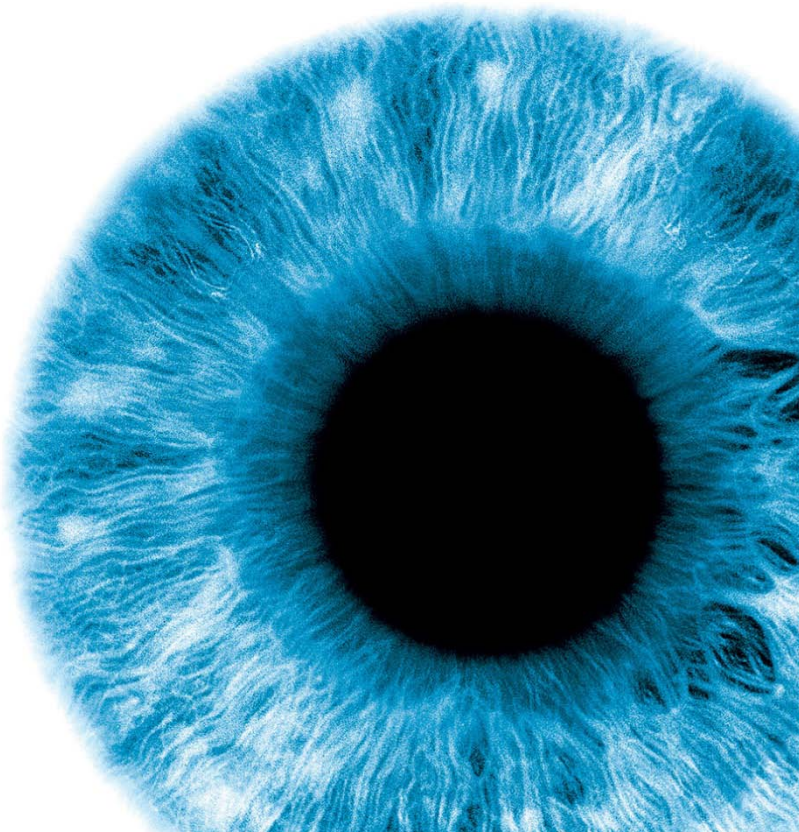
NICE National Institute for Health and Care Excellence

Lower limb peripheral arterial disease

Evidence Update November 2014

A summary of selected new evidence relevant to NICE clinical guideline 147 'Lower limb peripheral arterial disease: diagnosis and management' (2012)

Evidence Update 69



Contents

Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Lower limb peripheral arterial disease. NICE clinical guideline 147 (2012)**

A search was conducted for new evidence from 9 January 2012 to 26 June 2014. A total of 3128 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 37 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 8 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods. This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 147 (NICE CG147). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guidelines development methods guides for further information about updating clinical guidelines.

NICE Pathways

NICE Pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- Lower limb peripheral arterial disease. NICE Pathway

Quality standards

- Peripheral arterial disease. NICE quality standard 52

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG147. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG147.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Management of intermittent claudication		
Exercise programmes		
• Supervised exercise is associated with increases in maximum walking distance compared with home-based or other unsupervised exercise programmes.		✓
• Supervised exercise is associated with greater increases in walking distance in people with aorto-iliac disease than either stenting or optimum medical care.		✓
• Supervised exercise appears to be more cost effective than either angioplasty alone or supervised exercise plus angioplasty in people with intermittent claudication due to femoro-popliteal occlusion.		✓
Additional technologies to enhance angioplasty		
• Conventional and drug-eluting stents may reduce the likelihood of restenosis, and drug-coated balloons may reduce the need for revascularisation, after angioplasty. However, further research on outcomes such as symptoms, quality of life and re-intervention is needed.		✓
Ramipril[2] for intermittent claudication		
• Ramipril appears to be associated with increases in pain-free and maximum walking times in people with intermittent claudication, but further studies are needed to confirm this finding.		✓

[2] At the time of publication of this Evidence Update, ramipril did not have UK marketing authorisation for this indication and was not considered by NICE CG147.

1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from NICE CG147.

