KCE REPORT 221

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

REVASCULARIZATION FOR LOWER LIMB PERIPHERAL ARTERIAL DISEASE

KCE REPORT 221
GOOD CLINICAL PRACTICE

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REVASCULARIZATION FOR LOWER LIMB PERIPHERAL ARTERIAL DISEASE

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COLOPHON

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ABPI	Ankle brachial pressure index
ACCP	American College of Chest Physicians
BMS	Bare metal stent
BSTH	Belgian Society on Thrombosis and Haemostasis
BSVS	Belgian Society for Vascular Surgery
CDT	Clinical decision threshold
CEBAM	Belgian Centre for Evidence Based Medicine
CE-MRA	Contrast enhanced - magnetic resonance angiography
CI	Confidence interval
CLI	Critical limb ischemia
CPG	Clinical practice guideline
CTA	Computed tomography angiography
DCB	Drug coated balloon
DES	Drug eluting stent
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
IC	Intermittent claudication
KCE	Belgian Healthcare Knowledge Centre
MRA	Magnetic resonance angiography
NCGC	National Clinical Guideline Centre
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
PAD	Peripheral arterial disease
PICO	Population – Intervention – Comparator – Outcome
PIRT	Patient/Problem – Index Test – Reference Standard – Target Condition

PTFE	Polytetrafluoroethylene
PVI	Peripheral vascular intervention
RBRS	Royal Belgian Society of Radiology
RCT	Randomised controlled trial
ROC	Receiver-operator curve
RRR	Relative risk ratio
SIGN	Scottish Intercollegiate Guidelines Network
TLR	Total lesion revascularisation
TOF MRA	Time-of-flight magnetic resonance angiography
TVR	Total venous revascularisation
UK	United Kingdom
UNAMEC	La fédération belge de l’industrie des technologies médicales

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

The most common initial symptom of lower limb peripheral arterial disease (PAD) is pain in the leg on walking, known as intermittent claudication (IC)[73]. The incidence of PAD increases with age. In the majority of those with IC the symptoms remain stable, but approximately 20% will progress to develop increasingly severe symptoms with the development of critical limb ischemia (CLI). Those with CLI are at significant risk of developing irreversible ischemic damage to the leg or foot if they do not receive appropriate treatment and this may lead to the need for amputation. Overall, approximately 1% to 2% of people with IC will eventually undergo amputation, although the risk is higher (about 5%) in people with diabetes.

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

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

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

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

Mild symptoms are generally managed in primary care, with referral to secondary care when symptoms do not resolve or deteriorate. There are several treatment options for people with IC. These include advice to exercise and management of elevated cardiovascular risk (for example, aspirin, statins, smoking cessation, etc). There is considerable variation in the utilisation of these treatment options. Whilst supervised exercise programmes can improve walking distance and quality of life, access to such programmes is limited in Belgium because they are not reimbursed. Treatments for secondary prevention are less commonly offered to people with PAD than for those with other cardiac and cerebrovascular risk factors.

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

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

1.2 The need for a guideline

According to data of the RIZIV – INAMI, a continuous increase is noticed in the number of percutaneous revascularizations of peripheral arteries since 1990, with an increase of 22% between 2006 and 2009. In view of a small increase of 'classical' surgical interventions (+2.39% between 2006 and 2009), the RIZIV – INAMI questions the appropriateness of these evolutions. A clinical practice guideline (CPG) on revascularization of lower limb peripheral arterial disease:

- Will assist clinicians in making appropriate choices when treating patients with the disorder;
- May provide scientific arguments for a change in the nomenclature to reduce the number of inappropriate interventions.

1.3 Scope

The guideline focuses on the diagnostic evaluation and revascularization of patients with lower limb peripheral arterial disease. The following diagnostic interventions are addressed:

- Duplex ultrasound;
- Magnetic resonance angiography;
- Computed tomography angiography;
- Ankle/brachial index.

In addition, the following revascularization techniques are addressed:

- Angioplasty with or without stenting (selective vs. primary; bare metal vs. drug eluting; drug coated balloons);
- Bypass surgery (autologous vein vs. prosthetic bypass).

This guideline does not cover:

- Screening of asymptomatic peripheral arterial disease;
- Treatment of (cardio)vascular risk factors;
- Patients with acute ischaemia of the lower limb.

Furthermore, as this guideline focuses on revascularization, best medical treatment and/or supervised exercise were only evaluated against revascularization. The comparison between supervised exercise and best medical treatment was considered out of scope.

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence both for the diagnostic evaluation and revascularization of patients with lower limb peripheral arterial disease. It is intended to provide clear recommendations about when and how to revascularize these patients. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

1.4.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of patients with lower limb peripheral arterial disease, including vascular surgeons, (interventional) radiologists, cardiologists and physiotherapists. It will also be of particular interest for patients and their families, for general practitioners, for hospital managers and policy makers.

The guidelines are based on clinical evidence and may not always be in line with the current criteria for NIHDI (RIZIV – INAMI) reimbursement of diagnostic and therapeutic interventions. The NIHDI may consider adaptation of reimbursement/financing criteria based on these guidelines.

1.5 Statement of intent

CPGs are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with lower limb peripheral arterial disease.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline should be fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

The KCE is a federal institution which is financed for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and the Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of the guidelines is paid by KCE budget, the sole mission of the KCE is providing scientifically valid information. The KCE has no interest in companies (commercial or not, e.g. hospital, university), associations (e.g. professional association, syndicate), individuals or organisations (e.g. lobby group) on which the guidelines could have a positive or negative impact (financial or other).

All clinicians involved in the guideline development group (GDG) or the peer-review process completed a declaration of interest form. The information of possible conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available on request.

2 METHODOLOGY

2.1 Introduction

The present guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with the members of the Guideline Development Group (GDG). Secondly, a literature review was made (including search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

2.2 The Guideline Development Group

This guideline was developed in collaboration between a multidisciplinary group of practising clinicians and KCE experts. The composition of the GDG is documented in Appendix 1. Guideline development and literature review expertise, support and facilitation were provided by the NCGC (UK) and the KCE expert team.

The roles assigned to the GDG were:

- The definition of the clinical questions, in close collaboration with the KCE expert team and stakeholders;
- The identification of important outcomes;
- The feedback on the selection of papers and identification of papers that were missed;
- The feedback on the content of the guideline;
- The judgement about indirectness of evidence;
- The feedback on the first draft of recommendations;
- The concerns that have to be reported under 'other considerations'.

2.3 General approach and clinical research questions

First, a search was done to identify recent (i.e. published after 2010) high-quality guidelines addressing the topic. In addition to a search in OVID Medline, the National Guideline Clearinghouse and the GIN database (see Appendix 2.1 for search strategies), the websites of NICE and SIGN were searched to identify relevant guidelines. The search resulted in 152 hits, from which seven potentially relevant guidelines were selected. These seven guidelines were appraised with the AGREE II instrument by two researchers independently (see Appendix 3.2). Only two guidelines were found to be of sufficient quality[1,73]. However, since the ACCP guidelines addressed antithrombotic therapy[1], it was decided to only use the NICE 2012 guideline for adaptation[73]. Relevant recommendations were extracted to an Excel-file and the members of the GDG and stakeholders group were asked to score their agreement with these recommendations using a 5-point scale. The scores were summarized and served as a basis for discussion during an initial stakeholder meeting at KCE on May 13, 2013. During this meeting, using the NICE 2012 guideline as a basis for the scoping phase, the following twelve clinical questions were selected:

Diagnostic evaluation:

1. What is the most clinically effective method of assessment of PAD (intermittent claudication and critical limb ischemia)?

Treatment of intermittent claudication:

1. What is the clinical effectiveness of endovascular or surgical techniques compared to or in combination with exercise or best medical treatment for the treatment of adults with intermittent claudication?
2. What is the clinical effectiveness of angioplasty compared to bypass surgery for the treatment of intermittent claudication in adults with PAD?
3. What is the clinical effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with intermittent claudication?
4. What is the clinical effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with intermittent claudication?

5. What is the clinical effectiveness of drug coated balloon angioplasty for the treatment of PAD in adults with intermittent claudication?
6. What is the clinical effectiveness of autologous vein versus prosthetic bypass for the treatment of PAD in adults with intermittent claudication?

Treatment of critical limb ischemia:

1. What is the clinical effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of critical limb ischemia in adults with PAD?
2. What is the clinical effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with critical limb ischemia?
3. What is the clinical effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with critical limb ischemia?
4. What is the clinical effectiveness of drug coated balloon angioplasty for the treatment of PAD in adults with critical limb ischemia?
5. What is the clinical effectiveness of autologous vein versus prosthetic bypass for the treatment of PAD in adults with critical limb ischemia?

For four research questions (question 2, 3, 8 and 12) it was decided to use the evidence from the NICE 2012 guideline without performing an update, because it was considered to be sufficiently up-to-date by the guideline development group (GDG). For six research questions (question 1, 4, 5, 7, 9 and 10) a literature search was done by NCGC to identify new studies published since the NICE 2012 guideline and the original evidence reviews were updated. Two additional research questions (question 6 and 11) were proposed by the GDG, and since these were not addressed by the NICE 2012 guideline they were answered with a new literature search.

2.4 Literature review and quality appraisal

For each clinical question requiring a literature search a protocol was developed using the PICO/PIRT framework (see Appendix 2.2). In general, primary studies were searched in Medline, Embase and the Cochrane Library. Detailed search strategies per database can be found in the same Appendix. For the diagnostic question, diagnostic accuracy studies and RCTs were searched, for the other research questions RCTs were searched. Only articles published in Dutch, English and French were included. The results of the selection process are provided in the Appendix 3.3.

The quality appraisal was performed by two researchers independently:

- **Systematic reviews** were assessed using the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php);
- **RCTs** were assessed with the Cochrane Collaboration's tool for assessing risk of bias;[39]
- **Diagnostic accuracy studies** were assessed with the QUADAS-2 checklist[105] for the new studies. An update of the HTA quality assessment from the NICE 2012 guideline, which was based on the QUADAS-1 checklist, was carried out by undertaking a mapping process to map all studies onto QUADAS-2 (see Appendix).

The tools used for the quality appraisal are reported in Appendix 3.1, while the results of the quality appraisal are available in Appendix 3.2 and 3.3.

2.5 Data extraction

Data extraction was performed by two researchers independently and entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion or, if required, by a third party.

All evidence tables are reported in Appendix 4.

2.6 Analysis

2.6.1 Therapeutic research questions

- Where there were 0 events (or less than 1% event rate) in one arm, instead of analysing data using the risk ratio, the Peto odds ratio was employed. When there was only one study, the absolute effect was calculated using the risk difference in Review Manager.
- Where there were 0 events in both arms, there is no estimate for relative effect. The absolute effect was calculated using the risk difference in Review Manager.
- Where time to event data has been analyzed for the applicable outcomes (mortality, amputation rate & wound healing) hazard ratios have been used.

2.6.2 Diagnostic research question

- For the 'test and treat' part of the diagnostic review, the same methods were used as for the therapeutic research questions.
- Results were reported separately for the different lesion locations in the leg: below the knee, above the knee, the whole leg and the foot separately, where reported. Arteries included in these classifications varied with studies and the arteries examined were recorded where reported.
- Data for arterial segments were not combined with data for whole arteries (information on the latter is found in the HTA report and not reported here[17].
- 2x2 tables were obtained as raw data or calculated from the numbers of patients who were positive and negative with the reference standard and the sensitivity and specificitiy. Occasionally, the 2x2 table was calculated algebraically using the number of patients and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV); where this was the case the study was considered to be at risk of bias and data were only used if there was insufficient other data. Such studies were labelled 'calc' in forest plots.
- Diagnostic meta-analysis was conducted if there were more than four studies per comparison, following sensitivity analyses as below. Methods are described in Appendix 7. Where there were zero events in any of the 2x2 cells, a value of 1 was substituted to allow the model to run, but the zeros were kept in the Review Manager entries.
- Data were plotted as coupled forest plots of sensitivity and specificity and on ROC curves. Wherever possible, the plots compared the different imaging tests, including a separate forest plot for comparisons within the same study.
- If there were fewer than five studies, the sensitivity with its 95% confidence interval was reported for the median study, together with the range of sensitivities across all studies; and the corresponding specificity with its 95% confidence interval was also reported, alongside the range of specificities.
- Sensitivity analyses on the basis of risk of bias were peformed before conducting meta-analyses, excluding studies at very high risk of bias, unless this reduced the numbers to fewer than five studies (so that a diagnostic meta-analysis was prohibited) or if the evidence was reduced to only one study.

Modified GRADE profiles were produced, reporting the sensitivity and specificity pairs in the same row. Imprecision was assessed by considering the confidence interval around the sensitivity: regions of acceptability were defined – so that if the confidence interval lay entirely within a region, the evidence was considered precise, but if the confidence interval crossed into two or three regions, the evidence was downgraded by one and two increments respectively. These regions were defined as 90-100%, 80-90% and below 80%. If a diagnostic meta-analysis was conducted, the summary statistics were used to assess imprecision, otherwise the study with the median sensitivity was assessed. Additionally, if a diagnostic meta-analysis was conducted the extent of the confidence ellipse was examined by inspecting the ROC curves.

2.7 Grading of evidence

2.7.1 Therapeutic research questions

For each recommendation, the strength and the quality of the supporting evidence was provided[6]. According to GRADE, we classified the quality of evidence into four categories: high, moderate, low, and very low (Table 1 and Table 2). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 1). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain[38].

Observational studies were by default considered low level of evidence (Table 1 and Table 2). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: the presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 3. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles in the Appendix 5.

Table 1 – A summary of the GRADE approach to grading the quality of evidence for each outcome[7]

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⨁⨁⨁⨁) Moderate (⨁⨁⨁⊖) Low (⨁⨁⊖⊖) Very low (⨁⊖⊖⊖)
Observational studies	Low			

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Table 3 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention.

Quality element	Reasons for downgrading
	Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

In addition, the following points were taken into account:

- GRADE tables provide estimates of absolute effects using the moderate risk category rather than the control group for baseline risk.
- Where there were dichotomous data for outcomes that should be time to event data (mortality, amputation rate and wound healing) the evidence was downgraded for indirectness.
- Target lesion revascularisation (TLR) and re-intervention rates have often been interchangeable in the studies. These have been grouped in the analyses where possible. These outcomes have been described in this report as described in the studies. Where an analysis combined studies where it was reported as re-intervention in some studies and target lesion revascularisation in others this has been made clear.
- Some studies report TLR or re-intervention data as time to event. This has been reported the data whichever way it is reported in the study and not downgraded for indirectness.
- The default categories in GRADE have been used when assessing imprecision.
- Data were reported as patient randomized unless otherwise indicated. In the few studies where data were reported by limb or lesion randomized it was indicated as such in the title of the outcome of the GRADE tables.
- The following template has been used for downgrading evidence when blinding was unclear or usually described as inadequate for participants and/or the outcome assessor:

Table 4 – Outcome assessments

Outcome(s)	Minimally important difference	Risk of bias assessment considerations objective or subjective
Mortality	1%	Objective outcome so low risk of bias if blinding inadequate
Amputation rate	1%	Objective outcome so low risk of bias if blinding inadequate
Perioperative Complications	10%	Dependant on how the study assesses these outcomes: • Objective if they predefine how they measure this and systematically assess everyone the same way, otherwise - low risk of bias for outcome assessor if blinding inadequate • Subjective if they do not predefine how they measure this or do not systematically assess everyone the same way – high risk of bias for outcome assessor if blinding inadequate • Low risk of bias for patient blinding if inadequate method used
Complications	10%	
Re-intervention & target lesion or vessel revascularisation	10%	
Wound healing	Grade default values.	
Adverse events		Subjective outcome unless they have specifically reported how they categorise this. High risk of bias if blinding inadequate
Quality of life	EQ-5D – change of 0.5 (mean difference, continuous outcome) Any other quality of life score uses GRADE defaults	Subjective outcome so high risk of bias if blinding inadequate
Walking distance	Doubling in baseline distance (mean difference, continuous outcome)	Subjective outcome so high risk of bias if blinding inadequate
Pain measures	0.5 standardised mean difference	Subjective outcome so high risk of bias if blinding inadequate

2.7.2 Diagnostic research question

Modified GRADE profiles were produced, reporting the sensitivity and specificity pairs in the same row:

- Risk of bias and indirectness were assessed by considering the majority of the evidence. This method took into account the size of the studies, as well as the number of them;
- Inconsistency was assessed by examining the forest plots and ROC curves;
- Imprecision was assessed by considering the confidence interval around the sensitivity: regions of acceptability were defined – so that if the confidence interval lay wholly within a region, the evidence was considered precise, but if the confidence interval crossed into two or three regions, the evidence was downgraded by one and two increments respectively. These regions were arbitrarily defined as 90-100%, 80-90% and below 80%. If a diagnostic meta-analysis was conducted, the summary statistics were used to assess imprecision, otherwise the study with the median sensitivity was assessed. Additionally, if a diagnostic meta-analysis was conducted the extent of the confidence ellipse was examined by inspecting the ROC curves.

