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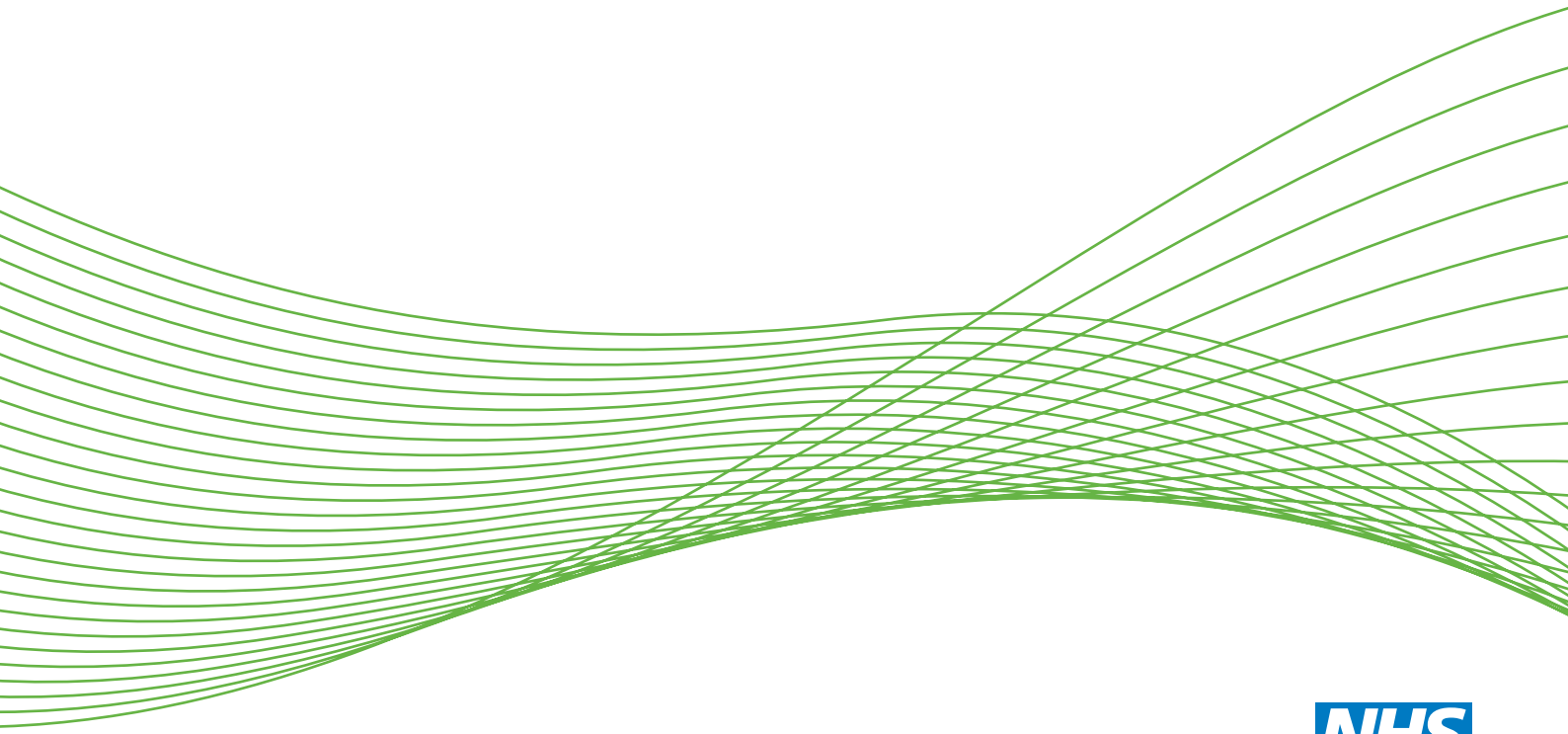

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This report

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Abstract

Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis

Emma L Simpson, Benjamin Kearns, Matthew D Stevenson, Anna J Cantrell, Chris Littlewood and Jonathan A Michaels*

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Background: There have been rapid technological developments aimed at improving short- and long-term results of percutaneous transluminal balloon angioplasty (PTA) in peripheral arterial occlusive disease (PAD).

Objectives: To assess current clinical effectiveness and cost-effectiveness evidence of additional techniques to standard PTA for PAD, develop a health economic model to assess cost-effectiveness and to identify where further research is needed.

Data sources: Relevant electronic databases, including MEDLINE, EMBASE and The Cochrane Library were searched from inception to 2011, between May and October 2011.

Methods: Systematic reviews were conducted of clinical effectiveness and cost-effectiveness. The population was participants with symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament. Interventions were modifications of and adjuncts to PTA in the peripheral circulation, compared with conventional PTA. Outcomes included measures of clinical effectiveness and costs. Data were extracted from randomised controlled trials (RCTs), which were quality assessed using standard criteria. Where appropriate, meta-analyses using fixed- and random-effects methods produced relative risks (RRs). A discrete-event simulation model was developed to assess the relative cost-effectiveness of the interventions from a NHS perspective over a lifetime. The patient populations of intermittent claudication (IC) and critical limb ischaemia (CLI) were modelled separately. Univariate and probabilistic sensitivity analyses were undertaken.

Results: In total, 40 RCTs were included, many of which had small sample sizes. Significantly reduced restenosis rates were shown in meta-analyses of self-expanding stents (SES) {RR 0.67 [95% confidence interval (CI) 0.52 to 0.87]}, endovascular brachytherapy (EVBT) [RR 0.63 (95% CI 0.48 to 0.83)] at 12 months and drug-coated balloons (DCBs) at 6 months [RR 0.40 (95% CI 0.23 to 0.69)], and single studies of stent-graft or drug-eluting stent (DES), compared with PTA; a single study showed improvements with DES versus bare-metal stents (BMSs). Compared with PTA, walking capacity was not significantly affected by cutting balloon, balloon-expandable stents or EVBT; in SES, there was evidence of improvement in walking capacity after up to 12 months. The use of DCBs dominated both the assumed standard practice of PTA with bailout BMS and all other interventions because it lowered lifetime costs and improved quality of life (QoL). These results were seen for both patient populations (IC and CLI). Sensitivity analyses showed that the results were robust to different assumptions about the clinical benefits attributable to the interventions, suggesting that the use of DCBs is cost-saving.

Limitations: Differing definitions of restenosis made direct comparison across trials difficult. There were few data available for walking capacity and QoL.

Conclusions: The evidence showed a significant benefit to reducing restenosis rates for self-expanding and DESs, stent-graft, EVBT and DCBs. If it is assumed that patency translates into beneficial long-term clinical outcomes, then DCB and bail-out DES are most likely to be the cost-effective enhancements to PTA. A RCT comparing current recommended practice (PTA with bail-out BMS) with DCB and bail-out DES could assess long-term follow-up and cost-effectiveness. Data relating patency status to the need for reintervention and to the probability of symptoms returning should be collected, as should health-related QoL measures [European Quality of Life-5 Dimensions (EQ-5D) and maximum walking distance].

Study registration: This study is registered as PROSPERO CRD42012002014.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Dominated (simple) When an intervention is less effective and more expensive than its comparator.

Meta-analysis A statistical method whereby the results of a number of studies are pooled to give a combined summary statistic.

Posterior distribution A representation of the knowledge associated with the true value of a population parameter after combining the prior distribution with sample data.

Prior distribution A representation of the knowledge associated with the true value of a population parameter in addition to any sample data.

Relative risk The ratio of the probability of an event occurring in an exposed group relative to a non-exposed or control group.

List of abbreviations

ABPI	ankle–brachial pressure index
ABSOLUTE	randomized balloon angioplasty versus stenting with nitinol stents in the superficial ankfemoral artery
AMS	absorbable metal stent
AMS INSIGHT	bio-absorbable metal stent investigation in chronic limb ischaemia treatment
BES	balloon-expandable stent
BMS	bare-metal stent
BS	bypass surgery
CB	cutting balloon
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CLI	critical limb ischaemia
DCB	drug-coated balloon
DES	drug-eluting stent
DESM	discrete-event simulation model
EBRT	external beam radiotherapy
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	EuroQol visual analogue scale
ESC	European Society of Cardiology
EVBT	endovascular brachytherapy
EVPI	expected value of perfect information
FAST	Femoral Artery Stenting Trial
FemPac	Femoral Paclitaxel trial
IC	intermittent claudication
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LEVANT I	the Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis trial
MACE	composite outcome for adverse events including death, stroke, myocardial infarction, revascularisation, embolisation in treated limb, worsening of 1+ Rutherford category
NICE	National Institute for Health and Care Excellence
PAD	peripheral arterial occlusive disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTA	percutaneous transluminal balloon angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
QVA	quantitative vessel analysis
RCT	randomised controlled trial
RESILIENT	randomised study comparing the Edwards self-expanding LifeStent with angioplasty alone in lesions involving the superficial femoral artery and/or proximal popliteal artery
RR	relative risk
SES	self-expanding stent
SF-36	Short Form questionnaire-36 items

SF-8	Short Form questionnaire-8 items
SIROCCO	SIROlimus-Coated COrdis self-expandable stent trial
TASC	Trans-Atlantic Inter-Society Consensus
THUNDER	local taxane with short exposure for reduction of restenosis in distal arteries
TLR	target lesion revascularisation
TTO	time trade-off
TVR	target vessel revascularisation
VARA	VAscular RAdiotherapy trial
VascuCoil	intracoil femoropopliteal stent trial
VSGBI	The Vascular Society of Great Britain and Ireland

Scientific summary

Background

Peripheral arterial occlusive disease (PAD) is a cause of major morbidity in the UK. There have been rapid technological developments aimed at improving the short- and long-term results of percutaneous transluminal balloon angioplasty (PTA).

Objectives

This report aimed to assess current evidence on the clinical effectiveness and cost-effectiveness of additional techniques designed to improve the results of standard transluminal balloon angioplasty for PAD, to develop a health economic model to assess cost-effectiveness and to identify areas where further primary research is needed.

Data sources

The following electronic databases were searched from inception to 2011: MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library; Cumulative Index to Nursing and Allied Health Literature (CINAHL); Science Citation Index (via ISI Web of Science); Social Science Citation Index (via ISI Web of Science); Conference Proceedings Citation Index – Science (CPCI-S) (via ISI Web of Science); UK Clinical Research Network Portfolio Database; Current Controlled Trials; and ClinicalTrials.gov. Searches were conducted between May and October 2011.

Methods

Systematic reviews were conducted of clinical effectiveness and cost-effectiveness of enhancement to angioplasty. Additional focused searches were conducted on the natural history and quality of life (QoL) for PAD.

The population was participants with symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament. Interventions were techniques used as an adjunct to, or as a replacement for, balloon angioplasty in the peripheral circulation. Conventional PTA was the main comparator. An expert group of clinicians assisted in the identification of relevant technologies, known trials and important outcome measures. Outcomes included measures of clinical effectiveness, restenosis and the need for reintervention, and costs. Data were extracted from randomised controlled trials (RCTs), which were quality assessed using standard criteria.

A discrete-event simulation model was developed to assess the relative cost-effectiveness of the interventions from a NHS perspective over a lifetime. The patient populations of intermittent claudication (IC) and critical limb ischaemia (CLI) were modelled separately. Univariate and probabilistic sensitivity analyses were undertaken.

Results

In total, 40 RCTs were included, although many had small sample sizes. Significantly reduced restenosis rates were shown in meta-analyses of self-expanding stents (SES) {relative risk (RR) 0.67 [95% confidence interval (CI) 0.52 to 0.87]}, endovascular brachytherapy (EVBT) [RR 0.63 (95% CI 0.48 to 0.83)] at 12 months and drug-coated balloons (DCBs) at 6 months [RR 0.40 (95% CI 0.23 to 0.69)], and single studies of stent-graft or drug-eluting stent (DES), compared with PTA; a single study showed improvement of DES versus bare-metal stents (BMSs). Compared with PTA, walking capacity was not significantly affected by cutting balloon, balloon-expandable stents or EVBT; in SES, there was evidence of improvement in walking capacity after up to 12 months.

The use of DCBs dominated both the assumed standard practice of PTA with bail-out BMSs and all other interventions because it lowered lifetime costs and improved QoL. These results were seen for both patient populations (IC and CLI). Sensitivity analyses showed that the results were robust to different assumptions about the clinical benefits attributable to the interventions, suggesting that the use of DCBs is cost-saving.

Discussion

Despite many studies being identified, there remains uncertainty in the results of the report. Clinically, there was evidence of a significant benefit to reducing restenosis rates for SES, stent-graft, EVBT and DCB compared with PTA and for DES compared with BMS. If it is assumed that patency translates into beneficial long-term clinical outcomes, then DCB and bail-out DES are most likely to be the cost-effective enhancements to PTA.

A RCT comparing current recommended practice (PTA with bail-out BMS) with DCB and bail-out DES could assess long-term follow-up and cost-effectiveness. Data relating patency status to the need for reintervention and to the probability of symptoms returning should be collected, as should health-related QoL measures [European Quality of Life-5 Dimensions (EQ-5D) and maximum walking distance].

Study registration

This study is registered as PROSPERO CRD42012002014.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Peripheral arterial occlusive disease (PAD) is a cause of major morbidity in the UK. Disease in the arteries to the legs causes a reduction in the circulation and can present clinically as intermittent claudication (IC; pain on walking), which can severely impair lifestyle. More severe disease may present as critical ischaemia with rest pain, ulceration or gangrene in the lower extremities.

In recent years, there has been a rapid increase in the use of endovascular treatment, particularly percutaneous transluminal balloon angioplasty (PTA). In this procedure, a device is inserted through a small puncture under local anaesthetic and a narrowed or blocked area of artery is opened up by the inflation of balloons. There is a high demand for PTA for PAD, with in excess of 20,000 procedures per annum in England (based on data for 2010–11).[1] Revascularisation strategy is individual to the patient, and treatment by vascular specialists, or within specialised vascular centres, is recommended by the European Society of Cardiology (ESC) guidelines[2] and the Vascular Society of Great Britain and Ireland (VSGBI).[3]

There have also been rapid technological developments aimed at improving the short- and long-term results of this treatment. Such developments include the use of stents, drug-eluting stents (DESs), drug-eluting balloons, cryotherapy, atherectomy and drug treatments. Many of these techniques have been developed for use in the coronary circulation and extended to the peripheral circulation or may be evaluated in the peripheral circulation with a view to using similar methods in the coronary circulation.

The purpose of this report was to evaluate the range of additional technologies that are available and identify the clinical situations in which they are most likely to be of benefit, or those technologies for which further research studies are justified.

When considering the introduction of new technologies, there are a number of considerations regarding the clinical situation that may be relevant to the applicability and outcome of particular techniques and may therefore be important in defining subgroups that are important in the consideration of the new technologies. These are particularly the clinical stage or symptomatic presentation of the condition being treated, the anatomical distribution of disease and the place of the endovascular procedure in the treatment pathway.

Clinical presentation

The majority of patients with PAD will present with symptoms of IC (pain in the muscle of the leg brought about by walking). This may vary in severity from mild pain that occurs only after considerable exercise or when going uphill, to severe pains that stop activity after only a few paces. It may also affect one or both legs.

More severe PAD may result in insufficient blood supply to the legs, even at rest. In these circumstances, the patient may develop rest pain, particularly nocturnal pain when the legs are elevated in bed and, in the more advanced stages, tissue loss, ulceration and gangrene. The severity of the symptoms of PAD may be classified using a variety of scales, the most common being the Fontaine or Rutherford classifications. These may be used in research settings, although they are consistently used in routine clinical practice. The classifications divide up patients depending upon the severity of the condition based upon IC and critical limb ischaemia (CLI) and then further subdivide them. The Fontaine classification uses subdivisions based upon pain-free walking distance, whereas the Rutherford classification uses the results of the treadmill exercise test and ankle–brachial pressure index (ABPI) measurements.

In addition, PAD is associated with other forms of arterial disease, particularly ischaemic heart disease and cerebrovascular disease. In many patients with generalised atherosclerosis, there is some degree of

asymptomatic PAD, and mild degrees of IC are quite common in the general population: the Edinburgh Artery Study reported a prevalence of 4.5% [95% confidence interval (CI) 3.5% to 5.5%] in people aged 55–74 years.[4] Those with IC may go on to develop worsening symptoms, although it is quite common for symptoms to remain static for many years and only a small proportion, probably around 5–10% over 5 years,[5] will go on to develop critical ischaemia, about a quarter of whom may eventually require amputation.

As the clinical presentation has a significant bearing on outcome and particularly the risk of reocclusion following an endovascular procedure, this is an important aspect to be taken into consideration when evaluating new technologies.

Anatomical distribution

Both IC and CLI may be the result of a reduction in blood flow due to narrowing or occlusion of the arteries to the lower limb at any level. From the point of view of management, the levels of arterial disease are often divided into aortoiliac, that is affecting anywhere in the aorta or common and external iliac arteries, and infrainguinal, those arteries below the inguinal ligament. Disease below the inguinal ligament is also often further subdivided into femoropopliteal disease, that is disease in the femoral arteries and popliteal artery above or below the knee and infrageniculate or distal disease, referring to those vessels below the popliteal artery (anterior and posterior tibial and peroneal arteries).

Owing to the differences in arterial calibre and blood flow, the natural history and outcomes of treatments may be expected to differ among the different anatomical sites. The position, size and accessibility of different vessels may also give rise to particular technical challenges. There are many other ways in which the anatomical distribution of disease may be important in determining treatment; these include:

- whether there is a partial or complete occlusion of a vessel
- the length of any area of disease that requires treatment
- the accessibility of the diseased area of artery
- the eccentricity of any residual lumen
- the presence or absence of calcification.

The presence or absence of disease either proximal or distal to the area being treated is also a major determinant of the potential success of any procedure. It is therefore important to consider all these issues when evaluating a new technology, particularly as some technologies may be especially useful for dealing with a specific clinical situation, such as when there is calcification or a very eccentric lumen.

Treatment pathway

Many of the new technologies that are considered in this report have been evaluated primarily in relatively simple, short stenotic or occluded areas of a single vessel. However, in practice, PAD is a chronic condition in which there are often multiple areas of disease, and the patient may undergo a series of different treatments over many years. Endovascular treatments may be used for multiple areas of disease as an adjunct to other interventions. This may be either simultaneous or as part of a planned series of procedures for disease at different sites. They may also be used for the retreatment of areas that have previously been treated by endovascular means or in the treatment of stenosis in arterial bypass grafts.

Although these are relevant areas in which some of the technologies considered in this report may be used, these situations are often specifically excluded or simply not represented in the clinical trials.

Limitations of current techniques

Percutaneous transluminal angioplasty has been widely adopted and is a common and useful procedure in the management of peripheral arterial disease; however, it has certain limitations and potential risks that may be addressed by some of the new technologies considered in this report.

The site and extent of disease may determine whether or not endovascular treatments are possible. Longer occlusions of small distal arteries are increasingly difficult to treat and have poor outcomes. However, there is no absolute criterion to determine suitability, as is demonstrated by the variability of clinicians' readiness to randomise patients in some trials.[6]

When endovascular treatment is attempted, there may be failure or complications at any stage of the procedure:

- There may be failure to gain access to the site of the disease.
- It may prove impossible to cross the occluded segment with the device used for treatment.
- It may prove impossible to reopen the vessel sufficiently to obtain a suitable lumen.
- Procedural complications may occur, including bleeding at the puncture site, embolisation of material from the diseased segment of artery, dissection, perforation or immediate reocclusion.
- After a successful initial procedure, there is a risk of late restenosis and reocclusion causing recurrence of symptoms.

New techniques associated with angioplasty may address any of these potential difficulties in carrying out the procedure. The technologies that are considered in this report are primarily concerned with either increasing the effectiveness of the initial recanalisation or preventing late restenosis. For example, stents, laser and atherectomy devices are intended to improve the immediate result, whereas DESs, drug-coated balloons (DCBs) and radiotherapy are unlikely to affect the immediate anatomical result but are aimed at reducing the rate of subsequent restenosis and reocclusion.

In addition to these there are other technologies that have not been considered in this report, such as developments in catheters and guide-wire technology, which may improve access and closure devices, which may reduce the risk of the complication of postprocedure bleeding.

Chapter 2 Definition of decision problem

Purpose of assessment

This report aimed to answer the following research questions:

What are the clinical effectiveness and cost-effectiveness of additional techniques designed to improve the results of endovascular treatment (standard transluminal balloon angioplasty) for PAD?

For which of these techniques is further primary research likely to lead to information that will improve the clinical effectiveness and cost-effectiveness of care for this condition?

Place of the intervention in the treatment pathway

The techniques under consideration in this assessment were those that are used either as a replacement for or in conjunction with conventional balloon angioplasty. In general, treatments were considered that occupy the same place as balloon angioplasty in the treatment pathway for PAD.

Included interventions

This assessment is of new endovascular techniques that may be used to either supplement or replace existing endovascular procedures to improve the circulation of the lower limb in cases of PAD.
The following interventions were included.

Absorbable stents
This is a type of stent that is bio-absorbable.[7]

Self-expanding stents
This is a type of bare-metal stent (BMS) that expands when implanted.

Balloon-expandable stents
This is a type of BMS that requires expansion with a balloon.

Drug-eluting stents
There are a number of designs of metal stents that are coated with drugs that are gradually released and may reduce the rate of restenosis. These include stents that release cytotoxic or immunosuppressant drugs. These have been quite widely used in the coronary circulation and various configurations are now available that are suitable for use in the peripheral circulation.

Stent-graft
Stents may be covered with graft material, usually ePTFE (expanded polytetrafluoroethylene), to produce stent-grafts. Large stent-grafts are now commonly used for treating aneurysms and smaller-diameter versions are available for use in the peripheral arteries. Such devices may be inserted by a percutaneous route or may be used as a part of surgical procedures.

Atherectomy
Whereas conventional balloon angioplasty or stenting does not remove the occluding material but opens up and stretches the lumen of the vessel, atherectomy is a technique that attempts to remove some of the

occluding material. There are a number of proprietary devices for this technique, including the Simpson catheter, the Rotablator® (Boston Scientific Corporation, Natick, MA, USA) and the SilverHawk™ (ev3 Endovascular Inc., Plymouth, MN, USA) atherectomy device. Again, these may be divided into subgroups depending upon the mechanism of action, with available devices being either 'rotational', removing material in a concentric fashion, or 'directional' in nature, removing material from one aspect of the arterial wall.

Cutting balloon

The cutting balloon (CB) is a device that combines a conventional angioplasty balloon with small blades that cut the atheroma at the time of dilatation.

Cryoplasty

This is a method that combines transluminal angioplasty using a balloon with the cryotherapy by cooling the vessel wall. The technique uses inflation of the balloon with a cooling mixture rather than the standard use of contrast medium.

Radiation

Radiation therapy has been used to try and reduce restenosis following angioplasty. This may be carried out through different techniques. Endovascular brachytherapy (EVBT) uses small radioactive probes that can be inserted through an endovascular route. External beam radiotherapy (EBRT) applies radiation from outside the body.

Drug-coated balloon

A recent development has been the use of balloons coated in drugs similar to those used for DESs in order to deliver the agent at the time of angioplasty. Paclitaxel-coated balloons have been used elsewhere and have recently become available in the UK.

Laser angioplasty

There was a considerable body of research published in the late 1980s regarding the use of lasers to unblock arteries. The majority of devices that were used at that time have subsequently been withdrawn. However, there are some devices still available that use excimer lasers as part of an atherectomy procedure to ablate occluding material.

Excluded interventions

Pharmacological interventions

The separate effects of pharmacological measures aimed at altering patency were not specifically considered, except when the use of a particular agent was required as an integral part of a new endovascular technique.

Combined surgical procedures

Some new techniques, such as remote femoral endarterectomy, require a combined surgical and endovascular approach. Many of the others may also be combined with surgical procedures and, in some cases, may be used for different indications in patients who would not necessarily be amenable to conventional endovascular techniques.

Other techniques

There are a number of other new endovascular techniques that may be used as an adjunct to angioplasty. These include closure devices, devices to protect from embolisation and techniques for thrombolysis or thrombectomy. These will be considered only when they are a component of one of the other techniques referred to above.

Interventions above the inguinal ligament (aortoiliac segment)

The outcome of endovascular treatment is also known to be heavily influenced by the site and distribution of arterial occlusive disease. Aortoiliac disease affects the larger vessels above the inguinal ligament. Conventional angioplasty, with or without the use of stents, has been common practice in this area for some years and clinical results are generally good, with lower rates of restenosis or reocclusion. In view of this, the potential advantages of new techniques to improve outcomes are likely to be very much smaller in absolute terms, with very large clinical studies being required to demonstrate significant clinical benefit. The current assessment will therefore focus on disease below the inguinal ligament.

Relevant comparators

The comparator was conventional PTA. Bail-out stenting was included as a possible comparator for any of the interventions, BMSs were considered as a comparator for DESs and sham radiation was included as a possible comparator for radiation interventions.

Population

The population was participants with symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament. Patients with either IC or CLI were included.

Methods for assessment

Review stage 1

A comprehensive search was undertaken to systematically identify clinical effectiveness and cost-effectiveness literature concerning endovascular techniques to supplement or replace balloon angioplasty in the infrainguinal arterial circulation. Systematic reviews were conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[8]

The clinical effectiveness review methods and results are reported in *Chapter 3* and *Appendices 1–4*. The clinical effectiveness review is registered as Prospero registration number CRD42012002014 (www.crd.york.ac.uk/prospero/index.asp).

The cost-effectiveness review is reported in *Chapter 4*.

Review stage 2

Where utility data were unavailable from studies identified in review stage 1, literature reviews were conducted to provide data to populate the economic model. This comprised data on the utilities associated with health states relating to the natural history of treated and untreated PAD. The results of this review are reported in *Chapter 4*.

Development of a health economic model

A new economic evaluation of the cost-effectiveness of technologies for the management of PAD was developed. The model is reported in *Chapter 4*.

Chapter 3 Systematic review of the clinical effectiveness of enhancements to angioplasty

Methods

Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning enhancement to angioplasty in adults with PAD. The search involved combining terms for the population (PAD) with terms for the interventions and then combining these terms with filters designed to retrieve systematic reviews, randomised control trials (RCTs) and economic evaluations as appropriate. The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The preliminary list of interventions included the following: BMSs, DESs, drug-eluting balloons, stent-grafts, cryotherapy, brachytherapy, external beam radiation, CBs and atherectomy. Following consultation with experts and scoping searches, the search terms of scoring balloons and ultrasonic angioplasty were added.

The following electronic databases were searched from inception for published and unpublished research evidence:

- MEDLINE (Ovid) 1950–present
- MEDLINE In-Process & Other Non-Indexed Citations (Ovid) (for latest publications)
- EMBASE (Ovid) 1980–present
- The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and NHS Economic Evaluation Database (NHS EED) databases 1991–present
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) 1982–present
- Science Citation Index (via ISI Web of Science) 1900–present
- Social Science Citation Index (via ISI Web of Science) 1956–present
- Conference Proceedings Citation Index-Science (CPCI-S) (via ISI Web of Science) 1990–present
- UK Clinical Research Network (UKCRN) Portfolio Database
- Current Controlled Trials
- ClinicalTrials.gov.

Other online searches included the US Food and Drug Administration's website, the European Medicines Agency's website and relevant conference proceedings. These included the proceedings of the VSGBI, the European Society of Vascular and Endovascular Surgery, the British Society of Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe, the Society of Interventional Radiology and the Society for Vascular Surgery.

Searches for clinical effectiveness studies were performed by an information specialist (AC) in May 2011. References were collected in a database, and duplicates removed.

Searches for cost-effectiveness were conducted in May 2011 and are discussed in *Chapter 4*. Additional focused searches were conducted on MEDLINE to find literature on the natural history of PAD and

literature on restenosis and quality of life (QoL) in October 2011. Published data were used, and trial authors were not contacted. Bibliographies of included studies were searched for potential additional trials.

The search strategy for MEDLINE is provided in *Appendix 1*.

Inclusion criteria

Population
The population was participants with symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament. Patients with either IC or CLI were included.

Interventions
Interventions were techniques used as an adjunct to, or as a replacement for, balloon angioplasty in the peripheral circulation.

These were as follows: absorbable stents, self-expanding stents (SESs), balloon-expandable stents (BESs), DESs, stent-graft, atherectomy, CB, cryoplasty, radiation by EVBT or EVRT, DCB and laser angioplasty.

Comparator
The comparator was conventional PTA. Bail-out stenting was included as a possible comparator for any of the interventions, BMSs were considered as a comparator for DESs, and sham radiation was included as a possible comparator for radiation interventions.

Outcomes
Reported outcomes included patency or restenosis measures, need for reintervention, disease-specific and generic measures of QoL, clinical status, exercise tolerance or walking distance, pain (patient-reported pain scores and analgesic use), limb salvage, complications and adverse events. Cost outcomes are discussed in *Chapter 4*.

Study design
Initially, RCTs were searched. As data were available from these, other study types from further down the accepted hierarchy of evidence were not sought. Meta-analyses and systematic reviews of RCTs were sought to identify RCTs that met the inclusion criteria of this review.

Exclusion criteria

Interventions
Pharmacological interventions, combined surgical procedures and devices that have been withdrawn, such as older laser angioplasty devices, were not considered, as well as interventions above the inguinal ligament (aortoiliac segment).

Publication types
Studies that were published only in languages other than English, studies based on animal models, and preclinical and biological studies were excluded, as were narrative reviews, editorials and opinion pieces. Reports published as meeting abstracts were excluded only when insufficient details were reported to allow inclusion.

Study selection was made by one reviewer and checked by another, based on the above inclusion and exclusion criteria. Citations were sifted by title and abstract, and those remaining after abstract sift were sifted by full papers. Studies excluded at full-paper screening were placed in *Appendix 2*.

Data extraction, critical appraisal and synthesis

Data were extracted by one reviewer and checked by another, using a standardised form. The forms are shown in *Appendix 3*. Data were extracted with no blinding to authors or journal. Quality was assessed according to criteria based on NHS Centre for Reviews and Dissemination (CRD) Report No. 4.[9] Quality assessment forms are shown in *Appendix 4*. Prespecified outcomes were tabulated and discussed within a descriptive synthesis. For some interventions, meta-analyses were precluded as a result of differences in outcomes. For example, definitions of patency varied across trials and there were also differences in populations, interventions and length of follow-up. When appropriate, meta-analyses were undertaken using fixed- and random-effects methods. Meta-analyses were carried out using Review Manager 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark). The Mantel–Haenszel methods have been shown to be more reliable than other methods when there are relatively few studies with small sample sizes, so these were employed, with both fixed and random effects, as recommended by the Cochrane Collaboration.[10]

Results

Quantity and quality of studies

Study selection

The search of electronic databases yielded 9501 article citations with duplicates removed. Additional searching yielded one reference and two conference presentations. The sifting process is shown in *Figure 1*, a flow diagram adapted from PRISMA recommendations.[8] Title sifting excluded 8175 citations. There were 1329 abstracts sifted. In total, 95 references were full-text screened. *Appendix 2* shows 34 studies that were excluded at the full-paper sifting stage with reasons for exclusions.

There were 40 RCTs accepted into the review, published in 61 references, comprising 53 articles from peer-reviewed journals with additional data in eight conference presentations (*Table 1*). Following literature

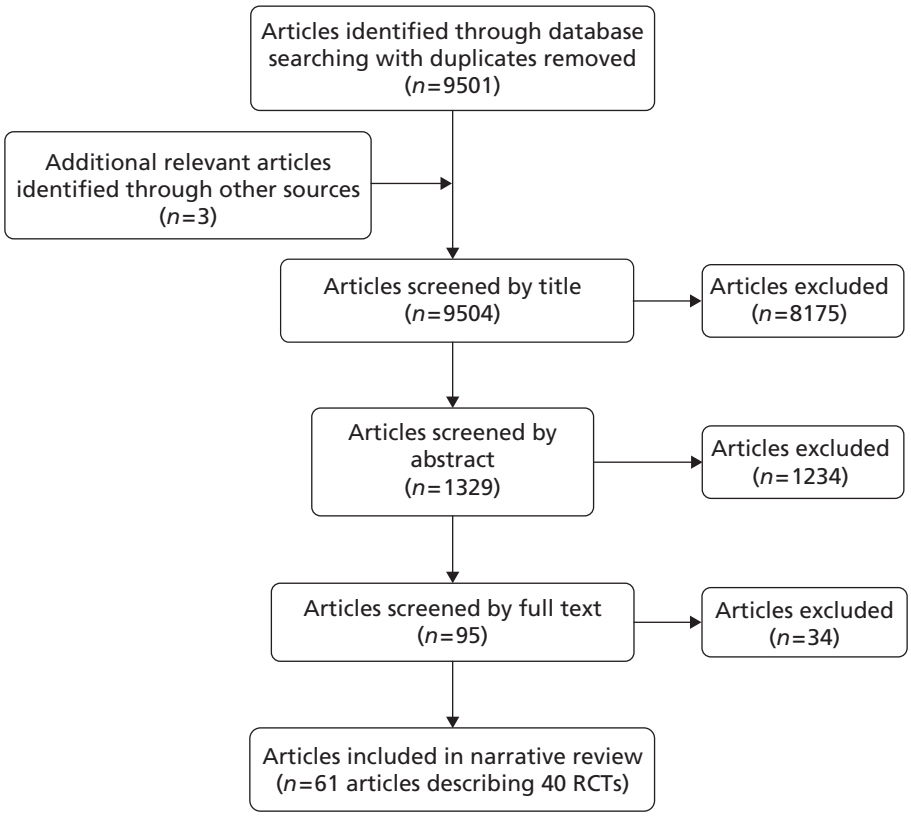

FIGURE 1 Flow diagram of study selection (based on a revised version of the PRISMA diagram).[8]

TABLE 1 Summary of included trials

Trial (trial name, author, date)	Sample size	Intervention	Comparator	Follow-up	Outcomes reported
AMS INSIGHT, Bosiers *et al*. 2009[11]	117 CLI	AMS	PTA	6 months	Patency, late lumen loss, complications
Dick *et al*. 2009[12]	73 (of whom 69 IC, 4 CLI)	SES	PTA	12 months	Restenosis, walking capacity, complications
VascuCoil, Greenberg *et al*. 2004[13]	266 'symptomatic leg ischaemia'	SES (IntraCoil®, Sulzer/ IntraTherapeutics, St. Paul, MN, USA)	PTA	9 months	TLR, complications
FAST, Krankenberg *et al*. 2007[14]	244 (of whom 226 IC, 7 CLI, 11 data unavailable)	SES (nitinol)	PTA	12 months	Restenosis, TLR, Rutherford category, walking capacity, complications
RESILIENT, Laird *et al*. 2010[15]	206 IC	SES	PTA	12 months	Restenosis, TLR/TVR, walking capacity, QoL, complications
ABSOLUTE, Schillinger *et al*. 2006,[16] 2007,[17] Sabeti *et al*. 2007[18]	104 (of whom 91 IC, 13 CLI)	SES (nitinol)	PTA	24 months	Restenosis, reintervention, Rutherford category, walking capacity, QoL, complications
Becquemin *et al*. 2003[19]	227 (of whom 180 IC, 47 CLI)	BES (Palmaz®, Cordis, a Johnson & Johnson interventional systems company)	PTA	12 months	Restenosis, complications
Cejna *et al*. 2001[20]	141 (154 limbs of which 108 IC, 46 CLI)	BES (Palmaz)	PTA	24 months	Patency, complications
Grimm *et al*. 2001[21]	53 IC	BES (Palmaz)	PTA	24 months	Patency, need for reintervention, walking capacity, complications
Rand *et al*. 2006[22]	51 CLI	BES (Carbostent™, Sorin, Biomedica, Italy)	PTA	6 months	Patency, complications
Vroegindeweij *et al*. 1997[23]	51 IC	BES (Palmaz)	PTA	12 months	Patency, complications
Zdanowski *et al*. 1999[24]	32 CLI	BES (tantalum)	PTA	12 months	Restenosis, need for reintervention, complications
Zilver PTX, Dake *et al*. 2010,[25] Ansell 2011,[26] Dake *et al*. 2008[27]	479 (Rutherford category 2 or above)	DES (paclitaxel)	PTA (with potential second randomisation to DES or BMS)	12 months	Patency, complications

TABLE 1 Summary of included trials (*continued*)

Trial (trial name, author, date)	Sample size	Intervention	Comparator	Follow-up	Outcomes reported
SIROCCO, Duda *et al*. 2002,[28] 2005,[29] 2006[30]	93 (of whom 46 Rutherford category 1 or 2, 47 Rutherford category 3 or 4)	DES (sirolimus)	SES	24 months	Restenosis, TLR/TVR, complications
Rastan *et al*. 2011[31]	161 (of whom 86 IC, 75 CLI)	DES (sirolimus)	BMS (placebo coated)	12 months	Patency, TLR, Rutherford category, complications
Saxon *et al*. 2003,[32] 2008[33]	197 (of whom 175 IC, 21 CLI, 1 unknown)	Stent-graft (nitinol covered)	PTA	12 months	Patency, Rutherford category, complications
Nakamura *et al*. 1995[34]	39 IC	Atherectomy (transcutaneous extraction catheter)	PTA	6 months	Patency, complications
Vroegindeweij *et al*. 1992,[35] 1995,[36] Tielbeck *et al*. 1996[37]	73 IC	Atherectomy (directional)	PTA	24 months	Patency, Rutherford category, complications
Amighi *et al*. 2008[38]	43 (of whom 35 IC, 8 CLI)	CB	PTA	6 months	Restenosis, symptoms, walking capacity, complications
Dick *et al*. 2008[39]	39 (of whom 30 IC, 9 CLI)	CB	PTA	6 months	Restenosis, need for reintervention, walking capacity, complications
Jahnke *et al*. 2010[40]	86 (of whom 66 IC, 20 CLI)	Cryoplasty	PTA	9 months	Patency, symptoms, complications
Spiliopoulos *et al*. 2010[41]	50 (60 limbs included, of which 36 IC, 24 CLI)	Cryoplasty	PTA	36 months	Patency, TLR, complications
Gallino *et al*. 2004,[42] Bonvini *et al*. 2003[43] (results of Diehm *et al*. 2005[44] and Zehnder *et al*. 2003[45])	156 IC (in two arms relevant to this review, from four-arm trial)	Radiation (EVBT) plus PTA	PTA and placebo drug	36 months	Patency, need for reintervention, Rutherford category, complications
Zehnder *et al*. 2003[45] (results of Diehm *et al*. 2005[44] and Gallino *et al*. 2004[42]/ Bonvini *et al*. 2003[43])	100 (of whom 92 IC, 8 CLI)	Radiation (EVBT) plus PTA	PTA and placebo drug	36 months	Restenosis, need for reintervention, Rutherford category
Hagenaars *et al*. 2002[46]	24 (of whom 12 IC, 12 CLI)	Radiation (EVBT) plus PTA	PTA	6 months	Restenosis, late lumen loss
Krueger *et al*. 2002,[47] 2004[48]	30 (unclear how many IC/CLI; all Fontaine 2a-3)	Radiation (EVBT) plus PTA	PTA plus sham radiation	24 months	Restenosis, need for reintervention, walking capacity
Vienna-2, Wolfram *et al*. 2006,[49] Minar *et al*. 2000,[50] Wolfram *et al*. 2005[51]	113 (of whom 88 IC, 25 CLI)	Radiation (EVBT) plus PTA	PTA	60 months	Restenosis, TLR/TVR

continued

TABLE 1 Summary of included trials (*continued*)

Trial (trial name, author, date)	Sample size	Intervention	Comparator	Follow-up	Outcomes reported
Vienna-3, Pokrajac *et al*. 2005,[52] 2000,[53] Wolfram *et al*. 2005[51]	96 (of whom 77 IC, 19 CLI)	Radiation (EVBT) plus PTA	PTA plus sham radiation	12, 24 months	Restenosis, TLR/TVR, complications
VARA, van Tongeren *et al*. 2005[54]	60 (of whom 52 IC, 8 CLI)	Radiation (EVBT) plus PTA	PTA	12 months	Restenosis, need for reintervention, Rutherford category, complications
Wyttenbach *et al*. 2007,[55] 2004[56]	20 (unclear how many IC/CLI, but all Rutherford category 3 or above)	Radiation (EVBT) plus PTA	PTA	3, 24 months	Late lumen loss
Fritz *et al*. 2004[57]	95 (of whom 94 IC, 1 CLI)	Radiation (external beam) plus PTA	PTA plus sham radiation	12 months	Restenosis, Fontaine stage
Therasse *et al*. 2005[58]	99 (of whom 27 IC, 72 CLI)	Radiation (external beam, three doses) plus PTA	PTA plus sham radiation	12 months	Restenosis, need for reintervention
LEVANT I, Scheinert *et al*. 2010[59,60]	101 (of whom 94 IC, 7 CLI)	DCB (paclitaxel)	PTA with uncoated balloon	6 months	Late lumen loss, TLR
THUNDER, Tepe *et al*. 2008[61–63]	102 (in two relevant arms of three-arm trial), Rutherford categories 1–5	DCB (paclitaxel)	PTA with uncoated balloon	24 months	Restenosis, late lumen loss, TLR, Rutherford category, complications
FemPac, Werk *et al*. 2008[64]	87 (of whom 82 IC, 5 CLI)	DCB (paclitaxel)	PTA with uncoated balloon	24 months	Restenosis, TLR, Rutherford category, complications
Belli *et al*. 1991[65,66]	68 (of whom 48 IC, 20 CLI)	Laser angioplasty (thermal)	PTA	12 months	Symptoms, complications
Fisher *et al*. 1996[67]	82 (of whom 76 IC, 6 CLI)	Laser angioplasty (hot-tip)	PTA	24 months	Restenosis
Lammer *et al*. 1992[68]	116 (of whom 84 IC, 32 CLI)	(1) Laser angioplasty (pulsed XeCl); or (2) laser angioplasty (Nd:YAG, thermal)	PTA	12 months	Patency, complications
Spies *et al*. 1990[69]	25 IC	Laser angioplasty (Nd:YAG, thermal)	PTA	2 weeks	Complications
Tobis *et al*. 1991[70]	40 (of whom 35 IC, 5 CLI)	Laser angioplasty	PTA	12 months	Patency, complications

AMS, absorbable metal stent; FemPac, Femoral Paclitaxel trial; SIROCCO, SIROlimus-Coated COrdis self-expandable stent trial; TLR, target lesion revascularisation; TVR, target vessel revascularisation; VARA, VAscular RAdiotherapy trial.

searches, the Zilver PTX[25–27] trial published an additional paper,[71] which confirmed the results included from abstracts.

There was one RCT of absorbable metal stents (AMSs), five RCTs of SESs and six RCTs of BESs. There were three trials of DESs, of which one concerned paclitaxel and two sirolimus. There was one trial of stent-graft, two of atherectomy, two of CB and two of cryoplasty. Of the 10 RCTs of radiation, eight employed EVBT and two employed EBRT. Three RCTs of DCB were included and five RCTs of laser angioplasty. Trials of stents, stent-graft, CB, cryoplasty and DCB versus PTA allowed bail-out stenting in the PTA group, when deemed medically necessary. Bail-out atherectomy was permitted in one atherectomy trial (Vroegindeweij *et al.*[36]), and, of the radiation trials, the comparator PTA group had oral placebo in two RCTs (Gallino *et al.*, [42] Zehnder *et al.*[45]) and sham radiation in four RCTs (Krueger *et al.*,[47,48] Vienna-3,[51–53] Fritz *et al.*,[57] Therasse *et al.*[58]).

Further study details are shown in *Appendix 3*.

Critical appraisal

Appendix 4 shows the quality assessment for the included studies. Method of allocation concealment was considered adequate in 11 of the trials [AMS INSIGHT (bio-absorbable metal stent investigation in chronic limb ischaemia treatment),[11] Becquemin *et al.*,[19] Grimm *et al.*,[21] Rand *et al.*,[22] Vroegindeweij *et al.*,[23,35,36] Rastan *et al.*,[31] Tielbeck *et al.*,[36] Amighi *et al.*,[38] Dick *et al.*,[39] VARA (VAscular RAdiotherapy trial),[54] FemPac (Femoral Paclitaxel trial)[64]]. Both the method used to generate allocation sequences and the method of allocation concealment were considered adequate in seven of these trials (AMS INSIGHT,[18] Becquemin *et al.*,[19] Grimm *et al.*,[21] Rastan *et al.*,[31] Amighi *et al.*,[38] Dick *et al.*,[39] VARA,[54] FemPac[64]). For other trials, reporting of randomisation methods was unclear.

There was blinding for assessors in at least one of the study outcomes in 20 trials [Dick *et al.*,[12] FAST (Femoral Artery Stenting Trial),[14] ABSOLUTE (randomized balloon angioplasty vs. stenting with nitinol stents in the superficial femoral artery),[16–18] Becquemin *et al.*,[19] Rand *et al.*,[22] SIROCCO (SIROlimus-Coated COrdis self-expandable stent trial),[28–30] Rastan *et al.*,[31] Amighi *et al.*,[38] Spiliopoulous *et al.*,[41] Diehm *et al.*[44] analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials, Krueger *et al.*,[47,48] Vienna-3,[51–53] Wyttenbach *et al.*,[55,56] Fritz *et al.*,[57] Therasse *et al.*,[58] THUNDER (local taxane with short exposure for reduction of restenosis in distal arteries),[61–63] FemPac,[64] Lammer *et al.*[68]]. Blinding of clinicians to the endovascular techniques used in these studies would have been difficult or impossible. One trial (FemPac[64]) mentioned that the blinding of clinicians was attempted, but the difference in appearance of DCB and uncoated balloons meant that clinicians were likely to know which intervention was being used. There was explicit blinding of patients in eight trials (SIROCCO,[28–30] Rastan *et al.*,[31] Krueger *et al.*,[47,48] Vienna-3,[51–53] Fritz *et al.*,[57] Therasse *et al.*,[58] THUNDER,[61–63] FemPac[64]).

Intervention and control groups were largely comparable at baseline in all trials. Some trials reported one variable that was not equal across treatment groups at baseline [AMS INSIGHT,[11] Dick *et al.*,[12] RESILIENT (randomised study comparing the Edwards self-expanding LifeStent with angioplasty alone in lesions involving the superficial femoral artery and/or proximal popliteal artery),[15] Zilver PTX,[25–27] SIROCCO,[28–30] Rastan *et al.*,[31] Nakamura *et al.*,[34] Vroegindeweij's group,[35–37] THUNDER,[60–62] Fisher *et al.*[67]]. When studies measured more outcomes than they reported, this was because of future expected reports [LEVANT I (the Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis trial),[59,60] Spies *et al.*[69]].

Only one trial had an imbalance in dropouts between treatment groups (Hagenaars *et al.*[46]). An analysis of patients in their allocated groups according to the intention-to-treat (ITT) principle was available for all trials, although for two trials (Gallino *et al.*, [42] Zehnder *et al.*[45]) this was only available for the combined analysis of these two trials (Diehm *et al.*[44]).

Clinical effectiveness results

Results are presented according to the 11 included interventions (see *Appendix 5*).

Absorbable metal stent

One RCT identified compared AMS with PTA (AMS INSIGHT[11]) in CLI patients. The AMS INSIGHT[11] trial provided patency data on 94 lesions at 6-month follow-up (*Tables 2* and *3*). AMS fared significantly worse than PTA ($p = 0.013$) in terms of restenosis measured by core-lab quantitative vessel analysis (QVA). A patency measure including major amputation or target lesion revascularisation (TLR) as failure showed no significant difference between treatment groups. For adverse events, a measure including major amputation or death did not find any significant difference between groups at 1-month follow-up (*Table 4*).

Self-expanding stent

Five RCTs compared SESs with PTA. The populations comprised mostly IC patients, but also some CLI patients.

Three RCTs (Dick *et al.*,[12] RESILIENT,[15] ABSOLUTE[16–18]) showed an advantage for SES over PTA in terms of restenosis (*Table 5*). Of these, one study (ABSOLUTE[16–18]) had only a trend favouring SES at 6 months but significant results at 1 and 2 years, whereas the other studies reached and maintained significance at 3–6 months (Dick *et al.*[12]) and 6–12 months (RESILIENT[15]). One RCT found no significant difference between groups at 1-year follow-up (FAST[14]). Meta-analysis (*Figures 2–7*) for restenosis at 6 months

TABLE 2 Absorbable-metal-stent and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA lesions analysed (*n*)	PTA lesions with restenosis (%)	AMS lesions analysed (*n*)	AMS lesions with restenosis (%)	Comparative statistic
AMS INSIGHT (Bosiers *et al.* 2009[11])	6 months	Patency was defined as the absence of a haemodynamically significant restenosis (> 50%) documented by digital subtraction angiography and confirmed by the core-lab QVA	50	42[a]	44	68.2[a]	$p = 0.013$
		Primary patency rates determined by colour-flow Doppler ultrasound and defined as the absence of a haemodynamically significant restenosis (> 50%), derived from the ratio of the PSV at the lesion segment to that at the proximal part, a major amputation or a TLR	50	11.9[a]	44	19.8[a]	$p = 0.270$

PSV, peak systolic velocity.
a Restenosis rates calculated from reported patency.

TABLE 3 Absorbable-metal-stent and late lumen loss

Study	Follow-up	Definition of late lumen loss	PTA lesions analysed (*n*)	PTA size (mm; mean ± SD)	AMS lesions analysed (*n*)	AMS size (mm; mean ± SD)	Comparative statistic
AMS INSIGHT[11]	6 months	Difference between the in-stent MLD post procedure and the MLD at follow-up measured with angiography	50	0.7 ± 0.7	44	1.4 ± 0.8	$p < 0.0001$

MLD, minimal lumen diameter; SD, standard deviation.

TABLE 4 Absorbable-metal-stent and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	AMS analysed (*n*)	AMS patients with complications (%)	Comparative statistic
AMS INSIGHT[11]	1 month	Major amputation and/or death within 30 days of intervention	57	5.3	60	5	$p = 1.0$

TABLE 5 Self-expanding-stent and restenosis

Study	Follow-up	Definition of restenosis/patency	PTA analysed (*n*)	PTA patients with restenosis (%)	SES analysed (*n*)	SES patients with restenosis (%)	Comparative statistic
Dick *et al.* 2009[12]	6 months	Restenosis defined as a > 50% lumen diameter reduction at the most narrow site within the limits of the treated segment plus the adjacent 10 mm proximal and distal to the treated segment by computed tomography angiography	39	50.0	34	18.2	$p = 0.006$

continued

TABLE 5 Self-expanding-stent and restenosis (*continued*)

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	SES analysed (*n*)	SES patients with restenosis (%)	Comparative statistic
	3 months	Secondary end point restenosis measured by ultrasound binary restenosis > 50% by duplex ultrasonography defined as PSV of at least 2.4	39	18.9	34	2.9	$p = 0.033$
	6 months	a/a	39	55.6	34	21.9	$p = 0.005$
	12 months	a/a	39	61.1	34	34.4	$p = 0.028$
FAST[14]	12 months	The primary study end point was binary restenosis, defined as a PVR proximal ≥ 2.4 on duplex ultrasound	101	38.6	101	31.7	$p = 0.377$
RESILIENT[15]	6 months	Restenosis was defined as a loss of primary patency, i.e. PSVR ≥ 2.5, suggesting > 50% reduction in luminal diameter	63	52.6[a]	121	5.8[a]	$p < 0.0001$
	12 months	a/a	59	63.3[a]	112	18.7[a]	$p < 0.0001$
ABSOLUTE[16–18]	6 months	Restenosis was defined as > 50% restenosis measured by duplex ultrasound	53	45.0	51	25.0	$p = 0.06$
	12 months	a/a	53	63.0	51	37.0	$p = 0.01$
	24 months	a/a	52	69.2	46	45.7	$p = 0.031$

a/a, as above; PSV, peak systolic velocity; PSVR, peak systolic velocity ratio; PVR, peak velocity ratio.
a Restenosis rates calculated from reported patency.

Study or subgroup	SES Events	SES Total	PTA Events	PTA Total	Weight	RR M-H, fixed, 95% CI
ABSOLUTE 2007[16–18]	13	51	24	53	55.8%	0.56 (0.32 to 0.98)
Dick 2009[12]	7	34	20	39	44.2%	0.40 (0.19 to 0.83)
Total (95% CI)		**85**		**92**	**100.0%**	**0.49 (0.32 to 0.76)**
Total events	20		44			

Heterogeneity: χ^2=0.53, df=1 (p=0.47); I^2=0%

Test for overall effect: z=3.16 (p=0.002)

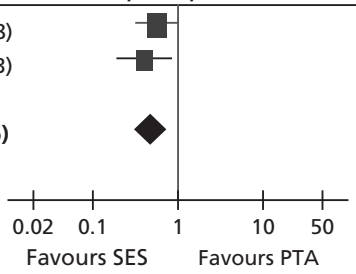

FIGURE 2 Forest plot of comparison: 1 SES vs. PTA, restenosis 6 months fixed two studies.

Study or subgroup	SES Events	SES Total	PTA Events	PTA Total	Weight	RR M-H, random, 95% CI
ABSOLUTE 2007[16–18]	13	51	24	53	63.2%	0.56 (0.32 to 0.98)
Dick 2009[12]	7	34	20	39	36.8%	0.40 (0.19 to 0.83)
Total (95% CI)		**85**		**92**	**100.0%**	**0.50 (0.32 to 0.77)**
Total events	20		44			

Heterogeneity: τ^2=0.00, χ^2=0.53, df=1 (p=0.47); I^2=0%

Test for overall effect: z=3.11 (p=0.002)

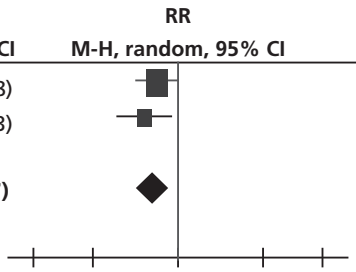

FIGURE 3 Forest plot of comparison: 1 SES vs. PTA, restenosis 6 months random two studies.

Study or subgroup	SES Events	SES Total	PTA Events	PTA Total	Weight	RR M-H, fixed, 95% CI
ABSOLUTE 2007[16–18]	18	49	33	52	35.0%	0.58 (0.38 to 0.88)
Dick 2009[12]	11	34	22	39	22.4%	0.57 (0.33 to 1.00)
FAST 2007[14]	32	101	39	101	42.6%	0.82 (0.56 to 1.20)
Total (95% CI)		**184**		**192**	**100.0%**	**0.68 (0.53 to 0.87)**
Total events	61		94			

Heterogeneity: χ^2=1.87, df=2 (p=0.39); I^2=0%

Test for overall effect: z=3.01 (p=0.003)

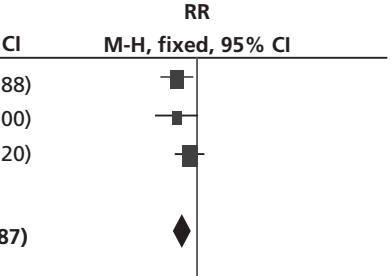

FIGURE 4 Forest plot of comparison: 1 SES vs. PTA, restenosis 12 months fixed three studies.

Study or subgroup	SES Events	SES Total	PTA Events	PTA Total	Weight	RR M-H, random, 95% CI
ABSOLUTE 2007[16–18]	18	49	33	52	35.5%	0.58 (0.38 to 0.88)
Dick 2009[12]	11	34	22	39	20.2%	0.57 (0.33 to 1.00)
FAST 2007[14]	32	101	39	101	44.3%	0.82 (0.56 to 1.20)
Total (95% CI)		**184**		**192**	**100.0%**	**0.67 (0.52 to 0.87)**
Total events	61		94			

Heterogeneity: τ^2=0.00, χ^2=1.87, df=2 (p=0.39); I^2=0%

Test for overall effect: z=3.08 (p=0.002)

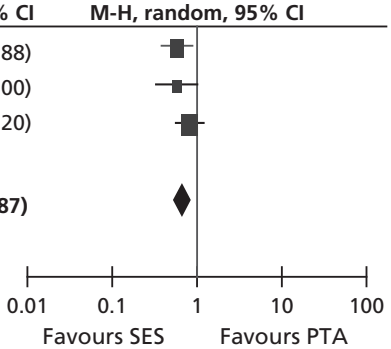

FIGURE 5 Forest plot of comparison: 1 SES vs. PTA, restenosis 12 months random three studies.

	SES		PTA			RR	RR
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI	M-H, fixed, 95% CI
ABSOLUTE 2007[16–18]	18	49	33	52	61.0%	0.58 (0.38 to 0.88)	
Dick 2009[12]	11	34	22	39	39.0%	0.57 (0.33 to 1.00)	
Total (95% CI)		**83**		**91**	**100.0%**	**0.58 (0.41 to 0.81)**	
Total events	29		55				

Heterogeneity: χ^2=0.00, df=1 (p=0.98); I^2=0%

Test for overall effect: z=3.20 (p=0.001)

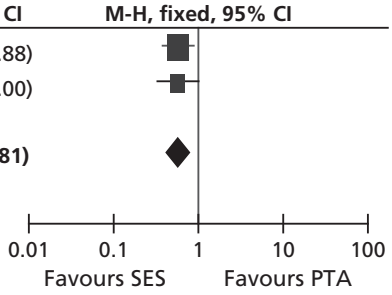

FIGURE 6 Forest plot of comparison: 1 SES vs. PTA, restenosis 12 months fixed two studies.

	SES		PTA			RR	RR
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
ABSOLUTE 2007[16–18]	18	49	33	52	63.8%	0.58 (0.38 to 0.88)	
Dick 2009[12]	11	34	22	39	36.2%	0.57 (0.33 to 1.00)	
Total (95% CI)		**83**		**91**	**100.0%**	**0.58 (0.41 to 0.81)**	
Total events	29		55				

Heterogeneity: τ^2=0.00, χ^2=0.00, df=1 (p=0.98); I^2=0%

Test for overall effect: z=3.20 (p=0.001)

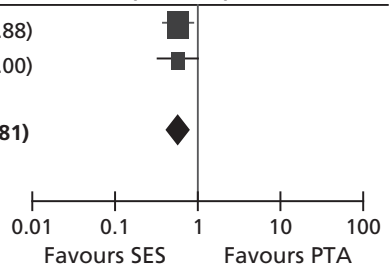

FIGURE 7 Forest plot of comparison: 1 SES vs. PTA, restenosis 12 months random two studies.

using the studies ABSOLUTE[16–18] and Dick *et al.*[12] produced a relative risk (RR) for SES with reference to PTA of 0.49 with a 95% CI of 0.32 to 0.76 by fixed-effect analysis. By random-effect analysis, the RR was 0.50 (95% CI 0.32 to 0.77). Both analyses significantly favoured SES over PTA ($p = 0.002$). Restenosis at 12 months, using the studies ABSOLUTE,[16–18] Dick *et al.*[12] and FAST[14], produced a RR of 0.68 (95% CI 0.53 to 0.87) by fixed-effect analysis ($p = 0.003$). By random-effect analysis, the RR was 0.67 (95% CI 0.52 to 0.87), significantly favouring SES over PTA ($p = 0.002$).

Of the four RCTs that reported a need for reintervention, three showed no significant difference between groups [VascuCoil (intracoil femoropopliteal stent trial),[13] FAST,[14] ABSOLUTE[16–18]] (*Table 6*). One study found an advantage for SES over PTA, with fewer SES participants needing TLR/target vessel revascularisation (TVR) at 6–12 months following the procedure (RESILIENT[15]). Rutherford category was studied by two RCTs, neither of which found a significant difference between SES and PTA treatment groups (FAST,[14] ABSOLUTE[16–18]) (*Table 7*).

Treadmill protocols were used by two studies (FAST,[14] ABSOLUTE[16–18]) to assess walking capacity (*Table 8*) and both found a significant advantage for SES over PTA at 6–12 months. ABSOLUTE[16–18] found that by 24 months the difference between treatment groups was no longer significant. Maximum walking capacity, as reported by the patients, was reported as significantly better with SES than PTA in one study (Dick *et al.*[12]). One study (RESILIENT[15]) found no significant difference between groups, as measured by the walking impairment questionnaire, as both groups improved significantly from baseline. RESILIENT[15] reported that the PTA group reported more claudication pain at 12 months ($p = 0.009$).

TABLE 6 Self-expanding stent and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	SES analysed (*n*)	SES patients undergoing reintervention (%)	Comparative statistic
VascuCoil[13]	9 months	TLR	131	1.5	135	0.7	Reported as NS only
FAST[14]	12 months	TLR	115	18.3	114	14.9	$p = 0.595$
RESILIENT[15]	6 months	TLR/TVR	63	47.4	121	1.5	$p < 0.0001$
	12 months	TLR/TVR	59	44.9	112	12.7	$p < 0.0001$
ABSOLUTE[16–18]	12 months	Need for ipsilateral reintervention within 12 months; PTA, stent implantation or bypass surgery	53	31.0	51	28.6	NS (PTA $p = 0.45$, stent $p = 0.99$, bypass $p = 0.22$)
	24 months	a/a	52	53.8	46	37.0	$p = 0.14$

a/a, as above; NS, non-significant.

TABLE 7 Self-expanding stent and Rutherford classification

Study	Follow-up	Definition of pain	PTA analysed (*n*)	PTA outcome	SES analysed (*n*)	SES outcome	Comparative statistic
FAST[14]	12 months	Rutherford category improvement	75	91% of patients improved	61	89% of patients improved	Reported as NS between groups
ABSOLUTE[16–18]	24 months	Rutherford category	52	4.2% CLI	46	4.4% CLI	$p = 0.74$

NS, non-significant.

TABLE 8 Self-expanding stent and walking capacity

Study	Follow-up	Definition of walking capacity	PTA analysed (*n*)	PTA outcome	SES analysed (*n*)	SES outcome	Comparative statistic
Dick *et al.* 2009[12]	6 months	Maximum walking capacity (m) (mean) (as reported by patient)	39	600	34	800	$p = 0.042$
	12 months	a/a	39	550	34	800	$p = 0.002$
FAST[14]	12 months	Absolute walking distance (median) (treadmill test 2 mph on a 12% incline)	52	185	20	150	$p = 0.0283$
RESILIENT[15]	12 months	Improvement from baseline as defined by the walking impairment questionnaire	59	29.4 ± 37.4	112	25.6 ± 34.6	NS
ABSOLUTE[16–18]	6 months	Maximal treadmill walking capacity (m) (median) (3.2 km/h, 12-degree slope)	53	270	51	362	$p = 0.041$
	12 months	a/a	53	267	51	387	$p = 0.040$
	24 months	a/a	52	196	46	302	$p = 0.12$

a/a, as above; NS, non-significant.

The two RCTs investigating QoL (RESILIENT,[15] ABSOLUTE[16–18]) found no significant differences between treatment groups SES and PTA on measures of Short Form questionnaire-8 items (SF-8) or Short Form questionnaire-36 items (SF-36) by ITT analysis (*Table 9*). There were no significant differences between treatment groups SES and PTA in terms of complications, in any of the five included RCTs (Dick *et al.*,[12] VascuCoil,[13] FAST,[14] RESILIENT,[15] ABSOLUTE[16–18]) (*Table 10*).

Meta-analyses

Self-expanding stent versus percutaneous transluminal balloon angioplasty Restenosis at 6 months: using the studies ABSOLUTE[16–18] and Dick *et al.*,[12] there was no substantial heterogeneity between studies. Fixed- and random-effect analyses gave similar results (see *Figures 2* and *3*).

Restenosis at 12 months: using the studies ABSOLUTE,[16–18] Dick *et al.*[12] and FAST,[14] there was no significant heterogeneity among studies. The overall effect was similar for fixed- and random-effect analyses (see *Figures 4* and *5*).

Restenosis at 12 months – using the studies ABSOLUTE[16–18] and Dick 2009,[12] which had been used for the 6-month restenosis analyses – gave non-significant heterogeneity. Overall effect was similar for fixed- and random-effect analyses (see *Figures 6* and *7*).

Balloon-expandable stent

Six RCTs compared BESs with PTA.

All six included RCTs reported restenosis, and four of these studies, of which two had only IC patients and two had approximately twice as many IC as CLI patients (Becquemin *et al.*,[19] Cejna *et al.*,[20] Grimm *et al.*,[21] Vroegindeweij *et al.*[23]), found no significant difference between BES and PTA (*Table 11*). One study of CLI patients (Rand *et al.*[22]) reported a significant advantage for BES over PTA, whereas one study of CLI patients (Zdanowski *et al.*[24]) reported that PTA had an advantage over BES. Meta-analyses for restenosis at 6 months, using the studies of Cejna *et al.*[20] and Rand *et al.*,[22] gave a RR of 0.49 (95% CI 0.24 to 1.02) for both fixed- and random-effect analyses, with a non-significant trend favouring BES ($p = 0.06$) (*Figures 8–11*).