1.1 Information requirements

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 Secondary prevention of cardiovascular disease in people with peripheral arterial disease

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.3 Diagnosis

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.4 Imaging for revascularisation

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.5 Management of intermittent claudication

Exercise programmes

Supervised exercise versus home-based exercise

NICE CG147 recommends offering a supervised exercise programme to all people with intermittent claudication. The guideline does not recommend any home-based exercise programmes.

Al-Jundi et al. (2013) did a systematic review of 17 studies of home-based exercise programmes for people with intermittent claudication (n=1457). Home-based exercise was compared with supervised exercise in 5 studies, and was compared with usual care in 4 studies. One 3-arm study compared home-based exercise with both supervised exercise and with usual care. Seven studies had a single-group design.

Heterogeneity in trial design meant that a meta-analysis was not possible. Exercise regimens varied in the duration (range 10–60 minutes) and frequency (from 3 times a week to daily). Follow-up with a healthcare professional in 12 studies was either face-to-face or by telephone, but the frequency ranged from weekly to once every 2 months. Most studies assessed walking capacity by incremental treadmill test (11 studies), constant-load treadmill test (2 studies) or both (2 studies). No study reported adverse events.

For home-based exercise compared with supervised exercise, 5 studies (n=382) reported that supervised exercise improved walking capacity and quality of life to a greater extent. Two of these 5 studies reported that home-based exercise resulted in little change from baseline. In 1 additional study (n=119), improvements in walking capacity were higher in the supervised exercise group than in the home-based exercise group. Although these differences may have been clinically significant, they were not statistically significant.

In 5 studies of home-based exercise versus usual care (n=479), 3 studies concluded that home exercise improved walking capacity compared with usual care, the remaining 2 studies found little change within or between groups. The 7 single-group trials (n=596) were all rated as being low quality, and all reported improvements in walking capacity.

Overall 15 of the 17 included trials were rated as low quality. Limitations of individual studies included lack of description of randomisation, no blinding of outcome assessors, small sample size, recruitment to strict criteria in a single site, uncertainty about consistency of intervention delivery, no intention-to-treat analysis, and short-term follow-up.

Fokkenrood et al. (2013) conducted a Cochrane review of 14 studies of supervised versus unsupervised exercise therapy in adults with intermittent claudication (n=1002). The primary outcome was maximum treadmill walking time or distance. For inclusion, supervised exercise programmes needed to run for at least 6 weeks and have more than 50% of the time spent on walking or lower leg training, but frequency or intensity of exercise was not specified as inclusion criteria. Unsupervised exercise control groups could receive advice to walk or a structured home-based exercise programme, but studies with usual care as control were excluded.

In 11 studies peripheral arterial disease was determined by ankle–brachial pressure index, 2 studies used clinical history plus ultrasound, and 1 used clinical history only. Exclusion criteria in individual trials varied, but included ischaemic pain at rest, comorbidities affecting exercise ability, and recent vascular surgery or percutaneous transluminal angioplasty. Supervised exercise was most commonly done by walking on a treadmill until moderate or intense pain, 3 times a week with variable duration (20–70 minutes) for differing lengths of programme (6 weeks, 3 months or 12 months). In 9 trials the control group received walking advice, and 4 trials used home-based exercise as the control; 1 trial had 2 control arms so used both of these methods.

After 6 weeks of exercise therapy, maximum treadmill walking distance was increased with supervised exercise compared with control, with an effect size of 0.52 (95% confidence interval [CI] 0.24 to 0.81, p=0.00031; 5 studies, n=234). By 3 months the effect size was 0.69 (95% CI 0.51 to 0.86, p<0.00001; 10 studies, n=592), which equates to about 180 m extra walking distance in the supervised exercise group.

In subgroup analysis, the improvement in walking distance with supervised exercise compared with walking advice had an effect size of 0.76 (95% CI 0.56 to 0.96, p<0.00001; 5 studies, n=439). The improvement in walking distance with supervised exercise compared with home-based exercise had an effect size of 0.50 (95% CI 0.17 to 0.83, p=0.0032; 5 studies, n=153). The results for walking advice and home-based exercise did not differ significantly from each other.

