Peripheral arterial disease

Search date May 2010

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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 May 2010. 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 70 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 large trials 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.

  Cilostazol may reduce the incidence of cerebrovascular events compared with placebo but may be no more effective at reducing cardiac events.

  Cilostazol may be more effective than pentoxifylline at improving claudication distance.

  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. Adding a stent to PTA may confer additional benefit over PTA alone.

- Bypass surgery may improve arterial patency at 12 months compared with PTA, but there seems to be no long-term benefit. Bypass surgery may be associated with improved survival in severe limb ischaemia in the longer term (3–7 years) compared with angioplasty.
- Prostaglandins may improve amputation-free survival in critical ischaemia at 6 months when surgical revascularisation is not an option.

  Prostaglandins may not be of benefit in intermittent claudication.

  Prostaglandins are associated with higher rates of adverse effects, including headache, vasodilation, diarrhoea, tachycardia, and vasodilation compared with placebo.

Clinical context

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, sex, 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

Mortality (all cause and cardiovascular); **Cardiovascular events**; **Claudication distance/time measures** (initial claudication distance, absolute claudication distance, pain-free or maximal walking time, etc); **Post-intervention patency (e.g., arterial occlusion, arterial reocclusion, restenosis, patency, reintervention rates, ulcer healing, and limb amputation)**; **Physiological measures** (ankle brachial index); **Generic/disease-specific quality of life**; and **Adverse effects**.

METHODS

Clinical Evidence search and appraisal May 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2010, Embase 1980 to May 2010, and The Cochrane Database of Systematic Reviews May 2010 (online) 1966 to date of issue. When editing this review we used The Cochrane Database of Systematic Reviews 2010, issue 3. An additional search within The Cochrane Library was carried out 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 predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to contain 20 or more individuals, of whom 80% or more were followed up. RCTs had to be at least single blinded where blinding was possible. 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 we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (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 71). 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

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Antiplatelet agents reduce major cardiovascular events, arterial occlusion, and revascularisation compared with placebo, but 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.

Benefits and harms

Antiplatelet agents versus placebo or control:

We found 9 systematic reviews (search dates 1999, [8] 1997, [9] [10] 1990, [11] 1998, [12] 2004, [13] 2008, [14] 2008, [15] 2009 [16]). The systematic reviews all identified many of the same RCTs; however, they used different inclusion/exclusion criteria and performed different meta-analyses, and so we report on them all; although the third systematic review [10] described the results presented in the second review [9] and so we include the data only once and reference both papers. One systematic review looked at only aspirin versus placebo. [15]

Mortality

Antiplatelet agents compared with placebo/control Aspirin may be no more effective than placebo at reducing all-cause mortality or cardiovascular mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis One RCT (1276 people) included in the meta-analysis was in people with diabetes	**All-cause mortality , up to 6.7 years** 114/1516 (7.5%) with aspirin (100 to 1500 mg/day) 118/1503 (7.9%) with placebo or control Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	RR 0.96 95% CI 0.75 to 1.22 P = 0.74 Results should be interpreted with caution; over one third of people in the analysis had diabetes	⟷	Not significant
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis One RCT (1276 people) included in the meta-analysis was in people with diabetes	**Cardiovascular mortality , up to 6.7 years** 55/1516 (3.6%) with aspirin (100 to 1500 mg/day) 49/1503 (3.3%) with placebo or control Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	RR 1.15 95% CI 0.78 to 1.68 P = 0.48 Results should be interpreted with caution; over one third of people in the analysis had diabetes	⟷	Not significant

No data from the following reference on this outcome. [10] [8] [9] [11] [12] [13] [14] [16]

Cardiovascular events

Antiplatelet agents compared with placebo/control Antiplatelet agents as a class may be more effective at reducing major cardiovascular events (non-fatal MI, non-fatal stroke, or vascular death). Aspirin may be more effective than placebo at reducing non-fatal stroke but may be no more effective at reducing MI (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vascular events					
[8] Systematic review	6036 people with intermittent claudication 24 RCTs in this analysis	**Proportion of people with a vascular event (non-fatal MI, non-fatal stroke, or vascular death)** 202/3100 (7%) with antiplatelet agents 238/2936 (8%) with placebo Antiplatelet agents included ticlopidine, suloctidil, indobufen, picotamide, and aspirin (with or without dipyridamole)	OR 0.78 95% CI 0.63 to 0.96	●○○	Antiplatelet agents
[9] Systematic review	9214 people with peripheral arterial disease 42 RCTs in this analysis	**Proportion of people with a serious vascular event** 280/4844 (6%) with antiplatelet agents 347/4862 (7%) with control (not further defined) Antiplatelet agents included ticlopidine, dipyridamole, clopidogrel, picotamide, and aspirin (with or without dipyridamole)	P <0.004	○○○	Antiplatelet agents
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis One RCT (1276 people) included in the meta-analysis was in people with diabetes	**Proportion of people with a vascular event (non-fatal MI, non-fatal stroke, or vascular death) , up to 6.7 years** 125/1516 (8%) with aspirin (100 to 1500 mg/day) 144/1503 (10%) with placebo or control Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	RR 0.75 95% CI 0.48 to 1.18 P = 0.21 Results should be interpreted with caution; over one third of people in the analysis had diabetes	⟷	Not significant
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis One RCT (1276 people) included in the meta-analysis was in people with diabetes	**Proportion of people with MI , up to 6.7 years** 59/1516 (3.9%) with aspirin (100 to 1500 mg/day) 67/1503 (4.4%) with placebo or control Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	RR 0.88 95% CI 0.36 to 2.14 P = 0.78 Results should be interpreted with caution; over one third of people in the analysis had diabetes	⟷	Not significant
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis One RCT (1276 people) included in the meta-analysis	**Proportion of people with non-fatal stroke , up to 6.7 years** 32/1516 (2%) with aspirin (100 to 1500 mg/day) 51/1503 (3%) with placebo or control Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	RR 0.64 95% CI 0.42 to 0.99 P = 0.04 Results should be interpreted with caution; over one third of people in the analysis had diabetes	●○○	Aspirin (100 to 1500 mg/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	was in people with diabetes				

No data from the following reference on this outcome. [10] [11] [12] [13] [14] [16]

Claudication distance/time

Antiplatelet agents compared with placebo/control Antiplatelet agents (including ticlopidine, cloricromen, mesoglycan, indobufen, and defibrotide) may be more effective at increasing maximum walking distance at 5 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain-free walking distance					
[16] Systematic review	1077 people with moderate intermittent claudication and ankle brachial index <0.9 5 RCTs in this analysis	**Maximum walking distance , 5 to 12 months** with antiplatelet agents with placebo Absolute results not reported Antiplatelet agents included ticlopidine, cloricromen, mesoglycan, indobufen, and defibrotide	WMD 59 metres 95% CI 36.92 m to 81.28 m	○○○	Antiplatelet agents

No data from the following reference on this outcome. [8] [9] [10] [11] [12] [13] [14] [15]

Post-intervention patency

Antiplatelet agents compared with placebo/control Antiplatelet agents seem to be more effective at reducing the risk of arterial occlusion (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Arterial occlusion					
[12] Systematic review	2810 people Data from 1 RCT	**Arterial occlusion or revascularisation procedures , 3 months** with aspirin with placebo Absolute results not reported	OR 0.46 95% CI 0.27 to 0.77	●●○	Antiplatelet agents (aspirin)
[13] Systematic review	356 people undergoing peripheral endovascular intervention 2 RCTs in this analysis	**Rates of restenosis or reocclusion , 6 months** with low-dose aspirin plus dipyridamole with placebo Absolute results not reported	OR 0.69 95% CI 0.44 to 1.10	⟷	Not significant
[14] Systematic review	966 people 6 RCTs in this analysis	**Proportion of people with arterial occlusion of either venous or artificial peripheral bypass grafts , 12 months** 114/501 (23%) with antiplatelet agents (aspirin or aspirin plus dipyridamole) 156/465 (34%) with placebo	OR 0.59 95% CI 0.45 to 0.79	●○○	Antiplatelet agents (aspirin or aspirin plus dipyridamole)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] Systematic review	222 people 4 RCTs in this analysis Subgroup analysis	**Proportion of people with arterial occlusion of artificial peripheral bypass grafts , 12 months** 21/115 (18%) with antiplatelet agents (aspirin or aspirin plus dipyridamole) 57/107 (53%) with placebo	OR 0.22 95% CI 0.12 to 0.38	●●○	Antiplatelet agents (aspirin or aspirin plus dipyridamole)
[14] Systematic review	642 people 2 RCTs in this analysis Subgroup analysis	**Proportion of people with arterial occlusion of venous peripheral bypass grafts , 12 months** 71/335 (21%) with antiplatelet agents (aspirin or aspirin plus dipyridamole) 86/307 (28%) with placebo	OR 0.68 95% CI 0.48 to 0.99 Result is of borderline significance	●○○	Antiplatelet agents (aspirin or aspirin plus dipyridamole)
[11] Systematic review	3226 people with intermittent claudication, or having bypass surgery of the leg, or peripheral artery angioplasty 14 RCTs in this analysis	**Arterial occlusion , 19 months** with antiplatelet agents with placebo or no additional treatment Absolute results not reported Antiplatelet agents included dipyridamole, ticlopidine, suloctidil, and aspirin (with or without dipyridamole)	RRR 37% P <0.00001	○○○	Antiplatelet agents
[12] Systematic review	1302 people 2 RCTs in this analysis	**Arterial occlusion or revascularisation procedures , up to 7 years** with ticlopidine with placebo Absolute results not reported	OR 0.62 95% CI 0.41 to 0.93	●○○	Antiplatelet agents (ticlopidine)

No data from the following reference on this outcome. [8] [9] [10] [15] [16]

Physiological measures

No data from the following reference on this outcome. [8] [9] [10] [11] [12] [13] [14] [15] [16]

Quality of life

No data from the following reference on this outcome. [8] [9] [10] [11] [12] [13] [14] [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Bleeding					
[8] Systematic review	8449 people with claudication undergoing surgery or percutaneous transluminal angioplasty (PTA) 36 RCTs in this analysis	**Proportion of people with major bleeding** 47/4349 (1.1%) with antiplatelet agents 33/4100 (0.8%) with placebo Antiplatelet agents included ticlopidine, suloctidil, indobufen, picotamide, and aspirin (with or without dipyridamole)	OR 1.40 95% CI 0.90 to 2.20 The number of events was likely to have been too low to detect a clinically important increase in major bleeding	⟷	Not significant
[9] Systematic review	94,326 people (number of RCTs in analysis not reported)	**Proportion of people with a major extracranial bleed** 535/47,158 (1.1%) with antiplatelet agents 333/47,168 (0.7%) with control (not further defined) Antiplatelet agents included ticlopidine, dipyridamole, clopidogrel, picotamide, and aspirin (with or without dipyridamole)	OR 1.6 95% CI 1.4 to 1.8 The review pooled results for all identified RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone	●○○	Placebo
[11] Systematic review	6425 people (number of RCTs in analysis not reported)	**Proportion of people with a non-fatal "major" bleed** 70/3214 (2%) with antiplatelet agents 29/3201 (1%) with control	P = 0.002 The review pooled results for all identified RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone	○○○	Placebo
[11] Systematic review	3999 people (number of RCTs in analysis not reported)	**Proportion of people requiring re-operation, or with haematoma or infection caused by bleed** 109/1997 (6%) with antiplatelet agents 72/2002 (4%) with control	P = 0.02 The review pooled results for all identified RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone	○○○	Placebo
[11] Systematic review	6529 people (number of RCTs in analysis not reported)	**Proportion of people with fatal bleed** 5/3267 (0.15%) with antiplatelet agents 1/3262 (0.03%) with control	P = 0.06 Result was of borderline significance The review pooled results for all identified RCTs (also including coronary and other conditions) rather than for people with peripheral arterial disease alone	⟷	Not significant
[13] Systematic review	Number of people in RCT not reported Data from 1 RCT	**Bleeding at the puncture site after endovascular treatment** with antiplatelet agents with placebo	OR 1.52 95% CI 0.47 to 4.96	⟷	Not significant
[14] Systematic review	598 people 2 RCTs in this analysis	**Proportion of people with major bleeding** 19/318 (6%) with antiplatelet agents 9/280 (3%) with placebo	OR 1.88 95% CI 0.85 to 4.16 P = 0.12	⟷	Not significant
[15] Systematic review	3019 people with peripheral arterial disease 9 RCTs in this analysis	**Occurrence of major bleeding** 42/1516 (3%) with aspirin (100 to 1500 mg/day) 37/1503 (2%) with placebo or control	P = 0.86 RR 1.04 95% CI 0.66 to 1.62 Results should be interpreted with caution; over one third of	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	One RCT (1276 people) included in the meta-analysis was in people with diabetes	Definition of major bleeding varied across RCTs Placebo in 8 RCTs, control in 1 RCT (200 people) not specified	people in the analysis had diabetes.		
Adverse effects (general)					
[10] Systematic review	Number of people and RCTs in analysis not reported	**Adverse effects (general)** with ticlopidine with control Absolute results not reported The 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 Results for the control group were not reported		
[14] Systematic review	966 people 6 RCTs in this analysis	**Proportion of people with an adverse effect** 58/501 (12%) with antiplatelet agents 36/465 (7%) with placebo	OR 1.55 95% CI 1.00 to 2.41 P = 0.052 Result was of borderline significance	⟷	Not significant
[14] Systematic review	966 people 6 RCTs in this analysis	**Proportion of people with GI adverse effects** 54/501 (11%) with antiplatelet agents 36/465 (7%) with placebo	OR 1.44 95% CI 0.92 to 2.24 P = 0.11	⟷	Not significant

No data from the following reference on this outcome. [12] [16]

Antiplatelet agents other than aspirin (alone or in combination with aspirin) versus aspirin alone:

We found one systematic review (search date 1999) [8] and one subsequent RCT. [17]

Cardiovascular events

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vascular events					
[8] Systematic review	6928 people with peripheral arterial disease 5 RCTs in this analysis	**Proportion of people with a vascular event (non-fatal MI, non-fatal stroke, or vascular death)** 227/3461 (7%) with antiplatelet agents other than aspirin 292/3467 (8%) with aspirin Antiplatelet agents assessed were ticlopidine, clopidogrel, or aspirin plus dipyridamole	OR 0.76 95% CI 0.64 to 0.91	●○○	Antiplatelet agents other than aspirin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARIS-MA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people who had an MI , 26 months** 36/1545 (2%) with clopidogrel plus aspirin 57/1551 (4%) with placebo plus aspirin	OR 0.63 95% CI 0.42 to 0.96 P = 0.03	●○○	Clopidogrel plus aspirin
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARIS-MA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people with a cardiovascular event (cardiovascular death, MI, or stroke) , 26 months** 117/1545 (8%) with clopidogrel plus aspirin 138/1551 (9%) with placebo plus aspirin	HR 0.85 95% CI 0.66 to 1.08 P = 0.18	⟷	Not significant

