ClinicalEvidence

Peripheral arterial disease

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ABSTRACT

INTRODUCTION: Up to 20% of adults aged over 55 years have detectable peripheral arterial disease of the legs, but this may cause symptoms of intermittent claudication in only a small proportion of affected people. The main risk factors are smoking and diabetes mellitus, but other risk factors for cardiovascular disease are also associated with peripheral arterial disease. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for people with chronic peripheral arterial disease? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2009. (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 59 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antiplatelet agents; bypass surgery; cilostazol; exercise; pentoxifylline; percutaneous transluminal angioplasty (PTA); prostaglandins; smoking cessation; and statins.

QUESTIONS

INTERVENTIONS

TREATMENTS

Footnote

*Based on observational evidence and consensus.

Key points

- Up to 20% of adults aged over 55 years have detectable peripheral arterial disease of the legs, but this may cause symptoms of intermittent claudication in only a small proportion of affected people.

  The main risk factors are smoking and diabetes mellitus, but other risk factors for CVD are also associated with peripheral arterial disease.

  Overall mortality after the diagnosis of peripheral arterial disease is about 30% after 5 years and 70% after 15 years.

- Antiplatelet agents reduce major cardiovascular events, arterial occlusion, and revascularisation compared with placebo, with the overall balance of benefits and harms supporting treatment of people with peripheral arterial disease.

- Regular exercise increases maximal walking distance compared with no exercise.

  Stopping smoking and taking vitamin E may also increase walking distance when combined with exercise.

- Statins have been shown to reduce cardiovascular events in studies including people with PVD, and they may increase walking distance and time to claudication compared with placebo.

  Cilostazol may improve walking distance compared with placebo.

  We don't know whether pentoxifylline improves symptoms compared with placebo, and it may be less effective than cilostazol.

- Percutaneous transluminal angioplasty (PTA) may improve walking distance compared with no intervention, but the benefit may not last beyond 6 months.

- Bypass surgery may improve arterial patency for 12 to 24 months compared with PTA, but there seems to be no longer term benefit.

- Prostaglandins may improve amputation-free survival in critical ischaemia at 6 months when surgical revascularisation is not an option.

Prostaglandins are unlikely to be of benefit in intermittent claudication.

DEFINITION

Peripheral arterial disease arises when there is significant narrowing of arteries distal to the arch of the aorta. Narrowing can arise from atheroma, arteritis, local thrombus formation, or embolisation from the heart, or more central arteries. This review includes treatment options for people with symptoms of reduced blood flow to the leg that are likely to arise from atheroma. These symptoms range from calf pain on exercise (intermittent claudication) to rest pain, skin ulceration, or symptoms of ischaemic necrosis (gangrene) in people with critical limb ischaemia.

INCIDENCE/ PREVALENCE

Peripheral arterial disease is more common in people aged over 50 years than in younger people, and is more common in men than in women. The prevalence of peripheral arterial disease of the legs (assessed by non-invasive tests) is about 14% to 17% in men and 11% to 21% in women over 55 years of age. [1] [2] The overall annual incidence of intermittent claudication is 4.1 to 12.9 per 1000 men and 3.3 to 8.2 per 1000 women. [3]

AETIOLOGY/ RISK FACTORS

Factors associated with the development of peripheral arterial disease include age, gender, cigarette smoking, diabetes mellitus, hypertension, hyperlipidaemia, obesity, and physical inactivity. The strongest associations are with smoking (RR 2.0–4.0) and diabetes mellitus (RR 2.0–3.0). [4]

PROGNOSIS

The symptoms of intermittent claudication can resolve spontaneously, remain stable over many years, or progress rapidly to critical limb ischaemia. About 15% of people with intermittent claudication eventually develop critical limb ischaemia, which endangers the viability of the limb. The annual incidence of critical limb ischaemia in Denmark and Italy in 1990 was 0.25 to 0.45 per 1000 people. [5] [6] CHD is the major cause of death in people with peripheral arterial disease of the legs. Over 5 years, about 20% of people with intermittent claudication have a non-fatal cardiovascular event (MI or stroke). [7] The mortality rate of people with peripheral arterial disease is two to three times higher than that of age- and sex-matched controls. Overall mortality after the diagnosis of peripheral arterial disease is about 30% after 5 years and 70% after 15 years. [7]

AIMS OF INTERVENTION

To reduce intermittent claudication; symptoms of critical limb ischaemia (arterial leg ulcers, rest pain); and general complications (MI and stroke), and improve quality of life, while minimising adverse effects of interventions.

OUTCOMES

Claudication distance/time measures (initial claudication distance, absolute claudication distance, pain-free or maximal walking time, etc); generic/disease-specific quality of life; physiological measures (ankle brachial index); clinical end points (intervention rates, post-intervention morbidity/mortality); cardiovascular morbidity/mortality; and all-cause mortality; adverse effects.

METHODS

Clinical Evidence search and appraisal March 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2009; Embase 1980 to March 2009; and The Cochrane Database of Systematic Reviews, Issue 1, 2009. An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) website — for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for people with chronic peripheral arterial disease?

OPTION ANTIPLATELET AGENTS TO PREVENT CARDIOVASCULAR EVENTS OR PERIPHERAL ARTERIAL DISEASE

Post-intervention morbidity
Compared with placebo/no treatment Antiplatelet agents (aspirin and ticlopidine) are more effective at reducing the risk of arterial occlusion. However, low-dose aspirin plus dipyridamole is no more effective than placebo at preventing arterial reocclusion at 6 months in people undergoing peripheral endovascular intervention (high-quality evidence).

Cardiovascular events
Compared with placebo/control Antiplatelet agents (including dipyridamole, ticlopidine, clopidogrel, picotamide, and aspirin with or without dipyridamole) are more effective at reducing major cardiovascular events (high-quality evidence).

Antiplatelet agents (other than aspirin alone) compared with aspirin alone Antiplatelet agents (other than aspirin alone) may be more effective at reducing the risk of cardiovascular events and MI in people with intermittent claudication (low-quality evidence).

Note
Antiplatelet agents increase the risk of serious haemorrhage. The balance of benefits and harms is in favour of treatment for most people with symptomatic peripheral arterial disease, because as a group they are at much greater risk of cardiovascular events.

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Antiplatelet agents versus placebo or no antiplatelet agents:
We found seven systematic reviews (search dates 1999, [8] 1997, [9] [10] search date 1990, [11] 1998, [12] 2004, [13] 2008 [14]).

Cardiovascular event studies:
The first and second systematic reviews [8] [9] identified many of the same RCTs assessing antiplatelet agents in preventing cardiovascular events. However, they included different inclusion/exclusion criteria and performed different meta-analyses, so we report on both reviews here. The third systematic review [10] described the results presented in the second review. [9]

The first systematic review found that antiplatelet agents (including ticlopidine, suloctidil, indobufen, picotamide, and aspirin with or without dipyridamole) significantly reduced vascular events (non-fatal MI, non-fatal stroke, or vascular death) compared with placebo (24 RCTs; 6036 people with intermittent claudication: vascular events: 202/3100 [7%] with antiplatelet agents *v* 238/2936 [8%] with placebo; OR 0.78, 95% CI 0.63 to 0.96). [8] The second systematic review found that antiplatelet agents (including ticlopidine, dipyridamole, clopidogrel, picotamide, and aspirin with or without dipyridamole) significantly reduced serious vascular events compared with control (not defined) (42 RCTs; 9214 people with peripheral arterial disease: 280/4844 [6%] with antiplatelet agents *v* 347/4862 [7%] with control; P <0.004). [9]

Post-intervention morbidity studies:
The fourth systematic review (14 RCTs; 3226 people with intermittent claudication, or having bypass surgery of the leg, or peripheral artery angioplasty) found that antiplatelet agents (including dipyridamole, ticlopidine, suloctidil, and aspirin with or without dipyridamole) significantly reduced the risk of arterial occlusion over 19 months compared with placebo or no additional treatment (arterial occlusion: RRR 37%; P <0.00001). [11] The fifth systematic review found that aspirin significantly reduced arterial occlusion or revascularisation procedures compared with placebo at 3 months (1 RCT; 2810 people: arterial occlusion or revascularisation procedures: OR 0.46, 95% CI 0.27 to 0.77). [12] It also found that ticlopidine significantly reduced arterial occlusion or revascularisation procedures compared with placebo at up to 7 years (2 RCTs; 1302 people: OR 0.62, 95% CI 0.41 to 0.93). [12] The sixth systematic review found that the administration of low-dose aspirin plus dipyridamole in people undergoing peripheral endovascular intervention did not significantly reduce the risk of restenosis or reocclusion at 6 months compared with placebo (2 RCTs; 356 people: OR 0.69, 95% CI 0.44 to 1.10). [13] The seventh systematic review (15 RCTs; 4384 people) assessed antiplatelet agents after peripheral bypass surgery. [14] It found that antiplatelet agents (aspirin or aspirin plus dipyridamole) significantly reduced arterial occlusion of both venous and artificial peripheral bypass grafts compared with placebo at 12 months (6 RCTs; 966 people: occlusion: 114/501 [23%] with antiplatelet agents *v* 156/465 [34%] with placebo; OR 0.59, 95% CI 0.45 to 0.79). [14] Subgroup analyses of RCTs by the type of graft found that antiplatelet agents significantly reduced arterial occlusion for artificial grafts, and modestly but borderline significantly reduced arterial occlusion for venous grafts at 12 months, compared with placebo (artificial grafts: 4 RCTs; occlusion:

21/115 [18%] with antiplatelet agents *v* 57/107 [53%] with placebo; OR 0.22, 95% CI 0.12 to 0.38; venous grafts: 2 RCTs; occlusion: 71/335 [21%] with antiplatelet agents *v* 86/307 [28%] with placebo; OR 0.68, 95% CI 0.48 to 0.99). [14]

Antiplatelet agents (other than aspirin alone) versus aspirin alone:
We found one systematic review (search date 1999) [8] and one subsequent RCT. [15] The review found that antiplatelet agents (ticlopidine, clopidogrel, or aspirin plus dipyridamole) significantly reduced vascular events (non-fatal MI, non-fatal stroke, or vascular death) compared with aspirin (5 RCTs; 6928 people with peripheral arterial disease; vascular events: 227/3461 [7%] with other antiplatelet agents *v* 292/3467 [8%] with aspirin; OR 0.76, 95% CI 0.64 to 0.91). [8] The subsequent RCT (3096 people with symptomatic or asymptomatic peripheral arterial disease) was a post-hoc subgroup analysis from the CHARISMA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors). It found significantly lower MI rates with clopidogrel plus aspirin compared with placebo plus aspirin after 26 months (36/1545 [2%] with clopidogrel plus aspirin *v* 57/1551 [4%] with placebo plus aspirin; OR 0.63, 95% CI 0.42 to 0.96; P = 0.029). However, it found no significant difference in the overall rate of cardiovascular death, MI, or stroke between groups (117/1545 [8%] with clopidogrel plus aspirin *v* 138/1551 [9%] with placebo plus aspirin; HR 0.85, 95% CI 0.66 to 1.08; P = 0.18). [15]

Harms:

Antiplatelet agents versus placebo or no antiplatelet agents:
The first systematic review found no significant difference between antiplatelet agents and placebo in major bleeding (36 RCTs; 8449 people with claudication undergoing surgery or percutaneous transluminal angioplasty [PTA]: major bleeds: 47/4349 [1%] with antiplatelet agents *v* 33/4100 [0.8%] with placebo; OR 1.40, 95% CI 0.90 to 2.20). [8] The number of events was likely to have been too low to detect a clinically important increase in major bleeding. The second systematic review pooled results for all included RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone. It found that antiplatelet agents significantly increased the risk of a major extracranial bleed compared with control treatment (535/47,158 [1.1%] with antiplatelet agents *v* 333/47,168 [0.7%] with control; OR 1.6, 95% CI 1.4 to 1.8). [9] The third systematic review found that adverse effects associated with ticlopidine included rash (25%), neutropenia (1–2%), and thrombotic thrombocytopenic purpura (0.025–0.05%; significance not reported for any outcome). [10] Results for the control group were not reported. The fourth systematic review reported pooled harms for all included RCTs using antiplatelet agents (also including coronary and other conditions) rather than for people with peripheral arterial disease alone. It found that the risk of non-fatal "major" bleed and reoperation, haematoma, or infection caused by bleed was significantly increased with antiplatelet agents compared with control (non-fatal "major" bleed: 70/3214 [2%] with antiplatelet agents *v* 29/3201 [1%] with control; P = 0.002; reoperation, haematoma, or infection caused by bleed: 109/1997 [6%] with antiplatelet agents *v* 72/2002 [4%] with control; P = 0.02). [11] It found no significant difference between groups in fatal bleeding, although the result was of borderline significance (5/3267 [0.15%] with antiplatelet agents *v* 1/3262 [0.03%] with control; P = 0.06). [11] The fifth systematic review did not report on harms. [12] The sixth systematic review reported that one included RCT found no significant difference between antiplatelet agents and placebo in bleeding at the puncture site after endovascular treatment (OR 1.52, 95% CI 0.47 to 4.96). [13] The seventh systematic review found increased adverse effects with antiplatelet agents, which was of borderline significance (6 RCTs: 58/501 [12%] with antiplatelet agents *v* 36/465 [7%] with placebo; OR 1.55, 95% CI 1.00 to 2.41; P = 0.052). There was no significant difference in GI adverse effects or major bleeding between groups (GI adverse effects: 6 RCTs; 54/501 [11%] with antiplatelet agents *v* 36/465 [7%] with placebo; OR 1.44, 95% CI 0.92 to 2.24; P = 0.11; major bleeding: 2 RCTs; 19/318 [6%] with antiplatelet agents *v* 9/280 [3%] with placebo; OR 1.88, 95% CI 0.85 to 4.16; P = 0.12). [14]

Antiplatelet agents (other than aspirin alone) versus aspirin alone:
The systematic review found no significant difference between aspirin and other antiplatelet agents (ticlopidine, clopidogrel, or dipyridamole plus aspirin) in major bleeding (5 RCTs; 7028 people with peripheral arterial disease: major bleeds: 68/3467 [2.0%] with aspirin *v* 50/3561 [1.4%] with other antiplatelet agents; OR 0.73, 95% CI 0.51 to 1.06). [8] The number of events was likely to have been too low to detect a clinically important increase in major bleeding. The subsequent RCT found that minor bleeding was significantly increased with clopidogrel plus aspirin compared with placebo plus aspirin (531/1545 [34%] with clopidogrel plus aspirin *v* 323/1551 [21%] with placebo plus aspirin; HR 1.99, 95% CI 1.69 to 2.34; P <0.001). However, there was no significant difference in fatal, severe, or moderate bleeding or primary intracranial haemorrhage between groups (fatal bleeding: 7/1545 [0.5%] with clopidogrel plus aspirin *v* 6/1551 [0.4%] with placebo plus aspirin; HR 1.17, 95% CI 0.39 to 3.49; P = 0.776; primary intracranial haemorrhage: 3/1545 [0.2%] with clopidogrel plus aspirin *v* 6/1551 [0.4%] with placebo plus aspirin; HR 0.50, 95% CI 0.12 to 2.01; P = 0.507; severe bleeding: 26/1545 [1.7%] with clopidogrel plus aspirin *v* 27/1551 [1.7%] with placebo plus aspirin; HR 0.97, 95% CI 0.56 to 1.66; P = 0.90; moderate bleeding: 38/1545 [3%] with clopidogrel

plus aspirin *v* 29/1551 [2%] with placebo plus aspirin; HR 1.32, 95% CI 0.81 to 2.16; P = 0.26). [15]

Comment:

Clinical guide:
Across a wide range of people, antiplatelet agents have been found to increase significantly the risk of major haemorrhage. Peripheral arterial disease increases the risk of cardiovascular events; for most people, the risk of bleeding is outweighed by the benefits of regular antiplatelet use.

OPTION EXERCISE

Claudication distance/time
Compared with usual care/placebo Regular exercise may be more effective at improving measures of walking distance and time in people with chronic stable claudication. We don't know whether resistance training is more effective than control at improving walking distance (assessed by a 6-minute walk test) at 6 months (low-quality evidence).

Exercise as part of a multicomponent intervention compared with usual care/placebo Regular exercise plus vitamin E may be more effective than placebo at increasing walking duration at 6 months. A "stop smoking and keep walking" intervention may be more effective than usual care at increasing the maximal walking distance at 12 months (low-quality evidence).

Different types of exercise compared with each other We don't know whether upper-limb exercises are more effective than lower-limb exercises at improving claudication distance and maximum walking distance. Cycling three times a week for 6 weeks may be less effective than walking exercise at increasing maximum walking time and pain-free walking time in people with intermittent claudication (low-quality evidence).

Quality of life
Compared with usual care/placebo We don't know whether exercise (supervised treadmill or resistance training) is more effective than usual care at improving quality of life (assessed by the short form-36 [SF-36] or the Walking Impairment Questionnaires) at 6 months (low-quality evidence).

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Exercise versus usual care/placebo:
We found three systematic reviews (search date 1996, [16] 2006, [17] and 2008 [18]) comparing exercise versus control treatments (placebo tablets or instructions "to continue with normal lifestyle"). We found one additional RCT, [19] and one subsequent RCT. [20] The systematic reviews identified many of the same RCTs; however, they applied different inclusion criteria and performed different meta-analyses, so we report all three here. The first review (6 RCTs; 2 RCTs in people also being treated with surgery, aspirin, or dipyridamole) found that exercise programmes significantly increased both the initial claudication distance and the absolute claudication distance compared with usual care or placebo after 3 to 12 months (mean increase in initial claudication distance between exercise and no exercise: 4 RCTs; 94 people with chronic, stable intermittent claudication: 139 metres, 95% CI 31 metres to 247 metres; mean increase in absolute claudication distance between exercise and no exercise: 5 RCTs; 115 people: 179 metres, 95% CI 60 metres to 298 metres). Exercise programmes involved at least 30 minutes of walking as far as claudication permitted, at least 3 times a week, for 3 for 6 months. [16] The second review (10 RCTs; 577 people) compared supervised exercise therapy, for between 12 weeks and 2 years, with usual care. It found that exercise significantly increased pain-free walking distance and maximum walking distance compared with usual care (pain-free walking distance: 8 RCTs: WMD 81.29 metres, 95% CI 35.45 metres to 127.14 metres; P = 0.0005; maximum walking distance: 9 RCTs: WMD 155.79 metres, 95% CI 80.84 metres to 230.74 metres; P <0.0001). [17] The third review (16 RCTs; 811 people) found that exercise, for between 12 weeks and 2 years, significantly increased maximum walking distance and pain-free walking distance compared with usual care/placebo (mean increase in maximal walking distance between exercise and no exercise: 6 RCTs; 391 people: 113.2 metres, 95% CI 94.96 metres to 131.43 metres; mean increase in pain-free walking distance between exercise and no exercise: 6 RCTs; 322 people: 82.19 metres, 95% CI 71.73 metres to 92.65 metres). It also found that exercise significantly improved maximum walking time compared with usual care/placebo (7 RCTs; 255 people: 136 minutes with exercise *v* 119 minutes with usual care/placebo; WMD 5.12 minutes, 95% CI 4.51 minutes to 5.72 minutes). There was no significant difference between groups in the ankle brachial index (7 RCTs; 228 people: mean difference –0.01, 95% CI –0.05 to +0.04). [18]

