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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 (exercise-induced lower limb pain relieved by rest). These patients have a three- to six-fold increase in cardiovascular mortality. Cilostazol is a drug licensed for the use of improving claudication distance and, if shown to reduce cardiovascular risk, could offer additional clinical benefits. This is an update of the review first published in 2007.

Objectives

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

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and AMED databases, and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registries, on 9 November 2020.

Selection criteria

We considered double-blind, randomised controlled trials (RCTs) of cilostazol versus placebo, or versus other drugs used to improve claudication distance 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 assessed the risk of bias with the Cochrane risk of bias tool. Certainty of the evidence was evaluated using GRADE. For dichotomous outcomes, we used odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and for continuous outcomes we used mean differences (MDs) and 95% CIs. We pooled data using a fixed-effect model, or a random-effects model when heterogeneity was identified. Primary outcomes were initial claudication distance (ICD) and quality of life (QoL). Secondary outcomes were absolute claudication distance (ACD), revascularisation, amputation, adverse events and cardiovascular events.

Main results

We included 16 double-blind, RCTs (3972 participants) comparing cilostazol with placebo, of which five studies also compared cilostazol with pentoxifylline. Treatment duration ranged from six to 26 weeks. All participants had intermittent claudication secondary to PAD.

Cilostazol dose ranged from 100 mg to 300 mg; pentoxifylline dose ranged from 800 mg to 1200 mg. The certainty of the evidence was downgraded by one level for all studies because publication bias was strongly suspected. Other reasons for downgrading were imprecision, inconsistency and selective reporting.

Cilostazol versus placebo

Participants taking cilostazol had a higher ICD compared with those taking placebo (MD 26.49 metres; 95% CI 18.93 to 34.05; 1722 participants; six studies; low-certainty evidence). We reported QoL measures descriptively due to insufficient statistical detail within the studies to combine the results; there was a possible indication in improvement of QoL in the cilostazol treatment groups (low-certainty evidence). Participants taking cilostazol had a higher ACD compared with those taking placebo (39.57 metres; 95% CI 21.80 to 57.33; 2360 participants; eight studies; very-low certainty evidence). The most commonly reported adverse events were headache, diarrhoea, abnormal stools, dizziness, pain and palpitations. Participants taking cilostazol had an increased odds of experiencing headache compared to participants taking placebo (OR 2.83; 95% CI 2.26 to 3.55; 2584 participants; eight studies; moderate-certainty evidence).Very few studies reported on other outcomes so conclusions on revascularisation, amputation, or cardiovascular events could not be made.

Cilostazol versus pentoxifylline

There was no difference detected between cilostazol and pentoxifylline for improving walking distance, both in terms of ICD (MD 20.0 metres, 95% CI -2.57 to 42.57; 417 participants; one study; low-certainty evidence); and ACD (MD 13.4 metres, 95% CI -43.50 to 70.36; 866 participants; two studies; very low-certainty evidence). One study reported on QoL; the study authors reported no difference in QoL between the treatment groups (very low-certainty evidence). No study reported on revascularisation, amputation or cardiovascular events. Cilostazol participants had an increased odds of experiencing headache compared with participants taking pentoxifylline at 24 weeks (OR 2.20, 95% CI 1.16 to 4.17; 982 participants; two studies; low-certainty evidence).

Authors' conclusions

Cilostazol has been shown to improve walking distance in people with intermittent claudication. However, participants taking cilostazol had higher odds of experiencing headache. There is insufficient evidence about the effectiveness of cilostazol for serious events such as amputation, revascularisation, and cardiovascular events. Despite the importance of QoL to patients, meta-analysis could not be undertaken because of differences in measures used and reporting. Very limited data indicated no difference between cilostazol and pentoxifylline for improving walking distance and data were too limited for any conclusions on other outcomes.

PLAIN LANGUAGE SUMMARY

Cilostazol for peripheral arterial disease

Background

Blockages in the arteries to the legs - peripheral arterial disease - affect 20% of people aged over 70 years and 4% to 12% of people aged 55 to 70 years. Approximately 40% of those with peripheral arterial disease complain of pain in the legs or buttocks that occurs with exercise and subsides with rest. This is known as intermittent claudication and these symptoms are an indicator for the development of blocked arteries elsewhere in the body. People with intermittent claudication have a three- to six-fold increased chance of dying as a result of cardiovascular events compared to people of the same age without intermittent claudication.

People with intermittent claudication are treated with best medical management which includes modifying risk factors, such as stopping smoking, and doing structured exercise. Further cardiovascular risk modification includes treatment for high blood pressure, 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, such as cilostazol, are used to help improve symptoms of intermittent claudication and so we examined the evidence to see if cilostazol improved walking distance, quality of life and other important outcomes compared to placebo (dummy pill) or other drugs used for intermittent claudication.

Study characteristics and key results

We included 16 double-blind, randomised controlled trials, with 3972 adults (search up to 9 November 2020). Participants taking cilostazol for three to six months could walk approximately 26 metres further before calf pain and 40 metres further in total compared to participants taking placebo. However, participants taking cilostazol had nearly three times the odds of experiencing headache related to study medication. There is currently not enough information about the effectiveness of cilostazol for serious events such as amputation, revascularisation and cardiovascular events. Despite its importance, only four studies reported quality of life, using different tools and ways of reporting. Very limited data indicated no difference between cilostazol and pentoxifylline for improving walking distance, and there was not enough information comparing cilostazol with pentoxifylline, for any other outcomes.

Certainty of the evidence

We judged the evidence to be 'very low' to 'low-certainty' for all outcomes except headaches, which were 'moderate-certainty'. All studies were downgraded because we strongly suspected publication bias from drug company involvement.

Conclusion

Cilostazol can increase the distance walked both in total and before the onset of pain, compared to placebo. Cilostazol was associated with increased headaches and there was a lack of evidence for other important outcomes such as amputation, revascularisation and cardiovascular events.

SUMMARY OF FINDINGS

Summary of findings 1. Cilostazol compared with placebo for intermittent claudication

Cilostazol compared with placebo for intermittent claudication

Patient or population: intermittent claudication
Setting: all outpatient settings
Intervention: cilostazol
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with cilostazol				
Initial claudication distance (change in metres) 12 to 24 weeks follow-up	The mean change in initial claudication distance was 32.28	MD 26.49 higher (18.93 higher to 34.05 higher)	-	1722 (6 RCTs)	⊕⊕⊖⊖ LOW [1, 2]	
Quality of life (change in points/ percentage; COM, SF-36, VascuQol, WIQ) 16 to 24 weeks follow-up	There appeared to be a general improvement of cilostazol over placebo across four studies that used the SF-36 (Beebe 1999; Dawson 2000; Money 1998; O'Donnell 2009). There were inconsistent results for walking impairment according to the WIQ (4 studies), three studies showed no difference between groups for walking impairment (Beebe 1999; Dawson 2000; O'Donnell 2009) and one study reported a 20% increase in walking speed for the cilostazol group (Money 1998). There were modest improvements across the domains of the COM in one study (Beebe 1999). There was no difference between groups in one study using the VascuQol questionnaire (O'Donnell 2009).		-	1163 (4 RCTs)	LOW [2, 3]	Meta-analysis was not undertaken because of differences in measures used and how they were reported. See Table 1 for further details.
Absolute claudication distance (change in metres) 12 to 24 weeks follow-up	The mean change in absolute claudication distance was 37.45	MD 39.57 higher (21.8 higher to 57.33 higher)	-	2360 (8 RCTs)	⊕⊖⊖⊖ VERY LOW [2, 4, 5]	

Arterial revascularisation (number of cases) 24 weeks follow-up	Study population 6 per 1,000	1 per 1000 (0 to 24)	OR 0.16 (0.01 to 4.07)	516 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2, 6]
Amputation (number of cases) 24 weeks follow-up	Study population 6 per 1000	1 per 1000 (0 to 24)	OR 0.16 (0.01 to 4.07)	516 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2, 6]
Adverse event related to study medication - headache (number of cases) 12 to 26 weeks follow-up	Study population 105 per 1000	250 per 1000 (210 to 295)	OR 2.83 (2.26 to 3.55)	2584 (8 RCTs)	⊕⊕⊕⊖ MODERATE [2, 7]
Cardiovascular event (number of cases) 24 to 26 weeks follow-up	Study population 16 per 1000	23 per 1000 (8 to 66)	OR 1.50 (0.51 to 4.47)	692 (2 RCTs)	⊕⊕⊖⊖ LOW [2, 8]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **COM:** Claudication Outcome Measure; **OR**: odds ratio; **SF-36:** self-administered Short-form 36; **VascuQol:** Vascular Quality of Life; **WIQ:** Walking Impairment Questionnaire.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] downgraded by one level for risk of bias because 3 studies (Dawson 1998; Otsuka Study 21-95-201; Strandness 2002) rated at high risk for selective reporting
[2] downgraded by one level for publication bias because pharmaceutical sponsors involvement in most of these studies raises questions of whether unpublished studies that suggest no benefit exist
[3] downgraded by one level for imprecision because a range of quality of life measurement tools were used and results were reported in different ways (meta-analysis was not undertaken for these reasons)
[4] downgraded by one level for risk of bias because 4 studies (Dawson 1998; Elam 1998; Otsuka Study 21-95-201; Strandness 2002) rated at high risk for selective reporting

[5] downgraded by one level for inconsistency because of heterogeneity: I^2 = 72% cilostazol 100 mg twice daily versus placebo subgroup - heterogeneity reduced to 0% when 2 studies removed (Otsuka Study 21-95-201; Otsuka Study 21-98-213)
[6] downgraded by two levels for imprecision due to low number of participants and events from 1 RCT (Beebe 1999)
[7] see Table 2 for other adverse events related to study medication
[8] downgraded by one level for imprecision due to low number of participants and events from 2 RCTs (Beebe 1999; Brass 2012)

Summary of findings 2. Cilostazol compared with pentoxifylline for intermittent claudication

Cilostazol 100 mg twice daily compared with pentoxifylline 400 mg twice daily for intermittent claudication

Patient or population: intermittent claudication
Setting: all outpatient settings
Intervention: cilostazol 100 mg twice daily
Comparison: pentoxifylline 400 mg three times daily

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with pentoxifylline 400 mg twice daily	Risk with cilostazol 100 mg twice daily				
Initial claudication distance (change in meters) 24 weeks follow-up	The mean change in initial claudication distance was 73.6	MD 20.00 higher (2.57 lower to 42.57 higher)	-	417 (1 RCT)	⊕⊕⊖⊖ LOW [1, 2]	
Quality of life (change in points, SF-36, WIQ) 24 weeks follow-up	Quote "None of the treatments significantly affected the Medical Outcomes Scale Short Form-36 scores on Mental Health Concepts, General Health Perception, Physical Health Concepts, or Vitality Scores. There were also no significant differences in patient-reported walking distance or speed as determined by the Walking Impairment Questionnaire." (Dawson 2000).		-	317 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2, 3]	
Absolute claudication distance (change in metres) 24 weeks follow-up	The mean change in absolute claudication distance was 70.0	MD 13.43 higher (43.50 lower to 70.36 higher)	-	866 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [2, 4, 5]	
Arterial revascularisation	-	-	-	-	-	no studies

Amputation	-	-	-	-	-	no studies
Adverse event related to study medication - headache (number of cases) 24 weeks follow-up	Study population 111 per 1000	 216 per 1000 (127 to 343)	OR 2.20 (1.16 to 4.17)	982 (2 RCTs)	⊕⊕⊖⊖ LOW [2 4]	
Cardiovascular event	-	-	-	-	-	no studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **SF-36:** self-administered Short-form 36; **WIQ:** Walking Impairment Questionnaire.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] downgraded one level for imprecision because 1 RCT had a low number of participants (Dawson 2000)
[2] downgraded one level because publication bias strongly suspected
[3] downgraded by two levels for imprecision because 1 RCT had a low number of participants (Dawson 2000) and imprecision could not be evaluated
[4] downgraded one level for inconsistency because of heterogeneity: $I^2 \geq 50\%$
[5] downgraded one level for imprecision due to very wide CIs

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). About 4% of people with intermittent claudication will require amputation over five years of follow-up (Leng 1996).

The majority of patients with intermittent claudication are treated with best medical treatment (Khan 2005), and the mainstay of treatment for patients with PAD is cardiovascular risk factor modification. This consists of smoking cessation, prescribed exercise (Lane 2017), 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; Niu 2016; 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

Treatment of intermittent claudication includes best medical treatment (BMT), lifestyle changes, physical exercise and angioplasty, if appropriate (Haile 2020). A recent review demonstrated that angioplasty and supervised exercise were 'more or less comparable treatment options' (Fakhry 2018). In practice, compliance with BMT is poor and most people remain symptomatic with intermittent claudication. There are various pharmacological agents, as well as cilostazol, used in the treatment of intermittent claudication including anticoagulants (Cosmi 2014), antiplatelets (Wong 2011), and pentoxifylline (Broderick 2020). However, there is a degree of uncertainty as to which, if any, of these medications provides the most clinical benefit. The National Institute for Health and Care Excellence (NICE) (clinical guideline 147, last updated December 2020), recommends the use of naftidrofuryl for people with intermittent claudication caused by PAD; cilostazol is licensed for the treatment of PAD in selected patients who do not respond to other treatments (NICE 2012). NICE clinical guidelines are underpinned by cost-effectiveness analysis which is outside the remit of this review. If cilostazol is found to reduce the symptoms of claudication, as well as cardiovascular risk in patients with PAD, it would offer some patients another clinical option. This is an update of the review first published in 2007 (Robless 2007) and incorporates the most recent literature and advances in Cochrane methodology, with respect to grading of the evidence.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blind, randomised controlled trials of cilostazol versus placebo, or versus other drugs used to improve claudication distance.

Types of participants

We included participants 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

We included studies that compared cilostazol versus placebo, or other drugs used to improve claudication distance, e.g. pentoxifylline. The interventions must have been given for at least four weeks. We excluded 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)

- Health-related quality of life (QoL), including general and disease-specific QoL, measured by a validated questionnaire

Secondary outcomes

- Absolute claudication distance (ACD) (the maximum distance walked on a treadmill)
- Revascularisation (angioplasty or surgical bypass)
- Amputation
- Adverse events related to study medication
- Cardiovascular events (defined as stroke, unstable angina, acute myocardial infarction (MI))
- All-cause mortality
- Ankle brachial index (ABI)
- Major Adverse Limb Event (MALE) defined as major vascular amputation or any vascular re-intervention, including surgical or endovascular re-intervention

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for randomised controlled trials and controlled clinical trials without language, publication year or publication status restrictions.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched from inception to 10 November 2020).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO 2020, Issue 10).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to present) (searched 9 November 2020).
- Embase Ovid (searched 9 November 2020).
- CINAHL Ebsco (searched 9 November 2020).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Search strategies for major databases are provided in Appendix 1.
The information Specialist also searched the following trials registries on 10 November 2020.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch)
- ClinicalTrials.gov

Searching other resources

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

Data collection and analysis

Selection of studies

For this update, two review authors (TB and MS), independently evaluated studies for inclusion based on selection criteria. Disagreements were resolved by discussion between the two review authors.

Data extraction and management

For this update, two review authors (TB and RBF), independently extracted the data. We identified one new eligible study for this update. We collected information regarding the trial design, participant characteristics, therapy type, dosages and treatment periods. We collected information for the primary outcomes of ICD and QoL and secondary outcomes including ACD, revascularisation, amputation, adverse events, cardiovascular events, all-cause mortality, and ABI. We resolved disagreements through discussion between the two review authors. Data were entered into and analysed using Review Manager (RevMan Web 2019).

Assessment of risk of bias in included studies

For this update, two review authors (TB and RBF), independently assessed the methodological quality using Cochrane's risk of bias tool (Higgins 2011). We assessed the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. We classified the domains as low risk, high risk, or unclear risk of bias, according to the guidelines in Higgins 2011. Disagreements were resolved by discussion between the two review authors.