Mortality

No data from the following reference on this outcome. [8] [17]

Claudication distance/time

No data from the following reference on this outcome. [8] [17]

Post-intervention patency

No data from the following reference on this outcome. [8] [17]

Physiological measures

No data from the following reference on this outcome. [8] [17]

Quality of life

No data from the following reference on this outcome. [8] [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Bleeding					
[8] Systematic review	7028 people with peripheral arterial disease 5 RCTs in this analysis	**Proportion of people with a major bleed** 50/3561 (1%) with antiplatelet agents other than aspirin 68/3467 (2%) with aspirin Antiplatelet agents assessed were ticlopidine, clopidogrel, or aspirin plus dipyridamole	OR 0.73 95% CI 0.51 to 1.06 The number of events was likely to have been too low to detect a clinically important increase in major bleeding	⟷	Not significant
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARISMA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people with minor bleeding , 26 months** 531/1545 (34%) with clopidogrel plus aspirin 323/1551 (21%) with placebo plus aspirin	HR 1.99 95% CI 1.69 to 2.34 P <0.001	●○○	Placebo plus aspirin
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARISMA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people with a fatal bleed , 26 months** 7/1545 (0.5%) with clopidogrel plus aspirin 6/1551 (0.4%) with placebo plus aspirin	HR 1.17 95% CI 0.39 to 3.49 P = 0.776	⟷	Not significant
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARISMA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people with a primary intracranial haemorrhage , 26 months** 3/1545 (0.2%) with clopidogrel plus aspirin 6/1551 (0.4%) with placebo plus aspirin	HR 0.50 95% CI 0.12 to 2.01 P = 0.507	⟷	Not significant
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease	**Proportion of people with severe bleeding , 26 months** 26/1545 (1.7%) with clopidogrel plus aspirin	HR 0.97 95% CI 0.56 to 1.66 P = 0.90	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	RCT is a post-hoc subgroup analysis from the CHARIS-MA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	27/1551 (1.7%) with placebo plus aspirin			
[17] RCT	3096 people with symptomatic or asymptomatic peripheral arterial disease RCT is a post-hoc subgroup analysis from the CHARIS-MA trial (15,603 people with CAD, CVD, peripheral arterial disease, or multiple atherothrombotic risk factors)	**Proportion of people with moderate bleeding , 26 months** 38/1545 (3%) with clopidogrel plus aspirin 29/1551 (2%) with placebo plus aspirin	HR 1.32 95% CI 0.81 to 2.16 P = 0.26	⟷	Not significant

Further information on studies

Comment: **Clinical guide:**
Across a wide range of people, antiplatelet agents have been found to cause a clinically meaningful increase 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

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- 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.

Benefits and harms

Exercise versus usual care/placebo:

We found three systematic reviews (search date 1996, [18] 2006, [19] and 2008 [20]) comparing exercise versus control treatments (placebo tablets or instructions "to continue with normal lifestyle"). We found one additional RCT, [21] and two subsequent RCTs. [22] [23] 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.

Claudication distance/time

Regular exercise compared with usual care/placebo Regular exercise (including supervised treadmill exercise, an arm crank exercise programme, or undefined 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain-free walking distance					
[18] Systematic review	94 people with chronic, stable intermittent claudication 4 RCTs in this analysis Two RCTs identified by the review were in people also being treated with surgery, aspirin, or dipyridamole	**Mean increase in initial claudication distance , 3 to 12 months** with exercise programmes with usual care or placebo Absolute results not reported Exercise programmes involved at least 30 minutes of walking as far as claudication permitted, at least three times a week, for 3 to 6 months	Common difference of the mean (not further defined) 139 metres 95% CI 31 m to 247 m	○○○	Exercise
[19] Systematic review	409 people 8 RCTs in this analysis	**Increase in pain-free walking distance** with supervised exercise therapy with usual care Absolute results not reported Exercise therapy was supervised for between 12 weeks and 2 years	WMD 81.29 m 95% CI 35.45 m to 127.14 m P = 0.0005	○○○	Exercise
[23] RCT	57 men with stable intermittent claudication	**Change in pain-free walking distance , 12 weeks** From 147 m to 225 m with 12-week supervised arm-crank exercise programme From 177 m to 192 m with control group Exercise programme consisted of twice weekly 40-minute sessions with 20 minutes' exercise per session	P = 0.03	○○○	Arm-crank exercise programme
[20] Systematic review	322 people 6 RCTs in this analysis	**Mean increase in pain-free walking distance** with exercise with usual care or placebo Absolute results not reported Exercise therapy was given for between 12 weeks and 2 years	Mean difference 82.19 m 95% CI 71.73 m to 92.65 m	○○○	Exercise
[18] Systematic review	115 people 5 RCTs in this analysis Two RCTs identified by the review were in people also being treated with surgery, aspirin, or dipyridamole	**Mean increase in absolute claudication distance , 3 to 12 months** with exercise programmes with usual care or placebo Absolute results not reported Exercise programmes involved at least 30 minutes of walking as far as claudication permitted, at least three times a week, for 3 to 6 months	Common difference of the mean (not further defined) 179 m 95% CI 60 m to 298 m	○○○	Exercise
[19] Systematic review	499 people 9 RCTs in this analysis	**Increase in maximum walking distance** with supervised exercise therapy with usual care Absolute results not reported	WMD 155.79 m 95% CI 80.84 m to 230.74 m P <0.0001	○○○	Exercise

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Exercise therapy was supervised for between 12 weeks and 2 years			
[20] Systematic review	391 people 6 RCTs in this analysis	**Mean increase in maximal walking distance** with exercise with usual care or placebo Absolute results not reported Exercise therapy was given for between 12 weeks and 2 years	Mean difference 113.2 m 95% CI 94.96 m to 131.43 m	○○○	Exercise
[23] RCT	57 men with stable intermittent claudication	**Change in maximum walking distance , 12 weeks** From 496 m to 661 m with 12-week supervised arm-crank exercise programme From 600 m to 626 m with control group Exercise programme consisted of twice weekly 40-minute sessions with 20 minutes' exercise per session	P = 0.01	○○○	Arm-crank exercise programme
[22] RCT **3-armed trial**	156 people The third arm assessed resistance training (3 times/week)	**Increase in walking distance (assessed by a 6-minute walk test; change from baseline) , 6 months** +20.9 m with supervised treadmill exercise (3 times/week) –15.0 m with control Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference 35.9 m 95% CI 15.3 m to 56.5 m P <0.001 for treadmill *v* control	○○○	Exercise
[22] RCT **3-armed trial**	156 people The third arm assessed supervised treadmill exercise (3 times/week)	**Increase in walking distance (assessed by a 6-minute walk test; change from baseline) , 6 months** –2.6 m with resistance training (3 times/week) –15.0 m with control Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference +12.4 m 95% CI –8.42 m to +33.3 m P = 0.24 for resistance training *v* control	⟷	Not significant
Walking time					
[20] Systematic review	255 people 7 RCTs in this analysis	**Mean change in walking time** 136 minutes with exercise 119 minutes with usual care or placebo Exercise therapy was given for between 12 weeks and 2 years	WMD 5.12 minutes 95% CI 4.51 minutes to 5.72 minutes	○○○	Exercise
[21] RCT **4-armed trial**	52 people with intermittent claudication The third and fourth arms assessed pole-striding exercise plus vitamin E and vitamin E alone	**Increase in walking duration from baseline , 6 months** From 804 seconds to 2020 seconds with pole-striding exercise plus placebo From 612 seconds to 623 seconds with placebo	P value not reported for pole-striding *v* placebo		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Pole-striding exercise took place for 45 to 60 minutes, three times/week for 24 weeks			

Physiological measures

Regular exercise compared with usual care/placebo Regular exercise for 12 weeks to 2 years may be no more effective at improving ankle brachial index (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial index					
[20] Systematic review	228 people 7 RCTs in this analysis	**Ankle brachial index** with exercise with usual care or placebo Absolute results not reported Exercise therapy was given for between 12 weeks and 2 years	Mean difference –0.01 95% CI –0.05 to +0.04	⟷	Not significant
[23] RCT	57 men with stable intermittent claudication	**Resting ankle brachial index , 12 weeks** 0.71 with 12-week supervised arm-crank exercise programme 0.69 with control group Exercise programme consisted of twice weekly 40-minute sessions with 20 minutes' exercise per session Baseline ankle brachial index: 0.68 arm-crank group and 0.69 control group	P = 0.12	⟷	Not significant

No data from the following reference on this outcome. [18] [19] [21] [22]

Quality of life

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[22] RCT **3-armed trial**	156 people The third arm assessed resistance training (3 times/week)	**Change in SF-36 physical functioning score , 6 months** with supervised treadmill exercise (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 7.50 95% CI 0 to 15.0 P = 0.02 for treadmill *v* control	○○○	Treadmill exercise

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	156 people The third arm assessed the effects of supervised treadmill exercise (3 times/week)	**Change in SF-36 physical functioning score , 6 months** with resistance training (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 7.50 95% CI 0 to 15.0 P = 0.04 for resistance training *v* control	○○○	Resistance training
[22] RCT **3-armed trial**	156 people The third arm assessed resistance training (3 times/week)	**Change in Walking Impairment Questionnaire distance score , 6 months** with supervised treadmill exercise (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 10.7 95% CI 1.56 to 19.9 P = 0.02 for treadmill *v* control	○○○	Exercise
[22] RCT **3-armed trial**	156 people The third arm assessed the supervised treadmill exercise (3 times/week)	**Change in Walking Impairment Questionnaire distance score , 6 months** with resistance training (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 6.92 95% CI 1.07 to 12.8 P = 0.03 for resistance training *v* control	○○○	Resistance training
[22] RCT **3-armed trial**	156 people The third arm assessed resistance training (3 times/week)	**Change in stair-climbing score , 6 months** with supervised treadmill exercise (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 8.33 95% CI 0 to 16.7 P = 0.06 for treadmill *v* control	⟷	Not significant
[22] RCT **3-armed trial**	156 people The third arm assessed supervised treadmill exercise (3 times/week)	**Change in stair-climbing score , 6 months** with resistance training (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: 10.4 95% CI 0 to 20.8 P = 0.02 for resistance training *v* control	○○○	Resistance training
[22] RCT **3-armed trial**	156 people The third arm assessed resistance training (3 times/week)	**Change in speed score , 6 months** with supervised treadmill exercise (3 times/week) with control Absolute results not reported	Difference between groups: +3.80 95% CI –4.35 to +12.0 P = 0.39 for treadmill *v* control	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Control arm was 11 nutritional information sessions; not designed to change behaviour			
[22] RCT **3-armed trial**	156 people The third arm assessed supervised treadmill exercise (3 times/week)	**Change in speed score , 6 months** with resistance training (3 times/week) with control Absolute results not reported Control arm was 11 nutritional information sessions; not designed to change behaviour	Difference between groups: +1.63 95% CI –5.43 to +8.70 P = 0.55 for resistance training *v* control	⟷	Not significant

No data from the following reference on this outcome. [18] [19] [20] [21] [23]

Mortality

No data from the following reference on this outcome. [18] [19] [20] [21] [22] [23]

Cardiovascular events

No data from the following reference on this outcome. [18] [19] [20] [21] [22] [23]

Post-intervention patency

No data from the following reference on this outcome. [18] [19] [20] [21] [22] [23]

Adverse effects

No data from the following reference on this outcome. [18] [19] [20] [21] [22] [23]

Exercise as part of a multicomponent intervention versus usual care or placebo:

We found two RCTs. [21] [24]

Claudication distance/time

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum walking distance					
[24] RCT	882 men with early PVD identified by population screening	**Increase in self-reported maximal walking distance (assessed using the Edinburgh Claudication Questionnaire; change from baseline) , 12 months** 23% with "stop smoking and keep walking" intervention package 15% with usual care The intervention package involved an educational package, a brochure about community physiotherapy services, and information about the benefits of smoking cessation (see further information on studies for more details)	P = 0.008	○○○	Exercise (as part of a multicomponent intervention)
Walking time					
[21] RCT **4-armed trial**	52 people with intermittent claudication The third and fourth arms assessed pole-striding exercise plus placebo and vitamin E alone	**Increase in walking duration on a constant work-rate treadmill test (change from baseline) , 6 months** From 486 seconds to 1886 seconds with pole-striding exercise plus vitamin E From 612 seconds to 623 seconds with placebo Pole-striding exercise took place for 45 to 60 minutes, three times/week for 24 weeks	Significance not assessed		
Claudication grade					
[24] RCT	882 men with early PVD identified by population screening	**Intermittent claudication grade (assessed using the Edinburgh Claudication Questionnaire) , 12 months** with "stop smoking and keep walking" intervention package with usual care Absolute results not reported The intervention package involved an educational package, a brochure about community physiotherapy services, and information about the benefits of smoking cessation (see further information on studies for more details)	P = 0.26	⟷	Not significant

Mortality

No data from the following reference on this outcome. [21] [24]

Cardiovascular events

No data from the following reference on this outcome. [21] [24]

Post-intervention patency

No data from the following reference on this outcome. [21] [24]

Physiological measures

No data from the following reference on this outcome. [21] [24]

Quality of life

No data from the following reference on this outcome. [21] [24]

Adverse effects

No data from the following reference on this outcome. [21] [24]

Different types of exercise versus each other:

We found three RCTs. [25] [26] [27]

Claudication distance/time

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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Claudication distance					
[25] RCT **3-armed trial**	67 people with moderate to severe intermittent claudication The third arm assessed no treatment	**Improvement in initial claudication distance from baseline , 6 weeks** 122% with arm exercises 93% with leg exercises Absolute results reported graphically 48 people in analysis	Reported as not significant for arm *v* leg exercises P value not reported	⟷	Not significant
[25] RCT **3-armed trial**	67 people with moderate to severe intermittent claudication The third arm assessed no treatment	**Improvement in absolute claudication distance from baseline , 6 weeks** 147% with arm exercises 150% with leg exercises Absolute results reported graphically	Reported as not significant for arm *v* leg exercises P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		48 people in analysis			
[26] RCT **3-armed trial**	94 people The third arm assessed no exercise	**Improvement in claudication distance , 24 weeks** 51% with upper-limb exercises (twice weekly) 57% with lower-limb exercises (twice weekly) Absolute numbers not reported	Significance not assessed		
[26] RCT **3-armed trial**	94 people The third arm assessed no exercise	**Improvement in maximal walking distance , 24 weeks** 29% with upper-limb exercises (twice weekly) 31% with lower-limb exercises (twice weekly) Absolute numbers not reported	Significance not assessed		
Maximum/pain free walking time					
[27] RCT **3-armed trial**	42 people The third arm assessed no supervised training programme	**Increase in maximum walking time , 24 weeks** +240 seconds with treadmill training +48 seconds with cycle training Each exercise regimen was carried out three times/week for 6 weeks	Significance not assessed		
[27] RCT **3-armed trial**	42 people The third arm assessed no supervised training programme	**Change in pain-free walking time , 24 weeks** +195 seconds with treadmill training –8 seconds with cycle training Each exercise regimen was carried out three times/week for 6 weeks	Significance not assessed		

Mortality

No data from the following reference on this outcome. [25] [26] [27]

Cardiovascular events

No data from the following reference on this outcome. [25] [26] [27]

Post-intervention patency

No data from the following reference on this outcome. [25] [26] [27]

Physiological measures

No data from the following reference on this outcome. [25] [26] [27]

Quality of life

No data from the following reference on this outcome. [25] [26] [27]

Adverse effects

No data from the following reference on this outcome. [25] [26] [27]

Further information on studies

[24] The general practitioners of the people 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.

