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Pentoxifylline for intermittent claudication (Review)

Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA

Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA.
Pentoxifylline for intermittent claudication.
Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD005262.
DOI: 10.1002/14651858.CD005262.pub3.

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[Intervention Review]

Pentoxifylline for intermittent claudication

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Editorial group: Cochrane Vascular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2015.

Citation: Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD005262. DOI: 10.1002/14651858.CD005262.pub3.

ABSTRACT

Background

Intermittent claudication (IC) is a symptom of peripheral arterial disease (PAD) and is associated with high morbidity and mortality. Pentoxifylline, one of many drugs used to treat IC, acts by decreasing blood viscosity, improving erythrocyte flexibility and promoting microcirculatory flow and tissue oxygen concentration. Many studies have evaluated the efficacy of pentoxifylline in treating individuals with PAD, but results of these studies are variable. This is an update of a review first published in 2012.

Objectives

To determine the efficacy of pentoxifylline in improving the walking capacity (i.e. pain-free walking distance and total (absolute, maximum) walking distance) of individuals with stable intermittent claudication, Fontaine stage II.

Search methods

For this update, the Cochrane Vascular Group Trials Search Co-ordinator searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (2015, Issue 3).

Selection criteria

All double-blind, randomised controlled trials (RCTs) comparing pentoxifylline versus placebo or any other pharmacological intervention in patients with IC Fontaine stage II.

Data collection and analysis

Two review authors separately assessed included studies,. matched data and resolved disagreements by discussion. Review authors assessed the methodological quality of studies by using the Cochrane 'Risk of bias' tool and collected results related to pain-free walking distance (PFWD) and total walking distance (TWD). Comparison of studies was based on duration and dose of pentoxifylline.

Main results

We included in this review 24 studies with 3377 participants. Seventeen studies compared pentoxifylline versus placebo. In the seven remaining studies, pentoxifylline was compared with flunarizine (one study), aspirin (one study), Gingko biloba extract (one study), nylidrin hydrochloride (one study), prostaglandin E1 (two studies) and buflomedil and nifedipine (one study). The quality of the evidence was generally low, with large variability in reported findings.. Most included studies did not report on random sequence

generation and allocation concealment, did not provide adequate information to allow selective reporting to be judged and did not report blinding of assessors. Heterogeneity between included studies was considerable with regards to multiple variables, including duration of treatment, dose of pentoxifylline, baseline walking distance and participant characteristics; therefore, pooled analysis was not possible.

Of 17 studies comparing pentoxifylline with placebo, 14 reported TWD and 11 reported PFWD; the difference in percentage improvement in TWD for pentoxifylline over placebo ranged from 1.2% to 155.9%, and in PFWD from -33.8% to 73.9%. Testing the statistical significance of these results generally was not possible because data were insufficient. Most included studies suggested improvement in PFWD and TWD for pentoxifylline over placebo and other treatments, but the statistical and clinical significance of findings from individual trials is unclear. Pentoxifylline generally was well tolerated; the most commonly reported side effects consisted of gastrointestinal symptoms such as nausea.

Authors' conclusions

Given the generally poor quality of published studies and the large degree of heterogeneity evident in interventions and in results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain. Pentoxifylline was shown to be generally well tolerated.

Based on total available evidence, high-quality data are currently insufficient to reveal the benefits of pentoxifylline for intermittent claudication.

PLAIN LANGUAGE SUMMARY

Pentoxifylline for intermittent claudication

Background

Atherosclerosis, or hardening of the arteries, results in narrowing and blockage of the arteries and can reduce the blood supply to the legs, causing peripheral arterial disease. Intermittent claudication (IC) is a cramp-like pain felt in the leg muscles that is brought on by walking and is relieved by standing still or resting. Pentoxifylline is a drug that is used to relieve IC while improving people's walking capacity. It decreases blood viscosity and improves red blood cell flexibility, promoting microcirculatory blood flow and increasing oxygen in the tissues. This review looked at all available evidence from randomised controlled trials on the efficiency of pentoxifylline for treatment of IC.

Study characteristics and key results

This review included 24 studies with 3377 participants (current until April 2015). Seventeen studies compared pentoxifylline with placebo, and the remaining studies compared pentoxifylline with flunarizine (one study), aspirin (one study), Gingko biloba extract (one study), nylidrin hydrochloride (one study), prostaglandin E1 (two studies) and buflomedil and nifedipine (one study). Large differences between included studies in how investigators measured and reported study findings made it impossible to combine results.

Most of the included studies suggested mild to moderate improvement in pain-free walking distance and total walking distance for pentoxifylline over placebo (and other treatments, which included Gingko biloba, buflomedil, iloprost, nylidrin, aspirin and prostaglandin E1). The statistical significance of findings from individual trials was unclear, and researchers observed large variability between studies in the effects of pentoxifylline. The most commonly reported side effects were gastrointestinal symptoms, mainly nausea, and the drug was well tolerated.

Quality of the evidence

The quality of included studies was generally low, and very large variability between studies was noted in reported findings including duration of trials, doses of pentoxifylline and distances participants could walk at the start of trials. Most included studies did not report on randomisation techniques or how treatment allocation was concealed, did not provide adequate information to permit judgement of selective reporting and did not report blinding of outcome assessors. Given all these factors, the role of pentoxifylline in intermittent claudication remains uncertain, although this medication was generally well tolerated by participants.

BACKGROUND

Description of the condition

Intermittent claudication (IC) is a cramp-like pain felt in the leg muscles that is brought on by walking, is relieved by rest and is a result of reduced circulation (NICE 2012). Intermittent claudication is a common presentation of peripheral arterial disease (PAD) caused by atherosclerosis. From 2000 to 2010, the number of people living with PAD increased across all age groups by a mean of 23.51% (Fowkes 2013). These data include high-income countries, as well as low- and middle-income countries. Peripheral arterial disease is a progressive disease associated with significant morbidity and mortality. The main cause of mortality is associated cerebrovascular and coronary artery disease. Patients with IC have reduced quality of life and increased risks of stroke and myocardial infarction (NICE 2011).

Description of the intervention

Primary health care plays an important role in the treatment of individuals with intermittent claudication. First steps in treating IC include conservative risk factor control, exercise therapy and pharmacotherapy (Tendera 2011). Revascularisation intervention, in the form of open or endovascular surgery, is usually reserved for incapacitating disease (Bachoo 2010; Fowkes 1998). In one study, 63% of newly diagnosed claudicants were treated by general practitioners with lifestyle advice or drugs, or both; only 37% required referral to hospital specialists (Meijer 2002). Understanding treatment options and their effectiveness is vital for controlling the disease at an early stage and preventing its progression.

Different types of medications have been used for treatment of IC. Vasodilators and antiplatelets reduce the chance of blood clots at the blockage site (Wong 2011); other drugs help reduce the symptoms of claudication, improve walking distance and reduce disability associated with the condition (de Backer 2012; de Backer 2013; Robertson 2013).

How the intervention might work

Pentoxifylline is a vasoactive drug that has been authorised for the medical treatment of individuals with IC. Pentoxifylline decreases blood viscosity, improves erythrocyte flexibility and promotes microcirculatory flow, while increasing tissue oxygen concentration. It is a methylxanthine derivative that works by inhibiting the enzyme phosphodiesterase and by potentiating the effects of endogenous prostacyclin, a prostaglandin that possesses anti-aggregatory, fibrinolytic (decreased fibrinogen concentrations) and vasodilatory properties and increases cyclic adenosine monophosphate (cAMP) levels in red blood cells, platelets and arterial cell walls (Micromedex 2002).

Why it is important to do this review

Intermittent claudication is a marker of increased morbidity and mortality, and treating symptoms is becoming ever more important with the increased prevalence of PAD. Previous studies and reviews have evaluated the efficacy of pentoxifylline in the treatment of IC and peripheral vascular disease, compared with other treatment options including other pharmacological interventions and exercise, yielding variable results (Bedenis 2014; Lane 2014; Moher 2000; Stevens 2012). Continued evaluation of pentoxifylline through evidence-based systematic reviews will result in improved understanding of available pharmacological interventions for IC.

Recently, the National Institute for Health and Care Excellence (NICE) recommended naftidrofuryl oxalate as the leading pharmacological treatment for IC on studies of effectiveness and costs (NICE 2011; NICE 2012). In this review, we will not address cost-effectiveness.

OBJECTIVES

To determine the efficacy of pentoxifylline in improving the walking capacity (i.e. pain-free walking distance and total (absolute, maximum) walking distance) of individuals with stable intermittent claudication, Fontaine stage II (Fontaine 1954).

METHODS

Criteria for considering studies for this review

Types of studies

We included all double-blind, randomised controlled trials of pentoxifylline versus placebo or versus other pharmacological interventions. We excluded comparisons with diet, exercise or surgery. We excluded single-blind and open studies.

Types of participants

We included patients with symptoms of stable IC (no change in symptoms for six months), Fontaine stage II (Fontaine 1954), due to peripheral vascular disease. We excluded those with symptoms of critical ischaemia (rest pain, skin ulcers or gangrene) or who had undergone previous surgical or percutaneous catheter interventions.

Types of interventions

We included studies that compared pentoxifylline versus placebo or some other pharmacological intervention and lasted at least four weeks. We excluded comparisons with surgery, angioplasty or exercise. We included all doses and routes of administration of pentoxifylline.

Types of outcome measures

Primary outcomes

Walking capacity is one of the most important outcome measures used to assess intermittent claudication.

According to Moher 2000, walking capacity can be assessed by

- pain-free walking distance (PFWD) or initial claudication distance (ICD), which is the distance walked on a treadmill before the onset of pain; and
- total walking distance (TWD) or absolute claudication distance (ACD), which is the maximum or absolute distance walked on a treadmill.

Secondary outcomes

- Ankle-brachial pressure index (ABI).
- Quality of life, as measured by questionnaires.
- Side effects.

In this review, we excluded outcome measures such as blood viscosity and microcirculation.

Search methods for identification of studies

We applied no language restrictions in our searches, and we sought translation of non-English trials.

Electronic searches

For this update, the Cochrane Vascular Group Trials Search Coordinator (TSC) searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (CRS) (http://www.metaxis.com/CRSWeb/Index.asp) (2015, Issue 3), which is part of the *Cochrane Library* (www.cochranelibrary.com). See Appendix 1 for details of the search strategy used in searching the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular Group module in the *Cochrane Library* (www.cochranelibrary.com).

Searching other resources

We reviewed the reference lists of all relevant, identified studies.

Data collection and analysis

Selection of studies

Two review authors (KS and RF) used the eligibility criteria provided above to independently assess all potentially relevant articles identified by the search strategy described. We resolved differences by consensus.

Data extraction and management

KS and RF collected information from each included trial. Information collected included trial design, participant characteristics, inclusion and exclusion criteria, interventions and controls used, treatment periods, methods of assessment and PFWD and TWD results. We also collected data on the secondary outcomes of ankle-brachial pressure index (ABI), quality of life and side effects.

Assessment of risk of bias in included studies

For the update of this review, two review authors (RF and KS) assessed the quality of included studies using the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011); we assessed allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. We assigned a score of high risk, unclear risk or low risk of bias, according to Higgins 2011.

Measures of treatment effect

We planned to pool the data on pain-free walking distance (PFWD) and absolute (total) walking distance (TWD) from each trial to arrive at an overall estimate of the effectiveness of pharmacological interventions. We planned to calculate the percentage change in walking distance before and after the interventions. When possible, we planned to calculate the mean difference between pentoxifylline and control groups.

Unit of analysis issues

For all included studies, the unit of randomisation was the individual participant.

Dealing with missing data

When data were not available or were missing, we contacted study authors to request missing data.

Assessment of heterogeneity

We planned to perform all analyses on an intention-to-treat basis. We planned to evaluate outcome data for appropriateness for the meta-analysis on the basis of heterogeneity by using the Chi^2 test and the I^2 statistic, both of which describe the percentage of variability in estimates of effect that is due to heterogeneity rather than to chance. If the I^2 value was greater than 50%, we planned to evaluate data for heterogeneity. We planned to use a random-effects model for meta-analyses if no reason was found for heterogeneity. We planned to use a fixed-effect model if the I^2 value was lower than 50%.

Assessment of reporting biases

We planned to assess reporting bias by using funnel plots if more than 10 studies were included in the meta-analysis.

Data synthesis

We intended to perform a pooled, fixed-effect model meta-analysis of included trials with subgroup analyses using variables such as duration of treatment and dose and route of administration. However, in the light of clinical heterogeneity, we judged that a pooled meta-analysis was not appropriate.

Subgroup analysis and investigation of heterogeneity

We anticipated that trials would not be homogeneous. Therefore, we planned to perform a subgroup analysis of included trials using variables such as duration of treatment and dose and route of administration.

Sensitivity analysis

We planned to perform sensitivity analyses to evaluate the effects on meta-analysis of studies of low quality due to risk of bias, as well as studies with unclear inclusion criteria or methods.

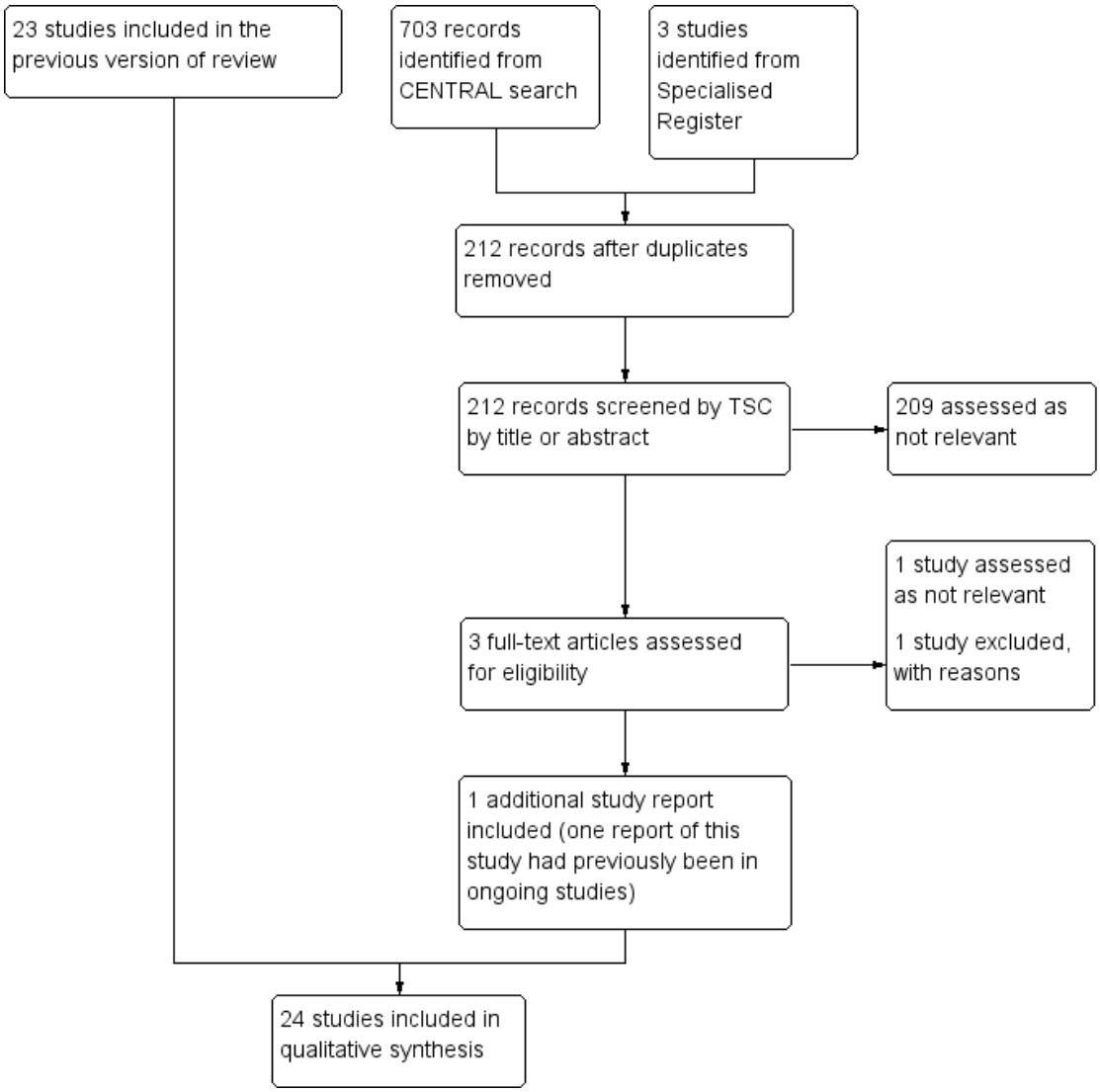
RESULTS

Description of studies

Results of the search

See Figure 1 for details of the search results. For this update of the review, we identified three additional reports of studies. One study was considered to be not relevant, another was excluded (Singh 2009) and the third consisted of an abstract that correlated with a study previously listed in 'Ongoing Studies' (Schellong 2012), from which data are now available. This review update identified 24 included studies and 39 excluded studies. It should be noted that several excluded studies from the previous version of the review have been removed, as they are now considered not relevant.