TABLE 9 Self-expanding stent and QoL

Study	Follow-up	Definition of QoL	PTA analysed (*n*)	PTA outcome	SES analysed (*n*)	SES outcome	Comparative statistic
RESILIENT[15]	12 months	Improvement from baseline defined by SF-8	59	5.9 ± 11.2	112	5.7 ± 11.2	Statistically significant changes within groups, but not between group
ABSOLUTE[16–18]	12 months	SF-36 physical component summary [median (IQR)]	53	37 (27–49)	51	35 (30–48)	$p = 0.9$
	12 months	SF-36 mental component summary [median (IQR)]	53	51 (35–58)	51	54 (45–59)	$p = 0.1$

IQR, interquartile range.

TABLE 10 Self-expanding stent and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	SES analysed (*n*)	SES patients with complications (%)	Comparative statistic
Dick *et al.* 2009[12]	1 day (perioperative)	Presence of small pseudoaneurysm at the puncture site	39	2.6	34	0	NS
VascuCoil[13]	9 months	Death	131	0.8	135	0	Reported as NS only
		Myocardial infarction	131	0	135	0	Reported as NS only
		Amputation	131	0.5	135	0	Reported as NS only
		Major bleeding	131	0.8	135	0.7	Reported as NS only
		Abrupt closure	131	1.5	135	0	Reported as NS only
		Renal failure	131	0.5	135	0	Reported as NS only
		Major vascular complications	131	4.6	135	3	Reported as NS only
FAST[14]	12 months	Stent fracture	n/a	n/a	83	12	n/a
	Perioperative	Procedural complications	121	4	123	7	
RESILIENT[15]	6 months	MACE: death within 30 days, stroke, myocardial infarction, significant distal embolisation, emergent surgical revascularisation of target limb, thrombosis and worsening Rutherford category	63	7.2	121	6.9	$p = 0.95$
	12 months	MACE; a/a	59	13.4	112	14.2	$p = 0.88$
		Amputation	59	2	112	0	
ABSOLUTE[16–18]	6 months	Stent fracture	17	0	51	2	$p = 0.99$
	12 months	a/a	17	0	49	2	$p = 0.99$
	6 months	Amputation	47	0	51	0	
	12 months	a/a	47	0	51	0	
	6 months	Death	47	0	51	0	
	12 months	a/a	47	0	51	2	$p = 0.99$

a/a, as above; n/a, not applicable; NS, non-significant.

TABLE 11 Balloon-expandable stent and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	BES analysed (*n*)	BES patients with restenosis (%)	Comparative statistic
Becquemin *et al.* 2003[19]	12 months	Presence of > 50% stenosis at 1-year angiographic follow-up	65	32.3[a]	75	34.7[a]	$p = 0.85$
Cejna *et al.* 2001[20]	1 month	Presence of ≥ 70% stenosis as defined by angiography	42 limbs	16[a]	38 limbs	8[a]	
	6 months	a/a	29 limbs	27[a]	25 limbs	16[a]	
	12 months	a/a	16 limbs	37[a]	17 limbs	37[a]	
	24 months	a/a	11 limbs	47[a]	8 limbs	47[a]	$p = 0.09$
Grimm *et al.* 2001[21]	12 months	Primary patency, narrowing ≤ 20%	23	15.8[a]	30	25[a]	$p > 0.41$
	24 months	a/a	23	22.8[a]	30	27.6[a]	$p > 0.41$
	39 months	a/a	23	30.4[a]	30	26.7[a]	$p > 0.41$
Rand *et al.* 2006[22]	6 months	Stenosis > 70% as defined by angiography; critical	20 (32 lesions)	38.9 (lesions)[a]	17 (25 lesions)	16.3 (lesions)[a]	$p = 0.02$
	6 months	Stenosis > 50% as defined by angiography; subcritical	20 (32 lesions)	54.4 (lesions)[a]	17 (25 lesions)	20.3 (lesions)[a]	$p = 0.02$
Vroegindeweij *et al.* 1997[23]	12 months	Primary patency was determined by colour-flow duplex surveillance. All lesions that recurred during follow-up within the same treated arterial segment are considered restenoses. Progression of disease in untreated arterial segments is considered as new lesions. These lesions are not considered for the analysis of patency	27	26[a]	24	38[a]	$p = 0.22$

continued

TABLE 11 Balloon-expandable stent and restenosis (*continued*)

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	BES analysed (*n*)	BES patients with restenosis (%)	Comparative statistic
Zdanowski *et al.* 1999[24]	12 months	Restenosis was defined if the inner diameter was decreased by > 50% compared with the state immediately after stenting defined by angiography	8	25	12	50	$p = 0.033$

a/a, as above.
a Restenosis rates calculated from reported patency.

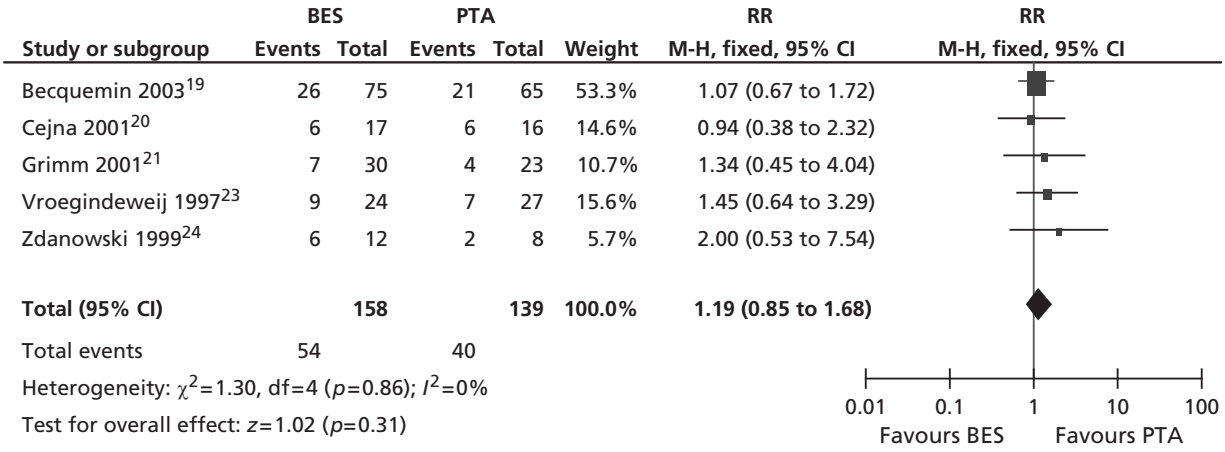

FIGURE 8 Forest plot of comparison: 2 BES vs. PTA, restenosis at 12 months fixed.

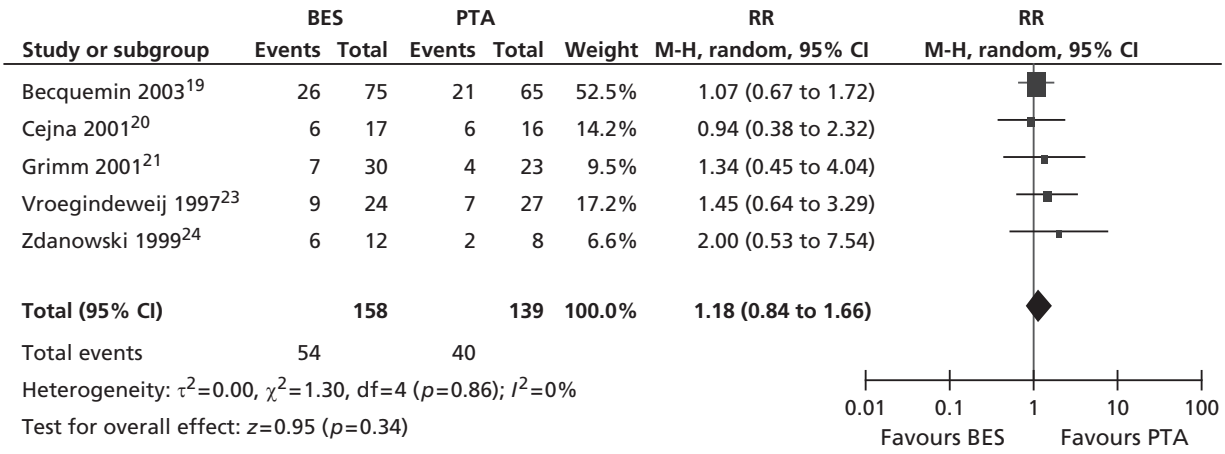

FIGURE 9 Forest plot of comparison: 2 BES vs. PTA, restenosis at 12 months random.

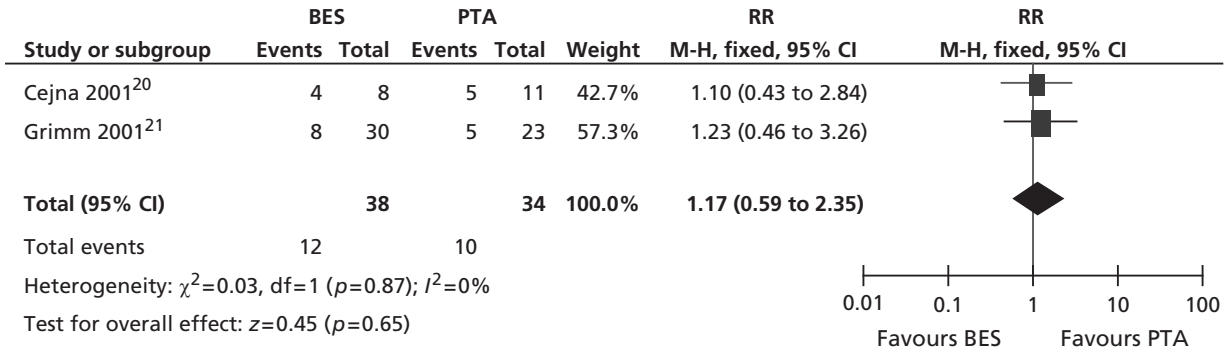

FIGURE 10 Forest plot of comparison: 2 BES vs. PTA, restenosis at 24 months fixed.

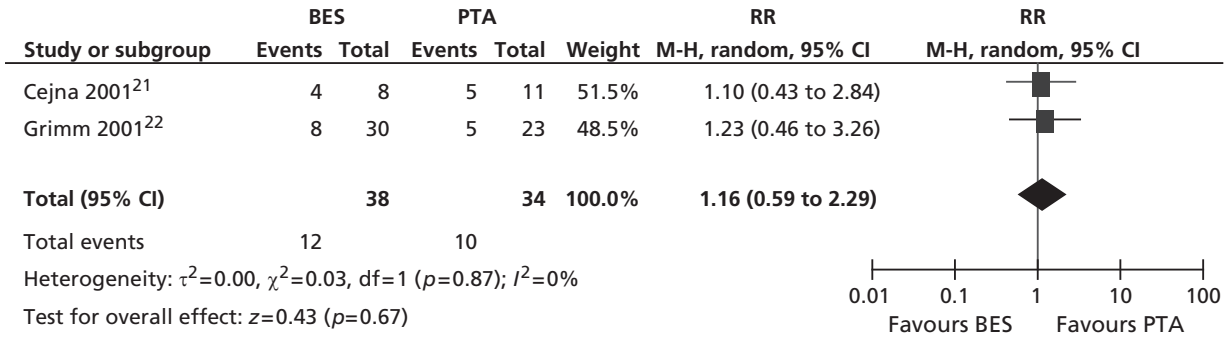

FIGURE 11 Forest plot of comparison: 2 BES vs. PTA, restenosis at 24 months random.

Restenosis at 12 months, using the studies Becquemin *et al.*,[19] Cejna *et al.*,[20] Grimm *et al.*,[21] Vroegindeweij *et al.*[23] and Zdanowski *et al.*,[24] gave a non-significant treatment group difference by fixed-effect (RR 1.19; 95% CI 0.85 to 1.68; $p = 0.31$) and random-effect analyses (RR 1.18; 95% CI 0.85 to 1.66; $p = 0.34$). Restenosis at 24 months, using the studies of Cejna *et al.*[20] and Grimm *et al.*,[21] gave a non-significant treatment group difference by fixed-effect (RR 1.17; 95% CI 0.59 to 2.35; $p = 0.65$) and random-effect analyses (RR 1.16; 95% CI 0.59 to 2.29; $p = 0.67$).

Neither of the two studies (Grimm *et al.*,[21] Zdanowski *et al.*[24]) that reported a need for reintervention found a significant difference between BES and PTA treatment groups (*Table 12*). One study (Grimm *et al.*[21]) investigated walking distance, and found similar results between groups. Although the PTA group had a slightly larger increase in walking distance, no statistic for the difference between groups was reported (*Table 13*). All six included RCTs reported complications (*Table 14*), and none of the studies showed a significant difference between groups for BES and PTA.

TABLE 12 Balloon-expandable stent and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	BES analysed (*n*)	BES patients undergoing reintervention (%)	Comparative statistic
Grimm *et al.* 2001[21]	Within 12 months	Need for second angioplasty	23	30	30	27	$p = 0.3$
Zdanowski *et al.* 1999[24]	Within 7 months	Underwent femorodistal bypass	17	11.8	15	13.3	

TABLE 13 Balloon-expandable stent and walking capacity

Study	Follow-up	Definition of walking capacity	PTA analysed (*n*)	PTA outcome	BES analysed (*n*)	BES outcome
Grimm *et al.* 2001[21]	Within 29 months	Change in mean walking distance (m)	23	316.4	30	217.1

TABLE 14 Balloon-expandable stent and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	BES analysed (*n*)	BES patients with complications (%)	Comparative statistic
Becquemin *et al.* 2003[19]	Perioperative	Perioperative complications	112	4.9	115	8.6	$p = 0.2$
	1 month	Death	86	0	89	0	
	12 months	Death	112	14	115	11	
	1 month	Minor complications at the puncture site	112	6.3	115	6.1	
	1 month	Major amputation	112	0.9	115	0	
	1 month	Minor amputation	112	4	115	1.7	$p = 0.73$
	12 months	Number of failed procedures (death or > 50% stenosis)	86	33%	89	34%	$p = 0.9$
Cejna *et al.* 2001[20]	1 month	Major complications: defined as causing a change in the level of care, surgery or prolonged stay in the hospital or death	77 limbs	2.6	77 limbs	1.3	$p = 1.0$
	1 month	Procedure-related complications	77 limbs	1.3	77 limbs	3.9	
	1 month	Minor amputations	77 limbs	5.2 (digital amputations)	77 limbs	2.6 (crural amputations)	
	1 month	Peripheral embolism < 30 days post intervention	77 limbs	3.9	77 limbs	5.2	(Any minor complications at 1 month, $p = 0.55$)

TABLE 14 Balloon-expandable stent and complications (*continued*)

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	BES analysed (*n*)	BES patients with complications (%)	Comparative statistic
Grimm *et al.* 2001[21]	1 month	Major complications: events requiring therapy and prolonged hospitalisation (> 24 hours) and/or an unplanned increase in the level of care or permanent adverse sequelae or death	23	0	30	0	
Rand *et al.* 2006[22]	1 month	Major amputation	53 lesions	0	42 lesions	2.4	
	1 month	Minor amputation	53 lesions	1.8	42 lesions	2.4	
Vroegindeweij *et al.* 1997[23]	Within 1 month	Occurrence of embolus	27	0	24	4.2	
	1 month	Occurrence of thrombus	27	3.7	24	0	
Zdanowski *et al.* 1999[24]	Perioperative	Major complications: myocardial infarction, bleeding, emboli	17	23.5%	15	6.7	

Meta-analyses

Balloon-expandable stent versus percutaneous transluminal balloon angioplasty Restenosis at 12 months: using the studies of Becquemin *et al.*,[19] Cejna *et al.*,[20] Grimm *et al.*,[21] Vroegindeweij *et al.*[23] and Zdanowski *et al.*,[24] there was no significant heterogeneity. The overall effect was similar for fixed- and random-effect analyses (see *Figures 8* and *9*).

Restenosis at 24 months: using the studies of Cejna *et al.*[20] and Grimm *et al.*,[21] there was no significant heterogeneity. The overall effect was similar for fixed- and random-effect analyses (see *Figures 10* and *11*).

Drug-eluting stent

Three RCTs of DESs were included. One RCT compared paclitaxel-eluting stents with PTA, with participants in the PTA arm having the potential to be further randomised to DES or BMS.[25] One RCT compared sirolimus-eluting stents with SESs.[30] One RCT compared sirolimus-eluting stents with stents coated with placebo.[31]

The RCT of paclitaxel-eluting stents (Zilver® PTX®, Cook Medical, Bloomington, IN, USA) reported a significant advantage for DES over PTA for restenosis at 12 months (*Table 15*), and also for survival free of amputation, TLR or worsening of Rutherford category (*Table 16*). Of the two RCTs of sirolimus-eluting stents, one study found no treatment effect for DES and BMS for restenosis (SIROCCO[28–30]), and the other found a significant advantage of DES over BMS for luminal narrowing (Rastan *et al.*[31]) (*Table 17*). Neither of these studies found significant differences between groups in terms of the need for reintervention (*Table 18*).

TABLE 15 Paclitaxel-eluting stent and restenosis

Study	Follow-up	Definition of restenosis/patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Paclitaxel-eluting stent analysed (*n*)	Paclitaxel-eluting stent patients with restenosis (%)	Comparative statistic
[a]Zilver PTX[25–27]	12 months	Patency: duplex ultrasonography, patent = PSVR < 2.0 (or angiography, if available; patent = diameter stenosis < 50%). Group randomised to PTA, with second randomisation to stents	251 lesions (*n* = 236)	67.2[a]	247 lesions (*n* = 235)	16.9[a]	$p = 0.01$
		Patency: Duplex ultrasonography, patent = PSVR < 2.0 (or angiography if available, patent = diameter stenosis < 50%). Patients receiving only PTA not undergoing second randomisation	126 lesions (on treatment, PTA alone)	34.7[a] (PTA alone)	a/a	a/a	$p < 0.01$

a/a, as above; PSVR, peak systolic velocity ratio.
a Restenosis rates calculated from reported patency.

TABLE 16 Paclitaxel-eluting stent and survival from adverse events

Study	Follow-up	Definition of adverse events	PTA analysed (*n*)	PTA patient survival (%)	Paclitaxel-eluting stent analysed (*n*)	Paclitaxel-eluting stent patient survival (%)	Comparative statistic
Zilver PTX[25–27]	12 months	Event-free survival; freedom from death, amputation, TLR, worsening Rutherford classification	236	82.6	235	90.4	$p < 0.01$

a 0.9% stent fracture rate for all stents including DES and BMS.

TABLE 17 Sirolimus-eluting stent and restenosis

Study	Follow-up	Definition of restenosis/patency	BMS analysed (*n*)	BMS patients with restenosis [% (95% CI)]	Sirolimus-eluting stent analysed (*n*)	Sirolimus-eluting stent patients with restenosis [% (95% CI)]	Comparative statistic
SIROCCO[28–30]	6 months	Restenosis defined as >50% stenosis as determined by duplex ultrasonography	42	4.8 (0.6 to 16.2)	44	4.5 (0.6 to 16.2)	NS
	9 months	a/a	42	7.1 (1.5 to 19.5)	36	11.1 (3.1 to 26.1)	
	12 months	a/a	38	18.4 (7.7 to 34.3)	39	12.8 (4.3 to 27.4)	
	24 months	a/a	35	22.9 (10.4 to 40.1)	38	21.1 (9.6 to 37.3)	$p = 1.0$
Rastan *et al.* 2011[31]	6 months	Luminal narrowing of ≥ 50% detected with duplex ultrasound if not appropriate with angiography	67	31.3[a]	64	14.1[a]	$p = 0.02$
	12 months	a/a	63	44.4[a]	62	19.4[a]	$p = 0.004$

a/a, as above; NS, non-significant.
a Restenosis rates calculated from reported patency.

TABLE 18 Sirolimus-eluting stent and need for reintervention

Study	Follow-up	Definition of reintervention	BMS analysed (*n*)	BMS patients undergoing reintervention (%)	Sirolimus-eluting stent analysed (*n*)	Sirolimus-eluting stent patients undergoing reintervention (%)	Comparative statistic
SIROCCO[28–30]	24 months	TLR	46 SES	13 SES	47	6	$p = 0.30$
	24 months	TVR	46 SES	22 SES	47	13	$p = 0.33$
Rastan *et al.* 2011[31]	12 months	Target limb reintervention	63	17.5	62	9.7	$p = 0.29$

One study (Rastan *et al.*[31]) found a significant advantage for SES over BMS for improving Rutherford category (*Table 19*), although this advantage appeared at 12 months and was not seen 6 months post intervention. The two RCTs of sirolimus-eluting stents found no significant differences between groups for adverse events (*Table 20*).

Stent-graft

One RCT was identified that compared stent-graft with PTA (Saxon *et al.*[32,33]). IC and CLI patients were included, with most having IC. This RCT reported significantly superior results for stent-graft compared with PTA in terms of restenosis, after up to 24 months follow-up (*Table 21*). This RCT also reported significantly superior results for stent-graft compared with PTA in terms of clinical status (*Tables 22* and *23*). Complications were similar between treatment groups, although there was a borderline significant effect of increased rates of thigh pain for stent-graft compared with PTA (*Table 24*).

TABLE 19 Sirolimus-eluting stent and Rutherford classification

Study	Follow-up	Definition of clinical status	BMS analysed (*n*)	BMS outcome	Sirolimus-eluting stent analysed (*n*)	Sirolimus-eluting stent outcome	Comparative statistic
Rastan *et al.* 2011[31]	6 months	Change in Rutherford–Becker classification [median (IQR)]	67	–1 (–2 to 0)	64	–2 (–3 to –1)	$p = 0.12$
	12 months	a/a	62	–1 (–2 to 0)	63	–2 (–3 to –1)	$p = 0.004$

a/a, as above; IQR, interquartile range.

TABLE 20 Sirolimus-eluting stent and complications

Study	Follow-up	Definition of complication	BMS analysed (*n*)	BMS patients with complications (%)	Sirolimus-eluting stent in analysis (*n*)	Sirolimus-eluting stent patients with complications (%)	Comparative statistic
SIROCCO[28–30]	24 months	Serious adverse event related to procedure (death or prolonged hospitalisation)	25	4	40	15	a
	18 months	Device-related adverse events and minor complications (related to stent fractures)	25	36	40	20	$p = 0.245$
Rastan *et al.* 2011[31]	12 months	Death	63	13.9	62	17.1	$p = 0.66$
		Major amputation	63	3.2	62	1.6	
		Minor amputation	63	3.2	62	1.6	

a Deaths not related to the procedure.

TABLE 21 Stent-graft and restenosis

Study	Follow-up	Definition of restenosis/patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Stent-graft analysed (*n*)	Stent-graft patients with restenosis (%)	Comparative statistic
Saxon *et al.* 2003,[32] 2008[33]	6 months; *n* = 28 from report of single-centre study	> 50% stenosis on duplex ultrasound	12	58[a]	15	7[a]	$p = 0.002$
	24 months; *n* = 28 from report of single-centre study	> 50% stenosis on duplex ultrasound	12	75[a]	15	13[a]	$p = 0.002$
	12 months[b]	No TVR; no evidence of restenosis or occlusion within treated vessel from Doppler ultrasound (where target lesion not identified, vessel patency from SFA to popliteal artery was applied); angiography demonstrating < 30% residual diameter stenosis	100	60[a]	97	35[a]	$p = 0.0003$

SFA, superficial femoral artery.
a Restenosis rates calculated from reported patency.
b From entire multicentre study.

TABLE 22 Stent-graft and clinical success

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA patients with clinical success (%)	Stent-graft analysed (*n*)	Stent-graft patients with clinical success (%)	Comparative statistic
Saxon *et al.* 2003,[32] 2008[33]	12 months	Clinical success rate via Rutherford–Becker classification. Where change in clinical status was 'improved' = +3 to +1, 'no change' = 0, 'worse' = –1 to –3	100	69	97	84	$p = 0.025$

TABLE 23 Stent-graft and Rutherford classification

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA outcome	Stent-graft analysed (*n*)	Stent-graft outcome	Comparative statistic
Saxon *et al.* 2003,[32] 2008[33]	24 months; *n* = 28 from report of single-centre study	Mean clinical status via Rutherford–Becker classification	100	1.9 (95% CI 1.02 to 2.78)	97	2.8 (95% CI 2.46 to 3.14)	$p = 0.08$

TABLE 24 Stent-graft complications

Study	Follow-up	Definition of complication	PTA (*n*)	PTA patients with complications (%)	Stent-graft (*n*)	Stent-graft patients with complications (%)	Comparative statistic
Saxon *et al.* 2003,[32] 2008[33]	1 month	Major adverse event	100	5	97	11.3	Reported as NS
	12 months	a/a	100	16	97	9.3	Reported as NS
	1 month	Minor adverse event: haematoma	100	7	97	13.4	$p = 0.161$
	1 month	Minor adverse event: thigh pain	100	3	97	10.3	$p = 0.047$

a/a, as above; NS, non-significant.

Atherectomy

Two RCTs comparing atherectomy with PTA in IC patients were included. One RCT (Nakamura *et al.*[34]) found no significant difference in restenosis rates between atherectomy and PTA at 6 months (*Table 25*). One RCT (Vroegindeweij *et al.*,[35,36] Tielbeek *et al.*[37]) found an advantage for PTA over atherectomy for restenosis at 1-year follow-up, although this no longer reached significance at 2-year follow-up.

One RCT (Vroegindeweij *et al.*,[35,36] Tielbeek *et al.*[37]) found no significant difference in clinical status between atherectomy and PTA, with both groups showing improvement after 1 month, and some continuation of improvement after 12 months (*Table 26*). Between-group statistics were not reported for complications (*Table 27*), but neither study (Nakamura *et al.*,[34] Vroegindeweij *et al.*,[35,36] Tielbeek *et al.*[37]) suggests significant differences between atherectomy and PTA.

Cutting balloon

Two RCTs were identified that compared CB with PTA, with mostly IC, but some CLI, patients. All patients in the trial of Dick *et al.*[39] had prior stents and the study investigated femoropopliteal in-stent restenosis, whereas the study of Amighi *et al.*[38] looked at short de novo superficial femoral artery lesions. One RCT (Amighi *et al.*[38]) showed a borderline significant trend favouring PTA over CB for restenosis. The other RCT (Dick *et al.*[39]) found no significant difference in restenosis between CB and PTA (*Table 28*).

One study (Dick *et al.*[39]) showed similar rates of need for reintervention for CB and PTA groups (*Table 29*). One RCT (Amighi *et al.*[38]) showed a trend favouring PTA over CB for rates of asymptomatic patients (*Tables 30* and *31).* Both studies (Amighi *et al.*[38] and Dick *et al.*[39]) showed similar levels of complications between CB and PTA groups (*Table 32*).

TABLE 25 Atherectomy and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Atherectomy analysed (*n*)	Atherectomy patients with restenosis (%)	Comparative statistic
Nakamura 1995[34]	6 months	Patency was defined as improvement in clinical symptoms as well as sustained improvement in the ABPI	10	50[a]	2.7-mm TEC, $n = 13$; 4.0-mm TEC, $n = 8$	With 2.7-mm TEC: 54[a]. With 4.0-mm TEC: 62[a]	$p = 0.16$
Vroegindeweij's group 1995[35–37]	12 months	PSV index = ratio of PSV stenosis to PSV artery. PSV index ≤ 0.5 indicates $\geq 50\%$ diameter reduction. Assessed by colour-flow duplex scanning	14	23[a]	16	75[a]	$p = 0.017$
	24 months	PSVR ≥ 2.5 assessed by colour-flow duplex scanning	35	66[a]	38	44[a]	$p = 0.07$
		Angiographically determined diameter reduction $\geq 50\%$	35	33[a]	38	56[a]	$p = 0.06$

PSV, peak systolic velocity; PSVR, peak systolic velocity ratio; TEC, transcutaneous extraction catheter.
a Restenosis rates calculated from reported patency.

TABLE 26 Atherectomy and improvement of clinical category

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA outcome (%)	Atherectomy analysed (*n*)	Atherectomy outcome (%)	Comparative statistic
Vroegindeweij's group 1995[35–37]	1 month	Improvement defined by the Society for Vascular Surgery/ International Society for Cardiovascular Surgery criteria	35	97	38	89	Reported as NS
	12 months	Maintenance of clinical category according to Society for Vascular Surgery/ International Society for Cardiovascular Surgery criteria	14	74	16	57	$p = 0.52$

NS, non-significant.

TABLE 27 Atherectomy and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	Atherectomy analysed (*n*)	Atherectomy patients with complications (%)
Nakamura 1995[34]	Perioperative	Minor procedural complication	13	23.1	2.7-mm TEC, *n* = 13; 4.0-mm or 4.7-mm TEC, *n* = 13	2.7-mm TEC, 0; 4.0-mm or 4.7-mm TEC, 38.5
Vroegindeweij's group 1995[35–37]	Perioperative	Minor procedure-related complications; dissections	35	14.3	38	0
		Major procedure-related complications	35	2.9	38	7.9

TEC, transcutaneous extraction catheter.

TABLE 28 Cutting balloon and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	CB analysed (*n*)	CB patients with restenosis (%)	Comparative statistic
Amighi *et al.* 2008[38]	6 months	> 50% restenosis of the treated vessel segment determined by duplex ultrasound	22	32	21	62	$p = 0.048$
Dick *et al.* 2008[39]	1 month	a/a	22	27	17	12	$p = 0.42$
	3 months	a/a	22	41	17	47	$p = 0.75$
	6 months	a/a	22	73 (95% CI 54 to 92)	17	65 (95% CI 42 to 88)	$p = 0.73$

a/a, as above.

TABLE 29 Cutting balloon and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	CB analysed (*n*)	CB patients undergoing reintervention (%)
Dick *et al.* 2008[39]	6 months	Ipsilateral reintervention with repeat balloon angioplasty or bypass surgery	22	36.4	17	41

TABLE 30 Cutting balloon and clinical symptoms

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA outcome (%)	CB analysed (*n*)	CB outcome (%)	Comparative statistic
Amighi *et al.* 2008[38]	6 months	Clinically asymptomatic	22	73	21	38	$p = 0.059$

TABLE 31 Cutting balloon and walking capacity

Study	Follow-up	Definition of walking capacity	PTA analysed (*n*)	PTA outcome	CB analysed (*n*)	CB outcome	Comparative statistic
Amighi *et al.* 2008[38]	6 months	Pain-free walking distance (m) [median (IQR)]	22	> 1000 (200 to > 1000)	21	600 (100 to > 1000)	$p = 0.17$
Dick *et al.* 2008[39]	6 months	Maximum walking capacity on the treadmill (m)	22	103	17	117	$p = 0.97$

IQR, interquartile range.

TABLE 32 Cutting balloon complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	CB analysed (*n*)	CB patients with complications (%)	Comparative statistic
Amighi *et al.* 2008[38]	6 months	Minor procedure-related complications: peripheral embolism or pseudoaneurysm	22	4.5	21	9.5	
Dick *et al.* 2008[39]	Perioperative	Major complications: access site complications requiring surgical intervention, bleeding complications, amputation, macroembolism, death	22	0	17	0	
		Minor complications: spontaneously resolving	22	18	17	18	$p = 0.99$

Cryoplasty

Two RCTs were included that compared cryoplasty with PTA in IC and CLI patients. Neither RCT (Jahnke *et al.*,[40] Spiliopoulos *et al.*[41]) found a significant treatment group effect between cryoplasty and PTA for restenosis (*Table 33*).

One study (Spiliopoulos *et al.*[41]) found a significant advantage for PTA over cryoplasty, in terms of fewer patients needing reintervention (*Table 34*). One study (Jahnke *et al.*[40]) showed similar levels of improvement in clinical status for cryoplasty and PTA (*Table 35*). Both studies (Jahnke *et al.*,[40] Spiliopoulos *et al.*[41]) showed similar levels of complications between cryoplasty and PTA groups (*Table 36*).

Radiation

In this review, 10 RCTs were included that compared radiation with PTA in majority IC and CLI patients. Of these, eight employed EVBT, and two used EBRT.

TABLE 33 Cryoplasty and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Cryoplasty analysed (*n*)	Cryoplasty patients with restenosis (%)	Comparative statistic
Jahnke *et al.* 2010[40]	3 months	> 2.5-fold increase in PSVR across the treated segment indicative of > 50% luminal narrowing	37	9.2[a]	31	3.2[a]	
	6 months	a/a	33	20.2[a]	27	17.1[a]	
	9 months	a/a	23	33.3[a]	23	20.7[a]	$p = 0.14$
Spiliopoulos *et al.* 2010[41]	12 months	Binary in-lesion restenosis > 50%	31 limbs	32.4[a]	29 limbs	33.4[a]	
	24 months	a/a	31 limbs	45.4[a]	29 limbs	40.8[a]	
	36 months	a/a	31 limbs	45.4[a]	29 limbs	40.8[a]	$p = 0.894$

a/a, as above; PSVR, peak systolic velocity ratio.
a By log-rank test.

TABLE 34 Cryoplasty and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	Cryoplasty analysed (*n*)	Cryoplasty patients undergoing reintervention (%)	Comparative statistic
Spiliopoulos *et al.* 2010[41]	36 months	TLR	31 limbs	52.3	29 limbs	66.5	$p < 0.04$

TABLE 35 Cryoplasty and improvement

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA mean score	Cryoplasty analysed (*n*)	Cryoplasty mean score	Comparative statistic
Jahnke *et al.* 2010[40]	9 months	Improvement defined by the Society for Vascular Surgery/ International Society for Cardiovascular Surgery criteria for lower-limb ischaemia ranging from –3 (markedly worse) to +3 (markedly improved)	23	2.43 ± 1.16	23	2.73 ± 0.55	Only within-group analysis offered

TABLE 36 Cryoplasty and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	Cryoplasty analysed (*n*)	Cryoplasty patients with complications (%)	Comparative statistic
Jahnke *et al.* 2010[40]	Perioperative	Major complication: distal embolisation, side branch perforation	46	2.7	40	5	
		Minor complication: groin haematoma	46	2.7	40	2.5	
Spiliopoulos *et al.* 2010[41]	Perioperative	Minor puncture-site-related complications	31 limbs	3.2	29 limbs	3.5	$p = 0.4$
		Major puncture-site-related complications	31 limbs	0	29 limbs	0	NS
		Procedure-related adverse events	31 limbs	0	29 limbs	0	NS
		Minor amputation	31 limbs	9.7	29 limbs	6.9	$p = 0.3$

NS, non-significant.

Endovascular brachytherapy studies

For restenosis (*Table 37*), three studies (Zehnder *et al.*,[45] Krueger *et al.*,[47,48] Vienna-3[51–53]) showed a significant advantage for EVBT over PTA, although, for one of these studies (Krueger *et al.*[47,48]), the advantage at 6 months was not maintained at 2 years, and two studies (Gallino *et al.*,[42] Hagenaars *et al.*[46])

TABLE 37 Endovascular brachytherapy and restenosis

Study	Follow-up	Definition of restenosis/patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Radiation analysed (*n*)	Radiation patients with restenosis (%)	Comparative statistic
Gallino *et al.* 2004,[42] Bonvini *et al.* 2003,[43] Diehm *et al.* 2005[44]	6 months	> 50% restenosis measured by duplex ultrasound	84	42[a]	81	17[a]	
Zehnder *et al.* 2003,[45] Diehm *et al.* 2005[46]	12 months	> 50% recurrent obstruction defined by duplex ultrasound	56	42	44	23	$p < 0.028$
Gallino *et al.* 2004,[42] Zehnder *et al.* 2003,[45] Diehm *et al.* 2005[44]	12 months	50% or more diameter reduction by digital subtraction angiography	75	29.3[a]	72	17.3[a]	$p = 0.16$
	24 months	a/a	75	36.9[a]	72	35.7[a]	$p = 0.16$
	36 months	a/a	75	52.9[a]	72	35.7[a]	$p = 0.16$
Hagenaars *et al.* 2002[46]	6 months	> 50% diameter stenosis defined by angiography	16	31.3	8	0	$p = 0.08$
Krueger *et al.* 2002, 2004[47,48]	6 months	> 50% diameter reduction within the former stenotic section defined by angiography	15	46.7	15	0	$p = 0.006$
	12 months	a/a	15	33.3	15	0	$p = 0.042$
	24 months	a/a	15	33.3	15	13.3	$p = 0.39$
Vienna-2[49–51]	6 months	Angiographically verified stenosis of > 50% narrowing of the luminal diameter within the recanalised segment compared with the diameters of normal segments. In a patient who only underwent duplex ultrasound a PSVR ≥ 2.4 was used to indicate restenosis	29	69	15	73.4	
	60 months	a/a	37	32.4	37	43.2	
Vienna-3[51–53]	12 months	> 50% reduction of arterial lumen determined angiographically or, when patients refused, with duplex ultrasound. PSVR > 2.4 indicated 50% restenosis	67	67.1	67	41.7	$p < 0.05$
VARA[54]	6 months	≥ 50% restenosis of the treated segment	29	31	23	22	$p = 0.45$

showed a trend favouring EVBT (Gallino *et al.*[42] trial significance value not calculated between two arms presented here, as it was part of a four-arm trial). Two studies (Vienna-2,[49–51] VARA[54]), and one combined analysis with long-term follow-up of two included studies (Diehm *et al.*[44] analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials), found no significant difference between EVBT and PTA (*Table 38*). Meta-analyses of restenosis at 6 months using VARA[54] and Vienna-2[49–51] trials (*Figures 12–15*) gave a RR of 0.93 (95% CI 0.62 to 1.39; $p = 0.72$) by fixed-effect analysis. By random-effect analysis, the RR was 1.00 (95% CI 0.70 to 1.44; $p = 1.00$). At 12-month follow-up, restenosis rates based on the meta-analyses of Diehm *et al.*,[44] VARA[54] and Vienna-3[51–53] had a RR of 0.63 (95% CI 0.48 to 0.83) by both fixed-effect ($p = 0.001$) and random-effect ($p = 0.0008$) analyses, significantly favouring EVBT over PTA.

TABLE 38 Endovascular brachytherapy and late lumen loss

Study	Follow-up	Definition of late lumen loss	PTA analysed (*n*)	PTA lumen	Radiation analysed (*n*)	Radiation lumen	Comparative statistic
Hagenaars *et al.* 2002[46]	6 months	Change in lumen area from immediately post procedure to 6-month follow-up (mm^2)	16	mean –1.6 mm (SD 5.1)	8	mean 4.3 mm (SD 6.8)	$p = 0.03$
Wyttenbach *et al.* 2004, 2007[55,56]	24 hours	Lumen area gain (%) from baseline detected via cross-sectional MRI	10	86%	10	67%	Reported as NS
	3 months	a/a	10	40%	10	106%	$p = 0.026$
	24 months	a/a	10	30%	10	82%	$p = 0.047$

a/a, as above; MRI, magnetic resonance imaging; NS, non-significant; SD, standard deviation.

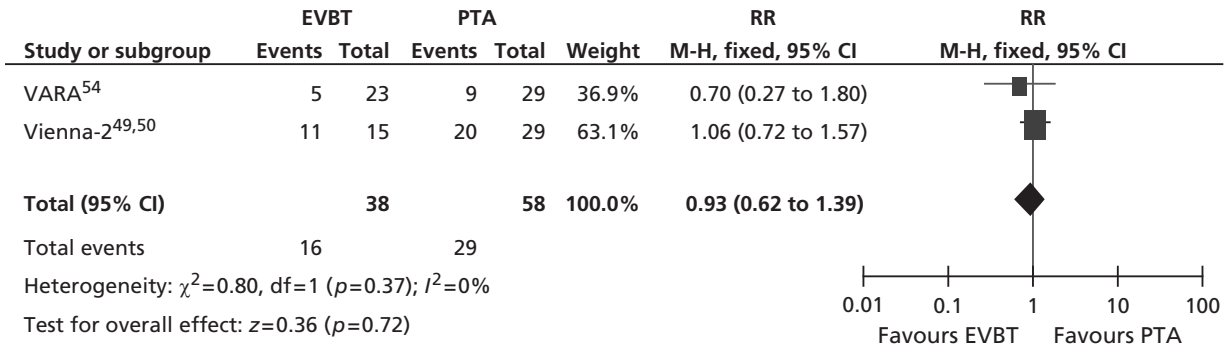

FIGURE 12 Forest plot of comparison: 4 EVBT vs. PTA, restenosis at 6 months fixed two studies.

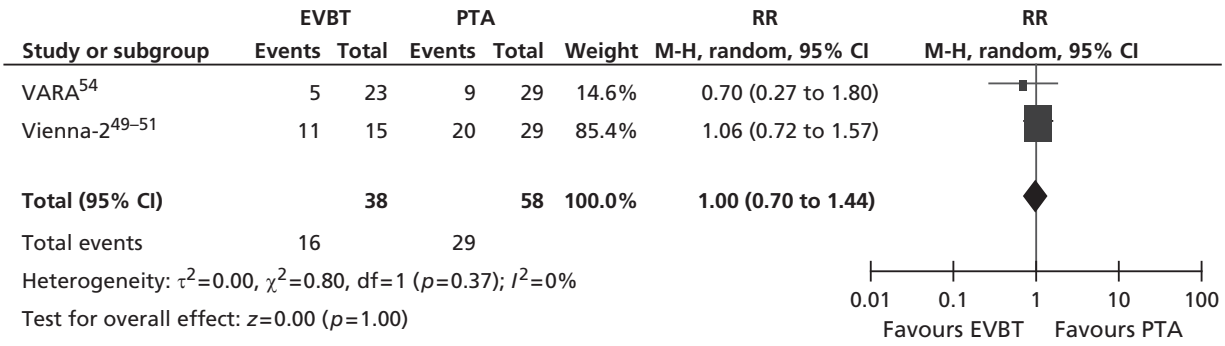

FIGURE 13 Forest plot of comparison: 4 EVBT vs. PTA, restenosis at 6 months random two studies.

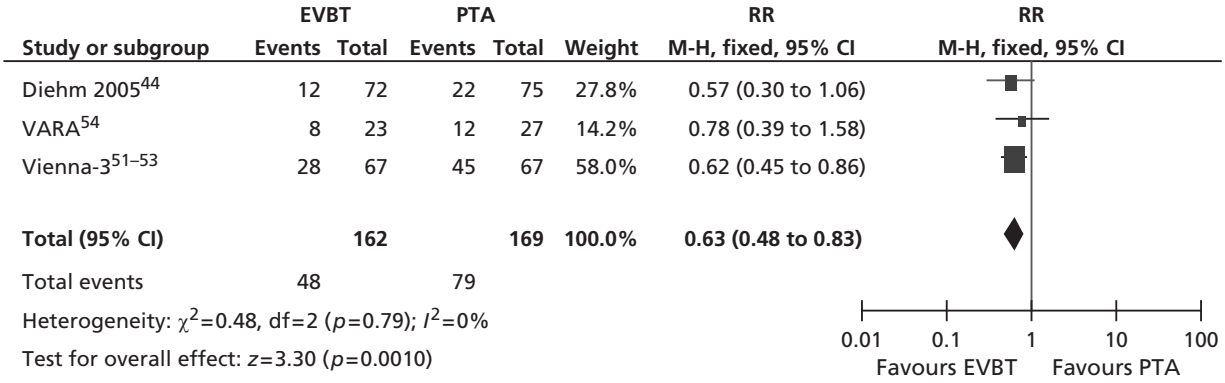

FIGURE 14 Forest plot of comparison: 4 EVBT vs. PTA, restenosis at 12 months fixed three studies.

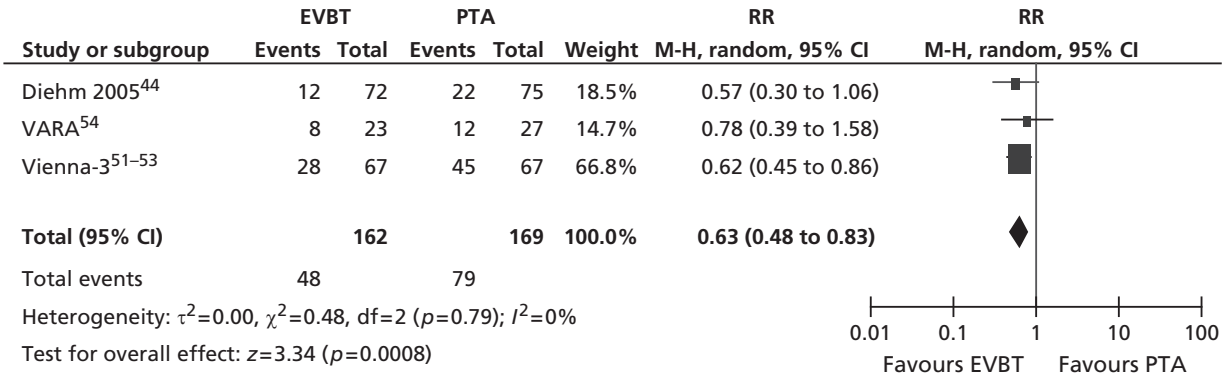

FIGURE 15 Forest plot of comparison: 4 EVBT vs. PTA, restenosis at 12 months random three studies.

Need for reintervention rates were not significantly different between EVBT and PTA (Gallino *et al.*,[42] Krueger *et al.*,[47,48] Vienna-2,[49–51] Vienna-3,[51–53] VARA,[54] and the combined Gallino *et al.*[42]/Zehnder *et al.*[45] analysis reported by Diehm *et al.*[44]) (*Table 39*). One RCT (VARA[54]) and one combined analysis with long-term follow-up of two included studies (Diehm *et al.*[44] analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials) found no significant difference between EVBT and PTA in terms of clinical improvement (*Table 40*).

The RCT (Krueger *et al.*[47,48]) reporting walking capacity found no significant differences between groups for EVBT and PTA on measures of pain-free walking distance or total walking distance up to 12 months post intervention (*Table 41*), with similar results up to 24 months. The patient-reported leg pain scores

TABLE 39 Endovascular brachytherapy and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	Radiation analysed (*n*)	Radiation patients undergoing reintervention (%)
Gallino *et al.* 2004,[42] Bonvini *et al.* 2003,[43] Diehm *et al.* 2005[44]	6 months	Revascularisation needed	75	11	69	6
Zehnder *et al.* 2003[45]	12 months	Repeat dilatation or surgery	56	23.2	44	6.8
Krueger *et al.* 2002, 2004[47,48]	6 months	TLR	15	0	15	0
	12 months	a/a	15	0	15	0
	24 months	a/a	15	13.3	15	6.7
	6 months	TVR	15	0	15	6.7
	12 months	a/a	15	0	15	13.3
	24 months	a/a	15	13.3	15	26.7
Vienna-2[49–51]	60 months	TLR	51	64.7	51	62.7
	60 months	TVR	51	72.5	51	70.6
Vienna-3[51–53]	12 months	TLR	46	30.4	50	10
	12 months	TVR	46	0	50	4
	12 months	Bypass surgery	46	0	50	2
VARA[54]	12 months	Mandatory TLR; PTA or bypass surgery	29	21	22	18

a/a, as above.

TABLE 40 Endovascular brachytherapy and clinical improvement

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA outcome (95% CI)	Radiation analysed (*n*)	Radiation outcome (95% CI)	Comparative statistic
Gallino *et al*. 2004,[42] Zehnder *et al*. 2003,[45] Diehm *et al*. 2005[44]	12 months	Sustained clinical improvement was defined as survival without repeat revascularisation and with an ABPI > 0.1 and/or an upwards categorical shift in clinical symptoms according to the Rutherford classification	75	84.3 (72.7 to 91.3)	72	82.4 (71.1 to 89.6)	$p = 0.26$ by log-rank (cumulative rates)
	24 months	a/a	34	82.1 (69.8 to 89.8)	37	69.8 (56.5 to 79.7)	$p = 0.26$ by log-rank (cumulative rates)
	36 months	a/a	25	76.4 (62 to 86)	25	67.5 (53.9 to 77.9)	$p = 0.26$ by log-rank (cumulative rates)
VARA[54]	6 months	Change in Rutherford classification (median)	27	2	23	2	$p = 0.75$
	12 months	a/a	27	2	23	2	$p = 0.39$

a/a, as above.

TABLE 41 Endovascular brachytherapy and walking capacity

Study	Follow-up	Definition of walking capacity	PTA analysed (*n*)	PTA outcome	Radiation analysed (*n*)	Radiation outcome	Comparative statistic
Krueger *et al*. 2002, 2004[47,48]	1 month	Pain-free walking distance (m) (mean) (treadmill 3 km/h, slope 12 degrees)	15	288.1 ± 193.9	15	308 ± 191.2	$p = 0.68$
	6 months	a/a	15	307.0 ± 170.2	15	339.4 ± 185.3	
	12 months	a/a	15	297.9 ± 205.8	15	329.2 ± 185.5	$p = 0.72$
	1 month	Total walking distance (m) (mean) (treadmill 3 km/h, slope 12 degrees)	15	321.1 ± 176.0	15	344.5 ± 171.7	$p = 0.72$
	6 months	a/a	15	345.4 ± 174.8	15	395.9 ± 140.1	
	12 months	a/a	15	357.8 ± 170.4	15	393.0 ± 143.0	$p = 0.59$
	1 month	Walking distance leg pain scores at interview (max. 35)	15	25.7 ± 5.9	15	28.4 ± 4.5	$p = 0.18$
	6 months	a/a	15	25.7 ± 6.2	15	27.3 ± 5.3	$p = 0.28$
	12 months	a/a	15	22.2 ± 8.1	15	26.1 ± 3.7	$p = 0.05$

a/a, as above.

(Krueger *et al.*[47,48]) were also similar between EVBT and PTA following intervention, although there was a borderline significant trend ($p = 0.05$) at 12 months favouring EVBT over radiation. Reported complications (*Table 42*) were similar for EVBT and PTA (Gallino *et al.*,[42] Vienna-3,[51–53] VARA[54]).

External beam radiotherapy studies

Two RCTs (Fritz *et al.*,[57] Therasse *et al.*[58]) found no significant treatment group effect for restenosis rates between EBRT and PTA (*Table 43*). One of these studies (Therasse *et al.*[58]) reported a treatment group effect for minimum lumen diameter, which was significantly larger in the 14 Gy dose EBRT group than in the PTA group for the dilated zone ($p = 0.0039$) and the irradiated zone ($p = 0.037$).

TABLE 42 Endovascular brachytherapy and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	Radiation analysed (*n*)	Radiation patients with complications (%)
Gallino *et al.* 2004,[42] Bonvini *et al.* 2003[43]	6 months	Late acute thrombotic occlusion	75	0	69	4.3
Vienna-3[51–53]	12 months	Amputation	46	2.2	50	0
VARA[54]	Perioperative	Vessel thrombosis/ early occlusion	33	3	27	3.7

TABLE 43 External beam radiation and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Radiation analysed (*n*)	Radiation patients with restenosis (%)	Comparative statistic
Fritz *et al.* 2004[57]	12 months	Restenosis was assumed if the ABPI was < 0.8 and only a max. of 0.2 > the value before PTA. If the ABPI was not meaningful, then the peak velocity ratio determined by duplex ultrasound or the resulting stenosis using a nomogram and the clinical stage according to Fontaine. > 50% restenosis was regarded as significant	48	33.3	46	45.7	$p = 0.292$

continued

TABLE 43 External beam radiation and restenosis (*continued*)

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Radiation analysed (*n*)	Radiation patients with restenosis (%)	Comparative statistic
Therasse *et al.* 2005[58]	12 months	> 50% reduction of lumen diameter within the dilated segment determined angiographically	22	50	7 Gy, *n* = 23; 10.5 Gy, *n* = 23; 14 Gy, *n* = 20	7 Gy, 65; 10.5 Gy, 48; 14 Gy, 25	*p* = 0.072
		> 50% reduction of lumen diameter within the irradiated zone determined angiographically	22	50	7 Gy, *n* = 23; 10.5 Gy, *n* = 23; 14 Gy, *n* = 20	7 Gy, 65; 10.5 Gy, 48; 14 Gy, 30	*p* = 0.15

There was no significant treatment effect for the need for reintervention (*Table 44*) between EBRT and PTA at 18 months post intervention (Therasse *et al.*[58]). Clinical change reported by one RCT (Fritz *et al.*[57]) showed similar improvement in Fontaine stage in EBRT and PTA groups (*Table 45*). One RCT (Therasse *et al.*[58]) reported that there were no major complications in either EBRT or PTA treatment groups.

Meta-analyses

Endovascular brachytherapy versus percutaneous transluminal balloon angioplasty Restenosis at 6 months: a meta-analysis using the VARA[54] and Vienna-2[49–51] studies gave non-significant heterogeneity. The overall effect was similar for fixed- and random-effect analyses.

Restenosis at 12 months: using the trials Diehm *et al.* 2005,[44] VARA[54] and Vienna-3,[51–53] there was no significant heterogeneity. The overall effect was similar for fixed- and random-effect analyses.

TABLE 44 External beam radiation and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	Radiation analysed (*n*)	Radiation patients undergoing reintervention (%)	Comparative statistic
Therasse *et al.* 2005[58]	18 months	Repeat PTA or surgery	24	25	25	in 14 Gy group: 12	*p* = 0.24

TABLE 45 External beam radiation and clinical change

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	PTA outcome	Radiation analysed (*n*)	Radiation outcome
Fritz *et al.* 2004[57]	12 months	Mean change in Fontaine classification	48	–0.8	47	–0.6

Drug-coated balloon

Three RCTs were identified that compared DCB angioplasty with conventional (uncoated balloon) PTA. For all studies, the type of drug utilised was paclitaxel. Most of the patients across the studies had IC, although some had CLI.

Two studies (THUNDER,[61–63] FemPac[64]) reported a significant advantage for DCB over PTA for restenosis rates (*Table 46*). When meta-analysed for restenosis at 6-month follow-up, these studies gave an RR of 0.40 (95% CI 0.23 to 0.69; $p = 0.001$), by both fixed- and random-effect analyses. Late lumen loss (LEVANT I[59,60]) and postintervention lumen diameter difference (THUNDER[61–63]) showed a significant treatment effect favouring DCB over PTA (*Table 47*).

TABLE 46 Drug-coated balloon and restenosis

Study	Follow-up	Definition of restenosis/patency	PTA analysed (*n*)	PTA patients with restenosis (%)	DCB analysed (*n*)	DCB patients with restenosis (%)	Comparative statistic
THUNDER[61–63]	6 months	Angiographically determined ≥ 50% stenosis of the diameter of the reference-vessel segment	48	44	41	17	$p = 0.01$
	12 months	a/a	36	50	33	24	NR
FemPac[64]	6 months	Angiographically determined ≥ 50% stenosis in the treated lesion	34	47	31	19	$p = 0.035$

a/a, as above; NR, not reported.

TABLE 47 Drug-coated balloon and late lumen loss

Study	Follow-up	Definition of late lumen loss	PTA analysed (*n*)	PTA late lumen loss (mm; mean)	DCB analysed (*n*)	DCB late lumen loss (mm; mean)	Comparative statistic
LEVANT I[59,60]	6 months	Late lumen loss (mm)	35	1.09	39	0.46	$p = 0.016$
THUNDER[61–63]	6 months	The difference between the minimum lumen diameters after dilatation and at the 6-month follow-up	54	1.7 ± 1.8	48	0.4 ± 1.2	$p < 0.001$

Need for reintervention rates were lower in DCB than in PTA treatment groups (*Table 48*), significantly favouring DCB over PTA in two RCTs (THUNDER,[61–63] FemPac[64]); the significance level was not reported in the other study (LEVANT I[59,60]) for TLR. Rates of TVR were also lower in the DCB than in the PTA group (LEVANT I[59,60]). TLR at 6-month follow-up, by meta-analysis of FemPac,[64] LEVANT I[59,60] and THUNDER[61–63] trials, which showed some heterogeneity (*Figures 16–21*), produced a RR of 0.26 (95% CI 0.10 to 0.68; $p = 0.006$) by random-effect analysis. This significantly favoured DCB over PTA, which was also the case at 24-month follow-up using the FemPac[64] and THUNDER[61–63] trials (RR 0.27; 95% CI 0.16 to 0.47; $p < 0.00001$).

TABLE 48 Drug-coated balloon and need for reintervention

Study	Follow-up	Definition of reintervention	PTA analysed (*n*)	PTA patients undergoing reintervention (%)	DCB analysed (*n*)	DCB patients undergoing reintervention (%)	Comparative statistic
LEVANT I[59,60]	6 months	TLR	47	22	41	13	NR
THUNDER[61–63]	6 months	a/a	54	37	48	4	$p < 0.001$
	12 months	a/a	54	48	48	10	
	24 months	a/a	54	52	48	15	$p < 0.001$
FemPac[64]	6 months	a/a	42	33	45	7	$p = 0.0024$
	24 months	a/a	42	50	45	13	$p = 0.001$

a/a, as above; NR, not reported.

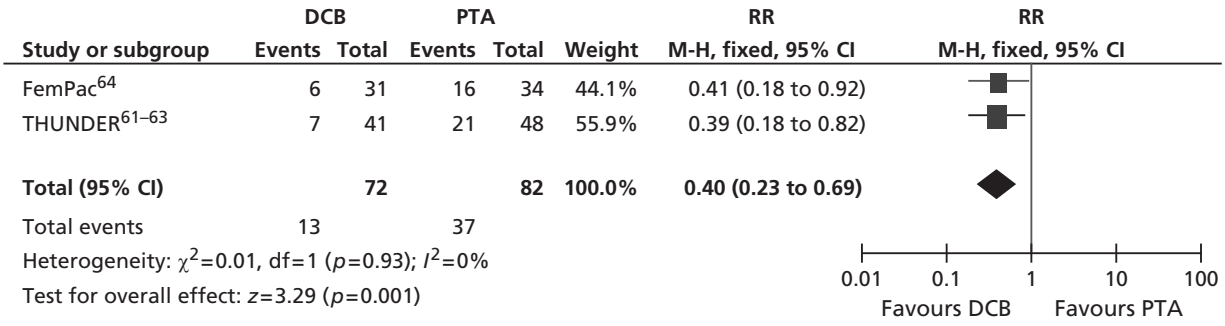

FIGURE 16 Forest plot of comparison: 5 DCB vs. PTA, restenosis at 6 months fixed.

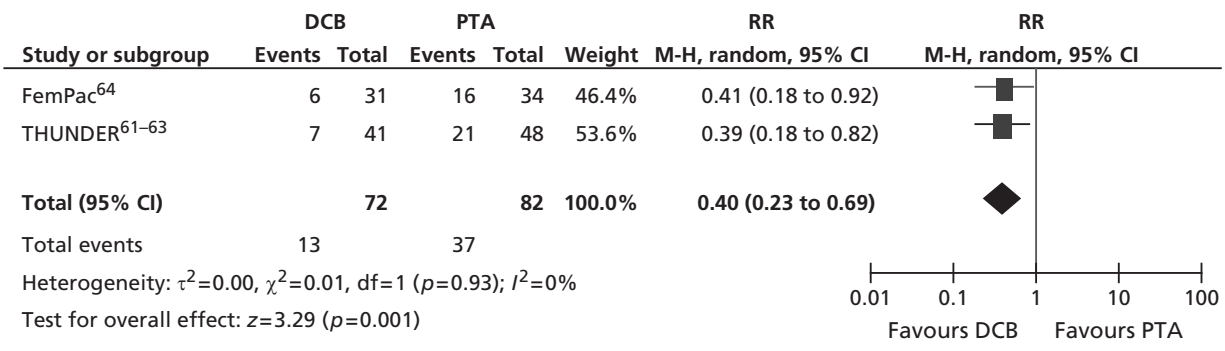

FIGURE 17 Forest plot of comparison: 5 DCB vs. PTA, restenosis at 6 months random.

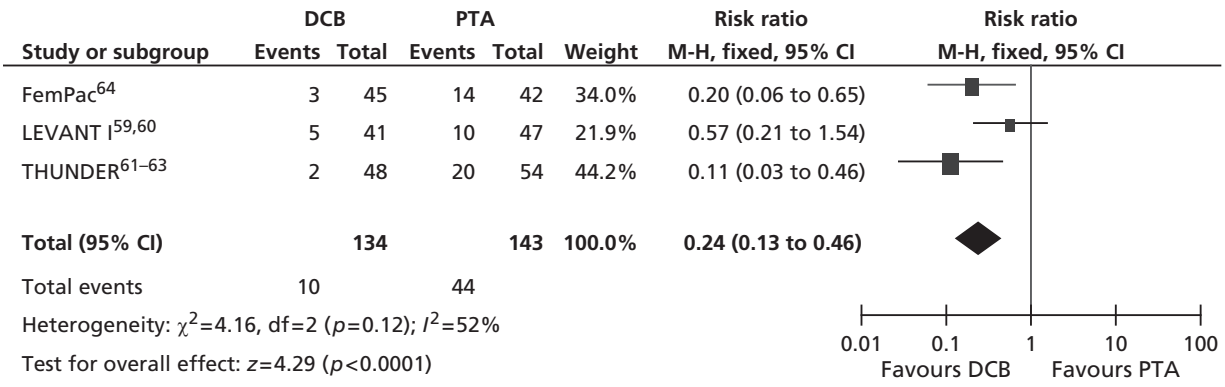

FIGURE 18 Forest plot of comparison: 5 DCB vs. PTA, TLR at 6 months fixed.

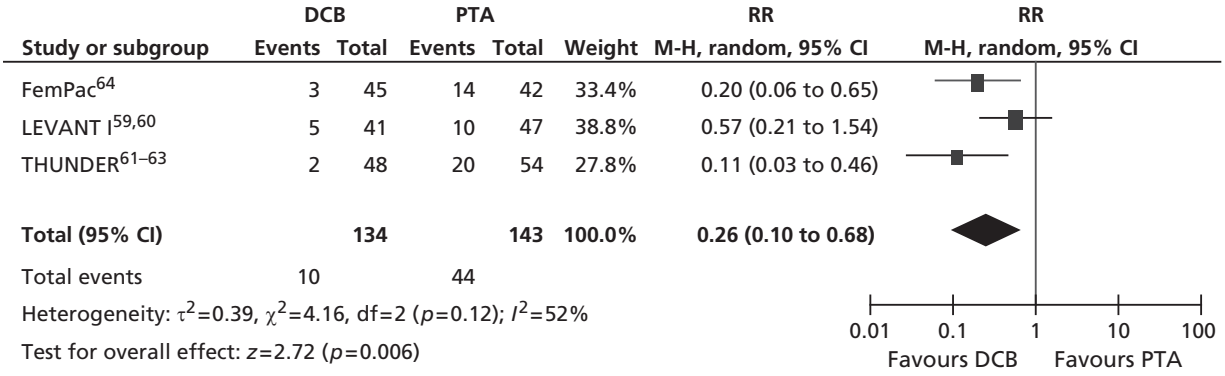

FIGURE 19 Forest plot of comparison: 5 DCB vs. PTA, TLR at 6 months random.

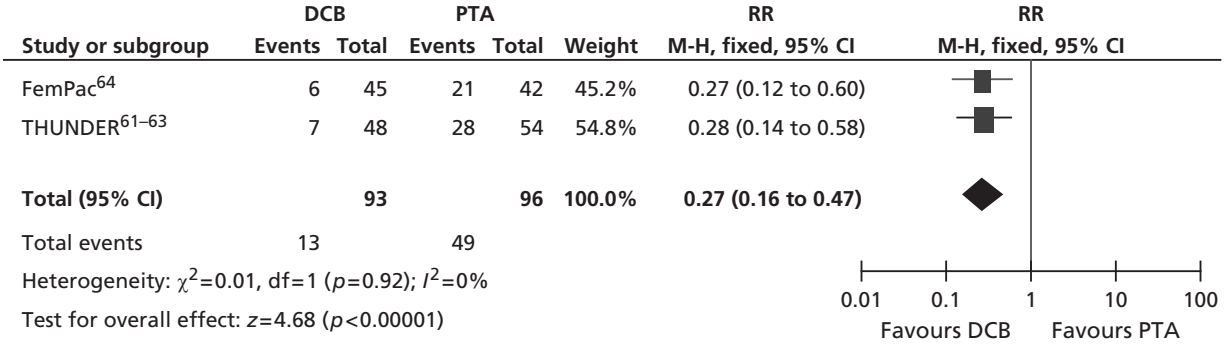

FIGURE 20 Forest plot of comparison: 5 DCB vs. PTA, TLR at 24 months fixed.