All trials were judged to have a high risk of bias from lack of blinding of participants or investigators. However, the nature of the interventions made participant blinding impossible. Most trials had unclear risk of bias related to blinding of outcome assessors or allocation concealment. Most studies had low risk of bias related to random sequence generation, incomplete outcome data or selective reporting. No publication bias was detected. The results at 3 months had moderate heterogeneity, but a random-effects analysis produced similar results to the original analysis, suggesting that the heterogeneity was not important.

These studies suggest that supervised exercise is associated with increases in maximum walking distance compared with home-based or other unsupervised exercise programmes. This evidence is consistent with the recommendation in NICE CG147 to offer supervised exercise to all people with intermittent claudication.

Key references

Al-Jundi W, Madbak K, Beard JD et al. (2013) Systematic review of home-based exercise programmes for individuals with intermittent claudication. European Journal of Vascular & Endovascular Surgery 46: 690–706

Fokkenrood HJ, Bendermarcher BL, Jan Lauret G, et al. (2013) Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. Cochrane Database of Systematic Reviews issue 8: CD005263

Supervised exercise versus stent revascularisation or medical care

NICE CG147 recommends offering a supervised exercise programme to all people with intermittent claudication. Primary revascularisation with stents is recommended for people whose intermittent claudication is caused by complete aorto-iliac occlusion (rather than stenosis).

Murphy et al. (2012) reported a multicentre randomised controlled trial (RCT) conducted in the USA and Canada that compared optimum medical care with supervised exercise and with stent revascularisation in people with moderate-to-severe intermittent claudication. Participants had the ability to walk for 2–11 minutes only on a graded treadmill test and had a haemodynamically significant aorto-iliac arterial stenosis. Participants were excluded if they had critical limb ischaemia, comorbidities affecting walking ability, total aorto-iliac occlusion from the renal arteries to the inguinal ligaments, or results on repeated baseline treadmill testing that deviated by more than 25%. The primary outcome was change in peak walking time on a graded treadmill test at 6 months.

Randomisation was in a 2:1 ratio for both stenting (n=46) and supervised exercise (n=43) versus usual care (n=22). Optimum medical therapy was based on the 2005 guidelines from the American College of Cardiology/American Heart Association and included cilostazol 100 mg twice daily and advice on home exercise and diet. Supervised exercise was a 1-hour session 3 times a week for 26 weeks. Stenting was done with any self-expanding or balloon expandable stent approved by the US Food and Drug Administration (FDA).

Baseline characteristics were similar between groups apart from previous stroke, which applied to 19% of the supervised exercise group, 2% of the stenting group and 0% of the optimum medical care group ($p<0.007$). No participants crossed over to another treatment during the study period. In the exercise group, 29 (67%) of the 43 enrolled patients completed at least 70% of the 78 scheduled exercise sessions.

Supervised exercise resulted in a 4.6 minute increase in walking time compared with optimum medical care (95% CI 2.7 to 6.5 minutes, $p<0.001$). Stenting resulted in a 2.5 minute increase in walking time compared with optimum medical treatment (95% CI 0.6 to 4.4 minutes, $p=0.022$). Supervised exercise resulted in a 2.1 minute increase in walking time compared with stenting (95% CI 0.0 to 4.2, $p=0.04$). Serious adverse events occurred in 4 people in the stenting group and none in the supervised exercise group.

Limitations included that the 6-month results are fairly short term. Additionally, the study was stopped early because of slow recruitment, reducing the sample size. The participants may also have been a population that performed well on treadmill tests through selection of those whose tests were consistent at baseline and that the exercise programme could act as further training for the treadmill test. The authors noted that slow recruitment could have been caused by clinician bias towards a particular treatment or differing reimbursements across treatment types.

The evidence suggests that supervised exercise is associated with greater increases in walking distance than either stenting or optimum medical care in people with aorto-iliac disease. These results are consistent with the recommendation in NICE CG147 to offer supervised exercise to all people with intermittent claudication.