Figure 1. Study flow diagram.



Included studies

For details of included studies, see Characteristics of included studies.

We included a total of 24 studies with 3377 participants. Fourteen studies compared pentoxifylline versus placebo alone (Belcaro 2002; Bollinger 1977; Cesarone 2002b; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983; Donaldson 1984; Ernst 1992; Gallus 1985; Kiesewetter 1988; Lindgarde 1989; Porter 1982a; Porter 1982b; Volker 1978), one versus flunarizine (Perhoniemi 1984), one versus aspirin (Ciocon 1997), one versus Gingko biloba extract (GBE) (Bohmer 1988), one versus nylidrin hydrochloride (Accetto 1982) and two versus prostaglandin E1 (PGE1) (Hepp 1992; Schellong 2012). Two studies compared pentoxifylline versus placebo and cilostazol (Dawson 2000; Lee 2001), one compared pentoxifylline versus placebo and iloprost (Creager 2008) and one compared pentoxifylline versus buflomedil and nifedipine (Chacon-Quevedo 1994).

The treadmill protocol for assessment of PFWD and TWD varied between studies. The treadmill speed most commonly used in included studies was 3 km/h, with gradients ranging from 0% (Accetto 1982) to 5% (Bohmer 1988), 10% (Chacon-Quevedo

1994) and 12% (Belcaro 2002; Cesarone 2002b; De Sanctis 2002a; De Sanctis 2002b; Schellong 2012). Other studies used a treadmill speed of 3.2 km/h - three with a gradient of 12.5% (Bollinger 1977; Lee 2001; Lindgarde 1989) and two starting at a 0% gradient and gradually increasing the inclination during testing (Creager 2008; Dawson 2000). One study used a treadmill speed of 3.6 km/h at 0% gradient (Perhoniemi 1984), and two used a treadmill speed of 4 km/h - one at a 0% gradient (Donaldson 1984) and the other at a 10% gradient (Gallus 1985). Three studies used different units of speed; Di Perri 1983 used a walking test of 120 steps per minute on a horizontal treadmill, and Porter 1982a and Porter 1982b used a speed of 1.5 mph - both at a 7% gradient. Four studies did not provide information on the treadmill protocol used (Ernst 1992; Hepp 1992; Kiesewetter 1988; Volker 1978).

Two studies reported use of an exercise programme (Bollinger 1977; Ernst 1992). Remaining studies did not report use of an exercise programme, or reported that no specific instructions were given to participants.

Excluded studies

We excluded 39 studies because they did not meet the inclusion criteria. See the Characteristics of excluded studies table for reasons for exclusion. In brief, 18 studies were not double-blinded (Bieron 2005; Dawson 1999; Dettori 1989; Hepp 1996; Milio 2003; Milio 2006; Panchenko 1997; Pignoli 1985; Regenthal 1991; Reilly 1987; Rodin 1998; Rodin 1998a; Scheffler 1991; Scheffler 1994; Shustov 1997; Singh 2009; Strano 2002; Triebe 1992), two included participants with critical limb ischaemia (Schubotz 1976; Thomson 1990), four included participants with Fontaine stage III and did not present results separately for the different Fontaine stages (Kellner 1976; Roekaerts 1984; Strano 1984; Tonak 1977), four were short-term studies (Farkas 1993; Rudofsky 1987; Rudofsky 1988; Rudofsky 1989), 10 described non-relevant outcomes (Ciuffetti 1991; Ehrly 1986; Ehrly 1987; Fossat 1995; Guest 2005; Incandela 2002; Luk'Janov 1995; Poggesi 1985; Tsang 1994; Wang 2003) and one used variable doses of pentoxifylline (Horowitz 1982).

Risk of bias in included studies

Risk of bias in included studies is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

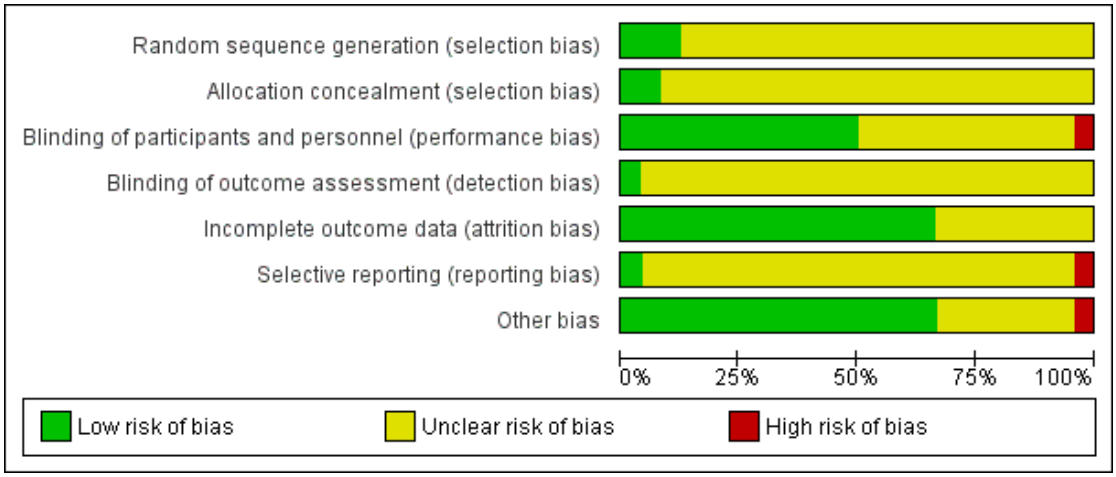
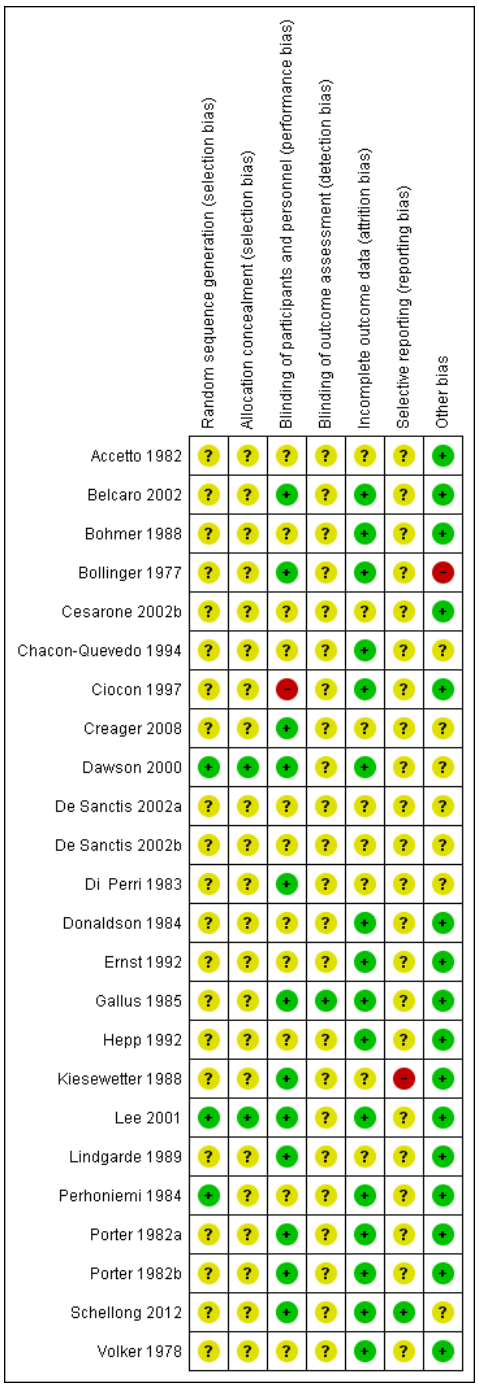


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Selection bias was deemed to involve low risk in only two studies (Dawson 2000; Lee 2001). Another study (Perhoniemi 1984) indicated low risk of bias for random sequence generation. For all other studies, available information was insufficient to permit judgement of low or high risk of bias.

Blinding

Blinding of participants and personnel was achieved in 12 studies (Belcaro 2002; Bollinger 1977; Creager 2008; Dawson 2000; Di Perri 1983; Gallus 1985; Kiesewetter 1988; Lee 2001; Lindgarde 1989; Porter 1982a; Porter 1982b; Schellong 2012), which therefore were classed as having low risk of bias. Eleven studies were classed as having unclear risk of bias (Accetto 1982; Bohmer 1988; Cesarone 2002b; Chacon-Quevedo 1994; De Sanctis 2002a; De Sanctis 2002b; Donaldson 1984; Ernst 1992; Hepp 1992; Perhoniemi 1984; Volker 1978), mainly because of insufficient reporting, and one study (Ciocon 1997) was deemed to be at high risk of bias because different treatment regimens were provided for the study medication.

For all but one study (Gallus 1985), risk of bias for blinding of outcome assessment (detection bias) was classed as unclear because of insufficient reporting. For the study by Gallus 1985, blinding of outcome assessment was deemed to present low risk of bias because study authors reported that results were withheld from investigators during the study.

Incomplete outcome data

For most included studies, no evidence suggested incomplete outcome data (Belcaro 2002; Bohmer 1988; Bollinger 1977; Chacon-Quevedo 1994; Ciocon 1997; Dawson 2000; Donaldson 1984; Ernst 1992; Gallus 1985; Hepp 1992; Lee 2001; Perhoniemi 1984; Porter 1982a; Porter 1982b; Schellong 2012; Volker 1978), or information was insufficient to indicate whether outcome data were missing (Accetto 1982; Cesarone 2002b; Creager 2008; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983; Kiesewetter 1988; Lindgarde 1989).

Selective reporting

For all included studies except Kiesewetter 1988 and Schellong 2012, available information, such as a study protocol, was insufficient to permit judgement of selective reporting. Kiesewetter 1988 was judged at high risk of bias because TWD results were reported in the abstract but were not mentioned in the remainder of the paper, either as an outcome variable or as a result. Schellong 2012 was judged to have low risk, as all outcomes described in the ClinicalTrials.gov protocol were reported.

Other potential sources of bias

Most studies were deemed free of other bias (Accetto 1982; Belcaro 2002; Bohmer 1988; Cesarone 2002b; Ciocon 1997; Donaldson 1984; Ernst 1992; Gallus 1985; Hepp 1992; Kiesewetter 1988; Lee 2001; Lindgarde 1989; Perhoniemi 1984; Porter 1982a; Porter 1982b; Volker 1978). All other studies (Chacon-Quevedo 1994; Creager 2008; Dawson 2000; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983; Schellong 2012) were determined to have unclear risk of bias for a variety of reasons, such as unclear reporting (Chacon-Quevedo 1994; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983) or sponsoring of the study by a pharmaceutical company (Creager 2008; Dawson 2000; Schellong 2012). One study was assigned high risk of bias because of differences in clinical baseline data between study groups (Bollinger 1977).

Effects of interventions

Pentoxifylline versus placebo

A total of 17 studies compared pentoxifylline versus placebo (Belcaro 2002; Bollinger 1977; Cesarone 2002b; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983; Donaldson 1984; Ernst 1992; Gallus 1985; Kiesewetter 1988; Lindgarde 1989; Porter 1982a; Porter 1982b; Volker 1978). Two of these studies also compared pentoxifylline versus cilostazol (Dawson 2000; Lee 2001), and one compared pentoxifylline with iloprost (Creager 2008).

Pain-free walking distance (PFWD)

A total of 11 studies (Cesarone 2002b; Creager 2008; Dawson 2000; Donaldson 1984; Ernst 1992; Gallus 1985; Kiesewetter 1988; Lindgarde 1989; Porter 1982a; Porter 1982b; Volker 1978) that compared pentoxifylline with placebo measured PFWD. The duration of these studies varied from four to 40 weeks. Most studies used a pentoxifylline dose of 1200 mg per day. We analysed studies according to duration and dose levels. See Table 1 for details on PFWD by study. Results for PFWD are reported as percentage improvement in mean PFWD during treatment for both pentoxifylline and placebo groups. To formally compare improvement in PFWD between groups, data on both mean improvement and standard deviation of mean improvement were required. Of the 11 included studies, only one (Lindgarde 1989) presented data on standard deviation of the percentage change in PFWD; therefore, statistical analysis was performed only for this study. A pooled analysis was not conducted because data were lacking levels of heterogeneity between included studies were high with regards to multiple variables, including duration of treatment, dose of pentoxifylline, baseline walking distance and participant characteristics.

Four weeks

At four weeks, Volker 1978 was the study of shortest duration; investigators included 50 participants (25 in each arm) and gave a dose of 1200 mg pentoxifylline. Baseline PFWD was 331 m for the pentoxifylline group compared with 230 m for the placebo group. At the end of the study, mean PFWD for participants who received pentoxifylline improved by 40.3% compared with 26.0% for those given placebo, for a difference of 14.3% in favour of pentoxifylline.

Eight weeks

Three studies had a duration of eight weeks (Donaldson 1984; Gallus 1985; Kiesewetter 1988). One study (Donaldson 1984) used 600 mg of pentoxifylline, and the other two used 1200 mg. Gallus 1985 was a cross-over study consisting of two periods of eight weeks.

Donaldson 1984 included 40 participants in each group. The increase in mean PFWD in the pentoxifylline group, from 108.2 m to 119.3 m (10.3%), was 22.6% less than in the placebo group, from 97.1 m to 129 m (32.9%).

Gallus 1985 performed a cross-over study. Fifty participants were recruited, but only 38 finished the study and were included in the analysis (19 participants in each group). Study authors reported no statistically significant improvement in PFWD for pentoxifylline compared with placebo but did not present the results of significance tests. In the first phase of the study (eight weeks), PFWD in the pentoxifylline group improved by 7.7% more than in the placebo group (76.0% vs 68.3%). After the second portion of the study, participants treated with pentoxifylline in phase 1 and placebo in phase 2 showed a decrease of 9.4% in PFWD after cross-over. Those treated with placebo in phase 1 and pentoxifylline in phase 2 improved by 10.4% after cross-over.

