# Exercise for intermittent claudication (Review)

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**[Intervention Review]**

# Exercise for intermittent claudication

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## ABSTRACT

### Background

Exercise programmes are a relatively inexpensive, low-risk option compared with other more invasive therapies for leg pain on walking (intermittent claudication (IC)).

### Objectives

To determine the effects of exercise programmes on IC, particularly in respect of reduction of symptoms on walking and improvement in quality of life.

### Search methods

The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last search February 2008) and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* 2008, Issue 1.

### Selection criteria

Randomised controlled trials of exercise regimens in people with IC due to peripheral arterial disease.

### Data collection and analysis

Two authors independently extracted data and assessed trial quality.

### Main results

Twenty-two trials met the inclusion criteria involving a total of 1200 participants with stable leg pain. Follow-up period was from two weeks to two years. There was some variation in the exercise regimens used, all recommended at least two sessions weekly of mostly supervised exercise. All trials used a treadmill walking test for one of the outcome measures. Quality of the included trials was good, though the majority of trials were small with 20 to 49 participants. Fourteen trials compared exercise with usual care or placebo; patients with various medical conditions or other pre-existing limitations to their exercise capacity were generally excluded.

Compared with usual care or placebo, exercise significantly improved maximal walking time: mean difference (MD) 5.12 minutes (95% confidence interval (CI) 4.51 to 5.72;) with an overall improvement in walking ability of approximately 50% to 200%; exercise did not affect the ankle brachial pressure index (ABPI) (MD -0.01, 95% CI -0.05 to 0.04). Walking distances were also significantly improved: pain-free walking distance MD 82.19 metres (95% CI 71.73 to 92.65) and maximum walking distance MD 113.20 metres

(95% CI 94.96 to 131.43). Improvements were seen for up to two years. The effect of exercise compared with placebo or usual care was inconclusive on mortality, amputation and peak exercise calf blood flow due to limited data.

Evidence was generally limited for exercise compared with surgical intervention, angioplasty, antiplatelet therapy, pentoxifylline, iloprost and pneumatic foot and calf compression due to small numbers of trials and participants. Angioplasty may produce greater improvements than exercise in the short term but this effect may not be sustained.

**Authors' conclusions**

Exercise programmes were of significant benefit compared with placebo or usual care in improving walking time and distance in selected patients with leg pain from IC.

## PLAIN LANGUAGE SUMMARY

**Exercise for reducing intermittent claudication symptoms**

Intermittent claudication is a cramping leg pain that develops when walking and is relieved with rest. It is caused by inadequate blood flow to the leg muscles because of atherosclerosis (fatty deposits blocking blood flow through the arteries). People with mild-to-moderate claudication are advised to keep walking, stop smoking and reduce cardiovascular risk factors. Other treatments include antiplatelet therapy and pentoxifylline, angioplasty (inserting a balloon into the artery to open it up) and bypass surgery.

The present review shows that exercise programmes clearly improve walking time and distance for people considered fit for exercise regimens. This benefit appears to be sustained over two years. The review authors identified 22 controlled trials that randomised some 1200 adults with stable leg pain to exercise, usual care or placebo, or the other interventions. Outcomes were measured at times ranging from 14 days to two years. The types of exercise varied from strength training to polestriding and upper or lower limb exercises, in generally supervised sessions, at least twice weekly. Compared with usual care, exercise therapy improved maximal walking time on a treadmill by some 5 minutes (range 4.5 to 5.7 minutes) in a total of 255 participants. Pain-free walking distance was increased overall by 82.2 metres (range 71.7 to 92.7) and the maximum distance participants could walk by 113.2 metres (range 95.0 to 131.4) in six trials. Exercise did not improve ankle to brachial blood pressure index. No data were given on non-fatal cardiovascular events; data on deaths and amputation were inconclusive.

Comparisons of exercise with surgical intervention, angioplasty, antiplatelet therapy, pentoxifylline, iloprost and pneumatic foot and calf compression were limited because of small numbers of trials and participants. Exercise programmes are relatively inexpensive and low risk compared with other more invasive therapies for improving leg pain on walking and related quality of life. People with intermittent claudication are often elderly and have other pre-existing medical conditions, which would compromise an exercise programme or make it impractical.

## BACKGROUND

Peripheral arterial disease is an important cause of morbidity and mortality for people in many Western countries. It is estimated that most adults have some degree of atherosclerosis by the time they reach middle age, and that approximately 4% will have intermittent claudication (Leng 1993). Risk factors for the development of lower limb arterial disease are similar to those for coronary heart disease and include smoking, raised cholesterol levels, hypertension and diabetes. Several epidemiological studies have also demonstrated an association between sedentary habits and increased risk of claudication (Leng 1993).

Treatment options for intermittent claudication include bypass surgery, angioplasty and drug therapy but the mainstay of treatment for many patients with mild-to-moderate claudication remains as advice to 'stop smoking and keep walking' (Housley 1988) in addition to modification of cardiovascular risk factors. Numerous studies of exercise therapy have been conducted using various regimens that differed in duration and intensity; many of these studies suggested that exercise can benefit patients with intermittent claudication (Ernst 1992). Underlying mechanisms through

which exercise may mediate an improvement include an increased and more effective distribution of blood flow to the legs (Ernst 1982), improved rheological characteristics of the blood (Ernst 1987b), less reliance on anaerobic metabolism (Ruell 1984) and a greater use of oxygen (Dahllof 1974b).

A meta-analysis of exercise rehabilitation programmes for claudication pain demonstrated that exercise training to near-maximal pain for at least six months was beneficial in improving claudication (Gardner 1995). That review provided good evidence for the best type of exercise therapy but did not compare the findings with non-exercised control groups. The present Cochrane analysis has concentrated on randomised controlled trials (RCTs) only and has encompassed additional end points. If exercise proves to be a beneficial treatment, more exercise programmes should be made available for people with intermittent claudication as they may represent a relatively cheap, low-risk option compared with other more invasive therapies.

# OBJECTIVES

The prime objective of this review was to determine whether an exercise programme in people with intermittent claudication was effective in alleviating symptoms and increasing walking distances and times. Secondary objectives were to determine whether exercise was effective in preventing deterioration of underlying disease, reducing cardiovascular events and improving quality of life.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All randomised controlled trials (RCTs) of an exercise regimen versus control, or versus medical or surgical therapy, were included. Trials which used alternation (for example allocation by date of birth or days of the week) were excluded; trials that were not analysed on an intention-to-treat basis were included provided all randomised patients were accounted for. For this update, trials where numerical data in a usable format were not available, despite contacting the authors, but which were otherwise suitable were excluded.

### Types of participants

Trials involving participants with intermittent claudication due to atherosclerotic disease were included (diagnosed either by questionnaire or clinically). Studies of participants with asymptomatic lower limb atherosclerosis that was identified by testing were excluded.

### Types of interventions

Any exercise programme used in the treatment of intermittent claudication, including walking, skipping and running. Inclusion of trials was not affected by the duration, frequency or intensity of the exercise programme but these issues were taken into account in the meta-analysis. This review did not consider supervised versus unsupervised exercise because this is the subject of another Cochrane review Bendermacher 2006.

### Types of outcome measures

The prime outcome measure was treadmill walking distance (time to onset of pain, maximal walking distance).
The following outcome measures were also considered: mortality; cardiovascular events; direct measurement of disease progression (for example using angiography, duplex ultrasound); indirect tests of disease (for example ankle pressure measurements); and subjective measures (for example symptom progression, quality of life).

## Search methods for identification of studies

The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Specialised Register (February 2008) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 1) using the search strategy shown in Appendix 1 for publications describing (or which might describe) RCTs of exercise therapy in intermittent claudication. The PVD Group Specialised Register is compiled from electronic searches of MEDLINE (1966 to date), EMBASE (1980 to date) and CINAHL (1982 to date) and through handsearching relevant journals. The full list of journals that have been handsearched, as well as the search strategies used, are described in the 'Search strategies for the identification of studies' section of the editorial information about the Cochrane PVD Group in *The Cochrane Library*, http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html.
In addition, trials were identified from references in a published meta-analysis of exercise therapy (Gardner 1995), in reports of exercise trials and by direct contact with principal investigators of trials (wherever possible).

## Data collection and analysis

For the update, one of the authors identified possible trials and their eligibility for inclusion in the review was checked by another author. Additional information was sought from trial authors, as necessary, for all trials that appeared to meet the inclusion criteria.

Quality of included trials was determined primarily by method of allocation concealment, as described by Schultz (Schulz 1995); blinding and by losses to follow up. In the original review, trials were also assessed for internal and external validity using a modified standard scoring sheet developed by the PVD group and evaluated using the Chalmers method of quantitative evaluation (Chalmers 1981). For the update we scored all trials, including those in the original review, using Jadad criteria (Jadad 1996).

Data were extracted independently by at least two of the authors. Disagreements were resolved by discussion and the final results were included in the review.

Heterogeneity between trial results was tested subjectively by clinical judgement of differences in patient populations, interventions (including type, duration and intensity of exercise programmes) and outcome assessments. Heterogeneity was also assessed statistically using the chi-squared test. Where appropriate, trial results were pooled in a statistical meta-analysis using guidelines published by the PVD group. Continuous data were analysed by determining mean difference, using both fixed-effect and random-effects models. Dichotomous data were analysed by determining the risk ratio using a fixed-effect model, unless heterogeneity was suspected.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Originally 10 trials were included, however for this update the number rose to 22. In many cases trials were reported in two or more publications. Some trials were excluded because relevant numerical data were not available. This included one of the original trials (Holm 1973).

In total the number of participants increased from almost 250 to over 1200. Exercise was compared to seven different modes of treatment, the most common being usual care or placebo. Fifteen trials had less than 50 participants and two trials had over 100 (Gelin 2001; Zwierska 2005).

Two early trials compared exercise with placebo tablets (Dahllof 1974b; Larsen 1966) but in more recent studies usual care was used as the control comparator. Exercise was compared with the following drug therapies: antiplatelet agents (Mannarino 1991); pentoxifylline (Ciuffetti 1994) and iloprost (Arosio 2001). Two trials compared exercise with surgical intervention (Gelin 2001; Lundgren 1989). Gelin 2001 used a three-way randomisation with usual care and compared surgery or an endovascular procedure, depending on angiographic findings, rather than surgery alone. Of 76 participants in the surgery arm of the trial, 15 were considered unsuitable for an invasive procedure with 17 patients receiving angioplasty; therefore it is difficult to make direct comparisons between the two studies.

Two trials compared exercise and angioplasty (Creasy 1990; Hobbs 2006). Tisi 1997 also included an exercise versus angioplasty comparison but only eight of the 28 patients randomised to receive this intervention actually did. No results for this comparison have been published other than the quality of life data. The exercise versus angioplasty arm of this trial (Tisi 1997) has therefore not been included in the review. One study compared exercise with pneumatic foot and calf compression (Kakkos 2005).

Inclusion and exclusion criteria varied widely but usually those people with serious co-morbidities which would compromise an exercise programme, or make it impractical, were excluded.

There was some variation in the exercise regimens used, although all recommended at least two sessions weekly. All specified some element of supervision, except the earliest trial (Larsen 1966) where patients were simply advised to exercise at home; and involved some training or walking regimen. The duration of treatment generally fell within three to 12 months. The types of exercise varied from strength training to polestriding, cycling and upper or lower limb exercises. Outcomes were measured at times ranging from 14 days to 2 years. Compliance with exercise was variable and was low at 49% in one trial (Gelin 2001).

