Appendix A: Summary of new evidence from surveillance

Information requirements for people with peripheral arterial disease

CG147 – 01 What are people's experiences of living with PAD and people's preferences for information requirements?

Recommendations derived from this question

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

- the causes of their symptoms and the severity of their disease
- the risks of limb loss and/or cardiovascular events associated with peripheral arterial
- disease the key modifiable risk factors, such as smoking, control of diabetes, hyperlipidaemia, diet, body weight and exercise (see also recommendation 1.2.1)
- how to manage pain
- all relevant treatment options, including the risks and benefits of each
- how they can access support for dealing with depression and anxiety.

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

1.1.2 NICE has produced guidance on the components of good patient experience in adult NHS services. Follow the recommendations in patient experience in adult NHS services (NICE guideline CG138).

1.2.1 Offer all people with peripheral arterial disease information, advice, support and treatment regarding the secondary prevention of cardiovascular disease, in line with published NICE guidance (see 'Related NICE guidance'; section 2.6) on:

- smoking cessation
- diet, weight management and exercise
- lipid modification and statin therapy
- the prevention, diagnosis and management of diabetes
- the prevention, diagnosis and management of high blood pressure
- antiplatelet therapy.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Diagnosis of peripheral arterial disease

CG147 – 02 In people with suspected PAD, is ABPI as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining the diagnosis and severity of PAD?

Recommendations derived from this question

1.3.1 Assess people for the presence of peripheral arterial disease if they:

- have symptoms suggestive of peripheral arterial disease or
- have diabetes, non-healing wounds on the legs or feet or unexplained leg pain or
- are being considered for interventions to the leg or foot or
- need to use compression hosiery.

1.3.2 Assess people with suspected peripheral arterial disease by:

- asking about the presence and severity of possible symptoms of intermittent claudication and critical limb ischaemia
- examining the legs and feet for evidence of critical limb ischaemia, for example ulceration
- examining the femoral, popliteal and foot pulses
- measuring the ankle brachial pressure index.

1.3.3 Measure the ankle brachial pressure index in the following way:

- The person should be resting and supine if possible.
- Record systolic blood pressure with an appropriately sized cuff in both arms and in the posterior tibial, dorsalis pedis and, where possible, peroneal arteries.
- Take measurements manually using a Doppler probe of suitable frequency in preference to an automated system.
- Document the nature of the Doppler ultrasound signals in the foot arteries.
- Calculate the index in each leg by dividing the highest ankle pressure by the highest arm pressure.

Surveillance decision

This review question should be updated for people with diabetes.

Measuring the ankle brachial pressure index

2-year surveillance summary
No relevant evidence was identified.

4-year surveillance summary
A systematic review [1] was identified that evaluated the performance of index non-invasive diagnostic tests (including ankle brachial index, toe brachial index, pulse oximetry and wave form analysis) against reference standard imaging techniques (magnetic resonance angiography, computed tomography angiography, digital subtraction angiography and colour duplex ultrasound) for the detection of PAD among patients with diabetes. Ten studies were included in the systematic review. Two studies reported exclusively on patients with symptomatic feet, two on patients with asymptomatic (intact) feet only, and the remaining six on patients both with and without foot ulceration. Ankle brachial index (ABI) was the most widely assessed index test. The authors concluded that the reported performance of ABI for the diagnosis of PAD in patients with diabetes mellitus is varied and is adversely affected by the presence of neuropathy. They also concluded that limited evidence from their study suggests that toe brachial index, pulse oximetry and wave form analysis may be superior to ABI for

diagnosing PAD in patients with neuropathy with and without foot ulcers.

Topic expert feedback
One topic expert stated that the value of ABPI might differ in those with diabetes. The issue also raised by an external expert indicating that most major diabetic foot assessment guidelines recommend pulse palpation rather than ABI and if NICE intended to make ABI a mandated part of routine diabetic foot examination it should be assured that this is based on good evidence and is likely to be cost effective.

Impact statement
New evidence on diagnosis of PAD among people with diabetes suggests that toe brachial index, pulse oximetry and wave form analysis may be superior to ankle brachial index for diagnosing PAD in patients with diabetes who have neuropathy with and without foot ulcers. NICE guidance on diabetic foot problems NG19 refers to CG147 for the diagnosis of peripheral vascular disease in people with diabetes.

CG147 recommends the ankle brachial pressure index measurement as an assessment tool in people with suspected PAD. Therefore, new evidence may have an impact on current CG147 recommendations on peoples with diabetes.

New evidence identified that may change current recommendations.

Imaging for revascularisation in peripheral arterial disease

CG147 – 03 What is most clinical and cost-effective method of assessment of PAD (intermittent claudication and critical limb ischemia)?

Recommendations derived from this question

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

1.4.2 Offer contrast-enhanced magnetic resonance angiography to people with peripheral arterial disease who need further imaging (after duplex ultrasound) before considering revascularisation.

1.4.3 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.

Surveillance decision

This review question should not be updated.

Imaging for revascularisation in peripheral arterial disease

2-year surveillance summary
No relevant evidence was identified.

4-year surveillance summary
A randomised controlled trial (RCT)[2] was identified that investigated the noninferiority in terms of diagnostic performance of gadoterate meglumine-enhanced versus gadobutrol-enhanced 3-T MR angiography (MRA) using digital subtraction angiography as the reference standard in patients with peripheral arterial occlusive disease. A total of 189 patients were enrolled. The diagnostic accuracy was evaluated and compared using a noninferiority analysis. Sensitivity in detecting significant stenosis (> 50%) was 72.3% for gadoterate meglumine versus 70.6% for gadobutrol meglumine, and specificity was 92.6% for gadoterate versus 92.3% for gadobutrol. Signal-to-noise ratio, and contrast-to-noise did not differ statistically significantly between the two groups.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement
Gadoterate meglumine was found to be not inferior to gadobutrol in terms of diagnostic performance in patients with peripheral arterial occlusive disease undergoing 3-T contrast-enhanced MRA.
CG147 recommends contrast-enhanced magnetic resonance angiography to people with PAD who need further imaging (after duplex ultrasound) before considering revascularisation.

Different types of contrasts were not reviewed in CG147. Therefore the evidence on different types of contrasts has no impact on current recommendations.

New evidence is unlikely to change guideline recommendations.

Management of intermittent claudication

CG147 – 04 What is the clinical and cost effectiveness of supervised exercise therapy compared to unsupervised exercise therapy for the treatment of PAD in adults with intermittent claudication?

Recommendations derived from this question

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

1.5.2 Consider providing a supervised exercise programme for people with intermittent claudication which involves:

- 2 hours of supervised exercise a week for a 3-month period
- encouraging people to exercise to the point of maximal pain.

Surveillance decision

This review question should not be updated.

Supervised exercise compared to unsupervised exercise

2-year surveillance summary
A systematic review[3] of 17 studies of home-based exercise programmes for people with intermittent claudication (n=1457) was identified. Home-based exercise was compared with supervised exercise (SE) in 5 studies, and was compared with usual care in 4 studies. One 3-arm study compared home-based exercise with both SE and with usual care. For home-based exercise compared with SE, 5 studies (n=382) reported that SE 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 SE group than in the home-based exercise group. 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.

A Cochrane review[4] of 14 studies of supervised versus unsupervised exercise therapy in adults with intermittent claudication (n=1002) was identified. 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 SE compared with control, with an effect size of 0.52. By 3 months the effect size was 0.69, which equates to about 180 m extra walking distance in the SE group. In subgroup analysis, the improvement in walking distance with SE compared with walking advice had an effect size of 0.76. The improvement in walking distance with SE compared with home-based exercise had an effect size of 0.50. The results for walking advice and home-based exercise did not differ significantly from each other.

4-year surveillance summary

A systematic review[5] of RCTs was identified that examined whether an exercise programme in people with intermittent claudication was effective in improving symptoms and increasing walking treadmill distances and walking times. Thirty (30) trials comprising of 1816 participants identified. Twenty trials compared exercise with usual care or placebo, the remainder of the trials compared exercise to medication (pentoxifylline, iloprost, antiplatelet agents and vitamin E) or pneumatic calf compression. Overall, when taking the first time point reported in each of the studies, exercise significantly improved maximal walking time when compared with usual care or placebo: with an overall improvement in walking ability of approximately 50% to 200%. Walking distances were also significantly improved. Improvements were seen for up to two years. Exercise did not improve the ABI. At three months, physical function, vitality and role physical all significantly improved with exercise; however this measure was only reported in two trials. At six months five trials reported outcomes of a significantly improved physical summary score and mental summary score secondary to exercise. Only two trials reported improvements in physical function and general health.

Two systematic reviews of RCTs[6,7] were identified that evaluated the various methods and outcomes of community walking programmes for PAD. One systematic review [6] investigated the effect of structured home-based exercise (SHE) programmes on maximal walking time (MWT), pain-free walking time, and self-reported walking ability in patients with PAD. Five (5) RCTs covering 547 patients included. SHE programmes significantly improved maximal walking time by mean difference of 66.78 seconds. Following the sensitivity analysis for heterogeneity, SHE programmes still significantly improved maximal walking time by mean difference of 91.21 seconds. SHE programmes improved significantly both pain-free walking time, and self-reported walking ability scores.

A systematic review[7] that evaluated the various exercise methods was identified. Ten RCTs examining peak walking outcomes in 558 patients with PAD demonstrated that SE programmes were more effective than community walking programmes that consisted of general recommendations for patients with intermittent claudication to walk at home.