Key reference

Murphy TP, Cutlip DE, Regensteiner JG et al. (2012) Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation 125: 130–9

Cost effectiveness of supervised exercise, angioplasty, or both

NICE CG147 recommends offering a supervised exercise programme to all people with intermittent claudication. Angioplasty is an option for people with intermittent claudication only when:

- advice on the benefits of modifying risk factors has been reinforced **and**
- a supervised exercise programme has not led to a satisfactory improvement in symptoms **and**
- imaging has confirmed that angioplasty is suitable for the person.

Mazari et al. (2013) reported an economic analysis based on the results of a UK-based RCT (Mazari et al. 2012) of percutaneous angioplasty (n=60), supervised exercise (n=60), or both (n=58) in people with intermittent claudication due to femoro-popliteal occlusion. Cost–utility analysis was based on NICE's methods for technology appraisals. Quality-adjusted life years were derived from the Short-Form Health Survey 36 (SF-36) quality of life questionnaire, which was administered at every follow-up appointment.

Costs were calculated for outpatient clinics, follow-up appointments, investigations and medical treatments. Costs of clinics and procedures were taken from the NHS payment by results tariff 2009–10. Investigation costs were taken from the UK National Institute of Health Research's clinical research network investigation pricing index. Drug costs were taken from the British National Formulary. Costs per quality-adjusted life year were calculated for each individual treatment and the incremental cost-effectiveness ratio was calculated for comparisons between treatments. Cost effectiveness had a threshold of €25,000 to €35,000.

The RCT found that all treatments were associated with improvements in clinical and quality of life outcomes at 12 months; however, there were no significant differences between the 3 treatment groups. In the supervised exercise group, 6 people (10%) needed revascularisation; 9 people (15%) in the angioplasty group needed repeat revascularisation; no patients in the angioplasty plus exercise group needed repeat revascularisation. No difference in improvement in quality of life was noted between groups. Costs were significantly lower in for supervised exercise (€3866) compared with angioplasty (€7302) or both treatments (€6912, $p<0.001$).

With supervised exercise as the baseline treatment, supervised exercise plus angioplasty had an incremental cost-effectiveness ratio of €152,260 per quality-adjusted life year, higher than the threshold for cost effectiveness of €35,000. Angioplasty alone was rejected by simple discounting because it was more expensive and had a lower gain in quality-adjusted life years (0.62) than either supervised exercise alone (0.63) or supervised exercise plus angioplasty (0.65).

All results were robust in sensitivity analyses, including replacing missing data with best, worst, mean or baselines values. The authors noted that they did not study stenting after angioplasty, so the costs of this adjunctive treatment were not included in the cost-effectiveness analysis. Additionally, the study used standard angiography for diagnosis, but current practice now uses duplex ultrasound or magnetic resonance angiography. However, the sensitivity analysis included replacing diagnostic angiography with magnetic resonance angiography. Patients were followed up more often in the trial than would be clinically necessary, which affected the costs of all treatment options.

The study did not include participants with aorto-iliac disease, critical ischaemia, femoro-popliteal disease that was not suitable for angioplasty, or severe comorbidities affecting

exercise ability, so the results might not be generalisable to these populations. Additionally, the follow-up period was 12 months, so longer-term costs are not known. The analysis also did not include indirect costs, such as time off work for patients to have treatment.

This study suggests that supervised exercise appears to be more cost effective than either angioplasty alone or supervised exercise plus angioplasty in people with intermittent claudication due to femoro-popliteal occlusion. This finding is consistent with the recommendation in NICE CG147 to offer supervised exercise to all people with intermittent claudication.

Additional information about the study by Mazari et al. (2013) is also available from an independent critical appraisal report produced for the Centre for Reviews and Dissemination's NHS Economic Evaluation Database.

Key references

Mazari FA, Khan JA, Carradice D et al. (2013) Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. British Journal of Surgery 100: 1172–79

Supporting reference

Mazari FA, Khan JA, Carradice D et al. (2012) Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. British Journal of Surgery 99: 39–48

Additional technologies to enhance angioplasty

NICE CG147 recommends offering angioplasty to people with intermittent claudication only when:

- advice on the benefits of modifying risk factors has been reinforced **and**
- a supervised exercise programme has not led to a satisfactory improvement in symptoms **and**
- imaging has confirmed that angioplasty is suitable for the person.