2.8 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and subcontractor). This first draft together with the evidence tables was circulated to the guideline development group 2 weeks prior to the face-to-face meetings (5 November 2013; 3 December 2013; 6 January 2014). Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval.

A grade of recommendation was assigned to each recommendation using the GRADE system (Table 5). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and cost (resource utilization). Factors that influence the strength of a recommendation are reported in Table 6

Table 5 – Strength of recommendations according to the GRADE system.

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Table 6 – Factors that influence the strength of a recommendation.

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not [4]. Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make the best decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate[7].

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 7[13,31].

Table 7 – Interpretation of strong and conditional (weak)* recommendations[8, 9]

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms ''conditional'' and ''weak'' can be used synonymously*

2.9 External review

2.9.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to the relevant stakeholders (Table 8). Each professional association was asked to assign one or two key representatives to discuss the recommendations during an open meeting (20th January 2014). All expert referees made declarations of interest.

In total, seven clinical experts and representatives of professional associations were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to score each recommendation on a 5-point Likert scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the panellists were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case a panellist disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. In Appendix 8, an overview is provided of how the comments of the stakeholders were taken into account.

Table 8 – List of stakeholders to whom the recommendations were communicated.

- **Belgian Society for Vascular Surgery (BSVS)**
- **Belgian Society on Thrombosis and Haemostatis (BSTH)**
- **Royal Belgian Society of Radiology (RBRS)**
- **RIZIV – INAMI**
- **UNAMEC**

2.9.2 Patient representatives

Since no association of patient representatives is available in Belgium for this disease, it was decided to supplement the literature searches with a specific search for patient issues (see Appendix 2.3). If relevant, information from this search was included in the factor 'Values and preferences' during the GRADEing process.

2.10 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. This validation process was done on 24th February 2014. The current guideline was reviewed prior to its publication by three independent validators (cfr. names in the colophon), making use of the AGREE II checklist. The validation process was chaired by CEBAM. The validation of the report resulted from a consensus or a voting process between the validators.

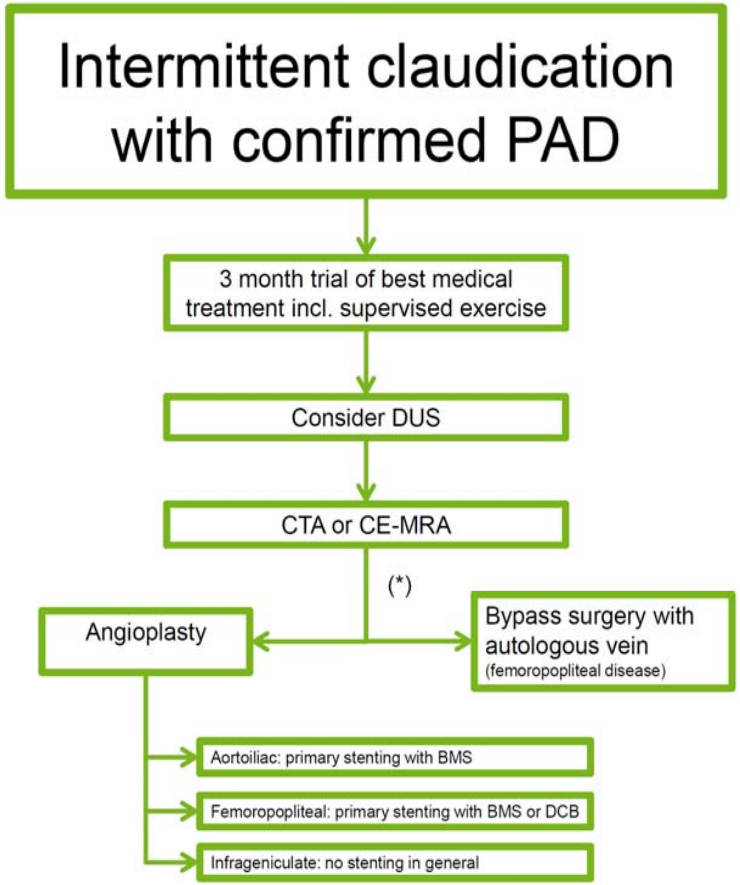
After this validation meeting a final GDG and stakeholders meeting was organised on 25th April 2014 to discuss the final changes. At this meeting a representative of Domus Medica and Société Scientifique de Médecine Générale was invited to obtain the opinion of the general practitioners.

3 RECOMMENDATIONS

3.1 General algorithm

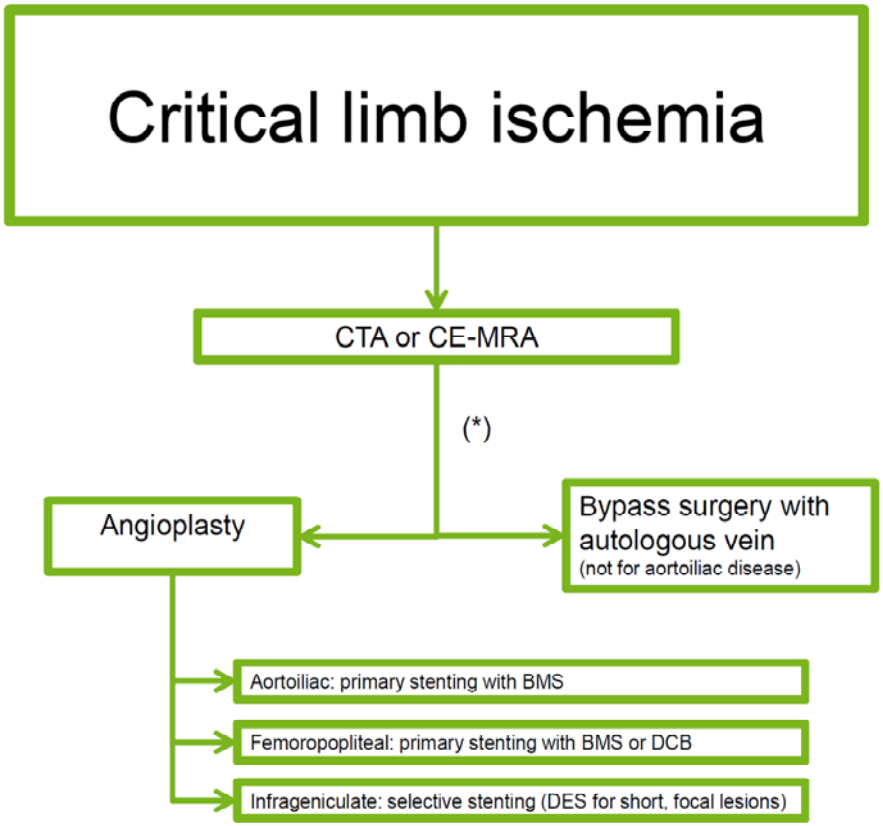
3.1.1 Intermittent claudication

The diagnosis of PAD is confirmed based on clinical symptoms and/or imaging and/or the ankle brachial pressure index, and by ruling out the presence of other diseases presenting with claudication.



(*) In addition to best medical treatment.

3.1.2 Critical limb ischemia



(*) In addition to best medical treatment.

3.2 Imaging for revascularization in peripheral arterial disease

3.2.1 Introduction

Lower limb PAD is characterized by atheromatous narrowing (stenosis) or blocking (occlusion) of one or more of the arteries of the leg. Narrowing of the arteries reduces blood flow to distal tissues and may result in symptoms, which may range from pain when walking (intermittent claudication) to tissue necrosis (ulceration and gangrene), and ultimately may lead to amputation and significant impact on quality of life. Management of PAD will depend largely on the extent of this narrowing, with the invasive procedures of angioplasty (with or without a stent) and surgical reconstruction being reserved for people with more severe disease. It is therefore necessary to determine the degree of narrowing of the arteries in people who are likely candidates for angioplasty or surgery, on the basis of their symptoms and quality of life, so that they can be offered appropriate treatment, balancing the risks of having an invasive procedure.

It is important to determine accurately the degree of stenosis or occlusion, balanced against the risks associated with measurement techniques, but ultimately the best test of this is to compare strategies of assessment coupled with treatment on the basis of the findings (the so-called 'test and treat' strategies). The disadvantage of investigating diagnostic test accuracy alone is that we cannot determine the effect on patient outcomes following subsequent treatment, without making assumptions about the effectiveness of treatment in people with significant stenosis and in people with non-significant stenosis. Test and treat approaches make no assumptions about this interaction. However, the limitation of test and treat approaches is that they may not use the most accurate tests and they may not use the most effective treatments. The combination of these two types of evidence will help inform practice.

The gold standard assessment test is digital subtraction angiography (DSA), which is an invasive procedure entailing the injection of contrast agent into the arteries, coupled with X-ray imaging. This has associated risks of arterial puncture, ionizing radiation, the potential nephrotoxicity of the contrast agents (particularly those with renal impairments) and allergic

reactions to the contrast agent. DSA requires insertion of a catheter usually via the femoral artery and is now infrequently performed as a primary imaging modality.

Available alternative diagnostic imaging modalities include duplex ultrasound scanning (DUS), magnetic resonance angiography (MRA), and computed tomographic angiography (CTA); DUS and MRA resonance imaging offer the least invasive options and avoid the use of ionizing radiation. DUS offers the unique advantage of functional assessment of arterial stenosis, but it is the most operator dependent of the available techniques. MRA imaging provides a three dimensional map of the imaged vessels and is able to image the pelvic vessels with more reproducibly than DUS. However, MRA may be contraindicated in some patients, for instance those with pacemakers and advanced renal insufficiency. CTA requires injection of contrast media, with attendant risks to renal function, and exposure to ionizing radiation.

Choice of imaging technique may also be affected by the part of the leg in which significant stenosis is suspected, and this review considers the evidence for imaging below the knee, above the knee, the foot alone and for the whole leg.

3.2.2 Search strategy

One search was conducted to cover both the test and treat and diagnostic test accuracy parts to the question. The search was limited to English, Dutch, and French languages in Medline and Embase. No time limit was placed on the literature search and there were no limitations on sample size. The search strategy is presented in Appendix 2.2.1. When selecting studies for inclusion, a selection of the studies included in the NICE guideline Lower Limb Peripheral Arterial Disease (CG147[73]) were also ordered.

The flow chart and reasons for exclusion are presented in Appendix 3.3.1.

3.2.3 Clinical evidence for diagnostic test accuracy

Seventy-one studies were included in this review. The NICE guideline was an update of the HTA, “A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease”[17], in which there were 58 test accuracy studies. The NICE guideline added a further seven studies (Bueno 2010[14], Eiberg 2010[29]; Gjonnaess 2006[33], Kos 2009[53], Kreitner 2008[55], Napoli 2011[72], Schernthaner 2008[87]). Six more papers were identified for inclusion in the review, three are new studies published since 2012 (Burbelko 2013[15], Iezzi 2013[45], Wang 2012[103]), one study was not identified by the NICE guideline review (Balzer 2005[7]) and two studies were identified in the reference list of a systematic review identified for this update (Andreisek 2007[3] and Lapeyre 2005[60]) and these papers were extracted separately. Studies were included only if there was sufficient information to extract a 2x2 table.

This current review updates both the HTA and the NICE guideline reviews, but further review and checking of the seven NICE papers was carried out, particularly to allow quality assessment using QUADAS 2. The HTA review data were used without obtaining the original papers, but the HTA quality assessments were mapped from QUADAS 1 to QUADAS 2, using a process developed for this review. Evidence for the 13 extra studies is given in the Appendix 3.3.1.4.1.

Overall, 23 studies investigated Contrast Enhanced (CE) MRA, of which two used a time resolved sequence MRA (Andreisek 2013[3] and Kos 2009[53]) and one (Wang 2012[103]) used a 3 Tesla 3D CE-MRA technique; data from these different techniques were reported separately. Eleven studies evaluated 2D time of flight MRA; ten studied CTA and 31 DUS.

Five studies compared more than one test with the reference standard (DSA) in the same population; these are reported in Appendix 3.3.1.3. One study (Iezzi 2013[45]) considered the effect of assessor experience.

The clinical GRADE evidence profiles are represented in Appendix 5.1. Stratification by symptoms (intermittent claudication or critical limb ischemia), test details (e.g. field strength for MRA), population subgroups such as diabetes, and inclusion/exclusion of the foot in the analysis of whole leg or below knee was not done because the HTA reported there was insufficient information in the primary studies. However, the results were reported separately for lesion location (above the knee, below the

knee, foot, whole leg) and according to the degree of stenosis. For the latter, subdivisions were 100% (occlusion), 70-100% stenosis and 50-100% stenosis; some other degrees of stenosis were reported in the HTA review.

The severity of symptoms varied within and between studies. Eighteen studies from the HTA review and two additional studies (Aly 1998[2], Andreisek 2007[3], Currie 1995[20], Davies 1992[23], Gjonnaess 2006[33], Hirai 1998[40], Laissy 1998[59], Legemate 1991[61], Linke 1994[63], Lundin 2000[65], Meaney 1999[71], Puls 2002[78], Rieker 1997[84], Sensier 1996[90], Steffens 1997[93], Sueyoshi 1999[94], Timonina 1999[98], Winterer 1999[111], Vavrik 2004[102], Whyman 1992[108]) had at least 80% patients with Fontaine stage II (intermittent claudication); eleven studies from the HTA review and one additional study (Cronberg 2003[19], Grassbaugh 2003[35], Hoch 1996[41], Hofmann 2004[42], Karacagil 1996[46], Koelemay 1998[51], Koelemay 1997[52], Kreitner 2000[55], Lapeyre 2005[60], McDermott 1995[68], Wilson 1997[110], Yucel 1993[113]) had more than 80% patients with Fontaine stage III or IV. The other studies either reported a mixed population or did not state the Fontaine classification.

Three studies reported in the HTA review and two additional studies were conducted in patients with diabetes (Andreisek 2007[3], Hofmann 2004[42], Kreitner 2008[55], Lapeyre 2005[60], McDermott 1995[68]).

All study evidence tables, forest plots and Receiver Operating Characteristics (ROC) curves are presented in respectively Appendix 4.1 and Appendix 6.1.