Measures of treatment effect

We pooled the data on ICD, ACD and ABI, to obtain an overall estimate of the effectiveness of cilostazol therapy. We used 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 mean differences (MDs) with 95% confidence intervals (CIs), and dichotomous data as odds ratios (ORs) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant in all studies included in this review. For studies with more than two treatment arms of relevance to the same meta-analysis and with one control arm, we included data from both treatment arms. To avoid double counting of participants, we halved the number of participants in the control arm. For dichotomous outcomes, both the number of events and the total number of participants were divided up. For continuous outcomes only the total number of participants was divided up (means and standard deviations remained unchanged). This method only partially overcomes the unit of analysis error because the resulting comparisons remain correlated (Higgins 2021a). However, we were interested in evaluating all doses of drug intervention as well as drug interventions per se, so we did not feel it was appropriate to pool the intervention group data within each study.

Dealing with missing data

In previous versions of the review, when data were not available or missing, study authors were contacted to request missing data. Data imputation was not carried out and reasons for study data not being included in meta-analyses were recorded (Table 3). All of the analyses were based on the number of participants accessed for each outcome within each study.

Assessment of heterogeneity

We evaluated trial heterogeneity using Chi^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 2021). If tests for heterogeneity found $I^2 > 50\%$, we planned to use a random-effects model, otherwise, we planned to use a fixed-effect model. We are aware there can be uncertainty around the value of I^2 and using thresholds for interpretation, and so we also considered the direction and magnitude of effects and degree of overlap between CIs.

Assessment of reporting biases

We hoped to assess reporting bias by funnel plots if more than ten studies were included in the meta-analysis (Higgins 2021). As we did not include more than ten studies in any analysis, we did not do this.

Data synthesis

We used a pooled fixed-effect model meta-analysis with subgrouping, where appropriate. We used a random-effects model when tests for heterogeneity found $I^2 > 50\%$. We also considered the direction and magnitude of effects and degree of overlap between CI. For outcomes where we were unable to pool data, we described the results narratively.

Subgroup analysis and investigation of heterogeneity

For this update, we synthesised the data by drug comparison and so it was appropriate to subgroup by drug dose.

Sensitivity analysis

In order to determine that robust conclusions could be drawn using meta-analyses, we removed studies of a lower methodological 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. We planned to undertake sensitivity analysis only if sufficient studies remained in the analyses to provide a meaningful result.

Summary of findings and assessment of the certainty of the evidence

For this update, we prepared a summary of findings table to present the findings from our review for the comparisons 'Cilostazol versus placebo' (Summary of findings 1) and 'Cilostazol versus pentoxifylline' (Summary of findings 2), using GRADEpro software (GRADEpro). We used the GRADE method, to evaluate the evidence based on the risk of bias of the individual studies, inconsistency, imprecision, indirectness and publication bias (Schünemann 2021). We evaluated the following outcomes because they were the most clinically relevant:

- ICD
- health-related QoL
- ACD
- revascularisation
- amputation
- adverse events related to study medication - headache
- cardiovascular events

Where meta-analysis was not undertaken, we described the evidence using a narrative approach. GRADE assessments for the other outcomes of adverse events that were not included in the summary of findings tables are presented in an additional table (Table 2).

RESULTS

Description of studies

Results of the search

See Figure 1. For this update of the review, we identified one new study (Lee 2001), one additional report of a previously included study (Brass 2012), and one study is awaiting classification (Sapelkin 2013). We excluded 23 new studies. This review update involved a total of 16 included studies and 31 excluded studies.

Figure 1. Study flow diagram.

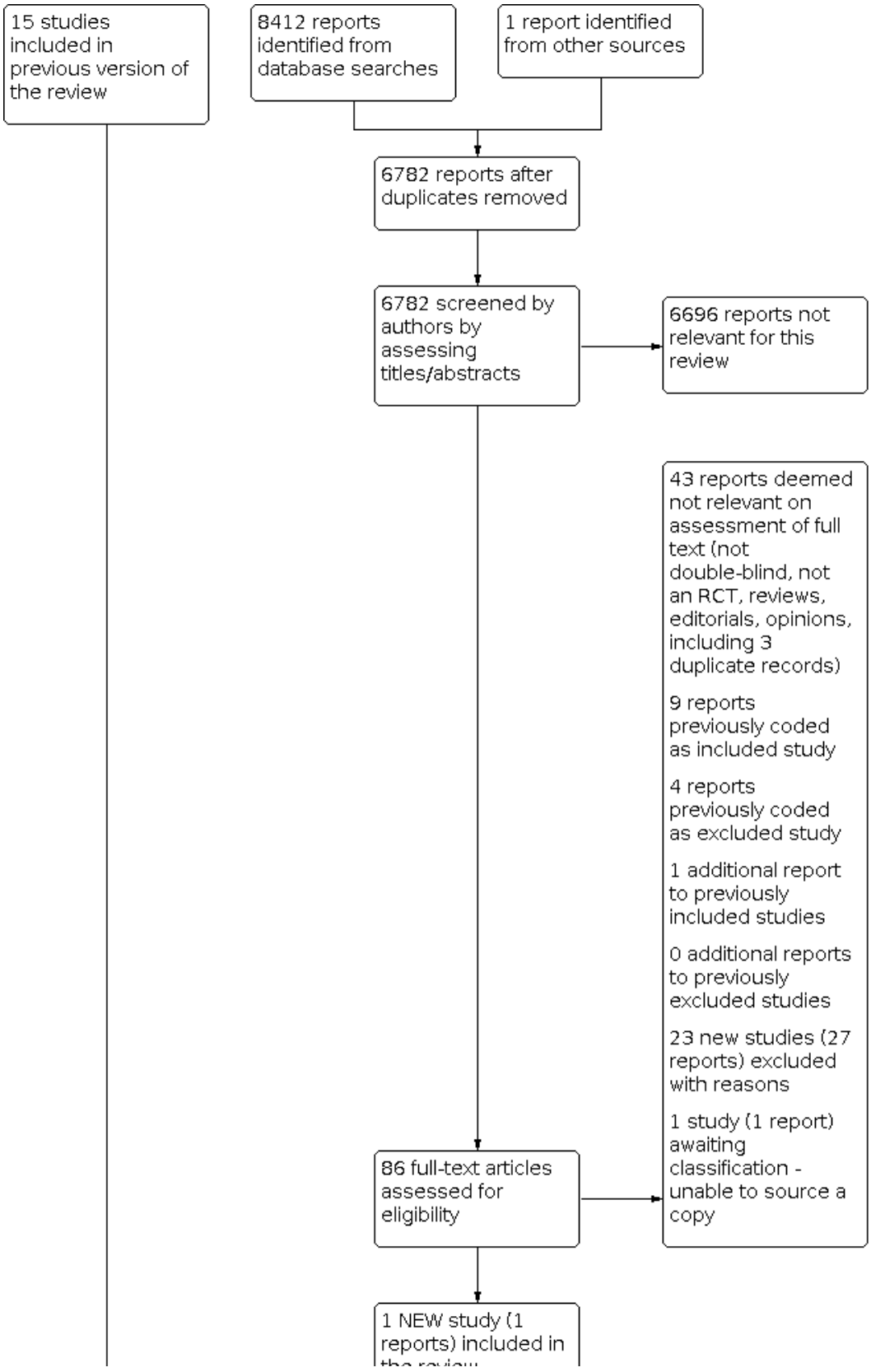
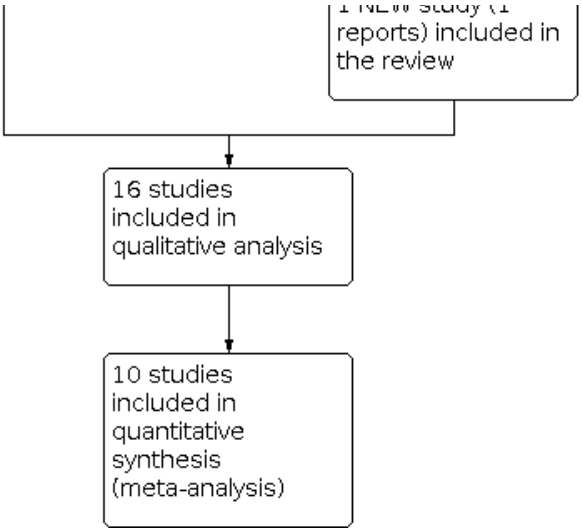


Figure 1. (Continued)



Included studies

See Characteristics of included studies for more detail. We included 16 studies with 3972 participants. Treatment duration ranged 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. Two studies also 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 also 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 pentoxifylline 400 mg twice daily (Lee 2001). Brass 2012 had treatment groups excluded from our analyses (K-134, 50 mg and 100 mg twice daily) because K-134 is not an alternative antiplatelet agent or medication currently known to increase walking distance.

Seven studies were published in journal articles and six studies were not published as journal articles, with sources of data being a medical review by the FDA in five cases (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), and a pharmaceutical submission to NICE in the other case (Otsuka Study 21-98-213). All 16 studies received funding from pharmaceutical companies, 13 of which received funding from Otsuka Pharmaceuticals, the company that formulated cilostazol. Lee 2001 was the only study to report a declaration of interest (no conflicts declared). Five studies had study authors employed by a pharmaceutical company; including Otsuka Pharmaceuticals in four cases (Dawson 2000; Elam 1998; Money 1998; Strandness 2002), and Kowa Research Institute in another case (Brass 2012). One study (O'Donnell 2009), reported that a study author received financial support from Otsuka Pharmaceuticals for travel costs to attend conferences to present data from the trial.

For two studies, the duration of treatment was six weeks (Otsuka Study 21-86-101; Otsuka Study 21-86-103), and for one study the treatment duration was eight weeks (Lee 2001). 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, in 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). Six 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; Lee 2001; 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 that 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.

Excluded studies

See Characteristics of excluded studies for more detail.

Studies that were not RCTs or were not double-blinded were judged not relevant. For this update, we excluded 23 new studies making a total of 31 excluded studies. There were nine previously excluded studies; one of these was non-randomised and was removed from the list of studies excluded with reasons.

Briefly, 15 studies included the wrong patient population (Chao 2014; Chao 2016; Chen 2017; ChiCTR-TRC-09000441; Chisari 2019; Hsieh 2009; JPRN-C000000215; JPRN-UMIN000001198; Kim 2013; NCT00573950; NCT00886574; NCT00912756; NCT01952756; NCT01188824; Xiao 2010). Eleven studies were excluded due to the wrong intervention, for example, iloprost, olmesarten, sildenafil, ticagrelor and valsarten (Goldenberg 2012; JPRN-UMIN000011869; JPRN-UMIN000014307; Mazzone 2013; NCT00102050; NCT02373462; NCT02407314; NCT02636283; NCT02930811; NCT03318276; NCT03686306). We excluded the NCT00443287 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 were not available (CASTLE 2008). The NCT00300339 study was discontinued early, and no outcome data were available for the trial. We were unable to determine if the Otsuka Study PUIC-1 was double-blind, and the Otsuka Study PUIC-2 abstract did not contain enough information on the methods and results of the study to be included.

One study is awaiting classification because we could not source the publication (Sapelkin 2013).

Risk of bias in included studies

Figure 2 and Figure 3 offer graphical summaries of risk of bias for the 16 included studies.

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

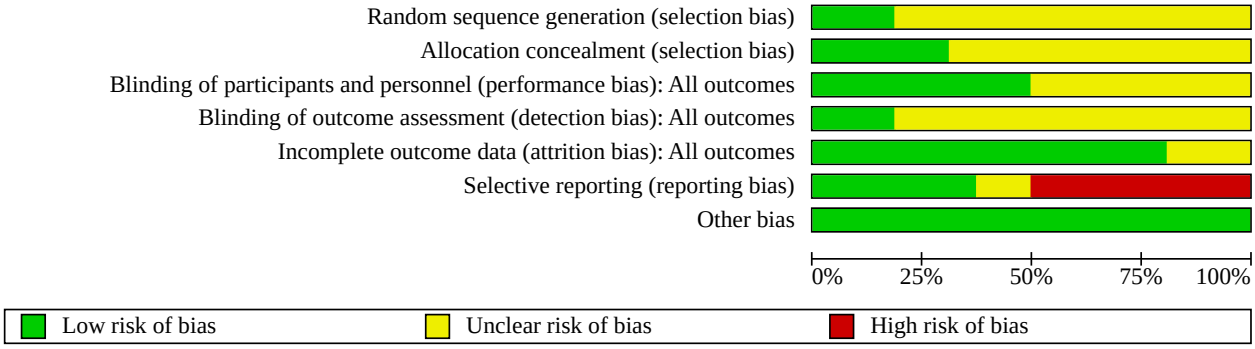
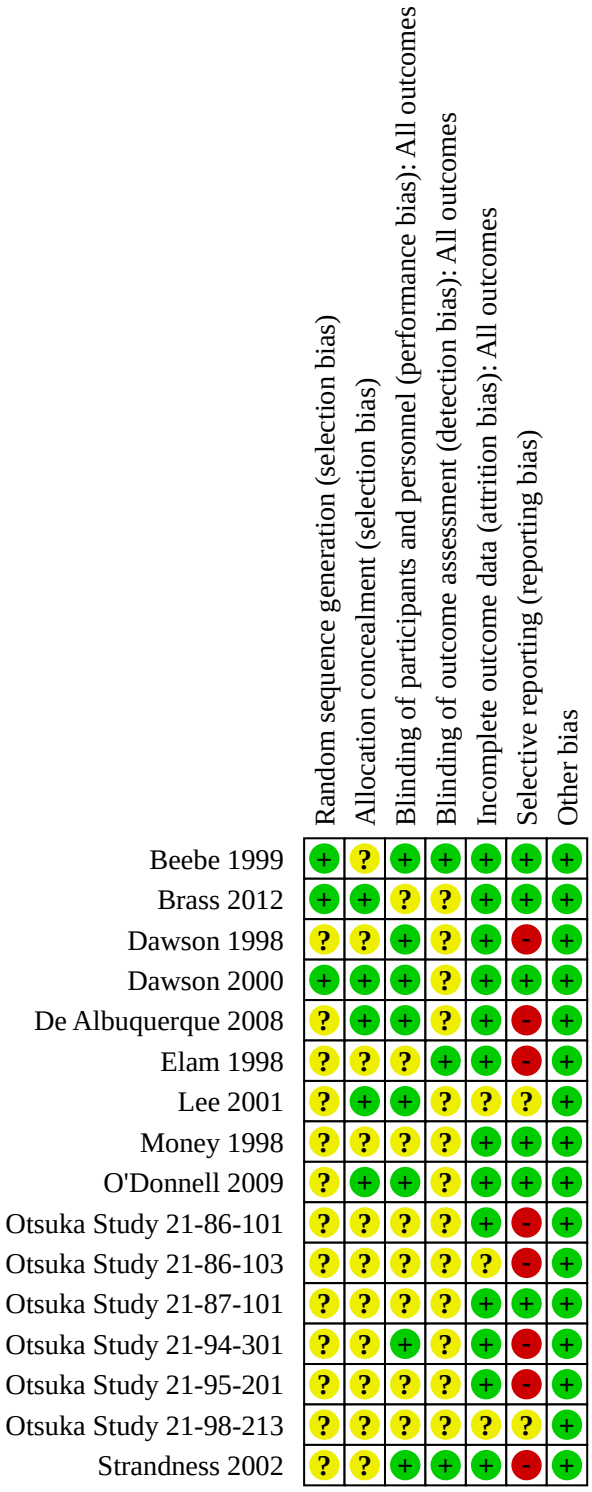


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Thirteen studies did not clearly describe randomisation sequence generation methods, leading to a rating of unclear risk of bias. Randomisation sequence generation was low risk in only three studies: two studies reported voice-interactive computerised methods of randomisation (Brass 2012; Dawson 2000), and Beebe 1999 reported the use of a coded randomisation list. Eleven studies provided insufficient information to permit judgement of risk of bias and were rated as being unclear.