The additional RCT compared four treatments: polestriding exercise (45–60 minutes, 3 times/week for 24 weeks) plus vitamin E; polestriding exercise plus placebo; vitamin E alone; and placebo alone. [19] It found that exercise improved walking duration on a constant work-rate treadmill test compared with placebo alone at 6 months (52 people with intermittent claudication; walking duration: 804 seconds at baseline to 2020 seconds with exercise *v* 612 seconds to 623 seconds with

placebo; P value not reported). The subsequent RCT (156 people) compared supervised treadmill exercise or resistance training (both 3 times/week) versus control (11 nutritional information sessions; not designed to change behaviour). It found that supervised treadmill exercise significantly increased walking distance (assessed by a 6-minute walk test) compared with control at 6 months (change from baseline: 20.9 metres with treadmill exercise *v* –15.0 metres with control; difference 35.9 metres, 95% CI 15.3 metres to 56.5 metres; P <0.001). There was no significant difference between resistance training and control in walking distance (change from baseline: –2.6 metres with resistance training *v* –15.0 metres with control; difference +12.4 metres, 95% CI –8.42 metres to +33.3 metres; P = 0.24). The RCT found that supervised treadmill exercise significantly improved some domains of quality-of-life questionnaires compared with control at 6 months (difference between groups in change from baseline: short form-36 [SF-36] physical functioning score: 7.50 with treadmill exercise *v* control, 95% CI 0 to 15.0; P = 0.02; Walking Impairment Questionnaire distance score: 10.7 with treadmill exercise *v* control, 95% CI 1.56 to 19.9; P = 0.02). However, it found no significant difference between groups in other domains of quality of life at 6 months (difference between groups in change from baseline: Walking Impairment Questionnaire stair: climbing score: 8.33 with treadmill exercise *v* control, 95% CI 0.0 to 16.7; P = 0.06; speed score: +3.80 with treadmill exercise *v* control, 95% CI –4.35 to +12.0; P = 0.39). It found that resistance training also significantly improved some domains of quality-of-life questionnaires compared with control at 6 months (difference between groups in change from baseline: SF-36 physical functioning score: 7.50 with resistance training *v* control, 95% CI 0 to 15.0; P = 0.04; Walking Impairment Questionnaire distance score: 6.92 with resistance training *v* control, 95% CI 1.07 to 12.8; P = 0.03; stair-climbing score: 10.4 with resistance training *v* control, 95% CI 0.0 to 20.8; P = 0.02). However, it found no significant difference between groups in other domains of quality of life at 6 months (difference between groups in change from baseline: Walking Impairment Questionnaire speed score: +1.63 with resistance training *v* control, 95% CI –5.43 to +8.70; P = 0.55). [20]

Exercise as part of a multicomponent intervention versus usual care or placebo:
We found two RCTs. [19] [21] The first RCT compared four treatments: polestriding exercise (45–60 minutes 3 times/week for 24 weeks) plus vitamin E; polestriding exercise plus placebo; vitamin E alone; and placebo alone. [19] It found that exercise plus vitamin E improved walking duration on a constant work-rate treadmill test compared with placebo alone at 6 months (52 people with intermittent claudication; walking duration: 486 seconds at baseline to 1886 seconds at 6 months with exercise plus vitamin E *v* 612 at baseline to 623 seconds at 6 months with placebo; P value not reported).

The second RCT compared a "stop smoking and keep walking" intervention package versus usual care. [21] The intervention package involved an educational package, a brochure about community physiotherapy services, and information on the benefits of smoking cessation. The general practitioners of these participants received a letter plus educational material (including information about the effects of stopping smoking, nicotine replacement products, and peripheral arterial disease) and a recommendation to refer the person to community physiotherapy. The community physiotherapist received details about likely referrals. Physiotherapists provided a community-based mobility programme for senior citizens, consisting of supervised or home-based exercise sessions, and advice to walk for at least 30 minutes per day. All participants completed the Edinburgh Claudication Questionnaire at randomisation and at follow-up (2 months and 12 months). The questionnaires were used to compare self-reported maximum walking distance at baseline and at follow-up. It found that the intervention significantly increased self-reported maximal walking distance compared with usual care at 12 months (882 men with early PVD identified by population screening; 23% with intervention *v* 15% with control; P = 0.008). It found no significant difference between intervention and usual care in intermittent claudication grade (Edinburgh Claudication Questionnaire: P = 0.26). [21]

Different types of exercise versus each other:
We found three RCTs. [22] [23] [24] The first RCT (67 people with moderate-to-severe intermittent claudication) compared arm exercises versus leg exercises of similar intensity versus no treatment. [22] The RCT found no significant difference between arm and leg exercises in improvement in initial claudication distance or absolute claudication distance, although both groups improved after 6 weeks (48 people: improvement in initial claudication distance from baseline: 122% with arm exercises *v* 93% with leg exercises; absolute results presented graphically, P value not reported; improvement in absolute claudication distance from baseline: 147% with arm exercises *v* 150% with leg exercises; absolute results presented graphically, P value not reported). The second RCT (94 people) compared upper-limb exercise versus lower-limb exercise versus no exercise. [23] It found that twice-weekly upper or lower-limb exercises significantly improved claudication distance and maximal walking distance compared with control, and the improvements were similar with the two exercise groups after 24 weeks (improvement in claudication distance: 51% with upper-limb exercise *v* 57% with lower-limb exercise *v* 0% with control; P [exercise *v* control] <0.001, significance for upper-limb *v* lower-limb exercise not reported; improvement in maximal walking distance: 29%

with upper-limb exercise *v* 31% with lower-limb exercise *v* 0% with control; P [exercise *v* control] <0.001, significance for upper-limb *v* lower-limb exercise not reported). The third RCT (42 people) compared cycle training versus treadmill training (each 3 times/week for 6 weeks) versus control (no supervised training programme). [24] It found that treadmill training significantly improved maximum walking time and pain-free walking time compared with cycle training (maximum walking-time increase: +240 seconds with treadmill training *v* +48 seconds with cycle training *v* –10 seconds with control; between-group P value not reported; pain-free walking-time increase: +195 seconds with treadmill training *v* –8 seconds with cycle training *v* +55 seconds with control; between-group P value not reported).

Harms:

Exercise versus usual care/placebo:
The reviews [16] [17] [18] and additional [19] and subsequent [20] RCTs did not report on the harms of the exercise programmes.

Exercise as part of a multicomponent intervention versus usual care or placebo:
The RCTs did not report on the harms of the exercise programmes as part of a multicomponent intervention. [19] [21]

Different types of exercise versus each other:
The RCTs did not report on the harms of the exercise programmes. [22] [23] [24]

Comment:

The RCTs in the systematic reviews had low withdrawal rates, but it is unclear whether those assessing the outcomes were blind to the group allocation. Concealment of the allocation to participants was not possible. [16] [17] [18] We found one further systematic review (search date 1993; 21 observational studies or RCTs of exercise; 564 people with peripheral arterial disease). [25] It calculated effects based on the differences in claudication distance before and after exercise treatment, but made no allowance for any spontaneous improvement that might have occurred in the participants. It reported large increases with exercise in the initial claudication distance (126–351 metres) and in the absolute claudication distance (325–723 metres), but these estimates were based on observational data. The benefit from arm exercise may be caused by generally improved cardiovascular function rather than local changes in the peripheral circulation.

OPTION BYPASS SURGERY

Post-intervention morbidity
Compared with percutaneous transluminal angioplasty (PTA) Bypass surgery may be more effective at improving primary arterial patency after 12 to 24 months, but we don't know whether it is more effective after 4 years. We don't know whether bypass surgery is more effective than PTA at decreasing amputation rates (low-quality evidence).

Compared with PTA plus stent placement We don't know whether bypass surgery is more effective than PTA plus stent placement at improving primary patency rates at 6–24 months in people with superficial femoral artery occlusive disease (low quality-evidence).

Mortality
Compared with PTA We don't know whether bypass surgery is more effective than PTA at decreasing mortality within 30 days in people with intermittent claudication or critical limb ischaemia (low quality-evidence).

Note
The risk of serious postoperative complications and mortality may be greater after bypass surgery compared with PTA. We found no clinically important results about the effects of bypass surgery compared with PTA plus stent placement.