Kiesewetter 1988 compared 1200 mg of pentoxifylline versus placebo over eight weeks in a study with 40 participants. Results showed that PFWD in the pentoxifylline group improved by 44 m (43.6%) compared with 3 m (3.1%) in the placebo group. Authors of this paper did not present data on baseline walking distance for the two groups.

Twelve weeks

One study, which lasted 12 weeks (Ernst 1992), used 1200 mg pentoxifylline daily and included 40 participants (20 in each arm). Both groups of participants exercised regularly for one hour twice a week. Study authors stated that both groups showed significant improvement in walking distance, although they did not present the results of statistical tests. The pentoxifylline group improved by 152.8% (144 m to 364 m) and the placebo group by 186.6% (134 m to 384 m), for a difference of 33.8% in favour of placebo.

Twenty-four weeks

All studies with a duration of 24 to 26 weeks (six months) used 1200 mg of pentoxifylline (Creager 2008; Dawson 2000; Lindgarde 1989; Porter 1982a; Porter 1982b).

In a large multi-centre study, Creager 2008 compared pentoxifylline versus placebo (and vs various doses of iloprost) over six months. In this study, 430 participants were randomly assigned to five groups: iloprost 50 µg (87 participants), iloprost 100 µg (86 participants), iloprost 150 µg (87 participants), pentoxifylline 1200 mg (86 participants) and placebo (84 participants). Only 214 participants (50%) completed the entire six months of the study. Three hundred seventy participants were included in what was called an intention-to-treat analysis on the basis that they had received at least one dose of the study drug and had undergone at least one follow-up test, that is, within two to four weeks. Walking distance in the pentoxifylline group improved by 34.3% from a baseline PFWD of 118 m compared with a 21.2% improvement in the placebo group from a baseline PFWD of 120 m. Overall, pentoxifylline improved PFWD by 13.1% more than placebo, but this difference could not be analysed statistically because data were insufficient. Study authors reported that after one month, the difference between groups was statistically significant, but P values for significance results were not provided.

Dawson 2000 included 232 participants in the pentoxifylline group and 239 in the placebo group. The pentoxifylline group improved by 12.8% more than the placebo group (60.3% vs 47.5%).

Lindgarde 1989 included 76 participants in the pentoxifylline group and 74 in the placebo group. Results showed a net improvement for pentoxifylline of 20% (95% confidence interval (CI) 16.3 to 23.7) over placebo (80% vs 60%). This improvement was statistically significant (P value < 0.0001).

Porter 1982a was a relatively large study with no intention-to-treat analysis. Gillings 1987 performed an intention-to-treat analysis on data from the Porter 1982a study. Initially, Porter 1982a double-blinded 128 participants (including one who was randomly assigned twice) but included only 82 participants in the analysis (pentoxifylline 42, placebo 40); remaining participants were withdrawn from the study because of side effects and loss to follow-up. In the initial analysis, PFWD distance improved in the pentoxifylline group from 111 m to 195 m (75.7%) and in the placebo group from 117 m to 180 m (53.8%), yielding a statistically significant difference of 21.9% (P value = 0.18) in favour of pentoxifylline. Gillings 1987 included 124 participants who had follow-up data (63 in the pentoxifylline group and 61 in the placebo group). In this intention-to-treat analysis, PFWD improved in the pentoxifylline group by 47% and in the placebo group by 26% (difference of 21% in favour of pentoxifylline). The authors of this paper did not present data on end-of-trial PFWD.

Another, smaller study by Porter et al. (Porter 1982b) consisted of 22 participants (11 in each arm). In this study, PFWD in the pentoxifylline group improved by 73.9% more than in the placebo group (108.8% vs 34.9%, respectively).

Forty weeks

Cesarone 2002 used 1600 mg of pentoxifylline daily for 40 weeks. The pentoxifylline group consisted of 88 participants, and the placebo group 90 participants. Total PFWD in the pentoxifylline group improved from 43 m to 166 m (286%), and in the placebo group from 42 m to 155 m (269%), for a small difference of 17% in favour of pentoxifylline.

Total walking distance (TWD)

A total of 14 studies comparing pentoxifylline with placebo (Belcaro 2002; Bollinger 1977; Cesarone 2002b; Creager 2008; Dawson 2000; De Sanctis 2002a; De Sanctis 2002b; Di Perri 1983; Ernst 1992; Gallus 1985; Lee 2001; Lindgarde 1989; Porter 1982a; Porter 1982b) assessed TWD. The duration of these studies ranged from eight weeks to 52 weeks. See Table 2 for details on TWD by study. As was done for PFWD, TWD was reported as percentage change in mean TWD from baseline to end of study for pentoxifylline and placebo groups separately, and as the difference in percentage change between groups. Again, data on mean change in TWD and standard deviation of the change were required to compare improvement in TWD between groups. In all 14 included studies, trial authors failed to report the standard deviation of the percentage change in mean TWD, so a statistical analysis could not be performed. Meta-analysis of TWD results for pentoxifylline compared with placebo was not performed for reasons similar to those described for PFWD results.

Eight weeks

Four studies had a duration of eight weeks. One study used 600 mg (Bollinger 1977), one 800 mg (Lee 2001) and two 1200 mg pentoxifylline (Di Perri 1983; Gallus 1985).

In Bollinger 1977, the sample size was 19 participants (10 pentoxifylline and nine placebo) with a dose of 600 mg of pentoxifylline. The quality of the study was poor; initially 26 participants were included, but results for only 19 were included in the analysis. No intention-to-treat analysis was performed. The two groups varied in terms of duration of claudication and extent of disease. Participants in the pentoxifylline group had more unilateral disease, and more bilateral and extensive disease was noted in the placebo group. All participants in this study were advised to stop smoking and to walk daily for at least one hour. Investigators reported improvement with pentoxifylline over placebo of 155.9% (208.4% vs 52.5%).

Lee and colleagues published two reports on the same study (Lee 2001; Lee 2001a). Only a very slight difference was apparent between reports in that the sample size was larger by two participants in the later report (17 in the pentoxifylline group, 16 in the placebo group and 17 in the cilostazol group). Results from Lee 2001 are included in both reports. TWD improved in the pentoxifylline group from 114 m to 147 m (28.9%) compared with 116 m to 121 m (4.3%) in the placebo group, for an overall difference of 24.6% in favour of pentoxifylline.

Di Perri 1983 examined 1200 mg of pentoxifylline in 24 participants using a cross-over design (12 participants in each group over two periods of eight weeks). A 61% increase in TWD was described for the pentoxifylline group compared with 3.5% for the placebo group after the first period. This was confirmed after the cross-over, when the pentoxifylline group again increased by 61% compared with an increase of 1.9% in the placebo group.

In Gallus 1985, also a cross-over study, TWD showed a pattern similar to PFWD. After the first phase of the study, TWD improved by 33.3% in the pentoxifylline group compared with 13.5% in the placebo group (difference of 19.8% in favour of pentoxifylline). After the cross-over phase, participants who were treated with pentoxifylline in phase 1 and placebo in phase 2 improved by just 1.88% over those treated with placebo before pentoxifylline.

Twelve weeks

One study reported findings at 12 weeks (Ernst 1992). Both groups of participants also received regular exercise, for one hour twice a week. TWD in the pentoxifylline group (1200 mg daily) improved from 166 m to 504 m (203.6%) compared with improvement in the placebo group from 151 m to 420 m (178.1%), yielding a difference of 25.5% in favour of pentoxifylline.

Twenty-four to twenty-six weeks

Six studies (Belcaro 2002; Creager 2008; Dawson 2000; Lindgarde 1989; Porter 1982a; Porter 1982b) had a duration of 24 to 26 weeks (six months). Apart from Belcaro 2002, which used a dose of 1600 mg, and Creager 2008, which used 400 mg, studies used 1200 mg of pentoxifylline.

Belcaro 2002 compared 1600 mg daily of pentoxifylline versus placebo. TWD improved in the pentoxifylline group from 56 m to 161 m (187.5%), and TWD in the placebo group improved from 59 m to 103 m (74.6%), showing a difference of 112.9% in favour of pentoxifylline.

Creager 2008 presented baseline TWD and percentage improvement rather than TWD at the end of the study. The pentoxifylline versus placebo result showed significant improvement for pentoxifylline of 13.9% (from baseline TWD of 316 ± 191 m) compared with placebo, which resulted in improvement of only 3.3% (from baseline TWD of 292 ± 161 m), for a difference of 10.6% in favour of pentoxifylline.

Dawson 2000 did not show significant improvement in TWD for pentoxifylline over placebo (29.4% vs 28.2%).

In Lindgarde 1989, TWD improved by 50% in the pentoxifylline group compared with 29% in the placebo group, for a difference of 21% in favour of pentoxifylline. Data on TWD at the end of the study were not presented, and improvement in TWD between groups could not be analysed statistically.

In the original analysis of Porter 1982a, TWD improved from 172 m to 268 m (55.8%) in the pentoxifylline group and from 181 m to 250 m (38.1%) in the placebo group, for a net difference of 17.7% in favour of pentoxifylline. In Gillings 1987 (the intention-to-treat analysis of the Porter 1982a study) and Reich 1984 (a publication based on the Porter 1982a study), TWD in the pentoxifylline group improved by 32% compared with 20% in the placebo group (difference of 12% in favour of pentoxifylline). Data on TWD at the end of this study were not presented.

In Porter 1982b, the net improvement in TWD observed in the pentoxifylline group over the placebo group was 66.5% (P value = 0.002). TWD in the pentoxifylline group improved by 69.4% compared with just 2.9% in the placebo group.

Forty weeks

Investigators in one study with a duration of 40 weeks gave 1600 mg of pentoxifylline daily (Cesarone 2002b). This study included 88 participants in the pentoxifylline group and 90 in the placebo group. Very large improvement in TWD of 229.9% was seen in the pentoxifylline group (from 87 ± 11 m to 287 ± 340 m) compared with 83.7% (from 98 ± 14 m to 180 ± 120 m) in the placebo group, for a net difference of 146.2%.

Fifty-two weeks

Two studies were reported by De Sanctis in 2002 (De Sanctis 2002a; De Sanctis 2002b). The former study looked at participants with a baseline TWD between 50 m and 200 m, and the latter study examined participants with a greater baseline TWD (> 500 m). Investigators in both studies administered 1800 mg of pentoxifylline daily.

In De Sanctis 2002a, each group consisted of 60 participants initially, but only 56 of those in the pentoxifylline group and 45 in the placebo group completed the study. In this study, baseline walking distance was short, and the effect of pentoxifylline was more prominent. The pentoxifylline group improved by 304.5% (66 ± 13 m to 267± 38 m), and the placebo group by 180.6% (67 ± 11 m to 188 ± 19 m), for a net difference of 123.9% in favour of pentoxifylline.

De Sanctis 2002b included 98 participants in the pentoxifylline group (75 of whom completed the study) and 96 in the placebo group (60 of whom completed the study). Significant improvement in TWD from baseline was reported in both groups, and the pentoxifylline group improved by 39.1% more than the placebo group. In the pentoxifylline group, TWD increased by 70.2% (554 ± 66 m to 943 ± 78 m) versus 31.1% (576 ± 71 m to 755 ± 67 m) in the placebo group.

Ankle-brachial pressure index (ABI)

Five studies comparing pentoxifylline versus placebo (Bollinger 1977; Dawson 2000; Donaldson 1984; Gallus 1985; Lee 2001) measured ABI. Three of these looked only at pre-exercise or resting ABI (Bollinger 1977; Dawson 2000; Lee 2001), and two looked at both pre-exercise and post-exercise ABI (Donaldson 1984; Gallus 1985). Authors of all five studies presented mean ABI at baseline and at end of treatment for both pentoxifylline and placebo groups. However, as the standard deviation for the change in ABI was not presented in any of the studies, statistical analysis could not be conducted to compare improvement in ABI. Furthermore, none of the five studies reported results of their own statistical tests. ABI results were not amenable to meta-analysis because of lack of data, differences in ABI measurements and differences in pentoxifylline doses and study duration.

In Bollinger 1977, pre-exercise ABI improved from 0.57 to 0.64 in the pentoxifylline group, and in the placebo group it dropped from 0.62 to 0.59 on the basis of measurements from the posterior tibial artery. Trialists stated that although a tendency toward better results was evident in the pentoxifylline group, results were not statistically significant.

Dawson 2000 reported that ABI increased in the pentoxifylline group from 0.66 ± 0.21 at baseline to 0.71 ± 0.24 at 24 weeks. In the placebo group, ABI did not improve (0.68 ± 0.42 at baseline, 0.67 ± 0.19 at 24 weeks). Study authors reported that improvement in ABI in the pentoxifylline group was not significantly different from that in the placebo group but did not present the level of significance.

In Lee 2001, mean pre-exercise ABI improved in the pentoxifylline group from 0.66 ± 0.13 to 0.7 ± 0.14, and in the placebo group from 0.69 ± 0.12 to 0.71 ± 0.13. Study authors reported no significant changes in ABI across all groups (including cilostazol).

In Donaldson 1984, no difference in ABI was reported in the pentoxifylline group nor in the placebo group before and after exercise. In the pentoxifylline group, pre-exercise ABI remained the same at 0.52 ± 0.26 before and after treatment. Post-exercise ABI dropped from 0.3 ± 0.27 before treatment to 0.27 ± 0.25 after treatment. In the placebo group, pre-exercise ABI improved from 0.52 ± 0.25 to 0.57 ± 0.24, and in the treatment group from 0.32 ± 0.26 to 0.34 ± 0.30. Study authors stated that none of these results were statistically significant (P values not presented).

Gallus 1985 reported no differences in the pentoxifylline group nor in the placebo group before and after exercise at the end of a cross-over study. In the pentoxifylline group, pre-exercise ABI improved from 0.59 ± 0.14 before treatment to 0.61 ± 0.16 after treatment; and post-exercise ABI dropped from 0.13 (range 0.03 to 0.60) before treatment to 0.10 (range 0.02 to 0.55) after treatment. In the placebo group, pre-exercise ABI remained similar at 0.59 ± 0.14 before and 0.59 ± 0.16 after treatment. Post-exercise ABI increased slightly, from 0.13 (range 0.03 to 0.60) before treatment to 0.14 (range 0.03 to 0.63) after treatment. None of these results were reported as statistically significant, and the level of significance used was not reported in the paper.

Quality of life

Three studies comparing pentoxifylline versus placebo reported on quality of life (Creager 2008; Dawson 2000; Volker 1978).
Both Dawson 2000 and Creager 2008 reported no differences between treatment groups in Short Form 36 (SF36) scores. Scores on the walking impairment questionnaire (WIQ) - a measure of degree of handicap caused by the disease - were similar between pentoxifylline and placebo groups in the Dawson 2000 study.
Creager 2008 reported that stair climbing was the only domain of the WIQ questionnaire that significantly improved when the pentoxifylline group and the placebo group were compared (9% increase in score; P value = 0.04).
Volker 1978 reported that in the pentoxifylline group, 18 participants reported improvement and seven reported no improvement. Six participants in the placebo group showed improvement, 18 showed no improvement and one showed a decline. Differences between treatment groups were statistically significant (P value < 0.01).