Nearly all trials used a treadmill walking test to assess one of the outcome measures, but there was considerable variation in outcomes. Some reported walking distance, others reported walking times. Calf blood flow and ankle brachial pressure index (ABPI) were reported and often haematological and biochemical measures were given. There was little information about mortality, amputations and fatal or non-fatal cardiovascular events. Six studies reported quality of life and functional measures. As these were measured on a variety of different scales they were not included in the meta-analysis but are shown in Table 1.

Additional information was sought from trialists of the majority of the included studies.

## Risk of bias in included studies

All studies were randomised controlled trials but in many reports no details were available on the method of allocation other than a statement of "randomised". Trials which had high concealment of allocation scores (A) were: Ciuffetti 1994; Hiatt 1994; Lundgren 1989; Collins 2005; Gelin 2001; Hobbs 2005; Hobbs 2006; Kakkos 2005; Sanderson 2006; and Zwierska 2005.

All studies, including the original included trials, were scored using Jadad criteria. Jadad scores varied from 1 to 3 as blinding was generally not employed. Inevitably in trials of exercise blinding was not possible; therefore, significant placebo responses may have occurred in trials comparing exercise with usual care.

There were either no or minimal loses to follow up in most trials. In the largest trial (Gelin 2001) movement between the three arms (exercise, surgery and usual care) was allowed within the trial design; of 253 participants, 39 were lost to follow up at 1 year and 90 did not receive the treatment allocated, although results were given on an intention-to-treat basis.

## Effects of interventions

### Exercise regimen compared with placebo or usual care

#### Maximal walking time: Analysis 1.1

For 255 participants there was a highly statistically significant overall improvement in walking time (MD 5.12 min, 95% CI 4.51 to 5.72; fixed-effect model). The results were similar when calculated by the random-effects model (MD 5.17 min, 95% CI 4.05 to 6.29). Sanderson 2006 employed a combination of cycling and treadmill training, which may account for the lack of effect seen in this trial compared to the others.The walking time improvement in the other six trials ranged from 50% to over 200%, which is likely to be of clinical significance.

#### Pain-free walking time: Analysis 1.2

Two studies reported similar improvements for the exercise groups (MD 2.91 min, 95% CI 2.51 to 3.31) using a fixed-effect model. This was a 100% improvement, which is likely to be of clinical significance.

#### Ankle brachial pressure index (ABPI): Analysis 1.3

The seven trials included in the meta-analysis uniformly showed no change in ABPI (MD -0.01, 95% CI -0.05 to 0.04) using a fixed-effect model.

#### Exercise calf blood flow: Analysis 1.4

The meta-analysis showed no significant overall improvement in blood flow (MD 0.94 ml/100 ml/min, 95% CI -0.81 to 2.69; fixed-effect model). Using a random-effects model the MD was 1.90 ml/100 ml/min (95% CI -1.21 to 5.01).

#### Pain-free walking distance: Analysis 1.5

Six trials were included and a significant improvement was seen (MD 82.19 m, 95% CI 71.73 to 92.65; fixed-effect model). The smallest study (Hobbs 2006) showed least effect and using a random-effects model the MD was 74.82 m (95% CI 45.9 to 103.7). Excluding this study the improvement seen was 75% to 200%, which is likely to be clinically significant.

#### Maximum walking distance: Analysis 1.6

Six trials reported this outcome and there was significant statistical heterogeneity. The overall result was a statistically significant improvement (MD 113.2 m, 95% CI 94.96 to 131.43) using a fixed-effect model and a MD of 115.96 m (95% CI 26.67 to 205.26) using a random-effects model. Improvements of up to 100% were seen, which is likely to be clinically significant.

#### Amputation: Analysis 1.7

One trial (Gelin 2001) reported on amputation but only two events occurred. The difference between groups was not significant (RR 0.20, 95% CI 0.01 to 4.15).

#### Mortality: Analysis 1.8

One study (Gelin 2001) reported this outcome but there was no significant difference between groups.

### Exercise regimen compared with surgery

Two trials compared exercise with surgery (Gelin 2001; Lundgren 1989) (see comments in 'Description of studies' above).

#### Maximal walking time: Analysis 2.1

Lundgren 1989 found no significant difference between the exercise and surgery groups (MD -1.66 min, 95% CI -4.55 to 1.23).

#### Maximum walking distance: Analysis 2.2

In Gelin 2001 there was a significant improvement in walking distance in the surgery group compared to exercise with a MD of -97 m (95% CI -142.74 to -51.26), an improvement of 40%.

#### Ankle brachial pressure index (ABPI): Analysis 2.3

There was a significant improvement in ABPI in the surgery group compared with those receiving exercise in Lundgren 1989 (MD -0.27, 95% CI -0.37 to -0.17).

#### Exercise calf blood flow: Analysis 2.4

In Lundgren 1989 there was no significant difference between the exercise and surgery groups at the end of the study (MD -2.70 ml/100 ml/min, 95% CI -6.47 to 1.07).

#### Amputation: Analysis 2.5

Gelin 2001 reported one amputation in the control group, the result was not significant (RR 0.33, 95% CI 0.01 to 7.98).

#### Mortality: Analysis 2.6

Lundgren 1989 reported two deaths in the surgery group and Gelin 2001 reported five deaths in each group. There was no significant difference (RR 0.74, 95% CI 0.25 to 2.17).

#### Adverse events:

These included (Lundgren 1989) three wound haematomas, thrombectomies and three participants required a further reconstruction; the overall complication rate following surgery was therefore 18%. There were no direct complications of exercise although two participants developed worsening ischaemia and required surgery. In Gelin 2001 patency of reconstructions at one year were 89% for supra-inguinal sites and 76% for infra-inguinal sites, although further details of complications were not given.

### Exercise regimen compared with angioplasty (PTA)

Two trials investigated this comparison. Creasy 1990 gave outcomes at one year and Hobbs 2006 gave outcomes at six months.

#### Maximal walking time: Analysis 3.1

In Creasy 1990 walking time showed an initial increase in the angioplasty group so that after six months it was higher than in the exercise group, but not significantly so. Walking time then gradually declined in the PTA group compared with a steady increase in the exercise group so that after 12 months it was significantly longer in those receiving exercise therapy (MD 3.30 min, 95% CI 2.21 to 4.39). This involved a doubling of mean walking time in the exercise group.

#### Ankle brachial pressure index (ABPI): Analysis 3.2

After 12 months, the ABPI did not differ significantly between the two groups (Creasy 1990). In the exercise group the ABPI was relatively constant throughout the 12 month period, whereas in the PTA group the mean resting ABPI increased significantly in the first three to nine months ($P < 0.01$) but then subsequently declined. The results at six months (Hobbs 2006) were better in the angioplasty group giving an overall combined MD of -0.15 (95% CI -0.19 to -0.10) which is a statistically significant effect although the difference in timing of these results must be noted. Furthermore the heterogeneity between the trials was significant ($P<0.00001$; $I^2$ =96%) which may be related to the very small numbers of patients and trials.

#### Pain-free walking distance: Analysis 3.3

In the small study of Hobbs 2006 a dramatic improvement was seen in the angioplasty group (MD -542.80 m, 95% CI -815.43 to -270.17).

#### Maximum walking distance: Analysis 3.4

In Hobbs 2006 a significant increase was seen in the angioplasty group (MD -436.6 m, 95% CI -797.88 to -75.32 m).

#### Mortality: Analyis 3.5

There were six deaths in the treatment group and four in the control group (Creasy 1990) but this was not significant (RR 1.73, 95% CI 0.55 to 5.47).

#### Adverse events:

In the PTA group (Creasy 1990), two angioplasties were not successful (one due to failure to pass a guide wire across a stenosis in the superficial femoral artery, the other due to thrombosis of the superficial femoral artery following angiography). There were four complications: three groin haematomas, all treated conservatively, plus a rupture of an external iliac artery requiring an emergency ilio-femoral graft. One other patient had an elective aorto-bifemoral graft for deterioration six months after the PTA. There were no adverse events in the exercise group although one patient requested PTA after three months because maximal walking distance had increased only marginally. Hobbs 2006 did not report any serious side effects.

### Exercise regimen compared with antiplatelet therapy

In the one trial which compared exercise with antiplatelet therapy (Mannarino 1991) the following results were reported.

#### Maximal walking time: Analysis 4.1

After six months treatment maximal walking time was significantly greater in the exercise group than for those treated with antiplatelets (MD 1.06 min, 95% CI 0.15 to1.97). Maximum walking time was increased by 86% in the exercise group and by 38% in those on antiplatelet therapy.

#### Ankle brachial pressure index: Analysis 4.2

There was no significant difference between the exercise and antiplatelet therapy groups at the end of the trial (MD 0.00, 95% CI -0.22 to 0.22).

#### Exercise calf blood flow: Analysis 4.3

There was no significant difference in calf blood flow between antiplatelet therapy and exercise groups after six months, although flow tended to be higher in the exercise group (MD 2.18 ml/100 ml/min, 95% CI -0.28 to 4.64).

### Exercise regimen compared with pentoxifylline

In the one trial which compared exercise with pentoxifylline ( Ciuffetti 1994) the following results were reported.

#### Maximal walking time: Analysis 5.1

After 13 weeks therapy, maximal walking time was significantly greater in the pentoxifylline group than the exercise group (MD -0.45 min, 95% CI -0.66 to -0.24). Walking distance increased by 62% in the exercise group and by 88% for those on pentoxifylline.

#### Adverse events:

Two patients experienced gastroenteritis during treatment with pentoxifylline but this was not considered to be a side effect of treatment.

### Exercise regimen compared with iloprost therapy

Arosio 2001 investigated this comparison.

#### Pain free walking distance: Analyisis 6.1

There is a significant improvement in pain free walking distance (MD 188.7 m, 95% CI 15.38 to 362.02)

#### Maximum walking distance: Analysis 6.2

There was a non-significant increase in this measure in the exercise group (MD 196.80 m, 95% CI -83.8 to 477.40).

### Exercise regimen compared with pneumatic foot and calf compression

Kakkos 2005 described this comparison.

#### Pain-free walking distance: Analysis 7.1

There was a non-significant increase in the pneumatic compression group (MD -160.30 m, 95% CI -438.88 to 118.28).

#### Maximum walking distance: Analysis 7.2

There was a non-significant slight increase in the pneumatic compression group (MD -61.90 m, 95% CI -391.59 to 267.79).

## DISCUSSION

The data presented in this update generally confirms the findings of the previous review, that exercise has a significant positive effect on walking times and walking distances in people considered to be fit for exercise intervention compared to placebo or usual care. While most studies examined outcomes at three or six months, importantly this benefit would appear to be sustained for up to two years (Jansen 1991). Mean improvements in walking distance and walking time with exercise were clinically and statistically significant, however, in most cases the data were not normally distributed. Some individuals responded with improvements of considerably larger magnitude than the mean whereas others responded less well, which may reflect varying compliance with exercise programmes. Successful programmes generally comprised physiotherapy, supervised exercise two or three times per week for 30-60 minutes, often with walking, leg exercises or treadmill training. Some encouraged additional home exercise.