3.2.4 *Clinical evidence for diagnostic test-and-treat*

One multicenter, pragmatic, randomized trial (Ouwendijk 2008[76]; Ouwendijk 2005[76]; de Vries 2007[24]) compared three imaging techniques in a test and treat study (the DIPAD trial). Patients were randomized to CE-MRA or to the currently used imaging test, which varied between hospitals (DUS in three hospitals and CTA in a fourth); the trial was stratified by hospital. Findings from the imaging tests were discussed at a weekly vascular conference, alongside patient history, physical examination results, and vascular laboratory results, and this information was used to make decisions about further imaging and treatment. Following the vascular conference, patients were offered additional vascular imaging and then surgical intervention, percutaneous intervention or exercise therapy. Outcomes were quality of life at 6 months and therapeutic confidence of the clinicians; the number of interventional procedures was also recorded. Further details are given in the Appendix.

It is noted that the design of the trial is such that the comparison of DUS and CTA is not randomized, but can be addressed as an indirect comparison: both these imaging modalities are part of the 'usual care' arm and assignment is according to what was commonly used in the particular hospital; the same protocol was used for the two comparisons of MRA versus CTA and MRA versus DUS. The most recent paper (Ouwendijk 2008[76]) combines the results from the MRA arm for all hospitals and compares all three index tests head to head, which is inappropriate. In this review we have chosen to report the stratified randomized comparisons from the original papers (Ouwendijk 2005 for MRA versus CTA,[76] and de Vries 2007 for MRA versus CTA[24]).

Conclusions

Comparison of assessment tools for people with PAD who are likely candidates for angioplasty or surgical intervention

- This review compares the diagnostic test accuracy of several index tests in relation to the reference standard, digital subtraction angiography (DSA). These tests are: contrast enhanced magnetic resonance angiography (CE-MRA), duplex ultrasound (DUS), computed tomography angiography (CTA) and 2-dimensional time-of-flight MRA.
- Based on the generally low-to-very-low-level evidence, for examining 50-100% stenosis whilst imaging the whole leg, diagnostic meta-analysis showed sensitivities between 89 and 99%, with specificities between 86 and 99% across all tests. The ROC curves and summary statistics suggested that CTA and CE-MRA are the most accurate tools and that 2D TOF MRA is the least accurate.
- For the threshold of 70-100% stenosis in the whole leg, there was less evidence (and none at all for DUS), but the moderate and high quality evidence for CTA and CE-MRA showed similar sensitivities to each other (96-99%) and comparable specificities (99%). The single study for 2D TOF MRA gave very low quality evidence giving a sensitivity point estimate of 90% and specificity of 97%.
- Based on the available low-moderate-level evidence for occlusion in the assessment of the whole leg, all tests showed similar specificities of around 99%, but the sensitivity was higher for the CE-MRA and CTA tests (96%), with DUS and 2D TOF MRA giving lower values (90%). This is illustrated clearly in the ROC curve.
- For examining peripheral vessels above the knee, and considering the threshold 50-100% stenosis, there was low-very-low-level evidence, with much inconsistency between studies for DUS and CE-MRA, to show CTA was the most accurate test (median 97% sensitivity) followed by CE-MRA (92%), with DUS and the single study reporting 2D TOF MRA having sensitivities centred around 86% and 81% respectively. For examining occlusion, the generally low-level evidence again showed higher sensitivity for CTA (96% median), with DUS and CE-MRA having similar values (93%) and the single TOF MRA study showing around 87% (95%CI 60 to 98).
- For examining peripheral vessels below the knee, the low-very-low evidence showed much inconsistency between studies. For the threshold of 50-100% stenosis, DUS had lower sensitivity than CE-MRA and this is illustrated well in the ROC curve. There was limited evidence for occlusion below the knee, particularly for CTA, but the very low and moderate quality evidence suggested DUS has a sensitivity about 10% lower than that for CE-MRA (with lower specificities too). This is also clearly shown in the ROC curve.
- Based on limited low-very-low-level evidence for examining the foot, it is unclear whether there are differences between techniques, but sensitivities are generally low for DUS and CE-MRA. Low-level evidence from one study suggests there may be an advantage to using a time-resolved approach to MRA, but it may be preferable to retain DSA for vessels in the foot.
- Three studies compared different imaging tools directly in the same patients, and for each of these there was evidence to suggest that CE-MRA is more accurate than DUS, particularly for measuring 50-100% stenosis.

Comparison of test-and-treat strategies of assessment tools plus treatment for people with PAD who are likely candidates for angioplasty or surgical intervention

- One multicentre randomised trial compared three test-and-treat strategies, in two randomised comparisons. Patients received an imaging modality (DUS, CTA or CE-MRA) and on the basis of the findings from these imaging techniques, and in the context of a vascular conference, appropriate treatment was assigned (exercise, percutaneous intervention (PCI) or surgery). The impact of these strategies on quality of life and 'economic / process outcomes' was examined.
- Evidence of low-very-low-level suggests that there is no clinically relevant difference in impact of CTA imaging compared with CE-MRA on quality of life (EQ-5D) and maximum walking distance.
- Based on the available low-level evidence, no firm conclusion can be drawn about the impact of CTA imaging compared with CE-MRA on amputation rate in patients with PAD who are likely candidates for angioplasty or surgical intervention.
- There may be more additional imaging required for people who had MRA as an initial imaging technique, compared with people receiving CTA, but again there was uncertainty in the evidence because of the large confidence interval around the point estimate.
- There was low-level evidence to show that considerably fewer people had surgical interventions when the imaging technique was CTA, compared with CE-MRA and, also potential for fewer PCIs. Taking into consideration the test accuracy evidence above, it may be that the increased surgical interventions are an indication of initial under-treating.
- For the comparison of CE-MRA with DUS, in the context of the vascular conference and treatment on the basis of findings, there was low-very-low-level evidence on patient outcomes (EQ-5D and walking distance) to suggest little difference between CE-MRA and DUS as part of a test-and-treat strategy.
- However, DUS led to a much increased requirement for further imaging within 6 months, and particularly in advance of therapy, reflecting a possible lack of confidence in DUS. This was moderate-level evidence. On the other hand, moderate-low-level evidence showed there was no important difference between CE-MRA and DUS in the number of PCIs and surgical procedures.
- There appears to be enough evidence to also support further research into strategies of this type, in which the role of the vascular conference could perhaps be explored.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Of all tests CTA imaging and CE MRA seem to have the best diagnostic accuracy in general. CE MRA imaging is potentially associated with an increased number of angioplasties or surgical interventions compared with CTA. However, CTA is associated with an increased radiation exposure. This consideration made MRA imaging first choice above CTA. DUS is easily accessible in most centres treating patients with peripheral arterial disease, but is highly rater-dependent. For critical limb ischemia, invasive treatment is almost always necessary, and more extensive evaluation (with CTA or CE MRA) is commonly needed. This consideration was the determining factor for the first recommendation.
Quality of evidence	The evidence is of very low to moderate quality.
Costs (resource allocation)	NCGC identified one decision analytic model (Collins 2007[17]) and three trial-based economic evaluations. For whole leg and below the knee imaging, the decision model concluded that DUS was more cost effective than 2D TOF MRA, CE MRA and CTA. For above the knee imaging, the same economic decision model found that 2D TOF MRA was more cost effective than DUS, CE MRA and CTA.
Patients values and preferences	Nielsen et al. prospectively evaluated patient acceptance of whole-body MRA versus digital subtraction angiography with a postal questionnaire in 79 consecutive patients with symptomatic PAD (Nielsen 2010). Overall discomfort scores were higher in DSA compared to MRA (mean 2.1 and 1.7, respectively; p=0.06). In MRA, overall discomfort was strongly correlated to feeling confined in the MRI system. In DSA, discomfort was strongly correlated to arterial puncture and contrast injection. Injection of iodinated contrast agent at DSA was graded more uncomfortable than injection of gadolinium-based contrast agent at WB-MRA (mean 2.1 vs. 1.5, respectively; p<0.001). Sixty-two patients (90%) were willing to repeat MRA, and 64 patients (93%) would repeat DSA if they needed another vascular examination. Forty-one patients preferred MRA (60%), 12 patients preferred DSA (17%), and 16 patients had no preference (23%). Patient preference of MRA over DSA was statistically significant (p<0.001).

Recommendations	Strength of Recommendation	Level of Evidence
Consider duplex ultrasound as first-line imaging in people with intermittent claudication for whom revascularisation is being considered.	Weak	Low - Very low
Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) before considering revascularization.	Strong	Moderate - Low
Offer computed tomography angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) if contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.	Strong	Moderate - Low

3.3 Management of intermittent claudication

3.3.1 Revascularization compared with or in combination with exercise or best medical treatment

Best medical treatment for patients with peripheral arterial disease usually consists of one or more of the following components:

- secondary prevention of cardiovascular disease (e.g. smoking cessation, improved glycaemic control in diabetic patients, cholesterol management, hypertensive treatment, anti-platelet agents, other lifestyle changes)
- exercise advice [73].

3.3.1.1 Best medical treatment versus best medical treatment plus angioplasty

NCGC identified two RCTs reported in four articles (NICE 2012[73], Nylaende M 2007[74], Nylaende M 2007[75],Whyman MR 1997[107], Whyman MR 1996[106]). Nyelande et al. included 56 patients and randomised them to optimal medical treatment (OMT) alone or OMT combined with percutaneous transluminal angioplasty (PTA). 45/56 patients had combined lesions of the femoropopliteal and aortoiliac segment, ten had lesions in aortoiliac segment and one in the femoropopliteal segment. Follow-up was performed at 3, 12 and 24 months. It was not possible to perform an anatomical subgroup analysis based on the data provided. The study had a high risk of bias (no blinding, insufficient sample size calculation). Whyman et al. included 62 patients with femoral stenosis or occlusions (n=47) or iliac stenosis (n=15) and randomised them to conventional medical treatment alone (n=32) or conventional medical treatment with angioplasty (n=30). Follow-up duration was performed at 6 and 24 months. The study had a high risk of bias (no blinding, no ITT analysis). More details on these studies can be found in the evidence tables (NICE 2012 appendices, chapter H.4.2, p. 239-244) and forest plots (NICE 2012 appendices, chapter J.3.2, p. 400). The GRADE tables can be found in appendix 5.2.1.

Conclusions

Intermittent claudication with aortoiliac or femoropopliteal lesion (mixed population)

- There is very low level evidence that optimal medical treatment with angioplasty significantly improves the maximum walking distance and pain-free walking distance at 3 months, 1 year and 2 years compared with optimal medical treatment alone. The effect appears to be clinically important for pain-free walking distance at 3 months, but not for the other time point measures.
- There is very low level evidence that optimal medical treatment with angioplasty significantly increases quality of life on the following SF-36 subscales compared with optimal medical treatment alone: “physical functioning” (3 and 24 months), “bodily pain” and “reported health transition (3 months), and “role emotional” (24 months). For the other time point measures on these subscales no significant group differences were observed. For the remaining SF-36 subscales (physical role, general health vitality, and mental health) no difference was found (3, 12 or 24 months).
- There is very low level evidence that optimal medical treatment with angioplasty does not result in complications at 1 year.
- There is very low level evidence that optimal medical treatment with angioplasty does not result in re-interventions at 1 year.

Intermittent claudication with femoropopliteal lesion

- There is low level evidence that optimal medical treatment with angioplasty does not result in complications at 6 months.
- There is low level evidence that optimal medical treatment with angioplasty does not result in re-interventions at 6 months, and 3% re-interventions at 2 years.
- No evidence from RCTs is available on the effect of optimal medical treatment with angioplasty on functional outcomes and quality of life compared with optimal medical treatment alone.

Intermittent claudication with infrageniculate disease

- No evidence from RCTs is available on the effectiveness of optimal medical treatment with angioplasty compared with optimal medical treatment alone.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Best medical treatment with angioplasty appears to be more effective than best medical treatment alone in terms of functional capacity and some areas of quality of life with complications and re-intervention rates remaining at very low levels.
Quality of evidence	The evidence is limited to small RCTs and observational studies with a high risk of bias and an overall low to very low level of evidence, and there is limited evidence with respect to lesion location
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study.
Patients values and preferences	None identified from the literature.

3.3.1.2 Best medical treatment with supervised exercise and angioplasty versus best medical treatment with supervised exercise

NCGC identified three RCTs (NICE 2012[73], Mazari FAK 2012[67], Mazari FA 2010[66], Greenhalgh RM 2008[37]). Greenhalgh et al.[37] performed two separate trial for patients with aortoiliac lesions (34 patients randomised) and patients with femoropopliteal lesions (93 patients randomised). Patients were allocated to best medical treatment, smoking cessation advice supervised exercise with angioplasty or to best medical treatment, smoking cessation advice plus supervised exercise. Follow-up was carried out at 6, 12 and 24 months. The study had a high risk of bias (allocation concealment not stated, no blinding, and no ITT analysis). Mazari et al. [66] randomised 178 patients with femoropopliteal disease to supervised exercise alone, to angioplasty alone or to supervised exercise with angioplasty. All patients had been on best medical treatment for >3 months. Follow-up was performed after 3 months. The study had a high risk of bias (no reporting of blinding, or ITT analysis, drop-out >15 %).

Mazari et al. [67] randomised 118 patients with femoropopliteal disease to supervised exercise alone, to angioplasty alone or to angioplasty + supervised exercise. Patients had follow-up at 1, 3, 6 and 12 months, however, only 12 months data is reported. The study had a high risk of bias (no reporting on randomisation, allocation concealment and blinding). More details on these studies can be found in the evidence tables (NICE 2012 appendices, chapter H.4.2, p. 249-252) and forest plots (NICE 2012 appendices, chapter J.3.2, p. 403).

Conclusions

Intermittent claudication with aortoiliac lesion

- There is low to very low level evidence that best medical treatment and supervised exercise combined with angioplasty has no significant effect on the walking distance at 24 months compared with best medical treatment and supervised exercise alone.
- Based on the available low-level evidence, no conclusion can be drawn on the effect of best medical treatment and supervised exercise combined with angioplasty on quality of life compared with best medical treatment and supervised exercise alone.
- There is low level evidence of a post-procedure complication rate of approximately 21 % after best medical treatment and supervised exercise combined with angioplasty
- No evidence from RCTs was found on re-intervention rates after best medical treatment and supervised exercise combined with angioplasty.

Intermittent claudication with femoropopliteal lesion

- There is moderate to low level evidence that best medical treatment and supervised exercise combined with angioplasty significantly improves the walking distance at 24 months compared with best medical treatment and supervised exercise alone.
- Based on the available low-level evidence, no conclusion can be drawn on the effect of best medical treatment and supervised exercise combined with angioplasty on quality of life compared with best medical treatment and supervised exercise alone.
- There is low level of evidence of an immediate post-procedure complication rate of 12.5 % after best medical treatment and supervised exercise combined with angioplasty. There is low level of evidence of a complication rate of 0 % after 3 months and 1 year.
- No evidence from RCTs was found for re-intervention rates after best medical treatment and supervised exercise combined with angioplasty.

Intermittent claudication with infrageniculate disease

- No evidence from RCTs is available on the effectiveness of best medical treatment and supervised exercise combined with angioplasty compared with best medical treatment and supervised exercise alone.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The addition of angioplasty to supervised exercise seems to have some effects on walking distance for femoropopliteal patients but not aortoiliac patients.
Quality of evidence	The evidence is limited to three studies with a high risk of bias and an overall moderate - very low level of evidence.
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study.
Patients values and preferences	None identified from the literature.