Side effects

Nine studies comparing pentoxifylline versus placebo reported on side effects (Belcaro 2002; Cesarone 2002b; Creager 2008; Dawson 2000; De Sanctis 2002b; Lee 2001; Porter 1982a; Porter 1982b; Volker 1978).
Belcaro 2002, Cesarone 2002b, De Sanctis 2002b and Lee 2001 reported that no side effects or serious side effects were observed.
Creager 2008 reported that the most common adverse events observed in the pentoxifylline group were headache at 19%, pain in extremity at 14% and dyspepsia at 13%, compared with 16%, 7% and 5%, respectively, in the placebo group. The frequency of premature discontinuation of pentoxifylline was similar to that of placebo. Serious adverse events were reported in 14% of the pentoxifylline group compared with 17% of the placebo group.
Dawson 2000 reported that the withdrawal rate from placebo was 16% (38/239) compared with 26% (60/232) from pentoxifylline. Most of the commonly reported side effects, such as headache and diarrhoea, were similar between pentoxifylline and placebo groups, except for pharyngitis, which was reported by 14% in the pentoxifylline group and 7% in the placebo group.
Porter 1982a reported that 55% (37/67) of participants in the pentoxifylline group and 39% (24/61) of those in the placebo group reported side effects. Side effects reported were mainly gastrointestinal complaints; the most commonly reported complaint was nausea.
Porter 1982b reported that no participants discontinued as a result of drug-related side effects, which were minimal in the two treatment groups. According to trialists, the only statistically significant (P value not presented) side effect was nausea, which was reported by seven pentoxifylline participants.
Volker 1978 reported similar numbers of side effects in the two treatment groups. In the pentoxifylline group (25 participants), two participants reported headaches, two dizziness, two stomach pains and two itching, and in the placebo group (25 participants), two participants reported headaches, two dizziness and three stomach pains.

Pentoxifylline versus flunarizine

Perhoniemi 1984 compared 1200 mg of pentoxifylline daily versus 15 mg of flunarizine daily over six months (three-month crossover design). Seventeen participants started on flunarizine, and 14 started on pentoxifylline.

Pain-free walking distance

In Perhoniemi 1984, PFWD increased for both pentoxifylline and flunarizine groups (P value < 0.01) when compared with baseline, but no statistically significant difference was found between pentoxifylline and flunarizine groups (Table 3).

Total walking distance

In Perhoniemi 1984, statistically significant improvement in TWD was noted in both groups (43% for pentoxifylline and 18% for flunarizine), but no statistically significant differences were observed between groups (Table 4).

Ankle-brachial pressure index

No difference in ABI was found by Perhoniemi 1984 between baseline measurements (0.63 ± 0.20) and measurements after treatment (pentoxifylline 0.63 ± 0.19; flunarizine 0.62 ± 0.20), nor between treatment groups.

Quality of life

Perhoniemi 1984 did not measure quality of life.

Side effects

In Perhoniemi 1984, 32 participants reported side effects (tiredness, diarrhoea, gastrointestinal symptoms, sweating, itching and allergic reactions), but no statistically significant differences were noted between flunarizine and pentoxifylline groups. One participant in the pentoxifylline group discontinued the study because of gastrointestinal symptoms.

Pentoxifylline versus aspirin

Ciocon 1997 compared 325 mg of aspirin versus 1200 mg of pentoxifylline over six weeks. Each group included 45 participants.

Pain-free walking distance

Ciocon 1997 did not measure PFWD.

Total walking distance

Baseline TWD was one mile for the pentoxifylline group. This increased to two miles after the treatment period, showing improvement of 100%. The aspirin group showed improvement of 50%, from 0.8 miles to 1.2 miles. Study authors reported that 50% improvement in TWD after treatment with pentoxifylline versus placebo was statistically significant (P value < 0.05) (Table 4).

Ankle-brachial pressure index

ABI testing showed very slight improvement in the pentoxifylline group, from 0.6 ± 0.1 to 0.7 ± 0.2, and in the aspirin group, ABI remained similar (0.6 ± 0.3 at baseline, 0.6 ± 0.5 after treatment).

Quality of life

Ciocon 1997 did not measure quality of life.

Side effects

Ciocon 1997 did not measure side effects.

Pentoxifylline versus Ginkgo biloba extract (GBE)

Bohmer 1988 compared pentoxifylline with GBE. A total of 27 participants were included: 13 received 1200 mg of pentoxifylline daily, and 14 received 160 mg of GBE, over 24 weeks.

Pain-free walking distance

In Bohmer 1988, PFWD significantly improved in both groups after treatment, but no statistically significant difference was observed between treatment groups. PFWD increased in the pentoxifylline group from 80.1 m to 325.6 m (P value < 0.05), and in the GBE group from 94.6 m to 327.5 m (P value < 0.01) (Table 3). A statistically significant difference between treatment groups was not detected, according to Bohmer 1988.

Total walking distance

TWD significantly improved in both groups after treatment, but no statistically significant difference was observed between treatment groups. TWD increased in the pentoxifylline group from 189.5 m to 472.3 m (P value < 0.01), and in the GBE group from 203 m to 436.5 m (P value < 0.01) (Table 4). A statistically significant difference between treatment groups was not detected, according to Bohmer 1988.

Ankle-brachial pressure index

Bohmer 1988 reported that ABI increased slightly in both treatment groups but did not present the data.

Quality of life

Bohmer 1988 did not measure quality of life.

Side effects

Bohmer 1988 did not measure side effects.

Pentoxifylline versus nylidrin hydrochloride

Accetto 1982 compared 400 mg of pentoxifylline daily versus 3 mg of nylidrin hydrochloride daily, over eight weeks.

Pain-free walking distance

Accetto 1982 did not measure PFWD.

Total walking distance

Compared with baseline, TWD increased in the pentoxifylline group from 132.6 m to 193.4 m (46.7%), and in the nylidrin group from 163.4 m to 168.9 m (1%) (P value = 0.006). Study authors also expressed TWD in seconds, with the pentoxifylline group improving from 160 seconds at baseline to 240 seconds after treatment. TWD in the nylidrin group at baseline was 197 seconds, and after treatment 220 seconds. Improvement in walking distance was observed in 17 of 23 in the pentoxifylline group and in 11 of 24 in the nylidrin hydrochloride (HCl) group (Table 4). Accetto 1982 reported that at the end of treatment, a significant difference favoured pentoxifylline (P value = 0.006).

Ankle-brachial pressure index

Accetto 1982 did not measure ABI.

Quality of life

Accetto 1982 did not measure quality of life.

Side effects

Accetto 1982 reported that 6 of 23 pentoxifylline participants and 3 of 24 nylidrin HCl participants reported side effects. Most of these were gastrointestinal in nature, and all were transient and of mild severity.

Pentoxifylline versus prostaglandin E1 (PGE1)

Two studies compared pentoxifylline versus prostaglandin E1 (Hepp 1992; Schellong 2012).

Hepp 1992 compared intravenous pentoxifylline (400 mg) versus intravenous PGE1 (80 mg) over four weeks. Schellong 2012 compared pentoxifylline (600 mg twice daily for a total of 1200 mg) versus intravenous PGE1 (20 µg alprostadil) over a total of eight weeks, which was broken down into two four-week treatment periods; four weeks of PGE1 injections given daily were followed by four weeks of bi-weekly injections. It should be noted that for the Schellong 2012 study, all data were retrieved from the ClinicalTrials.gov website, which offered no actual walking distances - only ratios - and no findings of statistical analysis. It is hoped that future publications planned for this study will provide additional information on data and collection methods.

Pain-free walking distance

Median PFWD increased in the pentoxifylline group from 72 m to 133 m (85%) compared with an increase in the PGE1 group from 80 m to 175 m (119%) (Table 3). According to Hepp 1992, the difference between treatments was statistically significant (P value < 0.001).

Results from Schellong 2012 were presented as ratios for PFWD at the specified time point compared with baseline PFWD with standard deviations. After the first four-week treatment period (daily PGE1), the ratio of PFWD compared with baseline for pentoxifylline-treated participants was 1.58 ± 2.59, and for PGE1-treated participants 1.58 ± 1.92. After the second four-week treatment period (bi-weekly PGE1), the PFWD ratio was 1.98 ± 3.61 compared with baseline for pentoxifylline-treated participants, and 2.60 ± 12.22 for those treated with PGE1. After six months of post-treatment follow-up, the ratio was 2.36 ± 2.69 for pentoxifylline, and 2.27 ± 3.00 for PGE1.

Total walking distance

Median TWD increased in the pentoxifylline group from 115 m to 190 m (65%) and in the PGE1 group from 129 m to 230 m (78%) (Table 4). According to Hepp 1992, the difference between treatments was statistically significant (P value < 0.01).

As with PFWD, Schellong 2012 reported TWD as a ratio of the time point measurement compared with baseline. Following the first four-week treatment period (daily PGE1), the ratio of TWD compared with baseline for pentoxifylline-treated participants was 1.43 ± 1.34, and for PGE1-treated participants 1.39 ± 0.53. After the second four-week treatment period (bi-weekly PGE1), TWD ratio compared with baseline was 1.76 ± 1.78 for pentoxifylline-treated participants and 1.64 ± 0.86 for those treated with PGE1. Six months after treatment, the ratio for pentoxifylline was 1.99 ± 1.61, and for PGE1 1.89 ± 1.40.

Ankle-brachial pressure index

Hepp 1992 and Schellong 2012 did not measure ABI.

Quality of life

Hepp 1992 did not measure quality of life.

Schellong 2012 measured mean changes in quality of life using the Peripheral Arterial Occlusive Disease 86 quality of life questionnaire (PAVK 86) and reported changes from baseline to the end of the six-month follow-up period for eight domains, along with standard deviations. A change in the pain domain of -0.41 ± 0.58 was noted for the pentoxifylline group, and -0.28 ± 0.57 for the PGE1 group. Functional status showed a change of -0.35 ± 0.57 for the pentoxifylline group, and -0.26 ± 0.58 for the PGE1 group. A change in the anxiety domain of -0.22 ± 0.66 was reported for the pentoxifylline group, and -0.20 ± 0.64 for the PGE1 group. For the pentoxifylline group, a change of -0.12 ± 0.53 in mood and a smaller change of -0.04 ± 0.45 in social life were observed, and the PGE1 group showed changes of -0.06 ± 0.48 and -0.09 ± 0.43, respectively. For expectation of treatment, investigators reported an increase of 0.11 ± 0.49 for the pentoxifylline group and 0.07 ± 0.51 for the PGE1 group. State of general health during the last week showed a change of -0.48 ± 1.98 for the pentoxifylline group, with change in quality of life of -0.39 ± 2.20 during the last week, and the PGE1 group recorded mean changes of -0.43 ± 1.83 and -0.36 ± 2.09, respectively.

Side effects

Hepp 1992 reported that one PGE1 participant experienced nausea, and two others discontinued study medication for reasons unrelated to the medication. In total, six participants discontinued pentoxifylline treatment early because of nausea. In both treatment groups, no cardiovascular side effects were observed.

Schellong 2012 reported 17 total serious adverse events in 28 (5.96%) participants in the pentoxifylline group and 19 among 276 (6.88%) participants in the PGE1 group, which included, but were not limited to, coronary artery disease, angina, carotid artery stenosis and peripheral arterial occlusive disease (although it is noted that many of these are not necessarily events, but rather co-morbidities with events during the trial). Other adverse events were reported in 55 of 285 (19.30%) participants in the pentoxifylline group and in 60 of 276 (21.74%) in the PGE1 group; these included, but were not limited to, vertigo, gastrointestinal symptoms, peripheral oedema and hyperlipidaemia.

Pentoxifylline versus cilostazol

Two studies compared pentoxifylline versus cilostazol (Dawson 2000; Lee 2001).

Pain-free walking distance

One study (Dawson 2000) examined PFWD. This study compared 232 participants who received 1200 mg of pentoxifylline versus 227 who received 200 mg of cilostazol daily over 24 weeks. PFWD in the cilostazol group improved by 75.8% (124 ± 81 m to 218 ± 149 m) compared with 60.3% in the pentoxifylline group (126 ± 79 m to 202 ± 139 m), with a net difference of 15.5%. As standard deviations were not presented in the paper, it was not possible to compare improvement in PFWD between treatment groups (Table 3).

Total walking distance

Both studies examined TWD (Table 4). In Dawson 2000, TWD improved in the cilostazol group by 45.2% (241 ± 123 m to 350 ± 209 m) compared with the pentoxifylline group, which improved by 29.4% (238 ± 119 m to 308 ± 183 m), with a net difference of 15.8%. Statistical analysis comparing improvement in TWD between treatment groups could not be performed because data on standard deviations were insufficient.

Lee 2001 compared 17 participants who received 800 mg of pentoxifylline daily versus another 17 who received 200 mg of cilostazol. The pentoxifylline group improved by 29% (114 ± 51 m to 147 ± 81 m) versus 30% improvement in the cilostazol group (111 ± 30 m to 145 ± 53 m). Differences in improvement between treatment groups could not be tested statistically because data were insufficient.

Ankle-brachial pressure index

Lee 2001 reported that ABI in the cilostazol group dropped from 0.73 ± 0.12 to 0.69 ± 0.11, and the pentoxifylline group improved from 0.66 ± 0.13 to 0.7 ± 0.14. Study authors stated that none of these results were statistically significant, although they did not present test results. Dawson 2000 reported that ABI increased in the cilostazol group from 0.66 ± 0.18 at baseline to 0.70 ± 0.18 at 24 weeks, and in the pentoxifylline group, ABI increased from 0.66 ± 0.21 to 0.71 ± 0.24. ABI after 24 weeks was not statistically significantly different between treatment groups (P value not presented).

Quality of life

Lee 2001 did not measure quality of life. Dawson 2000 reported that no treatment significantly affected SF36 and WIQ scores.

Side effects

Dawson 2000 reported that rates of withdrawal due to adverse effects were similar in pentoxifylline (43/232) and cilostazol groups (36/227). Headache, diarrhoea and abnormal stools were significantly more common among participants receiving cilostazol than among those receiving pentoxifylline or placebo. Dawson 2000 reported that these adverse events were generally mild to moderate, were self-limiting and did not appear to affect the dropout rate.

Pentoxifylline versus iloprost

Creager 2008 compared iloprost (50 µg, 100 µg and 150 µg) versus pentoxifylline (1200 mg) and placebo over six months.

Pain-free walking distance

PFWD increased by 24%, 28.9% and 31.2% for the iloprost 50 µg, 100 µg and 150 µg groups, respectively, and the increase for the pentoxifylline group was 34.3% (Table 3). Creager 2008 reported no significant differences when comparing treatment groups versus placebo (P value = NS) but did not report on differences between iloprost and pentoxifylline.

Total walking distance

Iloprost comparisons showed that TWD increased in 50 µg, 100 µg and 150 µg groups by 7.7%, 8.8% and 11.2%, respectively. None of these changes were significant. Improvement with pentoxifylline over placebo was significant, as reported above, but trialists did not report on differences between iloprost and pentoxifylline (Table 4).

Ankle-brachial pressure index

Creager 2008 did not measure ABI.

Quality of life

Quality of life was measured using the WIQ and the SF36. According to Creager 2008, the SF36 showed no differences between treatment groups, and the WIQ showed significant differences only in stair climbing between iloprost and placebo, and between pentoxifylline and placebo. Again, trialists did not report on differences between iloprost and pentoxifylline.

Side effects

Creager 2008 reported side effects for the iloprost, pentoxifylline and placebo groups. The most common side effects in the pentoxifylline group were headache (19%), pain in extremity (14%) and dyspepsia (13%), and side effects in the iloprost groups were mainly headache, vasodilation or flushing, pain in extremity, jaw pain, nausea and diarrhoea. For most adverse events, severity increased with increasing dose of iloprost.