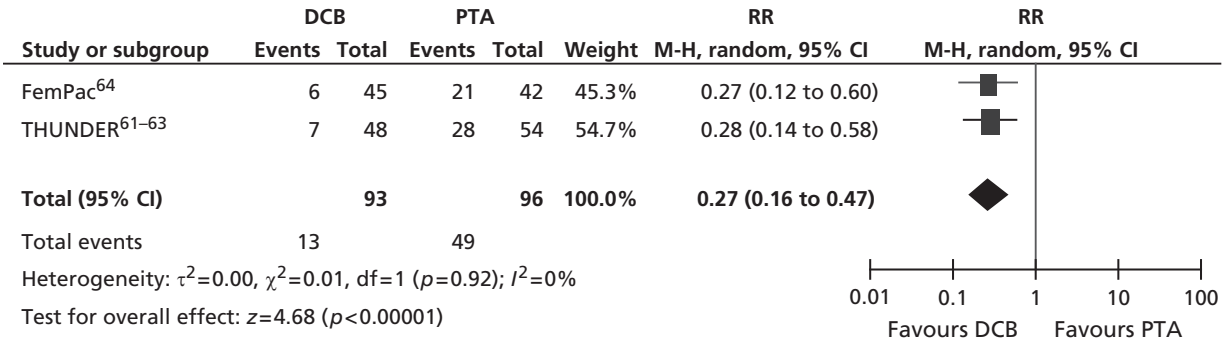

FIGURE 21 Forest plot of comparison: 5 DCB vs. PTA, TLR at 24 months random.

Two studies reported Rutherford category (*Table 49*). One study found no treatment group effect (THUNDER[61–63]), and one study (FemPac[64]) reported a borderline significant group difference, with more patients improving in the DCB group than in the PTA group at 6 months. However, in the latter study, by 18–24 months post intervention there was no significant difference between the groups, with the PTA group remaining stable and the improvement lessening in the DCB group, although both groups still improved from pre intervention. Complications and adverse events (*Table 50*) showed no significant treatment effects between DCB and PTA groups (LEVANT I,[59,60] THUNDER,[61–63] FemPac[64]).

Meta-analyses

Drug-coated balloon versus percutaneous transluminal balloon angioplasty Restenosis at 6 months: using the trials FemPac[64] and THUNDER,[61–63] there was no significant heterogeneity. The overall effect was similar for fixed- and random-effect analyses.

TLR at 6 months: there was some heterogeneity across the three included trials, although this did not reach significance.

TLR at 24 months: non-significant heterogeneity was found using FemPac[64] and THUNDER[61–63] trials. The overall effect was similar for fixed- and random-effect analyses.

Laser angioplasty

Five RCTs were included that compared laser angioplasty with PTA. Restenosis at 12-month follow-up was reported by one trial (Lammer *et al.*[68]), which found no significant treatment effect between laser and PTA (*Table 51*).

One study reported clinical success (Belli *et al.*[65,66]) measured by symptoms and peripheral pulses, and found a borderline significant trend favouring PTA over laser angioplasty (*Table 52*). Procedural complications were similar in laser and PTA groups (Belli *et al.*,[65,66] Lammer *et al.*,[68] Spies *et al.*,[69] Tobis *et al.*[70]), with the exception of dissection, which was significantly more frequent with laser angioplasty than with PTA (*Table 53*).

TABLE 49 Drug-coated balloon and clinical change

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	Clinical status of PTA patients	DCB analysed (*n*)	Clinical status of DCB patients	Comparative statistic
THUNDER[61–63]	6 months	Change in Rutherford category from baseline to follow-up (mean)	54	–1.9	48	–2.3	Reported as NS
FemPac[64]	6 months	Improvement in Rutherford category from baseline to follow-up	42	36% of patients improved	45	58% of patients improved	0.045
	18–24 months	Improvement in Rutherford category from baseline to follow-up	42	36% of patients improved	35	35% of patients improved	0.98

NS, non-significant.

TABLE 50 Drug-coated balloon and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	DCB analysed (*n*)	DCB patients with complications (%)	Comparative statistic
LEVANT I[59,60]	1 month	Adverse device effects	52	NR	49	NR	NS
THUNDER[61–63]	< 2 weeks	Embolic complication or thrombosis	54	5.6	48	4.2	
	6 months	Amputation	54	0	48	4.2	$p = 0.22$
	6 months	Death	54	2	48	4.2	$p = 0.59$
FemPac[64]	6 months	Major amputation of target leg, excluding toes	42	2	45	0	$p = 0.48$
	18–24 months	Major amputation of target leg, excluding toes	42	0	45	0	$p = 1.0$
	6 months	Death	42	0	45	2	$p = 1.0$
	18–24 months	Death	42	7	45	13	$p = 0.49$
	Perioperative	Adverse events: PE, skin rash, allergic reaction, temporary serum creatinine increase	42	2	45	2	

NR, not reported; NS, non-significant; PE, peripheral embolism.

TABLE 51 Laser and restenosis

Study	Follow-up	Definition of restenosis/ patency	PTA analysed (*n*)	PTA patients with restenosis (%)	Laser analysed (*n*)	Laser patients with restenosis (%)	Comparative statistic
Lammer *et al.* 1992[68]	12 months	Angiographic reobstruction was defined as an increase in diameter stenosis > 30%, an immediate post-PTA diameter stenosis of < 50% increasing to > 70% at follow-up, an increase in stenosis severity to ≤ 10% of predilation obstruction and a loss of > 50% of the gain in luminal diameter achieved by PTA	Unclear (77 across all groups)	50*	Unclear (77 across all groups)	Pulsed, 55; continuous, 64	NS

NS, non-significant.

TABLE 52 Laser and clinical success

Study	Follow-up	Definition of clinical status	PTA analysed (*n*)	Clinical status of PTA patients (%)	Laser analysed (*n*)	Clinical status of laser patients (%)
Belli *et al.* 1991[65,66]	1 month	Clinical success was defined as relief of symptoms and improved peripheral pulses	34	82	34	79
	3 months	a/a	34	72	34	56
	6 months	a/a	26	56	30	42
	12 months	a/a	24	47	26	39

a/a, as above.

TABLE 53 Laser and complications

Study	Follow-up	Definition of complication	PTA analysed (*n*)	PTA patients with complications (%)	Laser analysed (*n*)	Laser patients with complications (%)
Belli *et al.* 1991[65,66]	Perioperative	Small embolus	34	5.9	34	2.9
		Spasm	34	5.9	34	5.9
Lammer *et al.* 1992[68]	Perioperative	Embolus	39	7.7	Pulsed, *n* = 37; continuous, *n* = 40	Pulsed, 0; continuous, 5
		Dissection	39	15.4	Pulsed, *n* = 37; continuous, *n* = 40	Pulsed, 35.1; continuous, 20
		Perforation	39	7.7	Pulsed, *n* = 37; continuous, *n* = 40	Pulsed, 5.4; continuous, 5
		Spasm	39	2.6	Pulsed, *n* = 37; continuous, *n* = 40	Pulsed, 0; continuous, 0
Spies *et al.* 1990[69]	Perioperative	Embolus	13	0	14 procedures	7.1
Tobis *et al.* 1991[70]	Perioperative	Procedural complication; arterial wall perforation	20	5	20	15

Discussion

Data were available from RCTs for the technologies AMSs, SESs, BESs, DES, stent-graft, atherectomy, CB, cryoplasty, radiation by EVBT or EBRT, DCBs and laser angioplasty. The trials of atherectomy and laser angioplasty were older than those of other technologies. An ITT analysis was available from all trials, and treatment groups within trials were comparable at baseline. Of the 40 RCTs included, 20 included blinding for assessors for at least one of the study outcomes. Method of allocation concealment was considered adequate in 11 of the trials, with unclear reporting in the others. Most trials had small sample sizes and short durations.

Most trials reported measures of restenosis in terms of rates of restenosis or patency, although there was some variation of definitions of patency or restenosis, making direct comparison difficult. Direct comparison was also limited by differences in lesion types between trials. Most trials reported complications or adverse events for the procedures. Some trials reported the need for reintervention and clinical symptoms, and a few trials reported walking capacity or QoL. Not all outcomes were reported for all technologies. Most trials had a majority of IC participants with few CLI participants. Most of the trials recruited participants requiring angioplasty to the superficial femoral arteries or femoropopliteal arteries.

There was evidence of a significant benefit to reducing restenosis rates for SES, stent-graft, EVBT and DCB compared with PTA and for DES compared with BMS. In addition, significantly lower rates of the need for reintervention were reported for DCB, as well as a significant benefit in clinical stage for stent-graft, and a significant benefit to walking capacity at up to 1-year follow-up for SES compared with PTA. PTA was reported as having a significant advantage over AMS for restenosis rates, and over cryoplasty in terms of the need for reintervention.

No significant differences for restenosis rates between technologies and PTA were reported for BES, atherectomy, CB, cryoplasty, EBRT and laser angioplasty. There were also similar results between treatment groups in terms of the need for reintervention for AMS, SES, BES, DES, CB, EVBT and EBRT and in terms of measures of clinical symptoms for SES, DES, atherectomy, cryoplasty, EVBT, EBRT and DCB. Walking capacity did not differ significantly between PTA and BES or EVBT; nor was QoL found to differ significantly between SES and PTA. None of the studies reported significant differences between groups for procedural complications.

A Cochrane review of RCTs regarding stents for IC found no significant advantage for stents over PTA.[72] However, as this was restricted to trials of IC alone, the Cochrane review included only two RCTs of BESs[72] (Grimm *et al.*[21] and Vroegindeweij *et al.*[23]), meaning the lack of positive findings for BESs in this report concurs with the findings of the Cochrane review.[72] Another Cochrane review looked at RCT regarding stents for superficial femoral artery lesions[73] and reported a small but statistically significant improvement in patency at 6 months, but non-significant improvement at 12 and 24 months. This Cochrane review included six RCTs of BESs (Becquemin *et al.*,[19] Cejna *et al.*,[20] Grenacher 2004,[74] Grimm *et al.*,[21] Vroegindeweij *et al.*,[23] Zdanowski *et al.*[24]) and two RCTs (FAST,[14] ABSOLUTE[16–18]) of SESs.[73] A systematic review of stents in femoropopliteal lesions[75] found a non-significant trend favouring stents for restenosis rates; however, this was based on combining SES, BES and stent-graft trials.

The positive finding for SESs in this report concurs with ESC guidelines,[2] which recommend primary nitinol stenting as the first-line intervention for intermediate length, superficial femoral artery lesions. ESC guidelines[2] recommend that, for infrapopliteal arteries, stents are used where PTA has been suboptimal, although they refer to favourable outcomes for DES based on evidence from a non-randomised study. ESC guidelines also suggest that, owing to difficulties in producing RCTs for the rapidly developing endovascular treatment options, IC and CLI patients undergoing angioplasty should be entered into a clinical surveillance programme.[2]

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Searches

A systematic literature search was undertaken to identify economic evaluations of techniques used as an adjunct to, or as a replacement for, PTA in people with PAD.

The methods of the search strategy used (including inclusion and exclusion criteria) and databases searched are the same as those for the assessment of clinical effectiveness, as described in *Methods* in *Chapter 3*. Key details are reproduced in *Table 54*.

Results

The literature searches identified 1306 potentially relevant citations. Of these, only 102 appeared to relate to an economic evaluation comparing the use of PTA with an alternative in the treatment of PAD. In total, 16 full papers were screened, only one of which (Sculpher *et al.*[76]) met the inclusion criteria. The other 15 studies were excluded for being abstracts (five), being in a foreign language (two), relating to an excluded population (coronary; one) or having only an excluded comparator (seven). *Figure 22* shows the summary of the study selection and exclusion employed. The studies accepted were evaluated using both the Drummond–Jefferson quality assessment criteria and CHEC-list criteria (details of this evaluation are presented in *Appendix 6*).

As only one study was identified, the inclusion criteria were relaxed to also include bypass surgery (BS) as an intervention. This intervention was included because it was decided that BS should be considered as a possible second-line treatment (following failure of the initial treatment). The only other second-line treatment considered was PTA. This identified a further five economic evaluations (Hunink *et al.*,[77] de Vries *et al.*,[78] Holler *et al.*,[79] Muradin and Myriam Hunink,[80] Visser *et al.*[81]). In addition, two further economic evaluations were manually identified: the BASIL trial (Forbes *et al.*[82]) and the National Institute for Health and Care Excellence (NICE) cost-effectiveness analysis (CEA),[83] which is part of the draft NICE guidelines on lower limb peripheral arterial disease (released for consultation). Neither of these evaluations was available at the time of the original systematic review. The research team were aware of the pending NICE guidelines; when they were released for consultation, they were used to identify the journal article by Forbes *et al.*[82]

In two instances, two economic evaluations were generated based on the same underlying model. In the first instance, Muradin and Hunink[80] use the model of Hunink *et al.*[77] to look at the cost-effective price required for a hypothetical new endovascular device. In the second instance, Visser *et al.*[81] extended the economic evaluation of de Vries *et al.*[78] to include diagnostic imaging. In both instances the extended evaluations are not of relevance to this study and thus only the original evaluation is considered.

In total, six existing economic evaluations were used to inform this economic evaluation; they are briefly summarised below.

Hunink *et al.*[77]

- *Indication*: IC and CLI.
- *Lesion type*: stenosis and occlusion.
- *Site*: femoropopliteal.
- *Comparator*: PTA.
- *Interventions*: BS or no treatment.

TABLE 54 Inclusion criteria for the systematic review of economic evaluations

Study design	Cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis or cost–utility analysis
Population	Patients with PAD (any type)
Comparator	PTA
Interventions	BMSs, DESs, stent-grafts, atherectomy, cryoplasty, radiation therapy, CB, DEB, laser angioplasty
Outcome	Cost-effectiveness

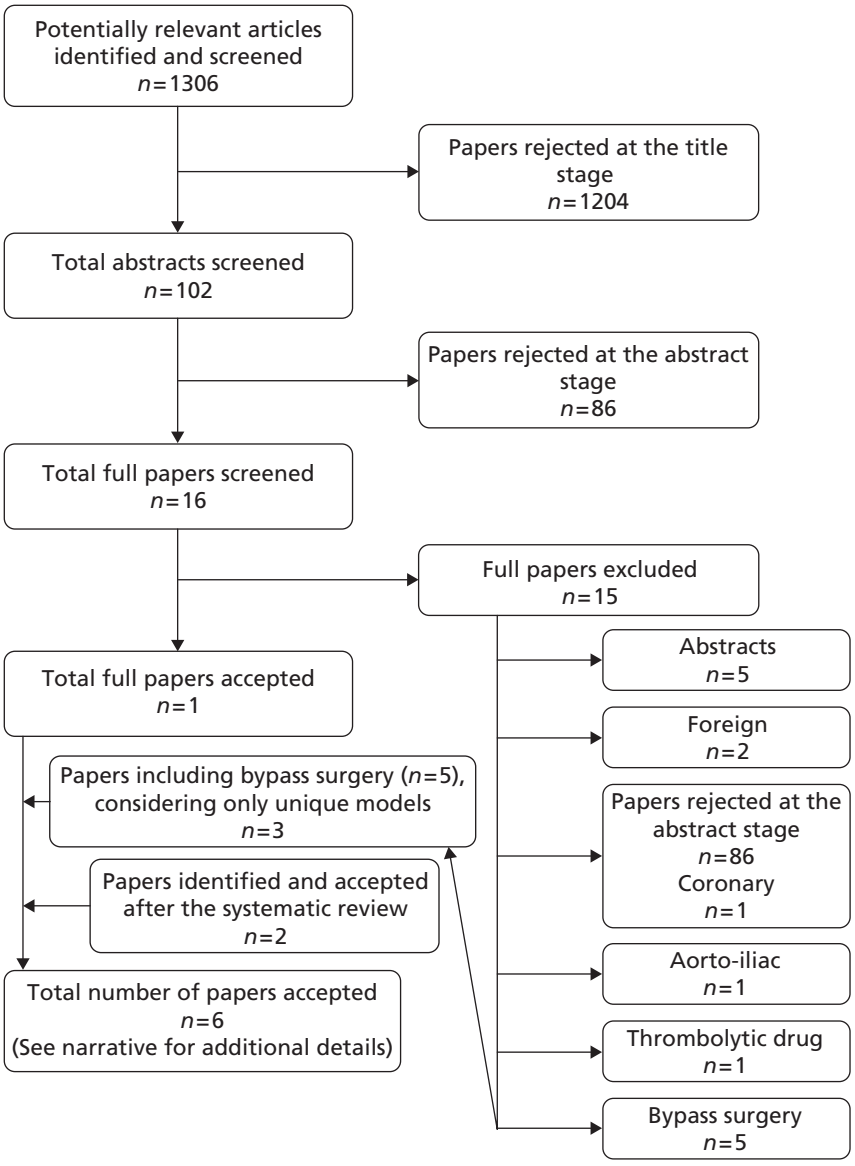

FIGURE 22 Summary of economic evaluation selection and exclusion.

- *Costs*: 1990 US dollars.
- *Health utilities*: Torrance multiattribute scale.

(1990 US dollars presented in Hunink *et al.*[77] These values were updated to 1999 US dollars in Muradin and Hunink.[80])

Together the comparator and interventions constitute three treatments. Six specific treatment strategies were compared. Initial PTA could be followed by any of the three treatments. Initial BS could be followed only by NT or graft revision. No treatment completed the strategies under consideration. A maximum of two treatments per patient were modelled.

The authors used a patient-level 'multistate transition model' using a lifetime horizon programmed in Borland C (Borland, Scotts Valley, CA, USA). The perspective was that of the health-care system. Input and results were disaggregated by lesion type and graft material. CLI was subdivided into 'rest pain' and 'necrosis'.

Costs for repeat procedures are assumed to be equal to the initial procedure cost. Annual follow-up costs are also provided, depending on whether or not the patient maintained patency, or if they had an amputation.

Quality of life was based on the Torrance multiattribute scale as valued by two vascular surgeons, two interventional radiologists and an internist. Utility values are based on the patient's indication, and are also altered if the patient receives successful treatment or if the patient receives an amputation. These states are further divided depending on whether or not major morbidity (see below) is present. Procedure-specific decrements are also applied.

Initial success and patency rates are based on a previous systematic review. Disease progression was not modelled. Operative mortality rates were based on 26 studies, and depended on the type of operation and whether or not the patient was 'high risk' – defined as being aged 65 years and over with CLI and/or documented coronary artery disease. Procedure-related complications were modelled as the development of non-fatal systemic morbidity (which includes major cardiopulmonary, renal or cerebrovascular complications). Long-term mortality was modelled as an excess per cent, based on the ABPI (2% above the annual risk for individuals with ABPI > 0.3, 12% above the annual risk for individuals with ABPI ≤ 0.3). For a sensitivity analysis, a RR of 3.1 is used, regardless of indication.

Based on an incremental cost-effectiveness ratio (ICER) threshold of US$50,000 per quality-adjusted life-year (QALY), the authors come to the following conclusions:

- Initial PTA is recommended for all patients with stenoses, and claudicants with occlusive lesions.
- Initial BS is recommended for patients with both CLI and occlusions.

The authors only presented selected results. QALYs gained range from 2.7 to 7.4 for stenosis and 2.6 to 7.0 for occlusions. Costs range from US$15,000 to US$43,000 for stenosis and US$24,000 to US$51,000 for occlusions.

A variety of univariate sensitivity analyses were performed, with most of the parameters varied according to observed ranges within the literature. Multiway sensitivity analyses considered 'optimistic' and 'pessimistic' scenarios. Results were found to be most sensitive to procedural mortality and morbidity rates.

Sculpher *et al.*[76]

- *Indication*: IC and CLI.
- *Lesion type*: occlusions.
- *Site*: not stated.
- *Comparator*: PTA.
- *Interventions*: PTA with laser-assisted PTA on acute failure.
- Costs: 1993/94 UK pounds.
- Health utilities: European Quality of Life-5 Dimensions (EQ-5D) used; SF-36 values also available.

(Intervention uses data from a study on disease in the femoropopliteal arteries.)

For this cost–utility analysis, a two-part model was used, with a decision tree for initial revascularisation outcomes; these outcomes are then used as the starting health states in a Markov model that employed a lifetime horizon. Only the decision tree explicitly modelled the effects of the intervention. With the exception of death, all probabilities in the decision tree were taken from a single RCT (Lammer *et al.*[68]). This RCT also showed that primary laser-assisted PTA was dominated by primary PTA, so this intervention was not considered.

If the initial operation (with or without laser assistance) failed, then patients may have BS and/or an amputation. There does not seem to be a limit on the number of BS operations that a patient may receive; in addition, patients with IC are able to receive repeat PTA (with or without laser assistance). Bilateral disease is not considered.

A crucial limitation concerning the cost-effectiveness data is that the cost-effectiveness of the laser when used as a secondary intervention (on immediate failure) is based on only seven patients. Long-term cost-effectiveness is based on a Markov model with a cycle length of 1 month, with a time horizon of 25 years. Disease progression was not modelled. General mortality is based on a Gompertz function, adjusted for an increased RR owing to having PAD (RR = 2 for IC and 3 for CLI). All other transition probabilities are independent of time and based on a mixture of published studies, an audit of patients' notes at John Radcliffe Hospital in Oxford (where a co-author worked) or the clinical judgement of one of the co-authors. The paper does not state which probabilities came from which source. Procedure-related mortality is dependent on indication (IC or CLI) for BS but not for PTA. The secondary use of the laser is assumed not to result in any procedure-related deaths. Procedure-related complications are not modelled.

Utility values were elicited for four health states (IC, CLI and amputation above/below the knee) using both the time trade-off (TTO) method and the EuroQol visual analogue scale (EQ-VAS). Values for successfully treated patients were assumed to equal one. Two samples were used during elicitation: one of 36 health-care professionals (with a 100% response rate), and a random sample of the public (size not stated). As the values elicited were very similar for the two samples, only the results from the latter are used. In the base case, TTO values were used, with EQ-VAS values used in a sensitivity analysis; this did not have a noticeable impact on the results.

Costs are broken down into one-off costs based on procedure type (with an additional cost of angiography for any procedures during the Markov model) and monthly costs based on health state (cured, IC, CLI, amputee). For one-off costs, a breakdown of inpatient and outpatient costs is presented.

For each indication, the numbers in each health state and the numbers receiving a repeat operation (PTA or BS) are presented in 5-yearly increments.

For IC, the secondary use of a laser increases life-years from 6.78 to 6.79 and QALYs from 5.78 to 5.87, while increasing cost from £3669 to £3929. This gives an ICER of £3040 per QALY.

For CLI, the secondary use of a laser increases life-years from 5.44 to 5.46 and QALYs from 4.40 to 4.46, while increasing cost from £8716 to £8823. This gives an ICER of £1180 per QALY.

Sensitivity analyses showed that the following uncertainties had the greatest effect on results:

- The proportion of patients 'cured' following a successful operation (assumed = 100%).
- Annual utilisation of the laser (affecting its cost per operation).
- The proportion of patients in whom CLI recurs after reocclusion (assumed = 100%).
- Patency rates following PTA among CLI patients.
- The effectiveness of the laser.

de Vries *et al.*[78]

- *Indication*: IC.
- *Lesion type*: stenosis and occlusion.
- *Site*: above tibia.
- *Comparator*: PTA.
- *Interventions*: exercise and bypass surgery.
- *Costs*: 1995 US dollars.
- *Health utilities*: EQ-5D.

The authors compared five different treatment strategies involving sequences of exercise and PTA. BS was also included as an option in some of the strategies when PTA was deemed to be unsuitable. Exercise is an excluded intervention in our research, so results for this are not discussed here. The study presented an in-depth breakdown of outcomes for PTA and BS, broken down by site and lesion type, which are discussed here.

The authors presented results at both the aortoiliac level and the femoropopliteal level; the latter are of interest for this report. Rates of procedural mortality and systemic complications are taken from Hunink *et al.*,[77] as previously described. In addition, de Vries *et al.*[78] also include rates for angiographic investigations. For an amputation, mortality rates are presented separately for patients below and above the age of 75 years; rates for systemic complications were assumed not to vary with age.

As regards patency data, only 2-year results are provided. These are broken down by indication and intervention (PTA or BS). For BS, there is a further subdivision by graft type and, for PTA, there is a further subdivision by lesion type. The values used for the femoropopliteal level are taken from Hunink *et al.*[77]

Health utility values for amputation and CLI are taken from Sculpher *et al.*[76] Values for IC and asymptomatic disease are taken from two other studies. Utility values associated with systemic complications are based on reported values for myocardial infarction survivors. Costs are taken from a mixture of published studies and the Medicare database. They are different from the costs used in any of the previous economic evaluations.

Holler *et al.*[79]

- *Indication*: CLI.
- *Lesion type*: occlusions. (Not entirely clear.)
- *Site*: not stated.
- *Comparator*: PTA.
- *Interventions*: BS, prostaglandin E_1 (PGEI) or no treatment.
- *Costs*: euros, year not stated.
- *Health utilities*: EQ-5D.

This study looked at treatment strategies, with patients able to experience a maximum of two treatments. As PGE1 is an excluded intervention, only the information provided for PTA and BS are considered.

Cost-effectiveness data were based on a systematic review of German- and English-language literature. Values from studies were weighted by their sample size and the median value was taken. The probability of staying within the same health state (CLI or IC) is calculated based on the logical constraint that transition probabilities must sum to one. For patients with IC, the probability of dying was assumed to be the same as that for a 70-year-old German male (taken from life tables). Mortality rates vary depending on the initial treatment, unless a patient receives an amputation, in which case the probability of mortality is independent of initial treatment. It is assumed that patients with IC do not have an amputation.

Cost data are based on a survey of a patient sample (time period and setting not stated), which included 147 patients with IC, 92 with CLI and 40 who had had an amputation. Treatment costs are applied on a yearly basis, and are different for the two indications. The cost of an amputation is independent of the initial treatment.

Data on QoL are based on the EQ-5D questionnaire given to a sample of 280 patients with PAD. Separate values are given depending on initial treatment and indication. As with cost, the value for having had an amputation is independent of the initial treatment.

The BASIL trial (Forbes *et al.*[82])

- *Indication*: Severe ischaemia. (CLI, but without the restriction that ABPI < 50 mmHg.)
- *Lesion type*: stenosis and occlusion.
- *Site*: infrainguinal.
- *Comparator*: PTA.
- *Interventions*: BS.
- *Costs*: 2006/07 US dollars.
- *Health utilities*: EQ-5D used; SF-36 values also available.

This is the only economic evaluation that was conducted alongside a clinical trial (ISRCTN 45398889). Detailed 12-month outcomes for the BASIL trial have been published (Bradbury *et al.*[84]). Data from further follow-up have been presented in a number of publications (Forbes *et al.*,[82] Bradbury *et al.*[85–88]).

The authors note that their inclusion criteria are different from the technical definition of CLI, but it was felt by our clinical expert (JAM) that they reflect CLI as defined in every-day practice, and thus the results of the BASIL trial are assumed for this evaluation to apply to CLI patients.

Between August 1999 and June 2004, the BASIL trial randomised 452 patients to a treatment strategy of either PTA first or BS first. There were a small number of crossovers; the economic evaluation uses an ITT analysis.

All of the data used in the model come from the BASIL trial. QoL was measured using the Vascular Quality of Life Questionnaire, the generic SF-36 health survey and EQ-5D. The EQ-5D is used within the economic evaluation. Cost data are based on hospital-related activity only. Both costs and utilities are discounted at 3.5% per annum.

Statistical regression methods were used to calculate incremental costs and incremental QALYs, with non-parametric bootstrapping used to assess uncertainty. As the costs data exhibited a heavy skew, the results from three different regression methods were reported. These are reproduced in *Table 55*, along with the corresponding ICERs. Although the results are not presented in UK pounds, it is clear that BS would not be considered cost-effective by decision-makers such as NICE using any of the three methods given current, and historic, exchange rates.

TABLE 55 Cost-effectiveness results from the BASIL trial

BS vs. PTA[a]	Least squares	Robust regression	Median regression
Incremental costs	5521	9132	11,507
Incremental QALYs	0.03	0.03	0.03
Incremental cost per QALY	184,492	304,400	383,567

2006/7 US dollars. $n = 448$.
a Positive values indicate that surgery is more costly/more effective.

The National Institute for Health and Care Excellence cost-effectiveness analysis[83]

- *Indication*: IC.
- *Lesion type*: stenosis and occlusion.
- *Site*: iliac/femoropopliteal. (Analysed separately; only the latter is considered here.)
- *Comparator*: PTA (with selective stenting).
- *Interventions*: PTA (with primary stenting), unsupervised exercise, supervised exercise, BS.
- *Costs*: 2009/10 UK pounds.
- *Health utilities*: EQ-5D.

This economic evaluation considered two-stage treatment strategies. BS is considered only as a second-line treatment (giving four different first-line treatments). Neither PTA with primary stenting nor unsupervised exercise is considered as a second-line treatment (giving three different second-line treatments), resulting in (3 × 4) 12 different treatment strategies. A 13th strategy of PTA with selective stenting and supervised exercise (and no secondary treatment) is also evaluated.

A Markov model is employed using 3-monthly cycles. The analysis takes the perspectives of the NHS and personal social services. Both costs and QALYs are discounted at 3.5% per year.

Procedural costs (for PTA, BS and amputation) were taken from 2009/10 NHS Reference Costs.[89] For PTA and BS, the proportion of procedures that were elective or non-elective was based on expert opinion, with slight differences between the initial and repeat procedures. Ongoing costs were modelled only for patients who had undergone an amputation. Costs incurred in the first year were different from those incurred in follow-up years; both were based on a mixture of expert opinion and the 2010 Personal Social Services Research Unit.[90]

Quality of life data for patients with IC were based on the values reported by the studies included in the evaluation. Only reports of EQ-5D or SF-36 (when sufficient data were available for them to be mapped to EQ-5D) were included, the final values used being the average of the included values. Data for patients with CLI or an amputation were taken from Sculpher *et al.*[76]

It is assumed that PTA does not affect subsequent rates of mortality or morbidity and that repeat procedures have the same effectiveness as the initial procedure. Failure was taken to include both a loss of patency and symptom deterioration requiring reintervention. Perioperative complications, amputations and deaths were taken from an audit reported by the Royal College of Surgeon's of England.[91] For patients with IC, there were no amputations or deaths. Based on expert opinion, these probabilities were felt to be non-zero, and therefore values of 0.5 amputations and 0.5 deaths were added to the numerator (and subtracted from the denominator) of the audit. Rates of failure and the amount of patients needing a reintervention are based on expert opinion and are modelled as fixed (time-invariant) amounts. The requirement for reintervention is assumed to vary depending on lesion type (stenosis or occlusion); the prevalence of lesions among patients with IC is based on expert opinion.

Progression to CLI was assumed to be independent of treatment strategy, with a 3-month probability of 0.1% (based on a value of 2% over 5 years). It was assumed that 25% of patients with CLI will receive an amputation as a primary intervention and that 25% will die each year (modelled by 3-month probabilities of 6.9% and 3.9%, respectively).

For patients with IC and femoropopliteal disease, the NICE CEA concluded that there were only four treatment strategies that were neither dominated nor extendedly dominated. These are detailed in *Table 56*.

TABLE 56 Cost-effectiveness results from the NICE CEA

Strategy	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALYs	Cost-effectiveness (£)
UE | SE	4059	Baseline	4.374	Baseline	Baseline
SE | SE	4276	217	4.466	0.092	2362
SE | PTA	5378	1102	4.534	0.069	16,024
PTA | PTA	6603	1225	4.572	0.037	32,898

SE, supervised exercise; UE, unsupervised exercise.
A 'I' divides initial and secondary treatment.
All the listed PTA procedures are with secondary stenting.

Summary

There are currently no economic evaluations that include all of the relevant interventions considered in this report. There is only one economic evaluation (Sculpher *et al.*[76]) that includes any of the relevant interventions, but this includes only a subgroup of the relevant population. A de novo economic evaluation is therefore required.

Independent economic assessment

Methods

This section provides details of a model developed by the assessment team and used to evaluate the cost-effectiveness of enhancements to angioplasty in the treatment of PAD.

Model description

A discrete-event simulation model (DESM) was developed in Simul8© 17.0 (Simul8 Corporation, Boston, MA, USA) to determine the cost-effectiveness of each enhancement compared with conventional angioplasty alone. A DESM was used in preference to a state-transition model primarily because of the large number of patient characteristics that required tracking over time. A DESM also more appropriately models time to event based on stochastic distributions.

Patient population

The population considered was patients with symptomatic PAD suitable for endovascular treatment for disease distal to the inguinal ligament. A lifetime horizon was used.

The patient population was subdivided into those with IC and those with CLI. The clinical classifications of these subgroups are presented in *Table 57*.

Differences in anatomical features were not explicitly modelled. These include features such as proximity to bifurcations, stenosis versus complete occlusions and length of occlusion. These differences were not considered because of a lack of available evidence for the comparator and interventions.

With two exceptions, the effectiveness of all interventions was evaluated in the femoropopliteal arteries. The exceptions were BMSs, which were evaluated in both the femoropopliteal and infrapopliteal arteries, and sirolimus-eluting stents, which were evaluated in the infrapopliteal arteries. As base-case data (for PTA) were available only for the femoropopliteal arteries, the results of evaluations considering the infrapopliteal arteries should be viewed as exploratory.

TABLE 57 Clinical classifications of PAD used in this assessment

Clinical stage (indication)	Fontaine classification	Rutherford classification		Classification used in this evaluation
		Grade	Category	
Asymptomatic	Stage I	0	0	Asymptomatic
Mild claudication	Stage II	I	1	IC
Moderate claudication			2	
Severe claudication			3	
Ischaemic rest pain	Stage III	II	4	CLI
Minor tissue loss	Stage IV	III	5	
Major tissue loss			6	

Interventions and comparators

The base-case analysis considers patients receiving conventional PTA with secondary bare-metal stenting if immediate (acute) failure occurs. Acute failure is defined as either failure of the operation or restenosis within 30 days of the operation. The interventions considered for this research are listed and described in Clinical effectiveness results in *Chapter 3* on clinical effectiveness. Based on the results of the clinical effectiveness research, it was decided that there would be little value in including some of the interventions in the economic evaluation, as they were likely to be dominated by either the base case or a comparator (as they were less effective and likely to be more costly). Explicit costs for these comparators were not calculated; instead, it was noted that, because they are all enhancements to PTA, they will be more expensive than PTA. Hence, the following interventions were immediately excluded in the assessment of cost-effectiveness (the sections describing their clinical effectiveness can be found in *Clinical effectiveness results* in *Chapter 3*):

- AMSs
- atherectomy
- EBRT
- laser angioplasty.

No distinction was made between SESs and BESs, as (in general) use of the former has replaced use of the latter. As with the NICE CEA, the use of either of these stents is referred to as use of BMSs. CBs were not included in the economic evaluation, as they were recalled by their manufacturer because of a potential shaft separation of the catheter during operation (www.fda.gov/MedicalDevices/Safety/RecallsCorrectionsRemovals/ListofRecalls/ucm062951.htm referenced in White and Grey[92]).

The two patient populations (IC and CLI) are analysed separately. Owing to a lack of evidence, the treatment effect of each intervention is assumed to be the same for the two patient populations. It should be noted that in most trials the majority of participants have IC. Natural history data for the two patient populations (for example, patency rates for the comparator and time to amputation) vary. The effectiveness of BS (modelled as a second-line treatment) also varies by patient population.

Each intervention may be used as the initial treatment instead of (or with) PTA, with secondary stenting if required. In addition, the use of conventional PTA with secondary DESs (paclitaxel) was also reported in one study (Dake *et al.*[71]). Because of this, paclitaxel-eluting stents were included as two interventions: one for their use as the initial treatment (no secondary stenting was required, so no distinction is made for this intervention) and one for their use only on acute failure.

To summarise, the base-case comparator and included interventions in the femoropopliteal arteries are:

- PTA with secondary BMSs (*base case*)
- primary BMSs
- PTA using a DCB
- primary DESs (paclitaxel)
- PTA with secondary DESs (paclitaxel)
- stent-graft
- cryoplasty
- EVBT.

In the infrapopliteal arteries they are:

- PTA with secondary BMSs (*base case*)
- primary BMSs
- primary DESs (sirolimus).

Outcomes

The main model outcome is the incremental cost per QALY gained. A secondary outcome of incremental cost per life-year gained is also presented.

Model structure

The structure of the decision model is presented in *Figure 23*. Events are modelled such that each event triggers changes in a patient's health state. Patients can enter the model with either one leg or two; if the patient has two legs, the status of both legs is modelled. For simplicity, on receiving an amputation (to either leg), the only possible events for a patient are procedure-related death or general mortality. Patients can enter the model with either IC or CLI; these two groups are modelled and analysed separately.

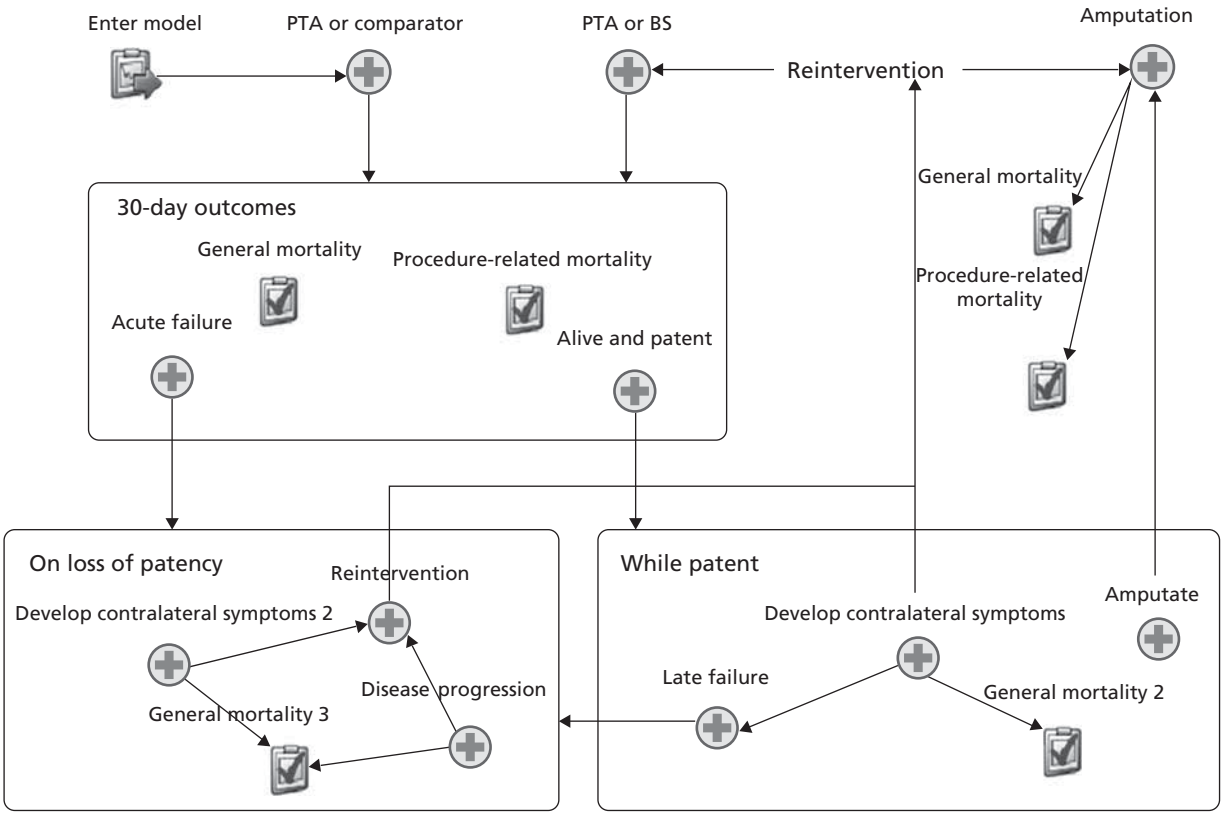

FIGURE 23 Diagram of the structure of the decision model.

For illustrative purposes, *Figure 23* has been depicted with three groups of events, entitled '30-day outcomes', 'While patent' and 'On loss of patency'. On entering a group, the time to each event (or the probability that it occurs) is calculated, with the event occurring first being the next simulated event.

For example, upon entering the 'On loss of patency' group, the time to develop contralateral symptoms and experience disease progression and time to general mortality are all calculated. The probabilities of requiring and receiving a reintervention are also calculated and compared with random numbers (drawn from the uniform distribution on [0,1]) to see if they occur. If a patient were modelled as receiving a reoperation, this is given a time to event of 1 week. The event with the shortest time to occurrence then becomes the next simulated event.

In the following discussion, a reoperation refers to receiving PTA or BS only; it does not include receiving an amputation. For the purposes of brevity, the term 'reoperation' is also used to include the situation in which an individual receives an operation on a contra-lateral limb while the first limb remains asymptomatic.

The structure of the model from the perspective of a patient is presented in *Figure 24*, which shows the health states modelled. Patients enter the model with either IC or CLI. It is assumed that after a successful operation patients move into the asymptomatic health state, where they remain until they either die or suffer a loss of patency (failure). If a failure occurs, then, as with Sculpher *et al.*[76] and Hunink *et al.*,[77] it is assumed that the patient returns to their health status prior to the operation.

As with Sculpher *et al.*[76] and Hunink *et al.*[77] it is assumed that spontaneous improvement from CLI to IC (in the absence of an operation) does not occur. It should be noted that, if a patient's operation fails (at any time), then they return to their health state prior to the operation, not their health state when entering the model. This affects IC patients; if they progress to CLI, then it is not possible for them to enter the IC health state again.

Patients may also develop contralateral symptoms (PAD in their other leg), so, for example, a patient with CLI in one leg may also develop IC in their other leg. As the status of each leg is tracked separately, *Figure 24* actually represents the health states (and permissible transitions) for each leg.

Patients enter the model when undergoing their initial endovascular operation (which varies depending on the intervention or comparator considered). During the 30 days following an operation (the perioperative period), the following events may occur:

1. mortality attributable to the intervention or comparator
2. mortality not attributable to the intervention or comparator (general mortality)
3. acute failure (loss of patency)
4. success; defined as none of the above.

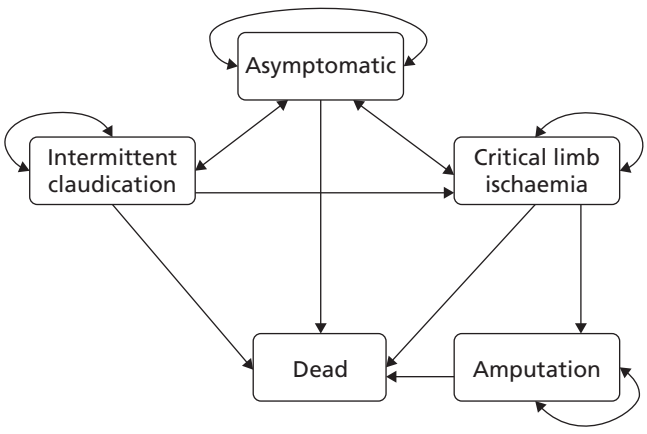

FIGURE 24 Diagram of the health states modelled.

In addition, there is a probability of the patient developing a complication during the perioperative period. This is assumed to result in a (ongoing) utility decrement and cost, but it does not affect subsequent transitions, so it is not modelled as a separate event. Once a patient develops a complication, it is assumed that they remain with this complication for life.

General mortality is taken from life tables.[93] Mortality attributable to the intervention or comparator is not removed from the life tables, as the numbers are small. The life tables are adjusted to reflect an increased RR of dying due to having PAD. Separate RRs are modelled for IC and CLI. It is assumed that this excess risk remains even if a patient experiences a successful operation, as it is based on the patient's disease prior to the operation.

If the initial operation is a success, then the patient moves into the asymptomatic PAD health state, and postprocedural events-while-patent are modelled:

1. Late failure (loss of patency).
2. Develop contralateral symptoms: these may be either IC or CLI and are influenced by the patient's disease prior to their last operation.
3. Amputation: this is the risk of amputation owing to progression of disease in the limb (not owing to the result of loss of patency at the treated site).
4. General mortality.

If a patient suffers a failure (loss of patency) at any time point, then the following events are possible:

1. A reintervention (PTA, BS or amputation) is required and received.
2. The patient's disease progresses to CLI. (This is applicable only for patients with IC.)
3. The patient develops contralateral symptoms (as previously described).
4. General mortality.

There are three situations for which a patient may require a reoperation:

1. After loss of patency, a proportion of patients are modelled as experiencing the (immediate) return of symptoms. If symptoms do return, then the patient requires a reintervention.
2. The patient develops contralateral symptoms.
3. The patient experiences disease progression (to CLI).

It should be noted that loss of patency on its own is not sufficient to require a reoperation; the patient must also experience a return of symptoms. In contrast, the data used to inform the transition probabilities for developing contralateral disease or disease progression both imply that a reoperation will be required as a result of the event.

If patency is lost, the probability of experiencing a return of symptoms is modelled as an immediate event and is independent of the type of operation received. It does, however, depend on the patient's health state prior to the operation. If symptoms do return, then the patient moves into their health state prior to the operation. If symptoms do not return (but patency is lost), then patients with prior IC remain in the asymptomatic health state, but patients with prior CLI return to the CLI health state. This is because there is evidence to suggest that alternative forms of therapy (exercise and pharmacotherapy) are effective in improving the QoL of patients with IC but not patients with CLI.[83,94]

There are three situations for which a patient may require a reoperation but not receive it (for further details, see the section 'Probability of reintervention following failure'):

1. The patient dies before the operation is received.
2. The assumed maximum number of permissible reoperations (two) has already been reached.
3. The patient's lesion is not suitable for reoperation.

Patients may receive an amputation at any time, with higher rates of amputation observed for patients with CLI. It is assumed that the low risk of amputation for those with IC is a result of the progression of disease, rather than being directly attributable to restenosis at the site of the original lesion causing IC. The model does not distinguish between below-knee and above-knee amputations but uses average costs and utilities for amputation based upon the proportions in the BASIL Trial.[84]

Time horizon, perspective and discounting

The time horizon of the model was 100 years to ensure that all differences in costs and benefits are captured within the model. The analysis takes the perspectives of the NHS and personal social services. Both costs and QALYs were discounted at a rate of 3.5% per year.

Assessment of cost-effectiveness

The main results are an estimate of the lifetime costs and total QALYs of each intervention and the comparator, and the ICERs, presented as cost per QALY gained and cost per life-year gained. Results are reported separately for the IC and CLI populations. In incremental analyses, one intervention may be dominated or extendedly dominated by another. Dominance is defined to occur when an intervention is less effective and more expensive than another intervention. Extended dominance is defined to occur when the ICER for a given treatment alternative is higher than that of the next most effective intervention.[95] To estimate costs and QALYs, 1000 probabilistic sensitivity analysis runs were implemented. A cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness plane are included to give a measure of the uncertainty incorporated into the model. To explore the sensitivity of the model results to parameter values and assumptions, a range of univariate sensitivity analyses were performed. These sensitivity analyses are:

- exploring the sensitivity of the results to different starting ages
- no amputation-related costs
- assume no intervention effect except for lower reintervention rates
- results for the infrapopliteal arteries.

Estimate of base-case model parameters

Details of the parameters used, their distributions and their sources are discussed on the following pages and summarised in *Tables 58–61*. Additional details are provided in *Appendix 7*. For the probabilistic sensitivity analyses, all parameters were independently sampled.

Starting age

The starting age was based on data reported from the Swedish Vascular Registry,[96] which was the only identified source that gave stratified estimates by indication (IC or CLI). The average (mean) age of a patient with IC receiving PTA was 66 years; for patients with CLI, the average age was 74 years. For comparison, where economic evaluations use (or state) their starting ages, for IC they range from 60 (de Vries *et al.*[78]) to 67 (NICE CEA[83]). Neither Sculpher *et al.*[76] nor Hunink *et al.*[77] stratify their starting age by indication, both use a value of 65 years. Starting/average ages for CLI patients are not stated in the Holler *et al.*[79] and BASIL trials.[82]

Starting age was not varied in probabilistic sensitivity analysis; the sensitivity of the base-case results to starting age was explored in a sensitivity analysis. For this, the variation reported in the Swedish Vascular Registry data[96] was used to estimate a plausible range of ages. For patients with IC, a standard deviation of 10.4 about the mean of 66 was reported. For patients with CLI, a standard deviation of 9.3 about the mean of 74 was reported.

General mortality and excess risk

Patients with PAD were assumed to be at greater risk of general mortality than patients without PAD. In the majority of economic evaluations, this increased mortality was modelled as a RR, although the values employed, or suggested by the literature, can vary substantially. Further details are provided in *Appendix 7*.

TABLE 58 Effectiveness data, specific to patients with IC, used in the economic analysis

Parameter	Value	Range used in probabilistic sensitivity analysis	Source
Starting age	66	Fixed	Bergqvist *et al.* 1998[96]
Mortality: RR (compared to general population)	3.1	Fixed	Criqui *et al.* 1992[97]
PTA failure			
Perioperative period	6.6%	Beta(42,592)	Hunink *et al.* 1994[98]
Year 1	20.7%	Beta(115,443)	Hunink *et al.* 1994[98]
After year 1	Weibull (1.415, 17.923)	Only varying beta parameter: Beta(5.35,1.65) – scaled to be between 9.97 and 20.38	Hunink *et al.* 1994[98]
Complications during PTA[a]	0.51%	Beta(4.29,841)[a]	Axisa *et al.* 2002[91]
30-day mortality following PTA	0.2%[b]	Log-normal[ln(0.2),1.30]	Hunink *et al.* 1995[77]
BS failure			
Perioperative period	Fixed probability (0%)	Beta(0.5,1194.5)	Hunink *et al.* 1994[98]
Post-perioperative period	Weibull (0.612, 59.607)	Only varying beta parameter: Beta(5.35,1.65) – scaled to be between 33.17 and 67.77[d]	Hunink *et al.* 1994[98]
30-day mortality following BS	0.8%[b]	Log-normal(ln[0.8],0.70)	Hunink *et al.* 1995[77]
Probability of requiring reintervention following failure[c]	28.27%	Beta(62.44,160.56)	NICE CEA 2012[83]
Probability of not being suitable for a reintervention	5%	Beta(5,95)[d]	de Vries *et al.* 2002[78]
Time to amputation	Exponential (400)	Exponential parameter varied by ± 20%[d]	TASC-II,[99] ACC/AHA[100]
Annual rate of progression to CLI	Exponential (28.65)	Exponential parameter varied by ± 20%[d]	Sculpher *et al.* 1996[76]

a Conditional on the corresponding values for CLI (see *Appendix 7* for more details).
b If a patient develops a complication or is aged over 65 years, then his or her mortality owing to either PTA or BS is the same as a patient with CLI.
c Following failure during the perioperative period, the probability of reintervention is 100% and it is always BS (or the comparator, if applicable).
d Arbitrary variation.

Relative risks for IC (compared with the general population) vary from 1.6 to 4. The value of 3.1 quoted by Criqui *et al.*[97] is used for the base case; this source was also used by Hunink *et al.*[77] and in the NICE CEA.[83] It is also very similar to the value of 3.14 used by de Vries *et al.*[78]

To ensure that patients with CLI do not have a lower probability of death than patients with IC, the RR of mortality for CLI is compared to that for IC. Two economic evaluations (de Vries *et al.*[78] and

TABLE 59 Effectiveness data, specific to patients with CLI, used in the economic analysis

Parameter	Value	Range used in probabilistic sensitivity analysis	Source
Starting age	74	Fixed	Bergqvist *et al.* 1998[96]
Mortality: RR (compared to patients with IC)	2	Fixed	Norgren *et al.* 2007[99]
PTA failure			
Perioperative period	23.9%	Beta(88,281)	Hunink *et al.* 1994[98]
Year 1	59.5%	Beta(193,131)	Hunink *et al.* 1994[98]
After year 1	Weibull (1.369, 6.871)	Only varying beta parameter: Beta (0.75,6.25) – scaled to be between 6.12 and 13.12	Hunink *et al.* 1994[98]
Complications during PTA	6.75%	Beta(16,221)	Bradbury *et al.* 2005[84]
30-day mortality following PTA	3.2%	Log-normal(ln[3.2],1)	Hunink *et al.* 1995[77]
BS failure			
Perioperative period	Fixed probability (0%)	Beta(0.5,1194.5)	Hunink *et al.* 1994[98]
Post-perioperative period	Weibull (0.608, 21.101)	Only varying beta parameter: Beta (0.75,6.25) – scaled to be between 18.81 and 40.30[c]	Hunink *et al.* 1994[98]
30-day mortality following BS	4.7%	Log-normal(ln[4.7],0.71)	Hunink *et al.* 1995[77]
Probability of requiring reintervention following failure[a]	72.7%	Beta(72,27)	Bradbury *et al.*, 2005[84] Hunink *et al.* 1994[98]
Probability of not being suitable for a reintervention[b]	1.55%	Beta(7,445)	Bradbury *et al.* 2005[84]
Time to amputation			
Within first 2 years	Weibull (0.536, 7.239)	Only varying beta parameter: Beta (0.75,6.25) – scaled to be between 6.45 and 13.82[c]	Bradbury *et al.* 2010[86]
After 2 years	Exponential (4.86)	Exponential parameter varied by ± 20%[c]	Bradbury *et al.* 2010[86]

a Following failure during the perioperative period, the probability of reintervention is 100% and it is always BS (or the comparator, if applicable).
b Based on the probability of not being suitable for any initial intervention, following randomisation.
c Arbitrary variation.

Hunink *et al.*[77]) assume that this RR is 0; other values reported imply that the RR may be as high as 2.8. For the base case, a RR of 2 is used [based on data presented in the TASC-II (Trans-Atlantic Inter-Society Consensus II) guidelines (Norgren *et al.*[99])].

The RRs were included in the model by modifying 2009/10 UK life tables.[93]

For the majority of the economic evaluations, it is not clear whether a successful operation reduces or removes any of this excess risk. The NICE CEA[83] assumes that it does not reduce the risk at all, a view shared by our clinical expert (JAM). Hence, RRs after an operation (including amputation) remain the same

TABLE 60 Effectiveness data, applicable to all patients, used in the economic analysis

Parameter	Value	Range used in probabilistic sensitivity analysis	Source
RR of complications (BS vs. PTA)	1.80	Log-normal(ln[1.80],0.09)	Bradbury *et al.* 2005[84]
Mortality during amputation			
Age < 75	9.8%	Normal(9.8,0.011)	de Vries *et al.* 2002[78]
Age ≥ 75	14.7%	Normal(14.7,0.017)	de Vries *et al.* 2002[78]
Annual rate of developing contralateral disease	Exponential (16.42)	Exponential parameter varied by ± 20%[a]	de Vries *et al.* 1998[78]
Probability that contralateral disease is CLI	Patient has IC: 10%	Beta(15,135)	de Vries *et al.* 2002[78]
	Patient has CLI: 67%	Beta(257,126)	de Vries *et al.* 2002[78]

a Arbitrary variation.

TABLE 61 Data on health-related QoL (as measured by EQ-5D) and costs (2009/10 UK pounds) used in the economic analysis

Parameter	Value	Range used in probabilistic sensitivity analysis	Source
QoL data			
IC (requiring intervention)	0.70	Normal(0.70,0.23/280)	Sculpher *et al.* 1996[76]
CLI (any)	0.35	Normal(0.35,0.23/280)	Sculpher *et al.* 1996[76]
Above-knee amputation	0.20	Normal(0.20,0.22/280)	Sculpher *et al.* 1996[76]
Below-knee amputation	0.61	Normal(0.61,0.20/280)	Sculpher *et al.* 1996[76]
Proportion of amputations above knee	31.7%	Normal(0.70,0.23/280)	Bradbury *et al.* 2005[84]
Asymptomatic[a]	Age-matched UK population norms	Fixed	Ara and Brazier 2010[101]
Systemic complication[b]	0.72	Log-normal(ln[0.72],0.10)	de Vries *et al* (2002)[78]
Costs data			
PTA – no complications	3661	Normal(3661,581)	NICE CEA 2012[83]
PTA – with complications	9367	Normal(9367,3079)	NICE CEA 2012[83]
BS – no complications	5988	Normal(5988,665)	NICE CEA 2012[83]
BS – with complications	7139	Normal(7139,882)	NICE CEA 2012[83]
Amputation – operation	9224	Normal(9224,923)	NICE CEA 2012[83]
Angiography – no complications	2169	Normal(2169,380)	NHS reference costs 2009/10[89]

TABLE 61 Data on health-related QoL (as measured by EQ-5D) and costs (2009/10 UK pounds) used in the economic analysis (*continued*)

Parameter	Value	Range used in probabilistic sensitivity analysis	Source
Angiography – with complications	6270	Normal(6270,1205)	NHS reference costs 2009/10[89]
Monthly costs – IC	102	Normal(305,40.61)/3	[c]Sculpher *et al.* 1996[76]
Monthly costs – CLI	321	Normal(305,40.61) + Normal (14.56,1.13) × 13/12	[c]Sculpher *et al.* 1996[76]
Monthly costs – amputee	1958.5	Gamma(400,50.756)	NICE CEA 2012[83]
Monthly costs – complication	141	Fixed	NICE CEA 2012[83]

a After a successful operation. Also includes IC not requiring an intervention.
b This is a multiplicative effect.
c Updated with NHS reference costs 2009/10.

as before the operation. It should be noted that this is a potential limitation; for example, for patients with CLI, successful treatment should remove some of the effects related to ischaemia of the limb.

Percutaneous transluminal balloon angioplasty failure

The meta-analysis of Hunink *et al.*[98] is employed in this evaluation; it was also used in four of the six economic evaluations. Of the alternatives, the NICE CEA[83] bases its value on expert opinion and uses a fixed annual rate, whereas the BASIL trial[82] reports failures only at 1 and 3 years. Further details of the Hunink *et al.*[98] meta-analysis are presented in *Appendix 7*.

Failure is defined as loss of patency; estimated failure rates over time are reproduced in *Figure 25*. To improve fit, failure during the perioperative period is modelled as a probability, as is failure during the first year (conditional on not failing during the perioperative period). Failure after the first year is modelled using a Weibull distribution (conditional on not failing during the first year).

It should be noted that, if PTA fails during the perioperative period, then it is assumed that BS is always required and received. This assumption was employed in the economic evaluation of Hunink *et al.*,[77] and is used to reflect the fact that failures during the perioperative period usually indicate that repeat PTA would not be feasible (but it may be for longer-term failure).

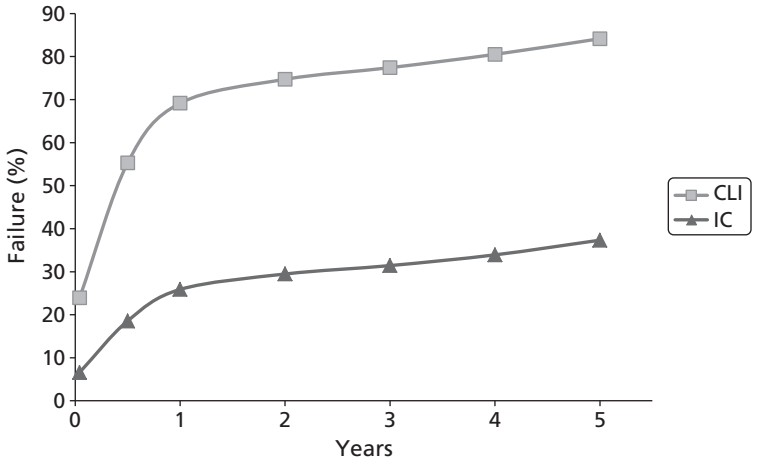

FIGURE 25 Percutaneous transluminal balloon angioplasty; cumulative failure rates over time for the two patient populations. Based on the meta-analysis of Hunink *et al.*[98]

30-day mortality following percutaneous transluminal balloon angioplasty or bypass surgery

Hunink *et al.*[77] provide the only economic evaluation to stratify mortality rates by patient status; this stratification is used within the model. Patients are deemed to be at 'high risk' of mortality if they are aged over 65, if they have a complication (as defined below) or if they have CLI; otherwise, they are at 'low risk' of mortality. High-risk patients have a probability of 30-day mortality following PTA of 3.2% and following BS of 4.7%. For low-risk patients, these values are 0.2% and 0.8%, respectively. It should be noted that, as the starting age of patients with IC is 65 years, all patients in the base case start with a high risk of mortality. The range of alternatives reported by Hunink *et al.*[77] is used to model uncertainty in these probabilities.

Complications during percutaneous transluminal balloon angioplasty or bypass surgery

A complication is defined as a non-fatal systemic complication (such as stroke, myocardial infarction and renal failure). For PTA, the BASIL trial (Bradbury *et al.*[84]) is used to estimate the probability of a complication for the CLI population (6.75%), whereas the Royal College of Surgeon's audit (Axisa *et al.*[91]) is used for the IC population. These two sources are used because they reflect observed rates of complications. Axisa *et al.*[91] do not break down the complications by IC or CLI status, but the number of operations is broken down. This information is used with data from the BASIL trial[84] to estimate a rate for IC (0.51%). For more details, see *Appendix 7*.

The number of complications reported by these two studies is reproduced in *Table 62*.

Estimates of complications during BS were modelled using a RR of 1.80, taken from the BASIL trial.[84] Although these data only relate to patients with CLI, they were used as it was felt that they provided the most plausible estimates. See *Appendix 7* for more details.

Bypass surgery failure

This is modelled using the same meta-analysis as was used to model PTA failure.[98] This source was also used in four of the six economic evaluations. Of the alternatives, the NICE CEA[83] did not model BS failure, and the BASIL trial[84] reports failures only at 1 and 3 years.

As with PTA, life table estimates of patency for patients with IC and stenosis were presented. For BS, there was no statistically significant difference in patency by lesion type (hazard ratio not reported), so only the RR associated with having CLI was employed. The results are presented in *Figure 26*.

The meta-analysis[98] also found that there was no difference between above-knee and below-knee operations, but that the type of graft material used affected the operation (with separate life tables presented for different graft types). Values for saphenous vein bypass are used in this analysis for two reasons:

- This type of operation was the most frequent in the BASIL trial (76%; 136/179).[84]
- The NICE guidelines for PAD recommend using this type of graft when possible.[83]

It should be noted that BS has a modelled perioperative failure rate of 0%.

TABLE 62 Details of the two studies used for complication rates

Bradbury *et al.* 2005[84] (PTA and CLI)	Axis *et al.* 2002[91] (PTA and IC and CLI)
Sample: 237	Sample: 717
Stroke/TIA: 3 (1.3%)	Stroke/TIA: 1 (0.1%)
Angina: 5 (2.1%)	Renal failure: 5 (0.7%)
Myocardial infarction: 8 (3.4%)	Myocardial infarction: 5 (0.7%)
	Bronchopneumonia: 6 (0.8%)

TIA, transient ischaemic attack.