The lack of effect of exercise on ABPI is also consistent. Data relating to other important outcomes is more sparse as there were no data on non-fatal cardiovascular events and inconclusive data regarding mortality and amputation. The criteria for patient selection excluded many patients with stable claudication for whom exercise was not practical or safe due to pre-existing medical conditions. As most patients with intermittent claudication are elderly, co-morbidities are common. For up to a third of patients exercise may not be a suitable option. Other research and reviews have examined the optimum modes of exercise regimen for those with intermittent claudication; for example a Cochrane review (Bendermacher 2006) explored supervised versus unsupervised exercise for intermittent claudication. The present review cannot resolve uncertainties about different exercise regimes although the effect of cycling may not give the same benefits as other types of exercise.

In one trial comparing exercise with surgery (Lundgren 1989), ABPI significantly improved in the surgery group, compared with exercise, and there was a non-significant increase in walking time in the surgery group compared with exercise at 12 to 15 months. The rapid benefit achieved by surgery must be weighed up against the increased adverse events, however, surgical methods may have changed since this trial. The more recent study (Gelin 2001) also reported an increase in ABPI in the invasive treatment (surgery or angioplasty) group compared with exercise at one year; with a significant increase in walking distance in the invasive treatment group compared with exercise. In constrast to other studies, this trial found no improvement in walking distance in the arms comparing exercise to usual care, which may reflect the pragmatic design of the study and low compliance with exercise. It is, therefore, difficult to compare this trial with others.

Data relating to exercise versus angioplasty are limited and recent

trials have experienced difficulty in recruitment (Hobbs 2006a). There would appear to be a greater improvement in walking time and walking distance for those receiving angioplasty compared with exercise in the first six months but the data from Creasy 1990 suggests that this may not be sustained at one year, indeed the exercise group did significantly better at this time. The intial improvement in ABPI, also noted at six months (Hobbs 2006), was also not sustained in Creasy 1990. These trials are separated in time by 16 years and it is possible that angioplasty techniques have developed in sophistication over that time. The lack of data regarding non-fatal cardiovascular events means that uncertainty remains around whether exercise or invasive intervention alters the propensity for cardiovascular events in other sites in patients with intermittent claudication (Hobbs 2006; Hobbs 2006a). A cost effectiveness study of exercise versus angioplasty found that a twice weekly exercise programme was cost saving when outcomes were measured at six months (Treesak 2004). Angioplasty versus non-surgical management is the topic of another Cochrane review, Fowkes 1996.

Antiplatelet therapy was less effective than exercise in improving walking distance and other measures of lower limb function but no data were presented in terms of fatal and non-fatal events. A previous meta-analysis has shown antiplatelet agents to reduce the incidence of cardiovascular events in patients with claudication (Trialists 1994). Therefore, aspirin should be of benefit despite the lack of effect on the lower limb.

The one small trial comparing pentoxifylline with exercise showed participants on drug therapy to have significantly greater walking distances after three months than those on exercise therapy (Ciuffetti 1994). There were no cardiovascular or adverse events reported in those on pentoxifylline but disadvantages of drug treatment might include cost and lack of general cardiovascular improvement. Arosio 2001 showed that exercise improved pain-free walking time significantly more than iloprost, however this was a small study (24 participants).

Pneumatic foot and calf compression gave non-significant improvements in walking distances compared with exercise, again in a small trial (Kakkos 2005). This may be a promising area for future investigation as people who are unsuitable for exercise programmes may be able to undertake this treatment.

Quality of life data were reported in a range of scales and this made it difficult to incorporate into a meta-analysis. Results were variable depending on the comparisons made and this is an area for future research.

# AUTHORS' CONCLUSIONS

## Implications for practice

This review suggests that exercise therapy should play an important part in the care of selected patients with intermittent claudication, to improve walking times and distances. Effects were demonstrated following three months of supervised exercise although some programmes lasted over one year. There are limited data to suggest that an effect is sustained for up to two years. Further information is required on the cost effectiveness of exercise programmes.

Angioplasty may be more beneficial than exercise in improving walking capacity in the short term but it is uncertain whether this effect is sustained over 12 months. Evidence comparing exercise and surgery is limited and it is difficult to draw firm conclusions.

Antiplatelet agents were less effective than exercise in improving walking distance but should continue to be used because of benefits in reducing cardiovascular events and death. In contrast, pentoxifylline was more effective than exercise but may have fewer beneficial effects on the cardiovascular system in general. Iloprost gave less improvement in walking time than exercise. Pneumatic foot and calf compression showed non-significant increases in walking distances over exercise.

## Implications for research

An important question is the degree of supervision required in any exercise regimen and how long any change in exercise habits can be expected to last. A trial is, therefore, required with a long follow up, of five years, to compare the effectiveness of different supervised and unsupervised regimens in changing long-term exercise patterns. Research should also focus on compliance with exercise and how this could be improved. Outcome measures should include fatal and non-fatal cardiovascular events. Further cost-effective analysis is also required, to determine whether the cost of supervised sessions might offset the cost of deterioration in terms of surgery or occupation of inpatient beds for other complications such as myocardial infarction.

Further research is required to determine the role of angioplasty and surgery in the management of intermittent claudication, particularly to determine effects one or more years after the procedure.

A trial is also required to compare exercise treatment with pentoxifylline to determine whether the benefit of drug treatment is sustained over a longer period and whether there are any differences in cardiovascular events. Further investigation of pneumatic foot and calf compression in the treatment of intermittent claudication is also needed. Consistency in use of quality of life measures in different trials would be helpful in linking the outcomes to patient-assessed improvements.

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Arosio 2001**

| | |
|---|---|
| Methods | Study design: RCT. Method of randomisation: 'randomly divided'. Exclusions post-randomisation: not reported. Losses to follow up: not reported. Jadad score: 1/5 |
| Participants | Country: Italy<br>Setting: hospital<br>No: 24<br>Age: mean 65 years; 64.5 (55-69) years in exercise group; 66.4 (57-72) years in iloprost group<br>Sex: all male<br>Inclusion criteria: Fontaine stage II PAOD with IC during past 4 to 6 years, confirmed by Doppler ultrasound, angiography and ABI<br>Exclusion criteria: not clearly stated but inferred to be smoking, severe hypertension, stroke, ischaemic attack, cerebral vascular disease, any drugs for PAOD or other disease except transdermal clonidine for mild to moderate hypertension |
| Interventions | Intervention 1: physical exercise (n = 10) - walking, running, squat thrusts, 2 x day for 30 mins, cycle ergometer for 30 mins, plus 30 mins constant load treadmill (2 mph, slope 0%)<br>Intervention 2: iloprost (0.5-2 ng/kg/min) (n = 10)<br>Duration: 14 days |
| Outcomes | Endogenous NO products, neutrophil adhesion, ICD, ACD (m) from constant load treadmill test |
| Notes | Exercise was interrupted at onset of pain, participant rested for 3 min, or until pain had gone, then resumed activity until each 30 min block was completed.<br>Information from authors - same study as Arosio 1999. |

**Ciuffetti 1994**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: allocated by pre-determined computer code. Not blinded<br>Exclusions post-randomisation:<br>Losses to follow up:<br>Jadad score: 3/5. |
| Participants | Country: Italy<br>Setting:<br>No. of participants: 30<br>Age: 48-64 years<br>Sex: male and female<br>Inclusion criteria: stable maximal walking time (90-130 s) at 2 previous 6 monthly checks, plus stage II PAOD confirmed by velocimetry and angiography<br>Exclusion criteria: no h/o vascular surgery, coronary or cerebrovascular disease, DM; no factors affecting oxygen demand (eg anaemias); recent infections; treatment with vasodilators, antiplatelets, anticoagulants or drugs affecting haemorrheological parameters for previous 1 mth |

**Ciuffetti 1994** (*Continued*)

| | |
|---|---|
| Interventions | Treatment: 1 h exercise at home daily plus twice weekly supervision at outpatients. Home regimen: week 1, 500 m in 20 min; week 2, 1000 m in 40 min; week 3, 2000 m in 60 min on the flat<br>Control: pentoxifylline 800 mg tds<br>Duration: 3 mths |
| Outcomes | Primary: treadmill test maximal walking distance (2 km/h on 12 degree slope) |
| Notes | |

**Collins 2005**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: states 'randomised' but method not reported in this article (is reported in previous article though)<br>Exclusions post-randomisation:<br>Losses to follow up: 6 (4 PS, 2 control).<br>Jadad score: 3/5. |
| Participants | Country: USA<br>Setting: community<br>No: 52 (49 analysed)<br>Age: 65.8 ± 7.1 years polestriding group; 68.0 ± 8.6 control group<br>Sex: 51 M, 1 F<br>Inclusion criteria: history of IC, ABI < 0.95 at rest or < 0.85 after exercise, IC pain a factor for arrested walking<br>Exclusion criteria: vascular surgery, angioplasty in previous 6 months, other co-morbid conditions that would interfere with participation in an exercise programme, currently taking vitamin E, warfarin or pentoxifylline, unable to give informed consent |
| Interventions | Treatment: polestriding (n = 27) supervised training 3 times per week for 4 weeks, twice weekly for 8 weeks, once weekly for 4 weeks, biweekly for 4 weeks, unsupervised for 4 weeks<br>Control: no exercise (n = 25) usual care. Seen biweekly for 3 months and monthly thereafter<br>Duration: 24 weeks |
| Outcomes | Primary: ABPI, maximum walking distance, oxygen uptake<br>Secondary: health-related quality of life |
| Notes | All participants given $6 travel for each visit and $5 for each test battery completed, starting at $25.<br>Secondary analysis of the 2 x 2 factorial design of Collins 2003 since there was no influence of vitamin E on exercise they combined the exercise groups together and compared with the non-exercise groups. Also reported as Langbein 1998, 2002 |

**Creasy 1990**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: "Simple" randomisation method. Not blinded<br>Exclusions post-randomisation: not described.<br>Losses to follow up: at 6 years 19 of whom 10 had died, 2 had amputation, others uncontactable or too ill<br>Jadad score: 2/5. |
| Participants | Country: England<br>Setting: university department<br>No. of participants: 36 (56 in Perkins paper and Creasy 1992)<br>Age: mean 62.9 years<br>Sex: male and female<br>Inclusion criteria: stable unilateral IC with failure of conservative treatment for >3 mths; treadmill walking distance <375 m; lesion on angiogram suitable for PTA<br>Exclusion criteria: none stated. |
| Interventions | Treatment: 30 min sessions of dynamic leg exercises twice weekly for first 6 mths, and on a regular basis afterwards (supervised by physiotherapist); encouraged to exercise daily at home<br>Control: PTA by experienced radiologist using conventional guidewire and balloon catheter technique, producing overdilation by ~10% more than normal, for at least 45 s with heparin cover<br>Duration: 12 mths, then at 6 years range 45-83 months |
| Outcomes | Primary: treadmill test pain-freeMD and maximal walking distance (3 km/h at 10% incline).<br>ABPI.<br>Secondary: complications of treatment.<br>Also reported mortality with usable data in Perkins paper. |
| Notes | Authors contacted for more information as 6 year results given as graphs but data no longer available. ICD and ACD reported to be significantly greater for patients in exercise group, ABPI significantly increased in PTA group |