3.3.1.3 Best medical treatment with supervised exercise and angioplasty versus best medical treatment and angioplasty

NCGC identified two RCTs (NICE[73], Mazari 2012[67], Kruidenier 2011[56]). Mazari et al. [67] randomised 118 patients with femoropopliteal disease to best medical treatment and supervised exercise alone, to best medical treatment and angioplasty alone or to best medical treatment, angioplasty and supervised exercise. Patients had follow-up at 1, 3, 6 and 12 months, however, only 12 months data is reported. The study had a high risk of bias (no reporting on randomisation, allocation concealment and blinding). Kruidenier [56] randomised 70 patients with aortoiliac or femoropopliteal disease. All patients received medical treatment and percutaneous vascular intervention (PVI) and were subsequently randomised to the PVI alone group or to PVI + supervised exercise therapy. The study had a high

risk of bias (no blinding, high number of patient cross-over). Follow-up was performed at 3 and 6 months.

More details on these studies can be found in the evidence tables (NICE 2012 appendices, chapter H.4.2, p. 251-255) and forest plots (NICE 2012 appendices, chapter J.3.2, p. 403). The GRADE tables can be found in appendix 5.2.3.

Conclusions

Intermittent claudication with aortoiliac or femoropopliteal lesion (mixed population)

- There is very low level evidence that best medical treatment with supervised exercise and angioplasty significantly improves maximum walking distance at 6 months and pain-free walking distance at 3 months and 6 months compared with best medical treatment and angioplasty. There is very low level evidence of a non significant difference in maximum walking distance at 3 months. The differences were not clinically important.
- Based on the available very low level evidence, no conclusion can be drawn on the effect of the addition of supervised exercise to best medical treatment and angioplasty on quality of life.
- There is very low level evidence of a significant effect of adding supervised exercise to best medical treatment and angioplasty on re-intervention rates, and the results are clinically important.
- No evidence from RCTs was found on complication rates after best medical treatment with supervised exercise and angioplasty.

Intermittent claudication with femoropopliteal lesion

- Based on the available very low level evidence, no conclusion can be drawn on the effect of the addition of supervised exercise to best medical treatment and angioplasty on quality of life.
- No evidence from RCTs was found for functional capacity, peri-procedural complications or re-intervention rates after best medical treatment with supervised exercise and angioplasty.

Intermittent claudication with infrageniculate disease

- No evidence from RCTs is available on the effectiveness of best medical treatment and supervised exercise combined with angioplasty compared with best medical treatment and angioplasty.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The addition of supervised exercise to best medical treatment and angioplasty in comparison with best medical treatment and angioplasty alone appears to have effects on functional capacity and re-intervention rates without the addition of major adverse events.
Quality of evidence	The evidence is limited to two studies with a high risk of bias and an overall low- very low level of evidence.
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study. Supervised exercise is currently not reimbursed in Belgium.
Patients values and preferences	None identified from the literature.

3.3.1.4 Angioplasty versus supervised exercise

NCGC identified five RCTs (NICE[73], Mazari FAK 2012[67], Mazari FA 2010[66], Spronk S 2009[92], Perkins JM 1996[77], Creasy 1990[18]). Mazari et al. 2010[66] randomised 178 patients with femoropopliteal disease to supervised exercise alone, to angioplasty alone or to supervised exercise with angioplasty. All patients had been on best medical treatment for >3 months. Follow-up was performed after 3 months. The study had a high risk of bias (no reporting of blinding, or ITT analysis, drop-out >15 %). Mazari et al. [67] randomised 118 patients with femoropopliteal disease to supervised exercise alone, to angioplasty alone or to angioplasty + supervised exercise. Patients had follow-up at 1, 3, 6 and 12 months, however, only 12 months data is reported. The study had a high risk of bias (no reporting on randomisation, allocation concealment and blinding). Spronk et al. [92] randomised 151 patients with aortoiliac and/or femoropopliteal disease (mixed population) to angioplasty using 10% oversized balloon or to hospital based exercise twice a week. Follow-up was performed at 6 and 12 months. The study had a high risk of bias (no reporting of allocation concealment or blinding). Perkins et al. [77] randomised 56 patients with superficial femoral artery or iliac artery lesions to angioplasty using conventional guide-wire and balloon catheter technique or to two weekly supervised exercise sessions for 6 months. Follow-up was performed at 3, 6, 9 and 15 months. The study had a high risk of bias (no description of randomisation, allocation concealment or blinding, no ITT analysis). Similarly, Creasy et al. [18] randomised 36 patients with aortoiliac and/or femoropopliteal disease (mixed population) to angioplasty using conventional guide-wire and balloon catheter technique or to two weekly supervised exercise sessions for 6 months. Follow-up was performed at 3, 6, 9 and 12 months. The study had a high risk of bias (no description of randomisation, allocation concealment or blinding, no ITT analysis). More details on these studies can be found in the evidence tables (NICE 2012 appendices, chapter H.4.2, p. 256-269) and forest plots (NICE 2012 appendices, chapter J.3.2, p. 405).

Conclusions

Intermittent claudication with aortoiliac or femoropopliteal lesions (mixed population)

- There is very low level evidence that supervised exercise is significantly better than angioplasty for maximum walking distance and pain free walking distance at 6 and 12 months. The results were not clinically important. Based on very low level evidence no conclusion can be made on the effect of angioplasty vs. supervised exercise on the number of people who doubled their maximum walking distance.
- Based on the available very low level evidence, no conclusion can be drawn on the effect of angioplasty versus supervised exercise with respect to quality of life.
- There is very low level evidence of a complication rate after angioplasty of approximately 11.6 % at 1 year.
- There is very low level evidence of re-intervention rates after angioplasty of 6.6 % at 6 months, 8.4 % at 1 year, and 10 % at 15 months.

Intermittent claudication with femoropopliteal lesion

- There is low level evidence of a re-intervention rate of approximately 15 % after angioplasty at 1 year.
- No evidence from RCTs was found for functional capacity, quality of life or peri-procedural complications after angioplasty compared with supervised exercise.

Intermittent claudication with infrageniculate disease

- No evidence from RCTs is available on the effectiveness of angioplasty compared with supervised exercise.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Supervised exercise appears to have an effect on functional outcomes in comparison with angioplasty. This was the determining factor to recommend a trial of supervised exercise first.
Quality of evidence	There is evidence from five trials but the majority of these are small, have a high risk of bias and are performed in patients with a mix of disease with respect to anatomical location.
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study. Supervised exercise is currently not reimbursed in Belgium.
Patients values and preferences	None identified from the literature.

3.3.1.5 Bypass surgery versus supervised exercise

NCGC identified one RCT (NICE[73], Lundgren 1989[64]). Lundgren et al. randomised 75 patients with aortoiliac and/ or femoropopliteal disease (mixed population) to surgery, to exercise or to a combination. Exercise sessions were performed for 3 session pr week. The study had a high risk of bias (no reporting of allocation concealment, small sample size). More details on this study can be found in the evidence tables (NICE 2012 appendices, chapter H.4.2, p. 269) and forest plots (NICE 2012 appendices, chapter J.3.2, p. 408). The GRADE tables can be found in appendix 5.2.5.

Conclusions

Intermittent claudication with aortoiliac or femoropopliteal lesion (mixed population)

- There is very low level evidence that bypass surgery is significantly better than supervised exercise for walking distance at 1 year. The difference seems to be clinically important.
- No evidence from RCTs was found for quality of life after bypass surgery compared with supervised exercise.
- There is very low level evidence of complication rates following bypass surgery of 24 % at 30 days.
- There is very low level evidence of re-intervention rates of 12 % following bypass surgery at 30 days.

Intermittent claudication with infrageniculate disease

- No evidence from RCTs is available on the effectiveness of bypass surgery compared with supervised exercise.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Bypass appears to have an effect on functional outcomes in comparison with supervised exercise, and the effect is clinically important.
Quality of evidence	There is evidence from one small trial including a mixed population. The study has a high risk of bias.
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study. Supervised exercise is currently not reimbursed in Belgium.
Patients values and preferences	None identified from the literature.

Recommendation	Strength of Recommendation	Level of Evidence
• **Consider a trial period of best medical treatment including supervised exercise in patients presenting with intermittent claudication.**	Weak	Very low

3.3.2 *Angioplasty versus bypass surgery*

NCGC identified four RCTs reported in seven articles (NICE 2012[73], Kedora 2007[47], McQuade 2010[70], McQuade 2009[69], Wilson 1989[109], Wolf 1993[112], Holm 1991[43], van der Zaag 2004[101]). McQuade et al. included 86 patients with atherosclerotic stenotic or occlusive lesions of the superficial femoral artery with no significant aortoiliac disease (Kedora 2007[47], McQuade 2010[70], McQuade 2009[69]). Patients were randomized by limb (N=100) to angioplasty with stenting or bypass surgery. This study had a high risk of bias due to an unclear randomization method, unreported allocation concealment and no blinding. Wolf et al. randomized 256 patients with a significant stenosis (>80%) or an occlusion <10 cm in length of the iliac, superficial femoral, or popliteal arteries to angioplasty or bypass surgery (Wilson 1989[109], Wolf 1993[112]). Due to unreported blinding, this study had a high risk of bias for subjective outcomes. In this study, randomization was stratified by disease localization and severity of symptoms. Holm et al. included 102 patients with either severe limb ischemia (rest pain or ischemic ulcerations; N=61) or severe claudication who had not benefited from exercise training (N=41) (Holm 1991[43]). Only occlusions or significant stenoses 6 cm or shorter in the common iliac, external iliac, femoral or popliteal artery were accepted for treatment. This study had a high risk of bias due to unclear allocation concealment and blinding. Finally, van der Zaag et al. included 56 patients with intermittent claudication not responding to conservative therapy for at least 3 months and a stenosis or occlusion of the superficial femoral artery with a length between 5 and 15 cm (van der Zaag 2004[101]). Patients were randomized to angioplasty or bypass surgery. The study had a high risk of bias because of unclear allocation concealment and blinding.

More details on these four RCTs can be found in the evidence tables (NICE 2012 appendices, chapter H.4.3, p. 271-284) and forest plots (NICE 2012 appendices, chapter J.3.3, p. 409-414). The GRADE tables can be found in appendix 5.3.

Conclusions

Aortoiliac disease

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on the re-intervention rate at 2 years compared with bypass surgery in patients with intermittent claudication due to aortoiliac disease.
- There is low-level evidence that angioplasty is associated with significantly more post-procedure complications than bypass surgery in patients with intermittent claudication due to aortoiliac disease. This difference is clinically important.
- No evidence from RCTs is available on the effect of angioplasty on quality of life or functional capacity or pain compared with bypass surgery in patients with intermittent claudication due to aortoiliac disease.

Femoropopliteal disease

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on the re-intervention rate at 1, 2 and 4 years compared with bypass surgery in patients with intermittent claudication due to femoropopliteal disease.
- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on minor post-procedure complications and major adverse events at 1 year compared with bypass surgery in patients with intermittent claudication due to femoropopliteal disease.

- No evidence from RCTs is available on the effect of angioplasty on quality of life or functional capacity or pain compared with bypass surgery in patients with intermittent claudication due to femoropopliteal disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	In general, the choice between angioplasty and bypass surgery should be made when a trial of best medical treatment with supervised exercise fails and when the claudication is incapacitating. Claudication becomes incapacitating when it significantly hampers quality of life and activities of daily living, over and above the general condition of the patient taking into account comorbidities and biological age. For aortoiliac disease, no clear benefits were found, but angioplasty was associated with more post-procedure complications than bypass surgery. These complications include acute thrombosis, puncture site bleeding, contrast extravasations, etc. For femoropopliteal disease, no firm conclusions could be drawn. The choice should be made after multidisciplinary discussions. Once a choice is made, the necessary medical expertise should be available to carry out the procedure. If the necessary expertise is not available in the same centre, the patient should be referred.
Quality of evidence	Overall low to very low.
Costs (resource allocation)	NCGC identified one cost-utility analysis for this comparison (Hunink 1995[44]). Hunink 1995 evaluated the cost-effectiveness of revascularisation for femoropopliteal disease using angioplasty, bypass surgery and combinations of the two treatments in people with disabling claudication. Only patients requiring revascularisation were included and strategies such as exercise, medical therapy or amputation were not considered. The results of bypass surgery were sub-grouped according to graft material (autologous vein vs. prosthetic bypass) and lesion type. Although the results of the analysis are different for each subgroup, the conclusions are broadly the same. NCGC did a new cost-effectiveness analysis (NICE 2012[73]). The model was designed to compare 13 alternative treatment strategies for people with intermittent claudication. The results of the model suggest that supervised exercise followed by angioplasty with selective stent placement has the highest probability of being cost effective in both the aortoiliac and femoropopliteal artery. If angioplasty does not represent a treatment option for people with intermittent claudication, supervised exercise followed by bypass surgery is the next most cost-effective option. Information about the reimbursement in Belgium can be found in appendix 9. Results of a comparison of the immediate costs related to angioplasty and bypass surgery in Belgium can be found in appendix 10. This comparison does not include costs related to re-interventions, and does not distinguish between lesion site and severity. Therefore, they should be interpreted with caution.
Patients values and preferences	Zafar et al. used a standard gamble-type survey to explore patient preferences in regard to treatment for PAD (Zafar 2011). Twenty patients with suspected PAD were asked to indicate their threshold for risk of amputation during a curative procedure for intermittent

Factor	Comment
	claudication. Up to 1% risk of above-knee amputation was found to be the median risk acceptable to patients for undergoing a curative procedure.

Recommendation	Strength of Recommendation	Level of Evidence
In patients with incapacitating claudication in whom, after a trial of best medical treatment including supervised exercise treatment, clinical results are insufficient, consider angioplasty or bypass surgery in addition, taking into account the following factors: • **Type and length of lesion;** • **Availability of vein;** • **Patient preferences;** • **Symptoms;** • **Costs.**	Weak	Very low

3.3.3 *Angioplasty with selective stenting versus primary stent placement*

3.3.3.1 *Introduction*

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

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

3.3.3.2 *Search strategy*

One search was conducted to cover three questions: selective stenting with angioplasty versus primary stenting with angioplasty (for intermittent claudication and critical limb ischemia); and drug coated balloon angioplasty versus any other endovascular procedure (for critical limb ischemia). The search was limited to English, Dutch and French languages in Medline and Embase. No time limit was placed on the literature search and there were no limitations on sample size. The search strategy is presented in Appendix 2.2.2. When selecting studies for inclusion papers a selection of the studies included in the NICE guideline Lower Limb Peripheral Arterial Disease (CG147[73]) were ordered to check for additional outcomes.

The flow chart and reason for exclusion are presented in Appendix 3.3.2.

3.3.3.3 *Clinical evidence*

Fourteen studies reported in 20 papers (for selective stenting with angioplasty versus primary stenting with angioplasty in intermittent claudication and critical limb ischemia) were included in this review [9,16,22,25,34,36,48,49,54,57,58,79,80,82,85,86,88,89,96,100]. Eleven of the studies reported in 16 papers were included in the NICE guideline [9,16,22,25,36,48,49,54,57,79,80,85,88,89,96,100]. Four additional papers were identified for inclusion in the review, three are new studies published since 2012 [34,82,86] and one study, Laird 2012 [58] provided further data for Laird 2010 [57]. Evidence of these studies is summarized in Appendix 4.2 and the clinical GRADE evidence profiles are represented in Appendix 5.4. Studies were only included if the paper described that bailout stents were used in the event of angioplasty failure. Outcomes were stratified according to diagnosis (intermittent claudication or critical limb ischemia) and lesion location (aortoiliac, femoropopliteal or infrageniculate). The majority of

studies included in the analysis of intermittent claudication and femoropopliteal arterial lesions included a mixed population of intermittent claudication and critical limb ischemia. In these studies the majority of patients had intermittent claudication. Only one study (reported in 2 papers) investigated patients with intermittent claudication alone [57,58]. Where this study is meta-analyzed with other studies the forest plots are subgrouped into 2 categories: intermittent claudication and critical limb ischemia combined; and intermittent claudication alone.

