse events

ABPI

reintervention</td><td rowspan="2">Funding source: No details</td></tr>
<tr><td colspan="3"><table>
<tr><td>Parameter</td><td>Saphenous vein</td><td>PTFE</td></tr>
<tr><td>Total</td><td>25</td><td>24</td></tr>
<tr><td>Male : Female</td><td>19:6</td><td>21:3</td></tr>
<tr><td>Mean age (yrs)</td><td>65±9</td><td>61±9</td></tr>
<tr><td>Indication</td><td></td><td></td></tr>
<tr><td>Interm.</td><td>9</td><td>11</td></tr>
</table></td><td colspan="2">All bypass operations were carried out by two surgeons using identical operative techniques
All operations were carried out under cefamandole prophylaxis
All patients were kept on fenprocoumon or acenocoumarol after surgery</td></tr>
</table>

	claudication			The operations were carried out only if before surgery the anticoagulation was in the therapeutic range of 10% (Thrombotest).		
	Rest pain	7	7			
	Tissue loss	9	6			
	Risk Factors					
	Smokers	21	21			
	Chronic pulmonary disease	4	5			
	ASHD	12	11			
	Diabetes mellitus	3	2			
	Anastomosis					
	Above-knee	7	8			
	Below-knee	18	16			
	Mean ABI	0.49±0.17	0.49±0.20			

Effect size

- In the PTFE group, two reoperations were necessary: one for control of bleeding on the distal anastomosis and one for thrombectomy of an early occlusion of the PTFE bypass (perioperative rates).
- Wound infections grades 1 and 2, according to Szilagyi et al., (Ann Surg 1972;176:321-33) were seen in nine patients, four in the PTFE group and five in the SV group, and were of no clinical consequence.
- After operation, the mean ABI for the PTFE group was 0.95 (SD: 0.13) and 0.88 (SD: 0.20) for the SV group. This difference was not significant (p > 0. 10)
- During a late follow-up period from 3 to 5 years, eight major amputations had to be carried out in the PTFE group, two of them in patients primarily operated on for intermittent claudication. No operations were necessary in the saphenous vein group
- There were no operative or postoperative deaths in either group.

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1 Appendix I: Economic evidence tables

I.1 Information requirements

3 No cost-effectiveness evidence was identified for this question.

I.2 Diagnosis of peripheral arterial disease

5 No cost-effectiveness evidence was identified for this question.

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I.3 Imaging for revascularisation

R.C. Collins. G. Cranny, J. Burch, R. Aguiar-Ibanez, D. Craig, K. Wright, E. Berry, M. Gough, J. Kleijnen, M. Westwood. 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. Health Technology Assessment Programme. 2007. 11(20). {Collins, 2010 16292 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: Cost utility analysis **Study design:** Decision model **Approach to analysis:** After a 50% to 100% degree of stenosis was detected, patients may proceed to one of three possible events: amputation, bypass or angioplasty. Patients with less than 50% stenosis were assumed to be treated with medical management. It was assumed that after an inconclusive test result (or where MRA was contraindicated), CA would be undergone to obtain a final result. Inaccurate diagnostic reading s may lead to inappropriate treatment plans, which	**Population:** All patients with PAD who were referred for imaging work-up to evaluate the feasibility and choice of revascularisation procedure. N: 352 Age (mean): 65 years Men: 68% CLI: 11% ABPI (mean): 0.60 **Intervention 1:** 2D TOF MRA **Intervention 2:** Contrast enhanced MRA **Intervention 3:** DUS **Intervention 4:** CA	**Total costs (mean per patient):** Intvn 1: £12, 492 Intvn 2: £10, 626 Intvn 3: £10, 208 Intvn 4: £13, 451 Incremental (3-1): £-2, 284 (p= NR) **Currency & cost year:** 2004 UK pounds (presented here as 2010 UK pounds‡) **Cost components incorporated:** 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.	**Primary outcome measure:** Quality adjusted life years (QALYs) Intvn 1: 0.61 Intvn 2: 0.64 Intvn 3: 0.64 Intvn 4: 0.64 Incremental (3-1): 0.03 (p = NR) **Other outcome measures (mean):** None	**Primary ICER:** Whole leg: DUS was the dominant strategy (lowest cost and greatest QALY gain) with a 95% probability of being cost-effective at a threshold of £20k. **Other:** **Short term analysis:** DUS vs. 2D TOF MRA: £2, 260 per QALY (Therefore DUS is the most cost effective strategy) **Subgroup analyses:** **Above the knee:** CE MRA vs. 2D MRA: £122, 687 per QALY (Therefore, 2D TOF MRA was the most cost-effective strategy with a 75% probability of being cost effective at a threshold of £20k) **Below the knee** 2D MRA vs. DUS: £37, 024 per QALY (Therefore DUS is the most cost-effective strategy with a 70% probability of being cost-effective at a threshold of £20k) **Analysis of uncertainty:**

will lead to a change in treatment strategy. Final health states were determined by whether the initial treatment plan was correct and whether complications such as graft failure, amputation or death occurred. **Perspective:** UK NHS **Time horizon:** 1 year **Treatment effect duration:** 1 year **Discounting:** Not relevant				Enderarterectomy included as a PTA procedure:

Data sources

Health outcomes: The probabilities associated with the treatment plans chosen by surgeons according to the results of each imaging procedure were obtained from four studies included in the systematic review. Two provided information about how patients would be managed using the results of the MRA test compared to the CA and two provided information about treatment plans for patients undergoing DUS.

Quality-of-life weights: Patients could end in one of six possible health states: fully ambulant; limited ambulance and independent; limited ambulance and dependant; non-ambulant and using a wheelchair; bedridden; or dead. The health utility values assigned to each of the possible health states were obtained from those used by Berry et al (2002), which were adapted from those reported in a study by Michaels et al (2001), which used the standard gamble to measure health preferences for 110 people in the UK for the included health states (Full mobility = 0.83; limited mobility, independent = 0.56 following amputation, 0.73 fir CLI and 0.78 for IC; limited mobility, dependant = 0.56 following amputation, 0.69 for CLI and IC; wheelchair, dependant = 0.46; bedridden = 0.33).

Cost sources: All costs were obtained from the original HTA on this topic by Berry et al (2002) and inflated to 2004 prices. In turn, the costs used by Berry et al were obtained from the UK National Hospital Episode Statistics and health Resource Groups and estimates published by Michaels et al (2001).

Comments

Source of funding: NHS Health Technology Assessment Programme; **Limitations:** 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; Analysis did not include all relevant comparators; downstream consequences differ from those considered appropriate by the GDG. **Other:** None.
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; Duplex US = duplex ultrasound; MRA = magnetic resonance imaging.

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

M.C.J.M. Kock, M.E.A.P.M. Adriaensen, P.M.T. Pattynama, M.R.H.M. van Sambeek, H. van Urk, T. Stijen, M.G.M. Hunick. DSA versus multi-detector row CT angiography in peripheral arterial disease: randomised controlled trial. Radiology. 2005. 237: 727-737. {Kock, 2005 358 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** RCT **Approach to analysis:** This study was designed to assess the consequences of replacing DSA with CTA for the primary imaging of PAD. Patients were randomly assigned to each group. **Perspective:** Netherlands, Hospital perspective **Time horizon:** 6 months	**Population:** All patients had either severe disabling intermittent claudication that was unresponsive to exercise therapy or critical ischaemia. N: 144 Age (mean): 64 Men: 73% CLI: 36% ABPI (mean): 0.64 **Intervention 1:** DSA **Intervention 2:** CTA	**Total costs** **Unadjusted mean and mean difference (per patient):** Intvn 1: £5, 324 Intvn 2: £7, 102 Incremental (2-1): £1, 778 (CI, -£588 to £4, 146; p=NR) **Adjusted mean difference (per patient):** -547 **Currency & cost year:** 2000 Euros (presented here as 2010 UK pounds‡) **Cost components incorporated:** Diagnostic costs: DSA £549, CTA £353 Interventional costs:	**Primary outcome measure:** Quality of life (change in EQ-5D at 6 months) Intvn 1: 0.07 Intvn 2: 0.11 Incremental (2-1): 0.04 (CI, -0.1 to 0.17; p=NR) **Adjusted mean difference (per patient):** 0.07 **Other outcome measures (mean):** Therapeutic confidence score Intvn 1: 8.2 Intvn 2: 7.2 (CI, NR: p= 0.001) Additional imaging:	**Primary ICER (Intvn 2 vs Intvn 1):** Unadjusted: CTA costs £44, 450 per QALY. Adjusted: CTA is the dominant treatment strategy. **Other:** None **Subgroup analyses:** None **Analysis of uncertainty:** None

Discounting: Not relevant		DSA £502, CTA £505 Surgical costs: DSA £1, 522; CTA £1, 346 Hospital costs: DSA £2, 750; CTA £4, 897	Intvn 1: 19/71 (27%) Intvn 2: 33/73 (45%) (p = 0.02)	
Data sources				
Health outcomes: Therapeutic confidence was assessed at weekly vascular conferences, where therapeutic decisions were made in consensus by three vascular radiologists and four vascular surgeons (study authors). Each clinician was asked to rate his or her individual confidence in making a well-founded therapeutic choice with the available diagnostic information on a 10 point scale, where a rating of 5 implies that there is insufficient information to make a therapeutic choice. **Quality-of-life weights:** Changes in quality of life were assessed using the SF-36 and EQ-5D. These measures were completed at baseline and after 3 and 6 months follow-up. Only 4 'most responsive' domains of the SF-36 were reported: physical functioning, role physical, bodily pain, and health perceptions and health change. **Cost sources:** The cost of imaging and vascular interventions were collected from the participating hospital six months after the date of the initial imaging work-up.				
Comments: The main driver of cost differences between the two interventions was the higher rate of additional imaging and intervention in the CTA group.				
Source of funding: Health Care Efficiency Grant from the Health Care insurance Board and a Program Grant from the Netherlands Organisation for Scientific Research; **Limitations:** should match checklist. **Other:** Therapeutic confidence was assessed during weekly vascular conferences with respect to the confidence of radiologists (n = 3) and vascular surgeons (n = 4) to make a decision on the basis of the results from each imaging modality. Therapeutic confidence was rates on a scale from 0 (no confidence) to 10 (extremely confident). The final therapeutic confidence score was based on a consensus between the radiologist and vascular surgeon. Each radiologist and vascular surgeon involved in the study had at least 7 years of experience in either vascular radiology or vascular surgery.				
Overall applicability*: Potentially serious limitations **Overall quality**: Partially applicable**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; DSA = digital subtraction angiography; CTA = computed tomography angiography.

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

R. Ouwendijk, M. de Vries, P.M.T. Pattynama, M.R.H.M. van Sambeek, M.W. de Haan, T. Stijnen, J.M.A. van Engelshoven, M.G.M Hunick. Imaging peripheral arterial disease: a randomised controlled trial comparing contrast-enhanced MR angiography and multi-detector row CT angiography. Radiology. 2005. 236: 1094-1103. {Ouwendijk, 2005 15954 /id}				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost analysis **Study design:**	**Population:** All patients with PAD who were referred for imaging work-up to evaluate the	**Total costs** **Unadjusted mean and mean difference (per patient):** Intvn 1: £6, 666	**Primary outcome measure:** Quality of life (change in EQ-5D at 6 months): Intvn 1: 0.08	**Primary ICER (Intvn 1 vs Intvn 2):** **Unadjusted:** CE MRA costs £9, 033 per QALY gained. **Adjusted:** CTA is the dominant treatment

RCT **Approach to analysis:** The aim of this study was to compare outcomes following CE MRA and CTA as the initial imaging test in the diagnostic work-up of patients with PAD. Patients were randomly assigned to each group. **Perspective:** Hospital, Netherlands **Time horizon:** 6 months **Treatment effect duration:** NR **Discounting:** Not relevant	feasibility and choice of revascularisation procedure. Patients had to have either severe disabling intermittent claudication or CLI. N: 156 Age (mean): 64 years Men: 65% CLI: 21% ABPI (mean): 0.63 **Intervention 1:** Contrast enhanced MRA **Intervention 2:** CTA	Intvn 2: £3, 956 Incremental (1-2): £2, 710 (p= NR) **Adjusted mean difference (per patient):** £2, 425 **Currency & cost year:** 2002 Euros (presented here as 2010 UK pounds‡) **Cost components incorporated:** Initial diagnostic imaging: MRA, £500; CTA, £159 Additional diagnostic imaging: DSA, £1, 190 ; DUS, £41	Intvn 2: 0.05 Incremental: (1-2): 0.03 (p=NR) **Adjusted mean difference (per patient):** -0.02 **Other outcome measures (mean):** Therapeutic confidence Intvn 1: 7.7 Intvn 2: 8.0 Incremental (1-2): NA (p = 0.8)	strategy. **Other:** None **Subgroup analyses:** None **Analysis of uncertainty:** One way sensitivity analyses: If the investment costs for the MR imager were reduced by 50%, CT is £266 less costly than CE MRA. If the investment costs for the CT equipment are increased by 200%, CT is £334 less costly than CE MRA. Two way sensitivity analysis: If the investment cost for MR technology is reduced by 50% and the initial cost of CT equipment is increased by 200%, CTA remains the less costly option by £251.
Data sources				
Health outcomes: All clinical outcomes were obtained from the current trial. Therapeutic confidence was assessed by a group of experienced radiologists and vascular surgeons during weekly vascular conferences. **Quality-of-life weights:** The EQ-5D was administered at the time of randomisation and 2 weeks, 3 months, and 6 months after initial imaging. **Cost sources:** All relevant costs accumulated over the 6 month follow-up were calculated; source not directly stated.				
Comments				
Source of funding: Supported by a grant from nonMw, Netherlands Organisation for Health Research and Development, and Netherlands Organisation for Scientific Research; **Limitations:** Patients were not considered for exercise therapy, only revascularisation, which is inconsistent with the alternatives considered by the GDG; cut-off criteria and intervention pathways not reported; sensitivity and specificity not reported, therefore not possible to compare to results of clinical review; insufficiently long				

time horizon; **Other:** None.	
Overall applicability*: Partially applicable	**Overall quality**: Potentially serious limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; MRA = magnetic resonance imaging; CTA = computed tomography angiography

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

I.4 Management of intermittent claudication

I.4.1 Supervised exercise compared to unsupervised exercise

H.L.D Lee, T. Mehta, B. Ray, M.S.T. Heng, P.T. McCollum and I.C. Chetter. A non-randomised controlled trial of the clinical and cost effectiveness of a supervised exercise programme for claudication. European Journal of Endovascular Surgery. 2007. 33;202-207. {Lee, 2007 901 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Non-randomised trial **Approach to analysis:** Quality of life was measured using the SF-36. The authors used the SF-36 index score to assess quality of life between 0 to 6 months and extrapolated between 6 to12 months based on previous studies (Currie 1995 and Perkins 1996) of exercise for the treatment of IC.	**Population:** People with IC who presented to an outpatient vascular clinic N = 70 Median age = 68 Male = 69% ABPI = 0.64 **Intervention 1:** Patients received an advice leaflet regarding exercise. **Intervention 2:** Patients attended three sessions of supervised exercise per week for a total of 12 weeks. Each session consisted of alternating exercise stations for two	**Total costs (mean per patient):** Intvn 1: NR: assumed £0 Intvn 2: £52 Incremental cost: £52 **Currency & cost year:** 2006 UK pounds (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** Cost of supervised exercise programme (three hours per week, 12 people per class, for three months) = £52 per supervised programme per patient.	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: NR Intvn 2: NR Incremental QALYs: 027 **Other outcome measures (mean):** NA None	**Primary ICER:** Intvn 2 vs Intvn 1: £1, 926 per QALY gained **Other:** NA **Subgroup analyses:** None **Analysis of uncertainty:** None

Perspective: UK NHS **Time horizon:** One year **Discounting:** NA	minutes with walking circuits of two minutes between stations.			
Data sources				
Health outcomes: Quality of life was measured using the SF-36 at baseline and 6 months. The mean index score of the SF-36 was used as a measure of utility. Quality of life between 6 months and one year was assumed to decline at a steady rate based on studies by Perkins 1996 and Currie 1995. The area between the curves was calculated to obtain the incremental QALY gain. **Quality-of-life weights:** No preference weighting was applied; SF-36 index scores were used. **Cost sources:** Costs were obtained from the finance department at the participating hospital (Hull Royal Infirmary). The supervised programme was provided for three hours per week for three months with 12 people per class and cost £52 per patient.				
Comments				
Source of funding: Not reported; **Limitations:** Non preference-based method of utility measurement based on extrapolated values from only one data point; short time horizon; cost of supervised exercise programme was considerably less than that estimated by the GDG; **Other:** When the SF-36 values reported by the authors are mapped to EQ-5D values using published algorithms by Ara and Brazier, the mean difference in change (0.025 QALYs) is close to that reported by the authors using the index value. Therefore, the results of the author's analysis are changed very little.				
Overall applicability*: Directly applicable Overall quality: Potentially serious limitations**				

NR = not reported; ABPI; ankle-brachial pressure index; ICER = incremental cost effectiveness ratio; WTP = willingness to pay; EVPI = expected value of perfect information; EQ-5D = EuroQol5D

† *Study reports societal perspective; however patient time costs reported in study have been subtracted from all results presented in evidence table*

‡ *Calculated based on reported incremental unadjusted mean costs and QALYs, excluding patient time costs*

‡ Converted to GBP using OECD Purchasing Power Parity Index*(OECD), 2010 16360 /id}* and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

A.D.I. van Asselt, S.P.A. Nicolai, M.A. Joore, M.H. Prins, J.A.W. Teijink. Cost-effectiveness of exercise therapy in patients with intermittent claudication: supervised exercise therapy versus 'go home and walk' advice. European Journal of Vascular Surgery. 2011. 41; 97-103.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:**	**Population:** People with IC and an ABPI of less than 0.9 and MWD of less than 500m. Patients were	**Total costs (mean per patient):** Intvn 1: £1, 664 Intvn 2: £2, 565	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 0.67 Intvn 2: 0.71	**Primary ICER:** Intvn 2 vs Intvn 1: £23, 695 per QALY gained **Other:**

RCT **Approach to analysis:** Patients were randomised to receive either walking advice, a supervised exercise programme or supervised exercise with feedback. The latter was not included in the current extraction. Costs and EQ-5D values were collected and assessed using bootstrap methods. **Perspective:** Netherlands, Healthcare system[±] **Time horizon:** Lifetime **Discounting:** NA	excluded if they had undertaken a previous supervised exercise programme, vascular intervention, limb amputation, serious cardiopulmonary limitations or other co-morbidity which would hinder physical training. N = 201 Mean age = 70 Male = 68% ABPI = 0.69 **Intervention 1:** Patients received oral walking advice and a brochure. They were instructed to complete three exercise sessions per day, walking until they reached their maximum pain level three times during each session. **Intervention 2:** Patients were referred to a local physiotherapist where they took part in interval training. Therapy took place over two to three sessions of 30 minutes per week for one year.	Incremental cost: £900 **Currency & cost year:** 2008 Euros (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** GP contacts, outpatient visits, A&E visits, hospital admissions, physical therapy sessions, and home/informal care.	Incremental QALYs: 0.038 97.5% CI: 0.003 to 0.0796 **Other outcome measures (mean):** Maximum walking distance (median and IQR per patient): Intvn 1: 400m (230 to 590) Intvn 2: 600m (435 to 1040) Incremental MWD: 200m p = 0.001	Intvn 2 vs Intvn 1: £4.5 per metre gained **Subgroup analyses:** None **Analysis of uncertainty:** At a threshold of £31, 000 (i.e. €40, 000), supervised exercise is cost-effective in 64% of bootstrap simulations. According to the CEAC, at a threshold of £20,000 (approximately €26, 000), there is a 35% probability that supervised exercise is the most cost-effective strategy.

Data sources
Health outcomes: Quality of life and walking distance was collected from the current study, as reported by Nicolai 2010.
Quality-of-life weights: The EQ-5D was scored based on preferences elicited from a UK population.
Cost sources: Retrospective cost questionnaire with 3 month recall period was used to collect data at each follow-up period. The questionnaire contained questions about GP contacts, outpatient visits, A&E visits, hospital admissions, physical therapy sessions, home and informal care, medications, devices such as special shoes or treadmill, and lost productivity due to absence from paid and unpaid employment. Participants were also asked to report their means of transportation and travel costs.
Comments
Source of funding: The Netherlands Organisation for Health Research and Development ; **Limitations:** Societal perspective; Dutch healthcare setting; short time horizon; **Other:** None
Overall applicability*: Partially applicable Overall quality: Minor limitations**

Abbreviations: CUA = cost utility analysis; RCT = randomised controlled trial; ABPI = ankle brachial pressure index; NA = not applicable; NR = not reported; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; m = metres; CEAC = cost effectiveness acceptability curve.

± Study reported costs from a societal perspective. All societal costs (out of pocket medications, paid and unpaid productivity) were subtracted from the cost of the interventions to calculate total and incremental costs presented in this table.

‡ Converted to GBP using OECD Purchasing Power Parity Index*(OECD), 2010 16360 /id}* and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable*

I.42 Naftidrofuryl oxalate

No cost-effectiveness evidence was identified for the question.

I.43 Comparisons of exercise, best medical treatment angioplasty and bypass surgery

J.L.Bosch, E. Tetteroo, W.P.T.M.Mali, M.G.M. Hunick. Iliac arterial occlusive disease: cost-effectiveness of stent placement versus percutaneous transluminal angioplasty. Radiology. 1998. 208:641-648. {Bosch, 1998 2459 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:**	**Population:** People with lifestyle limiting claudication due to stenosis in the iliac arteries for whom percutaneous intervention is indicated.	**Total costs (mean per patient):** Intvn 1: £3, 462 Intvn 2: £6, 031 Intvn 3: £6 756 Intvn 4: £7, 344 Intvn 5: £7, 713	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 10.30 Intvn 2: 11.03 Intvn 3: 11.29 Intvn 4: 11.36 Intvn 5: 11.47	**Primary ICER:** Strategy 2, 4,5, and 7 excluded by extended dominance. Intvn 3 vs. Intvn 1: £3, 327 per QALY gained Intvn 6 vs. Intvn 3: £12, 376 per QALY gained Probability cost-effective: NR

Alternative treatment strategies defined as initial endovascular intervention followed by secondary treatment performed in the event of long-term treatment failure. It was assumed that the patency results after repeated procedures were equivalent to patency results after the same procedure performed as initial treatment. Patients treated with conservative management after long-term treatment failure were assumed to develop symptoms similar to before treatment. Based on the trial, primary angioplasty was followed by stent placement in 43% of patients; this figure was used to estimate the proportion of patients requiring stent placement during the selective stent intervention. **Perspective:** Societal,	**Cohort settings:** Start age = 60 years M = 100% **Intervention 1:** No revascularisation (reference strategy) **Intervention 2:** Angioplasty followed by conservative management for long-term treatment failure **Intervention 3:** Angioplasty with selective stent placement followed by conservative management for long-term treatment failure **Intervention 4:** Angioplasty alone followed by angioplasty alone for long-term treatment failure **Intervention 5:** Angioplasty followed by angioplasty with selective stent placement for long-term treatment failure **Intervention 6:** Angioplasty with selective stent placement followed by angioplasty with selective	Intvn 6: £8, 023 Intvn 7: £9 007 Incremental (3 vs 1): £3, 294 Incremental 6 vs 3): £3, 960 (CI NR; p=NR) **Currency & cost year:** 1995 US dollars (presented here as 2010 UK pounds‡) **Cost components incorporated:**	Intvn 6: 11.61 Intvn 7: 11.61 Incremental (3 vs 1): 0.99 Incremental (6 vs 3): 0.32 (CI NR; p=NR) **Other outcome measures (mean):** None	**Other:** None **Subgroup analyses:** Lesion type (occlusion or stenosis): Results similar to basecase analysis Disease severity (intermittent claudication or ischaemia): Results similar to basecase analysis **Analysis of uncertainty:** The conclusion was robust to changes in the risk of long term failure following stent placement, proportion of patients requiring a stent, and stent cost. If stent placement and PTA yield very similar results (i.e. there is a 0%-1% reduction in failure risk associated with stent placement), the optimal strategy would be PTA followed by PTA for long term failures.

The Netherlands **Time horizon:** Lifetime **Treatment effect duration:** (e.g. 5 yrs) **Discounting:** Costs = 3%; Outcomes = 3%	stent placement for long-term treatment failure **Intervention 7:** Angioplasty with primary stent placement followed by angioplasty with selective stent placement for long term treatment failure			
Data sources				
Health outcomes: The model combined data from the randomised, controlled Dutch Iliac Stent Trial and a published meta-analysis (Bosch 1997). Procedural morbidity and mortality rates obtained from meta-analysis; post procedural long-term survival not affected by the procedure but long-term life expectancy was adjusted with age- and sex-specific mortality rates from standard life tables of the general population and excess mortality associated with PAD (Fowkes 1998, Howell 1989); 2-year patency probabilities obtained from the DIST trial; beyond 2 years, 4-year primary patency outcomes from the meta-analysis were used, and a constant annual failure rate was assumed thereafter; **Quality-of-life weights:** SF-36 questionnaires were administered to patients in the DIST trial and converted to EQ-5D valuations. QoL values after successful treatment were shown to remain constant over time and were not associated with age; no difference was observed between QoL after a procedure with complications compared to a procedure without complications, therefore no adjustment was made for QoL; **Cost sources:** Costs were collected alongside the trial and included both direct health care and non-healthcare related costs incurred by the radiology department, hospital and patient.				
Comments				
Source of funding: Supported by a PIONIER award from the Netherlands Organisation for Scientific Research and grant OG-93/001 from the Commission of Investigative Medicine of the Dutch National Health Insurance Council; **Limitations:** Societal perspective; Dutch healthcare setting; **Other:** Study by Bosch 2000 used the same model and effectiveness data with American costs. The conclusion of this analysis was the same.				
Overall applicability*: Partially applicable **Overall quality**: Minor limitations**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitation*

S.O. de Vries, K. Visser, J.A. de Vries, J. Wong, M. Donaldson, M.G. Hunink. Intermittent claudication: Cost-effectiveness of revascularisation versus exercise therapy. Radiology. 2002. 222:25-36. {de Vries, 2002 2460 /id}				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA	**Population:** 60 year old male patients with previously untreated	**Total costs (mean per patient):** Intvn 1: £17, 673	**Primary outcome measure:** QALYs (mean per patient)	**Primary ICER:** Interventions 2 & 5 excluded by extended dominance.

Study design: Decision analytic model **Approach to analysis:** Alternative treatment strategies defined as initial therapy combined with secondary treatment if initial treatment fails. Treatment failure defined as discontinuation of exercise programme combined with severe claudication; graft failure or restenosis in combination with severe claudication; or progression to CLI. Health states defined in terms of symptom severity. Patients transition between health states dependant on natural history and efficacy of intervention. Assumes that no or mild claudication does not require specific treatment; critical limb ischaemia may be treated with angioplasty if lesion is suitable (stenosis of 50-99% above the knee)	intermittent claudication of at least one year duration **Cohort settings:** Start age = 60 years old Male = 100% ABPI = 0.70 History of CAD = no **Intervention 1:** Unsupervised exercise programme only (patient asked to walk between 2-6km daily, depending on baseline ability. Instructed to pause when pain occurs. Four follow-up hospital visits scheduled over 6 months). **Intervention 2:** Unsupervised exercise programme + PTA with selective stent placement for treatment failure **Intervention 3** Unsupervised exercise programme + PTA selective stent placement or BS for treatment failure **Intervention 4:** PTA or unsupervised exercise programme + PTA for treatment failure	Intvn 2: £22, 218 Intvn 3: £43, 496 Intvn 4: £21, 511 Intvn 5: £43, 496 **Currency & cost year:** 1995 US dollars (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** *Medical costs:* Diagnostic and therapeutic procedures, professional services, short- and long-term care after complications, follow-up visits, long-term care for patients with amputations.	Intvn 1: 6.05 Intvn 2: 6.14 Intvn 3: 6.22 Intvn 4: 6.15 Intvn 5: 6.21 **Other outcome measures (mean):** NA	Intvn 4 (compared to Intvn 1): £38, 376 Intvn 3 (compared to Intvn 4): £314, 071 **Other:** NA **Subgroup analyses:** None **Analysis of uncertainty:** *One-way analysis:* When cost of exercise set to zero, Intvn 4 = £62,613° per QALY, Intvn 3 = £228,590° per QALY. 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. These results demonstrate that intervention 3 is not cost-effective in most situations either because it is dominated by Intvn 1 or Intvn 2 or the ICER is exceptionally high – especially for patients over 80 years of age or with a history of CAD.

and bypass if not; failure of three revascularisation procedures leads to amputation (above or below the knee). **Perspective:** Netherlands, Societal[†] **Time horizon:** Lifetime **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Intervention 5:** PTA if feasible, if not BS was considered. If neither feasible, entered unsupervised exercise + PTA or BS for treatment failure[‡]			
Data sources				
Health outcomes: Data from the literature was combined with original patient-level data from three databases. Probability of supraingual disease after first and second intervention, suitability of lesions for PTA, and 5-week probability of CLI following graft failure obtained from the vascular registry at Bringham and Women's Hospital, Boston, USA. Relative risk of severe claudication after stopping exercise obtained from exercise programme database at University Hospital Groningen, Netherlands. Relative risk of severe complication after graft failure obtained from a Dutch trial on oral anticoagulants conducted at the Dijkzigt Hospital, Rotterdam, Netherlands. Patency estimates for revascularisations obtained from published meta-analyses (de Vries 1997, Bosch, 1997, Hunink 1994) and adjusted for symptom severity and lesion type, level of anastomosis, and graft material. **Quality-of-life weights:** All EQ-5D values obtained from the literature: Quality of life for patients with systemic complications based on the average value for survivors of MI, angina values from the same source (Tsevat, 1991); critical ischaemia and amputation quality of life based on CUA by Sculpher (1996); severe, mild and no claudication values based on quality of life study by de Vries (1998). **Cost sources:** Estimates of the hospital costs for each revascularisation procedure were obtained from the Boston database (Jansen, 1998) and adjusted for age, sex, presenting symptoms and history of CAD. Costs for mortality and systemic infections obtained from same source. Costs associated with patient time based on estimates in literature (Gold 1996). It was assumed that long-term costs for patients with systemic complications are equal to yearly costs for survivors of myocardial infarction (Wittels 1990).			
Comments				
Source of funding: Supported by a PIONIER award from the Netherlands Organisation for Scientific Research; **Limitations:** Assumed that PTA always preceded by catheter angiography, a more expensive and higher risk imaging option than non-invasive options; **Other:** A maximum walking distance of 250m was used to distinguish severe claudication from no or mild claudication; treatment failure defined as discontinuation of the exercise programme in combination with severe claudication, graft failure or restenosis in combination with severe claudication, or progression to critical limb ischaemia.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CUA = cost utility analysis; CLI = critical limb ischaemia; ABPI = ankle brachial pressure index; CAD = coronary artery disease; PTA = percutaneous transluminal angioplasty; BS = bypass surgery; NA = not applicable; NR = not reported; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio.
† Societal costs were set to zero in the sensitivity analysis. These costs are reported in this table.
‡ It was assumed that 5% of patients would not be suitable for angioplasty based on angiographic findings. Suitability for BS unclear.
‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable*

M.G.M. Hunick, J.B.Wong, M.C Donaldson, M.F. Meyerovitz, J. De Vries, D.P. Harrington. Revascularisation for femoropopliteal disease: a decision and cost analysis. JAMA. 1995. 274:165-171.{Hunink, 1995 15926 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A Markov model developed to examine the initial treatment choice between angioplasty and bypass surgery for patients with lesions that appear suitable for either procedure. Secondary procedures for primary failures were included in the strategy. Each treatment strategy allowed at most two interventions. A loss of primary patency was assumed to lead to symptom recurrence. Patency results were	**Population:** People with disabling claudication of the femoro-popliteal arteries who desire revascularisation: **Cohort settings:** Start age = 65 M = 100% **Intervention 1:** No intervention **Intervention 2:** Angioplasty followed by no further treatment after primary failure. **Intervention 3:** Angioplasty followed by angioplasty for treatment failure. **Intervention 4:** Angioplasty followed by	**Total costs (mean per patient):** **Vein graft (IC stenosis)** Intvn 1: £26, 127 Intvn 2: NR Intvn 3: £15, 677 Intvn 4: £17, 767 Intvn 5: NR Intvn 6: £26, 128 **PTFE-AK (IC stenosis)** Intvn 1: £26, 128 Intvn 2: NR Intvn 3: £15, 677 Intvn 4: £18, 812 Intvn 5: NR Intvn 6: £27, 173 **PTFE-BK (IC stenosis)** Intvn 1: £26, 128 Intvn 2: NR Intvn 3: £15, 677 Intvn 4: £19, 857 Intvn 5: NR	**Primary outcome measure:** QALYs (mean per patient) **Vein graft (IC stenosis)** Intvn 1: 4.5 Intvn 2: NR Intvn 3: 7.3 Intvn 4: 7.4 Intvn 5: NR Intvn 6: 6.9 **PTFE-AK (IC stenosis)** Intvn 1: 4.5 Intvn 2: NR Intvn 3: 7.3 Intvn 4: 7.3 Intvn 5: NR Intvn 6: 6.7 **PTFE-BK (IC stenosis)** Intvn 1: 4.5 Intvn 2: NR Intvn 3: 7.3 Intvn 4: 7.2 Intvn 5: NR	**Primary ICER :** **Vein graft (IC stenosis)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **PTFE-AK (IC stenosis)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **PTFE-BK (IC stenosis)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **Subgroup analyses:** **Vein graft (IC occlusion)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **PTFE-AK (IC occlusion)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **PTFE-BK (IC occlusion)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **Other:** Using amputation-free and event-free life expectancy as measures of effectiveness yielded similar results (results NR).

pooled according to lesion type (stenosis & occlusion), indication (IC & CLI) and bypass graft material (vein & synthetic), and the site of graft placement (above & below the knee). It was assumed that long-term patency following primary angioplasty is equal to patency following repeat angioplasty. **Perspective:** USA healthcare system **Time horizon:** Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	bypass surgery for primary treatment failure. **Intervention 5:** Bypass surgery followed by no further treatment for primary failure. **Intervention 6:** Bypass surgery followed by bypass graft revision for primary failure.	Intvn 6: £30, 308 **Currency & cost year:** 1990 US dollars (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** Costs of angioplasty and bypass for patients with 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.	Intvn 6: 6.5 **Other outcome measures (mean):** None	**Analysis of uncertainty:** If angioplasty were associated with greater mortality, morbidity or higher cost or if venous grafting could be performed with a decreased morbidity, bypass surgery would be preferred as a first line treatment option. The presence of coronary artery disease or increased baseline risk of mortality did not change the conclusion of the analysis.
Data sources				
Health outcomes: Procedure-related morbidity and mortality obtained from published literature (Becker 1989; Donaldson 1991; Wolf 1993; Hunick 1993; Morse 1991; Henriksen 1988; Capek 1991; Belli 1990; Jeans 1990; Hasson 1990; Weibull 1987; Walden 1986; Milford 1988; Jorgensen 1988; Jones 1988; Kent 1988; Whittemore 1989; Quinines-Baldrich 1988; Taylor 1990; Hobson 1985; Veith 1986; Leather 1988; Bergamini 1981; Gupta 1991; Kram 1991); long-term mortality obtained from general population age- and sex- specific life tables and an annual excess mortality rate dependant on ABPI (Howell et al 1989; Fowkes et al 1988); patency (assumed to equal re-intervention) following angioplasty and bypass based on a meta-analysis by Hunick et al 1994; amputation rate assumed to depend on initial symptomatic status. **Quality-of-life weights:** Two vascular surgeons, two interventional radiologists, and an internist estimated the effect of alternative health states for patients with PAD using the Torrance Multi-Attribute Scale. Health states included: revascularisation failure (i.e. symptom recurrence); complications; and amputation. **Cost sources:** All costs were estimated using on administrative data from the Bringham and Women's hospital in Boston. The cost of each radiological procedure was based on microcosting estimates taking into account personnel time, time required, material costs, equipment use and overheads costs. Patient costs were estimated based on time and the average full-time earnings of 60-year old men. The cost of care for patients immobilised and dependant after amputation is based on studies by Gupta 1988, Callow 1988, and Cheshire 1992, assuming that 29% of all amputees require nursing home care at an average cost of £1562 per week.				
Comments				

Source of funding: Supported by a PIONEER award from the Netherlands Organisation for Scientific Research; an award from General Electric Radiolofy Research Academic Fellowships; grant 87269-3A from John A. Hartford Foundation; grant LM04493 from the National Library of Medicine; and grants HS-06503 and HS-06665 from the Agency for health Care Policy and Research; **Limitations:** Quality of life estimated using Torrence Multi Attribute Scale by healthcare workers; patency failure assumed to be equivalent to symptom progression & re-intervention **Other:** Progression of symptoms not modelled due to lack of data; studies included in meta-analysis of patency data predominantly based on studies of lesions less than 10cm in length; after revascularisation, a decreasing annual rate of revascularisation with a constant rate thereafter was assumed; it was assumed that the cost of repeat angioplasty and graft revision equalled that of the initial procedure.
Overall applicability*: Partially appliable Overall quality: Potentially serious limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitation*

S. Spronk, J.L. Bosch, P.T. den Hoed, H.F. Veen, P.M. Pattynama, M.G. Hunink. Cost-effectiveness of endovascular revascularisation compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomised controlled trial. J Vasc Surg. 2008. 48(6):1472-80. {Spronk, 2008 2451 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** RCT **Approach to analysis:** Statistical approach to interpretation of clinical trial results, including calculation of ICER, net benefit and value of information analysis. **Perspective:** Netherlands, Hospital† **Time horizon:** 1 year	**Population:** Patients with intermittent claudication suitable for revascularisation **Cohort settings:** Age (mean): 66 M: 40% ABPI: <0.9 History of CAD: No N = 150 **Intervention 1:** Supervised exercise program me(Two 30-min sessions per week for 24 weeks. Patient began walking on treadmill at 3.5km/hr until max claudication pain reached, then slowed down.	**Total costs (mean per patient):** Intvn 1: £1, 343 Intvn 2: £5, 211 Incremental (2-1): £3, 867 (CI , NR; p= <0.001) **Currency & cost year:** 2005 Euros (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** Procedure costs (materials, personnel, equipment, admission costs), follow-up (outpatient visits, imaging, therapeutic, and admissions), overhead costs†	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 0.07 Intvn 2: 0.11 Incremental (2-1): 0.02 (CI , -0.09 to 0.12; p= 0.63) **Other outcome measures (mean):** Maximum walking distance Intvn 1: 1034 Intvn 2: 826 (p= 0.34) Maximum pain free walking distance Intvn 1: 943 Intvn 2: 806 (p= 0.34)	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: £193, 374 Probability cost-effective: 95% probability that Intervention 2 is not cost effective at a cost effectiveness threshold of £40k°. **Other:** (e.g. £3454 per life year gained) **Subgroup analyses:** None. Analyses of baseline population characteristics determined that there were no significant differences in between group means, therefore no subgroup analyses explored. **Analysis of uncertainty:** At a threshold of approximately £60k, there was a 5% probability that angioplasty is more cost effective than supervised exercise.

Treatment effect duration: (e.g. 5 yrs) **Discounting:** Costs = 3%; Outcomes = 3%	Supervised by vascular technologist in a hospital setting. Patients instructed to walk an additional 30-mins three times weekly at home.) **Intervention 2:** Endovascular revascularisation (PTA with stent if balloon dilation inadequate based on ABPI of <10 (iliac) or results of follow-up angiogram (femoral)).			

Data sources
Health outcomes: Based on results of the current RCT conducted at the Erasmus Medical Center Department of Vascular Surgery, Ikazia Hospital, Rotterdam, Netherlands{Spronk, 2008 2451 /id;Spronk, 2009 134 /id}. **Quality-of-life weights:** Collected from the current RCT using EQ-5D and weighted using Dutch scoring algorithm derived from the general population{Spronk, 2008 2451 /id;Spronk, 2009 134 /id}. **Cost sources:** Staff costs calculated by multiplying time by mean wage rate plus social security costs; material costs assumed to equal material prices; equipment costs calculated as time multiplied by annualised hourly equipment and services costs (Oostenbrink, 2002). Non-healthcare costs included housing, overhead, transportation and patient time costs; these costs were not reported in any detail.
Comments
Source of funding: NR; **Limitations:** Societal perspective; short (one year) time horizon - QALYs are not calculated over a lifetime; Costs derived from US and Dutch databases; patency not reported, making between study comparison difficult. **Other:** None
Overall applicability*: Partially applicable Overall quality: Minor limitations**

NR = not reported; ABPI; ankle-brachial pressure index; ICER = incremental cost effectiveness ratio; WTP = willingness to pay; EVPI = expected value of perfect information; EQ-5D = EuroQol5D
† *Study reports societal perspective; however patient time costs reported in study have been subtracted from all results presented in evidence table*
‡ *Calculated based on reported incremental unadjusted mean costs and QALYs, excluding patient time costs*
‡ Converted to GBP using OECD Purchasing Power Parity Index*(OECD), 2010 16360 /id}* and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable*

K. Visser, S.O. de Vries, P.J.E.H.M. Kitslaar, J.M.A van Enelshoven, M.G.M. Hunick. Cost-effectiveness of diagnostic imaging work-up and treatment for patients with intermittent claudication in the Netherlands. 2003. 25;213-223. {Visser, 2003 809 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA	**Population:** 60 year old male patients	**Total costs (mean per patient):**	**Primary outcome measure:** QALYs (mean per patient)	**Primary ICER:** Interventions 2, 4, and 6 excluded by

Study design: Decision analytic model **Approach to analysis:** Alternative treatment strategies defined as initial imaging strategy combined with angioplasty for patients with suitable lesions. It was assumed that 95% of people had lesions suitable for angioplasty or bypass. For patients with unsuitable lesions for angioplasty, supervised exercise was prescribed. Bypass surgery was included as a possibility in 3 additional intervention arms; these have been excluded from the analysis in this evidence table. **Perspective:** Netherlands, Societal **Time horizon:** Lifetime **Treatment effect duration:** (e.g. 5 yrs)	with severe unilateral claudication of at least one year duration and no history of CAD **Cohort settings:** Start age = 60 years old M = 100% History of CAD = No **Intervention 1:** Supervised exercise only **Intervention 2:** Colour-guided DUS + PTA for patients with suitable lesions, otherwise supervised exercise **Intervention 3:** MRA + PTA for patients with suitable lesions, otherwise supervised exercise **Intervention 4:** DSA + PTA for patients with suitable lesions, otherwise supervised exercise **Intervention 5:** DUS + PTA for patients with suitable lesions, otherwise bypass or supervised exercise	*Intvn 1:* £6 975 *Intvn 2:* £8 775 *Intvn 3:* £8 796 *Intvn 4:* £9 223 Intvn 5: £19, 223 Intvn 6: £18, 936 Intvn 7: £19, 083 **Currency & cost year:** 1999 Euros (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** Costs for personnel, materials, equipment, housing, hospital admission, and overhead; travel expenses and patient time.	*Intvn 1:* 6.0606 *Intvn 2:* 6.1465 *Intvn 3:* 6.1487 *Intvn 4:* 6.1498 *Intvn 5: 6.6002* *Intvn 6: 6.2136* *Intvn 7:6.2254* **Other outcome measures (mean):** NA	extended dominance; Intervention 5 excluded Intvn 3 (compared to Intvn 1): £20, 670 Intvn 7 (compared to Intvn 3): £134, 120 Probability cost-effective: NR **Other:** NA **Subgroup analyses:** None **Analysis of uncertainty:** The results were sensitive to the costs of MRA; at higher costs for MRA and alternative assumptions about treatment, DUS followed by angioplasty or exercise was the most cost-effective strategy. Increasing the number of people suitable for angioplasty slightly decreases the ICER for strategies 3 and 7. Performing angioplasty in conjunction with DSA did not change the results of the model.

Discounting: Costs = 3%; Outcomes = NR	**Intervention 6:** MRA + PTA for patients with suitable lesions, otherwise bypass or supervised exercise **Intervention 7:** DSA + PTA for patients with suitable lesions, otherwise bypass or supervised exercise			
Data sources				
Health outcomes: All health outcome data obtained from the literature. Search strategy not specified. **Quality-of-life weights:** For patients with intermittent claudication, EQ-5D values were obtained from patients who participated in the supervised exercise programme (published in separate paper); for patients with critical limb ischaemia or amputation, values from the literature were used; quality of life scores for patients with systemic complications and angina pectoris were incorporated using multiplicative relation (in literature). **Cost sources:** Cost of radiological and surgical interventions obtained from the University Hospital Maastricht (Netherlands); cost of complications and follow-up after amputation based on literature; monetary value of patient time calculated using average gross earnings for men aged 55-65 in The Netherlands.				
Comments				
Source of funding: Netherlands Organisation for Scientific Research; **Limitations:** Societal perspective; Supervised exercise was not considered an initial treatment strategy (on the basis that de Vries 2002 did not find it to be cost effective compared to initial angioplasty strategies; It was assumed that severe symptoms of IC justified the use of invasive treatment (i.e. symptoms led to re-intervention); **Other:** Failure of angioplasty or bypass was defined as graft failure or restenosis in combination with CLI. Failure of supervised exercise was defined as development of CLI. A maximum walking distance of 250m was used to distinguish severe claudication from no or mild claudication				
Overall applicability*: Partially applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CUA = cost utility analysis; NR = not reported; NA = not applicable; MRA = magnetic resonance imaging; DUS = duplex ultrasonography; PTA = percutaneous transluminal angioplasty; ABPI = ankle brachial pressure index; QALY = quality adjusted life years; CAD = coronary artery disease; DSA= digital subtraction angiography; ICER = incremental cost-effectiveness ratio; NR = not reported

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable*

I.4.4 Bare metal compared to drug eluting stents

No cost-effectiveness evidence was identified for this question.

I.4.5 Autologous vein compared to prosthetic bypass

2 No cost-effectiveness evidence was identified for this question.

I.5 Management of critical limb ischaemia

I.5.1 Angioplasty compared to bypass surgery

A.W. Bradbury, D.J. Bell, J.F. Forbes, F.G.R. Fowkes, I. Gillespie. Et al. Multicenter randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health Technology Assessment. 2010. 14(14).{Bradbury, 2010 1356 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** RCT with economic evaluation **Approach to analysis:** Patients were randomised to receive either an angioplasty or bypass first treatment. Costs and quality of life data was collected at 3 years. Costs, amputation free survival, and overall survival were measured at 7 years. An economic analysis was conducted using patient-level data and non parametric bootstrap methods.	**Population:** Hospital inpatients with severe limb ischaemia (ischaemia rest and/or night pain requiring opiate analgesia and/or tissue loss) as a result of infrainguinal atherosclerosis. N (total) = 452 M = 60% **Intervention 1:** Balloon angioplasty N: 224 **Intervention 2:** Bypass surgery N: 228	**Total costs (mean per patient):** ***Over 3 years:*** *Intvn 1:* £27 357 *intvn 2: £31 152* *Incremental cost: £3, 795* ***Over 7 years:*** *Intvn 1:* £33 539 *Intvn 2:* £36 021 **Currency & cost year:** 2006/2007 US dollars (presented here as 2010 UK pounds‡) **Cost components incorporated:** Cost of rehabilitation was not included, but number and timing of amputations were similar between the two	**Primary outcome measure:** QALYs (mean per patient) ***Over 3 years:*** *Intvn 1:* 1.133 *Intvn 2:* 1.161 *Incremental QALYs: 0.028* **Other outcome measures (mean):** ***Over 7 years:*** Amputation free survival: *Intvn 1:* 2.694 (984 days) *Intvnn 2:* 2.784 (1017 days) Overall survival: *Intvn 1:* 3.105 (1134 days) *Intvn 2:* 3.162 (1155 days)	**Primary ICER:** **3 year horizon:** Intervention 2 is more costly and more effective at a cost of £135, 517 per QALY gained. **Other:** **7 year horizon:** Amputation free survival: Intervention 2 is more costly and more effective, with an ICER of £26 032 per (amputation free) year gained. Overall survival: Intervention 2 is more costly and more effective, with an ICER of £41, 401 per (overall) year gained. **Subgroup analyses:** None **Analysis of uncertainty:**

Perspective: UK, Healthcare system **Time horizon:** **Discounting:** Costs = 3.5%‡; Outcomes = 5%		groups; therefore there is likely to be little relative difference.		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.
Data sources				
Health outcomes: Obtained from the current RCT; **Quality-of-life weights:** Patients completed EQ-5D questionnaires at baseline, 3 months, 6 months, 12 months, 24 months and 36 months after randomisation. Missing data were imputed using the multivariate imputation model (assumes data are missing at random); **Cost sources:** Resource use data were collected following randomisation on the index intervention and all subsequent interventions, hospital stays and hospital clinic visits. These measures of hospital resource use were converted into cost estimates using NHS hospital costs for Scotland. Inpatient days were valued using the specialty-specific cost per day, outpatients on a per diem visit, procedure costs were measured using specific timings; staff time was valued using UK national pay scales. Costs incurred outside the hospital setting were not included.				
Comments				
Source of funding: NHS HTA Programme **Limitations:** 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; **Other:** cost and quality of life of amputation not considered as amputation reported to be equal between groups. However, no values were provided.				
Overall applicability*: Directly applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

‡ The authors' analysis used undiscounted costs to calculate ICERs. The costs presented here are the reported discounted costs at 3.5% over three years.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

T.E. Brothers, G.A. Rios, J.G. Roboson, B.M. Elliott. Justification of intervention for limb-threatening ischemia: a surgical decision analysis. Cardiovascular surgery. 1999; 7(1):62-69.{Brothers, 1999 438 /id}

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model	**Population:** Patients presenting with limb-threatening ischaemia caused by tibial-peroneal artery occlusive disease for the first time.	**Total costs (mean per patient):** Intervention 1:£25 839 Intervention 2:£22 559 Intervention 3:£20 373	**Primary outcome measure:** QALYs (mean per patient) Intervention 1: 3.30 Intervention 2: 2.20 Intervention 3: 2.14	**Primary ICER:** Amputation is excluded by extended dominance ICER (Bypass vs. Expectant management): £4, 712 per QALY

Approach to analysis: A decision tree was constructed to compare three principal options for management of patients with limb-threatening ischaemia. Within the first 30 days of bypass surgery, the occlusion may remain patent, thrombose, or the patient may die. Patent sites may or may not experience successful wound healing. If the heal, they may remain patient for up to 5 years. If they do not, the patient is assumed to require amputation. Amputation would result in either healing or non-healing, and the patient may or may not be ambulatory with a prosthesis. A patient who did not heal from a primary amputation **Perspective:** USA, hospital perspective **Time horizon:** 5 years	Patients with previously failed reconstructions, gangrene, fixed contractures, inadequate venous conduit, or unsuitable anatomy for one of the interventions were excluded from the model. **Cohort settings:** Start age = M = **Intervention 1:** Primary bypass surgery **Intervention 2:** Primary amputation **Intervention 3:** Non-operative expectant management	**Currency & cost year:** 1996/97 US dollars (presented here as 2010 UK pounds‡) **Cost components incorporated:** Procedural cost of interventions, thromectomy/ revision of failed revascularisation, post-intervention surveillance, revision amputation and amputation rehabilitation (including gait training for ambulatory amputees), clinical follow-up costs for patients not receiving intervention.	**Other outcome measures (mean):** NA	**Other:** NA **Subgroup analyses:** None **Analysis of uncertainty:** One- and two-way sensitivity analyses were preformed to evaluate the effect of varying expected utility, incremental costs, early patency, late patency and perioperative mortality rates. The authors reported the results of these analyses in graphical form only and did not exclude dominated options; therefore it is not possible to analyse the results of these analyses. The authors conclude 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%.

Discounting: Costs = NR; Outcomes = 5%				
Data sources				
Health outcomes: 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 (Brothers, 1005; Elliot, 1993; Robison, 1995; Robison 1995). **Quality-of-life weights:** Utility values were obtained from 64 patients with symptoms of infrainguinal vascular occlusive disease in a study by the authors (Brothers, 1996). **Cost sources:** Patient charges for all hospital, outpatient clinic and physician visits generated for 50 bypass and 50 primary amputations were converted to costs using a cost-to-charge ratio of 75%.				
Comments				
Source of funding: Office of Research and Development**,** Medical Research Service, Department of Veterans Affairs; **Limitations:** 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. Data informing the clinical efficacy parameters were obtained from retrospective analyses; there is no indication that a systematic search was undertaken to obtain these data; QALYs were estimated by people with CLI who were asked to imagine different health states rather than people who had experienced those health states. **Other:** Brothers et al have since published several expanded decision analyses (Brothers 2003; 2004; 2007). However, this is the only model that contains both costs and QALYs.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

‡ Cost year not reported; it was assumed that costs were reported for 1996/97, the year of study completion.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

M.G.M. Hunick, J.B.Wong, M.C Donaldson, M.F. Meyerovitz, J. De Vries, D.P. Harrington. Revascularisation for femoropopliteal disease: a decision and cost analysis. JAMA. 1995. 274:165-171.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A Markov model developed to examine the initial treatment choice between angioplasty and bypass	**Population:** People with CLI of the femoro-popliteal arteries who desire revascularisation: **Cohort settings:** Start age = 65 M = 100% **Intervention 1:** No intervention	**Total costs (mean per patient):** **Vein graft (Rest pain stenosis)** Intvn 1: £44, 940 Intvn 2: NR Intvn 3: £34, 489 Intvn 4: £34, 489 Intvn 5: NR Intvn 6: £36, 579 **PTFE-AK (Rest pain stenosis)**	**Primary outcome measure:** QALYs (mean per patient) **Vein graft (Rest pain stenosis)** Intvn 1: 2.5 Intvn 2: NR Intvn 3: 5.7 Intvn 4: 6.3 Intvn 5: NR Intvn 6: 5.9	**Primary ICER :** **Vein graft (Rest pain stenosis)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **PTFE-AK (Rest pain stenosis)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **PTFE-BK (Rest pain stenosis)** Intvn 3 vs Intvn 1: Intvn 3 is dominant **Subgroup analyses:**

surgery for patients with lesions that appear suitable for either procedure. Secondary procedures for primary failures were included in the strategy. Each treatment strategy allowed at most two interventions. A loss of primary patency was assumed to lead to symptom recurrence. Patency results were pooled according to lesion type (stenosis & occlusion), indication (IC & CLI) and bypass graft material (vein & synthetic), and the site of graft placement (above & below the knee). It was assumed that long-term patency following primary angioplasty is equal to patency following repeat angioplasty. **Perspective:** USA healthcare system **Time horizon:** Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	**Intervention 2:** Angioplasty followed by no further treatment after primary failure. **Intervention 3:** Angioplasty followed by angioplasty for treatment failure. **Intervention 4:** Angioplasty followed by bypass surgery for primary treatment failure. **Intervention 5:** Bypass surgery followed by no further treatment for primary failure. **Intervention 6:** Bypass surgery followed by bypass graft revision for primary failure.	Intvn 1: £44, 940 Intvn 2: NR Intvn 3: £34, 489 Intvn 4: £38, 669 Intvn 5: NR Intvn 6: £43, 895 **PTFE-BK (Rest pain stenosis)** Intvn 1: £44, 940 Intvn 2: NR Intvn 3: £34, 489 Intvn 4: £40, 759 Intvn 5: NR Intvn 6: £49, 120 **Currency & cost year:** 1990 US dollars (presented here as 2009/10 UK pounds‡) **Cost components incorporated:** Costs of angioplasty and bypass for patients with 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.	**PTFE-AK (Rest pain stenosis)** Intvn 1: 2.5 Intvn 2: NR Intvn 3: 5.7 Intvn 4: 5.8 Intvn 5: NR Intvn 6: 5.1 **PTFE-BK (Rest pain stenosis)** Intvn 1: 2.5 Intvn 2: NR Intvn 3: 5.7 Intvn 4: 5.5 Intvn 5: NR Intvn 6: 4.6 **Other outcome measures (mean):** None	**Vein graft (Rest pain occlusion)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **PTFE-AK (Rest pain occlusion)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **PTFE-BK (Rest pain occlusion)** Intvn 4 vs Intvn 1: Intvn 4 is dominant **Results were also reported for necrosis according to stenosis and occlusions.** **Other:** Using amputation-free and event-free life expectancy as measures of effectiveness yielded similar results (results NR). **Analysis of uncertainty:** If angioplasty were associated with greater mortality, morbidity or higher cost or if venous grafting could be performed with a decreased morbidity, bypass surgery would be preferred as a first line treatment option. The presence of coronary artery disease or increased baseline risk of mortality did not change the conclusion of the analysis.

Data sources
Health outcomes: Procedure-related morbidity and mortality obtained from published literature (Becker 1989; Donaldson 1991; Wolf 1993; Hunick 1993; Morse 1991; Henriksen 1988; Capek 1991; Belli 1990; Jeans 1990; Hasson 1990; Weibull 1987; Walden 1986; Milford 1988; Jorgensen 1988; Jones 1988; Kent 1988; Whittemore 1989; Quinines-Baldrich 1988; Taylor 1990; Hobson 1985; Veith 1986; Leather 1988; Bergamini 1981; Gupta 1991; Kram 1991); long-term mortality obtained from general population age- and sex- specific life tables and an annual excess mortality rate dependant on ABPI (Howell et al 1989; Fowkes et al 1988); patency (assumed to equal re-intervention) following angioplasty and bypass based on a meta-analysis by Hunick et al 1994; amputation rate assumed to depend on initial symptomatic status. **Quality-of-life weights:** Two vascular surgeons, two interventional radiologists, and an internist estimated the effect of alternative health states for patients with PAD using the Torrance Multi-Attribute Scale. Health states included: revascularisation failure (i.e. symptom recurrence); complications; and amputation. **Cost sources:** All costs were estimated using on administrative data from the Bringham and Women's hospital in Boston. The cost of each radiological procedure was based on microcosting estimates taking into account personnel time, time required, material costs, equipment use and overheads costs. Patient costs were estimated based on time and the average full-time earnings of 60-year old men. The cost of care for patients immobilised and dependant after amputation is based on studies by Gupta 1988, Callow 1988, and Cheshire 1992, assuming that 29% of all amputees require nursing home care at an average cost of £1562 per week.
Comments
Source of funding: Supported by a PIONEER award from the Netherlands Organisation for Scientific Research; an award from General Electric Radiolofy Research Academic Fellowships; grant 87269-3A from John A. Hartford Foundation; grant LM04493 from the National Library of Medicine; and grants HS-06503 and HS-06665 from the Agency for health Care Policy and Research; **Limitations:** Quality of life estimated using Torrence Multi Attribute Scale by healthcare workers; patency failure assumed to be equivalent to symptom progression & re-intervention **Other:** Progression of symptoms not modelled due to lack of data; studies included in meta-analysis of patency data predominantly based on studies of lesions less than 10cm in length; after revascularisation, a decreasing annual rate of revascularisation with a constant rate thereafter was assumed; it was assumed that the cost of repeat angioplasty and graft revision equalled that of the initial procedure.
Overall applicability*: Potentially serious limitations Overall quality: Partially applicable**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported

‡ Converted to GBP using OECD Purchasing Power Parity Index(OECD), 2010 16360 /id} and inflated to 2008/09 GBP using PRSSU Pay and Prices Index{Curtis, 2010 16346 /id}.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitation*

I.5.12 Angioplasty with primary compared to selective stent placement.

No cost-effectiveness evidence was identified for this question.

I.5.13 Bare metal compared to drug eluting stents

No cost-effectiveness evidence was identified for this question.

I.5.14 Autologous vein compared to prosthetic bypass

No cost-effectiveness evidence was identified for this question.

I.6 Management of ischaemic pain in critical limb ischaemia

No cost-effectiveness evidence was identified for this question.

I.7 Major amputation for critical limb ischaemia

Please refer to Brothers 1999{Brothers, 1999 438 /id}, above.