A follow up an RCT[8] was identified that examined whether a home-based walking exercise programme (that uses a group-mediated cognitive behavioural intervention, incorporating both group support and self-regulatory skills), can improve functional performance compared with a health education control group in patients with PAD with and without intermittent claudication. A total of 194 patients with PAD (72.2% without classic symptoms of intermittent claudication) were included. The findings indicated that home-based walking exercise programme significantly improved walking endurance, physical activity, and patient-perceived walking endurance and speed in PAD participants with and without classic claudication symptoms.

An RCT[9] was identified that evaluated the effectiveness of a SE programme plus at home non-supervised exercise therapy (non-SET) on functional status, quality of life (QoL) and hemodynamic response in 177 post-lower-limb bypass surgery patients. Patients in the intervention group received SE programme and also non-SET at home, whereas those assigned to the control group received just usual SE programme according to a common cardiovascular programme. The participants were assessed by a 6-min walking test, an ABI, and the Medical Outcomes Study Short Form-36 (SF-36) of QoL at baseline, at 1 and 6 months after surgery. A significant improvement was observed in the walked distance in the intervention group after 6 months compared with the control group. The intervention group had significantly higher QoL score in the physical and mental component of SF-36.

Further RCT[10] was identified that assessed the clinical effectiveness of self-monitored home exercise. One hundred eighty (180) patients were allocated to three groups; exercise

training using a step watch programme (NEXT Step), SE programme and light resistance training. The NEXT Step programme and the SE programme consisted of intermittent walking to mild-to-moderate claudication pain for 12 weeks, whereas the controls performed light resistance training. Both the NEXT Step home programme and the SE programme demonstrated a significant increase from baseline in claudication onset time, 6-minute walk distance, daily average cadence, and time to minimum calf muscle hemoglobin oxygen saturation. Only the NEXT Step home group had improvements from baseline in large-artery elasticity index, and high-sensitivity C-reactive protein.

An RCT [11] was identified that assessed the impact of treadmill-based supervised exercise therapy (SET) alone and treadmill-based SET combined with resistance training on pain-free walking distance, skeletal muscle mass (SMM), and calpain activity. 35 patients with intermittent claudication were allocated to 12 weeks of treadmill only SE training (group A), or combined treadmill and lower-limb resistance training (group B). Calpain activity increased and SMM decreased within group A compared with group B. Neither exercise programmes was superior in terms of walking performance.

Further RCT [12] was identified that assessed the impact of treadmill-based SE training alone or in combination with resistance training on pain free walking distance, flow-mediated dilatation, reactive hyperaemia index, nitric oxide and asymmetric dimethylarginine. Thirty-five patients with intermittent claudication were to 12 weeks of treadmill-only SE training (Group 1) or a combination of treadmill and lower-limb resistance SE training (Group 2). Pain free walking distance was assessed by six-minute walk test. Endothelial function was assessed by brachial artery flow-mediated dilatation, reactive hyperaemia index and serum analysis of asymmetric dimethylarginine and nitric oxide. Pain free walking distance improved within Group 1 (160 m to 204 m) but not Group 2 (181 m to 188 m). No significant change in flow-mediated dilatation or reactive hyperaemia index in either group. Nitric oxide decreased in Group 1 but not Group 2. Asymmetric dimethylarginine decreased in Group 2 but not Group 1. The differences were not statistically significant.

An RCT[13] compared the efficacy of Nordic pole walking (NPW) training with traditional treadmill training (TT) on a claudication and maximum walking distance in patients with PAD was identified. Patients with intermittent claudication were randomised into a two three-month rehabilitation programmes. TT was finished by 31 patients, NPW by 21. Walking capacity was measured by an exercise treadmill test with the Gardner-Skinner protocol (before and after the programme) and six-minute walk test (6MWT). In an exercise treadmill test both groups reached significant increase in claudication and maximum walking distance. In six-minute walk test, NPW group reached significant increase in both claudication and maximum walking distance, whereas the TT group only reached the significant increase in maximum walking distance.

An RCT[14] was identified that carried out to assess the effects of SE training after percutaneous transluminal angioplasty (PTA) compared with PTA alone on physical function, limb hemodynamics and health-related quality of life in patients with intermittent claudication. Fifty patients who all underwent PTA for intermittent claudication were included in the study. Both groups received usual post-operative care. In addition, the intervention group performed two sessions of hospital-based SE training and one home-based exercise session per week for 12 weeks after PTA. The control group did not receive any additional follow-up regarding exercise. The findings showed statistically significant positive changes from baseline to 3 months for both groups. At 3 months, there was a trend towards better results for the intervention group compared with the control group. The median improvement from baseline to 3 months for the 6-minute walk test was 66 meters for the intervention group and 45 meters for the control group.

An RCT[15] that examined health effects of programmed physical activities on blood fats in PAD of lower limbs was identified. One hundred patients with arterial disease of lower limbs were included in control group (n=50) and test group (n=50). Total level of cholesterol was assessed in patients after 28 weeks of applied programmed activity. Findings showed significant decrease in total cholesterol value and triglycerides levels in test group compared to control group.

A pilot RCT trial[16] was identified that assessed the efficacy of a community-based walking exercise programme with training, monitoring and coaching (TMC) components to improve exercise performance and patient-reported outcomes in PAD patients. Patients with PAD (n=25) who previously received peripheral endovascular therapy or presented with stable claudication were included. Patients randomised to the intervention group received a comprehensive community-based walking exercise programme with elements of TMC over 14 weeks. Patients in the control group did not receive treatment beyond standard advice to walk. Intervention group patients (n=10) did not significantly improve peak walking time when compared with the control group patients (n=10). Changes in claudication onset time and walking impairment questionnaire scores were greater for patients in the intervention group compared with the control group.

An RCT[17] was identified that examined whether a group-mediated cognitive behavioural intervention, prevented mobility loss and improved functional performance. One hundred ninety-four (194) PAD participants were randomised to intervention and control group. During months 1 to 6, the intervention group met weekly with a facilitator. Group support and self-regulatory skills were used to help participants in intervention group adhere to walking exercise. Ninety-percent of exercise was conducted at or near home. The control group attended weekly lectures. Compared to controls, fewer participants randomised to the intervention experienced mobility loss at 6-month follow-up: 6.3% versus 26.5%, and at 12-month follow-up: 5.2% versus 18.5%. The intervention improved fast-paced 4-meter walking velocity at 6-month follow-up and the Short Physical Performance Battery at 12-month follow-up, compared to controls.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
NICE CG147 recommends supervised exercise to all people with intermittent claudication.

The new evidence strongly supports supervised exercise for people with PAD which is consistent with the current recommendations.

New evidence is unlikely to change guideline recommendations.

CG147 – 05 What is the clinical and cost effectiveness of endovascular or surgical techniques compared to or in combination with exercise or best medical treatment for the treatment of people with intermittent claudication?

Recommendations derived from this question

1.5.3 Offer angioplasty for treating people with intermittent claudication only when:

- advice on the benefits of modifying risk factors has been reinforced (see recommendation 1.2.1) 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.

Surveillance decision

This review question should not be updated.

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

2-year surveillance summary

A multicentre RCT[18] was identified that compared optimum medical care with SE and with stent revascularisation in people with moderate-to-severe intermittent claudication. Randomisation was in a 2:1 ratio for both stenting (n=46) and SE (n=43) versus usual care (n=22). Optimum medical therapy 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. SE resulted in a 4.6 minute increase in walking time compared with optimum medical care. Stenting resulted in a 2.5 minute increase in walking time compared with optimum medical treatment. SE resulted in a 2.1 minute increase in walking time compared with stenting. Serious adverse events occurred in 4 people in the stenting group and none in the SE group.

A study [19] that reported an economic analysis based on the results of a UK-based RCT of PTA (n=60), SE (n=60), or both (n=58) in people with intermittent claudication was identified. There were no significant differences between the 3 treatment groups. In the SE 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 SE compared with angioplasty group.

4-year surveillance summary

A systematic review[20] was identified that examined the exact role of SET in management of symptomatic PAD and in particular to assess its role in comparison with or as an adjunct to invasive intervention. A total 11 studies inclusive of 969 patients were included. The study concluded that exercise is a complication-free treatment and it appears to offer significant improvements in patients walk distances with a combination of both SET and intervention offering a superior walking outcome to monotherapy in those requiring invasive measures.

Another systematic review[21] was identified that compared medical treatment to revascularise for treatment of ulcerated foot in patients with diabetes. Three non-randomised studies with a control group included. The major outcomes following endovascular or open bypass surgery were broadly similar among the studies. Following open surgery, the 1-year limb salvage rate was a median of 85% and following endovascular revascularisation, the rates was 78%. At 1-year follow-up, 60% or more of ulcers had healed following revascularisation with either open bypass surgery or endovascular revascularisation. Studies appeared to demonstrate improved rates of limb salvage associated with revascularisation compared with the results of medically treated patients in the literature.