Pentoxifylline versus buflomedil and nifedipine

Chacon-Quevedo 1994 compared pentoxifylline (1200 mg daily) versus buflomedil (600 mg daily) and nifedipine (60 mg daily) over 90 days (three months). A total of 45 individuals participated in the study (15 in each group).

Pain-free walking distance

PFWD increased in the pentoxifylline group from 109 ± 63 m to 194 ± 72 m, for improvement of 78%, compared with buflomedil (97 ± 73 m to 160 ± 73 m), which showed improvement of 64.9% and nifedipine (109 ± 56 m to 194 ± 65 m), with 78% improvement (Table 3).

Total walking distance

TWD increased in the pentoxifylline group from 180 ± 67 m to 226 ± 57 m compared with buflomedil (159 ± 76 m to 205 ± 66 m) and nifedipine (186 ± 54 m to 226 ± 49 m) (Table 4).
Chacon-Quevedo 1994 concluded that at 90 days, pentoxifylline was statistically better than buflomedil but not nifedipine in improving walking distance, but investigators did not specify the subtype (PFWD or TWD) nor the results of statistical tests.

Ankle-brachial pressure index

Chacon-Quevedo 1994 reported that improvement in ABI for the pentoxifylline group (0.64 ± 0.14 to 0.75 ± 0.17) was statistically greater than for the buflomedil or nifedipine group, but study authors did not provide complete data.

Quality of life

Chacon-Quevedo 1994 did not measure quality of life.

Side effects

Chacon-Quevedo 1994 did not measure side effects.

DISCUSSION

Intermittent claudication (IC) is a symptom of peripheral arterial disease (PAD) that is associated with increased morbidity and mortality and poor quality of life. It reflects the presence of an underlying disease process that results in narrowing or maybe blockage of lower limb blood vessels. It is associated with the presence of atherosclerosis elsewhere in the vascular tree, especially in the coronary and cerebral circulations.

As this pathology cannot be reversed, the main aims of treatment are (1) to stop or slow progression of the disease to critical ischaemia, to prevent adverse events, and (2) to alleviate the severity of symptoms to improve quality of life.

It is widely accepted, although at times controversial, that treatment of PAD at the stage of IC is medical, and that revascularisation is not the treatment of choice. Large numbers of interventions have been developed. Lifestyle changes and exercise are the basic essential interventions; they have a significant effect on both disease progression and symptoms. Other essential drugs like statins are very important for slowing the disease but have little effect on the symptoms. Pentoxifylline is one of many drugs used to relieve symptoms of IC and to improve quality of life.

Summary of main results

In comparing pentoxifylline with placebo, 11 studies reported pain-free walking distance (PFWD). The duration of studies ranged from four to 40 weeks, and the pentoxifylline dose from 600 mg to 1600 mg. Baseline PFWD ranged from 27.1 m to 460 m, with large variability in results. One study reported less improvement in PFWD over the duration of the trial in the pentoxifylline group than in the placebo group - with a difference as great as 33.8%. On the other hand, maximum improvement in PFWD among participants receiving pentoxifylline was 73.9% more than in those given placebo.
A total of 14 studies reported total walking distance (TWD) as an outcome when comparing pentoxifylline versus placebo. Studies varied in duration from eight weeks to 52 weeks, and pentoxifylline dose from 400 mg to 1800 mg, but most studies used 1200 mg. Baseline TWD ranged from 56 m to 678 m, and for PFWD, results were highly variable. The minimum benefit of pentoxifylline shown was 1%, and the maximum benefit was 155.9%.
In one study, pentoxifylline showed greater improvement in PFWD when compared with Gingko biloba extract (GBE), buflomedil and iloprost; cilostazol showed greater improvement when compared with pentoxifylline; and prostaglandin E1 (PGE1) showed greater improvement when compared with pentoxifylline. Data from the second study, which evaluated PGE1 and pentoxifylline, are too limited to allow meaningful conclusions. For TWD, greater improvement was shown for pentoxifylline than for nylidrin, GBE and aspirin, and for cilostazol and flunarizine than for pentoxifylline. PGE1 showed greater improvement in TWD in one study, and data in the second study are currently too limited to permit meaningful conclusions.
Pentoxifylline appeared to be well tolerated in most studies, with gastrointestinal side effects, mainly nausea, reported most commonly. These effects appeared mild.
Most included studies suggested improvement in PFWD and TWD for pentoxifylline over placebo (and other treatments), but the statistical significance of findings from individual trials is un-

clear, and pentoxifylline showed no improvement in ABI. It is important to appreciate the difference between statistical significance and clinical significance; even when a statistically significant improvement is described, improvement of a few metres might not make much difference to a patient.

Overall completeness and applicability of evidence

This review shows great variability between trial outcomes with pentoxifylline treatment. This helps to explain the large number of studies of pentoxifylline for IC that have been performed over three decades. Positive results in some studies were often only marginal, and across studies were generally inconsistent, encouraging further research to attain consistency.

Large variability in the results of studies included in this review was not unexpected. These studies used different doses of pentoxifylline, over variable durations, in different countries and by various study designs, but the variety of participant characteristics is most important. Investigators stated that they included individuals with IC Fontaine class II, but baseline walking distance varied from 27.1 m to 460 m for PFWD, and from 56 m to 678 m for TWD. This suggests considerable variation in the characteristics of participant groups across studies. Most researchers stated that baseline variables were comparable between intervention and control groups but did not specify these variables.

Only two studies reported use of an exercise programme in addition to pentoxifylline or comparison treatments. The remaining studies did not report an exercise programme or indicated that no formal programme was used. Some studies advised participants to stop smoking for the duration of the study. Advice on exercise and smoking appears inconsistent between studies, and effects of this on overall outcomes and placebo effects are unknown.

Quality of the evidence

We judged the overall quality of the evidence to be low. For most included studies, the risk of bias is unclear, mainly because insufficient information is available to permit judgement of low or high risk of bias. This was the case for selection bias, blinding, detection bias in particular, attrition bias and bias due to selective reporting. The quality of the evidence is severely limited by the heterogeneity of included studies. Study duration varied from four weeks to 52 weeks. Pentoxifylline doses used for the intervention group varied. Most studies used 1200 mg, but doses from 400 mg to 1800 mg were reported. Variability in outcomes was evident in that studies assessed PFWD, TWD or both. In addition, different treadmill protocols that ranged from constant load tests to graded tests were used to measure PFWD and TWD. Some studies did not report the treadmill protocol used. PFWD and TWD were reported as means, geometric means, seconds to percentage change from baseline and ratios. Thus we could not perform a pooled analysis.

Potential biases in the review process

In this systematic review, we identified all randomised controlled trials (RCTs) that compared pentoxifylline versus placebo or other pharmacological interventions. Open, cohort and single-blinded studies were not included because pentoxifylline has been studied extensively, and research authors identified a considerable number of RCTs. Comparisons of lifestyle changes and exercise were not included because no evidence has supported their inclusion in any treatment plan. As IC is a long-term condition, we included studies with a minimum duration of four weeks. We believe our search for RCTs has been comprehensive, and it is unlikely that our standardised methods of study selection and data extraction could have introduced major bias. Heterogeneity of included studies and variable presentation of outcomes by trialists (requiring substantial data imputation) precluded pooling of data.

Agreements and disagreements with other studies or reviews

A systematic review published in 2012 compared pentoxifylline, cilostazol and naftidrofuryl oxalate versus placebo, or versus one another, for the treatment of intermittent claudication in individuals with peripheral arterial disease (Stevens 2012). The Stevens 2012 review included four studies that were also included in our review - three comparing pentoxifylline versus placebo, and one comparing pentoxifylline versus cilostazol. Study authors employed imputation techniques to include study data in meta-analyses that we ourselves did not use because of heterogeneity. Their results revealed possible increases in both PFWD and TWD for pentoxifylline groups, with percent changes of 9% (95% credible interval 2% to 22%) and 11% (95% credible interval 1% to 24%), respectively. Adverse events were not reported in the meta-analysis, but with all vasoactive drugs, mild headaches and gastrointestinal issues were reported, and no increase in cardiovascular events or deaths was described for pentoxifylline, cilostazol or naftidrofuryl oxalate. Study authors noted that heterogeneity in quality of life reporting prevented them from reporting these findings in their review. However, these data are presented as part of Squires 2010 and Squires 2011, in technology assessment reports written for the National Institute for Health and Care Excellence (NICE) and in a recent study evaluating the cost-effectiveness of various treatments (Meng 2014; NICE 2011; NICE 2012).

Other systematic reviews on pentoxifylline for intermittent claudication have yielded results (Ernst 1994; Frampton 1995) similar to the findings of this review. Greater improvement in PFWD and TWD was shown for pentoxifylline versus placebo, but review authors concluded that clinical effects remain unclear and

may depend on patient characteristics, such as ABI, duration of intermittent claudication, whether risk factors were addressed and whether other treatment options had been investigated.

AUTHORS' CONCLUSIONS

Implications for practice

Given the generally poor quality of published studies and the large degree of heterogeneity apparent among interventions and results, the overall benefit of pentoxifylline for patients with Fontaine class II intermittent claudication remains uncertain, but the medication is generally well tolerated.

High-quality data are currently insufficient to show the benefits of pentoxifylline for intermittent claudication.

Implications for research

Numerous studies on pentoxifylline for intermittent claudication over more than 30 years have reported highly variable outcomes. Whilst this comprehensive review summarises and critiques all available RCT evidence, and should prove helpful to clinicians and healthcare professionals in making informed decisions regarding pentoxifylline for the treatment of patients with intermittent claudication, the role of pentoxifylline in treatment remains uncertain. However, valuable research resources might be better directed toward discovery of more effective treatments or prevention measures.

ACKNOWLEDGEMENTS

We would like to thank Cochrane Vascular for help provided in updating this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Accetto 1982

Methods	Study design: double-blinded, randomised Country: Yugoslavia Setting: single centre Intention-to-treat: no
Participants	Number of participants randomly assigned: 60 Number of participants analysed: 47 (23 pentoxifylline, 24 nylidrin HCL) Exclusions post randomisation: 13 Losses to follow-up: none Age: mean 61 years (range 30 to 80 years) Sex: 36 male, 14 female Inclusion criteria: Fontaine stage II or III; initial claudication distance > 50 m and < 500 m at 3 km/h at 0 degrees of inclination; severity of disorder unchanged for 6 months Exclusion criteria: advanced limb arterial occlusion; peripheral venous disorders; systemic haematological disorders; severely impaired renal function; GI disorders; hypersensitivities to methylxanthines; women of childbearing age; taking cardiac medication, glycosides and antihypertensives or antibiotics < 4 weeks before the study
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control: nylidrin HCl, 3 mg 3 times daily Duration: 8 weeks
Outcomes	Primary: mean TWD Secondary: side effects
Notes	Treadmill protocol: 3 km/h without inclination Mean TWD stated in metres and seconds

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reports 'double blinded'; no other information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned

Accetto 1982 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for withdrawals not provided
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Belcaro 2002

Methods	Study design: double-blinded, randomised Country: Italy/USA/UK Setting: 3 centres Intention-to-treat: no
Participants	Number of participants randomly assigned: 60 Number of participants analysed: 53 (27 pentoxifylline, 26 placebo) Exclusions post randomisation: 7 Losses to follow-up: none Age: pentoxifylline: 55 ± 7 years, placebo: 56 ± 11 years Sex: M:F: pentoxifylline: 16:11, placebo: 18:8 Inclusion criteria: severe intermittent claudication with total walking distance < 100 m; intermittent claudication > 3 months; resting Doppler ankle brachial index < 0.8; decrease in ankle pressure > 15 mmHg after standard exercise test on treadmill; age between 45 and 75 years; arterial stenoses, plaques and blood flow reduction due to arteriosclerosis (colour duplex); graded cardiac stress test showing no angina/MI; stable control of diabetes mellitus ≥ 5 years Exclusion criteria: presence of indication for vascular angioplasty or revascularisation; angina or cardiac ischaemia on effort; previous coronary or vascular surgery or angioplasty, aneurysm, congestive heart failure, renal failure (creatinine > 2 mg/dL) and diabetes requiring insulin; arthritis, pulmonary, cardiac, neoplastic inflammatory or immunologic disease Exclusion criteria after run-in phase: variance of maximal walking distance > 25% during 2-week run-in phase
Interventions	Treatment: oral pentoxifylline, 400 mg 4 times daily Control: placebo Duration: 6 months
Outcomes	Primary: mean TWD Secondary: side effects
Notes	Treadmill protocol: 3 km/h at 12% inclination Mean TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Belcaro 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	States 'randomized'; no other information available
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment allocation blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Bohmer 1988

Methods	Study design: double-blinded, randomised Country: Germany Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 27 (14 Ginkgo biloba extract, 13 pentoxifylline) Number of participants analysed: 26 Exclusions post randomisation: none Losses to follow-up: 1 Age: 60.3 ± 7.3 years (range 44 to 72 years) Sex: 24 males, 3 females Inclusion criteria: outpatient; high-grade stenosis for SFA; 1-side claudication; PFWD 50 to 200 m; < 30% variance in WD during 3-week placebo induction phase Exclusion criteria: not mentioned
Interventions	Treatment: pentoxifylline, 1200 mg/d Control: Ginkgo biloba extract, 160 mg/d Duration: 24 weeks
Outcomes	Primary: mean PFWD, TWD Secondary: ABI

Bohmer 1988 (*Continued*)

Notes	Treadmill protocol: 3 km/h at 5% inclination Mean PFWD and TWD expressed in metres only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reports 'double blind'; no other information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Bollinger 1977

Methods	Study design: double-blinded, randomised Country: Switzerland Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 26 Number of participants analysed: 19 Exclusions post randomisation: none Losses to follow-up: 7 Age: pentoxifylline: mean 63.9 years, placebo: mean 59.6 years Sex: pentoxifylline: 9 male, 1 female, placebo: 8 male, 1 female Inclusion criteria: intermittent claudication (Fontaine stage II) Exclusion criteria: malleolar arteries could not be compressed by a cuff (mediasclerosis)
Interventions	Treatment: oral pentoxifylline, 200 mg 3 times daily Control: placebo Duration: 8 weeks

Bollinger 1977 (*Continued*)

Outcomes	Primary: mean TWD Secondary: ABI
Notes	Treadmill protocol: 3.2 km/h at 12.5% inclination Mean TWD expressed in metres only Participants were instructed to refrain from smoking during the study and to walk daily for at least 1 hour

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'allocated at random to receive treatments'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Both pentoxifylline and placebo were presented in identical tablet form and supplied in containers of 40 tablets, identified only by a code number'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	High risk	Differences in clinical baseline data between treatment groups

Cesarone 2002b

Methods	Study design: double-blinded, randomised Country: Italy Setting: multi-centre - 7 centres Intention-to-treat: yes
Participants	Number of participants randomly assigned: 200 Number of participants analysed: 178 (88 pentoxifylline, 90 placebo) Exclusions post randomisation: none Losses to follow-up: 22 Age: pentoxifylline: 61 ± 9 years, placebo: 61 ± 10 years Sex: pentoxifylline: 55 males, 45 females, placebo: 56 males, 44 females

Cesarone 2002b (*Continued*)