Primary stent revascularisation may be considered for treating people with intermittent claudication caused by complete aorto-iliac occlusion (rather than stenosis). Bare metal stents should be used.

Simpson et al. (2013) reported a systematic review and meta-analysis of technologies that may enhance the efficacy of percutaneous transluminal balloon angioplasty for people with intermittent claudication or critical limb ischaemia. Outcomes of interest were restenosis and re-intervention. The systematic review included 40 RCTs, of which 16 were suitable for meta-analysis. Most trials were of angioplasty of the femoral or popliteal artery and generally included patients who had intermittent claudication, with only a few studies including people with critical limb ischaemia.

Interventions assessed were absorbable stents, self-expanding stents, balloon-expandable stents, drug-eluting stents, stent-grafts, atherectomy, cutting balloon, cryoplasty, brachytherapy, external beam radiotherapy, drug-coated balloon angioplasty, and laser angioplasty. Control comparators included conventional percutaneous angioplasty (with or without bail-out stenting); bare metal stents were comparators for drug-eluting stents, and sham radiation was included as a possible comparator for radiation interventions. Studies were excluded if they assessed drug treatments, multiple surgical procedures, methods no longer available, or intervention above the inguinal ligament.

At 12 months, self-expanding stents were associated with lower restenosis rates than conventional angioplasty (risk ratio [RR]=0.68, 95% CI 0.53 to 0.87, p=0.003; 3 studies, n=376). Brachytherapy was also associated with lower restenosis rates than conventional angioplasty (RR=0.63, 95% CI 0.48 to 0.83, p=0.001; 3 studies, n=331). However, balloon-

expanding stents were not significantly different from conventional angioplasty (RR=1.19, 95% CI 0.85 to 1.68, p=0.31; 5 studies, n=297). Revascularisation at 24 months was significantly lower with drug-coated than with conventional balloon angioplasty (RR=0.27, 95%CI 0.16 to 0.47, p<0.001; 2 studies, n=189).

Studies of drug-eluting stents were not suitable for meta-analysis, and none of the 3 identified showed a significant effect on revascularisation. Drug eluting stents had significantly lower rate of restenosis at 6 months compared with conventional angioplasty (17% versus 34% respectively, p<0.001; 1 trial, 373 lesions treated) and bare metal stents (14% versus 31%, p=0.02; 1 trial, n=131), but not in 1 trial (n=86) versus self-expanding stents (5% versus 5%, p=1.0).

This systematic review and meta-analysis was produced as part of a Health Technology Assessment commissioned by the National Institute of Health Research, published in full by **Simpson et al. (2014)**. The full assessment looked in depth at additional outcomes such as complications, adverse events, quality of life and walking distance.

All studies reported the outcome of complications due to the procedure, which did not differ between groups. Few trials reported on quality of life or walking outcomes. Self-expanding stents showed no significant difference from conventional angioplasty for quality of life or walking capacity at 24 months. Walking capacity similarly did not appear to be improved with cutting balloons, balloon-expandable stents or brachytherapy.

Meta-analysis was not possible for some outcomes in the systematic review and Health Technology Assessment because of heterogeneity; for example, populations, interventions and length of follow-up differed across studies. Half of the studies (20/40) had blinding of assessors for at least 1 outcome, but allocation concealment was considered to be adequate in only 11 of the 40 trials. The definitions of blood vessel patency or restenosis varied between trials. Even if consistent definitions were used, the mechanical effects of the treatments might not have been directly comparable, and the degree of restenosis may not directly affect clinical outcomes. Furthermore, specific interventions may be more or less suitable for a patient depending on the site or features of the stenosis.

Conventional and drug-eluting stents may reduce the likelihood of restenosis, and drug-coated balloons may reduce the need for revascularisation, after conventional angioplasty, but further research describing the impact on symptoms, quality of life and re-intervention is needed. Therefore no impact on NICE CG147 is expected.

Key references

Simpson EL, Michaels JA, Thomas SM et al. (2013) Systematic review and meta-analysis of additional technologies to enhance angioplasty for infrainguinal peripheral arterial occlusive disease. British Journal of Surgery 100: 1128–37

Simpson EL, Kearns B, Stevenson MD et al. (2014) Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. Health Technology Assessment 18 (10)

Ramipril[3] for intermittent claudication

NICE CG147 does not include recommendations on ramipril for intermittent claudication.

