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Cilostazol for intermittent claudication (Review)

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Cilostazol for intermittent claudication (Review)

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[Intervention Review]

Cilostazol for intermittent claudication

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ABSTRACT

Background

Peripheral arterial disease (PAD) affects between 4% and 12% of people aged 55 to 70 years, and 20% of people over 70 years. A common complaint is intermittent claudication, characterised by pain in the legs or buttocks that occurs with exercise and which subsides with rest. Compared with age-matched controls, people with intermittent claudication have a three- to six-fold increase in cardiovascular mortality. Symptoms of intermittent claudication, walking distance, and quality of life can be improved by risk factor modification, smoking cessation, and a structured exercise programme. Antiplatelet treatment is beneficial in patients with intermittent claudication for the reduction of vascular events but has not previously been shown to influence claudication distance. This is an update of a review first published in 2007.

Objectives

To determine the effect of cilostazol (an antiplatelet treatment) on improving initial and absolute claudication distances, and in reducing mortality and vascular events in patients with stable intermittent claudication.

Search methods

For this update, the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched October 2013) and CENTRAL (2013, Issue 9).

Selection criteria

Double-blind, randomised controlled trials (RCTs) of cilostazol versus placebo, or versus other antiplatelet agents in patients with stable intermittent claudication.

Data collection and analysis

Two authors independently assessed trials for selection and independently extracted data. Disagreements were resolved by discussion. We performed the meta-analysis as a fixed-effect model with weighted mean differences (WMDs) and 95% confidence intervals (CIs) for continuous data, and odds ratios (ORs) with 95% CIs for dichotomous data.

Main results

We included fifteen double-blind, RCTs comparing cilostazol with placebo, or medications currently known to increase walking distance e.g. pentoxifylline. There were a total of 3718 randomised participants with treatment durations ranging from six to 26 weeks. All participants had intermittent claudication secondary to PAD. Comparisons included cilostazol twice daily, with dosages of 50 mg, 100 mg and 150 mg compared with placebo, and cilostazol 100 mg, twice daily, compared with pentoxifylline 400 mg, three times daily. The

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methodological quality of the trials was generally low, with the majority being at an unclear risk for selection bias, performance bias, detection bias and other bias. Attrition bias was generally low, but reporting bias was high or unclear in the majority of the studies. For eight studies data were compatible for comparison by meta-analysis, but data for seven studies were too heterogeneous to be pooled. For the studies included in the meta-analysis, for initial claudication distance (ICD - the distance walked on a treadmill before the onset of calf pain) there was an improvement in the cilostazol group for the 100 mg and 50 mg twice daily, compared with placebo (WMD 31.41 metres, 95% CI 22.38 to 40.45 metres; $P < 0.00001$) and WMD 19.89 metres, 95% CI 9.44 to 30.34 metres; $P = 0.0002$), respectively. ICD was improved in the cilostazol group for the comparison of cilostazol 150 mg versus placebo and cilostazol 100 mg versus pentoxifylline, but only single studies were used for these analyses. Absolute claudication distance (ACD - the maximum distance walked on a treadmill) was significantly increased in participants taking cilostazol 100 mg and 50 mg twice daily, compared with placebo (WMD 43.12 metres, 95% CI 18.28 to 67.96 metres; $P = 0.0007$) and WMD 32.00 metres, 95% CI 14.17 to 49.83 metres; $P = 0.0004$), respectively. As with ICD, ACD was increased in participants taking cilostazol 150 mg versus placebo, but with only one study an association cannot be clearly determined. Two studies comparing cilostazol to pentoxifylline had opposing findings, resulting in an imprecise CI (WMD 13.42 metres (95% CI -43.51 to 70.35 metres; $P = 0.64$). Ankle brachial index (ABI) was lowered in the cilostazol 100 mg group compared with placebo (WMD 0.06, 95% CI 0.04 to 0.08; $P < 0.00001$). The single study evaluating ABI for the comparison of cilostazol versus pentoxifylline found no change in ABI.

There was no association between treatment type and all-cause mortality for any of the treatment comparisons, but there were very few events, and therefore larger, adequately powered studies will be needed to assess if there is a relationship. Only one study evaluated individual cardiovascular events, and from this study there is no clear evidence of a difference between any of the treatment groups and risk of myocardial infarction or stroke. We evaluated adverse side effects, and in general cilostazol was associated with a higher odds of headache, diarrhoea, abnormal stool, dizziness and palpitations. We only reported quality of life measures descriptively as there was insufficient statistical detail within the studies to combine the results, although there was a possible indication in improvement of quality of life in the cilostazol treatment groups.

Authors' conclusions

Cilostazol has been shown to be of benefit in improving walking distance in people with intermittent claudication secondary to PAD. Although there is an increase in adverse side effects, they are generally mild and treatable. There is currently insufficient data on whether taking cilostazol results in a reduction of all-cause mortality and cardiovascular events or an improvement in quality of life. Future research into the effect of cilostazol on intermittent claudication should carefully consider comparability, sample size and homogeneity when designing a study.

PLAIN LANGUAGE SUMMARY

Cilostazol for peripheral arterial disease

Blockages in the arteries to the legs - peripheral arterial disease - affect 20% of people over 70 years of age and 4% to 12% of the population aged 55 to 70 years. Approximately 40% of those affected with peripheral arterial disease complain of pain in the legs on walking, this is known as intermittent claudication. Intermittent claudication is characterised by pain in the legs or buttocks that occurs with exercise and which subsides with rest. The symptoms of intermittent claudication are an indicator for the development of blocked arteries elsewhere in the body. Compared with age-matched controls, people with intermittent claudication have a three- to six-fold increased chance of dying as a result of cardiovascular events.

The majority of patients with intermittent claudication are treated with best medical management. Symptoms of intermittent claudication, walking distance, and quality of life can be improved by risk factor modification, which includes smoking cessation and a structured exercise programme. Further cardiovascular risk modification includes treatment for hypertension, diabetes and cholesterol reduction. In practice, compliance with best medical treatment is poor and most people continue to have symptoms of intermittent claudication. Some drug therapies are used specifically to help improve walking distance in intermittent claudication and cilostazol is one of these. We have looked at the evidence supporting cilostazol in improving the symptoms of intermittent claudication.

This review included fifteen double-blind, randomised controlled trials, with a total of 3718 participants. The risk of bias was poor over all of the studies but the results from this review suggest that cilostazol improves walking distances and ankle-brachial pressure (blood pressure in the legs) for people with intermittent claudication. Side effects were mostly mild. There is currently not enough information to determine if there is an association between cilostazol and all-cause mortality, cardiovascular events or changes in quality of life.

BACKGROUND

Description of the condition

Lower limb peripheral arterial disease (PAD) is a manifestation of atherosclerosis in the lower extremities, affecting 20% of people over 70 years of age and 4% to 12% of the population aged 55 to 70 years (Dormandy 1999; PAD 2003). Patients with PAD commonly complain of intermittent claudication, which is characterised by pain in the legs or buttocks that occurs with exercise and subsides with rest, and occurs in 40% of PAD patients (Dormandy 1999). Despite the relatively benign prognosis for the affected limb, the symptoms of intermittent claudication are an indicator for systemic atherosclerosis. Compared with age-matched controls, people with intermittent claudication have a three- to six-fold increase in cardiovascular mortality (Leng 1996).

The majority of patients with intermittent claudication are treated with best medical management (Khan 2005), and the mainstay of treatment for patients with PAD is cardiovascular risk factor modification. This consists of smoking cessation, prescribed exercise (Watson 2008), antiplatelet treatment, lipid-lowering therapy and control of blood pressure and diabetes. Only two-thirds of compliant patients will achieve symptomatic relief of intermittent claudication after three to six months. Some patients may not be able to comply with prescribed exercise due to associated comorbidity or social reasons. As angioplasty or surgery are only used in severe, disabling or progressive intermittent claudication, these symptomatic patients may benefit from adjunctive therapy.

Description of the intervention

Cilostazol, with the trade name Pletal, is a phosphodiesterase-III inhibitor that has antiplatelet and antithrombotic actions (Sallustio 2010). Cilostazol also acts on smooth muscle cells as a vasodilator with beneficial effects on triglycerides and high-density lipoproteins (Chapman 2003). Cilostazol is indicated for intermittent claudication but there is also evidence to suggest that cilostazol may have a role in reducing restenosis after endovascular therapy and coronary stenting (Iida 2008; Lee 2013). The suggested dose of cilostazol for intermittent claudication is 100 mg taken orally twice daily. Cilostazol is contraindicated in patients with congestive heart failure and those with renal or hepatic impairment (Chapman 2003; Dawson 2001).

How the intervention might work

Antiplatelet therapy is effective in long term secondary prevention of vascular events in patients at high risk of vascular disease, including those who have had ischaemic stroke or acute myocardial infarction, and a benefit of antiplatelet treatment in patients with intermittent claudication in the reduction of vascular events has been previously observed (ATT 2002; PAD 2003; Robless 2001). It is unclear exactly how cilostazol works to improve claudication, but the mechanism is most likely multifactorial, involved with several of cilostazol's actions, specifically vasodilation, possible beneficial inhibition of platelet aggregation, and altering a patient's lipid profile (Chapman 2003; Rizzo 2011; Ueno 2011).

Why it is important to do this review

In practice, compliance with best medical treatment is poor and most people remain symptomatic with intermittent claudication.

Until recently there have been three options; supervised exercise, angioplasty or bypass surgery. Compliance with supervised exercise is poor, the durability of angioplasty is unproven and surgery carries significant morbidity and mortality (Fowkes 1998). Many pharmacological agents have been advocated for the symptomatic treatment of intermittent claudication but until recently none have gained acceptance. Cilostazol has been approved for the treatment of intermittent claudication and has been shown to improve pain-free walking distance (Barnett 2004). If cilostazol is found to reduce the symptoms of claudication, as well as cardiovascular risk in patients with PAD, it would be beneficial for patients whose options are otherwise limited, and possibly extreme. This is an update of a review first published in 2007 (Robless 2007).

OBJECTIVES

To determine the effect of cilostazol on improving initial and absolute claudication distances and in reducing mortality and vascular events in patients with stable intermittent claudication.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, RCTs of cilostazol versus placebo, or versus other antiplatelet agents.

Types of participants

We included patients with stable intermittent claudication (determined by a physician or investigator). We excluded studies that identified their participants as those with peripheral arterial disease (PAD), atherosclerosis obliterans, or similar, but did not specifically state that their study population had intermittent claudication.

Types of interventions

Cilostazol versus placebo, or versus an alternative antiplatelet agent or medications currently known to increase walking distance e.g. pentoxifylline. The cilostazol, antiplatelet or placebo interventions must have been given for at least four weeks. We did not include comparisons with exercise, anticoagulants or surgery.

Types of outcome measures

Primary outcomes

- Initial claudication distance (ICD) (the distance walked on a treadmill before the onset of calf pain)

Secondary outcomes

- Absolute claudication distance (ACD) (the maximum distance walked on a treadmill)
- All-cause mortality
- Ankle brachial index (ABI)
- Cardiovascular events (i.e. myocardial infarction and stroke)
- Progression to surgery
- Adverse effects
- Quality of life

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched October 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 9, part of *The Cochrane Library*, (www.thecochranelibrary.com). See [Appendix 1](#) for details of the search strategy used to search CENTRAL. 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 Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

We searched the reference lists of articles retrieved by electronic searches for additional citations.

Data collection and analysis

Selection of studies

For this update two review authors (RB and MS) independently evaluated studies for inclusion based on selection criteria. Disagreements were resolved with discussion between the two review authors. For the previous review version PR and GS selected the studies.

Data extraction and management

Two authors (RB and MS) independently extracted the data. From each included trial we collected information regarding the trial design, patient characteristics, therapy type, dosages and treatment periods. We collected information for ICD, ACD, ABI, all-cause mortality, cardiovascular events and quality of life for each study. We documented additional information on adverse effects from each trial. Where necessary, we contacted the principal authors of the included studies for information. We resolved disagreements through discussion.

Assessment of risk of bias in included studies

RB and MS independently assessed the methodological quality of included trials using the 'Risk of bias' tool from the Cochrane Collaboration ([Higgins 2011](#)). We assessed the following domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel and blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. We classified the domains as low risk of bias, high risk of bias, or unclear risk of bias, according to the guidelines in [Higgins 2011](#). Disagreements were resolved by discussion between the two review authors assessing bias.

Measures of treatment effect

We pooled the data on the initial claudication distances (ICDs) and absolute claudication distances (ACDs) and other available outcomes from each trial to obtain an overall estimate of the effectiveness of cilostazol therapy. We aimed to calculate mean

change from baseline for each trial, which is more informative of treatment effect than simply comparing final walking distances because it takes baseline measures into account. Due to the differences in treadmill testing methods between the studies, mean change from baseline is the only appropriate measure for treatment effect. The results for continuous data are presented as a weighted mean difference (WMD) with 95% confidence intervals (CIs), and dichotomous data as odds ratios (ORs) with 95% CIs. We performed statistical analyses according to the guidelines for reviews outlined in the Cochrane Peripheral Vascular Diseases Group's module (<http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html>).

Unit of analysis issues

The unit of analysis was the individual participant in all studies included in this review.

Dealing with missing data

All of the analyses were based on the intention-to-treat data from the individual trials. In order to maintain intent-to-treat analysis, all participants randomised to treatment based on the trial report were used in the analysis of this review. Where necessary, we contacted study authors for missing data.

Assessment of heterogeneity

We evaluated trial heterogeneity using χ^2 and I^2 testing, which describe the variability in effect estimates that are due to heterogeneity between studies, rather than chance. The I^2 is given as a percentage, with a measure of 0%, meaning little to no variability in effect estimates between the studies, and progressing amounts of variability with increased I^2 percentage values ([Higgins 2011](#)).

Assessment of reporting biases

Reporting bias was assessed by funnel plots if more than ten studies were included in the outcome meta-analysis.

Data synthesis

We used meta-analysis for data synthesis for outcomes that were adequately comparable between studies. For continuous data, we displayed results as WMD (95% CIs). For dichotomous data, we displayed results as OR (95% CIs). A P value of < 0.05 was considered statistically significant. If tests for heterogeneity found $I^2 > 50\%$, we used a random-effects model, otherwise, we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We did not plan to carry out subgroup analyses.