	Inclusion criteria: severe intermittent claudication with total walking distance between 50 and 200 m; intermittent claudication > 4 months; resting Doppler ankle-brachial index < 0.8; decrease in ankle pressure > 15 mmHg after standard exercise rest on treadmill (12% inclination, 3 km/h, 10 minutes of exercise); age between 45 and 75 years; documentation of arterial stenoses, plaques and flow reduction due to arteriosclerosis by colour-duplex imaging Exclusion criteria: indication for revascularisation or angioplasty; no angina or myocardial ischaemia on effort tested by bicycle ergometry, cardiac risk factors; previous coronary or vascular surgery or angioplasty; aneurysms; congestive heart failure NYHA III/IV; renal failure (creatinine > 2 mg/100 mL); insulin-dependent diabetes mellitus; change of > ± 25% during 2-week run-in period; arthritis; pulmonary, cardiac or neoplastic disease; inflammatory or immunologic disease
Interventions	Treatment: oral pentoxifylline, 400 mg 4 times daily Control: placebo Duration: 40 weeks
Outcomes	Primary: geometric mean TWD and PFWD Secondary: side effects
Notes	Treadmill protocol: 3 km/h at 12% inclination Geometric mean PFWD and TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomised into two treatment plans'; no further information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States 'double blind' and 'pentoxifylline and equivalent placebo were administered'; no other information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided on dropouts
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Chacon-Quevedo 1994

Methods	Study design: double-blinded, randomised Country: Spain Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 45 (15 in each arm) Number of participants analysed: 45 Exclusions post randomisation: none Losses to follow-up: none Age: 61 ± 8 years Sex: all men Inclusion criteria: PAD Fontaine stage II Exclusion criteria: not mentioned
Interventions	Treatment: pentoxifylline, 1200 mg/d Control: • Buflomedil, 600 mg/d • Nifedipine, 600 mg/d Duration: 90 days
Outcomes	Primary: mean PFWD, TWD Secondary: ABI
Notes	Treadmill protocol: 3 km/h at 10% inclination Mean PFWD and TWD expressed in metres only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'patients were divided randomly into three treatment groups'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided to permit judgement

Chacon-Quevedo 1994 (*Continued*)

Other bias	Unclear risk	Insufficient information provided to permit judgement

Ciocon 1997

Methods	Study design: randomised Country: USA Setting: 2 centres Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 90 Number of participants analysed: 90 (45 in each group) Exclusions post randomisation: not mentioned Losses to follow-up: not mentioned Age: 79 ± 3.5 years Sex: M:F: pentoxifylline: 10:34, aspirin: 12:34 Inclusion criteria: age ≥ 65 years; ankle-to-arm pressure < 0.8; not taken aspirin/pentoxifylline over previous 6 months; experienced leg claudication Exclusion criteria: took aspirin or pentoxifylline in previous 6 months; leg rest pain; vascular surgery; co-existing stable angina, severe osteoarthritis, peripheral neuropathy, leg surgery within previous 6 months; ankle-to-arm pressure ratio > 0.8
Interventions	Treatment: oral pentoxifylline, 400 mg twice daily Control: aspirin, 325 mg daily Duration: 6 weeks
Outcomes	Primary: TWD Secondary: ABI
Notes	Treadmill protocol: not specified TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'were randomly assigned to'; no further information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different treatments: pentoxifylline twice daily, aspirin once daily
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned

Ciocon 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Creager 2008

Methods	Study design: double-blinded, randomised Country: USA Setting: 32 centres Intention-to-treat: not mentioned: yes
Participants	Number of participants randomly assigned: 430 Number of participants analysed: 370 Exclusions post randomisation: none Losses to follow-up: 60 Age: 67 years Sex: M:F: 349:81 Inclusion criteria: age ≥ 40 years; Fontaine stage II; stable claudication for ≥ 3 months despite standard care; absolute claudication distance between 50 and 800 m; ABPI ≤ 0.90 in symptomatic leg and > 20% fall in ABPI within 1 minute following cessation of exercise; in non-compressible vessels, toe-brachial index at rest < 0.70; final inclusion criteria after run-in phase: absolute claudication distance within 20% of ACD on previous measurements before run-in phase; compliance with drug of 80% to 120% Exclusion criteria: ischaemic rest pain, ulcers, gangrene (Fontaine stage III and IV); evidence of non-atherosclerotic PAD; peripheral neuropathy impairing walking; revascularisation procedures within preceding 3 months; sympathectomy within 6 months; type 1 diabetes mellitus; myocardial infarction or major cardiac surgery within 3 months; unstable angina; heart failure; patients receiving low molecular weight heparin and warfarin in combination with aspirin, or any other drug for intermittent claudication
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control • Placebo • Iloprost 50 µg bd • Iloprost 100 µg bd • Iloprost 150 µg bd Duration: 6 months
Outcomes	Primary: TWD expressed as % change from baseline to follow-up Secondary: PFWD, quality of life (WIQ and SF36), side effects
Notes	Treadmill protocol: 3.2 km/h at 0% gradient, increased by 2% every 2 minutes TWD expressed in metres at baseline and % change at follow-up

Creager 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomised placebo controlled'; no further information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatments appropriately blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear why participants stopped medication; unclear whether data presented represent intention-to-treat or per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Sponsor: Berlex Pharmaceuticals Inc.

Dawson 2000

Methods	Study design: double-blinded, randomised Country: USA Setting: multi-centre - 54 centres Intention-to-treat: yes
Participants	Number of participants randomly assigned: 699 Number of participants analysed: 698 Exclusions post randomisation: 1 Losses to follow-up: 159 Age: 66 ± 9 years for all groups Sex: cilostazol: 172 male, pentoxifylline: 181 male, placebo: 176 male Inclusion criteria: > 6 months of symptoms with no substantial change within previous 3 months; baseline claudication distance > 53.6 m (1 minute on treadmill protocol) ; baseline walking distance < 537.6 m (10 minutes on treadmill protocol); peripheral arterial disease diagnosis confirmed by either a resting ABI ≤ 0.9 and a ≥ 10 mmHg decrease in ankle pressure measured 1 minute after walking to maximal walking distance or a ≥ 20 mmHg decrease in post-exercise ankle pressure in symptomatic extremity Exclusion criteria: Buerger's disease; critical ischaemia (II or III chronic lower extremity ischaemia); lower extremity arterial reconstruction (surgical or endovascular) or sympa-

Dawson 2000 (*Continued*)

	thectomy within previous 3 months; other conditions limiting exercise capacity; other medical conditions limiting participation; prior use of cilostazol or pentoxifylline within 30 days of start date; > 20% variation in maximal walking distance; use of anticoagulants or antiplatelet agents except for aspirin at a dose ≤ 81 mg/d
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control • Placebo • Cilostazol, 100 mg twice daily plus 1 identical placebo tablet Duration: 24 weeks
Outcomes	Primary: mean PFWD, TWD Secondary: ABI, side effects and QoL (SF36, WIQ)
Notes	Treadmill protocol: 3.2 km/h at 0% inclination, increased by 3.5% every 3 minutes Mean PFWD and TWD expressed in metres only Additional data on a subgroup of this study are presented in Dawson 2002

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified by clinical centre and patients assigned to 1 of 3 treatment regimes within each centre using permuted block design
Allocation concealment (selection bias)	Low risk	'Interactive voice randomization that blinded the investigator, patients and sponsor from treatment assignment'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatments appropriately blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Unclear risk	'Supported by Otsuka America Pharmaceuticals Inc., a US affiliate of the manufacturer of cilostazol'

De Sanctis 2002a

Methods	Study design: double-blinded, randomised Country: USA Setting: 5 centres Intention-to-treat: yes
Participants	Number of participants randomly assigned: 120 Number of participants analysed: 101 (56 pentoxifylline, 45 placebo) Exclusions post randomisation: 19 Losses to follow-up: none Age: pentoxifylline: 63 ± 4 years, placebo: 62 ± 3 years Sex: M:F: pentoxifylline: 36:20, placebo: 24:21 Inclusion criteria: severe intermittent claudication with total walking distance between 50 and 200 m; intermittent claudication > 4 months; resting Doppler ankle-brachial index < 0.8; decrease in ankle pressure > 15 mmHg after standard exercise test on treadmill; age between 45 and 75 years; documentation of arterial stenoses, plaques and flow reduction due to arteriosclerosis by colour-duplex imaging Exclusion criteria: presence of indication for revascularisation or angioplasty procedures; angina pectoris or myocardial ischaemia on effort at 80% of target heart rate; previous coronary or vascular surgery or angioplasty; aneurysms, congestive heart failure NYHA III-IV, renal failure (creatinine > 2 mg/dL), IDDM II; change > ± 25% during 2-week run in period; arthritis or other pulmonary, cardiac or neoplastic disease or inflammatory or immunologic disease
Interventions	Treatment: oral pentoxifylline, 600 mg 3 times daily Control: placebo Duration: 12 months
Outcomes	Primary: mean TWD Secondary: none
Notes	Treadmill protocol: 3 km/h at 12% inclination Mean TWD expressed in metres only Participants also took 300 mg antiplatelets as part of study treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'patients were randomised into two treatment plans'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement

De Sanctis 2002a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on dropouts provided other than due to low compliance
Selective reporting (reporting bias)	Unclear risk	No information on dropouts provided other than due to low compliance
Other bias	Unclear risk	Pentoxifylline dose unclear; study authors report both 1600 mg and 1800 mg. Assumed 1800 mg (3 × 600 mg) is actual treatment

De Sanctis 2002b

Methods	Study design: double-blinded, randomised Country: USA Setting: 5 centres Intention-to-treat: no
Participants	Number of participants randomly assigned: 194 Number of participants analysed: 135 (75 pentoxifylline, 60 placebo) Exclusions post randomisation: 59 Losses to follow-up: none Age: pentoxifylline: 62 ± 9 years, placebo: 61 ± 8 years Sex: M:F: pentoxifylline: 46:29, placebo: 28:22 Inclusion criteria: intermittent claudication with total walking distance > 400 m; claudication > 3 months; Doppler ankle-brachial index < 0.8; decrease in ankle pressure > 20 mm Hg after standard exercise test on treadmill; age between 50 and 65 years; arterial stenoses, plaques and flow reduction on colour duplex imaging Exclusion criteria: presence of Indication for revascularisation or angioplasty; angina or myocardial ischaemia on effort; previous coronary or vascular surgery or angioplasty, aneurysms, congestive heart failure NYHA III/IV, renal failure (creatinine > 2 mg/dL) , IDDM II; arthritis; other pulmonary cardiac neoplastic disease or inflammatory or immunologic disease
Interventions	Treatment: oral pentoxifylline, 600 mg 3 times daily Control: placebo Duration: 12 months
Outcomes	Primary: mean TWD Secondary: side effects
Notes	Treadmill protocol: 3 km/h at 12% inclination Mean TWD expressed in metres only Participants also took 300 mg antiplatelets as part of study treatment

De Sanctis 2002b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'patients were randomised into two treatment plans'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on dropouts provided other than due to low compliance
Selective reporting (reporting bias)	Unclear risk	No information on dropouts provided other than due to low compliance
Other bias	Unclear risk	Pentoxifylline dose unclear; study authors report both 1600 mg and 1800 mg. Assumed 1800 mg (3 × 600 mg) is actual treatment

Di Perri 1983

Methods	Study design: double-blinded, randomised. Cross-over after 8 weeks Country: Italy Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 24 Number of participants analysed: 24 Exclusions post randomisation: none Losses to follow-up: none Age: 59.3 years in both groups (range 40 to 71 years) Sex: group 1: 9 males, 3 females, group 2: 10 males, 2 females Inclusion criteria: walking capacity between 100 and 400 m; Fontaine II Exclusion criteria: pain at rest, paraesthesia and skin lesions; diabetes mellitus; severe hypertension; congestive heart failure

Di Perri 1983 (*Continued*)

Interventions	Treatment: oral pentoxifylline, 400 mg twice daily Control: placebo Duration: 8 weeks and cross-over after 2-week washout phase
Outcomes	Primary: mean TWD Secondary: none
Notes	Treadmill protocol: 120 steps/min at horizontal level Mean TWD expressed in metres only Participants stopped smoking at the start of the study Study authors reported a carryover effect that was not eliminated by the washout phase

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomly allotted into two groups to received either treatment A or treatment B'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pentoxifylline and placebo were of identical appearance and were provided as 1 tablet 3 times a day for each treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Adverse events reported only in the summary, not in the main paper
Selective reporting (reporting bias)	Unclear risk	Adverse events reported only in the summary, not in the main paper
Other bias	Unclear risk	Authors reported a carryover effect that was not eliminated by the washout phase

Donaldson 1984

Methods	Study design: double-blinded, randomised Country: UK Setting: single centre Intention-to-treat: not mentioned

Donaldson 1984 (*Continued*)

Participants	Number of participants randomly assigned: 80 (40 each arm) Number of participants analysed: not mentioned Exclusions post randomisation: none Losses to follow-up: 7 Age: pentoxifylline: 58.2 ± 11.7 years, placebo: 58.9 ± 9.1 years Sex: 31 males, 9 females in each group Inclusion criteria: typical intermittent claudication pain Exclusion criteria: rest pain (or incipient gangrene); severe ischaemic heart disease; postural hypotension; receiving any drugs likely to alter claudication distance within 4 weeks before inclusion in the study
Interventions	Treatment: oral pentoxifylline, 200 mg 3 times daily Control: placebo Duration: 8 weeks
Outcomes	Primary: mean PFWD, TWD Secondary: ABI, side effects
Notes	Treadmill protocol: 4 km/h at 0% inclination Mean PFWD and TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomised'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Ernst 1992

Methods	Study design: RCT Country: Austria, Hungary, Germany Setting: 3 centres Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 40 (20 each arm) Number of participants analysed: 40 Exclusions post randomisation: none Losses to follow-up: none Age: pentoxifylline: 53.3 ± 9.6 years, placebo: 55.9 ± 11.9 years Sex: M:F: pentoxifylline: 15:5, placebo: 19:1 Inclusion criteria: PAD stage II by clinical diagnosis, doppler pressures and angiography; pain-free walking distance < 200 m; stable ≥ 3 months Exclusion criteria: claudication due to non-vascular reasons; pre-treatment with drugs considered to be "rheologically active"
Interventions	Treatment: oral pentoxifylline, 600 mg twice daily Control: placebo Duration: 12 weeks
Outcomes	Primary: mean TWD and PFWD Secondary: none
Notes	Treadmill protocol: not specified Mean PFWD and TWD expressed in metres only Both groups received a supervised exercise programme for 1 hour, twice a week

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement

Ernst 1992 (*Continued*)

Other bias	Low risk	Study appears free of other bias

Gallus 1985

Methods	Study design: double-blinded, randomised. Cross-over after 8 weeks; no washout period Country: Australia Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 47 Number of participants analysed: 38 (19 in each group) Exclusions post randomisation: 9 Losses to follow-up: none Age: group A: 68 years, group B: 66 years Sex: group A: 17 males, 2 females, group B: 14 males, 5 females Inclusion criteria: stable claudication distance > 6 months; presence of peripheral vascular disease documented through clinical examination by vascular surgeon and supplemented by angiography or non-invasive testing; age > 50 years; pledge not to change smoking habits during trial; informed consent Exclusion criteria: vascular surgery or sympathectomy within previous 6 months; ischaemic leg ulcer or rest pain; exercise tolerance limited by conditions other than peripheral vascular disease; treatment with lipid-lowering or antiplatelet drugs
Interventions	Treatment: 400 mg twice daily for 1 week, then 400 mg 3 times daily for 7 weeks Control: placebo Duration: 8 weeks, then cross-over for another 8 weeks; no washout phase
Outcomes	Primary: geometric mean TWD and PFWD Secondary: ABI
Notes	Treadmill protocol: 4 km/h at 10% inclination Geometric mean PFWD and TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'A random number sequence was used to form the two treatment groups'
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded from allocation and held by hospital pharmacy