Ahimastos et al. (2013) reported results of a 24-week double-blind RCT of ramipril 10 mg/day versus placebo in people with peripheral arterial disease and claudication (n=212). The primary outcomes were pain-free walking time and maximum walking time, assessed by a standard treadmill test set at 3.2 km/hour at a gradient of 12°.

[3] At the time of publication of this Evidence Update, ramipril did not have UK marketing authorisation for this indication and was not considered for NICE CG147.

Inclusion criteria were ankle–brachial pressure index of less than 0.90 at rest in at least 1 leg, intermittent claudication that had been stable for at least 6 months, and stable drug regimen for at least 6 months. Exclusion criteria were resting brachial blood pressure of 160/100 mmHg or more, renal failure, renal artery stenosis, previous coronary or lower limb revascularisation, myocardial infarction in the previous 3 months, critical limb ischaemia or any other medical condition that affected walking ability. Additionally participants must not have used angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers, potassium-sparing diuretics or potassium supplements in the previous 6 months.

Participants were recruited from 3 hospitals in Australia. All patients received usual care according to their risk profile and symptoms, including lipid lowering therapy or antiplatelet treatments as needed. Participants were supervised by their doctors throughout the trial and received lifestyle advice before starting the trial. Adherence to treatment was assessed by monthly pill counts.

Participants had a mean age of 65.5 years, and no significant differences in baseline characteristics were detected between groups. At baseline about half (55%) were taking antiplatelet drugs and about half (55%) were taking lipid-lowering treatments. Resting ankle–brachial pressure index was 0.56.

Ramipril (n=106), compared with placebo (n=106), was associated with a significantly greater increase in pain-free walking time (75 seconds, 95% CI 60 to 89 seconds, p<0.001) and in maximum walking time (255 seconds, 95% CI 215 to 295 seconds, p<0.001). Ramipril, compared with placebo, was associated with a small increase in ankle–brachial pressure index at rest (0.1, 95% CI 0.08 to 0.13, p<0.001) and after exercise (0.11, 95% CI 0.08 to 0.14, p<0.001).

Overall, 12 patients reported dizziness after starting treatment (9 in the ramipril group and 3 in the placebo group). Persistent cough led to withdrawal of 7 people in the ramipril group. In the placebo group, 1 patient reported chest pain and 1 had pronounced ST-segment depression after the baseline treadmill test, resulting in a new diagnosis of unstable coronary artery disease; both of these patients withdrew from the trial. A further 3 participants in the placebo group were lost to follow-up. Missing data for the 12 participants lost to follow-up were accounted for using multiple imputation.

Limitations of the study included the short follow-up period of 6 months, so conclusions cannot be reached about the effects of ramipril over longer periods. The selection criteria for participants ensured a population that could be ethically randomised to placebo, but resulted in a population with lower blood pressure and less comorbidity than may be seen in the general population with lower limb peripheral arterial disease.

In a further report from this trial, **Ahimastos et al. (2014)** assessed biomarkers in participants from 1 site involved in the trial (n=165). At the end of the 24-week study period, biomarkers of angiogenesis were higher in the ramipril group than in the placebo group, including vascular endothelial growth factor A (38%, 95% CI 34 to 42%, p<0.001) and fibroblast growth factor 2 (64%, 95% CI 44 to 85%, p<0.001). Markers of thrombosis were lower in the ramipril group compared with the placebo group, including D-dimer (−24%, 95% CI −35 to −9%, p<0.001) and thrombin-antithrombin III (−16%, 95% CI −19 to −13%, p<0.001). The authors noted that these potential markers for the improvements in functional capacity could be targets for future studies. However, the relationships between changes in circulatory and functional parameters are associative, and cause and effect cannot be directly established.

This evidence suggests that ramipril may be associated with increases in pain-free and maximum walking times in people with intermittent claudication. Further studies are needed to confirm this finding, to establish safety in this population and to investigate whether this is a class effect of ACE inhibitors, so no impact on NICE CG147 is expected.