Appendix J: Forest plots

J.1 Diagnosis of peripheral arterial disease

Figure 1: Manual ABPI with Doppler (<0.5), reference standard angiography, diabetes

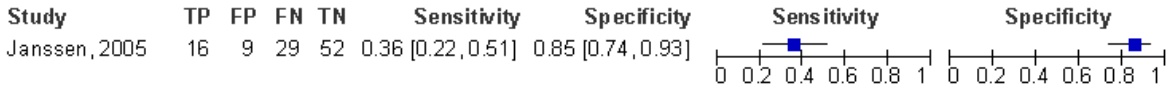


Figure 2: Manual ABPI with Doppler (<0.7), reference standard angiography, diabetes

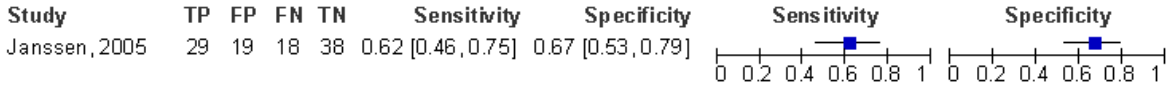


Figure 3: Manual ABPI with Doppler (<0.9), reference standard angiography, diabetes

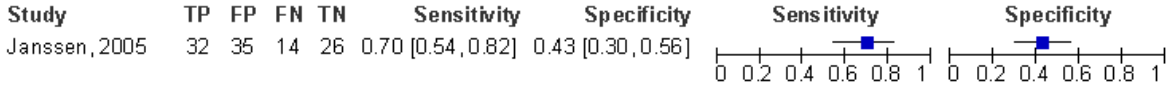


Figure 4: Manual ABPI with Doppler (<0.9), reference standard duplex ultrasound, diabetes

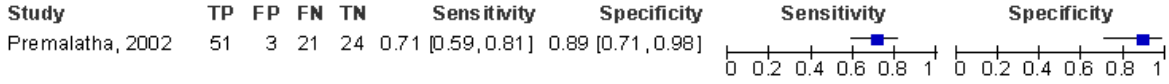


Figure 5: Manual ABPI with Doppler (<0.9), reference standard duplex ultrasound

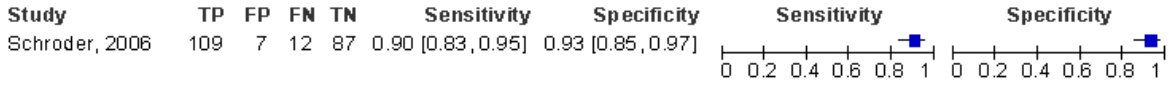
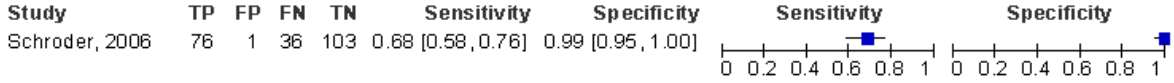


Figure 6: Manual ABPI with Doppler (>0.9), reference standard duplex ultrasound



J.2 Imaging for revascularisation

J.2.1 Diagnostic meta-analysis

Diagnostic meta-analysis was conducted where 5 or more studies were identified comparing the same diagnostic test to the reference standard. The sensitivity and specificity for the studies were pooled using WinBUGS® by the bivariate method; the advantage of this approach is that it produces summary estimates that account for the correlation between sensitivity and specificity. Other advantages of this method have been described elsewhere{Reitsma, 2005 16383 /id}{Van Houwelingen, 1993 16384 /id}{Van Houwelingen, 2002 16385 /id}.

J.2.1.1 Results

The results of each diagnostic meta-analysis are presented in chapter 7 of the full guideline, with the confidence regions presented below in section J.2.2.

J.2.1.2 Analysis

The bivariate method utilises a logistic regression on the true positives, true negatives, false positives and false negatives reported in the sudies and is parameterised as follows{Reitsma, 2005 16383 /id}{Van Houwelingen, 1993 16384 /id}{Van Houwelingen, 2002 16385 /id}:

Where:

and represent the true positives, true negatives, false positives and false negatives, respectively, reported in study i.

and represent the sensitivity and specificity calculated from the results of study i on the log odds scale.

represent the variance-covariance matrix of the pooled sensitivity and specificity on the log odds scale.

and represent the pooled sensitivity and specificity on the natural scale; these are the final summary estimates of interest.

The model above was fitted in WinBUGS®. Using the output from WinBUGS®, we constructed and plotted confidence regions and, where appropriate ROC curves, using methods outlined by Novelli et al{Novielli, 2010 16386 /id} in Microsoft Excel®.

As it was a Bayesian analysis, the evidence distribution is weighted by a distribution of prior beliefs. Vague non-informative priors were used for all parameters. For each analysis, a series of 50,000 burn-in simulations were run to allow convergence and then a further 50,000 simulations were run to produce the outputs. Convergence was assessed by investigating density plots, auto correlation plots and history plots for parameters of interest.

In cases where cell counts were 0, 1 was added to each category (true positives, false positives, true negatives, false negatives) to ensure the model was able to run, whilst not significantly distorting the results.

WinBUGS® code

Model

```
{

for (i in 1:NS)

        {

        TotP[i]<-TP[i] + FN[i]
        TotN[i]<-FP[i] + TN[i]
        TP[i] ~ dbin(p[i , 1] , TotP[i])
        TN[i] ~ dbin(p[i , 2]  , TotN[i])

                for (j in 1:2)

                {
                logit(p[i , j]) <- MeanS[i , j]

                }
MeanS[i , 1:2] ~ dmnorm(md[] , sigma[,])

        }
        sigma[1:2,1:2]~dwish(R[,] , 2)
        Sigma.sq[1:2,1:2] <- inverse(sigma[,])

                for (i in 1:2)
                        {
                        parms[i] <- exp(md[i])/(1+exp(md[i]))
                        }
```

```
            sens <- parms[1]
            spec<- parms[2]


                        for (i in 1:2)
                                {
                                md[i] ~ dnorm(0 , 0.001)
                                }

                        sensitivity.bar <- exp(md[1])/(1+ exp(md[1]))
            specificity.bar <- exp(md[2])/(1+exp(md[2]))


      }



}
```

Data

```
list(NS= Number of studies goes here)

list(R = structure(
          .Data = c(1, 0,
                0, 1), .
          Dim = c(2, 2))
```

Cell Counts for each strategy are entered below, in place of the ni values

```
TP=True positives
FP=False positives
FN=False negatives
TN=True negatives

TP[]      FP[]      FN[]      TN[]
n1        n2        n3        n4
END
```

Initial conditions

```
list(md=c(0,0))
```

J.2.3 Data set

Table 1: 2d TOF MRA, whole leg, 50-100% stenosis data set

Study	TP	FP	FN	TN
Baum, 1995	527	101	100	460
Houch, 1999	161	37	44	302
Houch, 1996	172	13	12	155
Snidow, 1995	80	76	7	215
Yucel, 1993	65	16	6	119

Table 2: 2D TOF MRA, below knee data set

Study	TP	FP	FN	TN
Cortell, 1996	172	10	3	208
Cortell, 1996	155	10	3	225
Cortell, 1996	125	7	3	258
McDermott, 1995	95	1	21	99
McDermott, 1995	124	7	15	70

Study	TP	FP	FN	TN
Eklof, 1998	59	2	14	31
Eklof, 1998	40	10	7	49

Table 3: CE MRA, whole leg, ≥50% stenosis data set

Study	TP	FP	FN	TN
Cronberg, 2003	227	62	20	109
Laissy, 1998	104	14	9	393
Lenhart, 2000	79	8	4	129
Schafer, 2003	138	13	9	416
Steffens, 2003	185	8	1	706
Sueyoshi, 1999	67	3	2	351
Winterer, 1999	362	43	14	1361
Gjonnaess, 2006	119	37	7	706
Bueno, 2010	306	14	34	1370
Kos, 2009	118	6	11	145

Table 4: CE MRA, whole leg, occlusion data set

Study	TP	FP	FN	TN
Lenhart, 2000	54	2	4	160
Meaney, 1999	83	16	15	526
Schafer, 2003	72	1	5	498
Steffens, 2003	85	7	4	804
Sueyoshi, 1999	40	2	1	384
Winterer, 1999	255	11	13	1502
Bueno, 2010	875	16	44	787
Kreitner, 2008	23	5	20	89

Table 5: CTA, whole leg, ≥50% stenosis data set

Study	TP	FP	FN	TN
Heuschmid, 2003	133	40	16	379
Martin, 2003	327	61	38	886
Puls, 1996	56	17	7	106
Rieker, 1996	111	20	3	193
Catalano, 2004	251	23	3	860
Portugaller, 2004	240	80	21	399

Table 6: CTA, whole leg, occlusion data set

Study	TP	FP	FN	TN
Heuschmid, 2003	49	6	5	508
Martin, 2003	202	2	26	1082
Puls, 1996	14	1	1	174
Rieker, 1996	61	1	1	264
Catalano, 2004	170	5	5	957

Table 7: DUS, whole leg, ≥50% stenosis data set

Study	TP	FP	FN	TN
Aly, 1998	404	27	34	2643
Beramini, 1995	94	13	24	273
Hatsukami, 1992	73	6	12	152
Linke, 1994	41	4	2	87
Sensier, 1996	214	26	28	201
El-Kayali, 2004	123	15	3	216
Legemate, 1991	179	30	33	676
Ashleigh, 1993	69	2	0	5
Baxter, 1993	32	1	3	5
Bueno, 2010	108	14	37	701
Gjonnaess, 2006	313	13	73	1322

Table 8: DUS, whole leg, occlusion data set

Study	TP	FP	FN	TN
Aly, 1998	272	18	25	2793
Beramini, 1995	76	10	13	305
Hatsukami, 1992	51	3	6	173
Linke, 1994	14	0	5	115
Sensier, 1996	166	11	21	271
Zeuchner, 1994	50	3	3	266
Legemate, 1991	103	6	9	800
Ashleigh, 1993	36	7	6	27
Bueno, 2010	837	24	101	766

Table 9: DUS, above knee, ≥50% stenosis data set

Study	TP	FP	FN	TN
Bergamini, 1995	83	12	8	194
Fletcher, 1990	59	12	8	89
Hatsukami, 1992	34	2	6	73
Lai, 1996	124	12	42	354
Lundin, 2000	27	7	11	207
El-Kayali, 2004	74	9	1	171
Whyman, 1992	42	2	1	2
Eiberg, 2001	50	8	1	35
Shaalan, 2003	97	12	5	100

Table 10: DUS, above knee, occlusion data set

Study	TP	FP	FN	TN
Currie, 1995	25	4	5	146
Fletcher, 1990	45	7	5	111
Hatcukami, 1992	30	1	2	86
Hirai, 1998	65	1	2	455
Lai, 1996	51	1	13	471

Lundin, 2000	13	1	1	237
Whyman, 1992	27	2	1	17
Davies, 1992	27	1	1	36
Mergelsberg, 1986	25	6	1	17

Table 11: DUS, below knee, occlusion data set

Study	TP	FP	FN	TN
Hatsukami, 1992	26	1	6	49
Karacagil, 1996	199	44	34	203
Koelemay, 1998	457	77	324	655
Koelemay, 1997	84	21	33	121
Wilson, 1997	80	1	5	36
Grassbaugh, 2003	36	6	12	56

J.22 Diagnostic imaging techniques – confidence ellipse of pooled diagnostic results

Figure 7: 2D TOF MRA – whole leg, 50-100% stenosis

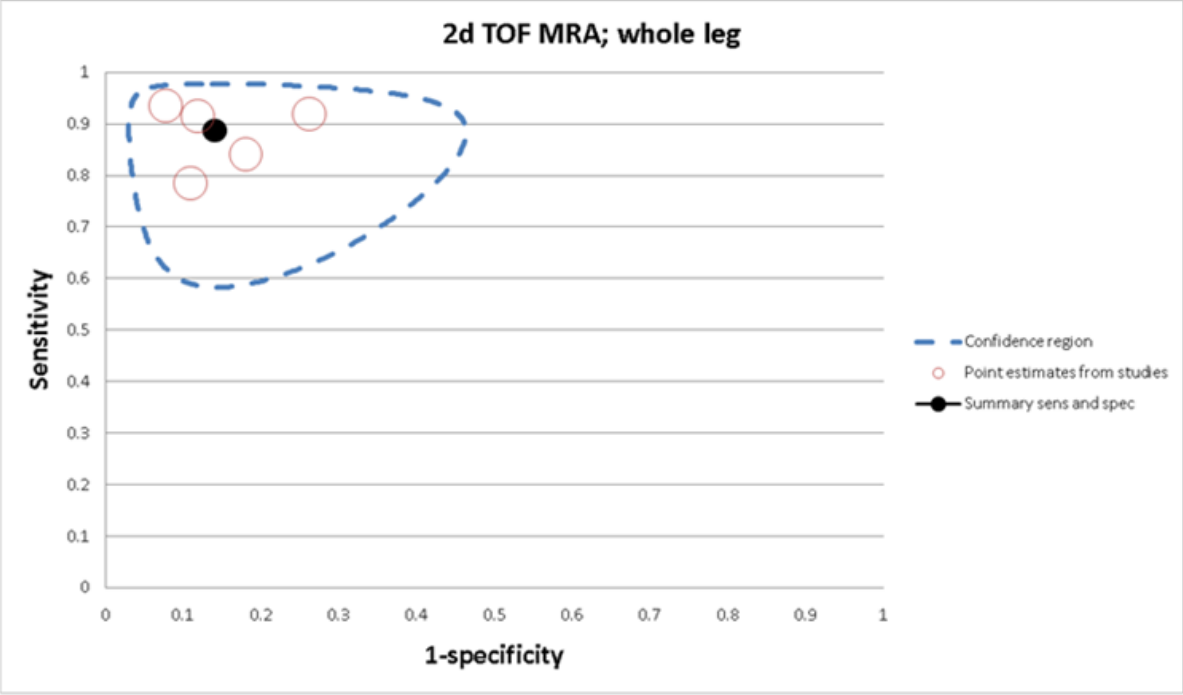
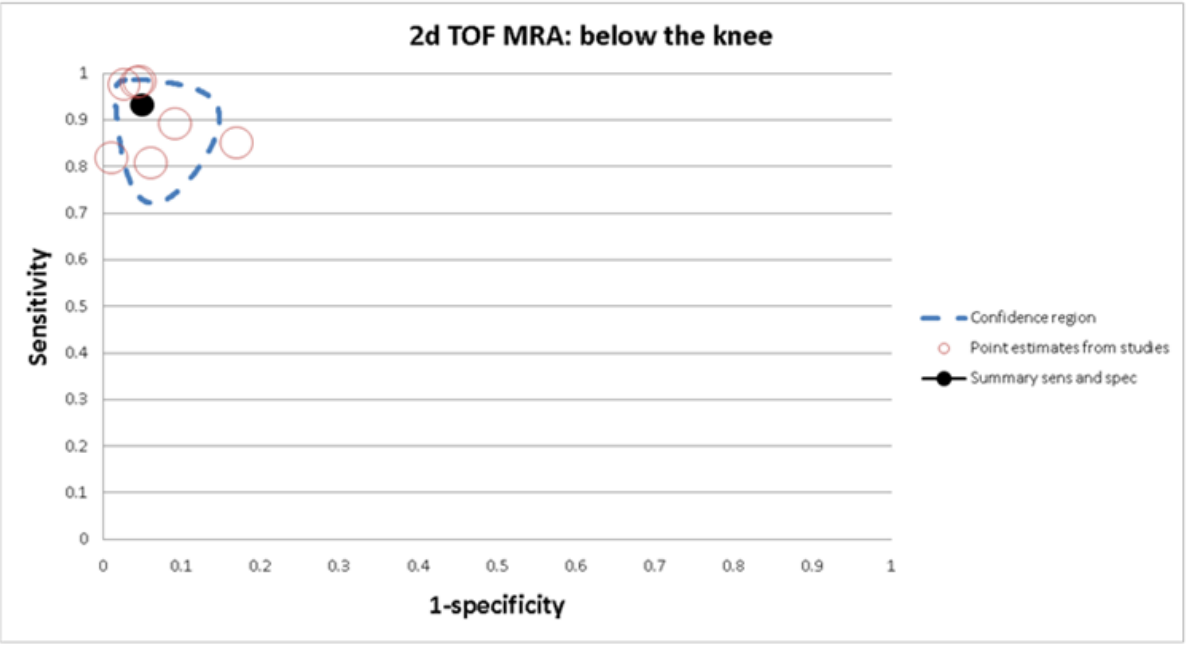
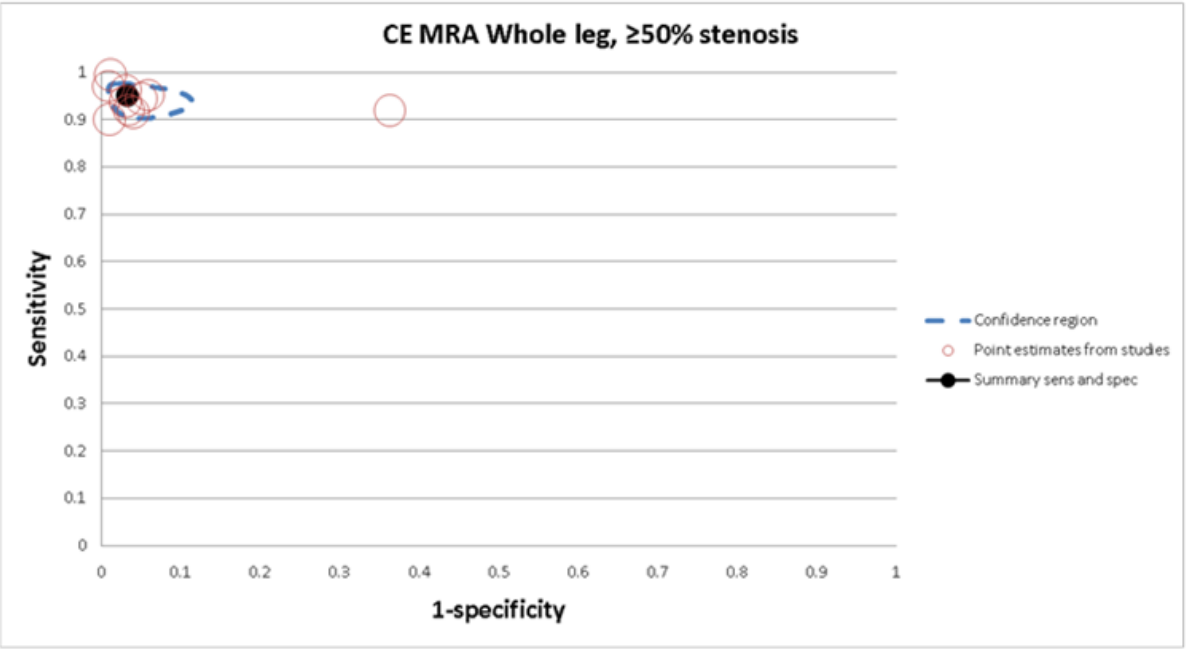


Figure 8: 2D TOF MRA – below knee



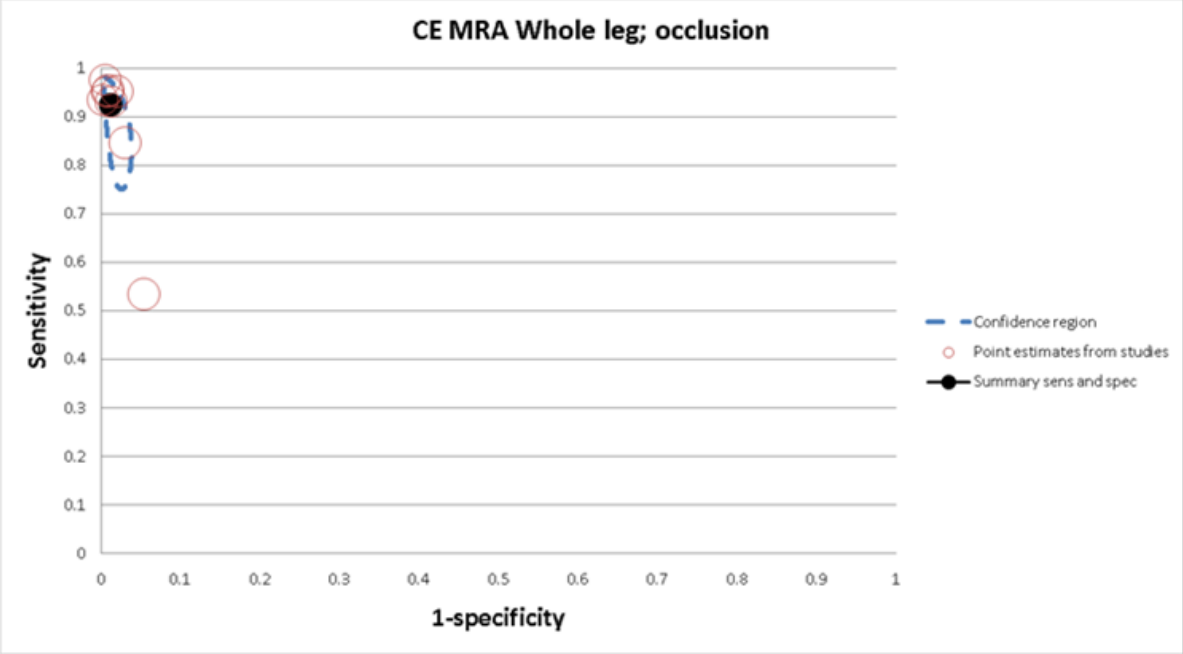
1

Figure 9: CE MRA – whole leg, ≥50% stenosis



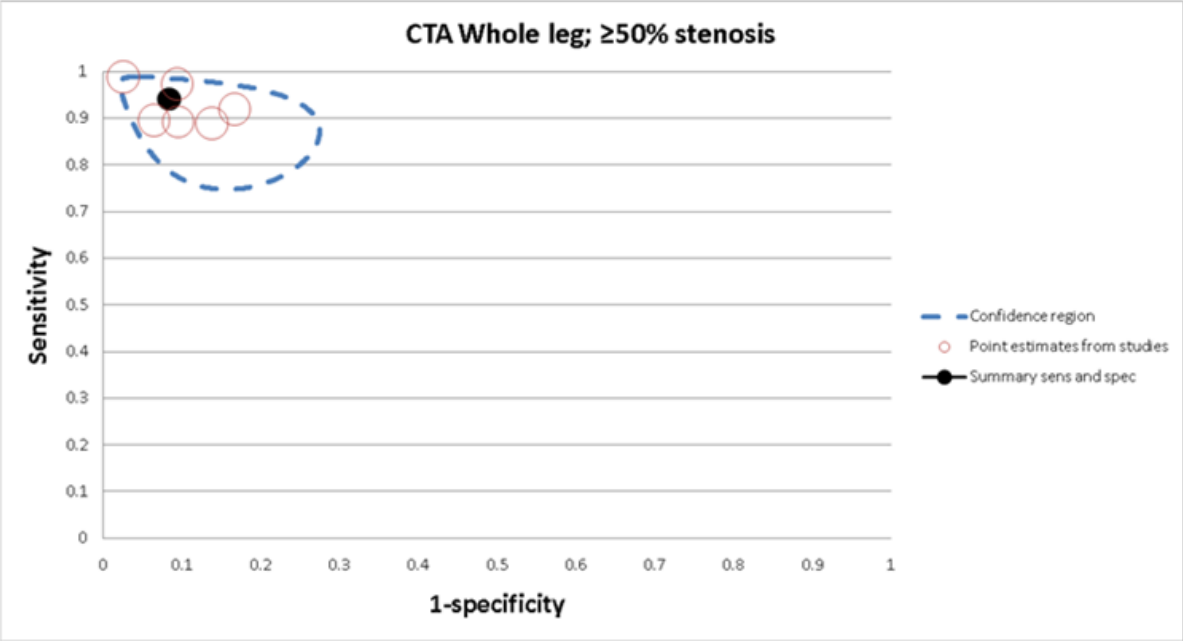
2

Figure 10: CE MRA – whole leg, occlusion



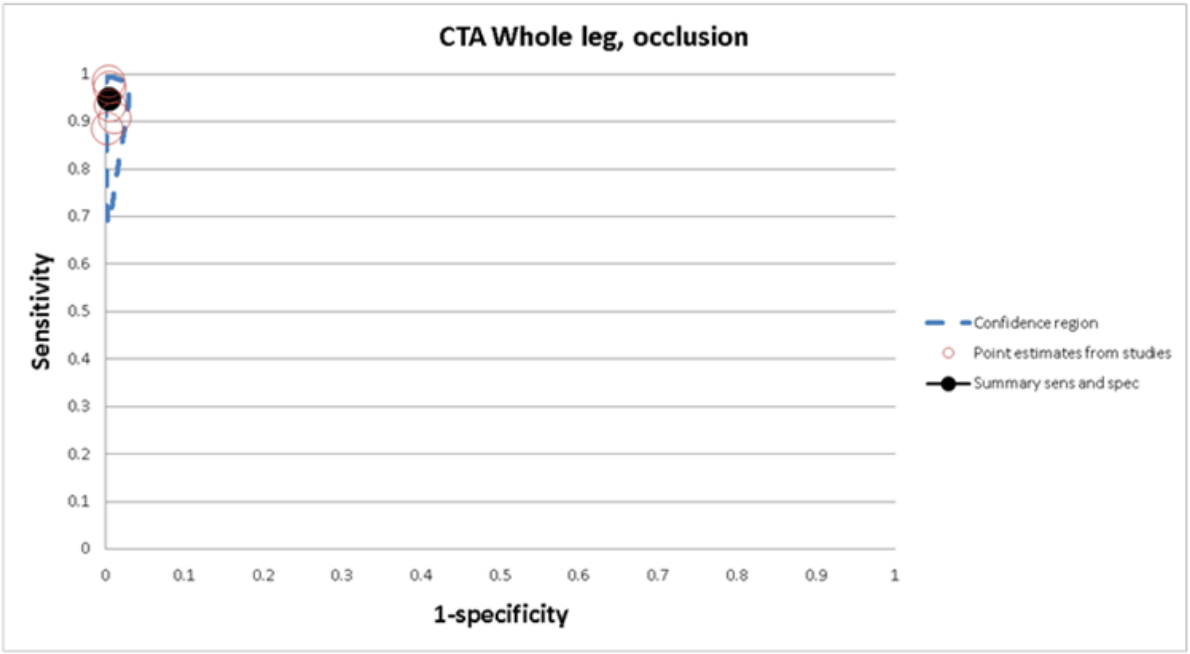
1

Figure 11: CTA – whole leg ≥50% stenosis



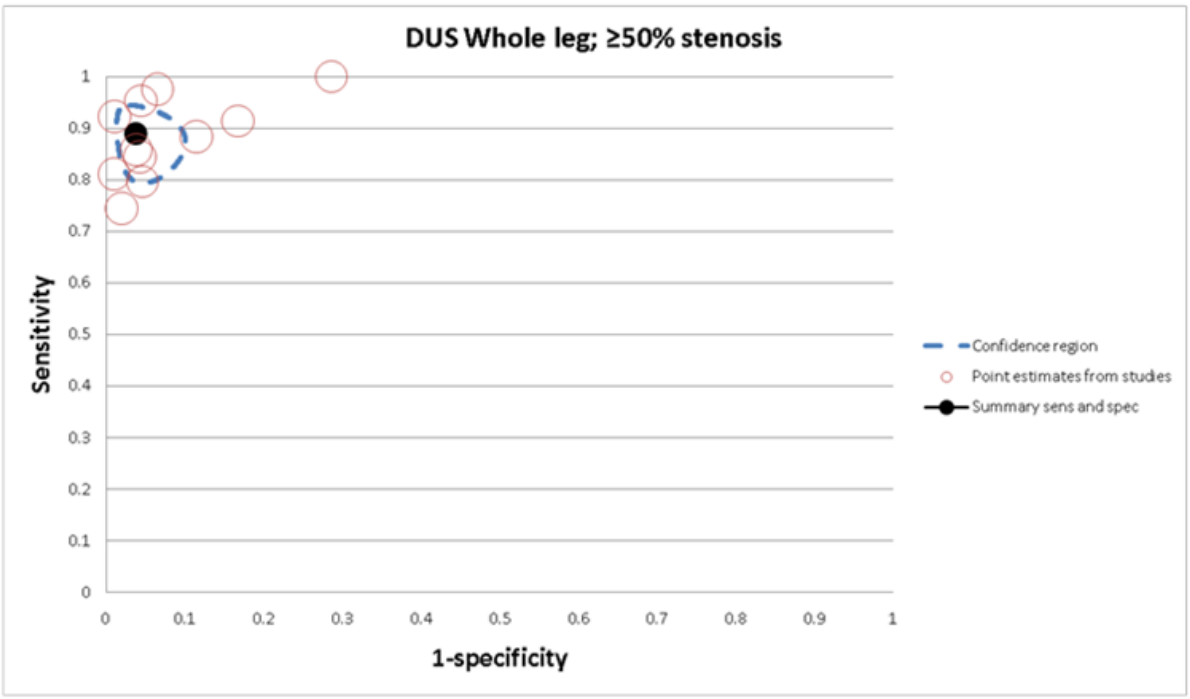
2

Figure 12: CTA – whole leg, occlusion



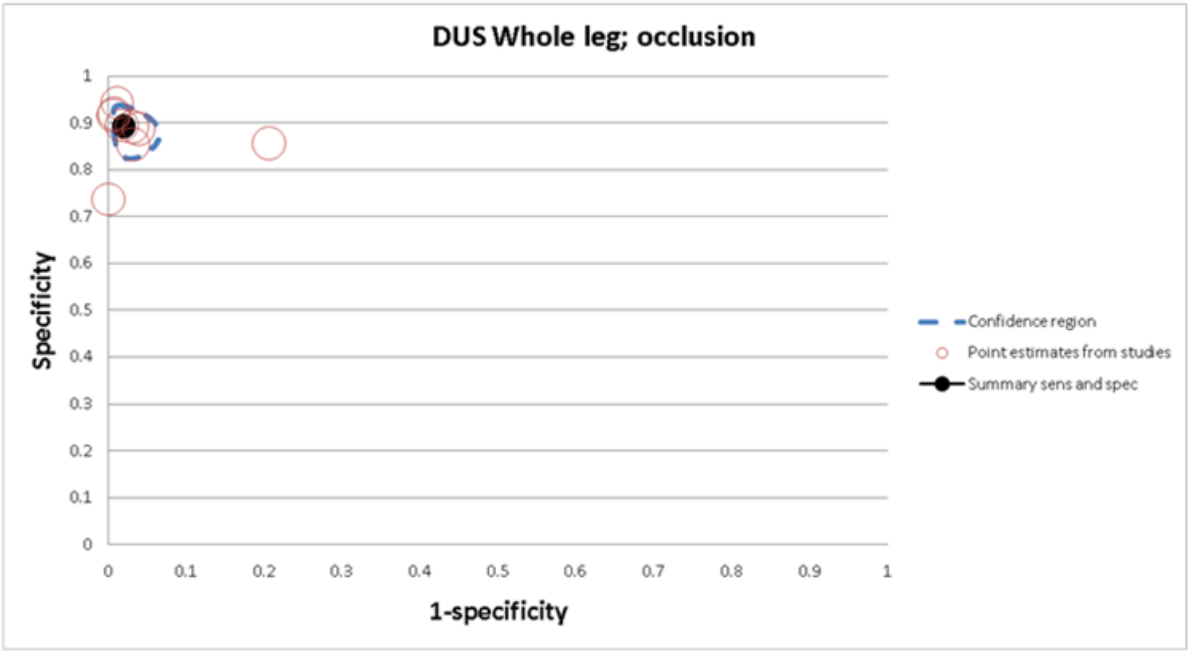
1

Figure 13: DUS – whole leg, ≥50% stenosis



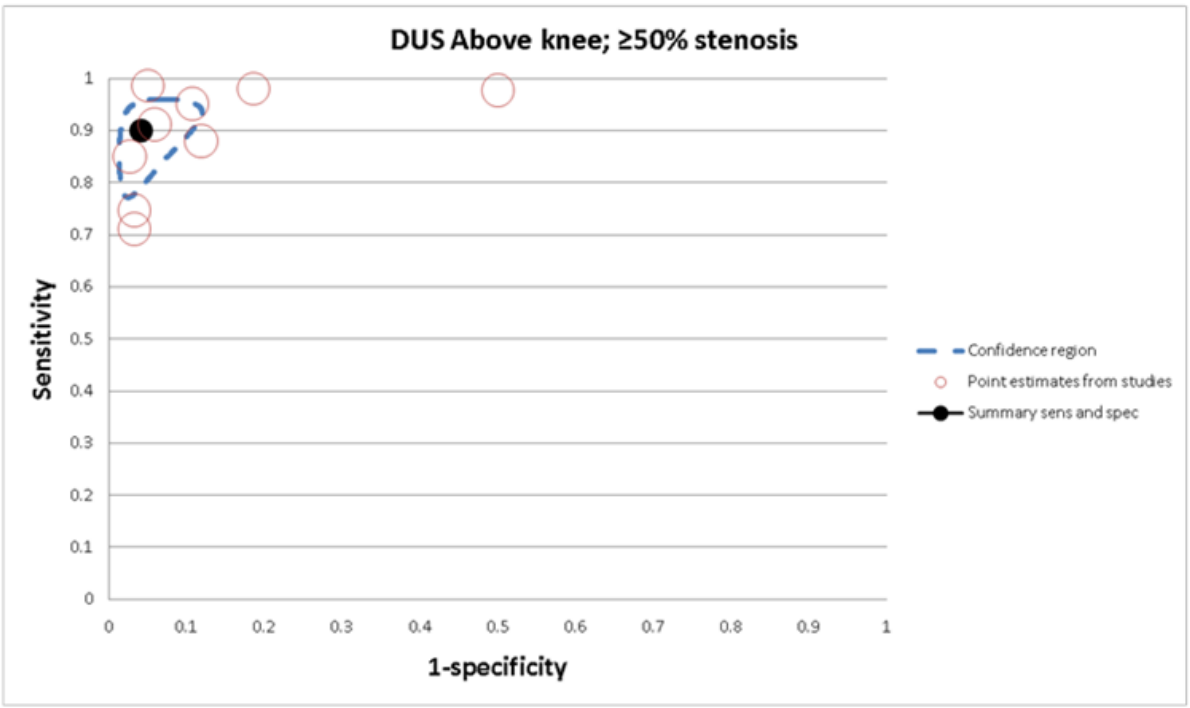
2

Figure 14: DUS – whole leg, occlusion



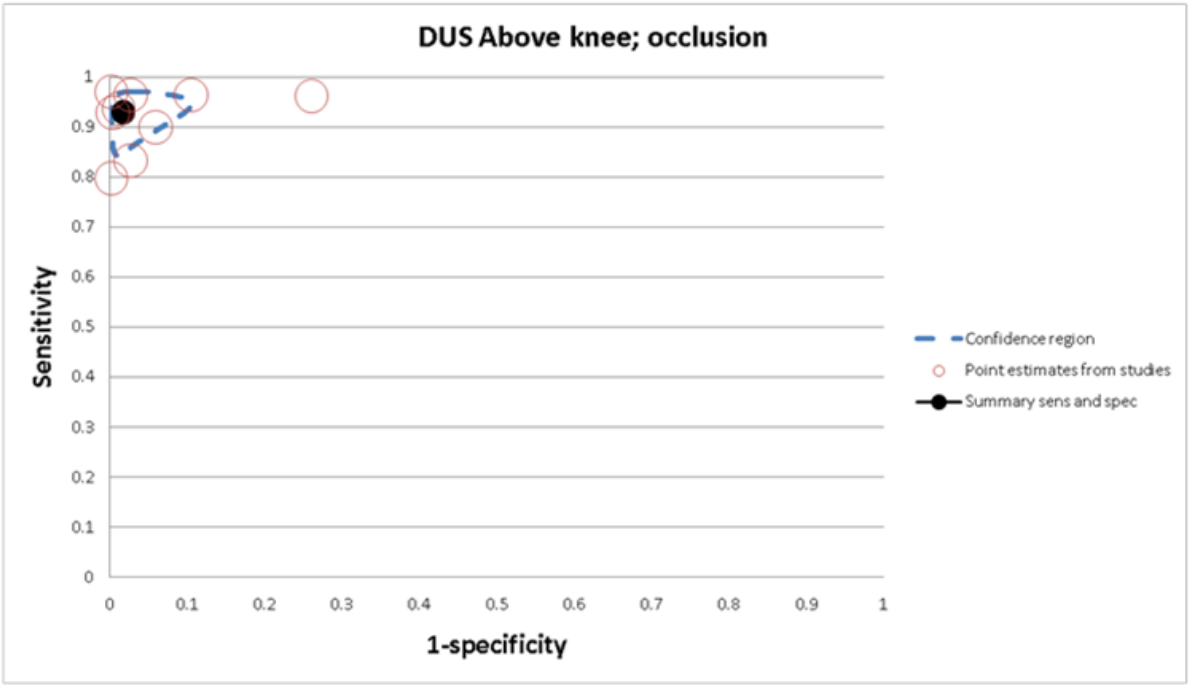
1

Figure 15: DUS – above knee, ≥50% stenosis



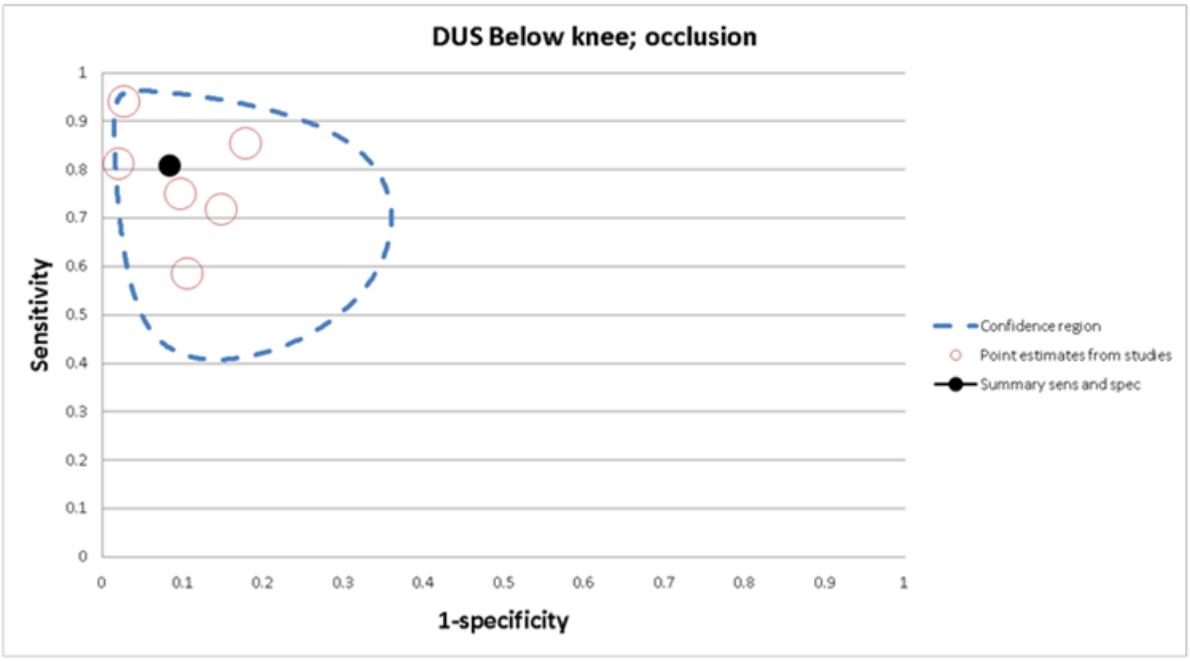
2

Figure 16: DUS – above knee, occlusion



1

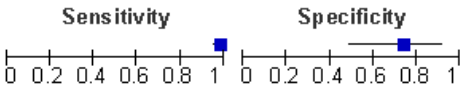
Figure 17: DUS – below knee, occlusion



2

Figure 18: 2D PC MRA, Whole leg, 50-100% stenosis

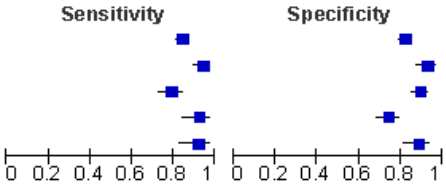
Study	TP	FP	FN	TN	Sensitivity	Specificity
Baum, 1995	229	5	5	14	0.98 [0.95, 0.99]	0.74 [0.49, 0.91]



1

Figure 19: 2D TOF MRA, Whole leg, 50-100% stenosis

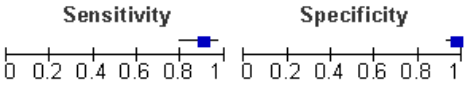
Study	TP	FP	FN	TN	Sensitivity	Specificity
Baum, 1995	527	101	100	460	0.84 [0.81, 0.87]	0.82 [0.79, 0.85]
Houch, 1996	172	13	12	155	0.93 [0.89, 0.97]	0.92 [0.87, 0.96]
Houch, 1999	161	37	44	302	0.79 [0.72, 0.84]	0.89 [0.85, 0.92]
Snidow, 1995	80	76	7	215	0.92 [0.84, 0.97]	0.74 [0.68, 0.79]
Yucel, 1993	65	16	6	119	0.92 [0.83, 0.97]	0.88 [0.81, 0.93]



2

Figure 20: 2D TOF MRA, Whole leg, ≥70% stenosis

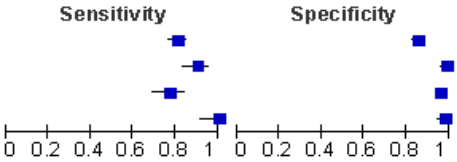
Study	TP	FP	FN	TN	Sensitivity	Specificity
Yucel, 1993	53	5	6	142	0.90 [0.79, 0.96]	0.97 [0.92, 0.99]



3

Figure 21: 2D TOF MRA, Whole leg, occlusion

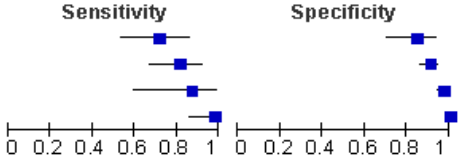
Study	TP	FP	FN	TN	Sensitivity	Specificity
Baum, 1995	322	118	76	672	0.81 [0.77, 0.85]	0.85 [0.82, 0.87]
Houch, 1996	101	4	11	236	0.90 [0.83, 0.95]	0.98 [0.96, 1.00]
Houch, 1999	103	17	31	393	0.77 [0.69, 0.84]	0.96 [0.93, 0.98]
Yucel, 1993	40	4	0	162	1.00 [0.91, 1.00]	0.98 [0.94, 0.99]



4

Figure 22: 2D TOF MRA, Above knee

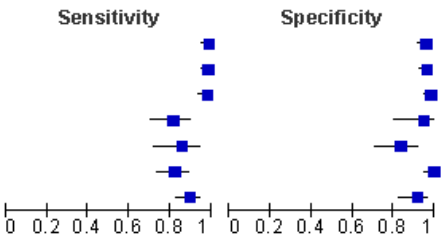
Study	TP	FP	FN	TN	Sensitivity	Specificity
Currie, 1995	25	7	10	38	0.71 [0.54, 0.85]	0.84 [0.71, 0.94]
Lundin, 2000	35	20	8	197	0.81 [0.67, 0.92]	0.91 [0.86, 0.94]
Lundin, 2000b	13	7	2	238	0.87 [0.60, 0.98]	0.97 [0.94, 0.99]
Timonina, 1999	36	0	1	163	0.97 [0.86, 1.00]	1.00 [0.98, 1.00]



5

Figure 23: 2D TOF MRA, Below knee

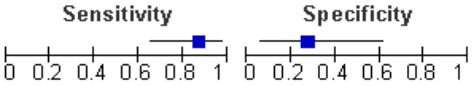
Study	TP	FP	FN	TN	Sensitivity	Specificity
Cortell, 1996	172	10	3	208	0.98 [0.95, 1.00]	0.95 [0.92, 0.98]
Cortell, 1996b	155	10	3	225	0.98 [0.95, 1.00]	0.96 [0.92, 0.98]
Cortell, 1996c	125	7	3	258	0.98 [0.93, 1.00]	0.97 [0.95, 0.99]
Eklof, 1998	59	2	14	31	0.81 [0.70, 0.89]	0.94 [0.80, 0.99]
Eklof, 1998b	40	10	7	49	0.85 [0.72, 0.94]	0.83 [0.71, 0.92]
McDermott, 1995	95	1	21	99	0.82 [0.74, 0.88]	0.99 [0.95, 1.00]
McDermott, 1995b	124	7	15	70	0.89 [0.83, 0.94]	0.91 [0.82, 0.96]



1

Figure 24: 2D TOF MRA, Foot

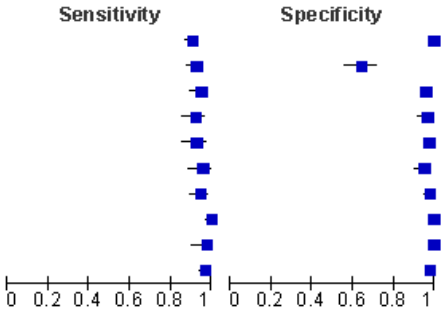
Study	TP	FP	FN	TN	Sensitivity	Specificity
Eklof, 1998	19	8	3	3	0.86 [0.65, 0.97]	0.27 [0.06, 0.61]



2

Figure 25: CE MRA, Whole leg, ≥50% stenosis

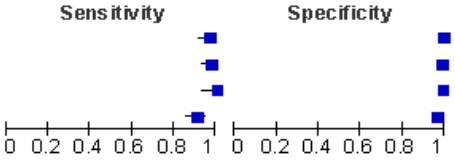
Study	TP	FP	FN	TN	Sensitivity	Specificity
Bueno, 2010	306	14	34	1370	0.90 [0.86, 0.93]	0.99 [0.98, 0.99]
Cronberg, 2003	227	62	20	109	0.92 [0.88, 0.95]	0.64 [0.56, 0.71]
Gjonnaess, 2006	119	37	7	706	0.94 [0.89, 0.98]	0.95 [0.93, 0.96]
Kos, 2009	118	6	11	145	0.91 [0.85, 0.96]	0.96 [0.92, 0.99]
Laissy, 1998	104	14	9	393	0.92 [0.85, 0.96]	0.97 [0.94, 0.98]
Lenhart, 2000	79	8	4	139	0.95 [0.88, 0.99]	0.95 [0.90, 0.98]
Schafer, 2003	138	13	9	416	0.94 [0.89, 0.97]	0.97 [0.95, 0.98]
Steffens, 2003	185	8	1	706	0.99 [0.97, 1.00]	0.99 [0.98, 1.00]
Sueyoshi, 1999	67	3	2	351	0.97 [0.90, 1.00]	0.99 [0.98, 1.00]
Winterer, 1999	362	43	14	1361	0.96 [0.94, 0.98]	0.97 [0.96, 0.98]



3

Figure 26: CE MRA, Whole leg, ≥70% stenosis

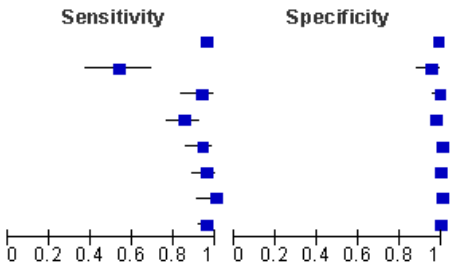
Study	TP	FP	FN	TN	Sensitivity	Specificity
Schafer, 2003	110	3	4	459	0.96 [0.91, 0.99]	0.99 [0.98, 1.00]
Steffens, 2003	147	11	4	738	0.97 [0.93, 0.99]	0.99 [0.97, 0.99]
Sueyoshi, 1999	53	4	0	366	1.00 [0.93, 1.00]	0.99 [0.97, 1.00]
Yavrik, 2004	170	26	17	661	0.91 [0.86, 0.95]	0.96 [0.95, 0.98]



4

Figure 27: CE MRA, Whole leg, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bueno, 2010	875	16	44	787	0.95 [0.94, 0.96]	0.98 [0.97, 0.99]
Kreitner, 2008	23	5	20	89	0.53 [0.38, 0.69]	0.95 [0.88, 0.98]
Lenhart, 2000	54	2	4	160	0.93 [0.83, 0.98]	0.99 [0.96, 1.00]
Meaney, 1999	83	16	15	526	0.85 [0.76, 0.91]	0.97 [0.95, 0.98]
Schafer, 2003	72	1	5	498	0.94 [0.85, 0.98]	1.00 [0.99, 1.00]
Steffens, 2003	85	7	4	804	0.96 [0.89, 0.99]	0.99 [0.98, 1.00]
Sueyoshi, 1999	39	1	0	383	1.00 [0.91, 1.00]	1.00 [0.99, 1.00]
Winterer, 1999	255	11	13	1502	0.95 [0.92, 0.97]	0.99 [0.99, 1.00]



1

Figure 28: CE MRA, Above knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hany, 1997	62	7	2	163	0.97 [0.89, 1.00]	0.96 [0.92, 0.98]
Lenhart, 2000	24	6	2	83	0.92 [0.75, 0.99]	0.93 [0.86, 0.97]
Lundin, 2000	35	18	8	204	0.81 [0.67, 0.92]	0.92 [0.87, 0.95]
Snidow, 1996	26	6	0	96	1.00 [0.87, 1.00]	0.94 [0.88, 0.98]

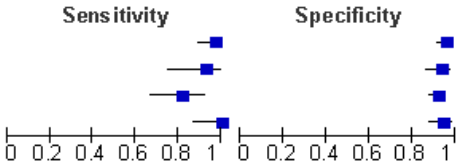


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Figure 29: CE MRA, Above knee, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Vavrik, 2004	86	13	9	468	0.91 [0.83, 0.96]	0.97 [0.95, 0.99]

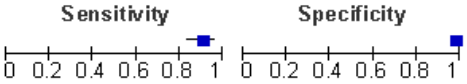

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Figure 30: CE MRA, Above knee, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hany, 1997	19	1	0	214	1.00 [0.82, 1.00]	1.00 [0.97, 1.00]
Lenhart, 2000	14	0	2	99	0.88 [0.62, 0.98]	1.00 [0.96, 1.00]
Lundin, 2000	13	0	2	250	0.87 [0.60, 0.98]	1.00 [0.99, 1.00]
Snidow, 1996	18	0	0	110	1.00 [0.81, 1.00]	1.00 [0.97, 1.00]

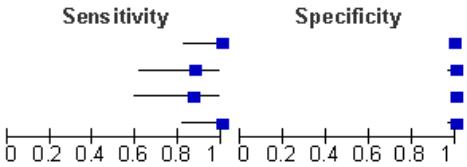

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Figure 31: CE MRA, Below knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kreitner, 2000	27	3	11	33	0.71 [0.54, 0.85]	0.92 [0.78, 0.98]
Lenhart, 2000	55	2	2	46	0.96 [0.88, 1.00]	0.96 [0.86, 0.99]
Zhang, 2005	252	31	52	207	0.83 [0.78, 0.87]	0.87 [0.82, 0.91]

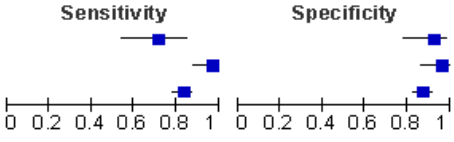

Figure 32: CE MRA, Below knee, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Vavrik, 2004	84	13	8	193	0.91 [0.84, 0.96]	0.94 [0.89, 0.97]

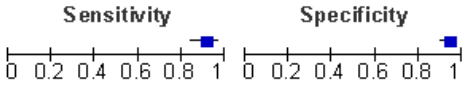

Figure 33: CE MRA, Below knee, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lenhart, 2000	40	2	2	61	0.95 [0.84, 0.99]	0.97 [0.89, 1.00]
Zhang, 2005	200	22	32	288	0.86 [0.81, 0.90]	0.93 [0.89, 0.95]

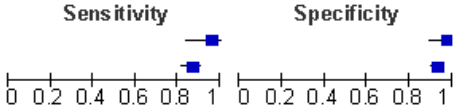

Figure 34: CE MRA, Foot

Study	TP	FP	FN	TN	Sensitivity	Specificity
Zhang, 2005	59	20	16	48	0.79 [0.68, 0.87]	0.71 [0.58, 0.81]
Zhang, 2005b	50	11	13	69	0.79 [0.67, 0.89]	0.86 [0.77, 0.93]

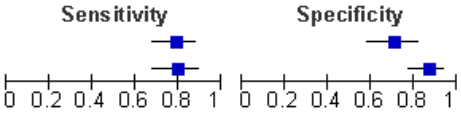

Figure 35: CTA, Whole leg, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Catalano, 2004	251	23	3	860	0.99 [0.97, 1.00]	0.97 [0.96, 0.98]
Heuschmind, 2003	133	40	16	379	0.89 [0.83, 0.94]	0.90 [0.87, 0.93]
Martin, 2003	327	61	38	886	0.90 [0.86, 0.93]	0.94 [0.92, 0.95]
Portugaller, 2004	240	80	21	399	0.92 [0.88, 0.95]	0.83 [0.80, 0.87]
Puls, 1996	56	17	7	106	0.89 [0.78, 0.95]	0.86 [0.79, 0.92]
Rieker, 1996	111	20	3	193	0.97 [0.93, 0.99]	0.91 [0.86, 0.94]

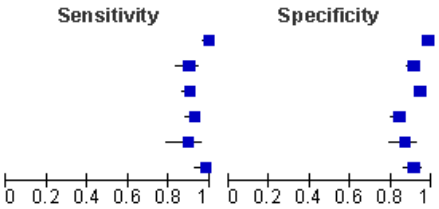

Figure 36: CTA, Whole leg, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Heuschmind, 2003	88	7	12	461	0.88 [0.80, 0.94]	0.99 [0.97, 0.99]
Martin, 2003	236	20	34	1022	0.87 [0.83, 0.91]	0.98 [0.97, 0.99]
Napoli, 2011	3072	115	39	4141	0.99 [0.98, 0.99]	0.97 [0.97, 0.98]
Rieker, 1996	91	6	6	224	0.94 [0.87, 0.98]	0.97 [0.94, 0.99]

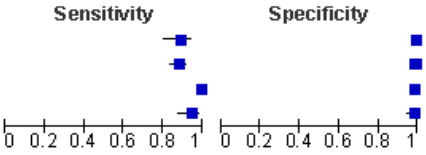

Figure 37: CTA, Whole leg, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Catalano, 2004	170	5	5	957	0.97 [0.93, 0.99]	0.99 [0.99, 1.00]
Heuschmind, 2003	49	6	5	508	0.91 [0.80, 0.97]	0.99 [0.97, 1.00]
Martin, 2003	202	2	26	1082	0.89 [0.84, 0.92]	1.00 [0.99, 1.00]
Puls, 1996	13	0	0	173	1.00 [0.75, 1.00]	1.00 [0.98, 1.00]
Rieker, 1996	61	1	1	264	0.98 [0.91, 1.00]	1.00 [0.98, 1.00]

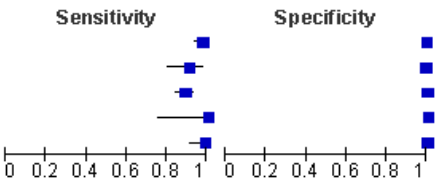

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Figure 38: CTA, Above knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Portugaller, 2004	86	23	3	238	0.97 [0.90, 0.99]	0.91 [0.87, 0.94]
Rieker, 1997	49	2	3	101	0.94 [0.84, 0.99]	0.98 [0.93, 1.00]
Rieker, 1997b	63	4	2	114	0.97 [0.89, 1.00]	0.97 [0.92, 0.99]

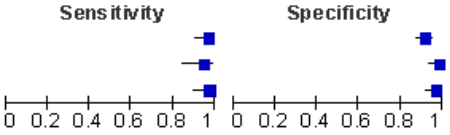

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Figure 39: CTA, Above knee, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rieker, 1997	30	0	0	153	1.00 [0.88, 1.00]	1.00 [0.98, 1.00]
Rieker, 1997b	28	0	0	127	1.00 [0.88, 1.00]	1.00 [0.97, 1.00]
Schernthaner, 2008	192	4	2	614	0.99 [0.96, 1.00]	0.99 [0.98, 1.00]

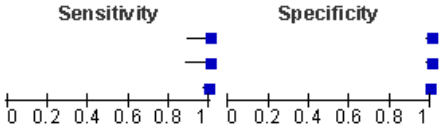

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Figure 40: CTA, Above knee, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rieker, 1997	39	0	2	114	0.95 [0.83, 0.99]	1.00 [0.97, 1.00]
Rieker, 1997b	48	1	2	132	0.96 [0.86, 1.00]	0.99 [0.96, 1.00]

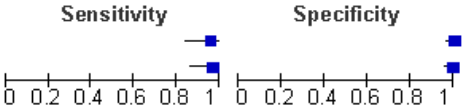

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Figure 41: CTA, Below knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Portugaller, 2004	154	57	18	161	0.90 [0.84, 0.94]	0.74 [0.67, 0.80]

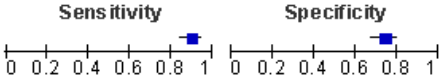

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Figure 42: CTA, Below knee, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Schernthaner, 2008	161	1	3	374	0.98 [0.95, 1.00]	1.00 [0.99, 1.00]

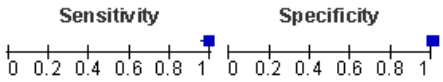

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Figure 43: DUS, Whole leg, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aly, 1998	404	27	34	2643	0.92 [0.89, 0.95]	0.99 [0.99, 0.99]
Ashleigh, 1993	69	2	0	5	1.00 [0.95, 1.00]	0.71 [0.29, 0.96]
Baxter, 1993	32	1	3	5	0.91 [0.77, 0.98]	0.83 [0.36, 1.00]
Beramini, 1995	94	13	24	273	0.80 [0.71, 0.87]	0.95 [0.92, 0.98]
Bueno, 2010	313	13	73	1322	0.81 [0.77, 0.85]	0.99 [0.98, 0.99]
El-Kayali, 2004	123	15	3	216	0.98 [0.93, 1.00]	0.94 [0.90, 0.96]
Gjonnaess, 2006	108	14	37	701	0.74 [0.67, 0.81]	0.98 [0.97, 0.99]
Hatsukami, 2002	73	6	12	152	0.86 [0.77, 0.92]	0.96 [0.92, 0.99]
Legemate, 1991	179	30	33	676	0.84 [0.79, 0.89]	0.96 [0.94, 0.97]
Linke, 1994	41	4	2	87	0.95 [0.84, 0.99]	0.96 [0.89, 0.99]
Sensier, 1996	214	26	28	201	0.88 [0.84, 0.92]	0.89 [0.84, 0.92]

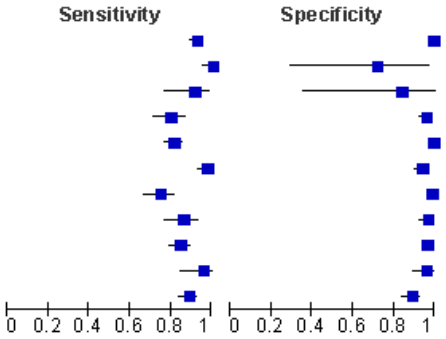

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Figure 44: DUS, Whole leg, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aly, 1998	272	18	25	2793	0.92 [0.88, 0.94]	0.99 [0.99, 1.00]
Ashleigh, 1993	36	7	6	27	0.86 [0.71, 0.95]	0.79 [0.62, 0.91]
Beramini, 1995	76	10	13	305	0.85 [0.76, 0.92]	0.97 [0.94, 0.98]
Bueno, 2010	837	24	101	766	0.89 [0.87, 0.91]	0.97 [0.96, 0.98]
Hatsukami, 2002	51	3	6	173	0.89 [0.78, 0.96]	0.98 [0.95, 1.00]
Legemate, 1991	103	6	9	800	0.92 [0.85, 0.96]	0.99 [0.98, 1.00]
Linke, 1994	14	0	5	115	0.74 [0.49, 0.91]	1.00 [0.97, 1.00]
Sensier, 1996	166	11	21	271	0.89 [0.83, 0.93]	0.96 [0.93, 0.98]
Zeuchner, 1994	50	3	3	266	0.94 [0.84, 0.99]	0.99 [0.97, 1.00]

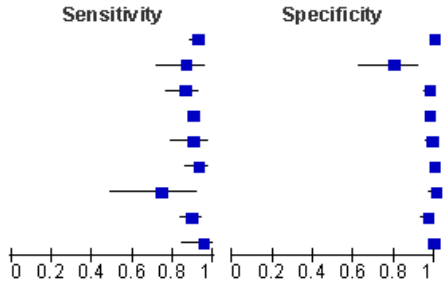

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Figure 45: DUS, Whole leg, other stenosis thresholds