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Bypass surgery versus percutaneous transluminal angioplasty (PTA):
We found one systematic review (search date 2007; 4 RCTs; 873 people with intermittent claudication or critical limb ischaemia) comparing bypass surgery with PTA. [26] The review did not pool data for all outcomes because of differences in symptoms of included participants and follow-up time between RCTs. One of the RCTs found no significant difference between surgery and PTA in mortality within 30 days (434 people: 11/197 [6%] with surgery *v* 7/237 [3%] with PTA; OR 1.93, 95% CI 0.75 to 4.99). Two of the RCTs (156 people) reported no deaths in either group within 30 days. Three of the RCTs found no significant difference in amputation rates between groups (pooled analysis not reported; reported as not significant). [26] The review found that surgery modestly but significantly improved primary patency after 12 months compared with PTA (2 RCTs; 355 people: 137/178 [77%] with bypass surgery *v* 119/177 [67%] with PTA; OR 1.6, 95% CI 1.0 to 2.6). It found no significant difference in primary patency after median 4 years (1 RCT; 263 people; absolute numbers not reported; P = 0.14). [26]

Bypass surgery versus PTA plus stent placement:
We found one RCT (100 limbs; 86 people with superficial femoral artery occlusive disease) comparing long-term outcomes of surgery versus PTA plus stent placement. [27] It found no significant difference in primary patency rates between femoro-above-knee popliteal bypass grafting and PTA plus stent placement at 6, 12, or 24 months (6 months: 84% with femoro-above-knee popliteal bypass grafting *v* 81% with PTA plus stent placement; 12 months: 83% with femoro-above-knee popliteal bypass grafting *v* 72% with PTA plus stent placement; 24 months: 76% with femoro-above-knee popliteal bypass grafting *v* 64% with PTA plus stent placement; absolute results not reported, P = 0.72). [27]

Harms:

Bypass surgery versus PTA:
The review found that surgery was associated with increased complications compared with angioplasty in people with critical limb ischaemia (2 RCTs; 472 people: 122/226 [54%] with surgery *v* 72/246 [29%] with PTA; OR 2.85, 95% CI 1.97 to 4.12). It found no significant difference in complications between groups (in people with intermittent claudication) in one of these RCTs (41 people: 1/18 [6%] with surgery *v* 3/23 [13%] with PTA; OR 0.44, 95% CI 0.06 to 3.40). The review defined complications in this RCT as bleeding, occlusion, infection, and embolism, but did not describe the complications in the other RCT. The review reported that three people having surgery died of causes related to the operation in one RCT (263 people; statistical assessment not reported). The review found that surgery significantly increased hospital stay compared with angioplasty (number of days: 46.1 with surgery *v* 36.4 with angioplasty; P <0.0001). [26]

Bypass surgery versus PTA plus stent placement:
The RCT found similar rates of early complications between groups (3/46 [7%] with femoro-above-knee popliteal bypass grafting *v* 4/40 [10%] with PTA plus stent placement; significance assessment not reported). Complications included: superior femoral artery dissection, transient leg oedema, transient thigh pain and a small groin haematoma with PTA plus stent, and groin lymphocoele and a small superficial groin wound dehiscence with bypass grafting.

Comment:

Clinical guide:
Although the consensus is that bypass surgery is the most effective treatment for people with debilitating symptomatic peripheral arterial disease, we found inadequate evidence from RCTs reporting long-term clinical outcomes to confirm this view. Long-term follow-up data from one of the RCTs included in the review [28] may provide better evidence in the future.

OPTION STATINS (HMG-COA REDUCTASE INHIBITORS)

Claudication distance/time
Compared with placebo Statins (simvastatin, atorvastatin) seem more effecting at increasing pain-free walking distance or time to onset of claudication at 6 to 12 months (moderate-quality evidence).

Quality of life
Compared with placebo Atorvastatin seems no more effective at improving quality of life scores (assessed by the Walking Impairment Questionnaire and short form-36 [SF-36] questionnaire) in people with peripheral arterial disease and intermittent claudication (moderate-quality evidence).

Cardiovascular events
Compared with placebo Statins (simvastatin, atorvastatin, and pravastatin) seem more effective at reducing major cardiovascular events in people with peripheral arterial disease (moderate-quality
evidence).

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Statins versus placebo:
Cardiovascular events studies:
We found no systematic review. We found three RCTs reported in four publications, comparing statins versus placebo. [29] [30] [31] [32]

The first RCT (20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus), comparing simvastatin versus placebo, was reported in two publications. [29] [30] It reported subgroup analyses of people with peripheral arterial disease (6748/20,536 [33%]), and also people with peripheral arterial disease but without diagnosed CHD (2701/20,536 [13%]). It found that in all people, simvastatin significantly reduced all-cause mortality, coronary death, non-fatal or fatal stroke, and coronary or non-coronary revascularisation compared with placebo at 5 years (20,536 people: all-cause mortality: 1328/10,269 [13%] with simvastatin *v* 1507/10,267 [15%] with placebo; P = 0.0003; coronary death: 587/10,269 [6%] with simvastatin *v* 707/10,267 [7%] with placebo; P = 0.0005; non-fatal or fatal stroke: 444/10,269 [4%] with simvastatin *v* 585/10,267 [6%] with placebo;

P <0.0001; coronary or non-coronary revascularisation: 939/10,269 [9%] with simvastatin *v* 1205/10,267 [12%] with placebo; P <0.0001). It found that simvastatin 40 mg daily significantly reduced the incidence of first major vascular events (major coronary event, stroke, and revascularisation) compared with placebo in people with peripheral arterial disease and in people with peripheral arterial disease but without prior CHD (6748 people with peripheral arterial disease: 895 [26%] with simvastatin *v* 1101 [33%] with placebo; absolute numbers in each group not reported, absolute reduction of 63 per 1000; P <0.001; 2701 people with peripheral arterial disease and no prior CHD; 327/1325 (25%) with simvastatin *v* 420/1376 (31%) with placebo; P <0.0001). [29] [30]

The second RCT (10,305 people with hypertension; 514 [5%] with peripheral arterial disease) compared atorvastatin versus placebo. [31] It did not separately report on the subgroup with peripheral arterial disease. It found that atorvastatin 10 mg daily significantly reduced total cardiovascular events (non-fatal MI and fatal CHD), total coronary events, and fatal and non-fatal stroke compared with placebo at median follow-up of 3.3 years (total cardiovascular events: 389/5168 [7.5%] with atorvastatin *v* 486/5137 [9.5%] with placebo; HR 0.79, 95% CI 0.69 to 0.90; total coronary events: 178/5168 [3.4%] with atorvastatin *v* 247/5137 [4.8%] with placebo; HR 0.71, 95% CI 0.59 to 0.86; fatal and non-fatal stroke: 89/5168 [1.7%] with atorvastatin *v* 121/5137 [2.4%] with placebo; HR 0.73, 95% CI 0.56 to 0.96; see comment). [31] There was no significant difference between atorvastatin and placebo in all-cause mortality or cardiovascular mortality at follow-up (all-cause mortality: 185/5168 [3.6%] with atorvastatin *v* 212/5137 [4.1%] with placebo; HR 0.87, 95% CI 0.71 to 1.06; cardiovascular mortality: 74/5168 [1.4%] with atorvastatin *v* 82/5137 [1.6%] with placebo; HR 0.90, 95% CI 0.66 to 1.23).

The third RCT (5804 people; aged 70–82 years; 513 [9%] with intermittent claudication or previous peripheral arterial surgery) compared pravastatin versus placebo. [32] It did not separately report on the subgroup with peripheral arterial disease. It found that pravastatin 40 mg daily significantly reduced the combined end point of coronary death, non-fatal MI, and fatal or non-fatal stroke compared with placebo at mean follow-up of 3.2 years (combined end point: 408/2891 [14%] with pravastatin *v* 473/2913 [16%] with placebo; HR 0.85, 95% CI 0.74 to 0.97). [32]

Claudication studies:
We found no systematic review. We found three RCTs comparing statins versus placebo. [33] [34] [35] The first RCT (69 people with intermittent claudication, aged 60–85 years) found that simvastatin 40 mg daily significantly increased time to onset of claudication compared with placebo at 12 months (increase in exercise time: 225 seconds at baseline to 320 seconds at 12 months with simvastatin *v* 231 seconds at baseline to 221 seconds at 12 months with placebo; P <0.0001). [33]

The second RCT (86 people with peripheral arterial disease and intermittent claudication) found that simvastatin 40 mg daily increased pain-free walking distance and total walking distance compared with placebo at 6 months (pain-free walking distance: 72 metres at baseline to 190 metres at 6 months with simvastatin *v* 74 metres at baseline to 100 metres at 6 months with placebo; P <0.0005; total walking distance: 96 metres at baseline to 230 metres at 6 months with simvastatin *v* 93 metres at baseline to 104 metres at 6 months with placebo; P <0.005). [34] It also found that simvastatin significantly improved ankle brachial index (ABI) both at rest and after exercise compared with placebo at 6 months (ABI at rest: 0.53 at baseline to 0.65 at 6 months with simvastatin *v* 0.55 at baseline to 0.56 at 6 months with placebo; P <0.01; ABI after exercise: 0.35 at baseline to 0.55 at 6 months with simvastatin *v* 0.39 at baseline to 0.36 at 6 months with placebo; P <0.01).

The third RCT (354 people with peripheral arterial disease and intermittent claudication) found that atorvastatin (80 mg daily) improved pain-free walking time compared with placebo at 12 months (mean improvement in pain-free walking time from baseline: 81 seconds with atorvastatin *v* 39 seconds with placebo; P = 0.025). [35] However, it found no significant difference between atorvastatin and placebo in maximal walking time after 12 months of treatment (increase in maximal walking time from baseline: 90 seconds with atorvastatin *v* 50 seconds with placebo; P = 0.37). There was no significant difference between treatments in quality of life (measured using the Walking Impairment Questionnaire and short form-36 [SF-36]; reported as not significant; no further data reported).