A Cochrane systematic review[22] was identified that assessed the efficacy of, and complications associated with, intravascular brachytherapy (IVBT) for maintaining patency after angioplasty or stent insertion in native vessels or bypass grafts of the iliac or infrainguinal arteries. Eight trials with a combined total of 1090 participants were included in this review. All studies compared PTA with or without stenting plus IVBT versus PTA with or without stenting alone. No trials were found comparing IVBT to technologies such as drug eluting stents (DES) or balloons, or cryoplasty. Follow-up ranged from six months to five years. For brachytherapy, cumulative patency was higher at 24 months. Significant difference was found for restenosis at six months, 12 months (and 24 months in favour of IVBT. No difference was found after five years as measured in one study. The need for re-interventions was reported in six studies. Target lesion revascularisation (TLR) was significantly reduced in trial participants treated with IVBT compared with angioplasty alone at six months after the interventions. No significant difference was found between the procedures on the need for re-intervention at 12 and 24 months after the procedures. Ankle brachial index was statistically significantly better for IVBT at the 12 month follow-up but no statistically significant differences were found at 24 hours and at six months. Quality of life, complications, limb loss, cardiovascular deaths, death from all causes, pain free walking distance and maximum walking distance on a treadmill were similar for the two arms of the trials.

Effectiveness of endovascular revascularisation plus SE for intermittent claudication was assessed in an RCT [23]. Two hundreds and twelve (212) patients allocated to either endovascular revascularisation plus SE or SE only. Patients were followed up for 12 months. Endovascular revascularisation plus SE (combination therapy) was associated with significantly greater improvement in maximum walking distance compared with the SE only group. Similarly, the combination therapy group demonstrated significantly greater improvement in the disease-specific Vascular Quality of Life Questionnaire (VascuQol) score and in the score for the SF-36 physical functioning No significant differences were found for the SF-36 domains of physical role functioning, bodily pain, and general health perceptions.

An RCT[24] was identified that examined the hypothesis that an invasive treatment strategy versus continued noninvasive treatment improves health-related quality of life after 1 year in unselected patients with intermittent claudication. Patients with intermittent claudication requesting treatment for claudication were randomly assigned to invasive (n=79) or noninvasive (n=79) treatment groups. Primary end point was health-related quality of life after 1 year, assessed with Medical Outcomes Study Short Form 36 version 1 and VascuQol, and secondary end points included walking distances on a graded treadmill. Overall, VascuQol score and 3 of 5 domain scores improved significantly more in the invasive versus the noninvasive treatment group. Intermittent claudication distance improved significantly in the invasive (+124 m) versus the noninvasive (+50 m) group, whereas the change in maximum walking distance was not significantly different between groups.

A follow up study[25] of a clinical trial was identified that carried out to report the longer-term (18-month) efficacy of SE compared with stent revascularisation and optimal medical care (OMC). Of 111 patients with aortoiliac PAD randomly assigned to receive OMC, OMC plus SE, or OMC plus stent revascularisation, 79 completed the 18-month clinical and treadmill follow-up assessment. The findings showed that the walking time improved from baseline to 18 months for both SE (5.0 ± 5.4 min) and stent revascularisation (3.2 ± 4.7 min) significantly more than for OMC alone (0.2 ± 2.1 min). The difference between SE and stent revascularisation was not significant. Improvement in claudication onset time was greater for SE compared with OMC, but not for stent revascularisation compared with OMC. Many disease-specific quality-of-life scales demonstrated durable improvements that were greater for stent revascularisation compared with SE or OMC.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The evidence from 2-year surveillance 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.

Evidence also 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 which is again consistent with the recommendation in CG147 to offer supervised exercise to all people with intermittent claudication.

New evidence is unlikely to change guideline recommendations.

CG147 – 06 What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of PAD in adults with intermittent claudication?

Recommendations derived from this question

1.5.4 Do not offer primary stent placement for treating people with intermittent claudication caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

1.5.5 Consider primary stent placement for treating people with intermittent claudication caused by complete aorto-iliac occlusion (rather than stenosis).

Surveillance decision

This review question should not be updated.

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

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

A systematic review[26] that assessed the effects of PTA versus primary stenting for stenotic and occlusive lesions of the iliac artery was identified. Two RCTs with a combined total of 397 participants identified. One study included mostly stenotic lesions (95%), whereas the second study included only iliac artery occlusions. Due to the heterogeneity among the two studies it was not possible to pool the data. In one study PTA with selective stenting and primary stenting resulted in similar improvement in the stage of PAD, resolution of symptoms and signs, improvement of quality of life, technical success of the procedure and patency of the treated vessel. In the other included trial, PTA of iliac artery occlusions resulted in a significantly higher rate of major complications, especially distal embolisation. The trial showed a significantly higher mean ABI at two years in the PTA group (1.0) compared to the mean ABI in the PS group (0.91). However, at other time points there was no difference. The authors concluded that there was insufficient evidence to assess the effects of PTA versus PS for stenotic and occlusive lesions of the iliac artery.

Another RCT[27] a sub-analysis of multicentre randomised trial (ACHILLES trial) was identified that assessed the health-related quality-of-life changes and quality-adjusted life-years (QALYs) gain in the 2 treatment arms of the angioplasty versus sirolimus-eluting stents (SES) in the treatment of patients with ischemic infrapopliteal arterial disease. A total of 200 patients were randomly assigned between SES and PTA for the treatment of infrapopliteal arterial occlusive lesions. Progression of wound healing was serially assessed by digital photography. Health-related quality-of-life scores were assessed with the self-administered EQ-5D questionnaire up to 1 year from randomisation. In total, 109 open wounds were documented at baseline. At 6 months, wound volume reduction was significantly higher in the SES group (95% healing compared with 60% healing in the PTA group). At 1 year, rates of complete wound closure were higher in the case of SES however the difference was not statistically significant. The recorded weighted EQ-5D score improved significantly up to 1 year in case of SES, but not in case of PTA. There was a trend of more QALYs gained with SES compared with PTA up to 1 year after randomisation. Relative QALY gain was 0.10 in the whole study and 0.17 in the wound subgroups comparison, which the findings were not statistically significant.

A systematic review [28] that assessed the outcomes of infrainguinal angioplasty with DES

or drug eluting balloons (DEB) was identified. Meta-analysis of studies comparing DEB with standard balloon angioplasty demonstrated a result in favour of DEBs for preventing binary primary restenosis and TLR.

A follow up an RCT[29] was identified that investigated the 2-year technical and clinical results of primary nitinol stent placement in comparison with PTA in the treatment of de novo lesions of the popliteal artery. In total, data from 183 patients (n=89 stent and n=94 PTA) were available for the 2-year analysis. The primary patency rate was significantly higher in the stent group than in the PTA group. TLR rate was 22.4% and 59.5%, respectively. A significant improvement in ABI and Rutherford category was observed at 2 years in both groups. The authors concluded that in treatment of obstructive popliteal artery lesions, provisional stenting shows equivalent patency in comparison to primary stenting. However, the 2-year results of this trial suggest the possibility of a shift toward higher patency rates in favour of primary stenting.

An RCT [30] that compared paclitaxel-coated balloons (PCB) versus DES was identified. Fifty patients with angiographically documented infrapopliteal disease were randomised to undergo infrapopliteal PCB angioplasty or primary DES placement. Immediate residual post-procedure stenosis was significantly lower in DES group. At 6 months, 5 patients died (2 in PCB vs. 3 in DES) and 3 suffered a major amputation (1 in PCB vs. 2 in DES). In total, 44 angiograms were evaluable with quantitative vessel analysis. Binary angiographic restenosis rate was significantly lower in DES compared with PCB. There were no significant differences with regard to TLR.

One RCT[31] was identified that investigated the efficacy and safety of a balloon expandable, SES in patients with symptomatic infrapopliteal arterial disease. Two hundred patients (total lesion length 27 ± 21 mm) were randomised to infrapopliteal SES stenting or PTA. Ninety-nine and 101 patients were randomised to SES and PTA, respectively. At 1 year, there were significantly lower angiographic restenosis rates, greater vessel patency rate in SES versus PTA. No differences observed between the two groups in death rates, repeat revascularisation, index-limb amputation rates, and proportions of patients with improved Rutherford class.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
There is insufficient evidence to assess the effects of percutaneous transluminal angioplasty versus primary stenting for stenotic and occlusive lesions of the iliac artery.

Evidence is generally consistent with the current recommendation of do not offer primary stent placement for treating people with intermittent claudication caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

New evidence is unlikely to change guideline recommendations.

CG147 – 07 What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of PAD in adults with intermittent claudication?

Recommendations derived from this question

1.5.6 Use bare metal stents when stenting is used for treating people with intermittent claudication.

Surveillance decision

This review question should not be updated at this time.

This review question should be considered for a future update after publication of the BASIL-3 study.

Bare metal compared to drug eluting stents- intermittent claudication

2-year surveillance summary

A systematic review and meta-analysis[32] of technologies that may enhance the efficacy of PTA for people with intermittent claudication or critical limb ischaemia was identified. Outcomes of interest were restenosis and re-intervention. The systematic review included 40 RCTs. Revascularisation at 24 months was significantly lower with drug-coated than with conventional balloon angioplasty. Drug eluting stents had significantly lower rate of restenosis at 6 months compared with conventional angioplasty and BMS.

4-year surveillance summary

An RCT[33] was identified that evaluated clinical durability of Zilver PTX, a paclitaxel-coated DES, for femoropopliteal artery lesions. Patients with symptomatic femoropopliteal artery disease were randomised to primary DES group (n=236) or PTA group (n=238). Patient with acute PTA failure were subsequently randomised to provisional DES (n=61) or provisional BMS placement (n=59). The 1-year primary endpoints of event-free survival and patency showed superiority of primary DES compared to PTA; these results were sustained through 5 years. Clinical benefit (freedom from persistent or worsening symptoms of ischemia, patency, and freedom from reintervention) for the overall DES group was superior to standard care. Similarly, clinical benefit, patency, and freedom from TLR with provisional DES were improved over provisional bare metal stent (BMS). These results represent >40% relative risk reduction for restenosis and TLR through 5 years for the overall DES compared to standard care and provisional DES compared to provisional BMS.