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ashleigh, 1993	25	7	4	42	0.86 [0.68, 0.96]	0.86 [0.73, 0.94]
Eiberg, 2010	1522	169	149	636	0.91 [0.90, 0.92]	0.79 [0.76, 0.82]
Lai, 1995	14	9	9	54	0.61 [0.39, 0.80]	0.86 [0.75, 0.93]
Zeuchner, 1994	12	1	4	305	0.75 [0.48, 0.93]	1.00 [0.98, 1.00]

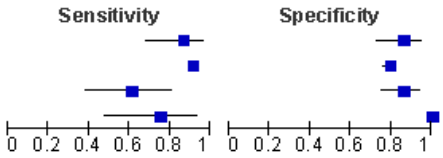

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Figure 46: DUS, Above knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Beramini, 1995	83	12	8	194	0.91 [0.83, 0.96]	0.94 [0.90, 0.97]
Eiberg, 2001	50	8	1	35	0.98 [0.90, 1.00]	0.81 [0.67, 0.92]
El-Kayali, 2004	74	9	1	171	0.99 [0.93, 1.00]	0.95 [0.91, 0.98]
Fletcher, 1990	59	12	8	89	0.88 [0.78, 0.95]	0.88 [0.80, 0.94]
Hatsukami, 2002	34	2	6	73	0.85 [0.70, 0.94]	0.97 [0.91, 1.00]
Lai, 1996	124	12	42	354	0.75 [0.67, 0.81]	0.97 [0.94, 0.98]
Lundin, 2000	27	7	11	207	0.71 [0.54, 0.85]	0.97 [0.93, 0.99]
Shaalan, 2003	97	12	5	100	0.95 [0.89, 0.98]	0.89 [0.82, 0.94]
Whyman, 1992	41	1	0	1	1.00 [0.91, 1.00]	0.50 [0.01, 0.99]

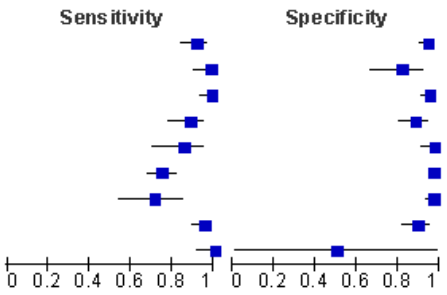

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Figure 47: DUS, above knee, ≥70% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fletcher, 1990	14	2	0	40	1.00 [0.77, 1.00]	0.95 [0.84, 0.99]
Lai, 1996	83	8	44	397	0.65 [0.56, 0.74]	0.98 [0.96, 0.99]

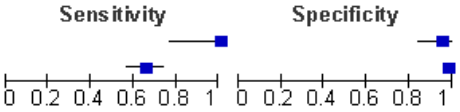

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Figure 48: DUS, Above knee, occlusion

Study	TP	FP	FN	TN	Sensitivity	Specificity
Currie, 1995	25	4	5	146	0.83 [0.65, 0.94]	0.97 [0.93, 0.99]
Davies, 1992	27	1	1	36	0.96 [0.82, 1.00]	0.97 [0.86, 1.00]
Fletcher, 1990	45	7	5	111	0.90 [0.78, 0.97]	0.94 [0.88, 0.98]
Hatsukami, 2002	29	0	1	85	0.97 [0.83, 1.00]	1.00 [0.96, 1.00]
Hirai, 1998	64	0	1	454	0.98 [0.92, 1.00]	1.00 [0.99, 1.00]
Lai, 1996	50	0	12	470	0.81 [0.69, 0.90]	1.00 [0.99, 1.00]
Lundin, 2000	13	1	1	237	0.93 [0.66, 1.00]	1.00 [0.98, 1.00]
Mergelsberg, 1986	25	6	1	17	0.96 [0.80, 1.00]	0.74 [0.52, 0.90]
Whyman, 1992	26	1	0	16	1.00 [0.87, 1.00]	0.94 [0.71, 1.00]

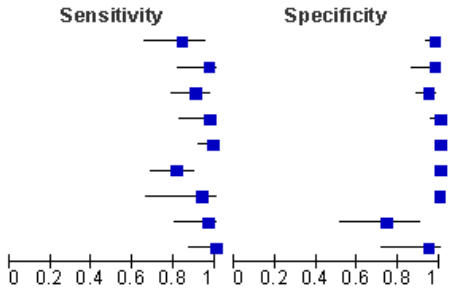

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Figure 49: DUS, above knee, other stenosis thresholds

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bostrom, 2001	93	11	6	53	0.94 [0.87, 0.98]	0.83 [0.71, 0.91]
Davies, 1992	16	1	1	47	0.94 [0.71, 1.00]	0.98 [0.89, 1.00]
Hirai, 1998	43	3	9	399	0.83 [0.70, 0.92]	0.99 [0.98, 1.00]

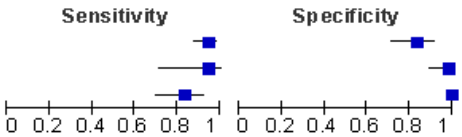

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Figure 50: DUS, Below knee, ≥50% stenosis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Beramini, 1995	11	1	16	79	0.41 [0.22, 0.61]	0.99 [0.93, 1.00]
El-Kayali, 2004	49	6	2	45	0.96 [0.87, 1.00]	0.88 [0.76, 0.96]
Hatsukami, 2002	27	1	6	44	0.82 [0.65, 0.93]	0.98 [0.88, 1.00]
Karacagil, 1996	211	47	36	186	0.85 [0.80, 0.90]	0.80 [0.74, 0.85]

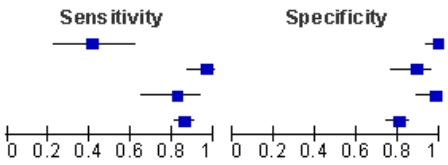

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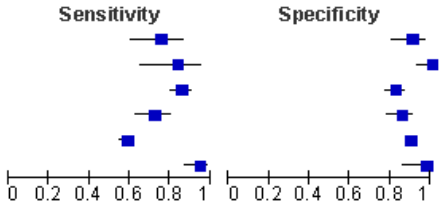
Figure 51: DUS, Below knee, occlusion

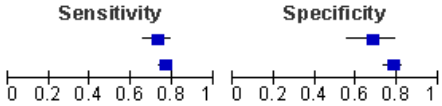
Study	TP	FP	FN	TN	Sensitivity	Specificity
Grassbaugh, 2003	36	6	12	56	0.75 [0.60, 0.86]	0.90 [0.80, 0.96]
Hatsukami, 2002	25	0	5	48	0.83 [0.65, 0.94]	1.00 [0.93, 1.00]
Karacagil, 1996	199	44	34	203	0.85 [0.80, 0.90]	0.82 [0.77, 0.87]
Koelemay, 1997	84	21	33	121	0.72 [0.63, 0.80]	0.85 [0.78, 0.91]
Koelemay, 1998	457	77	324	655	0.59 [0.55, 0.62]	0.89 [0.87, 0.92]
Wilson, 1997	80	1	5	36	0.94 [0.87, 0.98]	0.97 [0.86, 1.00]



2

Figure 52: DUS, Below knee, other stenosis thresholds

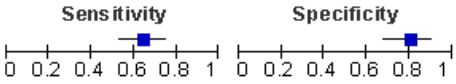
Study	TP	FP	FN	TN	Sensitivity	Specificity
Koelemay, 1997	136	23	52	48	0.72 [0.65, 0.79]	0.68 [0.55, 0.78]
Koelemay, 1998	813	99	257	344	0.76 [0.73, 0.79]	0.78 [0.73, 0.81]



3

Figure 53: DUS, Foot

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hofmann, 2004	54	11	30	45	0.64 [0.53, 0.74]	0.80 [0.68, 0.90]



4

J.3 Management of intermittent claudication

J.3.1 Supervised exercise compared to unsupervised exercise

J.3.1.1 Intermittent claudication due to femoro-politeal disease

Figure 54: Withdrawal at 3 months

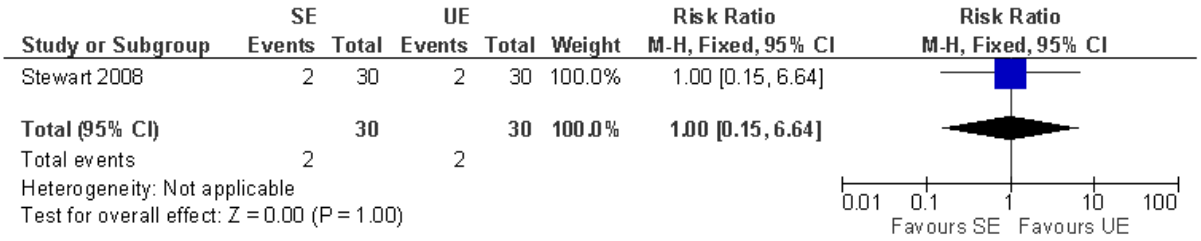


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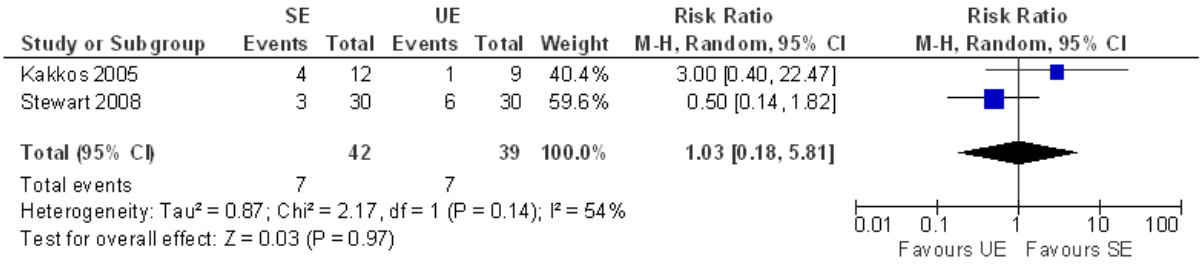
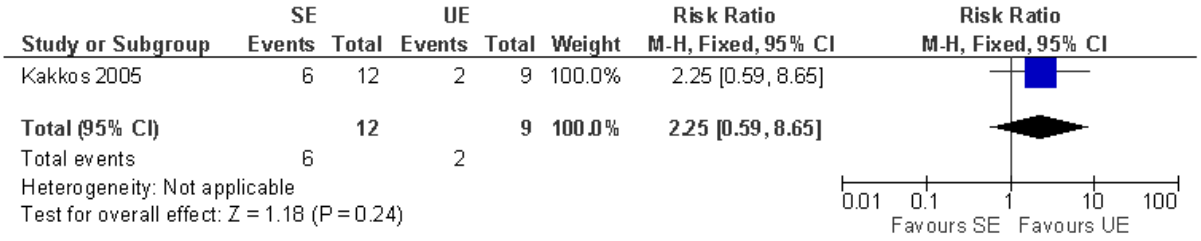
Figure 55: Withdrawal at 6 months (random effects)



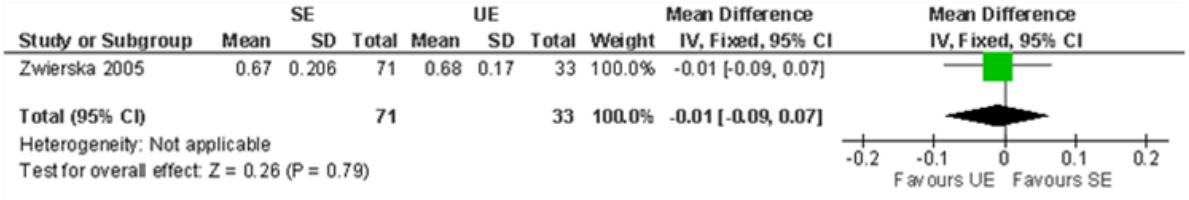
5

Figure 56: Withdrawal at 1 year



6

Figure 57: ABPI at 6 months



J.3.112 Intermittent claudication - unknown disease location

Figure 58: Maximum walking distance at 3 months (combined end and change results)

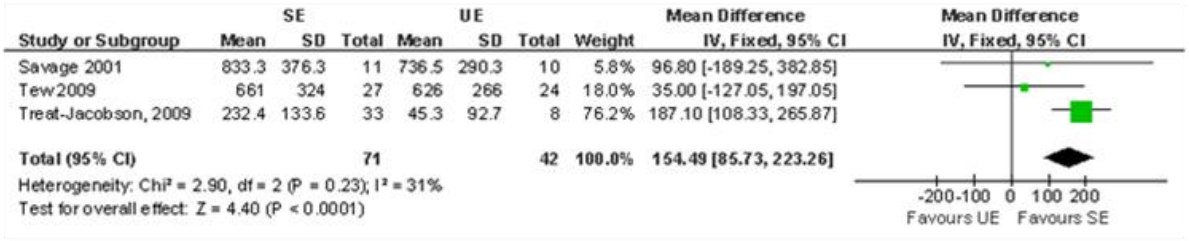


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Figure 59: Maximum walking distance at 6 months (combined end and change results)

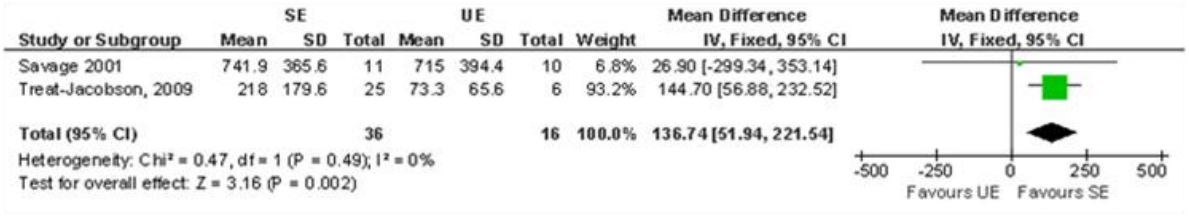

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Figure 60: Pain free walking distance at 3 months (combined end and change results)

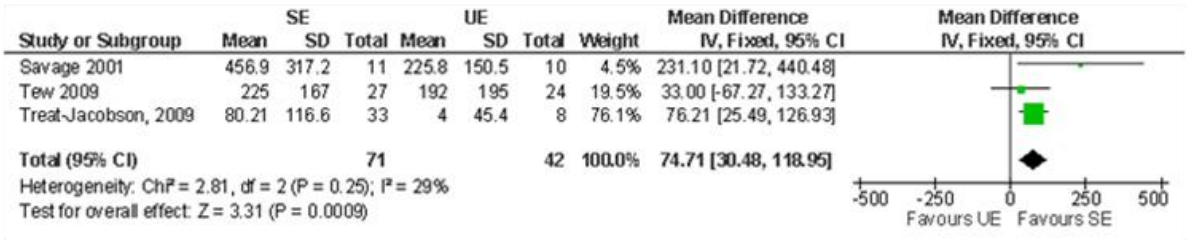

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Figure 61: Pain free walking distance at 6 months (combined change and end scores)

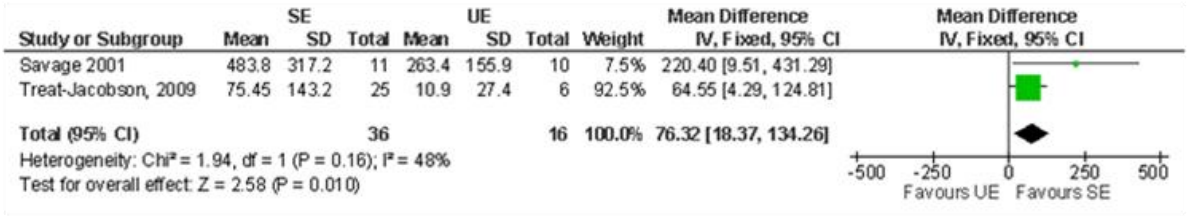

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Figure 62: Adverse events at 3 months

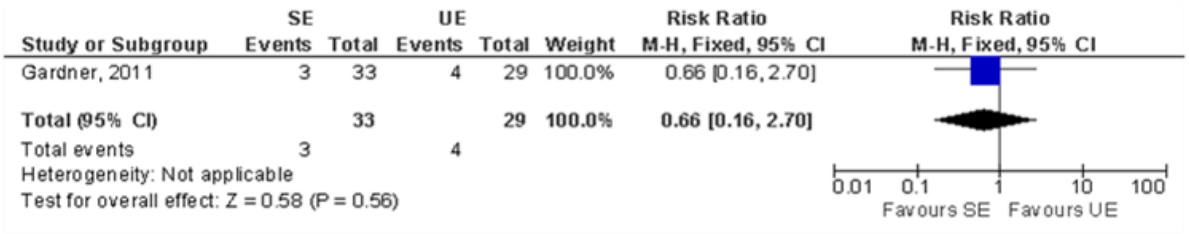

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Figure 63: Withdrawal at 3 months

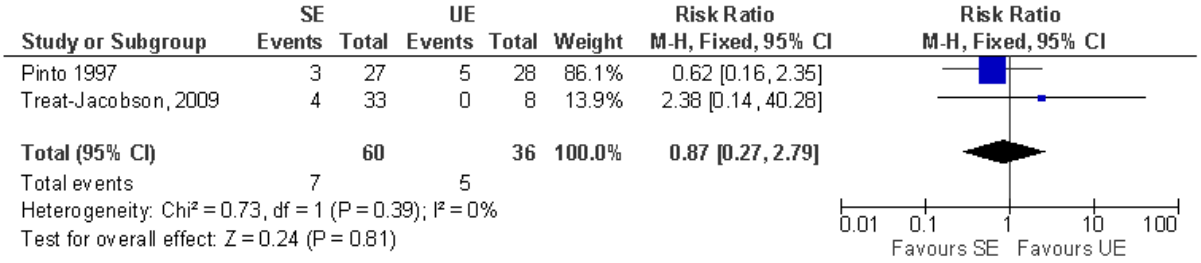

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Figure 64: Withdrawal at 6 months

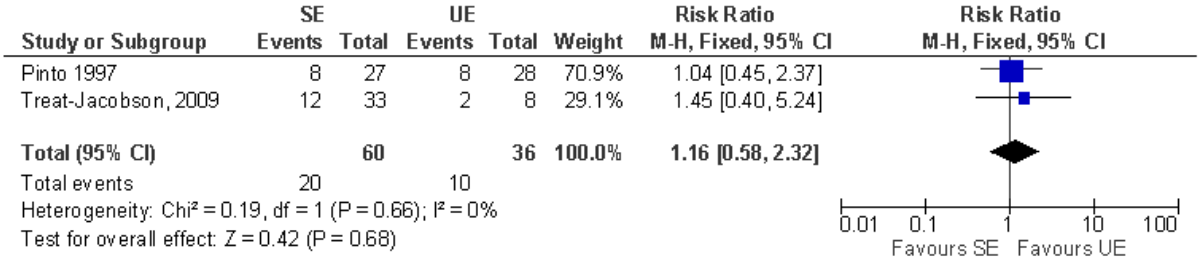

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Figure 65: Withdrawal at 1 year

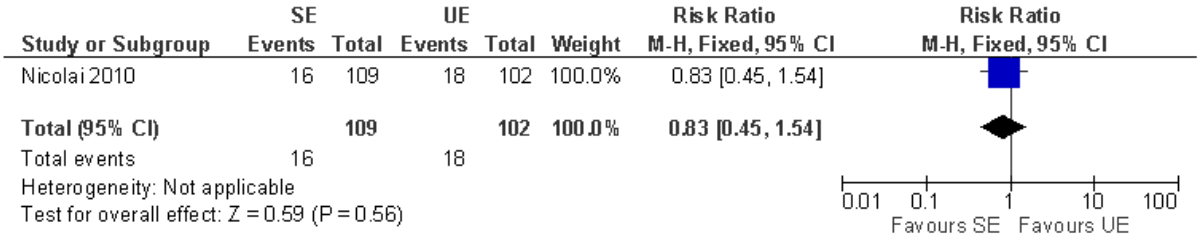

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Figure 66: ABPI at 3 months

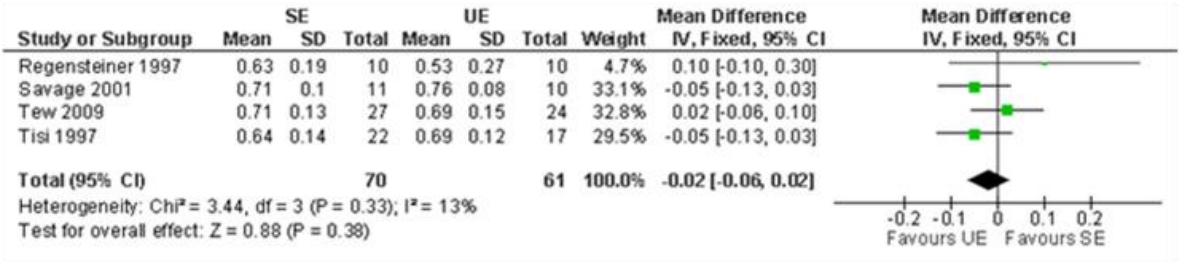

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Figure 67: ABPI at 6 months (random effects)

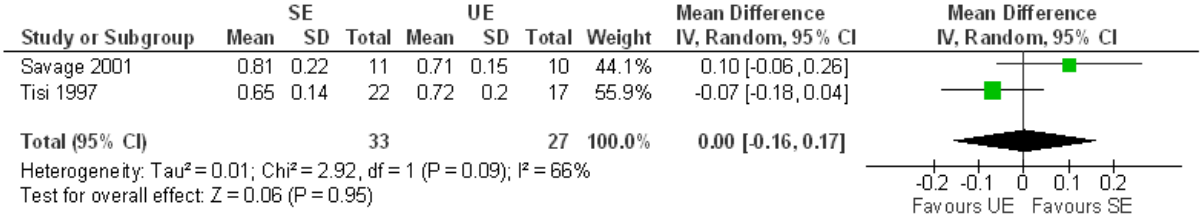

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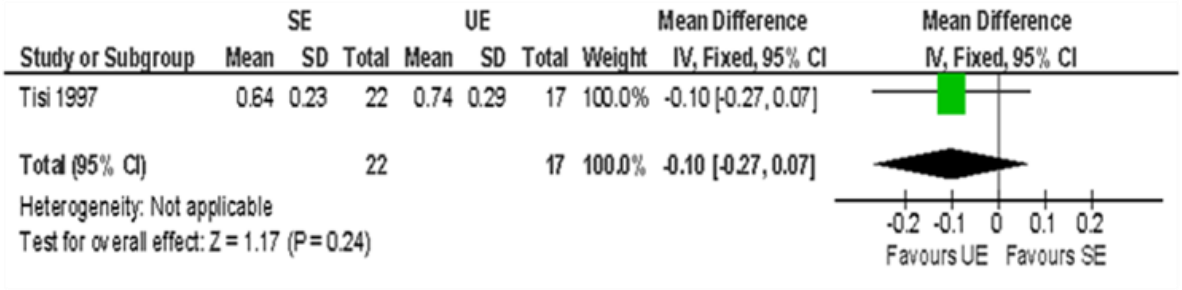
Figure 68: ABPI at 1 year



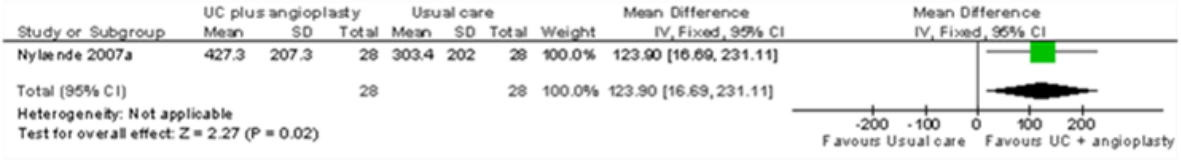
3

J.3.2 Comparisons of exercise, best medical treatment, angioplasty and bypass surgery

J.3.2.1 Best medical treatment compared to best medical treatment with angioplasty

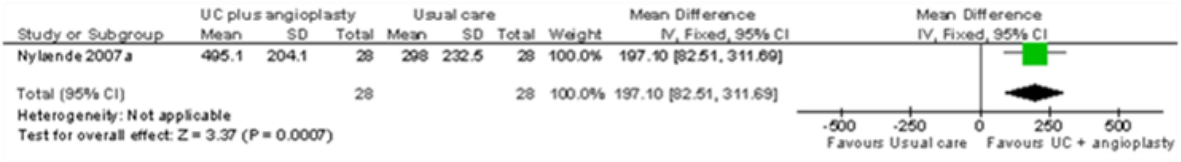
6 **Intermittent claudication due to femoro-popliteal and aorto-iliac disease**

Figure 69: Maximum walking distance at 3 months



7

Figure 70: Maximum walking distance at 1 year



1

Figure 71: Maximum walking distance at 2 years

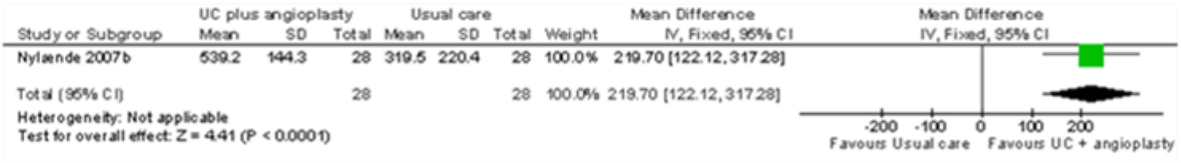


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Figure 72: Pain free walking distance at 3 months

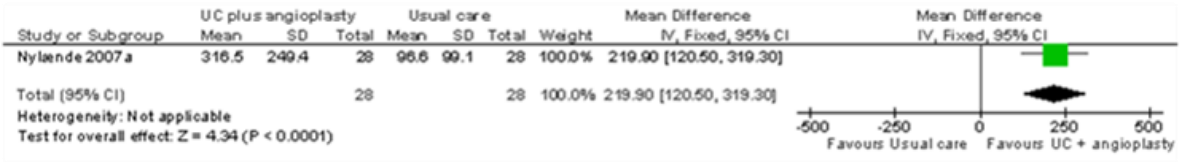

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Figure 73: Pain free walking distance at 1 year

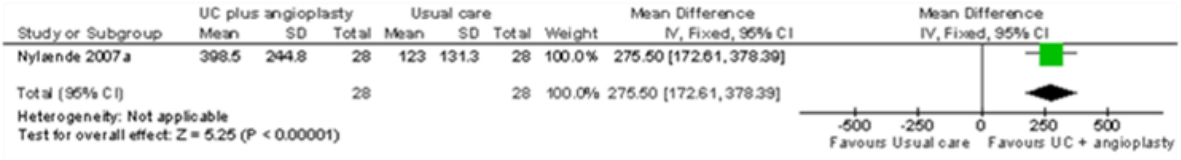

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Figure 74: Pain free walking distance at 2 years

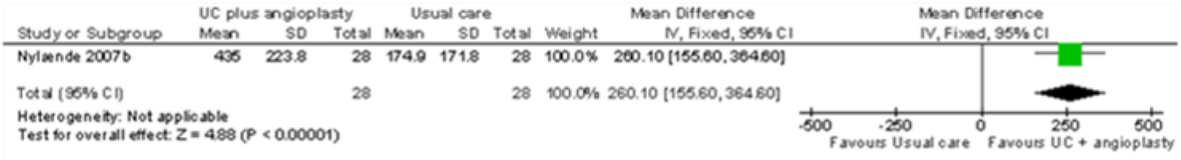

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Figure 75: ABPI at 3 months

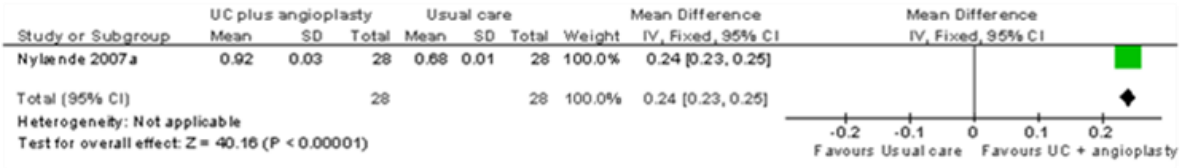

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Figure 76: ABPI at 1 year

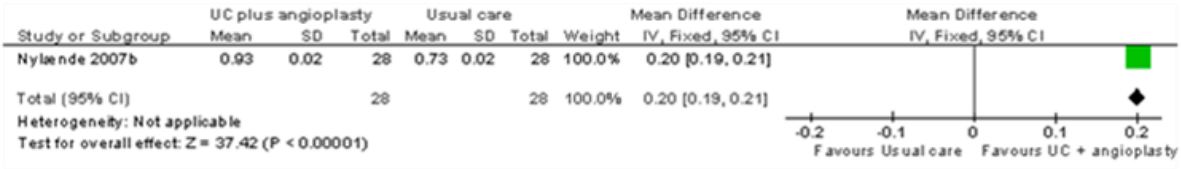

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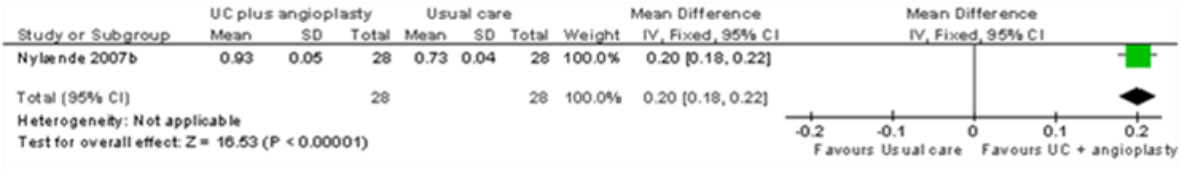
Figure 77: ABPI at 2 years



J.3.232 Intermittent claudication due to femoro-popliteal disease

Figure 78: Mortality at 2 years

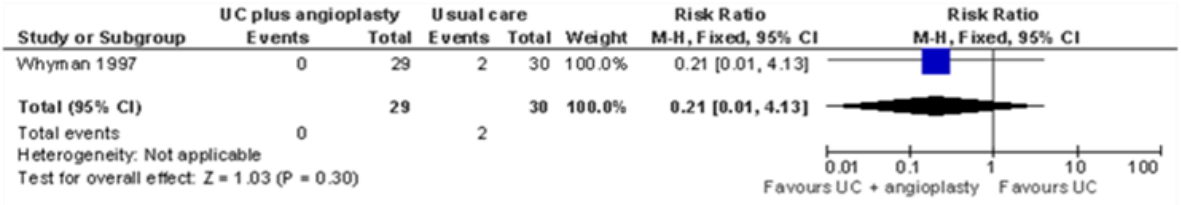


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Figure 79: ABPI at 6 months

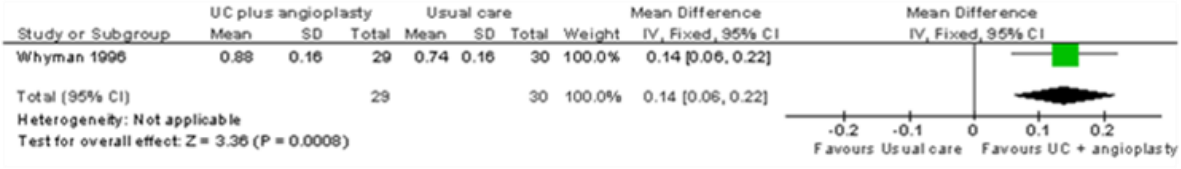

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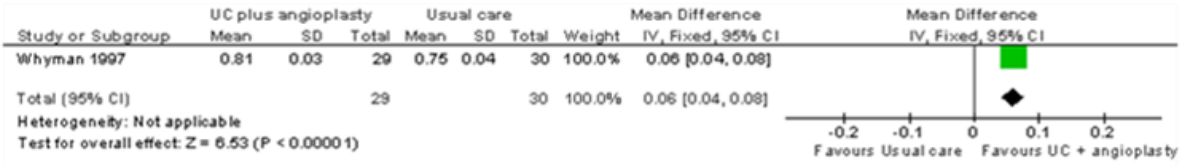
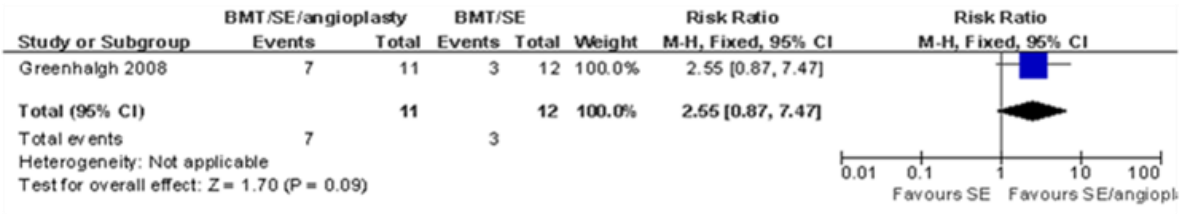
Figure 80: ABPI at 2 years



J.3.213 Supervised exercise with best medical treatment compared to supervised exercise, best medical 2 treatment and angioplasty

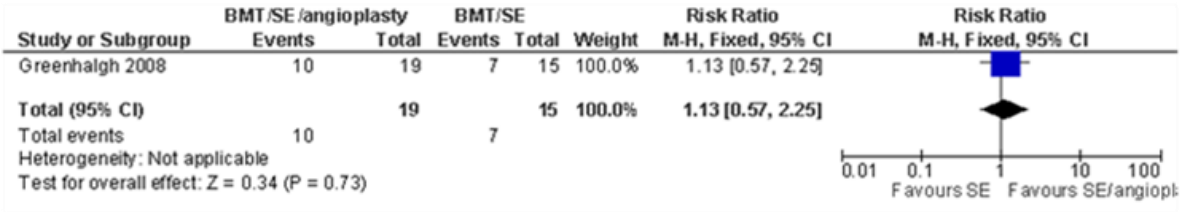
3 Intermittent claudication due to aorto-iliac disease

Figure 81: Pain free walking distance (% people who attained 200m without pain) at 2 years



4

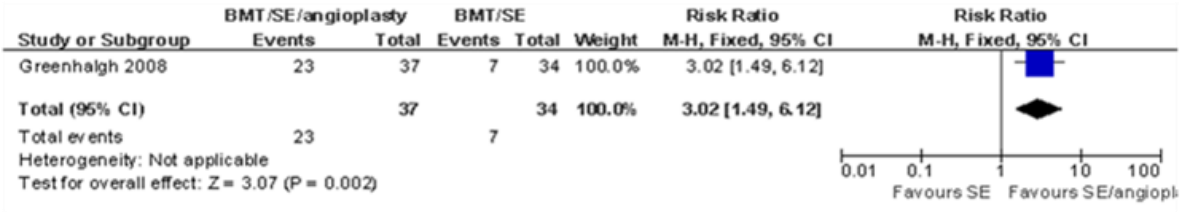
Figure 82: Compliance with an exercise programme



Source:

5 Intermittent claudication due to femoro-popliteal disease

Figure 83: Pain free walking distance (% people who attained 200m without pain) at 2 years



6

Figure 84: Compliance with an exercise programme

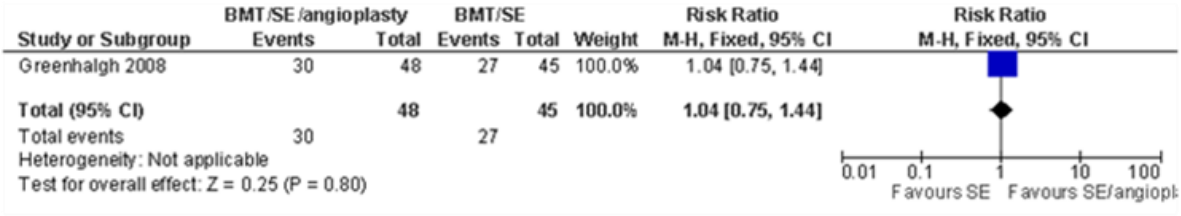


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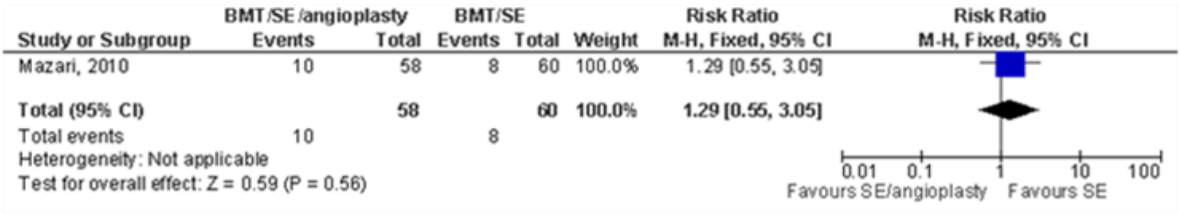
Figure 85: Withdrawal at 3 months

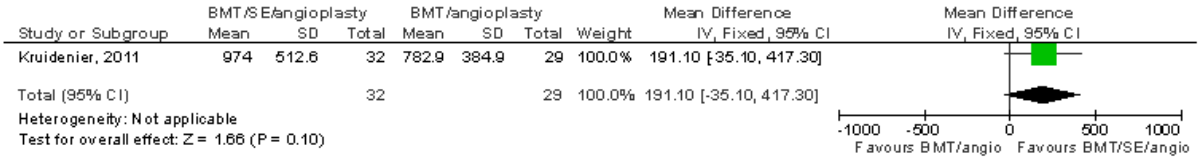


J.3.224 Best medical treatment with angioplasty compared to best medical treatment with angioplasty and supervised exercise

3

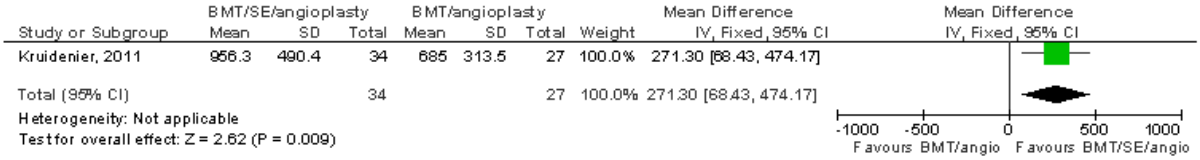
4 **Intermittent claudication due to aorto-iliac disease**

Figure 86: Maximum walking distance at 3 months



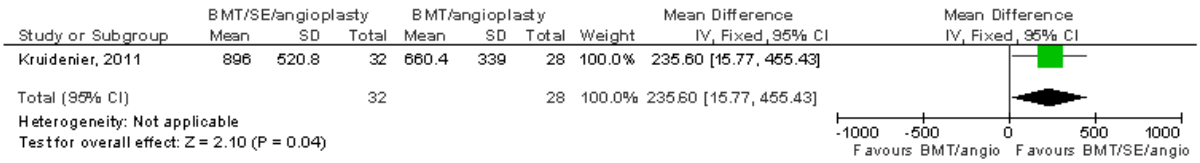
5

Figure 87: Maximum walking distance at 6 months



6

Figure 88: Pain free walking distance at 3 months



1

Figure 89: Pain free walking distance at 6 months

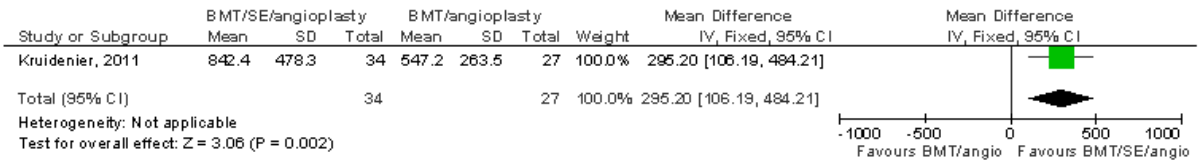


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Figure 90: Major adverse events at 6 months

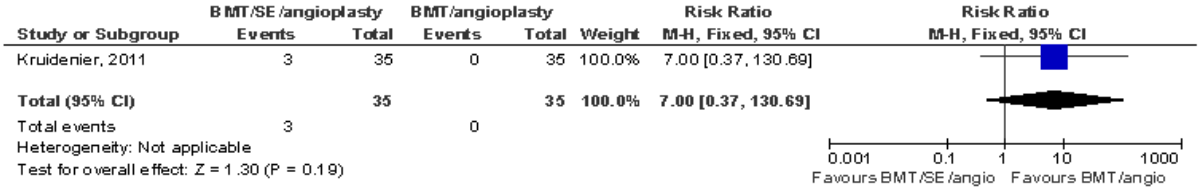

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Figure 91: Re-intervention at 12 months

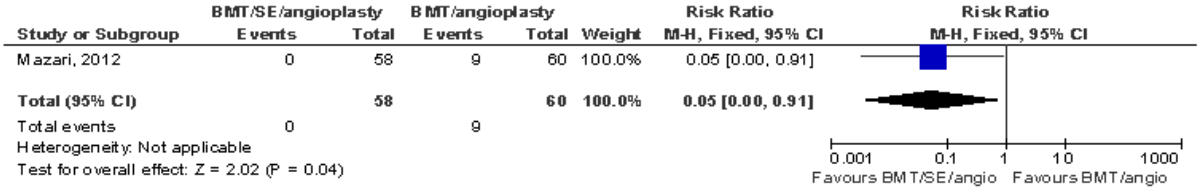

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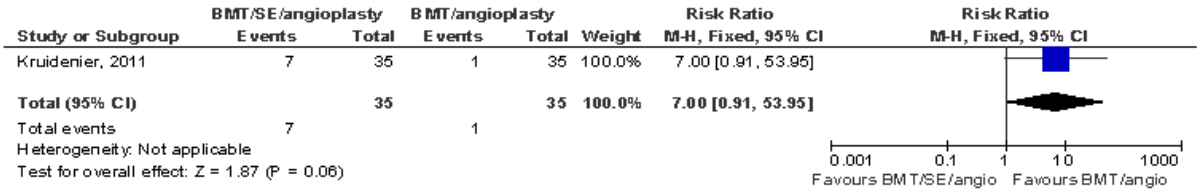
Figure 92: Withdrawal from treatment at 6 months



J.3.255 Angioplasty compared to supervised exercise

6 **Intermittent claudication due to aorto-iliac disease**

Figure 93: Maximum walking distance from baseline at 6 months

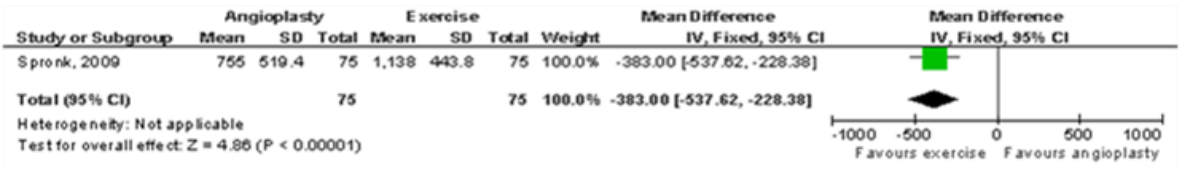
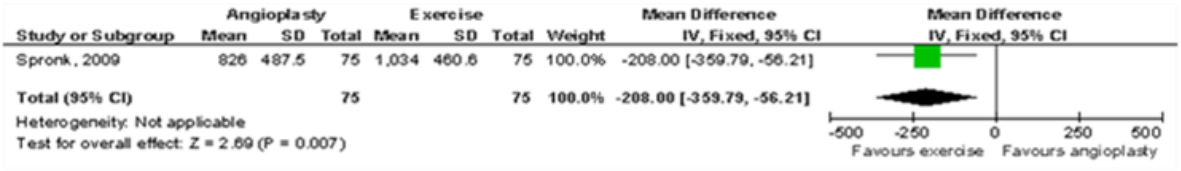
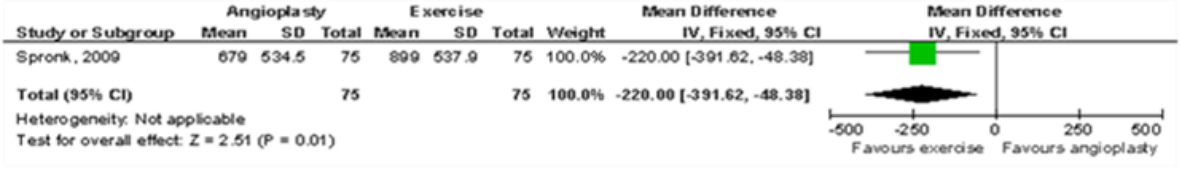


Figure 94: Maximum walking distance from baseline at 1 year



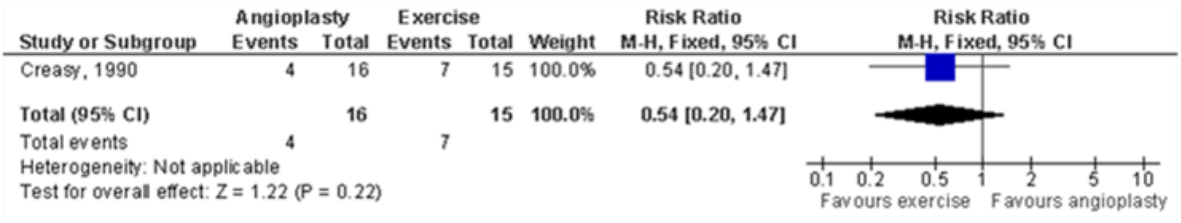
1

Figure 95: Pain free walking distance from baseline at 1 year



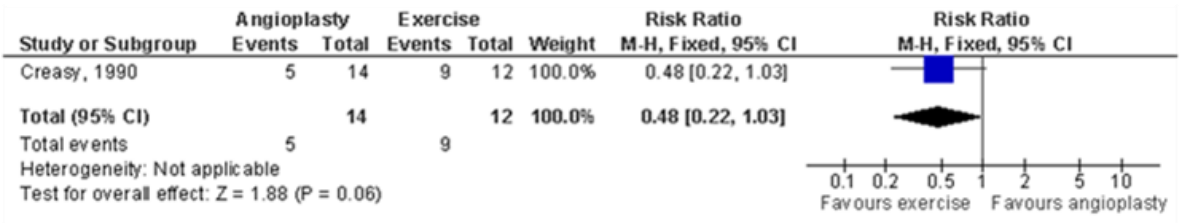
2

Figure 96: Number of people who doubled their maximum walking distance at 3 months



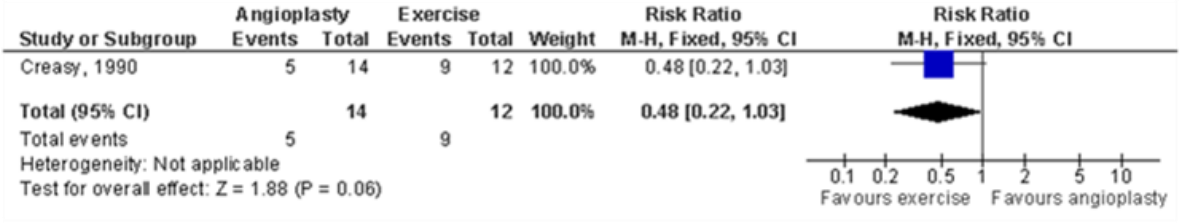
3

Figure 97: Number of people who doubled their maximum walking distance at 6 months



4

Figure 98: Number of people who doubled their maximum walking distance at 9 months



1

Figure 99: Number of people who doubled their maximum walking distance at 1 year

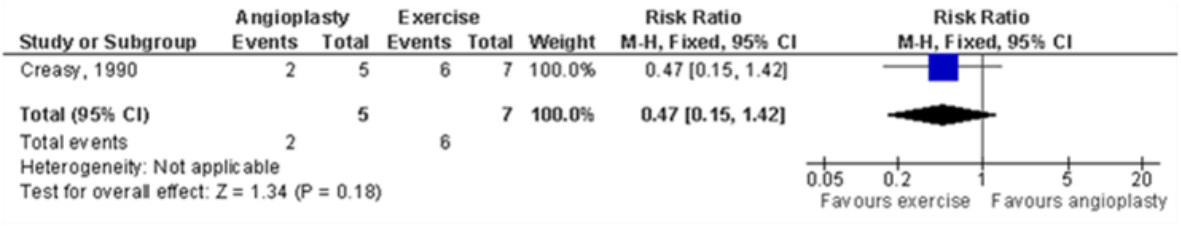


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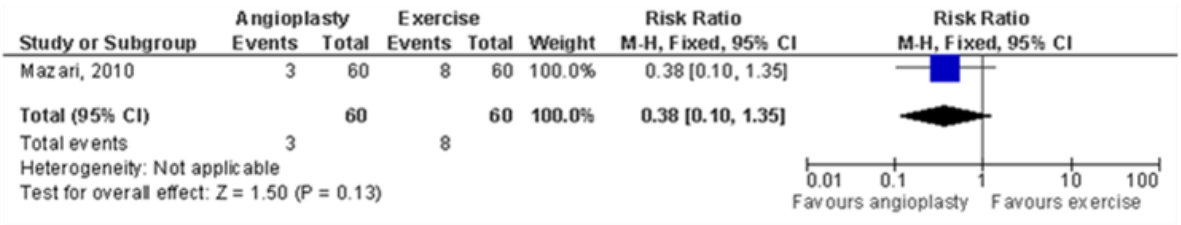
Figure 100: Withdrawal at 3 months



3

Figure 101: ABPI at rest from baseline at 6 months

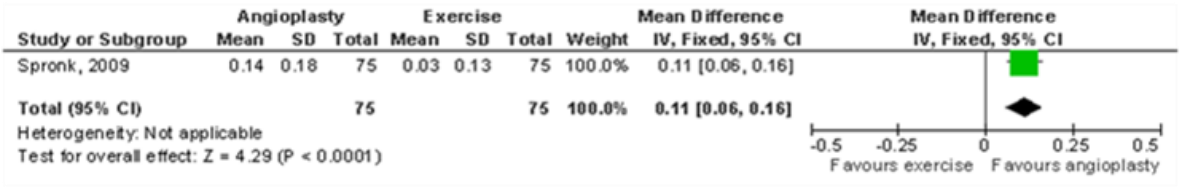


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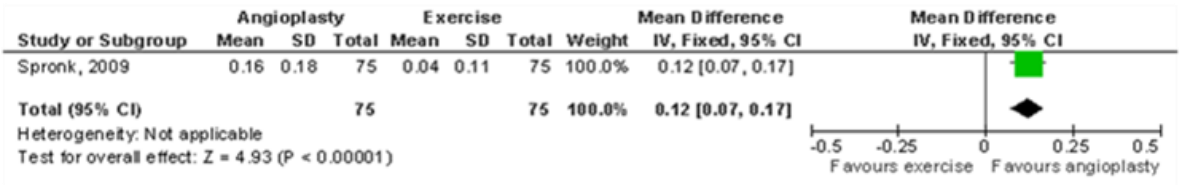
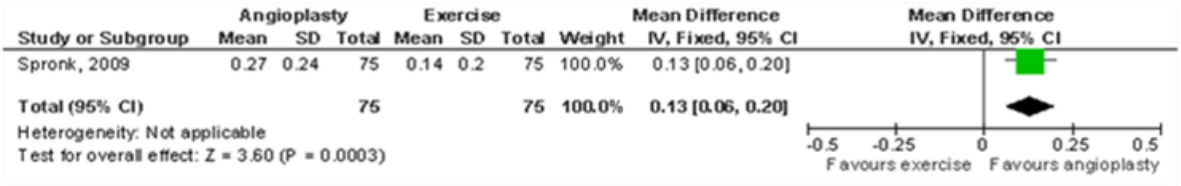
Figure 102: ABPI at rest from baseline at 1 year



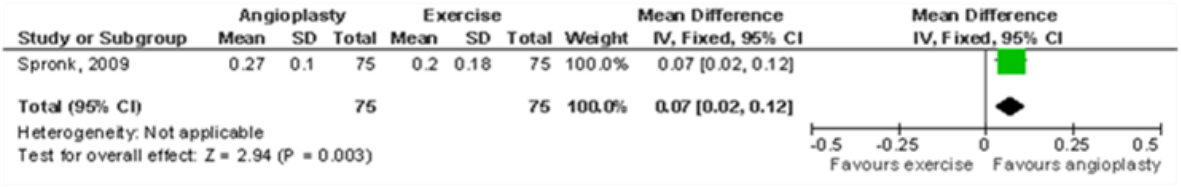
5

Figure 103: ABPI after exercise from baseline at 6 months



1

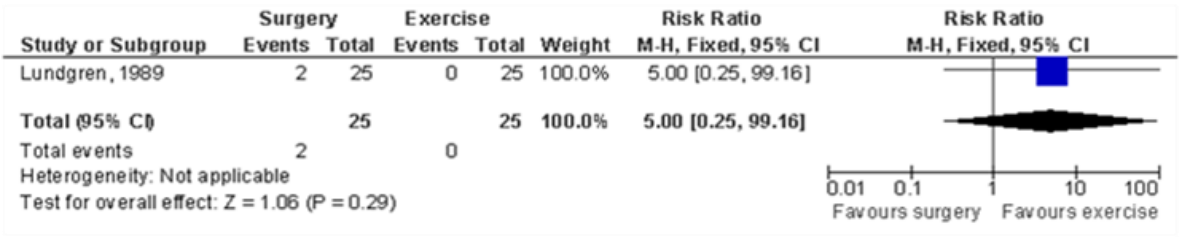
Figure 104: ABPI after exercise from baseline at 1 year



J.3.226 Bypass surgery compared to supervised exercise

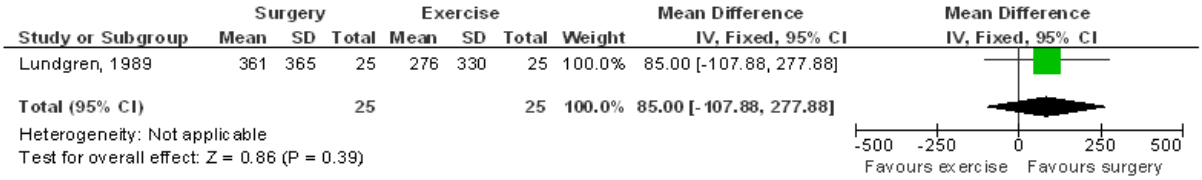
3 **Intermittent claudication due to aorto-iliac and femoro-popliteal disease**

Figure 105: Mortality at 1 year



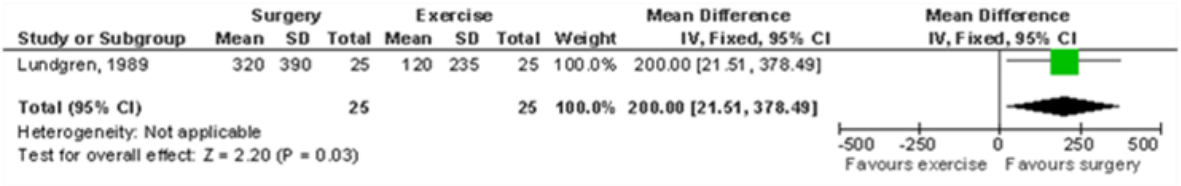
4

Figure 106: Maximum walking distance from baseline at 1 year



5

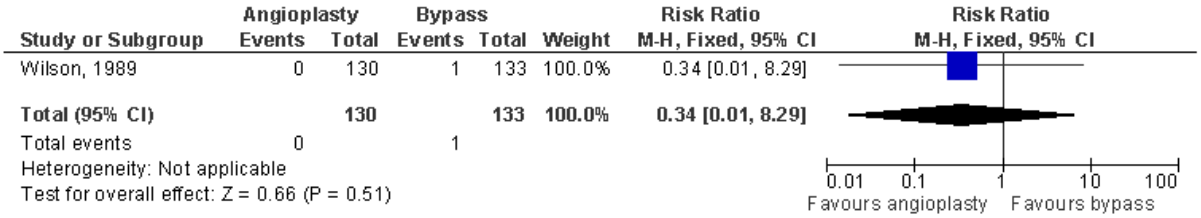
Figure 107: Pain free walking distance from baseline at 1 year



J.3.3 Angioplasty compared to bypass surgery

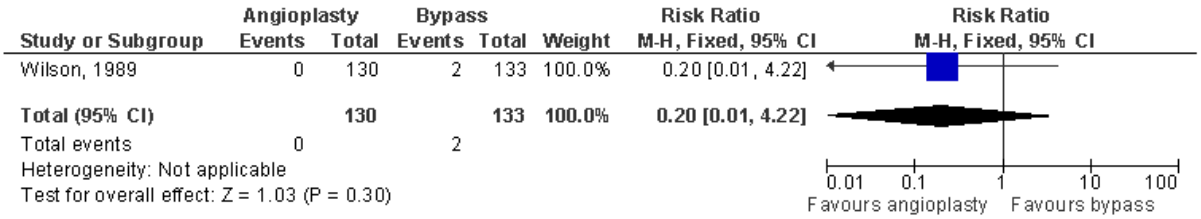
J.3.3.1 Intermittent claudication due to aorto-iliac disease

Figure 108: Mortality at 30 days



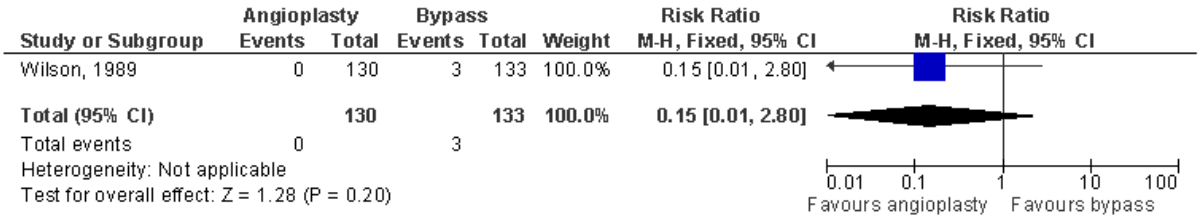
3

Figure 109: Mortality at 3 months



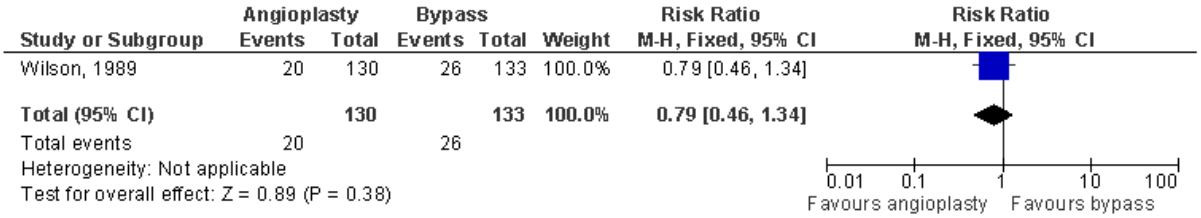
4

Figure 110: Mortality at 1 year



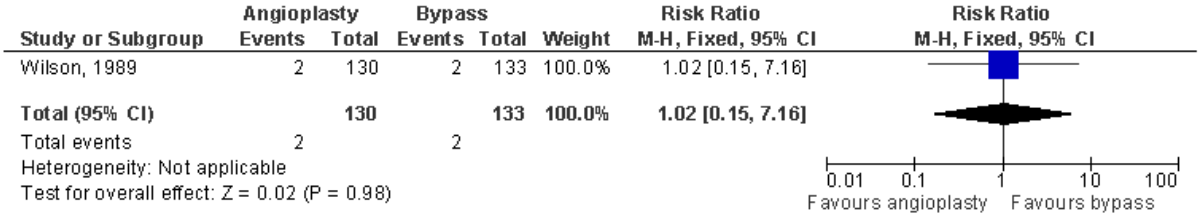
5

Figure 111: Mortality at 2 years



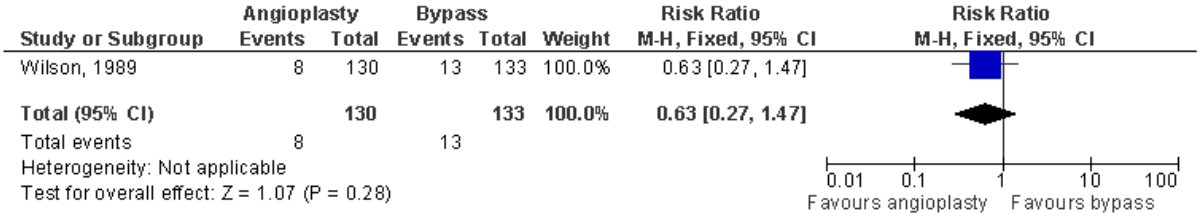
1

Figure 112: Amputation post procedure



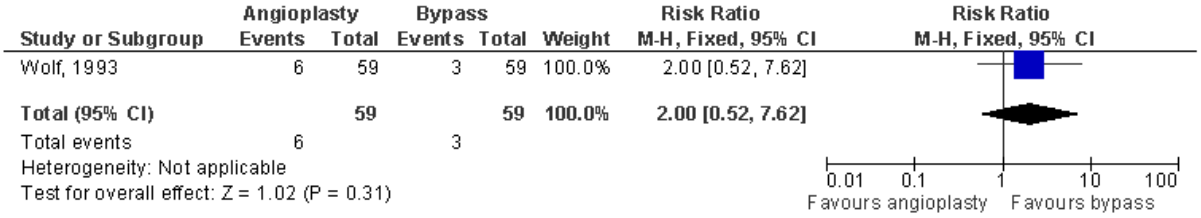
2

Figure 113: Amputation at 2 years



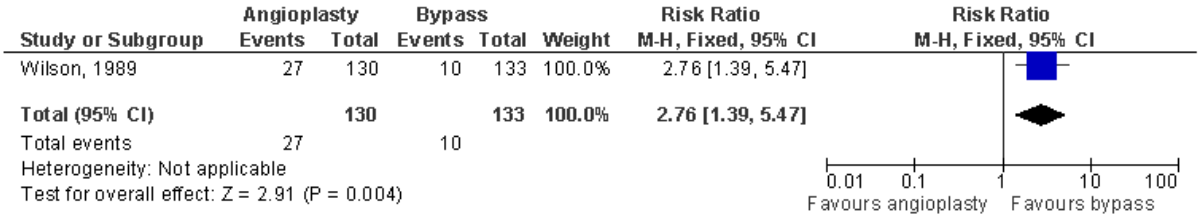
3

Figure 114: Amputation at 4 years



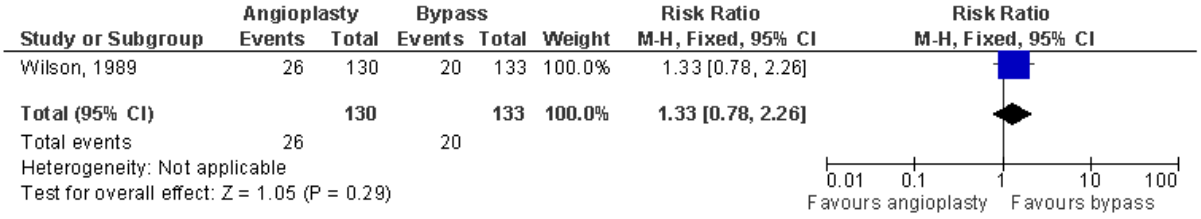
4

Figure 115: Complications post procedure



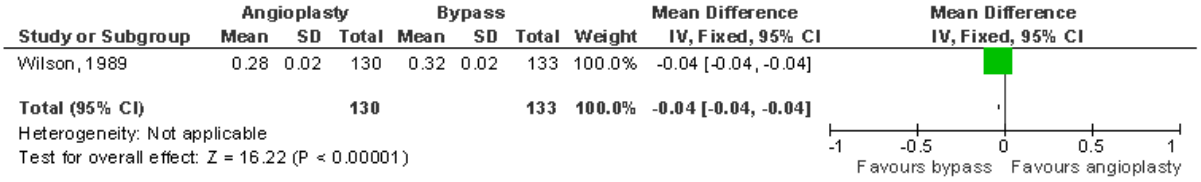
1

Figure 116: Re-intervention at 2 years



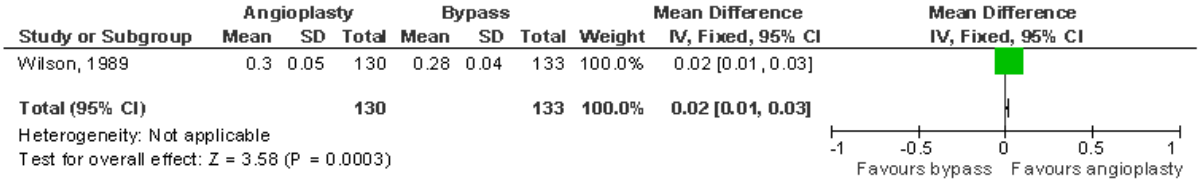
2

Figure 117: ABPI after treatment (no specific time point)