Sensitivity analysis

In order to determine that robust conclusions can be drawn using meta-analyses, we removed studies of a lower quality (defined as studies with five or more high risk or unclear risk ratings within the seven domains evaluated for risk of bias) from the analysis to determine the effect on the association.

RESULTS

Description of studies

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.

Included studies

See [Characteristics of included studies](#) for more detail.

We included an additional eight studies in this update ([Brass 2012](#); [de Albuquerque 2008](#); [O'Donnell 2009](#); [Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-98-213](#)). We had previously excluded the [Otsuka Study 21-94-301](#), but access to new data allowed us to reclassify this study as an included study. We added five references to five previously included studies ([Beebe 1999](#); [Dawson 1998](#); [Dawson 2000](#); [Elam 1998](#); [Money 1998](#)).

For this update we included 15 studies. A total of 3718 participants were randomised with treatment duration between six and 26 weeks. All participants had intermittent claudication secondary to peripheral arterial disease (PAD). All included studies compared cilostazol 100 mg twice daily with placebo. In addition, two studies compared cilostazol 50 mg twice daily with placebo ([Beebe 1999](#); [Strandness 2002](#)), and one study compared cilostazol 150 mg twice daily with placebo ([Otsuka Study 21-95-201](#)). Three studies compared cilostazol 100 mg twice daily with pentoxifylline 400 mg three times daily ([Dawson 2000](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-98-213](#)), one study compared cilostazol 100 mg twice daily with pentoxifylline 600 mg twice daily ([de Albuquerque 2008](#)) and one study compared cilostazol 100 mg twice daily with the antiplatelet K-134 50 mg and 100 mg twice daily ([Brass 2012](#)). It should be noted that the comparisons with pentoxifylline 600 mg twice daily and k-134 are not addressed in this review.

For two studies the duration of treatment was six weeks ([Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#)). Four studies had a treatment duration of 12 weeks ([Dawson 1998](#); [Elam 1998](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-95-201](#)), and one study treated participants for 16 weeks ([Money 1998](#)). The [de Albuquerque 2008](#) study had a treatment period of 20 weeks. The most common treatment duration was 24 weeks, with six studies ([Beebe 1999](#); [Dawson 2000](#); [O'Donnell 2009](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-98-213](#); [Strandness 2002](#)), and one study had a treatment duration of 26 weeks ([Brass 2012](#)). The number of participants in each study ranged from 19 in [Otsuka Study 21-87-101](#) to 780 in [Otsuka Study 21-98-213](#).

For the walking distance outcomes (initial claudication distance (ICD) and absolute claudication distance (ACD)) the treadmill test methods varied between three protocols. Five studies used a method with an immediate and constant gradient of 10% and a constant speed of 3.2 km/h ([O'Donnell 2009](#); [Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#)). Five studies used a similar method with an immediate and constant gradient of 12.5% and a constant speed of 3.2 km/h ([Beebe 1999](#); [Dawson 1998](#); [Otsuka Study 21-95-201](#); [Otsuka Study 21-98-213](#); [Strandness 2002](#)). Four studies adopted a delayed gradient treadmill method where the gradient began at 0% and increased by 3.5% every three minutes, with a constant

speed of 3.2 km/h ([Dawson 2000](#); [de Albuquerque 2008](#); [Elam 1998](#); [Money 1998](#)). It should be noted the [de Albuquerque 2008](#) study did not state the gradient by which the treadmill was increased, but it was assumed to be similar to the other three studies. The [Brass 2012](#) study only described their treadmill method as "graded" and referred to another study, but we were unable to determine from this which method was used.

Of the eight newly included studies seven do not include data on walking distances or ankle brachial index (ABI) that are appropriate to contribute to the meta-analysis of walking distances and ABI ([Brass 2012](#); [de Albuquerque 2008](#); [O'Donnell 2009](#); [Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#)). This is due to methodological differences in the reporting of outcomes that did not allow us to calculate mean change and standard deviations. Also, due to the large differences between studies, we deemed imputation inappropriate. Descriptions of the findings of these studies will be addressed under the appropriate outcome headings. [Table 1](#) describes reasoning for why these studies could not appropriately be included in the meta-analyses of walking distances and ABI. Data from five studies was gathered solely from unpublished study data ([Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-95-201](#)).

Excluded studies

See [Characteristics of excluded studies](#) for more detail.

For this update we excluded seven additional studies ([ACCELA](#); [Hsieh 2009](#); [Kim 2013](#); [MASCOT](#); [Otsuka Study PUIC-1](#); [Otsuka Study PUIC-2](#); [SPAD](#)), making a total of nine excluded studies, ([ACCELA](#); [CASTLE](#); [Hsieh 2009](#); [Kim 2013](#); [MASCOT](#); [Otsuka Study PUIC-1](#); [Otsuka Study PUIC-2](#); [Samra 2003](#); [SPAD](#)). We excluded the [ACCELA](#) study because the intervention arms were not clear, and we were unable to determine if clopidogrel was also used. We excluded one study because the duration of follow-up far exceeded that of the other included studies, and follow-up data at earlier time-points was not available ([CASTLE](#)). For the [Hsieh 2009](#), [Kim 2013](#) and [SPAD](#) studies it cannot currently be determined if their study population was of participants with intermittent claudication, and two of those studies did not report outcomes within the scope of this review. The [MASCOT](#) study was discontinued early, and there is no outcome data available for the trial. From the limited information provided for the [Otsuka Study PUIC-1](#) it cannot be determined if the study is double-blinded. The [Otsuka Study PUIC-2](#) abstract does not contain enough information on the methods and results of the study to be included at this time. A final study was non-randomised and was therefore excluded ([Samra 2003](#)).

Risk of bias in included studies

[Figure 2](#) and [Figure 3](#) offer graphical summaries of risk of bias for the 15 included studies. The main reason for an "unclear" rating was due to lack of description by the authors.

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beebe 1999	+	?	+	+	+	+	?
Brass 2012	+	+	?	?	+	+	+
Dawson 1998	?	?	+	?	+	-	?
Dawson 2000	+	+	+	?	+	+	?
de Albuquerque 2008	?	+	+	?	+	-	+
Elam 1998	?	?	?	+	+	-	?
Money 1998	?	?	?	?	+	+	?
O'Donnell 2009	?	+	+	?	+	+	+
Otsuka Study 21-86-101	?	?	?	?	+	-	?
Otsuka Study 21-86-103	?	?	?	?	?	-	?
Otsuka Study 21-87-101	?	?	?	?	+	+	?
Otsuka Study 21-94-301	?	?	+	?	+	-	?
Otsuka Study 21-95-201	?	?	?	?	+	-	?
Otsuka Study 21-98-213	?	?	?	?	?	?	?
Strandness 2002	?	?	+	+	+	-	?

Allocation

The majority of included studies did not clearly describe randomisation sequence generation methods, leading to a rating of unclear risk of bias, but two studies (Brass 2012; Dawson 2000) did describe use of voice interactive computerised methods of randomisation and the Beebe 1999 identified the use of a coded randomisation list, which would put them at a lower risk of bias.

For allocation concealment we considered the Brass 2012 and Dawson 2000 studies to be at low risk because the use of the

computerised methods helped to ensure that the participants and researchers could not determine the treatment allocation. The de Albuquerque 2008 and O'Donnell 2009 studies had adequate allocation concealment with the use of coded or sealed envelopes, but the remainder of the studies did not describe their allocation methods thoroughly enough to determine concealment.

Blinding

Although all 15 included studies used a placebo control, only seven studies adequately described their methods of blinding to

ensure that both participants and researchers would not be able to determine treatment (Beebe 1999; Dawson 1998; Dawson 2000; de Albuquerque 2008; O'Donnell 2009; Otsuka Study 21-94-301; Strandness 2002). None of the studies described blinding of assessors for all outcomes measured, but three studies (Beebe 1999; Elam 1998; Strandness 2002) did give a detailed description of assessor blinding for some of their outcomes, so we determined their risk of detection bias as low. The remainder of the studies to be at an unclear risk of detection bias.

Incomplete outcome data

Only two studies had unclear risk of attrition bias (Otsuka Study 21-86-103; Otsuka Study 21-98-213) and the remainder were at low risk. The Otsuka Study 21-86-103 study had an overlap of reasons for participants that dropped out, with no discussion of multiple reasons for dropouts. The data and information on the Otsuka Study 21-98-213 study was retrieved from a secondary NICE report, and not enough detail was provided to determine incomplete outcome data.

Selective reporting

Six studies had a low risk of reporting bias because all indicated outcomes and time-points were reported on (Beebe 1999; Brass 2012; Dawson 2000; Money 1998; O'Donnell 2009; Otsuka Study 21-87-101). One study had unclear risk of reporting bias because there was not adequate reporting of outcomes (Otsuka Study 21-98-213), and eight studies had a high risk of reporting bias because they described in the methods outcomes or time-points of interest that were not reported on (Dawson 1998; de Albuquerque 2008; Elam 1998; Otsuka Study 21-86-101; Otsuka Study 21-86-103; Otsuka Study 21-94-301; Otsuka Study 21-95-201; Strandness 2002).

Other potential sources of bias

The majority of studies received some form of support from Otsuka Pharmaceuticals, the company that formulated cilostazol, and therefore could potentially have biased design, collection or reporting of results (Beebe 1999; Dawson 1998; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-86-101; Otsuka Study 21-86-103; Otsuka Study 21-87-101; Otsuka Study 21-94-301; Otsuka Study 21-95-201; Otsuka Study 21-98-213; Strandness 2002).

Effects of interventions

We conducted sensitivity analysis by removing low quality studies (Dawson 1998; Elam 1998; Money 1998; Otsuka Study 21-86-101; Otsuka Study 21-86-103; Otsuka Study 21-87-101; Otsuka Study 21-94-301; Otsuka Study 21-95-201; Otsuka Study 21-98-213) in all outcomes, except cardiovascular events. However, we only performed this type of sensitivity analysis for analyses comparing cilostazol 100 mg versus placebo, as these were the only comparisons to have sufficient included studies to evaluate an association with and without studies of low quality.

Initial claudication distance (ICD)

Cilostazol 100 mg twice daily versus placebo

There were six studies comparing cilostazol 100 mg versus placebo eligible for inclusion in the meta-analysis (Beebe 1999; Dawson 1998; Dawson 2000; Money 1998; Otsuka Study 21-95-201; Strandness 2002). In the fixed-effect model, participants taking cilostazol had a statistically significant higher ICD, with a WMD of

31.41 metres (95% CI 22.38 to 40.45 metres; $P < 0.00001$), compared with those taking placebo (Analysis 1.1). When low quality studies were removed there was very little change in the meta-analysis results.

Eight additional studies reported data on change in ICD compared with baseline, but the data was not eligible for inclusion in the meta-analysis (Brass 2012; de Albuquerque 2008; O'Donnell 2009; Otsuka Study 21-86-101; Otsuka Study 21-86-103; Otsuka Study 21-87-101; Otsuka Study 21-94-301; Otsuka Study 21-98-213). Brass 2012 reported change in initial claudication time, with participants in the cilostazol group showing an increase of 60 seconds $\pm$ standard deviation (SD) of 95 seconds, and the placebo group showing a smaller increase of 44 seconds $\pm$ 102 seconds. The de Albuquerque 2008 report did not break down the ICD outcome by treatment group, and an estimate of change in ICD is meaningless for the whole study population. O'Donnell 2009 reported no difference in the change in effect between the cilostazol group and placebo, 67.0% and 51.6%, respectively, $P = 0.63$. Otsuka Study 21-86-101 reported an arithmetic placebo-corrected mean change of 41.9 metres and a statistically significant ratio of geometric mean changes of 1.32 (95% CI 1.07 to 1.64; $P = 0.01$), favouring cilostazol. In contrast, Otsuka Study 21-86-103 reported a mean change of -2.5 metres for the cilostazol group and 34.4 metres for the placebo group, and a statistically significant ratio of geometric mean changes of 0.69 (95% CI 0.53 to 0.91; $P = 0.01$), favouring the placebo group. Otsuka Study 21-87-101 also reported findings favouring placebo, with an arithmetic placebo-corrected mean change of -92 metres, and a non-significant ratio of geometric mean changes of 0.69 (95% CI 0.42 to 1.13; $P = 0.13$). Otsuka Study 21-94-301 reported a placebo-corrected mean change of 15 metres and a ratio of geometric mean changes of 1.01, favouring cilostazol. Otsuka Study 21-98-213 reported similar mean changes for the cilostazol and placebo groups of 47.3 metres and 45.3 metres, respectively, and a ratio of geometric mean changes of 1.02 (95% CI 0.92 to 1.13; $P = 0.769$).

Cilostazol 50 mg twice daily versus placebo

Two studies compared cilostazol 50 mg with placebo (Beebe 1999; Strandness 2002) and the fixed-effect model found a statistically significant higher ICD (WMD 19.89 metres, 95% CI 9.44 to 30.34 metres; $P = 0.0002$) in the cilostazol treatment group (Analysis 1.2).

Cilostazol 150 mg twice daily versus placebo

Only the Otsuka Study 21-95-201 study compared cilostazol 150 mg versus placebo. There was no observable difference between the treatment groups in ICD (WMD 15.70 metres, 95% CI -5.71 to 37.11 metres). As only one study is included in the analysis an overall association cannot be determined (Analysis 1.3).

Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily

A single study compared cilostazol 100 mg to pentoxifylline 400 mg (Dawson 2000), which found a WMD of 20.00 metres (95% CI -1.50 to 41.50 metres) (Analysis 1.4).

Additionally, two studies that could not be included in the meta-analysis compared change in ICD from baseline between cilostazol 100 mg and pentoxifylline 400 mg (Otsuka Study 21-94-301; Otsuka Study 21-98-213). Otsuka Study 21-94-301 reported a placebo-

corrected mean change of 10 metres in the pentoxifylline group and a ratio of geometric mean change from baseline of 1.02, favouring pentoxifylline. The [Otsuka Study 21-98-213](#) found an arithmetic mean change of 47.3 metres for the cilostazol group and 62.6 metres for the placebo group suggesting a greater increase for the pentoxifylline group. There was also a non-significant ratio of geometric means comparing cilostazol to pentoxifylline of 0.94 (95% CI 0.95 to 1.12; $P = 0.260$).