[18] [19] [20] 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.

Comment: We found one further systematic review (search date 1993; 21 observational studies or RCTs of exercise; 564 people with peripheral arterial disease). [28] 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 m) and in the absolute claudication distance (325–723 m), 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

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Bypass surgery may improve arterial patency at 12 months compared with PTA, but there seems to be no long-term benefit. Bypass surgery may be associated with improved survival in severe limb ischaemia in the longer term (3–7 years) compared with angioplasty.
- The risk of serious postoperative complications and mortality may be greater after bypass surgery compared with PTA.

Benefits and harms

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 versus PTA. [29] The review did not pool data for all outcomes because of differences in symptoms of included participants and follow-up time between RCTs. We also found long-term follow-up of one RCT (452 people with severe limb ischaemia) identified by the review. [30]

Mortality

Bypass surgery compared with percutaneous transluminal angioplasty (PTA) We don't know how bypass surgery and PTA compare at reducing mortality at 30 days or 2 years, but bypass surgery may be more effective at reducing mortality in the longer term (3–7 years) (low quality-evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[29] Systematic review	452 people Data from 1 RCT	**Mortality , within 30 days** 11/197 (6%) with bypass surgery 7/237 (3%) with percutaneous transluminal angioplasty (PTA)	OR 1.93 95% CI 0.75 to 4.99	⟷	Not significant
[29] Systematic review	54 people Data from 1 RCT	**Mortality , within 30 days** 0/24 (0%) with bypass surgery 0/30 (0%) with PTA			
[29] Systematic review	102 people Data from 1 RCT	**Mortality , within 30 days** 0/49 (0%) with bypass surgery 0/53 (0%) with PTA			
[30] RCT Further report of one RCT identified by review [29]	452 people with severe limb ischaemia due to infrainguinal disease	**All-cause mortality , 2 years** 70/228 (31%) with bypass surgery 61/224 (27%) with PTA	P = 0.85	⟷	Not significant
[30] RCT Further report of one RCT identified by review [29]	452 people with severe limb ischaemia due to infrainguinal disease	**All-cause mortality , 3 to 7 years (from 2 years after randomisation to trial end point)** 49/228 (21%) with bypass surgery 70/224 (31%) with PTA	P = 0.01	○○○	Bypass surgery

Post-intervention patency

Bypass surgery compared with percutaneous transluminal angioplasty (PTA) Bypass surgery may be more effective at improving primary arterial patency at 12 months, but we don't know whether it is more effective after 4 years. We don't know whether bypass surgery is more effective at decreasing amputation rates at 1 and 4 years in people with critical limb ischaemia or intermittent claudication (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Primary patency					
[29] Systematic review	355 people 2 RCTs in this analysis	**Proportion of people with improved primary patency , 12 months** 137/178 (77%) with bypass surgery 119/177 (67%) with percutaneous transluminal angioplasty (PTA)	OR 1.6 95% CI 1.0 to 2.6 P = 0.04	●○○	Bypass surgery
[29] Systematic review	263 people Data from 1 RCT	**Proportion of people with improved primary patency , median of 4 years of follow-up** with bypass surgery with PTA Absolute results not reported	P = 0.14	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Progression to amputation					
[29] Systematic review	41 people with intermittent claudication Data from 1 RCT	**Progression to amputation , 1 year** 0/18 (0%) with bypass surgery 1/23 (4%) with PTA	OR 0.17 95% CI 0 to 8.73	⟷	Not significant
[29] Systematic review	513 people with critical limb ischaemia 2 RCTs in this analysis	**Progression to amputation , 1 year** 74/257 (29%) with bypass surgery 56/256 (22%) with PTA	OR 1.45 95% CI 0.97 to 2.15	⟷	Not significant
[29] Systematic review	191 people with intermittent claudication Data from 1 RCT	**Progression to amputation , median follow-up of 49 months** 8/94 (8.5%) with bypass surgery 9/97 (9.3%) with PTA	OR 0.91 95% CI 0.34 to 2.46	⟷	Not significant
[29] Systematic review	525 people with critical limb ischaemia 2 RCTs in this analysis	**Progression to amputation , median follow-up of 49 months** 102/265 (38%) with bypass surgery 102/259 (39%) with PTA	OR 0.97 95% CI 0.69 to 1.39	⟷	Not significant

Cardiovascular events

No data from the following reference on this outcome. [29] [30]

Claudication distance/time

No data from the following reference on this outcome. [29] [30]

Physiological measures

No data from the following reference on this outcome. [29] [30]

Quality of life

No data from the following reference on this outcome. [29] [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] Systematic review	472 people with critical limb ischaemia 2 RCTs in this analysis	**Proportion of people with an operative complication** 122/226 (54%) with bypass surgery 72/246 (29%) with percutaneous transluminal angioplasty (PTA) The review defined complications in one RCT included in the meta-analysis as bleeding, occlusion, infection, and embolism; the review did not describe the complications in the other RCT	OR 2.85 95% CI 1.97 to 4.12	●●○	PTA
[29] Systematic review	41 people with intermittent claudication Data from 1 RCT	**Proportion of people with an operative complication** 1/18 (6%) with bypass surgery 3/23 (13%) with PTA	OR 0.44 95% CI 0.06 to 3.40	⟷	Not significant
[29] Systematic review	263 people Data from 1 RCT	**Procedure-related deaths** 3/133 (2%) with bypass surgery 0/130 (0%) with PTA The review reported that three people having surgery died of causes related to the operation in the RCT	Significance not assessed		
[29] Systematic review	452 people Data from 1 RCT	**Length of hospital stay** 46.1 days with bypass surgery 36.4 days with PTA	P <0.0001	○○○	PTA

Bypass surgery versus percutaneous transluminal angioplasty (PTA) plus stent placement:

We found one RCT comparing long-term outcomes of surgery versus PTA plus stent placement. [31]

Post-intervention patency

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Primary patency					
[31] RCT	86 people (100 limbs) with superficial femoral artery occlusive disease	**Rate of primary patency , 6 months** 84% with femoral to above-knee popliteal artery bypass with synthetic graft 81% with percutaneous transluminal angioplasty (PTA) plus stent placement Absolute numbers not reported	P = 0.72 P value reported for overall difference between groups (includes all time points)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT	86 people (100 limbs) with superficial femoral artery occlusive disease	**Rate of primary patency , 12 months** 83% with femoral to above-knee popliteal artery bypass with synthetic graft 72% with PTA plus stent placement Absolute numbers not reported	P = 0.72 P value reported for overall difference between groups (includes all time points)	⟷	Not significant
[31] RCT	86 people (100 limbs) with superficial femoral artery occlusive disease	**Rate of primary patency , 24 months** 76% with femoral to above-knee popliteal artery bypass with synthetic graft 64% with PTA plus stent placement Absolute numbers not reported	P = 0.72 P value reported for overall difference between groups (includes all time points)	⟷	Not significant

Mortality

No data from the following reference on this outcome. [31]

Cardiovascular events

No data from the following reference on this outcome. [31]

Claudication distance/time

No data from the following reference on this outcome. [31]

Physiological measures

No data from the following reference on this outcome. [31]

Quality of life

No data from the following reference on this outcome. [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT	86 people (100 limbs) with superficial femoral artery occlusive disease	**Proportion of people with an early complication** 3/46 (7%) with femoral to above-knee popliteal artery bypass with synthetic graft 4/40 (10%) with percutaneous transluminal angioplasty (PTA) plus stent placement 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	Significance not assessed		

Further information on studies

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.

OPTION STATINS (HMG-COA REDUCTASE INHIBITORS)

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Statins have been shown to reduce cardiovascular events in large trials including people with PVD, and they may increase walking distance and time to claudication compared with placebo.

Benefits and harms

Statins versus placebo:

We found one systematic review (search date 2009; 3 RCTs, 380 people) [16] and three additional RCTs (reported in 4 publications) comparing statins versus placebo. [32] [33] [34] [35] The review [16] did not pool data for statins as a class but reported the effects of atorvastatin versus placebo from one RCT [36] that it identified and pooled data for simvastatin from two RCTs it identified.

Mortality

Statins compared with placebo We don't know whether statins as a class are more effective at reducing all-cause or cardiovascular mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[32] [33] RCT	20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus; 6748 people with peripheral arterial disease	**Rate of all-cause mortality** 1328/10,269 (13%) with simvastatin 40 mg daily 1507/10,267 (15%) with placebo	P = 0.0003	○○○	Simvastatin 40 mg daily

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and 2701 people with peripheral arterial disease but without diagnosed CHD RCT did not separately report on the subgroup with peripheral arterial disease				
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 10 mg	**All-cause mortality** 1/120 (0.8%) with atorvastatin 80 mg daily 1/114 (0.9%) with placebo	Significance not assessed		
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 80 mg	**All-cause mortality** 4/120 (3%) with atorvastatin 10 mg daily 1/114 (1%) with placebo	Significance not assessed		
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease RCT did not separately report on the subgroup with peripheral arterial disease	**Rate of all-cause mortality , median follow-up of 3.3 years** 185/5168 (3.6%) with atorvastatin 10 mg daily 212/5137 (4.1%) with placebo	HR 0.87 95% CI 0.71 to 1.06	⟷	Not significant
Cardiovascular mortality					
[32] [33] RCT	20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus; 6748 people with peripheral arterial disease and 2701 people with peripheral arterial disease but without diagnosed CHD RCT did not separately report on the subgroup with peripheral arterial disease	**Rate of cardiovascular mortality** 587/10,269 (6%) with simvastatin 40 mg daily 707/10,267 (7%) with placebo	P = 0.0005	○○○	Simvastatin 40 mg daily
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease RCT did not separately report on the subgroup with peripheral arterial disease	**Rate of cardiovascular mortality , median follow-up of 3.3 years** 74/5168 (1.4%) with atorvastatin 10 mg daily 82/5137 (1.6%) with placebo	HR 0.90 95% CI 0.66 to 1.23	⟷	Not significant

No data from the following reference on this outcome. [35]

Cardiovascular events

Statins compared with placebo Statins (simvastatin, atorvastatin, and pravastatin) may be more effective at reducing major cardiovascular events and composite outcomes that include fatal cardiovascular events in people with peripheral arterial disease (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vascular event					
[32] [33] RCT	6748 people with peripheral arterial disease Subgroup analysis Total population was 20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus (see further information on studies for results for cardiovascular events in total population)	**Proportion of people with a first major vascular event (major coronary event, stroke, and revascularisation)** 895 (26%) with simvastatin 40 mg daily 1101 (33%) with placebo Absolute numbers not reported	Absolute reduction of 63 per 1000 P <0.001	○○○	Simvastatin 40 mg daily
[32] [33] RCT	2701 people with peripheral arterial disease but without diagnosed CHD Subgroup analysis Total population was 20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus (see further information on studies for results for cardiovascular events in total population)	**Proportion of people with a first major vascular event (major coronary event, stroke, and revascularisation)** 327/1325 (25%) with simvastatin 40 mg daily 420/1376 (31%) with placebo	P <0.0001	○○○	Simvastatin 40 mg daily
[35] RCT	5804 people; aged 70 to 82 years; 513 (9%) with intermittent claudication or previous peripheral arterial surgery RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with a non-fatal MI, fatal or non-fatal stroke, or coronary death , mean follow-up of 3.2 years** 408/2891 (14%) with pravastatin 40 mg daily 473/2913 (16%) with placebo	HR 0.85 95% CI 0.74 to 0.97	●○○	Pravastatin 40 mg daily
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with a cardiovascular event (non-fatal MI and fatal CHD) , median follow-up of 3.3 years** 389/5168 (8%) with atorvastatin 10 mg daily 486/5137 (9%) with placebo	HR 0.79 95% CI 0.69 to 0.90	●○○	Atorvastatin 10 mg daily
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease	**Proportion of people with a coronary event , median follow-up of 3.3 years**	HR 0.71 95% CI 0.59 to 0.86	●○○	Atorvastatin 10 mg daily

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	RCT did not separately report on the subgroup with peripheral arterial disease	178/5168 (3%) with atorvastatin 10 mg daily 247/5137 (5%) with placebo			
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with a fatal or non-fatal stroke , median follow-up of 3.3 years** 89/5168 (1.7%) with atorvastatin 10 mg daily 121/5137 (2.4%) with placebo	HR 0.73 95% CI 0.56 to 0.96	●○○	Atorvastatin 10 mg daily
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 10 mg	**Proportion of people with a cardiovascular event (MI and stroke)** 3/120 (2.5%) with atorvastatin 80 mg daily 3/114 (2.6%) with placebo	Significance not assessed		
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 80 mg	**Proportion of people with a cardiovascular event (MI and stroke)** 5/120 (4%) with atorvastatin 10 mg daily 3/114 (3%) with placebo	Significance not assessed		

Claudication distance/time

Statins compared with placebo Statins may be more effective at increasing maximum walking distance or pain-free walking time (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain free walking time					
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 80 mg	**Mean improvement in pain-free walking time (change from baseline) , 12 months** 74 seconds with atorvastatin 10 mg daily 39 seconds with placebo 234 people in this analysis (120 people in atorvastatin 10 mg group and 114 people in placebo group)	P = 0.13	⟷	Not significant
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 10 mg	**Mean improvement in pain-free walking time (change from baseline) , 12 months** 81 seconds with atorvastatin 80 mg daily 39 seconds with placebo 234 people in this analysis (120 people in atorvastatin 80 mg group and 114 people in placebo group)	P = 0.025 for atorvastatin 80 mg daily versus placebo	○○○	Atorvastatin 80 mg)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The review [16] noted that the baseline walking distance was considerably lower in the atorvastatin 80 mg group than in the placebo group. However, the RCT reported the baseline difference between groups as not significant			
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 80 mg	**Mean improvement in maximal walking time (change from baseline) , 12 months** 90 seconds with atorvastatin 10 mg daily 50 seconds with placebo 234 people in this analysis (120 people in atorvastatin 10 mg group and 114 people in placebo group)	P = 0.37	⟷	Not significant
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed atorvastatin 10 mg	**Mean improvement in maximal walking time (change from baseline) , 12 months** 90 seconds with atorvastatin 80 mg daily 50 seconds with placebo 234 people in this analysis (120 people in atorvastatin 80 mg group and 114 people in placebo group) The review [16] noted that the baseline walking distance was considerably lower in the atorvastatin 80 mg group than in the placebo group. However, the RCT reported the baseline difference between groups as not significant	P = 0.37	⟷	Not significant
Maximum/pain-free walking distance					
[16] Systematic review	146 people with moderate intermittent claudication and ankle brachial index <0.9 2 RCTs in this analysis	**Maximum walking distance , 6 to 12 months** with simvastatin with placebo Absolute results not reported	WMD 104.14 metres 95% CI 61.51 m to 146.77 m Results should be interpreted with caution; significant statistical heterogeneity between RCTs (P <0.001; no explanation of heterogeneity suggested)	◌◌◌	Simvastatin