Harms:

High doses of atorvastatin have been associated with an increased risk of haemorrhagic stroke in people with recent haemorrhagic stroke or lacunar infarct. In these people, commencing high-dose atorvastatin (80 mg) should be carefully considered as the balance of risks and benefits is uncertain. [36] [37]

Statins versus placebo:
Vascular events studies:
The first RCT found no significant difference between simvastatin and placebo in the proportion of people with muscular pain and weakness (32.9% with simvastatin *v* 33.2% with placebo; absolute

numbers not reported; P value not reported). [29] There were similar proportions of people who discontinued treatment because of adverse effects in both groups (4.8% with simvastatin *v* 5.1% with placebo; absolute numbers not reported; significance assessment not reported). There was no significant difference in the rate of new primary cancers between treatment groups (814/10,269 [7.9%] with simvastatin *v* 803/10,267 [7.8%] with placebo; RR 1.0, 95% CI 0.91 to 1.11). [29] The second RCT found similar rates of serious adverse effects between the placebo and statin groups (serious adverse effects not described; significance assessment not reported). [31] The RCT reported one incidence of fatal rhabdomyolysis in the statin group. The third RCT found that the frequency of serious adverse effects (including myalgia) was similar with pravastatin and placebo (myalgia: 36/2891 [1.2%] with pravastatin *v* 32/2913 [1.1%] with placebo; significance not reported). [32] However, the study did report a significant increase in the number of new cancers in the pravastatin group (245/2891 [9%] with pravastatin *v* 199/2913 [7%] with placebo; HR 1.25, 95% CI 1.04 to 1.51).

Claudication studies:
The first and second RCTs did not report on harms. [33] [34] The third RCT reported four deaths in people taking atorvastatin 10 mg , one in people taking atorvastatin 80 mg, and one in people taking placebo (significance assessment not reported). [35] The study also reported four MIs and one stroke in people taking atorvastatin 10 mg, two MIs and one stroke in people taking atorvastatin 80 mg, and three MIs in people taking placebo (significance assessment not reported). The number of discontinuations from the trial was similar between the three groups (33/120 [28%] with atorvastatin 10 mg *v* 25/120 [21%] with atorvastatin 80 mg *v* 28/114 [25%] with placebo; significance assessment not reported). [35]

Comment: People with peripheral arterial disease formed only a small proportion of the total number of people randomised. [29] [30] [31] [32] However, similar benefits were observed in this subgroup, suggesting that the results of the three RCTs may be generalisable to people with peripheral arterial disease. Follow-up was complete in more than 90% of people recruited in all three RCTs.

OPTION PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)

Claudication distance/time
Compared with no percutaneous intervention Percutaneous transluminal angioplasty (PTA) may be more effective at improving walking distance after 6 months, but not after 2 or more years, compared with no angioplasty or with exercise alone in people with mild-to-moderate intermittent claudication (low-quality evidence).

Quality of life
Compared with no percutaneous intervention We don't know whether percutaneous transluminal angioplasty (PTA) is more effective at improving quality of life (assessed by the Nottingham Health Profile or short form-36 [SF-36] questionnaire) at 3 to 24 months (very low-quality evidence).

PTA plus routine stent compared with PTA plus selective stent We don't know whether routine use of stents as part of PTA or selective use of stents are more effective at improving quality of life at 3 to 12 months (assessed using the RAND-36 questionnaire or the SF-36 questionnaire) (low-quality evidence).

Post-intervention morbidity
Compared with bypass surgery PTA may be less effective at improving primary arterial patency after 12 to 24 months, but we don't know whether it is more effective after 4 years. We don't know whether PTA is more effective than bypass surgery at decreasing amputation rates (low-quality evidence).

PTA plus stent compared with PTA alone PTA plus stent may be more effective than PTA alone at increasing patency rates at 6 months but we don't know whether it is more effective at 12 to 24 months (low-quality evidence).

PTA plus routine stent compared with PTA plus selective stent We don't know whether routine use of stents as part of PTA or selective use of stents are more effective at improving arterial occlusion rates or reintervention rates (low-quality evidence).

PTA plus statin compared with PTA alone PTA plus statin may be no more effective at reducing restenosis rates at 12 months (low-quality evidence).

Mortality
Compared with bypass surgery We don't know whether PTA is more effective than bypass surgery at decreasing mortality within 30 days in people with intermittent claudication or critical limb ischaemia (low-quality evidence).

PTA plus routine stent compared with PTA plus selective stent PTA plus routine stent seems no more effective than PTA plus selective stent at decreasing mortality at 1 year in people with severe claudication or limb-threatening stenosis of the superficial femoral artery (moderate-quality evidence).

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

PTA versus no percutaneous intervention:

We found one systematic review (search date 2006; 2 RCTs; 98 people) [38] and one subsequent RCT. [39] The review did not pool the results of the RCTs identified. The first RCT (62 people with mild-to-moderate intermittent claudication) identified by the review found that PTA significantly increased the median initial claudication distance after 6 months compared with no PTA, but found no significant difference in median initial claudication distance or quality of life after 2 years (median initial claudication distance at 6 months: 667 metres with PTA *v* 172 metres with no PTA; P <0.05; median initial claudication distance at 2 years: 383 metres with PTA *v* 333 metres with no PTA: P = 0.578; quality of life [assessed using the Nottingham Health Profile]: P >0.05, absolute results for combined quality of life measure not reported). [40] The second RCT identified by the review found that PTA significantly increased the absolute claudication distance at 6 months compared with an exercise programme (1 RCT; 36 people; 130 metres with PTA *v* 50 metres with exercise programme; WMD 80 metres; P <0.05). [41] The subsequent RCT (56 people with disabling intermittent claudication) compared PTA plus optimal medical treatment versus optimal medical treatment alone. It found a significant improvement in pain-free walking distance and maximum walking distance with optimal medical treatment alone compared with PTA plus optimal medical treatment at 24 months (pain-free walking distance: 174.9 metres with PTA plus optimal medical treatment *v* 435 metres with optimal medical treatment alone; P = 0.0001; maximum walking distance: 319.5 metres with PTA plus optimal medical treatment *v* 539.2 metres with optimal medical treatment alone; P = 0.0009). It found that PTA plus optimal medical treatment significantly improved some domains of quality-of-life questionnaires at 3 months (absolute results not reported; short form-36 [SF-36] physical functioning: P = 0.0003; SF-36 bodily pain: P <0.014; SF-36-reported health transition: P <0.0001; claudication scale pain during activity: P = 0.0014; claudication scale severity of pain: P = 0.001) but found no significant difference between groups in any other domain (absolute results not reported; SF-36: physical role, general health vitality, social functioning, mental health; claudication scale: everyday life, pain related to sleep, specific fears related to illness or psychological well-being; all reported as not significant; P values not reported). It found that PTA plus optimal medical treatment significantly improved only one domain of the SF-36 questionnaire at 24 months compared with optimal medical treatment alone (SF-36 physical functioning; absolute results not reported; P <0.0098), and found no significant difference between groups in any of the other domains of the SF-36 questionnaire or the claudication scale (absolute results not reported; all reported as not significant; P values not reported). Optimal medical treatment involved patient education regarding exercise, nutrition, and smoking cessation, and medication including antiplatelet agents, lipid-lowering agents, antihypertensives, and antidiabetic agents, when indicated. [39]

PTA plus stents versus PTA alone:

We found two systematic reviews (search date 2008, 7 RCTs; search date 2002, 2 RCTs; 1 RCT in common; 53 people). [42] [43] The first systematic review (7 RCTs; 519 people; 614 limbs) found that angioplasty plus stenting significantly improved patency rates compared with angioplasty alone at 6 months' follow-up (4 RCTs; 304 limbs; OR 0.47, 95% CI 0.27 to 0.84; P <0.05) but found no significant difference between groups at 12 and 24 months' follow-up (12 months: 6 RCTs; 519 limbs: OR 1.27, 95% CI 0.87 to 1.86; 24 months: 4 RCTs; 417 limbs: OR 1.22, 95% CI 0.81 to 1.82). [42] The second earlier systematic review did not pool data, because the two RCTs used different techniques and different definitions of restenosis. [43] One RCT was also identified by the first review, so we only present data from the other included RCT here. The RCT (51 people with aorto-iliac or femoro-popliteal lesions on angiography who had received an intravenous bolus of heparin and oral aspirin) found no significant difference in patency or in occlusion rate between PTA alone and PTA plus stent after 1 year (patency: 74% with PTA alone *v* 62% with PTA plus stent; absolute results not reported, P = 0.22; occlusion rate: 2/27 [7%] with PTA alone *v* 5/24 [21%] with PTA plus stent; P = 0.16). [44]

PTA plus routine stent versus PTA plus selective stent:

We found three RCTs comparing PTA plus routine stenting versus PTA plus selective stenting. [45] [46] [47] [48] The first RCT (279 people with intermittent claudication and iliac artery stenosis) found no significant difference between PTA plus routine stenting and PTA plus selective stenting in reintervention rates (reintervention rate: 10/143 [7%] with PTA plus routine stent *v* 6/136 [4%] with PTA plus selective stent; ARR +3%, 95% CI –3% to +8%). [45] It also found no significant difference between groups in quality of life (assessed using the RAND-36 questionnaire) after 3 months' follow-up (absolute results not reported, reported as not significant). The second RCT (227 people with severe claudication or limb-threatening stenosis of the superficial femoral artery) found no significant difference between treatments in death or restenosis after 1 year (death or >50% restenosis: 29/86 [33%] with PTA plus selective stent *v* 30/89 [34%] with PTA plus routine stent; P = 0.9). [46] The third RCT (104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery) was reported in two publications. [47] [48] The first publication [47] reported on restenosis and clinical outcomes; the second publication [48] reported on quality-of-life outcomes.