Absolute claudication distance (ACD)

Cilostazol 100 mg twice daily versus placebo

Eight studies were included in the meta-analysis for ACD comparing cilostazol 100 mg versus placebo ([Beebe 1999](#); [Dawson 1998](#); [Dawson 2000](#); [Elam 1998](#); [Money 1998](#); [Otsuka Study 21-95-201](#); [Otsuka Study 21-98-213](#); [Strandness 2002](#)). The results of the random-effects model showed a statistically significant higher ACD in the cilostazol arm (WMD 43.11 metres, 95% CI 18.27 to 67.95 metres; $P = 0.0007$; $I^2 = 78\%$) ([Analysis 2.1](#)). When low quality studies were removed there was very little change in the meta-analysis results.

Seven additional studies reported on ACD, but their data was incompatible for meta-analysis ([Brass 2012](#); [de Albuquerque 2008](#); [O'Donnell 2009](#); [Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#)). [Brass 2012](#) measured peak walking time, similar to ACD, and found that the mean change ($\pm$ standard deviation) from baseline for the cilostazol group was 122 seconds $\pm$ 190 seconds, and for the placebo group a mean change of 72 seconds $\pm$ 196 seconds. The [de Albuquerque 2008](#) study reported a mean change in maximal walking distance, 'expressed as per cent of control' of approximately 130% to 140%. This data was read from a graph, and no further information was given on the placebo arm. [O'Donnell 2009](#) reported a statistically significant increased change in effect between the cilostazol group and placebo, 161.7% and 79.0%, respectively, $P = 0.048$. [Otsuka Study 21-86-101](#) reported a placebo-corrected arithmetic mean change for the cilostazol group of 49.7 metres, and a non-significant ratio of geometric means of 1.17 (95% CI 0.97 to 1.42; $P = 0.09$). [Otsuka Study 21-86-103](#)'s results did not support cilostazol for increased ACD, with a mean change of -6.9 metres for the cilostazol group and 30.3 metres for the placebo group, and a statistically significant ratio of geometric means of 0.83 (95% CI 0.70 to 0.98; $P = 0.03$), favouring the placebo arm. [Otsuka Study 21-87-101](#) also reported ACD results that do not support cilostazol with a placebo-corrected mean change for the cilostazol group of -99.1 metres, and a ratio of geometric means of 0.83 (95% CI 0.46 to 1.51; $P = 0.52$). [Otsuka Study 21-94-301](#) reported a placebo-corrected arithmetic mean change for the cilostazol group of 33.6 metres and a ratio of geometric means of 1.06, favouring cilostazol.

Cilostazol 50 mg twice daily versus placebo

Two studies compared cilostazol 50 mg to placebo ([Beebe 1999](#); [Strandness 2002](#)), and their resulting fixed-effect meta-analysis found a statistically significant higher ACD in the cilostazol arm (WMD 32.00 metres, 95% CI 14.17 to 49.83 metres; $P = 0.0004$) ([Analysis 2.2](#)).

Cilostazol 150 mg twice daily versus placebo

Only the [Otsuka Study 21-95-201](#) compared cilostazol 150 mg with placebo, and found a WMD of 51.80 metres with a wide 95% CI spanning 0.01 to 103.59 metres ([Analysis 2.3](#)).

Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily

Two studies comparing cilostazol 100 mg with pentoxifylline 400 mg could be included in the ACD meta-analysis ([Dawson 2000](#); [Otsuka Study 21-98-213](#)). The resulting random-effects model found no difference between the treatment groups with a WMD of 13.41 metres (95% CI -43.52 to 70.34 metres; $P = 0.64$; $I^2 = 91\%$) ([Analysis 2.4](#)).

[Otsuka Study 21-94-301](#) found similar placebo-corrected mean changes of 33.6 metres for the cilostazol group and 34 metres for the pentoxifylline group, with a treatment effect ratio of cilostazol to pentoxifylline of 0.99, favouring pentoxifylline.

All-cause mortality

Cilostazol 100 mg twice daily versus placebo

All-cause mortality was reported in eight studies for this treatment profile ([Beebe 1999](#); [Brass 2012](#); [Dawson 1998](#); [Dawson 2000](#); [Money 1998](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-98-213](#); [Strandness 2002](#)). The results of the fixed-effect model found no difference between the treatment groups, with an OR of 1.14 (95% CI 0.48 to 2.71; $P = 0.77$) ([Analysis 3.1](#)). When low quality studies were removed the association remained non-significant.

Cilostazol 50 mg twice daily versus placebo

Two studies ([Beebe 1999](#); [Strandness 2002](#)) comparing cilostazol 50 mg to placebo found, with a fixed-effect model, no difference between the treatment groups (OR 0.49, 95% CI 0.04 to 5.50; $P = 0.57$), but with few events, the CI is wide and uninformative ([Analysis 3.2](#)).

Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily

Three studies reported on all-cause mortality comparing cilostazol and pentoxifylline ([Dawson 2000](#); [Otsuka Study 21-94-301](#); [Otsuka Study 21-98-213](#)). The resulting fixed-effect model found no association between the treatment groups, (OR 0.58, 95% CI 0.17 to 1.98; $P = 0.38$) ([Analysis 3.3](#)).

Ankle brachial index (ABI)

Cilostazol 100 mg twice daily versus placebo

Three studies were included in the meta-analysis for ABI for this treatment profile ([Dawson 2000](#); [Elam 1998](#); [Money 1998](#)), and the results from the random-effects model was a statistically significant higher ABI in the cilostazol arm of 0.06 (95% CI 0.04 to 0.08; $P < 0.00001$; $I^2 = 92\%$) ([Analysis 4.1](#)). When low quality studies were removed only the [Dawson 2000](#) study remained, so no overall association could be determined, yet the OR and 95% CI still favoured cilostazol.

The [O'Donnell 2009](#) study reported on ABI, but because they only reported interquartile range for the baseline and follow-up measurements, and they only reported ABI in a subgroup of normoglycaemic participants, the data was not comparable. The

cilostazol group had a median change of ABI of -0.05 in the right side of the body and median change of -0.04 on the left side of the body. In comparison, the placebo group had a median ABI change of -0.03 on the right side of the body and -0.08 on the left.

Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily

Only a single study was included in the ABI meta-analysis for the comparison of cilostazol 100 mg to pentoxifylline 400 mg (Dawson 2000), which found an ABI WMD of -0.01 (95% CI -0.12 to 0.10), but no overall association can be determined (Analysis 4.2).

Cardiovascular events

Cardiovascular events were reported adequately in the Beebe 1999 study, which compared cilostazol 100 mg twice daily and cilostazol 50 mg twice daily with placebo, and in the Brass 2012 study, comparing 100 mg cilostazol to placebo. For myocardial infarction there was no difference between cilostazol and placebo, for both the 100 mg and 50 mg dosages, (OR 0.97, 95% CI 0.14 to 6.97 and OR 2.01, 95% CI 0.36 to 11.13, respectively) (Analysis 5.1; Analysis 5.2). For stroke, there were also no differences between the treatment groups, for both 100 mg and 50 mg, compared to placebo (OR of 1.76, 95% CI 0.37 to 8.36; $P = 0.47$) and (OR 0.99, 95% CI 0.14 to 7.14), respectively (Analysis 5.3; Analysis 5.4).

Brass 2012 reported serious adverse cardiac events, but did not offer a break down of the types of events included. The cilostazol group experienced one cardiac event and the placebo group had three, but they were not statistically different; $P = 0.365$.

Progression to surgery

None of the included studies reported on progression to surgery.

Adverse effects

Eight of the included studies recorded data on side effects in a format eligible for meta-analysis (Beebe 1999; Brass 2012; Dawson 1998; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002). The side effects reported varied between the studies, but the most common events were headache, diarrhoea, abnormal stools, dizziness, pain and palpitations, which are discussed below. The O'Donnell 2009 study reports several side effects, but were mentioned in a combined events outcome, and it would not be appropriate to combine these in the meta-analyses.

Combined adverse events were reported in Otsuka Study 21-86-101, Otsuka Study 21-86-103, Otsuka Study 21-87-101, Otsuka Study 21-94-301 and Otsuka Study 21-95-201, but only for participants who dropped out of the study. These events were not considered in the meta-analyses.

Headache

Eight studies reported on headache when comparing cilostazol 100 mg twice daily to placebo (Beebe 1999; Brass 2012; Dawson 1998; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002), and two studies comparing cilostazol 50 mg twice daily to placebo (Beebe 1999; Strandness 2002). Both meta-analyses were performed using a fixed-effect model and showed a statistically significant increased odds of headache in the cilostazol group with OR 3.10 (95% CI 2.46 to 3.91; $P < 0.00001$) for the 100 mg versus placebo group and OR 2.07 (95% CI 1.36 to 3.15;

$P = 0.0007$) for the 50 mg versus placebo comparison (Analysis 6.1; Analysis 6.2). The Dawson 2000 and Otsuka Study 21-98-213 studies compared cilostazol 100 mg twice daily with pentoxifylline 400 mg three times daily, and the random-effects model found an increased odds of headache in the cilostazol group, OR 2.20 (95% CI 1.16 to 4.17; $P = 0.02$; $I^2 = 69\%$) (Analysis 6.3). When low quality studies were removed there was very little change in the meta-analyses results.

Diarrhoea

Seven studies comparing cilostazol 100 mg twice daily with placebo measured the adverse effect of diarrhoea among their study participants (Beebe 1999; Brass 2012; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002) and two studies comparing cilostazol 50 mg to placebo (Beebe 1999; Strandness 2002). The fixed-effect model found a statistically significant increased odds in the cilostazol group for both comparisons: OR 2.86 (95% CI 2.10 to 3.89; $P < 0.000001$) for the 100 mg comparison and OR 2.16 (95% CI 1.14 to 4.08; $P = 0.02$) for the 50 mg comparison (Analysis 6.4; Analysis 6.5). The two studies comparing cilostazol 100 mg to pentoxifylline 400 mg found, with a random-effects model, no difference between the treatment groups, OR 1.80 (95% CI 0.79 to 4.12; $P = 0.16$; $I^2 = 77\%$) (Dawson 2000; Otsuka Study 21-98-213) (Analysis 6.6). When low quality studies were removed there was very little change in the meta-analyses results.

Dawson 1998 collected data on gastrointestinal complaints compilation, which included diarrhoea and abnormal stools, but the data was not broken down into individual adverse events and could not be used in meta-analysis.

Abnormal stools

Five studies comparing cilostazol 100 mg to placebo found a statistically significant increased odds of abnormal stool in the cilostazol group, OR 4.02 (95% CI 2.69 to 6.01; $P < 0.00001$), performed with a fixed-effect model (Beebe 1999; Dawson 2000; Elam 1998; Money 1998; Strandness 2002) (Analysis 6.7). The two studies comparing cilostazol 50 mg versus placebo found no difference between the treatment groups, OR 2.35 (95% CI 0.58 to 9.54; $P = 0.23$; $I^2 = 75\%$), using a random-effects model (Beebe 1999; Strandness 2002) (Analysis 6.8). Only one study recorded abnormal stools for the comparison between cilostazol and pentoxifylline, which found an increased odds of abnormal stool in the cilostazol group, OR 3.12 (95% CI 1.57 to 6.21), although with no overall association (Dawson 2000) (Analysis 6.9).

Dizziness

For the comparison between cilostazol 100 mg and placebo, four studies recorded data on dizziness (Beebe 1999; Brass 2012; Elam 1998; Money 1998). The results of the fixed-effect meta-analysis found a statistically significant increased odds of dizziness in the cilostazol group, OR 2.53 (95% CI 1.48 to 4.34) (Analysis 6.10). A single study compared cilostazol 50 mg with placebo and found no difference between the two treatment groups, OR 1.95 (95% CI 0.80 to 4.72) (Beebe 1999) (Analysis 6.11). When low quality studies were removed there was very little change in the meta-analysis results.

Pain

Pain was reported as an adverse outcome in four studies comparing cilostazol 100 mg to placebo (Dawson 2000; Elam 1998; Otsuka Study 21-98-213; Strandness 2002), one study comparing cilostazol 50 mg to placebo (Strandness 2002) and two studies comparing cilostazol to pentoxifylline (Dawson 2000; Otsuka Study 21-98-213). There was no difference in the fixed-effect models for cilostazol 100 mg versus placebo and cilostazol versus pentoxifylline, OR 0.88 (95% CI 0.64 to 1.21; $P = 0.42$) and OR 0.85 (95% CI 0.57 to 1.26; $P = 0.41$), respectively (Analysis 6.12; Analysis 6.14). The 50 mg versus placebo comparison also saw no difference between treatment groups in the single study, OR 1.51 (95% CI 0.78 to 2.92) (Analysis 6.13). When low quality studies were removed there was very little change in the meta-analyses results.

Palpitations

The occurrence of palpitations was measured in four studies comparing cilostazol 100 mg to placebo (Beebe 1999; Brass 2012; Dawson 2000; Otsuka Study 21-98-213), one study comparing cilostazol 50 mg to placebo (Beebe 1999) and two studies comparing cilostazol to pentoxifylline (Dawson 2000; Otsuka Study 21-98-213). The random-effects model comparing cilostazol 100 mg to placebo found a statistically significant increased odds of palpitations in the cilostazol group, OR 6.98 (95% CI 1.79 to 27.25; $P = 0.005$; $I^2 = 66\%$) (Analysis 6.15). The comparison between cilostazol 50 mg and placebo found a slightly higher odds in the cilostazol group, with a very wide CI, OR 17.73 (95% CI 1.02 to 309.62), but with only a single study an overall association could not be determined (Analysis 6.16). The studies comparing cilostazol to pentoxifylline found a statistically significant increase in palpitations in the cilostazol group, with a fixed-effect model, OR 8.35 (95% CI 4.11 to 16.98; $P < 0.00001$) (Analysis 6.17). When low quality studies were removed there was very little change in the meta-analysis results.

Quality of life

Quality of life measures were evaluated in four studies (Beebe 1999; Dawson 2000; Money 1998; O'Donnell 2009) using the self administered Short-form 36 (SF-36), Walking Impairment Questionnaire (WIQ), Claudication Outcome Measure (COM), and Vascular Quality of Life (VascuQol) questionnaires. The O'Donnell 2009 study only reported quality of life measures in a subgroup of normoglycaemic patients. Due to the differences of quality of life measures taken, as well as how they were reported, we could not compile a meta-analysis to describe the association at this time. Table 2 provides basic change in quality of life measures as either points or percentages, as reported in the individual studies. This table should be interpreted with caution, as no hypothesis testing has been performed, and the data format differs between studies.