No data from the following reference on this outcome. [32] [33] [34] [35]

Physiological measures

Atorvastatin compared with placebo We don't know whether atorvastatin is more effective than placebo at improving ankle brachial index after exercise at 12 months in people with peripheral arterial disease and intermittent claudication (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial index					
[36] RCT	354 people with peripheral arterial disease and intermittent claudication	**Improvement in ankle brachial index after exercise (change from baseline) , 12 months**	P = 0.57 across all groups		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	In review [16]	From 0.62 to 0.64 with atorvastatin 80 mg daily From 0.62 to 0.64 with atorvastatin 10 mg daily From 0.59 to 0.63 with placebo	Significance of between group differences not assessed		

No data from the following reference on this outcome. [32] [33] [34] [35]

Quality of life

Atorvastatin 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed the effects of atorvastatin 10 mg	**Quality of life assessed using the Walking Impairment Questionnaire** with atorvastatin 80 mg daily with placebo Absolute results not reported 234 people in this analysis (120 people in atorvastatin 80 mg group and 114 people in placebo group)	Reported as not significant No further data reported	⟷	Not significant
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed the effects of atorvastatin 80 mg	**Quality of life assessed using the Walking Impairment Questionnaire** with atorvastatin 10 mg daily with placebo Absolute results not reported 234 people in this analysis (120 people in atorvastatin 10 mg group and 114 people in placebo group)	Reported as not significant No further data reported	⟷	Not significant
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed the effects of atorvastatin 10 mg	**Quality of life assessed using the short form-36 (SF-36) questionnaire** with atorvastatin 80 mg daily with placebo Absolute results not reported 234 people in this analysis (120 people in atorvastatin 80 mg group and 114 people in placebo group)	Reported as not significant No further data reported	⟷	Not significant
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16] The third arm assessed the effects of atorvastatin 80 mg	**Quality of life assessed using the SF-36 Questionnaire** with atorvastatin 10 mg daily with placebo Absolute results not reported 234 people in this analysis (120 people in atorvastatin 10 mg group and 114 people in placebo group)	Reported as not significant No further data reported	⟷	Not significant

No data from the following reference on this outcome. [32] [33] [34] [35]

Post-intervention patency

No data from the following reference on this outcome. [16] [32] [33] [34] [35] [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[34] RCT	10,305 people with hypertension; 514 (5%) with peripheral arterial disease RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with a serious adverse effect** with atorvastatin 10 mg daily with placebo Absolute results not reported The RCT found similar rates of serious adverse effects between the placebo and statin groups Serious adverse effects not described The RCT reported one incidence of fatal rhabdomyolysis in the statin group	Significance not assessed		
[32] [33] RCT	20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus; 6748 people with peripheral arterial disease and 2701 people with peripheral arterial disease but without diagnosed CHD RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people discontinuing treatment because of adverse effects** 4.8% with simvastatin 40 mg daily 5.1% with placebo Absolute numbers not reported	Significance not assessed		
[36] RCT **3-armed trial**	354 people with peripheral arterial disease and intermittent claudication In review [16]	**Proportion of people discontinuing study drug due to adverse events , 12 months** 3/120 (3%) with atorvastatin 80 mg daily 7/120 (6%) with atorvastatin 10 mg daily 2/114 (2%) with placebo	Significance not assessed		
[32] [33] RCT	20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus; 6748 people with peripheral arterial disease and 2701 people	**Proportion of people with a new primary cancer** 814/10,269 (7.9%) with simvastatin 40 mg daily 803/10,267 (7.8%) with placebo	RR 1.0 95% CI 0.91 to 1.11	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	with peripheral arterial disease but without diagnosed CHD RCT did not separately report on the subgroup with peripheral arterial disease				
[35] RCT	5804 people; aged 70 to 82 years; 513 (9%) with intermittent claudication or previous peripheral arterial surgery RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with a new cancer** 245/2891 (9%) with pravastatin 40 mg daily 199/2913 (7%) with placebo	HR 1.25 95% CI 1.04 to 1.51	●○○	Placebo
[32] [33] RCT	20,536 people with CHD, other occlusive arterial disease, or diabetes mellitus; 6748 people with peripheral arterial disease and 2701 people with peripheral arterial disease but without diagnosed CHD RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with muscular pain and weakness** 32.9% with simvastatin 40 mg daily 33.2% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[35] RCT	5804 people; aged 70 to 82 years; 513 (9%) with intermittent claudication or previous peripheral arterial surgery RCT did not separately report on the subgroup with peripheral arterial disease	**Proportion of people with myalgia** 36/2891 (1.2%) with pravastatin 40 mg daily 32/2913 (1.1%) with placebo	Significance not assessed		

Further information on studies

[32] [33] The RCT found that in all people, simvastatin significantly reduced non-fatal or fatal stroke, and coronary or non-coronary revascularisation compared with placebo at 5 years (20,536 people: 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).

Comment: **Clinical guide:**
In most of the RCTs we identified evaluating statins, people with peripheral arterial disease formed only a small proportion of the total number of people randomised. However, similar benefits were

observed in this subgroup, suggesting that the results of the RCTs may be generalisable to people with peripheral arterial disease. [32] [33] [34] [35]

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. [37] [38]

OPTION PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Percutaneous transluminal angioplasty (PTA) may improve walking distance compared with no intervention, but the benefit may not last beyond 6 months.
- Adding a stent to PTA may confer additional benefit over PTA alone.

Benefits and harms

Percutaneous transluminal angioplasty (PTA) versus no percutaneous intervention:

We found one systematic review (search date 2006; 2 RCTs; 98 people) [39] and one subsequent RCT. [40] The review [39] did not pool the results of the RCTs identified and so we report data from the individual RCTs. [41] [42]

Claudication distance/time

Percutaneous transluminal angioplasty (PTA) compared with no percutaneous intervention 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Claudication distance					
[42] RCT	36 people In review [39]	**Increase in mean claudication distance , 6 months** with Percutaneous transluminal angioplasty (PTA) with exercise programme Absolute results reported graphically	No direct statistical comparison between groups No significant difference with PTA compared with baseline P <0.01 with exercise programme compared with baseline		
[42] RCT	36 people In review [39]	**Increase in mean maximum walking distance , 6 months** with PTA with exercise programme Absolute results reported graphically	No direct statistical comparison between groups No significant difference with PTA compared with baseline P <0.01 with exercise programme compared with baseline		
[41] RCT	62 people with mild to moderate intermittent claudication In review [39]	**Median initial claudication distance , 6 months** 667 metres with PTA 172 m with no PTA	P <0.05	○○○	PTA
[41] RCT	62 people with mild to moderate intermittent claudication In review [39]	**Median initial claudication distance , 2 years** 383 m with PTA 333 m with no PTA	P = 0.578	⟷	Not significant
[40] RCT	56 people with disabling intermittent claudication	**Pain-free walking distance , 24 months** 174.9 m with PTA plus optimal medical treatment 435 m with optimal medical treatment alone	P = 0.0001	○○○	Optimal medical treatment alone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for details of optimal treatment			
[40] RCT	56 people with disabling intermittent claudication	**Maximum walking distance , 24 months** 319.5 m with PTA plus optimal medical treatment 539.2 m with optimal medical treatment alone See further information on studies for details of optimal treatment	P = 0.0009	○○○	Optimal medical treatment alone

Quality of life

Percutaneous transluminal angioplasty (PTA) compared with no PTA We don't know whether 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[41] RCT	62 people with mild to moderate intermittent claudication In review [39]	**Quality of life assessed using the Nottingham Health Profile , 2 years** with percutaneous transluminal angioplasty (PTA) with no PTA Absolute results not reported	P >0.05	⟷	Not significant
[40] RCT	56 people with disabling intermittent claudication	**Change in physical functioning component of short form-36 (SF-36) questionnaire , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported See further information on studies for details of optimal treatment	P = 0.0003	○○○	PTA plus optimal medical treatment
[40] RCT	56 people with disabling intermittent claudication	**Change in bodily pain component of SF-36 questionnaire , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported See further information on studies for details of optimal treatment	P <0.014	○○○	PTA plus optimal medical treatment
[40] RCT	56 people with disabling intermittent claudication	**Change in health transition component of SF-36 questionnaire , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported	P <0.0001	○○○	PTA plus optimal medical treatment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for details of optimal treatment			
[40] RCT	56 people with disabling intermittent claudication	**Change in pain during activity component of claudication scale questionnaire , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported See further information on studies for details of optimal treatment	P = 0.0014	○○○	PTA plus optimal medical treatment
[40] RCT	56 people with disabling intermittent claudication	**Change in severity of pain component of claudication scale questionnaire , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported See further information on studies for details of optimal treatment	P = 0.001	○○○	PTA plus optimal medical treatment
[40] RCT	56 people with disabling intermittent claudication	**Various components of SF-36 and claudication scale questionnaires , 3 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported Other domains assessed using the SF-36 were physical role, general health vitality, social functioning, and mental health. Domains assessed using the claudication scale were everyday life, pain related to sleep, and specific fears related to illness or psychological well-being See further information on studies for details of optimal treatment	Difference between groups in listed domains reported as not significant P values not reported	⟷	Not significant
[40] RCT	56 people with disabling intermittent claudication	**Change in physical functioning component of SF-36 questionnaire , 24 months** with PTA plus optimal medical treatment with optimal medical treatment alone Absolute results not reported See further information on studies for details of optimal treatment	P <0.0098	○○○	PTA plus optimal medical treatment
[40] RCT	56 people with disabling intermittent claudication	**Various components of SF-36 and claudication scale questionnaires , 24 months** with PTA plus optimal medical treatment with optimal medical treatment alone	Difference between groups in listed domains reported as not significant P values not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported Other domains assessed using the SF-36 were bodily pain, health transition, physical role, general health vitality, social functioning, and mental health. Domains assessed using the claudication scale were pain during activity, severity of pain, everyday life, pain related to sleep, and specific fears related to illness or psychological well-being See further information on studies for details of optimal treatment			

No data from the following reference on this outcome. [42]

Mortality

No data from the following reference on this outcome. [41] [42] [40]

Cardiovascular events

No data from the following reference on this outcome. [39] [40] [41] [42]

Post-intervention patency

No data from the following reference on this outcome. [39] [40] [41] [42]

Physiological measures

No data from the following reference on this outcome. [39] [40] [41] [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] Systematic review		**Adverse effects** with percutaneous transluminal angioplasty (PTA) with no PTA Absolute results not reported The review reported no major complications requiring surgical			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		correction or delay in discharge in one identified RCT The review reported two unsuccessful angioplasties, three groin haematomas, and one rupture of the external iliac artery			

No data from the following reference on this outcome. [40]

Percutaneous transluminal angioplasty (PTA) plus stent versus PTA alone:

We found two systematic reviews (search date 2008, 7 RCTs, 519 people, 614 limbs; [43] and search date 2009, 8 RCTs, 968 people [44]). The second review includes three of the RCTs reported in the first review but as it reports on different outcomes we include both reviews here. The second review also includes two of the RCTs we report separately in the PTA plus routine stent versus PTA plus selective stent comparison [45] [46] [47]). It is unclear in either of the reviews [43] [44] whether they included any additional RCTs that randomised people to PTA plus routine stent versus PTA plus selective stent.

Claudication distance/time

Percutaneous transluminal angioplasty (PTA) plus stent compared with PTA alone PTA plus stent may be more effective at increasing mean treadmill walking distance at 6 and 12 months but we don't know whether it is more effective at 24 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain-free walking distance					
[44] Systematic review	104 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion Data from 1 RCT	**Mean treadmill walking distance , 6 months** 271 m with percutaneous transluminal angioplasty (PTA) plus stent 183 m with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference 88.00 metres 95% CI 74.54 m to 101.46 m Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	○○○	PTA plus stent
[44] Systematic review	240 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 2 RCTs in this analysis	**Mean treadmill walking distance , 12 months** with PTA plus stent with PTA alone Absolute results not reported Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference 62.52 m 95% CI 48.36 m to 76.68 m Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial. Results should be interpreted with caution because of statistical heterogeneity (P <0.00001) as one large RCT in the analysis reported much higher results for walking distance in the PTA plus stent group than did the other RCTs	○○○	PTA plus stent

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[44] Systematic review	98 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 2 RCTs in this analysis	**Mean treadmill walking distance , 24 months** 180 m with PTA plus stent 163 m with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference +17.00 m 95% CI –123.23 m to +157.23 m P = 0.81 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant

No data from the following reference on this outcome. [43]

Post-intervention patency

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patency					
[43] Systematic review	230 people (304 limbs) 4 RCTs in this analysis	**Patency rate , 6 months** 106/128 limbs (83%) with percutaneous transluminal angioplasty (PTA) plus stenting 122/176 limbs (69%) with PTA alone	OR (PTA *v* PTA plus stent) 0.47 95% CI 0.27 to 0.84 P <0.05	●●○	PTA plus stenting
[44] Systematic review	325 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 4 RCTs in this analysis	**Patency on duplex USS , 6 months** 127/158 (80%) with PTA plus stent 118/167 (71%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT.	OR 1.71 95% CI 1.03 to 2.85 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	●○○	PTA plus stent
[44] Systematic review	261 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 3 RCTs in this analysis	**Patency on angiography , 6 months** 113/141 (80%) with PTA plus stent 84/120 (70%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	OR 2.06 95% CI 1.15 to 3.72 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	●●○	PTA plus stent
[43] Systematic review	468 people (519 limbs) 6 RCTs in this analysis	**Patency rate , 12 months** 164/249 limbs (66%) with PTA plus stenting 190/270 limbs (70%) with PTA alone	OR (PTA *v* PTA plus stent) 1.27 95% CI 0.87 to 1.86	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] Systematic review	374 people (417 limbs) 4 RCTs in this analysis	**Patency rate , 24 months** 113/201 limbs (56%) with PTA plus stenting 131/216 limbs (61%) with PTA alone	OR (PTA *v* PTA plus stent) 1.22 95% CI 0.81 to 1.82	⟷	Not significant
[44] Systematic review	520 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 6 RCTs in this analysis	**Patency on duplex USS , 12 months** 178/254 (70%) with PTA plus stent 167/266 (63%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	OR 1.41 95% CI 0.97 to 2.04 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant
[44] Systematic review	384 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 5 RCTs in this analysis	**Patency on angiography , 12 months** 134/205 (65%) with PTA plus stent 109/179 (61%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	OR 1.31 95% CI 0.84 to 2.03 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant
[44] Systematic review	192 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 3 RCTs in this analysis	**Patency on duplex USS , 24 months** 57/91 (63%) with PTA plus stent 48/101 (48%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	OR 1.78 95% CI 0.98 to 3.24 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant
[44] Systematic review	74 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 2 RCTs in this analysis	**Patency on angiography , 24 months** 15/30 (50%) with PTA plus stent 26/44 (59%) with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	OR 0.70 95% CI 0.28 to 1.76 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant

Physiological measures

Percutaneous transluminal angioplasty (PTA) plus stent compared with PTA alone PTA plus stent may be more effective than PTA alone at improving ankle brachial index at 6 and 12 months but maybe no more effective at 24 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial pressure index					
[44] Systematic review	104 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion Data from 1 RCT	**Mean improvement in ankle brachial index , 6 months** 0.25 with percutaneous transluminal angioplasty (PTA) plus stent 0.18 with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference 0.07 95% CI 0.04 to 0.10 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	○○○	PTA plus stent
[44] Systematic review	291 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion 3 RCTs in this analysis	**Mean improvement in ankle brachial index , 12 months** with PTA plus stent with PTA alone Absolute results not reported Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference 0.07 95% CI 0.05 to 0.09 Results should be interpreted with caution because of statistical heterogeneity as one large RCT in the analysis reported much higher results for ankle brachial index in the PTA plus stent group than the other RCTs Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	○○○	PTA plus stent
[44] Systematic review	98 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion Data from 1 RCT	**Mean improvement in ankle brachial index , 24 months** 0.26 with PTA plus stent 0.23 with PTA alone Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference +0.03 95% CI –0.04 to +0.10 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant

No data from the following reference on this outcome. [43]

Quality of life

Percutaneous transluminal angioplasty (PTA) plus stent compared with PTA alone We don't know whether PTA plus stent is more effective than PTA alone at improving quality of life scores at 6 or 12 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[44] Systematic review	208 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion	**Improvement in quality of life score , 6 months** with percutaneous transluminal angioplasty (PTA) plus stent with PTA alone Absolute results not reported	Mean difference –1.13 95% CI –5.03 to +2.77 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (sec-	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	ondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial		
[44] Systematic review	208 people with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion Data from 1 RCT	**Improvement in quality of life score , 12 months** with PTA plus stent with PTA alone Absolute results not reported Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	Mean difference +0.96 95% CI –2.62 to +4.53 Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial	⟷	Not significant

No data from the following reference on this outcome. [43]

Mortality

No data from the following reference on this outcome. [43] [44]

Cardiovascular events

No data from the following reference on this outcome. [43] [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] Systematic review	People with intermittent claudication or critical limb ischaemia and superficial femoral artery stenosis or occlusion	**Intervention complication rates** with percutaneous transluminal angioplasty (PTA) plus stent with PTA alone Absolute results not reported Five RCTs reported intervention complication rates of between 4.0% and 7.8%. The review did not report pooled data for this outcome. Review commented that the type of antiplatelet medication varied between the included RCTs; clopidogrel was given in one large RCT	RCTs reported no significant difference in complication rates between groups; no pooled data reported Results should be interpreted with caution as it was unclear in some of the RCTs how many people in the PTA alone arm went on to have "bailout" (secondary) stenting and whether or not they were subsequently included in the PTA plus stent arm for analysis, or excluded from the trial		

No data from the following reference on this outcome. [43]

Percutaneous transluminal angioplasty (PTA) plus routine stent versus PTA plus selective stent:

We found 4 RCTs (reported in 5 publications) in which people were randomised to PTA plus routine stent or PTA plus selective stent, which we report here. [45] [46] [47] [48] [49] One of the systematic reviews [44] reported in the PTA plus stent versus PTA alone comparison included two of the RCTs that we also report here in its meta-analysis. [45] [46] [47]

Claudication distance/time

Percutaneous transluminal angioplasty (PTA) plus routine stent compared with PTA plus selective stent PTA plus routine stent may be more effective at improving walking distance at 6 and 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Walking distance					
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Patient-reported average maximum walking distance , 6 months** 800 metres with percutaneous transluminal angioplasty (PTA) plus routine stenting (nitinol self-expanding stents) 600 m with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	Intention-to-treat analysis P = 0.002	○○○	PTA plus routine stenting
[46] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [47]	**Walking distance , 12 months** 387 m with PTA plus routine stenting (primary nitinol self-expanding stents) 267 m with balloon angioplasty with optional secondary stenting 17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)	P = 0.04	○○○	PTA plus routine stenting
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Patient-reported average maximum walking distance , 12 months** 800 m with PTA plus routine stenting (nitinol self-expanding stents) 550 with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	Intention-to-treat analysis P = 0.042	○○○	PTA plus routine stenting

No data from the following reference on this outcome. [45] [48]

Post-intervention patency

Percutaneous transluminal angioplasty (PTA) plus routine stent compared with PTA plus selective stent PTA plus routine stenting may be more effective at reducing reintervention rates or rates of restenosis at 3, 6, and 12 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-intervention / restenosis					
[48] RCT	279 people with intermittent claudication and iliac artery stenosis	**Proportion of people requiring reintervention** 10/143 (7%) with percutaneous transluminal angioplasty (PTA) plus routine stenting 6/136 (4%) with PTA plus selective stenting 59/136 (43%) in PTA with selective stenting group had stenting due to residual mean pressure gradient greater than 10 mm Hg across the treated site following PTA	ARR +3% 95% CI –3% to +8%	⟷	Not significant
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Proportion of people with >50% restenosis according to duplex ultrasound , 3 months** 1/34 (3%) with PTA plus routine stenting (nitinol self-expanding stents) 7/37 (19%) with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	P = 0.033	○○○	PTA plus routine stenting
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Proportion of people with >50% restenosis , 6 months** 7/32 (22%) with PTA plus routine stenting (nitinol self-expanding stents) 20/36 (56%) with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation Unclear whether duplex ultrasound or CTA (computed tomography angiography) was used to measure restenosis	Intention-to-treat analysis P = 0.005	○○○	PTA plus routine stenting
[45] RCT	227 people with severe claudication or limb-threatening stenosis of the superficial femoral artery	**Proportion of people who died or had >50% restenosis , 1 year** 30/89 (34%) with PTA plus routine stenting 29/86 (33%) with PTA plus selective stenting 17/112 (15%) in PTA with selective stenting group had stenting after suboptimal results of PTA (not further defined)	P = 0.9	⟷	Not significant
[46] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [47]	**Proportion of people with restenosis , 12 months** 18/49 (37%) with PTA plus routine stenting (primary nitinol self-expanding stents) 33/52 (63%) with balloon angioplasty with optional secondary stenting	P = 0.01	○○○	PTA plus routine stenting

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)			
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Proportion of people with >50% restenosis according to duplex ultrasound , 12 months** 11/32 (34%) with PTA plus routine stenting (nitinol self-expanding stents) 22/36 (61%) with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	Intention-to-treat analysis P = 0.028	○○○	PTA plus routine stenting

Physiological measures

Percutaneous transluminal angioplasty (PTA) plus routine stent compared with PTA plus selective stent We don't know how PTA plus routine stenting and PTA plus selective stenting compare at improving ankle brachial index at 6 and 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial index					
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Ankle brachial index , 6 months** 1.20 with percutaneous transluminal angioplasty (PTA) plus routine stenting (nitinol self-expanding stents) 1.06 with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	Intention-to-treat analysis P = 0.84	⟷	Not significant
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Ankle brachial index , 12 months** 0.93 with PTA plus routine stenting (nitinol self-expanding stents) 0.89 with PTA with optional secondary stenting 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation	Intention-to-treat analysis P = 0.40	⟷	Not significant

No data from the following reference on this outcome. [48] [45] [46] [47]

Quality of life

Percutaneous transluminal angioplasty (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 is more effective at improving quality of life at 3 to 12 months (assessed using the RAND-36 questionnaire or the short form-36 [SF-36] questionnaire) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[48] RCT	279 people with intermittent claudication and iliac artery stenosis	**Improvement in quality of life (assessed using the RAND-36 questionnaire) , 3 months** with percutaneous transluminal angioplasty (PTA) plus routine stenting with PTA plus selective stenting Absolute results not reported 59/136 (43%) in PTA with selective stenting group had stenting due to residual mean pressure gradient greater than 10 mm Hg across the treated site following PTA	Reported as not significant P value not reported	⟷	Not significant
[47] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [46]	**Physical component of the short form-36 (SF-36) quality-of-life questionnaire , 6 months** 33 with PTA plus routine stenting (primary nitinol self-expanding stents) 37 with balloon angioplasty with optional secondary stenting Physical component of the SF-36 quality-of-life questionnaire has a scale of 0 to 100; higher scores indicate a better quality of life 17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)	P = 0.8	⟷	Not significant
[47] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [46]	**Mental component of the SF-36 quality-of-life questionnaire , 6 months** 53 with PTA plus routine stenting (primary nitinol self-expanding stents) 50 with balloon angioplasty with optional secondary stenting Mental component of the SF-36 quality-of-life questionnaire has a scale of 0 to 100; higher scores indicate a better quality of life 17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)	P = 0.5	⟷	Not significant
[47] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [46]	**Physical component of the SF-36 quality-of-life questionnaire , 12 months** 35 with PTA plus routine stenting (primary nitinol self-expanding stents) 37 with balloon angioplasty with optional secondary stenting Physical component of the SF-36 quality-of-life questionnaire has a scale of 0 to 100; higher scores indicate a better quality of life	P = 0.9	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)			
[47] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [46]	**Mental component of the SF-36 quality-of-life questionnaire , 12 months** 54 with PTA plus routine stenting (primary nitinol self-expanding stents) 51 with balloon angioplasty with optional secondary stenting Mental component of the SF-36 quality-of-life questionnaire has a scale of 0 to 100; higher scores indicate a better quality of life 17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)	P = 0.1	⟷	Not significant

No data from the following reference on this outcome. [45] [49]

Mortality

No data from the following reference on this outcome. [45] [46] [47] [48] [49]

Cardiovascular events

No data from the following reference on this outcome. [45] [46] [47] [48] [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] RCT	279 people with intermittent claudication and iliac artery stenosis	**Proportion of people with complications** 6/143 (4%) with percutaneous transluminal angioplasty (PTA) plus routine stenting 10/136 (7%) with PTA plus selective stenting 59/136 (43%) in PTA with selective stenting group had stenting due to residual mean pressure gradient greater than 10 mm Hg across the treated site following PTA Complications included haematoma at the puncture site,	95% CI (for difference between groups) –2% to +9%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		arterial wall perforation, acute occlusion of the treated arterial segment, embolism, and vasovagal collapse			
[49] RCT	73 people with severe intermittent claudication, chronic critical limb ischaemia or ischaemic ulcers, and superficial femoral artery stenosis or occlusion Excluded people with acute critical limb ischaemia	**Post-intervention complications** with PTA plus routine stenting (nitinol self-expanding stents) with PTA with optional secondary stenting Absolute results not reported One small pseudo-aneurysm noted at day 1 in PTA plus optional stenting group, no major complications reported in either group 10/39 (26%) in PTA with optional secondary stenting group had stenting after two attempts of balloon dilation			
[45] RCT	227 people with severe claudication or limb-threatening stenosis of the superficial femoral artery	**Risk of local vascular events , 1 year** with PTA plus routine stenting with PTA plus selective stenting Absolute results not reported 17/112 (15%) in PTA with selective stenting group had stenting after suboptimal results of PTA (not further defined)	P = 0.017	○○○	PTA plus selective stenting
[46] RCT	104 people with severe claudication caused by stenosis or occlusion of the superficial femoral artery Further report of reference [47]	**Adverse effects (any) , 12 months** with PTA plus routine stenting (primary nitinol self-expanding stents) with balloon angioplasty with optional secondary stenting Absolute results not reported The RCT reported a stent fracture rate of 2%, and one case (2%) of early stent thrombotic occlusion in the primary stenting group 17/53 (32%) in PTA with optional secondary stenting group had stenting; in most cases because of a suboptimal result after angioplasty (not further defined)			

Percutaneous transluminal angioplasty (PTA) alone versus PTA plus statins:

We found one RCT. [50]

Post-intervention patency

Percutaneous transluminal angioplasty (PTA) alone compared with PTA plus statin Adding a statin to PTA may be no more effective than PTA alone at reducing restenosis rates and limb amputation at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Restenosis					
[50] RCT	37 people taking aspirin 250 mg/day with critical ischaemia or severe claudication; Fontaine classification class IIb or II	**Proportion of people with restenosis , 12 months** 4/18 (22%) with percutaneous transluminal angioplasty (PTA) plus lovastatin 20 mg daily 8/19 (42%) with PTA alone	Reported as not significant P value not reported The RCT is likely to have been underpowered to detect a small but clinically important difference between the two groups	⟷	Not significant
Amputation					
[50] RCT	37 people taking aspirin 250 mg/day with critical ischaemia or severe claudication; Fontaine classification class IIb or II	**Proportion of people with amputation of a limb , 12 months** 4/18 (11%) with percutaneous transluminal angioplasty (PTA) plus lovastatin 20 mg daily 4/19 (21%) with PTA alone	Reported as not significant P value not reported The RCT is likely to have been underpowered to detect a small but clinically important difference between the two groups	⟷	Not significant

Mortality

No data from the following reference on this outcome. [50]

Cardiovascular events

No data from the following reference on this outcome. [50]

Claudication distance/time

No data from the following reference on this outcome. [50]

Physiological measures

No data from the following reference on this outcome. [50]

Quality of life

No data from the following reference on this outcome. [50]

Adverse effects

No data from the following reference on this outcome. [50]

Percutaneous transluminal angioplasty (PTA) versus bypass surgery:

See option on bypass surgery, p 20 .

Further information on studies

[40] Optimal medical treatment involved patient education regarding exercise, nutrition, and smoking cessation, and medication including antiplatelet agents, lipid-lowering agents, anti-hypertensives, and anti-diabetic agents, when indicated.

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. [46] [51] [52] [53]

Prospective cohort studies have found that complications of PTA include puncture site major bleeding (3.4%), pseudo-aneurysms (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%). [54] [55]

OPTION SMOKING CESSATION

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Stopping smoking may increase walking distance when combined with exercise.
- We found no clinically important results from RCTs about the effects of advice to stop smoking in people with peripheral arterial disease.

Benefits and harms

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). [18]

Further information on studies

Comment:

Clinical guide:

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 m, 95% CI –19.3 m to +112.7 m). 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). [18] 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

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- Cilostazol may improve walking distance compared with placebo.
- Cilostazol may reduce the incidence of cerebrovascular events compared with placebo but may be no more effective at reducing cardiac events.
- Cilostazol may be more effective than pentoxifylline at improving claudication distance.
- Adverse effects of cilostazol are common, and include headache, diarrhoea, and palpitations.