The RCT found that primary nitinol self-expanding stents significantly improved patency and clinical results of superficial femoral artery stenoses or occlusions at 12 months compared with balloon angioplasty with optional secondary stenting (proportion of people with restenosis: 18/49 [37%] with primary stenting *v* 33/52 [63%] with balloon angioplasty; P = 0.01; walking distance: 387 metres with primary stenting *v* 267 metres with balloon angioplasty; P = 0.04). [47] It found no significant difference in physical or mental components of the SF-36 quality-of-life questionnaire (scale of 0 to 100; higher scores indicate a better quality of life) at 6 or 12 months between balloon angioplasty with optional secondary stenting and primary nitinol self-expanding stents (6 months: physical component: 37 with balloon angioplasty *v* 33 with primary stenting; P = 0.8; mental component: 50 with balloon angioplasty *v* 53 with primary stenting; P = 0.5; 12 months: physical component: 37 with balloon angioplasty *v* 35 with primary stenting; P = 0.9; mental component: 51 with balloon angioplasty *v* 54 with primary stenting; P = 0.1; intention-to-treat analysis). [48]

PTA alone versus PTA plus statins:
We found one RCT (37 people taking aspirin 250 mg/day with critical ischaemia or severe claudication; Fontaine classification class IIb or II). It found no significant difference between PTA plus lovastatin (20 mg daily) and PTA alone in restenosis rates at 12 months (restenosis: 8/19 [42%] with PTA alone *v* 4/18 [22%] with PTA plus lovastatin; reported as not significant; P value not reported). [49] The RCT is likely to have been underpowered to detect a small but clinically important difference between the two groups. [49]

PTA versus bypass surgery:
See benefits of bypass surgery, p 7 .

Harms:

PTA versus no percutaneous intervention:
The review reported no major complications requiring surgical correction or delay in discharge in one identified RCT. [38] It reported two unsuccessful angioplasties, three groin haematomas, and one rupture of the external iliac artery. The subsequent RCT did not report on harms of PTA or optimal medical treatment. [39]

PTA plus stents versus PTA alone:
The first and second systematic reviews did not report on harms. [42] [43]

PTA plus routine stent versus PTA plus selective stent:
The first RCT found no significant difference in complication rate between groups (proportion of people with complications: 6/143 [4%] with PTA plus routine stent *v* 10/136 [7%] with PTA plus selective stent, 95% CI [for difference between groups] –2% to +9%). Complications included: haematoma at the puncture site, arterial wall perforation, acute occlusion of the treated arterial segment, embolism, and vasovagal collapse. [45] The second RCT found that routine stenting significantly increased the risk of local vascular events compared with selective stenting after 1 year (P = 0.017). [46] The third RCT reported a stent fracture rate of 2%, and one case (2%) of early stent thrombotic occlusion in the primary stenting group. [47] Prospective cohort studies have found that complications of PTA include puncture site major bleeding (3.4%), pseudoaneurysms (0.5%), limb loss (0.2%), renal failure secondary to intravenous contrast (0.2%), cardiac complications such as MI (0.2%), and death (0.2%). [50] [51]

PTA alone versus PTA plus statins:
The RCT found that limb loss was higher with PTA alone, but this difference was not significant. [49]

Comment:

Clinical guide:
Further large RCTs are warranted in the future to fully assess newer stents. The small number of large RCTs and their small sample sizes and methodological weaknesses suggest that further RCTs are needed in order to reliably establish clinical effects of newer stents.

This limited evidence suggests transient benefit from angioplasty compared with no angioplasty. The longer term effects of angioplasty or stent placement on symptoms, bypass surgery, and amputation remain unclear, and the available RCTs are likely to have been too small to detect clinically important effects of stent placement. The long-term patency of femoro-popliteal angioplasties is poor, and we found conflicting evidence as to whether the addition of stents confers any additional benefit. [47] [52] [53] [54]

OPTION SMOKING CESSATION

We found no clinically important results from RCTs about the effects of advice to stop smoking in people with peripheral arterial disease.

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Advice to stop smoking versus no advice:
We found no RCTs. We found one systematic review (search date 1996; 4 observational studies; 866 people) of advice to stop cigarette smoking versus no advice (see comment). [16]

Harms:

We found no RCTs.

Comment:

RCTs of advice to stop smoking are considered unethical. The consensus is that stopping smoking improves symptoms in people with intermittent claudication. One observational study included in the systematic review found no significant increase in absolute claudication distance after stopping smoking (+46.7 metres, 95% CI –19.3 metres to +112.7 metres). The second and third studies identified by the review found conflicting results about the risk of deteriorating from moderate to severe claudication in people who successfully stopped smoking compared with current smokers. The second study found that significantly more smokers deteriorated from Fontaine stage II to III compared with people who had stopped smoking (26/304 [9%] smokers *v* 0/39 [0%] non-smokers; ARR 8.6%, 95% CI 5.4% to 11.7%). However, the third study found no difference in deterioration in ankle brachial index at 1 year between smokers and people who had stopped smoking (data not reported). There was also no significant difference in the number of failed revascularisation procedures between smokers and non-smokers (P = 0.07). [16] The fourth study provided no numerical results. Overall, the review found no good evidence to confirm or refute the consensus that advice to stop smoking improves symptoms in people with intermittent claudication.

OPTION CILOSTAZOL

Claudication distance/time
Compared with placebo Cilostazol (100 mg twice daily) seems to be more effective than placebo at improving claudication distance measures at 12 to 24 weeks, but we don't know whether cilostazol (50 mg twice daily or 150 mg twice daily) are more effective (low-quality evidence).

Compared with pentoxifylline Cilostazol seems to be more effective at improving initial and absolute claudication distance after 24 weeks (moderate-quality evidence).

Quality of life
Compared with placebo We don't know whether cilostazol is more effective at quality of life (assessed using the short form-36 [SF-36] questionnaire and the Walking Impairment Questionnaire) at 12 to 24 weeks (very low-quality evidence).

Note
Adverse effects of cilostazol are common, and include headache, diarrhoea, and palpitations.

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Cilostazol versus placebo:
We found one systematic review (search date 2008; 7 RCTs; 1579 people with peripheral arterial disease). [55] The review did not pool results for claudication distance or ankle brachial index for different doses of cilostazol, and so we have reported these separately by dose.

It found that cilostazol (100 mg twice daily) significantly improved the initial claudication distance, absolute claudication distance, and ankle brachial index compared with placebo at 12 to 24 weeks (initial claudication distance: 6 RCTs; 1326 people: WMD 31.3 metres, 95% CI 21.3 metres to 40.9 metres; absolute claudication distance: 7 RCTs; 1579 people: WMD 49.7 metres, 95% CI 24.2 metres to 75.2 metres; ankle brachial index: 3 RCTs; 859 people: WMD 0.06 metres, 95% CI 0.03 metres to 0.09 metres). It found no significant difference in the initial claudication distance between cilostazol (50 mg twice daily) and placebo at 12 to 24 weeks (2 RCTs; 475 people: WMD +41.3 metres, 95% CI –7.1 metres to +89.7 metres). However, it found significantly increased absolute claudication distance with cilostazol (50 mg twice daily) compared with placebo (2 RCTs; 497 people: WMD 31.9 metres, 95% CI 12.4 metres to 51.5 metres). It found no significant difference in either the initial claudication distance or absolute claudication distance between cilostazol (150 mg twice daily) and placebo at 12 weeks in one RCT (1 RCT; 104 people: mean change in initial claudication distance from baseline: 50.1 metres with cilostazol *v* 34.4 metres with placebo; WMD +15.7 metres, 95% CI –9.6 metres to +41 metres; mean change in absolute claudication distance from baseline: 89.9 metres with cilostazol *v* 38 metres with placebo; WMD +51.8 metres, 95% CI –13.9 metres to +118 metres).The review reported significant improvements in physical health components of the short form-36 (SF-36) questionnaire (3 RCTs; sub-scales of physical function: P = 0.002; and bodily pain: P <0.05) but not mental health components of the SF-36 questionnaires, with cilostazol (50 mg and 100 mg twice daily) compared with placebo (absolute numbers and details

not reported). It also found significant improvement in people's perception of walking speed with cilostazol in the Walking Impairment Questionnaire (50 mg and 100 mg twice daily; 2 RCTs; P <0.05; absolute numbers and details not reported). [55] The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results. [56] [57] [58] [59] Firstly, none of the RCTs evaluated cilostazol beyond 24 weeks. In addition, some of the RCTs had high withdrawal rates after randomisation (up to 29%). [58] In most of the RCTs, withdrawals were more common with cilostazol than with placebo. [56] [57] [58] [59] [60] To allow for these problems, the authors performed intention-to-treat analyses using "last available observation carried forward". However, the analyses did not include people with no observations to carry forward, and the effect of the difference in withdrawals between the groups was not explored adequately. If people with worsening claudication were more likely to withdraw, then the observed differences might have been artefactual.

Cilostazol versus pentoxifylline:
See benefits of pentoxifylline, p 15 .