The SF-36 is a multi-purpose, general health questionnaire made of 36 questions from eight subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Each subscale is scored on a scale of zero to 100. The WIQ scale is intended for patients with intermittent claudication and gathers data on walking distance and speed using degree of difficulty scoring from zero to four, with zero being unable to perform the task and four representing no difficulty. The COM is another disease specific testing method for scoring participants with intermittent claudication. It assesses severity of walking pain and discomfort with short and long distances and how participants feel the disease impacts other

aspects of their life, including emotional and social. VascuQol is designed for participants with PAD and consists of 25 questions with answer options of one to seven, spanning five domains of interest: physical activity, symptoms, pain, emotion and social aspects.

For the SF-36 subscales there appeared to be a general improvement of cilostazol over placebo. For the WIQ, there was no improvement of cilostazol over placebo for the Beebe 1999 study, but there was a reported 20% increase in walking speed for the cilostazol group in the Money 1998 study. COM results were only reported for the Beebe 1999 study, and showed modest improvements across the domains. The VascuQol questionnaire was only utilised in the O'Donnell 2009 study and the cilostazol group showed improvements over placebo for the activity, pain and emotional domains.

The Strandness 2002 study also reported on quality of life, with inadequate numerical data to support, but mentioned greater improvement in the cilostazol groups, compared with placebo, in the physical function, role-physical and bodily pain scales. Otsuka Study 21-95-201 only briefly indicated no difference between the two groups for the endpoint quality of life, but the authors did not indicate which questionnaires were used. Otsuka Study 21-98-213 reported a statistically significant difference at 12 weeks, favouring cilostazol, compared with placebo, but no data was reported.

DISCUSSION

Summary of main results

We included fifteen double-blind, RCTs with a total of 3718 participants with intermittent claudication in this review. The results from the meta-analysis indicate that cilostazol improves both initial claudication distance (ICD) and absolute claudication distance (ACD) over placebo. Few studies were included comparing cilostazol to pentoxifylline, so any conclusions drawn regarding this association should be done guardedly. Reviewing the results of the studies not included in the meta-analysis showed a less clear result, with a variability of positive and negative data regarding cilostazol and its effects on ICD and ACD. However, these studies were not included in the meta-analysis due to large variations in reporting that would make direct comparisons inappropriate. Cilostazol significantly improved ankle brachial index (ABI) over placebo, but there was no difference found between cilostazol and pentoxifylline. There were very few deaths in any of the studies, and the meta-analyses found no differences in all-cause mortality for any of the treatment comparisons. Cardiovascular events (myocardial infarction and stroke) were reported in only a single study, with few events that were fairly even between the treatment groups. More data would be needed to understand the association between cilostazol and cardiovascular events. For adverse events, participants in the cilostazol treatment groups had a greater odds of experiencing headaches, diarrhoea, abnormal stool, dizziness and palpitations than placebo or pentoxifylline, but were possibly less likely to experience pain symptoms. While participants in the cilostazol group did experience more adverse events, these symptoms were mild to moderate in intensity and resolved with symptomatic treatment without requiring cessation of therapy.

Overall completeness and applicability of evidence

This review addressed whether the use of cilostazol reduced symptoms of intermittent claudication (specifically ICD and ACD) in participants with peripheral arterial disease (PAD). All 15 included studies evaluated the effects of cilostazol compared with placebo, within similar study populations. However, due to the lack of consistency in reporting of clear data, seven studies could not be utilised for comparison in the ICD and ACD meta-analyses ([Brass 2012](#); [de Albuquerque 2008](#); [O'Donnell 2009](#); [Otsuka Study 21-86-101](#); [Otsuka Study 21-86-103](#); [Otsuka Study 21-87-101](#); [Otsuka Study 21-94-301](#)). The [Otsuka Study 21-98-213](#) could be used for ACD analysis, but not ICD. The inability to use these studies for direct comparison reduces the thoroughness of this review. Attempts were made to contact study authors and sponsors to obtain further information. The seven studies that were included in the meta-analyses for ICD and ACD ([Beebe 1999](#); [Dawson 1998](#); [Dawson 2000](#); [Elam 1998](#); [Money 1998](#); [Otsuka Study 21-95-201](#); [Strandness 2002](#)) did allow robust associations to be derived for the ICD and ACD outcomes, specifically for the treatment comparison of cilostazol 100 mg twice daily versus placebo. These results should be interpreted with the consideration that seven studies evaluating the same issue could not be included in the meta-analyses results.

The ability of the included studies to assess both all-cause mortality and cardiovascular morbidity is limited by the few events reported, resulting in inadequate power to assess these outcomes. Also, treatment duration ranged from six to 26 weeks, with the most common treatment time at 24 weeks. Most of the included studies only reported change from baseline for the final time-point, so we are currently unable to compare studies at a common time-point. Treadmill protocols ranged between three main protocols. The aberrations between the testing protocols were addressed by using change in mean walking distances, rather than absolute follow-up distance, which does not account for baseline. These differences and limitations alter the strength of the applicability of the evidence, and should be kept in mind when interpreting the findings.

Only two of the included studies defined their baseline treadmill test values when multiple baseline values were obtained ([Brass 2012](#); [Dawson 2000](#)). Both studies used the highest baseline treadmill value for analysis, while the remaining studies did not indicate their methods. Possible variations in treadmill testing baseline definition could reduce the applicability of the findings.

Quality of the evidence

From the electronic search results we included 15 studies, with a total of 3718 participants. The quality of the studies was low to moderate, with most of the studies not adequately reporting on randomisation of sequence generation, allocation concealment or blinding. Also, many studies did not report on outcomes set out in their methods, possibly indicating a high risk of reporting bias. Furthermore, seven of the 15 studies did not present data on ICD and ACD in a form which could be used for direct comparison, limiting the robustness of the results of this review. The inability to compare these studies confuses the overall findings of the meta-analyses, making associations difficult to determine.

Potential biases in the review process

Study selection and data extraction was performed independently by two authors in order to minimise bias in the review process. The

inclusion and exclusion criteria set out in the protocol were strictly adhered to in order to limit subjectivity. All participants randomised in a study were used in our analyses to reduce bias from subjective definitions of intention-to-treat used by study authors. There was the possibility of imputation for the seven studies whose data was not in a readily available format for inclusion in meta-analysis, but after consultation with a statistician this was not done in order to reduce large scale subjectivity being introduced into the study results.

The [Brass 2012](#) study provided data on adverse events in percentages, which were converted to number of participants in order to use in analyses. For the [Dawson 2000](#) study there were standard deviations provided for the ABI outcome for mean change for the comparison between cilostazol and placebo, but not for cilostazol compared to pentoxifylline. Correlation coefficients were calculated using the existing mean change standard deviations and imputed to calculate mean change standard deviations for the comparison between cilostazol and pentoxifylline. Other forms of imputation were avoided due to large differences between the studies and their methods of reporting results.

Agreements and disagreements with other studies or reviews

The [Pratt 2001](#) study reviewed data from the cilostazol safety database, representing eight RCTs. However, it was unclear which eight trials were evaluated, so it cannot be determined if they are similar to the studies in our review. The [Pratt 2001](#) review found similar results regarding adverse effects that we found: participants taking cilostazol had an increased risk of headache, diarrhoea, abnormal stool, dizziness and palpitations, and a decreased risk of pain, compared with participants taking placebo or pentoxifylline. The [Pratt 2001](#) review also found very few reports of cardiovascular events, which we also noted, with only a single study reporting.

A systematic review published in 2002 evaluated the effects of cilostazol on walking distances and health related quality of life measures, using six studies that were also included in our review ([Regensteiner 2002](#)). Although this study analysed data in a different manner, they also concluded increased ICDs and ACDs in the participants taking cilostazol compared with those taking placebo. The [Regensteiner 2002](#) review found an increase in WIQ scores and most SF-36 subscale scores for the participants taking cilostazol compared to placebo. Our study did not perform any compilation of quality of life scores, so we cannot directly comment on the similarity to our results.

Another systematic review ([Thompson 2002](#)), published in 2002 investigating the role of cilostazol in increasing walking distances and quality of life in patients with intermittent claudication, used similar inclusion and exclusion criteria as our review and included eight studies in their analysis that were also used in ours. For their analysis they did not include all participants randomised, but rather the modified intention-to-treat population accounting for withdrawals and incomplete treadmill testing. It should be kept in mind when making direct comparisons with our results that the [Thompson 2002](#) review reported percentage change from baseline, rather than weighted mean change in metres. For ICD (reported as pain-free walking distance) the placebo-treated group had a 40% change from baseline increase, and the cilostazol-treated groups experienced a 60% increase from baseline for the 50 mg twice daily group, and 67% for the 100 mg twice daily

group. Both cilostazol groups were statistically significantly greater compared with placebo ($P < 0.05$). For ACD (reported as maximal walking distance) there were statistically significant increases in the cilostazol 50 mg and 100 mg twice daily treatment groups compared with the placebo-treated group, 44%, 50% and 21.4%, respectively ($P < 0.05$). The results for ICD and ACD in [Thompson 2002](#) are similar to our own findings. Two trials in the [Thompson 2002](#) review compared pentoxifylline to placebo, and found no difference between the two groups. Also, similar to our review, there was increased headache, diarrhoea and abnormal stools in the cilostazol-treated groups. Finally, quality of life results showed improvement in the cilostazol group for the SF-36 physical function subscale, as well as for the role-physical and bodily pain subscales, and for WIQ there were improvements in both walking distance and speed for the cilostazol treatment groups.

A systematic review published in 2012 comparing cilostazol, naftidrofuryl oxalate and pentoxifylline to placebo for the treatment of intermittent claudication in patients with PAD included six of the same studies as our review ([Stevens 2012](#)). For inclusion in meta-analysis the study authors employed imputation techniques that we ourselves did not use and they reported their findings for ICD (reported as maximum walking distance) and ACD (reported as pain-free walking distance) as geometric mean changes compared with placebo. However, their results also found increases in both ICD and ACD for the cilostazol groups, compared with placebo, with an increase in ICD of 25% (95% credible interval 11% to 40%) and an ACD increase of 13% (95% credible interval 2% to 26%). Adverse events were not reported in the meta-analysis, but headaches and gastrointestinal issues that were mild were noted in the intervention arms and there was no increase in cardiovascular events or deaths for cilostazol, naftidrofuryl oxalate or pentoxifylline. The authors noted that the heterogeneity of quality of life reporting did not allow them to report those findings in their review. This data is also presented as part of [Squires 2010](#) and [Squires 2011](#) as technology assessment reports written for the National Institute for Health and Care Excellence (NICE). Although the data supports the use of cilostazol for the treatment of intermittent claudication in people with PAD, as well as pentoxifylline and inositol nicotinate, current NICE guidelines

only recommend naftidrofuryl as treatment in this population ([NICE 2011](#); [NICE 2012](#)). The NICE guidelines were also based on cost-effectiveness data, which was not evaluated in our own review.

AUTHORS' CONCLUSIONS

Implications for practice

Cilostazol, 50 mg to 100 mg twice daily, has been shown to improve walking distances compared with placebo, and the adverse side effect profile is limited to conditions that are mild and often treatable. Cilostazol can be considered as an option for claudicants whom conservative or interventional treatments have failed to sufficiently alleviate their symptoms. However, cilostazol is contraindicated in patients with congestive cardiac failure due to its mechanism of action as a phosphodiesterase enzyme III inhibitor. Cilostazol is also contraindicated in patients with moderate to severe renal or hepatic impairment ([Chapman 2003](#)). There is insufficient data at this time to comment on whether treatment with cilostazol results in a reduction of adverse cardiovascular events or mortality, or its superiority to pentoxifylline.

Implications for research

Future research on cilostazol for the treatment of intermittent claudication should ideally be performed such that comparisons can be made with other studies. Currently, there is little consensus with treatment duration, treadmill test protocol, and outcome measurement/reporting, which inhibits direct comparisons. This is apparent in this review with the significant number of studies that could not be included in the meta-analysis due to outcome reporting being inconsistent, and other variations making imputation inappropriate. Also, further studies in relation to the impact of cilostazol on quality of life, and prevention of adverse cardiovascular events are required, as well as its comparison to other antiplatelet therapies, such as pentoxifylline.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Beebe 1999

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention-to-treat: yes Country: USA
Participants	Number randomised: 516 (cilostazol 100 mg n = 175; cilostazol 50 mg n = 171; placebo n = 170) Age (mean years $\pm$ SE): cilostazol 100 mg = 64.3 $\pm$ 8.5; cilostazol 50 mg = 64.5 $\pm$ 9.9; placebo = 65.1 $\pm$ 9.3 Sex M/F: cilostazol 100 mg 130/45; cilostazol 50 mg = 131/40; placebo = 131/39 Inclusion criteria: $\geq$ 40 years of age; $\geq$ 6 months history of stable symptomatic intermittent claudication secondary to lower extremity arterial occlusive disease; reproducible walking distances on screening treadmill tests; treadmill tests terminated solely because of claudication pain; ICD in screening period between 30 and 200 m on two consecutive tests; resting ABI of 0.90 or less and a 10 mmHg or more decrease in ankle artery blood pressure following the onset of ACD Exclusion criteria: ischaemic pain at rest; gross obesity; childbearing potential; hypertension; current metastatic malignant neoplasm; exercise-limiting cardiac disease; history of bleeding tendencies; or concomitant use of antiplatelet, anticoagulant, vasoactive or NSAIDs
Interventions	Treatment 1: cilostazol 100 mg, twice daily, orally Treatment 2: cilostazol 50 mg twice daily, orally Control: placebo Duration: 24 weeks
Outcomes	PFWD and MWD by treadmill testing, doppler-measured bilateral peripheral limb pressures, patient-based quality of life questionnaires (SF-36, WIQ, COM), patient and physician end-of-treatment global therapeutic assessments, cardiovascular morbidity, all-cause mortality, and adverse events. Outcomes evaluated at baseline (three times), 4, 8, 16, 20 and 24 weeks
Notes	Constant-rate, constant-grade treadmill test design, with 12.5% incline and speed of 3.2 km/h

Beebe 1999 (Continued)