A systematic review [34] that evaluated the clinical effectiveness, safety, cost-effectiveness and budget impact of Zilver paclitaxel self-expanding DES for the treatment of de novo or restenotic lesions in above-the-knee peripheral arterial disease was identified. One RCT reported a significantly higher patency rate with Zilver paclitaxel DES for lesions ≤ 14 cm than with angioplasty or BMS.

A randomised multicentre study[35] was identified that evaluated the patency rates in 141 patients with symptomatic PAD after treatment with heparin-bonded covered stents (VIABAHN Endoprosthesis) and BMS. Patency rates were assessed at 1, 6, 12, and 24 months. The 24-month primary patency rates in the heparin-bonded covered stents were significantly higher compared with BMS group in both intention to treat analysis and treatment per protocol analysis. For the treatment per protocol group in lesions ≥20 cm, the 24-month patency rates were significantly higher in heparin-bonded covered stents compared with BMS group, however there was no difference observed in freedom from TLR and ABI between the two groups.

A systematic review[36] was identified that evaluated the economic impact on payers and providers of the four main endovascular strategies BMS, DES, and DCB, PTA for the treatment of infrainguinal peripheral artery disease. Thirteen studies with 2,406 patients were included. The reported probability of TLR in the identified studies varied widely, particularly following treatment with PTA or BMS. The pooled 24-month probabilities were 14.3%, 19.3%, 28.1%, and 40.3% for DCB, DES, BMS, and PTA, respectively. The drug-eluting strategies had a lower projected budget impact over 24 months compared to BMS and PTA.

A systematic review [37] was estimated the clinical and economic impact of drug-eluting endovascular treatment strategies for femoropopliteal artery disease compared with current standard of care at the NHS setting. Most patients suffered from intermittent claudication (about 80%). Twenty-eight studies, reporting on 5167 femoropopliteal lesions were identified. Over 24 months, DCB, DES and BMS reduced TLRs of de novo lesions from 36.2% to 17.6%, 19.4% and 26.9%, respectively, at an increased cost of £43, £44 and £112. Number needed to treat (NNT) to avoid 1 TLR in 24 months were 5.4, 6.0 and 10.8, resulting in cost per TLR avoided of £231, £264 and £1204. DCB was estimated to add 0.011 QALYs, DES 0.010 QALYs and BMS 0.005 QALYs, resulting in estimated incremental cost-effectiveness ratio (ICERs) of £3983, £4534 and £20 719 per QALY gained. A modest reduction of 10% in DCB and DES prices made drug-eluting treatments dominant. The authors concluded that the widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS. They stated that

based on currently available data, DCBs offer the highest clinical and economic value.

A meta-analysis of RCTs[38] performed comparing DEB angioplasty and DES for infrainguinal PAD was identified. Eight RCTs for a DEB angioplasty and 12 RCTs for DES in PAD were identified. Meta-analysis demonstrated significant superiority of DEB over plain balloon angioplasty (PTA) for late lumen loss, restenosis, and TLR, with no benefit in major amputation or mortality. The authors concluded that DEB and DESs demonstrated superior outcomes compared to PTA and BMS, with no difference in amputation or mortality.

Topic expert feedback
Topic experts indicated that there is an increasing body of evidence which supports the use of drug eluting technologies in the management of femoropoliteal disease and it would be incorrect if NICE was to continue with the existing recommendations. They also highlighted several trials [37, 33, 39, 30] related to drug eluting technologies that were included in the 4 year surveillance evidence summary.

Impact statement
Evidence from 2- year surveillance review suggests that drug-eluting stents may reduce the likelihood of restenosis.

New evidence from the four year surveillance review suggests that that drug-eluting stents are cost effective and may also improve the patency rate better than the bare metal stents.

Further evidence provided persistent safety and clinical durability for drug-eluting stents compared to standard endovascular treatments. This is in contrast with CG147 recommendation that use of bare metal stent was recommended when stenting for treating people with intermittent claudication. Topic experts indicated that a review of this area is necessary to establish whether there are benefits associated with use of drug-eluting stents for treating people with intermittent claudication**.**

However, the topic experts also indicated that the decision of if this questions should be updated may be influenced by the evidence from an ongoing NIHR HTA-funded BASIL-3 study, which is a RCT of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and balloon angioplasty with bail-out bare metal stent revascularisation strategies. Based on the feedback from topic experts, this question should be considered for inclusion after completion of BASIL-3 trial. The study is in the recruiting stage and reviewing the question now could potentially impact on the recruitment process. NICE will track the findings of the BASIL-3 trail.

New evidence identified that may change current recommendations.

CG147 – 08 What is the clinical effectiveness of autologous vein versus prosthetic bypass for the treatment of intermittent claudication in adults?

Recommendations derived from this question

1.5.7 Offer bypass surgery for treating people with severe lifestyle-limiting intermittent claudication only when:

- angioplasty has been unsuccessful or is unsuitable and
- imaging has confirmed that bypass surgery is appropriate for the person.

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

CG147 – 09 What is the clinical and cost effectiveness of naftidrofuryl oxalate compared to exercise therapy, angioplasty or stents for the treatment of intermittent claudication in adults with PAD?

Recommendations derived from this question

1.5.9 Consider naftidrofuryl oxalate for treating people with intermittent claudication, starting with the least costly preparation, only when:

- supervised exercise has not led to satisfactory improvement and
- the person prefers not to be referred for consideration of angioplasty or bypass surgery.

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Management of critical limb ischaemia

CG147 – 10 What is the clinical and cost effectiveness of angioplasty compared to bypass surgery or amputation for the treatment of critical limb ischaemia in adults with PAD?

Recommendations derived from this question

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

1.6.2 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.

Surveillance decision

This review question should not be updated.

Angioplasty compared to bypass surgery

2-year surveillance summary
No relevant evidence was identified.

4-year surveillance summary
A systematic review [40] was identified that assessed clinical outcomes of angioplasty versus bypass surgery in patients with critical limb ischemia. Seven clinical trials were selected for meta-analysis. No significant difference was found in the primary outcome-amputation free survival, between angioplasty and bypass surgery groups. The amputation free survival in 1, 3 and 5 years were 332/498 (66.7%), 169/346 (48.8%) and 21/60 (35%) in angioplasty group, versus 484/749 (64.6%), 250/494 (50.6%) and 46/132 (34.8%), in bypass group, respectively. The 30 days mortality rate was significantly higher in bypass treatment group (79/1304 [6.1%]) than in angioplasty group (30/918 [3.3%]). However, there was no statistical significance in 1, 3 and 5 years mortality between these two groups. Two clinical trials showed that there was no difference in leg salvage between angioplasty and bypass surgery groups either. In addition, no difference was observed in revascularisation between the two groups. The authors concluded that angioplasty is non-inferior to bypass surgery in regarding the amputation free survival, revascularisation, leg amputation and overall mortality. However, angioplasty is safer, simple, and less invasive and less cost procedure. It should be considered as the first choice for feasible patients with critical limb ischemia patients.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence from a systematic review is consistent with the CG147 recommendation that indicates to offer angioplasty or bypass surgery to people with critical limb ischaemia who require revascularisation, taking into account individual clinical condition and preference. Therefore, no impact on current recommendations is anticipated.

New evidence is unlikely to change guideline recommendations.

CG147 – 11 What is the clinical and cost effectiveness of angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of critical limb ischemia in adults with PAD?

Recommendations derived from this question

1.6.3 Do not offer primary stent placement for treating people with critical limb ischaemia caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

1.6.4 Consider primary stent placement for treating people with critical limb ischaemia caused by complete aorto-iliac occlusion (rather than stenosis).

Surveillance decision

This review question should not be updated.

Angioplasty with selective stent placement compared to angioplasty with primary stent placement for the treatment of critical limb ischemia

2-year surveillance summary

No relevant evidence was identified.

4-year surveillance summary

A systematic review[41] was identified that investigated the effect of PTA compared with PTA with BMS in people with symptomatic lower limb peripheral vascular disease.

Eleven trials with total of 1387 participants included. All included studies examined angioplasty alone versus angioplasty with BMS for the treatment of superficial femoral artery stenosis. Participants were followed for up to two years. There was an improvement in primary duplex patency at 6 and 12 months in participants treated with PTA plus stent over lesions treated with PTA alone. No differences observed in primary duplex patency by 24 months. Ankle brachial index and treadmill walking distance showed no improvement at 12 months between participants treated with PTA alone or PTA with stent insertion. Three trials (660 participants) reported quality of life, which showed no significant difference between participants treated with PTA alone or PTA with stent insertion at any time interval.

An RCT[42] was identified that assessed the effect of PTA with primary stenting in infrapopliteal arteries in patients with critical limb ischemia, concerning 1-year clinical benefit and reobstruction rate. Patients were either randomised for primary stenting (balloon expandable stent) or PTA alone, 33 patients were assigned to the PTA group, 21 patients to the stent group. Improvement by at least one Rutherford classification was observed at 12 months for 22 (81.5 %) patients in PTA group and 11 (64.7 %) in the stent group. Half of all patients showed re-obstruction over the follow-up period, 39.4 % of the PTA and 66.7 % of the stent group. At month 3 primary patency rate was nearly equal in both groups (76.7 % PTA vs 75.0 % stent), but drifted apart with the duration of the follow-up period. As for secondary patency at month 12 the PTA group showed a patency rate of 70.4 %, vs 52.9 % in the stent group. The authors concluded that primary stenting with balloon expandable stents in the infrapopliteal arteries does not outweigh the benefit of PTA alone with the application of modern hydrophilic balloon catheters in patients with critical limb ischemia.