Harms:

Cilostazol versus placebo:
The review reported that headache, diarrhoea, peripheral oedema, rhinitis, and infection were reported significantly more frequently with cilostazol (100 mg and 50 mg twice daily) compared with placebo (P <0.05; absolute numbers not reported). [55] Two RCTs identified by the review found that cilostazol significantly increased the risk of withdrawal from the trial because of adverse effects or concerns about safety compared with placebo (1 RCT: 39/227 [17%] with cilostazol 200 mg *v* 24/239 [10%] with placebo; RR 1.71, 95% CI 1.06 to 2.75; NNH 14, 95% CI 8 to 111; 1 RCT: 22.6% with cilostazol 200 mg *v* 12.1% with cilostazol 100 mg *v* 10.1% with placebo; significance assessment not reported). [57] [60] The second of these RCTs reported that more people taking cilostazol 200 mg withdrew because of headache and cardiovascular events compared with people taking placebo (headache: 4.5% with cilostazol 200 mg *v* 0% with placebo; cardiovascular events: 12/133 with cilostazol *v* 5/129 with placebo; CI not reported). A third RCT identified by the review found that more people taking cilostazol 100 mg reported GI complaints compared with people taking placebo (44% with cilostazol *v* 15% with placebo; significance assessment not reported). [56] Cilostazol is a phosphodiesterase inhibitor; RCTs have found that other phosphodiesterase inhibitors (milrinone, vesnarinone) are associated with increased mortality in people with heart failure. However, results aggregated from other studies have not found an excess of cardiovascular events with cilostazol. [61]

Cilostazol versus pentoxifylline:
See harms of pentoxifylline, p 15 .

Comment:

The review did not describe the outcomes of cardiovascular morbidity and mortality from the included trials. However, it commented on a separate review of the same RCTs comparing cilostazol versus placebo, which included a summary of adverse effects and cardiovascular events from these trials. It found a similar incidence of cardiovascular events (incidence of MI: 1.0% with cilostazol *v* 0.8% with placebo; incidence of stroke: 0.5% with cilostazol *v* 0.5% with placebo; statistical assessment not reported). It also found a similar incidence of total cardiovascular morbidity and all-cause mortality (6.5% with cilostazol 100 mg twice daily *v* 6.3% with cilostazol 50 mg twice daily *v* 7.7% with placebo; statistical assessment not reported; absolute numbers not reported). [55]

OPTION PROSTAGLANDINS (SEVERE PERIPHERAL ARTERIAL DISEASE)

Claudication distance/time
Compared with placebo Oral beraprost sodium may be no more effective at improving walking distance in people with intermittent claudication (moderate-quality evidence).

Post-intervention morbidity
Compared with placebo Prostaglandin E1 may be more effective at reducing the composite outcome of major amputation or mortality and at reducing pain and improving ulcer healing in people with severe peripheral arterial disease (stage III and IV) not eligible for arterial reconstruction. We don't know whether lipo-ecraprost is more effective at reducing major amputation in people with critical limb ischaemia (very low-quality evidence).

Mortality
Compared with placebo Prostaglandin E1 may be more effective at reducing the composite outcome of mortality or major amputation in people with severe peripheral arterial disease (stage III and IV) not eligible for arterial reconstruction. We don't know whether lipo-ecraprost is more effective at reducing mortality in people with critical limb ischaemia undergoing endovascular or surgical revascularisation (very low-quality evidence).

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits: We found one systematic review, [62] one additional RCT, [63] and two subsequent RCTs. [64] [65] The review (search date 2004; 7 RCTs; 643 people) reported on prostaglandin E1 (PGE1) for treating severe peripheral arterial occlusive disease (stage III and IV). It found that PGE1 significantly improved ulcer healing and reduced pain compared with placebo after 6 months in people not eligible for arterial reconstruction (response for ulcer healing and/or pain reduction: 48% with PGE1 *v* 25% with placebo; P = 0.0294). Major amputation or death was significantly lower in the PGE1 group compared with placebo at 6 months' follow-up (incidence of major amputation or death: 23% with PGE1 *v* 36% with placebo; P = 0.015). [62]

The additional RCT (762 people with intermittent claudication) found that oral beraprost sodium did not significantly improve symptoms of intermittent claudication in people with peripheral arterial disease at 24 weeks (maximum walking distance improvement at 24 weeks: 17% with beraprost *v* 15% with placebo; pain-free walking distance improvement at 24 weeks: 19% with beraprost *v* 15% with placebo; absolute results not reported; reported as not significant; P values not reported). [63]

The first subsequent RCT (379 people) found no significant difference for lipo-ecraprost (a lipid-encapsulated PGE1 prodrug) on 6-month amputation rates in people with critical limb ischaemia who were not candidates for revascularisation (amputation rate: 29/179 [16%] with lipo-ecraprost *v* 23/177 [13%] with placebo; P value not reported). [64] However, 46% of people in the lipo-ecraprost group received fewer than 35 of the 40 intended treatment doses. The second subsequent RCT (322 people with critical limb ischaemia undergoing endovascular or surgical revascularisation) found no significant difference in major amputation rates or death with lipo-ecraprost (intravenously for 8 weeks) compared with placebo at 6 months (major amputation: 17/141 [12%] with ecraprost *v* 19/143 [13%] with placebo; reported as not significant; P value not reported; death: 13/141 [9%] with ecraprost *v* 19/143 [13%] with placebo; P = 0.279). [65] However, significantly fewer people in the ecraprost group adhered to study medication compared with people in the placebo group (proportion of people who received at least 35 of the intended 40 treatment doses: 37/141 [26%] with ecraprost *v* 73/143 [51%] with placebo; reported as significant; P value not reported). [65]

Harms: The systematic review reported a higher rate of adverse effects with PGE1 compared with placebo (39.6% with PGE1 *v* 15.4% with placebo; specific effects and P value not reported). [62] The additional RCT found that several adverse effects were significantly more common in people taking beraprost sodium versus people taking placebo, and included headaches (27.5% with beraprost *v* 5% with placebo; P <0.001), vasodilation (13.5% with beraprost *v* 4% with placebo; P <0.001), diarrhoea (7.3% with beraprost *v* 1.3% with placebo; P <0.02), pain (5.5% with beraprost *v* 1.1% with placebo; P <0.02), and nausea (4.4% with beraprost *v* 1.3% with placebo; P <0.02). There was no significant difference in serious adverse effects or in compliance between the two groups. A total of 29% of people taking beraprost discontinued treatment because of adverse effects, compared with 15% of people taking placebo. [63] The first subsequent RCT reported a higher number of adverse effects in people taking lipo-ecraprost compared with people taking placebo (7094 [202 serious] for 189 people with lipo-ecraprost *v* 1594 [235 serious] for 190 people with placebo; P value not reported). The most common adverse effects reported included headache, nausea, vomiting, diarrhoea, pain, hypotension, tachycardia, and vasodilation. [64] The second subsequent RCT did not directly compare adverse effects of lip-ecraprost versus placebo. Common adverse effects in the lipo-ecraprost group included headache, pain, hypotension, tachycardia, vasodilation, diarrhoea, nausea, and vomiting. [65]

Comment: The seven studies included in the systematic review [62] were conducted between 1987 and 1992, and therefore did not comply with current guidelines regarding the conducting of clinical trials in peripheral arterial disease. Four of the included studies were not double-blind, placebo-controlled studies, and the end point of ulcer healing and pain relief used in some of these studies is somewhat subjective.

OPTION PENTOXIFYLLINE

Claudication distance/time

Compared with placebo Pentoxifylline seems no more effective at increasing walking distance (moderate-quality evidence).

Compared with cilostazol Pentoxifylline seems less effective at improving initial and absolute claudication distance after 24 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for peripheral arterial disease, see table , p 19 .

Benefits:

Pentoxifylline versus placebo:
We found one systematic review [66] and one subsequent RCT. [57] The review (search date 1999) identified two RCTs (192 people), but did not meta-analyse the results. Neither RCT in the review found a significant difference between pentoxifylline and placebo in change in initial claudication distance or absolute claudication distance (improvement in mean initial claudication distance for pentoxifylline *v* placebo: 1st RCT: +15 metres, 95% CI –5 metres to +35 metres; 2nd RCT: –30 metres, 95% CI –138 metres to +78 metres; improvement in mean absolute claudication distance: 1st RCT: +21 metres, 95% CI –10 metres to +52 metres; 2nd RCT: +69 metres, 95% CI –44 metres to +182 metres). [66] The subsequent RCT was a three-armed trial, comparing pentoxifylline, cilostazol, and placebo. [57] It found no significant difference between pentoxifylline and placebo in the proportion of people who had either no change or deterioration in the claudication distance (438 people: 72/212 [34%] with pentoxifylline *v* 68/226 [30%] with placebo; RR 1.13, 95% CI 0.86 to 1.48). The RCT had a high withdrawal rate after randomisation, which could be a source of bias (60/232 [26%] with pentoxifylline *v* 38/239 [16%] with placebo). [57]

Pentoxifylline versus cilostazol:
We found one RCT comparing pentoxifylline, cilostazol, and placebo. [57] The RCT found that pentoxifylline significantly increased the proportion of people who had either no change or deterioration in claudication distance compared with cilostazol (438 people: 72/212 [34%] with pentoxifylline *v* 47/205 [23%] with cilostazol; RR 1.48, 95% CI 1.08 to 2.03; ARR 11%, 95% CI 2.4% to 20.0%; NNT 9, 95% CI 5 to 42). It found that pentoxifylline was significantly less effective at increasing the initial claudication distance and the absolute claudication distance compared with cilostazol after 24 weeks (202 metres with pentoxifylline *v* 218 metres with cilostazol; mean difference –16 metres; P = 0.0001; absolute claudication distance: 308 metres with pentoxifylline *v* 350 metres with cilostazol; mean difference –42 metres; P = 0.0005). The RCT had a high withdrawal rate after randomisation, which could be a source of bias (60/232 [26%] with pentoxifylline *v* 61/237 [26%] with cilostazol). [57]

Harms:

Pentoxifylline versus placebo:
One RCT found that pentoxifylline significantly increased the risk of withdrawal from the RCT because of adverse effects or concerns about safety compared with placebo (44/232 [19%] with pentoxifylline *v* 24/239 [10%] with placebo; RR 1.89, 95% CI 1.19 to 3.00; NNH 12, 95% CI 7 to 39). [57] Adverse effects of pentoxifylline included sore throat (14% with pentoxifylline *v* 7% with placebo) and dyspepsia, nausea, and diarrhoea (8% with pentoxifylline *v* 5% with placebo; P = 0.31). No life-threatening adverse effects of pentoxifylline have been reported, although to date RCTs have been too small to assess this reliably.