**Dahllof 1974**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: states "randomised". Not blinded.<br>Exclusions post-randomisation:<br>Losses to follow up:<br>Jadad score: 2/5. |
| Participants | Country: Sweden<br>Setting:<br>No. of participants: 18<br>Age: 54-71 years<br>Sex: male and female<br>Inclusion criteria: IC for >1 year<br>Exclusion criteria: DM or IHD |
| Interventions | Treatment: 30 min training sessions 3 times weekly, supervised by a physiotherapist, including dynamic leg exercises beyond the appearance of pain<br>Control: placebo tablets<br>Duration: 6 mths |

**Dahllof 1974** (*Continued*)

| | |
|---|---|
| Outcomes | Primary: treadmill test pain-free and maximal walking distance (max. 1000 m), at 4 km/h<br>Secondary: calf blood flow - venous occlusion plethysmography after ischaemic foot exercises |
| Notes | |

**Gardner 2002**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: not described.<br>Exclusions post-randomisation: nil.<br>Losses to follow up: 3 in treatment group, 6 in control group dropped out. More at 18 months - 31 remained<br>Jadad score: 2/5. |
| Participants | Country: US<br>Setting: vascular clinics, newspaper and radio adverts<br>No. of participants: 61 originally, 31 remained at 18 months<br>Age: over 60 years<br>Sex: 90% male<br>Inclusion criteria: Fontaine II PAOD Rose questionnaire.ABPI <0.97 at rest. IC limiting factor on treadmill<br>Exclusion criteria: other significant medical conditions limiting exercise tolerance, poorly controlled DM |
| Interventions | Treatment: 30 min training sessions 3 times weekly for 6 months then twice weekly for 12 months<br>Control: usual care<br>Duration: 6 months and 18 months |
| Outcomes | Treadmill distance to claudication<br>maximum claudication distance<br>ABPI<br>peak oxygen uptake<br>walking economy<br>6-minute walking distance<br>accelerometer derived physical activity<br>walking impairment questionnaire<br>calf blood flow<br>health-related quality of life on SF-36<br>self-perceived ambulatory measures. |
| Notes | |

**Gelin 2001**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: block, computer.<br>Exclusions post-randomisation: nil stated.<br>Losses to follow up: 39 (13 control, 15 training, 11 invasive therapy) did not complete evaluation at 1 year. A total of 90 patients did not complete treatment as allocated, although analysis was based on intention to treat. 15 were unsuitable for surgery and 17 recieved angioplasty in surgery arm<br>25 withdrew from quality of life section.<br>Jadad score: 3/5. |
| Participants | Country: Sweden<br>Setting: vascular outpatients<br>No: 253<br>Age: mean 67 (range 45-81) years<br>Sex: 67% male<br>Inclusion criteria: stable intermittent claudication for > 6 months, ABI < 0.6. Maximum post-ischaemic blood flow < 25 ml/min/100g, willing to undergo operations<br>Exclusion criteria: contraindication to surgery; other disorder limiting treadmill walking |
| Interventions | Treatment:<br>1. supervised exercise training 30 min 3 times per week for 6 months then 6-12 months 2 sessions per week;<br>2. invasive surgery/endovascular procedure, based on angiographic findings<br>Control: observation only<br>Duration: 1 year |
| Outcomes | Primary:<br>mortality, ABI, amputation, treadmill distance;<br>max post-ischaemic calf blood flow;<br>big toe systolic pressure.<br>Secondary:<br>blood pressure;<br>haemoglobin, cholesterol, triglycerides, creatine;<br>quality of life. |
| Notes | Quality of life (data for 171 only, 18 changed group but were analysed in original).<br>Randomised before pre-treatment investigations. Low compliance in exercise group but classes offered for longer than most studies.<br>Results for ABPI omitted standard deviations. |

**Hiatt 1990**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: randomised in sealed envelopes in pairs matched by ABPI and walking distance. Not blinded<br>Exclusions post-randomisation:<br>Losses to follow up: 6 in treatment group and 2 in control.<br>Jadad score: 2/5. |

**Hiatt 1990** (*Continued*)

| | |
|---|---|
| Participants | Country: USA<br>Setting:<br>No. of participants: 29<br>Age: mean 67 years<br>Sex: all male<br>Inclusion criteria: IC due to PAOD (ABPI <0.95 at rest or <0.85 after exercise)<br>Exclusion criteria: critical limb ischaemia; unable to walk on the treadmill; DM; vascular intervention in previous year; treatment with beta blockers or pentoxifylline |
| Interventions | Treatment: programme of exercise 3 times each week (5 min warm up, 50 min intermittent isotonic, resistive exercise, 5 min cool down)<br>Control: maintain usual level of exercise<br>Duration: 12 weeks |
| Outcomes | Primary: treadmill test maximal walking time (2 mph at 0% slope, with a subsequent 3.5% increase in slope every 3 min until forced to stop)<br>Secondary: calf blood flow venous occlusion plethysmography.<br>Subjective indicators: perceived pain during exercise; walking-limited distance |
| Notes | The Hiatt 1990 trial included distance walked and claudication pain. Unfortunately these results were not reported by treatment group but simply correlated with treadmill performance. The correlation was good, therefore it may be assumed that a significant improvement was experienced in those receiving exercise therapy |

**Hiatt 1994**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: sealed envelope. Not blinded.<br>Exclusions post-randomisation:<br>Losses to follow up: 2 in control group.<br>Jadad score: 2/5. |
| Participants | Country: USA<br>Setting:<br>No. of participants: 29<br>Age: mean 60 years<br>Sex: male only<br>Inclusion criteria: 3 mth h/o stable IC (Rose questionnaire) limiting exercise sufficiently to affect ability to perform routine activity; ABPI <0.94 at rest, <0.73 after exercise<br>Exclusion criteria: rest pain, ulcer, gangrene; unable to walk on treadmill at >2 mph; exercise limited by angina, CHF, COAD or arthritis; no DM, vascular surgery or PTA in previous year |
| Interventions | Treatment: either supervised treadmill walking exercise (n=10) or strength training (n=9), and encouraged to walk alone for 2 days each week (treadmill - 1 h 3 times a week, walking until moderate pain, then rest)<br>Control: maintain usual level of activity<br>Duration: 12 weeks |

**Hiatt 1994** (*Continued*)

| | |
|---|---|
| Outcomes | Primary: treadmill test pain-free and maximal walking distance (2 mph, 0% slope, with a subsequent 3.5% increase in slope every 3 min until forced to stop).<br>ABPI (resting and post-exercise). |
| Notes | Trial continued after 12 weeks without a control group, therefore later results not included.<br>Strength training was less effective than treadmill exercise, only the latter was included in the meta-analysis for statistical reasons |

**Hobbs 2005**

| | |
|---|---|
| Methods | Study design: RCT.<br>Randomisation: yes 2x2 factorial design, random number table<br>Concealment of allocation: yes.<br>Exclusions post-randomisation: not reported.<br>Losses to follow up: 4 of original 38 withdrew<br>Intention to treat: yes.<br>Jadad score 3/5. |
| Participants | Country: UK<br>Setting: university department of vascular surgery, patients referred to IC clinic from primary or secondary care<br>No. of participants: 34<br>Age: median 67 (63-72) years<br>Sex: 27 men, 7 women<br>Inclusion criteria:<br>IC diagnosed by Edinburgh claudication questionnaire and reduced ABPI <0.9, reviewed after 3-6 months;<br>max walking distance 20-500 m.<br>Exclusion criteria:<br>significant aorto-iliac disease, unable to complete treadmill distance to absolute claudication distance, MI, transient ischaemic attack, strole or PTA in last 3 months, CHF, bellding diathesis, glomerular filtration rate <20mL/min, CYP3A4 or CYP2C19 inhibitor use |
| Interventions | Treatment:<br>1. supervised exercise - 3 month, twice weekly 1 hour physiotherapist-led exercise programme. Given video tape of programme and encourage to take log of exercise at home;<br>2. cilostazole 100mg twice daily, if side effects dosing halved for 1 week;<br>3. exercise as above plus cilastozole.<br>Control:<br>best medical therapy<br>Duration: 6 months |
| Outcomes | Maximum walking distance<br>pain-freeMD walking distance<br>ABPI<br>thrombin anti-thrombin complex<br>prothrombin fragments 1 and 2<br>plasminogen activator inhibitor<br>tissue plasminogen activator. |

**Hobbs 2005** (*Continued*)

| | |
|---|---|
| Notes | Authors contacted for means and SDs - received for best medical therapy and supervised exercise groups |

**Hobbs 2006**

| | |
|---|---|
| Methods | Study design: RCT.<br>Randomisation: random number table.<br>Concealment of allocation: yes.<br>Exclusions post-randomisation: not reported.<br>Losses to follow up: not reported.<br>Intention to treat: yes.<br>Jadad score 3/5. |
| Participants | Country: UK<br>Setting: university department of vascular surgery, patients referred to IC clinic from primary or secondary care<br>No. of participants: 23<br>Age: median 67 (57-77) years<br>Sex: 15 men, 7 women<br>Inclusion criteria:<br>IC diagnosed by Edinburgh claudication questionnaire and reduced ABPI <0.9, reviewed after 3-6 months;<br>max walking distance 20-500 m.<br>Exclusion criteria:<br>significant aorto-iliac disease, unable to complete treadmill distance to absolute claudication distance, MI, transient ischaemic attack, stroke or PTA in last 3 months, CHF, bellding diathesis, glomerular filtration rate <20mL/min, CYP3A4 or CYP2C19 inhibitor use |
| Interventions | Treatment:<br>1. supervised exercise - 3 month, twice weekly 1 hour physiotherapist-led exercise programme. Given video tape of programme and encourage to take log of exercise at home;<br>2. PTA.<br>Control:<br>best medical therapy<br>Duration: 6 months |
| Outcomes | Maximum walking distance<br>pain-freeMD walking distance<br>ABPI<br>thrombin anti-thrombin complex<br>plasminogen activator inhibitor<br>tissue plasminogen activator. |
| Notes | Authors contacted for means and SDs - received. |

**Jansen 1991**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: not described.<br>Exclusions post-randomisation: not described.<br>Losses to follow up: not described.<br>Jadad score: 1/5. |
| Participants | Country: Germany<br>Setting: community<br>No: 48<br>Age: not described<br>Sex: not described<br>Inclusion criteria: PAOD stage II<br>Exclusion criteria: not stated |
| Interventions | Treatment: training on treadmill 3.5 km/hr 10% slope for 2 hours twice per week under medical/physiotherapy supervision<br>Control: no training<br>Duration: 2 years |
| Outcomes | Primary:<br>treadmill walking distance, pain-free and maximum.<br>Secondary:<br>ultrasound Doppler of arm and leg arteries. |
| Notes | |