Minimum three-week screening period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of eligible patients was stratified by each clinical center. A master randomization list of patient code assignments to the test medication... was developed using a permuted-block design"
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The master list was forwarded to the drug packaging company, where separate medication supply was prepared for each unique patient code. All 3 test medications had a similar appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"For all-cause mortality and cardiovascular morbidity assessment, an independent study committee, blinded to treatment assignment, adjudicated all patient deaths and serious adverse event...". Although it was not directly addressed for other outcomes, it is assumed blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Table 1 describes patient flow with all participants included in safety outcomes, and participants excluded for efficacy endpoints were similar across treatment groups
Selective reporting (reporting bias)	Low risk	Although no protocol was available all outcomes included in description of methods are reported on
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Brass 2012

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention to treat: yes; LOCF method Country: USA and Russia
Participants	Number randomised: 387 (cilostazol n = 89; K-134 25 mg n = 42; K-134 50 mg n = 85; K-134 100 mg n = 84; placebo n = 87) Age (mean years): cilostazol = 64.5; K-134 25 mg = 63.3; K-134 50 mg = 63.8; K-134 100 mg = 62.8; placebo = 62.9 Sex (M%): cilostazol = 94.6; K-134 25 mg = 83.3; K-134 50 mg = 86.8; K-134 100 mg = 82.3; placebo = 89.7 Inclusion criteria: aged ≥ 40 years; had PAD as documented by an ABI ≤ 0.90 or an ABI between 0.90 and 1.00 that fell by ≤ 0.20 within one minute following termination of treadmill exercise; patients with a peak walking time at baseline between one and 12 minutes Exclusion criteria: critical limb ischaemia, amputation or other non-claudication limitation to treadmill performance; revascularization ≤ 3 months; poorly controlled hyperlipidaemia or hypertension; major surgical procedure ≤ 6 months; myocardial infarction ≤ 4 months; history or evidence of congestive heart failure; electrocardiogram abnormalities; clinically significant laboratory or other medical conditions that pose a safety risk; use of warfarin aspirin monotherapy, aspirin combined with clopidogrel or ticlopidine, strong inhibitors of cytochrome P3A4, use of other PDE inhibitors, use of pentoxifylline or L-carnitine

Brass 2012 (Continued)

Interventions	<p>Treatment 1: cilostazol 100 mg, twice daily</p> <p>Treatment 2: K-134 25 mg, twice daily</p> <p>Treatment 3: K-134 50 mg, twice daily (initially started on 25 mg twice daily and then increased after two weeks)</p> <p>Treatment 4: K-135 100 mg, twice daily (initially started on 50 mg twice daily and then increased after two weeks)</p> <p>Control: placebo, twice daily</p> <p>Duration: 26 weeks</p>
Outcomes	Peak walking time, claudication onset time, inflammatory bio-markers, safety and adverse events; measured at baseline (twice) and weeks 2, 4, 14 and 26
Notes	<p>Treadmill test was only described as "graded" with a reference to another study, but we were unable to determine which of the treadmill tests from the referred to paper the authors used</p> <p>The K-134 arm of 25 mg twice daily was discontinued early due because it was found to be minimally informative, and no outcome data recorded. Due to the scope of this review, only data on the cilostazol and placebo groups are used for comparison</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was conducted through a central interactive voice response system and used block randomization by site to minimize risk of imbalances"
Allocation concealment (selection bias)	Low risk	"Randomization was conducted through a central interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The highest rates of discontinuations were observed in the 100-mg K-134 and cilostazol arms... but there were no statistical differences in discontinuation rates across arms". Reasons for discontinuation were similar across treatment groups
Selective reporting (reporting bias)	Low risk	All outcomes included in description of methods are reported on
Other bias	Low risk	No indication of other bias

Dawson 1998

Methods	<p>Study design: multicentre, randomised, double-blind, placebo-controlled</p> <p>Intention to treat: yes; LOCF method</p>
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Dawson 1998 (Continued)

Country: USA

Participants	<p>Number randomised: 81 (cilostazol n = 54; placebo n = 27)</p> <p>Age (mean years $\pm$ SE): cilostazol = 66 ± 1.1; placebo = 67 ± 2.0</p> <p>Sex M/F: cilostazol = 38/16; placebo = 24/3</p> <p>Inclusion criteria: ≥ 40 years; stable intermittent claudication secondary to chronic occlusive arterial disease ≥ 6 months; ICD on treadmill between 30 and 200 m and had to be within $\pm 35\%$ value of previous visit; confirmation of diagnosis of chronic occlusive arterial disease; doppler-measured ankle systolic blood pressure ≥ 20 mmHg</p> <p>Exclusion criteria: limb-threatening chronic limb ischaemia (ischaemic rest pain, ulceration or gangrene); lower extremity surgical or endovascular arterial reconstruction or sympathectomy in previous 6 months; uncontrolled hypertension; inability to complete the treadmill walking test for reasons other than intermittent claudication; MI within previous 6 months; DVT within previous 3 months; severe concomitant disease; substance abuse; or gross obesity</p>
Interventions	<p>Treatment: cilostazol 100 mg, twice daily, orally</p> <p>Control: placebo, twice daily</p> <p>Duration: 12 weeks</p>
Outcomes	<p>ICD, ACD, ABI, and subjective assessments of symptoms by patient and physician</p> <p>Outcomes evaluated at baseline (multiple visits), 2, 4, 8 and 12 weeks after initiation of therapy</p>
Notes	<p>Constant speed treadmill test at 3.2 km/h and a fixed incline of 12.5%</p> <p>Two-week baseline period to stabilise concomitant medications, followed by a two to four week single-blind placebo lead-in phase</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was stratified by treatment center and patients use of calcium channel blocker". Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study used an 'identical' placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Table 2 gives explanations for withdrawals and exclusions, which were similar between treatment groups and unlikely to affect outcomes
Selective reporting (reporting bias)	High risk	Authors only briefly mention ABI results in the abstract with no explicit description
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Dawson 2000

Methods	<p>Study design: multicentre, randomised, double-blind, placebo-controlled</p> <p>Intention to treat: yes; LOCF method</p> <p>Country: USA</p>
Participants	<p>Number randomised: 698 (cilostazol n = 227; pentoxifylline n = 232; placebo n = 239)</p> <p>Age (mean years $\pm$ SD): cilostazol = 66 $\pm$ 9; pentoxifylline = 66 $\pm$ 9; placebo = 66 $\pm$ 9</p> <p>Sex M/F: cilostazol = 172/55; pentoxifylline = 181/51; placebo = 176/63</p> <p>Inclusion criteria: stable, moderate to severe symptoms of intermittent claudication for previous 6 months; confirmed PAD; baseline ICD $\geq$ 53.6 m (one minute); ACD $\leq$ 537.6 m (ten minutes)</p> <p>Exclusion criteria: patients with Buerger's disease; critical ischaemia; lower extremity surgical or endovascular reconstruction or sympathectomy in previous 3 months; limited exercise capacity due to conditions other than intermittent claudication; medical problems judged likely to preclude study completion; use of pentoxifylline or any investigational drug within 30 days of study enrolment; prior use of cilostazol</p>
Interventions	<p>Treatment: cilostazol 100 mg, twice daily with a third placebo for blinding</p> <p>Treatment: pentoxifylline 400 mg, three times daily</p> <p>Control: placebo</p> <p>Duration: 24 weeks</p>
Outcomes	ACD, ICD, resting doppler limb pressures, quality of life questionnaires (SF-36, WIQ); measured at baseline and weeks 2, 4, 8, 12, 16, 20 and 24
Notes	<p>Standardised treadmill test, beginning at 0% incline and 3.2 km/h, increasing incline 3.5% every three minutes while maintaining 3.2 km/h speed</p> <p>Two- to three-week baseline period</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of eligible patients was stratified by clinical center, and patients were assigned to one of the three treatment regimens within each center using a permuted-block design." "Patients were randomly assigned by using an interactive voice randomization system that blinded the investigator, patient and sponsor from treatment assignment"
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned by using an interactive voice randomization system that blinded the investigator, patient and sponsor from treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly assigned by using an interactive voice randomization system that blinded the investigator, patient and sponsor from treatment assignment". Study medications were identical in appearance and taken at similar intervals
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing patients were all accounted for and rates were similar between groups as to those who remained in the study

Dawson 2000 (Continued)

Selective reporting (reporting bias)	Low risk	Although no protocol was available all relevant outcomes appear to be reported on
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

de Albuquerque 2008

Methods	Study design: randomised, double-blind, placebo-controlled Intention to treat: unclear Country: Brazil
Participants	Number randomised: 48 (cilostazol n = 17; pentoxifylline n = 15; placebo n = 16) Age (mean years $\pm$ SD): cilostazol = 64.0 $\pm$ 9.0; pentoxifylline = 64.0 $\pm$ 10.0; placebo = 63.0 $\pm$ 9.0 Sex %M: cilostazol = 64.7%; pentoxifylline = 60.0% placebo = 50.0% Inclusion criteria: Age 45 to 85 years; intermittent claudication for at least 6 months; resting ABI $\leq$ 0.90; duplex evidence of PAD Exclusion criteria: Critical limb ischaemia (Fontaine classification III and IV); symptomatic coronary artery disease (angina); congestive heart failure; arterial revascularisation indication; less than 6 months of diagnosed PAD
Interventions	Treatment 1: cilostazol 100 mg, twice daily, orally Treatment 2: pentoxifylline 600 mg, twice daily Control: placebo, twice daily Duration: 20 weeks
Outcomes	PFWD, MWD, blood analysis (CRP, triglycerides, HDL, LDL), urine analysis (8-epi-prostaglandin F2a), endothelial function by forearm blood flow, adverse events, change in ABI; measured at baseline and then every 4 weeks until 20 weeks
Notes	Calibrated treadmill at a constant speed of 3.2 km/h; incline was increased every 3 min

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to 20 weeks of treatment...". Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Low risk	Use of coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients or researchers were not able to distinguish among treatment capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias)	Low risk	Appears all participants completed the trial, no loss-to-follow-up reported

Cilostazol for intermittent claudication (Review)

de Albuquerque 2008 (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	All outcomes included in description of methods are reported on, but for PFWD and MWD (Table 2) there is no breakdown for the different treatment groups
Other bias	Low risk	No indication of other bias

Elam 1998

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention to treat: yes Country: USA	
Participants	Number randomised: 189 (cilostazol n = 95; placebo n = 94) Age (mean years): cilostazol = 66.7; placebo = 65.8 Sex M/F: cilostazol = 83/12; placebo = 76/18 Inclusion criteria: men and women > 40 years; chronic stable intermittent claudication secondary to PAD Exclusion criteria: women with childbearing potential; gross obesity; poorly controlled hypertension or diabetes; history of malignancy; current alcohol or drug abuse; renal disease; bleeding tendencies	
Interventions	Treatment: cilostazol 100 mg, twice daily, orally Control: placebo, twice daily, orally Duration: 12 weeks	
Outcomes	Lipid profiles, ICD, ACD, ABI Outcomes evaluated at baseline 2, 4, 6, 8 and 12 weeks (treadmill tests conducted at two baseline visits, and weeks 8 and 12)	
Notes	"Delayed-incline" treadmill method, where incline loading was delayed until the third minute then gradually increased by 3.5% increments every three minutes, with a constant speed of 3.2 km/h Minimum two-week lead-in period	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate

Elam 1998 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All lipid analyses were blinded to the investigators and patients after randomization". Although it was not directly addressed for other outcomes, it is assumed blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who completed the study were comparable between treatment groups
Selective reporting (reporting bias)	High risk	In the methods the authors state both pain-free and maximum walking distances as primary exercise variables, but only maximum walking distance is reported on
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Money 1998

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention to treat: yes; LOCF method Country: USA
Participants	Number randomised: 239 (cilostazol n = 119; placebo n = 120) Age (mean years $\pm$ SD): cilostazol = 64.8 $\pm$ 9.4; placebo = 64.5 $\pm$ 8.8 Sex M/F: cilostazol = 90/29; placebo = 90/30 Inclusion criteria: > 40 years; intermittent claudication caused by lower extremity PAOD for at least 6 months; baseline ICD $\geq$ 54 m (one minute); ACD variance no greater than 20% between two screen visits and maximum allowable ACD of 805 m (15 minutes) Exclusion criteria: limb-threatening PAOD including gangrene or ischaemic rest pain; surgical or endovascular procedures during previous 3 months; gross obesity; hypertension; current malignancy; Buerger's disease or DVT in previous 3 months; inability to complete treadmill testing for reasons unrelated to intermittent claudication; bleeding problems
Interventions	Treatment: 100 mg cilostazol, twice daily Control: placebo Duration: 16 weeks
Outcomes	ACD, ICD, ABI, physician and patient perception of effect of study drug, quality of life (SF-36, WIQ) Treadmill tests performed at two baseline visits and weeks 8, 12 and 16 after randomisation
Notes	Variable-grade, constant-speed treadmill test, beginning at 0% incline with a speed of 3.2 km/h, increasing by 3.5% every 3 minutes Two-week screening period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods

Cilostazol for intermittent claudication (Review)

Money 1998 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for discontinuation are given and all participants accounted for
Selective reporting (reporting bias)	Low risk	Although no protocol was available all relevant outcomes are reported on
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

O'Donnell 2009

Methods	Study design: single-centre, randomised, double-blind, placebo-controlled Intention to treat: yes Country: Northern Ireland
Participants	Number randomised: 106 (cilostazol n = 51; placebo n = 55) Age (median years): cilostazol = 64.2; placebo = 66.1 Sex (M/F): cilostazol = 34/17; placebo = 39/16 Inclusion criteria: aged 30 to 90 years (both sexes); had PAD with intermittent claudication with an ABI < 0.9 stable on optimal medical therapy for 3 months Exclusion criteria: current or previous acute or critical limb ischaemia; severe claudication prohibiting treadmill testing; endovascular or surgical procedures within the preceding 6 months; non-atherosclerotic co-morbidity that had limited their walking before the onset of claudication pain; predisposition to bleeding; a history of uncontrolled cardiac, respiratory, renal or liver disease; use of omeprazole or diltiazem
Interventions	Treatment: cilostazol 100 mg, twice daily, oral route Control: placebo, twice daily, oral route Duration: 24 weeks
Outcomes	ICD, ACD, oxygen-derived free-radical generation, antioxidant consumption, other inflammatory cascade markers, quality of life (SF-36, WIQ, VasculQoL); measured at baseline and weeks 6 and 24
Notes	Calibrated treadmill test with a constant speed of 3.2 km/h and constant 10% gradient Four-week stabilisation run-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
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O'Donnell 2009 (Continued)