Five studies were rated as having low risk for allocation concealment: Brass 2012 and Dawson 2000 used computerised methods to help ensure that the participants and researchers could not determine the treatment allocation; De Albuquerque 2008, Lee 2001 and O'Donnell 2009 used coded or sealed envelopes to conceal allocation. The remaining eleven studies provided insufficient information to permit judgement of risk of bias and were rated as being unclear.

Blinding

Although all 16 included studies used a placebo control, only half (eight) of the studies adequately described their methods of blinding to ensure that both participants and researchers would not be able to determine treatment and these were rated as being at low risk of bias (Beebe 1999; Dawson 1998; Dawson 2000; De Albuquerque 2008; Lee 2001; O'Donnell 2009; Otsuka Study 21-94-301; Strandness 2002). The remaining eight studies were rated as being unclear.

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 was low. The other 13 studies were rated as having unclear risk of detection bias.

Incomplete outcome data

Thirteen studies were at low risk of attrition bias and three studies had unclear risk of attrition bias (Lee 2001; Otsuka Study 21-86-103; Otsuka Study 21-98-213). Study authors in one study (Lee 2001) stated analysis would be performed on participants that completed the study (not intention-to-treat), but did not specifically state the number of participants that completed the study. The Lee 2001 study has two publications; the results tables in one reference included values that would suggest all participants were included in the analysis, and therefore completed the trial. However, the number of participants reported in the other reference had two participants missing, with no explanation. 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 were 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). Two studies had an unclear risk of reporting bias; in one study, there was inadequate reporting of outcomes (Otsuka Study 21-98-213), and in another study two publications reported on different outcomes with no clear indication of what the preplanned outcomes were (Lee 2001). 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

All 16 studies had a low risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Cilostazol compared with placebo for intermittent claudication; **Summary of findings 2** Cilostazol compared with pentoxifylline for intermittent claudication

For the primary outcome of ICD, 14 of the 16 included studies reported this outcome. However, only six of these studies were reported in an adequate and appropriate manner to be included in the meta-analyses. This was due to methodological differences in the reporting of outcomes that did not allow us to calculate mean change and standard deviations (SD). Also, due to the large differences between studies, we deemed imputation inappropriate. Descriptions of the findings of these studies are addressed under the appropriate outcome headings. Table 3 describes the reasoning why these studies could not appropriately be included in the meta-analyses of walking distances and ABI. Data from five studies were 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).

We conducted sensitivity analyses by removing studies of a lower methodological quality (defined as studies with five or more high-risk or unclear-risk ratings within the seven domains evaluated for risk of bias). We only performed this type of sensitivity analysis for analyses and outcomes where there were sufficient data within the meta-analyses; this included the comparison of cilostazol versus placebo, and for the outcomes ICD, ACD, adverse events and all-cause mortality. For the adverse events of abnormal stools and dizziness, and for ABI there were no studies defined as low quality and so these sensitivity analyses were not undertaken.

Cilostazol versus placebo

Summary of findings 1 provides a summary of the results for the comparison of cilostazol versus placebo. We carried out subgroup analysis to investigate any overall effect of cilostazol and also to compare the different cilostazol doses. Two studies compared cilostazol 50 mg twice daily with placebo (Beebe 1999; Strandness 2002), all 16 included studies compared cilostazol 100 mg twice daily with placebo (Beebe 1999; Brass 2012; Dawson 1998; Dawson 2000; De Albuquerque 2008; Elam 1998; Lee 2001; 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) and one study compared cilostazol 150 mg twice daily with placebo (Otsuka Study 21-95-201).

Initial claudication distance

Two studies (400 participants) compared cilostazol 50 mg with placebo (Beebe 1999; Strandness 2002) and the fixed-effect model

found a higher ICD (MD 19.50 metres, 95% CI 6.80 to 32.21 metres) in the cilostazol treatment group compared with the placebo group (Analysis 1.1).

Six studies (1236 participant) comparing cilostazol 100 mg versus placebo were 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 higher ICD, with a MD of 32.19 metres (95% CI 22.20 to 42.18 metres), compared with those taking placebo (Analysis 1.1).

One study (86 participants) compared cilostazol 150 mg versus placebo (Otsuka Study 21-95-201) and the fixed-effect model found no observable difference between the treatment groups in ICD (MD 15.70 metres, 95% CI -12.20 to 43.60 metres). As only one study was included in the analysis, an overall association could not be determined (Analysis 1.1).

Overall, six studies (1722 participants) were included in the meta-analysis that compared cilostazol (all doses) versus placebo. In the fixed-effect model, participants taking cilostazol had a higher ICD, with a MD of 26.49 metres (95% CI 18.93 to 34.05 metres), compared with those taking placebo (Analysis 1.1). No differences were seen with subgroup analysis (test for subgroup differences: P = 0.22). When low-quality studies were removed in sensitivity analysis, there was an additional improvement of 3.03 meters in favour of cilostazol (MD 29.52, 95% CI 21.26 to 37.78) and there was a subgroup difference (P = 0.04).

Eight additional studies reported data on change in ICD compared with baseline, but the data were 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 ± standard deviation (SD) of 95 seconds, and the placebo group showing a smaller increase of 44 seconds ± 102 seconds. The report by De Albuquerque 2008 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).

Overall, the evidence for this outcome was of low certainty, downgraded one level because of risk of bias (selective reporting) and one level because publication bias was strongly suspected.

Health-related quality of life

Quality of life (QoL) 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 reported QoL measures in normoglycaemic patients and diabetic patients, separately. Due to the differences in QoL measures, as well as how they were reported, we did not undertake a meta-analysis. Table 1 provides information on change in QoL measures as reported in the individual studies. This table should be interpreted with caution, as no hypothesis testing has been performed, and the data format differed 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 representing inability 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.

There appeared to be a general improvement in QoL for cilostazol over placebo (various domains, not all domains measured within studies) (SF-36, Beebe 1999; Dawson 2000; Money 1998; O'Donnell 2009). There were inconsistent results for walking impairment according to the WIQ (four studies), three studies showed no difference between groups for walking impairment (Beebe 1999; Dawson 2000; O'Donnell 2009) and one study reported a 20% increase in walking speed for the cilostazol group (Money 1998). There were modest improvements across the domains of the COM in one study (Beebe 1999). There was no difference between groups in one study using the VascuQol questionnaire (O'Donnell 2009).

The Strandness 2002 study also reported on QoL, with inadequate numerical data to support, but mentioned greater improvement in the cilostazol group 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 QoL, 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 were reported.

Overall, the evidence for this outcome was of low certainty, downgraded one level for imprecision because a range of QoL measurement tools were used and results were reported in

different ways and one level for strongly suspected publication bias.

Absolute claudication distance

Two studies (400 participants) compared cilostazol 50 mg with placebo (Beebe 1999; Strandness 2002), and the resulting random-effect meta-analysis found a higher ACD in the cilostazol arm (MD 30.84 metres, 95% CI 8.81 to 52.86 metres) (Analysis 1.2).

Eight studies (1874 participants) 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 higher ACD in the cilostazol arm (MD 42.32 metres, 95% CI 18.12 to 66.51 metres) (Analysis 1.2).

One study of 86 participants (Otsuka Study 21-95-201), compared cilostazol 150 mg with placebo, and found a MD of 51.80 metres with a wide 95% CI spanning -10.59 to 114.19 (Analysis 1.2).

Overall, eight studies (2360 participants) were included in the meta-analysis that compared cilostazol (all doses) versus placebo. Heterogeneity was detected so we used the random-effects model. Participants taking cilostazol had a higher ACD, with a MD of 39.57 metres (95% CI 21.80 to 57.33 metres), compared with those taking placebo (Analysis 1.2). No differences were seen with subgroup analysis (test for subgroup differences: P = 0.70). When low-quality studies were removed in sensitivity analysis, there was there was an additional improvement of 8.87 meters in favour of cilostazol (MD 48.44, 95% CI 34.49 to 62.39).

Eight additional studies reported on ACD, but their data were incompatible for meta-analysis (Brass 2012; De Albuquerque 2008; Lee 2001; 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 (± SD) from baseline for the cilostazol group was 122 seconds ± 190 seconds, and for the placebo group a mean change of 72 seconds ± 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%. These data were 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 did 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. Lee 2001 reported a baseline ACD for the cilostazol group of 111 metres (SD 30) and follow-up of 145 (SD 53). The placebo group had a baseline ACD of 116 metres (SD 56) and follow-up of 121 (SD 62), with no difference between the time points.

Overall, the evidence for this outcome was of very low certainty, downgraded one level for risk of bias (selective reporting), one level for inconsistency (heterogeneity) and one level for strongly suspected publication bias.

Revascularisation (angioplasty or surgical bypass)

One study (516 participants) compared both cilostazol 50 mg twice daily and cilostazol 100 mg twice daily versus placebo (Beebe 1999) and found no clear difference in the odds of arterial revascularisation with OR 0.16 (95% CI 0.01 to 4.07, Analysis 1.3). The evidence for this outcome was of very low certainty, downgraded by two levels for imprecision and one level for strongly suspected publication bias.

Amputation

One study (516 participants) compared both cilostazol 50 mg twice daily and cilostazol 100 mg twice daily versus placebo (Beebe 1999), and found no clear difference in the odds of amputation with OR 0.16 (95% CI 0.01 to 4.07, Analysis 1.4). The evidence for this outcome was of very low certainty, downgraded by two levels for imprecision and one level for strongly suspected publication bias.

Adverse events related to study medication

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 reported several side effects in a combined events outcome, which was not appropriate to include 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. Lee 2001 reported no significant subjective side effects in the cilostazol or placebo group, but did not define what they considered a side effect.

Headache

Two studies (453 participants) reported on headache when comparing cilostazol 50 mg twice daily versus placebo (Beebe 1999; Strandness 2002). Meta-analysis using a fixed-effect model, showed an increased odds of headache in the cilostazol 50 mg twice daily group with OR 2.02 (95% CI 1.19 to 3.43) versus the placebo group (Analysis 1.5).

Eight studies (2131 participants) reported on headache when comparing cilostazol 100 mg twice daily versus placebo (Beebe 1999; Brass 2012; Dawson 1998; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002). Meta-analysis using a fixed-effect model, showed an increased odds of headache in the cilostazol 100 mg twice daily group with OR 3.05 (95% CI 2.38 to 3.92) versus the placebo group (Analysis 1.5).

Overall, eight studies (2584 participants) reported on headache when comparing cilostazol (all doses) versus placebo (Beebe 1999; Brass 2012; Dawson 1998; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002). Meta-analysis using a fixed-effect model, showed an increased odds of headache in the cilostazol group with OR 2.83 (95% CI 2.26 to 3.55) versus the placebo group (Analysis 1.5). Incidence rates were 380/1456 for cilostazol participants and 119/1128 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.17). When low-quality studies were removed in sensitivity analysis, there was very little change in the odds of headache in the cilostazol group versus placebo, OR 2.83, (95% CI 2.21 to 3.61, Analysis 1.16).

Overall, the evidence for this outcome was of moderate certainty, downgraded one level for strongly suspected publication bias. Table 2 grades the evidence for other adverse events related to study medication.

Diarrhoea

Two studies (453 participants) compared cilostazol 50 mg with placebo (Beebe 1999; Strandness 2002). The fixed-effect model found no clear difference between groups, OR 2.02 (95% CI 0.91 to 4.52) for the 50 mg comparison (Analysis 1.6).

Seven studies (2050 participants) compared cilostazol 100 mg twice daily with placebo (Beebe 1999; Brass 2012; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002). The fixed-effect model found an increased odds in the cilostazol group: OR 2.88 (95% CI 2.07 to 3.99, Analysis 1.6).

Overall, seven studies (2503 participants) compared cilostazol (all doses) with placebo (Beebe 1999; Brass 2012; Dawson 2000; Elam 1998; Money 1998; Otsuka Study 21-98-213; Strandness 2002). The fixed-effect model found an increased odds in the cilostazol group: OR 2.73 (95% CI 2.02 to 3.70, Analysis 1.6). Incidence rates were 190/1402 for cilostazol participants and 62/1101 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.43). When low-quality studies were removed in sensitivity analysis, there was very little change in the meta-analyses results, OR 2.91, (95% CI 2.05 to 4.12, Analysis 1.17).

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

Two studies (453 participants) compared cilostazol 50 mg versus placebo and found no difference between the treatment groups, OR 2.48 (95% CI 1.08 to 5.71) using a fixed-effect model (Beebe 1999; Strandness 2002) (Analysis 1.7).

Five studies (1351 participants) compared cilostazol 100 mg with placebo and found an increased odds of abnormal stools in the cilostazol group, OR 4.04 (95% CI 2.59 to 6.31), using a fixed-effect model (Beebe 1999; Dawson 2000; Elam 1998; Money 1998; Strandness 2002) (Analysis 1.7).

Overall, five studies (1804 participants) compared cilostazol (all doses) with placebo (Beebe 1999; Dawson 2000; Elam 1998; Money 1998; Strandness 2002). The fixed-effect model found an increased odds in the cilostazol group: OR 3.63 (95% CI 2.45 to 5.38, Analysis 1.7). Incidence rates of abnormal stools were 150/1052 for cilostazol participants and 33/752 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.31).

Dizziness

A single study compared cilostazol 50 mg with placebo and found no clear difference between the two treatment groups, OR 1.95 (95% CI 0.63 to 6.06) (Beebe 1999) (Analysis 1.8).

For the comparison between cilostazol 100 mg and placebo, four studies (864 participants) recorded data on dizziness (Beebe 1999; Brass 2012; Elam 1998; Money 1998). The results of the fixed-effect meta-analysis found an increased odds of dizziness in the cilostazol group, OR 2.57 (95% CI 1.42 to 4.63, Analysis 1.8).

Overall, four studies (1120 participants) compared cilostazol (all doses) versus placebo (Beebe 1999; Brass 2012; Elam 1998; Money 1998). The results of the fixed-effect meta-analysis found an increased odds of dizziness in the cilostazol group, OR 2.42 (95% CI 1.43 to 4.08, Analysis 1.8). Incidence rates were 63/649 for cilostazol participants and 20/471 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.67).

Pain

Pain was reported in one study (197 participants) comparing cilostazol 50 mg versus placebo (Strandness 2002); it found no clear difference between treatment groups, OR 1.53 (95% CI 0.67 to 3.48) (Analysis 1.9).

Pain was reported in four studies (1375 participants) comparing cilostazol 100 mg versus placebo (Dawson 2000; Elam 1998; Otsuka Study 21-98-213; Strandness 2002). There was no clear difference in the fixed-effect model for cilostazol 100 mg versus placebo: OR 0.88 (95% CI 0.64 to 1.23, Analysis 1.9).

Overall, four studies (1572 participants) compared cilostazol (all doses) with placebo (Dawson 2000; Elam 1998; Otsuka Study 21-98-213; Strandness 2002). There was no clear difference in the fixed-effect model for cilostazol versus placebo: OR 0.96 (95% CI 0.71 to 1.30, Analysis 1.9). Incidence rates were 107/848 for cilostazol participants and 92/724 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.23). When low-quality studies were removed in sensitivity analysis, there was very little change in the meta-analyses results, OR 1.07, (95% CI 0.75 to 1.54, Analysis 1.18).

Palpitations

The occurrence of palpitations was measured in one study (256 participants) comparing cilostazol 50 mg versus placebo (Beebe 1999); it found a higher odds in the cilostazol group, with a very wide CI, OR 8.89 (95% CI 0.51 to 155.87), but with only a single study, an overall association could not be determined (Analysis 1.10).

The occurrence of palpitations was measured in four studies (1425 participants) comparing cilostazol 100 mg versus placebo (Beebe 1999; Brass 2012; Dawson 2000; Otsuka Study 21-98-213). The fixed-effects model found an increased odds of palpitations in the cilostazol group, OR 7.06 (95% CI 3.85 to 12.96, Analysis 1.10).