Outcomes for re-intervention were sometimes reported as target lesion or target vessel revascularisation. Where possible, these have been analyzed as one outcome.

All study evidence tables and forest plots are presented in respectively Appendix 4.2 and 6.2.

Conclusions

Intermittent claudication with aortoiliac lesions

- Based on the available low-to-very-low-level evidence, no conclusion can be drawn on the effect of primary stenting on re-intervention compared with selective stenting in patients with intermittent claudication due to aortoiliac disease.
- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of primary stenting on complications/adverse events at 30 days compared with selective stenting in patients with intermittent claudication due to aortoiliac disease. However, there is very-low-level evidence that primary stenting is associated with significantly less major complications/adverse events at two years compared with selective stenting. The difference is clinically important.
- Based on the available moderate-level evidence, no conclusion can be drawn on the effect of primary stenting on walking distance compared with selective stenting in patients with intermittent claudication due to aortoiliac disease.
- No evidence from RCTs is available on the effect of primary stenting on quality of life compared with selective stenting in patients with intermittent claudication due to aortoiliac disease.

Intermittent claudication with femoropopliteal arterial lesions

- There is low-to-moderate-level evidence that primary stenting is associated with less re-intervention/target lesion/vessel revascularisations compared with selective stenting at all time points in patients with intermittent claudication due to femoropopliteal disease. The difference is statistically significant at 6 months and 1 year only, but seems to be clinically important at all time points.
- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of primary stenting on perioperative and/or major complications compared with selective stenting in patients with intermittent claudication due to femoropopliteal disease.
- Based on the available moderate-level evidence, no conclusion can be drawn on the effect of primary stenting on quality of life compared with selective stenting in patients with intermittent claudication due to femoropopliteal disease.
- There is low-to-moderate-level evidence that primary stenting is associated with a longer walking distance compared with selective stenting in patients with intermittent claudication due to femoropopliteal disease. The reported effects are not always statistically significant nor clinically important.

Intermittent claudication with infrageniculate arterial lesions

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of primary stenting on target lesion/vessel revascularisations at 1 year compared with selective stenting in patients with intermittent claudication due to infrageniculate disease.
- No evidence from RCTs is available on the effect of primary stenting on walking distance, peri-procedural complications and quality of life compared with selective stenting in patients with intermittent claudication due to infrageniculate disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	**Intermittent claudication due to aortoiliac disease:** • Benefits: effect of primary stenting on re-intervention rate and walking distance (and mortality + pain) is unclear (but appears to have lower amputation rate at 5 years, although CI is very broad) • Harms: less major complications at 2 years with primary stenting **Intermittent claudication due to femoropopliteal disease:** • Benefits: lower re-intervention rate and longer walking distance with primary stenting, effect on quality of life (and mortality + amputation rate + pain) is unclear • Harms: unclear effect on complications • Lesions up to 20 cm long can be treated with one stent **Intermittent claudication due to infrageniculate disease:** • Benefits: all results favour primary stenting, but none are statistically significant; however, stenting is not generally recommended for infrageniculate disease • Harms: no evidence The clinical benefit of primary stenting was the determining factor to recommend this treatment option.
Quality of evidence	Overall very low to moderate.
Costs (resource allocation)	NCGC identified one cost-effectiveness analysis (**Bosch 1998**[8]). Bosch et al. developed a decision model to evaluate the cost-effectiveness of treating claudication due to iliac arterial stenosis with primary stent placement, selective stent placement or angioplasty without stent placement. This model assumed that 40% of patients undergoing angioplasty require selective stent placement and that compared to angioplasty alone, the relative risk of failure associated with stent placement is 0.61. The results of this model suggested that angioplasty with selective stent placement for both primary and secondary treatment is more cost-effective than both selective stent placement followed by conservative management and primary stent placement followed by selective stent placement. This conclusion was robust to a wide range of sensitivity analyses. Information about the reimbursement in Belgium can be found in appendix 9.
Patients values and preferences	None identified from the literature.

Recommendation	Strength of Recommendation	Level of Evidence
Consider primary stenting in patients with intermittent claudication due to aortoiliac disease undergoing revascularization with angioplasty.	Weak	Very low
Consider primary stenting in patients with intermittent claudication due to femoropopliteal disease undergoing revascularization with angioplasty, taking into account the following factors: (*) • **Length of the lesion;** • **Complexity of the lesion;** • **Calcification;** • **Location of the lesion.**	Weak	Low

(*) In the summary, this recommendation is merged with the recommendation on drug coated balloons.

3.3.4 Bare metal versus drug eluting stents

3.3.4.1 Introduction

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

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

3.3.4.2 Search strategy

A literature search was conducted for RCTs that compared the effectiveness of bare metal stents to drug eluting stents (one search for intermittent claudication and critical limb ischemia). The search was limited to English, Dutch and French languages in Medline and Embase. No time limit was placed on the literature search and there were no limitations on sample size. The search strategy is presented in Appendix 2.2.3.

The flow chart and reason for exclusion are presented in Appendix 3.3.3.

3.3.4.3 Clinical evidence

Five studies were included in this review (for intermittent claudication and critical limb ischemia in total). Evidence of these studies is summarized in Appendix 4.3 and the clinical GRADE evidence profiles are represented in Appendix 5.5. Three of the studies, Dake 2011 [22], Duda 2002, 2005 and 2006 [26-28] and Rastan 2011 [83] were included in the previous PAD guideline. A paper by Dake [21] and another by Rastan [81] included further follow-up data for the respective studies. Two new studies were found from up-date searches, Bosiers [10] and Geraghty [32], and were added to the review. Outcomes were stratified according to diagnosis (intermittent claudication or critical limb ischemia) and lesion location (femoropopliteal or infrageniculate). All studies included in the analysis of intermittent claudication and femoropopliteal arterial lesions included a mixed population of intermittent claudication and critical limb ischemia. The majority of patients had intermittent claudication. The study included in the analysis for intermittent claudication and infrageniculate arterial lesions included only patients with intermittent claudication.

All study evidence tables and forest plots are presented in Appendix 4.3 and 6.3, respectively.

Conclusions

Femoropopliteal arterial lesions with intermittent claudication or critical limb ischemia

- There is low-level evidence that drug eluting stents are associated with significantly less target vessel revascularisations (hazard ratio results) at 24 months compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease. However, based on very-low-to-moderate level evidence, no conclusions can be drawn for other timepoints.
- Based on very-low-level evidence, no conclusions can be drawn on the effect of drug eluting stents on peri-procedural complications or major adverse events compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.
- Based on low-to-moderate-level evidence, no conclusions can be drawn on the effect of drug eluting stents on quality of life compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.
- No evidence from RCTs is available on the effect of drug eluting stents on walking distance compared with bare metal stents in patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.

Infrageniculate arterial lesions with intermittent claudication

- There is low-level evidence that drug eluting stents are associated with less target vessel revascularisations at 1200 days compared with bare metal stents in patients with intermittent claudication due to infrageniculate disease. Although the effect is not statistically significant, it seems to be clinically important. Based on low-to-very-low-level evidence, no conclusions can be drawn on the effect on target lesion revascularisations or re-interventions at 1 year.
- No evidence from RCTs is available on the effect of drug eluting stents on walking distance, quality of life or peri-procedural complications compared with bare metal stents in patients with intermittent claudication due to infrageniculate disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	**Intermittent claudication due to aortoiliac disease:** • Benefits: no evidence from RCTs available; however, good results can be achieved with bare metal stents • Harms: no evidence from RCTs available **Intermittent claudication or critical limb ischemia due to femoropopliteal disease:** • Benefits: DES lead to less TVR at 24 months; effect on other outcomes unclear • Harms: unclear **Intermittent claudication due to infrageniculate disease:** • Benefits: DES lead to less TVR at 1200 days; however, stenting is not generally recommended for infrageniculate disease • Harms**:** no evidence
Quality of evidence	Overall very low to moderate.
Costs (resource allocation)	NCGC identified no published cost-effectiveness analyses. Information about the reimbursement in Belgium can be found in appendix 9. Drug eluting stents are not separately reimbursed for PAD. Given the rather

Factor	Comment
	small positive effects reported in the literature and the costs associated with DES, they cannot be recommended at present for this indication.
Patients values and preferences	None identified from the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Given the absence of comparative RCTs, use bare metal stents instead of DES in patients with intermittent claudication due to aortoiliac disease undergoing revascularization with angioplasty and stenting.	Strong	Very low
Use bare metal stents in patients with intermittent claudication due to femoropopliteal disease undergoing revascularization with angioplasty and stenting.	Weak	Very low

3.3.5 Drug coated balloons

3.3.5.1 Introduction

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

3.3.5.2 Search strategy

One search was conducted to cover two questions: selective stenting with angioplasty versus primary stenting with angioplasty; and drug coated balloon angioplasty versus any other endovascular procedure. The search was limited to English, Dutch, French and German languages in Medline and Embase. No time limit was placed on the literature search and there were no limitations on sample size. The search strategy is presented in Appendix 2.2.5.

The flow chart and reason for exclusion are presented in Appendix 3.3.5.

3.3.5.3 Clinical evidence

Four studies were included in this review.[30,62,95,104] Evidence reported in these studies is summarized in Appendix 4.5 and the clinical GRADE evidence profiles are represented in Appendix 5.10. All four studies compared balloons coated with paclitaxel to uncoated balloons. One of the studies had three arms comparing drug coated and uncoated balloons to balloons with paclitaxel in a contrast medium.[95] Two of the studies[95,104] investigated patients with femoropopliteal arterial lesions where the majority had intermittent claudication (Rutherford Classes 1 to 3), though a minority were classified as Rutherford class 4. One of the studies[30] investigated patients with femoropopliteal or below the knee arterial lesions in a population where around 60% of patients had intermittent claudication (Fontaine IIB) and 40% had critical limb ischemia (Fontaine III or IV). The results for intermittent claudication and critical limb ischemia in this study were not reported separately. The fourth study investigated diabetic patients with critical limb ischemia and below the knee arterial lesions.

During the course of the review 13 uncompleted trials were identified investigating the effectiveness of drug coated balloons. These were in various stages from recruitment having not begun to a trial registered as finished but results yet to be reported. A comprehensive search for all ongoing trials was not carried out so more trials may be in progress. The identified trials are listed here with the ClinicalTrials.gov Identifier: LEVANT Study (http://clinicaltrials.gov/ct2/show/study/NCT00930813); PACIFIER Study (http://clinicaltrials.gov/ct2/show/NCT01083030); PACUBA 1 Trial

(http://clinicaltrials.gov/ct2/show/NCT01247402); PHOTOPAC study (http://clinicaltrials.gov/ct2/show/NCT01298947); DEFINITIVE AR study (http://clinicaltrials.gov/ct2/show/results/NCT01366482); LEVANT 2 Study (http://clinicaltrials.gov/ct2/show/NCT01412541); INPACT SFA II (http://clinicaltrials.gov/ct2/show/NCT01566461); LEVANT Japan Clinical Trial (http://clinicaltrials.gov/ct2/show/NCT01816412); FREERIDE Study (http://clinicaltrials.gov/ct2/show/NCT01960647); trial sponsored by Acotec Scientific (http://clinicaltrials.gov/ct2/show/NCT01850056); trial sponsored by Covidien (http://clinicaltrials.gov/ct2/show/NCT01858428); trial sponsored by Lutonix (http://clinicaltrials.gov/ct2/show/NCT01870401).

All study evidence tables and forest plots are presented in Appendix 4.5 and 6.5, respectively.

Conclusions

Intermittent claudication or critical limb ischemia with femoropopliteal arterial lesions

- There is low level evidence that drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons at 6, 12 and 18 to 24 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- Based on the available very low level evidence, no conclusion can be drawn on the effect of serious adverse events at 2 weeks and 6 months of drug coated balloons when compared with uncoated balloons in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- There is low level evidence that drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons and the same drug administered in a contrast medium at 12 and 18 to 24 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- Based on the available very low level evidence, no conclusion can be drawn on the effect of serious adverse events at 2 weeks and 6 months of drug coated balloons when compared with uncoated balloons and the same drug administered in a contrast medium in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- No evidence from RCTs is available on the effect of drug coated balloons on peri-procedural complications and quality of life compared with uncoated balloons in patients with intermittent claudication and femoropopliteal arterial lesions.

Intermittent claudication or critical limb ischemia with femoropopliteal and/or infrageniculate arterial lesions

- There is very low level evidence that drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons at 6 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal and/or infrageniculate arterial lesions.
- There is very low level evidence that drug coated balloons are associated with less total major adverse events compared with uncoated balloons at 2 weeks and 6 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal and/or infrageniculate arterial lesions.
- No evidence from RCTs is available on the effect of drug coated balloons on quality of life compared with uncoated balloons in patients with intermittent claudication and femoropopliteal and/or infrageniculate arterial lesions.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Mainly evidence is available for femoropopliteal lesions (mixed populations with intermittent claudication and critical limb ischemia, but mainly patients with intermittent claudication). Drug coated balloons seem to have a consistent positive effect on re-interventions, and possibly also on adverse events. This was the determining factor to consider this treatment option.
Quality of evidence	Generally low to very low. Many studies ongoing.
Costs (resource allocation)	Not reimbursed in Belgium.
Patients values and preferences	None identified in the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Consider drug coated balloon angioplasty in patients with intermittent claudication due to femoropopliteal disease undergoing revascularization with angioplasty. (*)	Weak	Very low

(*) In the summary, this recommendation is merged with the recommendation on primary stenting.

3.3.6 Autologous vein versus prosthetic graft

3.3.6.1 Introduction

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

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

3.3.6.2 Search strategy

A literature search was conducted for randomized clinical trials (RCTs) that compared the effectiveness of autologous vein to prosthetic bypass. The search was limited to English, Dutch, French and German languages in Medline and Embase. No time limit was placed on the literature search and there were no limitations on sample size. The search strategy is presented in Appendix 2.2.4.

The flow chart and reason for exclusion are presented in Appendix 3.3.4.

3.3.6.3 *Clinical evidence*

Four studies were included in this review (Balotta 2003[5], Klinkert 2003[50], Solakovic 2008[91] and Tofigh 2007[99]). Evidence from these studies is summarized in appendix 4.4 and the clinical GRADE evidence profiles are represented in Appendix 5.6. Two of the studies, were included in the 2011 NICE PAD guideline (Balotta 2003 and Klinkert 2003[50]), however Balotta 2003[5] was originally in the review of people with critical limb ischemia but the trial population consisted of people with disabling claudication which was not judged to be critical limb ischemia and more in line with intermittent claudication. Two new studies were found from up-date searches, which were not included in the previous PAD guideline, and were added to the review (Solakovic 2008[91] and Tofigh 2007[99]). All studies included in the analysis of intermittent claudication and femoropopliteal arterial lesions included a mixed population of intermittent claudication and critical limb ischemia. The majority of patients had intermittent claudication.

All study evidence tables and forest plots are presented in appendix 4.4 and appendix 6.4, respectively.