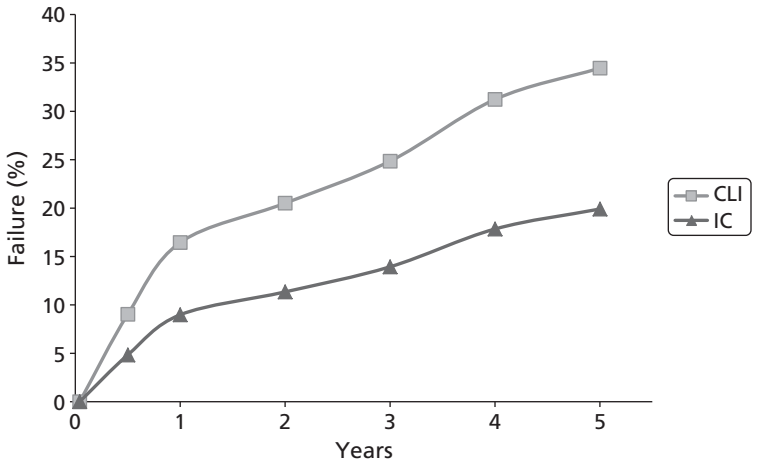

FIGURE 26 Bypass surgery; cumulative failure rates over time for the two patient populations. Based on the meta-analysis of Hunink *et al.*[98]

Probability of reintervention following failure

It is assumed that, following failure during the perioperative period, a reintervention always occurs and it is always BS. If a patient experiences late failure, then three criteria must be met for a reintervention to take place:

1. *Symptoms must return*. For patients with IC, the values from the NICE CEA[83] are used. It is assumed that 17.3% of patients with IC have an occlusion, as opposed to the 20% assumed by the NICE CEA[83] (for more details, see *Appendix 7*: Percutaneous transluminal balloon angioplasty failure). This gives a probability of 28.3% that symptoms will return.
   For patients with CLI there are no direct data on the probability of symptoms returning following failure. The BASIL trial[84] details the number of patients whose symptoms return, but not the number who lost patency. Instead, the failure rates used in this model are applied to the BASIL data, giving a probability of 72.7% that symptoms will return.
2. *The individual must be eligible for a reintervention*. Patients may be ineligible either because they have already received the maximum allowable number of interventions or because they are deemed to be physically ineligible. Based on discussions with our clinical expert (JAM), the maximum number of interventions (including the initial operation) was set at three; this is also the same number as was used by de Vries *et al.*[78]
   Probabilities for being physically ineligible were taken from the only available evidence. de Vries *et al.*[78] assume that 5% of individuals with IC will be unsuitable for a reintervention. For patients with CLI, the most relevant data come from the BASIL trial,[84] which states that, of 452 patients randomised to receive either PTA or BS, 14 did not receive any form of treatment. Removing the seven patients who did not receive a treatment because they died, the proportion ineligible is 1.55%.
3. *The individual must not die before the planned reintervention occurs*. Based on discussions with our clinical expert (JAM), it was assumed that the average time of reintervention following the return of symptoms was 1 week for patients with CLI and 1 month for patients with IC.

Type of reintervention and effectiveness

It is assumed that reinterventions are either PTA or BS. As previously mentioned, acute failure is always followed by a reintervention of BS. For the base-case analysis, reinterventions following late failure are always PTA; in a scenario analysis, this is changed to be always BS.

The BASIL trial[86] is the only economic evaluation to compare the effectiveness of interventions when used as either the initial (first-line) or a follow-up (post-first-line) intervention. There was no evidence to suggest that there is any difference in patency rates between first-line and post-first-line interventions. This applied to both PTA and BS; for further details, see *Appendix 7*.

Disease progression

This is assumed to occur only following failure. Data from the analysis of Sculpher *et al.*[76] are used, as, of the evaluations that model disease progression, their assumptions regarding failure and disease progression are the closest to those used in this model. For further details, see *Appendix 7*.

Developing contralateral symptoms

Data were taken from an article by de Vries *et al.*,[100] as used in the economic evaluation of de Vries *et al.*[78] This is the only evaluation to consider contralateral symptoms. Values for contralateral symptoms requiring a reintervention are used, and adjusted to account for the fact that only 87% of contralateral symptoms (following infrainguinal disease) will also be in the infrainguinal arteries. de Vries *et al.*[78] state that, for patients with previous CLI, 67% of the contralateral symptoms are CLI (the rest being IC), whereas, for patients with previous IC, 10% of the symptoms are CLI. These values are used in this analysis. The development of contralateral symptoms is independent of the patient's patency status.

Transition probabilities for a patient with CLI or IC are independent of how the disease was developed.

Amputations

The handling of amputation varies markedly across the economic evaluations. For this analysis, there are two key questions regarding the modelling of amputations.

Do patients with IC receive an amputation?

Five of the economic evaluations considered this; two (de Vries *et al.*,[78] Holler *et al.*[79]) assumed that it does not happen. Hunink *et al.*[77] applied an annual rate following failure, the NICE CEA[83] applied a fixed probability during PTA and Sculpher *et al.*[76] applied separate rates depending on whether or not patency was maintained.

In this evaluation, patients with IC are modelled as receiving amputations; this is in agreement with expert opinion (JAM), the majority of the economic evaluations and TASC-II guidance, which states that 'The concept that all patients who require an amputation have steadily progressed through increasingly severe claudication to rest pain, ulcers and, ultimately, amputation is incorrect'.

What is the relationship between patency and amputation?

Hunink *et al.*[77] assume that amputations only occur following failure. Sculpher *et al.*[76] stratify their rates by whether or not patency was maintained. It is unclear how De Vries *et al.* handled this.[78] The BASIL trial[84] did not explore this relationship. Both the NICE CEA[83] and Holler *et al.*[79] apply fixed probabilities irrespective of patency status for CLI patients (their handling of IC patients has been previously described).

Clinical guidelines[2] indicate that amputation may be a result of either failure (if reintervention is not possible) or infection or gangrene, irrespective of patency.

As there is no direct evidence that any of the interventions reduce amputation rates, time to amputation is modelled independently of patency status. For patients with CLI, time to amputation is based on data reported by the BASIL trial.[86] For patients with IC, an exponential distribution is used, based on values reported in clinical guidelines: TASC-II guidance[99] states that after 5 years 1% to 3.3% of patients with IC will experience an amputation, whereas ACC/AHA guidelines[102] say that only 2% of claudicants will ever require amputation. With the fitted distribution, 1.2% of claudicants receive an amputation after 5 years, with this value increasing to 2.4% after 10 years.

Amputation-related mortality

Only three economic evaluations provide data on procedural mortality (Hunink *et al.*,[77] de Vries *et al.*,[78] NICE CEA[83]). There are no reported differences in rates between patients with IC and patients with CLI. Hunink *et al.*[77] use a value of 11.5%, and the NICE CEA[83] uses a value of 12.9%. de Vries *et al.*[78] stratify

their rates by age, with a rate of 9.8% among patients below the age of 75 years, and 14.7% above; these values are used in the model.

The NICE CEA[83] is the only evaluation to model a change in the rates of general mortality following an amputation. Whereas the annual mortality rate of patients with CLI is 25%, patients experience a mortality rate of 35% in the first year following an amputation, followed by an annual rate of 19%. For this model, it is assumed that there is no difference in general mortality rates following an amputation.

Quality of life

There was wide variation in the QoL values employed in the existing economic evaluations. A detailed discussion of these is presented in *Appendix 7*. The values of Hunink *et al.*[77] are not used, as they were based on the abbreviated form of the Torrance multiattribute scale. All other evaluations used the EQ-5D.

Baseline (pre-treatment) values are taken from the analysis of Sculpher *et al.*[76] It is assumed that following patency failure an individual's QoL returns to his or her pre-treatment value.

For IC, the value elicited by Sculpher *et al.*[76] (0.70) is nearly identical to those elicited by de Vries *et al.*[78] (0.71) and Holler *et al.*[79] (0.70). The value used by the NICE CEA[83] is much lower (0.57 – this is the average of two studies); Spronk *et al.*[103] provide a value similar to that of Sculpher *et al.*[76] (12-month value: 0.77), whereas the value provided by Greenhalgh *et al.*[104] is much lower (12-month value: 0.48) – this is the only study to not directly measure EQ-5D (values are mapped from SF-36).

There is much variation in the reported values for CLI. The BASIL trial[82] (0.26) reports the most recent data, and directly elicits its values from CLI patients. However, there were high levels of comorbid cardiovascular disease in these patients. As the effect of cardiovascular disease is separately modelled, use of this data may not be appropriate. Sculpher *et al.*[76] elicited their value (0.35) from the general public, and thus the effect of comorbid disease should be less pronounced. This value was also used by de Vries *et al.*[78] and in the NICE CEA.[83] Holler *et al.*[79] elicited their value (0.60) from CLI patients; it is noted that this value is over twice that reported by the BASIL trial.[82]

Quality of life following an amputation is taken from the analysis of Sculpher *et al.*,[76] who separate their values by above-knee (0.20) and below-knee amputations (0.61). The proportions of these are taken from the BASIL trial (out of 41 amputations, 13 were above the knee and 28 were below the knee[84]). Both de Vries *et al.*[78] and the NICE CEA[83] use the values of Sculpher *et al.*[76] The only other evaluation to report EQ-5D values following an amputation is that of Holler *et al.*[79] (0.52), although it does not state the proportion of above- and below-knee amputations.

The effect of systemic complications is assumed to have a multiplicative decrement on QoL. Only the NICE CEA[83] and de Vries *et al.*[78] report the effects of these. The NICE CEA[83] reports the effect of both myocardial infarction and stroke, with separate values for the first and subsequent years. Values following the first year are based on the arbitrary assumption that they are half that of the first year. de Vries *et al.*[78] only report the effect of myocardial infarction, assuming a constant effect.

The utility decrement reported by de Vries *et al.*[78] is used. This is primarily to keep the model simple, as there are no data to suggest that any of the interventions alters the probability of experiencing a systemic complication. In addition:

- Both Axisa *et al.*[91] and the BASIL trial[84] indicate that an myocardial infarction is much more likely to occur than a stroke.
- The NICE CEA[83] states that the derived decrement following the first year is based on the arbitrary assumption that it is half that of the first year.

Costs

The NICE CEA[83] values costs using the same perspective and time frame (2009/10 NHS reference costs[89]) as this economic evaluation, so costs are taken from this with the following exceptions:

- The NICE CEA[83] assumes no long-term costs for patients with IC or CLI. In contrast, Hunink *et al.*[77], Sculpher *et al.*[76] and Holler *et al.*[79] all assume that there are costs. Of these, Sculpher *et al.*[76] is the only evaluation to base their costs on assumed resource use. The costs of these are updated using 2009/10 costs[89] and used in the model. For further details see *Appendix 7*.
- The long-term costs for patients following an amputation are 20.3% higher in the first year than in subsequent years in the NICE CEA.[83] To keep this model simple only the long-term costs are employed (these are applied at all years).
- The NICE CEA[83] uses a slight increase in the cost of repeat PTA procedures (less than 1%) due to an (assumed) increased number of non-elective admissions. In this evaluation all repeat PTAs cost the same as the initial PTA, with the weight given to non-elective admissions based on their observed frequency of occurrence in the NHS reference costs data.
- The cost of systemic complications is divided into myocardial infarction and stroke, with an increased cost in the first 3 months in the NICE CEA.[83] Only the costs for myocardial infarction are used in this evaluation for the reason described in the QoL section. As the presence of complications results in an increased procedural cost, the increased cost in the first 3 months is not included, as this may lead to double counting.

Data for interventions

Interventions are assumed to affect only the transition probabilities for acute failure, late failure and the return of symptoms following failure (loss of patency). The effects of interventions are assessed for two different sites: femoropopliteal (*Table 63*) and infrapopliteal (*Table 64*) arteries. In *Tables 63* and *64* interventions are ranked by their procedural cost. For both sites, the base case is PTA with bailout stenting. The effect of each intervention is assumed to be the same for patients with IC and CLI.

From the preceding tables it can be seen that interventions D to G are dominated by intervention C. However, as a result of the uncertainty in assuming mid-point values for the estimates of effectiveness, there is still a possibility that they may represent cost-effective options for the treatment of PAD. Therefore, they are retained in the analysis.

TABLE 63 Costs and effects for interventions: femoropopliteal arteries

Intervention		RR			Cost, no complications (£)
		Acute failure	Late failure	Return of symptoms	
X(f)	Base case (PTA with bail-out BMSs)	1	1	1	3837
A	PTA, no bail-out stenting	2	1	1	3661
B	PTA with bail-out paclitaxel-eluting stents	1	0.82	0.66	3949
C	Paclitaxel-coated balloon	1	0.40	0.68	4071
D	BMSs	1	0.58	1	4316
E	Paclitaxel-eluting stent	1	0.53	1	4525
F	EVBT	1	0.63	1	6171
G	Stent-graft	1	0.58	1	6561
H	Cryoplasty	0.35	2.2	1	7367

TABLE 64 Costs and effects for interventions: infrapopliteal arteries

Intervention		RR			Cost, no complications (£)
		Acute failure	Late failure	Return of symptoms	
X(i)	Base case (PTA with bail-out stenting)	1	1	1	3837
α	BMSs	1	0.42	1	4316
β	Sirolimus-eluting stent	1	0.18	1	4732

The effects of complications

There were no data available that showed how clinical effectiveness, QoL or costs were affected by the presence of a complication. Hence, these are assumed to have the same effect on interventions as they have on PTA, namely they:

- do not alter subsequent transition probabilities
- have a multiplicative decrement on QoL
- increase procedural costs by 91.7%. (In comparison the costs for BS increase by 44.2%.)

Data on costs

Costs data were derived from two main sources. The cost of interventions involving stents (A, B, D, E, α and β) is based on the base-case cost of PTA with bail-out stents (£3348), adjusted for the cost of a stent (£900 for DESs and £500 for BMSs) and their frequency of use (two per patient when used as the primary procedure, 0.324 per patient when used as a bail-out procedure). These data are taken from the NICE CEA.[83] It should be noted that both types of DES are assumed to have the same procedural cost; however, as the two are applied to different sites, it is not possible to compare the two. It is assumed that the cost of C (paclitaxel-coated balloon) is equal to the base case plus the incremental cost of drug coating (taken to be the difference in costs between a DES and a BMS).

Data for the remaining interventions (EVBT, stent-grafts and cryoplasty) were taken from the literature.[105–107] Instead of adjusting quoted costs to 2009/10 UK pounds, the costs were compared to the quoted costs for the base case and the excess cost applied as a ratio to the base-case cost employed in this evaluation.

Data on clinical effectiveness

With two exceptions, the data on clinical effectiveness come from studies previously discussed in the assessment of clinical effectiveness (see *Chapter 3, Results*) and, therefore, will not be discussed further here. For each intervention, if multiple studies were available, these were meta-analysed, with the results presented in *Results* in *Chapter 3*. Sometimes there were multiple time points with data that could be used to inform clinical effectiveness data. In all instances, the data were judged to be consistent over time, and thus only one result was used, typically the 12-month values. For example, results of the meta-analysis of TLR for DCBs were available for 6 months and 12 months, with RRs of 0.24 and 0.27, respectively – the latter value is used in this evaluation.

Differences in late failure rates are conditional on any differences in acute failure and any differences in the return of symptoms are conditional on any differences in failure. For example, for DCBs a TLR RR of 0.27 is used as a proxy value for the RR of the return of symptoms. As DCBs have a RR for late failure of 0.40, the RR for return of symptoms is calculated as 0.27/0.40 = 0.68.

Data on the clinical effectiveness (late failure and return of symptoms) of cryoplasty were taken from the trial of Spiliopoulos *et al.*[45] Although this study is included in the assessment of clinical effectiveness, the results used here are adjusted for other variables (as reported in table 5 of the paper of Spiliopoulos *et al.*[45]), and therefore differ from the unadjusted results reported in *Results* in *Chapter 3* of this evaluation.

Data on paclitaxel-eluting stents are taken from a 2012 publication by Dake *et al.*,[71] published after a systematic review of clinical effectiveness was undertaken.

Sources of evidence on each interventions used in the modelling are summarised in *Table 65*.

Results

Cost–utility analysis: base case

Intermittent claudication: femoropopliteal arteries

Total costs and total QALYs for each intervention are displayed in *Table 66*, which is sorted by ascending price. Because the options are mutually exclusive, ICERs are presented based on a fully incremental analysis.

Intervention C, paclitaxel (drug)-coated balloons, is both less expensive and more clinically effective than all of the other options and, therefore, it dominates them. Interventions C and B both dominate the comparator, whereas interventions A and H are dominated by it. The ICERs for the remaining interventions (vs. assumed standard care) are: D (£11,979), E (£28,701), F (£4150) and G (£46,318).

Any decisions regarding which interventions to adopt or fund would be based on the point estimates presented in *Table 66*. It is also important to look at uncertainty in the decision to adopt.

TABLE 65 Evidence sources for the clinical effectiveness of each intervention

Intervention		RR	Source
A	PTA, no bail-out stenting	Acute failure: 2.00	Cejna *et al.* 2001[20]
B	PTA with bail-out paclitaxel-eluting stents	Late failure: 0.82 Return of symptoms: 0.66	Dake *et al.* 2011[71]
C	Paclitaxel-coated balloon	Late failure: 0.40 Return of symptoms: 0.68	Meta-analysis of THUNDER[61–63] and FemPac[64] RCTs; value for 12 months (see *Chapter 3, Results*)
D	BMSs	Late failure: 0.58	Meta-analysis of ABSOLUTE[16–18] and Dick *et al.*[12] RCTs; value for 12 months (see *Chapter 3, Results*)
E	Paclitaxel-eluting stent	Late failure: 0.53	Dake *et al.* 2011[71]
F	EVBT	Late failure: 0.63	Meta-analysis of Vienna-3,[51–53] VARA[54] and Dick *et al.* RCTs; value for 12 months (see *Chapter 3, Results*)
G	Stent-graft	Late failure: 0.58	Saxon *et al.* 2003[32] (12-month results)
H	Cryoplasty	Acute failure: 0.35	Jahnke *et al.* 2010[40]
		Late failure: 2.20	Spiliopoulos *et al.*[41] (Table 5)
α	BMSs	Late failure: 0.43	Rand *et al.*[22]
β	Sirolimus-eluting stent	Late failure: 0.18	Rastan *et al.* 2010[108] (12-month results)

TABLE 66 Full incremental analysis of PTA and all the potential interventions

Intervention		Costs (£)	QALYs	Incremental analysis
C	Paclitaxel-coated balloon	12,668	6.120	–
B	PTA with bail-out paclitaxel-eluting stents	13,032	6.081	*Dominated by C*
X(f)	PTA with bail-out BMSs	14,637	5.956	*Dominated by C*
A	PTA, no bail-out stenting	14,787	5.931	*Dominated by C*
D	BMSs	15,030	5.989	*Dominated by C*
E	Paclitaxel-eluting stent	15,692	5.993	*Dominated by C*
F	EVBT	15,891	5.984	*Dominated by C*
G	Stent-graft	16,171	5.989	*Dominated by C*
H	Cryoplasty	17,578	5.934	*Dominated by C*

These uncertainties are explored in the following sections. As part of the estimate of uncertainty, probabilistic sensitivity analysis was performed, with 1000 runs.

Figure 27 presents the incremental CEAC for the interventions and assumed standard care. This shows the probability of each procedure being cost-effective at various levels of willingness to pay (maximum acceptable ICER). Thresholds from £0 to £100,000 were tested. Of all the procedures, use of a DCB has the highest probability of being most cost-effective, and use of bailout DESs has the second highest probability of being most cost-effective for all willingness-to-pay thresholds. The probability of any of the other interventions being cost-effective is never greater than 1%. The actual probabilities for each procedure are presented in *Table 67* for selected willingness-to-pay thresholds of £20,000, £30,000 and £50,000.

Based on the values presented in *Table 67*, interventions C and B have the highest probability of being the most cost-effective. The cost-effectiveness plane for these interventions is presented in *Figure 28*, which shows the incremental clinical effectiveness and incremental costs of these interventions versus the comparator.

The cost-effectiveness plane shows that both of the presented interventions fall in all four quadrants, suggesting that there is a non-zero probability that each intervention could be dominated by the comparator (represented by points falling in the top-left quadrant).

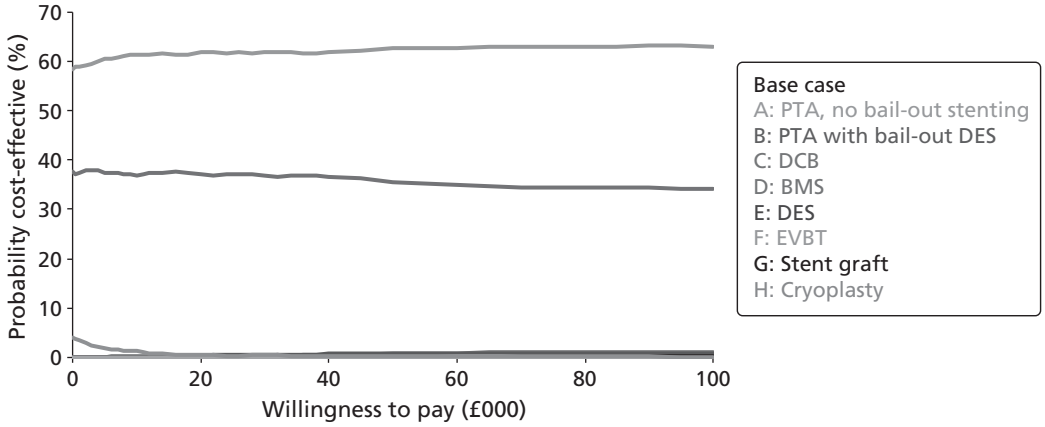

FIGURE 27 Incremental cost-effectiveness acceptability curve for the base-case model results (all but two of the interventions have probabilities ≈ 0 for all willingness-to-pay thresholds).

TABLE 67 Incremental probability (%) of being cost-effective for specified levels of willingness to pay

	Intervention								
Threshold (£)	C	B	X(f)	E	D	A	G	F	H
20,000	61.8	37.0	0.6	0.3	0.2	0.1	0.0	0.0	0.0
30,000	61.9	36.8	0.4	0.4	0.3	0.1	0.1	0.0	0.0
50,000	62.6	35.5	0.2	0.8	0.7	0.0	0.1	0.1	0.0

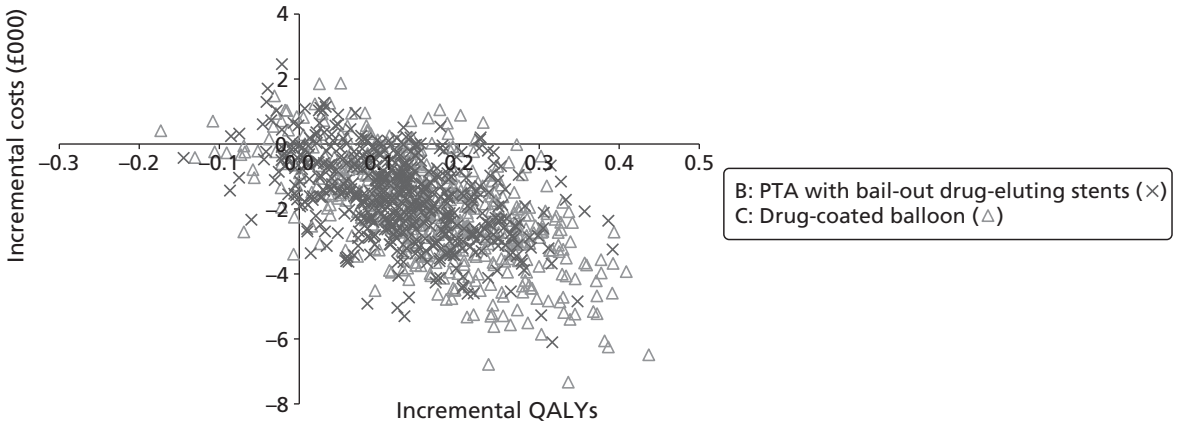

FIGURE 28 Cost-effectiveness plane showing incremental clinical effectiveness and costs of selected interventions vs. the comparator (base case).

Additional details of the two interventions B and C, along with the comparator, are presented in *Tables 68* and *69*. These show the main drivers for the observed differences in clinical and cost-effectiveness outcomes.

Table 68 shows that, although interventions B and C are both more expensive than the comparator, a large component of their cost saving comes from avoiding repeat procedures (by prolonging patency). These interventions also save costs by keeping patients out of the IC health state for longer.

Table 69 shows that, although there is no difference in extension to life offered by the interventions, they keep patients out of the IC health state for longer, resulting in greater QoL.

For both tables, differences in amputation outcomes are minimal, as expected given the assumption that all of the interventions are assumed to have no impact on time to amputation. As amputations are associated with large costs and decrements to QoL, if there is an effect of interventions on reducing these, the cost savings and increases in QoL shown here are likely to be even greater.

An analysis of the expected value of perfect information (EVPI) based on the method described in Claxton and Posnett[109] was undertaken and the results are shown in *Figure 29*.

Figure 29 may be interpreted as showing that there is uncertainty in which treatment is more efficacious, with the result that EVPI increases as willingness to pay increases. Often one treatment is more efficacious and, thus, EVPI reaches a maximum; its value decreases as willingness to pay increases and the more efficacious treatment is adopted. In this situation, the decision of which treatment is the most cost-effective does not appear to be dependent upon willingness to pay (the maximum acceptable ICER to a decision-maker). Instead, the most cost-effective treatment is dependent on the clinical effectiveness of the various treatments, and the uncertainty about these treatment effects. This is shown by the CEAC of

TABLE 68 Breakdown of costs

	Average costs per patient (£)		
Type of procedure	Comparator	Bail-out DESs	DCB
All procedures[a]	8361	7851	7656
First procedure	3348	3461	3580
Follow-up procedures	4816	4198	3885
Amputations	198	192	191
Amputees	2401	2403	2295
IC	801	502	411
CLI	124	109	84

a Procedures exclude amputations.

TABLE 69 Breakdown of utilities and life-years

	Average values per patient		
Health state	Comparator	Bail-out DESs	DCB
Life-years gained	7.80	7.78	7.78
QALYs	5.96	6.07	6.10
Asymptomatic	5.15	5.52	5.59
IC	0.73	0.47	0.44
Amputees	0.04	0.04	0.04
CLI	0.03	0.03	0.02

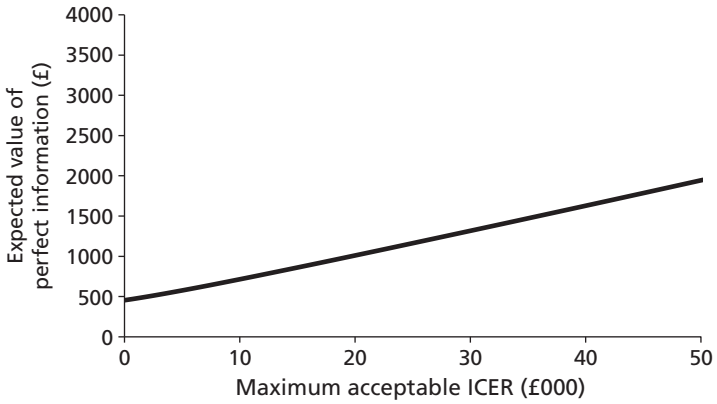

FIGURE 29 Results of EVPI.

Figure 27, as the two treatments with non-negligible probabilities of cost-effectiveness have essentially flat curves. Because of this, increasing the maximum acceptable ICER will lead to an increase in the EVPI, as shown in *Figure 29*. This is in contrast to more commonly seen figures in which there is a trade-off between the cost of an intervention and its efficacy.

It is estimated that about 7% of persons aged ≥ 60 years have IC.[2] Applying this value to 2010 mid-year population estimates for the UK,[1] and assuming that the information from this report will be of benefit for a 10-year horizon, gives a multiplier for the EVPI values of 9,847,740.

Critical limb ischaemia: femoropopliteal arteries

Total costs and total QALYs for each intervention are displayed in *Table 70*, which is sorted by ascending price. Because the options are mutually exclusive, ICERs are presented based on a fully incremental analysis.

As with the results for patients with IC, intervention C, paclitaxel (drug)-coated balloons, is both less expensive and more clinically effective than all of the other options and, therefore, it dominates them. Interventions A and H are again dominated by the comparator, being both more expensive and less clinically effective.

Procedures which include some form of drug and/or the primary use of stents (interventions B to E) are both less expensive and more effective than the comparator of PTA with bailout stenting.

Endovascular procedures that have a different mechanism of action from the comparator (interventions F, G and H) are all more expensive. Only intervention H (cryoplasty) is also less effective. However, the majority of the excluded interventions (atherectomy, EBRT and laser) similarly have a different mechanism of action from the base case, but were excluded because they were known to be both more expensive and less effective. The ICERs for interventions G and F (vs. the comparator) are £6681 (G) and £8341 (F).

Any decisions regarding which interventions to adopt or fund would be based on the point estimates presented in *Table 70*. It is also important to look at uncertainty in the decision to adopt. These uncertainties are explored in the following sections. As part of the estimate of uncertainty, probabilistic sensitivity analysis was performed, with 1000 runs.

Figure 30 presents the incremental CEAC for the interventions and comparator. This shows the probability of each procedure being cost-effective at various levels of willingness to pay (maximum acceptable ICER). Thresholds from £0 to £100,000 were tested. Of all the procedures, use of a DCB has the highest probability of being most cost-effective and use of bailout DESs has the second highest probability of being most cost-effective for all willingness-to-pay thresholds. The probability of any of the other interventions being cost-effective is never greater than 0.5%. The actual probabilities for each procedure are presented in *Table 71* for selected willingness-to-pay thresholds of £20,000, £30,000 and £50,000.

Based on the values presented in *Table 71*, interventions C and B have the highest probability of being the most cost-effective. The cost-effectiveness plane for these interventions is presented in *Figure 31*, which shows the incremental clinical effectiveness and incremental costs of these interventions versus the comparator.

TABLE 70 Full incremental analysis of PTA and all the potential interventions

Intervention		Costs (£)	QALYs	Incremental analysis
C	Paclitaxel-coated balloons	49,890	3.402	–
B	PTA with bail-out paclitaxel-eluting stents	52,335	3.297	*Dominated by C*
D	BMSs	54,775	3.144	*Dominated by C*
E	Paclitaxel-eluting stent	55,012	3.157	*Dominated by C*
X(f)	PTA with bail-out BMSs	55,199	3.047	*Dominated by C*
G	Stent-graft	55,852	3.144	*Dominated by C*
F	EVBT	55,928	3.134	*Dominated by C*
A	PTA, no bail-out stenting	56,539	2.988	*Dominated by C*
H	Cryoplasty	58,097	3.003	*Dominated by C*

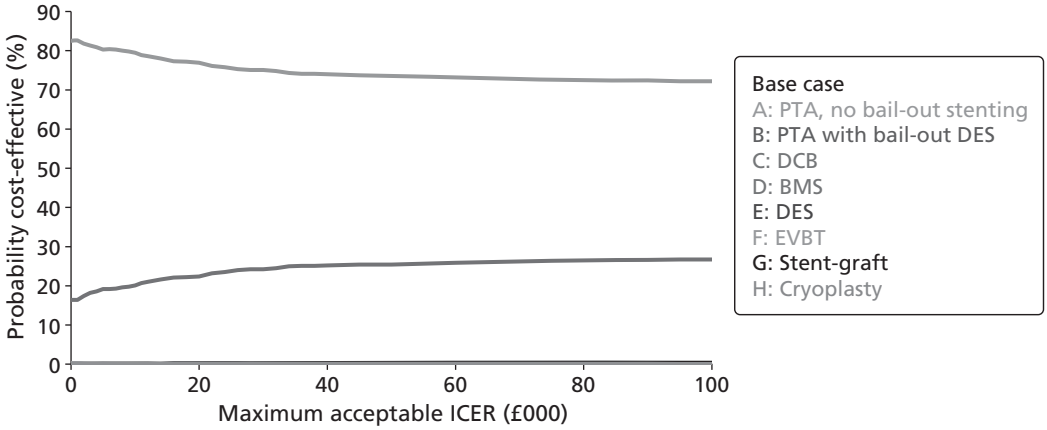

FIGURE 30 Incremental cost-effectiveness acceptability curve for the base-case model results (all but two of the interventions have probabilities ≈ 0 for all willingness-to-pay thresholds).

TABLE 71 Incremental probability (%) of being cost-effective for specified levels of willingness to pay

	Intervention								
Threshold (£)	C	B	E	D	F	G	X(f)	A	H
20,000	76.9	22.4	0.2	0.3	0.1	0.1	0.0	0.0	0.0
30,000	75.1	24.2	0.3	0.2	0.1	0.1	0.0	0.0	0.0
50,000	73.6	25.4	0.4	0.3	0.1	0.2	0.0	0.0	0.0

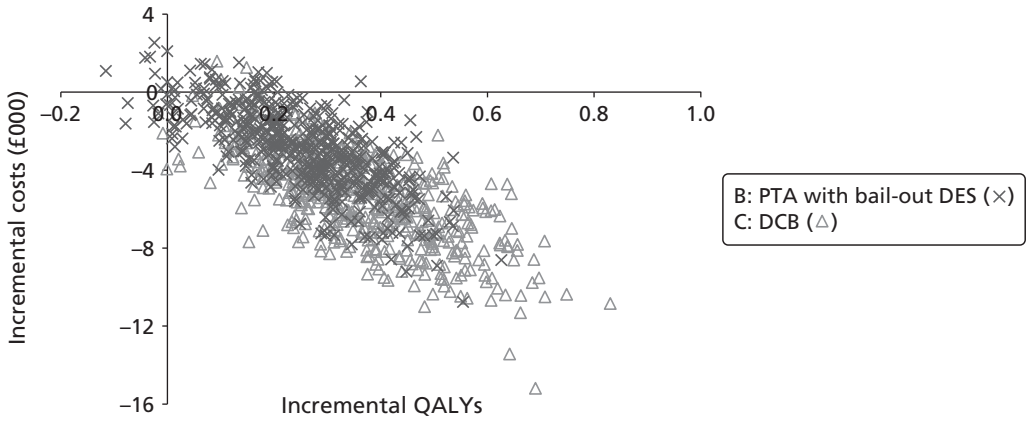

FIGURE 31 Cost-effectiveness plane showing incremental clinical effectiveness and costs of selected interventions vs. the comparator (base case).

The cost-effectiveness plane shows that, for some realisations of intervention B (but not intervention C), results fall in the top-left quadrants, suggesting that there is a non-zero probability that it could be dominated by the comparator.

Additional details of the two interventions B and C, along with the comparator, are presented in *Tables 72* and *73*. These show the main drivers for the observed differences in cost-effectiveness outcomes.

Table 72 shows that, although interventions B and C are both more expensive than the comparator, a large component of their cost saving comes from avoiding repeat procedures (by prolonging patency). These interventions also save costs by keeping patients out of the CLI health state for longer.

TABLE 72 Breakdown of costs

	Average costs per patient		
Type of procedure	Comparator (£)	Bail-out DESs (£)	DCB (£)
All procedures[a]	14,949	13,685	12,432
First procedure	3348	3461	3580
Follow-up procedures	8320	6877	5511
Amputations	3282	3347	3341
Amputees	32,478	33,731	32,600
IC	87	69	23
CLI	1262	808	668

a Procedures exclude amputations.

TABLE 73 Breakdown of utilities and life-years

	Average values per patient		
Health state	Comparator	Bail-out DESs	DCB
Life-years gained	5.17	5.25	5.20
QALYs	2.99	3.24	3.32
Asymptomatic	2.20	2.50	2.65
IC	0.03	0.02	0.01
Amputees	0.50	0.53	0.53
CLI	0.27	0.18	0.13

Whereas the costs for amputees are of similar magnitude for the comparator and both interventions, the increased costs for intervention B (owing to natural variation) are almost the same as the decreased procedural costs (owing to intervention effect). Therefore, setting amputation costs to zero will result in even greater cost savings for intervention B relative to the comparator. Setting amputation costs to zero will not make intervention B cheaper than intervention C however.

Table 73 shows that the main driver for differences in QoL is keeping patients out of the CLI health state and in the asymptotic health state for longer.

An analysis of the EVPI based on the method described in Claxton and Posnett[109] was undertaken and the results are shown in *Figure 32*.

The results of the EVPI analysis for patients with CLI are very similar to the results of the analysis for patients with IC. Again, there is an indication of some uncertainty over the results, with EVPI increasing as willingness to pay increases. In this situation, the decision of which treatment is the most cost-effective does not appear to be dependent upon willingness to pay (the maximum acceptable ICER to a decision-maker). Instead, the most cost-effective treatment is dependent on the inherent effectiveness of the various treatments, and the uncertainty about these treatment effects. This is shown by the CEAC of *Figure 30*, as the two treatments with non-negligible probabilities of cost-effectiveness have essentially flat curves. Because of this, increasing the maximum acceptable ICER will lead to an increase in the EVPI, as

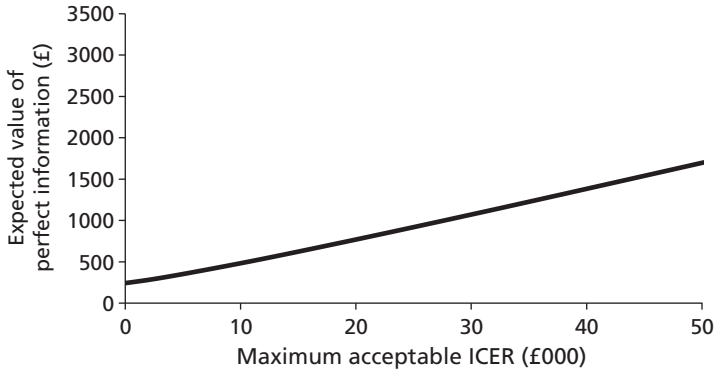

FIGURE 32 Results of EVPI analysis.

shown in *Figure 31*. This is in contrast to more commonly seen figures in which there is a trade-off between the cost of an intervention and its efficacy.

It is estimated that about 0.4% of persons aged ≥ 60 years have CLI.[2] Applying this value to 2010 mid-year population estimates for the UK,[1] and assuming that the information from this report will be of benefit for a 10-year horizon, gives a multiplier for the EVPI values of 562,728.

Scenario analysis 1: varying age

In the base-case analysis, the starting age for patients was 66 for those with IC and 74 for those with CLI. These values were not varied within probabilistic sensitivity analyses; instead, the sensitivity of the conclusions reached in the base case to starting age are explored here.

Incremental costs and incremental QALYs for each intervention relative to the comparator are shown in *Tables 74–77*. As many interventions either dominate or are dominated by the comparator, ICERs are not presented.

No intervention alters life-years gained; their effect on costs is to avoid repeat reinterventions and their effect on QALYs is to keep patients in the asymptomatic health state for longer. For QALYs, effectiveness (or lack of it) shows a mostly smooth relationship with age, with effects becoming more (less) pronounced at younger (older) ages. This pattern can be seen for both patient populations.

TABLE 74 Incremental costs (vs. comparator) for each intervention against age in patients with IC

	Intervention							
Age (years)	A	B	C	D	E	F	G	H
45–49	–£621	–£1516	–£2795	–£413	£398	£781	£738	£3331
50–54	–£419	–£1251	–£2500	–£244	£518	£945	£907	£2993
55–59	–£548	–£1220	–£2181	–£203	£581	£950	£947	£2759
60–64	–£465	–£994	–£1684	£27	£893	£1117	£1178	£3027
65–69	–£152	–£762	–£1166	£314	£1027	£1276	£1464	£2682
70–74	–£171	–£643	–£847	£443	£1136	£1446	£1593	£2672
75–79	–£66	–£467	–£585	£587	£1330	£1531	£1737	£2728
80–84	–£130	–£403	–£462	£591	£1276	£1541	£1741	£2640
85–89	–£73	–£231	–£327	£687	£1369	£1608	£1837	£2638

TABLE 75 Incremental QALYs (vs. comparator) for each intervention against age in patients with IC

	Intervention							
Age (years)	A	B	C	D	E	F	G	H
45–49	–0.114	0.367	0.527	0.027	0.055	0.007	0.027	–0.039
50–54	–0.137	0.305	0.421	0.002	0.063	–0.026	0.002	–0.040
55–59	–0.114	0.230	0.311	0.038	0.041	0.002	0.038	0.001
60–64	–0.104	0.173	0.215	0.024	0.032	0.006	0.024	–0.007
65–69	–0.027	0.089	0.122	0.012	0.023	0.008	0.012	–0.029
70–74	–0.010	0.038	0.069	–0.005	0.011	0.011	–0.005	–0.038
75–79	–0.005	0.023	0.038	0.008	0.012	0.015	0.008	–0.022
80–84	–0.006	0.006	0.021	0.005	0.012	0.005	0.005	–0.006
85–89	–0.011	–0.005	0.006	–0.002	0.004	0.005	–0.002	–0.007

TABLE 76 Incremental costs (vs. comparator) for each intervention against age in patients with CLI

	Intervention							
Age (years)	A	B	C	D	E	F	G	H
45–49	£2441	–£927	–£4753	–£1395	£1138	£1826	–£245	£5905
50–54	£2178	–£1591	–£4586	–£1172	£601	£1487	–£22	£4707
55–59	£2700	–£1393	–£4119	–£641	£935	£1897	£509	£4560
60–64	£3040	–£603	–£3508	–£365	£1421	£2160	£785	£4276
65–69	£2902	–£642	–£3163	£25	£996	£2089	£1175	£4115
70–74	£2027	–£1114	–£3109	–£28	£790	£1717	£1123	£3540
75–79	£1853	–£933	–£2410	£387	£899	£1623	£1538	£3574
80–84	£1388	–£895	–£1979	£261	£862	£1337	£1411	£3058
85–89	£1197	–£798	–£1485	£505	£1093	£1442	£1655	£2612

TABLE 77 Incremental QALYs (vs. comparator) for each intervention against age in patients with CLI

	Intervention							
Age (years)	A	B	C	D	E	F	G	H
45–49	–0.159	0.573	0.847	0.110	0.150	0.088	0.110	–0.072
50–54	–0.118	0.514	0.730	0.124	0.168	0.121	0.124	–0.057
55–59	–0.109	0.407	0.583	0.114	0.152	0.118	0.114	–0.076
60–64	–0.099	0.336	0.446	0.084	0.140	0.111	0.084	–0.072
65–69	–0.087	0.245	0.324	0.057	0.087	0.084	0.057	–0.079
70–74	–0.080	0.153	0.213	0.032	0.060	0.060	0.032	–0.070
75–79	–0.052	0.098	0.127	0.024	0.035	0.052	0.024	–0.031
80–84	–0.029	0.053	0.064	0.013	0.026	0.036	0.013	–0.014
85–89	–0.018	0.016	0.022	0.005	0.009	0.014	0.005	–0.006

A similar pattern can be seen for costs, although it is less pronounced – particularly for patients with CLI. This is likely to be a result of the effect of amputations, which are both very costly and independent of the intervention used.

The tables show that interventions B and C dominate the comparator for all ages and for both patient populations. For patients with IC, this effect becomes very small after the age of (about) 80; for patients with CLI, the effect becomes very small after the age of (about) 85.

Scenario analysis 2: no amputation costs

The average costs of the interventions considered range from £3837 (A) to £7367 (H), whereas monthly costs for IC are £15 and for CLI are £52. In contrast, an amputation procedure costs an average of £9733, with follow-up monthly costs just under £2000.

The high costs associated with receiving an amputation mean that any variations in the rates of its occurrence are likely to overwhelm any intervention effects (with respect to costs). Convergence tests were performed to ensure that natural variation is unlikely to be an issue, and it is assumed that interventions do not affect time to amputation (as there is not enough evidence to suggest otherwise). Care was taken to minimise any indirect effects of interventions on amputation rates. For example, patent patients cannot experience ipsilateral disease progression and, hence, interventions prolonging patency also result in lower rates of progression to CLI. As patients with CLI have a shorter time to amputation, this could result in an indirect intervention effect on amputation rates. To avoid this, time to amputation is set based on a patient's characteristics at model entry, and is not changed upon disease progression (the same applies to time to general mortality).

There remains in the model one indirect intervention effect on amputation rates. Patency avoids the need for reinterventions and thus avoids the slight mortality risk associated with a reintervention. Because of this, more effective interventions will (on average) keep patients alive for a slightly longer time, meaning that patients are slightly more likely to receive an amputation.

This scenario analysis looks at the impacts on the base-case results when amputation-related costs are removed. Costs and QALYs for the comparator and each intervention are shown for each patient population in *Table 78*. As with the base-case, results are ordered by ascending price.

TABLE 78 Costs and QALYs when amputation costs are removed

IC				CLI			
Intervention		Costs	QALYs	Intervention		Costs (£)	QALYs
C	Paclitaxel-coated balloons	7920	6.120	C	Paclitaxel-coated balloons	16,433	3.402
B	PTA with bail-out paclitaxel-eluting stents	8117	6.081	B	PTA with bail-out paclitaxel-eluting stents	18,283	3.297
A	PTA, no bail-out stenting	8302	5.931	D	BMSs	18,348	3.144
X(f)	PTA with bail-out BMSs	8368	5.956	X(f)	PTA with bail-out BMSs	18,619	3.047
D	BMSs	8928	5.989	E	Paclitaxel-eluting stent	18,816	3.157
E	Paclitaxel-eluting stent	9607	5.993	A	PTA, no bail-out stenting	18,913	2.988
F	EVBT	9756	5.984	F	EVBT	19,505	3.134
G	Stent-graft	10,077	5.989	G	Stent-graft	19,589	3.144
H	Cryoplasty	12,314	5.934	H	Cryoplasty	22,030	3.003

There are some slight differences from the base-case results in the order of interventions ranked near the middle. For example, for patients with IC, in the base case intervention A was £150 more expensive than the comparator, but, in this analysis, it is now £67 cheaper.

The main conclusions of the base case – that intervention C dominates all others and intervention B also dominates the comparator – remain unchanged. This is to be expected, given that interventions are not assumed to effect amputation rates.

Scenario analysis 3: reduced clinical benefit owing to patency and cost-minimisation approach

The effects of interventions on prolonging patency are taken from the literature. However, there is some concern over the link between patency and clinical outcomes, such as the need for reinterventions and the effect on QoL. The available literature linking these two is very sparse, and the NICE CEA[83] did not include differences in patency because of a lack of evidence.

In the base-case analysis, prolonging patency has the following effects:

(a) It improves QOL by stopping the return of symptoms (either IC or CLI).
(b) It saves future costs by preventing the need for a reintervention.
(c) It stops patients with IC experiencing ipsilateral disease progression.

It is worth noting that each of these effects is diluted:

1. After losing patency, not all individuals will experience a return of symptoms.
2. After losing patency, not all individuals will require a reintervention.
3. Patients with IC can experience contralateral disease progression at any point.

This sensitivity analysis looks at the impact on the base-case results if assumptions C and A are removed. Assumption C was removed by setting time to ipsilateral progression at model entry, using an exponential distribution with a parameter of 249.5 (this is based on the rate of disease progression modelled in the NICE CEA). Results from this are shown in *Table 79*.

TABLE 79 Costs and QALYs when ipsilateral disease progression is not affected by the intervention

IC				CLI			
Intervention		Costs (£)	QALYs	Intervention		Costs (£)	QALYs
C	Paclitaxel-coated balloons	10,776	6.127	C	Paclitaxel-coated balloons	48,939	3.320
B	PTA with bail-out paclitaxel-eluting stents	10,877	6.094	B	PTA with bail-out paclitaxel-eluting stents	49,147	3.197
A	PTA, no bail-out stenting	11,688	6.124	D	BMSs	50,535	3.096
D	BMSs	12,129	6.072	E	Paclitaxel-eluting stent	51,129	3.098
X(f)	PTA with bail-out BMSs	12,369	6.052	F	EVBT	51,275	3.060
F	EVBT	12,952	6.109	X(f)	PTA with bail-out BMSs	51,286	2.975
E	Paclitaxel-eluting stent	13,002	6.080	G	Stent-graft	51,685	3.096
G	Stent-graft	13,279	6.072	A	PTA, no bail-out stenting	52,811	2.922
H	Cryoplasty	14,710	6.070	H	Cryoplasty	54,464	2.938

Relative to the base-case results, costs are slightly reduced and there are some slight differences in the ordering of the interventions near the middle. However, the main conclusions – that intervention C dominates all others and intervention B also dominates the comparator – remain unchanged.

If assumption A is removed, the effect would be that all interventions have the same QALYs. The only differences would then be in cost, with the cheapest intervention being chosen. Again, this would lead to intervention C being chosen, with intervention B the second cheapest (this conclusion holds for both the base case and the removal of assumption C.

Scenario analysis 4: results for the infrapopliteal arteries

The base case uses an underlying 'natural' history (time to patency for the comparator) model for PAD in the femoropopliteal arteries. This natural history is then affected by the interventions, with different underlying natural histories for the two patient populations (IC and CLI).

Data for each intervention considered in the base case were taken from studies that were identified in the systematic review and that looked at the role of the intervention in the femoropopliteal arteries, popliteal artery or superficial femoral artery.

Data for sirolimus-eluting stents were only available for the infrapopliteal arteries. After discussions with our clinical expert (JAM), it was felt that these should be analysed separately, as the underlying natural history was likely to be very different for this anatomical area.

This scenario analysis looks at the results for sirolimus-eluting stents versus the comparator. It should be stressed that these results should be seen as exploratory in nature, as data for the comparator are based on outcomes observed in the femoropopliteal arteries.

Only one study was found that considered the cost-effectiveness of sirolimus-eluting stents (Rastan *et al.*[108]). However, the comparator in this study was BMSs. One study identified in the systematic review considered the cost-effectiveness of BMSs in the infrapopliteal arteries (Rand *et al.*[22]); the cost-effectiveness of sirolimus-eluting stents relative to the comparator used in this analysis is indirectly estimated using the results of Rand *et al.*[22] BMSs are also included as an additional intervention (using only cost-effectiveness data from Rand *et al.*[22]). As the Rand *et al.*[22] study only considers patients with CLI, only results for this patient population are considered. Results for this scenario analysis are shown in *Table 80*.

Assuming the same natural history model as observed in femoropopliteal arteries, the use of BMSs in infrapopliteal arteries dominates the comparator. Relative to BMSs, the use of sirolimus-eluting stents generates 0.23 additional QALYs at an additional cost of £2416, giving an ICER of £10,571.

TABLE 80 Costs and QALYs for interventions applied to infrapopliteal arteries in patients with CLI

Intervention		Costs (£)	QALYs
α	BMSs	48,604	3.520
X(f)	PTA with bail-out BMSs	49,890	3.402
β	Sirolimus-eluting stents	51,020	3.750

Results for the comparator are based on the femoropopliteal arteries.

Chapter 5 Discussion

The review identified a large number of studies covering most of the technologies that have been included in the scope. However, many trials were small and the populations, clinical indications and nature of the lesions varied among studies. Although the review aimed to consider a range of potential outcome measures, very little evidence was found regarding disease-specific or generic measures of QoL and clinical outcomes such as walking distance or limb loss. For these outcomes and for complications and adverse events, there were no significant differences reported between any of the new technologies and PTA. This may reflect the limited outcome data collected in the trials and that the trials were not sufficiently large to be powered for identification of such outcomes. In addition, nearly all comparisons were with PTA, meaning that it was not possible to conduct a network meta-analysis. The only exceptions are the studies that looked at DESs; these included a comparison with BMSs. However, the studies considered different drugs and, therefore, including these in a network meta-analysis would not have been useful.

The main outcomes reported in the majority of trials were measures of patency or restenosis and the need for reintervention. Based upon this specific outcome, one technology, AMSs, was reported as being significantly worse than PTA and six others: BESs, atherectomy, CB, cryoplasty, EBRT and laser angioplasty showed no significant differences from PTA. There was, however, a group of technologies for which there was evidence of a significant benefit in reducing restenosis rates. These technologies were SESs, stent-grafts, EVBT and DCBs. Studies of DESs versus BMSs also demonstrated an advantage in terms of restenosis rates for DESs.

The health economic analysis considered the effects of eight interventions (PTA with no bail-out stenting, PTA with bail-out paclitaxel-eluting stents, paclitaxel-coated balloons, primary BMSs, primary paclitaxel-eluting stents, EVBT, stent-grafts and cryoplasty) in the femoropopliteal arteries, along with the comparator (PTA with bail-out BMSs). Two interventions (primary BMSs and primary sirolimus-eluting stents) were also considered in the infrapopliteal arteries, although the results for these can be interpreted only as an exploratory sensitivity analysis as data for both the comparator and natural history of PAD were based on the femoropopliteal arteries.

Results for the base-case analysis suggest that the use of paclitaxel-coated balloons dominates both the comparator and all other interventions. Taking account of the uncertainty in this result, of the other interventions, only the use of bail-out paclitaxel-eluting stents (which also dominate the comparator and all other comparators except for paclitaxel-coated balloons) is likely to be the most cost-effective intervention (all other interventions had probabilities of being the most cost-effective that were always less than 1% for willingness-to-pay values between £0 and £100,000).

Exploratory results for the infrapopliteal arteries suggest that the use of BMSs will be cost saving relative to the comparator, and it will also improve QoL for patients. Relative to BMSs, the use of sirolimus-eluting stents is associated with an ICER of £10,571.

A particular strength of this analysis was its consideration of a large number of interventions for peripheral arterial disease. Comparing all of the interventions in a single economic evaluation reduces uncertainty in the recommendations, as all of the alternatives are evaluated in a consistent manner. The use of discrete-event simulation is also a strength. Previous studies mainly used Markov models; the use of discrete-event simulation meant that, for this analysis, a large number of patient characteristics (such as both ipsilateral and bilateral disease progression) could be tracked over time, while still keeping the model relatively transparent.

The main weakness of this study is the lack of evidence and data. Many of the trials identified by the clinical systematic review were small, meaning that some potentially important intervention effects were

not detected due to a lack of power. For example, many trials measured differences in adverse events or mortality, but none found a significant difference. Moreover, trials varied in the patient populations, particularly as regards the anatomical distribution and extent of disease and the clinical indications for intervention. In the absence of these data, the modelling required a number of assumptions, which adds to the uncertainty around the results.

This analysis modelled the effect of the interventions by their impact on patency; the lack of evidence linking patency and clinical outcomes, such as claudication distance, QoL and reintervention, is a limitation to the current analysis. It appears to be common for research in this field to use patency as a surrogate for clinical effectiveness; however, this link was not accepted for most interventions in the recent NICE guidance on peripheral arterial disease.[81] There are considerable concerns about the validity of this assumption. Whereas it seems plausible that this relationship may hold for interventions that have very similar mechanical effects, for example two identical stents, with and without drug coating, it is less clear that the degree of restenosis within a stent will have the same clinical implications as a similar degree of stenosis in an area treated by balloon alone or atherectomy.

A further problem with the assumption that clinical outcomes can be implied from patency rates is that there was little evidence on which to base assumptions regarding the costs and clinical effectiveness of retreatment. As the options for retreatment and the outcomes may vary among different primary treatments, it is possible restenosis will have differing implications for downstream costs and outcomes. In the absence of evidence on this, the model assumes a relationship between patency and retreatment that is independent of the primary procedure.

In addition, the relationships between patency of the index lesion and clinical outcomes may not be constant over time, as assumed in the analysis. For example, late adverse outcomes of PAD in patients with claudication will often relate to progressive disease at sites other that the site of initial treatment. This is partly accommodated by modelling contralateral disease progression, which patients may experience at any time (i.e. independently of patency status). In a scenario analysis in which ipsilateral disease progression was also assumed to be independent of patency, the main conclusions of the base-case analysis were unchanged. In addition, the effects of stents (either BMSs or DESs) on the target vessel are very different from those of other interventions such as stent-grafts and cryoplasty. Because of this, the nature of the relationship between vessel diameter (patency) and clinical outcomes may vary for different interventions.

As the use of paclitaxel-coated balloons is less expensive than the comparator, the results of this study still support its use even if it is assumed that there is no link between patency and QoL. This decision remains if the more pessimistic scenario of no link between patency and ipsilateral disease progression is included. However, it does assume that prolonged patency will lead to cost savings as a result of fewer reinterventions. This is based on relatively little direct evidence, although the frequency with which patency is measured in trials of endovascular treatments for PAD suggests that it is an important consideration when deciding on whether or not to perform a reintervention. In addition, it is noted that in the model failed patency will not immediately require a reintervention; on average, 26.9% of patients with IC and 71.6% of patients with CLI will receive a reintervention following failure. The model also assumes that, while patency relates to the rate of reintervention, the nature of reinterventions, and thus their cost and outcome, is independent of the initial intervention. There was no data identified that would confirm or refute this assumption.

After the acute (30 days following operation) period, the effects of each intervention on patency are assumed to be constant over time; in other words, they are assumed to follow a proportional hazards model. While there were no data to suggest that the proportional hazards assumption would not hold, this was mostly because of a lack of data on the clinical effectiveness of interventions over time. It is plausible that the modelled benefits (in particular, for the two most cost-effective interventions: paclitaxel-coated balloons and bail-out paclitaxel-eluting stents) reduce over time, as the effect of the drug

may be expected to be most effective immediately after the initial treatment. The possible effects of this on the base-case results have not been explored.

Relative to the costs of the interventions, costs related to amputation are very large. For example, the cost of an amputation is between 32% and 154% greater than the intervention costs, and the yearly cost of being an amputee is between 219% and 513% greater. Because of this, any differences in amputation rates due to intervention are likely to overwhelm differences in any other costs. None of the trials reviewed showed any effect on amputation rates, but they had not been powered to demonstrate such an effect. Thus, assumptions about the relationship between amputation and patency have the potential to drive the results of modelling. In the base-case analysis, the only effect of interventions on amputations was due to higher/lower rates of reinterventions, which result in sooner/later deaths (owing to procedural-related deaths) and, therefore, a slight decrease/increase in the potential for progressing to amputation. It is noted that this will disfavour more clinically effective treatments. When amputation-related costs were removed from the base case, the interpretations of cost-effectiveness remained unchanged.

The main uncertainties about the results presented are the assumed associations between patency and clinical outcomes. While scenario analyses have showed that the base-case results remain fairly robust to changes in these assumptions, further study into these associations would allow for more accurate modelling of the potential cost-effectiveness of the interventions, in particular for paclitaxel-coated balloons and paclitaxel-eluting stents.

Chapter 6 Conclusions

Implications for practice

Despite many studies being identified, there remains uncertainty in the results of the report. Clinically, there was evidence of a significant benefit to reducing restenosis rates for SESs, stent-graft, EVBT and DEB compared with PTA and for DESs compared with BMSs. If it is assumed that patency translates into beneficial long-term clinical outcomes, then DCBs and bailout DESs are most likely to be the cost-effective enhancements to PTA. Of these, the use of DCBs resulted in the lowest lifetime costs and greatest improvement in QoL of all the interventions, hence dominating them.

Current NICE guidance recommends PTA with bailout BMSs.[83] The NICE guidance does not consider many of the interventions considered in this report, and hence this report does not call for changes to the NICE advice for practice, but suggests areas for further research. Research into these areas is important, as a key component of the economic evaluation is the assumption that prolonged patency was associated with improved clinical outcomes; this assumption was not used in the NICE guidelines.

Recommendations for future research

A RCT comparing current recommended practice (PTA with bail-out BMSs) with DCBs and bailout DESs could assess long-term follow-up and cost-effectiveness. In addition to patency, the inclusion of health-related QoL measures EQ-5D and maximum walking distance would be useful.

Our study also indicates that, of the interventions considered, AMSs, atherectomy, EBRT, laser angioplasty, EVBT, stent-grafts and cryoplasty are all unlikely to warrant further investigation.

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Contributions of authors

Jonathan A Michaels was the principal investigator and was involved in designing the project.

Anna J Cantrell conducted the literature searches.

Emma L Simpson and **Chris Littlewood** conducted the clinical effectiveness review.

Benjamin Kearns and **Matthew D Stevenson** conducted the clinical effectiveness modelling.

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Appendix 1 Search strategy

Databases searched

Database	Host/system	Date searched	No. of hits
CENTRAL/CCTR	Cochrane Library	24 May 2011	2205
CDSR	Cochrane Library	24 May 2011	35
CINAHL 1982–	EBSCO		1074
Citation Indexes (Science and Social Sciences)	Web of Science		RCTs 2000; systematic reviews 203; economics evaluations 703
DARE	Cochrane Library	24 May 2011	100
EMBASE 1980–	Ovid		RCTs 4428; systematic reviews 453; economics evaluations 761
MEDLINE 1966–	Ovid	24 May 2011	RCTs 1311; systematic reviews 74; economics evaluations 181
NHS EED	Cochrane Library		123
NHS HTA	Cochrane Library	24 May 2011	49
MEDLINE In-Process & Other Non-Indexed Citations	Ovid	24 May 2011	RCTs 10; systematic reviews 3; economics evaluations 4

CCTR, Cochrane controlled trials reports; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects.

Other sources searched

Other source	Date searched
ClinicalTrials.gov (http://clinicaltrials.gov/)	May 2011
Current Controlled Trials (www.controlled-trials.com/)	May 2011
EMEA (www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true)	May 2011
FDA (www.fda.gov/)	May 2011
National Research Register Archive (www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx)	May 2011
NIHR Clinical Research Network Portfolio Database (http://public.ukcrn.org.uk/search/)	May 2011

FDA, Food and Drug Administration.

Relevant conference proceedings, as determined by the project team, were searched May 2011.

Proceedings of the VSGBI, the European Society of Vascular and Endovascular Surgery, the British Society of Interventional Radiology, the Cardiovascular and Interventional Radiological Society of Europe, the Society for Interventional Radiology and the Society for Vascular Surgery.

MEDLINE search strategy

Population and intervention terms

1. Peripheral Arterial Disease/
2. peripheral arter$ occlusive disease$.tw.
3. peripheral occlusive arter$ disease$.tw.
4. paod.tw.
5. peripheral arter$ disease$.tw.
6. Arterial Occlusive Diseases/
7. Peripheral Vascular Diseases/
8. peripheral vascular disease$.tw.
9. pad.tw.
10. pvd.tw.
11. Ankle Brachial Index/
12. critical limb isch?emia.tw.
13. limb salvage.tw.
14. Limb Salvage/
15. Intermittent Claudication/
16. claudicat$.tw.
17. Constriction, Pathologic/
18. femoral artery/ or popliteal artery/ or tibial arteries/
19. 17 and 18
20. (narrow$ or obstruct$ or harden$ or steno$ or resteno$ or constric$ or occlus$).tw.
21. femoral arter$.tw.
22. leg arter$.tw.
23. peripheral arter$.tw.
24. popliteal.tw.
25. infrapopliteal.tw.
26. femoropopliteal.tw.
27. or/21–26
28. 20 and 27
29. Atherosclerosis/
30. Arteriosclerosis/
31. atheroma/
32. atherosclero$.tw.
33. (arteriosclero$ or athereosclero$ or atheroma$).tw.
34. or/29–33
35. 27 and 34
36. 18 and 20
37. 17 and 27
38. 18 and 34
39. femoral atheroma$.tw.
40. angiotome.tw.
41. or/1–16,19,28,35–40

42. endovascular procedures/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/ or atherectomy/ or catheterization, peripheral/
43. stents/ or drug-eluting stents/
44. stent$.tw.
45. drug eluting.tw.
46. stent graft$.tw.
47. sirolimus paclitaxel.tw.
48. paclitaxel-eluting stent$.tw.
49. sirolimus-eluting stent$.tw.
50. nitinol.tw.
51. palmaz.tw.
52. viabahn.tw.
53. pulsar-18.tw.
54. lifestent.tw.
55. protege.tw.
56. absolute.tw.
57. xpert.tw.
58. zilver.tw.
59. haemobahn.tw.
60. turbo elite.tw.
61. atherectomy.tw.
62. silverhawk.tw.
63. turbohawk.tw.
64. wholey.tw.
65. hi-torque.tw.
66. loc.tw.
67. tad.tw.
68. atherocath.tw.
69. transluminal extraction catheter.tw.
70. tec.tw.
71. predator 360 pad system$.tw.
72. dimondback 360 pad system$.tw.
73. dimondback.tw.
74. pad system$.tw.
75. balloon$.tw.
76. cutting balloon$.tw.
77. scoring balloon$.tw.
78. high pressure balloon$.tw.
79. drug-eluting balloon$.tw.
80. cryoplasty.tw.
81. polarcath.tw.
82. paccocath.tw.
83. dior.tw.
84. genie.tw.
85. advance 18 ptx.tw.
86. advance 18.tw.
87. laser angioplasty.tw.
88. spectranetics.tw.
89. radiotherapy/ or brachytherapy/
90. radiotherap$.tw.
91. brachytherap$.tw.
92. ultraso$.tw.
93. radioisotopes.tw.

94. or/42–93
95. 41 and 94

Terms 1–41 were terms for the population and terms 42–94 were terms for the different interventions. These terms were combined together to find relevant literature and then combined with filters designed to retrieve systematic reviews, RCTs and economic evaluations, as appropriate. The filters for MEDLINE are provided below.