A systematic review [43] evaluated the clinical value of primary stenting compared with balloon angioplasty in treating patients with infrapopliteal diseases. Comparisons were made with balloon angioplasty and primary stenting, and based on the different types of stents; they divided the primary stent group into the BMS group and DES group. A total of 3789 patients and 4339 limbs constituted to the final study population. The technical success rate of balloon angioplasty was 92.29%. Only 2 studies reported the technical failure rates as 4% and 5.2% in the primary stent group. The pooled estimates of 1-year primary patency and target vessel revascularisation-free rate were similarly low in the balloon angioplasty group and BMS group. The pooled estimates of 1-

year primary patency and target vessel revascularisation -free rate in DES group were 81.10% and 90.30% respectively, which were better than those of the BMS and balloon angioplasty groups. The pooled estimate of 1-year limb salvage in the balloon angioplasty, BMS, and drug eluted stent groups was 88.61%, 94.41%, and 95.20%, respectively. The BMS and DES groups had higher limb salvage rates than the balloon angioplasty group for both comparisons. The study concluded that primary BMS implantation had no advantage over balloon angioplasty in reducing restenosis or revascularisation for infrapopliteal disease.

A systematic review[44] was identified that examined whether treatment of infra-inguinal arterial occlusive disease with DES provides improved outcomes compared with BMS or PTA alone. Five studies included. The findings showed lower angiographic restenosis (22.4 vs 41.9%) and greater vessel patency (75 vs 57.1%) in the DES group at 1 year when compared to PTA group.

An RCT[31] was identified that investigated the efficacy and safety of a balloon expandable, SES in patients with symptomatic infrapopliteal arterial disease. Two hundred patients (200) were randomised to infrapopliteal SES stenting or PTA. At 1 year, there were lower angiographic restenosis rates (22.4% vs. 41.9%), greater vessel patency (75.0% vs. 57.1%), and similar death, repeat revascularisation, index-limb amputation rates, and proportions of patients with improved Rutherford class for SES versus PTA.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence suggests that primary stenting with balloon expandable stents in the infrapopliteal arteries does not outweigh the benefit of PTA alone with the application of modern hydrophilic balloon catheters in patients with critical limb ischemia.

Evidence is generally consistent with current recommendations, which recommends do not offer primary stent placement for treating people with critical limb ischaemia caused by aorto-iliac disease (except complete occlusion) or femoro-popliteal disease.

New evidence is unlikely to change guideline recommendations

CG147 – 12 What is the clinical and cost effectiveness of bare metal stents compared to drug eluting stents for the treatment of critical limb ischemia in adults with PAD?

Recommendations derived from this question

1.6.5 Use bare metal stents when stenting is used for treating people with critical limb ischaemia.

Surveillance decision

This review question should not be updated at this time.

This review question should be considered for a future update after publication of the BASIL-3 study.

Bare metal stents compared to drug eluting stents-critical limb ischemia

2-year surveillance summary

A systematic review and meta-analysis[32] of technologies that may enhance the efficacy of PTA for people with intermittent claudication or critical limb ischaemia was identified. Outcomes of interest were restenosis and re-intervention. The systematic review included 40 RCTs. Revascularisation at 24 months was significantly lower with drug-coated than with conventional balloon angioplasty. DES had significantly lower rate of restenosis at 6 months compared with conventional angioplasty and BMS.

4-year surveillance summary

An RCT[33] evaluated clinical durability of Zilver PTX, a paclitaxel-coated DES, for femoropopliteal artery lesions was identified. Patients with symptomatic femoropopliteal artery disease were randomised to primary DES group (n=236) or PTA group (n=238). Patient with acute PTA failure were subsequently randomised to provisional DES (n=61) or provisional BMS placement (n=59). The 1-year primary endpoints of event-free survival and patency showed superiority of primary DES compared to PTA; these results were sustained through 5 years. Clinical benefit (freedom from persistent or worsening symptoms of ischemia, patency, and freedom from reintervention) for the overall DES group was superior to standard care. Similarly, clinical benefit, patency, and freedom from target-lesion-revascularisation with provisional DES were improved over provisional BMS. These results represent >40% relative risk reduction for restenosis and target-lesion-revascularisation through 5 years for the overall DES compared to standard care and provisional DES compared to provisional BMS.

A systematic review [34] that evaluated the clinical effectiveness, safety, cost-effectiveness and budget impact of Zilver paclitaxel self-expanding DES for the treatment of de novo or restenotic lesions in above-the-knee PAD was identified. One RCT reported a significantly higher patency rate with Zilver paclitaxel DES for lesions ≤ 14 cm than with angioplasty or BMS.

A randomised multicentre study[35] was identified that evaluated the patency rates in 141 patients with symptomatic PAD after treatment with heparin-bonded covered stents (VIABAHN Endoprosthesis) BMS. Patency rates were assessed at 1, 6, 12, and 24 months. The 24-month primary patency rates in the heparin-bonded covered stents were significantly higher compared with BMS group in both intention to treat analysis and treatment per protocol analysis. For the treatment per protocol group in lesions ≥20 cm, the 24-month patency rates were significantly higher in heparin-bonded covered stents compared with BMS group, however there was no difference observed in freedom from TLR and ABI between the two groups.

A multicentre, randomised trial [45] was conducted to assess whether DES improve patency and clinical outcome of infrapopliteal lesions. Adults with critical limb ischemia (Rutherford category ≥4) and infrapopliteal lesions were randomised to receive PTA±BMS or DES with paclitaxel. Seventy-four limbs (73 patients) were treated with DES and 66 limbs

(64 patients) received PTA±BMS. Six-month patency rates were 48.0% for DES and 35.1% for PTA±BMS in the modified-intention-to-treat and 51.9% and 35.1% in the per-protocol analysis. The ordinal score showed significantly worse treatment failure for PTA±BMS versus DES. The observed major amputation rate remained lower in the DES group until 2 years post-treatment, with a trend toward significance. Fewer minor amputations occurred after DES until 6 months post-treatment.

A systematic review[36] was identified that evaluated the economic impact on payers and providers of the four main endovascular strategies BMS, DES and DCB, PTA for the treatment of infrainguinal peripheral artery disease. Thirteen studies with 2,406 patients were included. The reported probability of TLR in the identified studies varied widely, particularly following treatment with PTA or BMS. The pooled 24-month probabilities were 14.3%, 19.3%, 28.1%, and 40.3% for DCB, DES, BMS, and PTA, respectively. The drug-eluting strategies had a lower projected budget impact over 24 months compared to BMS and PTA.

A meta-analysis of RCTs[38] was identified that compared DEB angioplasty and DES for infrainguinal PAD. Eight RCTs for a DEB angioplasty and 12 RCTs for DES in PAD were identified. Meta-analysis demonstrated significant superiority of DEB over PTA for late lumen loss, restenosis, and TLR, with no benefit in major amputation or mortality. Study concluded that DEB and DES demonstrated superior outcomes compared to PTA and BMS, with no difference in amputation or mortality.

Topic expert feedback

Topic experts indicated that there is an increasing body of evidence which supports the use of drug eluting technologies in the management of femoropoliteal disease and it would be incorrect if NICE was to continue with the existing recommendations. They also highlighted several trials [37, 33, 39, 30] related to drug eluting technologies that were included in the 4 year surveillance evidence summary.

Impact statement

Evidence from 2- year surveillance review suggests that drug-eluting stents may reduce the likelihood of restenosis.

New evidence from the 4 year surveillance review suggests that that drug-eluting stents are cost effective and may also improve the patency rate better than the bare metal stents.

Further evidence provided persistent safety and clinical durability for drug-eluting stents compared to standard endovascular treatments. This is in contrast with CG147 recommendation that use of bare metal stents was recommended when stenting for treating people with critical limb ischemia. Topic experts indicated that a review of this area is necessary to establish whether there are benefits associated with use of drug-eluting stents for treating people with critical limb ischemia**.**

However, the topic experts also indicated that the decision of if this questions should be updated may be influenced by the evidence from an ongoing NIHR HTA-funded BASIL-3 study, which is a RCT of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and balloon angioplasty with bail-out bare metal stent revascularisation strategies. Based on the feedback from topic experts, this question should be considered for inclusion after completion of BASIL-3 trial. The study is in the recruiting stage and reviewing the question now could potentially impact on the recruitment process. NICE will track the findings of the BASIL-3 trail.

New evidence identified that may change current recommendations.

CG147 – 13 What is the clinical effectiveness of autologous vein versus prosthetic bypass graft for the treatment of CLI in adults with PAD?

Recommendations derived from this question

1.6.6 Use an autologous vein whenever possible for people with critical limb ischaemia having infra-inguinal bypass surgery.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

CG147 – 14 What is the clinical and cost effectiveness of chemical sympathectomy, opioids, gabapentin, pregabalin or tricyclic antidepressants compared to each other in any combination for the management of ischaemic pain in adults with critical limb ischemia?

Recommendations derived from this question

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

1.6.8 Offer drugs such as laxatives and anti-emetics to manage the adverse effects of strong opioids, in line with the person's needs and preferences.