Conclusions

Femoropopliteal disease

- Based on the available moderate-level evidence, meta-analysis of three studies showed a significant increase in re-interventions in the prosthetic bypass group compared to the autologous vein group at 5 years. The direction of the effect was also indicated by one study at 2 years, but there was uncertainty in this result because of the large confidence interval.
- Based on the available very low level evidence, no conclusions can be drawn on the effect of autologous vein versus prosthetic bypass on peri-operative complications at 30 days in patients with intermittent claudication due to femoropopliteal disease.
- No evidence from RCTs is available on the effect of autologous vein versus prosthetic bypass on walking distance or quality of life in patients with intermittent claudication.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Only studies on femoropopliteal disease are available (the question is irrelevant for aortoiliac and infrageniculate disease). There are significantly less re-interventions at 5 years with autologous vein bypass. Adverse events are not clearly different. This more positive benefit-risk balance was the determining factor to recommend autologous vein grafting.
Quality of evidence	Generally low to very low.
Costs (resource allocation)	NCGC identified no published cost-effectiveness analyses. Information about the reimbursement in Belgium can be found in appendix 9.
Patients values and preferences	None identified from the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Consider autologous vein grafting in patients with intermittent claudication due to femoropopliteal disease undergoing bypass surgery.	Weak	Low

3.4 Management of critical limb ischemia

3.4.1 Angioplasty versus bypass surgery

NCGC identified three RCTs reported in four articles [NICE 2012[73], Bradbury 2010[11], Holm 1991[43], Wilson 1989[109], Wolf 1993[112]]. No RCTs or observational studies comparing angioplasty to amputation were identified. Bradbury et al. included 452 patients with severe limb ischemia due to infrainguinal atherosclerosis [Bradbury 2010[11]]. Due to unreported blinding, this study had a high risk of bias for quality of life, but not for the other reported outcomes. Holm et al. included 102 patients with either severe limb ischemia (rest pain or ischemic ulcerations; N=61) or severe claudication who had not benefited from exercise training (N=41) [Holm 1991[43]]. Only occlusions or significant stenoses 6 cm or shorter in the common iliac, external iliac, femoral or popliteal artery were accepted for treatment. This study had a high risk of bias due to unclear allocation concealment and blinding. Finally, Wolf et al. included 256 patients with a significant stenosis (>80%) or an occlusion <10 cm in length of the iliac, superficial femoral, or popliteal arteries [Wilson 1989[109], Wolf 1993[112]]. Due to unreported blinding, this study had a high risk of bias for subjective outcomes. In this study, randomization was stratified by disease localization and severity of symptoms.

More details on these three RCTs can be found in the evidence tables (NICE 2012 appendices, chapter H.5.1, p. 319-331) and forest plots (NICE 2012 appendices, chapter J.4.4, p. 425-428). The GRADE tables can be found in appendix 5.7.

Conclusions

Aortoiliac disease

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on limb salvage at 4 years compared with bypass surgery in patients with critical limb ischemia due to aortoiliac disease.
- No evidence from RCTs is available on the effect of angioplasty on amputation-free survival, perioperative adverse events, re-intervention rate, quality of life, wound healing or pain compared with bypass surgery in patients with critical limb ischemia due to aortoiliac disease

Femoropopliteal disease

- Based on the available low to very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on amputation-free survival, amputation rate or limb salvage compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease.
- There is low-level evidence that angioplasty has no significant effect on quality of life compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease.
- There is moderate-level evidence that angioplasty is associated with less major adverse events at 30 days compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease. Although the difference is not statistically significant, it seems to be clinically important.
- There is high- and low-level evidence that angioplasty is associated with significantly less minor adverse events at 30 days and 1 year, respectively, compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease, and the difference is clinically important.
- There is high-level evidence that angioplasty is associated with a significantly higher re-intervention rate at 30 days compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease, and the difference is clinically important. However, based on very-low-level evidence, no conclusion can be drawn on the effect of angioplasty on the re-intervention rate at 1 year compared with bypass surgery.
- No evidence from RCTs is available on the effect of angioplasty on wound healing or pain compared with bypass surgery in patients with critical limb ischemia due to femoropopliteal disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	For aortoiliac disease, the evidence does not allow to balance the clinical benefits and harms. For femoropopliteal disease, adverse events were less frequently observed with angioplasty. However, the re-intervention rate at 30 days was found to be higher.
Quality of evidence	The evidence consisted of 3 studies. The quality was high to very low according to the GRADE criteria.
Costs (resource allocation)	NCGC identified three cost-effectiveness studies (**Bradbury 2010**[11], Hunink 1995[44]**, Brothers 1999**[12]). One study found that angioplasty is more cost effective than bypass surgery for the treatment of people with severe limb ischemia (**Bradbury 2010**[11]). A second study found that angioplasty followed by (autologous vein) bypass surgery is the most cost effective treatment option in people with critical limb ischemia due to stenoses and occlusions (Hunink 1995[44]). A third study found that primary bypass surgery may be more cost-effective than primary amputation in people with critical limb ischemia (**Brothers 1999**[12]). **Information about the reimbursement in Belgium can be found in appendix 9.**
Patients values and preferences	Zafar et al. used a standard gamble-type survey to explore patient preferences in regard to treatment for PAD (**Zafar 2011**). Twenty patients with suspected PAD were asked to indicate their threshold for risk of **mortality during a curative procedure for critical limb ischemia. Up to 1% risk of mortality was found to be the median risk acceptable to patients for undergoing a curative procedure.**

Recommendations	Strength of Recommendation	Level of Evidence
In addition to best medical treatment, offer angioplasty or bypass surgery for treating people with critical limb ischaemia who require revascularisation, taking into account factors including: • **Comorbidities;** • **Pattern of disease;** • **Availability of a vein;** • **Patient preference;** • **Costs.**	Weak	Very low

3.4.2 Angioplasty with selective versus primary stent placement

3.4.2.1 Introduction

See chapter 3.3.3.1.

3.4.2.2 Search strategy

See chapter 3.3.3.2.

3.4.2.3 Clinical evidence

Fourteen studies reported in 20 papers (on selective stenting with angioplasty versus primary stenting with angioplasty in intermittent claudication and critical limb ischemia) were included in this review [9,16,22,25,34,36,48,49,54,57,58,79,80,82,85,86,88,89,96,100]. Eleven of the studies reported in 16 papers were included in the NICE guideline [9,16,22,25,36,48,49,54,57,79,80,85,88,89,96,100]. Four additional papers were identified for inclusion in the review, three are new studies published since 2012 [34,82,86] and one study, Laird 2012 [58] provided further data for Laird 2010 [57]. Evidence of these studies is summarized in Appendix 4.2.2.1 and the clinical GRADE evidence profiles are represented in Appendix 5.8. Studies were only included if the paper described that bailout stents were used in

the event of angioplasty failure. Outcomes were stratified according to diagnosis (intermittent claudication or critical limb ischemia) and lesion location (aortoiliac, femoropopliteal or infrageniculate). The majority of studies included in the analysis of intermittent claudication and femoropopliteal arterial lesions included a mixed population of intermittent claudication and critical limb ischemia. In these studies the majority of patients had intermittent claudication. Only one study (reported in 2 papers) investigated patients with intermittent claudication alone [57,58]. Where this study is meta-analyzed with other studies the forest plots are subgrouped into 2 categories: intermittent claudication and critical limb ischemia combined; and intermittent claudication alone.

Outcomes for re-intervention were sometimes reported as target lesion or target vessel revascularisation. Where possible, these have been analyzed as one outcome.

All study evidence tables and forest plots are presented in respectively Appendix 4.2.2.1 and Appendix 6.2.

Conclusions

Infrageniculate disease

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of primary stenting on amputations or target lesion revascularisations compared with selective stenting in patients with critical limb ischemia due to infrageniculate disease.
- There is very-low-level evidence that selective stenting is associated with a significantly higher complete ulcer healing at 12 months compared with primary stenting in patients with critical limb ischemia due to infrageniculate disease. The effect is clinically important.
- No evidence from RCTs is available on the effect of primary stenting on quality of life, peri-procedural complications and pain compared with selective stenting in patients with critical limb ischemia due to infrageniculate disease.

Aoartiliac and femoropopliteal disease

- No evidence from RCTs is available on the effectiveness of primary stenting compared with selective stenting in patients with critical limb ischemia due to aortoiliac or femoropopliteal disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	In the absence of evidence for aortoiliac or femoropopliteal disease, recommendations analogous to those for intermittent claudication were formulated. **Critical limb ischemia due to infrageniculate disease**: • Benefits: better ulcer healing at 12 months with selective stenting; also lower amputation and re-intervention rate (and mortality) with selective stenting, but never statistically significant • Harms: no evidence • This more positive benefit-risk balance was the determining factor to recommend selective **stenting for infrageniculate disease.**
Quality of evidence	Overall very low.
Costs (resource allocation)	NCGC identified no published cost-effectiveness analyses. Information about the reimbursement in Belgium can be found in appendix 9.
Patients values and preferences	None identified from the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Consider primary stenting in patients with critical limb ischaemia due to aortoiliac disease undergoing revascularization with angioplasty.	Weak	Very low
Consider primary stenting in patients with critical limb ischaemia due to femoropopliteal disease undergoing revascularization with angioplasty, taking into account the following factors: (*) • **Length of the lesion;** • **Complexity of the lesion;** • **Calcification;** • **Location of the lesion**.	Weak	Very low
Consider balloon angioplasty with bail-out stenting in patients with critical limb ischaemia due to infrageniculate disease undergoing revascularization with angioplasty.	Weak	Very low

(*) In the summary, this recommendation is merged with the recommendation on drug coated balloons.

3.4.3 Bare metal versus drug eluting stents

3.4.3.1 Introduction

See chapter 3.3.4.1.

3.4.3.2 Search strategy

See chapter 3.3.4.2.

3.4.3.3 Clinical evidence

Five studies were included in this review (for intermittent claudication and critical limb ischemia in total). Evidence of these studies is summarized in Appendix 4.3 and the clinical GRADE evidence profiles are represented in Appendix 5.9. Three of the studies, Dake 2011 [22], Duda 2002, 2005 and 2006 [26-28] and Rastan 2011 [83] were included in the previous PAD guideline. A paper by Dake 2013 [21] and another by Rastan 2012 [81] included further follow-up data for the respective studies. Two new studies were found from up-date searches, Bosiers 2012 [10] and Geraghty 2013 [32], and were added to the review. Outcomes were stratified according to diagnosis (intermittent claudication or critical limb ischemia) and lesion location (femoropopliteal or infrageniculate). All studies included in the analysis of intermittent claudication and femoropopliteal arterial lesions included a mixed population of intermittent claudication and critical limb ischemia. The majority of patients had intermittent claudication. The study included in the analysis for intermittent claudication and infrageniculate arterial lesions included only patient with intermittent claudication.

All study evidence tables and forest plots are presented in Appendix 4.3 and Appendix 6.3 respectively.

Conclusions

Femoropopliteal arterial lesions with intermittent claudication or critical limb ischemia

- There is low-level evidence that drug eluting stents are associated with significantly less target vessel revascularisations (hazard ratio results) at 24 months compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease. However, based on very-low-to-moderate level evidence, no conclusions can be drawn for other timepoints.
- Based on very-low-level evidence, no conclusions can be drawn on the effect of drug eluting stents on peri-procedural complications or major adverse events compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.
- Based on low-to-moderate-level evidence, no conclusions can be drawn on the effect of drug eluting stents on quality of life compared with bare metal stents in a mixed population of patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.
- No evidence from RCTs is available on the effect of drug eluting stents on walking distance compared with bare metal stents in patients with intermittent claudication or critical limb ischemia due to femoropopliteal disease.

Infrageniculate arterial lesions with critical limb ischemia

- There is very-low-level evidence that drug eluting stents may lead to less amputations at 1200 days than bare metal stents in patients with critical limb ischemia due to infrageniculate disease. Although the effect is not statistically significant, it seems to be clinically important. Based on very-low-level evidence, no conclusions can be drawn on the effect on amputations at 1 year.
- Based on low-to-very-low-level evidence, no conclusion can be drawn on the effect of drug eluting stents on target lesion revascularisations compared with bare metal stents in patients with critical limb ischemia due to infrageniculate disease. Time-to–event data favour drug eluting stents, whereas the results are less clear for dichotomous data.
- Based on very low-level evidence, no conclusion can be drawn on the effect of drug eluting stents on wound healing compared with bare metal stents in patients with critical limb ischemia due to infrageniculate disease.
- No evidence from RCTs is available on the effect of drug eluting stents on pain, quality of life or peri-procedural complications compared with bare metal stents in patients with critical limb ischemia due to infrageniculate disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	**Intermittent claudication or critical limb ischemia due to femoropopliteal disease:** • Benefits: DES lead to less TVR at 24 months; effect on other outcomes unclear • Harms: unclear **Intermittent claudication due to infrageniculate disease:** • Benefits: DES lead to less TVR at 1200 days • Harms: no evidence
Quality of evidence	Overall very low to moderate.
Costs (resource allocation)	NCGC identified no published cost-effectiveness analyses. Information about the reimbursement in Belgium can be found in appendix 9. Drug eluting stents are

Factor	Comment
	not separately reimbursed for PAD. Given the rather small positive effects reported in the literature and the costs associated with DES, they cannot be recommended for femoropopliteal disease. For infrageniculate disease, DES can be considered because of the clinical benefits, but only for short focal lesions (that can be treated with one stent).
Patients values and preferences	None identified from the literature.

Recommendations	Strength of Recommendation	Level of Evidence
In the absence of evidence based on RCTs, do not use drug eluting stents in patients with critical limb ischemia due to aortoiliac disease undergoing revascularization with angioplasty and stenting.	Strong	Very low
Consider bare metal stents in patients with critical limb ischemia due to femoropopliteal disease undergoing revascularization with angioplasty and stenting.	Weak	Very low
Consider drug eluting stents in patients with critical limb ischemia and short, focal lesions due to infrageniculate disease undergoing revascularization with angioplasty and stenting.	Weak	Very low

3.4.4 Drug coated balloons

3.4.4.1 Introduction

See chapter 3.3.5.1.

3.4.4.2 Search strategy

See chapter 3.3.5.2.

3.4.4.3 Clinical evidence

See chapter 3.3.5.3.

Conclusions

Intermittent claudication or critical limb ischemia with femoropopliteal arterial lesions

- There is low level evidence that drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons at 6, 12 and 18 to 24 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- Based on the available very low level evidence, no conclusion can be drawn on the effect of serious adverse events at 2 weeks and 6 months of drug coated balloons when compared with uncoated balloons in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- There is low level evidence that drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons and the same drug administered in a contrast medium at 12 and 18 to 24 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.

- Based on the available very low level evidence, no conclusion can be drawn on the effect of serious adverse events at 2 weeks and 6 months of drug coated balloons when compared with uncoated balloons and the same drug administered in a contrast medium in patients with intermittent claudication or critical limb ischemia and femoropopliteal arterial lesions.
- No evidence from RCTs is available on the effect of drug coated balloons on peri-procedural complications and quality of life compared with uncoated balloons in patients with critical limb ischemia and femoropopliteal arterial lesions.

Intermittent claudication or critical limb ischemia with femoropopliteal and/or infrageniculate arterial lesions

- There is very low level evidence drug coated balloons are associated with less target lesion revascularisations compared with uncoated balloons at 6 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal and/or infrageniculate arterial lesions.
- There is very low level evidence drug coated balloons are associated with less total major adverse events compared with uncoated balloons at 2 weeks and 6 months in patients with intermittent claudication or critical limb ischemia and femoropopliteal and/or infrageniculate arterial lesions.
- No evidence from RCTs is available on the effect of drug coated balloons on quality of life compared with uncoated balloons in patients with critical limb ischemia and femoropopliteal and/or infrageniculate arterial lesions.