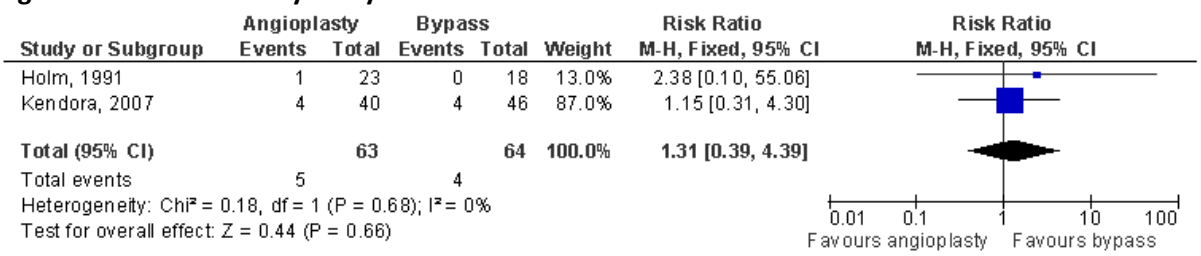
3

Figure 118: ABPI at 3 years



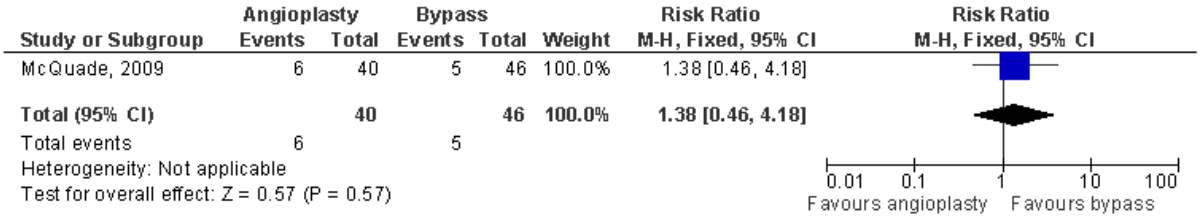
J.3.342 Intermittent claudication due to femoro-popliteal disease

Figure 119: Mortality at 1 year



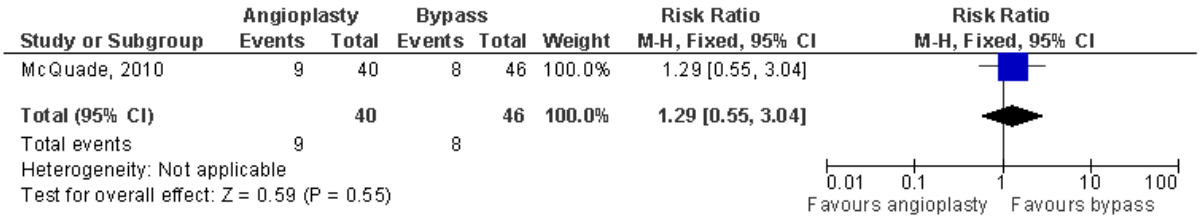
1

Figure 120: Mortality at 2 years



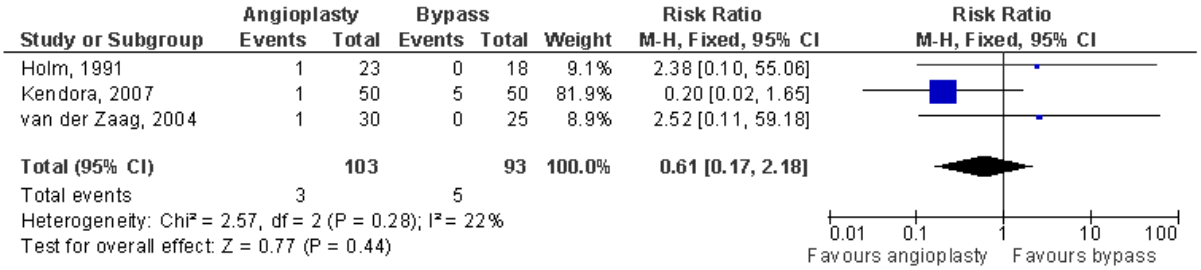
2

Figure 121: Mortality at 4 years



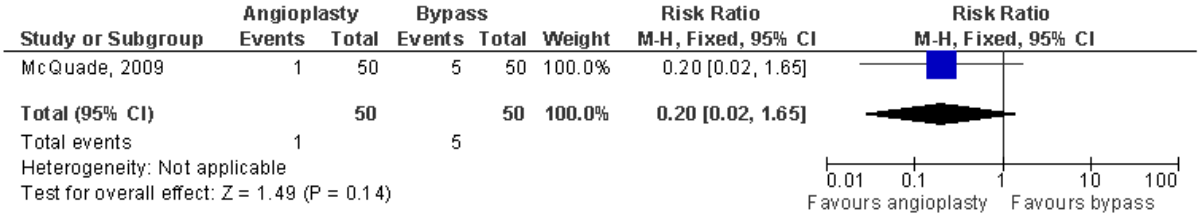
3

Figure 122: Amputation at 1 year



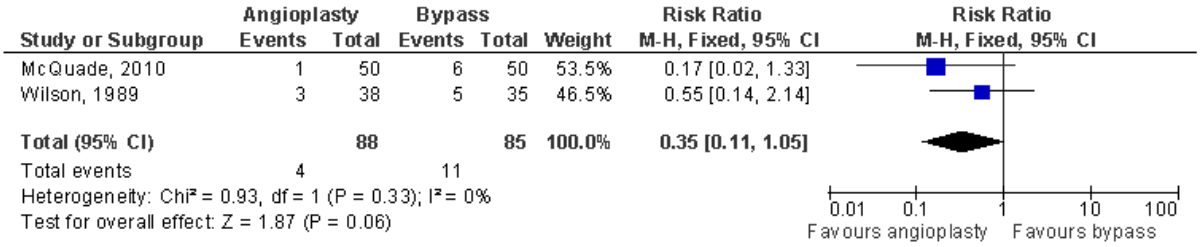
4

Figure 123: Amputation at 2 years



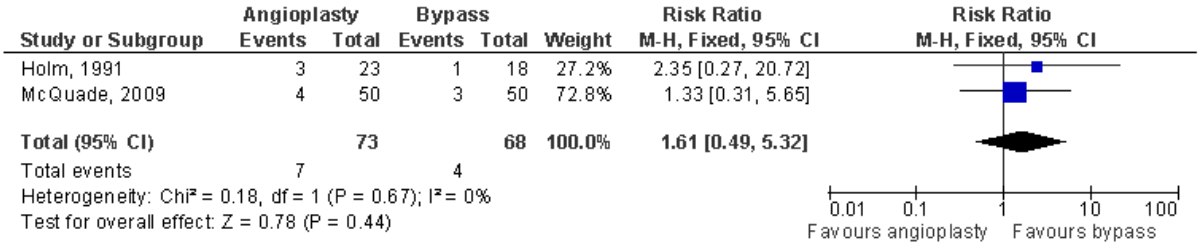
5

Figure 124: Amputation at 4 years



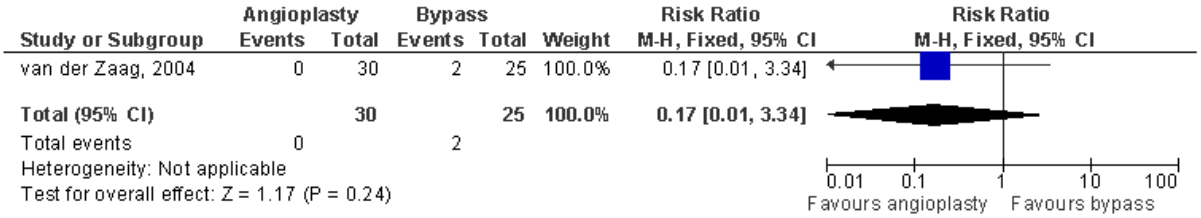
1

Figure 125: Minor complications post procedure



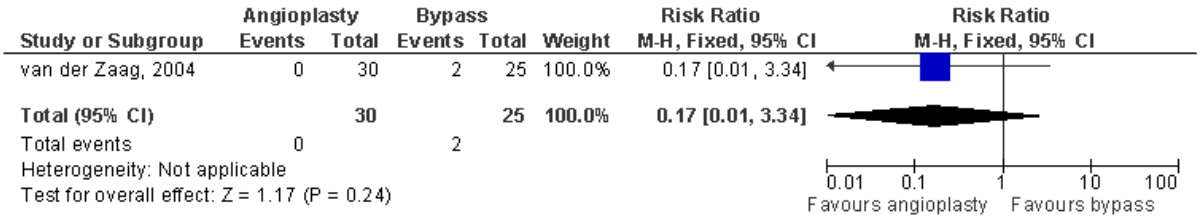
2

Figure 126: Major adverse events at 1 year



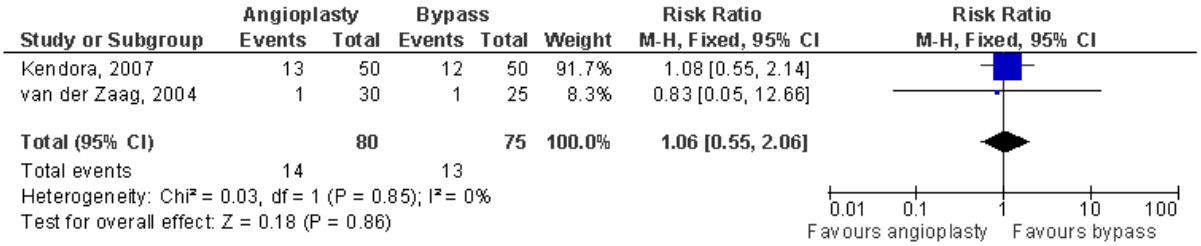
3

Figure 127: Minor adverse events at 1 year



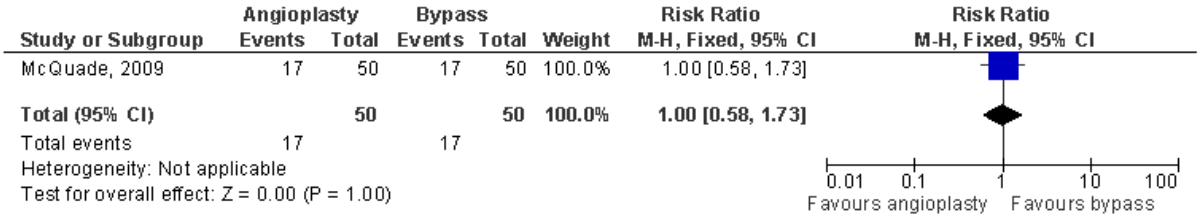
4

Figure 128: Re-intervention at 1 year



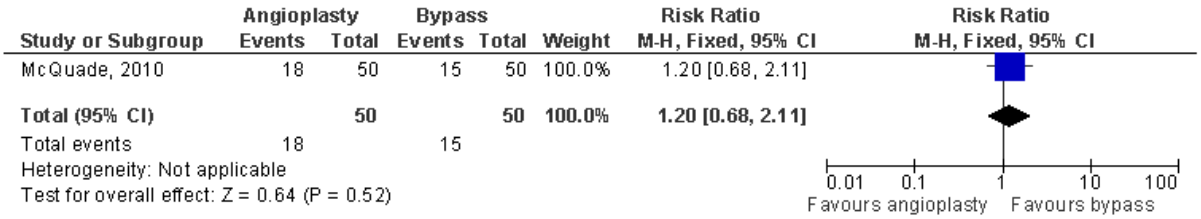
1

Figure 129: Re-intervention at 2 years



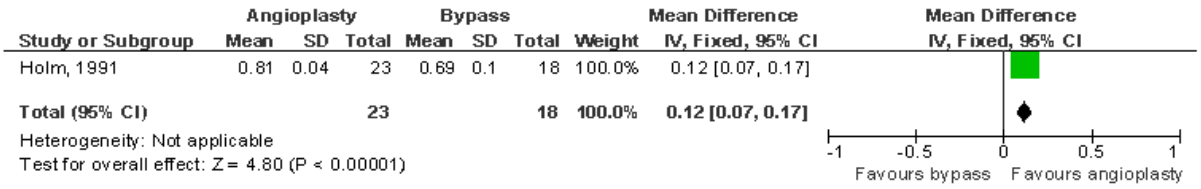
2

Figure 130: Re-intervention at 4 years



3

Figure 131: ABPI at 1 year



J.3.4 Angioplasty with selective stent placement compared angioplasty with primary stent placement

J.3.4.1 Intermittent claudication due to aorto-iliac disease – person randomised

Figure 132: Mortality at 1 year

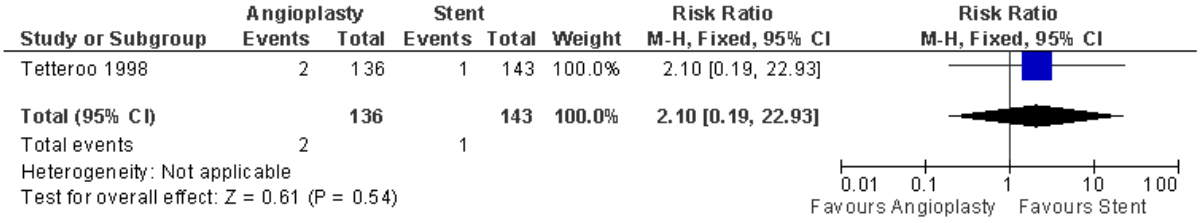


Figure 133: Mortality at 2 years

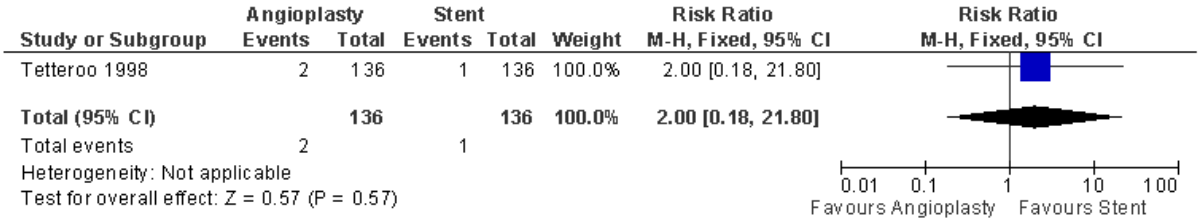


Figure 134: Mortality at 5 years

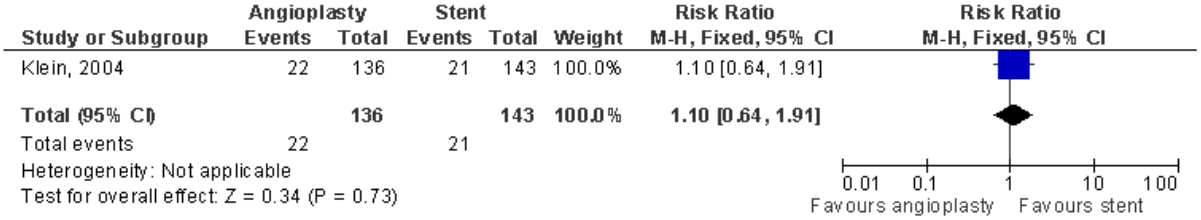


Figure 135: Amputation at 5 years

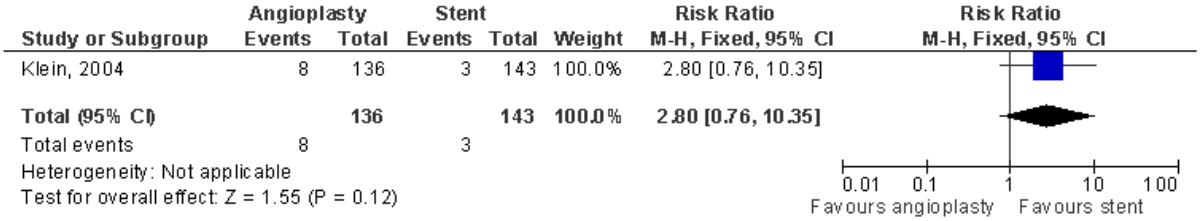
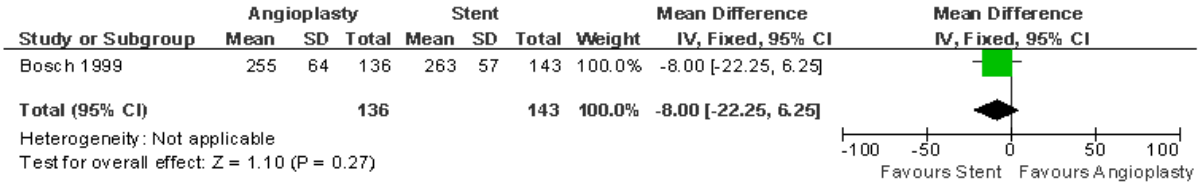
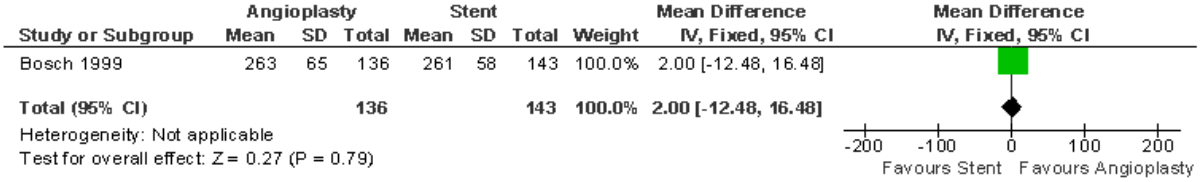


Figure 136: Maximum walking distance at 3 months



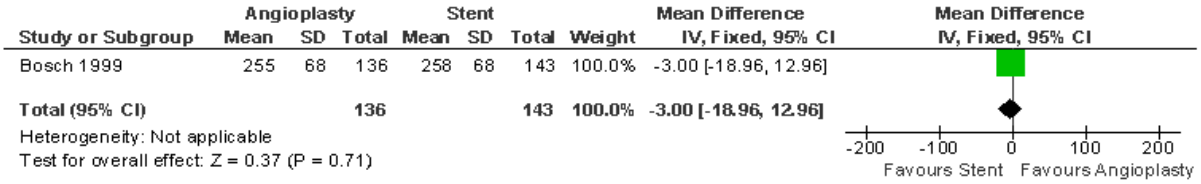
1

Figure 137: Maximum walking distance at 1 year



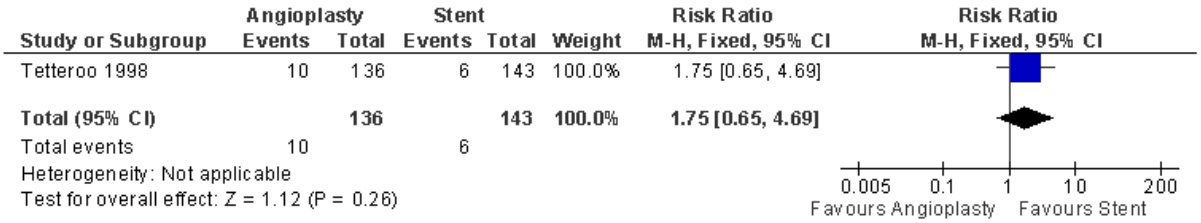
2

Figure 138: Maximum walking distance at 2 years



3

Figure 139: Adverse events at 30 days



4

Figure 140: Re-intervention at 3 months

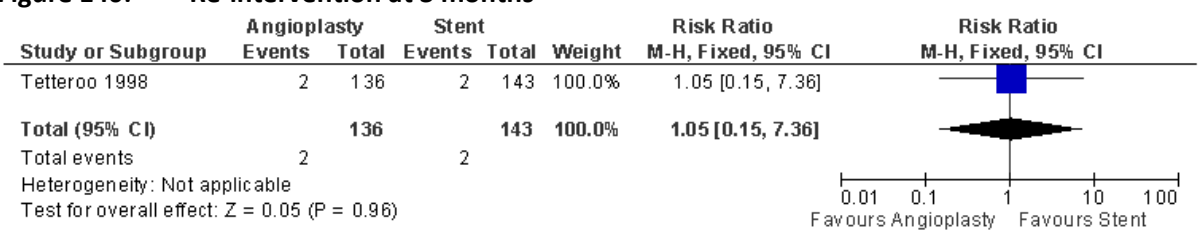
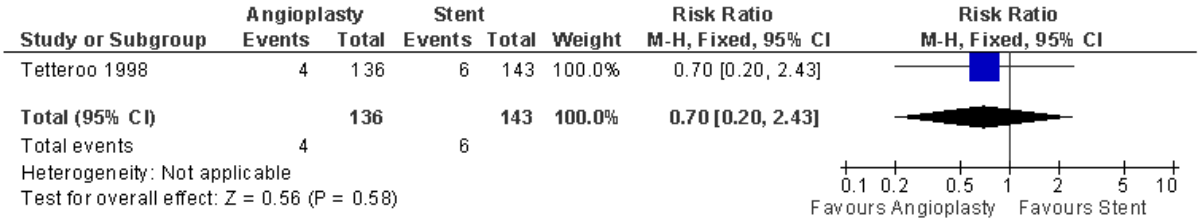
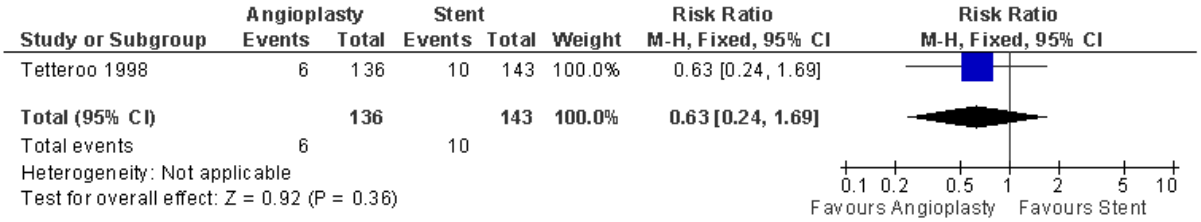


Figure 141: Re-intervention at 1 year



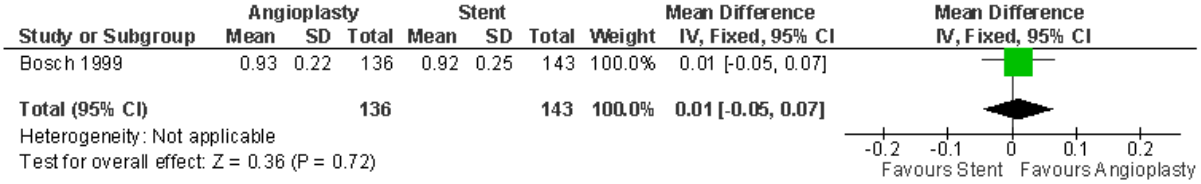
1

Figure 142: Re-intervention at 2 years



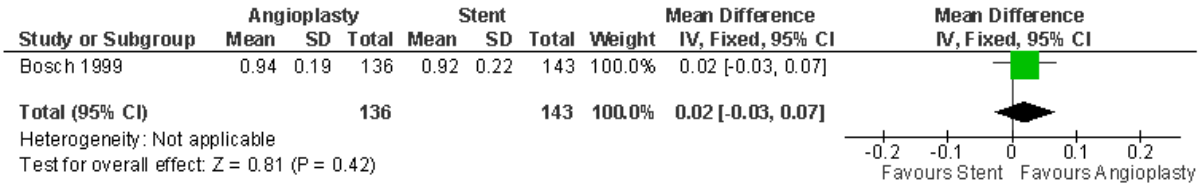
2

Figure 143: ABPI at 3 months



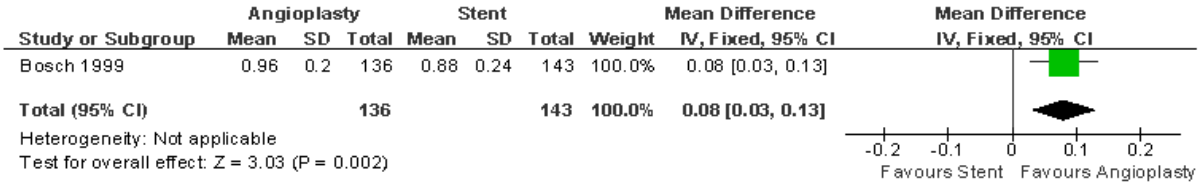
3

Figure 144: ABPI at 1 year



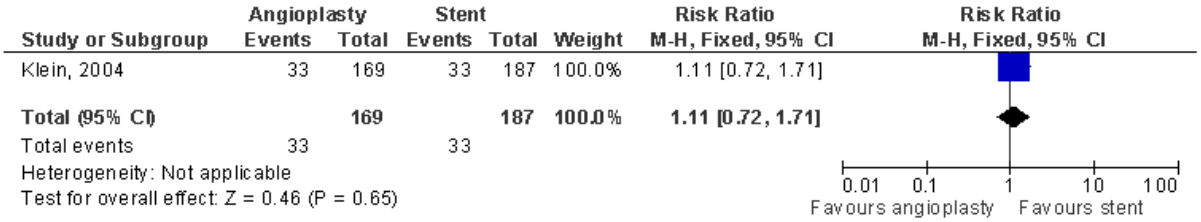
4

Figure 145: ABPI at 2 years



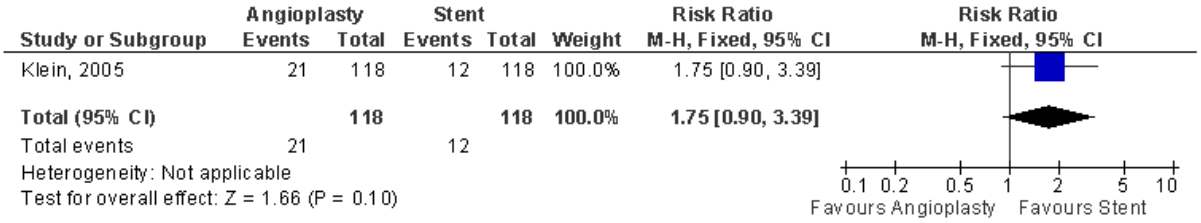
J.3.412 Intermittent claudication due to aorto-iliac disease (limb/lesion randomised)

Figure 146: Re-intervention at 5 years



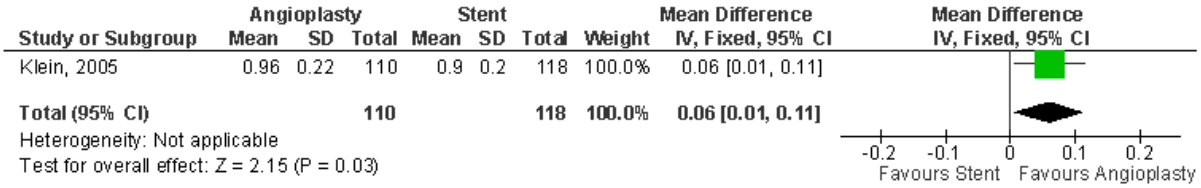
2

Figure 147: Re-intervention at 6 to 8 years



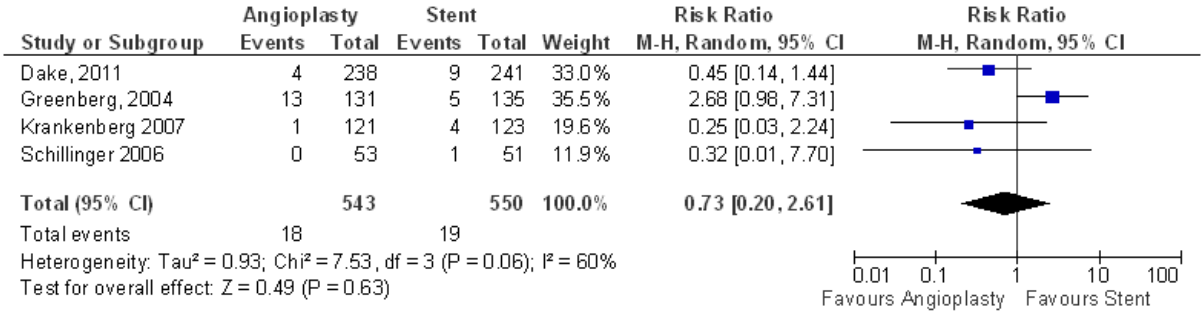
3

Figure 148: ABPI at 6 to 8 years



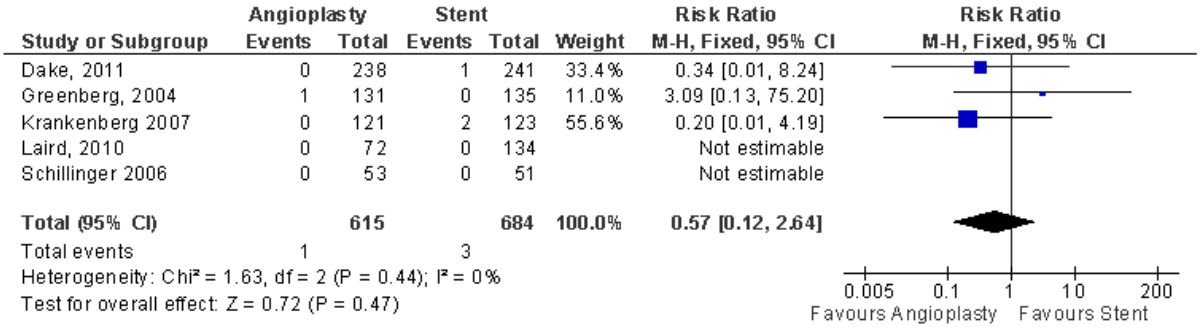
J.3.413 Intermittent claudication due to femoro-popliteal disease (person randomised)

Figure 149: Mortality at 1 year (random effects)



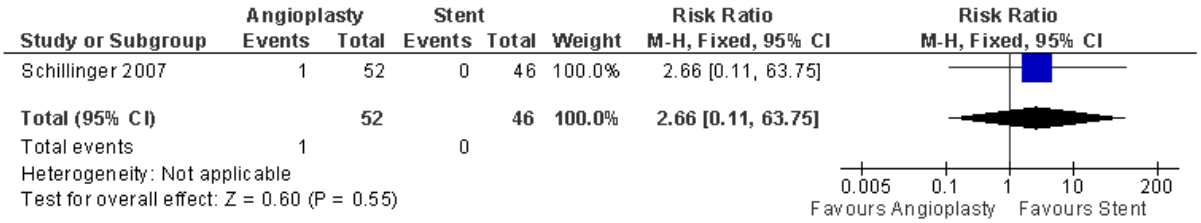
2

Figure 150: Amputation at 1 year



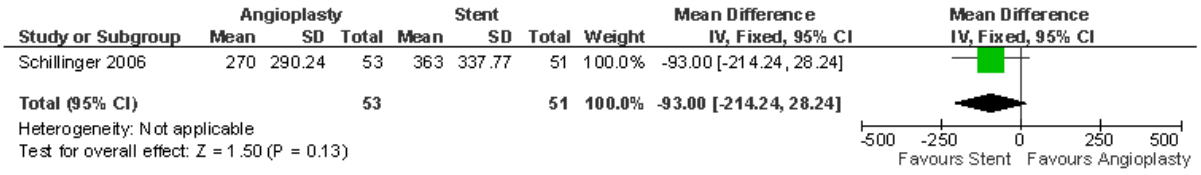
3

Figure 151: Amputation at 2 years



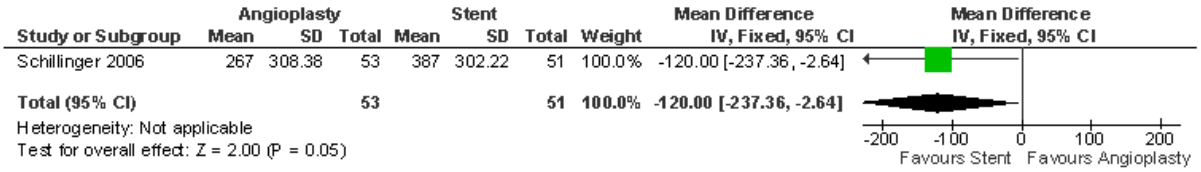
4

Figure 152: Maximum walking distance at 6 months



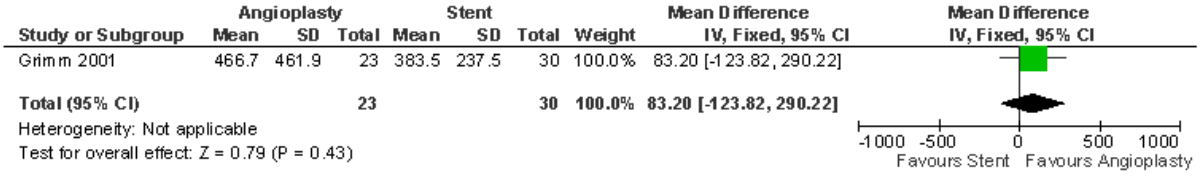
5

Figure 153: Maximum walking distance at 1 year



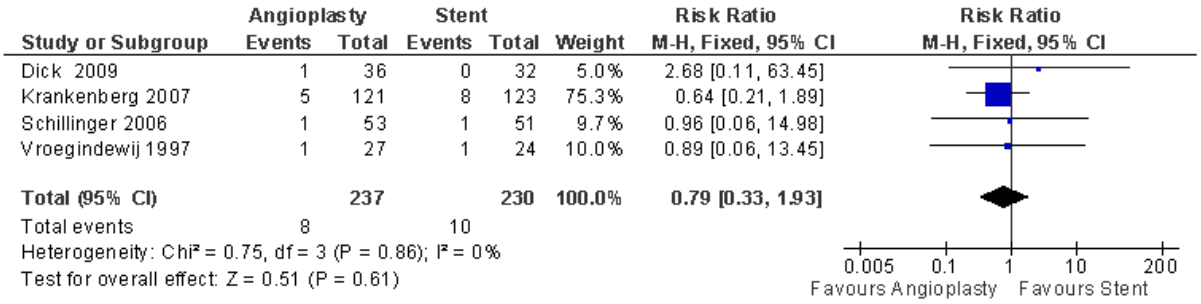
1

Figure 154: Pain free walking distance at 30 days



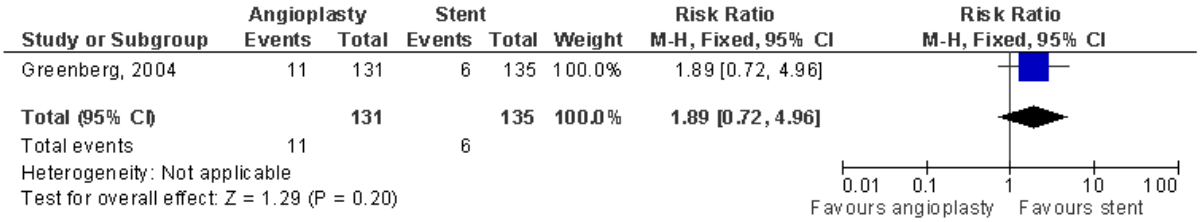
2

Figure 155: Major adverse events at 30 days



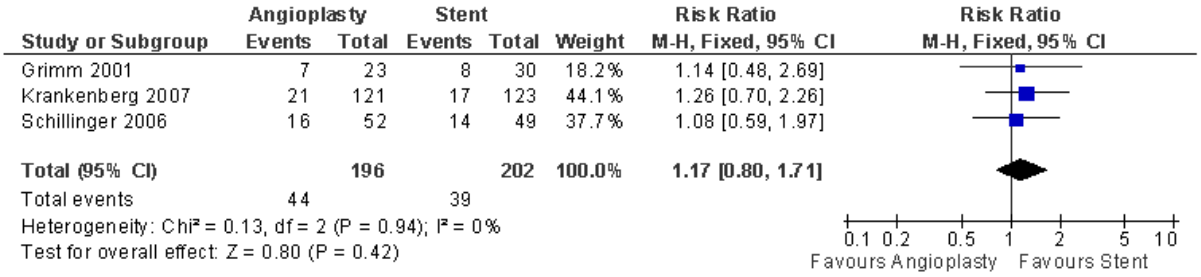
3

Figure 156: Major adverse events at 1 year



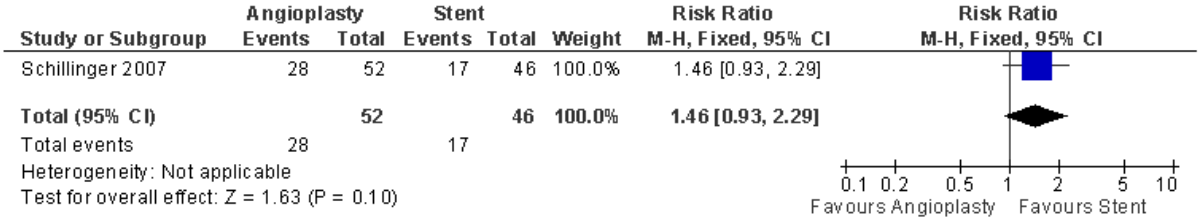
4

Figure 157: Re-intervention at 1 year



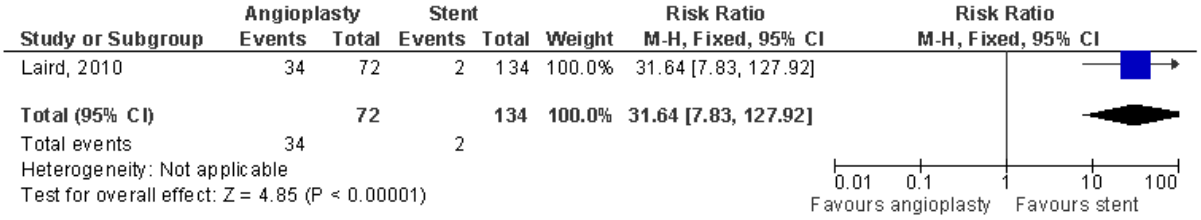
1

Figure 158: Re-intervention at 2 years



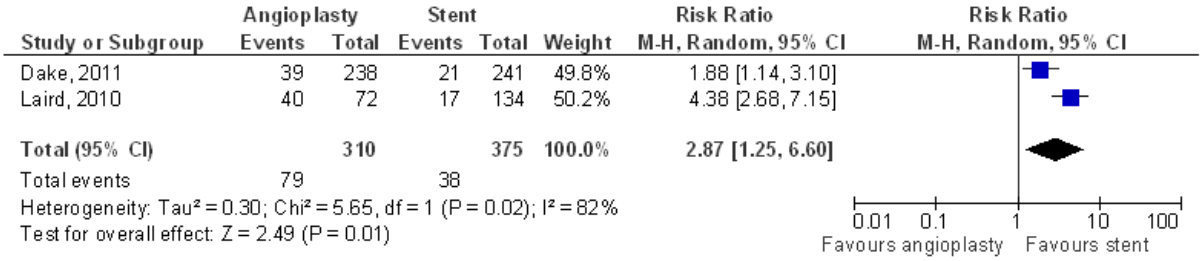
2

Figure 159: Target lesion revascularisation at 6 months



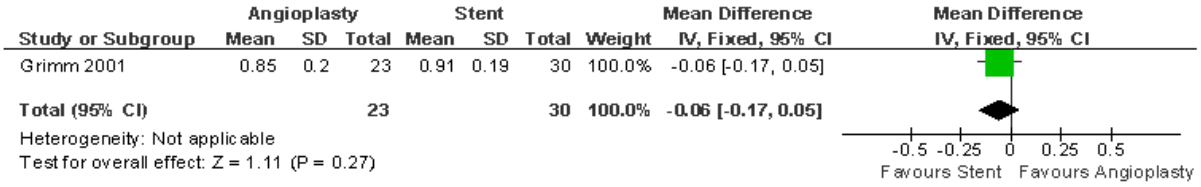
3

Figure 160: Target lesion revascularisation at 1 years (random effects)



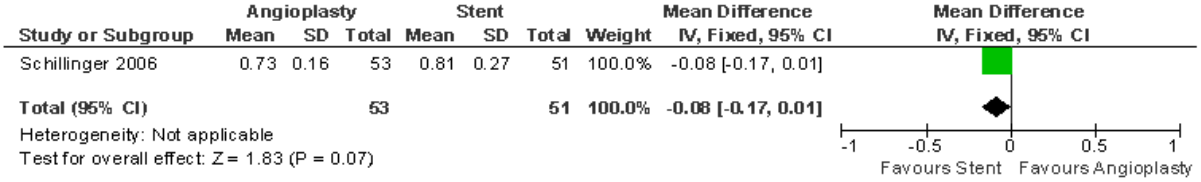
4

Figure 161: ABPI at 30 days



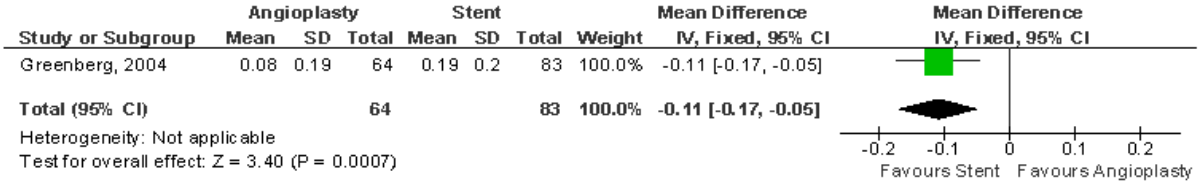
1

Figure 162: ABPI at 6 months



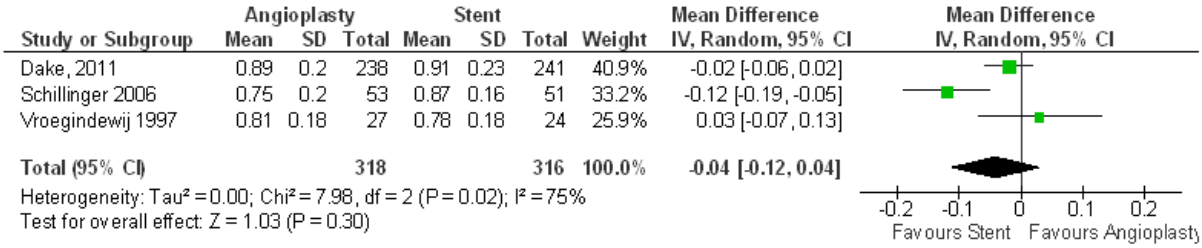
2

Figure 163: ABPI at 9 months



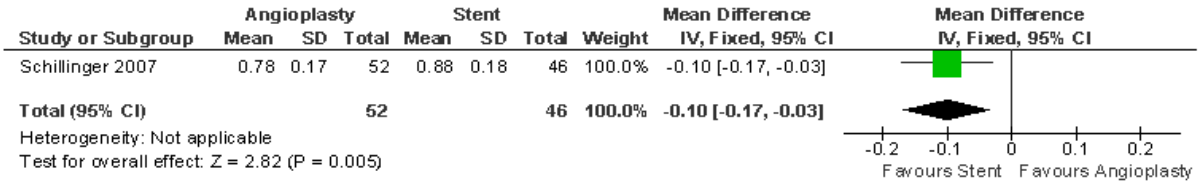
3

Figure 164: ABPI at 1 year (random effects)



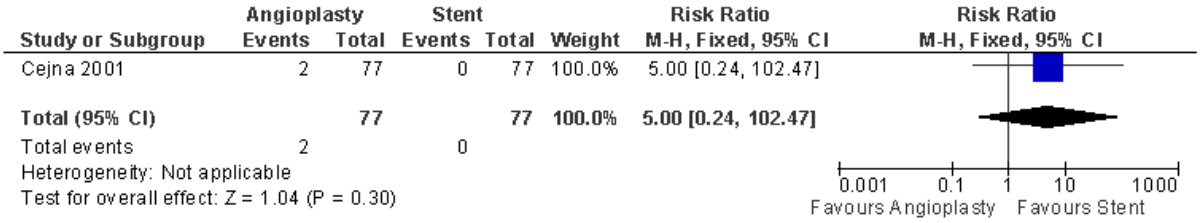
4

Figure 165: ABPI at 2 years



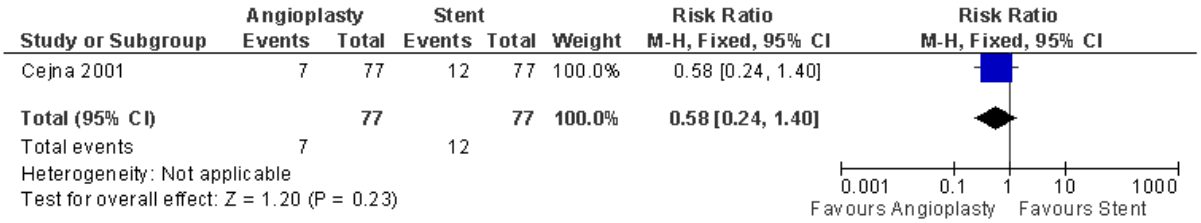
J.3.414 Intermittent claudication for femoro-popliteal disease (limb/lesion randomised)

Figure 166: Mortality at 30 days



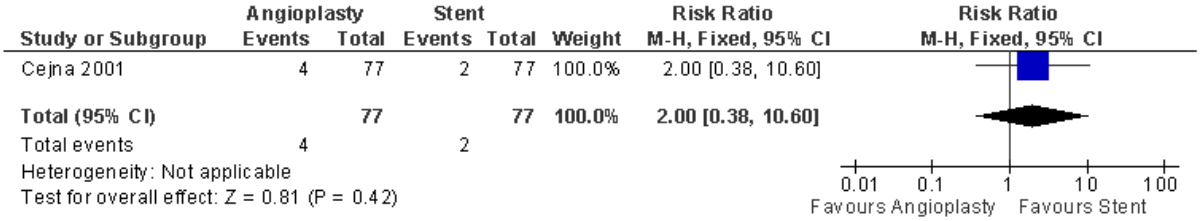
2

Figure 167: Morality at 1 year



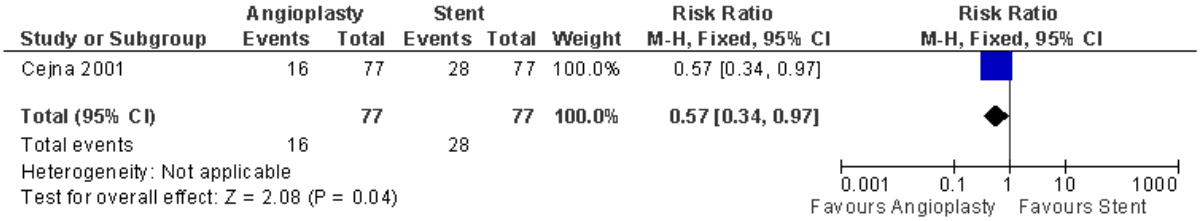
3

Figure 168: Amputation at 30 days



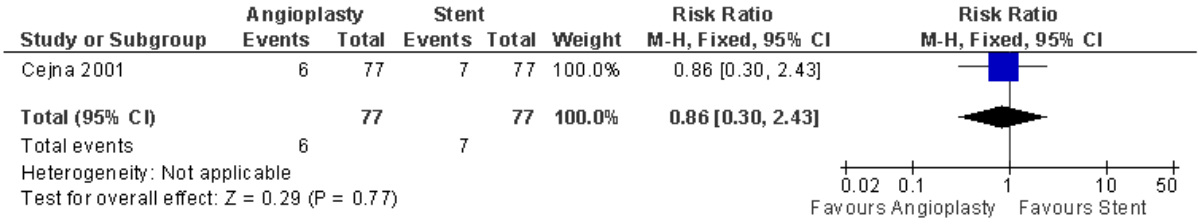
4

Figure 169: Re-intervention at 1 year



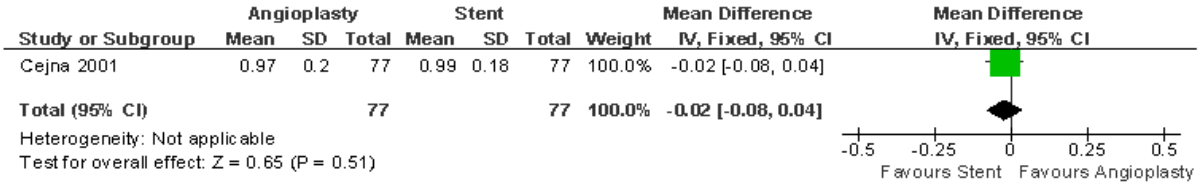
5

Figure 170: Major complications at 30 days



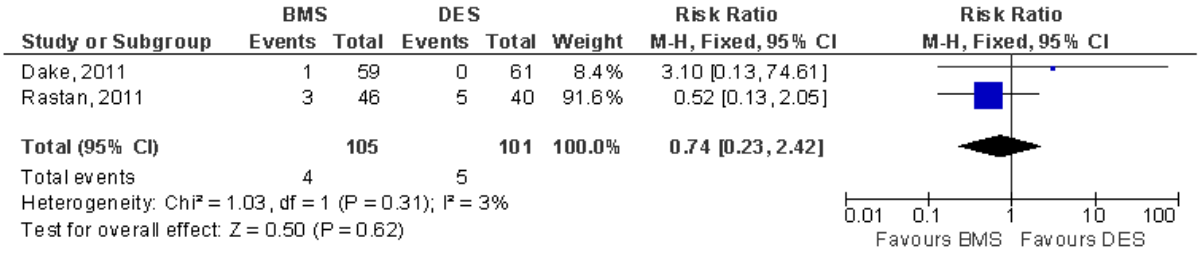
1

Figure 171: ABPI (time point not specified)



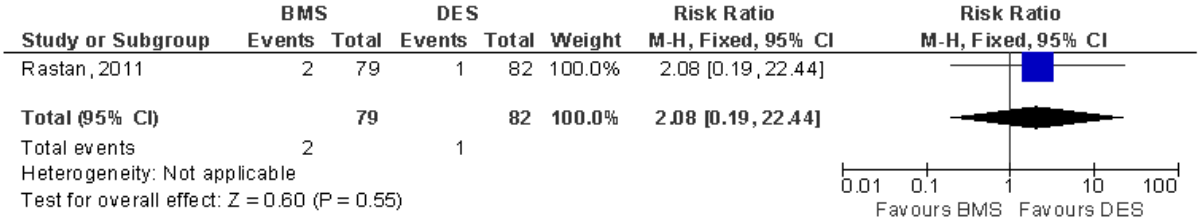
J.325 Bare metal compared to drug eluting stents for femoro-popliteal disease

Figure 172: Mortality at 1 year



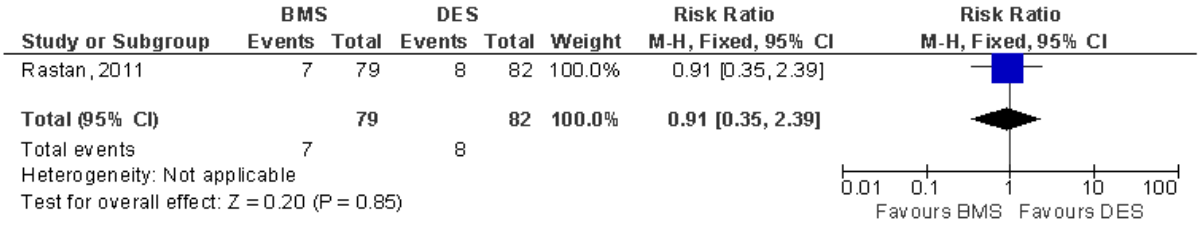
3

Figure 173: Amputation at 1 year



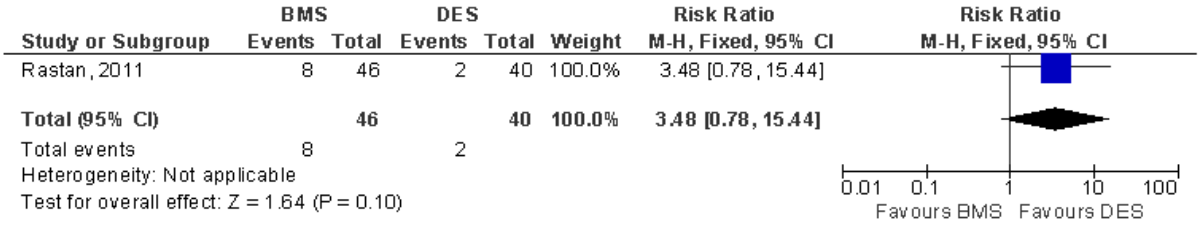
4

Figure 174: Re-intervention at 1 year



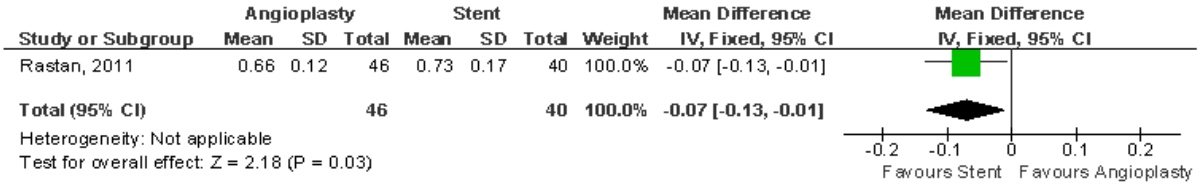
1

Figure 175: Target lesion revascularisation at 1 year



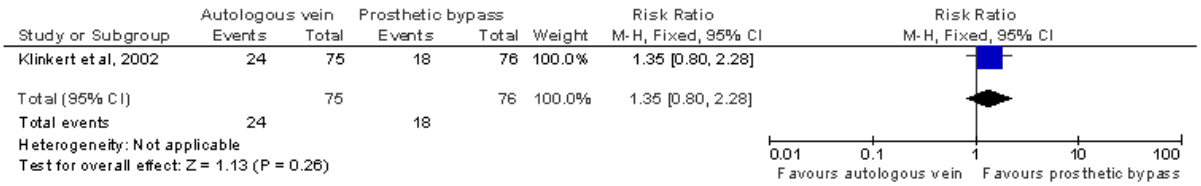
2

Figure 176: ABPI at 1 year



J.3.6 Autologous vein compared to prosthetic graft due to femoro-popliteal disease

Figure 177: Mortality at 5 years



4

Figure 178: Amputation at 5 years

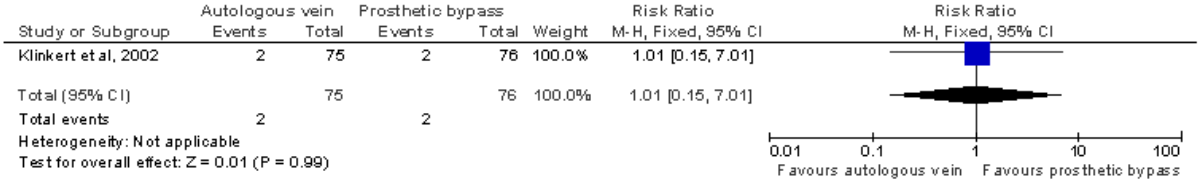
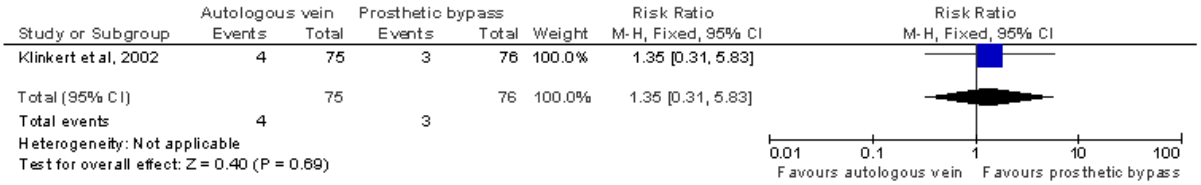
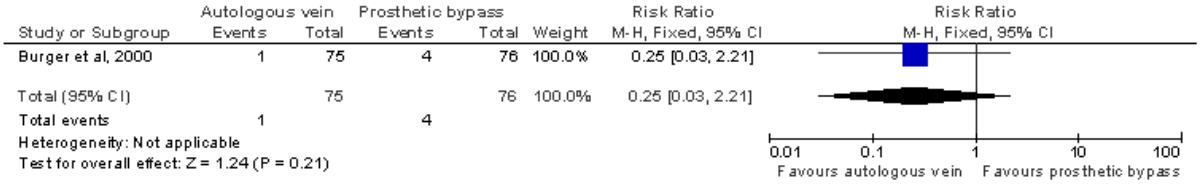