Randomised controlled trial filter

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/
7. clinical trial.pt.
8. exp Clinical Trial/
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
11. placebos/
12. placebos.ti,ab.
13. random.ti,ab.
14. research design/
15. or/1–14

Systematic review filter

1. Meta analysis/
2. Meta analys$.tw.
3. Metaanaly$.tw.
4. exp Literature review/
5. (systematic adj (review or overview)).tw.
6. or/1–5
7. Commentary.pt.
8. Letter.pt.
9. Editorial.pt.
10. Animals/
11. or/7–10
12. 6 not 11

Economic evaluations filter

1. Economics/
2. "costs and cost analysis"/
3. Cost allocation/
4. Cost-benefit analysis/
5. Cost control/
6. cost savings/
7. Cost of illness/

8. Cost sharing/
9. "deductibles and coinsurance"/
10. Health care costs/
11. Direct service costs/
12. Drug costs/
13. Employer health costs/
14. Hospital costs/
15. Health expenditures/
16. Capital expenditures/
17. Value of life/
18. exp economics, hospital/
19. exp economics, medical/
20. Economics, nursing/
21. Economics, pharmaceutical/
22. exp "fees and charges"/
23. exp budgets/
24. (low adj cost).mp.
25. (high adj cost).mp.
26. (health?care adj cost$).mp.
27. (fiscal or funding or financial or finance).tw.
28. (cost adj estimate$).mp.
29. (cost adj variable).mp.
30. (unit adj cost$).mp.
31. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
32. or/1–31

Appendix 2 Excluded studies

Reference	Reason for exclusion
Agostoni *et al.* 2007[110]	Population not PAD
Ahn *et al.* 1992[111]	Study design not RCT
Aldea *et al.* 1998[112]	Population not PAD
Allaqaband *et al.* 2009[113]	Study design not RCT
Aoki *et al.* 2008[114]	Population not PAD
Carreira *et al.* 2008[115]	Study design not RCT and population aortoiliac
Dalainas *et al.* 2006[116]	Study design not RCT
Das 2001[117]	Study design not RCT
Diehm *et al.* 2008[118]	Study design not RCT
Dieter *et al.* 2010[119]	Study design not RCT
Fleisher *et al.* 1987[120]	Study design not RCT
Gaines *et al.* 2005[121]	Population aortoiliac
Hall *et al.* 1993[122]	Study design not RCT
Hartnell *et al.* 1995[123]	Intervention access device
Hassan *et al.* 2010[124]	Population not PAD
Kaneda *et al.* 2009[125]	Population not PAD
Killewich 2006[126]	Study design not RCT
Jahnke *et al.* 2002[127]	Study design not RCT
Jahnke *et al.* 2003[128]	Study design not RCT
Jeans *et al.* 1990[129]	Intervention access device, and study design allocation to groups not random
Lammer *et al.* 2000[130]	Study design not RCT
London *et al.* 1993[131]	Study design not RCT
Nicholson 1998[132]	Intervention pharmacological, thrombolysis
Randon *et al.* 2010[133]	Interventions combined with other interventions that were not part of randomised allocation; no separate data for individual interventions
Roubin *et al.* 1997[134]	Population not PAD
Sen *et al.* 2005[135]	Population not PAD
Sgura *et al.* 2002[136]	Population not PAD
Tanabe *et al.* 2004[137]	Population not PAD
Tay *et al.* 2011[138]	Study design not RCT
Turco *et al.* 2006[139]	Population not PAD
Whyman *et al.* 1997[140]	Comparator medical treatment only
Wolfram *et al.* 2005[141]	Comparator combined PTA plus stent plus sham irradiation; intervention combined stent plus radiation
Zabakis *et al.* 2005[142]	Comparator combined PTA plus stent; intervention combined stent plus radiation

Appendix 3 Data extraction of included studies

Absorbable metal stent

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
AMS INSIGHT[11]	To investigate the safety of AMSs in the infrapopliteal arteries based on 1- and 6-month clinical follow-up and efficacy based on 6-month angiographic patency; and to prove the superiority of the AMS stent over PTA alone for infrapopliteal indications	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	The sponsor, BIOTRONIK AG, funded the total study costs and was responsible for the study administration and monitoring of the study	Belgium	Belgium, the Netherlands, Austria and Germany	Outcomes reported at 1 and 6 months; study follow-up 12 months

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
AMS INSIGHT[11]	AMSs vs. PTA	AMS: after measurement and then selection of a suitable balloon length, the lesion was pre-dilated with the Pleon Explorer (BIOTRONIK AG, Switzerland) balloon under angiographic control. Pre-dilatation was mandatory in this study. After dilatation, the stenosed area was treated by one AMS implant. Post-dilatation was allowed at the discretion of the physician, for cases in which angiographic control revealed suboptimal apposition of the AMS to the vessel wall or flow-limiting residual stenosis	PTA: the lesion was dilated with the Pleon Explorer balloon under angiographic control. In cases in which the residual stenosis after procedure was estimated to be > 50%, balloon inflation was repeated and prolonged. If the stenosis persisted to be > 50% or a flow-limiting dissection occurred, the patient underwent implantation of the AMS study stent and ended up in the crossover group

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
AMS INSIGHT[11]	The study population consisted of patients with symptomatic CLI (Rutherford categories 4 and 5). They were eligible if they had de novo stenotic (> 50%) or occlusive atherosclerotic disease of the infrapopliteal arteries and presented with a reference vessel diameter of between 3.0 and 3.5 mm and a lesion length of < 15 mm (i.e. less than one stent length)	Inclusion criteria: • Stenotic (> 50%) or occlusive atherosclerotic disease of the infrapopliteal arteries • Length of lesion < 15 mm (less than one stent length, changed during study to < 20 mm) • Reference vessel diameter 3.0–3.5 mm • A maximum of two lesions in one infrapopliteal vessel treated in the study, or in two vessels of two different legs (modified to allow PTA treatment of other infrapopliteal lesions in non-target vessels outside of the current study) • Symptomatic CLI (Rutherford categories 4 and 5) • Patient ≥ 50 years • Life expectancy of > 6 months • No child-bearing potential or negative serum pregnancy test within 7 days of the index procedure • Patient willing and able to return at the appropriate follow-up times for the duration of the study • Patient provision of written patient informed consent that is approved by the ethics committee Exclusion criteria: • Patient refusal of treatment • Reference segment diameter not suitable for available stent design • Length of lesion requiring more than one stent implantation • Previously implanted stent(s) or PTA at the same lesion site • Lesion lying within or adjacent to an aneurysm • Inflow-limiting arterial lesions left untreated	2005–7

Trial	Target population	Inclusion/exclusion criteria	Recruitment
		• Patient has a known allergy to heparin, aspirin or other anticoagulant/antiplatelet therapies, or a bleeding diatheses, or is unable, or unwilling, to tolerate such therapies • Patient taking phenprocoumon (Marcumar®, MEDA, Germany) • Patient history of prior life-threatening contrast medium reaction • Patient currently enrolled in another investigational device or drug trial • Patient currently breastfeeding, pregnant or intending to become pregnant • Patient had learning disability or mental health problems • Patient liable for military or civilian service	

Sample size

Trial	Numbers randomised	Number of participants in T1 (AMS)	Number of participants in T2 (PTA)	Power calculation (a priori sample calculation)	Attrition/loss to follow-up	Number followed up from each condition
AMS INSIGHT[11]	117 patients with 149 lesions	60 (74 lesions)	57 (of whom 7 crossed over to AMS) (75 lesions)	The sample size calculation for this study was based on the hypothesis of a superior efficacy of the first-generation AMS system in maintaining a patent vessel lumen at 6 months vs. PTA alone. The following were assumed at 6 months: a patency rate of 50% in the PTA arm and a clinical relevance effect of 25% in the AMS arm. With acceptance of a 10% dropout rate, a crossover rate of 30% in the PTA arm, a two-sided significance level of 0.05, and 80% statistical power, a total of 117 patients were required	Clinical follow-up at 6 months was assessed in 41 of 57 (71.9%) and 39 of 60 (65.0%) initially enrolled PTA and AMS patients, respectively. The number of patients who refused the 6-month angiogram was relatively high in both groups. Reasons for declination were diverse: patient renunciation to repeat angiography (16 patients), patient death (9 patients), major amputation (7 patients), health issues making the angiographic control problematic (5 patients) and difficulties analysing angiograms at the core lab (3 patients). One patient randomised for stenting (1/60) with a double lesion (2/74) underwent implantation of a non-study stent (SES) because of severe tortuosity of the iliac artery. Therefore, this patient is not considered in the on-treatment analysis	100% at 1-month follow-up. 6-month QVA results (regular or delayed follow-up or clinically indicated visits) were available for 50 PTA lesions (40 patients, 70%) and 44 AMS lesions (37 patients, 62%)

Baseline characteristics

Trial	Age	Gender	Classification of PAD	Presence of cardiovascular risk factors
AMS INSIGHT[11]	The mean age of patients enrolled in the study was 73.1 ± 8.5 (range, 53–91) and 74.7 ± 7.8 (55–87) years in the PTA and AMS groups, respectively	The baseline characteristics of the randomised patients are statistically not different in the two treatment groups except for gender ($p = 0.04$) (71.9% male PTA, 51.7% male AMS).	Rutherford category 4, 28.1% PTA and 26.7% AMS; category 5, 71.9% PTA and 73.3% AMS	Nicotine abuse was noted in 26 (45.6%) and 24 (40.0%) patients in the PTA and AMS groups, respectively. Comorbidities were arterial hypertension in 51 (89.5%) and 51 (85.0%), hyperlipidaemia in 35 (61.4%) and 32 (53.3%), and diabetes mellitus in 39 (68.4%) and 43 (71.7%) patients in the PTA and AMS groups, respectively

Outcomes

Trial	Complications including amputation	Patency measures
AMS INSIGHT[11]	The primary safety end point of the AMS INSIGHT was defined as the absence of clinical complications at 1 month post procedure. Complications were defined as major amputations or any cause of death. Major amputations were defined as amputations at or above the ankle. Secondary end point limb salvage was defined as lack of major amputations at the different prescheduled follow-up visits until 12 months after index intervention	The primary efficacy end point of this study was to analyse and compare the 6-month angiographic patency rate after PTA alone or PTA followed by AMS implantation in patients with stenotic or occlusive atherosclerotic disease of the infrapopliteal arteries. Patency was defined as the absence of a haemodynamically significant restenosis (> 50%), documented by digital subtraction angiography and confirmed by the core-lab QVA. The secondary end point was the primary patency rates at each visit as determined by colour-flow Doppler ultrasound and defined as either the absence of a haemodynamically significant restenosis (> 50%) derived from the ratio of the PSV at the lesion segment to that at the proximal part, a major amputation, or a TLR

PSV, peak systolic velocity.

Results

Trial	Results	Complications
AMS INSIGHT[11]	Patency: the study's primary efficacy end point was the 6-month angiographic patency rate. Six-month QVA results available for 50 PTA lesions (40 patients) and 44 AMS lesions (37 patients); ITT 58.0% (29/50 lesions) for the PTA, and 31.8% (14/44 lesions) for the AMS group ($p = 0.013$). Secondary end point was colour-flow Doppler ultrasound patency, Kaplan–Meier estimation of the primary patency rate, 6-month primary patency, ITT 88.1% for PTA only and 80.2% for AMS implantation ($p = 0.270$). Kaplan–Meier analysis of the QVA measurements resulted in an ITT-based primary patency of 61.2% after PTA and 47.2% after AMS ($p = 0.180$). Limb salvage (see also adverse events), according to the Kaplan–Meier estimation: 6-month cumulative patient limb salvage rates were calculated on an ITT basis as 92.4% PTA and 87.6% AMS ($p = 0.434$) Revascularisation: considering the ITT analysis, the incidence of TLR at 6 months was 16.0% (12/75) in the PTA group and 31.1% (23/74) in the AMS group ($p = 0.052$), where, for PTA, 66.7% (8/12) and, for AMS, 78.3% (18/23) of lesion revascularisations were clinically indicated	The primary safety end point, i.e. absence of major amputation and/or death within 30 days after index intervention, was not significantly different between the AMS study group and the PTA control group. At 1 month, major amputation was undertaken in four patients: two in the PTA group (2/57) and two in the AMS arm (2/60). 1 of 57 PTA patients and 1 of 60 AMS patients died before the 1-month follow-up. The ITT analysis of the complication rate within 30 days yielded values of 5.3% (3/57) and 5.0% (3/60) in patients randomised for PTA alone and PTA followed by AMS implantation, respectively ($p = 1.0$)

Self-expanding stent

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Dick *et al.* 2009[12]	To investigate whether primary nitinol stenting is associated with a morphological and clinical benefit when compared with PTA with optional stenting in intermediate-length lesions	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	NR	Austria	Austria	Outcomes at 3, 6 and 12 months
VascuCoil[13]	To estimate and compare hospital costs associated with PTA and stent placement for patients with symptomatic peripheral arterial disease; the authors performed a prospective economic evaluation in conjunction with the Intracoil femoropopliteal stent trial (VascuCoil)	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	Supported in part by a grant from IntraTherapeutics, St Paul, MN, USA, the funding agreement ensured the authors' independence	USA	USA	Outcomes at 30 days and 9 months
FAST[14]	Designed to investigate the impact of nitinol stenting of SFA lesions, with a maximum length of 10 cm, on restenosis and clinical outcomes at 1 year	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	Sponsored by C.R. Bard Inc., Murray Hill, NJ, USA	Germany	11 European centres, Germany, Austria, Belgium, Switzerland	12 months
RESILIENT[15]	To compare a new, flexible nitinol stent to PTA for the treatment of obstructive lesions of the SFA and the proximal popliteal artery in patients with IC	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	From ClinicalTrials.gov; sponsored by C.R. Bard CardioVascular Research Foundation, Korea	USA	24 centres in the United States and Europe (Germany, Austria)	12 months
ABSOLUTE[16–18]	To determine whether primary implantation of a self-expanding nitinol (nickel titanium) stent yielded anatomical and clinical benefits superior to those afforded by PTA with optional secondary stenting	RCT, prospective, single centre	Full report in peer-reviewed journal	English	Supported by the Medical University of Vienna and the Vienna General Hospital (The authors have no commercial, proprietary or financial interest in any products or companies)	Austria	Austria	Outcomes at 6 months, 12 months and 24 months

NR, not reported; SFA, superficial femoral artery.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Dick *et al.* 2009[12]	Primary nitinol stenting is associated with a morphological and clinical benefit when compared with PTA with optional stenting	Stent group: self-expandable nitinol stents (Astron, Biotronik GmbH, Berlin, Germany) with a nominal diameter of 6 mm were used. Pre-dilatation with undersized balloons was performed restrictively in patients with very tight stenosis or heavily calcified 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. Post-dilatation after stenting was performed strictly within the stented segment with up to 10% oversizing of the post-dilatation balloon	PTA group: the minimal time for each balloon inflation was 2 minutes at 10–12 atm. After dilatation of the entire target segment, biplane control angiograms were obtained. In cases with a suboptimal primary result, defined as a residual stenosis > 30% or presence of a flow-limiting dissection in the worst angiographic view, a second prolonged balloon dilatation (> 2 minutes) of the target segment was performed. In patients with a persistent suboptimal result after the second balloon dilatation, secondary stenting was performed
VascuCoil[13]	PTA vs. IntraCoil stent	IntraCoil stent	PTA alone
FAST[14]	Nitinol stenting vs. PTA	Direct implantation without lesion pre-dilatation was preferably performed. In tight stenoses and totally occluded lesions that precluded stent advancement, angioplasty with a 3-mm-diameter balloon was done to enable stent placement. The stent dimensions were chosen such that the nominal diameter exceeded the reference vessel diameter by 1 mm and the length exceeded the lesion length by 5–10 mm proximal and distal. The intention was to cover the entire lesion with a single stent. Protocol-mandated post-dilatation utilised a balloon shorter than the stent. Technical success was defined on-site as a residual diameter stenosis < 30% by visual estimate. Deployment of a second study stent abutting the index stent was allowed in cases in which the latter was positioned incorrectly or a dissection extended beyond the stent margins	An over-the-wire PTA balloon was advanced into the lesion. Its nominal diameter had to be roughly the same as the reference vessel diameter, and its length had to match the lesion length, with a maximum proximal and distal balloon overhang of 5 mm. The balloon was gradually inflated until the lesion diameter appeared to be visually identical to the reference vessel diameter. When vessel recoil after balloon deflation was taken into account, the procedure was regarded as technically successful by the investigator if the residual diameter stenosis was estimated at < 50% (later validated off-site by independent ultrasound analysis). In cases in which this end point was not reached or a flow-limiting dissection occurred, balloon inflation was repeated once for at least 5 minutes. If technical failure persisted after repeat angioplasty, the patient underwent implantation of the study stent

Population inclusion

Trial	Target Population	Inclusion/exclusion criteria	Recruitment
Dick *et al.* 2009[12]	The clinical criterion for study entry was symptomatic PAD with either severe IC (Rutherford category 3) or chronic CLI with rest pain (Rutherford category 4) or ischaemic ulcers (Rutherford category 5)	The clinical criterion for study entry was symptomatic PAD with either severe IC (Rutherford category 3) or chronic CLI with rest pain (Rutherford category 4) or ischaemic ulcers (Rutherford category 5). Anatomical inclusion criteria, based upon findings on biplane digital subtraction angiography at the time of intervention, were a > 50% stenosis or occlusion of the SFA with a target lesion length between 30 and 200 mm, and at least one patent (< 50% stenosis) tibioperoneal run-off vessel. Exclusion criteria were acute CLI, previous BS 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	Consecutive patients; year NR
VascuCoil[13]	Patients with stenotic or occluded superficial femoral or popliteal arteries	Eligible patients were candidates for PTA with symptomatic leg ischaemia, requiring treatment of superficial femoral or popliteal vessel with an occluded lesion length of at least 12 cm or stenotic lesion length of at least 15 cm, and located proximal to the bifurcation of the tibial artery	Between May 1997 and December 1999
FAST[14]	A single SFA lesion and CLI	Patients were eligible for enrolment if they were ≥ 21 years and had a de novo SFA lesion located at least 1 cm from the 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 one of the infrapopliteal (below-the-knee) vessels had to be continuously patent for sustained distal runoff. Clinically, the patients had to suffer from CLI of at least Rutherford category 2 (moderate claudication). Major exclusion criteria were 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 occlusion; an untreated ipsilateral iliac artery stenosis; ongoing dialysis treatment; and treatment with oral anticoagulants other than antiplatelet agents	2004–2005

Trial	Target Population	Inclusion/exclusion criteria	Recruitment
RESILIENT[15]	Patients with obstructive lesions of the SFA, proximal popliteal artery or both	Patients eligible for inclusion in the study were aged ≥ 18 years; had symptoms of IC (Rutherford categories 1–3); were candidates for angioplasty or stenting; had de novo stenotic, occlusive, or restenotic lesions in the SFA, proximal popliteal artery, or both; and had at least one patent infrapopliteal runoff vessel to the foot. The treatment area in the SFA and popliteal artery extended from 1 cm below the origin of the profunda femoris artery to approx. 3 cm above the intercondylar notch of the femur. Target lesions were examined angiographically to verify stenosis or restenosis ≥ 50% and a total lesion length of ≤ 150 mm. More than one lesion in the target vessel could be treated as long as the total length of the lesions did not exceed 150 mm. To allow for proper stent sizing, the reference vessel diameter was required to be between 4 and 6.5 mm. If a restenosed or reoccluded lesion was treated, the previous intervention must have occurred > 6 months before the study procedure and must not have included stenting. If a patient had multiple lesions in the SFA and popliteal arteries of both limbs (i.e. bilateral disease), only one limb could be enrolled in the study. Exclusion criteria included a sensitivity to contrast media that was not amenable to pretreatment with steroids, antihistamines or both; known allergies to study medications or materials; renal failure (serum creatinine > 2.0 mg/dl) or hepatic insufficiency; previous BS of the target limb; extensive peripheral vascular disease that precluded safe insertion of an introducer sheath; aneurysmal disease in the vessel segment to be treated; thrombus in the area to be treated that could not be resolved; or angiographic evidence of poor inflow that was inadequate to support vascular bypass or patients who were receiving dialysis or immunosuppressive therapy	Between December 2004 and August 2006
ABSOLUTE[16–18]	Patients who had severe claudication or CLI due to stenosis or occlusion of the SFA	The clinical criteria for study entry were symptomatic peripheral artery disease with severe IC (Rutherford category 3), chronic CLI with pain while the patient was at rest (Rutherford category 4), or chronic CLI with ischaemic ulcers (Rutherford category 5). The anatomical inclusion criteria, based on biplane digital subtraction angiography performed at the time of intervention, were stenosis of > 50% or occlusion of the ipsilateral SFA, a target lesion length of > 30 mm, and at least one patent (< 50% stenosed) tibioperoneal runoff vessel. The exclusion criteria were acute CLI, previous BS or stenting of the SFA, untreated inflow disease of the ipsilateral pelvic arteries (> 50% stenosis or occlusion) and known intolerance to study medications or contrast agents	From June 2003 through August 2004, consecutive patients. A total of 252 patients were screened for participation in the study. Of these, 143 did not meet the inclusion criteria

NR, not reported; SFA, superficial femoral artery.

Sample size

Trial	Numbers included in the study	Number of participants in T1	Number of participants in T2	Power calculation (a priori sample calculation)	Number (%) followed up from each condition (or attrition)
Dick *et al.* 2009[12]	73	34 nitinol stent	39 PTA (of whom 10 had stenting)	A sample size of 70–80 patients was estimated necessary assuming a 6-month restenosis rate of 60% in the PTA group vs. 25% in the nitinol stent group. A two-sided *p*-value of 0.05 was considered statistically significant and a power of 80% was required with a 10% maximum dropout rate	Complete follow-up data could be obtained for 71 of 73 patients (97%) at 3 months, and in 68 of 73 patients (93%) at 6 and 12 months, respectively. Follow-up data were not available in two patients at 3 months (one died and one refused re-evaluation) and in five patients at 6 and 12 months (three died, two refused re-evaluation)
VascuCoil[13]	266	135 stent (177 lesions)	131 PTA (175 lesions)		
FAST[14]	244	123 stent	121 PTA (13 of whom crossed over to stent)	The sample size calculation for this trial was based on the assumptions of 12-month binary restenosis rates of 45% in the PTA arm and 25% in the stent arm (an absolute difference of 20%). With acceptance of a 15% lost to follow-up rate, a two-sided significance level of 0.05, and 80% statistical power, a total of 244 patients had to be enrolled	Clinical follow-up at 12 months was assessed in 115 PTA group patients (95%) and 114 stent group patients (93%). The change in the patients' clinical and haemodynamic statuses, in terms of absolute walking distance, ABPI at rest and Rutherford category, was assessed in a subset of 61 stent group patients (50%) and 75 PTA group patients (62%) who were able to undergo treadmill testing both at baseline and at 12 months

Trial	Numbers included in the study	Number of participants in T1	Number of participants in T2	Power calculation (a priori sample calculation)	Number (%) followed up from each condition (or attrition)
RESILIENT[15]	206	134 stent	72 PTA [of whom 29 (40.3%) underwent a secondary bail-out stenting procedure because of an inadequate PTA result]	A minimum sample size of 206 patients was needed to detect a 14% difference in the TVR and TLR rate at 6 months post procedure with a statistical power of 80% (one-sided simple log-rank test with a significance level of 0.05). The 14% difference was based on calculated TVR rates of 26% for the control group and 12% for the test group at 6 months post procedure. A crossover rate of $\leq$ 16% was assumed for the RESILIENT[15] trial. A dropout rate of 7% (2% death; 5% lost to follow-up) was assumed for the log-rank-test-based sample size calculation	Follow-up data were available on 87% of patients at 12 months (87.5% for the stent group and 86.8% for the angioplasty group). Seven patients died, nine patients withdrew consent to be evaluated, and three patients were lost to follow-up
ABSOLUTE[16–18]	104	51 stent	53 PTA [of whom 17 (32%) underwent secondary stenting]	We estimated that 100–110 patients would need to be enrolled for the study to have a statistical power of 80% to detect an absolute difference in restenosis rates of 25%, given 6-month rates of restenosis of 50% in the angioplasty group and 25% in the stent group and a maximal dropout rate of 10%	Complete follow-up data were obtained from all 104 patients at 3 and 6 months. Data were not available for three patients at 12 months (one died and two declined to be re-evaluated)

Baseline characteristics

Trial	Age (years) [mean (SD)]	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance	Other relevant information
Dick *et al.* 2009[12]	Stent 69 (9), PTA 69 (10)	Stent 74% male; PTA 64% male	Clinical stage of PAD (Rutherford): category 3 (IC), stent *n* = 31 (91%), PTA 38 (97%); category 4 (ischaemic rest pain), stent 1 (3%), PTA 0; category 5 (ischaemic ulcers) stent 2 (6%), PTA 1 (3%)		• Family history of atherosclerosis: stent 14 (42), PTA 19 (50) • Hypertension: stent 27 (79), PTA 33 (85) • Antihypertensive medication at baseline: stent 28 (82), PTA 31 (80) • Hyperlipidaemia: stent 31 (91), PTA 36 (92) • Statin treatment at baseline: stent 28 (82), PTA 32 (82) • Diabetes mellitus: stent 10 (29), PTA 12 (31) • Smoking at baseline: stent 12 (35), PTA 17 (44) • Symptomatic coronary artery disease: stent 12 (35), PTA 12 (31) • History of myocardial infarction: stent 7 (15), PTA 6 (15) • History of stroke: stent 2 (6), PTA 2 (5)	Maximum walking distance (m): stent mean 131 (SD 188), PTA 103 (92). Walking distance was assumed "0" in patients with CLI and ischaemic rest pain or ischaemic ulcers	Mean lesion length (SD) (mm): stent group 82 (67); PTA group 65 (46)

Trial	Age (years) [mean (SD)]	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance	Other relevant information
VascuCoil[13]	Stent 66.8 (10.6); PTA 68.1 (10.2)	Stent, 67.4% male; PTA, 63.4% male			• Diabetes mellitus: stent 35%, PTA 37.4% • History of smoking: stent 81.9%, PTA 80% • Prior myocardial infarction: stent 37.2%, PTA 29.1%		Total occlusion: stent 22.7%, PTA 16.8%
FAST[14]	66 (10)	168 men (69%), 76 women	Rutherford category of PAD; data available from 119 stent and 114 PTA patients: 1. 0 – asymptomatic: stent 0.8%, PTA 0.9% 2. 2 – mild/moderate claudication: stent 35/119 (29.4%), PTA 36/114 (31.6%) 3. 3 – severe claudication: stent 80/119 (67.2%), PTA 73/114 (64.0%) 4. 4 – ischaemic pain at rest: stent 1/119 (0.8%), PTA 3/114 (2.6%) 5. 5 – minor tissue damage: 2/119 (1.7), 1/114 (0.9)	Prior peripheral vascular intervention: stent 42 (34.1), PTA 49 (40.5)	• Diabetes mellitus: stent 44 (35.8), PTA 37 (30.6) • Insulin-dependent diabetes mellitus: stent 12 (9.8), PTA 12 (9.9) • Non-insulin-dependent diabetes mellitus: stent 32 (26.0), PTA 25 (20.7) • Hypertension: stent 102 (82.9), PTA 100 (82.6) • Hyperlipidaemia: stent 74 (60.2), PTA 74 (61.2) • Smoking (past/current): stent 84 (68.3), PTA 88 (72.7) • Renal insufficiency: stent 18 (14.6), PTA 7 (5.8) • History of coronary artery disease: stent 52 (42.3), PTA 38 (31.4) • History of stroke/TIA: stent 13 (10.6), PTA 7 (5.8)	Absolute walking distance (m) [median (IQR)]: stent 110 (68–163) (*n* = 97), PTA 100 (60–150) (*n* = 99)	In both treatment groups the mean lesion length was 45 mm

Trial	Age (years) [mean (SD)]	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance	Other relevant information
RESILIENT[15]	Stent 68 (10), PTA 66 (9)	Stent, 95 men (70.9%); PTA, 48 men (66.7%)	Rutherford category: 1. 1 – mild claudication: stent 4 (3.0%), PTA 5 (6.9%) 2. 2 – moderate claudication: stent 48 (35.8%), PTA 30 (41.7%) 3. 3 – severe claudication: stent 82 (61.2%), PTA 36 (50.0%)	Patients with restenosis: stent 4 (2.6), PTA 2 (2.5)	• Hypertension stent: 112 (83.6), PTA 68 (94.4) • Hypercholesterolaemia: stent 107 (79.9), PTA 55 (76.4) • Diabetes: stent 51 (38.1), PTA 28 (38.9) • Smoking status (current/past): stent 96 (71.6), PTA 60 (83.3) • Coronary artery disease: stent 75 (56.0), PTA 39 (54.2) • Myocardial infarction: stent 27 (20.1), PTA 19 (26.4)		Mean lesion length (SD) (mm): stent group 70.5 (44.3); PTA group 64.4 (40.7)
ABSOLUTE[16–18]	Stent 65 (10), PTA 68 (10)	Stent, 30 men (59%); PTA, 25 men (47%)	Rutherford category of PAD [*n* (%)]: category 3 – stent 45 (88), PTA 46 (87); category 4 – stent 1 (2), PTA 2 (4); category 5 – stent 5 (10), PTA 5 (9)		• Hypertension: stent 48 (94), PTA 47 (89). Hyperlipidaemia: stent 47 (92), PTA 46 (87) • Diabetes mellitus: stent 22 (43), PTA 17 (32) • Smoking at baseline: stent 27 (53), PTA 19 (36) • Coronary artery disease: stent 34 (67), PTA 40 (75) • History of myocardial infarction: stent 10 (20), PTA 4 (8) • History of stroke: stent 2 (4), PTA 5 (9)		Mean lesion length (SD) (mm): stent group 132 (71); PTA group 127 (55)

IQR, interquartile range; SD standard deviation; TIA, transient ischaemic attack.

Outcomes

Trial	QoL (disease specific or generic)	Exercise tolerance/ walking distance	Pain/ clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Dick *et al.* 2009[12]		Maximum walking capacity as reported by the patient (3, 6 and 12 months)		Amputation and death (until 12 months)	The primary study end point was the occurrence of restenosis in the treated segment within 6 months post intervention by CTA. Restenosis was defined as a > 50% lumen diameter reduction at the most narrow site within the limits of the treated segment plus the adjacent 10 mm proximal and distal to the treated segment. Secondary end point was restenosis measured by ultrasound binary restenosis of > 50% by duplex ultrasound defined as PSV of at least 2.4	
VascuCoil[13]				Death, myocardial infarctions, amputation, adverse events		TLR
FAST[14]		Absolute walking distance	Rutherford category	Complications	The primary study end point was binary restenosis, defined as a proximal PVR ≥ 2.4 on duplex ultrasound	TLRs were performed only if two conditions were met: (1) the patient complained of recurrent claudication, and (2) on-site duplex ultrasound revealed target lesion restenosis

Trial	QoL (disease specific or generic)	Exercise tolerance/ walking distance	Pain/ clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
RESILIENT[15]	Short Form 8 Question Health Survey	Walking Impairment Questionnaire		Adverse events composite measure (MACE)	Radiographs of the stented limbs were taken 6 and 12 months post procedure and assessed for stent fractures by the angiographic core laboratory	Survival from TLR/TVR
ABSOLUTE[16–18]	SF-36	Maximal walking capacity on the treadmill	Rutherford category of PAD	Complications: amputation by 6 or 12 months; and death by 6 or 12 months	The primary study end point was the rate of binary restenosis (stenosis of ≥ 50% of the luminal diameter) in the treated segment 6 months after intervention, as determined by CTA or digital subtraction angiography Restenosis was defined as a reduction in the luminal diameter of > 50% according to the worst angiographic view at the narrowest site within the treated segment plus the 10-mm segments proximal and distal to the treated segment. The anatomical end points were restenosis of > 50%, as determined by duplex ultrasound at 3, 6 and 12 months; the angiographic degree of restenosis (the per cent reduction in diameter at 6 months); and the occurrence of stent fractures, as determined by biplane radiography at 6 and 12 months	Need for ipsilateral PTA/stent/BS

CTA, computed tomographic angiography; PSV, peak systolic velocity; PVR, peak velocity ratio.

Results

Trial	Results	Complications
Dick *et al.* 2009[12]	Restenosis: at 6 months the angiographic binary restenosis rate by CTA was 21.9% in the stent group vs. 55.6% in the PTA group ($p = 0.005$) as analysed by ITT. By ultrasound, restenosis rates in the stent and PTA groups at 3, 6 and 12 months were 2.9% vs. 18.9% ($p = 0.033$), 18.2% vs. 50.0% ($p = 0.006$) and 34.4% vs. 61.1% ($p = 0.028$), respectively. Walking: Patients in the stent group reported a significantly higher maximum walking capacity than those in the PTA group at 6 months (average 800 m vs. 600 m, $p = 0.002$) and at 12 months (average 800 m vs. 550 m, $p = 0.042$)	In the PTA group, one small pseudoaneurysm at the puncture site was observed at day 1 after the intervention. This minor complication was resolved by prolonged ultrasound-guided compression without clinical sequelae. No major complication was encountered in either treatment group
VascuCoil[13]	Incidence of TLR (9 months): stent 0.7%, PTA 1.5%. Incidence of amputation: stent 0.0%, PTA 0.8%	Death (unclear if 30 days or 9 months): stent 0.0%, PTA 0.8%. Myocardial infarctions: stent 0.0%, PTA 0.0%. Major bleeding complications: stent 0.7%, PT 0.8%. Renal failure: stent 0.0%, PTA 0.8%. Major vascular complications: stent 3.0%, PTA 4.6%. Abrupt closure: stent 0.0%, PTA 1.5%. Subacute closure: stent 0.7%, PTA 1.5%. Abrupt and subacute closure were non-significant between groups
FAST[14]	Limb salvage: lower-limb amputations because of pre-existing gangrene had to be performed in two stent group patients (1.8%). Walking: at 12 months, PTA and stent group patients were able to maximally walk a median of 185 m and 150 m, respectively, on the treadmill, which corresponded to a statistically significant difference in median walking distance improvement (52 vs. 20 m, respectively; ANCOVA $p = 0.028$). Restenosis: duplex ultrasound recordings at 12 months were available from 101 PTA group patients (83%) and 101 stent group patients (82%). Intention-to-treat analysis yielded binary restenosis rates of 38.6% (39 patients) in the stent group and 31.7% (32 patients) in the PTA group (absolute treatment difference, 6.9%; 95% CI, 19.7% to 6.2%; $p = 0.377$). Revascularisation: the cumulative incidence of TLRs at 12 months was 18.3% (21 patients) in the PTA group and 14.9% (17 patients) in the stent group (absolute treatment difference, 3.4%; 95% CI, 13.0% to 6.4%; $p = 0.595$). Disease state: an improvement by ≥ 1 Rutherford category of peripheral arterial disease was observed at 12 months in a total of 122 patients (90%), with no statistically significant difference between treatment modalities	Mortality: There was one death (of a carcinoma) at 11.6 months in the PTA group (0.9%), and four deaths (3.5%) occurred at a median of 8.0 months (IQR, 4.9–9.1 months) in the stent group. The cause of death in the latter patients was a carcinoma, multiple organ failure and severe three-vessel coronary artery disease; the cause remains unknown in one patient. Stent integrity at 12 months was assessed in 83 of 101 patients; stent fractures were detected in 10 of 83 patients. Procedural complications: stent $n = 8$ (7%), PTA $n = 5$ (4%)

Trial	Results	Complications
RESILIENT[15]	Reintervention: freedom from TLR at 6 months post procedure was significantly better for the stent group than for the angioplasty group (98.5% vs. 52.6%; $p = 0.0001$) and remained significantly better for the stent group (87.3% vs. 45.1%; $p = 0.0001$) at 12 months. Patency: primary patency, a combination of ultrasound-confirmed patency and absence of TLR, was significantly better for the stent group than for the angioplasty group at 6 months and 12 months post procedure ($p = 0.0001$). The 6-month primary patency rate for the stent group was 94.2% compared with 47.4% for the angioplasty group, whereas the 12-month primary patency rate was 81.3% for the stent group vs. 36.7% for the angioplasty group. QoL: both treatment groups demonstrated a significant improvement in all QOL measures (i.e. both SF-8 Question Heath Survey and Walking Impairment Questionnaire) at 6 and 12 months compared with baseline. The baseline SF-8 Question Heath Survey physical score was 41.0 (SD 10.5) in the angioplasty group and 41.4 (SD 9.2) in the stent group. At 12 months, the Short Form 8 Question Heath Survey scores had increased similarly in both groups [5.9 (SD 11.2) vs. 5.7 (SD 11.2); $p < 0.0001$ vs. baseline]. Walking distance: the 12-month walking distance score was 22.3 (SD 23.2) in the angioplasty group and 22.8 (SD 24.2) in the stent group. At 12 months, walking distance scores had increased similarly in both groups [29.4 (SD 37.4) vs. 25.6 (SD 34.6); $p < 0.0001$ vs. baseline]. Patients in the angioplasty group reported more claudication pain at 12 months than patients in the stent group (Walking Impairment Questionnaire evaluation, $p = 0.009$), but there were no other significant differences in QOL measures between treatment groups (*t*-test $p > 0.05$)	No patients in either arm of the study died within 30 days of the procedure. There was no statistically significant difference between the MACE rates for the treatment groups Freedom from MACE at 6 months for the stent group was 93.1% and for the angioplasty group 92.8% ($p = 0.95$). At 12 months, freedom from MACE was 85.8% for the stent group and 86.6% for the angioplasty group ($p = 0.88$). There were two unplanned amputations reported in the angioplasty group over 12 months. Both were minor, below-the-level-of-the ankle (single-toe) amputations. No amputations were reported in the stent group

Trial	Results	Complications
ABSOLUTE[16–18]	Restenosis: at 6 months, the rate of restenosis on angiography was 24% in the stent group and 43% in the angioplasty group, according to the ITT ($p = 0.05$). At 6 months, the rate of restenosis on duplex ultrasonography was 25% in the stent group and 45% in the angioplasty group ($p = 0.06$). At 12 months, the restenosis rate on duplex ultrasonography was 37% in the stent group and 63% in the angioplasty group ($p = 0.01$). Multivariable analysis adjusted for age, sex, presence or absence of diabetes, smoking status, stage of PAD and lesion length confirmed that, as compared with patients who underwent angioplasty, patients who underwent stenting had a reduced risk of restenosis at 6 months (adjusted RR, 0.45; 95% CI, 0.20 to 0.94) and 12 months (adjusted RR, 0.40; 95% CI, 0.19 to 0.80). There was no significant interaction between treatment assignment and the risk of restenosis according to the stage of PAD or the length of the lesion, indicating that the benefit of stenting did not vary according to these strata. Restenosis rates at 2 years were 45.7% (21 of 46) vs. 69.2% (36 of 52) in favour of primary stenting over balloon angioplasty with optional secondary stenting by an ITT analysis ($p = 0.031$). Reintervention rates at 1 year tended to be lower after primary stenting [17 of 46 (37.0%) vs. 28 of 52 (53.8%); $p = 0.14$). At 2 years, reintervention rates tended to be lower after stenting than after balloon angioplasty, but this also was not statistically significant [26 of 63 (41.3%) vs. 19 of 35 (54.3%); $p = 0.30$). Walking distance: patients in the stent group were able to walk significantly further on a treadmill than those in the angioplasty group at 6 months (average distance, 363 vs. 270 m; $p = 0.04$) and 12 months (average distance, 387 vs. 267 m; $p = 0.04$). Clinical worsening was rare in both groups. Clinically, Rutherford categories of PAD at 2 years were not significantly different between the two groups. Stent vs. balloon QoL, analysed according to the ITT: no significant difference for any parameter of QoL at any time interval between the balloon angioplasty and stent groups when comparing the 51 patients with primary stenting vs. the 53 patients with balloon angioplasty and optional secondary stenting in 17 patients (role-emotional was lower for PTA than stent with borderline significance level; $p = 0.04$)	

ANCOVA, analysis of covariance; CTA, computed tomographic angiography; IQR, interquartile range; SD, standard deviation.

Balloon-expandable stent

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Becquemin *et al.* 2003[19]	To compare results of systematic or selective stenting of the superficial femoral artery after balloon angioplasty in patients with lesions < 7 cm and disabling claudication or lower limb critical ischaemia	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	Supported by grants from Cordis, a Johnson & Johnson company, Miami Lakes, FL, USA; Lafon; Aventis; and Societe Francaise de Chirurgie Vasculaire	France	France	Outcomes at 1 and 4 years. Median follow-up was 2.43 years (SE 0.08), ranging from 8 days to 4 years
Cejna *et al.* 2001[20]	To evaluate if stent placement is superior to PTA in the treatment of chronic symptoms in short femoropopliteal arterial lesions	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	Supported by the Ludwig Boltzmann Institute for Radiological Tumour Diagnosis and Johnson & Johnson Interventional Systems, Warren, NJ, USA	Austria	Four hospitals in Austria	Outcomes at 6, 12 and 36 months. Mean follow-up time was 352 days (range, 1–1252 days) for PTA group and 353 days (range, 1–1215 days) for the stent placement group
Grimm *et al.* 2001[21]	To evaluate whether PTA combined with Palmaz stent placement provides long-term advantages compared with PTA alone after 34 months of follow-up in the femoropopliteal region	RCT, prospective, single centre	Full report in peer-reviewed journal	English	NR	Germany	Germany	Maximum study follow-up 39 months; mean stent 29.1 months, PTA 33.8 months

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Rand *et al.* 2006[22]	To determine the primary success and short-term patency of stent application as a primary treatment modality for high-grade lesions of the infrapopliteal arteries compared with treatment with PTA in CLI	RCT, prospective, multicentre (pilot study)	Full report in peer-reviewed journal	English	This study was supported by the Ludwig Boltzmann Institute for Radiological Tumour Diagnosis and the Ludwig Boltzmann Institute of Interdisciplinary Vascular Research	Austria	Austria. 44 patients were consecutively investigated and randomised at one centre to treatment of lesions by either PTA or stent application. Seven patients were enrolled from two other centres. (It is unclear whether the other centres were in Austria or the USA)	Outcomes at 6 months
Vroegindeweij *et al.* 1997[23]	To evaluate whether balloon angioplasty combined with stenting of symptomatic femoropopliteal disease would provide better results than balloon angioplasty alone	RCT, prospective	Full report in peer-reviewed journal	English	NR	Netherlands	Netherlands	Outcomes at 1 year reported (survival curves up to 18 months). Median of 14.1 months (range 0–31 months) in patients with PTA and 13.4 months (range 0–27 months) in stent patients
Zdanowski *et al.* 1999[24]	To investigate the 1-year outcome of PTA and stenting and PTA alone for femoropopliteal occlusions	RCT, prospective	Full report in peer-reviewed journal	English	NR	Sweden	Sweden	The follow-up included clinical examination, measurement of ABPI and control angiography at 12 months or earlier when necessary (20 patients)

NR, not reported; SE, standard error.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Becquemin *et al.* 2003[19]	BESs vs. PTA (with selective stent)	Balloon expandable Palmaz stents (Cordis or Johnson & Johnson interventional systems) of various sizes. In the group of patients allocated to undergo primary stenting, the stent was placed either before or after dilatation of the lesion. Two stents were placed in lesions > 5 cm	Lesions were approached through an ipsilateral femoral puncture. With angiographic guidance, a 0.89-mm Terumo (Leuven, Belgium) guide wire was passed through the lesion. A balloon dilating catheter was placed in the lesion and inflated to 8–12 atm. Non-compliant balloon catheters (Ultra-thin™, Meditech, Boston Scientific, Boston, MA, USA) were used in 82% of patients, and Olbert balloon catheters (Cordis) were used in 18% of patients. Half a milligram per kilogram of body weight of standard heparin was administered before dilatation. In the group of patients randomised to undergo balloon angioplasty, if results were suboptimal as demonstrated on the control angiogram, i.e. residual stenosis > 30% or dissection, the balloon was inflated one more time in an attempt to model the lesions. According to the results, the physician had the choice of retracting the balloon catheter without any further intervention or placing a stent
Cejna *et al.* 2001[20]	PTA vs. PTA followed by implantation of balloon expandable Palmaz stents	BESs: the Palmaz stent (P294 or P394, Johnson & Johnson Interventional Systems, Warren, NJ, USA) was mounted on an Olbert balloon (4–6 mm diameter, 4 cm length). The stent was pressed under high-pressure conditions against the stenotic lesion for 30 seconds. In long lesions (4–5 cm in length), a second stent was placed overlapping the first by at least 5 mm	PTA: all interventions were performed with use of digital subtraction angiographic equipment. After antegrade puncture of the common femoral artery by means of the Seldinger technique, a 7-F introducer sheath was inserted into the superficial femoral artery. 5000 units of heparin were administered intra-arterially. The lesion was crossed with the use of a Bentson guide wire (Boston Scientific/ Meditech, Natick, MA, USA) or a Terumo wire (Radifocus®, Terumo Europe, Leuven, Belgium) with use of road mapping. Once the lesion was crossed, balloon dilatation was performed for 30 seconds with use of a Gruentzig-type balloon (2 or 4 cm length) 4–6 mm in diameter under high pressure (8–12 atm) (Smash balloon™, Glidex balloon, Boston Scientific/Meditech). Biplane angiography was performed to evaluate technical success

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Grimm *et al.* 2001[21]	Balloon expandable Palmaz stent vs. PTA	Stent: A balloon expandable Palmaz stent (P294, Cordis, Roden, The Netherlands) made from stainless steel (alloy 316L) was used. The thickness of its struts was 0.14 mm and its length, if not expanded, was 29 mm. Expanding the stent to a diameter of 5 or 6 mm leads to a reduction of its length to 28.7 or 27.8 mm, respectively. After a 7-F sheath (Super Arrow, Flex, 65 cm, Arrow, Reading, PA, USA) was placed via antegrade puncture of the common femoral artery, the femoropopliteal lesion was passed with a hydrophilic guide wire (0.81 mm, curved tip; Terumo, Tokyo, Japan) and a multipurpose catheter (5-F, 0.89-mm interior diameter, open tip; Cordis). The sheath was flushed continuously with heparinised (1 IU/ml) saline. Each lesion was dilated with a balloon catheter (5 or 6 mm in diameter, 20 or 40 mm in length, depending on the vessel diameter proximal and location of the lesion; Meditech/Boston Scientific, Watertown, MA, USA). After removing the catheter, the sheath was placed distal to the lesion and the stent (4 cm in length) was mounted on the appropriate balloon catheter and placed within the lesion inside the covering sheath. After cautiously retracting the sheath, the stent was deployed by inflating the balloon	PTA (angioplasty as for intervention without stent)
Rand *et al.* 2006[22]	PTA vs. carbofilm-coated (and balloon expandable) stents in infrapopliteal arteries	The Carbostent is a balloon expandable, stainless steel tubular stent with innovative multicellular design and a carbon coating. Stent applications were performed using a 0.36-mm guide wire (HI-Torque, Spartacore™ 14, Guidant Corporation, Santa Clara, CA, USA) and Carbostents with a diameter range of 2.0–4 mm and a length of 15–25 mm. Primary stenting was performed. Adjunct therapy for the stent group consisted of clopidogrel (Plavix), administered as a bolus of 300 mg on the day of the procedure and 75 mg per day orally for 4 weeks, and acetylsalicylic acid (ASA, ThromboAss) medication permanently	PTA: an ipsilateral, femoral antegrade puncture technique was primarily used (4-Fr or 5-Fr haemostatic introducer; Cook introducer set, William Cook, Europe and Ultimum, St. Jude Medical Diagnostic Division, Minnetonka, MN, USA). Contralateral femoral access was used only if the antegrade access was unsuitable. After arterial cannulation with an introducer sheath, 5000 units of heparin were administered intra-arterially. The lesions were assessed visually by the interventional radiologist and the balloon diameter was selected to equal the diameter of the artery. Lesions were routinely treated with a 5-Fr conventional balloon angioplasty catheter and guide wire. Postinterventional anticoagulation therapy for the PTA group consisted of low-molecular-weight heparin (Enoxoparin 2 × 40 mg) for 3 days and acetylsalicylic acid (ASA; ThromboAss, 100 mg per day permanently)

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Vroegindeweij *et al.* 1997[23]		Stent: Palmaz stents were placed at angiographically identified lesions and expanded by balloon angioplasty. The lesions were not pre-dilated before stent placement. We attempted to cover the entire diseased section of the vessel with one stent. The length of the stents ranged from 20–40 mm. Heparin was continued for ≥ 48 hours and until the anticoagulation therapy was within the therapeutic level, according to the international normalised ratio. After the procedure, all patients started on oral warfarin (Coumadin). Anticoagulation treatment was continued during the first 3 months, then the treatment was changed to aspirin 80 mg/day indefinitely	PTA: standard technique (described in another publication)
Zdanowski *et al.* 1999[24]	To investigate the 1-year outcome of PTA and stenting and PTA alone for femoropopliteal occlusions	Strecker stent: 6-mm stents (length 40 mm or 80 mm) were implanted with an overlap of about 5 mm. Size and number of stents chosen to fully cover dilatation of vessel	PTA: common femoral artery was punctured and the superficial femoral artery catheterised with a 5-F or 6-F straight catheter. Occlusion passed with straight stiff or Terumo guide wire, catheter changed to 8-F introducer and an Olbert balloon with 6 mm diameter

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Becquemin *et al.* 2003[19]	Patients with lesions < 7 cm and disabling claudication or lower limb critical ischaemia	Patients of either sex with severe claudication or limb-threatening ischaemia [stage IIb, III or IV (SVS-ISCVS)] and who had stenosis or occlusion of the superficial femoral artery, as demonstrated on a pre-treatment angiogram, were eligible. Inclusion criteria included inflow vessels free of significant lesion; single superficial femoral artery lesion located between 1 cm from the origin of the superficial artery and 5 cm proximal to the projection of the knee joint on anteroposterior angiographic views; lesion length between 1 and 7 cm; and sufficient outflow, with at least one patent leg artery. Exclusion criteria included pregnancy, acute ischaemia, previous endovascular or open surgery in the treated superficial femoral or popliteal artery, allergy to iodine, haemorrhagic diathesis, hypercoagulation and enrolment in an ongoing trial. For each patient, only one leg was included in the trial	June 1995 and December 1997. In 24 of 251 eligible patients, the guide wire could not be placed through the lesion
Cejna *et al.* 2001[20]	Included were patients aged 40–85 years, with a history of claudication (SVS-ISCVS categories 1–3) or chronic CLI (SVS-ISCVS categories 4–5)	The inclusion criteria allowed up to three lesions (stenosis and/or occlusions), ≤ 5 cm in length, located in the superficial femoral artery or in the above-knee segment of the popliteal artery At least one run-off vessel had to be patent at angiography. Excluded were pregnant women, or patients with an acute onset of symptoms (with an angiographic appearance resembling an acute thromboembolism). Furthermore, patients who had previous vascular surgery in the treated segments, with an untreated obstruction of the inflow vessels (e.g. iliac and common femoral arteries), or patients who were unable or unwilling to participate in follow-up examinations and drug therapy, were also excluded from the study	February 1994 and April 1997. Of 838 limbs treated for femoropopliteal obstruction between February 1994 and April 1997, 523 fulfilled the anatomical inclusion criteria

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Grimm *et al.* 2001[21]	Claudication in the femoropopliteal region, occlusion or severe stenosis of the superficial femoral artery including the P1 segment of the popliteal artery	Inclusion criteria: 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 (proximal third part, above the knee joint space) of the popliteal artery. The P2 segment (middle part of the popliteal artery at the height of the knee joint space) had to be free of disease at the time of the study. The length of the stenosis could not exceed 5 cm; the percentage of stenosis had to be > 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 > 5 cm in length requiring more than two stents, multifocal disease or complete obstruction (that could not be passed with the guide wire) of the superficial femoral artery, haemodynamically 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	

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Rand *et al.* 2006[22]	Chronic CLI stages III and IV of the Fontaine classification	Inclusion criteria: (1) patients suffering from chronic CLI stages III and IV of the Fontaine classification; (2) patients with isolated stenosis > 70% or occlusion of the tibial arteries; (3) patients with up to three lesions; and (4) lesions that were ≤ 3 cm with a cumulative lesion length of ≤ 9 cm, including the tibiofibular trunk, anterior and posterior tibial arteries, and peroneal artery Exclusion criteria: patients with a significant inflow obstruction at the pelvic or superficial femoral artery level, patients with evidence of a systemic coagulopathy in whom anticoagulant and antiplatelet treatment was contraindicated, patients with previously implanted stents in the target lesion, patients with total occlusion in the target vessel following the target lesion, patients without distal run-off, patients with inflammatory vascular disease, patients with peptic ulcer or gastric/intestinal bleeding in the previous 6 months and patients with a clinically assessed intolerance to contrast medium	Patients were enrolled during a period of 16 months
Vroegindeweij *et al.* 1997[23]	Patients with femoropopliteal obstructive disease	Inclusion criteria: (1) lesions confined to the femoropopliteal artery, excluding below-knee lesions; (2) lesions eligible for balloon angioplasty alone and balloon angioplasty combined with stenting, which excluded all patients with multisegmental disease and with no run-off; and (3) 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 colour-flow duplex surveillance protocol were selected	Between January 1993 and December 1995
Zdanowski *et al.* 1999[24]	Patients with femoropopliteal occlusions or who had CLI	Patients with femoropopliteal occlusions or who had CLI	During 3 years

SVS-ISCVS, Society for Vascular Surgery/International Society for Cardiovascular Surgery classification.

Sample size

Trial	Numbers randomised	Number of participants in T1 (stent)	Number of participants in T2 (PTA)	Power calculation	Number of patients followed up (or attrition)
Becquemin *et al.* 2003[19]	227	115 (systematic stent)	112 (PTA with selective stenting) [of whom, in the PTA group, 15 patients (13%) required stent placement because of unsatisfactory results after angioplasty alone]	NR	At 1 year, 81 patients (80%) in the angioplasty only group and 83 patients (75.5%) in the angioplasty plus stent group had, respectively, 65 and 75 angiograms available for evaluation
Cejna *et al.* 2001[20]	141 patients (154 limbs)	77 limbs	77 limbs (10 patients after PTA had secondary stent placement because of primary technical failures)	The clinical estimate was that stent placement might raise the 1-year patency rate from 60% with PTA to 80%. Thus, 148 lesions were calculated to be necessary for a power of 80% (α-error, β-error; $p < 0.05$)	Angiographic follow-up within 12 months was available in 91 of 154 limbs (59.1%) (45 limbs in the PTA group, 46 limbs in the stent placement group). 111 limbs (55 limbs in the PTA group vs. 56 in the stent placement group) had angiographic follow-up within 24 months
Grimm *et al.* 2001[21]	53	30	23	NR	Six patients were lost to follow-up (and six deaths)
Rand *et al.* 2006[22]	95 lesions in 51 patients	42 lesions in 24 patients	53 lesions in 27 patients (one lesion secondary stenting)	NR	37 patients underwent a follow-up study in which 57 lesions had been treated by PTA (32 procedures in 20 patients) or stent application (25 procedures in 17 patients) Of the 51 patients, 2 patients died, 3 patients underwent amputation, 1 patient underwent major heart surgery, which did not allow further follow-up, and 8 patients were lost to follow-up

Trial	Numbers randomised	Number of participants in T1 (stent)	Number of participants in T2 (PTA)	Power calculation	Number of patients followed up (or attrition)
Vroegindeweij *et al.* 1997[23]	51	24 [four patients (8%) had a crossover from the randomised technique (stent) to the opposite treatment]	27	NR	Unclear
Zdanowski *et al.* 1999[24]	32	15	17	NR	All patients available for analyses of technical success and complications; 20 patients available for angiography (8 PTA, 12 stent) Angiography refused by seven patients in PTA group (47%) and two patients in the stent group (14%) because of clinical improvement

NR, not reported.

Baseline characteristics

Trial	Age (mean, years)	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance	Other relevant information
Becquemin *et al.* 2003[19]	PTA 66.42 (SD 11.7), stent 66.54 (SD 11.15)	Angioplasty group, 66 (59%) men; angioplasty plus stent group, 76 (66%) men ($p = 0.265$)	PTA group: 89 patients (79%) had claudication, 7 patients (6.25%) had rest pain and 16 patients (14.29%) had gangrene or ulcer. Stent group: 91 patients (79%) had claudication, 7 patients (6.09%) had rest pain, and 17 patients (14.78%) had gangrene or ulcer	Previous vascular surgery (contralateral limb, aortoiliac segment, carotid artery): PTA 36 (32), stent 24 (20)	• Previous stroke: PTA 10 (9), stent 6 (7) • Hypertension: PTA 57 (51), stent 61 (53) • Diabetes: PTA 16 (14), stent 11 (10) • Dyslipidaemia: PTA 48 (44), stent 43 (38) • Smoking: PTA 69 (60), stent 79 (59)		Mean lesion length in the two groups: PTA 25.11 mm (SD 17.8 mm) (range, 20–70 mm), stent 25.36 mm (SD 18 mm) (range 30–70 mm)
Cejna *et al.* 2001[20]	PTA 65.5 (range 39.2–83), stent 68.6 (range 39.2–87)	PTA group, 46 (59.8%) men; stent group 49 (63.6%) men	SVS-ISCVS categories: mild and moderate – PTA 13 (16.9%), stent 11 (14.3%); severe claudication – PTA 45 (58.4%), stent 39 (50.6%); ischaemic rest pain – PTA 7 (9.0%), stent 11 (14.2%); minor tissue loss – PTA 12 (15.6%), stent 16 (20.8%)		• History of smoking: PTA 43 (61), stent 49 (62.4) • Hypertony: PTA 36 (44.2), stent 31 (36.4) • Diabetes: PTA 31 (40.2), stent 32 (39.0) • Hypercholesterolaemia: PTA 37 (46.8), stent 32 (35.0) • Adiposity: PTA 19 (24.6), stent 23 (31.2)		In the PTA group, lesion length 2 cm was found in 46 patients, compared with 38 patients in the stent placement group. The average lesion length for the PTA group was 2.2 cm (SD 1.2 cm), compared to 2.6 cm (SD 1.4 cm) in the stent placement group (non-significant between groups)
Grimm *et al.* 2001[21]	Palmaz stent group 71 (SD 10), PTA group 68 (SD 8)	Stent group, 22 men and 8 women; PTA group, 10 men and 13 women	Fontaine classification: stent, 2.6 (SD 0.5); PTA, 2.8 (SD 0.4). Rutherford classification: stent, 2.4 (SD 0.7); PTA, 2.1 (SD 0.7)			Preoperative claudication distance (m): stent, 166.4 (SD 140.1); PTA 150.3 (SD 160.5)	

Trial	Age (mean, years)	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance	Other relevant information
Rand *et al.* 2006[22]	72.0 (range 47–80) (across both groups)		Fontaine III: PTA 8, stent 4. Fontaine IV: PTA 19, stent 20		• Insulin-dependent diabetes mellitus: PTA 13, stent 11 • Non-insulin-dependent diabetes mellitus: PTA 6, stent 5 • Smoking: PTA 17, stent 14 • Cardiac disease: PTA 11, stent 9 • Renal failure: PTA 3, stent 5		Occlusion in four PTA patients and two stent patients
Vroegindeweij *et al.* 1997[23]	PTA 64 (range 41–82), stent 65 (range 46–78)	PTA group, 19 men; stent group, 17 men	22 patients randomised for balloon angioplasty alone had mild to moderate IC (class I1–2) and five patients had severe claudication (class I3). 20 patients randomised for primary stenting had mild to moderate IC (class I1–2) and four patients had severe claudication (class I3)		• Coronary heart disease: PTA 9, stent 6 • Diabetes mellitus: PTA 3, stent 3 • Smoking: PTA 18, stent 14 • Hypertension: PTA 6, stent 3 • Hypercholesterolaemia: PTA 7, stent 9		Occlusion in five PTA and four stent patients
Zdanowski *et al.* 1999[24]	Median age: stent 72, PTA 71	Stent group, 10 men and 5 women; PTA group, 4 men and 13 women	Across groups, all patients had CLI, 66% had tissue loss, 19% had rest pain and 15% had disabling claudication. The median ABPI was 0.45. The occlusion was confined to the superficial femoral artery in 30 cases and to the popliteal artery in two cases (both in PTA group). The median length of the occlusions was 7.3 cm		• Smoking: stent 5/15, PTA 6/17 • Diabetes: stent 5/15, PTA 5/17 • Hypertension: stent 4/15, PTA 4/17		

SD, standard deviation; SVS-ISCVS, Society for Vascular Surgery/International Society for Cardiovascular Surgery classification.

Outcomes

Trial	Exercise tolerance/ walking distance	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Becquemin *et al.* 2003[19]		Survival; occurrence of clinical disorders including cardiac events, transient ischaemic attack, stroke, deep venous thrombosis or pulmonary embolism, pulmonary or renal complications and miscellaneous life-threatening complications; occurrence, according to time of follow-up, of vascular events in the treated leg including acute ischaemia, worsening of clinical stage, trash foot and need for another vascular procedure or major amputation; and number of failed procedures at 1 year, defined as > 50% restenosis or death	The primary end point was the presence of > 50% stenosis at 1-year postoperative angiography	
Cejna *et al.* 2001[20]		Primary technical success rate, complication rate. Clinical success was defined by an improvement in the SVS-ISCVS category. Reobstruction at follow-up was defined either as occlusion or stenosis of ≥ 70% within the treated area, as defined by angiography	The primary end point was the 12-month primary patency rate. Technical success was defined as a successful PTA or stent placement procedure with maximal 30% residual stenosis of vessel lumen diameter, as defined by biplane angiography	
Grimm *et al.* 2001[21]	Claudication distance	Major complications	Primary patency rates, secondary patency rates	Reintervention
Rand *et al.* 2006[22]		Major amputation	The primary end point was the angiographic patency rate of treated lesions. Evaluation of the primary patency rate referred to lesion reocclusion, which was defined as stenosis of > 70% (threshold 1: critical stenosis) or > 50% (threshold 2: subcritical stenosis)	

Trial	Exercise tolerance/ walking distance	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Vroegindeweij *et al.* 1997[23]		Complications	Late anatomical success or primary patency was determined by colour-flow duplex surveillance. All lesions that recurred during follow-up within the same treated arterial segment were considered restenoses. Progression of disease in untreated arterial segments was considered as new lesions. These lesions were not considered for the analysis of patency. Symptoms due to new lesions in an untreated segment were considered not to be a clinical failure Patency rates were determined by the life table method, restenosis or occlusion being the end point. Only primary patency was considered; the success of reinterventions was not part of this analysis Technical success was defined as a residual stenosis of < 30% diameter reduction on the completion arteriogram by visual estimation on two projections taken at right angles. Clinical and haemodynamic outcomes were classified according to the SVS/ISCVS criteria	
Zdanowski *et al.* 1999[24]		Major complications	Restenosis was defined as a decrease by > 50% of the inner diameter compared with the state immediately after stenting. Clinical improvement required claudication distance to improve by ≥ 50%, resolution of rest pain or healing ulcers	Need for reintervention

SVS-ISCVS, Society for Vascular Surgery/International Society for Cardiovascular Surgery classification.