Critical limb ischemia in patients with diabetes and infrageniculate lesions

- Based on the available very low level evidence, no conclusion can be drawn on the effect on major amputations or minor amputations at 12 months of drug coated balloons when compared with uncoated balloons in diabetic patients with criticial limb ischemia and infrageniculate arterial lesions.
- There is very low level evidence drug coated balloons are associated with less major adverse events compared with uncoated balloons at 12 months in diabetic patients with criticial limb ischemia and infrageniculate arterial lesions.
- There is very low level evidence drug coated balloons are associated with more complete ulcer healing compared with uncoated balloons at 12 months in diabetic patients with criticial limb ischemia and infrageniculate arterial lesions.
- No evidence from RCTs is available on the effect of drug coated balloons on target lesion revascularisation, perioperative complications, quality of life or pain compared with uncoated balloons in patients with criticial limb ischemia and infrageniculate arterial lesions.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Mainly evidence is available for femoropopliteal lesions (mixed populations with intermittent claudication and critical limb ischemia, but mainly patients with intermittent claudication). Drug coated balloons seem to have a consistent positive effect on re-interventions, and possibly also on adverse events. In patients with diabetes and CLI due to infrageniculate disease, there is also a positive effect on ulcer healing. This was the determining factor to consider this treatment option.
Quality of evidence	Generally low to very low. Many studies ongoing.
Costs (resource allocation)	Not reimbursed in Belgium.
Patients values and preferences	None identified in the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Consider drug coated balloon angioplasty in patients with critical limb ischaemia due to femoropopliteal disease undergoing revascularization with angioplasty. (*)	Weak	Very low

(*) In the summary, this recommendation is merged with the recommendation on primary stenting.

3.4.5 Autologous vein compared with prosthetic graft

NCGC identified two RCTs (NICE 2012[73], Ballotta 2003[5], Tilanus 1985[97]). Ballotta et al. included 51 patients with disabling claudication after failure of a nonsurgical protocol for a long superficial femoral artery occlusion [Ballotta 2003[5]]. Treatment consisted of reversed saphenous vein graft in one limb and PTFE graft in the controlateral limb. All bilateral procedures were generally performed 6-8 weeks apart. Tilanus et al. included 49 patients with peripheral ischemia due to an occlusion of the superficial femoral artery (Tilanus 1985[97]). Both studies had a high risk of bias because no details were provided on blinding, intention-to-treat analysis and the number of drop-outs. Allocation concealment was also not clear in the study of Tilanus et al. More details on these studies can be found in the evidence tables (NICE 2012 appendices, chapter H.5.4, p. 345-348) and forest plots (NICE 2012 appendices, chapter J.4.4, p. 439). However, since the patients included by Ballotta et al. had disabling claudication, this study was more appropriate for the research question on autologous vein versus prosthetic bypass for patients with intermittent claudication. Therefore, the original GRADE tables were adapted. The GRADE tables can be found in appendix 5.11.

Conclusions

Femoropopliteal disease

- There is low-level evidence that autologous vein bypass significantly improves the amputation rate at 5 years compared with prosthetic bypass in patients with critical limb ischemia due to a superficial femoral artery occlusion, and the difference is clinically important.
- There is very-low-level evidence that autologous vein bypass improves the re-intervention rate at 5 years compared with prosthetic bypass in patients with critical limb ischemia due to a superficial femoral artery occlusion. Although the difference is not statistically significant, it seems to be clinically important.

- Based on the available very-low-level evidence, no conclusion can be drawn on the effect of autologous vein bypass on perioperative adverse events compared with prosthetic bypass in patients with critical limb ischemia due to a superficial femoral artery occlusion.
- No evidence from RCTs is available on the effect of autologous vein bypass on quality of life, wound healing or pain compared with prosthetic bypass in patients with critical limb ischemia due to a superficial femoral artery occlusion.

Infrageniculate disease

- No evidence from RCTs is available on the effectiveness of autologous vein bypass compared with prosthetic bypass in patients with critical limb ischemia due to infrageniculate disease.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Autologous vein bypass appears to be more effective than prosthetic bypass in terms of amputation rate and re-intervention rate at 5 years. However, the confidence in the effect estimates is low. No firm conclusion can be drawn regarding adverse events. Infrageniculate lesions should preferentially be treated with autologous vein graft. In case of high urgency, prosthetic bypass is preferred. Clearly, if no vein is available, or if the vein is of low quality, prosthetic bypass is also preferred. The more positive benefit-risk balance was the determining factor to recommend autologous vein grafting.
Quality of evidence	The evidence is limited to one small study with a high risk of bias and an overall low to very low level of evidence.
Costs (resource allocation)	NCGC did not identify a cost-effectiveness study. A cost-utility analysis by Hunick et al. [**Hunink 1995**[44]] subgrouped the results of their clinical analysis by graft material. Although the study was not designed to directly compare the cost-effectiveness of one type of material to another, according to the results of the model, bypass surgery using autologous vein grafts results in higher quality of life and lower cost than bypass surgery using synthetic grafts. Information about the reimbursement in Belgium can be found in appendix 9.
Patients values and preferences	None identified from the literature.

Recommendations	Strength of Recommendation	Level of Evidence
Consider autologous vein graft in patients with critical limb ischemia due to femoropopliteal or infrageniculate disease taking into account the following factors: • **Availability of a vein;** • **Quality of the vein;** • **Location of the lesion (above or below the knee);** • **Comorbidity;** • **Urgency of the intervention.**	Weak	Very low

4 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

4.1 Implementation

The implementation of this guideline will be conducted by the professional associations involved in this guideline (Belgian Society for Vascular Surgery, Belgian Society on Thrombosis and Haemostatis, Royal Belgian Society of Radiology). An implementation plan will need to be developed in collaboration with the RIZIV – INAMI. This implementation plan should also target general cardiologists, general practitioners and physiotherapists.

For some recommendations, implementation could be hampered by the absence of specific reimbursement criteria:

- Drug eluting stents and drug coated balloons are currently not reimbursed in Belgium for peripheral arterial disease;
- Supervised exercise programmes are currently not reimbursed in Belgium for peripheral arterial disease.

Some recommendations contain a list of factors to be taken into account when considering a specific treatment. Experts from the GDG and stakeholders group stressed that the exact definition of these factors (e.g. length of lesion, calcification, etc) continue to be a matter of debate.

Most recommendations are based on evidence of low to very low quality, and clinicians may be reluctant to implement such recommendations.

4.2 Monitoring the quality of care

This guideline could be considered as a starting point to develop quality improvement programs that target all caregivers concerned.

On the one hand it can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators. On the other hand the scientific material of this guideline is intended to be disseminated by scientific and professional organisations. They can transform this material into attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.

4.3 Guideline update

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

REFERENCES

1 Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e669S-e690S

2 Aly SAAF. Duplex ultrasound in the assessment of peripheral arterial disease. PhD thesis. London, 1998

3 Andreisek G, Pfammatter T, Goepfert K, Nanz D, Hervo P, Koppensteiner R et al. Peripheral arteries in diabetic patients: standard bolus-chase and time-resolved MR angiography. Radiology. 2007; 242(2):610-620

4 Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. Journal of Clinical Epidemiology. United States: Vanderbilt Evidence-based Practice Center, Vanderbilt University, #27166-719 Thompson Lane, Nashville, TN 37204-3195, USA. jeff.andrews@vanderbilt.edu. 2013; 66(7):726-735

5 Ballotta E, Renon L, Toffano M, Da Giau G. Prospective randomized study on bilateral above-knee femoropopliteal revascularization: Polytetrafluoroethylene graft versus reversed saphenous vein. Journal of Vascular Surgery. 2003; 38(5):1051-1055

6 Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. United States: Oregon Evidence-based Practice Center, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA. balshemh@ohsu.edu. 2011; 64(4):401-406

7 Balzer JO, Gundelsheimer V, Khan V, Mack MG, Peters J, Schmitz-Rixen T et al. Treatment planning in patients with PAOD:Comparison of CE-MRA employing a dedicated peripheral MRA coil and high dose single volume contrast material application with i.a. DSA. EuroIntervention. 2005; 1(3):296-304

8 Bosch JL, Tetteroo E, Mali WP, Hunink MG. Iliac arterial occlusive disease: cost-effectiveness analysis of stent placement versus

percutaneous transluminal angioplasty. Dutch Iliac Stent Trial Study Group. Radiology. 1998; 208(3):641-648

9 Bosch JL, Van Der Graaf Y, Hunink MG. Health-related quality of life after angioplasty and stent placement in patients with iliac artery occlusive disease: results of a randomized controlled clinical trial. The Dutch Iliac Stent Trial Study Group. Circulation. 1999; 99(24):3155-3160

10 Bosiers M, Scheinert D, Peeters P, Torsello G, Zeller T, Deloose K et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrageniculate arterial occlusive disease. Journal of Vascular Surgery. 2012; 55(2):390-398

11 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making. Journal of Vascular Surgery. 2010; 51(5 Suppl):52S-68S

12 Brothers TE, Rios GA, Robison JG, Elliott BM. Justification of intervention for limb-threatening ischemia: a surgical decision analysis. Cardiovascular Surgery. 1999; 7(1):62-69

13 Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. The Journal of Allergy and Clinical Immunology. United States: Department of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada. 2010; 126(3):466-476

14 Bueno A, Acin F, Canibano C, Fernandez-Casado JL, Castillo E. Diagnostic accuracy of contrast-enhanced magnetic resonance angiography and duplex ultrasound in patients with peripheral vascular disease. Vascular and Endovascular Surgery. 2010; 44(7):576-585

15 Burbelko M, Augsten M, Kalinowski MO, Heverhagen JT. Comparison of contrast-enhanced multi-station MR angiography and digital subtraction angiography of the lower extremity arterial disease. Journal of Magnetic Resonance Imaging. 2013; 37(6):1427-1435

16 Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K et al. PTA versus Palmaz stent placement in femoropopliteal artery obstructions: a multicenter prospective randomized study. Journal of Vascular and Interventional Radiology. 2001; 12(1):23-31

17 Collins R, Cranny G, Burch J, Guiar-Ibanez R, Craig D, Wright K et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. Health Technology Assessment. 2007; 11(20):iii-iiv

18 Creasy TS, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. European Journal of Vascular Surgery. 1990; 4(2):135-140

19 Cronberg CN, Sjoberg S, Albrechtsson U, Leander P, Lindh M, Norgren L et al. Peripheral arterial disease. Contrast-enhanced 3D MR angiography of the lower leg and foot compared with conventional angiography. Acta Radiologica. 2003; 44(1):59-66

20 Currie IC, Jones AJ, Wakeley CJ, Tennant WG, Wilson YG, Baird RN et al. Non-invasive aortoiliac assessment. European Journal of Vascular and Endovascular Surgery. 1995; 9(1):24-28

21 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the zilver PTX randomized and single-arm clinical studies. Journal of the American College of Cardiology. 2013; 61(24):2417-2427

22 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circulation: Cardiovascular Interventions. 2011; 4(5):495-504

23 Davies AH, Magee TR, Parry R, Hayward J, Murphy P, Cole SE et al. Duplex ultrasonography and pulse-generated run-off in selecting claudicants for femoropopliteal angioplasty. British Journal of Surgery. 1992; 79(9):894-896

24 de Vries M, Ouwendijk R, Flobbe F, Nelemans PJ, Kessels AGH, Schurink GWH et al. Peripheral artery disease: Clinical and cost

comparison between duplex ultrasonography and contrast-enhanced magnetic resonance angiography - A multicenter randomized trial. Nederlands Tijdschrift Voor Geneeskunde. 2007; 151(32):1789-1794

25 Dick P, Wallner H, Sabeti S, Loewe C, Mlekusch W, Lammer J et al. Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. Catheterization and Cardiovascular Interventions. 2009; 74(7):1090-1095

26 Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Oliva VL et al. Drug eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. Journal of Endovascular Therapy. 2006; 13(6):701-710

27 Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Tielbeek A et al. Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: the SIROCCO II trial. Journal of Vascular and Interventional Radiology. 2005; 16(3):331-338

28 Duda SH, Pusich B, Richter G, Landwehr P, Oliva VL, Tielbeek A et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. Circulation. 2002; 106(12):1505-1509

29 Eiberg JP, Gronvall Rasmussen JB, Hansen MA, Schroeder TV. Duplex ultrasound scanning of peripheral arterial disease of the lower limb. European Journal of Vascular and Endovascular Surgery. 2010; 40(4):507-512

30 Fanelli F, Cannavale A, Boatta E, Corona M, Lucatelli P, Wlderk A et al. Lower limb multilevel treatment with drug eluting balloons: 6-month results from the DEBELLUM randomized trial. Journal of Endovascular Therapy. 2012; 19(5):571-580

31 Fiocchi A, Schunemann HJ, Brozek J, Restani P, Beyer K, Troncone R et al. Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA): a summary report. The Journal of Allergy and Clinical Immunology. United States: Department of Child and Maternal Medicine, Melloni Hospital, Milan, Italy. allerg@tin.it. 2010; 126(6):1119-1128

32 Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM, VIBRANT I. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. Journal of Vascular Surgery. 2013; 58(2):386-395

33 Gjonnaess E, Morken B, Sandbaek G, Stranden E, Slagsvold CE, Jorgensen JJ et al. Gadolinium-enhanced magnetic resonance angiography, colour duplex and digital subtraction angiography of the lower limb arteries from the aorta to the tibio-peroneal trunk in patients with intermittent claudication. European Journal of Vascular and Endovascular Surgery. 2006; 31(1):53-58

34 Goode SD, Cleveland TJ, Gaines PA, STAG tc. Randomized clinical trial of stents versus angioplasty for the treatment of iliac artery occlusions (STAG trial). British Journal of Surgery. 2013; 100(9):1148-1153

35 Grassbaugh JA, Nelson PR, Rzucidlo EM, Schermerhorn ML, Fillinger MF, Powell RJ et al. Blinded comparison of preoperative duplex ultrasound scanning and contrast arteriography for planning revascularization at the level of the tibia. Journal of Vascular Surgery. 2003; 37(6):1186-1190

36 Greenberg D, Rosenfield K, Garcia LA, Berezin RH, Lavelle T, Fogleman S et al. In-hospital costs of self-expanding nitinol stent implantation versus balloon angioplasty in the femoropopliteal artery (The VascuCoil Trial). Journal of Vascular and Interventional Radiology. 2004; 15(10):1065-1069

37 Greenhalgh RM, Belch JJ, Brown LC, Gaines PA, Gao L, Reise JA et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. European Journal of Vascular and Endovascular Surgery. 2008; 36(6):680-688

38 Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. Journal of Clinical Epidemiology. United States:

Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario L8N 3Z5, Canada. guyatt@mcmaster.ca. 2013; 66(2):151-157

39 Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S (eds), Cochrane handbook for systematic reviews of interventions, Wiley, 2008: 187-241

40 Hirai T, Ohishi H, Kichikawa K, Yoshimura H, Uchida H. Ultrasonographic screening for arterial occlusive disease in the pelvis and lower extremities. Radiation Medicine. 1998; 16(6):411-416

41 Hoch JR, Tullis MJ, Kennell TW, McDermott J, Acher CW, Turnipseed WD. Use of magnetic resonance angiography for the preoperative evaluation of patients with infrainguinal arterial occlusive disease. Journal of Vascular Surgery. 1996; 23(5):792-801

42 Hofmann WJ, Walter J, Ugurluoglu A, Czerny M, Forstner R, Magometschnigg H. Preoperative high-frequency duplex scanning of potential pedal target vessels. Journal of Vascular Surgery. 2004; 39(1):169-175

43 Holm J, Arfvidsson B, Jivegard L, Lundgren F, Lundholm K, Schersten T et al. Chronic lower limb ischaemia. A prospective randomised controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). European Journal of Vascular Surgery. 1991; 5(5):517-522

44 Hunink MG, Wong JB, Donaldson MC, Meyerovitz MF, de Vries J, Harrington DP. Revascularization for femoropopliteal disease. A decision and cost-effectiveness analysis. JAMA. 1995; 274(2):165-171

45 Iezzi R, Santoro M, Dattesi R, la Torre MF, Guerra A, Di Stasi C et al. Diagnostic accuracy of CT angiography in the evaluation of stenosis in lower limbs: comparison between visual score and quantitative analysis using a semiautomated 3D software. Journal of Computer Assisted Tomography. 2013; 37(3):419-425