Random sequence generation (selection bias)	Unclear risk	"Patient-treatment randomisation and allocation was performed independently by the Department of Research Pharmacology in the Belfast City Hospital". Insufficient information on sequence generation
Allocation concealment (selection bias)	Low risk	"Both, the patient and the primary investigator, were blinded to study-drug allocation, which was completed using the sealed-envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both, the patient and the primary investigator, were blinded to study-drug allocation". "Study-drug un-blinding was performed at the end of the study, following the completion of all clinical assessments and laboratory analyses for all patients"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were similar between treatment groups
Selective reporting (reporting bias)	Low risk	Although no study protocol is available, all outcomes appear to be reported on
Other bias	Low risk	Placebo provided by Otsuka Pharmaceutical Inc

Otsuka Study 21-86-101

Methods	Study design: single-centre, randomised, double-blind, placebo-controlled Intention to treat: yes Country: USA
Participants	Number randomised: 53 (cilostazol n = 28; placebo n = 25) Age (mean years): cilostazol = 62; placebo = 58 Sex %M: cilostazol = 89%; placebo = 84% Inclusion criteria: Aged 21 to 70 (both sexes), had atherosclerosis obliterans-induced intermittent claudication which was chronic (at least 6 months), stable (6 months); Evidence of PAOD; ICD $\leq$ 100 m on a constant load treadmill (10% incline, 3.5km/h); less than 30% variation in ICD during lead-in period Exclusion criteria: limb-threatening PAOD including gangrene or ischaemic rest pain; surgical or endovascular procedures during previous 3 months; gross obesity; hypertension; current malignancy; Buerger's disease or DVT in previous 3 months; inability to complete treadmill testing for reasons unrelated to intermittent claudication; bleeding problems
Interventions	Treatment: cilostazol 100 mg, twice daily, oral administration Control: placebo Duration: 6 weeks
Outcomes	ICD, ACD, subjective claudication improvement by patient, doppler-measured limb pressures; measured at baseline and weeks 3 and 6

Otsuka Study 21-86-101 (Continued)

Notes	Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with speed constant at 3.2km/h. Only to be stopped for claudication of sufficient severity to cause the subject to be unable to continue
	Three-week placebo lead-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were similar between the two treatment groups, as shown in Table 31
Selective reporting (reporting bias)	High risk	Subjective claudication improvement or doppler-measured limb pressures were not reported
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Otsuka Study 21-86-103

Methods	Study design: single-centre, randomised, double-blind, placebo-controlled Intention to treat: yes Country: USA
Participants	Number randomised: 33 (cilostazol n = 17; placebo n = 16) Age (mean years): cilostazol = 56; placebo = 59 Sex %M: cilostazol = 82%; placebo = 88% Inclusion criteria: Aged ≥ 21 years (both sexes); had atherosclerosis obliterans-induced intermittent claudication which was chronic (at least 6 months), stable (6 months); evidence of peripheral occlusive arterial disease; ICD ≤ 100 m on a constant load treadmill (10% incline, 3.5km/h); less than 30% variation in ICD during lead-in period Exclusion criteria: lower extremity ischaemic rest pain, severe ulceration or gangrene; female of child-bearing potential; malignancy; cardiac valve disorder or replacement; clinically significant abnormal lab value pre-treatment; renal insufficiency; a requirement for the uninterrupted use of platelet-active or vasoactive drugs; use of an investigational drug within the past 30 days; diabetes mellitus: either insulin-dependent or with duration > 5 years; status post vascular surgery, splenectomy, or gastrointestinal surgery within past 12 months

Otsuka Study 21-86-103 (Continued)

Interventions	Treatment: cilostazol 150 mg, twice daily, oral administration Control: placebo Duration: 21 weeks (from the text, change in ACD and ICD were measured and reported after 6 weeks)
Outcomes	Change in ACD and ICD (after 6 weeks of therapy), subjective claudication improvement as per patient, palpation of arterial pulses, doppler-measured limb pressure, sitting arm blood pressure; measured at baseline and then weeks 6, 9, 13, 17 and 21
Notes	Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with speed constant at 3.2km/h Dosage of cilostazol described as "fixed 150 mg bid oral dose... formulated as 50 mg cilostazol tablets". Assumption is that authors meant tablets were taken three times daily Three-week placebo lead-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts overlap without discussion
Selective reporting (reporting bias)	High risk	Subjective claudication improvement, palpitation of arterial pulses, doppler-measured limb pressures and sitting arm blood pressure were not reported
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Otsuka Study 21-87-101

Methods	Study design: single-centre, randomised, double-blind, placebo-controlled Intention to treat: yes Country: USA
Participants	Number randomised: 19 (cilostazol n = 10; placebo n = 9) Age (mean years): cilostazol = 62; placebo = 65 Sex (%M): cilostazol = 60%; placebo = 67%

Cilostazol for intermittent claudication (Review)

Otsuka Study 21-87-101 (Continued)

Inclusion criteria: Aged 45 to 70 years (both sexes); intermittent claudication which stable (3 months); ICD $\leq$ 100 m on a constant load treadmill test with no greater than 20% variation between observations in wash-out period

Exclusion criteria: lower extremity ischaemic rest pain, severe ulceration or gangrene; female of child-bearing potential; decompensated congestive heart failure or myocardial infarction within six months; cardiac valve disorder or replacement; respiratory insufficiency; vascular surgery, splenectomy, or gastrointestinal surgery within past 12 months; clinically significant abnormal lab value pre-treatment; decreased mobility due to joint disorders, or chronic lumbar vertebral column syndrome; malignancy; renal insufficiency; neuropathy; history of analgesic abuse or use of an investigational drug within the past 30 days; diabetes mellitus either insulin requiring or duration $>$ 5 years; a requirement for the uninterrupted use of pentoxifylline, dipyridamole, certain vasodilators, acetylsalicylic acid, PDE inhibitors or prostacyclin

Interventions	Treatment: cilostazol 100 mg, twice daily, oral route Control: placebo, twice daily, oral route Duration: 12 weeks
Outcomes	ACD, ICD, adverse events; measured at baseline and then weeks 4, 8 and 12
Notes	Immediate incline treadmill test where the incline load started immediately at 10% and remained constant with a constant 3.2 km/h Three-week placebo lead-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for all dropouts
Selective reporting (reporting bias)	Low risk	Although no study protocol is available, all outcomes appear to be reported on
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Otsuka Study 21-94-301

Methods	Study design: randomised, double-blind, placebo-controlled
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Otsuka Study 21-94-301 (Continued)

Intention to treat: yes; LOCF method

Country: USA

Participants	<p>Number randomised: 370 (cilostazol n = 123; pentoxifylline n = 123; placebo n = 124)</p> <p>Age (mean years): cilostazol = 66; pentoxifylline = 66; placebo = 66</p> <p>Sex %M: cilostazol = 70; pentoxifylline = 72; placebo = 73</p> <p>Inclusion criteria: Aged ≥ 40 years (both sexes); intermittent claudication which was chronic (at least 6 months), stable (3 months); Evidence of peripheral occlusive arterial disease; ACD ≤ 450 m in ≤ 8 minutes 28 seconds with no more than 20% variability in two consecutive tests during lead-in period; ICD of at least 30 m in 34 seconds during lead-in period; supine ABI of ≤ 0.80 after 10 minutes of rest</p> <p>Exclusion criteria: current use of pentoxifylline or previous discontinuation for inefficacy or adverse event; female of childbearing potential; greater than 60% above ideal body weight; supine arterial BP > 200 mmHg systolic or > 100 mmHg diastolic; sympathectomy or lower extremity arterial reparative surgery within the previous 3 months; DVT within the previous 3 months; termination of treadmill test for reasons other than intermittent claudication; history or current evidence of concomitant exercise-limiting disease other than intermittent claudication; history of bleeding tendencies; history of cerebrovascular bleed, cerebral or dissecting aortic aneurysm, pericarditis, or pericardial effusion; active peptic disease; recent or anticipated surgical procedures; platelet count $< 120 \times 10^9$/litre, twice the normal values for AST or ALT, or serum creatinine > 220 μmol/litre; current alcohol or other drug abuse, or use of an investigational drug within the past 30 days; a requirement for the uninterrupted use of platelet-active, anticoagulant, NSAIDs or haemorrhologic agents</p>
Interventions	<p>Treatment 1: cilostazol 100 mg, twice daily with third placebo dose to maintain blind, oral administration</p> <p>Treatment 2: pentoxifylline 400 mg, three times daily</p> <p>Control: placebo</p> <p>Duration: 24 weeks</p>
Outcomes	<p>ACD, ICD, subjective claudication improvement by physician and patient; all-cause death, cardiovascular events, safety endpoints (vital signs, 12-lead EKG, etc), adverse events; measured at baseline and weeks 2, 4, 8, 12, 16, 20 and 24</p>
Notes	<p>Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with a constant speed of 3.2 km/h</p> <p>Four- to eight-week lead-in period</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"CLZ, PTX and placebo tablets were encapsulated into identical capsule, and blinding of the dose interval was to be preserved by administered [sic] a third daily dose of placebo to CLZ-randomized subjects"
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of assessors is not adequately discussed

Otsuka Study 21-94-301 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for all dropouts
Selective reporting (reporting bias)	High risk	No reporting of all-cause death or cardiovascular events
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Otsuka Study 21-95-201

Methods	Study design: randomised, double-blind, placebo-controlled, clinical trial Intention to treat: yes; LOCF method Country: USA
Participants	Number randomised: 215 (cilostazol 150 mg n = 73; cilostazol 100 mg n = 72; placebo n = 70) Age (mean years): cilostazol 150 mg = 65; cilostazol 100 mg = 68; placebo = 66 Sex M/F: cilostazol 150 mg = 81%/19%; cilostazol 100 mg = 75%/25%; placebo = 81%/19% Inclusion criteria: > 40 years; atherosclerosis obliterans-induced intermittent claudication for ≥ 6 months, stable for ≥ 3 months. Exclusion criteria: intermittent claudication associated with lower extremity ischaemic rest pain, ischaemic ulceration, gangrene or Buerger's disease; women of childbearing potential; sympathectomy or lower extremity arterial reparative surgery, including endovascular procedures in previous 3 months; greater than 60% above ideal body weight; current metastatic malignancy; DVT within previous 3 months; other exercise-limiting disease; risk of or tendency to bleeding; pericarditis or pericardial effusions; platelet count < 130,000/cm ³ or haematocrit < 30%; twice the normal values for AST or ALT; serum creatinine > 2.5 mg/dL; current alcohol or other drug abuse, or use of investigational drug within the past 30 days; requirement for uninterrupted use of pentoxifylline, NSAIDs, certain antiplatelet and anticoagulant medications
Interventions	Treatment 1: cilostazol 150 mg, twice daily Treatment 2 : cilostazol 100 mg, twice daily Control: placebo, twice daily Duration: 12 weeks
Outcomes	Trough ACD and ICD, subjective claudication improvement as per patient and physician, doppler-measured limb pressures, quality of life questionnaires; measured at baseline then weeks 4, 8 and 12
Notes	Treadmill tests done by "immediate-incline" method: incline load started immediately at 12.5% (and remained constant) with speed constant at 3.2km/h. Tests were only to be stopped for claudication Two-week lead-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods

Otsuka Study 21-95-201 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for all dropouts
Selective reporting (reporting bias)	High risk	Report did not include ICD data at 4, 8 and 12 weeks, subjective claudication improvement or doppler limb pressures. Did not report quality of life results, but noted no significant differences between the groups
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Otsuka Study 21-98-213

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled, clinical trial Intention to treat: yes Country: USA
Participants	Number randomised: 785 (cilostazol n = 261; pentoxifylline n = 262; placebo n = 262) (several of the tables in the NICE report state 780 as the number of participants, 260 in each group, but the study characteristics on pg 177 of the report has n = 785 as the total number randomised) Age (mean years $\pm$ SE): cilostazol = 66.7 $\pm$ 9.9; pentoxifylline = 67.4 $\pm$ 9.4; placebo = not given Sex %M: cilostazol = 75.4; pentoxifylline = 76.9; placebo = 75.4 Inclusion criteria: $\geq$ 50 [sic] years or older, with PAD and intermittent claudication with stable symptoms for the preceding 3 months; PAD diagnosed as an abnormal resting ABI $\geq$ 0.4 and $\leq$ 0.9 in the reference leg with decline in post-exercise ABI $\geq$ 10 mmHg as confirmation; symptomatic patients with normal resting ABI but with pressure drop of $>$ 20 mmHg were also eligible; MWD varied by no more than 20% on two to three consecutive treadmill tests Exclusion criteria: limb-threatening ischaemia; limb revascularisation within 3 months; unstable coronary artery disease; coronary revascularisation within 6 months; thromboangiitis obliterans; DVT within 3 months; symptomatic arrhythmia; conditions other than PAD that might limit exercise ability or preclude completion of the study; congestive heart failure
Interventions	Treatment 1: cilostazol 100 mg, twice daily Treatment 2: pentoxifylline 400 mg, three times daily Control: placebo Duration: 24 weeks
Outcomes	MWD, PFWD, all-cause mortality, quality of life (SF-36, WIQ, COM), adverse events, vascular events; measured at baseline and then 4 weeks until 24 weeks
Notes	Constant workload treadmill test: 3.2 km/h at a constant 12.5% grade Study is also known under the trial name PACE

Cilostazol for intermittent claudication (Review)

Otsuka Study 21-98-213 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there is insufficient description to determine if blinding is adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors is not adequately discussed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No study report was available outside of the data collected from the NICE review
Selective reporting (reporting bias)	Unclear risk	No study protocol or report was available outside of the data collected from the NICE review
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

Strandness 2002

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled, phase III trial Intention to treat: yes; LOCF method Country: USA
Participants	Number randomised: 394 (cilostazol 100 mg n = 133; cilostazol 50 mg n = 132; placebo n = 129) Age (mean years $\pm$ SE): cilostazol 100 mg = 63.1 $\pm$ 10.2; cilostazol 50 mg = 63.9 $\pm$ 8.7; placebo = 64.4 $\pm$ 10.2 Sex M/F: cilostazol 100 mg = 102/31; cilostazol 50 mg = 98/34; placebo = 100/29 Inclusion criteria: $\geq$ 40 years; at least 6 month history of stable symptomatic intermittent claudication secondary to PAD; and reproducible walking distances on screening treadmill (20% or less variation in MWD on two consecutive tests); termination of all screening treadmill tests solely for reasons of claudication pain; ability to walk between 30 and 200 m; resting ABI less than 0.90 and at least a 10 mmHg decrease in ankle systolic blood pressure in the reference leg at completion of test Exclusion criteria: ischaemic pain at rest; gross obesity; childbearing potential; hypertension; malignancy; exercise limiting cardiac disease; history of bleeding tendencies; concomitant use of antiplatelet, anticoagulant, haemorrhagic or NSAIDs
Interventions	Treatment 1: cilostazol 100 mg, twice daily Treatment 2: cilostazol 50 mg, twice daily Control: placebo, twice daily Duration: 24 weeks