Results

Trial	Results	Complications
Becquemin *et al.* 2003[19]	The number of failed procedures at 1 year (death or > 50% stenosis) was as follows: PTA 29 of 86 (33%) and stent 30 of 89 (34%) (non-significant $p = 0.9$). At 1 year, 21 procedures (32%) in the PTA group and 26 (34%) in the stent group fulfilled the criteria for failure ($p = 0.85$). Total occlusion of the treated site was noted in seven patients (11%) and 12 patients (16%), respectively ($p = 0.3$). The differences were not statistically different. In 23 patients for whom no angiograms were available, a duplex scan was available at 1 year. 2 of 13 patients in the PTA group and 1 of 10 patients in the stent group had > 50% stenosis of the treated artery	Perioperative complications in the PTA and stent groups occurred, respectively, in 5 patients (4.9%) and 10 patients (8.6%) ($p = 0.2$) and included thrombosis [two patients (1.7%) vs. two patients (1.7%)], embolism [two patients (1.7%) vs. five patients (4%)], arterial rupture [one patient (0.9%) vs. 0 patients] and introducer site problems, defined as difficulty in puncturing the artery or in placing the introducer sheath or guide wire [0 patients vs. three patients (2.6%)]. Additional procedures to treat complications were performed on 20 PTA and 10 stent group patients. There were no statistically significant differences between the two groups ($p = 0.341$). Mortality (4 years): 29 patients died during follow-up, 16 (14%) in the PTA group and 13 (11%) in the stent group. Cumulative survival rate free of vascular events: there were more events in the PTA plus stent group ($p = 0.017$). Major amputation: one in each group
Cejna *et al.* 2001[20]	Patency: the cumulative 1- and 2-year angiographic primary patency rates were 63% and 53%, respectively, for both groups. The secondary 1- and 2-year angiographic patency rates were 86% and 74% in the PTA group vs. 79% and 73% in the stent group ($p = 0.5$). The cumulative primary angiographic patency rates in the PTA vs. stent placement groups were 84%, 73%, 63% and 53% vs. 92%, 84%, 63% and 53% after 30, 180, 360 and 720 days, respectively ($p = 0.09$). Secondary patency measure: secondary angiographic patency rates were 100%, 94%, 86% and 74% for the PTA group and 95%, 93%, 79% and 73% for the stent placement group after 30, 180, 360 and 720 days, respectively (non-significant, $p = 0.43$). Reintervention: in the stent placement group, seven patients underwent femoropopliteal bypass graft surgery after angiographically demonstrated reocclusion, compared with four patients in the PTA group. In one patient of the PTA group, a popliteopedal bypass had to be created. 12 patients in the PTA group had a second intervention in the treated limb, in three cases because of development of a new stenosis (unrelated to the prior intervention site), compared with 21 patients in the stent placement group (six new stenosis). Clinical: there was no difference between groups of treatment – haemodynamic/clinical success at 1 and 2 years in the PTA group was 72% and 65% vs. 77% and 65% in the stent group ($p = 0.26$)	There were 12 primary failures in the PTA group, resulting in a technical success rate of 84.4%, and the technical success rate of 'secondary' stent implantation (i.e. in PTA group) was 100%. In the stent placement group, only one primary failure was observed (technical success rate 98.7%), after incorrect crimping of a stent on the balloon. Major complications or death occurred in four (2.6%) of the PTA group compared with 2 (1.3%) of the stent group. Within 30 days of intervention, three early stent thromboses were observed (3.9%) compared with one early PTA thrombosis (1.3%). During the 36-month follow-up period, seven patients died in the PTA group compared with 12 patients in the stent placement group

Trial	Results	Complications
Grimm *et al.* 2001[21]	Walking distance: the mean walking distance increased in the PTA group from 150.3 m (SD 160.0 m) to 466.7 m (SD 461.9 m) ($p = 0.18$), and in the Palmaz group from 166.4 m (SD 140.0 m) to 383.5 m (SD 237.5 m) ($p = 0.04$). Reintervention: a second intervention was necessary in seven patients in the PTA group after 11 months and eight patients in the Palmaz stent group after 7 months, but this difference was not significant ($p = 0.3$). Stenosis: after dilatation or stent placement, respectively, the remaining stenosis percentage was 19.5% (SD 9.9%) in the PTA group and only 2.6% (SD 7.0%) in the Palmaz stent group. This difference of 17% is highly significant ($p = 0.0001$) and independent from the initial degree of stenosis because no correlation could be found between the degree of stenosis before and after intervention in both groups. Patency: after 12 months, the primary patency rates were 75% in the Palmaz stent group and 84.2% in the PTA group; after 24 months, they were 72.4% in the Palmaz stent group and 77.2% in the PTA group; after 39 months, they were 73.3% in the Palmaz stent group and 69.6% in the PTA group. There was no significant difference at any time ($p > 0.41$). Secondary patency rates at 12 months were 90% in the Palmaz stent group and 100% in the PTA group; after 24 months, they were 90% in the Palmaz stent group and 90.9% in the PTA group; after 39 months, they were 92.8% in the Palmaz stent group and 91.3% in the PTA group, again with no significant difference at any time ($p > 0.7$). To exclude a bias in favour of PTA (caused by the higher number of occlusions in the Palmaz stent group; 13 vs. 3), the subgroup of patients with a non-occlusive stenosis were compared, but, again, no significance between the patency rates in the Palmaz stent and PTA groups at 12 ($p = 0.83$), 24 ($p = 0.81$) and 39 ($p = 0.77$) months was found	(Six patients died during the follow-up period; all deaths were unrelated to the procedure and occurred > 30 days after the procedure)
Rand *et al.* 2006[22]	Patency: for the stent group the cumulative primary patency at 6 months was 83.7% at the 70% restenosis threshold, and 79.7% at the 50% restenosis threshold. For PTA, the primary patency at 6 months was 61.1% at the 70% restenosis threshold and 45.6% at the 50% restenosis threshold. Both results were statistically significant ($p = 0.02$). Total reocclusion was observed in two lesions (one PTA, one stent). Primary technical success: in one patient, stent application failed because the stent could not pass through a heavily calcified stenosis. In one lesion, PTA alone ended with a high-grade dissection and was unsatisfactory. This lesion was treated by secondary stenting	Amputation: one major amputation and one minor amputation were performed on patients in the stent group. One minor amputation was performed in a patient undergoing PTA. The comparison of cumulative limb salvage in the two groups using the Kaplan–Meier method revealed no significant difference between them

Trial	Results	Complications
Vroegindeweij *et al.* 1997[23]	Patency: the cumulative 1-year patency, determined by restenosis or occlusion in the overall group (ITT), was 69% (SE 9%) for all patients, 74% (SE 8%) in the PTA group and 62% (SE 9%) in the patients randomised to stent ($p = 0.22$). This difference did not reach statistical significance. Overall 19 (37%) of the patients developed a PSVR of ≥ 2.5 in an initially treated segment: eight balloon angioplasty patients after a mean follow-up of 7 months (range 1–18 months) and 11 stent patients after 6 months (range 0–15 months). Total occlusion occurred in two (7%) PTA patients and five (21%) stent patients. In eight patients (30%) treated by PTA and in nine patients (43%) treated by stent, a clinical deterioration occurred after 1 year of follow-up. When analysed by life table analysis, the cumulative rate of maintained improvement (class +1 or more according to the SVS/ISCVS criteria) after 1 year of follow-up was 80% (SE 9%) in all patients, 85% (SE 7%) in the balloon angioplasty group and 74% (SE 9%) in the stent group (non-significant, $p = 0.25$)	In one patient treated by stent an embolus occurred 10 days after stent placement, which was successfully managed with streptokinase. In one PTA patient a thrombosis occurred which was also successfully managed with thrombolysis
Zdanowski *et al.* 1999[24]	Clinical: the rate of clinical improvement was 71% after PTA and stent and 60% after PTA alone ($p = 0.17$). Restenosis: angiographic reocclusions were seen in 33% and 75% in the stent and PTA groups, respectively ($p = 0.17$), while the rate of restenosis was significantly higher in the stent group (50% vs. 25%) ($p = 0.033$)	No technical failure and no limb loss. In the PTA group, one patient had a myocardial infarction and three patients needed arteriography owing to bleeding. In the stent group, one patient required arteriography and embolectomy. The 1-year mortality was 6% (two patients, group not specified)and there were no amputations. Four patients (two in each group) were operated on with a femorodistal bypass

PSVR, peak systolic velocity ratio; SD, standard deviation; SE, standard error; SVS-ISCVS, Society for Vascular Surgery/ International Society for Cardiovascular Surgery classification.

Drug-eluting stent

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Zilver PTX[25,26]		RCT, prospective, multicentre	Dake – slides online (not peer reviewed)/ Ansel – abstract only	English	Cook Medical	USA	USA, Japan, Germany. 55 sites	Outcomes at 12 months (ongoing follow-up through 5 years)
SIROCCO[28–30]	To review clinical outcomes of patients with CLI and TASC type C lesions treated with sirolimus-eluting vs. bare SMART (Cordis) nitinol SESs	RCT, prospective, multicentre. SIROCCO trial conducted in two phases: phase one, Duda 2002[28] publication; phase two, Duda 2005[29] publication; and complete results presented in Duda 2006[30] publication	Full report in peer-reviewed journal, three publications	English	The study was sponsored by Cordis Corporation, a Johnson & Johnson company	Germany	Germany, Austria, Belgium, Canada, the Netherlands, Australia, the USA, France	Mean 24 months
Rastan *et al.* 2011[31]	The rationale of this double-blinded randomised study was to prove the concept of using sirolimus-eluting stents to improve primary patency rates after interventional therapy of focal lesions of infrapopliteal arteries	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	NR	Germany	Germany	Outcomes at 6 months and 12 months

NR, not reported.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Zilver PTX[25,26]	Paclitaxel-eluting stent vs. PTA (or BMS)	Zilver paclitaxel-eluting stent (PTX): paclitaxel 3 µg/mm^2 dose density, no polymer or binder	PTA: if suboptimal PTA (> 30% residual stenosis), then secondary randomisation to BMS or PTX
SIROCCO[28–30]	Sirolimus-eluting vs. bare SMART nitinol SESs	Sirolimus-eluting stent implantation procedure (for both groups): six or seven 80-mm stents implanted through a 7-F introducer sheath. A maximum of three stents were implanted in SIROCCO I and two stents in the SIROCCO II study. Patients not already on aspirin were to receive a 300-mg loading dose the day before the procedure; all received intra-arterial heparin boluses (3000–5000 units) at the time of the procedure, followed by a 750- to 1000-U/h infusion, as necessary. Overnight (24-hour) treatment with heparin was also permitted. After the procedure, either ticlopidine or clopidogrel was recommended for 4 weeks in addition to aspirin, which was continued for at least 12 months	Bare SMART nitinol SESs (Cordis) (implantation procedure as for T1)
Rastan *et al.* 2011[31]	Sirolimus-eluting stents vs. BMSs	A polymer-free sirolimus-eluting stent (Yukon™, Transluminal, Hechingen, Germany) was used. The polymer-free sirolimus-eluting stent was coated with a 2% sirolimus-containing solution	The BMS was coated with ethanol (placebo)

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Zilver PTX[25,26]	SFA, symptomatic disease of the above-the-knee femoropopliteal artery	Inclusion criteria: Rutherford category 2 or greater, proximal 1 cm below bifurcation, distal medial femoral epicondyle, reference vessel diameter 4–9 mm	
SIROCCO[28–30]	Symptomatic peripheral artery disease classified as Rutherford categories 1 (mild claudication) to 4 (rest pain)	Eligible patients were ≥ 30 years of age with symptomatic PAD classified as Rutherford categories 1 (mild claudication) to 4 (rest pain). All had obstructive (≥ 70%) de novo or restenotic lesions in the native SFA. The reference vessel diameter was 4–6 mm. The stenotic lesions varied in length from 7 to 20 cm in the first phase of the study and from 7 to 14.5 cm in the second phase. The occlusions varied in length from 4 to 20 cm in the first phase of the study and from 4 to 14.5 cm in the second phase. All lesions treated in SIROCCO I and II trials were classified as TASC type C. Signed informed consent Exclusion criteria included poor aortoiliac or common femoral inflow; uraemia; aneurysm in the target vessels; tandem lesions; previously stented lesions; ischaemic tissue loss; deep venous thrombosis; pregnancy; hepatic insufficiency; end-stage renal failure requiring dialysis; immunosuppressant therapy; recent haemorrhagic stroke (within the past 3 months); severe calcification that was deemed resistant to stenting; vessel tortuosity; revascularisation 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 an aortic, iliac or femoral vascular prosthesis; and a life expectancy of < 2 years. Female patients of childbearing potential had a documented negative pregnancy test within 3 days prior to randomisation	Phase one February to July 2001, phase two August to December 2001

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Rastan *et al.* 2011[31]	Focal lesions of infrapopliteal arteries	Patients were eligible for the study if they were ≥ 21 years old, were not pregnant and suffered from PAD with a Rutherford–Becker class (RC) of 3–5. Patients with lifestyle-limiting claudication, RC 2, could also be included after successful intervention of TASC A (single stenosis < 3 cm of the SFA or popliteal artery) femoropopliteal lesions to improve run-off status. Angiographic eligibility criteria were the presence of a single primary target lesion in a native infrapopliteal artery that was 2.5–3.5 mm in diameter and that did not exceed 45 mm in length to assure complete lesion coverage by the treatment with a maximum of two stents with a stent length of 25 mm; diameter stenosis of > 70%, as estimated by duplex-ultrasound and visually on angiography. Major exclusion criteria were a visible thrombus within the target lesion, known systemic coagulopathy, Buerger's disease, acute limb ischaemia and life expectancy of < 1 year, or an intolerance to aspirin, clopidogrel and heparin	Between April 2006 and April 2008

SFA, superficial femoral artery.

Sample size

Trial	Number of patients included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Number of patients followed up from each condition (or attrition)
Zilver PTX[25,26]	479	PTX, 241 from first randomisation; data presented from 238	PTA 238, of whom 120 unsuccessful and 61 allocated to PTX and 59 to BMS (analysed in PTA group); data presented from 236		Safety data from 236 PTA (of whom some had stents at second randomisation) and 235 PTX patients. Patency data from 251 lesions in PTA group, and 247 lesions in PTX group
SIROCCO[28–30]	93 (36 from phase one, 57 from phase two of trial)	Sirolimus-eluting stent, 47	Bare metal SES, 46	Planned sample size: 74 patients, which would provide 90% statistical power to detect 0.8-mm difference between groups at 6 months assuming SD of 1.0 mm in each group	DES: at 6 months 42/47, at 2 months 35/47. BMS: at 6 months 44/46, at 24 months 38/46
Rastan *et al.* 2011[31]	161	SES, 82	BMS, 79	Based on the published data, a patency rate of 50% was assumed with BMS. The study was designed to have a power of 95% to detect an elevation of the patency rate by the SES to 75% with a two-sided $p < 0.05$. Considering a dropout rate of 30%, total sample size of 155 patients	62 (76.5%) patients in the SES group and 63 (79.7%) patients in the BMS group completed 1-year follow-up. Owing to inappropriate duplex-ultrasound or TLR, angiography was performed in 55 (44%) patients 25 (15.5%) patients died, 8 (4.9%) patients were lost during the follow-up period, and 3 (1.9%) patients could only be contacted by telephone because of care dependency

PTX, paclitaxel-eluting stent; SD, standard deviation.

Baseline characteristics

Trial	Age (mean, years)	Gender	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors
Zilver PTX[25,26]	PTA 68 (SD 11), PTX 68 (SD 10)	PTA 64% male, PTX 66% male			• Diabetes: PTA 42%, PTX 49% • High cholesterol: PTA 70%, PTX 76% • Hypertension: PTA 82%, PTX 89% • Past/current smoker: PTA 84%, PTX 86%
SIROCCO[28–30]	47 patients [mean age 66.3 (SD 9.1), range 50–84] received the sirolimus-eluting SMART stent and 46 patients [mean age 65.9 (SD 10.8), range 38–83) received a bare SMART nitinol stent	47 patients (31 men; 66%) received the sirolimus-eluting SMART stent and 46 patients (36 men; 78%) received a bare SMART nitinol stent	• Rutherford categories 1 and 2: DES 20 (43%), BMS 26 (57%) • Rutherford categories 3 and 4: DES 27 (57%), BMS 20 (43%)	• Type of lesion de novo: DES 42 (89), BMS 44 (96) • Type of lesion restenotic: DES 5 (11), BMS 2 (4)	• Cardiomyopathy: DES 23 (49%), BMS 18 (39%) • Diabetes: DES 20 (43%), BMS 16 (35%) • Hyperlipidaemia: DES 30 (64%), BMS 29 (63%) • Hypertension: DES 32 (68%), BMS 32 (70%) • Current smoker: DES 22 (47%), BMS 14 (30%)
Rastan *et al.* 2011[31]	SES, 73.4 (SD 8); BMS, 72.3 (SD 9)	SES 67.9% male, BMS 64.9% male	CLI: SES 51.2%, BMS 41.8%		• Diabetes mellitus: SES 56.8%, BMS 50.6% • Dyslipidaemia: SES 76.5%, BMS 76.6% • Hypertension: SES 91.4%, BMS 88.3% • Current smoker: SES 28.4%, BMS 28.6%

PTX, paclitaxel-eluting stent; SD, standard deviation.

Outcomes

Trial	Clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Zilver PTX[25,26]		Primary safety end point: 12-month event-free survival – freedom from death, amputation, TLR or worsening Rutherford category (by two classes or to class 5 or 6), per-protocol cohort, Kaplan–Meier *p*-values from log-rank test	Primary effectiveness end point: 12-month primary patency duplex ultrasonography, patent = PSVR < 2.0 (or angiography if available, patent = diameter stenosis < 50%), intent-to-treat cohort, Kaplan–Meier *p*-values from log-rank test	
SIROCCO[28–30]		Adverse events	Primary end point was in-stent mean lumen diameter stenosis at 6 months as determined by QA. The in-lesion segment was defined as the in-stent segment plus 5 mm proximal and distal to the stent. Restenosis as determined by QA (> 50% stenosis) was defined as haemodynamic failure of the stented lesion (increase in PSV > 100% by duplex in the stenotic segment when compared with a reference segment proximal to the stenosis or absence of a Doppler signal) or incidence of serious adverse events (death or prolonged hospitalisation)	TLR/TVR
Rastan *et al.* 2011[31]	Rutherford–Becker classification	Death, major and minor amputations, TLR including need for surgical revascularisation and myocardial infarction were defined as major adverse events	The main study end point was primary patency rate after 1 year, defined as freedom from in-stent restenosis (luminal narrowing of < 50%) detected with duplex ultrasonography or angiography if appropriate. The definition of 50% restenosis was based on a PSVR (PSV within the stent divided by PSV ≥ 1 cm proximal of the stent in a healthy vessel segment) > 2.4. The presence of a significant restenosis was confirmed by intra-arterial angiography during clinically driven TLR in all cases Secondary end points included primary patency rate after 6 months and secondary patency rate, defined as patency following successful TLR after 12 months	Target limb reintervention

PSV, peak systolic velocity; PSVR, peak systolic velocity ratio; QA, quantitative angiography.

Results

Trial	Results	Complications
Zilver PTX[25,26]	Primary patency (PSVR < 2.0) at 12 months: PTX group 83.1%, PTA group (of 126 patients who actually had PTA alone) 65.3% ($p < 0.01$; significantly lower than PTX); PTA group of 125 lesions with stent implantation (bare metal or PTX) 32.8% (significantly lower than those randomised to PTX, $p < 0.01$); for the 62 lesions from patients randomised to PTA then BMS 67% patency at 12 months (significantly lower than those randomised to PTX, $p < 0.01$) – this group had a reported restenosis rate of 33% at 12 months, whereas the PTX restenosis rate was 12.9% (49% reduction). At 24 months, the patency rate of PTX vs. BMS was 81.2% vs. 62.7% ($p < 0.01$). Author notes relatively high acute PTA failure rate, and, for lesions < 14 cm, no in-stent restenosis	PTX and BMSs: 0.9% stent fracture rate over 12 months. Safety analysis – event-free survival at 12 months: PTX 90.4%, PTA 82.6% ($p < 0.01$)
SIROCCO[28–30]	Restenosis: at 24 months, the cumulative in-stent restenosis rates according to duplex ultrasound were 4.7%, 9.0%, 15.6% and 21.9%, respectively, at 6, 9, 18 and 24 months. The rates did not differ significantly between the treatment groups (duplex ultrasound restenosis rates and 95% CI): at 6 months DES 4.8%, 0.6% to 16.2% ($n = 42$), and BMS 4.5%, 0.6% to 15.5% ($n = 44$); at 9 months DES 7.1%, 1.5% to 19.5% ($n = 42$), and BMS 11.1%, 3.1% to 26.1% ($n = 36$); at 18 months DES 18.4%, 7.7% to 34.3% ($n = 38$), and BMS 12.8%, 4.3% to 27.4% ($n = 39$); at 24 months DES 22.9%, 10.4% to 40.1% ($n = 35$), and BMS 21.1%, 9.6% to 37.3% ($n = 38$); at 24 months TVR DES $n = 6$ (13%) and BMS $n = 10$ (22%), TLR DES $n = 3$ (6%), BMS $n = 6$ (13%). In both groups at 24 months, no amputations were performed as a complication of the stent procedure. Both groups of patients showed an improvement in Rutherford classification immediately after implantation of the stent, which was sustained over the 24-month follow-up	Seven patients died owing to stroke ($n = 1$), lung emboli ($n = 1$), cancer ($n = 1$), cardiac disease ($n = 2$) and natural causes ($n = 2$) in the sirolimus-eluting group, whereas only two patients died in the BMS group (complications of coronary BS and progressive cardiac failure). Stent fractures (defined as one broken strut) were detected by the independent angiographic and radiographic core laboratory ≤ 18 months post procedure in eight patients in the BMS group and 9 in the sirolimus stent group ($p = 0.245$)
Rastan *et al.* 2011[31]	Restenosis: the rates of ≥ 50% target lesion restenosis after 1 year were 19.4% ($n = 2$) for the SES group and 44.4% ($n = 28$) for the BMS group. Patency: the 1-year primary patency rates were 80.6% ($n = 50$) and 55.6% ($n = 35$; $p = 0.004$), and 6-month primary patency rates were 85.9% ($n = 55$) and 68.7% ($n = 46$; $p = 0.02$), respectively. The secondary 1-year patency rates were 91.9% ($n = 57$) for the SES group and 71.4% ($n = 45$; $p = 0.005$) for the BMS group. The BMS hazard ratio for restenosis was 3.2 (95% CI 1.5 to 6.7; $p = 0.003$) compared with SES after 1 year. The risk of restenosis associated with BMS prevailed after adjustment for diabetes mellitus, smoking status and body mass index. The corresponding adjusted hazard ratio was 3.0 (95% CI 1.4 to 6.4; $p = 0.005$). No significant interaction could be observed between stent type and stage of disease (CLI or IC). Clinical: the median (IQR) Rutherford category decreased from 4 (3–5) in the SES group and 3 (3–5) in the BMS group ($p = 0.40$) at baseline to 1 (1–3) and 2 (1–3; $p = 0.37$) at 6 months and 2 (0.75–3) and 2 (1–3; $p = 0.01$) at 1 year, respectively. Moreover, the median (IQR) change in Rutherford category in the SES and BMS groups was –2 (–3 to –1) and –1 (–2 to 0; $p = 0.12$) at 6 months and –2 (–3 to –1) and –1 (–2 to 0) at 1 year, respectively ($p = 0.004$). TLR: TLR was performed in 6 patients (9.7%) in the SES group and in 11 patients (17.5%) in the BMS group ($p = 0.29$)	Owing to study stent dislocation in one (1.2%) patient of the SES group and two (2.5%) patients of the BMS group, three stents had to be implanted to cover the target lesion. Adverse events: a total of 51 (31.5%) adverse events occurred, 22 (27.1%) in the SES group, and 29 (36.7%) in the BMS group. 14 patients (17.1%) in the SES group and 11 patients (13.9%, $p = 0.66$) in the BMS group died during the follow-up period: eight patients (5%) died because of major cardiac events (myocardial infarction, heart failure); five patients (3.1%) died as a result of gastrointestinal and pulmonary infections; and one patient (0.6%) had lung cancer. In 11 patients (6.8%) the cause of death remained uncertain. Limb salvage: owing to insufficiently controlled wound infection despite adequate antibiotic treatment, one lower-leg major amputation and one minor toe amputation of the target limb in the SES group (3.2%), and two lower-leg major amputations and two minor toe amputations in the BMS group (6.4%), were documented. Hence, the limb salvage rate was 98.4% in the SES group and 96.8% in the BMS group after 12 months ($p = 0.61$)

IQR, interquartile range; PSVR, peak systolic velocity ratio; PTX, paclitaxel-eluting stent.

Stent graft

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Saxon *et al.* 2003, 2008[32,33]	To compare the safety and effectiveness of the Viabahn® endoprosthesis (W. L. Gore, Flagstaff, AZ, USA) (ePTFE-covered stent) with those of PTA alone in the treatment of symptomatic peripheral arterial disease affecting the SFA	RCT, prospective, multicentre	Full report in peer-reviewed journal	English	NR (single-centre reference implies Gore and associates)	USA	USA, 25 centres	Outcomes at 12 months

ePTFE, expanded polytetrafluoroethylene; NR, not reported; SFA, superficial femoral artery.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Saxon *et al.* 2003, 2008[32,33]	Viabahn endoprosthesis (ePTFE-covered stent graft) vs. PTS	Viabahn endoprosthesis stent graft placement (ePTFE/nitinol SES graft): stent grafts were oversized 5–20% relative to native vessel diameter, placed preferably from a retrograde over-the-bifurcation approach, but also from antegrade approach. An angioplasty balloon with diameter equal to that of stent graft was inflated throughout entire length of device. Antiplatelet therapy at discretion of operator (aspirin, occasional ticlopidine)	PTA: patients with ≥ 30% residual stenosis after PTA could have uncovered stent as 'bail-out' (no crossover to ePTFE stent graft). In general, PTA was performed with 6-F sheaths. Patients in both groups given heparin during procedure

ePTFE, expanded polytetrafluoroethylene.

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Saxon *et al.* 2003, 2008[32,33]	Patients with symptomatic SFA PAD	Inclusion criteria: De novo or restenotic atherosclerotic or occlusive lesion of SFA up to 13 cm in length, chronic lifestyle-altering claudication or chronic lower limb ischaemia. Exclusion criteria: prior, planned or concurrent limb BS, intolerance to antiplatelet therapy, bleeding disorders, renal failure, bacteraemia, lesion within 0.5 cm of profunda femoris artery origin, prior stent implantation in target lesion, fewer than one continuously patent run-off infrapopliteal artery with stenosis of ≤ 50% diameter	From 1998 to 1999

SFA, superficial femoral artery.

Sample size

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
Saxon *et al.* 2003, 2008[32,33]	197	Stent graft, 97	PTA, 100	Originally designed to enrol a maximum of 415 patients and was statistically powered to show 15% increase in patency in the stent graft group		At 1 year patency results for 69/100 PTA and 78/97 stent graft patients

Baseline characteristics

Trial	Age (mean, years)	Gender (M/F)	Classification of PAD	Presence of cardiovascular risk factors (% of patients)
Saxon *et al.* 2003, 2008[32,33]	PTA 67 (range 40–84), stent graft 67 (46–88)	PTA 70/30, stent graft 80/17	PTA: 88% claudication; 12% CLI. Stent graft: 91% claudication; 9% CLI	• Smokers: PTA 51%, stent graft 46% • Coronary artery disease: PTA 46%, stent graft 49% • Prior myocardial infarction: PTA 30%, stent graft 24% • Congestive heart failure: PTA 8%, stent graft 14% • Stroke: PTA 7%, stent graft 10% • Hypertension: PTA 68%, stent graft 65% • Diabetes mellitus: PTA 34%, stent graft 37%

F, female; M, male.

Outcomes

Trial	Pain/clinical status	Complications including amputation	Patency measures
Saxon *et al.* 2003, 2008[32,33]	Rutherford–Becker classification	Major and minor adverse events	Primary outcome was primary patency at 12 months, which was defined as technical success without interrupted blood flow and no procedures performed (any major adverse events within 30 days led to a loss of primary patency), and > 50% stenosis on duplex ultrasound. *Redefined during study to*: no TVR, no evidence of restenosis or occlusion within treated vessel from Doppler ultrasound, where target lesion not identified vessel patency from SFA to popliteal artery was applied, angiography demonstrating < 30% residual diameter stenosis. Technical success defined as treatment success with no major adverse events within 30 days and improvement in limb pressure indexes of ≥ 0.15 relative to pre treatment. *Redefined during study to*: successful completion of randomised treatment with no rescue procedure on day of treatment and angiography demonstrating < 30% residual diameter stenosis

SFA, superficial femoral artery.

Results

Trial	Results	Complications
Saxon *et al.* 2003, 2008[32,33]	Technical success: the stent graft group had a significantly higher technical success rate (95% vs. 66%, $p < 0.0001$). Subgroup analysis non-significant for lesions < 3cm in length. Patency: the stent graft group had a significantly higher 1-year primary vessel patency rate at duplex ultrasonography (65% vs. 40%, $p = 0.0003$). A patency benefit was seen for lesions ≥ 3 cm in length. Clinical: at 12 months, chronic limb ischaemia status was 15% further improved for the stent graft group ($p = 0.003$)	There were no significant differences between treatment groups with regard to the occurrence of early or late major adverse events. 21 major adverse events for PTA group, and 20 in the stent graft group. Thigh pain in 10 cases in stent graft group and 3 in PTA group ($p = 0.047$); pain was transient and resolved within 2 months

Atherectomy

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Nakamura *et al.* 1995[34]	To test the hypothesis that, in occlusions of the superficial femoral artery, removal of atherosclerotic plaque would result in a higher long-term patency rate than that resulting from balloon dilatation alone. A secondary hypothesis was that long-term patency would be proportional to the amount of plaque removed	RCT, prospective, single centre	Full report in peer-reviewed journal	English	Supported in part by an NIH grant	USA	USA	Outcomes at 6 months
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	To evaluate whether directional atherectomy would provide better results than conventional balloon angioplasty in symptomatic femoropopliteal disease	RCT, prospective, single centre	Full report in peer-reviewed journal	English	NR	Netherlands	Netherlands	Outcomes at 2 years (median follow-up duration was 13 months)

NR, not reported.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Nakamura *et al.* 1995[34]	Atherectomy (TEC) vs. PTA, with 2 groups of TEC (2.7 or 4.0/4.7 mm)	Two groups of atherectomy: (1) a 2.7-mm or (2) a larger (4.0 or 4.7 mm) TEC atherectomy device followed by PTA. TEC: after successful recanalisation, guide wire inserted into femoral artery, a 2.7-mm atherectomy cutter was inserted and the rotating cutter was slowly advanced under fluoroscopic control. For patients in the large TEC group, TEC atherectomy was then performed with a 4- or 4.7-mm cutter. For both groups, the patients then had balloon dilatation with a 6- or 7-mm-diameter catheter	PTA: common femoral artery punctured in antegrade direction, 7.5-F sheath, heparin administered, 8-F introducing sheath. Balloon angioplasty performed using a balloon catheter 6 or 7 mm in diameter by 10 mm in length
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	DA vs. PTA	DA: the DA device consists of a hollow cutting cylinder with a window on one side and a balloon on the opposite side. Inflation of the balloon pushes the window against the diseased arterial wall, and obstructing plaque protrudes into the cylinder. A high-speed rotating cutter shaves off the plaque and pushes it into a collection chamber. An introducer sheath is advanced in an antegrade fashion through an arterial puncture in the common femoral artery either percutaneously (in the angiography suite) or via a 'cut down' approach (in the operating room). The patient receives 5000 IU of heparin intra-arterially, and, under fluoroscopic guidance, a 6-F to 8-F atherectomy catheter (Simpson's Atherocath™, Devices for Vascular Intervention, Inc., Redwood City, CA) is advanced distally. The size of the atherectomy catheter was chosen so that the working diameter, with the balloon inflated, was equal to slightly greater than a normal adjacent artery segment	PTA: introducing a 5-F non-compliant balloon catheter via a 6-F sheath, balloon length 2 cm except two cases of 4 cm, balloon diameter 5–7 mm. Use of only the technique selected by randomisation was attempted, although crossover was permitted if an acceptable result could be obtained only by the opposite technique or by combined techniques

DA, directional atherectomy; TEC, transcutaneous extraction catheter.

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Nakamura *et al.* 1995[34]	Patients with occluded superficial femoral arteries	Inclusion criteria: symptoms of claudication, evidence of peripheral vascular disease by diminished pulses and decreased ABPI, angiographic evidence of complete occlusion of an SFA. Exclusion criteria: prior peripheral bypass, insufficient distal run-off vessels	
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	All patients had segmental lesions of the femoropopliteal arteries	Eligible patients included those with IC of ≥ 3 months duration and obstructive lesions of the femoropopliteal arteries that appeared suitable for either atherectomy or balloon angioplasty, that is, lesions with a maximum length of 5 cm. This restriction was because atherectomy is applicable only in discrete stenoses or short occlusions. Therefore, any patient with a diffusely diseased femoropopliteal artery with a stenosis extending > 5 cm or an occlusion > 2 cm in length was not considered a good candidate for the trial and was relegated to an obligatory balloon dilatation. Only de novo lesions were admitted, and any previous ipsilateral femoropopliteal endovascular or operative intervention was considered an exclusion criterion, irrespective of whether this treatment had concerned a different segment from the one considered for intervention at the time of the study. Only patients were selected who would be able to comply with the frequent follow-up visits required by the involved colour-flow duplex surveillance protocol	From January 1990 until May 1993; 187 patients undergoing endovascular treatment; 114 did not meet inclusion criteria or refused to participate

Sample size

Trial	Numbers included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Number followed up from each condition (or attrition)
Nakamura *et al.* 1995[34]	39	TEC 2.7 mm, 13; TEC 4.0/ 4.7 mm, 13	PTA, 13	NR	6 months patency available from those with procedural success: PTA, 10/13; TEC 2.7 mm, 13/13; TEC 4.0/4.7 mm, 8/13
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	73	DA, 38	PTA, 35	NR	Follow-up ended because of death in three and because of surgical intervention for severe claudication or conversion to the stage of critical ischaemia in three patients. 19 patients had repeat endovascular treatment, and two of the patients were lost to follow-up

DA, directional atherectomy; NR, not reported.

Baseline characteristics

Trial	Age (mean, years)	Gender (male)	Classification of PAD [*n* (%)]	Presence of cardiovascular risk factors	Other relevant information
Nakamura *et al.* 1995[34]	PTA, 61 (SD 0.1); TEC 2.7 mm, 64 (SD 6); TEC 4.0/ 4.7 mm 70 (SD 6)	PTA 13/13; TEC 2.7 mm, 12/13; TEC 4.0/ 4.7 mm, 13/13		• Diabetes: PTA, 3/13; TEC 2.7 mm, 4/13; TEC 4.0/ 4.7 mm, 4/13 • Hypertension: PTA, 8/13; TEC 2.7 mm, 5/13; TEC 4.0/ 4.7 mm, 7/13 • History of smoking: PTA, 11/13; TEC 2.7 mm, 11/13; TEC 4.0/ 4.7 mm, 13/13	The mean occlusion length was 19.4 cm (SD 11.7 cm)
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	64 (range 49–77) in patients treated with atherectomy and 64 (range–80) in the PTA group	DA, 28 (74%); PTA, 27 (77%)	Mild to moderate claudication: DA 26 (68), PTA 27 (77) Severe claudication: 12 (32), PTA 8 (23)	• Diabetes mellitus DA 4 (10%), PTA 3 (9%) Hypertension DA 8 (21%), PTA 4 (11%) • History of smoking DA 19 (50%), PTA 20 (57%) • Hyperlipidaemia DA 11 (29%), PTA 8 (23%) • Coronary artery disease DA 15 (39%), PTA 15 (43%)	Occlusion: DA 3%, PTA 6%. 'It should be noted that the patients in this study comprised a primarily favourable group, with only IC and with lesions less than 5 cm in length'

DA, directional atherectomy; SD, standard deviation.

Outcomes

Trial	Clinical status	Complications including amputation	Patency measures
Nakamura *et al.* 1995[34]		Procedural complications	Improvement in clinical symptoms as well as sustained improvement in ABPI
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	Clinical and haemodynamic outcome was classified according to Society for Vascular Surgery/International Society for Cardiovascular Surgery criteria on a scale from –1 to –3 for deterioration of symptoms and ABPI: 0 for unchanged symptoms, +1 for either a categorical improvement of clinical classification of claudication or increase of ABPI > 0.10, +2 for at least a single category improvement of claudication combined with ABPI increase of > 0.10 and +3 for markedly improved symptoms combined with an ABPI > 0.90	Procedural complications	Primary patency ended if a restenosis with ≥ 50% diameter reduction developed Late anatomical success or patency was determined by colour-flow duplex surveillance. As a baseline characteristic, the severest lesion is considered the index lesion. All lesions that recurred during follow-up within the same arterial segment are considered restenoses. Lesions in different segments that are treated at the same time are associate lesions, and their recurrences also are defined as restenoses. The severest of the restenoses is the lesion whose velocity values are used for the patency analysis. When studied as a dichotomous variable, a PSV ratio greater than 2.5 was the criterion for restenosis. Progression of disease in non-treated arterial segments is defined as new lesions. These lesions are not considered for the analysis of late patency. The rate of restenosis or occlusion was assessed by use of colour-flow duplex scanning. Restenosis was defined on the basis of a PSVR of ≥ 2.5, and occlusion of the treated segment was diagnosed if flow signals were absent, that is, loss of patency

PSV, peak systolic velocity; PSVR, peak systolic velocity ratio.

Results

Trial	Results	Complications
Nakamura *et al.* 1995[34]	Across groups, the mean lumen area increased from 4.7 to 15.1 mm^2, primarily because of balloon dilatation, but the mean atheroma area of 19.8 mm^2 did not change with either size of TEC device. Although the initial procedure success rate was high (79%), the 6-month patency was only 45%. There was no difference in 6-month patency between the groups; at 6 months, the percentages of patients still patent were as follows: PTA, 50%; TEC 2.7 mm, 46%; TEC 4.0/4.7 mm, 38% ($p = 0.16$)	PTA: three perforations due to guide wire manipulation (no haematoma formation). TEC 4.0/4.7 mm: one perforation and two cases of distal embolisation with 4.7-mm device (4.0 mm used for all further patients)
Vroegindeweij *et al.* 1992, 1995,[35,36] Tielbeek *et al.* 1996[37]	The patency rate at 2 years of treated segments was 34% in the atherectomy group and 56% in PTA patients (non-significant, $p = 0.07$). In patients with lesions > 2 cm, the 1-year patency rate of atherectomy was significantly lower than that of balloon angioplasty ($p = 0.03$). Stenosis: residual stenoses (≥ 30% diameter reduction) resulted in five patients (13%) undergoing atherectomy and three patients (9%) undergoing balloon angioplasty. Clinical: at 1 month, clinical and haemodynamic improvement by Society for Vascular Surgery/ International Society for Cardiovascular Surgery criteria for lower-limb ischaemia was observed in 34 patients (89%) treated with atherectomy and in 34 (97%) treated with balloon angioplasty. By life table analysis, the cumulative rate of clinical and haemodynamic success at 2 years was 52% in patients treated with atherectomy and 87% in patients treated with balloon angioplasty ($p = 0.06$)	DA: one small dissection, one large dissection, one failure to pass guide wire, one thrombosis/ embolisation. PTA: five small dissections. Residual stenoses of ≥ 30% diameter reduction were seen in five patients treated with atherectomy and three treated with PTA. However, in none of these cases was the residual stenosis > 50% diameter reduction. Immediate operative intervention was not required in any patient

DA, directional atherectomy.

Cutting balloon

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Amighi *et al.* 2008[38]	To prospectively determine, in a RCT, whether CBA yields superior morphological and clinical outcomes at 6 months compared with the 6-month outcomes after conventional PTA in patients with short de novo SFA lesions	RCT, prospective, two centres	Full report in peer-reviewed journal	English	(From ClinicalTrials.gov. Sponsored by Medical University of Vienna, Vienna)	Austria	Austria, 2 centres	Outcomes at 6 months
Dick *et al.* 2008[39]	To prospectively determine whether CBA, when compared with conventional balloon angioplasty, improves morphological and clinical outcomes in patients with femoropopliteal in-stent restenosis	RCT, prospective, single centre	Full report in peer-reviewed journal	English	NR	Austria	Austria	Outcomes at 1, 3 and 6 months

CBA, CB angioplasty; NR, not reported; SFA, superficial femoropopliteal artery.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Amighi *et al.* 2008[38]	CBA vs. PTA	CBA: the diameter of the balloon for PTA or CBA corresponded to the proximal non-diseased vessel area in a 1 : 1 ratio. The CBs were inflated slowly to a pressure of up to 8 atm according to manufacturer (Boston Scientific, Natick, MA) recommendations. 0.018-inch peripheral CBs (5–6 mm in diameter, 10 or 20 mm in length) were used over a standard 0.018-inch guide wire. For 4-mm lesions, 0.014-inch CBs (15 mm in length) were used over a standard 0.014-inch guide wire	PTA: experienced staff interventionists with 6–15 years' experience in peripheral vascular intervention performed PTA by following a standardised protocol involving an antegrade or over-the-bifurcation approach with use of 5- to 7-F sheaths. Heparin (5000 IU) was routinely administered intra-arterially. The diameter of the balloon for PTA or CBA corresponded to the proximal non-diseased vessel area in a 1 : 1 ratio. The regular balloons were inflated to 8–10 atm for ≤ 2 minutes. As a bail-out procedure, self-expandable nitinol stent implantation was performed in patients who had > 30% residual stenosis after repeated angioplasty or because of flow-limiting dissection or elastic recoil in the worst angiographic view
Dick *et al.* 2008[39]	PCBA vs. PTA	PCBA: PCBA was performed by using a peripheral CB (Boston Scientific). The balloon diameter in both groups corresponded to the proximal non-diseased vessel area. Bail-out stenting using self-expanding nitinol stents was performed in patients with a residual stenosis of > 30% or flow-limiting dissection. All patients continuously received 100 mg of aspirin daily, in addition to 75 mg of clopidogrel daily for 1 month after intervention	PTA: interventions were performed percutaneously by one of three experienced interventionists from an over-the-bifurcation approach. After insertion of a 7-F sheath, 5000 IU of heparin was administered intra-arterially. Bail-out stenting using self-expanding nitinol stents was performed in patients with a residual stenosis of > 30% or flow-limiting dissection. All patients continuously received 100 mg of aspirin daily, in addition to 75 mg of clopidogrel daily for 1 month after intervention

CBA, CB angioplasty; PCBA, peripheral CB angioplasty.

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Amighi *et al.* 2008[38]	Patients with short (≤ 5cm) de novo SFA lesions	Patients with SFA lesions ≤ 5 cm in length who were referred for endovascular treatment of the SFA owing to IC or chronic CLI. Inclusion criteria: the clinical criterion for study entry was symptomatic PAD with severe IC (Fontaine stage IIb) or chronic CLI (Fontaine stage III or IV). The anatomical inclusion criterion was a single SFA target lesion – specifically, a SFA with > 50% stenosis or occlusion – ≤ 5 cm in length. Exclusion criteria were previous BS or stent placement at the ipsilateral lower limb; history of intolerance to antiplatelet therapy, heparin or contrast media; bleeding diathesis; active systemic bacterial infection; and severely impaired renal function (serum creatinine level > 2.5 mg/dl)	From August 2004 to June 2006; 45 recruited; two patients (one treated with CBA and one treated with PTA) had to be excluded because of their withdrawal from follow-up examinations
Dick *et al.* 2008[39]	Femoropopliteal in-stent restenosis (angiographic stenosis of > 50% of the vessel lumen diameter)	Entry criteria included symptomatic PAD with IC or CLI related to a recurrent stenosis in a previously stented segment of ≤ 20 cm in length. Only patients with a restenosis of a self-expanding nitinol stent (Absolute/Dynalink, Abbott Vascular, Abbott Park, IL, USA; Protege, EV3, Paris, France; Sentinol®, Boston Scientific, Galway, Ireland; or SMART CONTROL®, Cordis, Miami Lakes, FL, USA) implanted at our institution or others were eligible. Exclusion criteria were a history of intolerance to antiplatelet therapy, an adverse reaction to heparin, bleeding diathesis, a creatinine level of > 2.5 mg/dl, haemodialysis, active bacterial infection, allergy to contrast media, pregnancy; patients with stent fractures were not included in the study, as treatment of fractured stents frequently requires repeat stenting of the lesion. Patients with acute stent thrombosis were also not eligible, as these patients were treated with thrombolysis prior to angioplasty	Consecutive patients with femoropopliteal in-stent restenosis (angiographic stenosis of > 50% of the vessel lumen diameter) were enrolled from November 2004 to March 2007 – 40 enrolled, one lost to follow-up

CBA, CB angioplasty; SFA, superficial femoropopliteal artery.

Sample size

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Number followed up from each condition (or attrition)
Amighi *et al.* 2008[38]	43	CBA 21 (of whom four had secondary stent placement)	PTA 22 (of whom four had secondary stent placement)	Estimated that a sample size of 40–50 patients would be necessary to demonstrate any superiority of CBA over PTA. On the basis of data in the literature, expected restenosis rates of 40% in the PTA group (literature-reported restenosis rates of 35–45% in patients with short lesions) and 10–20% in the CBA group (estimated)	6-month outcomes for 22/23 enrolled for PTA, and 21/22 for CBA
Dick *et al.* 2008[39]	39 (40, 1 lost to follow-up)	PCBA 17	PTA 22	NR	One patient lost to follow-up, group not specified

CBA, CB angioplasty; NR, not reported; PCBA, peripheral CB angioplasty.

Baseline characteristics

Trial	Age (years)	Gender (male)	Classification of PAD [*n* (%)]	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance [median (IQR)]	Other relevant information
Amighi *et al.* 2008[38]	Median PTA, 71.4 (IQR 60.8–76.6); median CBA, 67.4 (62–75.6)	PTA 14 (64%); CBA 12 (57%)	• Claudication: PTA 17 (77), CBA 18 (86) • Rest pain: PTA 1 (4.5), CBA 0 (0) • Ischaemic ulcers: PTA 4 (18), CBA 3 (14)	• Hypertension: PTA 20 (91), CBA 20 (95) • Diabetes mellitus: PTA 13 (59), CBA 11 (52) • Smoker at baseline: PTA 13 (59), CBA 8 (38) • Hyperlipidaemia: PTA 19 (86), CBA 19 (91)	Pain-free walking distance (m): PTA 100 (0–200), CBA 100 (10–150)	Occlusion in 23% of PTA and 29% of CBA group. Across groups, mean length of the treated segments was 2.5 cm, and the mean degree of stenosis was 90%. Four (18%) patients in the PTA group vs. one (5%) patient in the CBA group ($p = 0.17$) underwent secondary stent placement owing to flow-limiting dissection or residual stenosis
Dick *et al.* 2008[39]	Mean PCBA, 70 (SD 10); mean PTA, 66 (SD 10)	PCBA 65%; PTA 55%	Clinical (Rutherford) classification of PAD: • Stage 3 (IC): PCBA 14 (82), PTA 16 (73) • Stage 4 (ischaemic rest pain): PCBA 2 (12), PTA 2 (9) • Stage 5 (ischaemic ulcers): PCBA 1 (6), PTA 4 (18)	• Hypertension: PCBA 17 (100), PTA 20 (91) • Antihypertensive medication at baseline: PCBA 17 (100), PTA 20 (91) • Hyperlipidaemia: PCBA 17 (100), PTA 19 (86) • Statin treatment at baseline: PCBA 15 (88), PTA 16 (73) • Diabetes mellitus: PCBA 7 (41), PTA 8 (36) • Smoking at baseline: PCBA 3 (18), PTA 4 (18) • History of myocardial infarction: PCBA 0, PTA 3 (14) • History of stroke: PCBA 1 (6), PTA 2 (9)	Maximum walking distance on treadmill (m): PCBA 42 (23–100), PTA 55 (10–92)	Average lesion length was 80 mm (SD 68). Average length of the treated segments was 85 mm (SD 70), with no significant difference between the two groups. Chronic occlusion: PCBA 12%, PTA 9%

CBA, CB angioplasty; IQR, interquartile range; PCBA, peripheral CB angioplasty; SD, standard deviation.

Outcomes

Trial	Exercise tolerance/ walking distance	Pain/ clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Amighi *et al.* 2008[38]	Patient-reported pain-free walking distance	Clinical stage of PAD	Complications, adverse events	The primary study end point was the occurrence of a duplex-ultrasonography-assessed relevant (> 50%) restenosis in the treated vessel segment(s) 6 months after treatment. Restenosis was defined according to haemodynamic criteria as a > 50% reduction in vessel diameter at the level of the previously treated lesion. A focal increase in PSV of ≥ 140% (corresponding to a PSVR of ≥ 2.4) was considered to be indicative of > 50% stenosis at that site	
Dick *et al.* 2008[39]	Maximum walking capacity on the treadmill (no further details of treadmill protocol)		Complications were classified as either major or minor. Major complications were access site complications requiring surgical interventions, bleeding complications with a decrease of serum haemoglobin of > 2 g/dl, amputation, macroembolism with the need for further revascularisation and any death before discharge. Minor complications were those that resolved spontaneously (e.g. superficial haematoma and groin pain owing to nerve injury)	The primary study end point was the occurrence of a > 50% restenosis at the treated segment at 6 months after intervention, as determined by duplex ultrasonography	Reintervention at the site of the treated segment or BS was also defined as a restenosis and loss of primary patency

PSV, peak systolic velocity; PSVR, peak systolic velocity ratio.

Results

Trial	Results	Complications
Amighi *et al.* 2008[38]	Restenosis: 6-month restenosis rate was 32% (seven patients) in the PTA group vs. 62% (13 patients) in the CBA group ($p = 0.048$). Clinical: 16 (73%) PTA group patients vs. 8 (38%) CBA group patients were asymptomatic at follow-up ($p = 0.059$). Walking distance: there was no significant difference for pain-free walking distance (median > 1000 m vs. 600 m for PTA vs. CBA group, respectively; $p = 0.17$) between the two groups. Pain-free walking distance (m) [median (IQR)]: PTA 1000 (200 to > 1000), CBA 600 (100 to > 1000) (non-significant, $p = 0.17$)	One patient randomly assigned to undergo CBA had the minor complication of peripheral embolism of the tibioperoneal trunk, which was successfully resolved with thrombus aspiration during the intervention without clinical sequelae. No patient died during the follow-up period. Three patients (group not specified) – all with CLI—underwent minor amputations (toe to distal forefoot) within 14 days of angioplasty
Dick *et al.* 2008[39]	Maximum walking capacity at 6 months, on the treadmill: PCBA 117 m vs. PTA 103 m (non-significant, $p = 0.97$). Restenosis: restenosis rates at 6 months were 65% (11 of 17; 95% CI 42% to 88%) after PCBA vs. 73% (16 of 22; 95% CI 54% to 92%) after PTA (non-significant, $p = 0.73$). Earlier restenosis rates in the PCBA vs. CBA groups were 12% (2 of 17; 95% CI 3% to 27%) vs. 27% (6 of 22; 95% CI 8% to 46%) at 1 month ($p = 0.42$); and 47% (8 of 17; 95% CI 23% to 71%) vs. 41% (9 of 22; 95% CI 20% to 62%) at 3 months ($p = 0.75$). Clinical: comparable outcomes between PCBA and CBA were observed until 6 months after intervention. Deterioration at 6 months: 1% PCBA, 3% PTA	Technical success could be achieved in all patients. No major complications were observed. Bail-out stenting was done infrequently in both groups (12% PCBA, 5% PTA). No amputations and no deaths at 6 months. Thrombosis and/or reocclusions at 6 months: PCBA 6%, PTA 23%. Ipsilateral reinterventions by 6 months: PCBA 41%, PTA 36%

CBA, CB angioplasty; IQR, interquartile range; PCBA, peripheral CB angioplasty.

Cryoplasty

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Jahnke *et al.* 2010[40]	To evaluate safety and efficacy of cryoplasty vs. conventional angioplasty for focal popliteal arterial occlusive disease	RCT, prospective, single centre	Full report in peer-reviewed journal	English	NR	Germany	Germany	Outcomes reported at 9 months
Spiliopoulos *et al.* 2010[41]	To investigate the immediate and long-term results of cryoplasty vs. conventional balloon angioplasty in the femoropopliteal artery of diabetic patients	RCT, prospective, single centre	Full report in peer-reviewed journal	English	NR	Greece	Greece	Follow-up visits at 6 months, 1 year and annually thereafter. The mean angiographic follow-up period was 23.5 months (SD 1.9 months) for the cryoplasty group vs. 25.3 months (SD 2.0 months) in the PTA group ($p = 0.6$), whereas the mean clinical follow-up period was 32 months (SD 9 months) in the cryoplasty group vs. 32 months (SD 2 months) in the PTA group ($p = 0.7$), with no significant differences in patient compliance between the two groups

NR, not reported; SD, standard deviation.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Jahnke *et al.* 2010[40]	Cryoplasty vs. PTA	Cryoplasty: from an ipsilateral antegrade puncture of the femoral artery, placement of 7-F sheath (Terumo, Tokyo, Japan) lesions were recanalised with guide wire and 5-F catheter (Berenstein, Cordis, Roden, the Netherlands). Correct intraluminal position verified with contrast medium, guide wire replaced with 0.9-mm Radifocus Glidewire, heparin administered. Cryoplasty balloon sizes chosen to be the same size as reference vessel diameter, and allowed to exceed luminal diameter of nearest normal appearing vessel by 20%, thus balloon-to-vessel ratios of 1.5 : 1 to 1.25 : 1. PolarCath® Peripheral Dilatation System (Boston Scientific, Natick, MA, USA) used. In the event of residual stenosis, conventional balloon angioplasty was performed; if persistent failure with > 30% residual stenosis, then a SES was implanted	PTA: from an ipsilateral antegrade or retrograde crossover approach, placement of 5- or 6-F sheath lesions were recanalised with guide wire and 5-F catheter. Correct intraluminal position verified with contrast medium, heparin administered, angioplasty with Sterling Balloon (Boston Scientific). Balloon sizes chosen to be the same size as reference vessel diameter, and allowed to exceed luminal diameter of nearest normal appearing vessel by 20%, thus balloon-to-vessel ratios of 1.5 : 1 to 1.25 : 1. In the event of residual stenosis, the balloon of next greatest diameter used or device inflated again for 3–5 minutes. If persistent failure with > 30% residual stenosis, then SES was implanted
Spiliopoulos *et al.* 2010[41]	Cryoplasty vs. PTA	Cryoplasty: cryoplasty therapy was performed with the use of the PolarCath Peripheral Dilatation System, which includes an over-the-wire, double-lumen dilatation balloon catheter manufactured of Pebax® (Atochem Inc., PA, USA) and an inflation system consisting of a microprocessor unit and a nitrous oxide cartridge. The cryoplasty catheter is formed by three layers (inner, middle and outer), and its fluoroscopic visibility is attained by radio-opaque markers placed in the middle layer. Balloon inflation is achieved by a specially designed apparatus that releases liquid nitrous oxide from the specially designed high-pressure cartridge through the catheter lumen and into the lower-pressure balloon chamber, where it changes state from liquid to gas and expands its volume	PTA: conventional balloon angioplasty with commercially available semi-compliant or non-compliant balloon catheters (inflation period 60–120 seconds). In all cases, balloon size was chosen according to reference vessel diameter per visual estimate. Balloon length was chosen to match lesion length, and, if that was not possible, to slightly exceed it, according to routine clinical practice. Stenting was reserved for bail-out in case of elastic recoil, post-dilatation residual stenosis > 30% or severe flow-limiting dissection (type C). An antegrade or retrograde femoral artery access using an appropriately sized sheath (6 F to 7 F) was performed. A bolus dose of unfractionated heparin (3000–5000 IU) was administered immediately after sheath placement, and an infusion rate of 1000 U/h was maintained during the rest of the procedure. Routine endovascular manoeuvres using standard guide wires and catheters were used to cross the SFA and/or the popliteal artery lesion as needed

SFA, superficial femoropopliteal artery.

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Jahnke *et al.* 2010[40]	Patients with focal atherosclerotic stenoses and occlusions of the popliteal artery	Inclusion criteria: lifestyle-limiting claudication (Rutherford–Becker 1–3), rest pain or ischaemic skin changes of the feet (Rutherford–Becker 4 or 5) induced by focal atherosclerotic stenoses or occlusions of popliteal artery. Exclusion criteria: haemodynamically relevant lesions (> 50% luminal stenosis) of the arterial in/out-flow, prior stent or graft placement into popliteal artery, lesions induced by former vascular surgery, fresh embolic occlusions, contraindications to contrast media, renal failure, hyperthyroidism, allergic diathesis	Over 2.5 years
Spiliopoulos *et al.* 2010[41]	Diabetic patients with femoropopliteal arterial occlusive disease	Inclusion criteria: non-insulin-dependent diabetes mellitus or insulin-dependent diabetes mellitus, severe claudication or CLI (Rutherford categories 3–6), stenosis ≥ 70% or occlusion of the SFA and/or the popliteal artery and de novo and in-stent restenotic lesions. Exclusion criteria: diet-controlled diabetes, history of severe contrast allergy or hypersensitivity, intolerance to aspirin and/or clopidogrel, systemic coagulopathy or hypercoagulation disorders, acute limb ischaemia, Buerger's disease, deep-vein thrombosis, infected tissue loss and absent pedal arch run-off	Between January 2005 and October 2007

Sample size

Trial	Numbers included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Number followed up from each condition (or attrition)
Jahnke *et al.* 2010[40]	86	Cryoplasty, 40 (crossover to long-term angioplasty in $n = 23$, 58%; bail-out stent placement $n = 12$, 30%)	PTA, 46 (bail-out stent placement $n = 18$, 39%)	NR	At time of publication, 23/40 cryoplasty and 23/46 PTA patients have reached 9 months follow-up
Spiliopoulos *et al.* 2010[41]	50	Cryoplasty, 24 patients with 31 lesions	PTA, 26 patients with 34 lesions	NR	Only one patient (1 of 24; 4.16%) assigned to the cryoplasty group was lost from angiographic but not from clinical follow-up after 6 months. This was due to an ischaemic stroke

NR, not reported.

Baseline characteristics

Trial	Age (mean, years)	Gender (%male)	Classification of PAD	Presence of cardiovascular risk factors	Other relevant information
Jahnke *et al.* 2010[40]	Across groups 72 (range, 50–94); cryoplasty group 73.6 (SD 9.7); PTA group 70.6 (SD 10.2)	Cryoplasty 43%, PTA 49%	• Claudication: cryoplasty 72.5%, PTA 80.% • CLI: cryoplasty 27.5%, PTA 19.6%	• Smoking cryoplasty: 38%, PTA 46% • Arterial hypertension: cryoplasty 85%, PTA 78% • Diabetes mellitus: cryoplasty 28%, PTA 33%	Mean lesion length (mm): cryoplasty 35 (SD 28.8), PTA 36.5 (SD 28.5)
Spiliopoulos *et al.* 2010[41]	Cryoplasty 65.3 (SE 10.4), PTA 70.3 (SE 7.8)	Cryoplasty 87.5%, PTA 84.6%	• 41.4% of patients in the cryoplasty group and 38.7% in the PTA group suffered from CLI ($p = 0.41$). Rutherford category of PAD: • Stage 3: cryoplasty 17 (58.6%), PTA 19 (61.3%) ($p = 0.42$) • Stage 4: cryoplasty 10 (34.5%), PTA 6 (19.4%) ($p = 0.09$) • Stage 5: cryoplasty 1 (3.4), PTA 4 (12.9) ($p = 0.09$) • Stage 6: cryoplasty 1 (3.4), PTA 2 (6.5) ($p = 0.29$)	• Smoking habit: cryoplasty 12 (50%), PTA 11 (42.3%) • Insulin-dependent diabetes mellitus: cryoplasty 10 (41.7%), PTA 9 (34.6%) • Hyperlipidaemia: cryoplasty 17 (71.0%), PTA 15 (58.0%) • Arterial hypertension: cryoplasty 23 (95.8%), PTA 23 (88.5%) • Cardiac disease: cryoplasty 7 (29.2%), PTA 10 (38.5%)	61.3% (19 of 31) of cryoplasty group lesions and 52.9% (18 of 34) of PTA group lesions were de novo lesions. > 70% of the lesions were TASC B and C in both groups. The average lesion length was 11.9 cm (SD 5 cm) in the cryoplasty group and 12.0 cm (SD 6 cm) in the PTA group ($p > 0.05$)

SD, standard deviation; SE, standard error.

Outcomes

Trial	Pain/clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Jahnke *et al.* 2010[40]	Improvement defined by Society for Vascular Surgery/International Society for Cardiovascular Surgery criteria for lower-limb ischaemia ranging from –3 (markedly worse) to +3 (markedly improved)	Procedural complications	The primary objective was target lesion patency. > 2.5-fold increase in PSVR across the treated segment indicative of > 50% luminal narrowing	
Spiliopoulos *et al.* 2010[41]		Procedural complications	Primary patency was defined as angiographic visualisation of a non-occluded lesion and no need for any additional repeat interventional procedure within the previously treated lesion. Absent or thread-like blood flow was classified as vascular occlusion. Binary in-lesion restenosis (> 50%)	Freedom from target lesion recanalisation. TLR included any additional recanalisation procedure within the area of the treated femoropopliteal lesion because of clinical deterioration and relapse of symptoms (i.e. clinically driven repeat procedures)

PSVR, peak systolic velocity ratio.

Results

Trial	Results	Complications
Jahnke *et al.* 2010[40]	Patency: the mean target lesion patency at 9 months was 79.3% (SD 7.5) for cryoplasty and 66.7% (SD 8.1) for conventional angioplasty (non-significant, $p = 0.14$). At 6 months, target lesion patency was 82.9% (SD 7.0) for cryoplasty and 79.8% (SD 6.4) for conventional angioplasty (non-significant). Clinical: improvement of clinical stage at 9 months – cryoplasty +2.73 (SD 0.55), PTA +2.43 (SD 1.16) (non-significant, $p = 0.29$). Optional long-term PTA was performed in 58% of cryoplasty patients. The rate of stent placement for dissection and/or residual stenosis was 30% after cryoplasty (including long-term dilatation) and 39% after conventional angioplasty ($p = 0.34$)	Initial success was 35% for cryoplasty vs. 54% for conventional angioplasty ($p = 0.02$). Minor complications: 2.5% cryoplasty, 2.7% PTA. Major complications: 5% cryoplasty, 2.7% PTA
Spiliopoulos *et al.* 2010[41]	Restenosis: there was a non-significant trend of increased binary restenosis in the cryoplasty group (HR 1.3; 95% CI 0.6 to 2.6; $p = 0.45$). Reintervention: significantly more repeat intervention events because of recurrent symptoms were required in the cryoplasty group (HR 2.5; 95% CI 1.2 to 5.3; $p = 0.01$). Patency: primary patency was significantly lower in the cryoplasty group than in the PTA group (HR 2.2; 95% CI 1.1 to 4.3; $p = 0.02$). Cox model adjusted for insulin-dependent diabetes mellitus, renal disease, smoking, hyperlipidaemia, lesion grade, lesion type (de novo or in-stent restenotic), heavy calcifications, TASC classification and type of treatment (cryoplasty or PTA)	Immediate technical success rate was 58.0% in cryoplasty group vs. 64.0% in PTA group ($p = 0.29$). According to 3-year Kaplan–Meier estimates, there were no significant differences with regard to patient survival (86.8% in cryoplasty group vs. 87.0% in PTA group; $p = 0.54$) and limb salvage (95.8% vs. 92.1% in cryoplasty and PTA groups, respectively; $p = 0.60$). None of the deaths was related to the procedure. Minor amputation rates were similar in the two study arms (6.9% in cryoplasty group vs. 9.7% in PTA group, $p = 0.3$)

HR, hazard ratio; SD, standard deviation.

Radiation

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	To evaluate the effect of probucol and/or EVBT on restenosis after PTA of femoropopliteal arteries	RCT	Full report	English	Swiss Heart Foundation	Switzerland	Switzerland	0-, 3-, 6-, 12- and 24-month follow-up post intervention
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	To evaluate the effect of EVBT on restenosis following secondary angioplasty of femoropopliteal segment	RCT	Full report	English	Not disclosed	Switzerland	Switzerland	1-day and 3-, 6-, 9- and 12-month follow-up post intervention. Annually up to 5 years (Diehm *et al.*[44] combined results of Gallino *et al.*[43] and Zehnder *et al.*[45])
Hagenaars *et al.* 2002[46]	To evaluate the effect of EVBT on the extent of plaque growth and vascular remodelling after PTA of the femoropopliteal artery	RCT	Full report	English	The Revolving Fund and Interuniversity Cardiology Institute of the Netherlands	Netherlands	Netherlands	6 months
Krueger *et al.* 2002, 2004[47,48]	To evaluate whether centred endovascular irradiation after PTA for de novo femoropopliteal stenoses reduces restenosis	RCT	Full report	English	Cologne Fortune	Germany	Germany	6, 12 and 24 months
Vienna-2[49,50]	To evaluate the efficacy of EVBT for prophylaxis of restenosis after femoropopliteal PTA.	RCT	Full report	English	Not disclosed	Austria	Austria	1 day, 1, 3, 6, 12, 18, 24 months and 5 years post procedure
Vienna-3[52]	To evaluate the effect of EVBT on restenosis after femoropopliteal angioplasty	RCT	Full report	English	Not disclosed	Austria	Austria	The primary end point of the study was arterial patency of the recanalised segment after 12 months and mean follow-up was 15.7 months

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
VARA[54]	To evaluate the efficacy of EVBT for prophylaxis of restenosis after femoropopliteal PTA	RCT	Full report	English	The Professor Michaël-van Vloten Foundation	Netherlands	Belgium/ Netherlands	6 and 12 months. The primary end point was a ≥ 50% restenosis at duplex ultrasound of the treated segment after 12 months
Wyttenbach *et al.* 2004, 2007[55,56]	To evaluate the short- and long-term effects of PTA on severely stenotic femoropopliteal lesions as well as the effect of brachytherapy on restenosis by means of serial MRI	RCT	Full report	English	Swiss Heart Foundation	Switzerland	Switzerland	24 hours, 3 and 24 months
Fritz *et al.* 2004[57]	To evaluate the effect of hypofractionated EBRT as a prophylaxis for restenosis	RCT	Full report	English	Not disclosed	Germany	Germany	1 day, 3, 6 and 12 months
Therasse *et al.* 2005[58]	To evaluate whether external beam radiation can prevent stenosis after femoropopliteal PTA	RCT	Full report	English	The study was supported by a grant from the Fonds de la recherche en sante du Quebec	Canada	Canada	The main study end point was the minimum lumen diameter within the dilated vessel segment 1 year after PTA

MRI, magnetic resonance imaging.