1.6.9 Refer people with critical limb ischaemic pain to a specialist pain management service if any of the following apply:

- their pain is not adequately controlled or revascularisation is inappropriate or impossible
- ongoing high doses of opioids are required for pain control
- pain persists after revascularisation or amputation.

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

CG147 – 15 What are the clinical indications for major amputation for the management of pain in people with critical limb ischaemia and does major amputation improve the quality of life in people with critical limb ischaemia?

Recommendations derived from this question

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Areas not currently covered in the guideline

NQ – 01 What is clinical and cost effectiveness of drug-eluting balloon angioplasty versus conventional balloon angioplasty for the treatment of patients with intermittent claudication?

Surveillance decision

This review question should be considered for inclusion after publication of the BASIL-3 study.

Drug-eluting angioplasty or stent angioplasty versus conventional angioplasty

2-year surveillance summary
No relevant evidence was identified.

4-year surveillance summary
A network meta-analysis [46] of RCTs was identified comparing bare nitinol stents, covered nitinol stents, paclitaxel- or sirolimus-eluting stents (PES or SES), and PCB with plain balloon angioplasty or with each other in the femoropopliteal artery. Sixteen RCTs comprising 2532 patients with 4227 person-years of follow-up were analysed on an intention-to-treat basis. Technical success was highest with covered stents (probability best 82%) followed by uncovered stents (probability best 18%) when compared with balloon angioplasty (reference treatment). Vascular restenosis was lowest with PES (probability best 45%) followed by PCB (probability best 42%). TLR was lowest with PCB (probability best 56%) followed by PES (probability best 33%). Major amputations were rare in all treatment and control groups (pooled amputation rate of 0.7 events per 100 person-years). The study concluded that immediate technical success is better with the use of covered stents, whereas PES and PCB offer the best long-term results in the femoropopliteal artery.

A meta-analysis [47] of RCTs was identified comparing DEB angioplasty and DES for infrainguinal PAD. Eight RCTs for DEB angioplasty and 12 RCTs for DES were identified. Meta-analysis demonstrated significant superiority of DEB over plain balloon angioplasty of femoral-popliteal disease for late lumen loss, restenosis, and TLR, with no benefit in major amputation or mortality.

A systematic review of RCTs[48] investigated PCB in the femoropopliteal artery was identified. Eleven RCTs with 1609 patients (1403 patients with intermittent claudication and 206 patients with critical limb ischemia) with medium-length femoropopliteal lesions (mean range 5.1–11.9 cm) were included.

There was consistently high-quality evidence supporting the clear superiority of PCBs in terms of reduced late lumen loss, less binary restenosis, and fewer TLR events. Major amputations were rare in both active and control arms (pooled event rate: 0.7%).

Five RCTs and a sub analysis of an RCT evaluated the safety and efficacy of PCB versus an uncoated balloon for treatment of patients with symptomatic femoral and popliteal artery disease.

The first RCT [49] evaluated the safety and efficacy of the novel Passeo-18 Lux paclitaxel-coated balloon compared with the Passeo-18 uncoated balloon in patients with symptomatic de novo or restenotic femoropopliteal lesions. Sixty patients in 5 European centres were enrolled in the BIOLUX P-I trial and randomised 1:1 to either the PCB or the uncoated balloon. At 6 months, patients treated with PCB had a significantly lower late lumen loss and binary restenosis than the control group. Correspondingly, clinically driven TLR was lower in the PCB group at 12 months for the intention-to-treat population and for the as protocol treated population. No death and one minor amputation were observed compared with two deaths and two minor amputations in the control group.

The second RCT [39] compared a DCB with PTA for the treatment of symptomatic superficial femoral and popliteal artery disease. Patients (n=331) with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven TLR at 12 months. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were similar. DCB resulted in significantly higher primary patency versus PTA. The rate of clinically driven TLR was significantly lower in the DCB arm in comparison with the PTA arm. There was a low rate of vessel thrombosis in both arms. There were no device- or procedure-related deaths and no major amputations.

The third RCT[50] was a 12 month follow up a multicentre; randomised trial to compare the safety and efficacy of DEB versus PTA in de novo or native restenotic lesions of the infrapopliteal arteries in patients with claudication and critical limb ischemia. Seventy-two patients were randomised 1:1 to either a Passeo-18 Lux DEB (n= 36) or Passeo-18 PTA (n= 36). Follow-up assessments were scheduled at 1, 6, and 12 months, with angiographic assessment at 6 months. The primary safety endpoint (a composite of all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularisation at 30 days) was 0% in the DEB group versus 8.3% in the PTA group. The primary performance endpoint (patency loss at 6 months) was 17.1% in the DEB group versus 26.1% in the PTA group, and major amputations of the target extremity occurred in 3.3% versus 5.6% of the patients at 12 months, respectively.

The forth RCT [51] a 24 month follow up an RCT investigated the longer-term outcomes of DCB compared to PTA for femoropopliteal lesions. Patients (n=331) were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA. The rates of TLR were significantly lower at DCB compared to PTA groups. The overall mortality rate in the DCB group was significantly higher (8.1%) compared to the PTA group (0.9%). No significant difference observed in the rate of vessel thrombosis in two groups. Both groups showed similar functional improvement (assessed by the EuroQOL-5D quality-of-life questionnaire, walking impairment questionnaire, and 6-min walk test) at 2 years, although DCB patients achieved this level of function with 58% fewer interventions.

The fifth RCT[52] evaluated the safety and efficacy of the Lutonix DCB coated with paclitaxel and a polysorbate/sorbitol carrier for treatment of femoropopliteal lesions. patients at 9 centres with Rutherford class 2 to 5 femoropopliteal lesions were randomised to treatment with Lutonix DCB (n = 49) versus uncoated balloons (control group [n = 52]), stratified by whether balloon-only treatment (n = 75) or stenting (n = 26) was intended. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group than for the control group. Composite 24-month major adverse events were 39% for the DCB group, including 15 TLR, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 TLR, 1 thrombosis, and 5 deaths.

A sub analysis of an RCT [53] performed to report the 12-month clinical outcomes of the DEBELLUM (Drug-Eluting-Balloon-Evaluation-for-Lower-Limb-mUltilevel-treatMent) randomised trial. Fifty patients were randomised between DEB (n= 25) and PTA (n= 25). One hundred and twenty-two lesions were treated. Twenty (40%) patients presented multilevel concomitant femoropopliteal and infra-popliteal lesions. Late lumen loss was significantly lower in DEB group versus the control group. In non-stented segment late lumen loss was also significantly lower in DEB versus PTA. In the stent subgroup late lumen loss was significantly lower in DEB versus PTA. In the femoropopliteal region the overall late lumen loss was also significantly lower in DEB versus PTA. The overall TLR was 12.2% for DEB and 35.3% for PTA. Amputation rate was 4% (DEB) vs. 12% (PTA). Thrombosis was 4% (DEB) vs. 8% (PTA). Major adverse events were 24% (DEB) vs. 60% (PTA). ABI improved more in the DEB group.

Topic expert feedback

Topic experts indicated that there is an increasing body of evidence which supports the use of drug eluting technologies in the management of femoropoliteal disease and it would be incorrect if NICE was to continue with the existing recommendations. They also highlighted several trials [37, 33, 39, 30] related to drug eluting technologies that were included in the 4 year surveillance evidence summary.

Impact statement

DEBs were not considered in the original guideline. Evidence form a network meta-analysis suggests that immediate technical success is better with the use of covered stents, whereas paclitaxel-eluting stents and paclitaxel-coated balloons offer the best long-term results in the femoropopliteal artery.

Evidence from other studies suggest that drug coated balloons may reduce rates of restenosis and target lesion revascularisation in the femoropopliteal artery regardless of stent placement and also prevents restenosis in the short term with higher reduction in amputation and no difference in mortality when compared with uncoated balloons.

There are general concerns among topic experts about evidence regarding the drug eluting technologies. A review of this area is necessary to establish whether there are benefits associated with use of drug-eluting balloons for treating people with intermittent claudication.

However, the topic experts also indicated that the decision of if this questions should be added may be influenced by the evidence from an ongoing NIHR HTA-funded BASIL-3 study, which is a RCT of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and balloon angioplasty with bail-out bare metal stent revascularisation strategies. Based on the feedback from topic experts, this question should be considered for inclusion after completion of BASIL-3 trial. The study is in the recruiting stage and reviewing the question now could potentially impact on the recruitment process. NICE will track the findings of the BASIL-3 trail.

New evidence identified that may impact on the guideline.

NQ – 02 **What is clinical and cost effectiveness of drug-eluting balloon angioplasty versus conventional angioplasty placement for the treatment of patients with critical limb ischemia?**

Surveillance decision

This review question should be considered for inclusion after publication of the BASIL-3 study.

Drug-eluting angioplasty or stent angioplasty versus conventional angioplasty

2-year surveillance summary
No relevant evidence was identified.

4-year surveillance summary
A meta-analysis of RCTs [47] (RCTs) was identified comparing DEB angioplasty and DES for infrainguinal PAD. Eight RCTs for DEB angioplasty and 12 RCTs for DES were identified. Meta-analysis demonstrated significant superiority of DEB over plain balloon angioplasty of femoral-popliteal disease for late lumen loss, restenosis, and TLR, with no benefit in major amputation or mortality.

A systematic review of RCTs[48] investigated PCB in the femoropopliteal artery was identified. Eleven RCTs with 1609 subjects (1403 patients with intermittent claudication and 206 patients with critical limb ischemia) with medium-length femoropopliteal lesions (mean range 5.1–11.9 cm) were included. There was consistently high-quality evidence supporting the clear superiority of PCBs in terms of reduced late lumen loss, less binary restenosis, and fewer TLR events. Major amputations were rare in both active and control arms (pooled event rate: 0.7%).