Overall, four studies (1681 participants) compared cilostazol (all doses) with placebo (Beebe 1999; Brass 2012; Dawson 2000; Otsuka Study 21-98-213). The fixed-effects model found an increased odds of palpitations in the cilostazol group, OR 7.16 (95% CI 3.95 to 12.98, Analysis 1.10). Incidence rates were 94/923 for cilostazol participants and 12/758 for placebo participants. No differences were seen with subgroup analysis (test for subgroup differences: P = 0.88). When low-quality studies were removed in sensitivity analysis, there was an increased odds in the cilostazol group versus placebo (OR 12.80, 95% CI 5.06 to 32.36, Analysis 1.19).

Cardiovascular events

Two studies (692 participants) reported cardiovascular events (myocardial infarction and stroke) that compared cilostazol (all doses) versus placebo (Beebe 1999; Brass 2012). Meta-analysis using a fixed-effect model, showed no clear difference in the odds of cardiovascular events with OR 1.50 (95% CI 0.51 to 4.47) versus the placebo group (Analysis 1.11). No differences were seen with subgroup analysis by cilostazol dose (test for subgroup differences: P = 1.0). Brass 2012 reported serious adverse cardiac events, but did not report a breakdown 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. Overall, the evidence for this outcome was of low certainty, downgraded one level for imprecision and one level for strongly suspected publication bias.

All-cause mortality

All-cause mortality was reported in eight studies (2642 participants) (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 clear difference between the treatment groups, with an OR of 0.97 (95% CI 0.41 to 2.30, Analysis 1.12). No differences were seen with subgroup analysis by cilostazol dose (test for subgroup differences: P = 0.62). When low-quality studies were removed, there was little change in the meta-analyses results (OR 1.21, 95% CI 0.47 to 3.13).

Ankle brachial index

Three studies were included in the meta-analysis for ABI (Dawson 2000; Elam 1998; Money 1998); the results from the random-effects model was a higher ABI in the cilostazol arm of 0.06 (95% CI 0.04 to 0.08, Analysis 1.13).

In addition, two studies reported ABI that could not be included in the meta-analysis (Lee 2001; O'Donnell 2009). 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 were not comparable. The cilostazol group had a median change of ABI of -0.05 on 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. Lee 2001 reported no differences from baseline to follow-up for any of the treatment groups. The cilostazol treatment group had a baseline measure of 0.73 (SD 0.12) and follow-up of 0.69 (SD 0.11), while the placebo group had a baseline of 0.69 (SD 0.12) and follow-up of 0.71 (SD 0.13).

Major Adverse Limb Event

None of the studies reported this outcome.

Cilostazol versus pentoxifylline

Summary of findings 2 provides a summary of the results for the comparison of cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily. Five studies were included for this comparison (Dawson 2000; De Albuquerque 2008; Lee 2001; Otsuka Study 21-94-301; Otsuka Study 21-98-213).

Initial claudication distance

A single study compared cilostazol 100 mg with pentoxifylline 400 mg (Dawson 2000), and the fixed-effect model found no observable difference between the treatment groups in ICD (MD 20.00 metres, 95% CI -2.57 to 42.57 metres). As only one study was included in the analysis, an overall association could not be determined (Analysis 2.1).

Additionally, three studies that could not be included in the meta-analysis compared change in ICD from baseline between cilostazol 100 mg and pentoxifylline 400 mg (De Albuquerque 2008; Otsuka Study 21-94-301; Otsuka Study 21-98-213). The report by De Albuquerque 2008 did not break down the ICD outcome by treatment group, and reported only an estimate of change in ICD for the whole study population split according to smoking status. 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 with pentoxifylline of 0.94 (95% CI 0.95 to 1.12; P = 0.260).

Overall, the evidence for this outcome was of low certainty because of imprecision and strongly suspected publication bias.

Health-related quality of life

One study reported this outcome (Dawson 2000). The study authors reported that none of the treatments significantly affected the scores on mental health concepts, general health perception, physical health concepts, or vitality scores (SF-36). There were no significant differences in patient-reported walking distance or speed (WIQ). Overall, the evidence for this outcome was of very low certainty because of very serious imprecision and strongly suspected publication bias.

Absolute claudication distance

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 MD of 13.41 metres (95% CI -43.50 to 70.36 metres, Analysis 2.2).

Additionally, three studies that could not be included in the meta-analysis compared change in ICD from baseline between cilostazol 100 mg and pentoxifylline 400 mg (De Albuquerque 2008; Lee 2001; Otsuka Study 21-94-301). The De Albuquerque 2008 study did not directly compare cilostazol with pentoxifylline, but reported a mean change in maximal walking distance via a graph, 'expressed

as per cent of control' of approximately 50%. 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. Lee 2001 reported a baseline ACD for the cilostazol group of 111 metres (SD 30) and follow-up of 145 (SD 53). The pentoxifylline group had a baseline ACD of 114 (SD 51) and follow-up of 147 (81). However, the authors of the study did not directly compare the change in ACD between the two treatment groups.

Overall, the evidence for this outcome was of very low certainty because of inconsistency, imprecision and strongly suspected publication bias.

Revascularisation (angioplasty or surgical bypass)

No study reported this outcome.

Amputation

No study reported this outcome.

Adverse events related to study medication

Headache

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, Analysis 2.3). Incidence rates were 106/488 for cilostazol participants and 55/494 for placebo participants.

Overall, the evidence for this outcome was of low certainty because of heterogeneity and strongly suspected publication bias.

Diarrhoea

The two studies comparing cilostazol 100 mg with pentoxifylline 400 mg found, with a random-effects model, no difference in the odds of diarrhoea between the treatment groups, OR 1.80 (95% CI 0.79 to 4.12) (Dawson 2000; Otsuka Study 21-98-213) (Analysis 2.4). Incidence rates were 78/488 for cilostazol participants and 48/494 for placebo participants.

Abnormal stools

Only one study (Dawson 2000) reported abnormal stools for the comparison between cilostazol and pentoxifylline; it found an increased odds of abnormal stools in the cilostazol group, OR 3.12 (95% CI 1.57 to 6.21) (Analysis 2.5). Incidence rates were 33/227 for cilostazol participants and 12/232 for placebo participants.

Pain

Pain was reported in two studies comparing cilostazol with pentoxifylline (Dawson 2000; Otsuka Study 21-98-213). There was no difference in the fixed-effect model results for cilostazol versus pentoxifylline, OR 0.85 (95% CI 0.57 to 1.26) (Analysis 2.6). Incidence rates were 52/488 for cilostazol participants and 61/494 for placebo participants.

Palpitations

The occurrence of palpitations was measured in two studies comparing cilostazol with pentoxifylline (Dawson 2000; Otsuka Study 21-98-213); there was an increase in palpitations in the cilostazol group, with a fixed-effect model, OR 8.35 (95% CI 4.11 to 16.98) (Analysis 2.7). Incidence rates were 65/488 for cilostazol participants and 9/494 for placebo participants.

Subjective side effects

Additionally, one study that could not be included in the meta-analysis (Lee 2001), reported no significant subjective side effects in the cilostazol or pentoxifylline group, but did not define what they considered a side effect.

Cardiovascular events

No study reported this outcome.

All-cause mortality

Three studies reported on all-cause mortality comparing cilostazol with pentoxifylline (Dawson 2000; Otsuka Study 21-94-301; Otsuka Study 21-98-213). The fixed-effect model results found no association between the treatment groups (OR 0.58, 95% CI 0.17 to 1.98) (Analysis 2.8).

Ankle brachial index

One study was included in the ABI meta-analysis for the comparison of cilostazol 100 mg to pentoxifylline 400 mg (Dawson 2000); it found an ABI MD of -0.01 (95% CI -0.12 to 0.10), but no overall association could be determined (Analysis 2.9).

Additionally, one study that could not be included in the meta-analysis (Lee 2001), reported no differences from baseline to follow-up for any of the treatment groups. The cilostazol treatment group had a baseline measure of 0.73 (SD 0.12) and follow-up of 0.69 (SD 0.11), while the pentoxifylline group had a baseline of 0.66 (SD 0.13) and follow-up of 0.70 (SD 0.14).

Major Adverse Limb Event

No study reported this outcome.

DISCUSSION

Summary of main results

Cilostazol versus placebo

There is very low to low-certainty evidence that cilostazol improves walking distance, both in terms of ICD and ACD, compared to placebo. Six studies reported ICD, with a study duration ranging from 12 to 24 weeks, and cilostazol dose ranging from 100 mg to 300 mg. Participants taking cilostazol had a higher ICD, with a MD of 26.49 metres (95% CI 18.93 to 34.05; 1722 participants; 6 studies), compared with those taking placebo. When lower quality studies were removed, there was an additional improvement of three metres in favour of cilostazol (MD 29.52, 95% CI 21.26 to 37.78; 1543 participants; 5 studies) and subgroup differences according to dose (P = 0.04). Participants taking 50 mg cilostazol twice daily had a MD of 19.50 metres (95% CI 6.80 to 32.21; 400 participants; 2 studies) and participants taking 100 mg cilostazol twice daily had a MD of 32.19 metres (95% CI 22.20 to 42.18; 1236 participants; 6 studies). Participants taking cilostazol had a higher ACD, with a MD of 39.57 metres (95% CI 21.80 to 57.33; 2360 participants; 8 studies) compared with those taking placebo. When lower quality studies were removed, there was an additional improvement of nine metres in favour of cilostazol (MD 48.44, 95% CI 34.49 to 62.39; 1732 participants; 6 studies).

The value of these increases in walking distance (26 metres further before the onset of calf pain and 40 metres further in terms of total distance) are subjective and depend on the individual patient; some patients may find not much benefit from this additional walking distance but some may find the additional extra walking distance enables them to undertake more daily activities.

Four studies reported on quality of life (QoL) but, due to the differences in QoL measures as well as how they were reported, we did not undertake a meta-analysis. Overall, cilostazol was associated with improvements in some domains of QoL compared to placebo. Very few studies reported on other outcomes making it impossible to draw any conclusions regarding the effectiveness of cilostazol versus placebo on arterial revascularisation, amputation, or cardiovascular events.

There was moderate-certainty evidence that participants taking cilostazol had an increased odds of experiencing headache compared to participants taking placebo, during 12 to 26 weeks intervention (OR 2.83, 95% CI 2.26 to 3.55; 2584 participants; 8 studies); and an increased odds of other commonly reported adverse events including diarrhoea, abnormal stools, dizziness and palpitations.

Eight studies reported very few deaths with no difference in all-cause mortality between cilostazol and placebo groups. Cilostazol (100 mg twice daily) improved ABI over placebo (MD 0.06, 95% CI 0.04 to 0.08; 859 participants; 3 studies).

The certainty of the evidence was downgraded by one level for all studies because publication bias was strongly suspected. Other issues that necessitated downgrading included risk of selective reporting, imprecision and inconsistency.

Cilostazol versus pentoxifylline

There is very low to low-certainty evidence of no difference between cilostazol and pentoxifylline for improving walking distance, both in terms of ICD (MD 20.00, 95% CI -2.57 to 42.57; 417 participants; 1 study) and ACD (MD 13.43, 95% CI -43.50 to 70.36; 866 participants; 2 studies).

One study reported on QoL; the study authors reported no difference in QoL between the treatment groups. No study reported on revascularisation, amputation or cardiovascular events. There was low-certainty evidence that cilostazol participants had an increased odds of experiencing headache compared to participants taking pentoxifylline at 24 weeks (OR 2.20, 95% CI 1.16 to 4.17; 982 participants; 2 studies); and an increased odds of experiencing abnormal stools, and palpitations, but there was no difference between treatment groups for diarrhoea or pain. There was no clear difference between treatment groups for all-cause mortality or ABI.

Certainty of the evidence was downgraded by one level for all studies because publication bias was strongly suspected. Other issues that necessitated downgrading included imprecision and inconsistency.

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 stable intermittent claudication. All 16 included studies evaluated the effects of cilostazol compared with placebo, within similar study populations. Most of the included evidence is for the comparison of cilostazol versus placebo, the two walking distance outcomes (ICD and ACD) and for the cilostazol dose of 100 mg twice daily. We identified very limited data on QoL, other serious outcomes of amputation, revascularisation and cardiovascular events, and all-cause mortality, both in terms of the number of studies reporting these outcomes and few events reported within those studies.

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 were 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 measures. 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.

Many included studies were quite 'old' and were carried out before best medical treatment was recommended or applied in patients with stable intermittent claudication and so a further limitation to this evidence is that it might not be an accurate representation of current practice. Also, dose recommendation for pentoxifylline is either 400 mg three times daily or 400 mg twice daily; one included study did not reflect current dosing practice as it used a pentoxifylline dose of 600 mg twice daily (De Albuquerque 2008). We only identified studies comparing cilostazol versus placebo, and cilostazol versus pentoxifylline; studies comparing cilostazol with other agents, such as naftidrofuryl, were not identified.

Quality of the evidence

We included 16 studies with 3972 participants. Using GRADE assessment, all studies (both comparisons) were downgraded one level because publication bias was strongly suspected, with pharmaceutical sponsors involved in all 16 studies (of which 13 involved the same pharmaceutical company (Otsuka)).

Using GRADE assessment, the body of evidence relating to cilostazol compared with placebo was judged to be of very low (ACD, revascularisation, amputation), low (ICD, QoL, cardiovascular outcomes) to moderate (adverse events - headache) certainty. Other issues that necessitated downgrading included risk of selective reporting, imprecision and inconsistency.

Using GRADE assessment, the body of evidence relating to cilostazol compared with pentoxifylline was judged to be of very low (QoL, ACD), to low (ICD, adverse events - headache) certainty. Other issues that necessitated downgrading included imprecision and inconsistency.

Certainty of the evidence was based on those studies in the summary of findings tables and (with the exception of QoL) this evidence comes from the meta-analyses. The risk of bias assessments of those studies not included in the meta-analyses

was consistent with risk of bias assessments of studies included in the meta-analyses. However, it should be noted that data in a significant proportion of studies was poorly reported, and we were unable to incorporate such data in any of the meta-analyses.

Six studies were never published as journal articles, with sources of data being a medical review by the FDA in five cases and a pharmaceutical submission to NICE in another case. Seven studies were published journal articles, however, the data used for six of these studies were derived from pharmaceutical data submitted to the FDA rather than the associated publications.

Potential biases in the review process

Study selection and data extraction were performed independently by two review authors in order to minimise bias in the review process. The inclusion and exclusion criteria of the review were strictly adhered to in order to limit subjectivity.

For the primary outcome of ICD, 14 of the 16 included studies reported this outcome. However, only six of these studies were reported in an adequate and appropriate manner to be included in the meta-analyses. Following consultation with a statistician, other forms of imputation were not carried out 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. For the Dawson 2000 study, standard deviations were provided for the ABI outcome for mean change in the comparison between cilostazol and placebo, but not for cilostazol compared to pentoxifylline. We calculated correlation coefficients using the existing mean change standard deviations and imputed values to calculate mean change standard deviations for the comparison between cilostazol and pentoxifylline.

Agreements and disagreements with other studies or reviews

The evidence presented here is consistent with the findings of two older reviews (Regensteiner 2002; Thompson 2002) which evaluated the effects of cilostazol for intermittent claudication and found similar improvements in walking distances for participants taking cilostazol. A systematic review published in 2012 comparing cilostazol, naftidrofuryl oxalate and pentoxifylline with 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 QoL reporting did not allow them to report those findings in their review.

The data from Stevens and colleagues (Stevens 2012) 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 2011). These assessment reports continue to underpin the current NICE guideline (CG147) and there has been no major change to this guideline in relation to treatment of intermittent claudication, since its publication in 2012 and last updated in December 2020 (NICE 2012). Our review confirms that there is very little new RCT evidence for cilostazol for people with intermittent claudication. We did not identify any newer systematic reviews of cilostazol for intermittent claudication.