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	PTA + EVBT vs. PTA + placebo drug. All groups received aspirin 100 mg/day	PTA with ipsilateral antegrade puncture and 6-F introducer sheath (Cordis Europe, Roden, The Netherlands) with 5- or 7-mm balloon catheters (Smash, Schneider Europe, Bulach, Switzerland) + EVBT with gamma irradiation (^{192}iridium, 14 Gy, 5-mm reference depth)	PTA + placebo drug given 1 g/day orally from 1 month before PTA and continued for 6 months post PTA
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	PTA + EVBT vs. PTA alone	PTA with ipsilateral antegrade approach to the common femoral artery using a 6-F sheath with 4- to 6-mm balloons. Stents were inserted if residual stenosis > 30% persisted or flow was obstructed. High-dose EVBT (^{192}iridium, 12-Gy reference dose, 5-mm reference depth) without a centring device	PTA as for intervention
Hagenaars *et al.* 2002[46]	PTA + EVBT vs. PTA alone	'Standard' PTA + EVBT (^{192}iridium, dose of 14 Gy with centring balloon) with an over-the-wire delivery catheter	PTA as for intervention
Krueger *et al.* 2002, 2004[47,48]	PTA + endovascular irradiation vs. PTA alone	PTA performed according to conventional practice using an ipsilateral or crossover approach with a short 8-F or flexible 8-F sheath, respectively. The balloon diameter was between 5 and 6 mm. EVBT was ^{192}iridium, 14 Gy, centred	PTA as for intervention
Vienna-2[49,50] Wolfram 2006	PTA + EVBT vs. PTA alone	PTA using an ipsilateral anterograde puncture and 6-F introducer sheath with 5- or 6-mm balloon catheters + EVBT (^{192}iridium, 12-Gy dose, 3 mm from the source axis, uncentred)	PTA as for intervention
Vienna-3[52]	PTA + EVBT vs. PTA + sham irradiation	PTA using an ipsilateral anterograde puncture and 6-F introducer sheath with 4- to 6-mm balloon catheters + EVBT (^{192}iridium, 18-Gy dose, 7-F centring catheter)	PTA as for intervention + sham irradiation, but no further detail about this process was reported
VARA[54]	PTA + EVBT vs. PTA alone	PTA via an ipsilateral antegrade puncture, 5-F catheter, 5- to 7-mm balloon. EVBT using ^{192}iridium, a dose of 14 Gy	PTA as for intervention
Wyttenbach *et al.* 2004, 2007[55,56]	PTA + EVBT vs. PTA alone	PTA via an ipsilateral anterograde puncture of the common femoral artery, 6-F introducer sheath, 5- to 6-mm balloon. EVBT using ^{192}iridium, reference dose of 14 Gy, non-centred	PTA as for intervention
Fritz *et al.* 2004[57]	PTA + EBRT vs. PTA + sham EBRT	PTA using conventional balloon catheter techniques with ipsilateral (femoropopliteal) or retrograde (iliac) puncture with balloon catheters 4–9 mm in diameter using a 6-F introducer sheath + EBRT daily in 3-Gy fractions to a total dose of 21 Gy	PTA as for intervention + sham ERBT
Therasse *et al.* 2005[58]	PTA + 7-Gy, 10.5-Gy, 14-Gy EBR vs. PTA + 0-Gy EBR	PTA + 7-Gy, 10.5-Gy, 14-Gy EBR (three groups) delivered in a single session 24 hours post PTA	PTA + 0-Gy EBR

EBR, external beam radiation.

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	Patients with IC of the femoropopliteal arteries	Inclusion criteria: (1) age > 50 years, (2) chronic, moderate to severe IC (Rutherford category 2 or 3), referable to > 50% stenosis or total occlusion. Exclusion criteria: (1) rest pain or CLI, (2) non-atherosclerotic arterial occlusive disease, (3) vascular surgery during the preceding 6 months, (4) uncontrolled arterial hypertension, (5) haemorrhagic diathesis, (6) liver disease, (7) impaired renal function (serum creatinine level > 180 µmol/l), (8) a prolonged corrected QT interval (≥ 480 ms) on electrocardiogram, (9) life expectancy < 6 months, (10) questionable compliance or an insufficient insonation window over the target lesion at duplex ultrasound, (11) patients who were non-compliant (> 20% of unused study drug at 4 weeks follow-up) during the run-in phase before angioplasty	Not reported
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	Patients with restenosis or reocclusion after primarily successful femoropopliteal PTA	Inclusion criteria: (1) restenosis > 50% after previously successful femoropopliteal PTA, (2) IC or CLI, (3) age > 50 years, (4) willingness to consent. Exclusion criteria: (1) acute or subacute occlusion of the vessel, (2) non-atherosclerotic occlusive disease, (3) vascular surgery or angioplasty during the preceding 3 months, (4) life expectancy < 6 months, (5) inadequate visualisation of the lesion on duplex images	Patients referred and meeting criteria
Hagenaars *et al.* 2002[46]	Patients with disabling claudication due to femoropopliteal arterial stenosis	Inclusion criteria: (1) angiographically proven femoropopliteal stenosis (> 50%) or occlusion, (2) lesion length < 10 cm, (3) age 40–85 years, (4) no inflow obstruction or significant stenosis in the iliac artery. Exclusion criteria: (1) impaired renal function, (2) acute ischaemia, (3) pregnancy, (4) life expectancy < 12 months	
Krueger *et al.* 2002, 2004[47,48]	Patients with de novo femoropopliteal stenosis Fontaine stage 2a to 3	Inclusion criteria: (1) age > 50 years, (2) femoropopliteal arterial occlusive disease Fontaine stage 2a to 3, (3) de novo stenosis of maximum length 8 cm. Exclusion criteria: (1) patients with untreated stenosis proximal to the region of PTA or with less than one run-off vessel, (2) exposure to endovascular treatments other than PTA, (3) patients with malignant disease	Consecutive patients

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Vienna-2[49,50]	Patients with de novo or recurrent femoropopliteal lesions	Inclusion criteria: (1) age > 40 years, (2) history of claudication (Rutherford category 2 or 3) for > 3 months or CLI with pain at rest with or without tissue damage, (3) de novo lesion in the femoropopliteal region with a minimal lesion length of 5 cm or a recurrent lesion (after former PTA) of any length, (4) technical success of the angioplasty procedure, which required angiographic patency with residual stenosis of > 30% diameter reduction, (5) no further stent implantation	Consecutive patients
Vienna-3[52]	Patients with de novo or recurrent femoropopliteal lesions	Inclusion criteria: (1) age > 45 years, (2) history of claudication (Rutherford category ≥ 2), (3) stenosis of ≥ 50%, (4) de novo lesion of ≥ 5 cm or recurrent lesion after prior angioplasty of any length, (5) successful angioplasty of < 30% residual stenosis. Exclusion criteria: (1) stenting and crossover approach, (2) in-stent restenosis, (3) former irradiation of superficial femoropopliteal artery, (4) life expectancy < 12 months, (5) thrombolysis at the time of randomisation	All patients admitted to the trial's host institutions with femoropopliteal lesions
VARA[54]	Patients with symptomatic stenotic or totally occluding lesions in the femoropopliteal artery	Inclusion criteria: (1) age between 40 and 80 years, (2) claudication or non-acute CLI (Rutherford category ≥ 2), (3) lesion in the femoropopliteal artery with a maximum length of 10 cm, (4) reference diameter of the segment 4–8 mm, (5) no significant haemodynamic iliac stenosis, (6) written informed consent. Exclusion criteria: (1) after randomisation of the revascularisation was unsuccessful; (2) where the maximum lesion length is 10 cm the dilated segment should not exceed 13 cm	Patients accessing the participating hospitals
Wyttenbach *et al.* 2004, 2007[55,56]	Patients with severe superficial femoropopliteal artery stenosis classified as Rutherford category ≥ 3	Patients were not eligible for the study if they had non-atherosclerotic occlusive disease, vascular surgery during the preceding 6 months, uncontrolled hypertension, haemorrhagic diathesis, impaired renal function (creatinine level ≥ 180 mmol/l), a life expectancy of < 6 months or a contraindication for MRI	Consecutive patients

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Fritz *et al.* 2004[57]	Patients who underwent successful PTA for claudication or CLI with Fontaine stage II to IV	Inclusion criteria: (1) age > 50 years, (2) claudication or CLI (Fontaine stage II to IV), (3) ABPI < 0.8 at rest, (4) focal de novo or recurrent lesion in the iliac or femoropopliteal region with a maximal lesion length of 10 cm, (5) PTA success, (6) no stent implantation or surgical intervention after PTA	
Therasse *et al.* 2005[58]	Patients with symptomatic, lifestyle-limiting vascular insufficiency, either claudication or CLI secondary to a de novo atherosclerotic obstructive lesion of the femoropopliteal artery	Inclusion criteria: (1) stenosis or occlusion of the femoropopliteal artery with a diameter reduction of ≥ 50% and ABPI < 0.9. Exclusion criteria: (1) age < 45 years, (2) women of child bearing age, (3) patients who had received a radiosensitising agent or radiation therapy to the lower limb in the past, (4) previous stent implantation, (5) residual stenosis > 50% after PTA	Patients referred for PTA by their physicians

MRI, magnetic resonance imaging.

Sample size

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	335 (includes all four treatments arms – only data related to two arms extracted here)	EVBT + placebo drug immediately after femoropopliteal PTA, 81	Placebo drug, 75	Assuming a 35% recurrence rate within 6 months, and treatment effect of 20% with $\alpha = 0.05$ and $\beta = 0.1$ and anticipating 10% loss to follow-up, it was estimated that 90 participants per group would be required	PTA + EVBT: 12/81 (14.8%) loss to follow-up. Control/placebo: 9/75 (12%) loss to follow-up. These figures include those excluded from final analysis owing to per protocol requirements (54). The authors report that six were lost to follow-up, but do not specify the arms from which they were lost. Only data for participants who completed the trial satisfactorily were analysed	PTA + EVBT: 69/81 (85.2%). Control/placebo: 66/75 (88.0%)
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	100 (Diehm *et al.*,[44] 147)	51 (Diehm *et al.*,[44] 72)	49 (Diehm *et al.*,[44] 75)	Not reported	12-month follow-up: 56/100. This is qualified as 'excluding patients with additional interventions'. The group distribution is unclear. Moreover, seven participants who did not receive adequate EVBT were added to the control group. [Diehm *et al.*:[44] at 31.8 months (range 12 days to 77.5 months) 30/72 from T1 (41.7%) and 34/75 from T2 (45.3%) were lost to follow-up.] Participants who did not provide follow-up data appear to have been excluded	For per protocol analysis, T1 44 (86.3%), T2 56 (114.3%; 49 randomised to PTA alone, and 7 originally randomised to EVBT). [Diehm *et al.*,[44] ITT: at 31.8 months (range 12 days to 77.5 months) T1 42/72 (58.3%) and T2 41/75 (54.7%)]

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
Hagenaars *et al.* 2002[46]	38	18	20	Not reported	14/38 were excluded or lost to follow-up: T1 = 10/18, T2 = 4/20. Data concerning those lost to follow-up were excluded from analysis	T1: 8/18 (44.4%). T2: 16/20 (80.0%)
Krueger *et al.* 2002, 2004[47,48]	30	15	15	The report refers to requiring 40 participants, but no further detail is provided	Minimal: 2/30 (6.7%) at 24-month follow-up	14/15 (93.3%) followed up in both groups. One participant in the control group refused and one participant in the intervention group died through gastric bleeding 15 months after randomisation
Vienna-2[49,50]	117	60	57	Assuming a 30% absolute difference between treatment arms with $\alpha = 0.05$ and $\beta = 0.15$, it was estimated that 82 patients would be needed	4/117 were excluded from further follow-up: one refused brachytherapy and three (T1 = 2, T2 = 1) suffered early recurrence within 24 hours. Subsequently, 107 patients were followed up with regards to 6-month patency. Missing data were excluded	T1: 53/60 (88.3%). T2: 54/57 (94.7%). At 5-year follow-up: T1 – 51/60 (85.0%); T2 – 51/57 (89.5%)
Vienna-3[52]	Only detail offered is that 134 were randomised	67	67	Not reported	38/134 were excluded for various reasons but maintained in the ITT. No additional attrition is reported. All excluded patients were treated as 'failures'	T1: 50/67 (74.6%). T2: 46/67 (68.7%)
VARA[54]	60	27	33	Assuming an incidence of restenosis of 50% in T2 and 20% in T1 with $\alpha = 0.05$ and power = 0.8, 38 participants per group were required	53/60 (88.3%). Missing data were excluded	T1: 23/27 (85.2%). T2: 30/33 (90.9%)

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
Wyttenbach *et al.* 2004, 2007[55,56]	20	10	10	Not reported	No apparent loss to follow-up at 3 months. At 24 months, 3/20 (15%) attrition	100% at 3 months in both groups. At 24 months: T1 – 9/10 (90%); T2 – 8/10 (80%)
Fritz *et al.* 2004[57]	100	47	48	Unclear whether an a priori calculation was undertaken, but the report states that a sample of 100 patients enables the detection of an absolute reduction in the failure rate from 40% to 15% with $\alpha = 0.05$ and $\beta = 0.2$	5/100 dropped out following first follow-up examination and were excluded from the analysis. Reason for attrition is not stated. One patient in the EBRT group had a stroke and was also excluded. Minimal attrition, but participants excluded from the analysis	Unclear because the number randomised to each group prior to first round of dropouts was not reported, but 94/100 followed up with regards to failure
Therasse *et al.* 2005[58]	99	7 Gy, 24; 10.5 Gy, 26; 14 Gy, 25	24	With power of 0.80 and a two-tailed significance level of 0.05 to detect an effect size of 0.40 between the control group and one of the EBR groups, 19 patients were required per group. To compensate for non-compliant patients and for those lost to follow-up, the sample size was increased to a total of 99 patients	88/99 (88.9%). Missing data were excluded for most analyses except the rate of restenosis of dilated segments	See attrition

EBR, external beam radiation.

Baseline characteristics

Trial	Age (mean, years)	Gender (male)	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]			Rutherford categories 2 and 3 referable to > 50% stenosis or total occlusion of the femoropopliteal arteries	Not reported	EVBT: diabetes mellitus 28 (35%), smoking 21 (26), hypertension 59 (73), hypercholesterolaemia 27 (53). PTA: diabetes mellitus 25 (30), smoking 26 (31), hypertension 50 (59), hypercholesterolaemia 41 (49)	Not reported
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	T1: 70.8 (± 8.0). T2: 70.7 (±9.0)	T1: 31 (62%). T2: 27 (55%)	IC or chronic limb ischaemia, > 50% restenosis documented by angiography or duplex ultrasound	At least one, but not reported more specifically	T1: diabetes mellitus 12 (23), smoking 21 (41), hypertension 32 (62), dyslipidaemia 27 (53). T2: diabetes mellitus 14 (29), smoking 19 (39), hypertension 29 (59), dyslipidaemia 25 (51)	Not reported
Hagenaars *et al.* 2002[46]	T1: 60.0 (±9.8). T2: 65.9 (± 9.9)	T1: 6/8 (75%). T2: 11/16 (68.8%)	Fontaine stages II to IV (T1: 6/1/1, respectively) (T2: 6/6/4, respectively)	Not reported	T1: diabetes mellitus 2 (25), smoker 7 (88.8), systemic hypertension 5 (63), hypercholesterolaemia 5 (63). T2: diabetes mellitus 3 (19), smoker 10 (63), systemic hypertension 7 (44), hypercholesterolaemia 4 (25)	Not reported

Trial	Age (mean, years)	Gender (male)	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance
Krueger *et al.* 2002, 2004[47,48]	T1: 60.4 (SD 5.7). T2: 61.3 (SD 5.4)	T1: 12/15 (80.0%). T2: 11/15 (73.3%)	Fontaine stage 2a to 3	None, de novo lesions included only	T1: diabetes mellitus 5 (33.3), smoker 8 (53.3), arterial hypertension 9 (60), hypercholesterolaemia 10 (66.7). T2: diabetes mellitus 4 (26.7%), smoker 9 (60), arterial hypertension 8 (53.3), hypercholesterolaemia 7 (46.7)	Treadmill testing undertaken pre intervention: mean pain-free walking distance for T1/T2 = 92.2m (SD 113.1m)/95.9m (SD 123.2m) ($p = 0.83$)
Vienna-2[49,50]	71 (range 43 to 89) for whole group only reported	T1: 29/57 (50.9%). T2: 34/56 (60.7%)	Rutherford category 2 or 3 for > 3 months or CLI with pain at rest with or without tissue damage. Duration of symptoms: T1 = 6 months (±6), T2 = 6 months (±5)	Recurrent stenosis following previous PTA: T1, 27/57 (47.4%); T2, 28/56 (50%)	T1: diabetes mellitus 26 (45.6), smoker 12 (21.1), arterial hypertension 42 (73.7). T2: diabetes mellitus 29 (51.8), smoker 13 (23.2), arterial hypertension 27 (48.2)	Not reported
Vienna-3[52]	Not reported	T1: 34/50 (68.0%). T2: 28/46 (60.9%)	Rutherford category 2, 3, 4 or 5. T1: *n* = 2/40/2/6. T2: *n* = 1/34/5/6	T1: 13/50 (26%) had recurrent lesions with previous angioplasty. T2: 8/46 (17.4%) had recurrent lesions with previous angioplasty	T1: diabetes mellitus 21 (42), smoker 16 (32), arterial hypertension 38 (76). T2: diabetes mellitus 22 (47.8), smoker 7 (15.2), arterial hypertension 37 (80.4)	Not directly reported – Rutherford classification reported
VARA[54]	T1: 63.2 (range 43 to 76). T2: 64.7 (range 50 to 85)	T1: 18 (63.0%). T2: 22 (67.0%)	Rutherford category ≥ 2. All had de novo stenosis	None	T1: diabetes mellitus 5 (19), smoker 24 (89), hypertension 9 (33), hypercholesterolaemia 10 (37). T2: diabetes mellitus 7 (21), smoker 30 (91), hypertension 14 (42), hypercholesterolaemia 11 (33)	Only the Rutherford classification reported

Trial	Age (mean, years)	Gender (male)	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors [*n* (%)]	Level of exercise tolerance
Wyttenbach *et al.* 2004, 2007[55,56]	T1: 68.7 ± 6.1. T2: 73.4 ± 6.6	T1: 7/10 (70%). T2: 7/10 (70%)	Rutherford category 3 or 4. T1: *n* = 9/1. T2: *n* = 7/3. Duration: T1, 6.3 months (± 5.5); T2, 5.9 months (± 5.0)	Only de novo lesions included	T1: diabetes mellitus 4 (40), smoker 5 (50), arterial hypertension 6 (60). T2: diabetes mellitus 6 (60), smoker 7 (70), arterial hypertension 6 (60)	Only the Rutherford classification reported
Fritz *et al.* 2004[57]	T1: 67.6 (± 8.3). T2: 69.3 (± 9.5)	T1: 30 (63.8%). T2: 22 (45.8%) ($p = 0.1$)	Fontaine stages II to IV	Former PTA: T1, 4/47 (8.5%); T2, 8/48 (16.7%)	T1: diabetes mellitus 17 (36.2), smoker 17 (36.2), arterial hypertension 29 (61.7). T2: diabetes mellitus 20 (41.7), smoker 18 (37.5), arterial hypertension 30 (62.5)	Not reported
Therasse *et al.* 2005[58]	63.7 (± 8.7)	65%	Patients with symptomatic, lifestyle-limiting vascular insufficiency, either claudication or CLI secondary to a de novo atherosclerotic obstructive lesion of the femoropopliteal artery	Not reported	Dyslipidaemia 62%, diabetes mellitus 31%, hypertension 65%, smoker 87%	Not reported

SD, standard deviation.

Outcomes

Trial	Pain/clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	Rutherford classification	Adverse events	> 50% restenosis on duplex ultrasonography	Revascularisation needed
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	Rutherford classification		> 50% restenosis on duplex ultrasonography	Repeat dilatation or surgery
Hagenaars *et al.* 2002[46]			> 50% restenosis. Change in lumen, vessel and plaque area and plaque dissections through an intravascular ultrasound scan	
Krueger *et al.* 2002, 2004[47,48]	Treadmill test for absolute and claudication distances; pain scores at structured interview		> 50% diameter reduction by angiography. Mean absolute change in degree of stenosis; rate of target lesion restenosis	Need for target lesion retreatment, TLR/TVR
Vienna-2[49,50]			> 50% diameter reduction by angiography, Doppler ultrasound, colour-flow duplex ultrasonography PSV	TVR was defined as further PTA or surgical bypass of the target vessel required because of the presence of > 50% diameter stenosis of the target lesion
Vienna-3[52]		Amputation	Restenosis was defined as > 50% reduction of arterial lumen. Arterial patency at 12 months was assessed angiographically or, if patients refused, with duplex ultrasonography. ABPI	TLR was defined as clinically manifested stenosis within intervention length which needed new recanalisation
VARA[54]	Rutherford classification	Complications	> 50% diameter reduction by angiography, Doppler ultrasound; PSVR > 2.4	Defined as need for further PTA or BS
Wyttenbach *et al.* 2004, 2007[55,56]			Lumen area and total vessel area by MRI	
Fritz *et al.* 2004[57]	Fontaine stage		> 50% diameter reduction	
Therasse *et al.* 2005[58]			> 50% diameter reduction by angiogram	Repeat lower-limb angioplasty

MRI, magnetic resonance imaging; PSV, peak systolic velocity; PSVR, peak systolic velocity ratio.

Results

Trial	Results	Complications
Gallino *et al.* 2004,[42] Bovini *et al.* 2003,[43] Diehm *et al.* 2005[44]	After successful PTA, 6-month patency according to the Kaplan–Meier life table method was 83% in the EVBT group and 58% in the control/placebo group	Late occlusion, QTc. Late occlusion occurred exclusively in patients receiving EVBT following stenting and always in concert with elimination of clopidogrel from the antiplatelet regimen. No other major EVBT-associated side effects were detected
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	ABPI: within-group improvement reported but no between-group differences. The per protocol life table analysis showed a longer recurrence-free time, 7.0 months (SD 2.2 months), for T1 than for T2, 5.8 months (SD 2.8 months) ($p = 0.028$). 33/100 needed reintervention owing to recurrent stenosis > 50% before the end of follow-up (T1 = 16, T2 = 17). But, per protocol analysis: T1 = 10 (23%), T2 = 23 (42%) ($p = 0.028$). [Diehm *et al.*[44] T1: cumulative sustained clinical success rates at 1, 2 and 3 years – 82.4% (95% CI 71.1% to 89.6%), 69.8% (95% CI 56.5% to 79.7%), 67.5% (95% CI 53.9% to 77.9%). T2: cumulative sustained clinical success rates at 1, 2 and 3 years – 84.3% (95% CI 72.7% to 91.3%), 82.1% (95% CI 69.8% to 89.8%), 76.4% (95% CI 62.0% to 86.0%) ($p = 0.26$). T1: freedom from restenosis at 1, 2 and 3 years – 82.7% (95% CI 67.1% to 91.4%), 64.3% (95% CI 47.2% to 77.2%) and 64.3% (95% CI 47.2% to 77.2%). T2: freedom from restenosis at 1, 2 and 3 years – 70.7% (95% CI 54.3% to 82.2%), 63.1% (95% CI 46.3% to 57.9%) and 47.1% (95% CI 31.0% to 61.7%) ($p = 0.16$)]	No adverse events reported
Hagenaars *et al.* 2002[46]	Lumen area change in mm^2: T1/T2, +4.3 (± 6.8)/−1.6 (± 5.1) ($p = 0.03$). Vessel area change in mm^2: T1/T2, +6.9 (± 8.7)/+ 0.8 (± 5.5) ($p = 0.05$). Change in plaque area in mm^2: T1/T2, +2.8 (± 6.0)/+2.2 (± 4.0) ($p = 0.80$)	
Krueger *et al.* 2002, 2004[47,48]	Mean absolute individual changes in degree of stenosis compared with the degree of stenosis shortly after PTA at 6 months, T1/T2 −10.6% (± 22.3)/39.6% (± 24.6) ($p < 0.001$); at 12 months, T1/T2 −2.0% (± 34.2)/40.6% (± 32.6) ($p = 0.002$); at 24 months, T1/T2 7.4% (± 43.2)/37.7% (± 34.5) ($p = 0.043$). Rate of target lesion restenosis at 6 months, T1/T2 – 0/15 = 0%/7/15 = 46.7% ($p = 0.006$); at 12 months, T1/T2 – 0/15 = 0%/5/15 = 33.3% ($p = 0.042$); at 24 months, T1/T2 – 2/15 = 13.3%/5/15 = 33.3% ($p = 0.39$). Target lesion retreatment at 24 months T1/T2 – 1/15 = 6.6%/2/15 = 13.3%. Target vessel retreatment at 24 months T1/T2 – 4/15 = 26.7%/2/15 = 13.3%. No significant differences in interview or treadmill testing between the groups	One patient developed a lower-limb thromboembolic occlusion during the procedure of brachytherapy

Trial	Results	Complications
Vienna-2[49,50]	Cumulative patency rates at 12 months: T1/T2 – 63.6%/35.3% ($p < 0.005$). Recurrence rate after 6 months: T1/T2 –15/53 = 28.3%/29/54 = 53.7% ($p < 0.05$). The mean ABPI increased from 0.50 (range 0.18 to 0.91) in the PTA group and 0.51 (range 0.1 to 0.92) in the PTA + brachytherapy group before PTA to 0.79 (range 0.40 to 1.13) and 0.85 (range 0.48 to 1.09), respectively, the day after PTA. Follow-up examinations demonstrated mean values of 0.77 (range 0.15 to 1.14) and 0.88 (range 0.47 to 1.20) in the PTA and PTA + brachytherapy groups, respectively, after 3 months and 0.74 (range 0.21 to 1.25) and 0.84 (range 0.27 to 1.25), respectively, after 6 months. (Values for patients with secondary interventions because of recurrence are not included.) TLR was performed during a mean follow-up period of 12 months in 22 patients (in 20 patients by further PTA and in two patients by BS) in the PTA group and in 14 patients (all with PTA) in the PTA + brachytherapy group. At 5-year follow-up, recurrence rate was 72.5% in each group ($p > 0.99$) but time to recurrence was significantly delayed in the PTA + EVBT group, 17.5 months (± 14.7) vs. 7.4 months (± 6.8) for the PTA alone group ($p < 0.05$). The mean PVR decreased from 7.3 (range 3.0 to 12.1) in the PTA group and 6.3 (range 2.7 to 11.9) in the PTA + brachytherapy group before PTA to 1.7 (range 1.05 to 2.2) and 1.7 (range 1.0 to 2.15), respectively, the day after PTA. The mean follow-up values were 2.50 (range 1.0 to 10.6) and 1.93 (range 1.0 to 11.8), respectively, after 3 months and 3.05 (range 1.1 to 9.8) and 2.41 (range 1.0 to 9.9), respectively, after 6 months. (Values for patients with secondary interventions because of recurrence are not included. Furthermore, in patients with occlusion, no PVR value can be calculated)	The report suggests that no adverse events were encountered in relation to brachytherapy, but describes two patients (one in each group) who developed small pseudoaneurysms at the puncture site and a further two patients (one in each group) who had haematoma at the puncture site
Vienna-3[52]	The binary restenosis rate was 41.7% (28/67 patients) in brachytherapy cohort and 67.1% (45/67 patients) in placebo cohort (χ^2 test, $p < 0.05$). The cumulative patency rates of the treated segment on intent-to-treat analysis, calculated by the Kaplan–Meier method at 24 months, were 54% in the brachytherapy group and 27% in the placebo group ($p < 0.005$). PVR improved from mean 6.0 (range 2.5–11.3) to mean 1.8 (range 1.0–2.3) in the placebo group the day after treatment. In the brachytherapy group, PVR decreased from mean 8.0 (range 3.0 to 12.0) to mean 1.8 (range 1.0 to 2.2). At 6 months, mean PVR in the placebo cohort was 1.8 (range 1.1 to 3.0) and at 12 months 2.4 (range 1.1 to 8.6). Mean PVR in the brachytherapy cohort was at 6 months 1.7 (range 1.1 to 4.3) and at 12 months 1.9 (range 1.0 to 4.8). A total of 14 patients in the placebo group and five in the brachytherapy group needed TLR (i.e. recurrence within treated segment) at 12 months. Further, two patients in the	Late thrombosis characterised by acute onset of symptoms was not diagnosed in this trial. Two of five patients in one centre treated with brachytherapy developed minor peripheral embolism post intervention

Trial	Results	Complications
	brachytherapy group had TVR (recurrence outside the initially treated segment) because of disease progression. No patient in placebo cohort had TVR. BS was necessary in one patient from brachytherapy cohort and amputation in one patient from placebo cohort	
VARA[54]	At 6 months, the restenosis rate was 9/29 (31%) in the PTA group vs. 5/23 (22%) in the PTA + EVBT group ($p = 0.045$). At 12 months, the restenosis rate was 12/27 (44%) in the PTA group vs. 8/23 (35%) in the PTA + EVBT group ($p = 0.049$). After 12 months, 6/29 (21%) in the PTA group and 4/22 (18%) in the PTA + EVBT group required revascularisation ($p = 0.82$). The alteration of the median Rutherford categories at 6 and 12 months compared with the pre-procedural score was not significantly different between the groups. ABPI and PSVR were not significantly different between groups	In two patients in the PTA + EVBT group a stent was placed owing to severe dissection with partial luminal obstruction. One patient in the PTA + EVBT group suffered from thrombosis of the treated vessel within 24 hours and an early occlusion was also seen in one patient in the PTA alone group
Wyttenbach *et al.* 2004, 2007[55,56]	At 24 hours, lumen area (86% and 67%), total vessel area (47% and 34%) and vessel wall area (37% and 25%) increased similarly in the PTA and PTA + EVBT groups (respectively) compared with baseline (reported as not significant but no *p*-value). At 3 months, there was a significant difference in lumen area change between the PTA and PTA + EVBT groups (40% and 106%, respectively; $p = 0.026$) and in the total vessel area (14% and 39%, respectively; $p = 0.018$). At 24 months, lumen area gain compared with baseline was + 30% in PTA vs. + 82% in PTA + EVBT ($p < 0.047$). Total vessel area returned to pre-treatment values in both groups; the difference was not significant	All patients showed severe splitting of the atherosclerotic plaque, resulting in an irregularly shaped lumen. At 3 months, plaque disruption was still present in 50% of the patients treated with PTA + EVBT. Otherwise, there were no procedural or radiation-related complications
Fritz *et al.* 2004[57]	No statistically significant differences between the groups. The day following the procedure, T1 ABPI increased from 0.59 (SD 0.12) to 0.92 (SD 0.12). T2 ABPI increased from 0.57 (SD 0.14) to 0.92 (SD 0.11). T1 failures 21 (45.7%), T2 failures 16 (33.3%) ($p = 0.292$)	One patient in the EBRT group had a stroke
Therasse *et al.* 2005[58]	The minimum lumen diameter in the dilated vessel segments (the primary efficacy end point) was significantly larger in the 14-Gy group (2.91 ± 1.32 mm) than in the placebo group (1.92 ± 1.22 mm, $p = 0.0072$), the 7-Gy group (1.64 ± 1.05 mm, $p < 0.001$) and the 10.5-Gy group (1.92 ± 0.95 mm, $p = 0.0071$). The difference between the 14-Gy and placebo groups was 0.98 mm, with a 95% CI of 0.27 to 1.69 mm. Reinterventions were performed in 6 of 24 (25%) patients in the placebo group (four PTAs and two surgeries) vs. 3 of 25 (12%) patients in the 14-Gy group (one PTA and two surgeries) at 18-months follow-up ($p = 0.24$)	Two patients in the 14-Gy group had transient thigh pain 2–4 months after EBR. The pain lasted a few months

EBR, external beam radiation; PSVR, peak systolic velocity ratio; PVR, peak velocity ratio; SD, standard deviation.

Drug-coated balloon

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
LEVANT I[59,60]	To evaluate the safety and efficacy of a paclitaxel + excipient-coated balloon vs. an uncoated balloon catheter for the treatment of femoropopliteal disease	RCT	Abstracts + PowerPoint delivered at the Transcatheter Cardiovascular Therapeutics conference 2010	English	Lutonix, Inc. (Minneapolis, MN, USA)	Germany	Germany	6 months
THUNDER (Tepe *et al.* 2008[61–63])	To evaluate the effect of paclitaxel on restenosis after angioplasty of stenotic or occluded superficial femoral or popliteal arteries	RCT (three-arm; one including uncoated balloon with paclitaxel dissolved in the contrast medium, which has been excluded from further data extraction)	One full report, plus abstracts	English	Sponsored by the Bavaria Medizin Technologie, Oberpfaffenhofen, and Schering, Berlin, Germany	Germany	Germany	The primary end point was late lumen loss, defined as the difference between the minimum lumen diameters after dilatation and at the 6-month follow-up
FemPac[64]	To evaluate the efficacy and safety of PTA balloons (Indena, Milan, Italy) coated with paclitaxel compared with conventional uncoated balloon catheters (Bavaria Medizin Technologie) in a patient population with short femoropopliteal artery occlusion or stenosis	RCT	Full report	English	The authors received balloon catheters for the study from Bavaria Medizin Technologie, Oberpfaffenhofen, Germany, and financial support from Bayer-Schering-Pharma AG, Berlin, Germany	Germany	Germany	The primary end point was late lumen loss at 6 months

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
LEVANT I[59,60]	Paclitaxel-coated balloon vs. uncoated balloon catheter	Paclitaxel + excipient-coated balloon catheter	Uncoated balloon catheter
THUNDER[61–63]	Standard balloon catheters coated with paclitaxel vs. uncoated balloon without paclitaxel	Balloon dilatation of the target lesion was performed with balloon catheters provided by Bavaria Medizin Technologie. The balloons were coated with paclitaxel at a dose of 3 μg/mm^2 balloon surface. To restore the reference diameter of the vessel, the balloons were inflated with a maximum of 12 atm for a standardised inflation time of 1 minute. All study balloons were inflated only once. Additional study balloons were used for lesions exceeding the length of the first balloon. If angiography after the procedure showed residual stenosis of > 30%, inflation with a conventional non-study balloon was repeated for 5 minutes. Nitinol stents were implanted in lesions that had persistent residual stenosis or as clinically needed	Uncoated balloon but, otherwise, as for intervention
FemPac[64]	Paclitaxel-coated balloon catheters vs. uncoated balloon catheters	Regular commercial PTA balloon catheters produced by Bavaria Medizin Technologie GmbH were used. Balloons were coated with paclitaxel at a dose of 3 μg/mm^2 balloon surface	As described for intervention, but uncoated balloons

Population inclusion

Trial	Target population	Inclusion/exclusion criteria
LEVANT I[59,60]		Inclusion criteria: (1) Rutherford categories 2–5, (2) > 70% stenosis, (3) lesion length 4–15 cm, (4) reference vessel diameter 4–6 mm. Exclusion criteria: (1) inadequate distal outflow, (2) severe calcification, (3) previous surgery of target lesion, (4) acute/subacute thrombosis
THUNDER[61–63]	Patients with stenotic or occluded superficial femoral or popliteal arteries	Eligible patients were between 18 and 95 years of age and had symptomatic PAD (Rutherford categories 1–5). All patients had one or more obstructive lesions, either new lesions or restenoses, ≥ 70% of vessel diameter and ≥ 2 cm in length, in the superficial femoral artery, the popliteal artery or both. If more than one lesion required intervention, only one was treated as the study lesion. Exclusion criteria included poor inflow, absence of a patent crural artery, acute onset of symptoms, pregnancy, life expectancy of < 1 year and contraindications to required medication
FemPac[64]	Patients with short femoropopliteal artery occlusion or stenosis	Eligible patients had an occlusion or stenosis ≥ 70% diameter of the superficial femoral artery and/or popliteal artery with clinical Rutherford categories 1–5. Study entry criteria also included adult age (18–90 years) and successful guide wire passage of the lesion. The main exclusion criteria were acute symptoms with an indication for thrombolytic therapy or operation, leg-threatening ischaemia, distal outflow over < 1 vessel, manifest hyperthyroidism, renal insufficiency (creatinine > 2.0 mg/dl) and major gastrointestinal bleeding within the last 6 months. Patients with known intolerance to study medications or contrast agents and additional severe disease that may have lead to non-compliance or was associated with reduced life expectancy (< 2 years) also were excluded. Further exclusion criteria were conditions requiring different treatment, serious safety concerns regarding the procedure or doubtful willingness or capability of patients to undergo the 6-month follow-up

Sample size

Trial	Numbers included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
LEVANT I[59,60]	101	49	52	Not reported	With regards to primary study end point at 6 months, 20% were lost in T1 and 31% in T2 (angiographic findings)	T1 at 30 days = 100%, angiographic at 6 months 80%, clinical at 6 months 96%. T2 at 30 days = 92%, angiographic at 6 months 69%, clinical at 6 months 87%
THUNDER[61–63]	154 were enrolled into the three-arm RCT. Data relating to the two relevant arms ($n = 102$) was extracted	48	54	It was estimated that 45 patients would have to be enrolled in each group to yield a statistical power of 80% for the detection of an absolute difference in late lumen loss of 15% of the reference diameter between study groups at a p-value of < 0.05. These calculations assumed a standard deviation for late lumen loss of 20% of the reference diameter and a 20% loss of patients to angiographic follow-up	It is reported that 128/154 (83%) underwent angiography at 6-month follow-up. No patients were excluded until they reached one of the defined end points	See attrition
FemPac[64]	87	45	42	To detect a 15% difference in late lumen loss between the equally sized treatment groups, which is considered to be clinically meaningful, e.g. 0.75 mm for a reference diameter of 5 mm at a level of $p < 0.05$ with a power of 80%, a standard deviation of ± 1.0 mm for late lumen loss was estimated to result in a raw total sample size of 58 patients. Assuming a loss to follow-up of 20%, at least 74 patients were to be enrolled. The ethics committee approved inclusion of up to 90 patients	Across both groups, at 6 months, 74.7% were followed up, and at 18–24 months 31% were followed up. Missing data were excluded	The 6-month follow-up angiography was performed in 31 of 45 (T1) and 34 of 42 (T2) patients

Baseline characteristics

Trial	Age (mean, years)	Gender (male)	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors	Level of exercise tolerance
LEVANT I[59,60]	T1: 67 ± 8. T2: 70 ± 10	T1: 69%. T2: 58%	Rutherford category 2, 3, 4 or 5: T1, 22%/71%/2%/4%; T2, 21%/71%/4%/4%	Unclear, but participants had not had any previous surgery to the target lesion. T1 presented 11% restenosis and T2 12%	T1: smoker 68%, diabetes mellitus 45%, hypertension 96%, dyslipidaemia 59%. T2: smoker 70%, diabetes mellitus 50%, hypertension 87%, dyslipidaemia 69%	Not reported
THUNDER[61–63]	T1: 69 ± 8. T2: 68 ± 9	T1: 31 (65%). T2: 34 (63%)	Rutherford categories 1–5. Mean score at baseline: T1, 3.4 ± 0.8; T2, 3.1 ± 0.8 ($p = 0.03$)	Not reported	T1: diabetes mellitus 24 (50%), smoker 11 (23%), hyperlipidaemia 33 (69%), hypertension 38 (79%). T2: diabetes mellitus 25 (46%), smoker 12 (22%), hyperlipidaemia 34 (63%), hypertension 45 (83%)	Rutherford classification only reported
FemPac[64]	T1: median age, 67.3 years. T2: median age, 70.2 years	T1: 27 (60%). T2: 25 (60%)	Rutherford categories 1–4. Rutherford 1, 2, 3 or 4: T1, $n = 2/10/31/2$; T2, $n = 1/7/31/3$	In T1 14/45 (31%) and in T2 10/42 (24%) presented with restenosis following previous PTA	T1: diabetes mellitus 18 (40%), smoker 21 (47%), hypertension 35 (78%), hypercholesterolaemia 26 (58%). T2: diabetes mellitus 23 (55%), smoker 15 (36%), hypertension 34 (81%), hypercholesterolaemia 24 (59%)	Rutherford classification only reported

Outcomes

Trial	Pain/clinical status	Complications including amputation	Patency measures	Need for reintervention or recurrence rate
LEVANT I[59,60]			Late lumen loss at 6 months	TLR
THUNDER[61–63]	Rutherford category	Amputation or death	> 50% restenosis on angiographic evaluation, late lumen loss	Incidence of TLR
FemPac[64]	Rutherford category	Amputation or death, adverse events	Late lumen loss was defined as the difference between the minimal luminal diameter after the procedure and at 6 months by quantitative angiography. Restenosis rate (defined as incidence of stenosis ≥ 50%) in the treated lesion at the 6-month follow-up angiography	TLR

Results

Trial	Results	Complications
LEVANT I[59,60]	Late lumen loss at 6 months: T1 0.46 mm vs. T2 1.09 mm ($p = 0.016$). TLR: T1 13% vs. T2 22%. 30-day safety was equal between the two groups (no data provided)	Brief report suggesting no reported incidents of acute or late thrombosis in T1
THUNDER[61–63]	The mean Rutherford category improved after the intervention from 3.1 ± 0.8 to 1.2 ± 1.5 in the control group, and from 3.4 ± 0.8 to 1.1±1.2 in the group treated with paclitaxel-coated balloons. The primary end point of mean late lumen loss was significantly lower in the group treated with paclitaxel-coated balloons than in the control group (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm; $p < 0.001$). The angiographic restenosis rate was significantly lower among patients treated with paclitaxel-coated balloons than among patients in the control group (17% vs. 44%; $p = 0.01$) at 6 months and (24% vs. 50%) at 12 months. There were no significant differences in the primary patency rate at 6 months between groups. TLR was performed in 20 of 54 patients in the control group (37%), and 2 of 48 patients in the group treated with paclitaxel-coated balloons (4%; $p < 0.001$). The rate of TLR at 12 months remained low in the group treated with paclitaxel-coated balloons. In this group, 5 of 48 patients (10%) underwent TLR during the first year, as compared with 26 of 54 (48%) in the control group. Only a few additional TLRs were reported between 12 and 24 months, for a total of 28 of 54 in the control group (52%) compared with 7 of 48 in the group treated with paclitaxel-coated balloons (15%; $p < 0.001$). Amputation of the target leg above the foot at 6 months was 0 in the control group and 2 (4%) in T1 ($p = 0.22$)	Embolic complications during the procedure or thrombosis ≤ 2 weeks afterwards occurred in three patients in the control group and two patients in the group treated with paclitaxel-coated balloons. No late thrombosis was recorded in any patient. During the period from 2 weeks after the intervention until follow-up angiography, 46% to 58% of patients in the three treatment groups had a serious adverse event ($p > 0.05$); most events were related to progression of atherosclerosis or underlying disease. In 75 of 80 patients, these events were judged by the investigators to be unrelated to the study medication. By 6 months after the intervention, five patients had died and four had undergone major amputation (above the foot or higher)

Trial	Results	Complications
FemPac[64]	The 6-month follow-up angiography showed less late lumen loss in the coated balloon group (0.5 ± 1.1 vs. 1.0 ± 1.1 mm; $p = 0.031$). The number of TLRs was lower in the paclitaxel-coated balloon group than in the control group (3 of 45 vs. 14 of 42 patients; $p = 0.002$). Improvement in Rutherford category was greater in the coated balloon group ($p = 0.045$), whereas the improvements in ABPI were not different. The difference in TLRs between treatment groups was maintained up to > 18 months	During and shortly after the intervention, four adverse events were reported: two events in the paclitaxel-coated balloon group (peripheral embolism, skin rash) and two in the control group (allergic reaction, temporary serum creatinine increase) During the 6-month follow-up period, one patient in the paclitaxel-coated balloon group died as a result of multiple organ failure, which was not related to the study medication or PTA. In one patient in the uncoated balloon group, bilateral below-knee amputation had to be performed within this time period. A comparable number of serious adverse events, including any hospitalisation or prolongation of hospitalisation according to the common definition (serious adverse events), were reported in the treatment groups: 22 patients (48.9%) in the paclitaxel-coated balloon group and 22 patients (52.4%) in the uncoated balloon group. Most of these serious adverse events were due to vascular disorders, including TLR, which was significantly more frequent in the control group (14 of 42, 33%) than in the coated balloon group (3 of 45, 7%) ($p = 0.002$). The majority of TLRs (10 of 14 in the control group and two of three in the coated balloon group) were stimulated by documented complaints the patients had before control angiography was performed; in the remaining cases, the decision was based on the angiographic result Neither of the two treatment groups showed unexpected adverse events or an unusual frequency of adverse events

All uncertainties are standard deviations.

Laser angioplasty

Study details

Trial	Objective	Study design	Publication type	Language of publication	Sources of funding	Country of corresponding author	Intervention site(s)	Length of follow-up
Belli *et al.* 1991[65,66]	To evaluate the efficacy of laser thermal recanalisation vs. conventional PTA in total occlusions of the femoropopliteal artery	RCT	Full report	English	Not disclosed	England	England	12 months
Fisher *et al.* 1996[67]	To evaluate the efficacy of laser-assisted balloon angioplasty compared with conventional balloon angioplasty alone in the treatment of localised disease in the superficial femoral artery	RCT	Full report	English	New South Wales Department of Health, Australia	Australia	Australia	Immediately post intervention and 1, 3 and 6 months. Median duration of follow-up was 350 days; for limbs with treatment success this was 430 days
Lammer *et al.* 1992[68]	To evaluate the efficacy of pulsed XeCl excimer laser vs. Nd:YAG laser vs. conventional PTA in patients with segmental femoropopliteal artery occlusions	RCT	Full report	English	Not disclosed	Austria	Austria	12 months
Spies *et al.* 1990[69]	To evaluate the efficacy of laser thermal angioplasty vs. standard balloon angioplasty in the femoropopliteal artery	RCT	Full report – initial results of a randomised trial	English	Not disclosed	USA	USA	Unclear – reported as initial technical success
Tobis *et al.* 1991[70]	To evaluate the efficacy of laser-assisted angioplasty vs. standard guide wire and catheter techniques and to see whether there is additional value in using thermal energy during laser intervention	RCT	Full report	English	National Institutes of Health, Bethesda, MD, USA, and from the Office of Naval Research, Arlington, VA, USA	USA		The study reports initial comparative technical success, and describes overall up to 12 months but offers no comparative analysis for these data

Interventions

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Belli *et al.* 1991[65,66]	Laser treatment vs. conventional PTA	Laser thermal angioplasty using a 2.5-mm hybrid laser probe (Spectraprobe PLR, Trimedyne, Santa Ana, CA, USA). During the initial study period (October 1988 to May 1989), the laser source was a continuous wave argon laser generator and between June 1989 and May 1990 the source was a continuous wave neodymium: yttrium aluminium garnet (Nd: YAG) generator. In both cases, 10–12 W of laser energy was used to heat the probe. Balloon dilatation was subsequently performed	Conventional treatment included crossing the occlusion with a guide wire of the operators choice before dilatation with a 7-F balloon catheter
Fisher *et al.* 1996[67]	Laser-assisted balloon angioplasty vs. conventional balloon angioplasty alone	Laser-assisted balloon angioplasty using a Trimedyne argon or Nd:YAG 'over-the-wire-hot-tip' laser system	No detail was provided in relation to conventional balloon angioplasty alone
Lammer *et al.* 1992[68]	Pulsed XeCI laser vs. Nd: YAG laser vs. conventional PTA	Excimer laser-assisted angioplasty: 308-nm XeCL excimer laser (MAX 10, Technolas, Grafeling, Germany) with a pulse width of 60–115 ns and a repetition rate of 20 Hz. A 2.2-mm catheter with 30 fibres, 200 µm in diameter. The energy fluence per pulse at the fibre tip was 45–60 mJ/mm^2. Nd:YAG laser-assisted angioplasty: continuous-wave laser (CL 60, Surgical Laser Technologies, Malvern, PA, USA) via a 1.064-nm laser. Exposure time of 0.5–1.0 s and a repetition rate of 0.5 Hz. A 2.2-mm single fibre catheter (600 µm) was used with a 'sapphire' contact probe. The energy fluence per pulse at the fibre tip was 35 J/mm^2. All procedures were carried out percutaneously through a 7-F introducer sheath. All patients had additional angioplasty with a 4- to 6-mm balloon	Conventional angioplasty: recanalisation via steerable guide wire followed by balloon angioplasty

Trial	Focus of interventions (comparisons)	T1: intervention group	T2: control group
Spies *et al.* 1990[69]	Laser thermal angioplasty (Nd:YAG laser, Optilase 1000, Trimedyne) vs. standard balloon angioplasty	Laser thermal angioplasty: a standard catheter and wire were initially used to cross the lesion followed by use of the laser probe (2.5-mm PLR Flex, Trimedyne) over it. Lasing lasted 30–60 seconds at 12–14 W followed by digital subtraction angiography. Then a standard balloon catheter was passed and inflated in the diseased segment in the standard fashion	Standard balloon angioplasty: an angiographic wire was passed through the lesion and angioplasty was performed with use of standard techniques
Tobis *et al.* 1991[70]	Laser-assisted angioplasty vs. standard guide wire and catheter techniques	Laser-assisted angioplasty: initially the laser probe was used as a cold, mechanical device without turning the laser on. The laser probe was a 1.5-mm-diameter laser probe model PLR-plus. Two different laser generating systems were used: an argon laser (Optilase model 900, Trimedyne) or a KTP-YAG laser model 532 (Laserscope, San Jose, CA, USA). The probe was inserted through a Y connector and passed along through the introducer sheath. Under fluoroscopic guidance, the probe was pushed into the occlusion, without activating the laser, with increasing force subjectively determined by the operator. If successful recanalisation was achieved, balloon dilatation angioplasty was then performed with a 4- to 7-mm-diameter balloon. If recanalisation was unsuccessful with the laser probe as a cold, mechanical device, then the laser was turned on at 10–12 W and gentle pressure was maintained at the level of occlusion for 5–10 seconds	Standard guide wire and catheter: a variety of guide wires were inserted through a 6-F or 7-F plastic catheter. The occlusion was probed under fluoroscopic guidance and the catheter was advanced over the guide wire as it progressed through the occlusion. Balloon angioplasty was undertaken as in intervention

Population inclusion

Trial	Target population	Inclusion/exclusion criteria	Recruitment
Belli *et al.* 1991[65,66]	Patients with total occlusions of the femoropopliteal artery	Inclusion criteria: (1) total occlusion of the femoropopliteal artery, (2) patients suitable for PTA via an ipsilateral approach. Exclusion criteria: patients in whom PTA was via a contralateral approach	Patients recruited but process is unclear
Fisher *et al.* 1996[67]	Patients with lower-limb PAOD	Inclusion criteria: patients with isolated occlusions < 3 cm or stenoses > 50% in the SFA, and with popliteal and two or three calf-vessel run-offs. Exclusion criteria: patients with iliac or popliteal artery occlusion or significant stenosis	
Lammer *et al.* 1992[68]	Patients with segmental femoropopliteal artery occlusions	Inclusion criteria: (1) femoropopliteal artery occlusion, (2) suitable for PTA, (3) unsuccessful conservative treatment, (4) symptoms for > 4 months, (5) length of obstruction between 1 and 20 cm, (6) anticoagulation therapy feasible. Exclusion criteria: (1) stenoses without occlusion, (2) acute thrombotic or embolic occlusions, (3) incomplete angiographic demonstration of run-off arteries, (4) cardiac or renal failure, (5) insulin-dependent diabetes mellitus	Consecutive symptomatic patients
Spies *et al.* 1990[69]	Patients presenting with treatment for IC	Inclusion criteria: (1) patients with IC, normal femoral pulses and either abnormal resting ABPI or a significant drop in ABPI after exercise, (2) no haemodynamically significant iliac stenosis or occlusion, (3) no more than three atherosclerotic lesions in the SFA or popliteal artery, (4) > 50% narrowing of the vessel, (5) maximum lesion length of 10 cm, (5) a lesion at least 2 cm proximal to the tibial trifurcation, (6) at least one continuous run-off vessel	Not reported
Tobis *et al.* 1991[70]	Patients with symptoms of claudication and angiographic evidence of an occluded SFA	Inclusion criteria: (1) patients with complete occlusions on angiography, (2) at least one patent tibial vessel for run-off. Exclusion criteria: stenotic lesions	Not reported

SFA, superficial femoral artery.

Sample size

Trial	Number included in the study	Number of patients in T1	Number of patients in T2	Power calculation (a priori sample calculation)	Attrition	Number followed up from each condition
Belli *et al.* 1991[65,66]	68	34	34	Not reported	At 6 months: 12/68 (17.6%). At 12 months: 18/68 (26.5%)	At 6 months: T1, 30/34 (88%); T2, 8/34 (76%). At 12 months: T1, 26/34 (76%); T2, 24/34 (71%)
Fisher *et al.* 1996[67]	82 (90 limbs)	Not reported	Not reported	Not reported	Not reported	Not reported
Lammer *et al.* 1992[68]	116	37 (group 2, 40)	39	To demonstrate a difference between 65% and 85% in the primary recanalisation rate at 79% power and $\alpha = 0.05$, 40 participants would be required in each group	At 3, 6 and 12 months, 103/116 (89%) for clinical data; follow-up angiography within 14 months was available in 80/116 (69%)	See attrition
Spies *et al.* 1990[69]	25 patients, 27 procedures	14 procedures	13 procedures	Not reported	None	100%
Tobis *et al.* 1991[70]	40	20	20	Not reported	None, the primary end point was immediate technical success	100%. This reduced at later follow-up, but individual group data were not published, only an overall summary

Baseline characteristics

Trial	Age (mean, years)	Gender (male)	Classification of PAD	Number of patients who have undergone previous revascularisation procedures	Presence of cardiovascular risk factors	Level of exercise tolerance
Belli *et al.* 1991[65,66]	Not reported	T1: 24/34 (70.6%). T2: 21/34 (61.8%)	T1: 24/34 (70.6%) IC; 10/34 (29.4%) rest ischaemia. T2: 24/34 (70.6%) IC; 10/34 (29.4%) rest ischaemia	Not reported	T1: diabetes mellitus 3 (8.8%), current smoker 10 (29.4%). T2: diabetes mellitus 9 (26.5%), current smoker 4 (11.8%)	Not reported
Fisher *et al.* 1996[67]	For whole group: 69 ± 9	Not reported adequately	44 patients were mild claudicants (Fontaine class IIa), 32 severe claudicants (Fontaine IIb), six had either rest pain or tissue loss (Fontaine III or IV)	Not reported	All five patients with diabetes mellitus were randomised to T1; otherwise, the data were inadequately reported	Not reported
Lammer *et al.* 1992[68]	T1: 68 ± 9.2. T2: 63 ± 10.9. T3: 66 ± 8.6	T1: 25/37 (67.6%). T2: 30/40 (75.0%). T3: 22/39 (56.4%)	Fontaine stage IIa, IIb, III or IV: T1 *n* = 9/11/6/11; T2 *n* = 13/22/1/4; T3 *n* = 7/22/2/8	Not reported	T1: diabetes mellitus 7 (18.9%), hyperlipidaemia 11 (29.7%), hypertension 16 (43.2%), smoking 24 (64.9%). T2: diabetes mellitus 9 (22.5%), hyperlipidaemia 18 (45.0%), hypertension 10 (25.0%), smoking 31 (77.5%). T1: diabetes mellitus 13 (33.3%), hyperlipidaemia 10 (25.6%), hypertension 17 (43.6%), smoking 28 (71.8%)	Not reported
Spies *et al.* 1990[69]	Age range 45 to 75 years	16/25 (64%)	Two patients had mild claudication, 23 had severe claudication	Not reported	Not reported	Not reported
Tobis *et al.* 1991[70]	65 (range 42 to 83)	36/40 (90%)	All patients had symptoms of claudication, but five patients had pain at rest without gangrene or an active skin ulcer due to vascular insufficiency. Duration range: 3 months to 17 years	Not reported	For the whole group (*n* = 40): diabetes mellitus 10 (25%), smokers 100%	Not reported

Outcomes

Trial	Pain/clinical status	Complications including amputation	Patency measures
Belli *et al.* 1991[65,66]	Clinical success was defined as relief of symptoms and improved peripheral pulses	Procedural complications	
Fisher *et al.* 1996[67]			Treatment failure was defined as restenosis of the original lesion to > 50% diameter stenosis or occlusion
Lammer *et al.* 1992[68]		Procedural complications	Angiographic reobstruction was defined as an increase in diameter stenosis > 30%, an immediate post-PTA diameter stenosis of < 50% increasing to > 70% at follow-up, an increase in stenosis severity to ≤ 10% of pre-dilatation obstruction, and a loss of > 50% of the gain in luminal diameter achieved by PTA
Spies *et al.* 1990[69]		Procedural complications	
Tobis *et al.* 1991[70]		Procedural complications	

Results

Trial	Results	Complications
Belli *et al.* 1991[65,66]	Cumulative clinical success (immediately and 1, 3, 6, 12 months): T1 88, 79, 56, 42, 39; T2 88, 82, 72, 56, 47, respectively. Kaplan–Meier analysis: no significant difference between the groups ($p = 0.81$). Clinical success at 2 weeks according to group to which they were randomised: T1 ($n = 29$) 85%; T2 ($n = 30$) 88% ($p = 0.67$). In T1, three (9%) received both interventions and in T2 six (18%). Technical success was reported as 91% in both groups when analysed according to the group to which they were randomised	In three cases (two conventional group, one laser) a small embolus was detected in the calf vessels. Spasm was induced in four patients (two conventional group, two laser). Haematoma formation, dissection and perforation were not considered significant complications unless they necessitated prolonged hospital stay or operative intervention or worsened the patient's clinical grade
Fisher *et al.* 1996[67]	Treatment failed in 40 limbs during follow-up – distribution between groups unclear. Median time to failure was 220 days. 21 limbs underwent repeat intervention	No direct adverse events were reported
Lammer *et al.* 1992[68]	Primary recanalisation rate by excimer laser (18/37, 49%) was lower than with Nd:YAG laser (31/40, 78%; $p < 0.01$) or PTA (32/39, 82%; $p < 0.003$). No significant difference between Nd:YAG and PTA. After excimer laser, there was no residual stenosis in 8/37, < 50% in 9/37 and 50% stenosis in one patient. For Nd:YAG the results are 21/40, 9/40 and 1/40, respectively, and for PTA 25/39, 5/39 and 2/39. Secondary recanalisation: PTA was successful in 13/19 patients in whom excimer laser failed and in 5/9 in whom Nd:YAG laser failed. Laser angioplasty was successful in 4/7 patients in whom PTA failed. At 12-month follow-up one patient had below-the-knee amputation, 13 had femoropopliteal bypass, eight had PTA for recurrent stenosis – individual group data not reported. Life table analysis based on clinical symptoms revealed a 12-month patency rate of 64% for patients treated successfully with excimer laser, 70% for Nd:YAG and 71% PTA. Life table analysis revealed a 12-month patency rate after successful primary recanalisation with excimer laser, Nd:YAG and PTA of 45%, 36% and 50%, respectively	Excimer laser, 15/37: embolus 0, dissection 13, perforation 2, spasm 0. Nd:YAG, 12/40: 2, 8, 2, 0, respectively. PTA 13/39: 3, 6, 3, 1. The number of dissections in the PTA group was significantly lower ($p = 0.005$)
Spies *et al.* 1990[69]	Laser: 9/14 initial technical success. Standard balloon angioplasty: 10/13 initial technical success. Of the five laser failures three were subsequently successfully treated with standard balloon angioplasty. Of the three standard balloon failures, none were subsequently successfully treated with laser	One patient in the laser group suffered an embolus and one further patient in the embolus group complained of severe procedural discomfort
Tobis *et al.* 1991[70]	The primary end point was recanalisation of the occluded segment of the artery with angiographic evidence of direct flow between the proximal and distal lumens. In T1 the success rate was 15/20 (75%), and in T2 it was 19/20 (95%). This difference was reported as not being statistically significant. No patient from T2 required crossover to T1. T1 initially used as a cold, mechanical device resulted in 13/20 (65%) successes with a further two successes when the probe was heated	Perforation of the arterial wall occurred in one patient in T2 and five patients in T1. Other adverse events included development of three arteriovenous fistulas, but it is unclear which groups these developed in. Haematomas developed in a further two patients

Appendix 4 Quality assessment of included studies

Quality was assessed according to criteria based on NHS CRD Report No. 4.[9]

Absorbable metal stent

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
AMS INSIGHT[11]	Computer-generated randomisation list	Adequate	Numbered, sealed envelopes	Adequate	Unblinded	Yes, apart from gender ($p = 0.04$): 71.9% male PTA, 51.7% male AMS	No	No	Yes

Self-expanding stent

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Dick *et al.* 2009[12]	Computer-generated randomisation list	Adequate	Sealed envelopes	Unclear	Outcome assessors blinded. Patients and clinicians unblinded	Yes, apart from the average length of the treated segments, which was 98 ± 54 mm and 71 ± 43 mm in the stent and PTA groups ($p = 0.011$), respectively	No	No	Yes
VascuCoil[13]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes
FAST[14]	Unclear	Unclear	Central allocation	Adequate	Unblinded, but blinded assessors for ultrasound analysis	Yes	No	No	Yes
RESILIENT[15]	Computer-generated randomisation list	Adequate	Unclear	Unclear	Unblinded	Yes, apart from more patients with hypertension in the PTA group	No	No	Yes
ABSOLUTE[16–18]	Computer-generated randomisation list	Adequate	Sealed envelopes	Unclear	Outcome assessors blinded. Patients and clinicians unblinded	Yes	No	No	Yes

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Balloon-expandable stent

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Becquemin *et al.* 2003[19]	Computer-generated randomisation list	Adequate	Central allocation	Adequate	Outcome assessors blinded. Patients and clinicians unblinded	Yes	No	No	Yes
Cejna *et al.* 2001[20]	Unclear	Unclear	Closed envelopes	Unclear	Unblinded	Yes	No	No	Yes
Grimm *et al.* 2001[21]	Randomisation list	Adequate	Numbered, sealed envelopes	Adequate	Unblinded	Yes	No	No	Yes
Rand *et al.* 2006[22]	Unclear	Unclear	Numbered, sealed envelopes	Adequate	Outcome assessors blinded. Patients and clinicians unblinded	Yes	No	No	Yes
Vroegindeweij *et al.* 1997[23]	Unclear	Unclear	Numbered, sealed envelopes	Adequate	Unblinded	Yes	No	No	Yes
Zdanowski *et al.* 1999[24]	Computer-generated randomisation list	Adequate	Unclear	Unclear	Unblinded	Yes	No	No	Yes

Drug-eluting stents

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Zilver PTX[25,26]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes, apart from more patients with hypertension in paclitaxel-eluting stent group ($p = 0.02$)	No	No	Yes
SIROCCO[28–30]	Unclear	Unclear	Unclear	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes, apart from more severe calcification for DES group. Calcification (moderate and severe): DES 27 (57%), BMS 16 (35%) ($p = 0.03$)	No	No	Yes
Rastan *et al.* 2011[31]	Computer-generated randomisation	Adequate	Central allocation	Adequate	Outcome assessors and patients blinded. Clinicians unblinded	Yes, with the exception of a significantly higher body mass index in the SES group	No	No	Yes

Stent graft

Trial name/ Study author and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Saxon *et al.* 2003, 2008[32,33]	Unclear	Unclear	Unclear	Unclear	Unblinded	Yes	No	No	Yes

Atherectomy

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Nakamura *et al.* 1995[34]	Random number table	Adequate	Unclear	Unclear	Unblinded	yes, except mean age older for TEC4mm than other groups	No	No	Yes
Vroegindeweij *et al.* 1992,[35] 1995,[36] Tielbeek *et al.* 1996[37]	Unclear	Unclear	Numbered, sealed envelopes	Adequate	Unblinded	Yes, although more patients in directional atherectomy group had hypertension	No	No	Yes

Cutting balloon

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Amighi *et al.* 2008[38]	Computer-generated randomisation list	Adequate	Numbered, sealed envelopes	Adequate	Outcome assessors blinded. Patients and clinicians unblinded	Yes	No	No	Yes
Dick *et al.* 2008[39]	Computer-generated randomisation list	Adequate	Numbered, sealed envelopes	Adequate	Unblinded, but blinded outcome assessors for ultrasound analysis	Yes	No	No	Yes

Cryoplasty

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Jahnke *et al.* 2010[40]	Unclear	Unclear	Sealed envelopes	Unclear	Unblinded	Yes	No	No	Yes
Spiliopoulos *et al.* 2010[41]	Unclear	Unclear	Sealed envelopes	Unclear	Unblinded, but independent angiographic image analysis	Yes	No	No	Yes

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Radiation

Trial name/Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Gallino *et al.* 2004,[42] Bonvini *et al.* 2003,[43] Diehm *et al.* 2005[44]	Unclear	Unclear	Unclear	Unclear	Unblinded (but blinded outcome assessors for angiographic analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials in Diehm *et al.*[44])	Yes	No	No	No (but ITT analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials in Diehm *et al.*[44])
Diehm *et al.* 2005,[44] Zehnder *et al.* 2003[45]	Unclear	Unclear	Unclear	Unclear	Unclear (but blinded outcome assessors for angiographic analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials in Diehm *et al.*[44])	Yes	No	No	No (only baseline characteristics analysed in ITT analysis) (but ITT analysis of Gallino *et al.*[42] and Zehnder *et al.*[45] trials in Diehm *et al.*[44])
Hagenaars *et al.* 2002[46]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes, more dropouts in radiation group	No	Yes
Krueger *et al.* 2002, 2004[47,48]	Computer-generated randomisation list	Adequate	Sealed envelopes	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes	No	No	Yes

Trial name/Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Vienna-2[49,50]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes
Vienna-3[52]	Unclear	Unclear	Unclear	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes	No	No	Yes
VARA[54]	Computer-generated randomisation list	Adequate	Central allocation	Adequate	Unclear	Yes	No	No	Yes
Wyttenbach *et al.* 2004, 2007[55,56]	Unclear	Unclear	Unclear	Unclear	Outcome assessors blinded. Patients and clinicians unblinded	Yes	No	No	Yes
Fritz *et al.* 2004[57]	Unclear	Unclear	Unclear	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes	No	No	Yes
Therasse *et al.* 2005[58]	Random number table	Adequate	Sealed envelopes	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes	No	No	Yes

Drug-coated balloon

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
LEVANT I[59,60]	Unclear	Unclear	Unclear	Unclear	Single blind, unclear if outcome assessors or patients blinded	Yes	No	Yes (but for future report)	Yes
THUNDER[61–63]	Lot-generated random list	Adequate	Unclear	Unclear	Outcome assessors and patients blinded. Clinicians unblinded	Yes, apart from some difference in baseline Rutherford classification	No	No	Yes
FemPac[64]	Random number list	Adequate	Central allocation	Adequate	Patients blinded, angiographic image assessors blinded (6-month outcome). Blinding of investigators attempted, but unlikely because of difference in appearance of balloons	Yes	No	No	Yes

Laser

Trial name/ Study authors and year	Method of randomisation	Was the method used to generate random allocations adequate?	Method of allocation concealment	Was the allocation adequately concealed?	Blinding	Were intervention and control groups comparable?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Were effectiveness outcomes analysed in allocated group according to ITT principle?
Belli *et al.* 1991[65,66]	Unclear	Unclear	Blind selection of a pre-marked card from a box	Unclear	Unblinded	Yes	No	No	Yes
Fisher *et al.* 1996[67]	Unclear	Unclear	Unclear	Unclear	Unblinded	Yes, except for diabetes mellitus, as all ($n = 5$) diabetes mellitus patients in laser group	No	No	Yes
Lammer *et al.* 1992[68]	Unclear	Unclear	Unclear	Unclear	Outcome assessors blinded. Patients and clinicians unblinded	No	No	No	Yes
Spies *et al.* 1990[69]	Coin toss	Adequate	Unclear	Unclear	Unblinded	Unclear	No	Yes (but for future report)	Only safety data reported, ITT
Tobis *et al.* 1991[70]	Computer-generated randomisation list	Adequate	Unclear	Unclear	Unblinded	Yes	No	No	Yes

There were too few studies for each comparison to produce funnel plots. Taking studies with any intervention that provided results for the outcome of restenosis, it appears that there is a spread of results from the larger studies, although overall they slightly favour intervention over PTA alone (*Figure 33*). The two small studies that favoured intervention were EVBT trials (Hagenaars *et al.* 2002[46] and Krueger *et al.* 2002,[47] 2004[48]) with very small sample sizes ($n = 24$ and $n = 30$, respectively). Given the differing interventions, and that not all studies reported the same outcomes, we cannot draw definite conclusions about the possibility of publication bias.