Five RCTs, a sub analysis of an RCT and follow up of an RCT evaluated the safety and efficacy of PCB versus an uncoated balloon for treatment of patients with symptomatic femoral and popliteal artery disease.

The first RCT [49] evaluated the safety and efficacy of the novel Passeo-18 Lux paclitaxel-coated balloon compared with the Passeo-18 uncoated balloon in patients with symptomatic de novo or restenotic femoropopliteal lesions. Sixty patients in 5 European centres were enrolled in the BIOLUX P-I trial and randomised 1:1 to either the PCB or the uncoated balloon. At 6 months, patients treated with PCB had a significantly lower late lumen loss and binary restenosis than the control group. Correspondingly, clinically driven TLR was lower in the PCB group at 12 months for the intention-to-treat population and for the as protocol treated population. No death and one minor amputation were observed compared with two deaths and two minor amputations in the control group.

The second RCT [39] compared a DCB with PTA for the treatment of symptomatic superficial femoral and popliteal artery disease. Patients (n=331) with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal peripheral artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. The primary efficacy end point was primary patency, defined as freedom from restenosis or clinically driven TLR at 12 months. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were similar. DCB resulted in significantly higher primary patency versus PTA. The rate of clinically driven TLR was significantly lower in the DCB arm in comparison with the PTA arm. There was a low rate of vessel thrombosis in both arms. There were no device- or procedure-related deaths and no major amputations.

The third RCT [50] was a 12 month follow up a multicentre; randomised trial to compare the safety and efficacy of a novel paclitaxel-coated DEB versus PTA in de novo or native restenotic lesions of the infrapopliteal arteries in patients with claudication and critical limb ischemia. Seventy-two patients were randomised 1:1 to either a Passeo-18 Lux DEB (n= 36) or Passeo-18 PTA (n= 36). Follow-up assessments were scheduled at 1, 6, and 12 months, with angiographic assessment at 6 months. The primary safety endpoint (a composite of all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularisation

at 30 days) was 0% in the DEB group versus 8.3% in the PTA group. The primary performance endpoint (patency loss at 6 months) was 17.1% in the DEB group versus 26.1% in the PTA group, and major amputations of the target extremity occurred in 3.3% versus 5.6% of the patients at 12 months, respectively.

The forth RCT [51] a 24 month follow up an RCT investigated the longer-term outcomes of a paclitaxel-eluting DCB compared to PTA for femoropopliteal lesions. Patients (n=331) were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA. The rates of TLR were significantly lower at DCB compared to PTA groups. The overall mortality rate in the DCB group was significantly higher (8.1%) compared to the PTA group (0.9%). No significant difference observed in the rate of vessel thrombosis in two groups. Both groups showed similar functional improvement (assessed by the EuroQOL-5D quality-of-life questionnaire, walking impairment questionnaire, and 6-min walk test) at 2 years, although DCB patients achieved this level of function with 58% fewer interventions.

The fifth RCT[52] evaluated the safety and efficacy of the Lutonix DCB coated with paclitaxel and a polysorbate/sorbitol carrier for treatment of femoropopliteal lesions. patients at 9 centres with Rutherford class 2 to 5 femoropopliteal lesions were randomised to treatment with Lutonix DCB (n = 49) versus uncoated balloons (control group [n = 52]), stratified by whether balloon-only treatment (n = 75) or stenting (n = 26) was intended. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group than for the control group. Composite 24-month major adverse events were 39% for the DCB group, including 15 TLR, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 TLR, 1 thrombosis, and 5 deaths.

A sub analysis of an RCT [53] performed to report the 12-month clinical outcomes of the DEBELLUM (Drug-Eluting-Balloon-Evaluation-for-Lower-Limb-mUltilevel-treatMent) randomised trial. Fifty patients were randomised between DEB (n= 25) and PTA (n= 25). One hundred and twenty-two lesions were treated. Twenty (40%) patients presented multilevel concomitant femoropopliteal and infra-popliteal lesions. Late lumen loss was significantly lower in DEB group versus the control group. In non-stented segment late lumen loss was also significantly lower in DEB versus PTA. In the stent subgroup late lumen loss was significantly lower in DEB versus PTA. In the femoropopliteal region the overall late lumen loss was also significantly lower in DEB versus PTA. The overall TLR was 12.2% for DEB and 35.3% for PTA. Amputation rate was 4% (DEB) vs. 12% (PTA). Thrombosis was 4% (DEB) vs. 8% (PTA). Major adverse events were 24% (DEB) vs. 60% (PTA). ABI improved more in the DEB group.

Follow up an RCT[54] assessed the efficacy and safety of IN.PACT Amphirion drug-eluting balloons (IA-DEB) compared to PTA for infrapopliteal arterial revascularisation in patients with critical limb ischemia. Patients (358) were randomised 2:1 to IA-DEB or PTA. There was a significant baseline difference between the IA-DEB and PTA arms in mean lesion length, impaired inflow, and previous target limb revascularisation. Primary efficacy results of IA-DEB versus PTA were TLR of 9.2% versus 13.1% and late lumen loss of 0.61 ± 0.78 mm versus 0.62 ± 0.78 mm. Primary safety endpoints were 17.7% versus 15.8% and met the noninferiority hypothesis. A safety signal driven by major amputations through 12 months was observed in the IA-DEB arm versus the PTA arm (8.8% vs. 3.6%). Study concluded that in patients with critical limb ischemia, IA-DEB had comparable efficacy to PTA while primary safety was met, there was a trend towards an increased major amputation rate through 12 months compared to PTA.

Topic expert feedback

Topic experts indicated that there is an increasing body of evidence which supports the use of drug eluting technologies in the management of femoropoliteal disease and it would be incorrect if NICE was to continue with the existing recommendations. They also highlighted several trials [37, 33, 39, 30] related to drug eluting technologies that were included in the 4 year surveillance evidence summary.

Impact statement

DEBs were not considered in the original guideline. Evidence from studies suggest that drug coated balloons may reduce rates of restenosis and target lesion revascularisation and also prevents restenosis in the short term with higher reduction in amputation and no

difference in mortality when compared with uncoated balloons.

There are general concerns among topic experts about evidence regarding the drug eluting technologies. A review of this area is necessary to establish whether there are benefits associated with use of drug-eluting balloons for treating people with critical limb ischemia.

However, the topic experts also indicated that the decision of if this questions should be added may be influenced by the evidence from an ongoing NIHR HTA-funded BASIL-3 study, which is a RCT of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and balloon angioplasty with bail-out bare metal stent revascularisation strategies. Based on the feedback from topic experts, this question should be considered for inclusion after completion of BASIL-3 trial. The study is in the recruiting stage and reviewing the question now could potentially impact on the recruitment process. NICE will track the findings of the BASIL-3 trail.

New evidence identified that may impact on the guideline.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the clinical and cost effectiveness of a 'bypass surgery first' strategy compared with an 'angioplasty first' strategy for treating people with critical limb ischaemia caused by disease of the infra-geniculate (below the knee) arteries?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 02 What is the clinical and cost effectiveness of supervised exercise programmes compared with unsupervised exercise for treating people with intermittent claudication, taking into account the effects on long-term outcomes and continuing levels of exercise?

New evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

New evidence was found but an update is not planned as the evidence supports the current guideline recommendations Therefore it is proposed to remove this research recommendation from the NICE research recommendations database and NICE version of the guideline

RR – 03 What is the effect of people's attitudes and beliefs about their peripheral arterial disease on the management and outcome of their condition?

The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).

Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 04 What is the clinical and cost effectiveness of selective stent placement compared with angioplasty plus primary stent placement for treating people with critical limb ischaemia caused by disease of the infra-geniculate arteries?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 05 What is the clinical and cost effectiveness of chemical sympathectomy in comparison with other methods of pain control for managing critical limb ischaemic pain?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

References

1. Brownrigg JR, Hinchliffe RJ, Apelqvist J et al. (2016) Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. Diabetes/Metabolism Research Reviews 32:Suppl-27.

2. Loewe C, Arnaiz J, Krause D et al. (2015) MR Angiography at 3 T of Peripheral Arterial Disease: A Randomized Prospective Comparison of Gadoterate Meglumine and Gadobutrol. AJR American:1311-1321.

3. 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.

4. Fokkenrood HJ, Lauret GJ, Verhofstad N et al. (2015) The effect of supervised exercise therapy on physical activity and ambulatory activities in patients with intermittent claudication. European Journal of Vascular & Endovascular Surgery 49:184-191.

5. Lane R, Ellis B, Watson L et al. (2014) Exercise for intermittent claudication. [Review][Update of Cochrane Database Syst Rev. 2008;(4):CD000990; PMID: 18843614]. Cochrane Database of Systematic Reviews 7:CD000990.

6. Li Y, Li Z, Chang G et al. (2015) Effect of structured home-based exercise on walking ability in patients with peripheral arterial disease: a meta-analysis. [Review]. Annals of Vascular Surgery 29:597-606.

7. Mays RJ, Hiatt WR, Casserly IP et al. (2015) Community-based walking exercise for peripheral artery disease: An exploratory pilot study. Vascular Medicine 20:339-347.

8. McDermott MM, Guralnik JM, Criqui MH et al. (2014) Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. Journal of the American Heart Association 3:e000711.