Two of the studies in our review that compared cilostazol versus pentoxifylline (Dawson 2000; Lee 2001) were included in another Cochrane review of pentoxifylline (Broderick 2020) where review authors concluded that the data from studies comparing cilostazol with pentoxifylline 'were too limited to allow meaningful conclusions'. In patients in whom symptoms do not improve with exercise and risk factor management, medical management using pharmacological interventions, such as cilostazol (Aboyans 2018; Gerhard-Herman 2017; Aboyans 2018), naftidrofuryl (Aboyans 2018; NICE 2012) and pentoxifylline (Aboyans 2018; Gerhard-Herman 2017; Aboyans 2018), are suggested by some national guidelines. A review of clinical guidelines published in 2016 showed that cilostazol was the most recommended drug (in five guidelines) as first option for pharmacological treatment (Barriocanal 2016).

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 (last updated December 2020) only recommend naftidrofuryl as treatment in this population (NICE 2012). Our review, alongside other reviews mentioned here, demonstrates that there remains a degree of uncertainty as to which, if any, of these medications provides most clinical benefit.

AUTHORS' CONCLUSIONS

Implications for practice

Participants taking cilostazol for three to six months could walk approximately 26 metres further before the onset of calf pain and 40 metres further in terms of total distance on a treadmill compared to participants taking placebo. However, participants taking cilostazol had nearly three times the odds of experiencing headache compared to participants taking placebo. The value of these increases in walking distance will be patient-specific. There is insufficient evidence about the effectiveness of cilostazol for serious events such as amputation, revascularisation, and cardiovascular events. Despite the importance of quality of life to patients, meta-analysis could not be undertaken because of differences in measures used and how they were reported.

Very limited data indicated no difference between cilostazol and pentoxifylline for improving walking distance, but the data were too limited to enable any meaningful conclusions to be drawn for any of the remaining outcomes reported.

Using GRADE methods, we judged the evidence to be of very low to low certainty for all of the outcomes except for adverse events related to study medication where some events were judged as being at moderate certainty. All studies for both comparisons were downgraded one level because publication bias was strongly suspected. Other issues that necessitated downgrading included risk of selective reporting, imprecision and inconsistency.

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 on 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. Suggestions for future research include research that is independently funded and which directly compares cilostazol with other active drugs. Quality of life is extremely important to patients and needs to be measured as a matter of course and consistently in future studies, with agreement of which tools to use and how to report the data to enable comparison across studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beebe 1999

Study characteristics	
Methods	Study design: multicentre, randomised, double-blind, placebo-controlled
	Intention-to-treat: yes
	Country: USA

Beebe 1999 *(Continued)*

Participants	Number randomised: 516 (cilostazol 100 mg, n = 175; cilostazol 50 mg, n = 171; placebo, n = 170) Age (mean years ± SE): cilostazol 100 mg = 64.3 ± 8.5; cilostazol 50 mg = 64.5 ± 9.9; placebo = 65.1 ± 9.3 Sex M/F: cilostazol 100 mg 130/45; cilostazol 50 mg = 131/40; placebo = 131/39 **Inclusion criteria:** ≥ 40 years of age; ≥ 6 months history of stable symptomatic IC 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 QoL questionnaires (SF-36, WIQ, COM), patient and physician end-of-treatment global therapeutic assessments, cardiovascular morbidity, all-cause mortality, amputation and adverse events. Outcomes evaluated at baseline (three times), 4, 8, 16, 20 and 24 weeks
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported
Notes	"The COM questionnaire was developed by the study sponsor and has not been independently validated." Constant-rate, constant-grade treadmill test design, with 12.5% incline and speed of 3.2 km/h 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 was assumed blinding was adequate.

Beebe 1999 *(Continued)*

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 were reported on.
Other bias	Low risk	No evidence of other bias

Brass 2012

Study characteristics	
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; revascularisation ≤ 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 or aspirin monotherapy, aspirin combined with clopidogrel or ticlopidine, strong inhibitors of cytochrome P3A4, use of other PDE inhibitors, use of pentoxifylline or L-carnitine
Interventions	Treatment 1: cilostazol 100 mg, twice daily Treatment 2: K-134 25 mg, twice daily Treatment 3: K-134 50 mg, twice daily (initially started on 25 mg twice daily and then increased after two weeks) Treatment 4: K-135 100 mg, twice daily (initially started on 50 mg twice daily and then increased after two weeks) Control: placebo, twice daily Duration: 26 weeks
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
Funding	Kowa Research Institute

Brass 2012 *(Continued)*

Declaration of interests	"Dr Morgan is an employee of the study's sponsor, Kowa Research Institute. Drs Brass, Cooper, and Hiatt were compensated by the study's sponsor, Kowa Research Institute, for their service on the project's steering committee. Dr Hiatt is president of the non-profit Colorado Prevention Center, which provided academic contract research organization services (paid for by Kowa Research Institute) for the reported trial".
Notes	Only data on the cilostazol and placebo groups were included in this review; the K-134 25 mg, 50 mg and 100 mg groups were excluded from this review because K-134 is not an alternative antiplatelet agent or medication currently known to increase walking distance. The 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 paper the authors used. The K-134 arm of 25 mg twice daily was discontinued early because it was found to be minimally informative, and no outcome data were recorded.

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 the study used a placebo, there was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was 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 the description of methods were reported on.
Other bias	Low risk	No evidence of other bias

Dawson 1998

Study characteristics

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention-to-treat: yes; LOCF method Country: USA
Participants	Number randomised: 81 (cilostazol n = 54; placebo n = 27) Age (mean years ± SE): cilostazol = 66 ± 1.1; placebo = 67 ± 2.0 Sex M/F: cilostazol = 38/16; placebo = 24/3

Dawson 1998 *(Continued)*

	Inclusion criteria: ≥ 40 years; stable IC secondary to chronic occlusive arterial disease ≥ 6 months; ICD on treadmill between 30 and 200 m and had to be within ± 35% value of previous visit; confirmation of diagnosis of chronic occlusive arterial disease; doppler-measured ankle systolic blood pressure ≥ 20 mmHg **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
Interventions	Treatment: cilostazol 100 mg, twice daily, orally Control: placebo, twice daily Duration: 12 weeks
Outcomes	ICD, ACD, ABI, and subjective assessments of symptoms by patient and physician Outcomes evaluated at baseline (multiple visits), 2, 4, 8 and 12 weeks after initiation of therapy
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported
Notes	Constant speed treadmill test at 3.2 km/h and a fixed incline of 12.5% Two-week baseline period to stabilise concomitant medications, followed by a two to four-week single-blind placebo lead-in phase

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 was 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 mentioned ABI results in the abstract with no explicit description.
Other bias	Low risk	No evidence of other bias

Dawson 2000

Study characteristics

Dawson 2000 *(Continued)*

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled Intention-to-treat: yes; LOCF method Country: USA
Participants	Number randomised: 698 (cilostazol n = 227; pentoxifylline n = 232; placebo n = 239) Age (mean years ± SD): cilostazol = 66 ± 9; pentoxifylline = 66 ± 9; placebo = 66 ± 9 Sex M/F: cilostazol = 172/55; pentoxifylline = 181/51; placebo = 176/63 **Inclusion criteria:** stable, moderate to severe symptoms of IC for previous 6 months; confirmed PAD; baseline ICD ≥ 53.6 m (one minute); ACD ≤ 537.6 m (ten minutes) **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 IC; 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
Interventions	Treatment: cilostazol 100 mg, twice daily with a third placebo for blinding Treatment: pentoxifylline 400 mg, three times daily Control: placebo Duration: 24 weeks
Outcomes	ACD, ICD, resting doppler limb pressures, QoL questionnaires (SF-36, WIQ); measured at baseline and weeks 2, 4,8, 12, 16, 20 and 24
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - two of the authors (EBB, WPF) were employed by Otsuka America Pharmaceutical Inc.
Notes	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 Two- to three-week baseline period

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 appeared to be reported on.
Other bias	Low risk	No evidence of other bias

De Albuquerque 2008

Study characteristics	
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 ± SD): cilostazol = 64.0 ± 9.0; pentoxifylline = 64.0 ± 10.0; placebo = 63.0 ± 9.0 Sex (% M): cilostazol = 64.7%; pentoxifylline = 60.0%; placebo = 50.0% **Inclusion criteria:** age 45 to 85 years; IC for at least 6 months; resting ABI ≤ 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
Funding	"Cilostazol, pentoxifylline, and placebo were generous gifts from LIBBS, Brazil." Study supported by grants from the National Research Council (CNPq 52 1850/96-7) and from Research Supporting Agency of Rio de Janeiro State (FAPERJ E-26/170. 522/00)
Declaration of interests	Not reported
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)	Unclear risk	Blinding of assessors was not adequately discussed.

De Albuquerque 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears all participants completed the trial; no loss-to-follow-up reported
Selective reporting (reporting bias)	High risk	All outcomes included in description of methods were reported on, but for PFWD and MWD (Table 2); there was no breakdown for the different treatment groups.
Other bias	Low risk	No evidence of other bias

Elam 1998

Study characteristics	
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 IC 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, 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)
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - three of the authors (JH, EBB, WPF) were employed by Otsuka America Pharmaceutical Inc.
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

Elam 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there was insufficient description to determine if blinding was adequate.
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 was 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 stated both pain-free and maximum walking distances as primary exercise variables, but only maximum walking distance was reported on.
Other bias	Low risk	No evidence of other bias

Lee 2001

Study characteristics	
Methods	Study design: single-centre, randomised, double-blind, placebo-controlled Intention-to-treat: no Country: Taiwan
Participants	Number randomised: 50 (cilostazol n = 17; pentoxifylline n = 17; placebo n = 16) Age (mean years (SD)): cilostazol = 66 (9); pentoxifylline = 68 (5); placebo = 69 (6) Sex M/F: cilostazol = 14/3; pentoxifylline = 14/3; placebo = 14/2 **Inclusion criteria**: men and women > 40 years old, IC with no symptomatic changes in previous 3 months, baseline ACD between 30 and 200 m, doppler measured ABI of ≤ 0.9, participants had to have a variance of ≤ 20% in their ACD between their two screening treadmill tests **Exclusion criteria**: Buerger's disease, category II or II chronic lower-extremity ischaemia, arterial surgery/angioplasty or sympathectomy within previous 3 months
Interventions	Treatment: Cilostazol 100 mg twice daily Pentoxifylline 400 mg twice daily Control: placebo twice daily Duration: 8 weeks (plus 2 weeks of placebo run-phase)
Outcomes	ABI, ACD, VEGF, IL6, neutrophils, monocytes, platelets, glucose and lipids
Funding	There were multiple study drug sponsors; no further details reported. "The patient received a randomized code number, according to which the sponsor supplied the study drug".
Declaration of interests	"There are neither financial nor other relations that could lead to a conflict of interest".
Notes	Treadmill tests performed at 2 baseline screening visits and at 8 weeks; 3.2 km/h with 12.5% gradient, under supervision by the same person at the same time of day for a given patient

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lee 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised code number according to which sponsor supplied the study drug, but how the numbers were generated was not described.
Allocation concealment (selection bias)	Low risk	A sealed envelope, with information on the treatment allocated, was kept in the clinical file of each patient.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Used special packaging to maintain blinding of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors stated analysis would be performed on participants that completed the study (not intention-to-treat), but did not specifically state the number that completed the study. The results tables in one reference included values that would suggest all participants were included in the analysis, and therefore completed the trial. However, the number of participants reported in the other reference had 2 patients missing (1 in the cilostazol group and 1 in the pentoxifylline group), with no explanation for the differences.
Selective reporting (reporting bias)	Unclear risk	The authors only stated their intention to measure ACD as a main outcome but did not specify the other outcomes they ultimately reported on. The two different references reported on different outcomes with no clear indication of what the preplanned outcomes were.
Other bias	Low risk	No evidence of other bias

Money 1998

Study characteristics	
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 ± SD): cilostazol = 64.8 ± 9.4; placebo = 64.5 ± 8.8 Sex M/F: cilostazol = 90/29; placebo = 90/30 **Inclusion criteria:** > 40 years; IC caused by lower extremity PAOD for at least 6 months; baseline ICD ≥ 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 IC; 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, QoL (SF-36, WIQ) Treadmill tests performed at two baseline visits and weeks 8, 12 and 16 after randomisation

Money 1998 *(Continued)*

Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported. Two of the authors (J Heckman and Dr. Forbes) were employed by Otsuka America Pharmaceutical Inc.
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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there was insufficient description to determine if blinding was 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 were given and all participants accounted for.
Selective reporting (reporting bias)	Low risk	Although no protocol was available all relevant outcomes were reported on.
Other bias	Low risk	No evidence of other bias

O'Donnell 2009

Study characteristics

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 IC 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 comorbidity 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

O'Donnell 2009 *(Continued)*

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, QoL (SF-36, WIQ, VascuQol); measured at baseline and weeks 6 and 24
Funding	Otsuka America Pharmaceutical Inc. provided the placebo. The study was funded by the Belfast City Hospital Vascular Research Fund and the Daisy Hill Hospital research fellowships and research grants from the Insulin Dependant Diabetes Trust and the Royal College of Surgeons Edinburgh.
Declaration of interests	Otsuka America Pharmaceutical Inc. provided the placebo for use in the study. Dr O'Donnell has received financial support from Otsuka Pharmaceuticals for travel costs to attend conferences to present data from this clinical trial.
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
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 was available, all outcomes appeared to be reported on.
Other bias	Low risk	No evidence of other bias

Otsuka Study 21-86-101

Study characteristics

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)

Otsuka Study 21-86-101 *(Continued)*

	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 IC which was chronic (at least 6 months), stable (6 months); evidence of PAOD; 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:** 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 IC; 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
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - source of the study data was a medical review by the FDA.
Notes	Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with speed constant at 3.2 km/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 was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was 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	Low risk	No evidence of other bias

Otsuka Study 21-86-103

Study characteristics	
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 IC which was chronic (at least 6 months), stable (6 months); evidence of POAD; 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 childbearing potential; malignancy; cardiac valve disorder or replacement; clinically significant abnormal lab value pretreatment; 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
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
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - source of the study data was a medical review by the FDA.
Notes	Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with speed constant at 3.2 km/h. Dosage of cilostazol described as "fixed 150 mg bid oral dose... formulated as 50 mg cilostazol tablets" Assumption was 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 was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was not adequately discussed.
Incomplete outcome data (attrition bias)	Unclear risk	Dropouts overlapped without discussion

Otsuka Study 21-86-103 *(Continued)*
All outcomes

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	Low risk	No evidence of other bias

Otsuka Study 21-87-101

Study characteristics	
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% **Inclusion criteria:** aged 45 to 70 years (both sexes); IC which was stable (3 months); ICD ≤ 100 m on a constant load treadmill test with no greater than 20% variation between observations in washout period **Exclusion criteria:** lower extremity ischaemic rest pain, severe ulceration or gangrene; female of childbearing potential; decompensated congestive heart failure or MI 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 pretreatment; 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 requiring insulin 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
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - source of the study data was a medical review by the FDA.
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

Otsuka Study 21-87-101 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was 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 was available, all outcomes appeared to be reported on.
Other bias	Low risk	No evidence of other bias

Otsuka Study 21-94-301

Study characteristics	
Methods	Study design: randomised, double-blind, placebo-controlled Intention-to-treat: yes; LOCF method Country: USA
Participants	Number randomised: 370 (cilostazol n = 123; pentoxifylline n = 123; placebo n = 124) Age (mean years): cilostazol = 66; pentoxifylline = 66; placebo = 66 Sex (% M): cilostazol = 70; pentoxifylline = 72; placebo = 73 **Inclusion criteria:** aged ≥ 40 years (both sexes); IC which was chronic (at least 6 months), stable (3 months); evidence of POAD; 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 **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 IC; history or current evidence of concomitant exercise-limiting disease other than IC; 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 x 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 haemorheologic agents
Interventions	Treatment 1: cilostazol 100 mg, twice daily with third placebo dose to maintain blind, oral administration Treatment 2: pentoxifylline 400 mg, three times daily Control: placebo Duration: 24 weeks
Outcomes	ACD, ICD, subjective claudication improvement by physician and patient; all-cause death, cardiovascular events, safety endpoints (vital signs, 12-lead ECG, etc.), adverse events; measured at baseline and weeks 2, 4, 8, 12, 16, 20 and 24
Funding	Otsuka America Pharmaceutical Inc.