**Kakkos 2005**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: "blind block telephone procedure" by means of computer<br>Exclusions post-randomisation:<br>Losses to follow up: 4 in supervised exercise group; 4 in pneumatic compression group<br>Jadad score: 3/5 (for now). |
| Participants | Country: England<br>Setting: vascular outpatients clinic<br>No: 34<br>Age: median and IQR: 66 (10.5) unsupervised exercise group; 69 (11.8) supervised exercise group; 66 (7) intermittent pneumatic compression group<br>Sex: 27 M in total; 8 M USE group, 11 M SE group, 8 M IPC group<br>Inclusion criteria: stable IC for > 6 months due to SFA occlusion of = 6 cm on ultrasound or angiogram<br>Exclusion criteria: duration of symptoms < 6 months, previous angioplasty or arterial surgery to symptomatic leg, myocardial infarction within previous 6 months, inability to manage treadmill or training, any psychiatric illness or other reason making follow-up difficult, ischaemic rest pain, gangrene, ischaemic ulceration, unable to attend supervised programme, severe peripheral neuropathy, ABPI > 0.9 at enrolment, non-compressible calf arteries, iliac occlusions or stenoses amenable to surgery or angioplasty, femoral artery occlusion < 6 cm, exercise capacity limited by angina, congestive heart failure, COPD, disease of spinal column, venous disease, neurological disease, mental illness or arthritis |

**Kakkos 2005** (*Continued*)

| | |
|---|---|
| Interventions | Treatment: supervised (n = 12) or unsupervised exercise (n = 9): constant load treadmill at 10% gradient, 3.5 km/hr<br>Control: pneumatic foot compression (n = 13)<br>Duration: 6 months treatment period plus further follow up at 12 months after treatment began (exercise advice given for second 6 month period) |
| Outcomes | Primary: ICD, ACD, ABPI<br>Secondary: SF-36, walking impairment questionnaire (WIQ), IC questionnaire |
| Notes | The authors contacted successfully for means and SDs. |

**Larsen 1966**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: randomised in pairs matched by age and disease. Not blinded<br>Exclusions post-randomisation:<br>Losses to follow up:<br>Jadad score: 2/5. |
| Participants | Country: Denmark<br>Setting:<br>No. of participants: 14<br>Age: 44-65 years<br>Sex: male and female<br>Inclusion criteria: typical IC, stable for >6 mths<br>Exclusion criteria: none stated |
| Interventions | Treatment: instructed to walk daily, in addition to normal activities<br>Control: 1 placebo (lactose) tablet bd<br>Duration: 6 mths |
| Outcomes | Primary: treadmill test maximal walking distance (4.6 km/h, elevation of 0, 8 or 16 cm/m)<br>Secondary: calf blood flow xenon clearance method. |
| Notes | |

**Lundgren 1989**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: randomised, balanced by age, sex and DM. Not blinded<br>Exclusions post-randomisation: not stated.<br>Losses to follow up: surgery not performed in 2 participants; exercise not carried out in 4<br>Jadad score: 2/5. |
| Participants | Country: Sweden<br>Setting: not stated<br>No. of participants: 50<br>Age: 40-80 years |

**Lundgren 1989** (*Continued*)

| | |
|---|---|
| | Sex: male and female<br>Inclusion criteria: IC >6 mths; maximal walking distance <600 m; BP in first toe >30 mmHg<br>Exclusion criteria: rest pain or ulcer |
| Interventions | Treatment: dynamic leg exercises beyond appearance of pain, supervised by physiotherapist, 30 min sessions 3 times each week; encouraged to exercise at leisure<br>Control: surgical intervention, including thrombendarterectomy, bypass with synthetic y-graft, saphenous vein or polytetrafluoroethylene graft<br>Duration: 12-15 mths |
| Outcomes | Primary: treadmill test pain-free and maximal walking distance (4 km/h at 0 slope to maximum of 1000 m);<br>ABPI.<br>Secondary: calf blood flow venous occlusion plethysmography. |
| Notes | A third group of 25 participants received surgery combined with an exercise regimen. These results are not included in formal meta-analysis |

**Mannarino 1991**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: states random. Not blinded.<br>Exclusions post-randomisation:<br>Losses to follow up: none.<br>Jadad score: 1/5. |
| Participants | Country: Italy<br>Setting:<br>No. of participants: 20<br>Age: 48-75 years<br>Sex: male and female<br>Inclusion criteria: IC for >2 yrs, stable for past 3 mths, pain-free walking distance <300 m<br>Exclusion criteria: h/o angina, recent MI or stroke; vascular surgery or PTA in previous 6 mths; impaired cardiac or lung function, major liver, kidney or metabolic disorders, infections, cancer or peptic ulcers |
| Interventions | Treatment: 1 h home exercises daily supervised via out-patients. Week 1 - 500 m in 20 min; week 2 - 1000 m in 40 min; week 3 - 2000 m in 60 min<br>Control: dipyridamole 75 mg tds plus aspirin 330 mg od.<br>Duration: 6 mths |
| Outcomes | Primary: treadmill test pain-free and maximal walking time (2 km/h on 12 degree slope);<br>ABPI.<br>Secondary: calf blood flow strain-gauge plethysmography. |
| Notes | A third group of 10 participants received antiplatelet treatment and exercise. These results are discussed but not formally included in a meta-analysis |

**Mika 2005**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: not described<br>Exclusions post-randomisation: not described.<br>Losses to follow up: 18 withdrew (10 control, 8 exercise).<br>Jadad score: 2/5. |
| Participants | Country: Poland<br>Setting: university department outpatient clinics<br>No. of participants: 98<br>Age: 50-70 years<br>Sex: male and female<br>Inclusion criteria: PAOD and IC (Fontaine stage II) stable for 3 months, pain-free walking distance 50-200 m at 3. 2 km/h<br>Exclusion criteria: angina, recent MI, vascular surgery in last 3 months, impaired cardiac or lung function, DM, cancer, kidney and liver disease, arthritis limiting walking, other contraindication to walking, those taking beta blockers, pentoxifylline or other haemorheologically active drugs |
| Interventions | Treatment: 12 week programme of supervised pain-free treadmill exercise, 1 hour per day three times a week of repetitive walking exercise<br>Control: usual care<br>Duration: 3 months |
| Outcomes | Pain-free walking distance<br>total leucocyte count<br>neutrophil count<br>microalbuminuria. |
| Notes | |

**Mika 2006**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: not described.<br>Exclusions post-randomisation: not described.<br>Losses to follow up: 5.<br>Jadad score: 2/5. |
| Participants | Country: Poland<br>Setting: university department clinics<br>No. of participants: 60<br>Age: 50-70 years<br>Sex: male and female<br>Inclusion criteria: Fontaine stage II PAOD, IC limiting walking and stable for 3 months, ABPI <0.9<br>Exclusion criteria: angina, recent MI, vascular surgery in last 3 months, impaired cardiac or lung function, DM, cancer, kidney and liver disease, arthritis limiting walking, unable to walk at 3.2 km/hour, those taking beta blockers, pentoxifylline or other haemorheologically active drugs |

**Mika 2006** (*Continued*)

| | |
|---|---|
| Interventions | Treatment: 12-week programme of supervised pain-freeMD treadmill exercise, 1 hour per day three times a week of repetative walking exercise<br>Control: usual care<br>Duration: 3 months |
| Outcomes | Pain-free walking time<br>maximum walking time<br>red cell deformability - erythrocyte elongation index. |
| Notes | |

**Sanderson 2006**

| | |
|---|---|
| Methods | Study design: RCT.<br>Blinded: no.<br>Exclusions post-randomisation: nil.<br>Losses to follow up: 1 in treadmill group.<br>Jadad score: 3/5. |
| Participants | Country: Australia<br>No.of participants: 42<br>Age: mean 63 years<br>Inclusion criteria: claudication lasting > 1 year, ABPI < 0.9<br>Exclusion criteria: reduced cardiac function, rest pain, recent surgery or cardiac event, other medical conditions rendering exercise unsuitable |
| Interventions | Treatment:<br>1. treadmill exercise;<br>2. cycling.<br>Both groups exercised three times a week for 6 weeks<br>Control: no exercise<br>Duration: 6 weeks |
| Outcomes | Maximal and pain-free walking and cycling tests<br>submaximal and peak physiological response<br>ABPI. |
| Notes | Stratified by gender, presence of diabetes, then randomised<br>results given as mean differences, contact authors. |

**Tisi 1997**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: randomised by sealed envelope, weighted 70:40:40 (angioplasty:exercise:observation).<br>19/25 randomised to PTA had unsuitable lesions and the technique failed in one other. Not blinded.<br>Intention-to-treat analysis.<br>Exclusions post-randomisation:<br>Losses to follow up:<br>Jadad score: 1/5. |
| Participants | Country: England<br>Setting: general hospital<br>No. of participants: 67<br>Age: mean 69.3 years<br>Sex: male and female<br>Inclusion criteria: stable IC >6 mths, positive Edinburgh Claudication Questionnaire, ABPI <0.8 and >30 mm Hg drop in ankle systolic pressure on exercise, and walking distance 50-250 m on treadmill (3 km/hr, 10% gradient)<br>Exclusion criteria: intervention for IC in past 6 mths, exercise limited by other factors, concurrent medical disease, treatment with steroids, or inability to complete assessment visits |
| Interventions | Treatment:<br>1. exercise - series of active and passive leg exercises performed to the limit of exercise pain, supervised by a physiotherapist once weekly for 4 weeks. Also encouraged to exercise for 45 min daily at home, plus to walk 1 mile a day;<br>2. PTA.<br>Control: observation, plus advice given to all 3 groups (leaflet advising on weight loss, smoking and exercise, plus 75 mg aspirin daily)<br>Duration 12 mths |
| Outcomes | Primary: treadmill test: pain-freeMD and maximal walking distance (3 km/h on 10% slope);<br>ABPI.<br>Secondary: Nottingham Health Profile |
| Notes | Results for the exercise vs angioplasty comparison have not been included in this review. This is because only a very small proportion of patients randomised to PTA actually received this treatment, and because the only published outcomes are for quality of life.<br>Claudication and walking distance results not in usable format |

**Tsai 2002**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: not described.<br>Exclusions post-randomisation: not described.<br>Losses to follow up: 11, 5 in treatment group.<br>Jadad score: 2/5. |
| Participants | Country: Taiwan<br>Setting: community<br>No. of participants: 64<br>Age: 76 years +/- 4<br>Sex: 81% male<br>Inclusion criteria: Fontaine II PAOD on Rose questionnaire. ABPI <0.95 |

**Tsai 2002** (*Continued*)

| | |
|---|---|
| | Exclusion criteria: intervention for IC in past 3 mths, exercise limited by other factors, rest pain, MI or unstable claudication in the last 3 months, history of angina on exertion |
| Interventions | Treatment: 12 weeks progressive rehabilitiation programme, three times a week. Up to 30 minutes on the treadmill<br>Control: usual care<br>Duration 12 weeks |
| Outcomes | Time to onset of pain<br>time to maximum pain<br>6-minute walking distance<br>walking impairment questionnaire<br>physical function<br>bodily pain<br>role limitation physical and emotional<br>general health<br>mental health<br>social function<br>vitality. |
| Notes | |

**Zwierska 2005**

| | |
|---|---|
| Methods | Study design: RCT.<br>Method of randomisation: randomisation was undertaken using the fishbowl technique (Baumgartner and Strong 1998). This involved drawing patient names out of a 'hat' and allocating them to the respective groups at random . Randomisation was undertaken by an independent academic based at another site in Sheffield<br>Intention-to-treat analysis: yes.<br>Exclusions post-randomisation: nil.<br>Losses to follow up: 10.<br>Jadad score: 2/5.<br>Exclusion criteria: not stated |
| Participants | Country: UK<br>Setting: not stated<br>No. of participants: 104<br>Age: median 69 (50-89)<br>Sex: not stated<br>Inclusion criteria: stable symptomatic peripheral arterial disease<br>Exclusion criteria: not stated. |
| Interventions | Treatment:<br>1. supervised upper limb aerobic exercise;<br>2. supervised lower limb aerobic exercise<br>Control:<br>no exercise.<br>Duration: 24 weeks |