Key references

Ahimastos AA, Latouche C, Natoli AK et al. (2014) Potential vascular mechanisms of ramipril induced increases in walking ability in patients with intermittent claudication. Circulation Research 114: 1144–55

Ahimastos AA, Walker PJ, Askew C et al. (2013) Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. JAMA 309: 453–60

1.6 Management of critical limb ischaemia

No new key evidence for this section was selected for inclusion in this Evidence Update.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Management of intermittent claudication

- Home-based exercise programmes for intermittent claudication
- Additional technologies to enhance angioplasty for infrainguinal peripheral arterial occlusive disease

Further evidence uncertainties for lower limb peripheral arterial disease can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Lower limb peripheral arterial disease. NICE clinical guideline 147 (2012)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 9 January 2012 (the end of the search period of NICE clinical guideline 147) to 26 June 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO

The Evidence Update search strategy replicates the strategy used by NICE CG147 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews, diagnostic and observational studies.

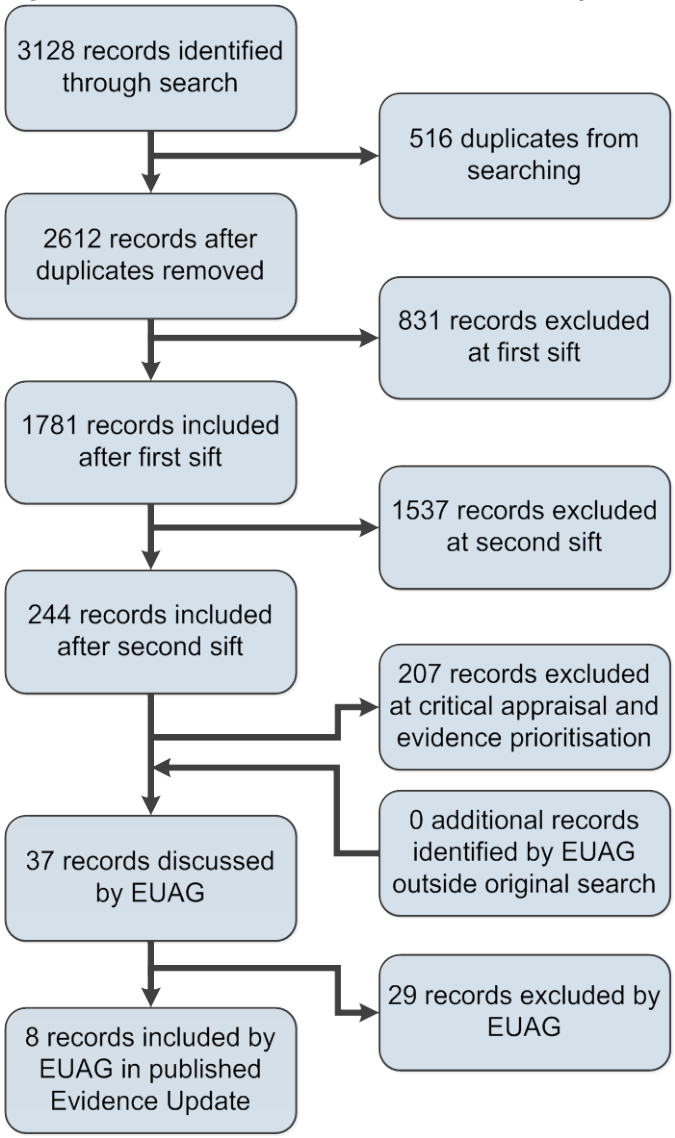
Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Peripheral Arterial Disease/ or Peripheral Vascular Diseases/
2	Intermittent Claudication/
3	(Pvd or pvod or paod or poad).ti,ab,hw.
4	(Claudication or claudicant*).ti,ab,hw.
5	Peripheral vascular disease.ti,ab,hw.
6	Peripheral arter* disease.ti,ab,hw.
7	Peripheral arter* occlusive disease.ti,ab,hw.
8	((severe or critical) adj limb isch?emia).ti,ab.
9	Fontaine stage.ti,ab.
10	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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