Otsuka Study 21-94-301 *(Continued)*

Declaration of interests	Not reported - source of the study data was a medical review by the FDA.
Notes	Immediate-incline treadmill method: incline load started immediately at 10% and remained constant with a constant speed of 3.2 km/h Four- to eight-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	"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) All outcomes	Unclear risk	Blinding of assessors was not adequately discussed.
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	Low risk	No evidence of other bias

Otsuka Study 21-95-201

Study characteristics

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 IC for ≥ 6 months, stable for ≥ 3 months. **Exclusion criteria:** IC 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; require-

Otsuka Study 21-95-201 *(Continued)*

	ment 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	ACD and ICD, subjective claudication improvement as per patient and physician, Doppler-measured limb pressures, QoL questionnaires; measured at baseline then weeks 4, 8 and 12
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - source of the study data was a medical review by the FDA.
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
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although study used a placebo, there was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was 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 QoL results, but noted no significant differences between the groups
Other bias	Low risk	No evidence of other bias

Otsuka Study 21-98-213

Study characteristics

Methods	Study design: multicentre, randomised, double-blind, placebo-controlled, clinical trial Intention-to-treat: yes Country: USA

Otsuka Study 21-98-213 *(Continued)*

Participants	Number randomised: 785 (cilostazol, n = 261; pentoxifylline, n = 262; placebo, n = 262) (several of the tables in the NICE report stated 780 as the number of participants, 260 in each group, but the study characteristics on pg 177 of the report had n = 785 as the total number randomised) Age (mean years ± SE): cilostazol = 66.7 ± 9.9; pentoxifylline = 67.4 ± 9.4; placebo = not given Sex (% M): cilostazol = 75.4; pentoxifylline = 76.9; placebo = 75.4 **Inclusion criteria:** 40 years or older, with PAD and IC with stable symptoms for the preceding 3 months; PAD diagnosed as an abnormal resting ABI ≥ 0.4 and ≤ 0.9 in the reference leg with decline in post-exercise ABI ≥ 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, QoL (SF-36, WIQ, COM), adverse events, vascular events; measured at baseline and then 4 weeks until 24 weeks
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported - source of the study data was a pharmaceutical submission to National Institute for Care and Excellence.
Notes	Constant workload treadmill test: 3.2 km/h at a constant 12.5% grade Study was also known under the trial name PACE.

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 was insufficient description to determine if blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors was 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	Low risk	No evidence of other bias

Strandness 2002

Study characteristics	
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 ± SE): cilostazol 100 mg = 63.1 ± 10.2; cilostazol 50 mg = 63.9 ± 8.7; placebo = 64.4 ± 10.2 Sex M/F: cilostazol 100 mg = 102/31; cilostazol 50 mg = 98/34; placebo = 100/29 **Inclusion criteria:** ≥ 40 years; at least 6 months history of stable symptomatic IC 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, haemorheologic or NSAIDs
Interventions	Treatment 1: cilostazol 100 mg, twice daily Treatment 2: cilostazol 50 mg, twice daily Control: placebo, twice daily Duration: 24 weeks
Outcomes	MWD, PFWD, Doppler-measured bilateral peripheral limb pressures, QoL 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
Funding	Otsuka America Pharmaceutical Inc.
Declaration of interests	Not reported. Two authors (P Zhang, WP Forbes) were employed by Otsuka America Pharmaceutical Inc.
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 50 mg 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 was assumed blinding was adequate.

Strandness 2002 *(Continued)*

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 were listed as a secondary outcome but not reported on, aside from a comment in the discussion for which no data were given to support it.
Other bias	Low risk	No evidence of other bias

ABI: ankle brachial index
ACD: absolute claudication distance
ALT: alanine transaminase
AST: aspartate aminotransferase
bid: twice daily
BP: blood pressure
CLZ: cilostazol
cm: centimetre
COM: Claudication Outcome Measures
CRP: C-reactive protein
DVT: deep vein thrombosis
ECG: electrocardiogram
FDA: Food and Drug Administration
HDL: high-density lipoprotein
IC: intermittent claudication
ICD: initial claudication distance
IL6: interleukin-6
km/h: kilometres per hour
LDL: low-density lipoprotein
LOCF: last observation carried forward
m: metres
M/F: male/female
mg: milligrams
MI: myocardial infarction
mph: miles per hour
MWD: maximum walking distance (equivalent to ACD)
NICE: National Institute for Health and Care Excellence
NSAIDs: non-steroidal anti-inflammatory agents
PAD: peripheral arterial disease
PAOD: peripheral arterial occlusive disease
PAR: Physical Activity Recall
PDE: phosphodiesterase
PFWD: pain-free walking distance (equivalent to ICD)
PTX: pentoxifylline
QoL: quality of life
SD: standard deviation
SE: standard error
SF-36: Medical Outcomes Scale Short Form-36
VascuQol: disease specific vascular quality of life
VEGF: vascular endothelial growth factor
WIQ: Walking Impairment Questionnaire

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

Study	Reason for exclusion
CASTLE 2008	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.
Chao 2014	Wrong patient population: PAD without obvious IC
Chao 2016	Wrong patient population: high risk for cardiovascular disease
Chen 2017	Wrong patient population: PAD or high risk of cardiovascular disease
ChiCTR-TRC-09000441	Wrong patient population: type 2 diabetes with ischaemic disease
Chisari 2019	Wrong patient population: PAD
Goldenberg 2012	Wrong intervention: L-cartinine + cilostazol versus cilostazol
Hsieh 2009	Wrong patient population: diabetic patients with POAD
JPRN-C000000215	Wrong patient population: type 2 diabetic patients with mild atherosclerosis
JPRN-UMIN000001198	Wrong patient population: patients with femoropopliteal stenting
JPRN-UMIN000011869	Wrong intervention: omega-3 fatty acid + cilostazol versus cilostazol
JPRN-UMIN000014307	Wrong intervention: new gene transfer vector based on nontransmissible recombinant Sendai virus expressing the human fibroblast growth factor-2 gene (DVC1-0101)
Kim 2013	Wrong patient population: type 2 diabetic patients with metabolic syndrome
Mazzone 2013	Wrong intervention: iloprost + usual care versus usual care
NCT00102050	Wrong intervention: phosphodiesterase inhibitor NM-702
NCT00300339	Study was discontinued early, and no outcome data were available.
NCT00443287	The specifics of the intervention arms are unclear at this time. We could not conclude which study arms also used clopidogrel.
NCT00573950	Wrong patient population: type 2 diabetic patients with metabolic syndrome
NCT00886574	Wrong patient population: type 2 diabetes mellitus
NCT00912756	Wrong patient population: chronic arteriosclerosis obliterans afflicting the femoropopliteal artery area
NCT01188824	Wrong patient population: ischaemic stroke patients with PAD
NCT01952756	Wrong patient population: POAD
NCT02373462	Wrong intervention: olmesartan
NCT02407314	Wrong intervention: ticagrelor
NCT02636283	Wrong intervention: valsartan

Study	Reason for exclusion
NCT02930811	Wrong intervention: sildenafil
NCT03318276	Wrong intervention: cilostazol 200 mg + ginkgo biloba leaf extract 160 mg versus cilostazol 100 mg + ginkgo biloba leaf extract 80 mg
NCT03686306	Wrong intervention: sildenafil
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
Xiao 2010	Wrong patient population: type 2 diabetes with lower limb ischaemic disease

IC: intermittent claudication
PAD: peripheral arterial disease
PAOD: peripheral arterial occlusive disease
RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Sapelkin 2013

Methods	Only title provided
Participants	Only title provided
Interventions	Only title provided
Outcomes	Only title provided
Notes	Library unable to source this material

DATA AND ANALYSES

Comparison 1. Cilostazol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Initial claudication distance (ICD)	6	1722	Mean Difference (IV, Fixed, 95% CI)	26.49 [18.93, 34.05]
1.1.1 Cilostazol 50 mg twice daily	2	400	Mean Difference (IV, Fixed, 95% CI)	19.50 [6.80, 32.21]
1.1.2 Cilostazol 100 mg twice daily	6	1236	Mean Difference (IV, Fixed, 95% CI)	32.19 [22.20, 42.18]
1.1.3 Cilostazol 150 mg twice daily	1	86	Mean Difference (IV, Fixed, 95% CI)	15.70 [-12.20, 43.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Absolute claudication distance (ACD)	8	2360	Mean Difference (IV, Random, 95% CI)	39.57 [21.80, 57.33]
1.2.1 Cilostazol 50 mg twice daily	2	400	Mean Difference (IV, Random, 95% CI)	30.84 [8.81, 52.86]
1.2.2 Cilostazol 100 mg twice daily	8	1874	Mean Difference (IV, Random, 95% CI)	42.32 [18.12, 66.51]
1.2.3 Cilostazol 150 mg twice daily	1	86	Mean Difference (IV, Random, 95% CI)	51.80 [-10.59, 114.19]
1.3 Arterial revascularisation	1	516	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 4.07]
1.3.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 4.07]
1.3.2 Cilostazol 100 mg twice daily	1	260	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 Amputation	1	516	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 4.07]
1.4.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 4.07]
1.4.2 Cilostazol 100 mg twice daily	1	260	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5 Adverse event related to study medication - headache	8	2584	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [2.26, 3.55]
1.5.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.19, 3.43]
1.5.2 Cilostazol 100 mg twice daily	8	2131	Odds Ratio (M-H, Fixed, 95% CI)	3.05 [2.38, 3.92]
1.6 Adverse event related to study medication - diarrhoea	7	2503	Odds Ratio (M-H, Fixed, 95% CI)	2.73 [2.02, 3.70]
1.6.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.91, 4.52]
1.6.2 Cilostazol 100 mg twice daily	7	2050	Odds Ratio (M-H, Fixed, 95% CI)	2.88 [2.07, 3.99]
1.7 Adverse event related to study medication - abnormal stools	5	1804	Odds Ratio (M-H, Fixed, 95% CI)	3.63 [2.45, 5.38]
1.7.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	2.48 [1.08, 5.71]

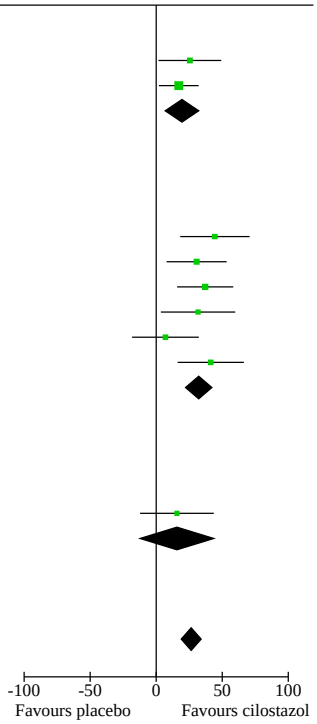
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 Cilostazol 100 mg twice daily	5	1351	Odds Ratio (M-H, Fixed, 95% CI)	4.04 [2.59, 6.31]
1.8 Adverse event related to study medication - dizziness	4	1120	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [1.43, 4.08]
1.8.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [0.63, 6.06]
1.8.2 Cilostazol 100 mg twice daily	4	864	Odds Ratio (M-H, Fixed, 95% CI)	2.57 [1.42, 4.63]
1.9 Adverse event related to study medication - pain	4	1572	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.30]
1.9.1 Cilostazol 50 mg twice daily	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.67, 3.48]
1.9.2 Cilostazol 100 mg twice daily	4	1375	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.23]
1.10 Adverse event related to study medication - palpitations	4	1681	Odds Ratio (M-H, Fixed, 95% CI)	7.16 [3.95, 12.98]
1.10.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	8.89 [0.51, 155.87]
1.10.2 Cilostazol 100 mg twice daily	4	1425	Odds Ratio (M-H, Fixed, 95% CI)	7.06 [3.85, 12.96]
1.11 Cardiovascular event	2	692	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.51, 4.47]
1.11.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.30, 7.64]
1.11.2 Cilostazol 100 mg twice daily	2	436	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.35, 6.52]
1.12 All-cause mortality	8	2642	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.41, 2.30]
1.12.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 8.00]
1.12.2 Cilostazol 100 mg twice daily	8	2189	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.42, 2.59]
1.13 Ankle brachial index (ABI)	3	859	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]
1.13.1 Cilostazol 100 mg twice daily	3	859	Mean Difference (IV, Random, 95% CI)	0.06 [0.04, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Initial claudication distance (ICD) sensitivity analysis	5	1543	Mean Difference (IV, Fixed, 95% CI)	29.52 [21.26, 37.78]
1.14.1 Cilostazol 50 mg twice daily	2	400	Mean Difference (IV, Fixed, 95% CI)	19.50 [6.80, 32.21]
1.14.2 Cilostazol 100 mg twice daily	5	1143	Mean Difference (IV, Fixed, 95% CI)	36.86 [25.98, 47.74]
1.15 Absolute claudication distance (ACD) sensitivity analysis	6	1732	Mean Difference (IV, Random, 95% CI)	48.44 [34.49, 62.39]
1.15.1 Cilostazol 50 mg twice daily	2	400	Mean Difference (IV, Random, 95% CI)	30.84 [8.81, 52.86]
1.15.2 Cilostazol 100 mg twice daily	6	1332	Mean Difference (IV, Random, 95% CI)	56.30 [40.37, 72.23]
1.16 Adverse event related to study medication - headache, sensitivity analysis	7	2061	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [2.21, 3.61]
1.16.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.19, 3.43]
1.16.2 Cilostazol 100 mg twice daily	7	1608	Odds Ratio (M-H, Fixed, 95% CI)	3.10 [2.35, 4.09]
1.17 Adverse event related to study medication - diarrhoea, sensitivity analysis	6	1980	Odds Ratio (M-H, Fixed, 95% CI)	2.91 [2.05, 4.12]
1.17.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.91, 4.52]
1.17.2 Cilostazol 100 mg twice daily	6	1527	Odds Ratio (M-H, Fixed, 95% CI)	3.16 [2.15, 4.67]
1.18 Adverse event related to study medication - pain, sensitivity analysis	3	1049	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.54]
1.18.1 Cilostazol 50 mg twice daily	1	197	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.67, 3.48]
1.18.2 Cilostazol 100 mg twice daily	3	852	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.66, 1.47]
1.19 Adverse event related to study medication - palpitations, sensitivity analysis	3	1158	Odds Ratio (M-H, Fixed, 95% CI)	12.80 [5.06, 32.36]
1.19.1 Cilostazol 50 mg twice daily	1	256	Odds Ratio (M-H, Fixed, 95% CI)	8.89 [0.51, 155.87]