Strandness 2002 (Continued)

Outcomes	MWD, PFWD, doppler-measured bilateral peripheral limb pressures, quality of life and functional status, end-of-treatment global therapeutic benefit (physician and participant), cardiovascular morbidity, all-cause mortality; Outcomes measured at baseline, weeks 2 and 4, then every 4 weeks until 24 weeks
Notes	Treadmill test consisted of standardised 2 mph at 12.5% incline Two-week lead-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient description of sequence generation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient description of allocation concealment methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Cilostazol was packaged as a 50mg tablet and a placebo dummy was given to maintain double blind conditions". "The blind was reportedly not broken during the course of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An independent committee, blinded to treatment assignment, adjudicated all patient death and any possible cardiovascular morbid events according to the predefined morbidity criteria". Although it was not directly addressed for other outcomes, it is assumed blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were no clinically or statistically significant differences events, serious or adverse events, discontinuation of therapy due to adverse events and death"
Selective reporting (reporting bias)	High risk	ABI data was listed as a secondary outcome but not reported on, aside from a comment in the discussion for which no data was given to support it
Other bias	Unclear risk	Study supported by Otsuka America Pharmaceutical Inc

ABI: ankle brachial index
 ACD: absolute claudication distance
 ALT: alanine transaminase
 AST: aspartate aminotransferase
 bid: twice daily
 CLZ: cilostazol
 cm: centimetre
 COM: Claudication Outcome Measures
 CRP: C-reactive protein
 DVT: deep vein thrombosis
 HDL: high-density lipoprotein
 ICD: initial claudication distance
 km/h: kilometres per hour
 LDL: low-density lipoprotein
 LOCF: last observation carried forward
 m: metres
 mg: milligrams
 MI: myocardial infarction
 mph: miles per hour
 MWD: maximum walking distance (equivalent to ACD)
 NSAIDs: non-steroidal anti-inflammatory agents

Cilostazol for intermittent claudication (Review)

PAD: peripheral arterial disease
 PAOD: peripheral arterial occlusive disease
 PAR: Physical Activity Recall
 PFWD: pain-free walking distance (equivalent to ICD)
 SE: standard error
 SF-36: Medical Outcomes Scale Short Form-36
 WIQ: Walking Impairment Questionnaire

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

Study	Reason for exclusion
ACCELA	The specifics of the intervention arms are unclear at this time. We cannot conclude which study arms also used clopidogrel. Also, no study outcomes are available at this time
CASTLE	This study was a safety study performed over 3.5 years, which is a much longer follow-up than other included studies. Authors were contacted for data from earlier time-points, but we received no response
Hsieh 2009	Currently unable to determine if the study was double blinded, or if the study population was made up of participants with intermittent claudication. Also, the outcomes reported are not within the scope of this review
Kim 2013	Cannot determine if study population was made up of participants with intermittent claudication. Also, the outcomes reported are not within the scope of this review
MASCOT	Study was discontinued early, and no outcome data is available
Otsuka Study PUIC-1	Currently cannot determine if the study was double-blinded
Otsuka Study PUIC-2	Currently not sufficient details of the study methods or outcomes to include
Samra 2003	Non-randomised study
SPAD	Cannot determine if study population was made up of participants with intermittent claudication

DATA AND ANALYSES

Comparison 1. Initial claudication distance (ICD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ICD cilostazol 100 mg twice daily versus placebo	6	1533	Mean Difference (IV, Fixed, 95% CI)	31.41 [22.38, 40.45]
2 ICD cilostazol 50 mg twice daily versus placebo	2	602	Mean Difference (IV, Fixed, 95% CI)	19.89 [9.44, 30.34]
3 ICD cilostazol 150 mg twice daily versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 ICD cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Initial claudication distance (ICD), Outcome 1 ICD cilostazol 100 mg twice daily versus placebo.

Analysis 1.2. Comparison 1 Initial claudication distance (ICD), Outcome 2 ICD cilostazol 50 mg twice daily versus placebo.

Analysis 1.3. Comparison 1 Initial claudication distance (ICD), Outcome 3 ICD cilostazol 150 mg twice daily versus placebo.

Analysis 1.4. Comparison 1 Initial claudication distance (ICD), Outcome 4 ICD cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Study or subgroup	Cilostazol		Pentoxifylline		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Dawson 2000	227	93.6 (127.4)	232	73.6 (106.4)		20[-1.5,41.5]

Comparison 2. Absolute claudication distance (ACD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACD cilostazol 100 mg twice daily versus placebo	8	2247	Mean Difference (IV, Random, 95% CI)	43.11 [18.27, 67.95]
2 ACD cilostazol 50 mg twice daily versus placebo	2	602	Mean Difference (IV, Fixed, 95% CI)	32.00 [14.17, 49.83]
3 ACD cilostazol 150 mg twice daily versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 ACD Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Mean Difference (IV, Random, 95% CI)	13.41 [-43.52, 70.34]

Analysis 2.1. Comparison 2 Absolute claudication distance (ACD), Outcome 1 ACD cilostazol 100 mg twice daily versus placebo.

Study or subgroup	Cilostazol		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Beebe 1999	175	129.1 (463.3)	170	26.8 (148.5)		7.02%	102.28[30.1,174.46]
Dawson 1998	54	84.6 (144.9)	27	4.6 (61.5)		11%	80.04[34.96,125.12]
Dawson 2000	227	107.3 (158.4)	239	64.7 (134.6)		14.38%	42.6[15.85,69.35]
Elam 1998	95	79.1 (134.5)	94	36.1 (141.6)		12.04%	42.95[3.58,82.32]
Money 1998	119	101.1 (154.9)	120	47.1 (124.9)		12.72%	54[18.31,89.69]
Otsuka Study 21-95-201	72	35.2 (72.1)	70	38.1 (69.7)		14.98%	-2.9[-26.21,20.41]
Otsuka Study 21-98-213	261	60.4 (108)	262	59 (137.7)		15.33%	1.4[-19.81,22.61]
Strandness 2002	133	96.4 (200.4)	129	23.2 (78.3)		12.54%	73.21[36.57,109.85]
Total ***	1136		1111			100%	43.11[18.27,67.95]
Heterogeneity: Tau ² =931.08; Chi ² =31.53, df=7(P<0.0001); I ² =77.8%							
Test for overall effect: Z=3.4(P=0)							

**Analysis 2.2. Comparison 2 Absolute claudication distance (ACD),
Outcome 2 ACD cilostazol 50 mg twice daily versus placebo.** **Analysis 2.3. Comparison 2 Absolute claudication distance (ACD),
Outcome 3 ACD cilostazol 150 mg twice daily versus placebo.** **Analysis 2.4. Comparison 2 Absolute claudication distance (ACD), Outcome 4
ACD Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.** **Comparison 3. All-cause mortality**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality cilostazol 100 mg twice daily versus placebo	8	2339	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.48, 2.71]
2 All-cause mortality cilostazol 50 mg twice daily versus placebo	2	602	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.04, 5.50]
3 All-cause mortality cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	3	1229	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.17, 1.98]

Analysis 3.1. Comparison 3 All-cause mortality, Outcome 1 All-cause mortality cilostazol 100 mg twice daily versus placebo.

Analysis 3.2. Comparison 3 All-cause mortality, Outcome 2 All-cause mortality cilostazol 50 mg twice daily versus placebo.

Analysis 3.3. Comparison 3 All-cause mortality, Outcome 3 All-cause mortality cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Comparison 4. Ankle brachial index (ABI)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ABI cilostazol 100 mg twice daily versus placebo	3	894	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]
2 ABI cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Ankle brachial index (ABI), Outcome 1 ABI cilostazol 100 mg twice daily versus placebo.

Analysis 4.2. Comparison 4 Ankle brachial index (ABI), Outcome 2 ABI cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Comparison 5. Cardiovascular events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction cilostazol 100 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Myocardial infarction cilostazol 50 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Stroke cilostazol 100 mg twice daily versus placebo	2	521	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [0.37, 8.36]
4 Stroke cilostazol 50 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Cardiovascular events, Outcome 1 Myocardial infarction cilostazol 100 mg twice daily versus placebo.

Study or subgroup	Cilostazol 100 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	2/175	2/170		0.97[0.14,6.97]
Favours cilostazol 100 mg 0.01 0.1 1 10 100 Favours placebo				

Analysis 5.2. Comparison 5 Cardiovascular events, Outcome 2 Myocardial infarction cilostazol 50 mg twice daily versus placebo.

Study or subgroup	Cilostazol 50 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	4/171	2/170		2.01[0.36,11.13]
Favours cilostazol 50 mg 0.01 0.1 1 10 100 Favours placebo				

Analysis 5.3. Comparison 5 Cardiovascular events, Outcome 3 Stroke cilostazol 100 mg twice daily versus placebo.

Study or subgroup	Cilostazol 100 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	3/175	2/170		80.04%	1.47[0.24,8.88]
Brass 2012	1/89	0/87		19.96%	2.97[0.12,73.81]
Total (95% CI)	264	257		100%	1.76[0.37,8.36]
Total events: 4 (Cilostazol 100 mg), 2 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.14, df=1(P=0.71); I ² =0%					
Test for overall effect: Z=0.72(P=0.47)					
Favours cilostazol 100 mg 0.002 0.1 1 10 500 Favours placebo					

Analysis 5.4. Comparison 5 Cardiovascular events, Outcome 4 Stroke cilostazol 50 mg twice daily versus placebo.

Study or subgroup	Cilostazol 50 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	2/171	2/170		0.99[0.14,7.14]

Comparison 6. Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache cilostazol 100 mg twice daily versus placebo	8	2281	Odds Ratio (M-H, Fixed, 95% CI)	3.10 [2.46, 3.91]
2 Headache cilostazol 50 mg twice daily versus placebo	2	602	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [1.36, 3.15]
3 Headache cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Odds Ratio (M-H, Random, 95% CI)	2.20 [1.16, 4.17]
4 Diarrhoea cilostazol 100 mg twice daily versus placebo	7	2200	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [2.10, 3.89]
5 Diarrhoea cilostazol 50 mg twice daily versus placebo	2	602	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [1.14, 4.08]
6 Diarrhoea cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Odds Ratio (M-H, Random, 95% CI)	1.80 [0.79, 4.12]
7 Abnormal stool cilostazol 100 mg twice daily versus placebo	5	1501	Odds Ratio (M-H, Fixed, 95% CI)	4.02 [2.69, 6.01]
8 Abnormal stool cilostazol 50 mg twice daily versus placebo	2	602	Odds Ratio (M-H, Random, 95% CI)	2.35 [0.58, 9.54]
9 Abnormal stool cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Dizziness cilostazol 100 mg twice daily versus placebo	4	949	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [1.48, 4.34]
11 Dizziness cilostazol 50 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12 Pain cilostazol 100 mg twice daily versus placebo	4	1440	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
13 Pain cilostazol 50 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Pain cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Palpitations cilostazol 100 mg twice daily versus placebo	4	1510	Odds Ratio (M-H, Random, 95% CI)	6.98 [1.79, 27.25]
16 Palpitations cilostazol 50 mg twice daily versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
17 Palpitations cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Odds Ratio (M-H, Fixed, 95% CI)	8.35 [4.11, 16.98]

Analysis 6.1. Comparison 6 Adverse effects, Outcome 1 Headache cilostazol 100 mg twice daily versus placebo.

Analysis 6.2. Comparison 6 Adverse effects, Outcome 2 Headache cilostazol 50 mg twice daily versus placebo.

Analysis 6.3. Comparison 6 Adverse effects, Outcome 3 Headache cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Analysis 6.4. Comparison 6 Adverse effects, Outcome 4 Diarrhoea cilostazol 100 mg twice daily versus placebo.

Analysis 6.5. Comparison 6 Adverse effects, Outcome 5 Diarrhoea cilostazol 50 mg twice daily versus placebo.

**Analysis 6.6. Comparison 6 Adverse effects, Outcome 6 Diarrhoea
cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.**

Analysis 6.7. Comparison 6 Adverse effects, Outcome 7 Abnormal stool cilostazol 100 mg twice daily versus placebo.

Analysis 6.8. Comparison 6 Adverse effects, Outcome 8 Abnormal stool cilostazol 50 mg twice daily versus placebo.

Analysis 6.9. Comparison 6 Adverse effects, Outcome 9 Abnormal stool cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Study or subgroup	Cilostazol 100 mg n/N	Pentoxifylline 400 mg n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	33/227	12/232		3.12[1.57,6.21]
Favours cilostazol 0.01 0.1 1 10 100 Favours pentoxifylline				

Analysis 6.10. Comparison 6 Adverse effects, Outcome 10 Dizziness cilostazol 100 mg twice daily versus placebo.

Study or subgroup	Cilostazol 100 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	18/175	8/170		40.52%	2.32[0.98,5.49]
Brass 2012	3/89	2/87		10.88%	1.48[0.24,9.1]
Elam 1998	12/95	4/94		19.55%	3.25[1.01,10.48]
Money 1998	15/119	6/120		29.06%	2.74[1.03,7.33]
Total (95% CI)	478	471		100%	2.53[1.48,4.34]
Total events: 48 (Cilostazol 100 mg), 20 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.57, df=3(P=0.9); I ² =0%					
Test for overall effect: Z=3.38(P=0)					
Favours cilostazol 100 mg 0.01 0.1 1 10 100 Favours placebo					

Analysis 6.11. Comparison 6 Adverse effects, Outcome 11 Dizziness cilostazol 50 mg twice daily versus placebo.

Study or subgroup	Cilostazol 50 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Beebe 1999	15/171	8/170		1.95[0.8,4.72]
Favours cilostazol 50 mg 0.01 0.1 1 10 100 Favours placebo				

Analysis 6.12. Comparison 6 Adverse effects, Outcome 12 Pain cilostazol 100 mg twice daily versus placebo.