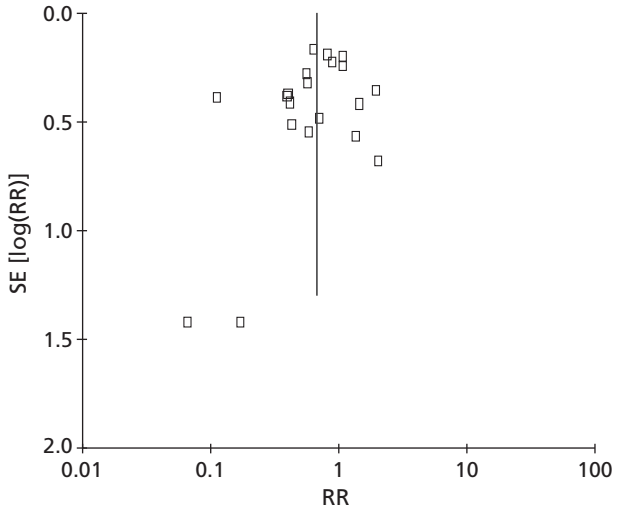

FIGURE 33 Funnel plot of studies reporting restenosis.

Appendix 5 Summary

Intervention	Trial (trial name, first author, date)	Sample size	Results (more detailed results shown in *Chapter 3, Results*)
AMS	AMS INSIGHT, Bosiers 2009[11]	117 CLI	Restenosis: AMS significantly worse than PTA ($p = 0.013$)
SES	Dick 2009[12]	73 (of whom 69 IC, 4 CLI)	Restenosis: SES significantly better than PTA ($p = 0.006$)
SES	VascuCoil, Greenberg 2004[13]	266 'symptomatic leg ischaemia'	TLR: non-significant between treatment groups
SES	FAST, Krankenberg 2007[14]	244 (of whom 226 IC, 7 CLI, 11 data unavailable)	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups
SES	RESILIENT, Laird 2010[15]	206 IC	Restenosis: SES significantly better than PTA ($p < 0.0001$). TLR/TVR: SES significantly better than PTA ($p < 0.0001$)
SES	ABSOLUTE, Schillinger 2006,[16] 2007,[17] Sabeti 2007[18]	104 (of whom 91 IC, 13 CLI)	Restenosis: SES significantly better than PTA at 12 months ($p = 0.01$). TLR: non-significant between treatment groups
BES	Becquemin 2003[19]	227 (of whom 180 IC, 47 CLI)	Restenosis: non-significant between treatment groups
BES	Cejna 2001[20]	141 (154 limbs, of which 108 IC, 46 CLI)	Restenosis: non-significant between treatment groups
BES	Grimm 2001[21]	53 IC	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups
BES	Rand 2006[22]	51 CLI	Restenosis: BES significantly better than PTA ($p = 0.02$)
BES	Vroegindeweij 1997[23]	51 IC	Restenosis: non-significant between treatment groups
BES	Zdanowski 1999[24]	32 CLI	Restenosis: PTA significantly better than BES ($p = 0.033$)
DES (paclitaxel)	Zilver PTX, Dake 2008,[27] 2010,[25] Ansell 2011[26]	479 Rutherford category 2 or above	Restenosis: DES significantly better than PTA ($p < 0.01$)
DES (sirolimus)	SIROCCO, Duda 2002,[28] 2005,[29] 2006[30]	93 (of whom 46 Rutherford category 1 or 2, 47 Rutherford category 3 or 4)	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups (DES, BMS)
DES (sirolimus)	Rastan 2011[31]	161 (of whom 86 IC, 75 CLI)	Restenosis: DES significantly better than PTA ($p = 0.02$). TLR: non-significant between treatment groups (DES, BMS)
Stent graft	Saxon 2003,[32] 2008[33]	197 (of whom 175 IC, 21 CLI, 1 unknown)	Restenosis: stent graft significantly better than PTA ($p = 0.0003$)
Atherectomy	Nakamura 1995[34]	39 IC	Restenosis: non-significant between treatment groups
Atherectomy	Vroegindeweij 1992,[35] 1995,[36] Tielbeck 1996[37]	73 IC	Restenosis: non-significant between treatment groups

Intervention	Trial (trial name, first author, date)	Sample size	Results (more detailed results shown in *Chapter 3, Results*)
CB	Amighi 2008[38]	43 (of whom 35 IC, 8 CLI)	Restenosis: CB significantly better than PTA ($p = 0.048$)
CB	Dick 2008[39]	39 (of whom 30 IC, 9 CLI)	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups
Cryoplasty	Jahnke 2010[40]	86 (of whom 66 IC, 20 CLI)	Restenosis: non-significant between treatment groups
Cryoplasty	Spiliopoulos 2010[41]	50 (60 limbs included, of which 36 IC, 24 CLI)	Restenosis: non-significant between treatment groups. TLR: cryoplasty significantly better than PTA ($p < 0.04$)
Radiation (EVBT)	Diehm 2005[44] (results of Gallino 2004[42] and Zehnder 2003[45])	Gallino 2004:[42] $n = 156$. Zehnder 2003:[45] $n = 100$	Restenosis: EVBT significantly better than PTA ($p = 0.16$). TLR: non-significant between treatment groups
Radiation (EVBT)	Hagenaars 2002[46]	24 (of whom 12 IC, 12 CLI)	Restenosis: EVBT significantly better than PTA ($p = 0.08$)
Radiation (EVBT)	Krueger 2002,[47] 2004[48]	30 (unclear how many IC/CLI, all Fontaine 2a to 3)	Restenosis: EVBT significantly better than PTA ($p = 0.006$). TLR: non-significant between treatment groups
Radiation (EVBT)	Vienna-2, Wolfram 2005,[51] 2006,[49] Minar 2000[50]	113 (of whom 88 IC, 25 CLI)	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups
Radiation (EVBT)	Vienna-3, Pokrajac 2000,[53] 2005,[52] Wolfram 2005[51]	96 (of whom 77 IC, 19 CLI)	Restenosis: EVBT significantly better than PTA ($p < 0.05$). TLR: non-significant between treatment groups
Radiation (EVBT)	VARA, van Tongeren 2005[54]	60 (of whom 52 IC, 8 CLI)	Restenosis: non-significant between treatment groups. TLR: non-significant between treatment groups
Radiation (external beam)	Fritz 2004[57]	95 (of whom 94 IC, 1 CLI)	Restenosis: non-significant between treatment groups
Radiation (external beam, three doses)	Therasse 2005[58]	99 (of whom 27 IC, 72 CLI)	Restenosis: EBRT significantly better than PTA ($p = 0.072$). TLR: non-significant between treatment groups
DCB (paclitaxel)	LEVANT I, Scheinert 2010[59,60]	101 (of whom 94 IC, 7 CLI)	TLR: non-significant between treatment groups
DCB (paclitaxel)	THUNDER, Tepe 2008[61–63]	102 (in two relevant arms of three-arm trial) (Rutherford categories 1–5)	Restenosis: DCB significantly better than PTA ($p = 0.01$). TLR: DCB significantly better than PTA ($p < 0.001$)
DCB (paclitaxel)	FemPac, Werk 2008[64]	87 (of whom 82 IC, 5 CLI)	Restenosis: DCB significantly better than PTA ($p = 0.035$). TLR: DCB significantly better than PTA ($p = 0.0024$)
Laser angioplasty	Lammer 1992[68]	116 (of whom 84 IC, 32 CLI)	Restenosis: non-significant between treatment groups

Appendix 6 Quality assessment forms (cost-effectiveness systematic review)

Drummond-adapted criteria (Drummond *et al.*[143])	Hunink *et al.* 1995[77]	Sculpher *et al.*[76]	de Vries *et al.* 2002[78]	Holler *et al.* 2006[79]	BASIL trial (Forbes *et al.* 2010[82])	NICE CEA 2012[83]
(1) Was a well-defined question posed in answerable form?	Yes	Partial	Partial	Yes	Yes	Yes
(2) Was a comprehensive description of the competing alternatives given?	Yes	Yes	Yes	Yes	Yes	Yes
(3) Was the effectiveness of the programme or services established?	Yes	Partial	Yes	Partial	Partial	Partial
(4) Were all the important and relevant costs and consequences for each alternative identified?	Yes	Partial	Partial	No	Yes	Yes
(5) Were costs and consequences measured accurately in appropriate physical units?	Yes	Yes	Yes	No	Yes	Yes
(6) Were the cost and consequences valued credibly?	Partial	Yes	Yes	Partial	Yes	Yes
(7) Were costs and consequences adjusted for differential timing?	Yes	Yes	Yes	No	Yes	Yes
(8) Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes	Yes	Yes	Yes	Yes
(9) Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Yes	Partial	Partial	Partial	Yes
(10) Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes	Yes	Partial	Yes	Yes

Consensus on Health Economic Criteria list (Evers *et al.*[144])	Hunink *et al.* 1995[77]	Sculpher *et al.*[76]	de Vries *et al.* 2002[78]	Holler *et al.* 2006[79]	BASIL trial (Forbes *et al.* 2010[82])	NICE CEA 2012[83]
(1) Is the study population clearly described?	Yes	Partial	Partial	Yes	Yes	Yes
(2) Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
(3) Is a well-defined research question posed in answerable form?	Yes	Partial	Yes	Yes	Yes	Yes
(4) Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Partial	Yes	Yes
(5) Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	No	Partial	Yes
(6) Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Unclear	Yes	Yes
(7) Are all important and relevant costs for each alternative identified?	Yes	Partial	Partial	Yes	Yes	Yes
(8) Are all costs measured appropriately in physical units?	Yes	Yes	Yes	No	Yes	Yes
(9) Are costs valued appropriately?	Yes	Yes	Yes	Unclear	Yes	Yes
(10) Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes
(11) Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
(12) Are outcomes valued appropriately?	Partial	Yes	Yes	Yes	Yes	Yes
(13) Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes	Yes	Yes	Yes
(14) Are all future costs and outcomes discounted appropriately?	Yes	Yes	Yes	No	Yes	Yes
(15) Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Partial	Yes	Partial	Partial	Partial	Yes
(16) Do the conclusions follow from the data reported?	Partial	Yes	Yes	Partial	Yes	Yes
(17) Does the study discuss the generalisability of the results to other settings and patient/client groups?	Yes	Yes	Yes	No	Yes	Yes
(18) Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	Yes	No	Yes	Not applicable
(19) Are ethical and distributional issues discussed appropriately?	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 7 Additional details for the base-case model parameters

This section provides additional information about the parameters used in the model developed for the independent economic assessment.

General mortality; excess risk

Holler *et al.*[79] model general mortality as fixed transition probabilities, depending on indication and initial operation. All the other evaluations model general mortality by applying an additional risk to general mortality rates. Hunink *et al.*[77] apply an excess mortality risk, stratified by level of ABPI; in a sensitivity analysis, they use a RR of 3.1, as reported by Criqui *et al.*[97] de Vries *et al.*[78] apply a RR of mortality of 3.14 for having PAD. Five references are provided for this value (none of them is Criqui *et al.*,[97] which also only reported the value to one decimal place). It is unclear how the RR of 3.14 was derived. Neither Hunink *et al.*[77] nor de Vries *et al.*[78] use separate RRs for patients with CLI, even though their referenced studies are all for patients with IC only. The NICE CEA[83] also uses the RR quoted by Criqui *et al.*[97] for patients with IC (although this is misquoted as 3.14). For CLI, the NICE CEA[83] uses an annual mortality rate of 25%, assuming that 70% of the population is male. Applying this proportion to general population life tales gives an annual probability of death of 2.87% for a 74-year-old. This is equivalent to assuming a RR of 8.7 for patients with CLI. TASC II[99] suggests that the annual mortality rate is actually 20%; this gives a relative of 7 for patients with CLI.

Sculpher *et al.*[76] use RRs of 2 for patients with IC and 3 for patients with CLI, based on data presented in Dormandy *et al.*[145]

In a previous HTA report looking at the use of drugs for treating patients with IC, Squires *et al.*[146] apply a RR of 1.6. TASC II[99] present data (see figure A8 in TASC II[99]) that suggest that the RRs for IC and CLI are about 3 and 6, respectively. Other journal articles have also reported different RRs; the following are all for IC: in addition to the value already quoted from Criqui *et al.*[97] (3.1), Jelnes *et al.*[147] say that the value is about 2, whereas Levy[148] quotes studies for which the values were about 3 and 4. There is little evidence of mortality rates being affected by lesion type.

For the base case, a RR (compared with the general population) of mortality due to having IC of 3.1 (Criqui *et al.*[97]) is used. It is felt that patients with CLI will have a RR at least equal to that of patients with IC, if not higher. Compared with patients with IC, patients with CLI have a RR of death of 0 (de Vries *et al.*,[78] Hunink *et al.*[77]), 1.5 (Schulpher *et al.*[76]), 2 (see figure A8 in TASC II[99]), 2.2 (TASC II[99] annual mortality of 20%) or 2.8 (NICE CEA[83] annual mortality of 25%). For the base case, the RR of 2 is used; this is equivalent to CLI patients having a RR of mortality of 6.2 compared with the general population.

PTA failure

The meta-analysis used in this evaluation (Hunink *et al.*[98]) uses data from 11 studies. A life table of yearly patency following PTA for 5 years is presented (patency at half a year and immediate technical and clinical failures are also included) for patients with IC and stenosis. The effects of having CLI or occlusions are assumed to act independently and follow a proportional hazards model. Hazard ratios for these two risk factors are presented and were used to derive yearly patency rates depending on indication (IC or CLI) and lesion type (stenosis or occlusion). These data are presented in *Table 81*.

TABLE 81 Life table of patency for patients with IC and stenosis of the femoropopliteal arteries

Interval (years)	Number at risk	Censored	Failures	Interval patency (%)	Cumulative patency (%)
0–0	1003	71	50	95	
0–0.5	882	72	89	89	95
0.5–1	721	49	52	93	85
1–2	620	45	24	96	79
2–3	551	150	11	98	75
3–4	390	60	11	97	74
4–5	319	138	11	96	71
5+	170				68

Hazard ratios; CLI vs. IC, 2.0; occlusion vs. stenosis, 2.7.

The authors do not present data on the prevalence of each lesion type for each indication; this was derived using the data presented for the 11 studies in Hunink *et al.*[98] These data are reproduced in *Table 82*.

An ordinary least squares regression was performed to judge the association between the proportion of patients with CLI and the proportion with occlusions. None of the studies reported restricting its sample by lesion type, but based on clinical opinion (JAM) the values from study 10 seen highly implausible, so this study is excluded from the analysis. The logit of occlusions (which was taken as the outcome variable) was used, where the logit is defined as follows: ln[Occ/(1 – Occ)], where 'Occ' is the proportion with occlusions. The results are presented in *Figure 34*.

The initial results are shown on the left; they predict that CLI does not have a statistically significant association with the percentage of occlusions. Using this model, it is predicted that 17.8% of claudicants and 27.1% of patients with CLI will have occlusions. The value for CLI was felt by our clinical expert (JAM) to not be plausible. As the studies 4 and 5 were potentially outliers, the analysis was repeated omitting

TABLE 82 Details of the studies used in Hunink *et al.*[98]

Study	Size	CLI (%)	Occlusions (%)
(1) Gallino *et al.*[42]	289	39	41
(2) Johnston[149]	254	20	39
(3) Capek *et al.*[150]	217	26	32
(4) Hunink *et al.*[151]	131	42	10
(5) Jørgenson *et al.*[152]	58	100	62
(6) Henriksen *et al.*[153]	31	0	42
(7) Walden *et al.*[154]	23	65	71
(8) Jeans *et al.*[155]	190	49	66
(9) Krepel *et al.*[156]	164	10	23
(10) Samson *et al.*[157]	89	90	0
(11) Murray *et al.*[158]	193	34	40

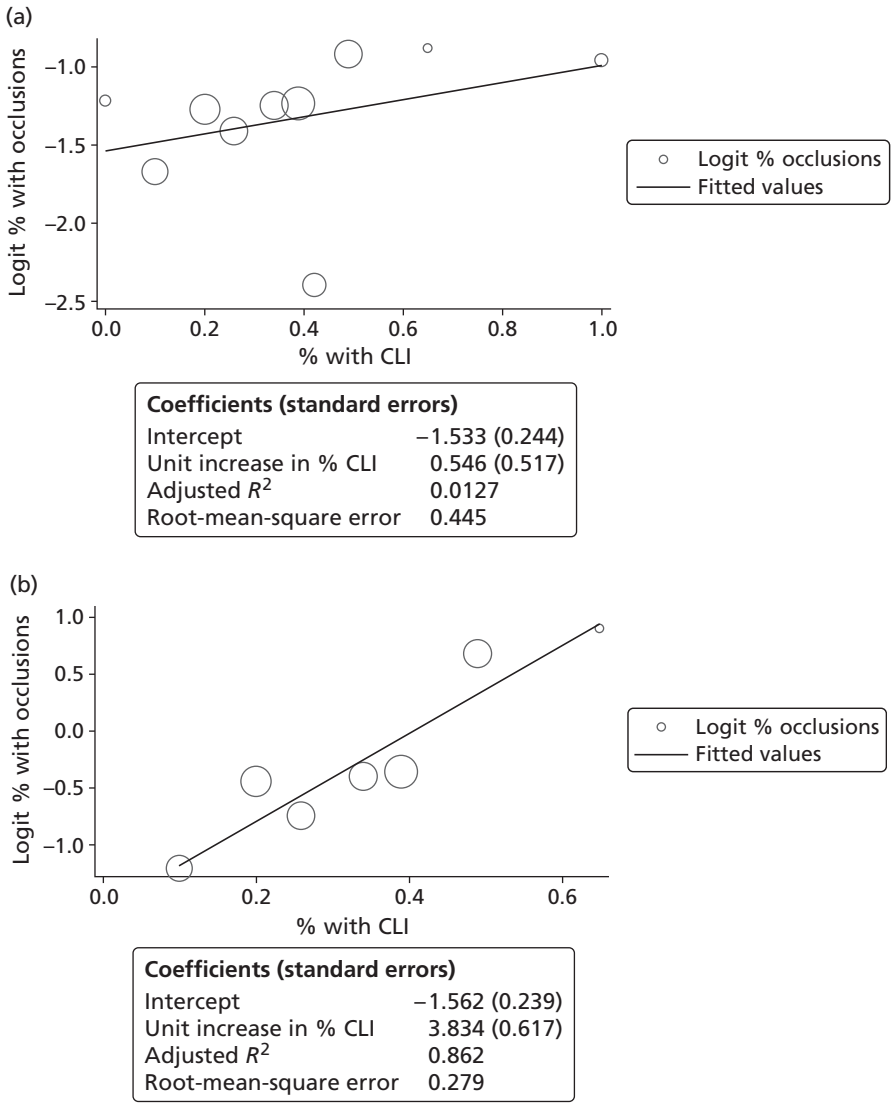

FIGURE 34 Regression analysis of the association between the proportion of patients with an occlusion and the proportion with CLI. (a) With possible outliers [weighted by sample size (see table for numbers)]; and (b) without (excluding study 4).

these, giving the results on the right. Using these it is predicted that among patients with IC, about 17.3% will have occlusions, with this value rising to 90.6% in the CLI population. These values are used in the base case.

In comparison, the NICE CEA[83] (released after this analysis was performed) assumes that 20% of patients with IC will have occlusions, based on expert opinion. The value of 17.3% for patients with IC estimated in this report is used for consistency with the value used for patients with CLI.

To extrapolate beyond the 5 years presented by Hunink *et al.*,[77] parametric survival models were fitted to the data (the parametric models were used to predict failure after the first year). Both Weibull and log-Normal models were fitted; the model which resulted in the smallest sum of squared residuals was selected. For both IC and CLI, a Weibull model was selected. Details of the fitted Weibull models are presented in *Figure 35*.

In comparison, in their economic evaluation Hunink *et al.*[77] state that for extrapolating failure beyond 5 years they use a constant rate (of failure), but this rate is not stated.

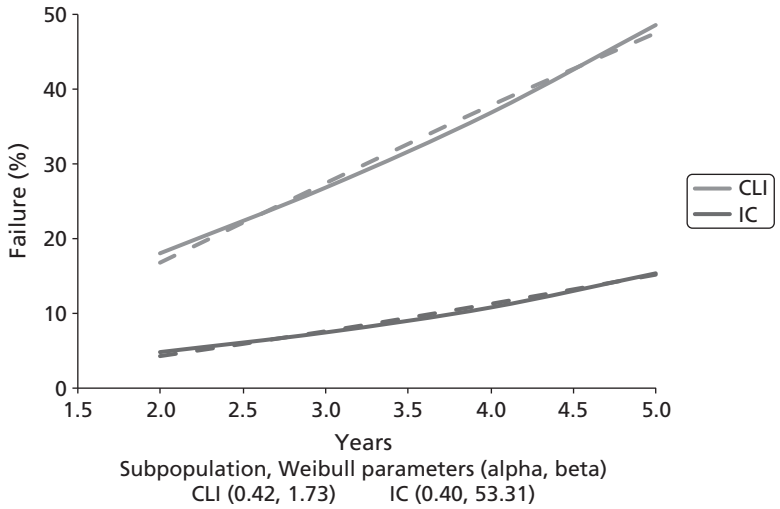

FIGURE 35 Weibull models used to predict failure. Conditional failure rates are conditional on surviving beyond year 1. Solid line = observed; dashed line = modelled (Weibull).

Complication during an operation

Hunink *et al.*,[77] the NICE CEA[83] and the BASIL trial[82] are the only economic evaluations to explicitly consider complications as a result of an operation. The values used by Hunink *et al.*[77] are also used by de Vries *et al.*[78]

Both Hunink *et al.*[77] and the NICE CEA[83] define a procedure-related complication as a non-fatal systemic complication (such as stroke, myocardial infarction and renal failure). Hunink *et al.*[77] use a value of 1.3%; the NICE CEA[83] uses a rate of 2.4%.

Alongside their value of 1.3%, Hunink *et al.*[77] also use a range of 0.2% to 11%. In total, 14 studies are referenced, but it is unclear where the value of 1.3% comes from. The authors state that this value includes 'major cardiopulmonary, renal or cerebrovascular complications'.

The NICE CEA[83] value of 2.4% comes from an audit published by the Royal College of Surgeon's of England in 2002.[91] This report includes a breakdown of the types of complication experienced; of 717 PTA procedures, 1 (0.14%) was a stroke or transient ischaemic attack, renal failure and myocardial infarction both occurred 5 (0.70%) times and the remaining 6 (0.84%) were bronchopneumonia.

The BASIL trial provides a detailed breakdown of the complications encountered during the perioperative period.[84] Following PTA (237 operations), an angina, myocardial infarction or stroke occurred 16 times, giving a probability of 6.75%. For BS, the probability is 12.18% (24/197).

Hunink *et al.*[77] use a base-case value of 8.5% for BS, along with a range of 2.7% to 13%. As with PTA, it is unclear where the base-case value comes from.

For BS, the NICE CEA[83] apply a RR of 0.60. However, there are weaknesses with this value; it is based on a single study that reports a small number of complications (4/40 for PTA and 3/46 for BS), none of which is a systemic complication (as defined here). This value also contradicts both the Hunink *et al.*[77] evaluation and the BASIL trial,[84] for which BS is associated with higher levels of complication.

The audit reported by the Royal College of Surgeon's for PTA[91] does not break down its results by indication. However, it does give the information that (excluding maintenance operations) 30.3% of PTAs were for CLI, with the remainder for IC. Applying the complication rate observed in the BASIL trial[84] to the

CLI population results in a complication rate of 0.51% for patients with IC. Applying the RR from the BASIL trial for BS (12.18/6.75 = 1.80) gives a complication rate of 0.92% for patients with IC.

As the BASIL trial[84] and the Royal College of Surgeon's audit[91] both use patients in the United Kingdom, and both are relatively recent (since 2000), they are used together to derive the complication rates.

Effectiveness of reintervention

With the exception of the BASIL trial[82], all the economic evaluations assumed that subsequent treatments were as effective as the initial treatment.

In the BASIL trial,[84] the 12-month success rate for initial PTA was 49.54% (107/216), and for repeat PTA it was 69.23% (9/13). This difference is not tested by the authors, but it is not statistically significant ($p = 0.168$, two-sided test).

The authors did compare initial BS with BS following a failed PTA. They found that both amputation-free survival and overall survival were both statistically significantly lower in the latter group. However, it is unclear whether these differences are due to the procedures or due to differing patient characteristics. The 12-month success rate for initial BS was 56.41% (110/195), and for BS following failed PTA it was 45.65% (21/46). This difference is not tested by the authors, but it is not statistically significant ($p = 0.188$, two-sided test). Hence, it is assumed that subsequent PTA reinterventions are as effective, with regards to maintaining patency, as the initial PTA intervention.

Patency following BS is taken from the same meta-analysis used to derive patency following PTA.[98] Values for saphenous vein bypass are used as these were most commonly experienced in the BASIL trial (76%; 136/179).[84] The meta-analysis reported differences in patency by indication (CLI or IC), but not by lesion status (stenosis or occlusion) or by site (above or below knee).

Disease progression

Only Sculpher *et al.*[76] and de Vries *et al.*[78] specifically model the progression from IC to CLI after PTA failure. Sculpher *et al.*[76] use a monthly probability of 0.0029%, giving a yearly probability of 3.43% in the absence of any other events. de Vries *et al.*[78] use a 5-week probability of 6.2%. It is unclear whether this probability is applied as a one-off or every 5 weeks. If the latter is the case, then it gives a yearly probability of 48.61% in the absence of any other events.

The NICE CEA[83] assumes that progression is independent of treatment, and uses a 5-yearly probability of 2%, giving a yearly probability of 0.4%. In addition, a yearly rate of 5.6% is used to model patients with IC whose symptoms deteriorate to the point where they require an operation.

The yearly probability of 3.43% from Sculpher *et al.*[76] is used because, of the three economic evaluations, the related assumptions employed by Sculpher *et al.*[76] are the most similar to the assumptions used in this analysis:

- Sculpher *et al.*[76] are the only ones to assume that on failure the patient returns to their pre-operation health state, and that progression to CLI varies depending on whether or not the patient is patent. These two assumptions are also employed in this analysis.
- The NICE CEA[83] assumes that progression to CLI is independent of patency.
- de Vries *et al.*[78] assume that on failure the patient is still asymptotic.

To model a yearly probability of 3.43%, an exponential distribution (mean: 28.65) is used.

Quality of life

An overview of the use of QoL values in the economic evaluations is presented in *Table 83*. In addition, two additional papers that were known to the authors are included.

TABLE 83 Overview of studies reporting QoL that were considered for this economic evaluation

Study	Method	Health states and values
Hunink *et al.*[77]	• Abbreviated form of the Torrance multiattribute scale • Values estimated by two vascular surgeons, two interventional radiologists and an internist	• Successful treatment: 0.93 • IC: 0.57 • Rest pain: 0.33 • Necrosis: 0.21 • Amputation: 0.19 • No PAD symptoms, but MM: 0.30 • IC and MM: 0.26 • Rest pain and MM: 0.24 • Necrosis and MM: 0.12 • Amputation and MM: 0.03

de Vries *et al.*[78]	• All values from previous articles
	• Values from CLI and amputation taken from Sculpher *et al.*[76]
	• Values for IC and asymptomatic from time trade-off (based on EuroQol questionnaire, $n = 92$)
	• The two types of complication are based on the results for myocardial infarction survivors (time trade-off, $n = 80$)
		• Asymptomatic: 0.79
		• IC: 0.71
		• CLI: 0.35
		• Amputation
		  ○ Below knee: 0.61
		  ○ Above knee: 0.20
		• Multiplicative effects
		  ○ Systemic complication: 0.72
		  ○ Angina pectoris: 0.90

Holler *et al.*[79]	• EQ-5D; 280 PAD patients • For clarity, only two decimal places shown; article reports values to four decimal places	• Amputation: 0.52 • IC, no treatment: 0.70 • CLI, no treatment: 0.60 • IC and PTA: 0.57 • CLI and PTA: 0.60 • IC and BS: 0.66 • CLI and BS: 0.53

Sculpher *et al.*[76]	• Time trade-off. Values also elicited for EQ-VAS (shown in brackets). Values were elicited from the general public (the sample size for these was not reported). It was stated that the resulting values were very similar to those elicited from 36 health-care professionals (the values for this group were not reported)
	• Values for asymptomatic assumed
	• Overall amputation value not estimated – calculated assuming a ratio of 0.84 (above) : 1 (below)
		• Asymptomatic: 1.00 (1.00)
		• IC: 0.70 (0.69)
		• CLI: 0.35 (0.41)
		• Amputation overall: 0.42 (0.47)
		  ○ below knee: 0.61 (0.62)
		  ○ above knee: 0.20 (0.30)

BASIL trial[82]	• Patients with CLI only • EQ-5D values (brackets: EQ-VAS) • Standard deviations for both measures also presented in the analysis	• Baseline: 0.26 (0.53) • 3 months: 0.53 (0.60) • 12 months: 0.56 (0.60) • 36 months: 0.61 (0.63)

NICE CEA[83]	• IC: weighted average of EQ-5D data from trials. Where possible, SF-36 values were mapped to EQ-5D
	• It is not explicitly stated, but it is assumed, that baseline scores reflect unsupervised exercise. All differences are relative to unsupervised exercise
	• Owing to a lack of EQ-5D data following BS, values were assumed to be the same as following PTA with primary stenting
		• IC: 0.573
		• (Additive) Differences between PTA and selective stents:
		  ○ 3 months: +0.014
		  ○ 6 months: +0.061
		  ○ 9 months: –0.005
		  ○ 12 months: +0.014

TABLE 83 Overview of studies reporting QoL that were considered for this economic evaluation (*continued*)

Study	Method	Health states and values

	• Amputation values taken from Sculpher *et al.*,[76] assuming that 52% are above the knee
	• The source of CLI values is not stated but appears to be Sculpher *et al.*[76]
	• Multipliers for cardiovascular events are based on the assumption that full health has an EQ-5D value of 1 (as used in the NICE guidance for hypertension). Multipliers are only applied to IC patients
		• BS/PTA and primary stents:
		  ○ 3 months: +0.064
		  ○ 6 months: +0.007
		  ○ 9 months: –0.059
		  ○ 12 months: –0.040
		• Amputation: 0.396
		• CLI: 0.350
		• (Multiplicative) effects:
		  ○ MI: 0.760
		  ○ Post MI: 0.880
		  ○ Stroke: 0.629
		  ○ Post stroke: 0.815

Dumville *et al.*[159]	Report that QoL among patients with asymptomatic PAD is no different from QoL among patients without PAD	
Sprengers *et al.*[160]	• Patients with CLI unsuitable for operation • Both SF-36 and EQ-5D values presented; only EQ-5D reported here (with 95% CI)	CLI: 0.34 (0.24 to 0.44)

MI, myocardial infarction; MM, major morbidity.

In the following discussion, the values presented by Hunink *et al.*[77] are not used, as it was not possible to map the Torrance multiattribute scale to EQ-5D.

Baseline values

For patients with IC, Holler *et al.*[79] and Sculpher *et al.*[76] both elicit values of 0.7, whereas de Vries *et al.*[78] elicit a value of 0.71. This is considerably higher than the value used in the NICE CEA (0.573). A value of 0.7 is used in the base case, with the NICE CEA value (which is based on the average of the RCTs used in the evaluation) used in a scenario analysis.

There is more variation in the baseline values used for CLI: Sculpher *et al.*[76] elicit a value of 0.35 (with this value used by de Vries *et al.*[78] and the NICE CEA[83]), Holler *et al.*[79] elicit a value of 0.60 and the BASIL trial[82] reports a value of 0.26. In this trial, 75% of patients had tissue loss; the remainder had rest pain.

As the value reported by Sculpher *et al.*[76] was also observed in the JUVENTAS trial (as reported by Sprengers *et al.*[160]), and appears to reflect a similar decrement (relative to an IC value of 0.7) to that reported by Hunink *et al.*,[77] this value is used in the base case. In addition, the Sculpher *et al.*[76] values were elicited by members of the general public, and thus can be assumed to reflect patients with CLI without any comorbidities. In the BASIL trial[84] comorbidities were generally high (with the prevalence of angina, previous myocardial infarction and previous stroke all being about 20%); this may be part of the reason for the lower observed EQ-5D values.

Values following successful treatment

Sculpher *et al.*,[76] de Vries *et al.*[78] and Hunink *et al.*[77] all assume that the values for asymptomatic patients are independent of the patients' prior disease, although the last two evaluations apply a utility decrement for having major morbidity or complications.

Sculpher *et al.*[76] assume that patients move to full health (EQ-5D = 1), which does not seem plausible. Neither do the values presented by Holler *et al.*,[79] which suggest that QoL reduces following successful treatment. The NICE CEA[83] suggests only moderate gains to QoL. However, there are also some possible problems with these values. They are taken from two sources, the RCTs of Greenhalgh *et al.*[104] and Spronk *et al.*[103] The increases in QoL modelled by NICE range from –0.005 to +0.061. In the Spronk *et al.*[103] RCT the increases observed range from +0.08 to +0.16, whereas in the Greenhalgh *et al.*[104] RCT they ranged from +0.042 to +0.088.

de Vries *et al.*[78] use a value of 0.79. This is based on patients with previous IC, and excludes those with severe comorbidities. The average age of the patients was 60. Population norms for the 50–59 and 60–69 years age groups are 0.798 and 0.774, respectively (median values 0.796 for both, Sullivan *et al.*[161]), suggesting that following a successful operation patients' QoL is comparable to that of the general population. This finding is supported by Dumville *et al.*[159]

The values following treatment with PTA reported in the BASIL trial[82] are much lower than those reported by de Vries *et al.*[78] This will be for two reasons; the BASIL trial[82] participants had major comorbidities and the treatment failures are included in the values. For example, at 12 months, a value of 0.56 is reported. This is based on a failure rate (among those still alive) of approximately 19% (about 35/180). Assuming that failures have the pre-treatment value of 0.26, the value for successfully treated patients is about 0.63.

Values following amputation

Hunink *et al.*,[77] Sculpher *et al.*[76] and Holler *et al.*[79] provide three separate estimates of the QoL associated with amputation. Sculpher *et al.*[76] elicited values based on whether the amputation was above or below the knee, and combined these to obtain an average value for the QoL associated with an amputation by using a ratio of above : below knee amputations of 0.84 : 1. de Vries *et al.*[78] used the same EQ-5D values and ratio, and the NICE CEA[83] used the same ED-5D values, but a ratio of 13 : 12.

The BASIL trial[82] does not explicitly report EQ-5D values, but (based on an ITT analysis of all patients) reports that, from 3 months onwards, values are consistently lower by about 0.06 (regardless of initial treatment); this would give a 12-month value of about 0.5 (there was no statistically significant difference in post-treatment values between PTA and BS). Of those alive at 12 months, 28 had a below-knee amputation, and 13 an above-knee amputation (patients who progressed from below to above are only included in the latter count). Applying these proportions to the EQ-5D values reported by Sculpher *et al.*[76] results in a value of 0.48.

As the QoL following an amputation reported in the BASIL trial[82] seems to be similar to that elicited by Sculpher *et al.*,[76] these values are used. As the ratio of above : below knee amputations used by the NICE CEA[83] is not referenced, the values observed in the BASIL trial[84] are used, giving a base-case value of 0.49.

It is noted that whereas Sculpher *et al.*[76] and the BASIL trial[82] both report that QoL following an amputation is higher than baseline QoL with CLI, Hunink *et al.*[77] and Holler *et al.*[79] report that it is lower (by 21% and 13%, respectively).

The effect of systemic complication

Both de Vries *et al.*[78] and the NICE CEA[83] assume that systemic complications have a multiplicative effect on QoL. The former use a value of 0.72 (based on survivors of myocardial infarction), whereas the latter use values between 0.629 and 0.880, depending on the type and timing of complication. Of the systemic complications observed by Axisa *et al.*,[91] myocardial infarctions were five times more likely to occur than a stroke, so only the effect of the former are considered in the model.

In the NICE CEA[83] it is stated that the effect of myocardial infarction after the first year is based on an arbitrary reduction in the effect of 50% relative to the first year. The (constant) effect of myocardial infarction reported by de Vries *et al.*[78] is in between the first-year and subsequent-year effects used by the NICE CEA,[83] so this effect is used at all time points in the model.

Costs

The NICE CEA[83] values costs using the same perspective and time frame as this economic evaluation, so, where possible, costs are based on it.

Procedure-related costs

The costs stated include the subsequent hospital stay. Costs from the BASIL trial[82] are not included, as they are not broken down into cost per procedure. Other sources of procedural costs are summarised in *Table 84*.

Both Hunink *et al.*[77] and Holler *et al.*[79] provide separate procedural costs for patients with IC and with CLI. In both of these analyses, it is assumed that the procedural cost is the same regardless of complication. Both the NICE CEA[83] and de Vries *et al.*[78] provide separate procedural costs for whether or not the patient has a complication. This approach is used in the model; it is assumed that the difference in cost between IC and CLI patients modelled by Hunink *et al.*[77] and Holler *et al.*[79] is a result of patients with CLI having more complications.

Subsequent operations are assumed to cost the same as the initial operation (unless the patient has developed a complication). This is the same assumption as that used by all of the economic evaluations, apart from the NICE CEA[83] for PTA, for which subsequent operations cost either £3695 (no complications) or £9385 (with a complication).

Any reinterventions are also assumed to be preceded by angiography. NHS 2009/10 reference costs[89] are used, which price diagnostic angiography at £202 (no complications) and £5101 (with a complication).

TABLE 84 Overview of studies reporting procedural costs that were considered for this economic evaluation

	Procedural costs		
Study (costs detail)	PTA	BS	Amputation
Sculpher *et al.*[76] (1993/94 UK pounds)	1186	2450	8106
Hunink *et al.*[77] (1999 US dollars[a])	10,168 (18,171)[a]	20,531 (25,881)[a]	34,384
de Vries *et al.*[78] (1998 US dollars[a])	4170 (13,940)[c]	16,490 (26,260)[c]	14,420 (7790)[b]
Holler *et al.*[79] (euros, year not stated)	2328 (3916)[a]	5309 (7778)[a]	4964
NICE CEA[83] (2009/10 UK pounds)	3661 (9367)[c]	5988 (7139)[c]	9733 (14,044)[c]

a First value is for patients with IC; value in brackets is for patients with CLI.
b First value is for above the knee; value in brackets is for below the knee.
c First value is for no complications; value in brackets is with complications.

Long-term costs

It is assumed that patent patients have no long-term costs. This assumption is also used by the NICE CEA,[83] de Vries *et al.*[78] and Sculpher *et al.*[76] In contrast, Holler *et al.*[79] and Hunink *et al.*[77] do model long-term costs for patent patients.

Long-term costs for each of the health states (other than asymptomatic) are summarised in *Table 85*. Costs from the BASIL trial[82] are not included, as no breakdown (by health state or patency status) is provided.

With the exception of Sculpher *et al.*,[76] the reported long-term costs are based on empirical (observed) data. Sculpher *et al.*[76] assume that long-term costs for IC patients take the form of an outpatient appointment once every 3 months. For CLI patients, it is assumed that there is an outpatient appointment once a month and half-an-hour of a 'Grade F' (agenda for change 6; assume point 24) nurse's time used every 2 weeks. This gives annual costs in 2009/10 UK pound of 1220 for IC and 3849 for CLI (it was not possible to update the costs for amputees).

For the base-case analysis, long-term costs for patients with IC or CLI are taken from the updated Sculpher *et al.*[76] values. After an amputation, a constant value of £23,502 is used for patients (the increased costs in the first year after an amputation are not modelled to keep the model simple).

As with QoL, it is assumed that any systemic complications are myocardial infarctions. Using the values reported by the NICE CEA,[83] this costs £5395 in the first year and £1692 in subsequent years. It is assumed that the initial high cost of having myocardial infarction is captured by the increased cost of any intervention (including angiography) due to having a complication. Hence, for the model only the fixed yearly cost of £1692 is used.

Number of runs required for stable results.

Figures 36–39 present the average costs and QALYs by run number for both patient populations considered in this analysis. Numerical results for the standard errors of each estimate are as follows:

Costs: IC, £51.17 (mean: £14,637); CLI, £191.73 (mean: £55,199).

QALYs: IC, 0.0105 (mean: 5.956); CLI, 0.0066 (mean: 3.047).

TABLE 85 Overview of studies reporting long-term costs that were considered for this economic evaluation

	Yearly costs			
Study (costs detail)	IC	CLI	Amputee	Systemic complication
Sculpher *et al.*[76] (1993/94 UK pounds)	180	648	744	–
Hunink *et al.*[77] (1999 US dollars[a])	543	543	48,877	7764
de Vries *et al.*[78] (1998 US dollars)	0	0	31,920	10,780
Holler *et al.*[79] (euros, year not stated)	1044	2721	4964	–
NICE CEA[83] (2009/10 UK pounds)	0	0	Year 1: 28,270. After year 1: 23,502	a

a Myocardial infarction (first 3 months, 4972; subsequent 3 months, 141). Stroke (first 3 months, 9630; subsequent 3 months, 559).

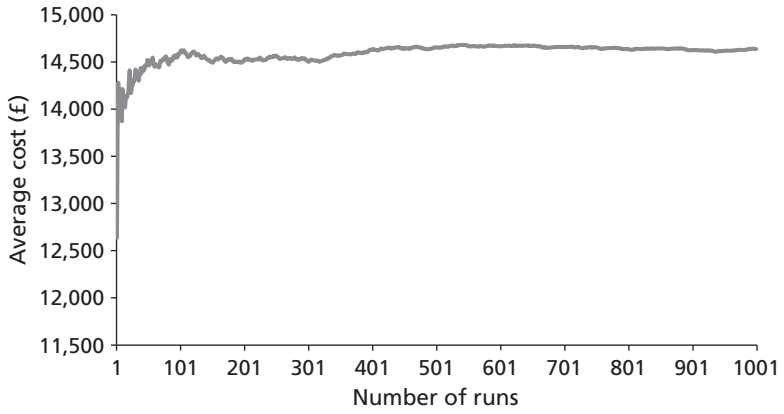

FIGURE 36 Average cost by run number for patients with IC.

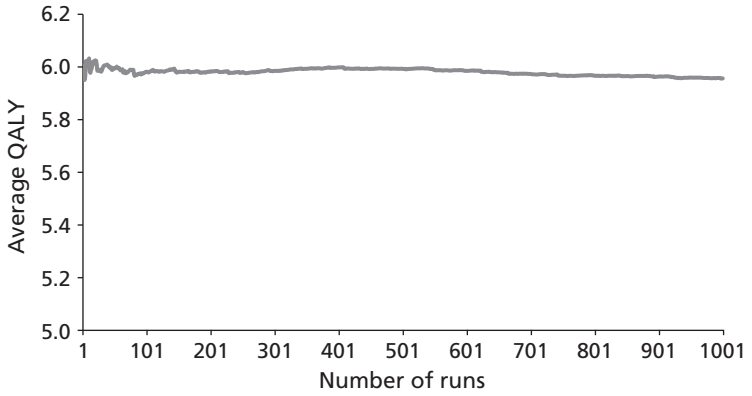

FIGURE 37 Average QALY by run number for patients with IC.

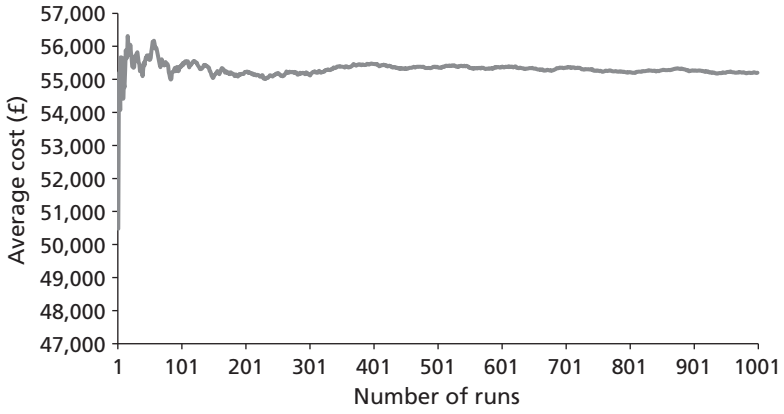

FIGURE 38 Average cost by run number for patients with CLI.

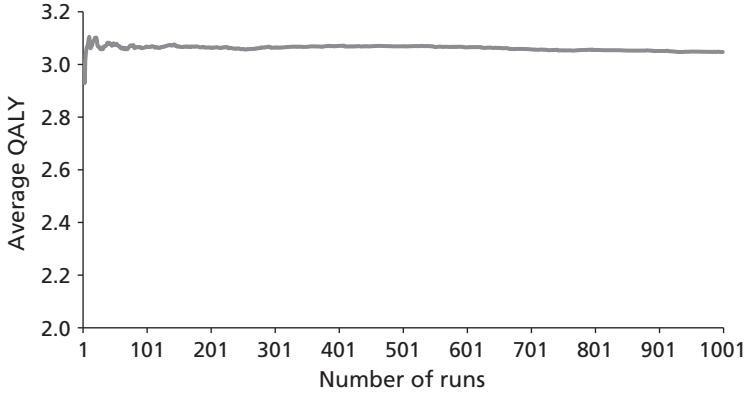

FIGURE 39 Average QALY by run number for patients with CLI.

Appendix 8 Protocol

ENHANCEMENTS TO ANGIOPLASTY FOR PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD): SYSTEMATIC REVIEW, COST-EFFECTIVENESS ASSESSMENT AND EXPECTED VALUE OF INFORMATION ANALYSIS.

Decision problem

Purpose of assessment

The planned assessment is to answer the following research questions:

- What is the clinical and cost effectiveness of additional techniques designed to improve the results of endovascular treatment (standard transluminal balloon angioplasty) for peripheral arterial disease?
- In which of these techniques is further primary research likely to lead to information that will improve the effectiveness and cost effectiveness of care in this condition?

Definition of interventions

This assessment is of new endovascular techniques that may be used to either supplement or replace existing endovascular procedures to improve the circulation of the lower limb in cases of PAOD.

Place of the intervention in the treatment pathway

The techniques under consideration in this assessment will be those that are either used as a replacement for, or in conjunction with, conventional balloon angioplasty. These cover a variety of different clinical settings and subgroups (see below). In general, treatments will be considered that occupy the same place as balloon angioplasty in the treatment pathway for PAOD. There are however several different potential situations that may need to be considered separately, particularly in relation to the assumptions of an economic model:

A technique intended to be used as a replacement or adjunct in all primary procedures;

A procedure or device that is intended to be used selectively in a subgroup of patients based upon anatomical or radiological features or an inadequate response to the initial balloon procedure; Those procedures intended to be used in cases of restenosis or failure of the primary procedure. The specific place in the pathway will therefore need to be considered individually for each of the technologies, depending upon their intended use and the available evidence.

Excluded interventions

In order for the review to be practicable some limitations will be placed on the interventions and devices that will be considered.

Pharmacological interventions

The separate effects of pharmacological measures aimed at altering patency will not be specifically considered, except where the use of a particular agent is required as an integral part of a new endovascular technique.

Combined surgical procedures

Some new techniques, such as remote femoral endarterectomy, require a combined surgical and endovascular approach. Many of the others may also be combined with surgical procedures and, in some cases, may be used for different indications in patients who would not necessarily be amenable to

conventional endovascular techniques. Inclusion would considerably extend the scope of the proposed reviews and require additional modelling.

These will therefore be excluded from the current review.

Other techniques

There are a number of other new endovascular techniques that may be used as an adjunct to angioplasty. These include closure devices, devices to protect from embolisation and techniques for thrombolysis or thrombectomy. These will only be considered where they are a component of one of the other techniques referred to above.

Relevant comparators

There are a large number of potential new technologies, many of which are mutually exclusive alternatives for the endovascular treatment of PAOD. The starting point for the evaluation will be direct comparisons with balloon angioplasty but where several treatments are appropriate to the same clinical subgroups mixed treatment comparisons will be carried out to compare all relevant technologies.

Population and subgroups

There are a number of different subgroups of population that may need to be considered separately within the review and modelling as they may have different clinical and economic implications. Subgroups will be identified where possible, within the published literature.

Modelling will include a consideration of appropriate subgroups as regards clinical presentation, anatomical site, demographic features and comorbidities. Several of these represent potentially important issues that will need to be addressed within the review.

Symptomatic presentation

Patients with PAOD may present either with intermittent claudication (pain on exercise) or with critical ischaemia which includes ulceration, gangrene and ischaemic rest pain. The Trans-Atlantic Inter-Society Consensus (TASC) has standardised the anatomical and symptomatic definitions of vascular disease, including the use of the Rutherford classification, which is often used to categorise the severity of ischaemia. The symptomatic classification has significant implications both for the appropriate treatment modalities and comparators and the likely outcome of treated and untreated disease. It is also closely related to the utilities associated with the relevant health states. It will therefore be necessary to consider separate subgroups within the review, and economic analysis will be based upon these factors.

Anatomical features

The outcome of endovascular treatment is also known to be heavily influenced by the site and distribution of arterial occlusive disease. Aortoiliac disease affects the larger vessels above the inguinal ligament. Conventional angioplasty, with or without the use of stents, has been common practice in this area for some years and clinical results are generally good with a lower rates of restenosis or reocclusion. In view of this, the potential advantages of new techniques to improve outcomes are likely to be very much smaller in absolute terms, with very large clinical studies being required to demonstrate significant clinical benefit. The current assessment will therefore focus on disease below the inguinal ligament.

The assessment will include all infrainguinal disease, but it is recognised that some technologies are used or designed specifically for certain areas within this and, where the evidence allows, subgroups will be considered separately for femoral, popliteal and infrageniculate disease.

Key factors to be addressed

The specific objectives of the review are:

1. To investigate by systematic review the effectiveness and cost effectiveness of endovascular techniques to supplement or replace balloon angioplasty in the infrainguinal arterial circulation (Review 1).
2. To investigate by systematic review the utilities associated with health states relating to the natural history of treated and untreated PAOD (Review 2).
3. To estimate the incremental cost effectiveness of the new technologies identified in Review 1.
4. To assess the potential value and optimum design for further research studies to collect data on areas of uncertainty identified by the above reviews.

Methods for synthesis of evidence

Description of reviews

Review stage 1: A comprehensive search will be undertaken to systematically identify clinical and cost effectiveness literature concerning endovascular techniques to supplement or replace balloon angioplasty in the infrainguinal arterial circulation.

Review stage 2: Where utility data are unavailable from studies identified in review stage 1, literature reviews will be conducted to provide data to populate the economic model. This will comprise data on the utilities associated with health states relating to the natural history of treated and untreated PAOD. This is likely to be necessary as it is expected that most published clinical research in this area will provide surrogate end points such as vessel patency or symptomatic and disease specific end points such as exercise tolerance, symptomatic state or amputation rates.

Identifying and systematic reviewing of clinical effectiveness evidence

Population

The population will be patients with symptomatic PAOD undergoing endovascular treatment for disease distal to the inguinal ligament.

Interventions

Clinical studies that evaluate techniques used as an adjunct to, or as a replacement for balloon angioplasty in the peripheral circulation. The identified procedures include but are not limited to those procedures identified in the inclusion criteria below.

Search strategy

The search strategy for both reviews will comprise the following main elements: searching of electronic databases; contact with experts in the field; scrutiny of bibliographies of retrieved papers. The electronic databases to be searched from inception will include MEDLINE; Medline in Process (for latest publications); EMBASE; Cochrane Database of Systematic

Reviews; Cochrane Controlled Trials Register; CINAHL; NHS EED, DARE, and HTA databases; NIHR Clinical Research Network Portfolio database; NRR (National Research Register) Archive; Web of Science Proceedings; Science Citation Index; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website; and relevant conference proceedings. These will include the proceedings of the Vascular Society of Great Britain and Ireland, The European Society of Vascular and Endovascular Surgery, The British

Society of Interventional Radiology, Cardiovascular and Interventional Radiological Society of Europe, The Society for Interventional Radiology and the Society for Vascular Surgery.

Searches will not be restricted by publication type, study design, date or language. In addition citations within relevant papers will be checked and hand searching of relevant journals, using the search strategy described by the Cochrane Peripheral Vascular Diseases Group, will be performed (Cochrane Collaboration 2006).

An initial draft search strategy based upon the identified technologies and relevant anatomical sites identified over 5,000 references. Standard methodological filters will be used to limit this to systematic reviews, randomised and controlled trials and cost effectiveness analyses. This is still expected to identify a large number of potentially relevant papers. Further limitation may be required to exclude papers referring to angioplasty at other sites. Limitation by publication date may also be necessary, but is likely to be different for individual technologies based upon expert advice regarding technological developments (see below).

Study selection

In both stages of the review citations will be imported into reference management software and screened for inclusion, based on inclusion/exclusion criteria below. Titles and abstracts will be examined for inclusion by one reviewer. Two reviewers will independently make decisions on inclusion of studies at full text stage and any discrepancies resolved by discussion.

Inclusion criteria

Interventions

Transluminal balloon angioplasty, self-expanding and balloon-expandable stent, drug eluting stent, drug eluting balloon angioplasty, percutaneous stent-graft insertion, laser angioplasty, atherectomy, cryoplasty, cutting balloon angioplasty, brachytherapy and external beam radiotherapy and other techniques used as an adjunct to, or replacement for, balloon angioplasty in the peripheral circulation.

Population

Adult patients with symptomatic PAOD suitable for endovascular treatment for disease distal to the inguinal ligament. Where data allows, patients with critical ischaemia will be considered as a separate group to those with only claudication. Other important subgroups will be identified from the included studies.

Comparator

Conventional balloon angioplasty. Other comparators will be considered if included interventions are specifically designed as alternatives to angioplasty for patients in whom conventional angioplasty has failed or is contraindicated, in which case the comparator will be current standard care as determined by the clinical evidence and expert advice.

Setting

Secondary care

Outcomes

Outcome measures will include: Disease-specific and generic measures of quality of life, exercise tolerance, pain (patient reported pain scores and analgesic use), limb salvage (for patients with critical ischaemia),

walking distance (for patients with claudication), patency measures, need for reintervention, complications, costs.

Study types

According to the accepted hierarchy of evidence, randomised controlled trials and meta-analyses from systematic reviews will be searched initially, as they provide the most authoritative forms of evidence. If data are not available from these, other study types will be included.

Exclusion criteria

Interventions: Pharmacological interventions, combined surgical procedures, devices that have been withdrawn, such as older laser angioplasty devices.

Publication types: Studies which are only published in languages other than English; studies based on animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and reports published as meeting abstracts only where insufficient details are reported to allow inclusion.

Data extraction and critical appraisal

Data will be extracted with no blinding to authors or journal. Data will be extracted by one reviewer using a standardised form. A standard proforma will be used and the data checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment will be subject to the types of studies identified but will be undertaken using appropriate and established tools, for example randomised controlled trials will be assessed according to criteria based on NHS CRD Report No.424

(http://www.york.ac.uk/inst/crd/report4.htm). The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis.

Data synthesis

Prespecified outcomes will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, meta-analysis will be conducted using fixed and random effect models, using RevMan software. If sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials affects the results.

Mixed treatment comparisons

If it is deemed appropriate a mixed treatment comparison will be undertaken to synthesise the direct and indirect evidence in a single network, and to provide an indirect comparison where head-to-head trials are not available.

Methods for synthesising cost effectiveness evidence

Identifying and reviewing published cost effectiveness studies The review above will be used to identify studies of cost effectiveness of balloon angioplasty and the new technologies. An economic search filter will be incorporated into the search strategy to identify relevant studies. Identified economic literature will be critically appraised and quality assessed using the critical appraisal checklist for economic evaluations proposed by Drummond et al (2005). Existing cost effectiveness analyses will also be used to identify

sources of evidence to inform structural modelling assumptions and parameter values for the de novo economic model.

Development of a health economic model

A new economic evaluation of the cost effectiveness of technologies for the management of PAOD will be developed. Cost effectiveness modelling will take account of potential benefits and harms of the new treatment and will identify subgroups of patients based upon the anatomical, radiological, symptomatic and other features discussed above where the data allows this.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life-year (QALY) gained associated with the use of new technologies to improve outcomes, used alongside or as alternatives for conventional balloon angioplasty of the infrainguinal arteries. A lifetime time horizon will be used in order to reflect the chronic effects of arterial disease and the on-going risk of vessel reocclusion, symptomatic deterioration, amputation and potential mortality. The perspective used will be that of the National Health Services and Personal Social Services. Costs and QALYS will be discounted at 3.5% as recommended in current guidelines. Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where required.

The ScHARR modelling team have published papers using different modelling techniques (such as discrete event simulation, transition state modelling and meta-modelling). The model structure and software used to construct the model will be determined following data collection in order that the most appropriate technique is used for this particular assessment. The expert advisory group will be consulted at the conceptual stage to ensure that the structure of the model is appropriate to clinical practice.

Ideally, health related quality of life evidence will be available directly from the review of the literature. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. In addition to the reviewed literature, national sources (e.g. NHS reference costs, national unit costs, *British National Formulary* (http://bnf.org)) and manufacturers' list prices will be used to estimate unit costs for use in the economic model. Where data on resource use associated with the new technologies are not available from the literature, advice will be sought from the expert advisory panel in the first instance. If uncertainty remains regarding the resources required for specific procedures, arrangements will be made for a member of the research team to observe and record the resource use associated with the procedures.

It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. The uncertainty in the central value for each required parameter will be represented by a distribution, enabling probabilistic sensitivity analysis to be undertaken. This will allow an assessment of the uncertainty to be made.

Value of information techniques will be undertaken within the work. The expected value of perfect information (EVPI) will be explicitly calculated. EVPI is defined as the maximum investment a decision-maker would be willing to pay to eliminate all uncertainty from the decision problem. It is initially calculated in terms of a defined unit (typically per patient) and then multiplied by the number of people expected to benefit from eliminating all uncertainty to form an estimate of total EVPI. EVPI per person is relatively high where there is large uncertainty in the adoption decision; conversely where there is only a small probability of error and the impact of an incorrect decision is small the EVPI per person will be relatively low.

Depending upon the resources required more complex methodologies (the expected value of partial perfect information (EVPPI) and the expected value of sample information (EVSI)) may be undertaken. EVPPI differs from EVPI as it evaluates the maximum value of removing all uncertainty in one, or a

subset of parameters, but it is more computationally expensive as it requires two nested Monte Carlo sampling levels.

EVSI is more advanced methodology for determining the value of information, which explicitly takes into account that uncertainty will not be removed even with large sample sizes. The EVSI methodology simulates the results from the proposed research and synthesises the simulated data with prior knowledge to form a posterior distribution: the larger the trial size the more the posterior distribution resembles the simulated data which is then used in probabilistic sensitivity analyses. The optimal trial size from the options evaluated can then be estimated based on the costs of conducting the trial and the expected net benefit of the sampled information. The application of EVSI is becoming more widespread and case studies employing this methodology have been published.

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