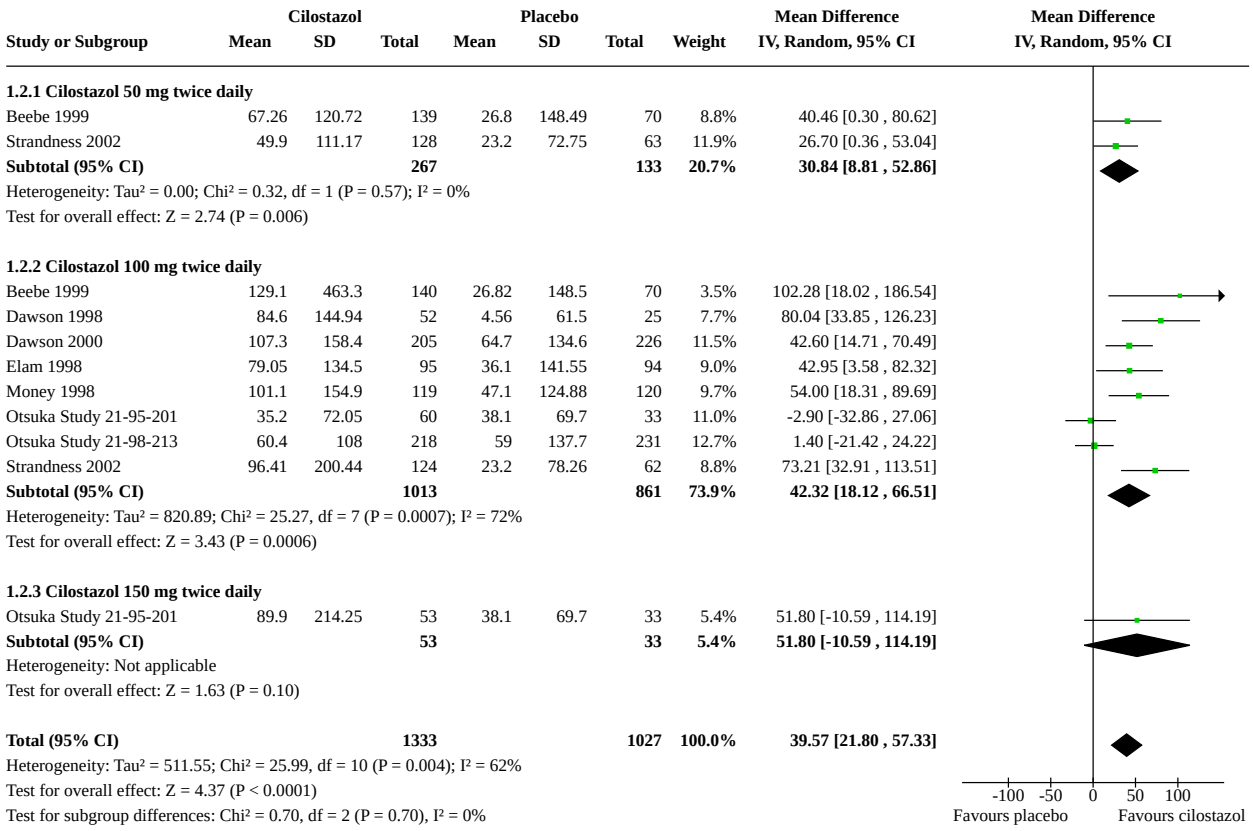
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.19.2 Cilostazol 100 mg twice daily	3	902	Odds Ratio (M-H, Fixed, 95% CI)	13.42 [5.05, 35.68]
1.20 All-cause mortality sensitivity analysis	7	2119	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.47, 3.13]
1.20.1 Cilostazol 50 mg twice daily	2	453	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 8.00]
1.20.2 Cilostazol 100 mg twice daily	7	1666	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.49, 3.75]

Analysis 1.1. Comparison 1: Cilostazol versus placebo, Outcome 1: Initial claudication distance (ICD)

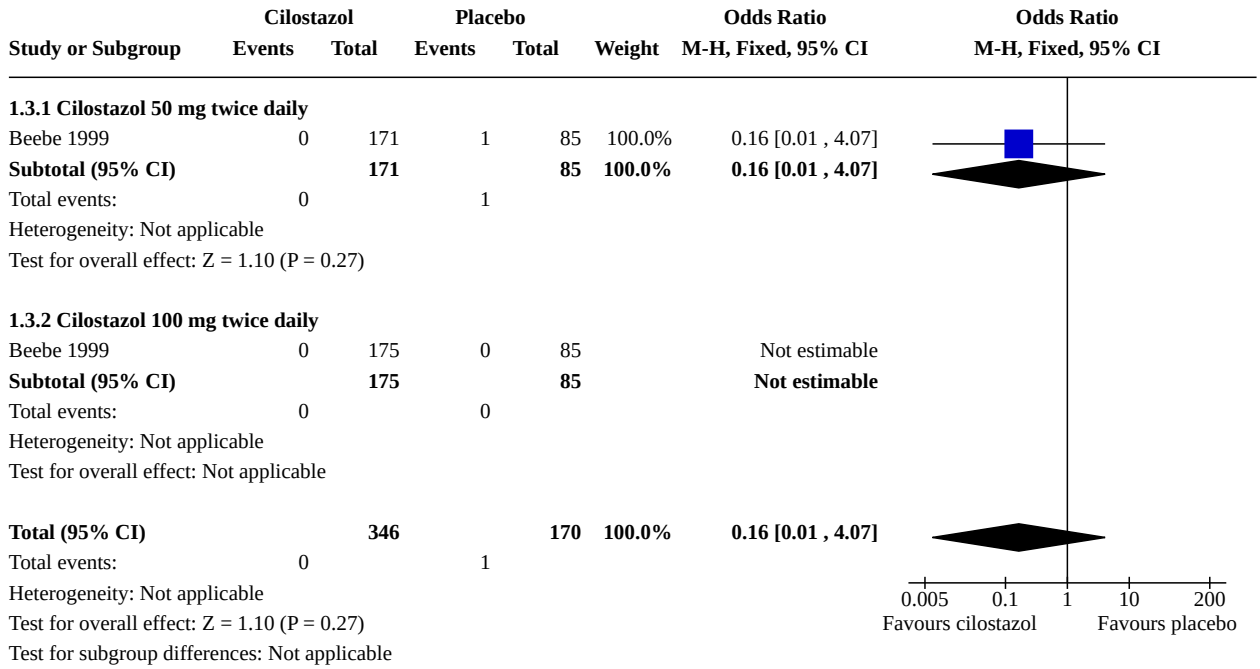
Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Cilostazol 50 mg twice daily								
Beebe 1999	48.6	93.13	139	23.1	76.9	70	10.1%	25.50 [1.75 , 49.25]
Strandness 2002	34.3	60.6	128	17.2	43.6	63	25.3%	17.10 [2.06 , 32.14]
Subtotal (95% CI)			**267**			**133**	**35.4%**	**19.50 [6.80 , 32.21]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 3.01 (P = 0.003)								
1.1.2 Cilostazol 100 mg twice daily								
Beebe 1999	67.5	130.4	140	23.04	63.78	70	8.3%	44.46 [18.20 , 70.72]
Dawson 1998	38.9	68.34	52	8.3	33.5	25	11.0%	30.60 [7.85 , 53.35]
Dawson 2000	93.6	127.4	205	56.5	93.1	226	12.7%	37.10 [15.85 , 58.35]
Money 1998	85.9	108	119	54.2	114	120	7.2%	31.70 [3.55 , 59.85]
Otsuka Study 21-95-201	41.4	63.2	60	34.4	57.3	33	9.0%	7.00 [-18.26 , 32.26]
Strandness 2002	58.5	128.3	124	17.2	43.6	62	9.1%	41.30 [16.25 , 66.35]
Subtotal (95% CI)			**700**			**536**	**57.3%**	**32.19 [22.20 , 42.18]**
Heterogeneity: Chi² = 5.39, df = 5 (P = 0.37); I² = 7%								
Test for overall effect: Z = 6.32 (P < 0.00001)								
1.1.3 Cilostazol 150 mg twice daily								
Otsuka Study 21-95-201	50.1	70.3	53	34.4	60.1	33	7.3%	15.70 [-12.20 , 43.60]
Subtotal (95% CI)			**53**			**33**	**7.3%**	**15.70 [-12.20 , 43.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.10 (P = 0.27)								
Total (95% CI)			**1020**			**702**	**100.0%**	**26.49 [18.93 , 34.05]**
Heterogeneity: Chi² = 8.72, df = 8 (P = 0.37); I² = 8%								
Test for overall effect: Z = 6.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.99, df = 2 (P = 0.22), I² = 33.0%								



Analysis 1.2. Comparison 1: Cilostazol versus placebo, Outcome 2: Absolute claudication distance (ACD)

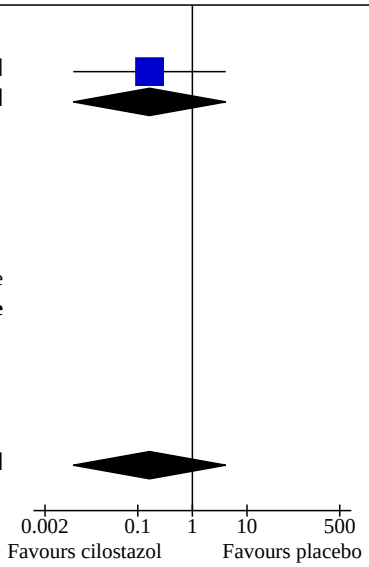


Analysis 1.3. Comparison 1: Cilostazol versus placebo, Outcome 3: Arterial revascularisation



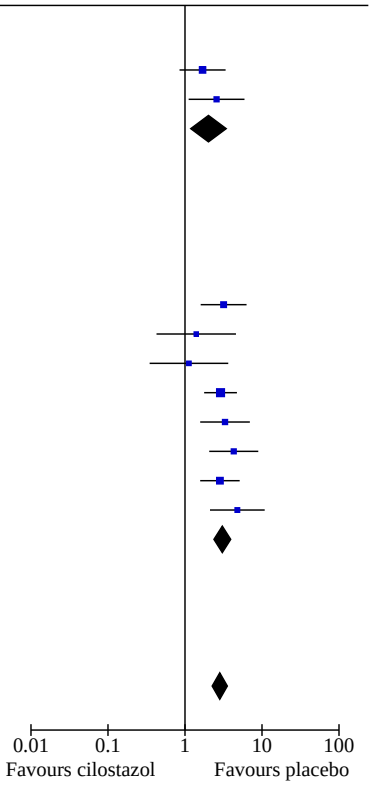
Analysis 1.4. Comparison 1: Cilostazol versus placebo, Outcome 4: Amputation

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Cilostazol 50 mg twice daily						
Beebe 1999	0	171	1	85	100.0%	0.16 [0.01 , 4.07]
Subtotal (95% CI)		**171**		**85**	**100.0%**	**0.16 [0.01 , 4.07]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
1.4.2 Cilostazol 100 mg twice daily						
Beebe 1999	0	175	0	85		Not estimable
Subtotal (95% CI)		**175**		**85**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**346**		**170**	**100.0%**	**0.16 [0.01 , 4.07]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						



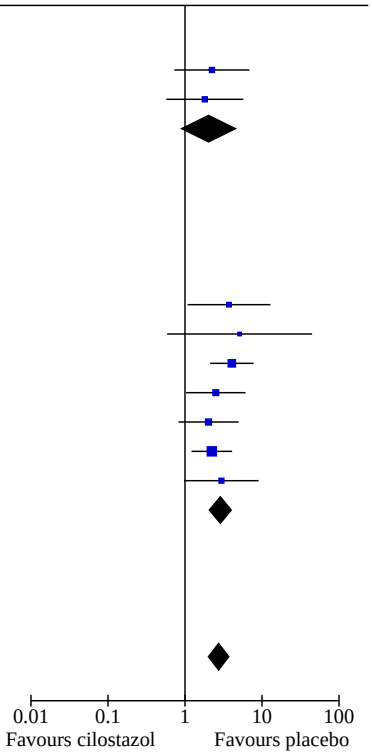
Analysis 1.5. Comparison 1: Cilostazol versus placebo, Outcome 5: Adverse event related to study medication - headache

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Cilostazol 50 mg twice daily						
Beebe 1999	40	171	13	85	13.6%	1.69 [0.85 , 3.37]
Strandness 2002	35	132	8	65	8.1%	2.57 [1.12 , 5.92]
Subtotal (95% CI)		**303**		**150**	**21.7%**	**2.02 [1.19 , 3.43]**
Total events:	75		21			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.5.2 Cilostazol 100 mg twice daily						
Beebe 1999	60	175	12	85	10.9%	3.17 [1.60 , 6.30]
Brass 2012	7	89	5	87	4.8%	1.40 [0.43 , 4.59]
Dawson 1998	11	54	5	27	5.4%	1.13 [0.35 , 3.65]
Dawson 2000	63	227	28	239	20.1%	2.89 [1.77 , 4.72]
Elam 1998	31	95	12	94	8.3%	3.31 [1.58 , 6.95]
Money 1998	36	119	11	120	7.8%	4.30 [2.06 , 8.95]
Otsuka Study 21-98-213	43	261	17	262	14.5%	2.84 [1.58 , 5.13]
Strandness 2002	54	133	8	64	6.6%	4.78 [2.11 , 10.84]
Subtotal (95% CI)		**1153**		**978**	**78.3%**	**3.05 [2.38 , 3.92]**
Total events:	305		98			
Heterogeneity: Chi² = 6.58, df = 7 (P = 0.47); I² = 0%						
Test for overall effect: Z = 8.74 (P < 0.00001)						
Total (95% CI)		**1456**		**1128**	**100.0%**	**2.83 [2.26 , 3.55]**
Total events:	380		119			
Heterogeneity: Chi² = 9.03, df = 9 (P = 0.43); I² = 0%						
Test for overall effect: Z = 9.01 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.8%						



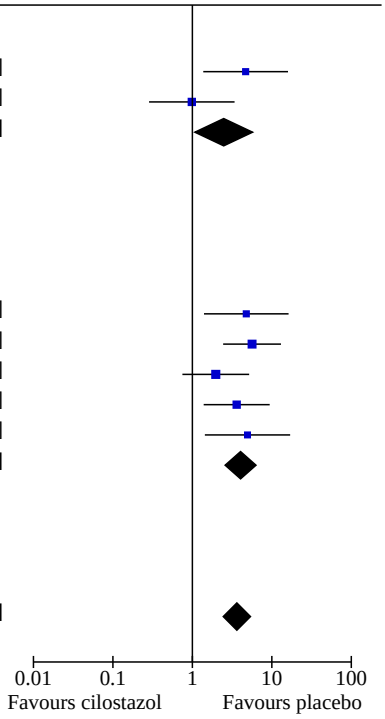
Analysis 1.6. Comparison 1: Cilostazol versus placebo, Outcome 6: Adverse event related to study medication - diarrhoea

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Cilostazol 50 mg twice daily						
Beebe 1999	17	171	4	85	8.4%	2.24 [0.73 , 6.86]
Strandness 2002	14	132	4	65	8.4%	1.81 [0.57 , 5.73]
Subtotal (95% CI)		**303**		**150**	**16.8%**	**2.02 [0.91 , 4.52]**
Total events:	31		8			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
1.6.2 Cilostazol 100 mg twice daily						
Beebe 1999	21	175	3	85	6.2%	3.73 [1.08 , 12.87]
Brass 2012	5	89	1	87	1.7%	5.12 [0.59 , 44.74]
Dawson 2000	43	227	13	239	18.0%	4.06 [2.12 , 7.78]
Elam 1998	18	95	8	94	11.4%	2.51 [1.03 , 6.11]
Money 1998	15	119	8	120	12.2%	2.02 [0.82 , 4.96]
Otsuka Study 21-98-213	35	261	17	262	25.7%	2.23 [1.22 , 4.10]
Strandness 2002	22	133	4	64	7.9%	2.97 [0.98 , 9.03]
Subtotal (95% CI)		**1099**		**951**	**83.2%**	**2.88 [2.07 , 3.99]**
Total events:	159		54			
Heterogeneity: Chi² = 2.88, df = 6 (P = 0.82); I² = 0%						
Test for overall effect: Z = 6.34 (P < 0.00001)						
Total (95% CI)		**1402**		**1101**	**100.0%**	**2.73 [2.02 , 3.70]**
Total events:	190		62			
Heterogeneity: Chi² = 3.53, df = 8 (P = 0.90); I² = 0%						
Test for overall effect: Z = 6.51 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%						