9. Jakubseviciene E, Vasiliauskas D, Velicka L et al. (2014) Effectiveness of a new exercise program after lower limb arterial blood flow surgery in patients with peripheral arterial disease: a randomized clinical trial. International Journal of Environmental Research & Public Health [Electronic Resource] 11:7961-7976.

10. Gardner AW. (2015) Exercise rehabilitation for peripheral artery disease: An exercise physiology perspective with special emphasis on the emerging trend of home-based exercise. Vasa - European Journal of Vascular Medicine.44 (6) (pp 405-417), 2015.Date of Publication: 2015. 405-417.

11. Delaney CL, Miller MD, Chataway TK et al. (2014) A randomised controlled trial of supervised exercise regimens and their impact on walking performance, skeletal muscle mass and calpain activity in patients with intermittent claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 47:304-310.

12. Delaney CL, Miller MD, Allan RB et al. (2015) The impact of different supervised exercise regimens on endothelial function in patients with intermittent claudication. Vascular.23 (6) (pp 561-569), 2015.Date of Publication: 01 Dec 2015. 561-569.

13. Bulinska K, Kropielnicka K, Jasinski T et al. (2016) Nordic pole walking improves walking capacity in patients with intermittent claudication: a randomized controlled trial. Disability & Rehabilitation 38:1318-1324.

14. Bo E, Bergland A, Stranden E et al. (2015) Effects of 12 Weeks of Supervised Exercise After Endovascular Treatment: A Randomized Clinical Trial. Physiotherapy Research International 20:147-157.

15. Baltic A, Baljic R, Radjo I et al. (2015) Health Effects of the Programmed Physical Activities on Lipid Profile in Peripheral Arterial Disease of the Lower Extremities. Medicinski Arhiv 69:311-314.

16. Mays RJ, Hiatt WR, Casserly IP et al. (2015) Community-based walking exercise for peripheral artery disease: An exploratory pilot study. Vascular Medicine 20:339-347.

17. McDermott MM, Guralnik JM, Criqui MH et al. (2015) Unsupervised exercise and mobility loss in peripheral artery disease: a randomized controlled trial. Journal of the American Heart Association 4:2015.

18. Murphy TP, Cutlip DE, Regensteiner JG et al. (2015) Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. Journal of the American College of Cardiology 65:999-1009.

19. 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 100:1172-1179.

20. Aherne T, McHugh S, Kheirelseid EA et al. (2015) Comparing Supervised Exercise Therapy to Invasive Measures in the Management of Symptomatic Peripheral Arterial Disease. [Review]. Surgery Research & Practice Print 2015:960402.

21. Hinchliffe RJ, Brownrigg JR, Andros G et al. (2016) Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes/Metabolism Research Reviews 32:Suppl-44.

22. Andras A, Hansrani M, Stewart M et al. (2014) Intravascular brachytherapy for peripheral vascular disease. [Review][Update of Cochrane Database Syst Rev. 2002;(4):CD003504; PMID: 12519600]. Cochrane Database of Systematic Reviews 1:CD003504.

23. Fakhry F, Spronk S, van dL et al. (2015) Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial. JAMA 314:1936-1944.

24. Nordanstig J, Taft C, Hensater M et al. (16-9-2014) Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. Circulation 130:939-947.

25. Murphy TP, Cutlip DE, Regensteiner JG et al. (2015) Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. Journal of the American College of Cardiology 65:999-1009.

26. Bekken J, Jongsma H, Ayez N et al. (2015) Angioplasty versus stenting for iliac artery lesions. [Review]. Cochrane Database of Systematic Reviews 5:CD007561.

27. Katsanos K, Spiliopoulos S, Diamantopoulos A et al. (2016) Wound Healing Outcomes and Health-Related Quality-of-Life Changes in the ACHILLES Trial: 1-Year Results From a Prospective Randomized Controlled Trial of Infrapopliteal Balloon Angioplasty Versus Sirolimus-Eluting Stenting in Patients With Ischemic Peripheral Arterial Disease. Jacc: Cardiovascular Interventions 9:259-267.

28. Canaud L, Ozdemir BA, Belli AM et al. (2014) Infrainguinal angioplasty with drug-eluting stents and balloons. [Review]. Journal of Vascular Surgery 59:1721-1736.

29. Rastan A, Krankenberg H, Baumgartner I et al. (2015) Stent placement vs. balloon angioplasty for popliteal artery treatment: two-year results of a prospective, multicenter, randomized trial. Journal of Endovascular Therapy 22:22-27.

30. Siablis D, Kitrou PM, Spiliopoulos S et al. (2014) Paclitaxel-coated balloon angioplasty versus drug-eluting stenting for the treatment of infrapopliteal long-segment arterial occlusive disease: the IDEAS randomized controlled trial. Jacc: Cardiovascular Interventions 7:1048-1056.

31. Scheinert D, Katsanos KF, Zeller TF et al. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial.

32. 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 100:1128-1137.

33. Dake MD, Ansel GM, Jaff MR et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial.

34. Health QO. (2015) Paclitaxel Drug-Eluting Stents in Peripheral Arterial Disease: A Health Technology Assessment. Ontario Health Technology Assessment Series 15:1-62.

35. Lammer J, Zeller T, Hausegger KA et al. (2015) Sustained benefit at 2 years for covered stents versus bare-metal stents in long SFA lesions: the VIASTAR trial.[Erratum appears in Cardiovasc Intervent Radiol. 2015 Jun;38(3):779-80; PMID: 25776757]. Cardiovascular & Interventional Radiology 38:25-32.

36. Pietzsch JB, Geisler BP, Garner AM et al. (1-10-2014) Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. [Review]. Catheterization & Cardiovascular Interventions 84:546-554.

37. Katsanos. (2016) Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK.

38. Baerlocher MO, Kennedy SA, Rajebi MR et al. (474) Meta-analysis of drug-eluting balloon angioplasty and drug-eluting stent placement for infrainguinal peripheral arterial disease. Journal of Vascular & Interventional Radiology 26:459-473.

39. Tepe G, Laird J, Schneider P et al. (3-2-2015) Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 131:495-502.

40. Fu X, Zhang Z, Liang K et al. (2015) Angioplasty versus bypass surgery in patients with critical limb ischemia-a meta-analysis. International journal of clinical and experimental medicine 8:10595-10602.

41. Chowdhury MM, McLain AD, and Twine CP. (2014) Angioplasty versus bare metal stenting for superficial femoral artery lesions. [Review][Update of Cochrane Database Syst Rev. 2009;(2):CD006767; PMID: 19370653]. Cochrane Database of Systematic Reviews 6:CD006767.

42. Brodmann M. (2014) Prime time for drug eluting balloons in SFA interventions? Journal of Cardiovascular Surgery.55 (4) (pp 461-464), 2014.Date of Publication: 01 Aug 2014. 461-464.

43. Yang X, Lu X, Ye K et al. (2014) Systematic review and meta-analysis of balloon angioplasty versus primary stenting in the infrapopliteal disease. [Review]. Vascular & Endovascular Surgery 48:18-26.

44. Antoniou GA, Georgakarakos E, I, Antoniou SA et al. (2014) Does endovascular treatment of infra-inguinal arterial disease with drug-eluting stents offer better results than angioplasty with or without bare metal stents? Interactive Cardiovascular and Thoracic Surgery.19 (2) (pp 282-285), 2014.Date of Publication: August 2014. 282-285.

45. Spreen MI, Martens JM, Hansen BE et al. (2016) Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) Trial. Circulation: Cardiovascular Interventions 9:e002376.

46. Katsanos K, Spiliopoulos S, Karunanithy N et al. (2014) Bayesian network meta-analysis of nitinol stents, covered stents, drug-eluting stents, and drug-coated balloons in the femoropopliteal artery. [Review]. Journal of Vascular Surgery 59:1123-1133.

47. Baerlocher MO, Kennedy SA, Rajebi MR et al. (1920) Meta-analysis of drug-eluting balloon angioplasty and drug-eluting stent placement for infrainguinal peripheral arterial disease. Journal of Vascular & Interventional Radiology 26:459-473.

48. Katsanos K, Spiliopoulos S, Paraskevopoulos I et al. (2016) Systematic Review and Meta-analysis of Randomized Controlled Trials of Paclitaxel-Coated Balloon Angioplasty in the Femoropopliteal Arteries: Role of Paclitaxel Dose and Bioavailability. Journal of Endovascular Therapy 23:356-370.

49. Scheinert D, Schulte KL, Zeller T et al. (2015) Paclitaxel-releasing balloon in femoropopliteal lesions using a BTHC excipient: twelve-month results from the BIOLUX P-I randomized trial. Journal of Endovascular Therapy 22:14-21.

50. Zeller T, Beschorner U, Pilger E et al. (2015) Paclitaxel-Coated Balloon in Infrapopliteal Arteries: 12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). Jacc: Cardiovascular Interventions 8:1614-1622.

51. Laird JR, Schneider PA, Tepe G et al. (1-12-2015) Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. Journal of the American College of Cardiology 66:2329-2338.

52. Scheinert D, Duda S, Zeller T et al. (2014) The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. Jacc: Cardiovascular Interventions 7:10-19.

53. Fanelli F, Cannavale A, Corona M et al. (2014) The "DEBELLUM"--lower limb multilevel treatment with drug eluting balloon--randomized trial: 1-year results. The Journal of cardiovascular surgery 55:207-216.

54. Zeller T, Baumgartner I, Scheinert D et al. (2014) Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. Journal of the American College of Cardiology 64:1568-1576.