Benefits and harms

Cilostazol versus placebo:

We found two systematic reviews (search date 2008, 7 RCTs, 1579 people with peripheral arterial disease; [56] and search date 2007, 12 RCTs, 5674 people [57]) and one subsequent RCT (80 people). [58] The first 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. The second review [57] identified all the RCTs identified by the first review [56] but reported on different outcomes and so we include both here.

Cardiovascular events

Cilostazol compared with placebo Cilostazol seems to be more effective at reducing all vascular events and cerebrovascular events, but seems no more effective than placebo at reducing cardiac events (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular events					
[57] Systematic review	5674 people with coronary stenting, cerebrovascular disease, or peripheral arterial disease; 3782 people (67%) with peripheral arterial disease 12 RCTs in this analysis	**Occurrence of all cardiovascular events , 12 to 144 weeks** 289/3038 (10%) with cilostazol 328/2636 (12%) with placebo Vascular events included stroke, TIA, carotid intervention, MI, unstable angina, sudden cardiac death, and coronary intervention	RR 0.86 95% CI 0.74 to 0.99 P = 0.038	●○○	Cilostazol
[57] Systematic review	5674 people with coronary stenting, cerebrovascular disease, or peripheral arterial disease; 3782 people (67%) with peripheral arterial disease 12 RCTs in this analysis	**Occurrence of cerebrovascular events , 12 to 144 weeks** 67/3038 (2%) with cilostazol 111/2636 (4%) with placebo Cerebrovascular events included stroke, TIA, and carotid intervention	RR 0.58 95% CI 0.43 to 0.78 P <0.001	●○○	Cilostazol
[57] Systematic review	5674 people with coronary stenting, cerebrovascular disease, or peripheral arterial disease; 3782 people (67%) with peripheral arterial disease	**Occurrence of cardiac events , 12 to 144 weeks** 222/3038 (7%) with cilostazol 217/2636 (8%) with placebo Cardiac events included MI, unstable angina, sudden cardiac death, and coronary intervention	RR 0.99 95% CI 0.83 to 1.17 P = 0.908	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	12 RCTs in this analysis				

No data from the following reference on this outcome. [56] [58]

Claudication distance/time

Cilostazol compared with placebo Cilostazol 100 mg twice daily may be more effective at improving initial and absolute claudication distance measures at 6 weeks and 12 to 24 weeks, but we don't know whether cilostazol 50 mg twice daily or 150 mg twice daily is more effective (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Claudication distance					
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Mean initial claudication distance , 6 weeks** 105.5 metres with cilostazol 100 mg twice daily 67.5 m with placebo Baseline initial claudication distance 69.7 m cilostazol group and 63.5 m placebo group	P = 0.02 Methods of randomisation not reported	○○○	Cilostazol 100 mg twice daily
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Mean absolute claudication distance , 6 weeks** 193.1 m with cilostazol 100 mg twice daily 168.5 m with placebo Baseline absolute claudication distance 144.4 m cilostazol group and 138.6 m placebo group	P = 0.04 Methods of randomisation not reported	○○○	Cilostazol 100 mg twice daily
[56] Systematic review	104 people Data from 1 RCT	**Mean change in initial claudication distance from baseline , 12 weeks** 50.1 m with cilostazol 150 mg twice daily 34.4 m with placebo	WMD +15.7 m 95% CI –9.6 m to +41 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	⟷	Not significant
[56] Systematic review	104 people Data from 1 RCT	**Mean change in absolute claudication distance from baseline , 12 weeks** 89.9 m with cilostazol 150 mg twice daily 38 m with placebo	WMD +51.8 m 95% CI –13.9 m to +118 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	⟷	Not significant
[56] Systematic review	475 people 2 RCTs in this analysis	**Improvement in initial claudication distance , 12 to 24 weeks** with cilostazol 50 mg twice daily with placebo Absolute results not reported	WMD +41.3 m 95% CI –7.1 m to +89.7 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[56] Systematic review	1326 people 6 RCTs in this analysis	**Improvement in initial claudication distance , 12 to 24 weeks** with cilostazol 100 mg twice daily with placebo Absolute results not reported	WMD 31.3 m 95% CI 21.3 m to 40.9 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 100 mg twice daily
[56] Systematic review	497 people 2 RCTs in this analysis	**Improvement in absolute claudication distance , 12 to 24 weeks** with cilostazol 50 mg twice daily with placebo Absolute results not reported	WMD 31.9 m, 95% CI 12.4 m to 51.5 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 50 mg twice daily
[56] Systematic review	1579 people 7 RCTs in this analysis	**Improvement in absolute claudication distance , 12 to 24 weeks** with cilostazol 100 mg twice daily with placebo Absolute results not reported	WMD 49.7 m, 95% CI 24.2 m to 75.2 m The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 100 mg twice daily
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Mean initial claudication distance , 24 weeks** 82.7 m with cilostazol 100 mg twice daily 85.0 m with placebo Baseline initial claudication distance 69.7 m cilostazol group and 63.5 m placebo group	P = 0.98 Methods of randomisation not reported	⟷	Not significant
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Mean absolute claudication distance , 24 weeks** 286.1 m with cilostazol 100 mg twice daily 227.1 m with placebo Baseline absolute claudication distance 144.4 m cilostazol group and 138.6 m placebo group	P = 0.22 Methods of randomisation not reported	⟷	Not significant

No data from the following reference on this outcome. [57]

Physiological measures

Cilostazol compared with placebo Cilostazol 100 mg twice daily may be more effective at improving ankle brachial index at 12 to 24 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial index					
[56] Systematic review	859 people 3 RCTs in this analysis	**Improvement in ankle brachial index , 12 to 24 weeks** with cilostazol 100 mg twice daily with placebo Absolute results not reported	WMD 0.06 95% CI 0.03 to 0.09 The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further	○○○	Cilostazol 100 mg twice daily

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			information on studies for more details)		
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Median ankle brachial index (left lower limb) , 24 weeks** 0.82 with cilostazol 100 mg twice daily 0.73 with placebo	P = 0.17 Methods of randomisation not reported	⟷	Not significant
[58] RCT	80 people with stable intermittent claudication Study excludes people with acute or critical limb ischaemia	**Median ankle brachial index (right lower limb) , 24 weeks** 0.80 with cilostazol 100 mg twice daily 0.80 with placebo	P = 0.45 Methods of randomisation not reported	⟷	Not significant

No data from the following reference on this outcome. [57]

Quality of life

Cilostazol compared with placebo We don't know whether cilostazol is more effective at improving quality of life (assessed using the short form-36 [SF-36], VascuQol, and the Walking Impairment Questionnaires) at 12 to 24 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[56] Systematic review	1149 people 3 RCTs in this analysis	**Improvement in physical function component of the short form-36 (SF-36) questionnaire** with cilostazol 50 mg and 100 mg twice daily with placebo Absolute results not reported	P = 0.002 No further details reported The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 50 mg and 100 mg twice daily
[56] Systematic review	1149 people 3 RCTs in this analysis	**Improvement in bodily pain component of the SF-36 questionnaire** with cilostazol 50 mg and 100 mg twice daily with placebo Absolute results not reported	P <0.05 No further details reported The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 50 mg and 100 mg twice daily
[56] Systematic review	1149 people 3 RCTs in this analysis	**Improvement in mental health component of the SF-36 questionnaire** with cilostazol 50 mg and 100 mg twice daily with placebo Absolute results not reported	Reported as not significant P value not reported No further details reported The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	⟷	Not significant
[58] RCT	80 people with stable intermittent claudication study excludes people with acute	**Mean percentage total improvement from baseline (assessed by the SF-36 questionnaire) , 24 weeks**	P = 0.50	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	or critical limb ischaemia	1.8% with cilostazol 100 mg twice daily 1.4% with placebo Absolute numbers not reported Methods of randomisation not reported			
[58] RCT	80 people with stable intermittent claudication Study excluded people with acute or critical limb ischaemia	**Mean percentage total improvement from baseline (assessed by the VascuQol questionnaire) , 24 weeks** 5.5% with cilostazol 100 mg twice daily 3.0% with placebo Absolute numbers not reported Methods of randomisation not reported	P = 0.78	⟷	Not significant
[56] Systematic review	755 people 2 RCTs in this analysis	**Improvement in people's perception of walking speed (assessed by Walking Impairment Questionnaire)** with cilostazol 50 mg and 100 mg twice daily with placebo Absolute results not reported	P <0.05 No further details reported The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Cilostazol 50 mg and 100 mg twice daily
[58] RCT	80 people with stable intermittent claudication Study excluded people with acute or critical limb ischaemia	**Speed component score of the Walking Impairment Questionnaire , 24 weeks** 39% with cilostazol 100 mg twice daily 38% with placebo Absolute numbers not reported Methods of randomisation not reported	P = 0.88	⟷	Not significant
[58] RCT	80 people with stable intermittent claudication Study excluded people with acute or critical limb ischaemia	**Distance component score of the Walking Impairment Questionnaire , 24 weeks** 38% with cilostazol 100 mg twice daily 37% with placebo Absolute numbers not reported Methods of randomisation not reported	P = 0.41	⟷	Not significant

No data from the following reference on this outcome. [57]

Mortality

No data from the following reference on this outcome. [56] [57] [58]

Post-intervention patency

No data from the following reference on this outcome. [56] [57] [58]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] Systematic review	Number of people and RCTs assessed not clear	**Adverse effects including headache, diarrhoea, peripheral oedema, rhinitis, and infection** with cilostazol 50 mg and 100 mg twice daily with placebo Absolute results not reported 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 The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	○○○	Placebo
[59] RCT **3-armed trial**	698 people In review [56] The third arm assessed pentoxifylline	**Proportion of people withdrawing because of adverse effects** 39/227 (17%) with cilostazol 100 mg twice daily 24/239 (10%) with placebo 466 people in this analysis	RR (cilostazol *v* placebo) 1.71 95% CI 1.06 to 2.75 NNH 14 95% CI 8 to 111 The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)	●○○	Placebo
[60] RCT **3-armed trial**	394 people In review [56]	**Proportion of people withdrawing because of adverse effects** 23% with cilostazol 100 mg twice daily 12% with cilostazol 50 mg twice daily 10% with placebo Absolute numbers not reported	Significance not assessed The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)		
[60] RCT **3-armed trial**	394 people In review [56] The third arm assessed cilostazol 50 mg twice daily	**Proportion of people withdrawing because of headache** 4.5% with cilostazol 100 mg twice daily 0% with placebo Absolute numbers not reported 262 people in this analysis	Significance not assessed The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)		
[60] RCT **3-armed trial**	394 people In review [56] The third arm assessed cilostazol 50 mg twice daily	**Proportion of people withdrawing because of cardiovascular events** 12/133 (9%) with cilostazol 100 mg twice daily 5/129 (4%) with placebo 262 people in this analysis	Significance not assessed The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[61] RCT	81 people In review [56]	**Proportion of people reporting a GI adverse effect** 44% with cilostazol 100 mg twice daily 15% with placebo Absolute numbers not reported	Significance not assessed The RCTs included in the review had some weaknesses in their methods that may limit the applicability of the results (see further information on studies for more details)		
[58] RCT	80 people with stable intermittent claudication Study excluded people with acute or critical limb ischaemia	**Number of medication-related adverse effects , 24 weeks** 36 with cilostazol 100 mg twice daily 7 with placebo Methods of randomisation not reported Adverse effects included headaches, diarrhoea, and palpitations. 34/36 in the cilostazol group resolved by 6 weeks	Significance not assessed		
[58] RCT	80 people with stable intermittent claudication Study excluded people with acute or critical limb ischaemia	**Proportion of people withdrawing from study , 24 weeks** 6/39 (15%) with cilostazol 100 mg twice daily 3/41 (7%) with placebo Methods of randomisation not reported 4 people withdrew from the cilostazol group because of adverse effects	Significance not assessed		
[57] Systematic review	5674 people with coronary stenting, cerebrovascular disease, or peripheral arterial disease; 3782 people (67%) with peripheral arterial disease 12 RCTs in this analysis	**Occurrence of serious bleeding , 12 to 144 weeks** 46/3038 (1.5%) with cilostazol 45/2636 (1.7%) with placebo Serious bleeding events defined as fatal, life threatening, or requiring admission to hospital	RR 1.00 95% CI 0.66 to 1.51 P = 0.996	⟷	Not significant

Cilostazol versus pentoxifylline:

See option on pentoxifylline, p 64 .

Further information on studies

[56] None of the RCTs evaluated cilostazol beyond 24 weeks. [59] [61] [62] [63] In addition, some of the RCTs had high withdrawal rates after randomisation (up to 29%). [62] In most of the RCTs, withdrawals were more common with cilostazol than with placebo. [59] [60] [61] [62] [63] 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.

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). [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. [64]

OPTION PROSTAGLANDINS

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- 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.
- Prostaglandins are associated with higher rates of adverse effects, including headache, vasodilation, diarrhoea, tachycardia, and vasodilation compared with placebo.

Benefits and harms

Prostaglandins versus placebo:

We found three systematic reviews, [65] [66] [67] and one additional RCT. [68] The first review (search date 2004; 5 RCTs, 300 people) reported on prostanoids for treating patients with intermittent claudication. [65] The second review (search date 2004; 3 RCTs, 254 people) reported on prostaglandin E1 (PGE1) for treating severe peripheral arterial occlusive disease (stage III and IV), [66] and the third review (search date 2010; 6 RCTs, 946 people) [67] reported on prostanoids for treating patients with critical limb ischaemia, without chance of rescue or reconstructive intervention and included two of the RCTs also reported in the second review, [66] but we report both here as they use the RCTs for different comparisons.