Gallus 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Results were withheld from investigators during the study'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Hepp 1992

Methods	Study design: double-blinded, randomised Country: Germany Setting: 9 centres Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 195 (98 pentoxifylline, 97 PGE1) Number of participants analysed: 195 Exclusions post randomisation: none Losses to follow-up: none Age: 65 years Sex: M:F: 2.8:1 Inclusion criteria: pain-free walking distance 50 to 200 m; stable stadium Fontaine IIb for 6 months; diagnosis of stenosis through digital substraction angiography or conventional angiography of lower limbs; signing an informed consent form; variance of walking distance at beginning < 20% Exclusion criteria: pregnancy; present heart failure; kidney failure; pre-stenosis (e.g. stenosis of the aorta abdominalis or iliacal arteries); necrosis or rest pain; pulmonary insufficiency; arthrosis; myocardial infarction within previous 6 months; orthostatic dysregulation and collapsing patients; severe cardiac rhythm problems; epilepsy
Interventions	Treatment: intravenous pentoxifylline, 200 mg twice daily Control: intravenous PGE1, 400 mg twice daily Duration: 4 weeks
Outcomes	Primary: mean TWD and PFWD Secondary: side effects
Notes	Treadmill protocol: not specified Mean PFWD and TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hepp 1992 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	States 'randomisation list'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reports 'blind', but no other information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Kiesewetter 1988

Methods	Study design: double-blinded, randomised Country: Germany Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 40 (20 in each arm) Number of participants analysed: 38 Exclusions post randomisation: 2 Losses to follow-up: none Age: pentoxifylline: 59.4 ± 11.4 years, placebo 62.1 ± 8.2 years Sex: 11 males, 8 females in each group Inclusion criteria: Fontaine II; already trained patients; 6 months stadium Fontaine IIb; all patients finished 3 months of exercise training still max walking distance < 300 m; max walking distance variation in the last 2 weeks (twice/wk) < 30% Exclusion criteria: other causes for walking problems (e.g. arthrosis, Parkinson's disease) ; operative therapy within previous 3 months (sympathectomy, vessel operations); myocardial infarction previous 3 months, also apoplexia; severe internistic diseases (e.g. heart, kidney or liver disease); polyneuropathy
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control: placebo Duration: 8 weeks
Outcomes	Primary: mean PFWD Secondary: none

Kiesewetter 1988 (*Continued*)

Notes	Treadmill protocol: not specified Mean PFWD expressed in metres only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised list'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets were identical and randomisation key was not known until end of study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	TWD result reported in abstract but not mentioned in remainder as outcome or result
Other bias	Low risk	Study appears free of other bias

Lee 2001

Methods	Study design: double-blinded, randomised Country: Taiwan Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 50 Number of participants analysed: 50 Exclusions post randomisation: none Losses to follow-up: none Age: cilostazol: 66 ± 9 years, pentoxifylline: 68 ± 5 years, placebo: 69 ± 6 years Sex: M:F: cilostazol: 14/3, pentoxifylline: 14/3, placebo: 14/2 Inclusion criteria: > 40 years old; stable PAD for last 3 months; baseline max walking distance > 30 m and < 200 m; variance < 20% in WMD in the 2 screening tests Exclusion criteria: Buerger's disease; category II or III chronic lower limb ischaemia; arterial surgery/angioplasty or sympathectomy within previous 3 months

Lee 2001 (*Continued*)

Interventions	Treatment: oral pentoxifylline, 400 mg twice daily Control • Oral cilostazol, 100 mg twice daily • Placebo Duration: 8 weeks
Outcomes	Primary: mean TWD Secondary: ABI, side effects
Notes	Treadmill protocol: 3.2 km/h at 12.5% gradient Mean TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomised code number according to which sponsor supplied the study drug'
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Special drug packaging was used to maintain the blindness of the treatment code'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Lindgarde 1989

Methods	Study design: double-blinded, randomised Country: Scandinavia Setting: multi-centre Intention-to-treat: yes
Participants	Number of participants randomly assigned: 150 (76 pentoxifylline, 74 placebo) Number of participants analysed: 150 Exclusions post randomisation: none Losses to follow-up: none

Lindgarde 1989 (*Continued*)

	Age: pentoxifylline: 65 ± 7 years, placebo: 64 ± 8 years Sex: pentoxifylline: 79% males, placebo: 80% males Inclusion criteria: ≥ 40 years of age; moderate to severe COAD; initial claudication distance 50 to 200 m; claudication history > 6 months; variance of walking distance < 35% in the last 2 treadmill tests with baseline walking distance < 100 m; variance of walking distance < 25% in the last 2 treadmill tests with baseline walking distance 101 to 200 m Exclusion criteria: complete occlusion of the aortoiliac segment, the femoral bifurcation or the popliteal artery without angiographically proven distal refilling of the respective segment; vascular reconstruction of sympathectomy within the past 12 months; peripheral neuropathy; Buerger's disease; marked post-phlebotic syndrome; diabetes; cardiac failure or severe rhythm disorders; major infections; abnormal values for platelets; history of xanthine hypersensitivity; addiction to analgesics; malignant disease
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control: placebo Duration: 6 months
Outcomes	Primary: geometric means of % change in TWD and PFWD from baseline to follow-up Secondary: ABI, side effects
Notes	Treadmill protocol: 3.2 km/h at 12.5% inclination PFWD and TWD expressed as geometric mean of % change

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomisation stratified by centres'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States 'During the double-blind period and according to a randomization plan, pentoxifylline or matching placebo was administered t.i.d.'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ABI data not provided for the main analysis
Selective reporting (reporting bias)	Unclear risk	ABI data not provided for the main analysis

Lindgarde 1989 (*Continued*)

Other bias	Low risk	Study appears free of other bias

Perhoniemi 1984

Methods	Study design: double-blinded, randomised. Cross-over after 3 months Country: Finland Setting: single centre Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 35 Number of participants analysed: 31 (17 group 1, 14 group 2) Exclusions post randomisation: none Losses to follow-up: 4 Age (mean): 60 years (range 45 to 80 years) Sex: 25 males, 6 females Inclusion criteria: typical history and objective symptoms of intermittent claudication; moderate claudication (IIb); max walking distance < 500 m Exclusion criteria: gangrene or ulcer of the legs; arterial reconstructive surgery within 6 months; symptomatic heart failure or symptomatic angina pectoris limiting exercise performance; severe hypertension WHO III
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control: flunarizine, 5 mg 3 times daily Duration: 3 months, then cross-over; no washout period
Outcomes	Primary: median TWD, PFWD Secondary: ABI, side effects
Notes	Treadmill protocol: 3.6 km/h at 0% inclination; in 3 participants, the speed was increased to 5.4 km/h Median PFWD and TWD expressed in metres at baseline and as % change at follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	States 'patients were randomized into two groups according to the system of randomized blocks'
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants received medication on a 'double-dummy basis'; no other information provided

Perhoniemi 1984 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Porter 1982a

Methods	Study design: double-blinded, randomised Country: USA Setting: 7 centres Intention-to-treat: no
Participants	Number of participants randomly assigned: 128 (127 + 1 randomised twice), but data presented for 124 participants (63 pentoxifylline, 61 placebo) Number of participants analysed: 82 Exclusions post randomisation: 46 Losses to follow-up: none Age (mean): pentoxifylline: 62.0 (range 47 to 77) years, placebo: 63.5 (range 45 to 81) years Sex: pentoxifylline: 51 males, 12 females, placebo: 50 males, 11 females Inclusion criteria: IC ≥ 6 months; able to walk on treadmill ≥ 50 m at 1.5 mph; ≤ 510 m in 9.5 minutes at a speed of 2 mph before onset of claudication; stable TWD - within 20% change of each other during run in phase Exclusion criteria: severe COAD with ischaemic pain at rest, ulceration, gangrene; sympathectomy within previous 6 months; severe peripheral neuropathy; chronic infection; hypersensitivity to methylxanthines (caffeine, theophylline, theobromine); women of childbearing potential/pregnant or using oral contraceptives
Interventions	Treatment: oral pentoxifylline, started at 600 mg, increased gradually to 1200 mg at 1 month Control: placebo Duration: 24 weeks
Outcomes	Primary: geometric mean of % change in PFWD, TWD Secondary: side effects
Notes	Treadmill protocol: 1.5 mph at 7% inclination PFWD and TWD expressed as geometric mean of % change Reich 1984 presents the same study, and an ITT analysis of this study is reported in Gillings 1987

Porter 1982a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomization was stratified by clinic'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reports the use of visibly identical placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Porter 1982b

Methods	Study design: double-blinded, randomised Country: USA Setting: single Intention-to-treat: not mentioned
Participants	Number of participants randomly assigned: 26 Number of participants analysed: 22 (11 in each group) Exclusions post randomisation: 4 Losses to follow-up: none Age (mean): 64 years in total group Sex: 20 males, 6 females Inclusion criteria: minimal walking distance > 50 m and < 200 m; lower extremity intermittent claudication); able to walk on a treadmill Exclusion criteria: ischaemic rest pain; ulceration; sympathectomy within 6 months; severe neuropathy; hypersensitivity to methylxanthines; females of childbearing potential; concomitant drugs known to have any arterial effect; peripheral vasodilators in the previous 3 months; variance > 20% in walking distance at the last 2 visits
Interventions	Treatment: oral pentoxifylline, 600 mg in first week, 800 mg in second week, 1000 mg in third week, then 1200 mg/d fourth to 24th week Control: placebo

Porter 1982b (*Continued*)

	Duration: 24 weeks
Outcomes	Primary: TWD, PFWD Secondary: side effects
Notes	Treadmill protocol: 1.5 mph at 7% inclination PFWD and TWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'randomised'; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States 'Placebo- and drug-treated patients received identical-appearing capsules on the same time schedule'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

Schellong 2012

Methods	Study design: double-blind, randomised controlled trial; parallel assignment Country: Germany Setting: multi-site Intention-to-treat: yes: participants who received ≥ 1 dose of trial medication and who had ≥ 1 valid measurement of pain-free walking distance under therapy
Participants	Number of participants randomly assigned: 561 (pentoxifylline 285, alprostadil 276) Number of participants analysed: 541 (pentoxifylline 272, alprostadil 269); completed study: 458 (pentoxifylline 233, alprostadil 225) Exclusions post randomisation: 103 (pentoxifylline 52, alprostadil 51) Losses to follow-up: 4 (pentoxifylline 3, alprostadil 1) Age (mean ± SD): 66.5 ± 8.7 years (pentoxifylline 66.8 ± 8.8 years, alprostadil 66.3 ± 8.6 years)

	Sex: M/F: 173/368 (pentoxifylline 89/183, alprostadil 84/185) Inclusion criteria: individuals with peripheral arterial occlusive disease (PAOD) of the lower extremity in Fontaine stage II; maximum walking distance on the treadmill (12%, 3 km/h) between 30 m and 150 m; stable intermittent claudication $\geq$ 6 months standing with no acute shortening of walking distance over the past 3 months; stenoses or occlusions below femoral bifurcation (above-knee or below-knee type) confirmed by duplex US or angiography; ankle/brachial index $\leq$ 0.90 with a decrease in systolic ankle pressure $\geq$ 10% after maximum loading (maximum walking distance on the treadmill at 3 km/h: 12%); patient physically and mentally capable of participating in the trial; patient age > 40 years, male and female; patient informed and given ample time and opportunity to think about her/his participation and provided written informed consent; patient willing and able to comply with all trial requirements Exclusion criteria: surgical or other interventional measures performed on affected extremity and prostaglandin treatment within the 6 months immediately before the trial; rest pain and necroses; systolic ankle pressure < 50 mmHg; change in maximum walking distance during 1-week run-in phase > ± 25% of baseline; successful physical walking training within the 6 months immediately before the trial; inflammatory vascular disease; polyneuropathy in diabetes mellitus; disease limiting walking distance (arthrosis, inflammatory disease of the joints, neurological disease, disease of the vertebral column, cardiopulmonary disease); history of pulmonary oedema; myocardial infarction within previous 6 months; pregnancy or nursing; known hypersensitivity to any components of trial medication or comparative drug; renal insufficiency, compensated retention (creatinine > 2.0 mg/dL); severe retinal haemorrhage; massive haemorrhage; known existing malignant disease; vasoactive concomitant medication (e.g. naftidrofuryl, pentoxifylline, buflomedil, cilostazol) or other prostaglandins; untreated or uncontrolled hypertension (systolic blood pressure $\geq$ 180 mmHg, diastolic blood pressure $\geq$ 110 mmHg); previous participation in the present trial
Interventions	Treatment: alprostadil (prostaglandin E1): 8 weeks total; 4 weeks of daily treatment (1 time daily IV infusion of 3 ampoules (20 μg) prostaglandin E1 in 50 to 250 mL physiological saline solution over 2 hours); 4-week interval treatment period (2 times weekly IV infusion of 3 ampoules (20 μg) of prostaglandin E1 in 50 to 250 mL physiological saline solution over 2 hours); received placebo tablets mimicking schedule of pentoxifylline Control: pentoxifylline: Trental, 8 weeks of 2-times-daily 600 mg tablets; received placebo infusions of saline mimicking the schedule of alprostadil Duration: 8 weeks
Outcomes	Pain-free walking distance, total walking distance, quality of life (PAVK 86 questionnaire) , side effects
Notes	Treadmill test: 12% grade and 3 km/h All data were retrieved from the ClinicalTrials.gov website, which offered no actual walking distances - only ratios - and no statistical analyses. A full report of the study including outcomes is currently being worked on by trialists and should provide additional information on bias issues and outcome data

Risk of bias

Bias	Authors' judgement	Support for judgement

Schellong 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not enough information given to determine adequate random sequence generation
Allocation concealment (selection bias)	Unclear risk	Not enough information given to determine adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind of participants and investigator using adequate techniques to maintain blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not discussed in abstract
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants were accounted for, and intention-to-treat analysis included nearly all participants; detailed table given to describe exclusions and loss to follow-up, although additional information should be provided regarding when these participants dropped out of the study
Selective reporting (reporting bias)	Low risk	All initially indicated outcomes were reported
Other bias	Unclear risk	Authors of the study reported that limitations of the study include early termination, leading to small numbers of participants analysed, and technical problems with measurement, leading to unreliable or uninterpretable data Although the work is sponsored by UCB Pharma, it has been indicated that the PI of the study is not employed by the sponsor, and that the sponsor cannot change communications or publications about the project

Volker 1978

Methods	Study design: double-blinded, randomised Country: Germany Setting: single centre Intention-to-treat: yes

Volker 1978 (*Continued*)

Participants	Number of participants randomly assigned: 50 (25 in each arm) Number of participants analysed: 50 Exclusions post randomisation: none Losses to follow-up: none Age: range 56 to 65 years Sex: pentoxifylline: 18 males, 7 females, placebo: 17 males, 8 females Inclusion criteria: Fontaine stage II, walking distance < 600 m; no vasoactive substances allowed Exclusion criteria: none reported
Interventions	Treatment: oral pentoxifylline, 400 mg 3 times daily Control: placebo Duration: 4 weeks
Outcomes	Primary: mean PFWD Secondary: quality of life, side effects
Notes	Treadmill protocol: not specified Mean PFWD expressed in metres only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned according to admission into the study; no other information provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported 'double-blind'; no other information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information available to permit judgement
Other bias	Low risk	Study appears free of other bias

ABI: ankle-brachial index.
ABPI: ankle-brachial pressure index.