Figure 179: Peri-operative minor adverse event



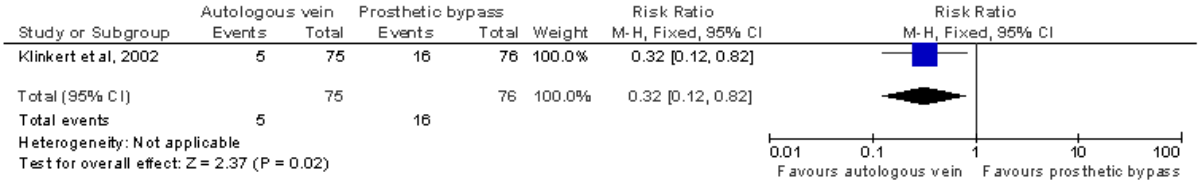
1

Figure 180: Re-intervention at 2 years



2

Figure 181: Re-intervention at 5 years

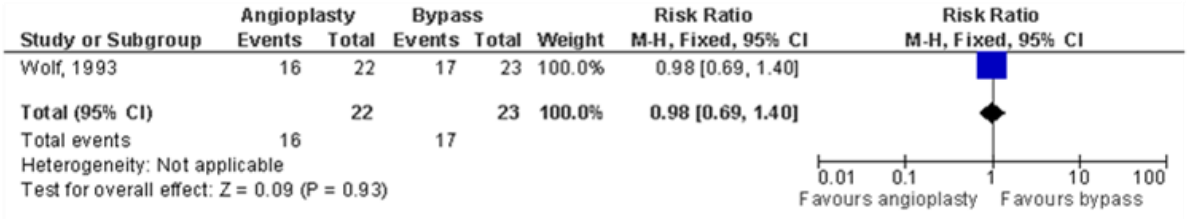


J.4 Critical limb ischaemia

J.4.1 Angioplasty compared to bypass surgery

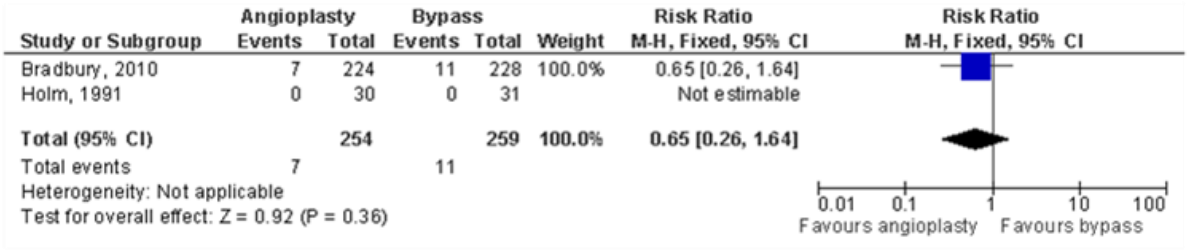
J.4.1.1 Critical limb ischaemia due to aorto-iliac disease

Figure 182: Limb salvage at 4 years



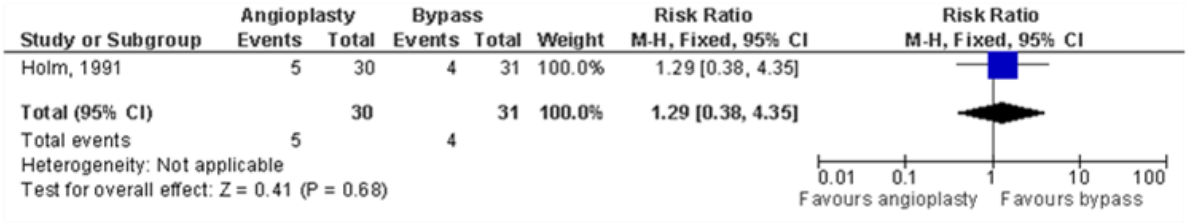
J.4.112 Critical limb ischaemia due to femoro-popliteal disease

Figure 183: Mortality at 30 days



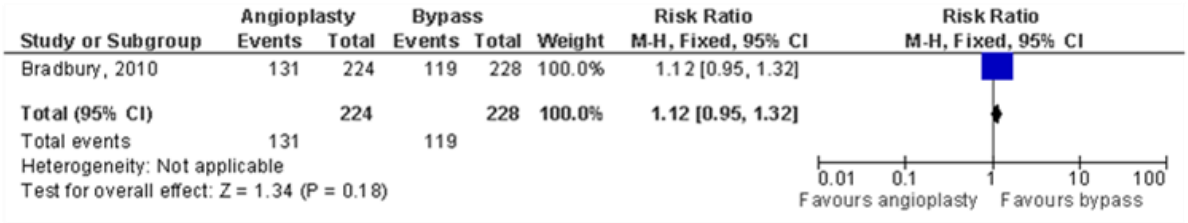
2

Figure 184: Mortality at 1 year



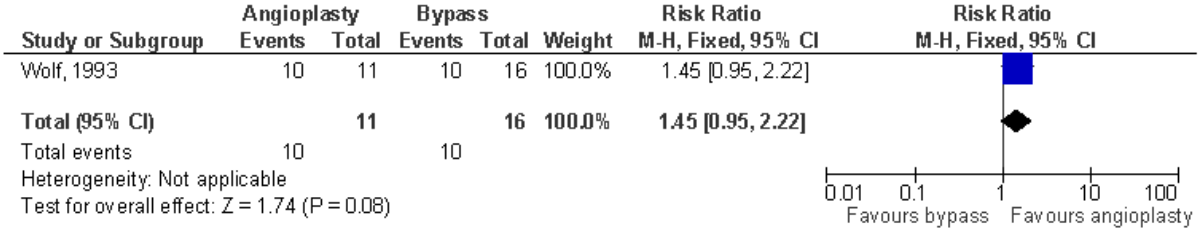
3

Figure 185: Mortality at 3 years



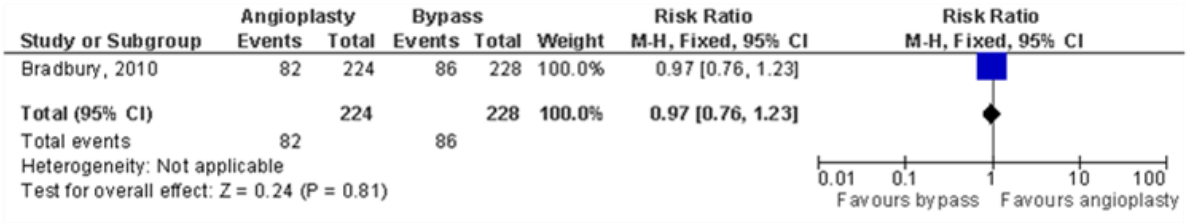
4

Figure 186: Amputation at 1 year



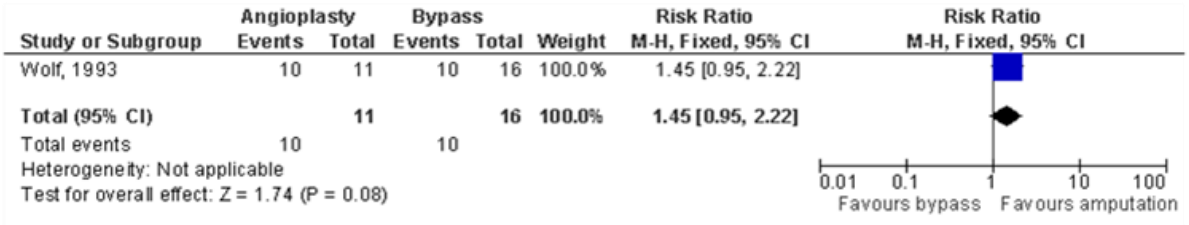
5

Figure 187: Amputation free survival at 3 years



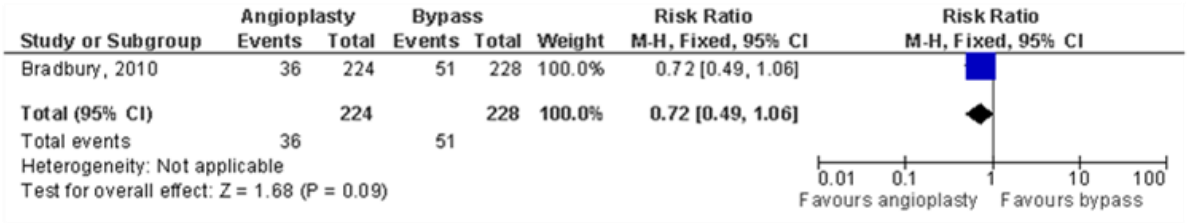
1

Figure 188: Limb salvage at 4 years



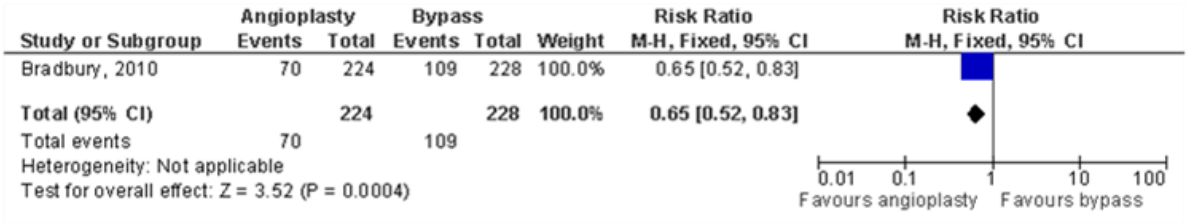
2

Figure 189: Major adverse events at 30 days



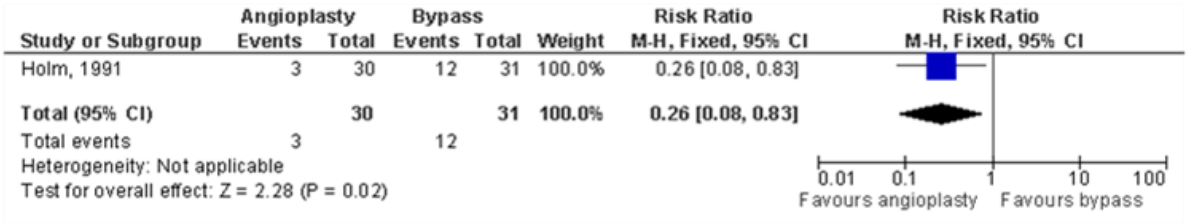
3

Figure 190: Minor adverse events at 30 days



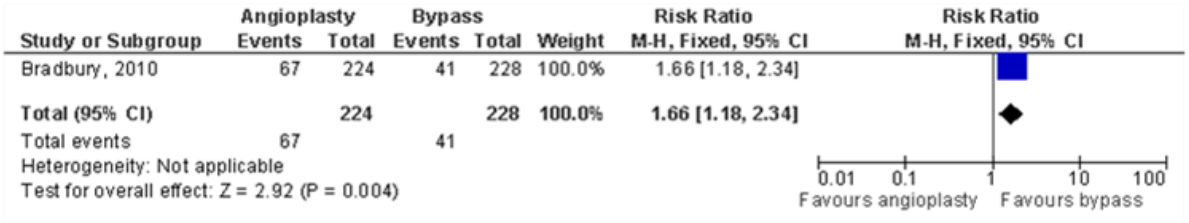
4

Figure 191: Minor adverse events at 1 year



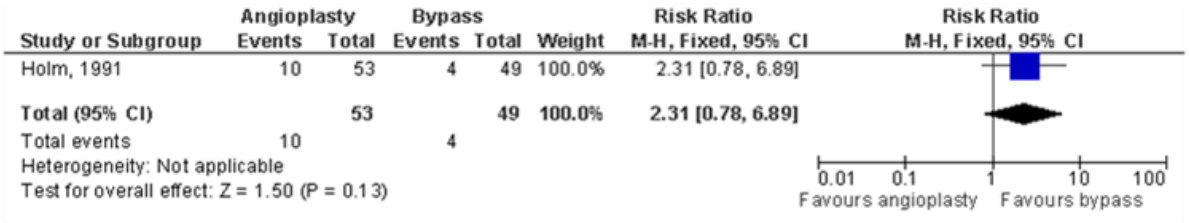
1

Figure 192: Re-intervention at 30 days



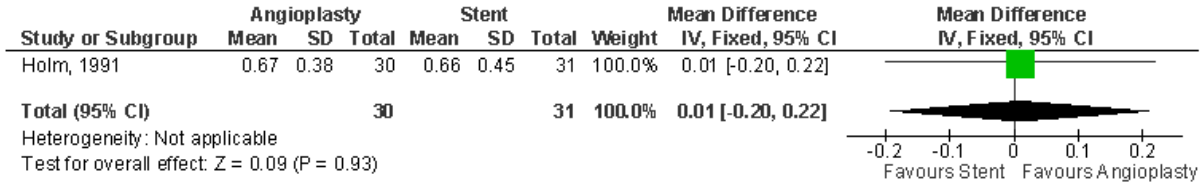
2

Figure 193: Re-intervention at 1 year



3

Figure 194: ABPI at 1 year



J.4.12 Angioplasty with primary stent placement compared to angioplasty with selective stent placement

J.4.2.1 Critical limb ischaemia due to femoro-popliteal disease (person randomised)

Figure 195: Mortality at 3 months

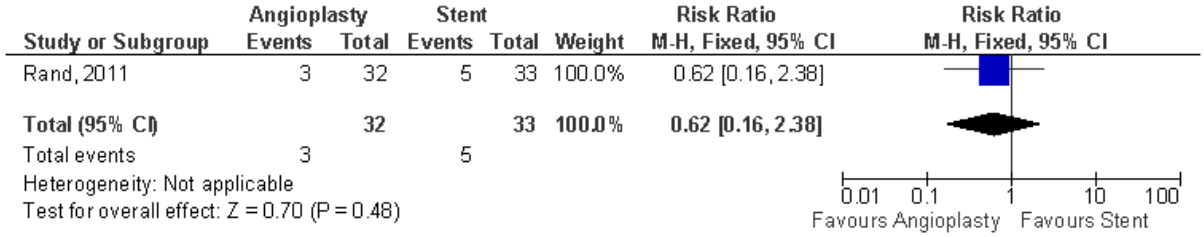


Figure 196: Mortality at 9 months

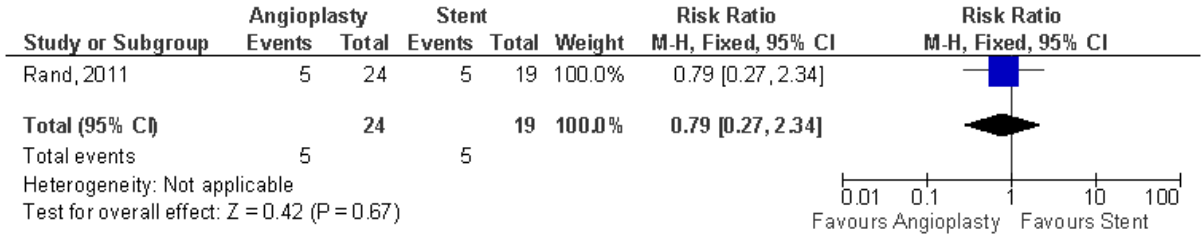


Figure 197: Amputation at 3 months

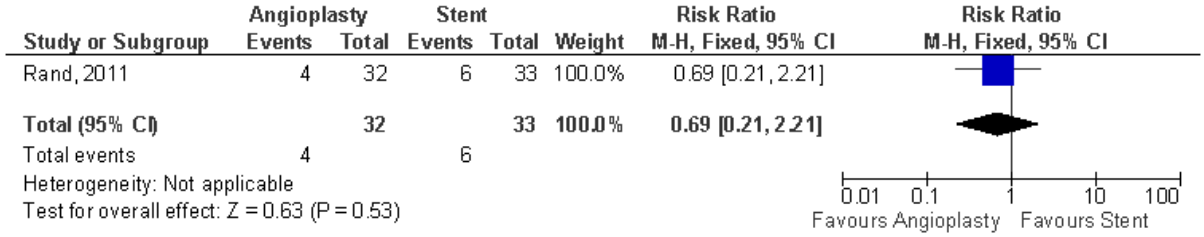


Figure 198: Amputation at 6 months

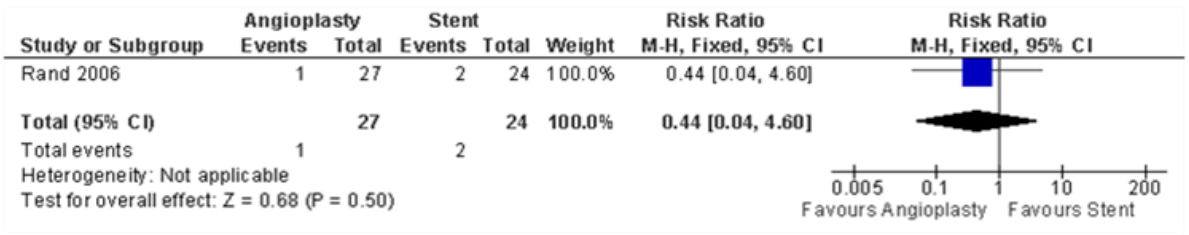
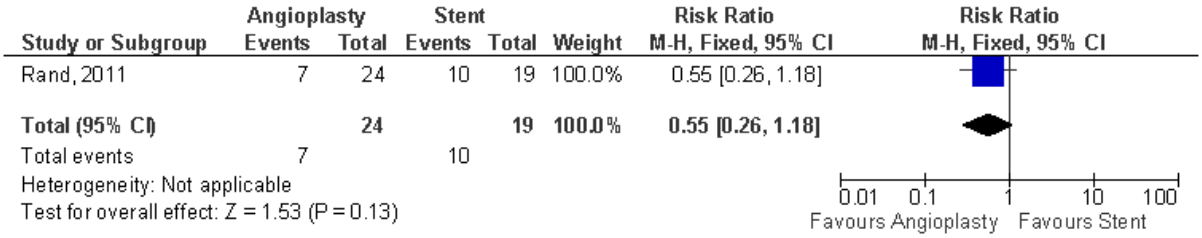
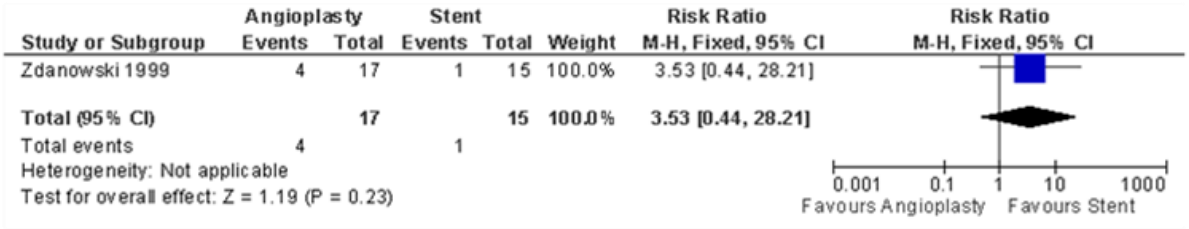


Figure 199: Amputation at 9 months



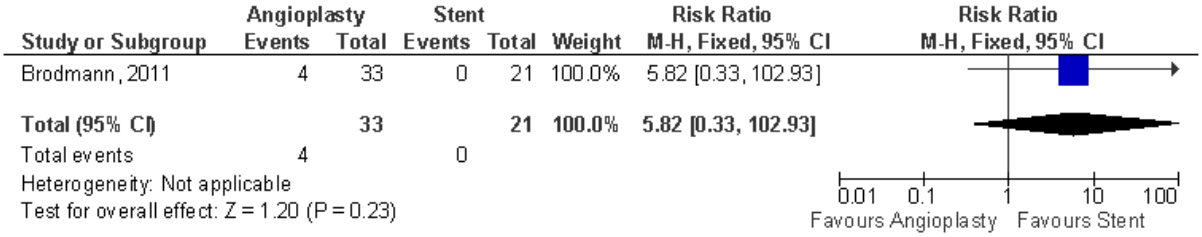
1

Figure 200: Major adverse events at 1 year



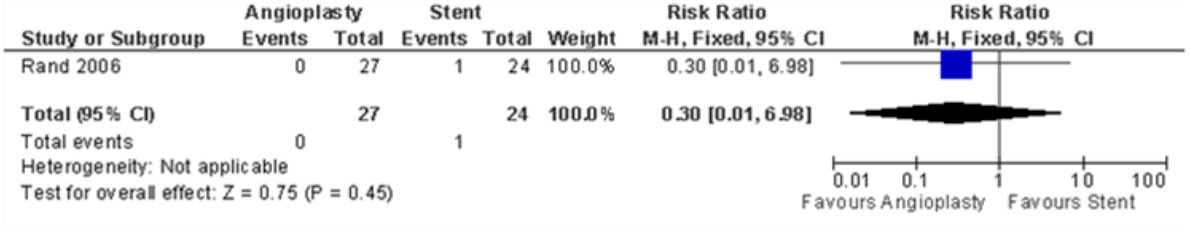
2

Figure 201: Minor adverse events at 1 year



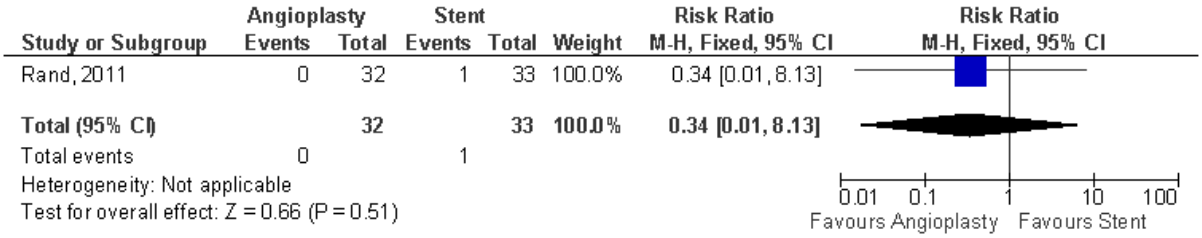
3

Figure 202: Re-intervention at 6 months



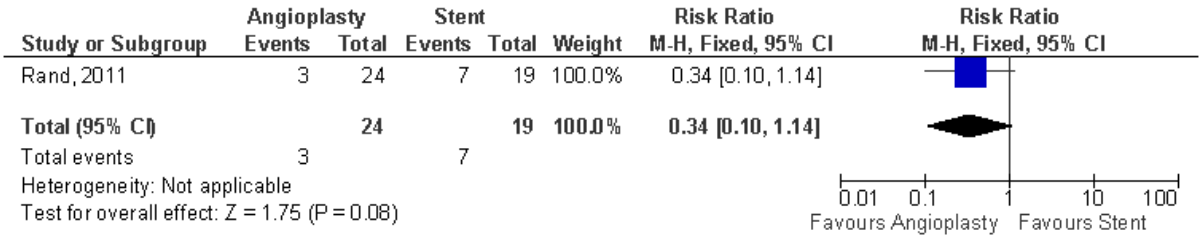
4

Figure 203: Target lesion revascularisation at 3 months



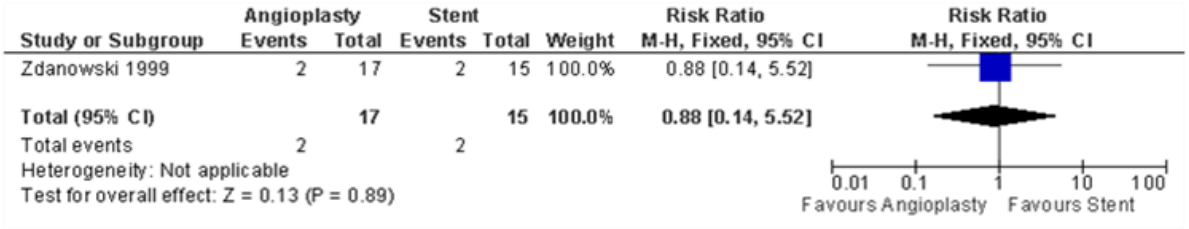
1

Figure 204: Target lesion revascularisation at 9 months



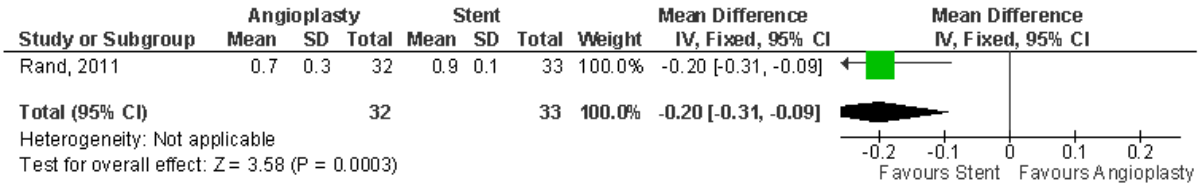
2

Figure 205: Re-intervention at 1 year



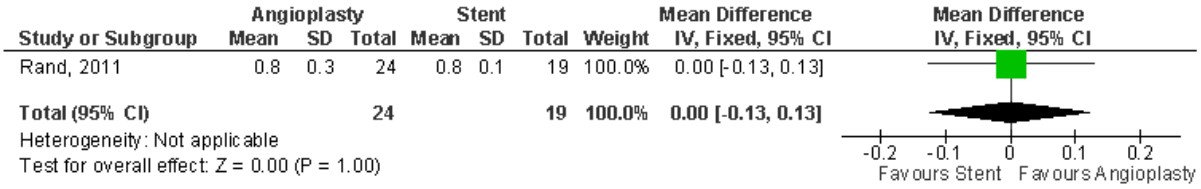
3

Figure 206: ABPI at 3 months



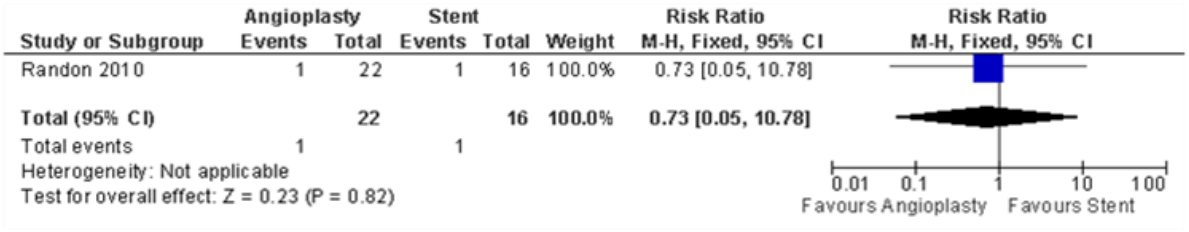
4

Figure 207: ABPI at 9 months



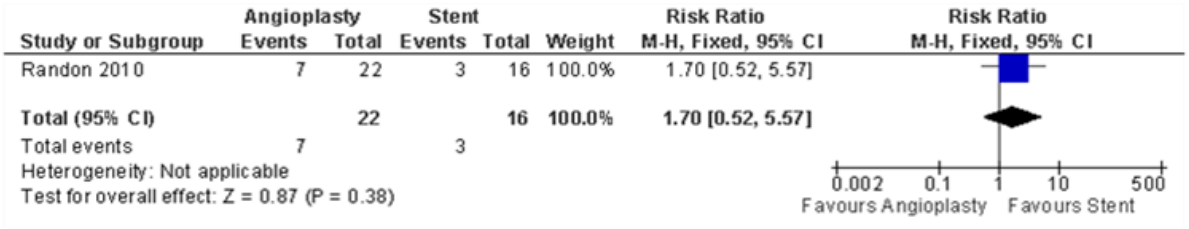
J.4.212 Critical limb ischaemia due to femoro-popliteal disease (limb/lesion randomised data)

Figure 208: Mortality at 30 days



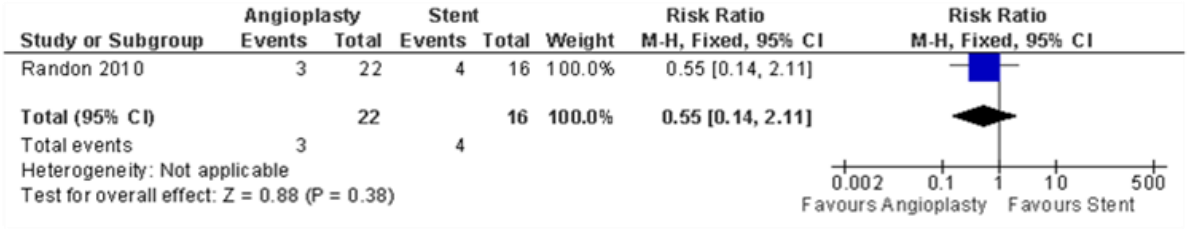
2

Figure 209: Mortality at 2 years



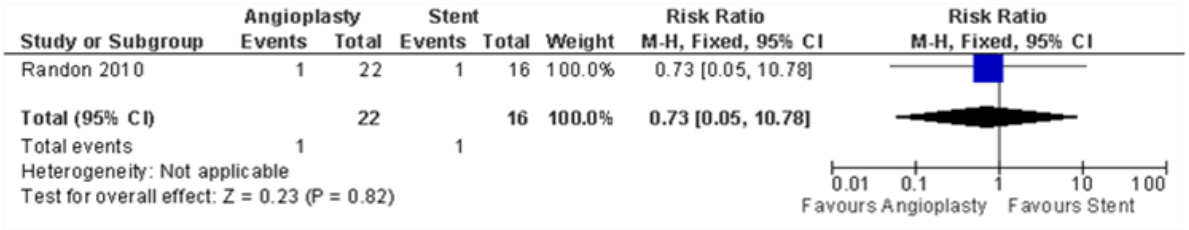
3

Figure 210: Amputation at 2 years



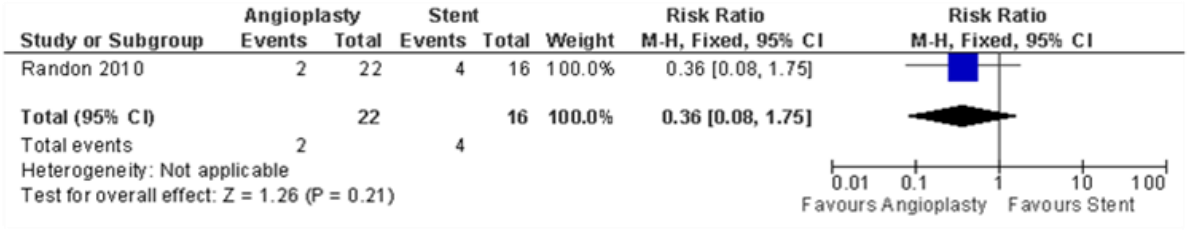
4

Figure 211: Major adverse events at 30 days



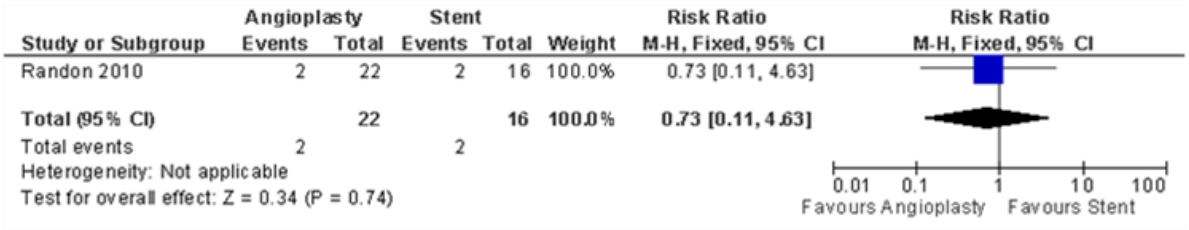
1

Figure 212: Minor adverse events at 30 days



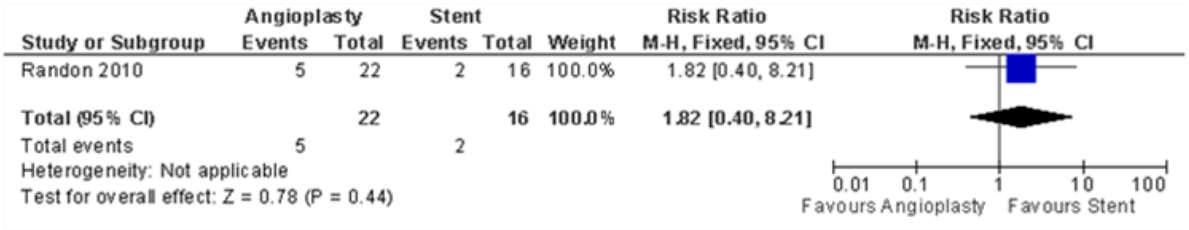
2

Figure 213: Major adverse event at 2 years



3

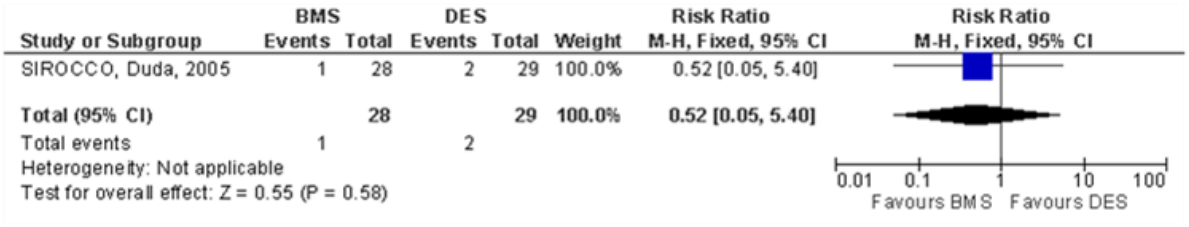
Figure 214: Re-intervention at 2 years



J.4.3 Bare metal compared to drug eluting stents

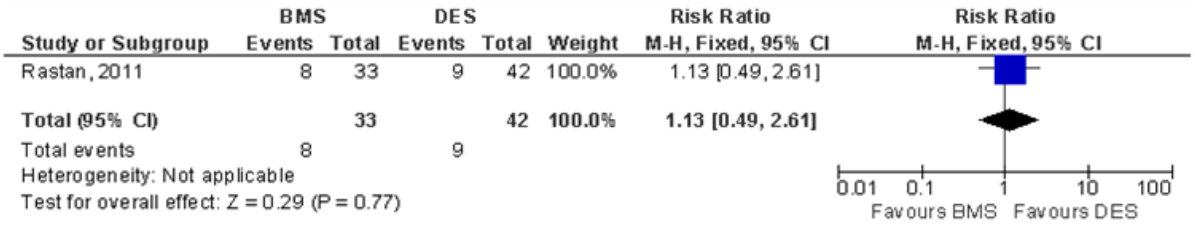
J.4.3.1 Critical limb ischaemia dut to femoro-popliteal diseaes

Figure 215: Mortality at 6 months



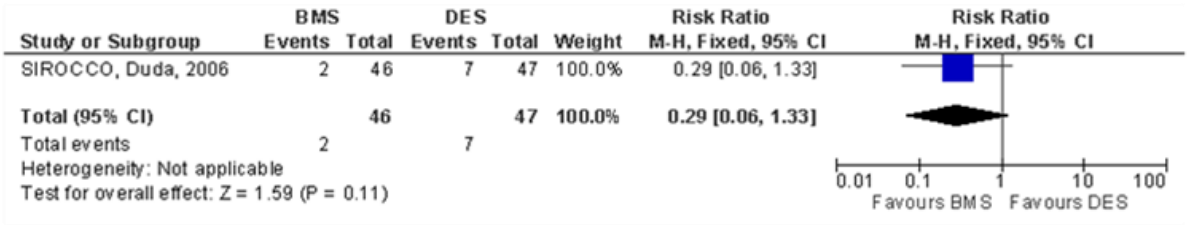
3

Figure 216: Mortality at 1 year



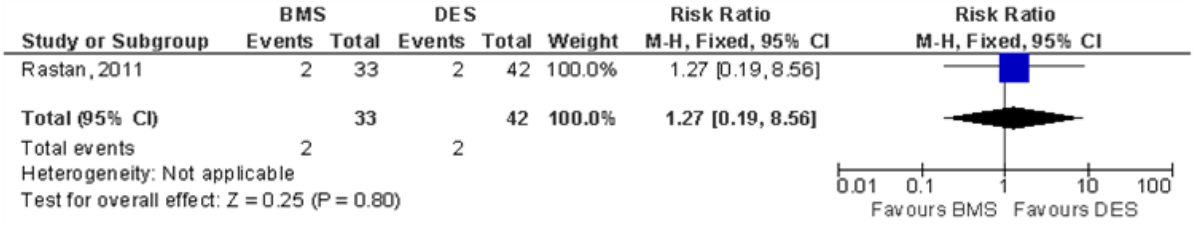
4

Figure 217: Mortality at 2 years



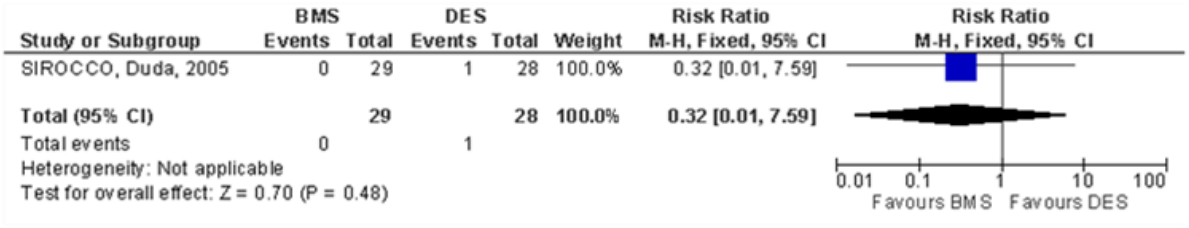
5

Figure 218: Amputation at 1 year



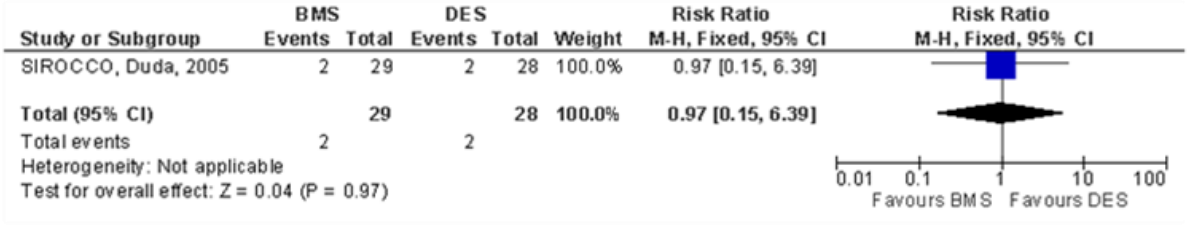
6

Figure 219: Major adverse events at 6 months



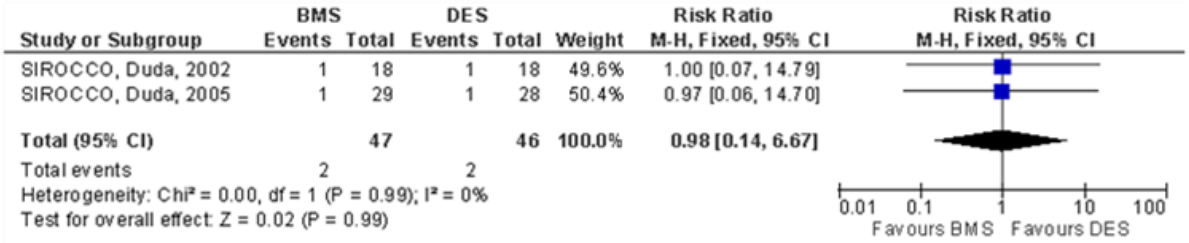
1

Figure 220: Minor adverse events during the procedure



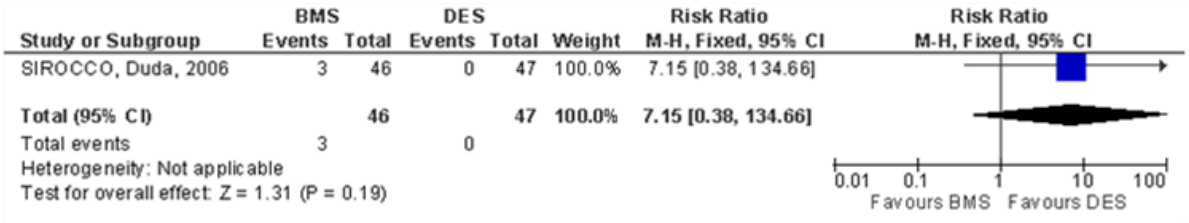
2

Figure 221: Minor adverse events at 6 months



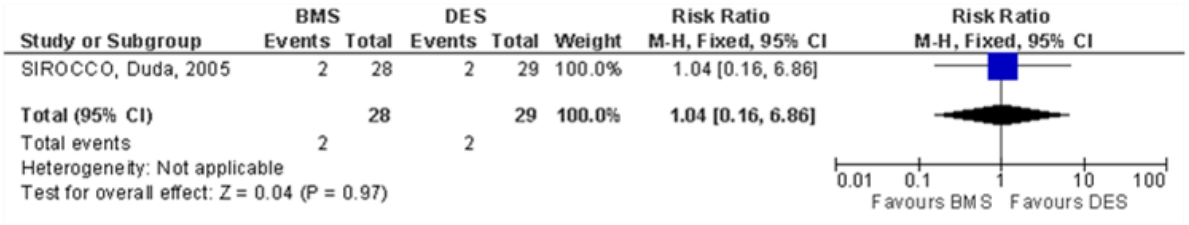
3

Figure 222: Minor adverse events at 2 years



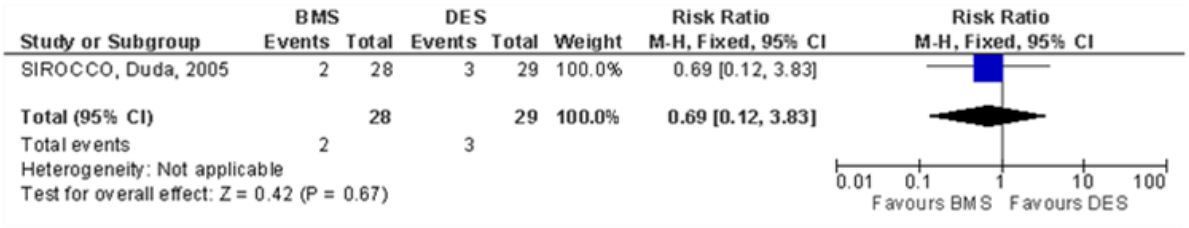
4

Figure 223: Revascularisation on the contralateral leg before discharge at 6 months



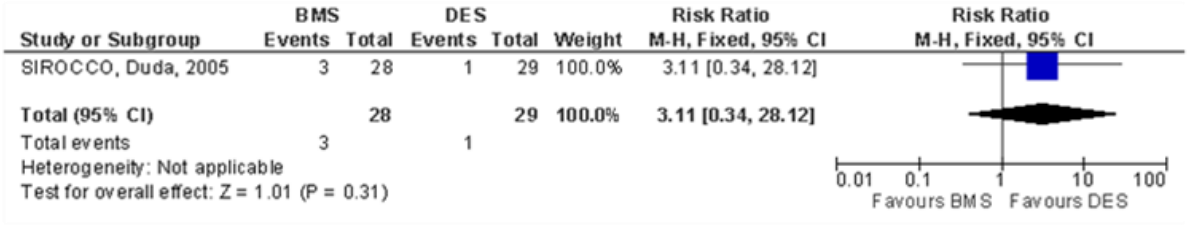
1

Figure 224: Revascularisation on the contralateral leg after discharge at 6 months



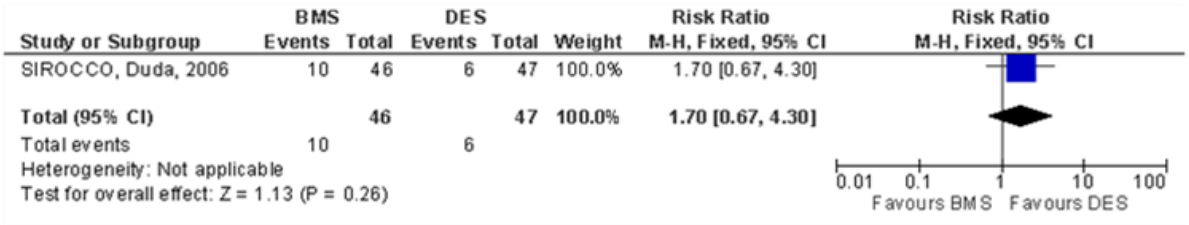
2

Figure 225: Target vessel revascularisation at 6 months



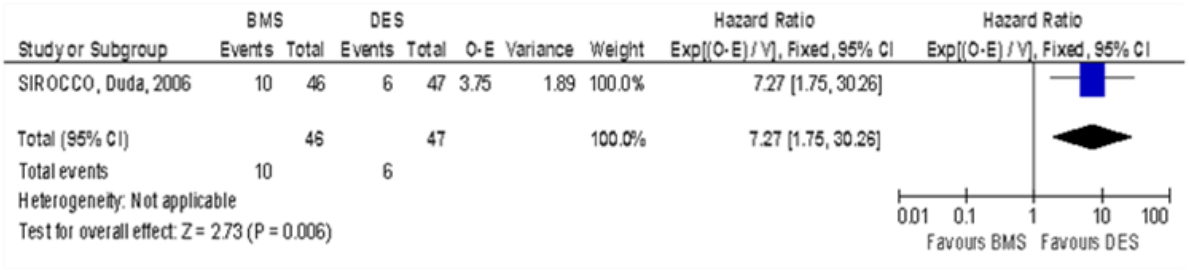
3

Figure 226: Target vessel revascularisation at 2 years (relative risk)



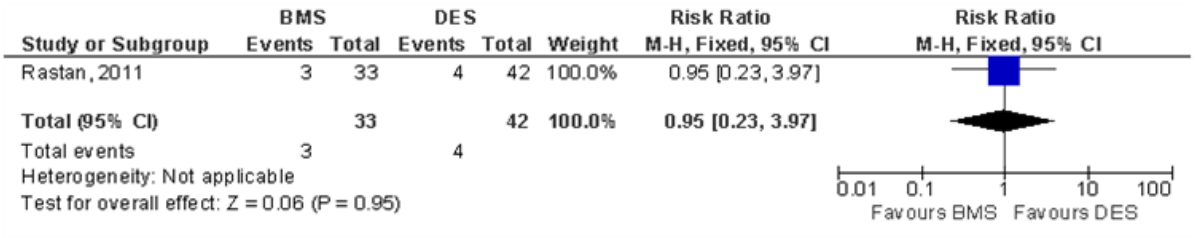
4

Figure 227: Target vessel revascularisation at 2 years (hazard ratio)



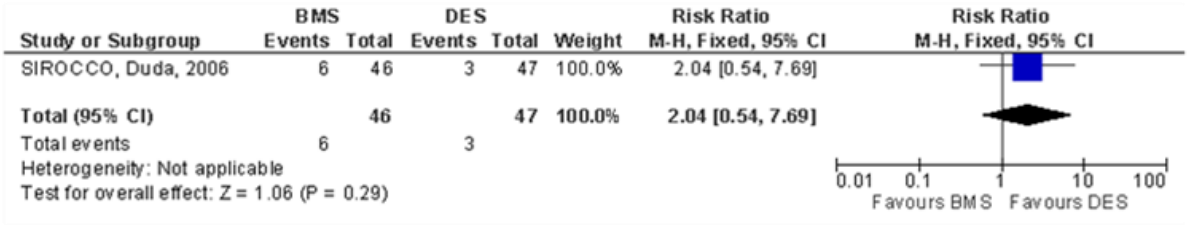
1

Figure 228: Target lesion revascularisation at 1 year



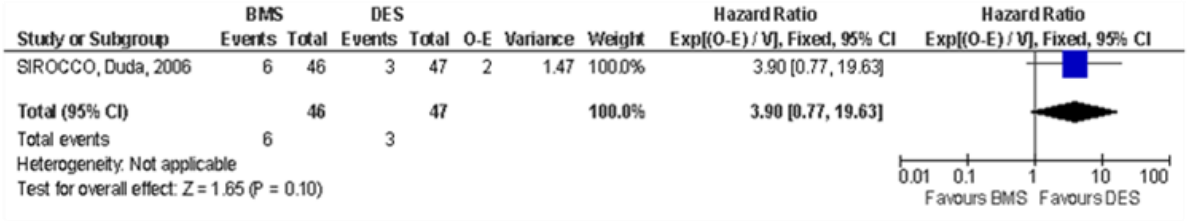
2

Figure 229: Target lesion revascularisation at 2 years (relative risk)



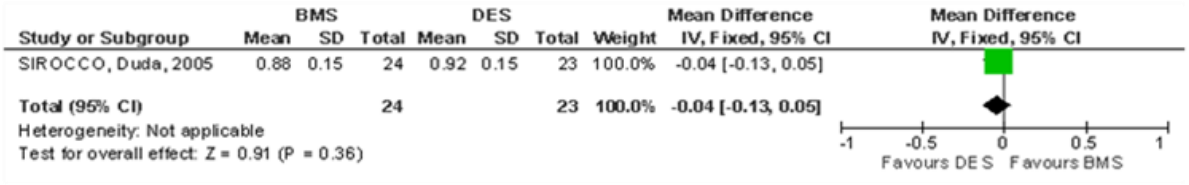
3

Figure 230: Target lesion revascularisation at 2 years (hazard ratio)



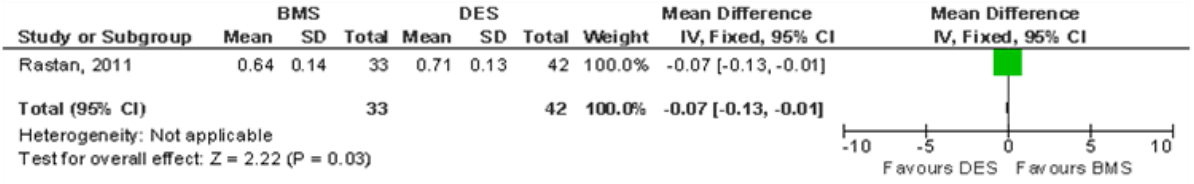
4

Figure 231: ABPI at 6 months



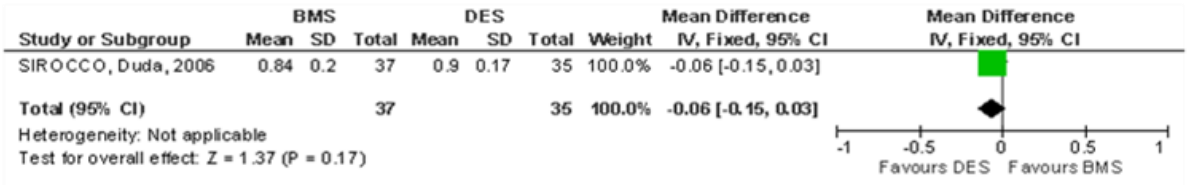
1

Figure 232: ABPI at 1 year



2

Figure 233: ABPI at 2 years



J.4.34 Autologous vein compared to prosthetic graft

J.4.441 Critical limb ischaemia due to femoro-popliteal disease

Figure 234: Amputation at 5 years

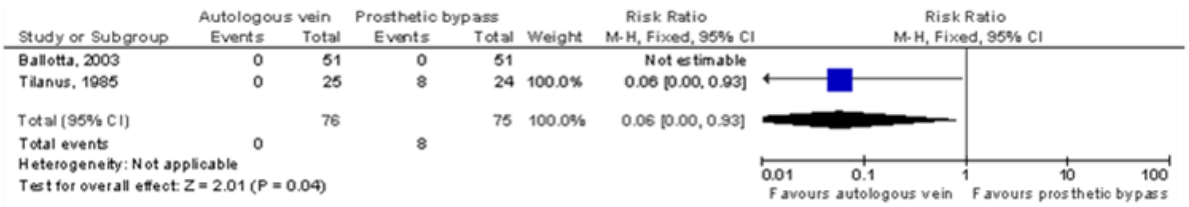


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Figure 235: Peri-operative minor adverse event

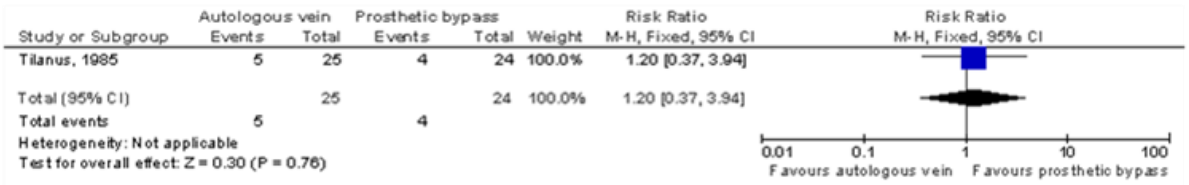

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Figure 236: Re-intervention at 5 years

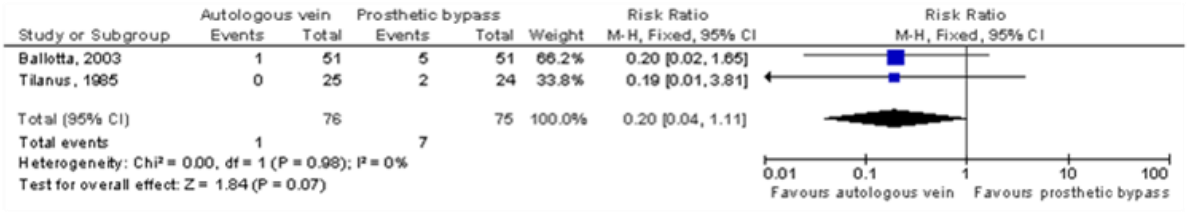

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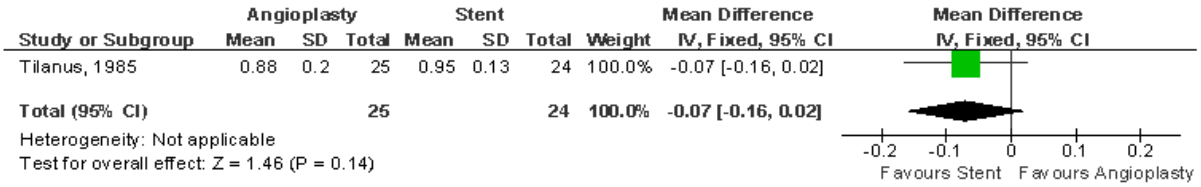
Figure 237: ABPI following surgery (no time point given)



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Appendix K: Cost-effectiveness analysis: Supervised exercise compared to unsupervised exercise for the treatment of people with intermittent claudication

K.1 Introduction

In most areas of England and Wales, the most common treatment for people with intermittent claudication (IC) is advice to exercise. Yet many clinical trials have demonstrated that supervised exercise programmes significantly improve walking performance and quality of life in people with IC compared to an unsupervised approach. The aim of this economic analysis was to determine which type of exercise programme represents the most cost-effective treatment strategy for the NHS by combining best available evidence of efficacy, costs, and quality of life.

K.2 Methods

K.2.1 Model overview

K.2.1.1 Comparators

This model evaluates the choice between two alternative interventions: unsupervised exercise and supervised exercise. Based on the studies included in the clinical 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 and resting to recover. Supervised exercise was defined as a community-based exercise programme supervised by healthcare professionals. In England and Wales, these programmes are typically supervised by two physiotherapists and have approximately 10 patients per group. The programme consists of approximately two hours of classes per week for a period of three months. Patients exercise until the onset of symptoms, then rest. They may walk on treadmills or outside, complete circuits, etc. The model did not evaluate different durations, intensities or modality of exercise programmes. A threshold analysis was undertaken to evaluate the likely cost-effectiveness of naftidrofuryl oxalate compared to supervised and unsupervised exercise (see section K.2.4.1).

K.2.1.2 Population

The hypothetical population included in the analysis was people with IC who are suitable for and willing to exercise. Not included were people with co-morbidities which prevent participation in an exercise programme, people who have recently undergone endovascular intervention, or people with severe IC or critical limb ischaemia (CLI).

People who refuse to participate in an exercise programme were not considered in the model. Decision models are designed to identify the optimal choice between two or more alternative strategies; the choice between unsupervised and supervised strategies only applies to people who agree to undertake an exercise regime. People who drop out after beginning an exercise programme are included in the model (see sections K.2.2, K.2.3.3 and K.2.3.6).

The population was not subdivided by lesion location and the model did not distinguish between people in primary and secondary care. 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.

K.2.13 Time horizon, perspective, discount rates used

The analysis was undertaken from the perspective of the NHS and personal social services in accordance with NICE guidelines methodology{National Institute for Health and Clinical Excellence, 2009 16359 /id}. 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.

K.2.12 Approach to modelling

Intermittent claudication is associated with an increased risk of mortality and cardiovascular events and decreased quality of life. In people with IC, exercise programmes have been shown to increase walking capacity and improve quality of life (chapter 9). Participation in regular physical activity is associated with an improvement in all of these outcomes.

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{Thompson, 2005 15996 /id} 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{Menard, 2004 341 /id}. 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.

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 M 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 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{Squires, 2010 16319 /id}, used maximum walking distance (MWD) as a

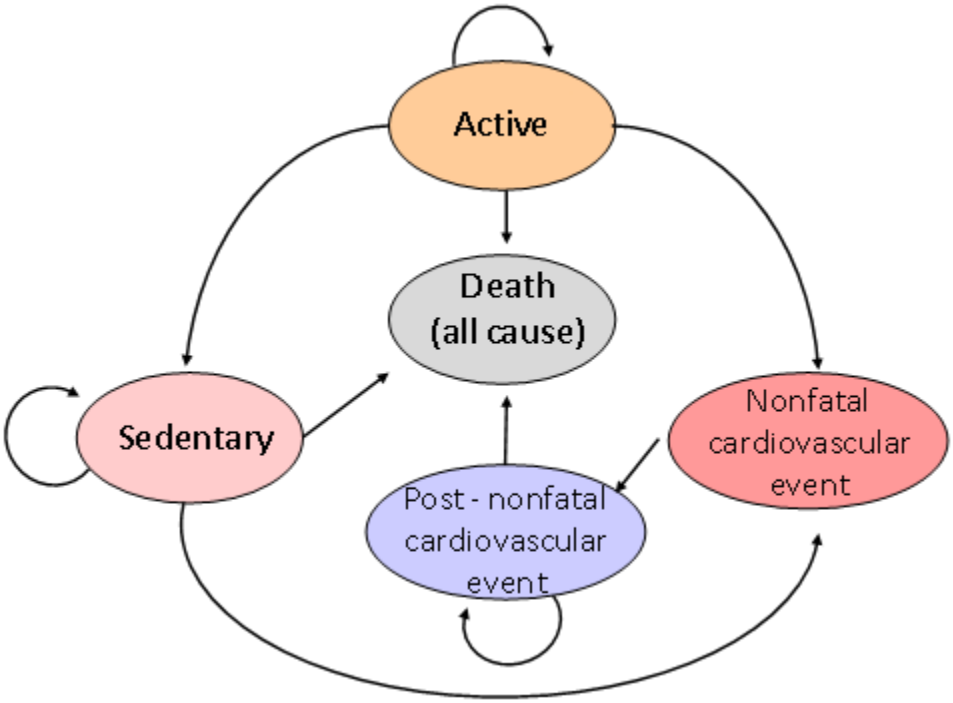
a The HSE defines an active lifestyle as undertaking 30 minutes or more of moderate vigorous physical activity on one to four days per week.

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.

K.2.231 Model structure

A simplified model structure is presented in Figure 238. The model includes four main health states: active (people who are physically active according to their prescribed exercise programme); sedentary (people who are inactive or less active than recommended); post-nonfatal cardiovascular event (stroke or MI); and death. The cycle length was three months and was chosen to reflect the most commonly reported follow-up intervals reported by the included RCTs.

Figure 238: 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.

K.2.232 Uncertainty

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 (see Table 12). When the model was run, a value for each input was randomly selected from its respective distribution. The model was run repeatedly (10k times) to obtain mean cost and QALY values.

Various sensitivity analyses were also undertaken to test the robustness of model assumptions and data sources. In these analyses, one or more inputs were changed and the analysis was rerun in order to evaluate the impact of these changes on the results of the model.

Table 12: Distributions used in probabilistic cost-utility analysis

Parameter	Type of distribution	Properties of distribution	Parameters for the distributions
Relative risk & odds ratios	Lognormal	Bound at zero	Log mean (LM) = Ln(RR) Log standard deviation (LSD) = $\frac{\text{Ln(Upper CI – Lower CI)}}{1.96 \times 2}$
Compliance to exercise (based on expert opinion)	Triangular	Minimum, mode, and maximum values	Min = minimum value Likeliest = mean Max = maximum value
Costs	Gamma	Bound between zero and infinity	α = (mean/standard error of the mean)2 γ = mean/standard error of the mean2
Probabilities (& mean baseline utility)	Beta	Bound between zero and one	α = events β = sample size - α

K.2.3 Model inputs

K.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review and supplemented by additional data sources as required. Model inputs were validated with members of the GDG. A summary of the model inputs used in the base case (primary) analysis is provided in Table 13 and Table 15. More details about sources, calculations and rationale for selection can be found in the sections following the summary tables.