Mortality

Prostaglandins compared with placebo We don't know whether lipo-ecraprost is more or less effective than placebo at reducing mortality in people with critical limb ischaemia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
All-cause mortality					
[68] RCT	322 people with critical limb ischaemia undergoing endovascular or surgical revascularisation	**Mortality rate , 6 months** 13/141 (9%) with lipo-ecraprost (intravenously for 8 weeks) 19/143 (13%) with placebo	P = 0.28 Significantly fewer people in the lipo-ecraprost group adhered to study medication compared with people in the placebo group (see further information on studies for absolute numbers)	⟷	Not significant

No data from the following reference on this outcome. [65] [66] [67]

Claudication distance/time

Prostaglandins compared with placebo We don't know whether prostaglandins are more effective at increasing pain-free and maximal walking distances in people with intermittent claudication (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain-free walking distance					
[65] Systematic review	100 people with intermittent claudication (peripheral arterial occlusive disease [PAOD] stage IIb) for > 6 months 2 RCTs in this analysis	**Pain-free walking distance** with intra-arterial prostaglandin E1 (PGE1) with placebo Absolute results not reported	Mean difference 95.7 metres 95% CI 76.35 m to 115.05 m P <0.00001 See further information on studies for details of methodological issues that may affect the results	○○○	Intra-arterial PGE1
[65] Systematic review	300 people with intermittent claudication 3 RCTs in this analysis	**Pain-free walking distance** with intravenous PGE1 with placebo Absolute results not reported	Mean difference 22.34 m 95% CI 21.78 m to 22.90 m P <0.00001 Results should be interpreted with caution as significant statistical heterogeneity and meta-analysis dominated by one large RCT (208 people), which was heavily weighted in the analysis. See further information on studies for further details	○○○	Intravenous PGE1
[65] Systematic review	43 people with intermittent claudication (PAOD stage IIb) Data from 1 RCT	**Median improvement of pain-free walking distance** 20 m with prostaglandin E1 prodrug (AS-013) 9 m with placebo	P >0.05	⟷	Not significant
[65] Systematic review	100 people with intermittent claudication (PAOD stage IIb) for >6 months 2 RCTs in this analysis	**Maximal walking distance** with intra-arterial PGE1 with placebo Absolute results not reported	Mean difference 126.92 m 95% CI 99.10 m to 154.73 m P <0.00001 See further information on studies for details of methodological issues that may affect the results	○○○	Intra-arterial PGE1
[65] Systematic review	300 people with intermittent claudication 3 RCTs in this analysis	**Maximal walking distance** with intravenous PGE1 with placebo Absolute results not reported	Mean difference 25.82 m 95% CI 25.29 m to 26.35 m P <0.00001 Results should be interpreted with caution as significant statistical heterogeneity and meta-analysis dominated by one large RCT (208 people), which was heavily weighted in the analysis. See further information on studies for further details	○○○	Intravenous PGE1
[65] Systematic review	43 people with intermittent claudication (PAOD stage IIb) Data from 1 RCT	**Median improvement of maximal walking distance** 28 m with prostaglandin E1 prodrug (AS-013) 4 m with placebo	P <0.05	○○○	Prostaglandin E1 prodrug (AS-013)

No data from the following reference on this outcome. [66] [68] [67]

Post-intervention patency

Compared with placebo We do not know whether prostaglandins are more effective than placebo at improving ulcer healing, reducing amputations, increasing rest pain relief, or reducing analgesic consumption in people with severe peripheral arterial disease or critical limb ischaemia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing/pain reduction					
[67] Systematic review	30 people with critical limb ischaemia presenting with rest pain, ischaemic ulceration, or both, and without chance of rescue or reconstructive intervention Data from 1 RCT	**Ulcer healing** 0/9 (0%) with intravenous infusion of prostaglandin E1 (PGE1) 3/10 (30%) with placebo	RR 0.16 95% CI 0.01 to 2.68 Review suggests that results should be interpreted with caution as the RCT had unclear methods	⟷	Not significant
[66] Systematic review	254 people with severe peripheral arterial disease (stage III or IV), not eligible for arterial reconstruction 3 RCTs in this analysis	**Response for ulcer healing and/or pain reduction , 6 months** 48% with PGE1 25% with placebo Absolute numbers not reported	P = 0.0294	○○○	PGE1
[67] Systematic review	85 people with type II diabetes and foot ulcers due to an arterial occlusive disease (critical limb ischaemia), without chance of rescue or reconstructive intervention Data from 1 RCT	**Ulcer healing** 6/36 (17%) with intravenous PGE1 2/37 (5%) with placebo	RR 3.08 95% CI 0.67 to 14.28 Review suggests that results should be interpreted with caution as the RCT had unclear methods	⟷	Not significant
[67] Systematic review	69 people under 70 years old with critical limb ischaemia without chance of rescue or reconstructive intervention 2 RCTs in this analysis	**Rest pain relief** 11/36 (31%) with PGE1 5/33 (15%) with placebo	RR 1.52 95% CI 0.69 to 3.34 Authors advise interpreting results with caution because of unclear methods in the RCTs	⟷	Not significant
[67] Systematic review	58 people under 70 years old with critical limb ischaemia without chance of rescue or reconstructive intervention 2 RCTs in this analysis	**Reduction in analgesics consumption** 21/33 (64%) with PGE1 10/25 (40%) with placebo	RR 1.58 95% CI 0.92 to 2.72 Authors advise interpreting results with caution because of unclear methods in the RCTs	⟷	Not significant
Limb amputation					
[67] Systematic review	85 people with type II diabetes and foot ulcers due to an arterial occlusive disease (critical limb ischaemia), without chance of rescue or reconstructive intervention Data from 1 RCT	**Total amputations** 4/36 (11%) with intravenous PGE1 10/37 (27%) with placebo	RR 0.41 95% CI 0.14 to 1.19 Review suggests interpreting results with caution as the RCT had unclear methods	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[66] Systematic review	207 people with severe peripheral arterial disease (stage III or IV), not eligible for arterial reconstruction 2 RCTs in this analysis	**Proportion of people with major amputation or death , 6 months** 23/102 (23%) with PGE1 38/105 (36%) with placebo	P = 0.02 Per-protocol analysis	○○○	PGE1
[69] RCT	379 people with critical limb ischaemia who were not candidates for revascularisation In review [67]	**Proportion of people who had a limb amputated , 6 months** 29/179 (16%) with lipo-ecraprost (a lipid-encapsulated PGE1 pro-drug) 23/177 (13%) with placebo 46% of people in the lipo-ecraprost group received fewer than 35 of the 40 intended treatment doses	Reported as not significant P value not reported	⟷	Not significant
[68] RCT	322 people with critical limb ischaemia undergoing endovascular or surgical revascularisation	**Proportion of people with amputation at or above the level of the ankle , 6 months** 17/141 (12%) with lipo-ecraprost (intravenously for 8 weeks) 19/143 (13%) with placebo	Reported as not significant P value not reported Significantly fewer people in the lipo-ecraprost group adhered to study medication compared with people in the placebo group (see further information on studies for absolute numbers)	⟷	Not significant
[67] Systematic review	30 people with critical limb ischaemia presenting with rest pain, ischaemic ulceration, or both, and without chance of rescue or reconstructive intervention Data from 1 RCT	**Total amputations** 7/14 (50%) with intravenous infusion of PGE1 5/16 (31%) with placebo	RR 1.60 95% CI 0.65 to 3.92 Review suggests interpreting results with caution as the RCT had unclear methods	⟷	Not significant

No data from the following reference on this outcome. [65]

Cardiovascular events

No data from the following reference on this outcome. [65] [66] [67] [68]

Physiological measures

No data from the following reference on this outcome. [65] [66] [67] [68]

Quality of life

No data from the following reference on this outcome. [65] [66] [67] [68]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[66] Systematic review	672 people with severe peripheral arterial disease (stage III or IV), not eligible for arterial reconstruction 7 RCTs in this analysis	**Rate of adverse effects , 6 months** 40% with prostaglandin E1 (PGE1) 15% with placebo Absolute numbers not reported Adverse effects not specified	P value not reported Analysis included non-placebo-controlled RCTs See further information on studies for potential methodological limitations in the RCTs identified		
[69] RCT	379 people with critical limb ischaemia who were not candidates for revascularisation In review [67]	**Proportion of people with an adverse effect , 6 months** 7094 (202 serious) for 189 people with lipo-ecraprost (a lipid-encapsulated PGE1 prodrug) 1594 (235 serious) for 190 people with placebo The most common adverse effects reported included headache, nausea, vomiting, diarrhoea, pain, hypotension, tachycardia, and vasodilation 46% of people in the lipo-ecraprost group received fewer than 35 of the 40 intended treatment doses	P value not reported		
[68] RCT	322 people with critical limb ischaemia undergoing endovascular or surgical revascularisation	**Adverse effects , 6 months** with lipo-ecraprost (intravenously for 8 weeks) with placebo Absolute results not reported The RCT did not directly compare adverse effects of lipo-ecraprost versus placebo Common adverse effects in the lipo-ecraprost group included headache, pain, hypotension, tachycardia, vasodilation, diarrhoea, nausea, and vomiting	Significantly fewer people in the lipo-ecraprost group adhered to study medication compared with people in the placebo group (see further information on studies for absolute numbers)		
[67] Systematic review	69 people under 70 years old with critical limb ischaemia without chance of rescue or reconstructive intervention 2 RCTs in this analysis	**Proportion of people reporting adverse events** 15/36 (42%) with PGE1 2/33 (6%) with placebo Most frequent adverse events were headache, facial flushing, and redness of the infused vein	RR 5.81 95% CI 1.62 to 20.86 Authors advise interpreting results with caution because of unclear methods in the RCTs	●●●	Placebo
[65] Systematic review	1255 people with intermittent claudication 16 RCTs in this analysis	**Adverse events** 54/392 (14%) with intra-arterial or intravenous PGE1 54/863 (6%) with placebo Review pooled adverse effects data from 17 RCTs that compared prostanoids (PGE1, PGI2, and their analogues) with placebo or any control treatment and re-			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		ported data separately for each drug Adverse events reported in the PGE1 group included facial flushing (12), local reactions at injection site (36), headache (1), gastrointestinal disorders (6), hypotension (2), dizziness (1), and influenza-like illness (2) Adverse events reported in placebo group included gastrointestinal disorders (16), headache (20), and local reactions at injection site (3)			

Prostaglandins versus pentoxifylline:

We found one systematic review (search date 2004; 2 RCTs, 277 people) comparing prostaglandin E1 (PGE1) versus pentoxifylline in people with intermittent claudication. [65]

Claudication distance/time

Prostaglandins compared with pentoxifylline Prostaglandin E1 may increase maximal and pain-free walking distances compared with pentoxifylline in people with intermittent claudication (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maximum/pain-free walking distance					
[65] Systematic review	195 people with intermittent claudication Data from 1 RCT	**Mean increase in pain-free walking distance** 181 metres with prostaglandin E1 (PGE1) 104 m with pentoxifylline	Reported as significant but no further details given	○○○	PGE1
[65] Systematic review	82 people with intermittent claudication Data from 1 RCT	**Mean increase in pain-free walking distance** 106 m with PGE1 71 m with pentoxifylline	Reported as significant but no further details given	○○○	PGE1
[65] Systematic review	195 people with intermittent claudication Data from 1 RCT	**Mean increase in maximal walking distance** 213 m with PGE1 191 m with pentoxifylline	Reported as significant but no further details given	○○○	PGE1

Physiological measures

Prostaglandins compared with pentoxifylline We don't know how prostaglandin E1 and pentoxifylline compare at improving ankle brachial index in people with intermittent claudication (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ankle brachial index					
[65] Systematic review	240 people with intermittent claudication 2 RCTs in this analysis	**Ankle brachial index** with PGE1 with pentoxifylline Absolute results not reported	Mean difference –0.05 95% CI –0.11 to +0.02 P = 0.14	⟷	Not significant

Mortality

No data from the following reference on this outcome. [65]

Post-intervention patency

No data from the following reference on this outcome. [65]

Cardiovascular events

No data from the following reference on this outcome. [65]

Quality of life

No data from the following reference on this outcome. [65]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] Systematic review	545 people with intermittent claudication This analysis includes data from 11 RCTs for prostaglandin E1 (PGE1) and two RCTs for pentoxifylline	**Gastrointestinal disorders** 6/392 (2%) with intra-arterial or intravenous PGE1 6/153 (4%) with pentoxifylline Review pooled adverse effects data from 17 RCTs that compared prostanoids (PGE1, PGI2, and their analogues) with placebo or any control treatment and reported data separately for each drug			

Further information on studies

[68] Proportion of people who received at least 35 of the intended 40 treatment doses was significantly less in the lipo-ecraprost group (37/141 [26%] with lipo-ecraprost *v* 73/143 [51%] with placebo; reported as significant; P value not reported).

[66] The 7 RCTs included in the systematic review 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.

[67] The review included 4 RCTs, all of which were of poor methodological quality and classified as moderate risk of bias. The review's authors suggest that this may be because the studies were done 15 to 30 years ago when current concepts from evidence-based medicine were not so well established.

[65] The review reported significant heterogeneity between the included studies because of variations in study design, including duration of interventions, drug doses, and use of different treadmills for measuring walking distances. The review also reported that many of the RCTs included had poor-quality methods including a lack of data on methods of randomisation and withdrawals, and several of the RCTs used baseline values for walking distance determined from a single measurement. This may have generated false results as other RCTs found variations of >20% between two measurements performed pre-treatment (baseline measurements) and excluded these people.

Comment:

OPTION PENTOXIFYLLINE

- For GRADE evaluation of interventions for Peripheral arterial disease, see table, p 71 .
- We don't know whether pentoxifylline improves symptoms compared with placebo, but it may be less effective than cilostazol.

Benefits and harms

Pentoxifylline versus placebo:

We found two systematic reviews [16] [70] and one additional RCT. [59] The first review (search date 1999; 2 RCTs,192 people) did not perform a meta-analysis and so we report data from the RCTs. The second review (search date 2009; 6 RCTs, 788 people) [16] pooled data and identified one RCT identified by the first review. [70]

Claudication distance/time

Pentoxifylline compared with placebo Pentoxifylline may be more effective than placebo at increasing maximum walking distance but may be no more effective at increasing initial claudication distance (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Claudication distance					
[70] Systematic review	40 people with peripheral arterial disease (Fontaine stage II) Data from 1 RCT	**Improvement in mean initial claudication distance** From 144 metres to 364 m with pentoxifylline From 134 m to 384 m with placebo	Mean difference –30 m 95% CI –138 m to +78 m	⟷	Not significant
[70] Systematic review	40 people with peripheral arterial disease (Fontaine stage II) Data from 1 RCT	**Improvement in mean absolute claudication distance** From 166 m to 504 m with pentoxifylline From 151 m to 420 m with placebo Absolute results not reported	Mean difference +69 m 95% CI –44 m to +182 m	⟷	Not significant
[59] RCT **3-armed trial**	698 people 471 people in this analysis The third arm assessed the effects of cilostazol	**Proportion of people who had either no change or had deterioration in the claudication distance** 72/212 (34%) with pentoxifylline 68/226 (30%) with placebo Withdrawal rates after randomisation: 60/232 (26%) with pentoxifylline *v* 38/239 (16%) 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	⟷	Not significant
[16] Systematic review	788 people with moderate intermittent claudication and ankle brachial index <0.9	**Maximum walking distance , 3 weeks to 12 months** with pentoxifylline with placebo	WMD 59.23 m 95% CI 37.46 m to 81.00 m	○○○	Pentoxifylline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	6 RCTs in this analysis	Absolute results not reported			

Mortality

No data from the following reference on this outcome. [16] [59] [70]

Cardiovascular events

No data from the following reference on this outcome. [16] [59] [70]

Post-intervention patency

No data from the following reference on this outcome. [16] [59] [70]

Physiological measures

No data from the following reference on this outcome. [16] [59] [70]

Quality of life

No data from the following reference on this outcome. [16] [59] [70]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[59] RCT **3-armed trial**	698 people The third arm assessed cilostazol	**Proportion of people withdrawing because of adverse effects or concerns about safety** 44/232 (19%) with pentoxifylline 24/239 (10%) with placebo 471 people in this analysis	RR 1.89 95% CI 1.19 to 3.00 NNH 12 95% CI 7 to 39 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)	●○○	Placebo
[59] RCT **3-armed trial**	698 people The third arm assessed the effects of cilostazol	**Proportion of people with sore throat**	Between group significance not assessed The RCT had a high withdrawal rate after randomisation, which could be a source of bias (60/232		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		32/232 (14%) with pentoxifylline 17/239 (7%) with placebo 471 people in this analysis	[26%] with pentoxifylline *v* 38/239 [16%] with placebo)		
[59] RCT **3-armed trial**	698 people The third arm assessed the effects of cilostazol	**Proportion of people with diarrhoea** 18/232 (8%) with pentoxifylline 13/239 (5%) with placebo 471 people in this analysis	Between group significance not assessed 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)		

No data from the following reference on this outcome. [16] [70]

Pentoxifylline versus cilostazol:

We found one systematic review (search date 2009; 1 RCT, 454 people). [16] The review found one RCT [59] comparing pentoxifylline, cilostazol, and placebo.