GI: gastrointestinal.
MI: myocardial infarction.
SFA: superficial femoral artery.
PAD: peripheral arterial disease.
ACD: absolute claudication distance.
WIQ: walking impairment questionnaire.
SF36: Short Form 36.
QoL: quality of life.
COAD: chronic occlusive artery disease.
tds: 3 times daily.
PFWD: pain-free walking distance.
SD: standard deviation.
TWD: total walking distance.

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

Study	Reason for exclusion
Bieron 2005	Not double-blinded
Ciuffetti 1991	Looked at biochemical properties, not TWD or PFWD
Dawson 1999	Single-blinded study
Dettori 1989	Single-blinded for acenocoumarol; therefore no true double-blinding of all trial agents. Outcomes measured in time, not distance
Ehrly 1986	Different outcome measures such as muscle tissue O2 pressure
Ehrly 1987	Different outcome measures such as muscle tissue O2 pressure
Farkas 1993	Duration of therapy only 2 weeks
Fossat 1995	Different outcome measures such as leucocyte activation
Guest 2005	Cost comparison with no clinical outcomes
Hepp 1996	Not double-blinded
Horowitz 1982	Variable doses of pentoxifylline
Incandela 2002	Looked at microcirculatory parameters
Kellner 1976	Participants with Fontaine stage II and III; results for the 2 groups not presented separately
Luk'Janov 1995	Different outcome measures such as haemorheologic and haemodynamic measures evaluated; minimal data on walking distance

(*Continued*)

Milio 2003	Not double-blinded
Milio 2006	Single-blinded study
Panchenko 1997	Open study - no blinding
Pignoli 1985	Not double-blinded
Poggesi 1985	Different outcomes such as circulatory changes and prostaglandin synthesis
Regenthal 1991	Not double-blinded
Reilly 1987	All included participants single-blinded after first 8 weeks; therefore no true randomisation
Rodin 1998	Not a double-blinded clinical trial
Rodin 1998a	Not a double-blinded clinical trial
Roekaerts 1984	Participants with Fontaine stage II and III; results not presented separately for the 2 groups
Rudofsky 1987	Only 1 to 2 weeks of treatment provided
Rudofsky 1988	Only 2 weeks of treatment provided
Rudofsky 1989	Only 2 weeks of treatment provided
Scheffler 1991	Not a double-blinded study. Training for participants provided
Scheffler 1994	Not a double-blinded study. Comparison with exercise performed
Schubotz 1976	Participants with symptoms of critical limb ischaemia
Shustov 1997	Open controlled trial
Singh 2009	Open study
Strano 1984	Participants with stage Fontaine stage II and III; results not presented separately for the 2 groups
Strano 2002	Open study
Thomson 1990	Participants with symptoms of critical limb ischaemia
Tonak 1977	Participants with Fontaine stage II and III; results not presented separately for the 2 groups
Triebe 1992	Open study
Tsang 1994	Different outcome measures such as albumin/creatinine ratio, etc

(*Continued*)

Wang 2003	Different outcome measures such as lipoprotein cholesterol concentrations

ADDITIONAL TABLES

Table 1. PFWD data for comparisons of pentoxifylline versus placebo

Study	Dose	Dur	Pxt	Plc	Px0	SD	Px-E	SD	%age	SD%	Plc0	SD	Plc-E	SD	%age	SD%	Diff
Cesarone 2002b	1600	40	88	90	43	70	166	220	286.0		42	10	155	440	269.0		17.0
Creager 2008	1200	24	86	84	118	83			34.3		120	88			21.2		13.1
Dawson 2000	1200	24	232	239	126	79	202	139	60.3		122	69	180	115	47.5		12.8
Donaldson 1984	600	8	40	40	108.2	85.1	119.3	73.7	10.3		97.1	66.2	129	109.4	32.9		-22.6
Ernst 1992	1200	12	20	20	144	54	364	236	152.8		134	64	384	228	186.6		-33.8
Gallus 1985 cross-over phase I*	1200	8	19	19	27.1		47.7		76.0		28.7		48.3		68.2		7.8
Kiesewter 1988	1200	8	20	20			(+44 m)		43.6				(+3 m)		3.1		40.5

Table 1. PFWD data for comparisons of pentoxifylline versus placebo (*Continued*)

Lindga 1989	1200	26	76	74	77	4			80	12	79	4			60	11	20
Porter 1982a	1200	24	40	42	111		195		76		117		180		54		22
Porter 1982b	1200	24	11	11	54.7		114.2		108.8		100.8		136		34.9		73.9
Volker 1978	1200	4	25	25	331.2	22.7	464.6	23.60	40.3		230.4	15.0	290.2	16.9	25.9		14.4

Dur: duration in weeks.
Pxt: pentoxifylline sample size.
Plc: placebo sample size.
Px0: baseline walking distance in meters for pentoxifylline group.
SD: standard deviation.
Px-E: end walking distance in meters for pentoxifylline group.
%age: percentage improvement in walking distance.
SD%: standard deviation percentage improvement in walking distance.
Plc0: baseline walking distance in meters for placebo group.
Plc-E: end walking distance in meters for placebo group.
Diff: difference in percentage of improvement for pentoxifylline and placebo groups.
*: data presented for phase I only.

Table 2. TWD data for comparisons of pentoxifylline versus placebo

Study	Dose	Dur	Pxt	Plc	Px0	SD	Px-E	SD	%age	SD%	Plc0	SD	Plc-E	SD	%age	SD%	Diff
Belcaro 2002	1600	24	27	26	56	8	161	21	187.5		59	12	103	22	74.6		112.9
Bolling 1977	600	8	10	9	226	33.6	697	125.3	208.0		177	29.2	270	201.8	52.5		155.9
Cesarone 2002b	1600	40	88	90	87	11	287	340	229.9		98	14	180	120	83.7		146.2

Table 2. TWD data for comparisons of pentoxifylline versus placebo (*Continued*)

Creager 2008	1200	24	86	84	316	191			13.9		292	161			3.3		10.6
Dawson 2000	1200	24	232	239	238	119	308	183	29.4		234	119	300	180	28.2		1.2
De Sanctis 2002a	1800	52	56	45	66	13	267	38	304.5		67	11	188	19	180.6		123.9
De Sanctis 2002b	1800	52	75	60	554	66	943	78	70.2		576	71	755	67	31.1		39.1
Di Perri 1983 cross-over phase I*	1200	8	12	12	223	20	359	29	61.00		208	24.6	215	25	3.4		57.6
Ernst 1992	1200	12	20	20	166	58	504	257	203.6		151	58	420	229	178.14		25.5
Gallus 1985 cross-over phase I*	1200	8	19	19	67.8		90.4		33.3		87.9		99.8		13.5		19.8
Lee 2001	800	8	17	16	114	51	147	81	28.9		116	56	121	62	4.3		24.6

Table 2. TWD data for comparisons of pentoxifylline versus placebo (*Continued*)

Lindga 1989	1200	26	76	74	132	9			50.0	9	155	11			29.0	8	21.0
Porter 1982a	1200	24	42	40	172		268		55.8		181		250		38.1		17.7
Porter 1982b	1200	24	11	11	92.1		156		69.4		182.1		187.4		2.9		66.5

Dur: duration in weeks.
Pxt: pentoxifylline sample size.
Plc: placebo sample size.
Px0: baseline walking distance in meters for pentoxifylline group.
SD: standard deviation.
Px-E: end walking distance in meters for pentoxifylline group.
%age: percentage improvement in walking distance.
SD%: standard deviation percentage improvement in walking distance.
Plc0: baseline walking distance in meters for placebo group.
Plc-E: end walking distance in meters for placebo group.
Diff: difference in percentage of improvement for pentoxifylline and placebo groups.
*: data presented for phase I only.

Table 3. PFWD data for comparisons of pentoxifylline versus other treatments

Study	Dose	Dur	Pxt	Oth	Px0	SD	Px-E	SD	%age	Oth0	SD	Oth-E	SD	%age	Diff
Bohme 1988 Gingko biloba	1200	24	13	14	80.1		325.6		306.5	94.6		327.5		246.2	60.3
Cha-con-Quevec 1994 Bu-flomedi	1200	13	15	15	109	63	194	72	78.0	97	73	160	73	64.9	13.1
Cha-con-Quevec	1200	13	15	15	109	63	194	72	78.0	109	56	194	65	78.0	0

Table 3. PFWD data for comparisons of pentoxifylline versus other treatments (*Continued*)

1994 Nifedipine															
Creager 2008* Iloprost	1200	24	86	87					34.3					31.2	3.1
Dawson 2000 Cilostazol	1200	24	232	227	126	79	202	139	60.3	124	81	218	149	75.8	-15.5
Hepp 1992 PGE1	400	4	98	97	72		133		84.7	80		175		118.8	-34.1
Perhoniem 1984 Flunarizine cross-over	1200	12	31	31	135		160		18.5	135		16		19	0
Schellong 2012 PGE1	1200	8	285	276			1.98**	3.61				2.60**	12.22		

*highest dose group iloprost.
**PFWD reported as ratio of distance after 8 weeks of treatment compared with baseline.
Dur: duration in weeks.
Pxt: pentoxifylline sample size.
Oth: other treatment group sample size.
Px0: baseline walking distance in meters for pentoxifylline group.
SD: standard deviation.
Px-E: end walking distance in meters for pentoxifylline group.
%age: percentage improvement in walking distance.
Oth0: baseline walking distance in meters for other treatment group.
Oth-E: end walking distance in meters for other treatment group.

Diff: difference in percentage improvement for pentoxifylline and other treatment groups.

Table 4. TWD data for comparisons of pentoxifylline versus other treatments

Study	Dose	Dur	Pxt	Oth	Px0	SD	Px-E	SD	%age	Oth0	SD	Oth-E	SD	%age	Diff
Accetto 1982 Nylidri HCL	1200	8	23	24	132.6		193.4		45.9	163.4		168.9		3.4	42.5
Bohme 1988 Gingko biloba	1200	24	13	14	189.5		427.3		125.5	203		436.5		115.0	10.5
Chacon-Quevec 1994 Buflomedi	1200	13	15	15	180	67	226	57	25.6	159	76	205	66	28.9	-3.3
Chacon-Quevec 1994 Nifedipine	1200	13	15	15	180	67	226	57	25.6	186	54	226	49	21.5	4.1
Ciocon 1997 Aspirin	1200	6	45	45	1 mile		2 miles		100	0.8 miles		1.2 miles		50	50
Creager 2008 Iloprost*	1200	24	86	87					13.9					11.2	2.7

Table 4. TWD data for comparisons of pentoxifylline versus other treatments (*Continued*)

Dawson 2000 Cilostazol	1200	24	232	227	238	119	308	183	29.4	241	123	350	209	45.2	-15.8
Hepp 1992 PGE1	400	4	98	97	115		190		65.2	129		230		78.3	-13.1
Lee 2001 Cilostazol	800	8	17	17	114	51	147	81	28.9	111	30	145	53	30.6	-1.7
Perhoniem 1984 Flunarizine cross-over	1200	12	31	31	255				18	255				43	-25
Schellong 2012 PGE1	1200	8	285	276			1.76**	1.78				1.64**	0.86		

*highest dose group iloprost.
**TWD reported as ratio of distance after 8 weeks of treatment compared with baseline.
Dur: duration in weeks.
Pxt: pentoxifylline sample size.
Oth: other treatment group sample size.
Px0: baseline walking distance in meters for pentoxifylline group.
SD: standard deviation.
Px-E: end walking distance in meters for pentoxifylline group.
%age: percentage improvement in walking distance.
Oth0: baseline walking distance in meters for other treatment group.
Oth-E: end walking distance in meters for other treatment group.
Diff: difference in percentage improvement for pentoxifylline and other treatment groups.

APPENDICES

Appendix 1. CRS search strategy

#1	MESH DESCRIPTOR Arteriosclerosis	863
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	69
#4	MESH DESCRIPTOR Atherosclerosis	489
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	695
#6	MESH DESCRIPTOR Intermittent Claudication	664
#7	MESH DESCRIPTOR Ischemia	718
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2072
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	7440
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	6179
#11	(peripheral near3 dis*):TI,AB,KY	2717
#12	(claudic* or IC):TI,AB,KY	2472
#13	(isch* or CLI):TI,AB,KY	18739
#14	arteriopathic:TI,AB,KY	7
#15	dysvascular*:TI,AB,KY	9
#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	75
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	110

(*Continued*)

#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	70
#19	((iliac or femoral or popliteal or femoro* or fempop* or crural) near3(occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	734
#20	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1061
#21	MESH DESCRIPTOR Iliac Artery	135
#22	MESH DESCRIPTOR Popliteal Artery	246
#23	MESH DESCRIPTOR Femoral Artery	723
#24	MESH DESCRIPTOR Tibial Arteries	30
#25	(((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*))):TI,AB,KY	858
#26	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	35405
#27	MESH DESCRIPTOR Pentoxifylline EXPLODE ALL TREES	408
#28	(pentox* OR oxypent*):TI,AB,KY	871
#29	MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES	4914
#30	(phosphodiesterase near2 inhibitor*):TI,AB,KY	1286
#31	BL-191:TI,AB,KY	5
#32	#27 OR #28 OR #29 OR #30 OR #31	5708
#33	#26 AND #32	703

WHAT'S NEW

Last assessed as up-to-date: 8 April 2015.

Date	Event	Description
4 May 2015	New search has been performed	Searches rerun. One new study excluded and one study that was previously recorded as 'Ongoing' now recorded as an included study
4 May 2015	New citation required but conclusions have not changed	Searches rerun. One new study excluded and one study that was previously recorded as 'Ongoing' now recorded as an included study, with limited data available from ClinicalTrials.gov (comparison pentoxifylline vs PGE1). New author added to the review team. Conclusions not changed

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 1, 2012

Date	Event	Description
22 October 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

For this review update:

RF evaluated studies for inclusion, performed data extraction, assessed risk of bias and updated manuscript text.

KS evaluated studies for inclusion, performed data extraction and assessed risk of bias.

ES, MAH, AB and JM provided editorial support.

DECLARATIONS OF INTEREST

JM: Chair of NICE guideline development group for PAD and co-author of several cited papers (Meng 2014; Squires 2010; Squires 2011; Stevens 2012).

KS: none known

RF: none known

ES: none known

MAH: none known

AB: none known

JM: Professor Michaels has received programme funding from the NIHR for research related to vascular disease and has received payments for secondment for committee work from the HTA Prioritisation Panel and the NICE Appraisal Committee, for consultancy from Michaels Consulting Limited (as director of company that provides consultancy for a number of companies - none directly related to the subject of this review) and for a review of practice guidelines from KCE (Belgian Health Care Knowledge Centre)

SOURCES OF SUPPORT

Internal sources

- Sheffield Vascular Institute, Northern General Hospital, Sheffield Teaching Hospital, UK.
- School of Health and Related Research (ScHARR), University of Sheffield, UK.

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

To adhere to updated Cochrane guidelines for assessment of bias, we have included an assessment of bias performed using the 'Risk of bias' tool of The Cochrane Collaboration and have removed the Jadad score.

We have removed eight studies from the 'Excluded studies' presented in the previous version of this review, as they were considered not relevant in the light of current Cochrane guidelines.

INDEX TERMS

Medical Subject Headings (MeSH)

Ankle Brachial Index; Intermittent Claudication [*drug therapy]; Pentoxifylline [*therapeutic use]; Platelet Aggregation Inhibitors [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Vasodilator Agents [*therapeutic use]; Walking

MeSH check words

Humans