Study or subgroup	Cilostazol 100 mg n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	30/227	33/239		34.46%	0.95[0.56,1.62]
Elam 1998	14/95	11/94		11.65%	1.3[0.56,3.04]
Otsuka Study 21-98-213	22/261	30/262		33.87%	0.71[0.4,1.27]
Strandness 2002	15/133	18/129		20.03%	0.78[0.38,1.63]
Total (95% CI)	716	724		100%	0.88[0.64,1.21]
Total events: 81 (Cilostazol 100 mg), 92 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =1.52, df=3(P=0.68); I ² =0%					
Test for overall effect: Z=0.8(P=0.42)					
Favours cilostazol 100 mg 0.01 0.1 1 10 100 Favours placebo					

Analysis 6.13. Comparison 6 Adverse effects, Outcome 13 Pain cilostazol 50 mg twice daily versus placebo.

Analysis 6.14. Comparison 6 Adverse effects, Outcome 14 Pain cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Analysis 6.15. Comparison 6 Adverse effects, Outcome 15 Palpitations cilostazol 100 mg twice daily versus placebo.

Analysis 6.16. Comparison 6 Adverse effects, Outcome 16 Palpitations cilostazol 50 mg twice daily versus placebo.

Analysis 6.17. Comparison 6 Adverse effects, Outcome 17 Palpitations cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

ADDITIONAL TABLES

Table 1. Reasoning for study not being included in meta-analyses of initial claudication distance (ICD), absolute claudication distance (ACD) and ankle brachial index (ABI)

Study	Reason for data not included in ICD, ACD or ABI outcomes
Brass 2012	Reported in peak walking time and initial claudication time with standard deviations, but the treadmill method is not clear, so we could not reliably convert from time to distance
de Albuquerque 2008	Outcomes of interest were only broken down between non-smokers and smokers, but not between treatment groups. Figures 2 and 3 of de Albuquerque 2008 do offer graphical information on the mean change in maximal walking distances, 'expressed as percent of control'
O'Donnell 2009	For ICD and ACD mean baseline and follow-up values were given, but no standard deviations were given. A P value was given for the overall treatment effect but that was for the comparison between cilostazol and placebo, not between baseline and follow-up. For ABI only interquartile ranges were given, which could not be adequately converted to standard deviation
Otsuka Study 21-86-101	Placebo-corrected mean change from baseline was provided for the treatment group, with no standard deviations. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but this data could not be re-calculated to mean change and standard deviation
Otsuka Study 21-86-103	Raw mean change from baseline was provided for the cilostazol and placebo groups, with no standard deviations. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but this data could not be re-calculated to mean change and standard deviation
Otsuka Study 21-87-101	Placebo-corrected mean change from baseline was provided for the treatment group, with no standard deviations. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but this data could not be re-calculated to mean change and standard deviation
Otsuka Study 21-94-301	For the ICD outcome only a ratio of the geometric means of change was calculated between cilostazol and the comparison, but this data could not be re-calculated to mean change and standard deviation
Otsuka Study 21-98-213	For ICD raw mean change from baseline was provided for the cilostazol and comparison groups, with no standard deviations. Also, a ratio of the geometric means of change was calculated between cilostazol and comparisons, but this data could not be re-calculated to mean change and standard deviation. Mean change data with standard deviations was available for the ACD outcome

Table 2. Change in quality of life status (change in points or percentage from baseline)

		Beebe 1999			Dawson 2000			Money 1998		O'Donnell 2009	
		Cilosta- zol 100 mg (n = 175)	Cilosta- zol 50 mg (n = 171)	Place- bo (n = 170)	Cilosta- zol 100 mg (n = 227)	Pen- tox 400 mg (n = 232)	Place- bo (n = 239)	Cilosta- zol 100 mg (n = 119)	Place- bo (n=120)	Cilosta- zol 100 mg (n = 51)	Place- bo (n = 55)
Short-form 36 (SF-36)	Physical function	7.1	8	2	3	1.8	0.8	8.3	2.3	11%	-0.30%
	Role-physical	5.3	4.4	-2.8	3.7	no im- prov	no im- prov	3.0	0.1	7.8%	5.4%
	Bodily pain	7.2	4.6	-1.8	5.2	1.6	1.0	-	-	3.7%	10.5%
	Social function	1.0	0.9	0.4	no diff	no diff	no diff	-	-	-	-
	Role-emotional	2.9	0.0	-1.7	no diff	no diff	no diff	-	-	-	-
	Mental health	2.5	-1.5	0.9	-0.7	-0.6	-1.3	-	-	-	-
	General health	-	-	-	-	-	-	-	-	2.7%	-1.0%
Walking Im- pairment Questionnaire (WIQ)	Walking speed	0.1	0.2	0.1	-	-	-	20.0%	0.0%	-	-
	Walking distance	0.2	0.2	0.1	-	-	-	-	-	-	-
Claudication Outcome Mea- sure (COM)	Change in pain/discomfort	2.8	2.7	2.4	-	-	-	-	-	-	-
	Pain/discomfort: daily activities	0.4	0.5	0.2	-	-	-	-	-	-	-
	Pain/discomfort: physical activities	0.5	0.5	0.2	-	-	-	-	-	-	-
	Pain/discomfort: social activities	0.3	0.4	0.3	-	-	-	-	-	-	-
	Walking pain/discomfort	0.7	0.7	0.4	-	-	-	-	-	-	-
	Worry/concern due to pain	0.8	0.6	0.5	-	-	-	-	-	-	-

Table 2. Change in quality of life status (change in points or percentage from baseline) *(Continued)*

Vascular Quality of Life (Vas-cuQol)	Activity	-	-	-	-	-	-	-	-	7.3	1.8
	Symptom	-	-	-	-	-	-	-	-	3.1	3.2
	Pain	-	-	-	-	-	-	-	-	10.4	13.2
	Emotion	-	-	-	-	-	-	-	-	5.7	1.8
	Social	-	-	-	-	-	-	-	-	1.1	3.4

diff: difference

improv: improvement

Pentox: pentoxifylline

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Arteriosclerosis] this term only	894
#2	MeSH descriptor: [Arteriolosclerosis] this term only	0
#3	MeSH descriptor: [Arteriosclerosis Obliterans] this term only	72
#4	MeSH descriptor: [Atherosclerosis] this term only	420
#5	MeSH descriptor: [Arterial Occlusive Diseases] this term only	772
#6	MeSH descriptor: [Intermittent Claudication] this term only	725
#7	MeSH descriptor: [Ischemia] this term only	767
#8	MeSH descriptor: [Peripheral Vascular Diseases] explode all trees	2195
#9	MeSH descriptor: [Vascular Diseases] this term only	394
#10	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	17891
#11	(arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	4988
#12	(vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1432
#13	(vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	753
#14	(veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1012
#15	(peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)	1389
#16	peripheral near/3 dis*	3394
#17	arteriopathic	20
#18	(claudic* or hinken*)	1488
#19	(isch* or CLI)	17409
#20	dysvascular*	29
#21	leg near/4 (obstruct* or occlus* or steno* or block* or obliter*)	191
#22	limb near/4 (obstruct* or occlus* or steno* or block* or obliter*)	243
#23	(lower near/3 extrem*) near/4 (obstruct* or occlus* or steno* or block* or obliter*)	149
#24	(aort* or iliac or femoral or popliteal or femoropop* or fempop* or crural) near/3 (obstruct* or occlus*)	335
#25	MeSH descriptor: [Femoral Artery] explode all trees	736

(Continued)

#26	MeSH descriptor: [Popliteal Artery] explode all trees	259
#27	MeSH descriptor: [Iliac Artery] explode all trees	152
#28	MeSH descriptor: [Iliac Vein] explode all trees	39
#29	MeSH descriptor: [Popliteal Vein] explode all trees	62
#30	MeSH descriptor: [Femoral Vein] explode all trees	205
#31	Fontaine	438
#32	#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 or #26 or #27 or #28 or #29 or #30 or #31	41098
#33	MeSH descriptor: [Vasodilator Agents] this term only	3273
#34	MeSH descriptor: [Platelet Aggregation Inhibitors] this term only	2762
#35	MeSH descriptor: [Phosphodiesterase Inhibitors] this term only	765
#36	MeSH descriptor: [Tetrazoles] this term only	1540
#37	vasodilator*	5388
#38	cilosta*	330
#39	OPC-13013	9
#40	platelet near/3 inhibitor	3044
#41	phosphodiesterase near/3 inhibitor	1196
#42	pletal or pletaal	14
#43	73963-72-1	3
#44	6-(4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy)-3,4-dihydro-2(1H)-quinolinone	2
#45	#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44	10738
#46	#32 and #45 in Trials	2629

FEEDBACK

Unpublished trials

Summary

The Cochrane review of cilostazol (1/2007) includes only one study of cilostazol (CLZ) and pentoxifylline (PTX, TRENTAL), (Dawson DL 2000), and states: the differences in ICD and ACD showed significant improvement for the cilostazol group over patients taking pentoxifylline.

Already in 1998 eight pivotal trials with cilostazol were analysed in the medical review by the FDA. One of these was trial 21-94-301 (P. 58), an unpublished trial of Otsuka with 370 patients: 247 CLZ or placebo, 123 pentoxifylline. In this study CLZ was not statistically distinguishable from either placebo or oxpentifylline (= pentoxifylline). A second study comparing cilostazol with pentoxifylline was the

Dawson DL 2000 (trial 21-96-202). The FDA states (p.231): There is not yet a convincing basis with which to conclude that CLZ is more efficacious than pentoxifylline in this regard (anti claudication efficacy).

Pentoxifylline is not recommended for claudication in some guidelines (SIGN 10/2006, CHEST 2/2007), therefore it is important to note that there is no difference between CLZ and PTX.

In a reply (21 March 2007) to my mail (23 February 2007) to the Cochrane peripheral vascular diseases group Prof. Stansby stated that "the medical review (of the FDA) does not come up if you put cilostazol into the FDA web page search".

This Cochrane review was published at the same time as marketing of cilostazol started in Germany and was part of the promotional material Schwarz Pharma sent to us. Prof. Stansby declared a conflict of interest with Otsuka pharmaceuticals, the developing company. For me this may be a problem. What does Cochrane think about it?

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We agree that there appears to be an additional and unpublished trial comparing cilostazol with pentoxifylline, referred to as study 21-94-301 in the FDA document of 1998. We were unaware of this when we prepared our original review. It did not come to light using standard search strategies. Unfortunately the data currently available to us is still not sufficient to allow inclusion of this trial at present. Otsuka have not made the data available to us, although it has been requested. The review has been altered to make it clear that this additional study exists and that any conclusions about a comparison with pentoxifylline should be guarded based on the one published trial. If in the future Otsuka do release further data to us, and the methodological quality is acceptable, we will consider including it in future updates.

The production of this review and its timing was entirely coincidental to the release date of cilostazol in Germany. Likewise there was no contact with Otsuka concerning these matters. Professor Stansby has declared his conflicts of interest, but has not had any contact with Otsuka in relation to the timing and release of this review. The main conclusions of the review are not altered by this additional trial but we have updated the review to include this study under "excluded studies".

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WHAT'S NEW

Date	Event	Description
15 April 2014	New citation required but conclusions have not changed	New authors joined review team. Risk of bias assessments added and methods updated to reflect current standards. Conclusions not changed
18 October 2013	New search has been performed	Searches rerun; eight new studies included and seven new studies excluded

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 1, 2007

Date	Event	Description
9 May 2008	Amended	Converted to new review format
11 November 2007	Feedback has been incorporated	Feedback and authors' response to feedback added. Unpublished trial Otsuka 1996b (Otsuka 21-94-201) is a duplicate reference to Strandness 2002
7 November 2007	New citation required but conclusions have not changed	Two excluded studies added. No change to conclusions
21 February 2007	Amended	Edited update. Abstract edited to include unit of measurement in results section

CONTRIBUTIONS OF AUTHORS

RB selected studies, assessed risk of bias, extracted data and drafted the review.

MS selected studies, assessed risk of bias, extracted data, and assisted in drafting the review.

MC, PR, DPM, and GS contributed to the review text.

In the previous version of the review:

PR selected studies, assessed the methodological quality of studies and extracted data.

GS selected studies, assessed the methodological quality of studies and extracted data.

DM resolved any conflicts regarding inclusion of trials and extracted data.

DECLARATIONS OF INTEREST

RB: none known.

MS: none known.

MC: Otsuka Ltd (producer of Cilostazol) made a donation (Approx. GBP 6000) to a research fund held by Newcastle University in 2003. This fund was used to support research in platelet studies (used to purchase chemicals e.g. antibodies) required for platelet activation laboratory research. The work was submitted as part of an MD thesis in 2006. These studies were not used in this Cochrane review.

PR: none known

DPM: Attended meetings and advisory boards and given some lectures sponsored by Merck, Sharp and Dohme (MSD) and Genzyme. I am editor-in-chief of several journals hence some royalties are paid to me (Bentham publications, SAGE publications and Informa publications).

GS: none known.

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The previous review version required the types of participants to be "Patients with stable intermittent claudication (Fontaine stage II) for more than six months..." In order to be as inclusive as possible we have changed the requirement to "Patients with stable intermittent claudication (determined by a physician or investigator)."

Cilostazol for intermittent claudication (Review)

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The title of the review has been changed from 'Cilostazol for peripheral arterial disease' to 'Cilostazol for intermittent claudication' in order to reflect the change in methods, in which included patients were 'patients with intermittent claudication or patients undergoing bypass surgery for peripheral arterial disease' was changed to only be 'patients with intermittent claudication'. This was done because patients undergoing surgery generally would have a more advanced disease stage than those with intermittent claudication, introducing bias and heterogeneity to the review. At the time of this update, no studies were included that included patients undergoing surgery, so no major changes had to be made. The originally planned subgroup analysis investigating differences between participants having intermittent claudication versus participants undergoing vascular surgical intervention is no longer relevant and has been removed.

INDEX TERMS

Medical Subject Headings (MeSH)

Cilostazol; Intermittent Claudication [*drug therapy]; Myocardial Infarction [prevention & control]; Pentoxifylline [therapeutic use]; Peripheral Vascular Diseases [drug therapy]; Platelet Aggregation Inhibitors [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [prevention & control]; Tetrazoles [adverse effects] [*therapeutic use]; Walking

MeSH check words

Aged; Humans; Middle Aged