Claudication distance/time

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Claudication distance					
[59] RCT **3-armed trial**	698 people In review [16] The third arm assessed the effects of placebo	**Proportion of people who had either no change or had deterioration in claudication distance , 24 weeks** 72/212 (34%) with pentoxifylline 47/205 (23%) with cilostazol 417 people in this analysis	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 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)	●○○	Cilostazol
[59] RCT **3-armed trial**	698 people In review [16] The third arm assessed the effects of placebo	**Initial claudication distance , 24 weeks** 202 metres with pentoxifylline 218 m with cilostazol 417 people in this analysis	Mean difference –16 m P = 0.0001 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)	○○○	Cilostazol
[59] RCT **3-armed trial**	698 people In review [16] The third arm assessed the effects of placebo	**Absolute claudication distance , 24 weeks** 308 m with pentoxifylline 350 m with cilostazol 417 people in this analysis	Mean difference –42 m 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)	○○○	Cilostazol

Mortality

No data from the following reference on this outcome. [16] [59]

Cardiovascular events

No data from the following reference on this outcome. [16] [59]

Post-intervention patency

No data from the following reference on this outcome. [16] [59]

Physiological measures

No data from the following reference on this outcome. [16] [59]

Quality of life

No data from the following reference on this outcome. [16] [59]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[59] RCT **3-armed trial**	698 people In review [16] The third arm assessed placebo	**Proportion of people withdrawing because of adverse effects or concerns about safety** 44/232 (19%) with pentoxifylline 39/227 (17%) with cilostazol 459 people in this analysis	Significance not assessed 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)		

Pentoxifylline versus prostaglandins:
See option on prostaglandins, p 57 .

Further information on studies

Comment: No life-threatening adverse effects of pentoxifylline have been reported, although to date RCTs have been too small to assess this reliably.

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.

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 Two new systematic reviews added comparing antiplatelet agents versus placebo. [15] [16] The first review found no significant difference between aspirin and placebo in cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death), all-cause mortality, or the occurrence of major bleeding. [15] The second review found that antiplatelet agents (ticlopidine, cloricromen, mesoglycan, indobufen, and defibrotide) increased maximal walking distance compared with placebo. [16] Categorisation unchanged (Beneficial).

Bypass surgery Long-term follow-up of one RCT [30] identified by an already reported review [29] added. The RCT found no significant difference in all-cause mortality at 2 years between bypass surgery and percutaneous transluminal angioplasty (PTA), although beyond 2 years up to the trial end point (maximum 7 years' follow-up), it found bypass surgery improved survival compared with PTA. Categorisation unchanged (Likely to be beneficial).

Cilostazol One systematic review [57] and one RCT [58] added both comparing cilostazol versus placebo. The review found cilostazol reduced all vascular and cerebrovascular events compared with placebo; however, it found no significant difference in cardiac events or serious bleeding episodes. [57] The RCT found cilostazol improved claudication distances at 6 weeks, although there was no significant difference at 24 weeks. [58] The RCT also found no significant difference between groups in ankle brachial index or quality-of-life scores at 24 weeks and reported more people withdrawing and reporting medication-related adverse effects at 24 weeks in the cilostazol group; however, the overall significance was not reported. Categorisation unchanged (Likely to be beneficial).

Exercise One RCT added, which found that a 12-week supervised arm crank exercise programme improved pain-free and maximal walking distances in men with stable intermittent claudication when compared with no exercise. [23] The RCT found no significant difference between exercise and control in resting ankle brachial index. [23] Categorisation unchanged (Beneficial).

Pentoxifylline One systematic review added, which reported on both pentoxifylline versus placebo and pentoxifylline versus cilostazol. [16] . The review found pentoxifylline increased maximal walking distance compared with placebo. [16] For the pentoxifylline versus cilostazol comparison, the review [16] identified only one RCT, [59] which we already report in this *Clinical Evidence* review. Categorisation unchanged (Unknown effectiveness).

Percutaneous transluminal angioplasty (PTA) One systematic review [44] and one RCT [49] added comparing PTA plus stenting versus PTA alone. The review found improved patency rates on duplex ultrasound scans and angiography with PTA plus stenting at 6 months compared with PTA alone but no significant difference at 1 or 2 years. It also found that PTA plus stenting increased walking distance at 6 and 12 months but not at 24 months. The review found no significant difference between groups in ankle brachial index, quality of life, and adverse effects. The RCT [49] compared PTA plus routine stenting versus PTA plus selective stenting. It found that PTA plus routine stenting reduced restenosis at 3, 6, and 12 months and increased patient-reported maximum walking distance at 6 and 12 months. Categorisation unchanged (Likely to be beneficial).

Prostaglandins Two systematic reviews added. [65] [67] The first review [65] found that prostaglandins increased maximal walking distance and pain-free walking distance compared with both placebo and with pentoxifylline in people with intermittent claudication. The second review [67] found no significant difference between prostaglandins and placebo in ulcer healing, amputations, rest pain relief, or reduction in analgesic consumption, although

prostaglandins were associated with more adverse effects. Categorisation unchanged (Trade off between benefits and harms).

Statins (HMG-CoA reductase inhibitors) One new systematic review [16] added comparing statins versus placebo. The review found that statins increased maximal walking distance compared with placebo. Categorisation unchanged (Likely to be beneficial).

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Competing interests: KC declares that he has no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Peripheral arterial disease.**

Important outcomes		Cardiovascular events, Claudication distance/time, Mortality, Physiological measures , Post-intervention patency, Quality of life							
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?									
9 (3019) [15]	Mortality	Antiplatelet agents versus placebo or control	4	0	0	–2	0	Low	Directness points deducted for large diabetic population reducing generalisability of results and small number of comparators
at least 42 (at least 9214) [8] [9] [15]	Cardiovascular events	Antiplatelet agents versus placebo or control	4	0	0	–2	0	Low	Directness points deducted for composite outcome in two reviews (inclusion of vascular death in vascular events) and combined regimens (aspirin plus dipyridamole) included in two reviews
5 (1077) [16]	Claudication distance/time	Antiplatelet agents versus placebo or control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results Directness point deducted for restricting population to moderate intermittent claudication
at least 14 (at least 3226) [11] [12] [13] [14]	Post-intervention patency	Antiplatelet agents versus placebo or control	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results in some reviews
6 (10,024) [8] [17]	Cardiovascular events	Antiplatelet agents other than aspirin (alone or in combination with aspirin) versus aspirin alone	4	–1	0	–1	0	Low	Quality point deducted for subgroup analysis of larger study. Directness point deducted for use of a composite outcome (review and RCT included mortality in event rate)
at least 9 (at least 656) [18] [19] [20] [21] [22] [23]	Claudication distance/time	Exercise versus usual care/placebo	4	–1	0	–1	0	Low	Quality point deducted for blinding flaws. Directness point deducted for range of different forms of exercise included
8 (285) [20] [23]	Physiological measures	Exercise versus usual care/placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for range of different interventions and length of treatment included; and 1 RCT restricting population to males.
1 (156) [22]	Quality of life	Exercise versus usual care/placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results for different outcomes with different types of exercise
2 (934) [21] [24]	Claudication distance/time	Exercise as part of a multicomponent intervention versus usual care or placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and subjective assessment of outcome in largest RCT
3 (203) [25] [26] [27]	Claudication distance/time	Different types of exercise versus each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no statistical assessment between groups
3 (590) [29] [30]	Mortality	Bypass surgery versus percutaneous transluminal angioplasty (PTA)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting and use of non-cumulative follow-up data in 1 large RCT. Directness point deducted for inclusion of different disease states

Important outcomes		Cardiovascular events, Claudication distance/time, Mortality, Physiological measures , Post-intervention patency, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
at least 2 (at least 525) [29]	Post-intervention patency	Bypass surgery versus percutaneous transluminal angioplasty (PTA)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for inclusion of different disease states
1 (86) [31]	Post-intervention patency	Bypass surgery versus percutaneous transluminal angioplasty (PTA) plus stent placement	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (31,195) [16] [32] [33] [34] [36]	Mortality	Statins versus placebo	4	0	–1	–1	0	Low	Consistency points deducted for different results with different statins. Directness point deducted for small proportion of people with peripheral arterial disease, which may affect generalisability of results
4 (at least 23,211) [16] [32] [33] [34] [35] [36]	Cardiovascular events	Statins versus placebo	4	0	0	–2	0	Low	Directness points deducted for use of a composite outcome (some outcomes assessed included fatal cardiovascular events) and because in two RCTs people with peripheral arterial disease represented only a small proportion of the total assessed, which may affect generalisability of results
5 (1442) [16] [36]	Claudication distance/time	Statins versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for uncertainty of benefit for different outcomes. Directness point deducted for statistical uncertainty regarding significance of baseline differences in 1 RCT so results may not be generalisable to the full population
1 (354) [16] [36]	Physiological measures	Statins versus placebo	4	–1	–1	0	0	Low	Quality point deducted for no statistical analysis of between group differences. Directness point deducted for limited number of drugs assessed (only atorvastatin)
1 (354) [16] [36]	Quality of life	Statins versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results.
3 (154) [39] [40] [41] [42]	Claudication distance/time	Percutaneous transluminal angioplasty (PTA) versus 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) [39] [40] [41]	Quality of life	Percutaneous transluminal angioplasty (PTA) versus 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
at least 2 (at least 240) [44]	Claudication distance/time	Percutaneous transluminal angioplasty (PTA) plus stent versus PTA alone	4	–1	–1	–2	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for statistical heterogeneity. Directness points deducted for uncertainty of interventions in PTA alone group and restricting population to superficial femoral disease.
at least 6 (at least 520) [43] [44]	Post-intervention patency	Percutaneous transluminal angioplasty (PTA) plus stent versus PTA alone	4	–1	0	–2	0	Very low	Quality point deducted for different diagnostic criteria. Directness points deducted for uncertainty of interventions in PTA alone group and restricting population to superficial femoral disease in one systematic review

Important outcomes		Cardiovascular events, Claudication distance/time, Mortality, Physiological measures , Post-intervention patency, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
at least 3 (at least 291) [44]	Physiological measures	Percutaneous transluminal angioplasty (PTA) plus stent versus PTA alone	4	–1	–1	–2	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for statistical heterogeneity. Directness points deducted for uncertainty of interventions in PTA alone group and restricting population to superficial femoral disease.
1 (208) [44]	Quality of life	Percutaneous transluminal angioplasty (PTA) plus stent versus PTA alone	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and not specifying quality of life score used. Directness points deducted for uncertainty of interventions in PTA alone group and restricting population to superficial femoral disease.
2 (177) [46] [49]	Claudication distance/time	Percutaneous transluminal angioplasty (PTA) plus routine stent versus PTA plus selective stent	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for excluding acute critical limb ischaemia in 1 RCT
4 (628) [45] [46] [48] [49]	Post-intervention patency	Percutaneous transluminal angioplasty (PTA) plus routine stent versus PTA plus selective stent	4	–1	–1	–2	0	Very low	Quality point deducted for unclear methods of measuring restenosis in 1 RCT. Consistency point deducted for conflicting results between RCTs assessing restenosis alone. Directness points deducted for assessment of composite outcome in one RCT and excluding acute critical limb ischaemia in 1 RCT
1 (73) [49]	Physiological measures	Percutaneous transluminal angioplasty (PTA) plus routine stent versus PTA plus selective stent	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for RCT excluding acute critical limb ischaemia
2 (383) [47] [48]	Quality of life	Percutaneous transluminal angioplasty (PTA) plus routine stent versus PTA plus selective stent	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and short follow-up
1 (37) [50]	Post-intervention patency	Percutaneous transluminal angioplasty (PTA) alone versus PTA plus statins	4	–2	0	0	0	Low	Quality points deducted for sparse data and RCT being underpowered to detect a clinically important result
12 (5674) [57]	Cardiovascular events	Cilostazol versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of three studies in the review with people without peripheral arterial disease, which may affect generalisabilty of results.
8 (1659) [56] [58]	Claudication distance/time	Cilostazol versus placebo	4	–1	–1	0	0	Low	Quality point deducted for methodological weaknesses of RCTs included in meta-analysis and one RCT not reporting method of randomisation. Consistency point deducted for different results with different doses
4 (939) [56] [58]	Physiological measures	Cilostazol versus placebo	4	–1	0	–1	0	Low	Quality point deducted for methodological weaknesses of RCTs included in meta-analysis and one subsequent RCT not reporting method of randomisation. Directness point deducted for RCT restricting population
at least 4 (at least 1229) [56] [58]	Quality of life	Cilostazol versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for methodological weakness of RCTs and incomplete reporting of results. Consistency point deducted for different results with different measures of quality of life

Important outcomes		Cardiovascular events, Claudication distance/time, Mortality, Physiological measures , Post-intervention patency, Quality of life							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (322) [68]	Mortality	Prostaglandins versus placebo	4	–1	0	–1	0	Low	Quality point deducted for statistically significant difference in adherence rates between treatment and placebo groups. Directness point deducted for population limited to critical limb ischaemia
5 (400) [65]	Claudication distance/time	Prostaglandins versus placebo	4	–3	0	0	0	Very low	Quality points deducted for statistical heterogeneity, incomplete reporting of results, and poor methodological quality in some RCTS
at least 7 (at least 1040) [66] [67] [68]	Post-intervention patency	Prostaglandins versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for methodological flaws. Consistency point deducted for conflicting results between studies. Directness point deducted for use of composite outcomes
2 (277) [65]	Claudication distance/time	Prostaglandins versus pentoxifylline	4	–2	0	0	0	Low	Quality points deducted for poor quality methods in the RCTs and incomplete reporting of results
2 (240) [65]	Physiological measures	Prostaglandins versus pentoxifylline	4	–2	0	0	0	Low	Quality points deducted for poor quality methods in the RCTs and incomplete reporting of results
8 (1299) [16] [59] [70]	Claudication distance/time	Pentoxifylline versus placebo	4	–2	0	0	0	Low	Quality points deducted for poor follow-up and incomplete reporting of results
1 (417) [59]	Claudication distance/time	Pentoxifylline versus cilostazol	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.