Table 13: Summary of base case model inputs and cohort settings

Input	Data	Source
Comparators	Unsupervised exercise (advice to exercise) versus supervised exercise programme	GDG consensus
Population	People with intermittent claudication who are suitable for either a supervised or unsupervised exercise programme	GDG consensus
Subgroups	None	
Initial cohort settings	Age: 67 Male: 66% ABPI: 0.67 Diabetes: 24% Current smokers: 43%	Weighted average across relevant RCTs{Cheetham, 2004 549 /id}{Nicolai, 2010 15927 /id}{Savage, 2001 3035 /id}
Perspective	NHS and PSSRU	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}
Time horizon	Lifetime	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}
Discount rate	Costs: 3.5% QALYs: 3.5%	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}

ABPI = ankle brachial pressure index; NHS = National Health Service; PSSRU = personal and social services research unit; QALYs = quality adjusted life years; RCT = randomised controlled trial.

Initial cohort settings

The cohort considered by the model is people with symptomatic intermittent claudication due to peripheral arterial disease. Of the 11 RCTs included in the clinical review, three included relevant quality of life outcomes which were relevant to the economic model (see section K.2.3.5). Based on the baseline characteristics of these studies, a starting age of 67 years was used to represent the average age of people with IC. The hypothetical cohort was 66% male and had an average ABPI of 0.67. 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 (see section K.2.3.2). The GDG considered this proportion of people with diabetes to be slightly greater than expected but thought that in light of the growing prevalence of diabetes across the UK it is likely to represent an accurate estimate in the near future. Table 14 contains a summary of the population characteristics and interventions of all studies included in the clinical review.

Table 14: Characteristics of studies included in the clinical review of unsupervised vs. supervised exercise

Study	N	Average age	Male	Diabetes	Smoking history		Resting ABPI	Type of analysis	Artery	Supervised exercise		Unsupervised exercise	
					Current	Former				Duration	Content	Duration	Content
Studies reporting relevant quality of life estimates (and therefore included in the current economic model)													
Cheetham 2004{Cheetham, 2004 549 /id}	59	67	73%	19%	NR	NR	0.68	OTA	NR	1 x 45 min per week for 6 months	Circuits	3 x 30 min per week for 6 months	Advice only
Nicolai 2010 & van Asselt 2011 (EXITPAD study){Nicolai, 2010 15927 /id;van Asselt, 2011 16275 /id}	211	67	64%	25%	43%	45%	0.66	Modified ITT **	NR	2-3 x 30 min per week for 12 months	Treadmill walking	3 x 3 times per day for 12 months	Advice only
Savage 2001{Savage, 2001 3035 /id}	21	66	71%	NR	NR	NR	0.73	Unclear	NR	3 x 40 min per week for 3 months	Treadmill walking	3 x 40 min per week for 3 months	Advice + monthly telephone support
WEIGHTED AVERAGE	**291**	**67**	**66%**	**24%**	**43%**	**45%**	**0.67**	**--**	**--**	**--**	**--**	**--**	**--**
All other studies included in the clinical review													
Kakkos 2005{Kakkos, 2005 453 /id}	34	68	90%	19%	24%	67%	0.56	OTA	FP	3 x 60 min per week for 6 months	Treadmill walking	45 min per day for 6 months	Advice only
Pinto 1997{Pinto, 1997 17 /id}	60	69	53%	35%	NR	NR	0.58	OTA	NR	3 x 60 min per week for 3 months	Treadmill walking + cycling + education	3 x 20-40 min per week for 3 months	Advice + journal + education + weekly in-person support
Regensteiner	20	65	100%‡	0%	55%	NR	0.60	ITT	NR	3 x 60 min	Treadmill	3 x 35-50	Advice +

1997{Regenstein er, 1997 931 /id}										per week for 3 months	walking	min per week for 3 months	weekly telephone support
Stewart 2008{Stewart, 2008 167 /id}	60	68	70%	22%	27%	62%	0.66	OTA	FP	2 x 60 min per week for 3 months + 3 months unsupervis ed exercise	Circuits	No details	Advice only
Treat-Jacobson 2009{Treat-Jacobson, 2009 91 /id}	45	67	71%	37%	NR	NR	0.67	OTA	NR	3 x 70 min per week for 3 months	Treadmill walking	Daily (no other details) for 3 months	Advice + journal + weekly in-person support
Tew 2009{Tew, 2009 81 /id}	57	69	NR	20%	29%	57%	0.68	OTA	NR	2 x 20-40 min per week for 3 months	Arm crank exercise s	No details	Advice only
Tisi 1997{Tisi, 1997 3042 /id}	67	69	69%	10%	30%	61%	0.67	Unclear	NR	1 x 60 min per week for 1 month	Leg exercises	No details	Advice only
Zwierska 2005{Zwierska, 2005 420 /id}	104	69	78%	18%	32%	63%	0.66	ITT	FP	2 x 20-40 min per week for 6 months	Leg and arm exercises	2 x 20-40 min per week for 6 months	Advice only

Abbreviations: ITT = intention to treat analysis; OTA = on treatment analysis; FP = femoro-popliteal; AI = aorto-iliac; NR = not reported; NA = not applicable
*** Analysis excluded drop outs unless they showed up to their final assessment. 5 control pts crossed over to EX group and were analysed in control group.*
‡Assumption based on the fact that the trial took place at a veteran's hospital.

1 **Table 15: Overview of parameters and parameter distributions used in the base case model**

Parameter		Point estimate	Value range	Probability distribution	Distribution parameters	Source
Baseline relative risk (people with IC compared to adjusted norms)						
All cause mortality		3.10	1.90 – 4.90	Lognormal	LM = 1.10219 LSD = 0.24167	Criqui 1992{Criqui, 1992 16328 /id}
Stroke & MI	M	2.16	1.76 – 2.66	Lognormal	LM = 0.76455 LSD = 0.10536	Ankle Brachial Index Collaboration{Fowkes, 2008 16329 /id}
	F	2.49	1.87 – 3.36	Lognormal	LM = 0.90048 LSD = 0.15361	Ankle Brachial Index Collaboration{Fowkes, 2008 16329 /id}
Exercise compliance¥						
Time period	**Unsupervised exercise**		**Supervised exercise**			**Source**
	Most likely value	**Lower and upper likely values**	**Most likely value**	**Lower and upper likely values**		
Scenario 1						
3 months	43%	17% - 56%	68%	40% - 83%		Expert opinion
6 months	33%	10% - 45%	50%	25% - 66%		Expert opinion
12 months	22%	7% - 37%	37%	14% - 54%		Expert opinion
24 months	16%	5% - 31%	31%	12% - 47%		Expert opinion
>24 months	16%	5% - 31%	31%	12% - 47%		Assumption
Scenario 2						
3 months	43%	17% - 56%	68%	40% - 80%		Expert opinion
6 months	33%	10% - 45%	40%	15% - 57%		Expert opinion
12 months	22%	7% - 37%	22%	4% - 40%		Expert opinion
24 months	16%	5% - 31%	16%	5% - 32%		Expert opinion
>24 months	16%	5% - 31%	16%	5% - 32%		Assumption
Relative risk (active compared to sedentary individuals)						
Mortality	0.87	0.75 – 0.99	Lognormal	LM = -0.14177 LSD = 0.07082		Cochrane review{Heran, 2011 16331 /id}
MI	0.97	0.82 – 1.15	Lognormal	LM = -0.03418 LSD = 0.08627		Cochrane review {Heran, 2011 16331 /id}
Stroke	0.80	0.74 – 0.86	Lognormal	LM = -0.22388 LSD = 0.03833		Meta-analysis{Lee, 2003 16333 /id}
Cost of exercise interventions						
Unsupervised	£0	NA	Fixed	NA		Expert opinion (see text)
Supervised	£288	£232 – £345	Gamma	α = 100.0000 β = 2.88600		Expert opinion (see text)

Cost of cardiovascular events					
Initial MI	£4, 792	£3, 853 – £5, 731	Gamma	α = 100.0000 β = 47.9200	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Post nonfatal MI	£141	£113 – £169	Gamma	α = 100.0000 β = 1.4100	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Initial stroke	£9, 630	£7, 743 – £11, 517	Gamma	α = 100.0000 β = 96.3000	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Post nonfatal stroke	£559	£449 – £669	Gamma	α = 100.0000 β = 5.5900	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Weighted mean baseline quality of life					
Baseline	0.654	0.631 – 0.678	Beta	α = 1049.090 β = 553.9091	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}, Savage 2001{Savage, 2001 3035 /id}
Weighted mean difference in change in quality of life					
Baseline to 3 months	-0.021	-0.086 – 0.046	Normal	Mean = -0.021 SD = 0.034	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}, Savage 2001{Savage, 2001 3035 /id}
3 months to 6 months	0.026	-0.038 – 0.090	Normal	Mean = 0.026 SD = 0.032	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927

					/id}, Savage 2001{Savage, 2001 3035 /id}
6 months to 9 months	0.010	-0.058 – 0.076	Normal	Mean = 0.010 SD = 0.034	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}
9 months to 12 months	0.029	-0.049 – 0.106	Normal	Mean = 0.029 SD = 0.039	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}
Quality of life *decrement* following a cardiovascular event					
MI	-0.157	-0.181 to -0.134	Beta	α = 143.0917 β = 768.0434	Based on Goodacre 2004{Goodacre, 2004 16276 /id}
Post MI	-0.079	-0.091 to -0.067	Beta	α = 156.5143 β = 1836.692	Assumption based on half the value observed in Goodacre{Goodacre, 2004 16276 /id}
Stroke	-0.243	-0.296 to -0.192	Beta	α = 63.94790 β = 199.2334	Based on Tengs 2003{Tengs, 2003 16277 /id}
Post stroke	-0.121	-0.148 to -0.096	Beta	α = 74.37100 β = 537.7856	Assumption based on half the value observed in Tengs 2003{Tengs, 2003 16277 /id}

¥Note that these values are cumulative and differ from the transition probabilities used in the model. LM = log mean; LSD = log standard deviation; RR = relative risk; MI = myocardial infarction.

K.2.3.2 Baseline event rates

Mortality

Age- and sex-specific all cause mortality was based on the most recent available life tables for England and Wales (2007-2009){Office for National Statistics, 2010 ONS2010 /id}. These rates were adjusted for people with IC by multiplying the standardised risk of all cause mortality observed over 10 years in people with IC by Criqui and colleagues (Table 15){Criqui, 1992 16328 /id}. This study was selected to inform the increased risk of mortality among people with IC as it reported an estimate which was considered clinically valid by the GDG and is consistent with existing cost effectiveness evaluations in this population. The resulting 5- and 10-year baseline cumulative mortality rates of 25% and 54% are consistent with those reported by several long term follow-up studies of people with claudication{Dormandy, 1999 16369 /id;Muluk, 2001 16096 /id}.

Cardiovascular events

The average baseline probability of stroke or 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 {Anderson, 1991 16344 /id;Payne, 2010 16343 /id}. Risk factor inputs for each sex were obtained from the 2006 Health Survey for England (HSE; Table 16){Craig, 2008 16342 /id}. Average age- and sex- specific blood pressure values were obtained from the 2011 NICE Hypertension update guideline{National Clinical Guideline Centre, 2011 16341 /id}, 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{Fowkes, 2008 16329 /id}. A limitation of this study for the purposes of our analysis was that the reported hazard ratios were not adjusted for age or cardiovascular risk factors. However, the values matched those expected by the GDG and were considered to be the best available estimates in the current literature. Sex-specific hazard ratios were incorporated into the analysis using lognormal distributions. Deterministic estimates of cumulative 10-year risk according to the Framingham equation and adjusted for people with IC are presented Table 17.

Table 16: Risk inputs used in the Framingham equations for stroke and MI

Age group	Mean total cholesterol	Mean HDL cholesterol	Mean systolic blood pressure	Mean prevalence of diabetes (1 & 2)	Mean prevalence of smoking (current)
Males					
65 to 74	5.2	1.3	137	15.7%	14.0%
Females					
65 to 74	5.9	1.6	138	10.4%	13.0%

Source/Note: 2006 Health Survey for England and 2009 NICE Hypertension update guideline.

Table 17: 10-year risk of MI and stroke

Sex	10 year risk of MI		10 year risk of stroke	
	According to Framingham equation	Adjusted for ABPI of 0.61 to 0.70	According to Framingham equation	Adjusted for ABPI of 0.61 to 0.70
Male	9.2%	25.4%	4.8%	13.2%
Female	3.1%	11.9%	3.6%	13.7%
Total (66% male)	7.2%	20.7%	4.4%	13.2%

K.2.3.3 Exercise compliance

The probability that people will maintain an increased level of physical activity after participation in an exercise regime is a key factor in determining overall cost and effectiveness of each type of intervention. The impact of compliance on the consequences of the model is captured by the assumption that the increased quality of life and decreased risk of mortality and cardiovascular events associated with exercise is maintained by those who continue to be physically active. Those who revert to a sedentary state are also assumed to revert to baseline quality of life, mortality and cardiovascular risk.

Although several studies identified in the clinical review reported either total dropout rates or dropouts associated with each study arm, Nicolai 2010 was the only study to report the number of people in each arm who withdrew due to a 'lack of motivation'. However, the GDG did not consider compliance within a trial setting to be representative of real world behaviour. Therefore, an

additional literature search was undertaken to identify estimates of short and long term compliance to supervised and unsupervised exercise programmes. All cardiovascular populations, 'older adult' populations and study types were considered. The aim was to identify estimates of the percentage of people who complete each exercise programme and the percentage who remain active over time.

In 2009, the Cochrane Collaboration published a systematic review comparing compliance to home vs. centre based exercise programmes in older adults{Ashworth, 2009 16370 /id}. The authors of this review concluded that home based programmes appear to have better adherence rates than centre based programmes (adherence was 68% for home-based programmes and 36% for centre based programmes after 2 years). However, adherence rates were defined by the percentage of prescribed exercise sessions that were completed by participants. This definition is quite different from our outcome of interest.

Bartelink 2004{Bartelink, 2004 16198 /id} conducted a review of 216 GP records in the Netherlands to identify people with IC. In those who reported that they had received advice about walking, 68% reported that they actually took part in a walking exercise, providing a possible baseline estimate for compliance to unsupervised exercise. However, based on their clinical experience, the GDG did not think that this sounded realistic. In addition, because the group did not think it relevant to use the compliance rates reported by the included clinical trials, there was no valid estimate of the relative rate of compliance to supervised compared to unsupervised exercise to complement this value.

An American study by Mouser 2009{Mouser, 2009 16371 /id} aimed to evaluate compliance to an unsupervised exercise programme for people with IC. Participants of this trial were instructed to walk for 30 minutes three times a week until near maximal pain. They were given a journal and received regular feedback (once every 2 months) and encouragement from staff at a vascular clinic. Of the 120 people who began the programme, 41 returned after 6 months, representing a primary completion rate of 34%. People were not told before enrolment that compliance data would be collected, leading to a more realistic picture of compliance among this group. However, this study did not compare supervised exercise to unsupervised, and so cannot be used to determine relative levels of compliance.

A decision analytic model of physical activity counselling in general practice by Dalziel and Elley 2006{Dalziel, 2006 16372 /id} assumed that 19.5% of people in the general population were physically active without counselling ('population baseline'). At the end of one year, an additional 4.9% of the control group and 14.4% of the intervention group were active (RR = 2.98). It was assumed that this rate declined at an even rate in both groups until the proportion of active people returned to baseline after 4 years. Although this assumption provided a useful precedent for the current model, neither the counselling therapy nor the control procedure was comparable with our interventions of interest.

Dorn 2000{Dorn, 2001 16020 /id} examined factors associated with exercise compliance over 3 years in male MI survivors. Subjects were participants who had been randomised to the supervised exercise treatment group in the National Exercise and Heart Disease Project and compliance was defined as the number of sessions attended compared to the number of sessions conducted. They found that for all age groups, compliance rates at 2 months were approximately 80%. By 6 months, this figure was 55%, steadily decreasing to 13% by 36 months, with the largest decrease observed after the first 8 weeks of the programme. Older men (58 - 65 year olds) were more compliant than younger men. Current smokers were less compliant than former smokers, and baseline work capacity was among the most consistent predictors of early and late compliance. Although these findings were interesting, they do not tell us of the relative levels of compliance between supervised and unsupervised exercise (the control group in this trial did not take part in regular exercise).

A paper by Sluijs and Knibbe 1991{Sluijs, 1991 16021 /id} explored theories surrounding exercise compliance. They noted that 'compliance with exercise regimens ranges from 30% to 57% and rates of compliance drop as time passes. The greatest drop is associated with the moment of discharge.

Physical therapists are aware of this drop in compliance. They estimate that on average 64% of their people complied with exercise prescription during the treatment period, while only 23% continued to do so after treatment had stopped'. Although, this paper provides an estimate of absolute levels of compliance to supervised exercise regimens over time, it does not allow an estimate of relative compliance between supervised and unsupervised programmes.

In the absence of directly applicable data, the GDG were presented with a choice between estimating values based on the available literature or conducting a wider survey of their clinical colleagues. The group elected to pursue the latter option in order to extend the reach of the 'expert opinion' used to inform this important parameter. The methods and results of this survey are described below.

Eliciting expert opinion using an on-line survey

Survey methods

A survey was created using a free website (www.SurveyMonkey.com) to elicit expert opinion from patients and healthcare professionals familiar with these programmes. The link to the survey was sent via email to the GDG, and subsequently forwarded to relevant colleagues of GDG members. The survey asked people to consider only people who had agreed to exercise and contained 10 questions:

Introduction

1. What is your job title and in what county or city are you based?
2. In general, do you think that supervised or unsupervised exercise programmes are more likely to lead to increased exercise levels
    a. Over the short term?
    b. Over the long term?

Supervised exercise

3. In your opinion, of the people who begin a supervised exercise programme, what percentage attends more than 75% of classes?
4. Following completion of a supervised exercise programme, what percentage do you think will continue to exercise at 6 months?
5. Following completion of a supervised exercise programme, what percentage do you think will continue to exercise at 1 year?
6. Following completion of a supervised exercise programme, what percentage do you think will continue to exercise at 2 years?

Unsupervised exercise

7. For people given an unsupervised programme, what percentage do you think will continue to follow the advice at 3 months?
8. For people given an unsupervised programme, what percentage do you think will continue to follow the advice at 6 months?
9. For people given an unsupervised programme, what percentage do you think will continue to follow the advice at 1 year?
10. For people given an unsupervised programme, what percentage do you think will continue to follow the advice at 2 years?

Questions 3 to 10 each contained a free text box where respondents were asked: 'What is your answer based on (personal opinion, clinical experience, audit data, published evidence, other)? If it is based on a source of data, would you be able to share it with us? If you have decided to pass on this question, is there any particular reason?' Respondents were provided with the email address of the guideline health economist to send additional data sources.

Question 2 was originally intended to allow a check of consistency between categorical answers and actual value estimates. However, for the first 23 respondents, the 'forced ranking' option of the survey was activated. This meant that respondents could not choose the same answer for both short and long term questions. Therefore, the results of this question were considered invalid and only answers to questions 3 to 10 were included in the analysis.

Survey results and scenario assumptions

Twenty nine people logged into the online survey. Five did not move beyond the first question and an additional seven did not progress past the second question. In one month, 17 people either partially or fully completed questions 3 to 10. Survey respondents included 9 physiotherapists, 9 vascular surgeons, 10 vascular nurses and one patient representative.

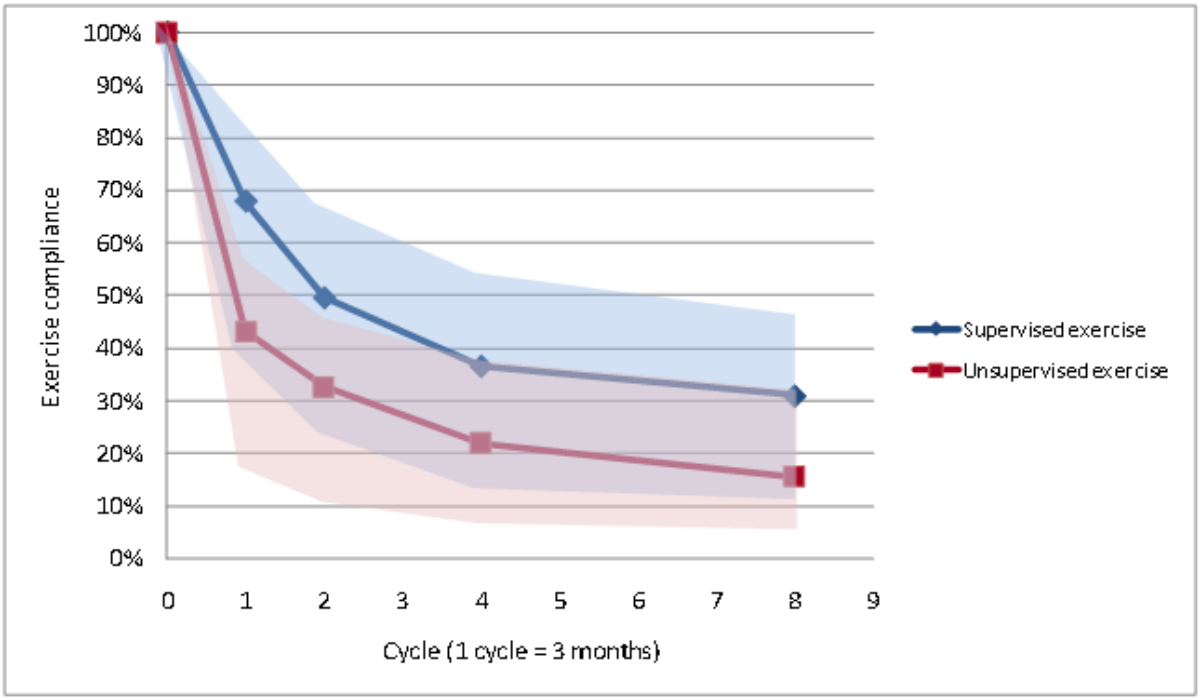
On average, respondents estimated that supervised exercise would lead to greater compliance over both the short and long term (Figure 239). Closer examination of individual answers reveals that the majority of respondents thought that supervised exercise would lead to greater short term compliance. However, there was much more uncertainty over long term compliance. This was reflected in the large proportion of people who chose not to answer this question and expressed differences of opinion among those who did.

Based on the results of the survey and discussions with the GDG, two different scenarios were developed in order to evaluate the effect of different rates of long-term compliance on the results of the model. In each scenario, supervised exercise was assumed to lead to greater compliance over the short term. Over the longer term, compliance to supervised exercise was assumed to be greater than unsupervised exercise in Scenario 1 (Figure 239) and equal to unsupervised exercise in Scenario 2 (Figure 240). The average results of the survey were used to inform the absolute probabilities used in scenario 1. For Scenario 2, the average results were used to inform the estimate for unsupervised exercise and the values for supervised exercise were adjusted accordingly.

The cumulative compliance estimates in each scenario were used to determine the transitional values used in the model. A triangular distribution, defined by its minimum, mode and maximum values, was chosen to represent the data elicited from the survey; the minimum and maximum values were adjusted so that the expected value matched the likeliest estimate.

The survey was subject to several limitations. Although an effort was made to elicit responses from a large and diverse group of people, the number of respondents was small and the majority were physicians, who have been reported to overestimate patient compliance to exercise.{Becker, 1985 16423 /id;Sluijs, 1991 16021 /id} The survey was edited by the GDG prior to distribution but the questions were not validated in a systematic way. In addition, the questions were not randomised and could be subject to question order bias. Due to the limitations in data collection associated with the survey, the GDG decided to use the results to inform estimates of absolute compliance levels and the relative difference between each programme was based on GDG discussion of likely scenarios.

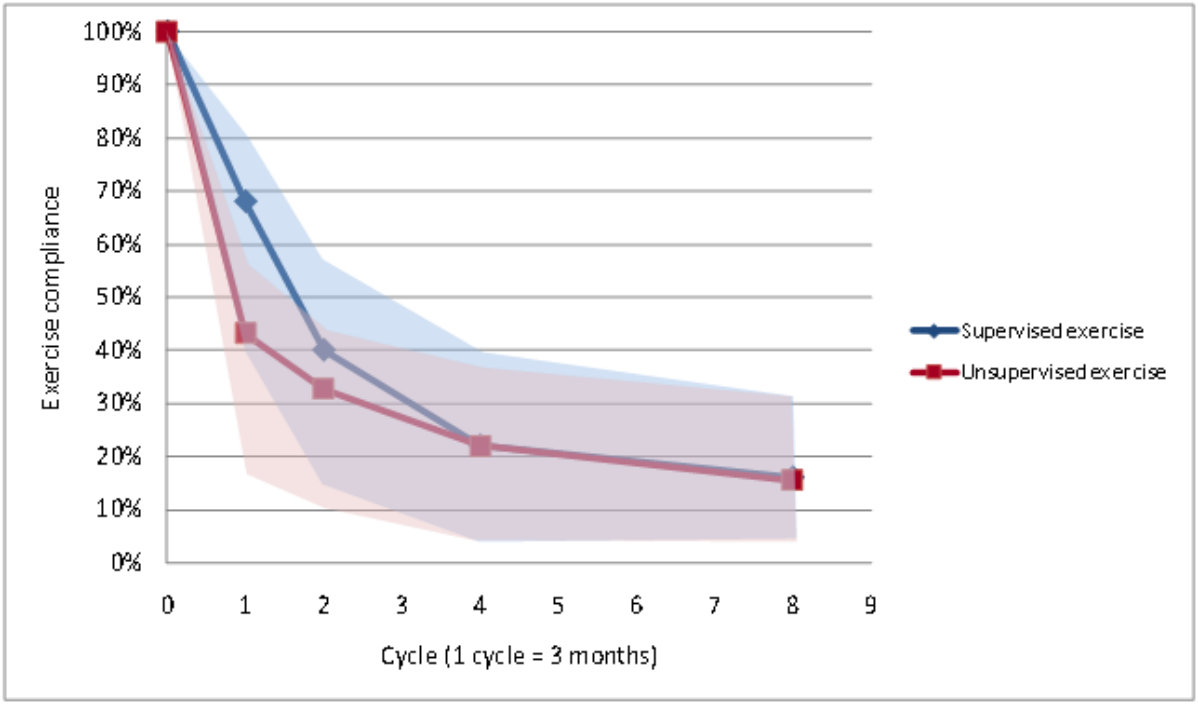
Figure 239: Scenario 1: Average survey results – greater long term compliance to supervised exercise



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%

1

Figure 240: Scenario 2: Equal long term compliance to supervised and unsupervised exercise



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	7%	22%	37%	7%	22%	37%
2 years	8	5%	16%	31%	5%	16%	31%

K.2.3.14 Relative treatment effects

Exercise-associated risk reduction for mortality and cardiovascular events

No randomised evidence of exercise-associated risk of mortality in people with IC was identified in the literature. Because the risk of CV events in individuals with PAD are comparable to the risk faced by people with established cardiovascular disease{Cacoub, 2009 16290 /id}, the GDG agreed that evidence from this population would represent a reasonable source of data in the absence of more direct data.

Recently, a Cochrane review of randomised controlled trials was conducted to determine the effects of exercise-based rehabilitation in people with coronary heart disease{Heran, 2011 16331 /id}. Thirty of the 47 included trials were conducted in people with previous MI. The remaining trials included either exclusively post-coronary revascularisation patients or both groups of patients. The ages of included participants ranged from 46 to 84 and 80% were men. The Cochrane review defined cardiac rehabilitation as an inpatient, outpatient, community or home based exercise intervention appropriate to a cardiac patient population. Interventions were grouped according to whether or not they included a psychosocial and/or educational intervention and trials were analysed according to the length of follow-up (less than or more than one year). For the purpose of our analysis, only trials evaluating the effect of exercise training alone over a period of more than one year were considered. Patients in the control groups received usual care, which could include standard medical care, such as drug therapy, but did not include any form of structured exercise training or advice. According to the results of the Cochrane review, in studies with a follow up of greater than one year total

mortality was reduced with exercise-based cardiac rehabilitation compared to control (RR 0.87 [95% CI 0.75, 0.99], p = 0.041).

The Cochrane review by Heran 2011{Heran, 2011 16331 /id} reported the incidence of MI in people with a follow up of longer than one year. There was no statistically significant difference between exercise-based cardiac rehabilitation and usual care (RR 0.97 [95% CI 0.82, 1.15], p = 0.73).

A meta-analysis of the effect of physical activity on stroke prevention was used to inform the risk of stroke for active compared to sedentary people in the model{Lee, 2003 16333 /id}. Nineteen cohort and case-control studies, including data from the Framingham cohort, Nurses' Health Study, and the Northern Manhattan Stroke Study, were included in this analysis. Overall, moderately active individuals were found to have a 20% lower risk of stroke incidence or mortality than controls (RR = 0.80; 95% CI, 0.74 to 0.86; p<0.001).

Although the GDG agreed that this represented the best available source of data, they also noted that there are several limitations associated with using estimates derived from an indirect patient population. For example, there is a difference in exercise capacity between the two groups which may affect the magnitude of the effect size{Hamer, 2008 16332 /id}. In addition, the GDG noted that many of the trials included in the review predate what is considered current 'best medical therapy'. The introduction of improved lipid modification medications, for example, may have an effect on observed outcomes. However, this limitation would equally apply to studies conducted in people with PAD.

K.2.3.5 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 was collected from all RCTs included in the clinical review (Table 18). One study included the EQ-5D as a measure of HRQoL. Five papers (representing an additional four trials) reported SF-36 data. According to the NICE reference case, 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{Ara, 2008 16334 /id} 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{Kakkos, 2005 453 /id;Savage, 2001 3035 /id} provided all the necessary values and the authors of the remaining three studies{Cheetham, 2004 549 /id;Nicolai, 2010 15927 /id;Pinto, 1997 17 /id} were contacted to request the required data (Table 18).

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{Cheetham, 2004 549 /id}, Nicolai 2010/van Asselt 2011{Nicolai, 2010 15927 /id;van Asselt, 2011 16275 /id} and Savage 2001{Savage, 2001 3035 /id} 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{Briggs, 2006 16373 /id}. Probabilistic mapped values were then calculated using Equation 4 from the paper by Ara and Brazier{Ara, 2008 16334 /id}, 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. The results of these simulations are reported in Table 21.

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 (see section K.3.2). 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. See Table 22 for study numbers and weights used to calculate these estimates. 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 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; the impact of assuming a greater cost of supervised exercise programme to reflect a longer average trial duration is explored in section K.3.2. The effect of using values from each individual trial in the model was explored in sensitivity analysis (section K.2.4 and K.3.2).

Table 18: Quality of life outcomes reported by RCTs included in clinical review

Studies included in clinical review	Generic quality of life measurement used	Additional data requested from authors?	Additional data obtained from authors?	Mapped to EQ-5D?	Included in cost-effectiveness analysis?	Notes/comments
Unsupervised exercise vs. supervised exercise						
EXITPAD	EQ-5D SF-36	Not necessary Yes	NA Yes	NA Yes	Yes No	EQ-5D data used in preference to mapped SF-36 data in base case analysis. Mapped data used in sensitivity analysis.
Cheetham 2004	SF-36	Yes	Yes	Yes	Yes	SE or SD not reported; assumed same SE as reported for each dimension by Nicolai 2010
Savage 2001	SF-36	Not necessary	NA	Yes	Yes	All relevant values reported by authors.
Pinto 1997	SF-36	Yes	Not available	NP	No	Authors replied that study data was collected over 10 years ago and is no longer available.
Kakkos 2005	SF-36	No	NA	NP	No	Data contained zero values which could not be mapped probabilistically.
Regensteiner 1997	SF-20	NA	NA	NA	No	No validated algorithms for mapping SF-20 to EQ-5D are currently available.
Stewart 2008	None	NA	NA	NA	NA	NA
Treat-Jacobson 2009	None	NA	NA	NA	NA	NA
Tew 2009	None	NA	NA	NA	NA	NA
Tisi 1997	None	NA	NA	NA	NA	NA
Zwierska 2005	None	NA	NA	NA	NA	NA

Abbreviations: EQ-5D = EuroQol 5 Dimensions; SF-36 = Short Form 36-item questionnaire; NA = not applicable; NP = not possible

Table 19: 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**
van Asselt{van Asselt, 2011 16275 /id} – 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

Table 20: SF 36: Individual domains and mapped EQ-5D values

	Unsupervised exercise					Supervised exercise				
	Baseline	**3 months**	**6 months**	**9 months**	**12 months**	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**
Cheetham2004¥ {Cheetham, 2004 549 /id} - 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±	**0.69 (0.02)**	**0.71 (0.02)**	**0.70 (0.02)**	**0.73 (0.02)**	**0.71 (0.02)**	**0.71 (0.02)**	**0.77 (0.02)**	**0.79 (0.02)**	**0.79 (0.02)**	**0.78 (0.02)**
Kakkos 2005¥ {Kakkos, 2005 453 /id} – 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°	**NE**	**NR**	**NE**	**NR**	**NE**	**NE**	**NR**	**NE**	**NR**	**NE**
Nicolai 2010{Nicolai, 2010 15927 /id} – 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±	**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{Savage, 2001 3035 /id} – 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±	**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**

Abbreviations: EQ-5D = EuroQol 5-Dimension; SF-36 = Short Form 36-item questionnaire; 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; NR = not reported; NE = not estimable.
±Mapped based on algorithm (Equation1) reported by Ara and Brazier 2008{Ara, 2008 ARA2008 /id}
° Not estimable based on median values of 0.
¥ No error estimates were provided in the paper/by the author. The standard deviation of each SF-36 dimension score reported by Nicolai 2010 was used to inform the standard error for these studies (SE = SD/SQRT n).

Table 21: Quality of life among people who complete supervised and unsupervised programmes

	Unsupervised exercise			Supervised exercise			Mean difference in change		
	Mean	95% CI	SE	Mean	95% CI	SE	Intvl	Mean	SE
van Asselt 2011{van Asselt, 2011 16275 /id} (EXITPAD)									
Baseline	0.620	0.58 – 0.66	0.023	0.660	0.62 – 0.70	0.019			
3 months	0.680	0.64 – 0.72	0.023	0.690	0.650 -0.730	0.020	B to 3	-0.030	0.042
6 months	0.690	0.65 – 0.73	0.019	0.720	0.68 – 0.76	0.016	3 to 6	0.019	0.039
9 months	0.680	0.64 – 0.72	0.023	0.730	0.69 – 0.77	0.020	6 to 9	0.020	0.039
12 months	0.660	0.61 – 0.71	0.028	0.740	0.69 – 0.79	0.021	9 to 12	0.030	0.047
Cheetham 2004*{Cheetham, 2004 549 /id}									
Baseline	0.687	0.65 - 0.72	0.017	0.711	0.68 - 0.74	0.017			
3 months	0.708	0.67 - 0.74	0.019	0.765	0.73 - 0.80	0.019	B to 3	0.055	0.059
6 months	0.704	0.67 - 0.74	0.019	0.789	0.75 - 0.83	0.020	3 to 6	0.038	0.062
9 months	0.733	0.69 - 0.77	0.021	0.792	0.75 - 0.83	0.020	6 to 9	-0.027	0.065
12 months	0.708	0.67 - 0.75	0.021	0.775	0.74 - 0.81	0.020	9 to 12	0.026	0.068
Savage 2001*{Savage, 2001 3035 /id}									
Baseline	0.659	0.61 - 0.71	0.027	0.679	0.63 - 0.73	0.027			
3 months	0.761	0.70 - 0.81	0.028	0.739	0.69 - 0.79	0.026	B to 3	-0.143	0.092
6 months	0.684	0.60 - 0.77	0.043	0.688	0.63 - 0.74	0.027	3 to 6	0.048	0.106
9 months	Not measured			Not measured			6 to 9	NA	
12 months	Not measured			Not measured			9 to 12	NA	
Weighted average									
Baseline	0.636	0.602 - 0.668	0.017	0.672	0.643 – 0.700	0.014			
3 months	0.692	0.658 - 0.725	0.017	0.709	0.649 – 0.738	0.015	B to 3	-0.021	0.033
6 months	0.692	0.664 - 0.720	0.014	0.732	0.707 – 0.756	0.013	3 to 6	0.026	0.032
9 months	0.692	0.654 - 0.727	0.018	0.744	0.711 – 0.775	0.016	6 to 9	0.010	0.034
12 months	0.671	0.625 – 0.714	0.023	0.748	0.714 – 0.780	0.017	9 to 12	0.029	0.039

Abbreviations:B = Baseline; 95% CI = 95% confidence interval; SE = standard error; Intvl = interval (equivalent to model cycle).

**Mapped from SF-36 to EQ-5D using Equation 1 from algorithm reported by Ara and Brazier 2008{Nicolai, 2010 15927 /id}.*

Table 22: Number of subjects per study and values used to calculate weighted average utilities

	Unsupervised exercise			Supervised exercise		
	Savage 2001	EXITPAD	Cheetham 2004	Savage 2001	EXITPAD	Cheetham 2004
	N (% total)	N (% total)	N (% total)	N (% total)	N (% total)	N (% total)
Baseline	10 (7.0%)	102 (71.8%)	30 (21.1%)	11 (7.4%)	109 (73.2%)	29 (19.5%)
3 months	10 (7.0%)	102 (71.8%)	30 (21.1%)	11 (7.4%)	109 (73.2%)	29 (19.5%)
6 months	10 (7.0%)	102 (71.8%)	30 (21.1%)	11 (7.4%)	109 (73.2%)	29 (19.5%)
9 months	0 (0.0%)	102 (77.3%)	30 (22.7%)	0 (0.0%)	109 (79.0%)	29 (21.0%)
12 months	0 (0.0%)	84 (73.7%)	30 (26.3%)	0 (0.0%)	93 (76.2%)	29 (23.8%)

Quality of life following a cardiovascular event

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{Squires, 2010 16319 /id} (Table 23).

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 0.654). 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 24. In the model, each utility decrease was divided by four to account for the three month cycle length. It was assumed that the quality of life decrement in the years following a cardiovascular event is half that experienced in the first year. In the model, the probabilistic mean utility decrement was divided by four to account for cycle length.

Table 23: Quality of life following cardiovascular events reported in literature

Event	Mean utility	SE	Source
MI	0.760	0.018	Goodacre 2004{Goodacre, 2004 16276 /id}
Stroke	0.629	0.040	Tengs 2003{Tengs, 2003 16277 /id}

MI = myocardial infarction; SE = standard error

Table 24: Simulated mean utility and mean utility decrements compared to baseline utility

	Utility associated with each health state			Corresponding utility decrease from baseline		
Health state	**Mean**	**SE**	**95% CI**	**Mean**	**SE**	**95% CI**
IC (baseline)	0.654	0.011	0.633 - 0.676			
MI	0.497	0.015	0.469 - 0.525	-0.157	0.012	- 0.181 to -0.134
Post MI	0.576	0.011	0.554 - 0.598	-0.079	0.006	- 0.091 to -0.067
Stroke	0.412	0.027	0.192 - 0.297	-0.243	0.026	- 0.296 to -0.192
Post stroke	0.533	0.016	0.502 - 0.564	-0.122	0.013	- 0.149 to -0.096

K.2.3.6 Resource use and cost

Cost of supervised and unsupervised exercise programmes

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{Curtis, 2010 CURTIS2010 /id}. A gamma distribution was fitted around the total cost by assuming a standard error of 10%. This standard error resulted in a range of costs that was thought a resaonable representation of the variation that might be expected in different programmes in different areas of the country (95% CI £232 to £345). A breakdown of the assumptions and unit costs used to calculate per-patient cost of a supervised exercise programme are provided in Table 25.

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 assumed to be £0. This was varied in sensitivity analysis to account for different levels of support provided by different types of unsupervised programmes.

Table 25: 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 3)
(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{Curtis, 2010 CURTIS2010 /id}

Cost of cardiovascular events

The approach to modelling cardiovascular events was based on the model developed for the most recent NICE hypertension guideline update{National Clinical Guideline Centre, 2011 16341 /id}. 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. In subsequent cycles they were assigned an ongoing cost representing the average costs following an event. In order to incorporate these values into the probabilistic analysis it was assumed that the standard error was 10% of the total cost and a gamma distribution was applied. The costs and original sources used to inform each health state are summarised in Table 26.

Table 26: Cost of MI and stroke per 3 month cycle

Event	Mean cost per 3 month cycle	SE[‡]	Original source of mean cost estimate
MI	£4 792	£497	Palmer 2002{Palmer, 2002 16339 /id}, inflated to 2009/10{Curtis, 2010 CURTIS2010 /id}
Post MI	£141	£14	Assumption from 2006 Hypertension guideline update{National Collaborating Centre for Chronic Conditions, 2006 16340 /id} inflated to 2009/10{Curtis, 2010 CURTIS2010 /id}
Stroke	£9 630	£963	Youman 2003{Youman, 2003 16338 /id} inflated to 2009/10{Curtis, 2010 CURTIS2010 /id}
Post stroke	£559	£56	Youman 2003{Youman, 2003 16338 /id} inflated to 2009/10{Curtis, 2010 CURTIS2010 /id}

‡Based on a standard error assumed to be 10% of the mean.

K.2.4 Sensitivity analyses

The following sensitivity analyses were undertaken to explore the effect of different parameter inputs and assumptions on the results of the model. The results of all sensitivity analyses are presented in section K.3.2.

SA1 and SA2: Baseline risk of total mortality in people with IC

In the base case analysis, the Framingham equations and data from the Ankle Brachial Collaboration was used to inform the risk of death in people with IC. However, several other sources of data are available, including a study evaluating the relationship between ABPI and mortality in people with PAD by Diehm and colleagues (2006){Diehm, 2006 16237 /id} and mortality rates reported by the Edinburgh Artery Study. Diehm 2006 reported an unadjusted hazard ratio of 4.41 (95% CI, 2.94 to 6.62){Diehm, 2006 16237 /id} for ABPIs of between 0.5 and 0.7 compared to people with normal ABPI, while the Edinburgh artery study observed a hazard ratio of 1.42 (95% CI, 1.15 to 1.74) in a community based sample of people with IC compared to those without IC. Both of these values were used to explore the effect of baseline mortality on the results of the model.

SA3: Relative risk of mortality in active people

The base case model assumes that the reduction in the beneficial effect of exercise observed in people with established cardiovascular disease applies equally to people with IC. The model also assumes that this effect is only relevant so long as people remain active. In sensitivity analysis, the probability of mortality for people who are active was set equal to the probability for those who are inactive in order to observe the effect of this assumption on the results of the model.

SA4: Risk of cardiovascular events in active people

The base case model also assumes that activity has an effect on cardiovascular risk in people with IC so long as they are active. To examine the effect of this assumption on the results of the model, the beneficial effect of exercise was removed from the model. Therefore, under this sensitivity analysis, exercise (either supervised or unsupervised) is not associated with a decreased risk of CV events.

SA5: Risk of mortality & cardiovascular events in active people

When the assumed benefit of exercise on mortality and cardiovascular events is removed, the result remains in favour of supervised exercise as the most cost-effective type of exercise programme for the treatment of IC.

SA6: Quality of life beyond one year in people who continue to exercise

In the absence of evidence to inform quality of life beyond the follow-up of included trials, a key assumption of the model is that at the end of one year, the gain in quality of life achieved by people in each exercise arm are maintained by those who continue to be active. The effect of this assumption was explored by running the model when there is no difference in quality of life between treatment strategies after one year.

SA7: All key assumptions

A sensitivity analysis was undertaken to examine the effect of removing all key assumptions (maintenance of quality of life gain and benefit to mortality and CV risk in those who are active) from the model. Under this analysis, the only major assumption external to the data collected from the included trials is the level of patient compliance, which is used to estimate the average cost and quality of life associated with each exercise programme.

SA8 to SA10: Methods of calculating quality of life

There are several other ways in which utility values could be calculated for this model, including using only the EQ-5D values reported by the EXITPAD study (as reported in Table 27), the weighted mean difference in change between absolute values as calculated using Equation 1 and EQ-5D from

the EXITPAD trial (Table 28), and the weighted mean difference in change using mapped values from all three trials (Table 29). Each of the corresponding utility values were entered into the model in turn in order to examine the impact of each method on the results of the model.

SA 11 to SA12: Cost of supervised exercise programme

The cost of a supervised exercise programme is likely to differ around the country. The GDG noted that in some centres only two staff members are involved in provision (one physiotherapist and one technician). In order to explore the effect of less costly and more costly supervised exercise programmes, the costs was set to the lower and upper limits of the 95% confidence interval (£232 to £345), which was derived from assumed 10% standard error around the mean cost estimate.

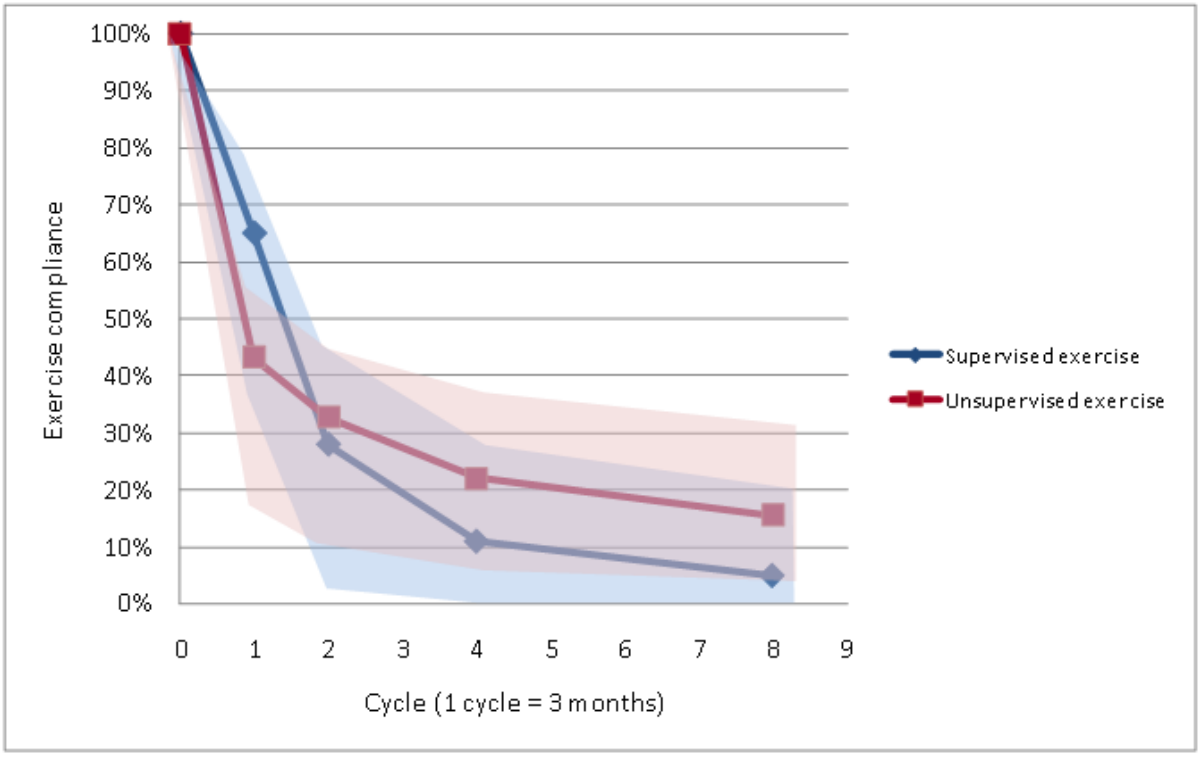
SA13: Discount rates

Currently, the NICE reference case states that both costs and QALYs should be discounted at a rate of 3.5% per year. Recently, there has been a debate surrounding this assumption. In order to test the impact of these rates on model results, each scenario was run with QALYs discounted at 1.5% and costs at 3.5%.

SA14: Cost of unsupervised exercise programmes

Different unsupervised exercise programmes may include different amounts of patient support, such as regular telephone calls, an exercise diary, or education component. The GDG noted that increased support may be associated with greater compliance to unsupervised exercise. In two way sensitivity analysis, an average cost of £25 was used to inform the cost of unsupervised exercise and compliance to unsupervised exercise was adjusted to be less than supervised exercise over the short term but greater than supervised exercise over the long term (Figure 241).

Figure 241: Sensitivity analysis: greater long term compliance to unsupervised exercise



SA15: Compliance to supervised and unsupervised exercise

Holding all other base case values constant, the model was run to determine which exercise programme is most cost effective when there is no relative difference in compliance. This scenario was run twice in order to illustrate the effect of absolute exercise compliance on the results of the model. In the first analysis, compliance in both programmes was equal to the level of compliance to unsupervised exercise in the base case analysis (as reported in Figure 239 and Figure 240). A second analysis was run in which compliance to both programmes was equivalent to that of supervised exercise in scenario 1 (Figure 239).

Table 27: Difference in change in quality of life – EQ 5D values from Nicolai 2010

	Quality of life								
	Savage 1995			Nicolai 2011			Cheetham 2004		
	Mean	95% CI	SE	Mean	95% CI	SE	Mean	95% CI	SE
Baseline to 3 months				-0.03	-0.12 – 0.06	0.04			
3 to 6 months				0.02	-0.07 – 0.11	0.04			
6 to 9 months				0.02	-0.07 – 0.11	0.04			
9 to 12 months				0.03	-0.06 – 0.12	0.05			

Table 28: Difference in change in quality of life – Calculated using absolute mapped values (Equation 1; Ara and Brazier 2008) and Nicolai 2010 EQ-5D

	Quality of life									Weighted average change in mean difference		
	Savage 1995			Nicolai 2011			Cheetham 2004					
	Mean	95% CI	SE	Mean	95% CI	SE	Mean	95% CI	SE	Mean	95% CI	SE
Baseline to 3 months	-0.04	-0.15 – 0.06	0.05	-0.03	-0.12 – 0.06	0.04	0.03	-0.04 – 0.10	0.04	-0.02	-0.08 – 0.05	0.03
3 to 6 months	0.03	-0.10 – 0.15	0.06	0.02	-0.07 – 0.11	0.04	0.03	-0.05 – 0.10	0.04	0.02	-0.04 – 0.09	0.03
6 to 9 months	Not measured			0.02	-0.07 – 0.11	0.04	-0.03	-0.10 – 0.05	0.04	0.01	-0.06 – 0.08	0.04
9 to 12 months	Not measured			0.03	-0.06 – 0.12	0.05	0.01	-0.07 – 0.09	0.04	0.03	-0.05 – 0.10	0.04

Table 29: Difference in change in quality of life – Calculated using mapped differences – SF-36 values from Nicolai 2010 (Equation 4; Ara and Brazier 2008)

	Quality of life									Weighted average change in mean difference		
	Savage 1995			Nicolai 2010			Cheetham 2004					
	Mean	95% CI	SE	Mean	95% CI	SE	Mean	95% CI	SE	Mean	95% CI	SE
Baseline to 3 months	-0.04	-0.15 – 0.06	0.05	0.05	-0.01 – 0.11	0.03	0.03	-0.04 – 0.10	0.04	0.04	-0.02 – 0.09	0.03
3 to 6 months	0.03	-0.10 – 0.15	0.06	0.02	-0.04 – 0.09	0.03	0.03	-0.05 – 0.10	0.04	0.03	-0.03 – 0.08	0.03
6 to 9 months	Not measured			0.05	-0.02 – 0.11	0.03	-0.03	-0.10 – 0.05	0.04	0.03	-0.03 – 0.09	0.03
9 to 12 months	Not measured			0.00	-0.08 – 0.07	0.04	0.01	-0.07 – 0.09	0.04	0.00	-0.06 – 0.07	0.03

K.2.411 Threshold analysis - Naftidrofuryl oxalate

The systematic clinical review did not identify any randomised controlled evidence comparing Naftidrofuryl oxalate to either supervised or unsupervised exercise. Without comparative evidence it was not possible to evaluate the relative effect of vasoactive drugs compared to exercise programmes in the base case analysis. Instead, naftidrofuryl oxalate was incorporated into the model by including all parameters of interest except evidence of comparative efficacy (as measured by quality of life). A threshold analysis was run to determine how many QALYs would be required for it to be considered cost-effective compared to supervised and unsupervised exercise. The assumptions and inputs used to inform this analysis were very similar to those used in the TA. These data are summarised in Table 30 and discussed below.

Table 30: 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{NHS Business Services Authority, 2011 16336 /id}
Discontinuation at 6 months	11%	NA	Fixed	NA	Squires 2010{Squires, 2010 16319 /id}
Discontinuation at 36 months	68%	NA	Fixed	NA	Squires 2010{Squires, 2010 16319 /id}
Relative effect on mortality	1	NA	Fixed	NA	Squires 2010{Squires, 2010 16319 /id}
Relative effect on stroke & MI	1	NA	Fixed	NA	Squires 2010{Squires, 2010 16319 /id}

Cost of naftidrofuryl oxalate

The cost of naftidrofuryl oxalate was based on the latest available NHS Drug Tariff list price. The May 2011 drug tariff lists only the generic version of the drug at a price of £4.68 per package of 84 100mg capsules. As in the TA, an average daily dose of 600mg per day was used to calculate a cost of £30.49 per 3 month model cycle.

Cost of cardiovascular events

The same cost of MI and stroke as used in the base case analysis was applied to the threshold analysis.

Discontinuation of treatment

The same rate of discontinuation reported in the TA was used to inform the threshold analysis in the current model. Because only two time points were reported in the TA, the 24 week probability was converted to a rate ($r = -Ln[1-P(t)]/t = 0.059$) and divided by 2 to obtain the 12 week probability of discontinuation ($p = 1 - e^{-rt} = 5.71\%$) in the first two cycles in the model. Thereafter, a constant discontinuation rate of 5.69% was applied to all subsequent cycles, resulting in a 36 month

probability of discontinuation of 68%. In the model, the discontinuation rate was used to modify the estimated total average cost of naftidrofuryl oxalate, as only those people who adhere to treatment incur the associated cost.

Relative effect on mortality & cardiovascular events

As in the TA, it was assumed that vasoactive drugs are for symptomatic relief only and do not have any impact on mortality or cardiovascular disease. Therefore, in the current model, adherence to drug treatment did not have any impact on life expectancy or the probability of experiencing a stroke or MI.

Quality of life

People in the naftidrofuryl arm were assigned the same baseline quality of life as those in the exercise arm. In threshold analysis, the gain in quality of life during each 3 month cycle was varied between 0 and 1.

K.2.5 Interpreting results

The results of cost-effectiveness analysis are presented as incremental cost-effectiveness ratios (ICERs). ICERs are calculated by dividing the difference in costs associated with two alternative treatments by the difference in QALYs:

$$\frac{\text{Difference in costs}}{\text{Difference in QALYs}}$$

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. In general, an intervention is considered to be cost-effective if either of the following criteria apply:

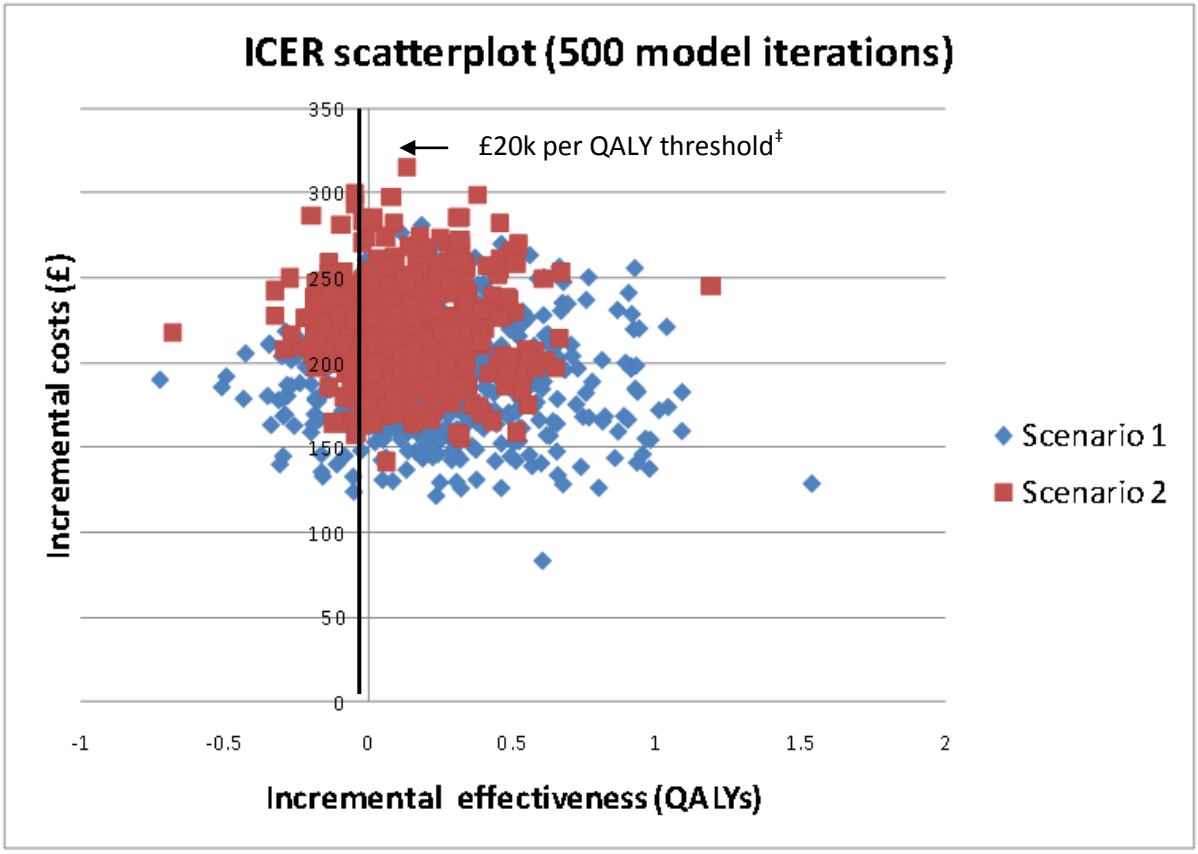
- The intervention dominates other relevant strategies (that is, is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

K.3 Results

K.3.1 Base case 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 31).

Figure 242: Distribution of incremental costs and effects



‡Points lying to the right of the £20k threshold are considered cost effective.

Table 31: Mean base case results (probabilistic)

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 32 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 CV 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 33 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 exercise on cardiovascular morbidity does not affect the results of the model.

Table 32: 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 33: 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

K.3.2 Sensitivity analyses

A wide range of probabilistic sensitivity analyses showed that supervised exercise is the most cost effective strategy in the majority of cases tested (Table 34 and Table 35). 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. When both cost and compliance to unsupervised exercise is increased, supervised exercise is unlikely to be cost-effective (Table 36). Table 37 shows the effect that varying absolute levels of compliance (with no relative difference between programmes) has on total costs and QALYs predicted by the model.

Table 34: SCENARIO 1: Results of probabilistic sensitivity analyses

	Δ Costs	Δ QALY	ICER	Probability supervised is CE
Base case				
Base case results	£191	0.268	£711	79%
Sensitivity analyses				
Baseline risk of mortality				
SA1: Baseline relative risk of mortality set to 4.41	£199	0.231	£858	79%
SA2: Baseline relative risk of mortality set to 1.42	£168	0.334	£502	79%
Key model assumptions				
SA3: No mortality benefit from exercise	£175	0.214	£818	76%

SA4: No CV event benefit from exercise	£237	0.263	£899	79%
SA5: No mortality or CV event benefit from exercise	£219	0.211	£1, 040	76%
SA6: No difference in QoL beyond one year	£190	0.051	£3, 754	83%
SA7: No difference in QoL beyond one year and no mortality or CV event benefit from exercise	£220	0.010	£21, 200	49%
Quality of life calculations				
SA8: Using only EXITPAD EQ-5D values to inform QoL	£191	0.270	£706	74%
SA9: Using mean difference in absolute mean QoL	£191	0.237	£805	78%
SA10: Using only mapped SF-36 values to inform QoL	£191	0.094	£2, 028	64%
Costs				
SA11: Decreased cost of supervised programme	£147	0.265	£556	80%
SA12: Increased cost of supervised programme	£233	0.265	£880	79%
Discount rates				
SA13: Rate of 1.5% for QALYs and 3.5% for costs	£190	0.304	£626	80%

Δ= difference between supervised and unsupervised exercise interventions; CE = cost effective; CV = cardiovascular; SA = sensitivity analysis; QoL = quality of life; EQ-5D = EuroQol 5-Dimension questionnaire.