46 Karacagil S, Lofberg AM, Granbo A, Lorelius LE, Bergqvist D. Value of duplex scanning in evaluation of crural and foot arteries in limbs with severe lower limb ischaemia--a prospective comparison with angiography. European Journal of Vascular and Endovascular Surgery. 1996; 12(3):300-303

47 Kedora J, Hohmann S, Garrett W, Munschaur C, Theune B, Gable D. Randomized comparison of percutaneous Viabahn stent grafts vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral arterial occlusive disease. Journal of Vascular Surgery. 2007; 45(1):10-16

48 Klein WM, Van Der Graaf Y, Seegers J, Moll FL, Mali WP. Long-term cardiovascular morbidity, mortality, and reintervention after endovascular treatment in patients with iliac artery disease: The Dutch Iliac Stent Trial Study. Radiology. 2004; 232(2):491-498

49 Klein WM, Van Der Graaf Y, Seegers J, Spithoven JH, Buskens E, Van Baal JG et al. Dutch Iliac Stent Trial: Long-term results in patients randomized for primary or selective stent placement. Radiology. 2006; 238(2):734-744

50 Klinkert P, Schepers A, Burger DHC, van Bockel JH, Breslau PJ. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: five-year results of a randomized controlled trial. Journal of Vascular Surgery. 2003; 37(1):149-155

51 Koelemay MJ, Legemate DA, de Vos H, van Gurp JA, Reekers JA, Jacobs MJ. Can cruropedal colour duplex scanning and pulse generated run-off replace angiography in candidates for distal bypass surgery. European Journal of Vascular and Endovascular Surgery. 1998; 16(1):13-18

52 Koelemay MJ, Legemate DA, van Gurp J, Ponson AE, Reekers JA, Jacobs MJ. Colour duplex scanning and pulse-generated run-off for assessment of popliteal and cruropedal arteries before peripheral bypass surgery. British Journal of Surgery. 1997; 84(8):1115-1119

53 Kos S, Reisinger C, Aschwanden M, Bongartz GM, Jacob AL, Bilecen D. Pedal angiography in peripheral arterial occlusive disease: first-pass i.v. contrast-enhanced MR angiography with blood pool contrast medium versus intraarterial digital subtraction angiography. American Journal of Roentgenology. 2009; 192(3):775-784

54 Krankenberg H, Schluter M, Steinkamp HJ, Burgelin K, Scheinert D, Schulte KL et al. Nitinol stent implantation versus percutaneous

transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation. 2007; 116(3):285-292

55 Kreitner KF, Kunz RP, Herber S, Martenstein S, Dorweiler B, Dueber C. MR angiography of the pedal arteries with gadobenate dimeglumine, a contrast agent with increased relaxivity, and comparison with selective intraarterial DSA. Journal of Magnetic Resonance Imaging. 2008; 27(1):78-85

56 Kruidenier LM, Nicola SP, Rouwet EV, Peters RJ, Prins MH, Teijink JAW. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: A randomized clinical trial. Journal of Vascular and Interventional Radiology. 2011; 22(7):961-968

57 Laird JR. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: Twelve-month results from the RESILIENT randomized trial. Circulation: Cardiovascular Interventions. 2010; 3(3):267-276

58 Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. Journal of Endovascular Therapy. 2012; 19(1):1-9

59 Laissy JP, Debray MP, Menegazzo D, Rangheard AS, Benamer H, Charlier P et al. Prospective evaluation of peripheral arterial occlusive disease by 2D MR subtraction angiography. Journal of Magnetic Resonance Imaging. 1998; 8(5):1060-1065

60 Lapeyre M, Kobeiter H, Desgranges P, Rahmouni A, Becquemin JP, Luciani A. Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. AJR. 2005; American Journal of Roentgenology. 185(6):1641-1650

61 Legemate DA, Teeuwen C, Hoeneveld H, Ackerstaff RG, Eikelboom BC. Spectral analysis criteria in duplex scanning of aortoiliac and femoropopliteal arterial disease. Ultrasound in Medicine and Biology. 1991; 17(8):769-776

62 Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K et al. Drug eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): A randomized trial in diabetic patients with critical limb ischemia. Circulation. 2013; 128(6):615-621

63 Linke RJ, Davies RP, Giles AJ, Walsh JA, Thompson BW. Colour duplex ultrasound: a screening modality for femoropopliteal disease in patients with intermittent claudication. Australasian Radiology. 1994; 38(4):320-323

64 Lundgren F, Dahllof AG, Lundholm K, Schersten T, Volkmann R. Intermittent claudication. Surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. Annals of Surgery. 1989; 209(3):346-355

65 Lundin P, Svensson A, Henriksen E, Jonason T, Forssell C, Backbro B et al. Imaging of aortoiliac arterial disease. Duplex ultrasound and MR angiography versus digital subtraction angiography. Acta Radiologica. 2000; 41(2):125-132

66 Mazari FA, Gulati S, Rahman MN, Lee HL, Mehta TA, McCollum P et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. Annals of Vascular Surgery. 2010; 24(1):69-79

67 Mazari FAK, Khan JA, Carradice D, Samuel N, Abdul Rahman MNA, Gulati S et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. British Journal of Surgery. 2012; 99(1):39-48

68 McDermott VG, Meakem TJ, Carpenter JP, Baum RA, Stolpen AH, Holland GA et al. Magnetic resonance angiography of the distal lower extremity. Clinical Radiology. 1995; 50(11):741-746

69 McQuade K, Gable D, Hohman S, Pearl G, Theune B. Randomized comparison of ePTFE/nitinol self-expanding stent graft vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of Vascular Surgery. 2009; 49(1):109-115

70 McQuade K, Gable D, Pearl G, Theune B, Black S. Four-year randomized prospective comparison of percutaneous ePTFE/nitinol self-expanding stent graft versus prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of Vascular Surgery. 2010; 52(3):584-590

71 Meaney JF, Ridgway JP, Chakraverty S, Robertson I, Kessel D, Radjenovic A et al. Stepping-table gadolinium-enhanced digital subtraction MR angiography of the aorta and lower extremity arteries: preliminary experience. Radiology. 1999; 211(1):59-67

72 Napoli A, Anzidei M, Zaccagna F, Cavallo Marincola B, Zini C, Brachetti G et al. Peripheral arterial occlusive disease: diagnostic performance and effect on therapeutic management of 64-Section CT angiography. Radiology. 2011; 261(3):976-986

73 National Clinical Guideline Centre. Lower limb peripheral arterial disease: Diagnosis and management. NICE clinical guideline 147. London. National Clinical Guideline Centre, 2012. Available from: http://guidance.nice.org.uk/CG147

74 Nylaende M, Abdelnoor M, Stranden E, Morken B, Sandbaek G, Risum O et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)--the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. European Journal of Vascular and Endovascular Surgery. 2007; 33(1):3-12

75 Nylaende M, Kroese AJ, Morken B, Stranden E, Sandbaek G, Lindahl AK et al. Beneficial effects of 1-year optimal medical treatment with and without additional PTA on inflammatory markers of atherosclerosis in patients with PAD. Results from the Oslo Balloon Angioplasty versus Conservative Treatment (OBACT) study. Vascular Medicine. 2007; 12(4):275-283

76 Ouwendijk R, de Vries M, Pattynama PM, Van Sambeek MRHM, De Haan MW, Stijnen T et al. Imaging peripheral arterial disease: A randomized controlled trial comparing contrast-enhanced MR angiography and multi-detector row CT angiography. Radiology. 2005; 236(3):1094-1103

77 Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. European Journal of Vascular and Endovascular Surgery. 1996; 11(4):409-413

78 Puls R, Knollmann F, Werk M, Gebauer B, Gaffke G, Steinkamp H et al. 3D multislice CT angiography for the assessment of relevant stenoses in patients with peripheral artery occlusive disease. Rontgenpraxis. 2001; 54(4):141-147

79 Rand T, Basile A, Cejna M, Fleischmann D, Funovics M, Gschwendtner M et al. PTA versus carbofilm-coated stents in infrageniculate arteries: pilot study. Cardiovascular and Interventional Radiology. 2006; 29(1):29-38

80 Rand T, Lammer J, Rabbia C, Maynar M, Zander T, Jahnke T et al. Percutaneous transluminal angioplasty versus turbostatic carbon-coated stents in infrageniculate arteries: InPeria II trial. Radiology. 2011; 261(2):634-642

81 Rastan A, Brechtel K, Krankenberg H, Zahorsky R, Tepe G, Noory E et al. Sirolimus-eluting stents for treatment of infrageniculate arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. Journal of the American College of Cardiology. 2012; 60(7):587-591

82 Rastan A, Krankenberg H, Baumgartner I, Blessing E, Muller-Hulsbeck S, Pilger E et al. Stent placement versus balloon angioplasty for the treatment of obstructive lesions of the popliteal artery: a prospective, multicenter, randomized trial. Circulation. 2013; 127(25):2535-2541

83 Rastan A, Tepe G, Krankenberg H, Zahorsky R, Beschorner U, Noory E et al. Sirolimus-eluting stents vs. bare-metal stents for treatment of focal lesions in infrageniculate arteries: a double-blind, multi-centre, randomized clinical trial. European Heart Journal. 2011; 32(18):2274-2281

84 Rieker O, Duber C, Neufang A, Pitton M, Schweden F, Thelen M. CT angiography versus intraarterial digital subtraction angiography for assessment of aortoiliac occlusive disease. AJR American Journal of Roentgenology. 1997; 169(4):1133-1138

85 Sabeti S, Czerwenka-Wenkstetten A, Dick P, Schlager O, Amighi J, Mlekusch I et al. Quality of life after balloon angioplasty versus stent implantation in the superficial femoral artery: Findings from a

randomized controlled trial. Journal of Endovascular Therapy. 2007; 14(4):431-437

86 Scheinert D, Katsanos K, Zeller T, Koppensteiner R, Commeau P, Bosiers M et al. A prospective randomized multicenter comparison of balloon angioplasty and infrageniculate stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. Journal of the American College of Cardiology. 2012; 60(22):2290-2295

87 Schernthaner R, Stadler A, Lomoschitz F, Weber M, Fleischmann D, Lammer J et al. Multidetector CT angiography in the assessment of peripheral arterial occlusive disease: accuracy in detecting the severity, number, and length of stenoses. European Radiology. 2008; 18(4):665-671

88 Schillinger M, Sabeti S, Dick P, Amighi J, Mlekusch W, Schlager O et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. Circulation. 2007; 115(21):2745-2749

89 Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. New England Journal of Medicine. 2006; 354(18):1879-1888

90 Sensier Y, Hartshorne T, Thrush A, Handford H, Nydahl S, London NJ. The effect of adjacent segment disease on the accuracy of colour duplex scanning for the diagnosis of lower limb arterial disease. European Journal of Vascular and Endovascular Surgery. 1996; 12(2):238-242

91 Solakovic E, Totic D, Solakovic S. Femoro-popliteal bypass above knee with saphenous vein vs synthetic graft. Bosnian Journal of Basic Medical Sciences. 2008; 8(4):367-372

92 Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training--randomized controlled trial. Radiology. 2009; 250(2):586-595

93 Steffens JC, Link J, Muller-Hulsbeck S, Freund M, Brinkmann G, Heller M. Cardiac-gated two-dimensional phase-contrast MR angiography of lower extremity occlusive disease. AJR American Journal of Roentgenology. 1997; 169(3):749-754

94 Sueyoshi E, Sakamoto I, Matsuoka Y, Ogawa Y, Hayashi H, Hashmi R et al. Aortoiliac and lower extremity arteries: comparison of three-dimensional dynamic contrast-enhanced subtraction MR angiography and conventional angiography. Radiology. 1999; 210(3):683-688

95 Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwälder U, Beregi JP et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. New England Journal of Medicine. 2008; 358(7):689-699

96 Tetteroo E, Van Der Graaf Y, Bosch JL, Van Engelen AD, Hunink MG, Eikelboom BC et al. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. The Lancet. 1998; 351(9110):1153-1159

97 Tilanus HW, Obertop H, van Urk H. Saphenous vein or PTFE for femoropopliteal bypass. A prospective randomized trial. Annals of Surgery. 1985; 202(6):780-782

98 Timoninia EA, Sinitsin VE, Shiryaev AA, Levitsky IV, Akchurin RS, Ternovoy SK. The use of magentic resonance angiography for assessment of stenotic and occlusive lesions of arteries of lower extremities in patients with intermittent claudication. Kardiologiya. 1999; 39(1):14-19

99 Tofigh AM, Warnier De Wailly G, Rhissassi B. Comparing vein with collagen impregnated woven polyester prosthesis in above-knee femoropopliteal bypass grafting. International Journal of Surgery. 2007; 5(2):109-113

100 US Food and Drug Administration. IntraCoil® self-expanding peripheral stent: summary of safety and effectiveness data. Silver Spring, MD. US Food and Drug Administration, 2002. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf/P000033b.pdf

101 van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. European Journal of Vascular and Endovascular Surgery. 2004; 28(2):132-137

102 Vavrik J, Rohrmoser GM, Madani B, Ersek M, Tscholakoff D, Bucek RA. Comparison of MR angiography versus digital subtraction angiography as a basis for planning treatment of lower limb occlusive disease. Journal of Endovascular Therapy. 2004; 11(3):294-301

103 Wang CY, Zhao B, Wuang GB, Lhang ZF, Qiu XL, Wu LB. Three-dimensional contrast-enhanced magnetic resonance angiography at 3.0T scanner: significance in the classification of peripheral arterial occlusive disease. International Angiology. 2012; 31(2):129-133

104 Werk M, Langer S, Reinkensmeier B, Boettcher HF, Tepe G, Dietz U et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation. 2008; 118(13):1358-1365

105 Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology. England: Centre for Reviews and Dissemination, University of York, England, UK. pfw2@york.ac.uk. 2003; 3:25

106 Whyman MR, Fowkes FG, Kerracher EM, Gillespie IN, Lee A, Housley E et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. European Journal of Vascular and Endovascular Surgery. 1996; 12(2):167-172

107 Whyman MR, Fowkes FG, Kerracher EM, Gillespie IN, Lee A, Housley E et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. Journal of Vascular Surgery. 1997; 26(4):551-557

108 Whyman MR, Gillespie I, Ruckley CV, Allan PL, Fowkes FG. Screening patients with claudication from femoropopliteal disease before angioplasty using Doppler colour flow imaging. British Journal of Surgery. 1992; 79(9):907-909

109 Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. Report of a prospective randomized trial in a selected group of patients. Journal of Vascular Surgery. 1989; 9(1):1-9

110 Wilson YG, Davies AH, Currie IC, McGrath C, Morgan M, Baird RN et al. Angioscopically-assisted in situ saphenous vein bypass for infrainguinal revascularisation. European Journal of Vascular and Endovascular Surgery. 1996; 12(2):223-229

111 Winterer JT, Laubenberger J, Scheffler K, Neumann K, Bayraktarli YR, Allmann KH et al. Contrast-enhanced subtraction MR angiography in occlusive disease of the pelvic and lower limb arteries: results of a prospective intraindividual comparative study with digital subtraction angiography in 76 patients. Journal of Computer Assisted Tomography. 1999; 23(4):583-589

112 Wolf GL, Wilson SE, Cross AP, Deupree RH, Stason WB. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. Journal of Vascular and Interventional Radiology. 1993; 4(5):639-648

113 Yucel EK, Kaufman JA, Geller SC, Waltman AC. Atherosclerotic occlusive disease of the lower extremity: prospective evaluation with two-dimensional time-of-flight MR angiography. Radiology. 1993; 187(3):637-641