**Zwierska 2005** (*Continued*)

| | |
|---|---|
| Outcomes | Claudication distance<br>Maximum walking distance<br>peak heart rate<br>peak oxygen consumption<br>perceived exertion and pain<br>physical activity status. |
| Notes | Results given as medians - authors contacted for more information, received |

PAOD = peripheral arterial occlusive disease
IC = intermittent claudication
mth(s)= month(s)
h/o = history of
DM = diabetes mellitus
IHD = ischaemic heart disease
CHF = congestive heart failure
COAD = chronic obstructive airways disease
MI = myocardial infarction
tds = three times a day
bd = twice a day
od = once a day
PTA = percutaneous transluminal angioplasty
ABPI = ankle brachial pressure index
ICD = intermittent claudication distance
ACD = absolute claudication distance (or maximum walking distance)

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Buchwalsky 1974 | Two training groups. |
| Bulling 1991 | Comparison of exercise plus gingko biloba and exercise versus placebo group. No non-exercise control group |
| Cachovan 1997 | Two exercise groups. |
| Cachovan 1999 | Comparison of two different sequences of exercise. No non-exercise control group |
| Carmeli 2004 | Not randomised. |
| Cheetham 2004 | Two exercise groups and no non-exercise control group. |
| Cina 1996 | Comparison of physical training with low dose heparin and physical training and placebo. No non-exercise control group |

(*Continued*)

| | |
|---|---|
| Dahllof 1976 | This trial was not fully randomised as the first ten of the 34 patients were allocated to exercise before randomisation was introduced. There were also several differences between the treatment and control groups, including significantly higher cholesterol levels and maximal calf blood flow in the control group. Treatment effects may also have been masked because many control subjects spontaenously undertook increased exercise during the trial period |
| Degischer 2002 | Not a randomised trial and both groups had exercise. |
| Dittmar 1977 | Exercise in addition to drug. |
| Ericsson 1970 | This trial compared exercise with no treatment but was excluded from the review because of insufficient evidence that patients were randomised. The paper stated that patients were "divided into two groups", and the trialists were approached to confirm the method of allocation. No reply was received, therefore it was decided to exclude the results from the review, unless evidence becomes available to the contrary |
| Ernst 1987 | This trial compared participants on an exercise programme with those not exercised but allocation was not strictly randomised as patients were "assigned according to space on the exercise programme" |
| Ernst 1990 | Comparison of treadmill exercise plus pentoxifylline and treadmill exercise plus placebo. No non-exercise control group |
| Ernst 1997 | Review of chelation therapy. |
| Fitzgerald 1971 | This trial compared an exercise regimen with no treatment but there is no evidence in the report that the groups were randomly allocated. The quality of the trial also appeared generally poor with a variable period of follow up and the inclusion of some patients who did not have intermittent claudication |
| Fowler 2002 | Some patients were asymptomatic and it was not possible to exclude these for the purposes of data extraction |
| Gardner 2005 | Two exercise groups compared. |
| Gibbellini 2000 | Satisfied inclusion criteria but no usable data despite attempting to contact authors. Results divided into asymptomatic and symptomatic groups, not aggregated |
| Gottstein 1987 | Both groups received training. |
| Holm 1973 | Suitable for review (originally excluded) but no usable numerical data despite attempt to contact author. Stated significant improvement in walking time in exercise group compared to placebo |
| Jones 1996 | Comparison of treadmill versus stairmaster. No non-exercise control group |
| Kiesewetter 1987 | Both groups received intensive physical therapy. No non-exercise control group |
| Krause 1976 | Combines exercise with drug. |
| Labs 1999 | Comparison of constant-load and graded-load treadmill testing with and without beraprost sodium. No non-exercise control group |

(*Continued*)

| | |
|---|---|
| Lee 2007 | Non-randomised (clinical and cost-effectiveness). |
| Lepantalo 1984 | Comparison of exercise plus flunarizine and exercise plus placebo. No non-exercise control group |
| Maejima 2005 | Satisfied inclusion criteria but no data available after attempt to contact authors. Reported improvement in walking time in exercise group at 12 weeks |
| Mannarino 1988 | Controlled, not randomised. |
| Mannarino 1989 | This trial compared an exercise regimen with nothing (placebo tablets) but the report suggested that the groups were not allocated by an acceptable randomisation method. Trialists have been approached to confirm the method of allocation, therefore it may become possible to include the trial at a later date |
| McDermott 2004 | Patients did not have intermittent claudication. |
| Nawaz 1999 | Both groups had exercise advice. No non-exercise control group |
| Nawaz 2001 | Comparison of upper limb and lower limb exercise. Separate non-randomised control group |
| Necker 2001 | Training after angioplasty. |
| Necker 2003 | Training after angioplasty. |
| Nielsen 1975 | Two exercise groups. |
| Nielsen 1977 | Both groups had exercise. No non-exercise control group. |
| Patterson 1997 | Comparison of supervised exercise programme plus lectures and home-based exercise plus lectures. No non-exercise control group |
| Pinto 1997 | Two exercise regimens. |
| Presern-Strukelj 200 | Comparison of standard exercise alone and standard exercise plus electrostimulation in amputees with peripheral arterial occlusive disease |
| Riebe 2001 | Comparison of two progressive treadmill tests. No non-exercise control group |
| Savage 2001 | Compared supervised exercise versus home-based exercise. No non-exercise control group |
| Scheffler 1991 | Each group received exercise training. No non-exercise control group |
| Schoneberger 1994 | Controlled study, not randomised |
| Silvestro 2002 | Age-matched control group. |
| Slordahl 2005 | Two exercise groups. |

(*Continued*)

| | |
|---|---|
| Streminski 1992 | Satisfied inclusion criteria but data not available in usable format despite attempt to contact author. Actovegin versus exercise. Results given as mean change. Reported improvement in pain-free walking distance in exercise group |
| Taft 2004 | This study was not truly randomised and did not contain any outcomes of relevance to this review |
| Thomson 1999 | Two exercise groups. |
| Walker 2000 | The non-exercise group was not randomised. |
| Waller 1988 | Comparison of exercise where patients had smoked immediately prior to treadmill test and exercise where patients had not smoked prior to treadmill test |
| Zwierska 2004 | Both groups had exercise. No non-exercise control group. |

## DATA AND ANALYSES

### Comparison 1. Exercise regimen compared with placebo/usual care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal walking time (minutes) | 7 | 255 | Mean Difference (IV, Fixed, 95% CI) | 5.12 [4.51, 5.72] |
| 1.1 Usual care | 6 | 241 | Mean Difference (IV, Fixed, 95% CI) | 5.12 [4.51, 5.72] |
| 1.2 Placebo | 1 | 14 | Mean Difference (IV, Fixed, 95% CI) | 5.13 [0.80, 9.46] |
| 2 Pain free walking time (minutes) | 3 | 150 | Mean Difference (IV, Fixed, 95% CI) | 2.91 [2.51, 3.31] |
| 3 Ankle brachial pressure index | 7 | 228 | Mean Difference (IV, Fixed, 95% CI) | -0.01 [-0.05, 0.04] |
| 4 Peak exercise calf blood flow (ml/100 ml/min) | 4 | 103 | Mean Difference (IV, Fixed, 95% CI) | 0.94 [-0.81, 2.69] |
| 4.1 Usual care | 2 | 71 | Mean Difference (IV, Fixed, 95% CI) | 2.83 [0.18, 5.49] |
| 4.2 Placebo | 2 | 32 | Mean Difference (IV, Fixed, 95% CI) | -0.52 [-2.85, 1.82] |
| 5 Pain free walking distance (m) | 6 | 322 | Mean Difference (IV, Fixed, 95% CI) | 82.19 [71.73, 92.65] |
| 6 Maximum walking distance (m) | 6 | 391 | Mean Difference (IV, Fixed, 95% CI) | 113.20 [94.96, 131.43] |
| 7 Amputation | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8 Mortality | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

### Comparison 2. Exercise regimen compared with surgery

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal walking time (minutes) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Maximum walking distance (m) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 Ankle brachial pressure index | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Peak exercise calf blood flow (ml/100 ml/min) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Amputation | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 6 Mortality | 2 | 219 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.25, 2.17] |

### Comparison 3. Exercise regimen compared with angioplasty

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal walking time (minutes) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Ankle brachial pressure index | 2 | 52 | Mean Difference (IV, Fixed, 95% CI) | -0.15 [-0.19, -0.10] |
| 3 Pain free walking distance (m) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Maximum walking distance (m) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

| | | | |
|---|---|---|---|
| 5 Mortality | 1 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

### Comparison 4. Exercise regimen compared with antiplatelet therapy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal walking time (minutes) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Ankle brachial pressure index | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 Peak exercise calf blood flow (ml/100 ml/min) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

### Comparison 5. Exercise regimen compared with pentoxifylline therapy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal walking time (minutes) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

### Comparison 6. Exercise regimen compared with iloprost therapy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Pain free walking distance (m) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Maximum walking distance (m) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

### Comparison 7. Exercise regimen compared with pneumatic foot and calf compression

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Pain free walking distance | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Maximum walking distance | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

## Analysis 1.1. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 1 Maximal walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 1 Maximal walking time (minutes)

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Usual care | | | | | | | |
| Collins 2005 | 27 | 15.73 (4.46) | 25 | 10.33 (4.67) | | 5.9 % | 5.40 [ 2.91, 7.89 ] |
| Hiatt 1990 | 10 | 13.9 (3.5) | 9 | 7.1 (2.9) | | 4.4 % | 6.80 [ 3.92, 9.68 ] |
| Hiatt 1994 | 10 | 14.7 (7.3) | 10 | 7.3 (2.7) | | 1.6 % | 7.40 [ 2.58, 12.22 ] |
| Mika 2006 | 27 | 10.93 (1.32) | 28 | 5.86 (1.28) | | 76.6 % | 5.07 [ 4.38, 5.76 ] |
| Sanderson 2006 | 28 | 19.43 (8.44) | 14 | 22.86 (11) | | 0.8 % | -3.43 [ -9.99, 3.13 ] |
| Tsai 2002 | 27 | 12.5 (3.7) | 26 | 7.6 (3.8) | | 8.9 % | 4.90 [ 2.88, 6.92 ] |
| **Subtotal (95% CI)** | **129** | | **112** | | | **98.1 %** | **5.12 [ 4.51, 5.72 ]** |
| Heterogeneity: $Chi^2$ = 8.81, df = 5 (P = 0.12); $I^2$ =43% | | | | | | | |
| Test for overall effect: Z = 16.50 (P < 0.00001) | | | | | | | |
| 2 Placebo | | | | | | | |
| Larsen 1966 | 7 | 8.17 (5.52) | 7 | 3.04 (1.94) | | 1.9 % | 5.13 [ 0.80, 9.46 ] |
| **Subtotal (95% CI)** | **7** | | **7** | | | **1.9 %** | **5.13 [ 0.80, 9.46 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.32 (P = 0.020) | | | | | | | |
| **Total (95% CI)** | **136** | | **119** | | | **100.0 %** | **5.12 [ 4.51, 5.72 ]** |
| Heterogeneity: $Chi^2$ = 8.81, df = 6 (P = 0.18); $I^2$ =32% | | | | | | | |
| Test for overall effect: Z = 16.66 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.00, df = 1 (P = 0.99), $I^2$ =0.0% | | | | | | | |

### Analysis 1.2. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 2 Pain free walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

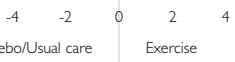
Outcome: 2 Pain free walking time (minutes)

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Mika 2006 | 27 | 6.43 (1) | 28 | 3.5 (0.47) | | 93.3 % | 2.93 [ 2.51, 3.35 ] |
| Sanderson 2006 | 28 | 7.05 (6.14) | 14 | 7.44 (7.38) | | 0.8 % | -0.39 [ -4.88, 4.10 ] |
| Tsai 2002 | 27 | 6.2 (2.7) | 26 | 3.2 (3.4) | | 5.9 % | 3.00 [ 1.34, 4.66 ] |
| **Total (95% CI)** | **82** | | **68** | | | **100.0 %** | **2.91 [ 2.51, 3.31 ]** |

Heterogeneity: $Chi^2$ = 2.10, df = 2 (P = 0.35); $I^2$ =5%

Test for overall effect: Z = 14.20 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 1.3. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 3 Ankle brachial pressure index.