Table 35: SCENARIO 2: Results of probabilistic sensitivity analyses

	Δ Costs	Δ QALY	ICER	Probability supervised is CE
Base case				
Base case results	£215	0.134	£1, 608	75%
Sensitivity analyses				
Baseline risk of mortality and CV events				
SA1: Baseline relative risk of mortality set to 4.41	£216	0.114	£1, 903	74%
SA2: Baseline relative risk of mortality set to 1.42	£212	0.166	£1, 275	75%
Key model assumptions				
SA3: No mortality benefit from exercise	£213	0.119	£1, 789	74%
SA4: No CV event benefit from exercise	£221	0.131	£1, 695	75%
SA5: No mortality or CV event benefit from exercise	£219	0.119	£1, 849	75%
SA6: No difference in QoL beyond one year	£215	0.009	£23, 479	47%
SA7: No difference in QoL beyond one year and no mortality or CV event benefit from exercise	£219	0.005	£48, 017	41%
Quality of life calculations				
SA8: Using only EXITPAD EQ-5D values to inform QoL	£215	0.128	£1, 685	69%
SA9: Using mean difference in absolute mean QoL	£215	0.115	£1, 874	73%
SA10: Using only mapped SF-36 values to inform QoL	£215	0.052	£4, 117	62%
Costs				
SA11: Decreased cost of supervised programme	£174	0.133	£1, 310	75%
SA12: Increased cost of supervised programme	£258	0.133	£1, 941	74%
Discount rates				
SA13: Rate of 1.5% for QALYs and 3.5% for costs	£215	0.145	£1, 483	74%

Δ= difference between supervised and unsupervised exercise interventions; CE = cost effective; CV = cardiovascular; SA = sensitivity analysis; QoL = quality of life; EQ-5D = EuroQol 5-Dimension questionnaire.

Table 36: SA14: Increased cost and compliance to unsupervised exercise

Strategy	Total cost	Incremental	Total	Incremental	ICER	Probability

		cost	QALYs	QALYs		CE
Unsupervised	£2, 499	Baseline	5.077	Baseline	Baseline	55%
Supervised	£2, 730	£231	5.087	0.010	£23, 718	45%

K.3.13 Threshold analysis of naftidrofuryl oxalate

The per-cycle QALY gain (compared to unsupervised exercise) necessary for naftidofuryl to be more cost effective than supervised exercise is reported in Table 37. According to the utility calculations undertaken by the NICE TA{Squires, 2010 16319 /id}, 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 gain of 0.0215 QALYs. Multiplying this value by 54% (13 /24 weeks) results in an average three month utility gain of 0.0116 QALYs. According to these estimates naftidrofuryl oxalate is not likely to be cost effective compared to supervised and unsupervised exercise, although it is difficult to make comparisons due to differences in the methods used to estimate utility values. Table 38 shows the comparative cost impact of the assumption that naftidrofuryl is does not affect the risk of cardiovascular events, as well as the total average lifetime cost of the drug based on compliance rates reported by the NICE TA.

Table 37: Threshold at which naftidrofuryl oxalate is more cost effective than supervised exercise

	Mean difference in change in utility threshold (per cycle)
Scenario 1	0.029
Scenario 2	0.017

Table 38: Breakdown of costs in naftidrofuryl oxalate treatment arm compared to exercise

	Unsupervised exercise	Supervised exercise	Naftidrofuryl oxalate
Scenario 1- Greater long term compliance to supervised exercise			
Intervention	£0	£219	£477
Initial CV events	£1, 186	£1, 176	£1, 199
Follow-up CV event	£1, 259	£1, 241	£1, 284
Scenario 2– Equal long term compliance			
Intervention	£0	£219	£477
Initial CV events	1, 186	£1, 184	£1, 199
Follow-up CV event	£1, 259	£1, 256	£1, 284

K.4 Discussion

K.4.1 Summary of results

This analysis found that supervised exercise is more cost effective than unsupervised exercise for the treatment of people with IC. This conclusion was robust to a wide range of sensitivity analyses.

The key cost difference between the programmes is the cost of the supervised exercise programme while key driver in the difference in effectiveness (QALYs) is the gain in quality of life associated with supervised exercise programmes.

The analysis is 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. Long-term follow-up of future trials is needed to inform this estimate.

Similarly, compliance to exercise is a key factor in determining overall cost and effect of each type of intervention. The main assumption of the model is that the gain in quality of life associated with each type of exercise, and the decrease in mortality and cardiovascular risk associated with exercise, are maintained by people who continue to be physically active. If in reality, either the relative and/or absolute levels of compliance to exercise are significantly different to the estimates used in the model, the cost-effectiveness of supervised exercise is much less certain.

In the absence of comparative clinical data, a threshold analysis was conducted to determine the QALY gain that would be needed to make naftidofuryl oxalate a more cost effective treatment than supervised exercise under the assumptions of the model. According to the results of the model and the utility gain estimated by the NICE TA{Squires, 2010 16319 /id}, naftidrofuryl oxalate is not likely to be cost effective compared to supervised exercise; however, this conclusion is subject to a number of limitations.

K.4.2 Limitations and interpretation

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.

K.4.3 Generalisability to other populations/settings

Intermittent claudication is defined as pain in the legs that is brought on by exertion and relieved by rest. As a result, exercise performance in people with claudication is approximately half that of age-matched controls(Regeneteiner 2002). Functional exercise capacity impacts people's ability to carry out day to day activities and is correlated with poor quality of life in this population{Bauman, 1997 15967 /id}. Due to the specific improvement in functional ability derived from exercise interventions, exercise programmes may have an effect on quality of life which is disproportionate to people with other conditions. Because the results of this analysis are largely dependent on the gain in quality of

life experienced by those undertaking supervised exercise programmes, the results of this analysis may not be applicable to other populations.

K.4.4 Comparisons with published studies

Two published cost-utility analyses were identified that compared unsupervised to supervised exercise for the treatment of IC{Lee, 2007 901 /id;van Asselt, 2011 16275 /id}. Both studies were based on clinical trials.

Lee 2007{Lee, 2007 901 /id} conducted a non-randomised trial with a follow-up of six months. Based on an extrapolation of the quality of life outcomes to one year, the authors concluded that supervised exercise is cost effective compared to unsupervised exercise in a UK NHS setting. However, this study used the SF-36 index score as a measure of utility; because the SF-36 does not accounting for preference weighting this is an invalid method of calculating QALYs. When the reported SF-36 scores are mapped to using the preference-based algorithm described by Ara and Brazier 2008{Ara, 2008 16334 /id}, supervised exercise results in slightly fewer QALYs but remains cost-effective compared to unsupervised exercise given the comparatively low estimate for the cost of a supervised exercise programme (£52).

The analysis by van Asselt 2011{van Asselt, 2011 16275 /id} was based on an RCT included in the clinical review (Nicolai 2010). Using bootstrap analysis, this study reported that supervised exercise cost £23, 695 per QALY with a 35% probability of being cost effective at a threshold of £20, 000. This analysis was undertaken from a Dutch healthcare perspective with a trial period of one year. On the basis of the results of this study, supervised exercise would not be considered cost effective for the NHS.

Neither of the included studies was thought to sufficiently capture the long-term effect of treatment nor were they designed to evaluate the benefit to cardiovascular health that is associated with exercise. Our analysis extrapolated costs, quality of life and the impact of exercise on CV events and mortality using best available data from the published literature in order to estimate the cost-utility of a supervised exercise programme from a UK NHS perspective. Sensitivity analysis shows that when these key assumptions are removed, the results of the model are similar to those of van Asselt 2011.

K.4.5 Conclusion = evidence statement

The results of our analysis suggest that compared to unsupervised exercise, supervised exercise programmes represent a cost effective treatment for people with IC.

K.4.6 Implications for future research

Research into the long term effects of exercise on cardiovascular events, mortality and quality of life in people with IC and how these outcomes differ between people undertaking supervised and unsupervised programmes is needed. In addition, future research into the most effective and cost effective content and method of programme delivery would ensure the most efficient use of NHS resources and best outcomes are achieved for people with claudication. High quality comparative evidence of real-world compliance to each type of exercise programme will form an essential element of this research

Appendix L: Cost-effectiveness analysis – Exercise compared to angioplasty for the treatment of intermittent claudication

L.1 Introduction

Claudication is the most frequent symptom of peripheral arterial disease (PAD). It is defined as discomfort or pain in the thigh or calf muscles that is brought on by walking and relieved by rest. All individuals with PAD experience some degree of functional impairment, but people with moderate to severe claudication often have severely limited physical functioning. PAD is also associated with an increased risk of mortality and cardiovascular events.

The primary treatment goals of IC are to alleviate symptoms, reduce risk factors and improve quality of life. Treatment strategies consist of non-interventional therapies, such as supervised and unsupervised exercise programmes, and endovascular treatments such as angioplasty and bypass surgery.

Currently, local patterns of referral and availability of exercise programmes largely dictate the treatment that people with IC receive. Conflicting results about the cost-effectiveness of different treatments have been reported (Chapter 9) and there are no published studies comparing all available intervention sequences based on randomised clinical data. The aim of this analysis was to determine the most cost-effective treatment pathway for patients with intermittent claudication in England and Wales who are suitable for both exercise and angioplasty as first-line treatment options.

L.2 Methods

L.2.1 Model overview

L.2.1.1 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 39).

Based on the studies included in the clinical 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 and resting to recover. Supervised exercise was defined as a community-based exercise programme supervised by healthcare professionals. In England and Wales, these programmes are typically supervised by two physiotherapists and have approximately 10 patients per group. The programme consists of approximately two hours of classes per week for a period of three months. Patients exercise until the onset of symptoms, then rest. They may walk on treadmills or outside, complete circuits, etc. The model did not evaluate different durations, intensities or modality of exercise programmes.

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 of the full guideline). 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 39: 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	

L.2.1.62 Population

The hypothetical population included in the analysis was people with IC who are suitable for and willing to undergo either exercise or angioplasty. Not included were people with co-morbidities which prevent participation in an exercise programme; 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.

L.2.1.83 Time horizon, perspective, discount rates used

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.

L.2.62 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) 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{Hirsch, 2006 16364 /id}. 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.

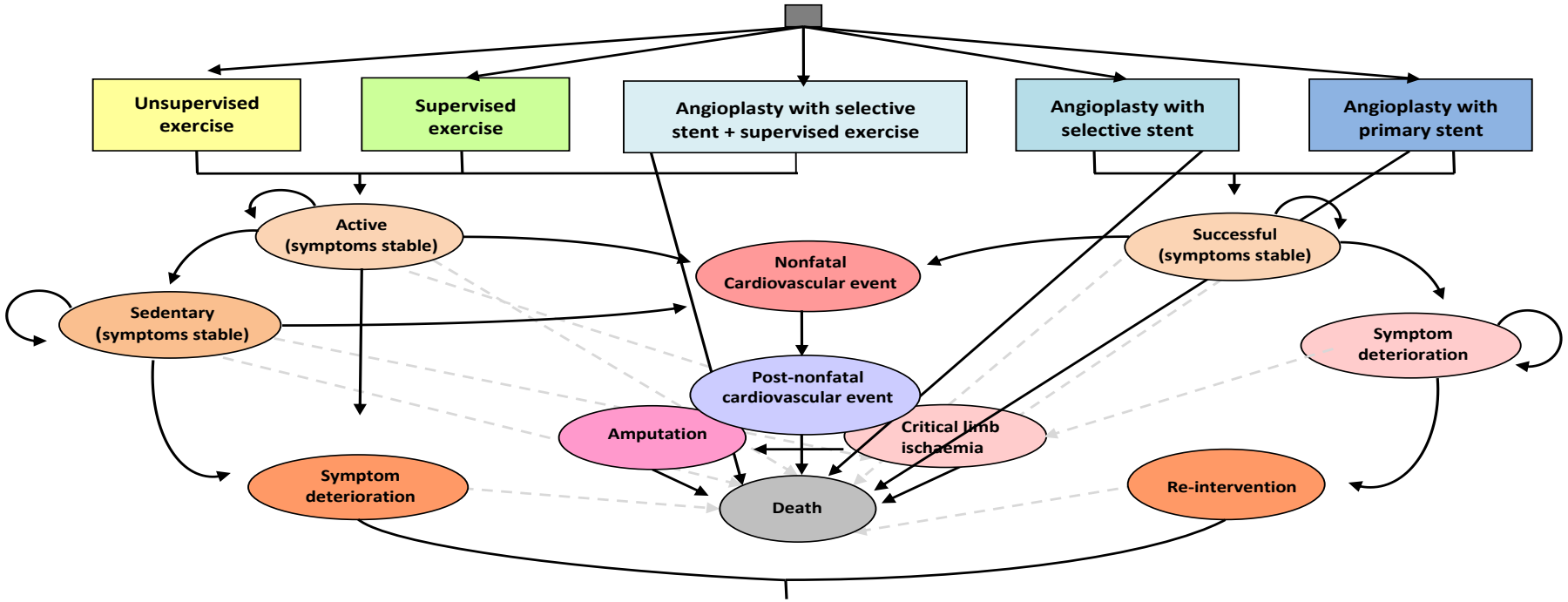
The GDG noted that currently there is no evidence to suggest a relationship between treatment for claudication and progression to critical limb ischaemia (CLI). In the base case analysis, the risk of progression to CLI was included as a constant background rate irrespective of treatment pathway, effectively '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 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.

Figure 243: Markov model



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 rat, represented by dashed grey arrows.

L.2.2.11 Uncertainty

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 (Table 40). 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.

Various sensitivity analyses were also undertaken to test the robustness of model assumptions and data sources. In these analyses, one or more inputs were changed and the analysis was rerun in order to evaluate the impact of these changes on the results of the model.

Table 40: Distributions used in probabilistic cost-utility analysis

Parameter	Type of distribution	Properties of distribution	Parameters for the distributions
Relative risk & odds ratios	Lognormal	Bound at zero	Log mean (LM) = Ln(RR) Log standard deviation (LSD) = $\frac{\text{Ln(Upper CI – Lower CI)}}{1.96 \times 2}$
Compliance to exercise (based on expert opinion)	Triangular	Minimum, mode, and maximum values	Min = minimum value Likeliest = mean Max = maximum value
Costs	Gamma	Bound between zero and infinity	α = (mean/standard error of the mean)2 γ = mean/standard error of the mean2
Probabilities (& mean baseline utility)	Beta	Bound between zero and one	α = events β = sample size - α

L.2.23 Model inputs

L.2.3.31 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review and supplemented by additional data sources as required. Model inputs were validated with members of the GDG. A summary of the model inputs used in the base case (primary) analysis is provided in Table 41. More details about sources, calculations and rationale for selection can be found in the sections following the summary tables.

Table 41: Summary of base case model inputs

Input	Data	Source
Comparators	Primary interventions: • Unsupervised exercise • Supervised exercise • Angioplasty (selective stent) • Angioplasty (primary stent) Secondary interventions: • Supervised exercise • Angioplasty	GDG consensus

	• Bypass Additional intervention • Angioplasty (selective stent) + supervised exercise	
Population	People with intermittent claudication who are considered suitable for either exercise or angioplasty.	GDG consensus
Subgroups (angioplasty and bypass only)	Aorto-iliac and femoro-politeal segments	GDG consensus
Initial cohort settings	Age: 67 Male: 70% ABPI: 0.64 Diabetes: 21% Current smokers: 43%	Average across included RCTs (Table 42)
Perspective	NHS and PSSRU	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}
Time horizon	Lifetime	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}
Discount rate	Costs: 3.5% QALYs: 3.5%	NICE reference case{National Institute for Health and Clinical Excellence, 2008 16387 /id}

L.2.3.12 Initial cohort settings

The cohort considered by the model is people with symptomatic intermittent claudication due to peripheral arterial disease. 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 (see section L.2.3.3). The GDG considered this proportion of people with diabetes to be slightly greater than expected but thought that in light of the growing prevalence of diabetes across the UK, it is likely to represent an accurate estimate in the near future. Table 42 contains summary of the population characteristics and interventions of all studies included in the clinical review.

Table 42: Study characteristics

Study	N	Average age	Male	Diabetes	Smoking history		Resting ABPI	Type of analysis	Artery	Supervised exercise		Unsupervised exercise	
					Current	Former				Duration	Content	Duration	Content
Supervised exercise vs. Unsupervised exercise													
Cheetham 2004{Cheetham, 2004 549 /id}	59	67	73%	19%	NR	NR	0.68	ITT	NR	1 x 45 min per week for 6 months	Circuits	3 x 30 min per week for 6 months	Advice only
Kakkos 2005{Kakkos, 2005 453 /id}	34	68	90%	19%	24%	67%	0.56	OTA	FP	3 x 60 min per week for 6 months	Treadmill walking	45 min per day for 6 months	Advice only
Nicolai 2010 & van Asselt 2011 (EXITPAD study){Nicolai, 2010 15927 /id;van Asselt, 2011 16275 /id}	211	67	64%	25%	43%	45%	0.66	Modified ITT **	NR	2-3 x 30 min per week for 12 months	Treadmill walking	3 x 3 times per day for 12 months	Advice only
Pinto 1997{Pinto, 1997 17 /id}	60	69	53%	35%	NR	NR	0.58	OTA	NR	3 x 60 min per week for 3 months	Treadmill walking + cycling + education	3 x 20-40 min per week for 3 months	Advice + journal + education + weekly in-person support
Regensteiner 1997{Regensteiner, 1997 931 /id}	20	65	100%‡	0%	55%	NR	0.60	ITT	NR	3 x 60 min per week for 3 months	Treadmill walking	3 x 35-50 min per week for 3 months	Advice + weekly telephone support
Savage 2001{Savage, 2001 3035 /id}	21	66	71%	NR	NR	NR	0.73	Unclear	NR	3 x 40 min per week for 3 months	Treadmill walking	3 x 40 min per week for 3 months	Advice + monthly telephone support
Stewart	60	68	70%	22%	27%	62%	0.66	OTA	FP	2 x 60 min	Circuits	No details	Advice only

2008{Stewart, 2008 167 /id}										per week for 3 months + 3 months unsupervised exercise			
Treat-Jacobson 2009{Treat-Jacobson, 2009 91 /id}	45	67	71%	37%	NR	NR	0.67	OTA	NR	3 x 70 min per week for 3 months	Treadmill walking	Daily (no other details) for 3 months	Advice + journal + weekly in-person support
Tew 2009{Tew, 2009 81 /id}	57	69	NR	20%	29%	57%	0.68	OTA	NR	2 x 20-40 min per week for 3 months	Arm crank exercises	No details	Advice only
Tisi 1997{Tisi, 1997 3042 /id}	67	69	69%	10%	30%	61%	0.67	Unclear	NR	1 x 60 min per week for 1 month	Leg exercises	No details	Advice only
Zwierska 2005{Zwierska, 2005 420 /id}	104	69	78%	18%	32%	63%	0.66	ITT	FP	2 x 20-40 min per week for 6 months	Leg and arm exercises	2 x 20-40 min per week for 6 months	Advice only

Study	N	Average age	Male	Diabetes	Smoking history		Resting ABPI	Type of analysis	Artery	Selective stent		Unsupervised exercise	
					Current	Former				Type	% placed	Duration	Content
Unsupervised exercise vs. Angioplasty													
Nylaende 2007 & Nylaende 2007 (OBACT study){Nylaende, 2007 59 /id;Nylaende, 2007 311 /id}	56	69	56%	18%	70%	25%	0.64	ITT	AI & FP	NR	0/28	2 x daily	Advice only
Whyman 1996 & Whyman 1997{Whyman, 1996 1082	62	62	82%	8%	50%	NR	0.73	OTA	AI & FP	NR	NR	No details	Advice only

/id;Whyman, 1997 640 /id}													
Study	**N**	**Average age**	**Male**	**Diabetes**	**Smoking history**		**Resting ABPI**	**Type of analysis**	**Artery**	**Supervised exercise**		**Selective stent**	
					Current	**Former**				**Duration**	**Content**	**Type**	**% placed**
Supervised exercise vs. Angioplasty with selective stent & supervised exercise													
Greenhalgh 2008 (MIMIC trial){Greenhalgh, 2009 924 /id}	127	65	48%	NR	NR	NR	0.67	OTA	AI & FP[Δ]	1 x 30 min per week for 6 months	Circuits	NA	NA
Mazari 2010 & Mazari 2012{Mazari, 2010 39 /id;Mazari, 2012 104 /id}	118	70	74%	14%	31%	NR	0.66	Unclear	FP	3 x 60 min per week for 3 months	Circuits	NA	NA
Study	**N**	**Average age**	**Male**	**Diabetes**	**Smoking history**		**Resting ABPI**	**Type of analysis**	**Artery**	**Selective stent**		**Selective stent + Supervised exercise**	
					Current	**Former**				**Type**	**% placed**	**Duration**	**Content**
Angioplasty with selective stent vs. Angioplasty with selective stent + supervised exercise													
Kruidenier 2011{Kruidenier, 2011 16326 /id}	70	62	62%	20%	56%	NR	0.70	ITT	AI & FP	NR	34.3%		
Study	**N**	**Average age**	**Male**	**Diabetes**	**Smoking history**		**Resting ABPI**	**Type of analysis**	**Artery**	**Supervised exercise**		**Selective stent**	
					Current	**Former**				**Duration**	**Content**	**Type**	**# placed**
Supervised exercise vs. Angioplasty with selective stent													
Spronk 2009{Spronk, 2009 134 /id}	151	66	55%	17%	19%	49%	0.63	ITT	AI & FP	2 x 30 min per week for 6 months	Treadmill walking	NA	NA
Perkins 1996{Perkins, 1996 984 /id}	56	NR	NR	NR	NR	NR	0.62	Unclear	AI & FP	2 x 30 min per week for 6 months	Leg exercise	NA	NA
Creasy 1990{Creasy, 1990 1160 /id}	36	63	75%	5.5%	64%	32%	0.64	Unclear		2 x 30 min per week for 6 months	Circuits	NA	NA

Mazari 2010	120	70	74%	14%	31%	NR	0.66	Unclear	FP	3 x 60 min per week for 3 months	Circuits	NA	NA

Study	N	Average age	Male	Diabetes	Smoking history		Resting ABPI	Type of analysis	Artery	Supervised exercise		Bypass surgery	
					Current	Former				Duration	Content	Type	# placed
Supervised exercise vs. Bypass surgery													
Lundgren 1989{Lundgren, 1989 2558 /id}	75	64	79%	8%	NR	NR	0.58	Unclear		3 x 30 min per week for 6 months	Leg exercises	Synthetic graft	NA

Study	N	Average age	Male	Diabetes	Smoking history		Resting ABPI	Type of analysis	Artery	Selective stent		Primary stent	
					Current	Former				Type	# placed	Type	# placed
Angioplasty with selective stent vs. Angioplasty with primary stent													
Krankenberg 2007{Krankenberg, 2007 200 /id}	244	67	68%	32%	NR	NR	0.70	ITT	FP	Self expanding nitinol stent	13/121	Self expanding nitinol stent	NR
Bosch 1999 & Tetteroo 1998 (Dutch Iliac Stent Tiral){Bosch, 1999 588 /id;Tetteroo, 1998 627 /id}	279	59	72%	10%	NR	NR	0.73	ITT	IA	Palmaz stent	59/136	Palmaz stent	142/143
Cejna 2001{Cejna, 2001 539 /id}	141	67	62%	40%	NR	NR	0.63	ITT	FP	NR	NR	NR	NR
Shillinger 2006 & Shillinger 2007 & Sabeti 2007{Sabeti, 2007 1983 /id;Schillinger, 2006 288 /id;Schillinger, 2007 209 /id}	104	66	53%	38%	45%	NR	0.56	ITT	FP	Self expanding nitinol stent	17/51	Self expanding nitinol stent	NR
Vroegindeweij 1997{Vroegindeweij, 1997 2255 /id}	51	65	71%	12%	63%	NR	NR	ITT	FP	Palmaz stent	NR	Palmaz stent	NR

Grimm 2001{Grimm, 2001 2254 /id}	53	69	60%	NR	NR	NR	0.54	ITT	FP	Palmaz stent	NR	Palmaz stent	NR
Dick 2009{Dick, 2009 32 /id}	73	69	69%	30%	40%	NR	0.63	ITT	FP	Self expanding nitinol stent	NR	Self expanding nitinol stent	NR
Study	**N**	**Average age**	**Male**	**Diabetes**	**Smoking history**		**Resting ABPI**	**Type of analysis**	**Artery**	**Selective stent details**		**Bypass surgery details**	
					Current	**Former**				**Type**	**# placed**	**Type**	
Angioplasty vs Bypass													
Kedora 2007 & McQuade 2010{Kedora, 2007 3060 /id;McQuade, 2010 15980 /id}	86	69	79%	40%	NR	NR	0.52	ITT	FP	NR	32/50	Synthetic graft	NA
Holm 1991{Holm, 1991 803 /id}	102	70	NR	27%	NR	NR	0.68	ITT	IA & FP	NR	NR	Synthetic & vein grafts	NA
Wilson 1989 & Wolf 1993{Wilson, 1989 847 /id;Wolf, 1993 3058 /id}	263	61	100%	26%	78%	20%	0.58	ITT	IA & FP	NR	NR	NR	NA
AVERAGE	**2 935**	**67**	**70%**	**21%**	**43%**	**48%**	**0.64**	**--**	**--**	**--**	**--**	**--**	**--**

ITT = intention to treat analysis; OTA = on treatment analysis; FP = femoro-popliteal; AI = aorto-iliac; NR = not reported; NA = not applicable

*Analysis does not include 4 pts who withdrew after randomisation

** Analysis excluded dropouts unless they showed up to their final assessment. 5 control patients crossed over to EX group and were analysed in control group.

‡Assumption based on the fact that the trial took place at a veteran's hospital.

Δ Results reported separately for patients with aorto-iliac and femoro-popliteal lesions.

1 **Table 43: Overview of parameters and parameter distributions used in the model**

Parameter		Point estimate	Value range	Probability distribution	Distribution parameters	Source
Baseline probabilities which apply equally to each intervention arm						
Relative risk of mortality and CV events for people with IC compared to age- and sex- adjusted norms						
All cause mortality		3.14	1.90 – 4.90	Lognormal	LM = 1.10219 LSD = 0.24167	Criqui 1992{Criqui, 1992 16328 /id}
Stroke & MI	M	2.16	1.76 – 2.66	Lognormal	LM = 0.76455 LSD = 0.10536	Ankle Brachial Index Collaboration{Fowkes, 2008 16329 /id}
	F	2.49	1.87 – 3.36	Lognormal	LM = 0.90048 LSD = 0.15361	Ankle Brachial Index Collaboration{Fowkes, 2008 16329 /id}
Cost of CV events						
Initial MI (first 3 months)		£4, 792	£3, 853 – £5, 731	Gamma	α = 100.0000 β = 47.9200	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Post nonfatal MI (subsequent 3 month cycles)		£141	£113 – £169	Gamma	α = 100.0000 β = 1.4100	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Initial stroke (first 3 months)		£9, 630	£7, 743 – £11, 517	Gamma	α = 100.0000 β = 96.30000	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Post nonfatal stroke (subsequent 3 month cycles)		£559	£449 – £669	Gamma	α = 100.0000 β = 5.5900	Hypertension guideline 2011{National Clinical Guideline Centre, 2011 16341 /id}
Probability of IC progressing to CLI						
3 month probability of CLI		0.1%	0.08% - 0.12%	Beta	α = 99.89803 β = 98845.74	ACC/AHA 2005 Practice Guidelines{Hirsch, 2006 16364

					/id}
CLI associated mortality					
3 month probability of mortality for CLI	3.9%	2.5% - 5.8%	Beta	α = 21.85105 β = 536.4443	Dormandy 1999{Dormandy, 1999 16025 /id}
Probability of amputation following development of CLI					
3 month probability of amputation for people with CLI	6.9%	6.3% - 7.6%	Beta	α = 372.1725 β = 4990.920	ACC/AHA 2005 Practice Guidelines{Hirsch, 2006 16364 /id}
Unsupervised and supervised exercise					
Intervention cost					
Unsupervised exercise	£0	NA	Fixed	NA	Expert opinion
Supervised exercise	£288	£232 – £345	Gamma	α = 100.0000 β = 2.886000	Expert opinion (see text)
Compliance to exercise¥					
Time period	**Unsupervised exercise**		**Supervised exercise**		**Source**
	Mode	**Min and Max**	**Mode**	**Min and Max**	
3 months	43%	17% - 56%	68%	40% - 80%	Expert opinion
6 months	33%	10% - 45%	40%	15% - 57%	Expert opinion
12 months	22%	7% - 37%	22%	4% - 40%	Expert opinion
24 months	16%	5% - 31%	16%	5% - 32%	Expert opinion
>24 months	16%	5% - 31%	16%	5% - 32%	Assumption
Relative risk of mortality and CV events (active compared to sedentary individuals)					
Mortality	0.87	0.75 – 0.99	Lognormal	LM = -0.14177 LSD = 0.07082	Cochrane review{Heran, 2011 16331 /id}
MI	0.97	0.82 – 1.15	Lognormal	LM = -0.03418 LSD = 0.08627	Cochrane review {Heran, 2011 16331 /id}
Stroke	0.80	0.74 – 0.86	Lognormal	LM = -0.22388 LSD = 0.03833	Meta-analysis{Lee, 2003 16333 /id}
Probability of symptom worsening following exercise					
3 month probability	1.4%	1.1% - 1.8%	Beta	α = 69.53812 β = 4800.078	ACC/AHA 2005 Practice Guidelines{Hirsch, 2006 16364 /id}
Angioplasty with primary and selective stent					
Intervention cost					
Diagnostic imaging	£90	£53 - £102	Gamma	α = 3.246680 β = 0.036037	NHS Reference Costs 2009/10{Department of Health,

					2011 5345 /id}
Stent (bare metal)	£550	£450 - £650	Gamma	α = 108.5069 β = 5.06880	Expert opinion
Primary angioplasty with no complications	£3, 661	£2, 204 - £4, 480	Gamma	α = 3.916705 β = 934.7800	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Primary angioplasty with major complications	£9, 367	£2, 200 - £14, 270	Gamma	α = 0.877416 β = 10675.72	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Secondary angioplasty with no complications	£3, 695	£2, 206 - £4, 524	Gamma	α = 3.412912 β = 1082.600	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Secondary angioplasty with major complications	£9, 385	£2, 329 - £14, 154	Gamma	α = 0.880720 β = 10655.68	NHS Reference costs 2009/10{Department of Health, 2011 5345 /id}
Proportion of patients receiving stents (selective stent)					
Aorto-iliac	35.2%	28.5% - 42.9%	Beta	α = 47.86838 β = 88.13162	Based on included RCTs{Bosch, 1998 2459 /id;Bosch, 1999 588 /id;Tetteroo, 1998 627 /id}
Femoro-popliteal	16.2%	10.5% - 24.4%	Beta	α = 16.50121 β = 85.49879	Based on included RCTs{Kedora, 2007 3060 /id;Krankenberg, 2007 200 /id;McQuade, 2010 15980 /id;Schillinger, 2006 288 /id;Schillinger, 2007 209 /id}
Average number of stents used where stents are placed					
Aorto-iliac	2	NA	Fixed	NA	Expert opinion
Femoro-popliteal	2	NA	Fixed	NA	Expert opinion
Probability of 30-day mortality for angioplasty with selective stent					
Baseline probability of 30-day mortality	0.06%	0.0% - 0.9%	Beta	α = 0.499851 β = 840.5001	Expert opinion informed by Royal College of Surgeons 2002{Axisa,

					2002 16361 /id}
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	Lognormal	LM = -2.79387 LSD = 1.53905	Cejna 2001{Cejna, 2001 539 /id}
Probability of major complications for angioplasty with selective stent					
Baseline probability of major complications	2.4%	1.7% - 3.3%	Beta	α = 32.60771 β = 1344.392	Royal College of Surgeons 2002{Axisa, 2002 16361 /id}
Relative risk of major complications for angioplasty with primary stent (compared to selective stent)					
Aorto-iliac	0.57	0.21 – 1.54	Lognormal	LM = -0.69129 LSD = 0.50827	Tetteroo 1998{Tetteroo, 1998 627 /id}
Femoro-popliteal	1.26	0.33 – 1.93	Lognormal	LM = 0.13422 LSD = 0.45055	Dick 2009{Dick, 2009 32 /id}, Krankenberg 2007{Krankenberg, 2007 200 /id}, Schillinger 2006{Schillinger, 2006 288 /id}, Vroegindewij 1997{Vroegindeweij, 1997 2255 /id}
Baseline probability of post operative amputation following angioplasty with selective stent					
Baseline probability of post operative amputation	0.06%	0.0% - 0.9%	Beta	α = 0.499851 β = 840.5001	Expert opinion informed by Royal College of Surgeons 2002{Axisa, 2002 16361 /id}
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	Lognormal	LM = -1.05362 LSD = 0.84909	Cejna 2001{Cejna, 2001 539 /id}
Probability of IC symptom worsening following angioplasty (selective stent & primary stent)					
Aorto-iliac	7.5%	5% - 10%	Beta	α = 24.67232 β = 304.2920	Expert opinion
Femoro-popliteal	34%	28% - 40%	Beta	α = 127.0500 β = 235.9500	Expert opinion
Baseline probability of reintervention following symptom worsening (selective stent only)					
Aorto-iliac	71%	66% - 76%	Beta	α = 233.1924 β = 95.24760	Expert opinion
Femoro-popliteal	28%	18% - 38%	Beta	α = 62.44000 β = 160.5600	Expert opinion
Odds ratio for re-intervention following angioplasty with primary stent (compared to selective stent)					

Aorto-iliac	1.63	0.58 – 4.61	Lognormal	LM = 0.34875 LSD = 0.52881	Tetteroo 1998{Tetteroo, 1998 627 /id}
Femoro-popliteal	0.50	0.22 – 1.13	Lognormal	LM = -0.78027 LSD = 0.41743	Schillinger 2007{Schillinger, 2007 690 /id;Schillinger, 2007 209 /id}
Bypass					
Cost of intervention					
Bypass with no/major complications	£5, 988	£4, 417 - £7, 025	Gamma	α = 8.963935 β = 668.0100	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Bypass with major complications	£7, 139	£5, 185 - £8, 641	Gamma	α = 5.662528 β = 1260.710	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Relative risk of 30-day mortality following bypass (compared to selective stent)					
Aorto-iliac	2.94	0.12 – 73.19	Lognormal	LM = -0.25992 LSD = 1.63605	Wilson 1989{Wilson, 1989 847 /id}
Femoro-popliteal	2.94	0.12 – 73.19	Lognormal	LM = -0.25992 LSD = 1.63605	Expert opinion (see text)
Relative risk of perioperative major complications following bypass (compared to selective stent)					
Aorto-iliac	0.31	0.14 – 0.67	Lognormal	LM = -1.25094 LSD = 0.39939	Wilson 1989{Wilson, 1989 847 /id}
Femoro-popliteal	0.60	0.17 – 2.17	Lognormal	LM = -0.72186 LSD = 0.64966	McQuade 2009{McQuade, 2009 94 /id}
Relative risk of amputation within 30-days of bypass (compared to selective stent)					
Aorto-iliac	0.98	0.14 – 7.04	Lognormal	LM = -0.51962 LSD = 0.99941	Wilson 1989{Wilson, 1989 847 /id}
Femoro-popliteal	Not reported. Assumed no difference between interventions (RR = 1)				
Amputation					
Procedural cost					
Cost of amputation without major complications	£9, 224	£6, 862 - £10, 481	Gamma	α = 6.945493 β = 1328.056	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Cost of amputation with major complications	£15, 001	£7, 862 - £18, 600	Gamma	α = 2.250302 β = 6666.219	NHS Reference Costs 2009/10{Department of Health, 2011 5345 /id}
Probability of procedural mortality and morbidity					

Probability of 30-day mortality	12.9%	11.9% - 13.9%	Beta	α = 526.5780 β = 3555.422	Vamos 2009{Vamos, 2009 16362 /id}
Probability of major complications	14.3%	12.2% - 16.6%	Beta	α = 137.1370 β =821.8630	Aulivola 2004{Aulivola, 2010 16055 /id}
Mortality and cost of care in first year following amputation					
3 month probability of mortality in first year	8.4%	5.6% - 11.7%	Beta	α = 25.87350 β = 282.1265	Aulivola 2004{Aulivola, 2010 16055 /id}
Cost of care during first year	£28, 270	£25, 499 - £31, 040	Gamma	α = 400.0000 β = 70.67470	Expert opinion; see text
Mortality and cost of care in subsequent years					
3 month probability of mortality in subsequent years	4.7%	2.7% - 7.4%	Beta	α = 14.59921 β = 293.4007	Aulivola 2004{Aulivola, 2010 16055 /id}
Annual cost of care in subsequent years	£23, 502	£21, 199 - £25, 806	Gamma	α = 400.0000 β = 58.75605	Expert opinion; see text
Quality of life					
Baseline quality of life (weighted average)					
Aorto-iliac	0.580	0.489 – 0.674	Beta	α = 61.24345 β = 44.39212	
Femoro-popliteal	0.573	0.489 – 0.659	Beta	α = 70.54923 β = 52.64679	
Mean difference in change associated with supervised exercise programme compared to unsupervised (Aorto-iliac + femoro-popliteal)					
3 months	-0.021	-0.086 – 0.046	Normal	Mean = -0.021 SD = 0.034	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}, Savage 2001{Savage, 2001 3035 /id}
6 months	0.026	-0.038 – 0.090	Normal	Mean = 0.026 SD = 0.032	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}, Savage 2001{Savage, 2001 3035 /id}
9 months	0.010	-0.058 – 0.076	Normal	Mean = 0.010 SD = 0.034	Cheetham 2004{Cheetham, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}
12 months	0.029	-0.049 – 0.106	Normal	Mean = 0.029 SD = 0.039	Cheetham 2004{Cheetham

					, 2004 549 /id}, Nicolai 2010{Nicolai, 2010 15927 /id}
Mean difference in change associated with angioplasty with selective stent compared to supervised exercise (Aorto-iliac + femoro-popliteal)					
3 months	0.035	-0.021 – 0.090	Normal	Mean = 0.035 SD = 0.028	Spronk 2009{Spronk, 2009 134 /id}
6 months	0.035	-0.021 – 0.090	Normal	Mean = 0.035 SD = 0.028	Spronk 2009{Spronk, 2009 134 /id}
9 months	-0.015	-0.081 – 0.050	Normal	Mean = -0.015 SD = 0.033	Spronk 2009{Spronk, 2009 134 /id}
12 months	-0.015	-0.081 – 0.050	Normal	Mean = -0.015 SD = 0.033	Spronk 2009{Spronk, 2009 134 /id}
Mean difference in change associated with angioplasty with primary stent compared to angioplasty with selective stent (Aorto-iliac + femoro-popliteal)					
3 months	0.050	-0.730 – 0.791	Normal	Mean = 0.050 SD = 0.391	Bosch 1999
6 months	-0.054	-0.323 – 0.231	Normal	Mean = -0.054 SD = 0.141	Bosch 1999
9 months	-0.054	-0.323 – 0.231	Normal	Mean = -0.054 SD = 0.141	Bosch 1999
12 months	-0.054	-0.323 – 0.231	Normal	Mean = -0.054 SD = 0.141	Bosch 1999
Mean difference in change associated with selective stent placement + supervised exercise compared to selective stent placement alone (aorto-iliac artery)					
3 months	0.077	0.037 – 0.117	Normal	Mean = 0.077 SD = 0.020	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
6 months	0.077	0.037 – 0.117	Normal	Mean = 0.077 SD = 0.020	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
9 months	0.004	-0.042 – 0.049	Normal	Mean = 0.004 SD = 0.023	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
12 months	0.004	-0.042 – 0.049	Normal	Mean = 0.004 SD = 0.023	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
24 months	-0.058	-0.158 – 0.043	Normal	Mean = -0.058 SD = 0.051	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
Mean difference in change associated with selective stent placement + supervised exercise compared to selective stent placement alone (femoro-popliteal artery)					
3 months	0.010	-0.015 – 0.035	Normal	Mean = 0.010 SD = 0.013	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
6 months	0.010	-0.015 – 0.035	Normal	Mean = 0.010	Greenhalgh

				SD = 0.013	2008{Greenhalgh, 2008 107 /id}
9 months	-0.001	-0.027 – 0.025	Normal	Mean = -0.001 SD = 0.013	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
12 months	-0.001	-0.027 – 0.025	Normal	Mean = -0.001 SD = 0.013	Greenhalgh 2008{Greenhalgh, 2008 107 /id}
24 months	0.014	-0.042 – 0.070	Normal	Mean = 0.014 SD = 0.028	Greenhalgh 2008{Greenhalgh, 2008 107 /id}

¥Note that these values are cumulative and differ from the transition probabilities used in the model. LM = log mean; LSD = log standard deviation; RR = relative risk; MI = myocardial infarction.

L.2.3.3 Baseline event rates

Mortality

Age- and sex-specific all cause mortality was based on the most recent available life tables for England and Wales (2007-2009){Office for National Statistics, 2010 ONS2010 /id}. These rates were adjusted for people with IC by multiplying the standardised risk of all cause mortality observed over 10 years in people with IC by Criqui and colleagues (1992){Criqui, 1992 16328 /id}. This study was selected to inform the increased risk of mortality among people with IC as it reported an estimate which was considered clinically valid by the GDG and is consistent with existing cost effectiveness evaluations in this population.

Cardiovascular events

The average baseline probability of stroke or MI was calculated by age and gender using the Framingham risk equations{Anderson, 1991 16344 /id;Payne, 2010 16343 /id}. Risk factor inputs (total cholesterol, HDL cholesterol, prevalence of smoking and diabetes) for each gender were obtained from the 2006 Health Survey for England (HSE){Craig, 2008 16342 /id}. Average age- and sex- specific blood pressure values were obtained from the 2009 NICE Hypertension update guideline, which used individual patient level data from the 2006 HSE. Ten-year risks were calculated using the risk calculator spreadsheet developed by Rupert Payne at the University of Edinburgh. Table 44 provides a summary of the inputs used in the Framingham risk calculator.

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{Fowkes, 2008 16329 /id}. A limitation of this study for the purposes of our analysis was that the reported hazard ratios were not adjusted for age or cardiovascular risk factors. However, the values matched those expected by the GDG and were considered to be the best available estimates in the literature. Sex-specific hazard ratios were incorporated into the analysis using lognormal distributions. Deterministic estimates of cumulative risk in the model are presented Table 45.

Table 44: Risk inputs used in the Framingham equations for stroke and MI

Age group	Mean total cholesterol	Mean HDL cholesterol	Mean systolic blood pressure	Mean prevalence of diabetes (1 & 2)	Mean prevalence of smoking (current)
Males					
65 to 74	5.2	1.3	137	15.7%	14.0%
Females					
65 to 74	5.9	1.6	138	10.4%	13.0%

Source/Note: *2006 Health Survey for England and 2009 Hypertension update guideline.*

Table 45: 10-year risk of MI and stroke

Sex	10 year risk of MI		10 year risk of stroke	
	According to Framingham equation	Adjusted for ABPI of 0.61 to 0.70	According to Framingham equation	Adjusted for ABPI of 0.61 to 0.70
Male	9.2%	25.4%	4.8%	13.2%
Female	3.1%	11.9%	3.6%	13.7%
Total (66% male)	7.2%	20.7%	4.4%	13.2%

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, 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 {Hirsch, 2006 16364 /id}

The one year mortality rate in people with CLI is approximately 25%{Dormandy, 1999 16025 /id}. 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{Aulivola, 2010 16055 /id}.

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.

Major complications as a result of angioplasty

A prospective audit by the Royal College of Surgeons of England evaluated the incidence of major medical complications in patients undergoing transluminal and subintimal angioplasty between 1995 and 1998{Axisa, 2002 16361 /id}. Of the 1337 interventions, 841 were for relief of disabling claudication. The majority (64%) of total procedures involved femoro-popliteal vessels, while 21% involved aorto-iliac vessels. 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 that was unrelated to the technique of angioplasty. This was used as the baseline probability of major complication following angioplasty with selective stent.

Mortality as a result of angioplasty

According to the results of the same RCS audit{Axisa, 2002 16361 /id}, 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; this probability was applied as the baseline probability for all patients undergoing angioplasty with selective stent in both arterial segments.

Amputation as a result of angioplasty

None of the patients included in the RCS audit{Axisa, 2002 16361 /id} experienced limb loss as a result of acute ischaemia following angioplasty. 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.

Re-intervention after angioplasty

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 estimates used to inform patency failure and reintervention rates for each artery, along with a weighted average probability of reintervention, are presented in Table 46.

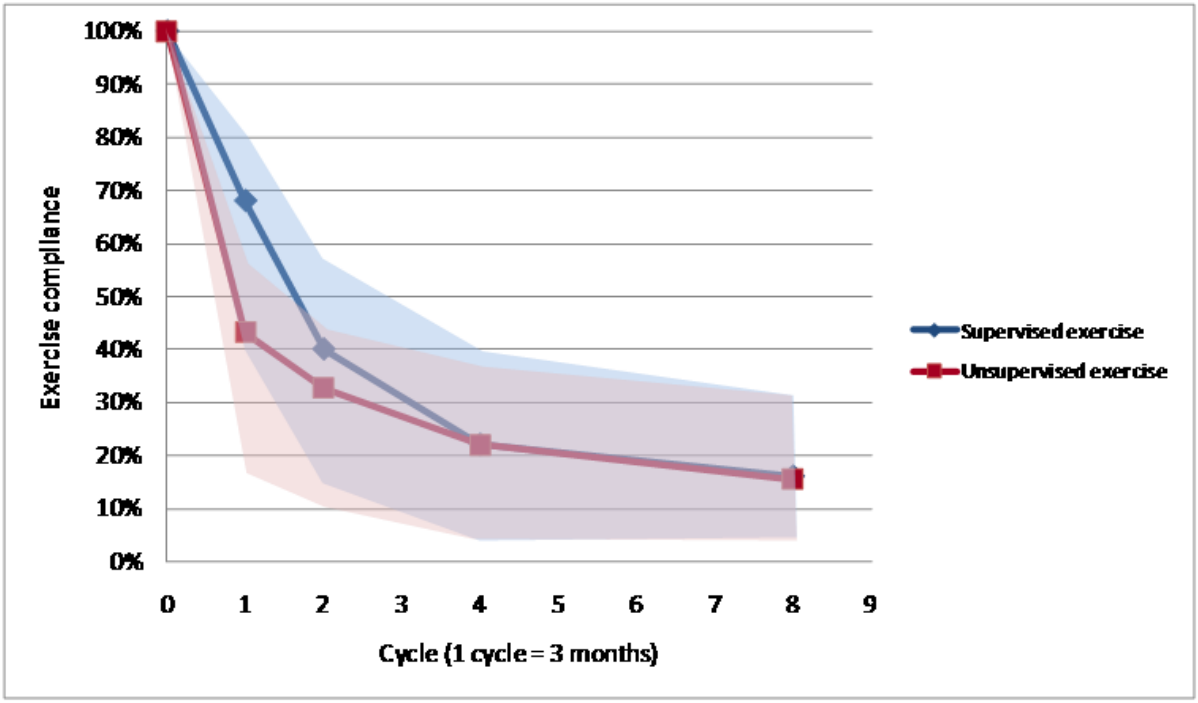
Table 46: Rates of secondary intervention following angioplasty

Annual rate of patency failure	Re-intervention after patency failure		Ratio of stenoses to occlusions	Weighted average probability of reintervention
	Stenosis	Occulsion		
Aorto-iliac				
7.5% (5% to 10%)	75% (70% to 80%)	55% (50% to 60%)	80:20	71%
Femoro-popliteal				
35% (30% to 40%)	30% (20% to 40%)	20% (10% to 30%)	80:20	28%

Compliance to supervised and unsupervised exercise

Levels of short- and long-term compliance to supervised and unsupervised exercise programmes 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 244). The impact of different levels of compliance on the outcome of the model was explored in sensitivity analysis.

Figure 244: Equal long term compliance



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%

L.2.3.14 Relative treatment effects

Exercise-associated risk reduction for mortality and cardiovascular events

No randomised evidence of exercise-associated risk of mortality in people with IC was identified in the literature. Because the risk of CV events in individuals with PAD are comparable to the risk faced by people with established cardiovascular disease{Cacoub, 2009 16290 /id}, the GDG agreed that evidence from this population would represent a reasonable source of data in the absence of more direct data.

Recently, a Cochrane review of randomised controlled trials was conducted to determine the effects of exercise-based rehabilitation in people with coronary heart disease{Heran, 2011 16331 /id}. Thirty of the 47 included trials were conducted in people with previous MI. The remaining trials included either exclusively post-coronary revascularisation patients or both groups of patients. The ages of included participants ranged from 46 to 84 and 80% were men. The Cochrane review defined cardiac rehabilitation as an inpatient, outpatient, community or home based exercise intervention appropriate to a cardiac patient population. Interventions were grouped according to whether or not they included a psychosocial and/or educational intervention and trials were analysed according to the length of follow-up (less than or more than one year). For the purpose of our analysis, only trials evaluating the effect of exercise training alone over a period of more than one year were considered. Patients in the control groups received usual care, which could include standard medical care, such as drug therapy, but did not include any form of structured exercise training or advice. According to the results of the Cochrane review, in studies with a follow up of greater than one year total

mortality was reduced with exercise-based cardiac rehabilitation compared to control (RR 0.87 [95% CI 0.75, 0.99], p = 0.041).

The Cochrane review by Heran 2011{Heran, 2011 16331 /id} reported the incidence of MI in people with a follow up of longer than one year. There was no statistically significant difference between exercise-based cardiac rehabilitation and usual care (RR 0.97 [95% CI 0.82, 1.15], p = 0.73).

A meta-analysis of the effect of physical activity on stroke prevention was used to inform the risk of stroke for active compared to sedentary people in the model{Lee, 2003 16333 /id}. Nineteen cohort and case-control studies, including data from the Framingham cohort, Nurses' Health Study, and the Northern Manhattan Stroke Study, were included in this analysis. Overall, moderately active individuals were found to have a 20% lower risk of stroke incidence or mortality than controls (RR = 0.80; 95% CI, 0.74 to 0.86; p<0.001).

Although the GDG agreed that this represented the best available source of data, they also noted that there are several limitations associated with using estimates derived from an indirect patient population. For example, there is a difference in exercise capacity between the two groups which may affect the magnitude of the effect size{Hamer, 2008 16332 /id}. In addition, the GDG noted that many of the trials included in the review predate what is considered current 'best medical therapy'. The introduction of improved lipid modification medications, for example, may have an effect on observed outcomes. However, this limitation would equally apply to studies conducted in people with PAD.

Risk of mortality, complications, amputation and re-intevention associated with selective stent placement, primary stent placement, and bypass surgery

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.

Relative treatment effects for the following outcomes were applied:

- 30-day mortality
- 30-day major adverse events
- 30-day amputation
- Re-intervention

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.

The GDG agreed that although the absolute risk of 30-day mortality and post-operative amputation is expected to be greater in the aorto-iliac artery than the femoro-popliteal, they did not expect this to have an effect on the relative risk of mortality between selective stent placement and primary stent placement. Similarly, the GDG agreed that there was no reason to expect a difference in post-operative amputation rates in the femoro-popliteal artery in bypass compared to angioplasty with selective stent placement.

In trials comparing angioplasty to bypass in the femoro-popliteal artery, Holm 1991 and van der Zaag 2004 reported zero deaths within 30 days in both groups (0/53 for angioplasty and 0/48 for bypass). Therefore, a pooled risk ratio for this outcome was not estimable. The GDG expected that because

bypass is a more invasive procedure and is associated with the known risks of general anaesthetic, the same relative risk reported for the aorto-iliac artery (RR 2.94) should be applied to the femoro-popliteal artery. Values for each RR are reported in Table 22.

L.2.3.5 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 (Table 49). 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{Ara, 2008 16334 /id} 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 (Table 49).

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{Briggs, 2006 16373 /id}. Probabilistic mapped values were then calculated using Equation 4 from the paper by Ara and Brazier{Ara, 2008 16334 /id}, 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 50.

The GDG noted that the trend in quality of life over time followed the pattern that would be expected from each intervention. Exercise showed a slow and steady increase in quality of life, reflecting the fact that the benefits of this treatment increase over time. Angioplasty resulted in an immediate increase in quality of life which declined over time.

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 each intervention (as calculated by the probabilistic simulation; Table 50) 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{Currie, 1995 15973 /id}, 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 47).

Table 47: Quality of life following cardiovascular events

Event	Mean utility	SE	Source
MI	0.760	0.018	Goodacre 2004{Goodacre, 2004 16276 /id}
Stroke	0.629	0.040	Tengs 2003{Tengs, 2003 16277 /id}

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 48. 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{Sculpher, 1996 2442 /id}. 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 48: 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

1 **Table 49: Quality of life outcomes reported by RCTs included in clinical review**

Studies included in clinical review	Generic quality of life measurement used	Additional data requested from authors?	Additional data obtained from authors?	Mapped to EQ-5D?	Included in cost-effectiveness analysis?	Notes/comments
Unsupervised exercise vs. supervised exercise						
EXITPAD	EQ-5D SF-36	Not necessary Yes	NA Yes	NA Yes	Yes No	EQ-5D data used in preference to mapped SF-36 data in base case analysis. Mapped data used in sensitivity analysis.
Cheetham 2004	SF-36	Yes	Yes	Yes	Yes	SE or SD not reported; assumed same SE as reported for each dimension by Nicolai 2010
Savage 2001	SF-36	Not necessary	NA	Yes	Yes	All relevant values reported by authors.
Pinto 1997	SF-36	Yes	Not available	NP	No	Authors replied that study data was collected over 10 years ago and is no longer available.
Kakkos 2005	SF-36	No	NA	NP	No	Data contained zero values, which could not be mapped probabilistically.
Regensteiner 1997	SF-20	NA	NA	NA	No	No validated algorithms for mapping SF-20 to EQ-5D are currently available.
Stewart 2008	None	NA	NA	NA	NA	NA
Treat-Jacobson 2009	None	NA	NA	NA	NA	NA
Tew 2009	None	NA	NA	NA	NA	NA
Tisi 1997	None	NA	NA	NA	NA	NA
Zwierska 2005	None	NA	NA	NA	NA	NA
Unsupervised exercise vs. angioplasty with selective stent placement						
Nylaende 2007 & Nylaende 2007 (OBACT study)	SF-36	Yes	No reply	No	No	Authors were contacted to request data for all 8 domains of the SF-36. No reply was received.
Whyman 1996 & Whyman 1997	None	NA	NA	NA	NA	
Supervised exercise vs. Angioplasty with selective stent placement + supervised exercise						
MIMIC trial	SF-36	Yes	Yes	Yes	Yes	Authors supplied data for both aorto-iliac and femoro-popliteal subgroups.

Studies included in clinical review	Generic quality of life measurement used	Additional data requested from authors?	Additional data obtained from authors?	Mapped to EQ-5D?	Included in cost-effectiveness analysis?	Notes/comments
Mazari 2010 & Mazari 2012	SF-36	Yes	No reply	No	No	Mazari 2010 reported SF-36 values at baseline and 3 months, which could not be mapped probabilistically. Mazari 2012 reported p values for the change in SF-36 values at 12 months. The authors were contacted for mean and standard errors but they did not reply.
Angioplasty with selective stent placement vs. Angioplasty with selective stent + supervised exercise						
Kruidenier 2011	EQ-5D SF-36	Not necessary Not necessary	NA NA	NA Yes	Yes No	EQ-5D data used in preference to mapped SF-36 data. Both values were used in sensitivity analysis.
Supervised exercise vs. Angioplasty with selective stent placement						
Spronk 2008 Spronk 2009	EQ-5D SF-36	Yes Yes	Not available Not available	No No	Yes No	Baseline EQ-5D and mean score improvement at 6 and 12 months were reported. Authors were asked for mean values at follow-up but these data were not available. A distribution was assigned to each improvement score and probabilistic simulation was used to estimate mean values and mean difference in change.
Mazari 2010 & Mazari 2012	SF-36	Yes	No reply	No	No	Mazari 2010 reported SF-36 values at baseline and 3 months, which could not be mapped probabilistically. Mazari 2012 reported p values for the change in SF-36 values at 12 months. The authors were contacted for mean and standard errors but they did not reply.
Perkins 1996	None	NA	NA	NA	NA	NA
Creasy 1990	None	NA	NA	NA	NA	NA
Angioplasty with selective stent placement vs. Angioplasty with primary stent placement						
Dutch Iliac Stent Tiral Bosch 1999 & Tetteroo 1998	EQ-5D SF-36	No Yes	No Not measured	NA NP	Yes No	Authors reported mean and 95% CI EQ-5D values at baseline, 3 months, 1 year and 2 years follow up. Also reported were the physical

Studies included in clinical review	Generic quality of life measurement used	Additional data requested from authors?	Additional data obtained from authors?	Mapped to EQ-5D?	Included in cost-effectiveness analysis?	Notes/comments
						domains of the SF-36. The authors were contacted to request all 8 domains. They replied that the emotional component was not measured as it was not thought relevant to this group of patients.
Shillinger 2006 & Shillinger 2007 & Sabeti 2007	SF-36	No	NA	NP	No	Data contained values which could not be mapped probabilistically.
Krankenberg 2007	None	NA	NA	NA	NA	
Cejna 2001	None	NA	NA	NA	NA	
Vroegindeweij 1997	None	NA	NA	NA	NA	
Grimm 2001	None	NA	NA	NA	NA	
ASTRON trial Dick 2009	None	NA	NA	NA	NA	
Supervised exercise vs. Bypass surgery						
Lundgren 1989	None	NA	NA	NA	NA	
Angioplasty vs. bypass						
Kedora 2007 & McQuade 2010	None	NA	NA	NA	NA	
Holm 1991	None	NA	NA	NA	NA	
Wilson 1989 & Wolf 1993	None	NA	NA	NA	NA	

EQ-5D = EuroQol 5 Dimensions; SF-36 = Short Form 36-item questionnaire; NA = not applicable; NP = not possible
Spronk et al{Spronk, 2008 2451 /id;Spronk, 2009 134 /id} To calculate 3 and 9 month values, a constant rate of change was assumed.
For those studies in which data was reported in 6 month (Greenhalgh 2008) or 9 month intervals (Bosch 1999), and it was assumed that the rate of change between time points was constant.

Table 50: 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-most column of each intervention pair.

L.2.3.16 Resource use and costs

Cost of supervised and unsupervised exercise programmes

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{Curtis, 2010 CURTIS2010 /id}. A gamma distribution was fitted around the total cost by assuming a standard error of 10%. This standard error resulted in a range of costs that was thought a resaonable representation of the variation that might be expected in different programmes in different areas of the country (95% CI £232 to £345). A breakdown of the assumptions and unit costs used to calculate per-patient cost of a supervised exercise programme are provided in Table 51.

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 assumed to be £0. This was varied in sensitivity analysis to account for different levels of support provided by different types of unsupervised programmes.

Table 51: 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 4)
(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{Curtis, 2010 CURTIS2010 /id}

Angioplasty

The average cost of angioplasty procedures was obtained from the most recent NHS Reference Costs from 2009/10. 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.

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. A standard error of 10% was assumed in order to assign a gamma distribution to this variable. Note that drug eluting stents were not included in the model as they were not recommended for routine clinical use by the group.

Table 52: Peripheral vascular stent cost

Vascular stent type	Approximate average cost	Source
Bare metal	£550	GDG opinion based on hospital records

Table 53: 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
Total 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 procedure with major complications	850	£255	£140	£338
QZ15C	Therapeutic endovascular procedure without complications	7, 054	£357	£229	£454
Total 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)		
First angioplasty (assuming 5% non elective)					
Angioplasty with major complications			**£9, 367 (£2, 200 to £14, 270)**		
Angioplasty without complications			**£3, 661 (£2, 204 to £4, 480)**		
Second angioplasty (assuming 10% 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{Department of Health, 2011 5345 /id}

Bypass

Bypass surgery was included only as a secondary procedure in people with IC. As a secondary procedure, the GDG assumed that 10% of operations would be non-elective procedures.

Table 54: Costs of bypass 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					
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{Department of Health, 2011 5345 /id}

Amputation

Amputation procedural costs were based on the most recent available NHS Reference Cost data. The GDG estimated that 55% of amputations preformed for people with CLI would be performed as emergency non-elective procedures.

Table 55: 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					
Amputations with major complications			**£14, 044**		
Amputations without major complications			**£9, 733**		

Source/Note: All costs obtained from 2009/10 NHS Reference Costs{Department of Health, 2011 5345 /id}

Post-amputation costs

The literature was reviewed for estimates of the cost of care following an amputation. Several UK{Collins, 2007 2434 /id;McWhinnie, 1994 16073 /id}, American{Brothers, 1999 438 /id;Hunink, 1995 15926 /id;Muradin, 2001 863 /id} and Dutch{Visser, 2003 809 /id} sources were identified. However, none included all relevant costs of hospital and social care and all were out of date.

In the absence of recent relevant estimates, 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 (Table 56) and those occurring in subsequent years (Table 57).