Pentoxifylline versus cilostazol:
The RCT found similar rates of withdrawal due to adverse effects or concerns about safety with pentoxifylline and cilostazol (44/232 [19%] with pentoxifylline *v* 39/227 [17%] with cilostazol, between group: significance assessment not reported). [57]

Comment:

None.

GLOSSARY

Ankle brachial index The ankle brachial index (ABI) is calculated by dividing the blood pressure recorded at the ankle by the blood pressure recorded in the arm. The ABI value is calculated both at rest and after exercise to determine the severity of peripheral arterial disease. A normal ABI value at rest is 1.0. A decrease in the ABI after exercise or a resting ABI below 0.9 indicates that peripheral arterial disease is present.
Initial claudication distance The distance a person can walk before the onset of claudication symptoms.
Intermittent claudication Pain, stiffness, or weakness in the leg that develops on walking, intensifies with continued walking until further walking is impossible, and is relieved by rest.
Absolute claudication distance Also known as the total walking distance. The maximum distance a person can walk before stopping.
Critical limb ischaemia Results in a breakdown of the skin (ulceration or gangrene) or pain in the foot at rest. Critical limb ischaemia corresponds to the Fontaine classification III and IV.
Fontaine classification I: asymptomatic; II: intermittent claudication; II-a: pain-free, claudication walking more than 200 metres; II-b: pain-free, claudication walking less than 200 metres; III: rest/nocturnal pain; IV: necrosis/gangrene.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antiplatelet agents One systematic review added, reporting that antiplatelet agents (aspirin or aspirin plus dipyridamole) reduced arterial occlusion of both venous and artificial peripheral bypass grafts versus placebo at 12 months. It found no significant difference in GI adverse effects, or major bleeding between groups. [14] One RCT added, reporting lower MI rates with clopidogrel plus aspirin versus placebo plus aspirin after 26 months, but no significant difference in the overall combined rate of cardiovascular death, MI, or stroke between groups. It found no significant difference in fatal, severe, or moderate bleeding or primary intracranial haemorrhage between groups. [15] Categorisation unchanged (Beneficial).

Bypass surgery One systematic review updated, [26] which now includes one RCT previously described separately in this *Clinical Evidence* review. Another RCT added, [27] which found no significant difference in primary patency between percutaneous transluminal angioplasty (PTA) plus stent placement versus femoro-above-knee popliteal bypass grafting at 6, 12, or 24 months. Categorisation unchanged (Likely to be beneficial).

Exercise Two systematic reviews and one subsequent RCT added. [17] [18] [20] One review found that exercise, for between 12 weeks and 2 years, increased maximum walking distance and pain-free walking distance versus usual care/placebo. It found no significant difference between groups in the ankle brachial index. [18] The other review also found increased pain-free walking distance and maximum walking distance with exercise versus usual care. [17] The RCT found improved quality of life, assessed by short form-36 (SF-36) physical functioning score and by the distance and stair-climbing scores of the Walking Impairment Questionnaire, with treadmill exercise or resistance training versus control. However, it found no significant difference between either exercise and control in the speed score of the Walking Impairment Questionnaire. [20] Categorisation unchanged (Beneficial).

Percutaneous transluminal angioplasty (PTA) One RCT added, comparing PTA versus optimal medical treatment. It found an improvement in both pain-free walking distance and maximum walking distance and visual analogue pain score with optimal medical treatment alone versus PTA at 24 months. However, it found no significant difference in quality of life between groups at 24 months. [39] Categorisation unchanged (Likely to be beneficial).

Prostaglandins One RCT added. It found no significant difference in major amputation rates or death with lipoecraprost (intravenously for 8 weeks) versus placebo at 6 months. [65] Categorisation unchanged (Trade-off between benefits and harms).

Statins One further report of one RCT, already included in this *Clinical Evidence* review, added. [30] Categorisation unchanged (Likely to be beneficial).

Cilostazol One systematic review added, [55] including RCTs already reported in this *Clinical Evidence* review. Evidence re-evaluated. Categorisation changed from Trade-off between benefits and harms to Likely to be beneficial.

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Disclaimer

TABLE **GRADE evaluation of interventions for peripheral arterial disease**

Important outcomes	Claudication distance/time, re-intervention rates, post-intervention morbidity (for example arterial occlusion, major amputation), cardiovascular events, mortality, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for people with chronic peripheral arterial disease?									
At least 18 (at least 4884) [11] [12] [13] [14]	Post-intervention morbidity	Antiplatelet agents *v* placebo/no treatment	4	0	0	0	0	High	
At least 42 (at least 9214) [8] [9]	Cardiovascular events	Antiplatelet agents*v* placebo/control	4	0	0	0	0	High	
6 (10,034) [8] [15]	Cardiovascular events	Antiplatelet agents (other than aspirin alone) *v* aspirin alone	4	–1	–1	0	0	Low	Quality point deducted for subgroup analysis of larger study. Consistency point deducted for different results between studies
11 (325) [16] [17] [18] [19] [20]	Claudication distance/time	Exercise *v* usual care/placebo	4	–1	0	–1	0	Low	Quality point deducted for blinding flaws. Directness point deducted for range of different interventions included
1 (156) [20]	Quality of life	Exercise *v* usual care/placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results for different outcomes
2 (934) [19] [21]	Claudication distance/time	Exercise as part of a multicomponent intervention versus usual care/placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and subjective assessment of outcome
3 (203) [22] [23] [24]	Claudication distance/time	Different types of exercise *v* each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups
at least 2 (355) [26]	Post-intervention morbidity	Bypass surgery *v* PTA	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness points deducted for inclusion of different disease states
3 (590) [26]	Mortality	Bypass surgery *v* PTA	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness points deducted for inclusion of different disease states
1 (86) [27]	Post-intervention morbidity	Bypass surgery *v* PTA plus stent placement	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (509) [33] [34] [35]	Claudication distance/time	Statins *v* placebo	4	0	–1	0	0	Moderate	Consistency point deducted for different results for different outcomes
1 (354) [35]	Quality of life	Statins *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (7775) [29] [30] [31] [32]	Cardiovascular events	Statins *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for subgroup analysis of larger study

Important outcomes	Claudication distance/time, re-intervention rates, post-intervention morbidity (for example arterial occlusion, major amputation), cardiovascular events, mortality, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (154) [38] [39] [40] [41]	Claudication distance/time	PTA *v* no percutaneous intervention	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results at different end points
2 (118) [38] [39] [40]	Quality of life	PTA *v* no percutaneous intervention	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for different results for different outcomes
3 (345) [42] [43] [44]	Post-intervention morbidity	PTA plus stent *v* PTA alone	4	–1	0	–1	0	Low	Quality point deducted for different diagnostic criteria. Directness point deducted for inclusion of different interventions
2 (383) [45] [48]	Quality of life	PTA plus routine stent *v* PTA plus selective stent	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and short follow-up
3 (610) [45] [46] [47]	Post-intervention morbidity	PTA plus routine stent *v* PTA plus selective stent	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results between studies. Directness point deducted for composite outcome of death and restenosis
1 (227) [46]	Mortality	PTA plus routine stent *v* PTA plus selective stent	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome of death and restenosis
1 (37) [49]	Post-intervention morbidity	PTA plus statin *v* PTA alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
6 (1832) [55]	Claudication distance/time	Cilostazol *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for poor follow-up. Consistency point deducted for different results at different outcomes
6 (1832) [55]	Quality of life	Cilostazol *v* placebo	4	–2	–1	0	0	Very low	Quality point deducted for poor follow-up and incomplete reporting of results. Consistency point deducted for different results at different outcomes
1 (762) [63]	Claudication distance/time	Prostaglandin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (1022) [62] [64] [65]	Post-intervention morbidity	Prostaglandin *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for methodological flaws (blinding and no placebo control). Consistency point deducted for conflicting results between studies. Directness point deducted for composite outcome of death or major amputation
8 (927) [62] [65]	Mortality	Prostaglandin *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for methodological flaws (blinding and no placebo control). Consistency point deducted for conflicting results between studies. Directness point deducted for composite outcome of death or major amputation
3 (630) [57] [66]	Claudication distance/time	Pentoxifylline *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
1 (438) [57]	Claudication distance/time	Pentoxifylline *v* Cilostazol	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up

Important outcomes	Claudication distance/time, re-intervention rates, post-intervention morbidity (for example arterial occlusion, major amputation), cardiovascular events, mortality, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evi-dence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
Type of evidence: 4 = RCT; 2 = Observational. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio PTA: percutaneous transluminal angioplasty.									