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 3 Ankle brachial pressure index

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Collins 2005 | 27 | 0.71 (0.22) | 25 | 0.71 (0.17) | | 14.6 % | 0.0 [ -0.11, 0.11 ] |
| Gardner 2002 | 28 | 0.67 (0.21) | 24 | 0.72 (0.24) | | 10.8 % | -0.05 [ -0.17, 0.07 ] |
| Hiatt 1990 | 10 | 0.71 (0.11) | 9 | 0.62 (0.12) | | 15.3 % | 0.09 [ -0.01, 0.19 ] |
| Hiatt 1994 | 10 | 0.53 (0.16) | 8 | 0.61 (0.18) | | 6.5 % | -0.08 [ -0.24, 0.08 ] |
| Hobbs 2005 | 16 | 0.71 (0.12) | 18 | 0.7 (0.19) | | 14.8 % | 0.01 [ -0.10, 0.12 ] |
| Hobbs 2006 | 7 | 0.7 (0.06) | 7 | 0.68 (0.14) | | 13.0 % | 0.02 [ -0.09, 0.13 ] |
| Tisi 1997 | 22 | 0.64 (0.14) | 17 | 0.69 (0.12) | | 24.8 % | -0.05 [ -0.13, 0.03 ] |
| **Total (95% CI)** | **120** | | **108** | | | **100.0 %** | **-0.01 [ -0.05, 0.04 ]** |

Heterogeneity: $Chi^2$ = 6.01, df = 6 (P = 0.42); $I^2$ =0%

Test for overall effect: Z = 0.25 (P = 0.80)

Test for subgroup differences: Not applicable

### Analysis 1.4. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 4 Peak exercise calf blood flow (ml/100 ml/min).

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 4 Peak exercise calf blood flow (ml/100 ml/min)

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Usual care | | | | | | | |
| Gardner 2002 | 28 | 17.6 (6.56) | 24 | 14.5 (6.52) | | 24.2 % | 3.10 [ -0.46, 6.66 ] |
| Hiatt 1990 | 10 | 14.2 (3.2) | 9 | 11.7 (5.3) | | 19.3 % | 2.50 [ -1.49, 6.49 ] |
| **Subtotal (95% CI)** | **38** | | **33** | | | **43.5 %** | **2.83 [ 0.18, 5.49 ]** |
| Heterogeneity: $Chi^2$ = 0.05, df = 1 (P = 0.83); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.09 (P = 0.037) | | | | | | | |
| 2 Placebo | | | | | | | |
| Dahllof 1974 | 10 | 16.9 (1.6) | 8 | 18.1 (3.2) | | 52.1 % | -1.20 [ -3.63, 1.23 ] |
| Larsen 1966 | 7 | 28 (9.63) | 7 | 20.43 (5.86) | | 4.4 % | 7.57 [ -0.78, 15.92 ] |
| **Subtotal (95% CI)** | **17** | | **15** | | | **56.5 %** | **-0.52 [ -2.85, 1.82 ]** |
| Heterogeneity: $Chi^2$ = 3.91, df = 1 (P = 0.05); $I^2$ =74% | | | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.66) | | | | | | | |
| **Total (95% CI)** | **55** | | **48** | | | **100.0 %** | **0.94 [ -0.81, 2.69 ]** |
| Heterogeneity: $Chi^2$ = 7.40, df = 3 (P = 0.06); $I^2$ =59% | | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.45, df = 1 (P = 0.06), $I^2$ =71% | | | | | | | |

### Analysis 1.5. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 5 Pain free walking distance (m).

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

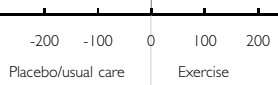
Outcome: 5 Pain free walking distance (m)

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Gardner 2002 | 28 | 402 (296) | 24 | 203 (211) | | 0.6 % | 199.00 [ 60.63, 337.37 ] |
| Hobbs 2005 | 16 | 181.7 (310) | 18 | 63.3 (20.5) | | 0.5 % | 118.40 [ -33.79, 270.59 ] |
| Hobbs 2006 | 7 | 115.2 (93.2) | 7 | 136.7 (94) | | 1.1 % | -21.50 [ -119.56, 76.56 ] |
| Jansen 1991 | 24 | 196 (26) | 24 | 111 (13) | | 80.9 % | 85.00 [ 73.37, 96.63 ] |
| Mika 2005 | 41 | 191.6 (94.8) | 39 | 101.6 (50.1) | | 10.0 % | 90.00 [ 57.00, 123.00 ] |
| Zwierska 2005 | 62 | 177 (117) | 32 | 134 (78) | | 6.9 % | 43.00 [ 3.27, 82.73 ] |
| **Total (95% CI)** | **178** | | **144** | | | **100.0 %** | **82.19 [ 71.73, 92.65 ]** |

Heterogeneity: $Chi^2$ = 11.43, df = 5 (P = 0.04); $I^2$ =56%

Test for overall effect: Z = 15.40 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 1.6. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 6 Maximum walking distance (m).

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 6 Maximum walking distance (m)

| Study or subgroup | Exercise N | Mean(SD) | Placebo/Usual care N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Gardner 2002 | 28 | 702 (302) | 24 | 425 (274) | | 1.4 % | 277.00 [ 120.38, 433.62 ] |
| Gelin 2001 | 73 | 247 (111) | 76 | 261 (131) | | 21.9 % | -14.00 [ -52.93, 24.93 ] |
| Hobbs 2005 | 16 | 248.6 (288.6) | 18 | 122.1 (42) | | 1.6 % | 126.50 [ -16.24, 269.24 ] |
| Hobbs 2006 | 7 | 254 (366.6) | 7 | 271.7 (331.9) | | 0.2 % | -17.70 [ -384.04, 348.64 ] |
| Jansen 1991 | 24 | 320 (50) | 24 | 171 (25) | | 66.5 % | 149.00 [ 126.64, 171.36 ] |
| Zwierska 2005 | 62 | 418 (179) | 32 | 281 (129) | | 8.3 % | 137.00 [ 73.89, 200.11 ] |
| **Total (95% CI)** | **210** | | **181** | | | **100.0 %** | **113.20 [ 94.96, 131.43 ]** |

Heterogeneity: $Chi^2$ = 56.12, df = 5 (P<0.00001); $I^2$ =91%

Test for overall effect: Z = 12.17 (P < 0.00001)

Test for subgroup differences: Not applicable


### Analysis 1.7. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 7 Amputation.

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 7 Amputation

| Study or subgroup | Exercise n/N | Placebo/Usual care n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Gelin 2001 | 0/88 | 2/89 | | 0.20 [ 0.01, 4.15 ] |

### Analysis 1.8. Comparison 1 Exercise regimen compared with placebo/usual care, Outcome 8 Mortality.

Review: Exercise for intermittent claudication

Comparison: 1 Exercise regimen compared with placebo/usual care

Outcome: 8 Mortality

| Study or subgroup | Exercise n/N | Placebo/Usual care n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Gelin 2001 | 5/88 | 4/89 | | 1.26 [ 0.35, 4.55 ] |


### Analysis 2.1. Comparison 2 Exercise regimen compared with surgery, Outcome 1 Maximal walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 1 Maximal walking time (minutes)

| Study or subgroup | Exercise N | Mean(SD) | Surgery N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Lundgren 1989 | 21 | 6.89 (4.53) | 23 | 8.55 (5.25) | | -1.66 [ -4.55, 1.23 ] |

### Analysis 2.2. Comparison 2 Exercise regimen compared with surgery, Outcome 2 Maximum walking distance (m).

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 2 Maximum walking distance (m)

| Study or subgroup | Exercise N | Mean(SD) | Surgery N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Gelin 2001 | 73 | 247 (111) | 76 | 344 (169) | | -97.00 [ -142.74, -51.26 ] |

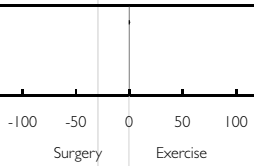

### Analysis 2.3. Comparison 2 Exercise regimen compared with surgery, Outcome 3 Ankle brachial pressure index.

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 3 Ankle brachial pressure index

| Study or subgroup | Exercise N | Mean(SD) | Surgery N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Lundgren 1989 | 21 | 0.63 (0.14) | 23 | 0.9 (0.19) | | -0.27 [ -0.37, -0.17 ] |



### Analysis 2.4. Comparison 2 Exercise regimen compared with surgery, Outcome 4 Peak exercise calf blood flow (ml/100 ml/min).