Table 56: 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 [(a)]	£1, 850 per above the knee prosthetic limb [(b)]
	£2, 650 per below the knee prosthetic limb [(b)]
3 prosthetist appointments per patient [(b)]	£343 per appointment [(c)]
Wheelchairs	
45% of amputees use wheelchairs [(d)]	
50% of these are non-motorised [(e)]	£58 per year per non-motorised wheelchair [(f)]
50% of these are motorised [(e)]	£287 per year per motorised wheelchair [(f)]
Inpatient rehabilitation	
1 assessment for rehabilitation per patient [(e)]	£306 per assessment [(c)]
50 days of rehabilitation per patient [(e)]	£290 per bed day for amputation rehabilitation [(c)]
Outpatient rehabilitation	
1 assessment for rehabilitation per patient [(e)]	£307 per assessment [(c)]
2 physiotherapists per class [(e)]	£37 (x 2) per hour [(f)]
1 physiotherapy technician [(e)]	£22 per hour [(g)]

Resource use	Unit cost
Room and equipment hire [e]	£15 per hour [e]
2 hours of class per week with 10 patients per class [e]	
8.5 weeks of rehabilitation for below the knee and 13 weeks for above the knee amputations [e]	
Wound care	
2.5 nurse visits per week [e]	£24 per home visit from a district nurse [g] and £10 of wound care supplies used per home visit [e]
90% have a non-complicated wound with an average healing time of 12 weeks [e]	
10% have a complicated wound with an average healing time of 32 weeks [e]	
Care home	
36% of formerly independent patients require a care home [h & e]	
47 weeks per year [e]	£986 per week [g]
Community care & home modifications	
64% of formerly independent patients remain in the community [h]	
Half of patients remaining in the community will require care in the community [e]	£296 per week [g]
All patients remaining in the community will have some form of home modification [e]	
1 concrete ramp [e]	£390 [g]
3 grab rails [e]	£53 each [g]
Relocation of toilet/other home renovation [e]	£1, 754 [g]
Total average cost per patient in the first year following amputation = £28, 270	

(a) Based on estimates of prosthesis use by amputation type{McWhinnie, 1994 16073 /id} and type of amputation data for people with IC{Moxey, 2010 16345 /id}
(b) Expert opinion (prosthestist)
(c) NHS Reference Costs 2009/10 {Department of Health, 2011 5345 /id}
(d) Assumed that those without prostheses have wheelchairs.
(e) Expert opinion (GDG)
(f) Annualised over 5 years according to PSSRU 2010{Curtis, 2010 CURTIS2010 /id}
(g) PSSRU 2010{Curtis, 2010 CURTIS2010 /id}
(h) Based on data suggesting that one year following amputation, 66.6% of people with below the knee amputations and 61.5% of people with below the knee amputations who were previously independent maintained their independent living status{Taylor, 2005 16395 /id} and a study reporting that 61% of people living independently prior to the operation returned to living independently after major amputation.{Larsson, 1998 16396 /id}

Table 57: 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 [a & b]	
47 weeks per year [b]	£986 per week [c]
Community care	
64% of formerly independent patients remain in the community [a]	
Half of patients remaining in the community will require care in the community [b]	£296 per week [c]

Wheelchair	
45% of amputees use wheelchairs [(d)]	
50% of these are non-motorised [(b)]	£58 per year per non-motorised wheelchair [(e)]
50% of these are motorised [(b)]	£287 per year per motorised wheelchair [(e)]
Total average cost per patient = £23, 502	

(a) Based on data suggesting that one year following amputation, 66.6% of people with below the knee amputations and 61.5% of people with below the knee amputations who were previously independent maintained their independent living status{Taylor, 2005 16395 /id} and a study reporting that 61% of people living independently prior to the operation returned to living independently after major amputation.{Larsson, 1998 16396 /id}
(b) Expert opinion (GDG)
(c) PSSRU 2010{Curtis, 2010 CURTIS2010 /id}
(d) Assumed that those without prostheses have wheelchairs.
(e) Annualised over 5 years according to PSSRU 2010{Curtis, 2010 CURTIS2010 /id}

L.2.4 Sensitivity analyses

The following sensitivity analyses were undertaken to explore the effect of different parameter inputs and assumptions on the results of the model. The results of all sensitivity analyses are presented in section L.3.2.

SA1 and SA2: Baseline risk of total mortality in people with IC

In the base case analysis, the Framingham equations and data from the Ankle Brachial Collaboration was used to inform the risk of death in people with IC. However, several other sources of data are available, including a study evaluating the relationship between ABPI and mortality in people with PAD by Diehm and colleagues (2006){Diehm, 2006 16237 /id} and mortality rates reported by the Edinburgh Artery Study. Diehm 2006 reported an unadjusted hazard ratio of 4.41 (95% CI, 2.94 to 6.62){Diehm, 2006 16237 /id} for ABPIs of between 0.5 and 0.7 compared to people with normal ABPI, while the Edinburgh artery study observed a hazard ratio of 1.42 (95% CI, 1.15 to 1.74) in a community based sample of people with IC compared to those without IC. Both of these values were used to explore the effect of baseline mortality on the results of the model.

SA3 & SA4: Baseline risk of 30-day mortality associated with angioplasty

Because no events were observed in the RCS audit, in the basecase analysis the probability of 30-day mortality associated with angioplasty was assigned a value of 0.5/840. In order to test the impact of this assumption within a range considered reasonable by the GDG, this value was set to 0% (0/840) and 0.02% (2/840).

SA5: Relative risk of mortality in active people

The base case model assumes that the beneficial effect of exercise observed in people with established cardiovascular disease applies equally to people with IC. The model also assumes that this effect is only relevant so long as people remain active. In sensitivity analysis, the probability of mortality for people who are active was set equal to the probability for those who are inactive in order to observe the effect of this assumption on the results of the model.

SA6: Risk of cardiovascular events in active people

The base case model also assumes that activity has an effect on cardiovascular risk in people with IC so long as they are active. To examine the effect of this assumption on the results of the model, the beneficial effect of exercise was removed from the model. Therefore, under this sensitivity analysis, exercise (either supervised or unsupervised) is not associated with a decreased risk of CV events.

SA7: Risk of mortality & cardiovascular events in active people

When the assumed benefit of exercise on mortality and cardiovascular events is removed, the result remains in favour of supervised exercise as the most cost-effective type of exercise programme for the treatment of IC.

SA8: Quality of life beyond one year in people who continue to exercise

In the absence of evidence to inform quality of life beyond the follow-up of included trials, a key assumption of the model is that at the end of one year, the gain in quality of life achieved by people in each exercise arm are maintained by those who continue to be active. The effect of this assumption was explored by running the model when there is no difference in quality of life between treatment strategies after one year.

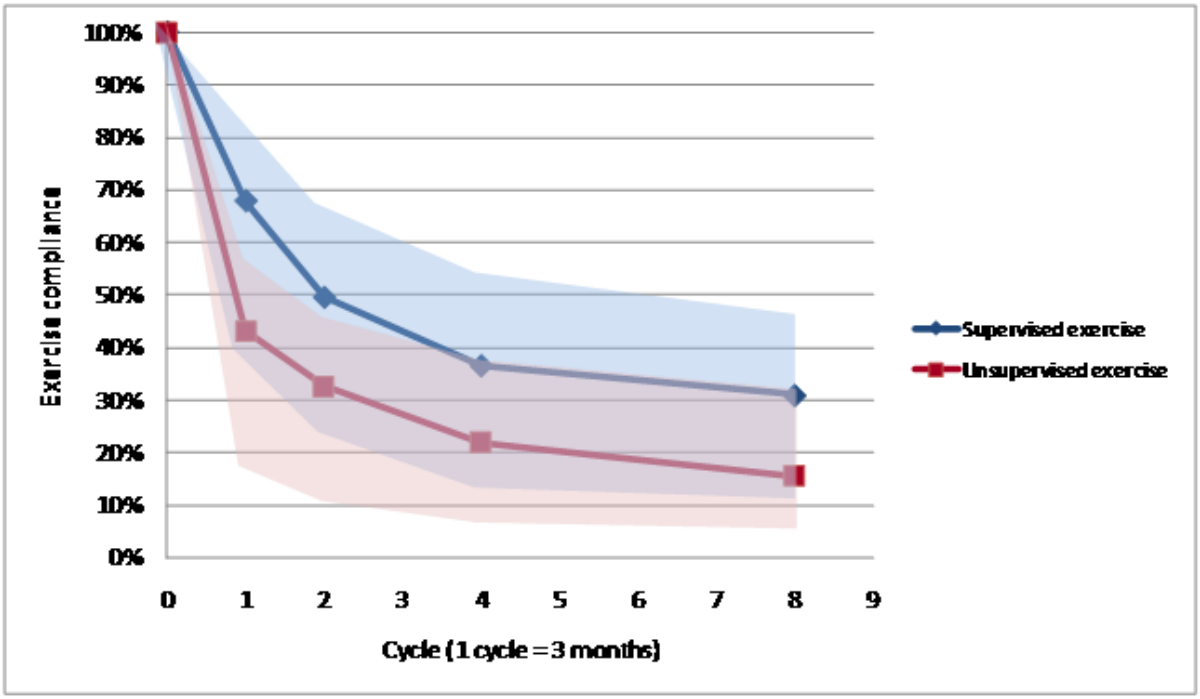
SA9: All key assumptions

A sensitivity analysis was undertaken to examine the effect of removing all key assumptions (maintenance of quality of life gain and benefit to mortality and CV risk in those who are active) from the model. Under this analysis, the only major assumption external to the data collected from the included trials is the level of patient compliance, which is used to estimate the average cost and quality of life associated with each exercise programme.

SA10: Greater long term compliance to supervised exercise programme

In order to test the impact of greater rates of long term compliance to supervised exercise on the outcome of the model, the average results of the survey described in Appendix K were used in sensitivity analysis.

Figure 245: Greater long term compliance to supervised



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%

SA11: Equal relative risks were data is missing in one artery

For outcomes (30-day mortality and post-operative amputation) where there was no data reported for one of the two arteries, the GDG decided that where 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. Where 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. To test the impact of this assumption on the results of the model, outcomes to which a risk of 1 was applied were assigned the same value as that observed in the other artery.

SA12: Risk of 30-day mortality associated with bypass

The GDG indicated that based on the very low baseline probability of mortality used for angioplasty, and the low relative risk observed in trials (2.97), the overall probability of 30-day mortality is lower than expected. To test the impact of this value on the results of the model, the probability of mortality associated with bypass was set to 5%

SA13 & SA14 & SA15: Progression to CLI

The GDG did not know of any evidence to suggest that progression to CLI is altered depending on the treatment undergone. In theory, the GDG thought that exercise may have a similar effect as that assumed for cardiovascular events. To test the impact of this assumption, the same relative risk as used for mortality (0.87) was applied to the probability of progression to CLI in SA 13. This relative risk was then applied to the probability of CLI after angioplasty in SA14.

SA16 & SA17: Cost of supervised exercise programme

The cost of a supervised exercise programme is likely to differ around the country. The GDG noted that in some centres only two staff members are involved in provision (one physiotherapist and one technician). In order to explore the effect of less costly and more costly supervised exercise programmes, the costs was set to the lower and upper limits of the 95% confidence interval (£232 to £345), which was derived from assumed 10% standard error around the mean cost estimate.

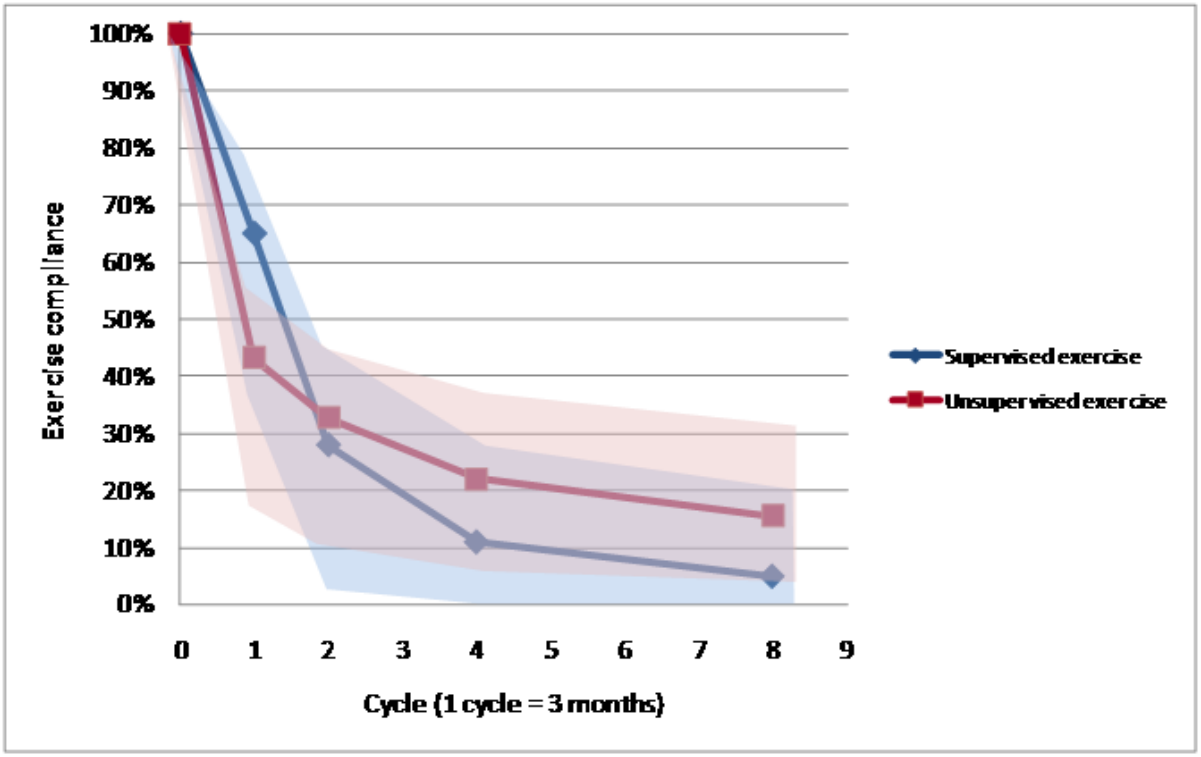
SA18: Increased cost of unsupervised exercise

Different unsupervised exercise programmes may include different amounts of patient support, such as regular telephone calls, an exercise diary, or education component. In order to test the impact of this cost on the outcome of the model, the cost of an unsupervised exercise programme was set to £25.

SA19: Increased compliance to unsupervised exercise

The GDG thought that it was very unlikely that greater long term compliance to an unsupervised exercise programme would be observed across a population of people with IC. However, in order to fully explore the uncertainty of the model, and to tease apart the impact of the results of SA20, this scenario was included in the sensitivity analysis for completeness.

Figure 246: Greater long term compliance to unsupervised exercise



SA20: Increased cost and compliance to unsupervised exercise

The GDG noted that increased support may be associated with greater compliance to unsupervised exercise. In two way sensitivity analysis, an average cost of £25 was used to inform the cost of unsupervised exercise and compliance to unsupervised exercise was adjusted to be less than supervised exercise over the short term but greater than supervised exercise over the long term (Figure 246).

SA21: Discount rates

Currently, the NICE reference case states that both costs and QALYs should be discounted at a rate of 3.5% per year. Recently, there has been a debate surrounding this assumption. In order to test the impact of these rates on model results, each scenario was run with QALYs discounted at 1.5% and costs at 3.5%.

L.2.5 Interpreting results

L.2.5.1 Incremental cost effectiveness ratios

The results of cost-effectiveness analysis are presented as incremental cost-effectiveness ratios (ICERs). ICERs are calculated by dividing the difference in costs associated with two alternative treatments by the difference in QALYs:

$$\frac{\text{Difference in costs}}{\text{Difference in QALYs}}$$

Where more than two interventions are being compared, the ICER is calculated according to the following process:

- The interventions are ranked in terms of cost, from least to most expensive.

- If an intervention is more expensive and less effective than the preceding intervention, it is said to be 'dominated' and is excluded from further analysis.
- ICERs are then calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next most effective strategy, then it is ruled out by 'extended dominance'
- ICERs are recalculated excluding any drugs subject to dominance or extended dominance.
- When there are multiple comparators, the option with the greatest average net benefit may also be used to rank comparators.

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. In general, an intervention is considered to be cost-effective if either of the following criteria applies:

- The intervention dominates other relevant strategies (that is, is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

L.2.5.2 Net benefit framework

The net benefit (NB) framework allows us to rearrange the decision rule using the threshold value.

The decision rule then becomes a simple question of maximising net benefit; the strategy with the greatest average NB is also the most cost effective option. This framework also eliminates the need to consider dominance and calculating ICERs with respect to the most appropriate comparator. As such, it allows us to rank order interventions according to cost-effectiveness.

Using the net benefit framework in probabilistic modelling, we are able to calculate the probability that a strategy will be cost effective (have the greatest NB) over a number of simulations. However, because this method does not take into account the magnitude of the simulations, the optimal treatment is not always the one with the greatest proportion of simulations in its favour. In order to calculate the optimal treatment when there are a large number of strategies, it is most useful to consider the cost-effectiveness frontier.

L.3 Results

L.3.1 Base case results

Results of probabilistic analysis were evaluated according to the decision rules outlined in section L.2.5. For reference, all evaluated strategies and the corresponding numbers used to represent each in base case and sensitivity analyses are presented in Table 58.

Table 58: 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

Strategy	Initial treatment	Secondary treatment
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	

L.3.111 Aorto-iliac artery

After excluding strategies that are dominated or extendedly dominated (Figure 245), 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 59). The cost effectiveness acceptability curve shows that at a threshold of between £20 and £30k, strategy 5 is the option with the greatest probability of being cost effective (Figure 246). Table 60 shows the total average net benefit associated with each treatment strategy.

Figure 247: Cost effectiveness plane: Aorto-iliac artery

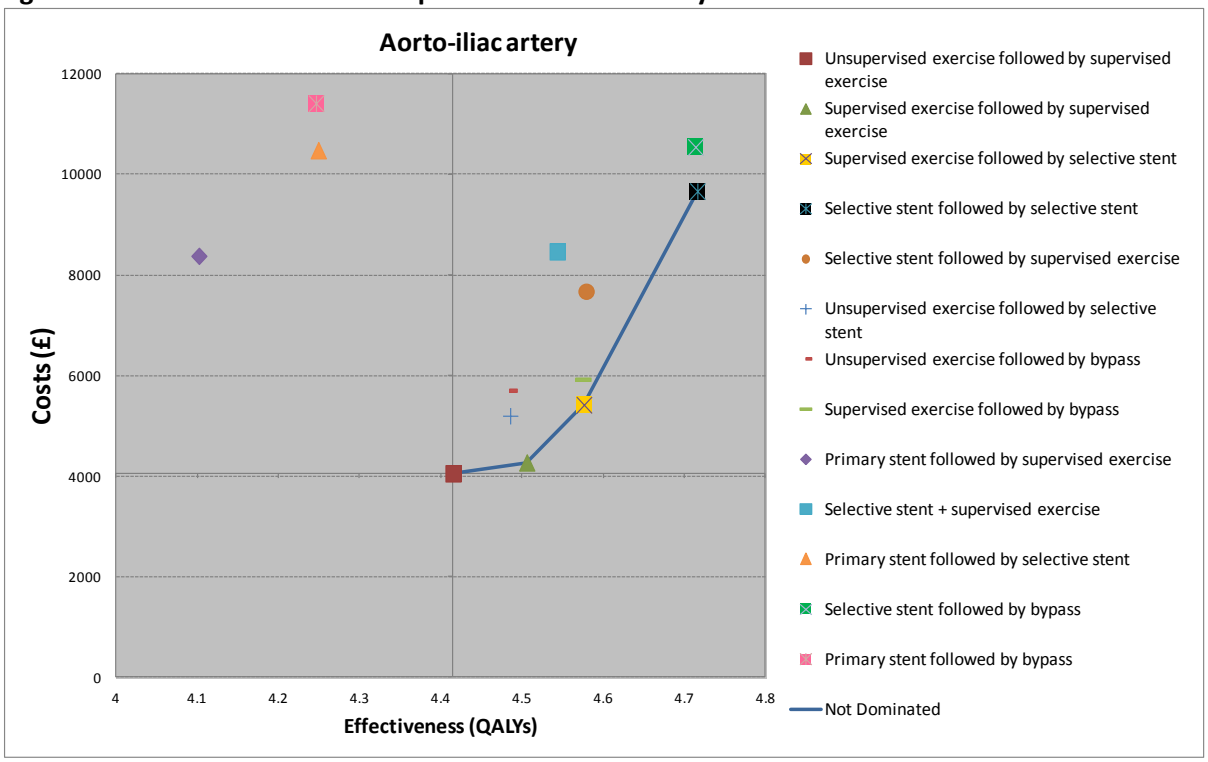
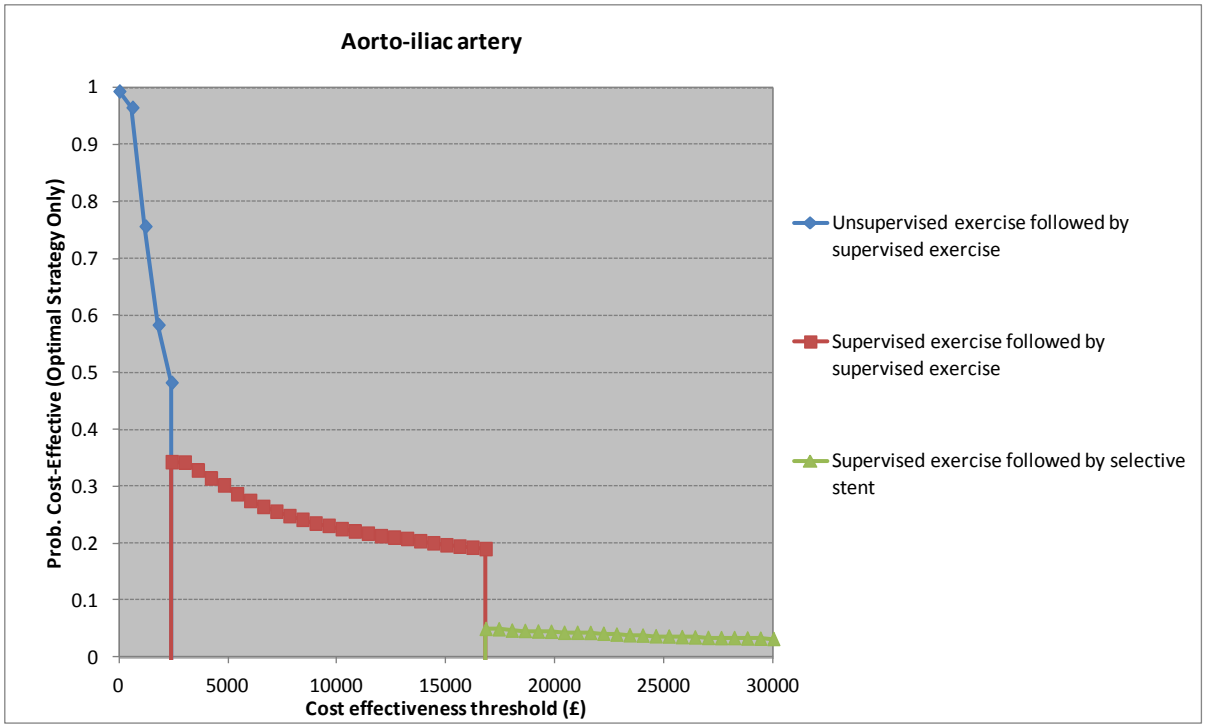


Figure 248: Cost effectiveness acceptability frontier: Aorto-iliac-artery



1 **Table 59: 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

2 **Table 60: Probabilistic net benefit ranking for each evaluated strategy: Aorto-iliac artery**

Ranking (most to least CE)	Strategy	Strategy description	Net Benefit
1	5	Supervised exercise followed by selective stent	£86, 110
2	4	Supervised exercise followed by supervised exercise	£85, 848
3	6	Supervised exercise followed by bypass	£85, 577
4	8	Selective stent followed by selective stent	£84, 655
5	2	Unsupervised exercise followed by selective stent	£84, 509
6	1	Unsupervised exercise followed by supervised exercise	£84, 248
7	3	Unsupervised exercise followed by bypass	£83, 978
8	7	Selective stent followed by supervised exercise	£83, 939
9	9	Selective stent followed by bypass	£83, 728
10	13	Selective stent + supervised exercise	£82, 400
11	11	Primary stent followed by selective stent	£74, 498
12	10	Primary stent followed by supervised exercise	£73, 658
13	12	Primary stent followed by bypass	£73, 508

L.3.112 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. 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 61). The cost effectiveness acceptability curve shows that at a threshold of between £20 and £30k, strategy 5 is the option with the greatest probability of being cost effective (Figure 250). Table 62 shows the total average net benefit associated with each treatment strategy.

Figure 249: Cost effectiveness plane: Femoro-popliteal artery

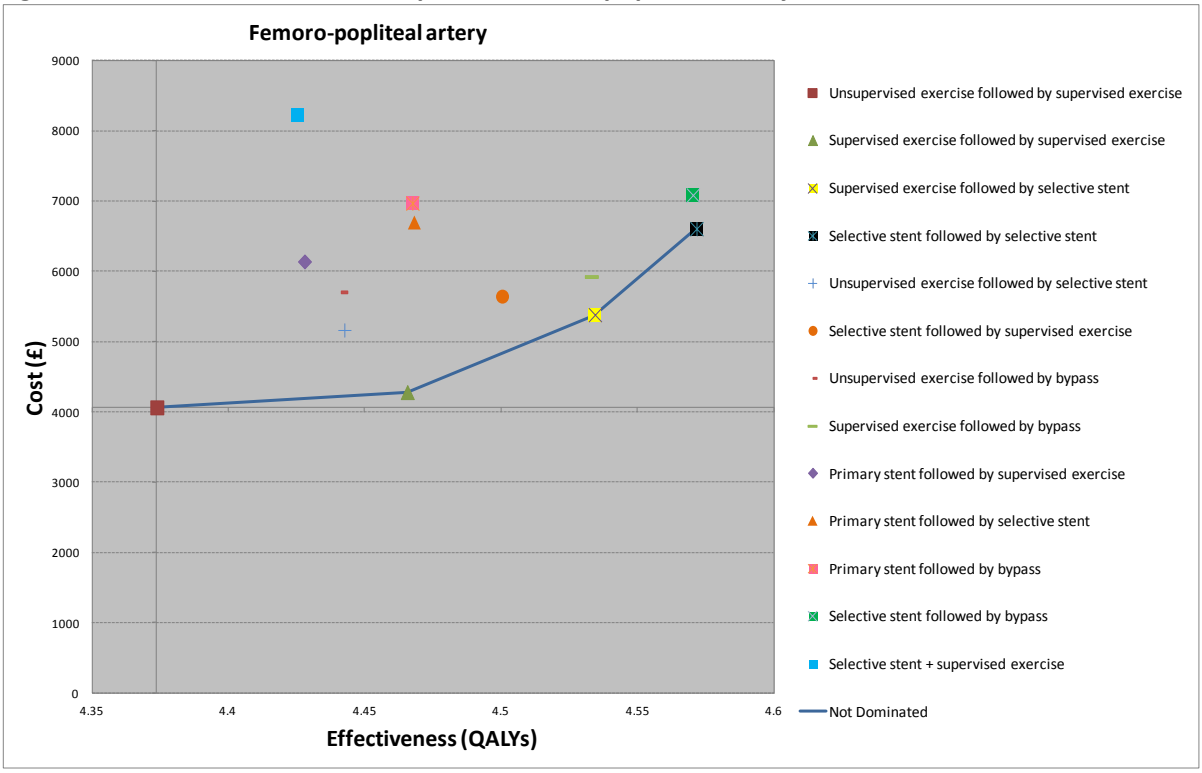
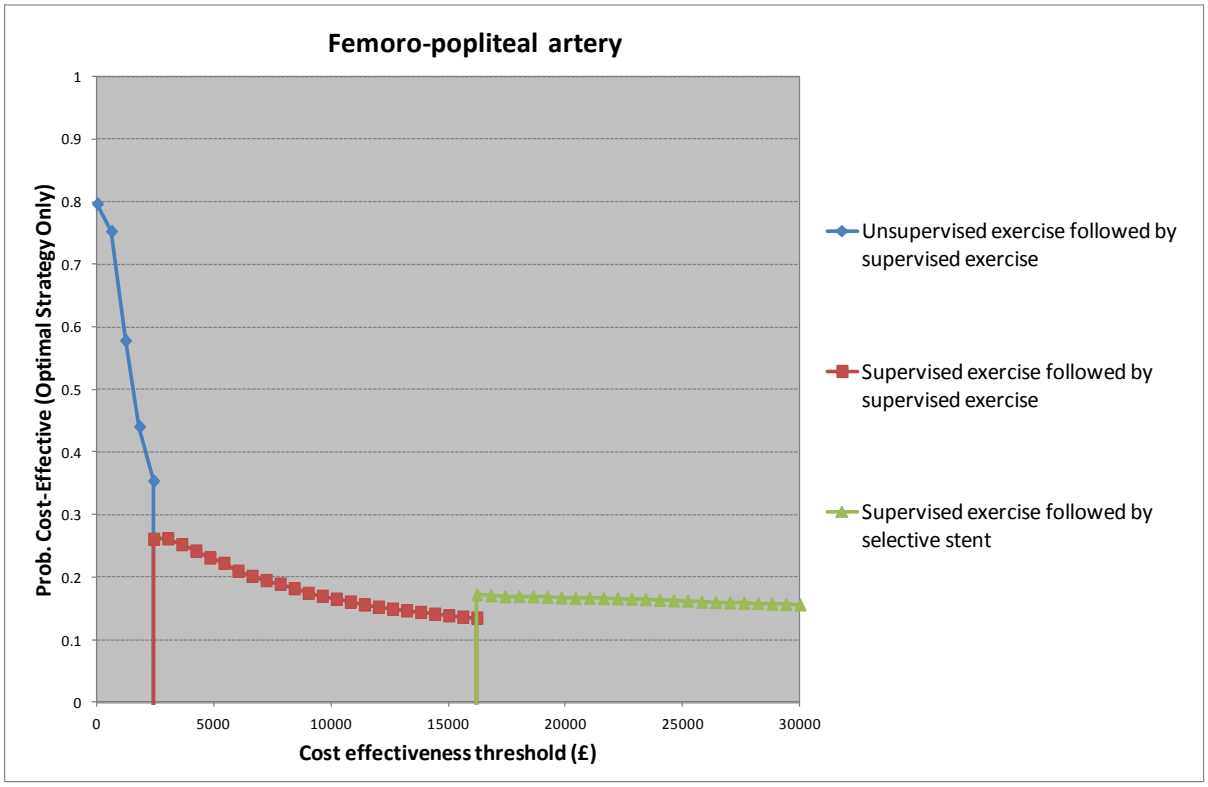


Figure 250: Cost effectiveness acceptability frontier: Femoro-popliteal artery



1 **Table 61: 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

2 **Table 62: Probabilistic net benefit ranking for each evaluated strategy: Femoro-popliteal artery**

Ranking (most to least CE)	Strategy	Strategy description	Net Benefit
1	5	Supervised exercise followed by selective stent	£85, 308
2	4	Supervised exercise followed by supervised exercise	£85, 035
3	8	Selective stent followed by selective stent	£84, 828
4	6	Supervised exercise followed by bypass	£84, 739
5	7	Selective stent followed by supervised exercise	£84, 374
6	9	Selective stent followed by bypass	£84, 323
7	2	Unsupervised exercise followed by selective stent	£83, 689
8	1	Unsupervised exercise followed by supervised exercise	£83, 415
9	3	Unsupervised exercise followed by bypass	£83, 120
10	11	Primary stent followed by selective stent	£82, 672
11	10	Primary stent followed by supervised exercise	£82, 421
12	12	Primary stent followed by bypass	£82, 382
13	13	Selective stent + supervised exercise	£80, 278

Table 63 and Table 64 provide a breakdown of total cost and QALY results predicted by the model for the aorto-iliac and femoro-popliteal arteries, respectively. Disaggregating costs into those associated with primary and secondary treatment shows the overall impact of different rates of complications, 30-day amputations, and reintervention between different endovascular treatments. Because the rate of amputation is constant throughout the model, the associated cost reflects the impact of different mortality rates on costs throughout the model. A higher mortality rate means that there are fewer people transitioning though the model. Therefore they do not incur additional costs. However, these strategies also result in fewer QALYs; this is reflected in the column reporting baseline QALYs. This effect of mortality complicates interpretation of the costs associated with CV events; strategies which include exercise decrease the cost associated with CV events but increase overall costs due to a decreased rate of mortality. The column titled treatment effect provides a summary of the lifetime intervention-specific QALY gain based on the clinical literature and assumptions of the model.

Table 63: Breakdown of total costs and QALYs: Aorto-iliac artery (deterministic)

Strategy (ordered from most to least cost effective according to average net benefit)	Total costs	Disaggregated costs				Total QALYs	Disaggregated QALYs		
		Primary treatment	Secondary treatment	CV events	Amputation		Baseline	Treatment effect	CV events
5. Supervised exercise followed by selective stent	£5, 307	£219	£1, 191	£2, 406	£1, 491	4.519	4.358	0.171	-0.010
4. Supervised exercise followed by supervised exercise	£4, 155	£219	£62	£2, 399	£1, 475	4.447	4.368	0.089	-0.010
6. Supervised exercise followed by bypass	£5, 809	£219	£1, 694	£2, 405	£1, 490	4.518	4.357	0.171	-0.010
8. Selective stent followed by selective stent	£9, 567	£4, 184	£2, 095	£2, 012	£1, 276	4.661	4.339	0.331	-0.009
2. Unsupervised exercise followed by selective stent	£5, 089	£0	£1, 190	£2, 410	£1, 489	4.427	4.357	0.080	-0.010
1. Unsupervised exercise followed by supervised exercise	£3, 938	£0	£62	£2, 403	£1, 473	4.355	4.364	0.001	-0.010
3. Unsupervised exercise followed by bypass	£5, 590	£0	£1, 692	£2, 409	£1, 489	4.426	4.356	0.080	-0.010
7. Selective stent followed by supervised exercise	£7, 548	£4, 184	£109	£2, 002	£1, 254	4.521	4.351	0.179	-0.009
9. Selective stent followed by bypass	£10, 449	£4, 184	£2, 980	£2, 011	£1, 274	4.659	4.765	-0.097	-0.009
13. Selective stent + supervised exercise	£8, 329	£4, 184	£213	£2, 411	£1, 521	4.484	4.338	0.156	-0.010
11. Primary stent followed by selective stent	£10, 702	£4, 839	£2, 360	£2, 143	£1, 360	4.269	4.376	-0.097	-0.010
10. Primary stent followed by supervised exercise	£8, 428	£4, 839	£122	£2, 131	£1, 336	4.112	4.257	-0.135	-0.010
12. Primary stent followed by bypass	£11, 696	£4, 839	£3, 356	£2, 142	£1, 359	4.267	3.946	0.331	-0.010

Table 64: Breakdown of total costs and QALYs: Femoro-popliteal artery (deterministic)

Strategy (ordered from most to least cost effective)	Total cost	Disaggregated costs				Total QALYs	Disaggregated QALYs		
		Primary treatment	Secondary treatment	CV events	Amputation		Baseline utility	Treatment effect	CV events
5. Supervised exercise followed by selective stent	£5, 248	£219	£1, 132	£2, 406	£1, 491	4.467	4.306	0.171	-0.010
4. Supervised exercise followed by supervised exercise	£4, 155	£219	£62	£2, 399	£1, 475	4.395	4.316	0.089	-0.010
8. Selective stent followed by selective stent	£6, 566	£3, 974	£1, 002	£961	£629	4.503	4.352	0.157	-0.006
6. Supervised exercise followed by bypass	£5, 811	£219	£1, 696	£2, 405	£1, 490	4.466	4.305	0.171	-0.010
7. Selective stent followed by supervised exercise	£5, 603	£3, 974	£55	£955	£618	4.427	4.351	0.082	-0.006
9. Selective stent followed by bypass	£7, 064	£3, 974	£1, 501	£961	£629	4.501	4.350	0.157	-0.006
2. Unsupervised exercise followed by selective stent	£5, 025	£0	£1, 131	£2, 409	£1, 485	4.374	4.304	0.080	-0.010

Strategy	Total	Disaggregated costs				Total	Disaggregated QALYs		
1. Unsupervised exercise followed by supervised exercise	£3, 938	£0	£62	£2, 403	£1, 473	4.303	4.312	0.001	-0.010
3. Unsupervised exercise followed by bypass	£5, 588	£0	£1, 695	£2, 408	£1, 485	4.373	4.303	0.080	-0.010
11. Primary stent followed by selective stent	£6, 687	£4, 932	£583	£722	£450	4.389	4.388	0.007	-0.006
10. Primary stent followed by supervised exercise	£6, 126	£4, 932	£32	£718	£444	4.345	4.360	-0.009	-0.006
12. Primary stent followed by bypass	£6, 946	£4, 932	£842	£722	£450	4.388	4.387	0.007	-0.006
13. Selective stent + supervised exercise	£8, 120	£3, 974	£213	£2, 411	£1, 521	4.351	4.285	0.076	-0.010

L.3.12 Sensitivity analyses

A wide range of deterministic sensitivity analyses showed that although supervised exercise followed by selective stent placement (strategy 5) is the most cost effective strategy in most analyses, the conclusion is sensitive to key model assumptions. The impact of each sensitivity analysis on the model is described below, with the results of each analysis for each artery presented in Table 65 and Table 66.

SA1 & SA2: When the relative risk of mortality from IC compared to the general population is increased/decreased in sensitivity analysis, there is a higher/lower background rate of mortality compared to that of the base case analysis. When mortality is increased, there are fewer people entering each stage of the model (because they die). Across the population, there are therefore fewer QALYs gained and fewer costs accrued. However, because exercise is assumed to have a beneficial effect on mortality, a higher baseline mortality rate means that the relative effectiveness of exercise is greater. Therefore, compared to strategy 4 (the next most cost-effective option), strategy 5 is not as effective as in the base case analysis. The converse is true when the baseline rate of mortality is decreased.

SA3 & SA4: Changing the baseline probability of operative mortality to 0% and 1% does not change the conclusions of the analysis.

SA5: Removing the assumed benefit of exercise on mortality demonstrates the importance of this assumption on the results of the model. Reducing the effectiveness of exercise increases the effectiveness of selective stent placement compared to strategies including supervised exercise. Under this sensitivity analysis, strategy 8 is most cost effective in both arteries.

SA6: Removing the assumed benefit of exercise on cardiovascular risk demonstrates the relative unimportance of this assumption on the results of the model. For the same reasons described above, removing this assumption increases the relative effectiveness of strategy 5, but does not have a great enough effect on the model for strategy 8 to fall under the £20, 000 threshold in either artery.

SA7: This sensitivity analysis demonstrates the combined effect of assumptions of mortality and cardiovascular benefit in people who are active. Under this assumption, and due more to assumptions about mortality than cardiovascular events, strategy 8 is both most the most effective and cost effective strategy in both arteries.

SA8: If we do not extrapolate quality of life beyond trial end dates, strategy 13 is most effective in the aorto-iliac artery and strategy 8 is most effective in the femoro-popliteal. However, neither of these strategies falls within the £20-£30k cost per QALY threshold. Under this sensitivity analysis, the baseline treatment option (strategy 1) is most cost effective in the aorto-iliac artery and strategy 5 is most cost effective in the femoro-popliteal. Please refer to section L.2.3.5 for details of the utility values used to inform the model.

SA9: If all key assumptions about the benefits of exercise were removed from the model, strategy 13 and 8 are again the most effective in the aorto-iliac and femoro-popliteal arteries, respectively. However, neither is cost effective according to our criteria and strategy 1 and 5 are the optimal options.

SA10: If we assume that a supervised programme leads to greater short term and long term compliance to exercise compared to an unsupervised programme, strategy 5 remains the most cost effective option. However, under this analysis strategy 4 (the next most cost effective option) almost doubles in incremental effectiveness compared to strategy 1. Therefore, strategy 5 is less effective compared to strategy 4 and incurs a greater cost per QALY than in the base case analysis.

SA11: Where evidence of intervention effectiveness is missing in one artery, setting the value equal to that observed in the other artery does not affect the conclusions of the model.

SA12: If the risk of operative-mortality associated with bypass surgery is increased to 5%, the results of the model are unchanged.

SA13 & SA14 & SA15: When the rate of progression to CLI is assumed to be reduced as a result of treatment with exercise and angioplasty, the result of the model is unchanged. Likewise when angioplasty increases the risk of progression to CLI.

SA16 & SA17: Increasing the risk of mortality associated with bypass surgery does not influence the results of the model because strategies involving bypass surgery are already ruled out by dominance (i.e. more costly and less effective than other interventions).

SA18: Increasing the cost of an unsupervised exercise programme by £25 has no effect on the results of the model.

SA19 & SA20: When compliance to unsupervised exercise is greater than supervised exercise over the long term, selective stent followed by selective stent is the most cost-effective treatment option in both arteries.

SA21: Using a different discount rate (1.5% for QALYs and 3.5% for costs) does not affect the conclusion of the model.

Table 65: AORTO-ILIAC: Results of deterministic sensitivity analyses

	Most CE strategy¥	Δ Costs	Δ QALY	ICER
Base case				
Base case results (deterministic)	**5**	£1, 152	0.072	£15, 949
Sensitivity analyses				
Baseline risk of mortality (total and 30-day)				
SA1: Baseline relative risk of mortality set to 4.41	**5**	£1, 021	0.054	£18, 864
SA2: Baseline relative risk of mortality set to 1.42	**5**	£1, 403	0.119	£11, 790
SA3: Baseline risk of 30-day mortality set to 0%	**5**	£1, 152	0.073	£15, 820
SA4: Baseline risk of 30-day mortality set to 1%	**5**	£1, 144	0.062	£18, 329
Key model assumptions				
SA5: No mortality benefit from exercise	**8**	£4, 303	0.181	£23, 751
SA6: No CV event benefit from exercise	**5**	£1, 140	0.072	£15, 726
SA7: No mortality or CV event benefit from exercise	**8**	£4, 257	0.184	£23, 128
SA8: No difference in QoL beyond one year	**1**	Baseline	Baseline	Baseline
SA9: No difference in QoL beyond one year and no mortality or CV event benefit from exercise	**1**	Baseline	Baseline	Baseline
SA10: Greater long term compliance to supervised compared to unsupervised exercise	**5**	£1, 159	0.052	£22, 147
SA11: Equal relative risk where data is missing	**5**	£1, 152	0.072	£15, 949
SA12: 5% rate of 30-day mortality in bypass surgery	**5**	£1, 152	0.072	£15, 949
SA13: Reduced progression to CLI for those who are active	**5**	£1, 158	0.072	£16, 083
SA14: Reduced progression to CLI after angioplasty	**5**	£1, 111	0.074	£15, 108
SA15: Increased risk of progression to CLI after angioplasty	**5**	£1, 198	0.071	£16, 955

	Most CE strategy¥	Δ Costs	Δ QALY	ICER
Costs				
SA16: Decreased cost of supervised programme	**5**	£1, 164	0.072	£16, 118
SA17: Increased cost of supervised programme	**5**	£1, 140	0.072	£15, 782
SA18: Increased cost of unsupervised exercise	**5**	£1, 152	0.072	£15, 949
SA19: Increased compliance to unsupervised exercise	**8**	£4, 478	0.234	£19, 149
SA 20: Increased cost and compliance to unsupervised exercise	**8**	£4, 478	0.234	£19, 149
Discount rate				
SA21: Rate of 1.5% for QALYs and 3.5% for costs	**5**	£1, 147	0.083	£13, 796

¥ At a threshold of £20k per QALY according to deterministic results

Table 66: FEMORO-POPLITEAL: Results of deterministic sensitivity analyses

	Most CE strategy¥	Δ Costs	Δ QALY	ICER
Base case				
Base case results (deterministic)	**5**	£1, 093	0.072	£15, 110
Sensitivity analyses				
Baseline risk of mortality				
SA1: Baseline relative risk of mortality set to 4.41	**5**	£969	0.054	£17, 858
SA2: Baseline relative risk of mortality set to 1.42	**8**	£992	0.106	£9, 339
SA3: Baseline risk of 30-day mortality set to 0%	**5**	£1, 093	0.073	£14, 990
SA4: Baseline risk of 30-day mortality set to 1%	**5**	£1, 080	0.062	£17, 487
Key model assumptions				
SA5: No mortality benefit from exercise	**8**	£1, 361	0.075	£18, 223
SA6: No CV event benefit from exercise	**5**	£1, 081	0.073	£14, 894
SA7: No mortality or CV event benefit from exercise	**8**	£1, 315	0.078	£16, 956
SA8: No difference in QoL beyond one year	**7**	£1, 664	0.110	£15, 066
SA9: No difference in QoL beyond one year and no mortality or CV event benefit from exercise	**7**	£1, 647	0.144	£11, 446
SA10: Greater long term compliance to supervised compared to unsupervised exercise	**5**	£1, 099	0.052	£20, 947
SA11: Equal relative risk where data is missing	**5**	£1, 093	0.072	£15, 110
SA12: 5% rate of 30-day mortality in bypass surgery	**5**	£1, 093	0.072	£15, 110
SA13: Reduced progression to CLI for those who are active	**5**	£1, 099	0.072	£15, 240
SA14: Reduced progression to CLI after angioplasty	**5**	£1, 052	0.074	£14, 291
SA15: Increased risk of progression to CLI after angioplasty	**5**	£1, 139	0.071	£16, 089
Costs				
SA16: Decreased cost of supervised programme	**5**	£1, 105	0.072	£15, 279
SA17: Increased cost of supervised programme	**5**	£1, 081	0.072	£14, 943
SA18: Increased cost of unsupervised exercise	**5**	£1, 093	0.072	£15, 110
SA19: Increased compliance to unsupervised exercise	**8**	£2, 628	0.215	£12, 244
SA 20: Increased cost and compliance to unsupervised exercise	**8**	£2, 628	0.215	£12, 244

	Most CE strategy¥	Δ Costs	Δ QALY	ICER
Discount rate				
SA21: Rate of 1.5% for QALYs and 3.5% for costs	**5**	£1, 088	0.083	£13, 065

¥ At a threshold of £20k per QALY according to deterministic results

The baseline difference in outcomes between the two lesion locations is due to the difference in baseline quality of life, proportion of patients receiving selective stent placement, and IC symptom progression. Table 67 shows total cost and QALYs when each of these variables is the same in each artery. Looking at the difference between each artery is useful to gain a sense of the magnitude of influence that the relative effect estimates obtained from the systematic review have upon each treatment strategy in the model. We can see that the slightly lower reported risk of operative complications associated with bypass (compared to selective stent placement) in the aorto-iliac artery leads to a very small difference in total cost. The studies included in the clinical review also reported a higher rate of reintervention, peri-operative amputation and 30-day mortality in the aorto-iliac artery, as well as a lower risk of operative complications for primary stent compared to selective stent placement. This is captured in both the costs and QALY difference between the two arteries. Strategy 10 is less affected by this difference as it includes supervised exercise as a secondary strategy. The effectiveness of exercise interventions included in the model are not subgrouped by lesion location.

Table 67: Total cost and QALYs in each artery when baseline differences are removed

	Aorto-iliac artery		Femoro-popliteal artery		Difference in costs and QALYs between arteries (Aorto – Fempop)	
Strategy	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**Δ costs**	**Δ QALYs**
1	£3, 938	4.355	£3, 938	4.355	£0	0.000
4	£4, 155	4.447	£4, 155	4.447	£0	0.000
5	£5, 307	4.519	£5, 307	4.519	£0	0.000
8	£9567	4.661	£9, 567	4.661	£0	0.000
7	£7, 548	4.521	£7, 548	4.521	£0	0.000
2	£5, 089	4.427	£5, 089	4.427	£0	0.000
3	£5, 590	4.426	£5, 593	4.426	£-3	0.000
6	£5, 809	4.518	£5, 811	4.518	£-3	0.000
13	£8, 329	4.484	£8, 329	4.403	£0	0.080
10	£8, 428	4.112	£7, 870	4.122	£559	-0.011
9	£10, 449	4.659	£10, 454	4.659	£-4	0.000
11	£10, 702	4.269	£9, 436	4.231	£1, 266	0.038
12	£11, 696	4.267	£10, 124	4.229	£1, 572	0.038

L.4 Discussion

L.4.1 Summary of results

The results of this analysis show that supervised exercise followed by angioplasty with selective stent placement for people with persistent or worsening claudication is the most cost-effective sequence of treatments for people with IC in the aorto-iliac and femoro-popliteal artery.

There was a high degree of uncertainty surrounding this conclusion and it 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.

L.4.2 Limitations & 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 research in this area is needed.

L.4.3 Generalisability to other populations / settings

Intermittent claudication is defined as pain in the legs that is brought on by exertion and relieved by rest. As a result, exercise performance in people with claudication is approximately half that of age-matched controls(Regeneteiner 2002). Functional exercise capacity impacts people's ability to carry out day to day activities and is correlated with poor quality of life in this population{Bauman, 1997 15967 /id}. Due to the specific improvement in functional ability derived from exercise interventions, exercise programmes may have an effect on quality of life which is disproportionate to people with other conditions. Because the results of this analysis are largely dependent on the gain in quality of life experienced by those undertaking supervised exercise programmes, the results of this analysis may not be applicable to other populations.

L.4.4 Comparison with published studies

Five cost-utility analyses were identified in the economic literature search that compared exercise and endovascular interventions for the treatment of IC. One was a pair-wise comparison based on an RCT{Spronk, 2008 2451 /id} and the remaining four were decision analytic models evaluating different intervention sequences{Bosch, 1998 2459 /id;de Vries, 2002 2460 /id;Hunink, 1995 15926 /id;Visser, 2003 809 /id}. None of the studies identified in the economic literature search included all comparators considered relevant by the GDG and none were directly applicable to the NHS setting. A brief description of the comparators and results of each included study are provided in Table 68. See Appendix I and section 9.4.8 of the full guideline for more details.

The results of the current analysis are consistent with conclusions reached by other published studies comparing exercise, angioplasty and/or bypass for the treatment of IC (Table 68). Uncertainty surrounding the cost-effectiveness of exercise compared to angioplasty with selective stent placement reported by Spronk 2008, Visser 2003, and de Vries 2002 is also observed in the current model. Consistent with Bosch 1998, selective stent placement was found to be more cost effective than primary stent placement. As reported by Hunick 1995, there is a greater probability that angioplasty is more effective than bypass as a secondary intervention, but this is associated with considerable uncertainty. What this model adds to the literature is a simultaneous comparison of all possible treatment options based on a systematic meta-analysis of all available RCT data and current UK unit costs.

Table 68: Published cost-utility analyses included in the economic literature review

Study	Study design	Comparators	Result	Quality and applicability
Spronk 2008{Spronk, 2008 2451 /id}	RCT	1. SEP 2. PTA(SS)	SEP is the most cost effective strategy in 95% of cases.	Partially applicable with minor limitations
Visser 2003{Visser, 2003 809 /id}	Model	1. SEP 2. DUS+PTA(SS) or SEP 3. MRA+PTA(SS) or SEP 4. DSA+PTA(SS) or SEP 5.DUS+PTA(SS) or BS or SEP 6.MRA+PTA(SS) or BS or SEP 7. DSA+PTA(SS) or Bp or SEP	MRA +PTA or SEP is most cost effective at a cost £20, 670 per QALY gained compared to SEP.	Partially applicable with potentially serious limitations

Study	Study design	Comparators	Result	Quality and applicability
de Vries 2002{de Vries, 2002 2460 /id}	Model	1. UEP 2. UEP and PTA(SS) 3. UEP and PTA(SS) or BP 4.PTA(SS) or UEP and PTA(SS) 5. PTA(SS) or BS or USP and PTA(SS) or BS	At a threshold of £20k, UEP is the most cost effective strategy.	Partially applicable with potentially serious limitations
Bosch 1998{Bosch, 1998 2459 /id}	Model	1. No treatment 2. PTA 3. PTA(SS) 4. PTA and PTA 5. PTA and PTA(SS) 6. PTA(SS) and PTA (SS) 7. PTA(PS) and PTA(SS)	PTA(SS) and PTA(SS) is the most cost effective strategy, at a threshold of £3, 960.	Partially applicable with minor limitations
Hunick 1995{Hunink, 1995 15926 /id}	Model	1. No treatment 2. PTA 3. PTA and PTA 4. PTA and BS 5. BS 6. BS and PTA	PTA and BS was the dominant treatment strategy	Partially applicable with potentially serious limitations

L.4.5 Conclusion = evidence statement

According to the model, 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.

L.4.6 Implications for future research

Research into the long term effects of exercise on cardiovascular events, mortality and quality of life in people with IC and how these outcomes differ between people undergoing different treatment pathways is needed. Comparative clinical (RCT) evidence of quality of life after angioplasty and bypass in people with IC is also needed, as is evidence of the effectiveness of secondary procedures or treatment sequences.

Appendix M: Research recommendations

M.1 Information requirements for people with peripheral arterial disease

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.

PICO question	**Population: People with peripheral arterial disease.** **Focus of interest: Attitudes and beliefs in relation to PAD, interventions that might influence these** **Comparison: None** **Outcomes: Impact on behavioural change in respect to cardiovascular risk modification.**
Importance to patients or the population	It is important to assess the impact of people's beliefs and attitudes towards peripheral arterial disease on outcomes and modifiable cardiovascular risk factors.
Relevance to NICE guidance	This research recommendation is relevant to all chapters within the guideline in particular the chapter on information requirements for people with peripheral arterial disease.
Relevance to the NHS	A better understanding of the attitudes and beliefs that people hold in relation to their disease and its treatment would allow clinicians to better tailor programmes of education and information to address the relevant concerns. This would be likely to aid shared decision-making and facilitate patient choice regarding lifestyle changes and treatment options.
National priorities	No relevant national priorities.
Current evidence base	The existing evidence base was systematically reviewed for literature related to information requirements for people with peripheral arterial disease. There was a lack of evidence of the 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.
Equality	Information needs to be tailored to the needs of patients and carers. This is particularly important for patients with specific cultural, religious, linguistic, or educational needs. Mental ability and physical capability should also be considered.
Study design	Qualitative study of a range people with PAD of their 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. The focus of the study should be in primary care.
Feasibility	The GDG thought it would be feasible to conduct a qualitative study in the area (a period of two years is suggested), so long as it was designed to be focused and specific.
Other comments	This area is of potential interest to psychosocial and educational research institutes, in addition to health and social care researchers.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

M.2 Exercise for intermittent claudication

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.

PICO question	**Population: People with intermittent claudication.** **Intervention: Supervised exercise** **Comparison: Unsupervised exercise** **Outcomes: Maximal walking distance, quality of life short and long-term engagement in physical activity, reasons for withdrawal, cardiovascular events, mortality.**
Importance to patients or the population	Exercise interventions have the potential to improve both the symptoms of peripheral arterial disease and the long term outcomes of cardiovascular disease
Relevance to NICE guidance	This research recommendation is relevant to the recommendation on supervised exercise for people with intermittent claudication.
Relevance to the NHS	Based on the current clinical evidence base and assumptions used to inform the economic model developed for this guideline, supervised exercise has been recommended as a clinical and cost-effective treatment for people with IC in the NHS. However, there is no long-term evidence of the effectiveness of exercise on mortality, cardiovascular health or quality of life in people with IC. The model was sensitive to the assumptions which were used to extrapolate existing data. If the long term effect of these programmes differs significantly from what was predicted by the model, it is possible that supervised exercise may not represent a cost-effective option for these treatments. Because supervised exercise programmes are likely to be associated with a large implementation cost, this

PICO question	**Population: People with intermittent claudication.** **Intervention: Supervised exercise** **Comparison: Unsupervised exercise** **Outcomes: Maximal walking distance, quality of life short and long-term engagement in physical activity, reasons for withdrawal, cardiovascular events, mortality.**
	represents a potentially significant opportunity cost to the NHS.
National priorities	No relevant national priorities.
Current evidence base	The current clinical evidence base includes several RCTs which demonstrate improved walking distance and quality of life in people who undertake supervised exercise programmes compared to those who are given advice to exercise (unsupervised). However, there is no data to inform the long term-compliance or effectiveness of this intervention. To date, no randomised trials have been conducted in the IC population to assess the impact of exercise on cardiovascular events or mortality.
Equality	None identified.
Study design	RCT based in the community with a minimum follow-up of two years. Longer follow up of the trial population should be considered if treatment effects remain evidence at 2 years. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size. Costs and resource use should be measured from a UK NHS perspective, taking into account all direct and social services costs incurred by patients over the time horizon of the study. Outcomes should include: • Walking distance (maximal and pain free walking distance) • Quality of life (measured by the EQ-5D and SF-36 as a minimum) • Short and long-term engagement in physical activity • Reasons for withdrawal • Cardiovascular events, including progression of PAD to CLI and limb loss • Mortality
Feasibility	The proposed research should be able to be carried out within realistic cost and timescale.
Other comments	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.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

M.3 Angioplasty compared to bypass surgery for critical limb ischaemia of the infra-geniculate arteries

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.

PICO question	**Population: People with critical limb ischaemia due to disease of the infra-geniculate arteries** **Intervention: Angioplasty** **Comparison: Bypass surgery** **Outcomes: Mortality, amputation free survival, quality of life, adverse events, re-intervention rates, change in ABPI**
Importance to patients or the population	People with critical limb ischaemia due to disease of the infra-geniculate arteries are at high risk of limb loss. Better knowledge about the best options for treatment would lead to better clinical outcomes.
Relevance to NICE guidance	This research recommendation is relevant to the recommendation on angioplasty and bypass for people with critical limb ischaemia.
Relevance to the NHS	Limb loss due to critical limb ischaemia is a major cause of morbidity and has high costs both to the NHS and social services
National priorities	No relevant national priorities.
Current evidence base	No RCT evidence was identified in the clinical review comparing angioplasty to bypass surgery in people with critical ischaemia due to disease of the infra-geniculate vessels.
Equality	None identified.
Study design	Multi-centre RCT. Power calculations should be conducted to establish the

	required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	The proposed research should be able to be carried out within realistic cost and timescale.
Other comments	None
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

M.4 Primary compared to secondary stenting for critical limb ischaemia of the infra-geniculate arteries

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.

PICO question	**Population: People with critical limb ischaemia due to disease of the infra-geniculate artery** **Intervention: Angioplasty with selective stent placement** **Comparison: Angioplasty with primary stent placement** **Outcomes: Mortality, amputation free survival, quality of life, adverse events, re-intervention rates, change in ABPI**
Importance to patients or the population	People with critical limb ischaemia due to disease of the infra-geniculate arteries are at high risk of limb loss. Better knowledge about the best options for treatment would lead to better clinical outcomes.
Relevance to NICE guidance	This research recommendation is relevant to the recommendation on angioplasty with or without primary placement for people with critical limb ischaemia.
Relevance to the NHS	Limb loss due to critical limb ischaemia is a major cause of morbidity and has high costs both to the NHS and social services
National priorities	No relevant national priorities.
Current evidence base	No RCT evidence was identified in the clinical review comparing angioplasty with selective stent placement to primary stent placement in people with critical ischaemia due to disease of the infra-geniculate vessels.
Equality	None identified.

Study design	RCT. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	The proposed research should be able to be carried out within realistic cost and timescale.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

M.5 Chemical sympathectomy for ischaemic pain

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. Destruction of the lumbar sympathetic chain (usually the L2 and L3 ganglia), chemical lumbar sympathectomy (CLS), 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.

PICO question	**Population: People with critical limb ischaemia** **Intervention: chemical lumbar sympathectomy** **Comparison: other methods of pain relief** **Outcomes: mortality, quality of life, adverse events, pain measures, pain control, patient satisfaction.**
Importance to patients or the population	Identification of the best methods of pain relief for people with critical ischaemia would have direct benefits in reducing symptoms and/or preventing unnecessary invasive procedures.
Relevance to NICE guidance	This research recommendation is relevant to the recommendation on pain relief for people with critical limb ischaemia.
Relevance to the NHS	There is currently considerable geographic variation in the use of chemical sympathectomy for pain relief in CLI. Better evidence in respect to its value would allow more consistent and cost effective practice.
National priorities	No relevant national priorities.
Current evidence base	There are no comparative trials (randomised or observational) comparing chemical lumbar sympathectomy to other methods of pain relief for people with critical limb ischaemia.

Equality	None identified.
Study design	RCT. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	The proposed research should be able to be carried out within realistic cost and timescale.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

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