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 4 Peak exercise calf blood flow (ml/100 ml/min)

| Study or subgroup | Exercise N | Mean(SD) | Surgery N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Lundgren 1989 | 21 | 19.7 (5.5) | 23 | 22.4 (7.2) | | -2.70 [ -6.47, 1.07 ] |

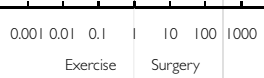

### Analysis 2.5. Comparison 2 Exercise regimen compared with surgery, Outcome 5 Amputation.

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 5 Amputation

| Study or subgroup | Exercise n/N | Surgery n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Gelin 2001 | 0/88 | 1/87 | | 0.33 [ 0.01, 7.98 ] |



### Analysis 2.6. Comparison 2 Exercise regimen compared with surgery, Outcome 6 Mortality.

Review: Exercise for intermittent claudication

Comparison: 2 Exercise regimen compared with surgery

Outcome: 6 Mortality

| Study or subgroup | Exercise n/N | Surgery n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Gelin 2001 | 5/88 | 5/87 | | 67.8 % | 0.99 [ 0.30, 3.29 ] |
| Lundgren 1989 | 0/21 | 2/23 | | 32.2 % | 0.22 [ 0.01, 4.30 ] |
| **Total (95% CI)** | **109** | **110** | | **100.0 %** | **0.74 [ 0.25, 2.17 ]** |

Total events: 5 (Exercise), 7 (Surgery)

Heterogeneity: $Chi^2$ = 0.87, df = 1 (P = 0.35); $I^2$ =0.0%

Test for overall effect: Z = 0.55 (P = 0.58)


### Analysis 3.1. Comparison 3 Exercise regimen compared with angioplasty, Outcome 1 Maximal walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 3 Exercise regimen compared with angioplasty

Outcome: 1 Maximal walking time (minutes)

| Study or subgroup | Exercise N | Mean(SD) | Angioplasty N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Creasy 1990 | 16 | 6.2 (2) | 20 | 2.9 (1.1) | | 3.30 [ 2.21, 4.39 ] |

### Analysis 3.2. Comparison 3 Exercise regimen compared with angioplasty, Outcome 2 Ankle brachial pressure index.

Review: Exercise for intermittent claudication

Comparison: 3 Exercise regimen compared with angioplasty

Outcome: 2 Ankle brachial pressure index

| Study or subgroup | Exercise N | Mean(SD) | Angioplasty N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Creasy 1990 | 16 | 0.7 (0.03) | 20 | 0.75 (0.13) | | 57.6 % | -0.05 [ -0.11, 0.01 ] |
| Hobbs 2006 | 7 | 0.7 (0.06) | 9 | 0.98 (0.08) | | 42.4 % | -0.28 [ -0.35, -0.21 ] |
| **Total (95% CI)** | **23** | | **29** | | | **100.0 %** | **-0.15 [ -0.19, -0.10 ]** |

Heterogeneity: Chi² = 24.87, df = 1 (P<0.00001); I² =96%

Test for overall effect: Z = 6.47 (P < 0.00001)

Test for subgroup differences: Not applicable


### Analysis 3.3. Comparison 3 Exercise regimen compared with angioplasty, Outcome 3 Pain free walking distance (m).

Review: Exercise for intermittent claudication

Comparison: 3 Exercise regimen compared with angioplasty

Outcome: 3 Pain free walking distance (m)

| Study or subgroup | Exercise N | Mean(SD) | Angioplasty N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Hobbs 2006 | 7 | 115.2 (93.2) | 9 | 658 (403.7) | | -542.80 [ -815.43, -270.17 ] |

### Analysis 3.4. Comparison 3 Exercise regimen compared with angioplasty, Outcome 4 Maximum walking distance (m).

Review: Exercise for intermittent claudication

Comparison: 3 Exercise regimen compared with angioplasty

Outcome: 4 Maximum walking distance (m)

| Study or subgroup | Exercise N | Mean(SD) | Angioplasty N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Hobbs 2006 | 7 | 254 (366.6) | 9 | 690.6 (364.7) | | -436.60 [ -797.88, -75.32 ] |


### Analysis 3.5. Comparison 3 Exercise regimen compared with angioplasty, Outcome 5 Mortality.

Review: Exercise for intermittent claudication

Comparison: 3 Exercise regimen compared with angioplasty

Outcome: 5 Mortality

| Study or subgroup | Exercise n/N | Angioplasty n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Creasy 1990 | 6/26 | 4/30 | | 1.73 [ 0.55, 5.47 ] |

### Analysis 4.1. Comparison 4 Exercise regimen compared with antiplatelet therapy, Outcome 1 Maximal walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 4 Exercise regimen compared with antiplatelet therapy

Outcome: 1 Maximal walking time (minutes)

| Study or subgroup | Exercise | | Antiplatelet therapy | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Mannarino 1991 | 10 | 4.51 (1.06) | 10 | 3.45 (1.01) | | 1.06 [ 0.15, 1.97 ] |

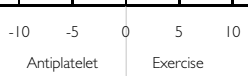

### Analysis 4.2. Comparison 4 Exercise regimen compared with antiplatelet therapy, Outcome 2 Ankle brachial pressure index.

Review: Exercise for intermittent claudication

Comparison: 4 Exercise regimen compared with antiplatelet therapy

Outcome: 2 Ankle brachial pressure index

| Study or subgroup | Exercise | | Antiplatelet therapy | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Mannarino 1991 | 10 | 0.68 (0.24) | 10 | 0.68 (0.27) | | 0.0 [ -0.22, 0.22 ] |



### Analysis 4.3. Comparison 4 Exercise regimen compared with antiplatelet therapy, Outcome 3 Peak exercise calf blood flow (ml/100 ml/min).

Review: Exercise for intermittent claudication

Comparison: 4 Exercise regimen compared with antiplatelet therapy

Outcome: 3 Peak exercise calf blood flow (ml/100 ml/min)

| Study or subgroup | Exercise N | Mean(SD) | Antiplatelet therapy N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Mannarino 1991 | 10 | 10.68 (0.34) | 10 | 8.5 (3.95) | | 2.18 [ -0.28, 4.64 ] |


### Analysis 5.1. Comparison 5 Exercise regimen compared with pentoxifylline therapy, Outcome 1 Maximal walking time (minutes).

Review: Exercise for intermittent claudication

Comparison: 5 Exercise regimen compared with pentoxifylline therapy

Outcome: 1 Maximal walking time (minutes)

| Study or subgroup | Exercise N | Mean(SD) | Pentoxifylline N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Ciuffetti 1994 | 15 | 3.15 (0.4) | 15 | 3.6 (0.08) | | -0.45 [ -0.66, -0.24 ] |

**Analysis 6.1. Comparison 6 Exercise regimen compared with iloprost therapy, Outcome 1 Pain free walking distance (m).**

Review: Exercise for intermittent claudication

Comparison: 6 Exercise regimen compared with iloprost therapy

Outcome: 1 Pain free walking distance (m)

| Study or subgroup | Exercise | | Iloprost | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Arosio 2001 | 12 | 344.5 (293.6) | 12 | 155.8 (87.4) | | 188.70 [ 15.38, 362.02 ] |

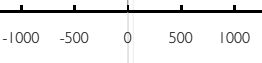

**Analysis 6.2. Comparison 6 Exercise regimen compared with iloprost therapy, Outcome 2 Maximum walking distance (m).**

Review: Exercise for intermittent claudication

Comparison: 6 Exercise regimen compared with iloprost therapy

Outcome: 2 Maximum walking distance (m)

| Study or subgroup | Exercise | | Iloprost | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Arosio 2001 | 12 | 598 (375.4) | 12 | 401.2 (324.1) | | 196.80 [ -83.80, 477.40 ] |



### Analysis 7.1. Comparison 7 Exercise regimen compared with pneumatic foot and calf compression, Outcome 1 Pain free walking distance.

Review: Exercise for intermittent claudication

Comparison: 7 Exercise regimen compared with pneumatic foot and calf compression

Outcome: 1 Pain free walking distance

| Study or subgroup | Exercise | | Pneumatic compression | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Kakkos 2005 | 12 | 92.9 (39.8) | 13 | 253.2 (510.8) | | -160.30 [ -438.88, 118.28 ] |


### Analysis 7.2. Comparison 7 Exercise regimen compared with pneumatic foot and calf compression, Outcome 2 Maximum walking distance.

Review: Exercise for intermittent claudication

Comparison: 7 Exercise regimen compared with pneumatic foot and calf compression

Outcome: 2 Maximum walking distance

| Study or subgroup | Exercise | | Pneumatic compression | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Kakkos 2005 | 12 | 417.1 (329.8) | 13 | 479 (500) | | -61.90 [ -391.59, 267.79 ] |

## ADDITIONAL TABLES

**Table 1. Functional status and Quality of life data (QoL)**

| Study | Measure reported | Effect reported | | |
|---|---|---|---|---|
| Collins | Walking impairment questionnaire (WIQ) - perceived distance and walking speed, Rand Short form 36 (SF-36) - perceived physical function | Exercise significant improvement in physical component summary score of SF-36 than usual care | | |
| Gardner | Peripheral arterial disease physical activity recall, Minnesota Leisure Time Physical Activity Questionnaire - daily physical activity, accelerometer measured free living daily activity, walking impairment questionnaire (WIQ), MOS SF-36 | No change in self-reported physical activity, or ambulation assessed by WIQ. Accelerometer measured free living daily activity increased in exercise group | | |
| Gelin | Health-related QoL, QoL overall | Exercise not superior to invasive therapy on any QoL, and superior to no treatment on only one dimension. Invasive therapy significantly greater improvements than training on aspects of physical functioning and walking related symptoms | | |
| Kakkos | Short-form 36 (SF 36), walking impairment questionnaire (WIQ), intermittent claudication questionnaire (ICQ) | Pneumatic compression improved ICQ score and speed score of WIQ signigicantly, exercise improved the WIQ claudication severity score significantly | | |
| Tisi | Nottingham Health Profile (NHP) | Exercise greater improvement in subjective health than angioplasty | | |
| Tsai | Self-reported ambulatory ability, perceived health-related quality of life, walking impairment questionnaire<br>physical function<br>bodily pain<br>role limitation physical and emotional | Perception of QoL increased significantly in the exercise group compared to usual care | | |

**Table 1. Functional status and Quality of life data (QoL)** (*Continued*)

| | | | | |
|---|---|---|---|---|
| | general health<br>mental health<br>social function<br>vitality | | | |

# APPENDICES

## Appendix 1. Search strategy for CENTRAL in *The Cochrane Library*

| |
|---|
| #1 MeSH descriptor Arterial Occlusive Diseases explode all trees |
| #2 MeSH descriptor Peripheral Vascular Diseases explode all trees |
| #3 peripheral near (vascular or arter*) or atherosclerosis or arteriosclerosis or PVD or PAOD or PAD |
| #4 arter* near occlus* |
| #5 obstruct* near arter* |
| #6 MeSH descriptor Intermittent Claudication explode all trees |
| #7 claudica* |
| #8 limb* near isch* |
| #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) |
| #10 MeSH descriptor Exercise explode all trees<br>#11 MeSH descriptor Exercise Therapy explode all trees<br>#12 walk* or runni* or exerc* or train* or treadmill<br>#13 activi*<br>#14 (#10 OR #11 OR #12 OR #13)<br>#15 (#9 AND #14) |

## WHAT'S NEW

Last assessed as up-to-date: 7 April 2008.

| Date | Event | Description |
|---|---|---|
| 18 June 2008 | New search has been performed | 12 new trials considered. Conclusions confirm the findings of the previous review |
| 29 April 2008 | New citation required but conclusions have not changed | Two new authors. |
| 8 April 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 1, 1998

| Date | Event | Description |
|---|---|---|
| 25 October 1999 | New citation required but conclusions have not changed | Substantive update |
| 17 June 1998 | New citation required and minor changes | After consultation with GCL, original November 1997 version substituted for June 1998 'update' as latter was an incorrect version. Some phrasing changed in June 1998, no changes to figures so earlier version more appropriate. Edited abstract added too, 24.2.99 |

## CONTRIBUTIONS OF AUTHORS

Lorna Watson: selected trials, assessed quality, extracted data and revised text of review.

Brian Ellis: selected trials, assessed quality and extracted data.

Gillian Leng checked the content of the updated review.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT


### Internal sources

- The University of Edinburgh, UK.

### External sources

- The Chief Scientist Office, Scottish Executive Health Directorates, The Scottish Government, UK.
- The British Heart Foundation, UK.


## INDEX TERMS

### Medical Subject Headings (MeSH)

Exercise Therapy [*methods]; Intermittent Claudication [*therapy]; Randomized Controlled Trials as Topic; Walking

### MeSH check words

Female; Humans; Male