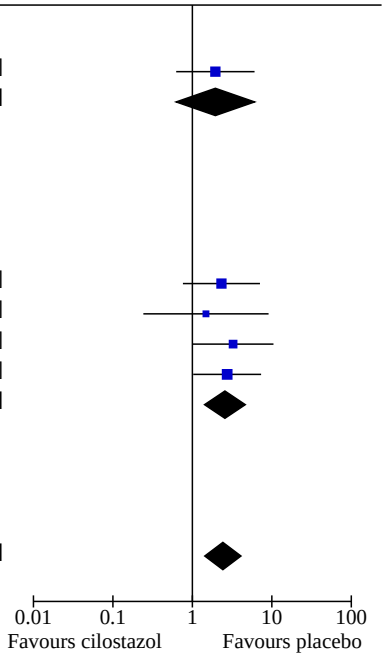
Analysis 1.7. Comparison 1: Cilostazol versus placebo, Outcome 7: Adverse event related to study medication - abnormal stools

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Cilostazol 50 mg twice daily						
Beebe 1999	25	171	3	85	10.7%	4.68 [1.37 , 15.98]
Strandness 2002	8	132	4	65	15.7%	0.98 [0.29 , 3.40]
Subtotal (95% CI)		**303**		**150**	**26.4%**	**2.48 [1.08 , 5.71]**
Total events:	33		7			
Heterogeneity: Chi² = 3.17, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 2.13 (P = 0.03)						
1.7.2 Cilostazol 100 mg twice daily						
Beebe 1999	26	175	3	85	10.7%	4.77 [1.40 , 16.24]
Dawson 2000	33	227	7	239	18.2%	5.64 [2.44 , 13.03]
Elam 1998	13	95	7	94	18.9%	1.97 [0.75 , 5.18]
Money 1998	19	119	6	120	15.7%	3.61 [1.39 , 9.39]
Strandness 2002	26	133	3	64	10.2%	4.94 [1.44 , 17.00]
Subtotal (95% CI)		**749**		**602**	**73.6%**	**4.04 [2.59 , 6.31]**
Total events:	117		26			
Heterogeneity: Chi² = 2.95, df = 4 (P = 0.57); I² = 0%						
Test for overall effect: Z = 6.13 (P < 0.00001)						
Total (95% CI)		**1052**		**752**	**100.0%**	**3.63 [2.45 , 5.38]**
Total events:	150		33			
Heterogeneity: Chi² = 7.46, df = 6 (P = 0.28); I² = 20%						
Test for overall effect: Z = 6.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² = 2.2%						



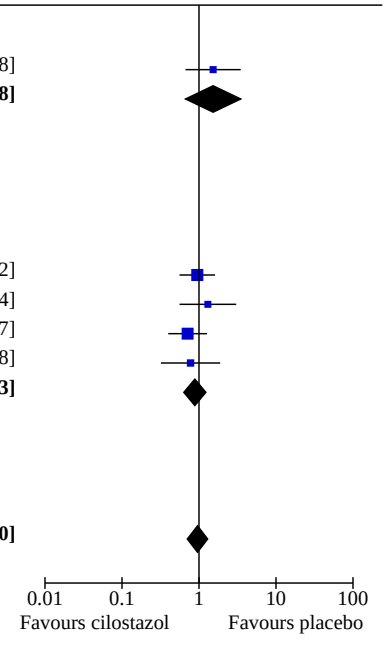
Analysis 1.8. Comparison 1: Cilostazol versus placebo, Outcome 8: Adverse event related to study medication - dizziness

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 Cilostazol 50 mg twice daily						
Beebe 1999	15	171	4	85	23.9%	1.95 [0.63 , 6.06]
Subtotal (95% CI)		**171**		**85**	**23.9%**	**1.95 [0.63 , 6.06]**
Total events:	15		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.8.2 Cilostazol 100 mg twice daily						
Beebe 1999	18	175	4	85	23.7%	2.32 [0.76 , 7.09]
Brass 2012	3	89	2	87	9.6%	1.48 [0.24 , 9.10]
Elam 1998	12	95	4	94	17.2%	3.25 [1.01 , 10.48]
Money 1998	15	119	6	120	25.6%	2.74 [1.03 , 7.33]
Subtotal (95% CI)		**478**		**386**	**76.1%**	**2.57 [1.42 , 4.63]**
Total events:	48		16			
Heterogeneity: Chi² = 0.56, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)		**649**		**471**	**100.0%**	**2.42 [1.43 , 4.08]**
Total events:	63		20			
Heterogeneity: Chi² = 0.73, df = 4 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						



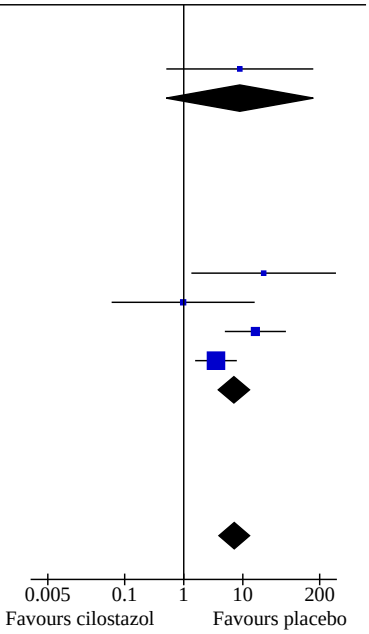
Analysis 1.9. Comparison 1: Cilostazol versus placebo, Outcome 9: Adverse event related to study medication - pain

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.9.1 Cilostazol 50 mg twice daily						
Strandness 2002	26	132	9	65	11.4%	1.53 [0.67 , 3.48]
Subtotal (95% CI)		**132**		**65**	**11.4%**	**1.53 [0.67 , 3.48]**
Total events:	26		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.9.2 Cilostazol 100 mg twice daily						
Dawson 2000	30	227	33	239	32.7%	0.95 [0.56 , 1.62]
Elam 1998	14	95	11	94	11.1%	1.30 [0.56 , 3.04]
Otsuka Study 21-98-213	22	261	30	262	32.2%	0.71 [0.40 , 1.27]
Strandness 2002	15	133	9	64	12.7%	0.78 [0.32 , 1.88]
Subtotal (95% CI)		**716**		**659**	**88.6%**	**0.88 [0.64 , 1.23]**
Total events:	81		83			
Heterogeneity: Chi² = 1.50, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**848**		**724**	**100.0%**	**0.96 [0.71 , 1.30]**
Total events:	107		92			
Heterogeneity: Chi² = 2.96, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.5%						



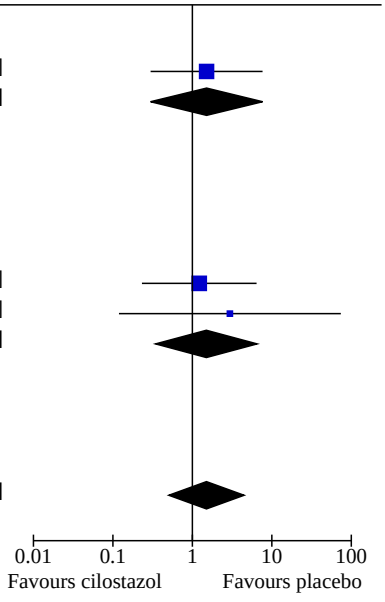
Analysis 1.10. Comparison 1: Cilostazol versus placebo, Outcome 10: Adverse event related to study medication - palpitations

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.10.1 Cilostazol 50 mg twice daily						
Beebe 1999	8	171	0	85	5.4%	8.89 [0.51 , 155.87]
Subtotal (95% CI)		**171**		**85**	**5.4%**	**8.89 [0.51 , 155.87]**
Total events:	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.10.2 Cilostazol 100 mg twice daily						
Beebe 1999	20	175	0	85	5.0%	22.54 [1.35 , 377.37]
Brass 2012	1	89	1	87	8.4%	0.98 [0.06 , 15.87]
Dawson 2000	39	227	3	239	20.4%	16.32 [4.97 , 53.63]
Otsuka Study 21-98-213	26	261	8	262	60.7%	3.51 [1.56 , 7.91]
Subtotal (95% CI)		**752**		**673**	**94.6%**	**7.06 [3.85 , 12.96]**
Total events:	86		12			
Heterogeneity: Chi² = 7.33, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 6.31 (P < 0.00001)						
Total (95% CI)		**923**		**758**	**100.0%**	**7.16 [3.95 , 12.98]**
Total events:	94		12			
Heterogeneity: Chi² = 7.41, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 6.48 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



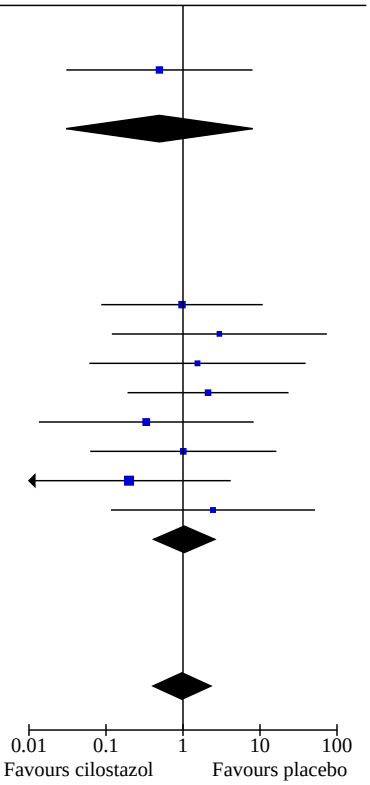
Analysis 1.11. Comparison 1: Cilostazol versus placebo, Outcome 11: Cardiovascular event

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.11.1 Cilostazol 50 mg twice daily						
Beebe 1999	6	171	2	85	45.3%	1.51 [0.30 , 7.64]
Subtotal (95% CI)		**171**		**85**	**45.3%**	**1.51 [0.30 , 7.64]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.11.2 Cilostazol 100 mg twice daily						
Beebe 1999	5	175	2	85	46.0%	1.22 [0.23 , 6.42]
Brass 2012	1	89	0	87	8.7%	2.97 [0.12 , 73.81]
Subtotal (95% CI)		**264**		**172**	**54.7%**	**1.50 [0.35 , 6.52]**
Total events:	6		2			
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**435**		**257**	**100.0%**	**1.50 [0.51 , 4.47]**
Total events:	12		4			
Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



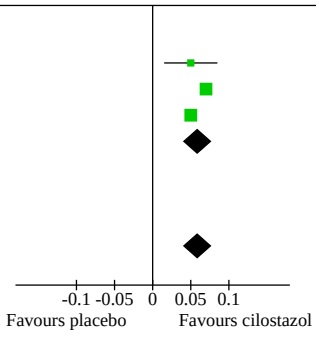
Analysis 1.12. Comparison 1: Cilostazol versus placebo, Outcome 12: All-cause mortality

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.12.1 Cilostazol 50 mg twice daily						
Beebe 1999	1	171	1	85	12.8%	0.49 [0.03 , 8.00]
Strandness 2002	0	132	0	65		Not estimable
Subtotal (95% CI)		**303**		**150**	**12.8%**	**0.49 [0.03 , 8.00]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.12.2 Cilostazol 100 mg twice daily						
Beebe 1999	2	175	1	85	12.8%	0.97 [0.09 , 10.86]
Brass 2012	1	89	0	87	4.8%	2.97 [0.12 , 73.81]
Dawson 1998	1	54	0	27	6.2%	1.54 [0.06 , 39.12]
Dawson 2000	2	227	1	239	9.3%	2.12 [0.19 , 23.49]
Money 1998	0	119	1	120	14.3%	0.33 [0.01 , 8.26]
Otsuka Study 21-94-301	1	123	1	124	9.5%	1.01 [0.06 , 16.30]
Otsuka Study 21-98-213	0	261	2	262	24.0%	0.20 [0.01 , 4.17]
Strandness 2002	2	133	0	64	6.4%	2.45 [0.12 , 51.83]
Subtotal (95% CI)		**1181**		**1008**	**87.2%**	**1.04 [0.42 , 2.59]**
Total events:	9		6			
Heterogeneity: Chi² = 2.72, df = 7 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)		**1484**		**1158**	**100.0%**	**0.97 [0.41 , 2.30]**
Total events:	10		7			
Heterogeneity: Chi² = 2.99, df = 8 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



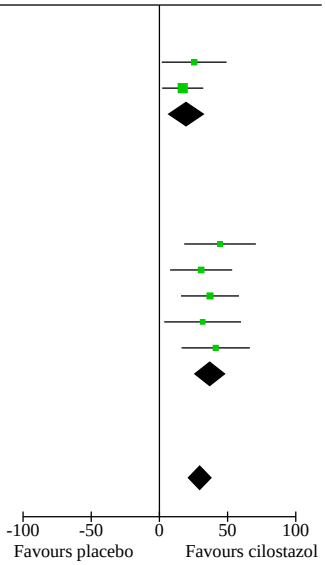
Analysis 1.13. Comparison 1: Cilostazol versus placebo, Outcome 13: Ankle brachial index (ABI)

Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 Cilostazol 100 mg twice daily								
Dawson 2000	0.04	0.18	205	-0.01	0.19	226	15.9%	0.05 [0.02 , 0.08]
Elam 1998	0.07	0.02	95	0	0.02	94	41.9%	0.07 [0.06 , 0.08]
Money 1998	0.06	0.02	119	0.01	0.02	120	42.3%	0.05 [0.04 , 0.06]
Subtotal (95% CI)			**419**			**440**	**100.0%**	**0.06 [0.04 , 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 26.63, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 6.57 (P < 0.00001)								
Total (95% CI)			**419**			**440**	**100.0%**	**0.06 [0.04 , 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 26.63, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 6.57 (P < 0.00001)								
Test for subgroup differences: Not applicable								



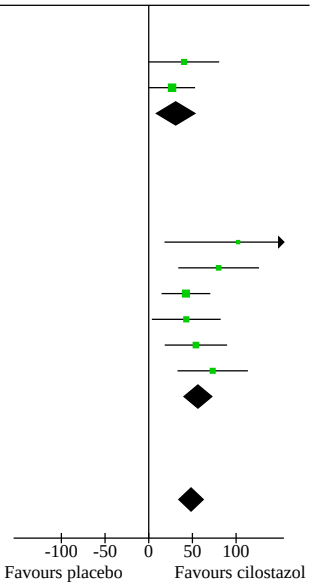
Analysis 1.14. Comparison 1: Cilostazol versus placebo, Outcome 14: Initial claudication distance (ICD) sensitivity analysis

Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Cilostazol 50 mg twice daily								
Beebe 1999	48.6	93.13	139	23.1	76.9	70	12.1%	25.50 [1.75 , 49.25]
Strandness 2002	34.3	60.6	128	17.2	43.6	63	30.2%	17.10 [2.06 , 32.14]
Subtotal (95% CI)			**267**			**133**	**42.3%**	**19.50 [6.80 , 32.21]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 3.01 (P = 0.003)								
1.14.2 Cilostazol 100 mg twice daily								
Beebe 1999	67.5	130.4	140	23.04	63.78	70	9.9%	44.46 [18.20 , 70.72]
Dawson 1998	38.9	68.34	52	8.3	33.5	25	13.2%	30.60 [7.85 , 53.35]
Dawson 2000	93.6	127.4	205	56.5	93.1	226	15.1%	37.10 [15.85 , 58.35]
Money 1998	85.9	108	119	54.2	114	120	8.6%	31.70 [3.55 , 59.85]
Strandness 2002	58.5	128.3	124	17.2	43.6	62	10.9%	41.30 [16.25 , 66.35]
Subtotal (95% CI)			**640**			**503**	**57.7%**	**36.86 [25.98 , 47.74]**
Heterogeneity: Chi² = 0.86, df = 4 (P = 0.93); I² = 0%								
Test for overall effect: Z = 6.64 (P < 0.00001)								
Total (95% CI)			**907**			**636**	**100.0%**	**29.52 [21.26 , 37.78]**
Heterogeneity: Chi² = 5.34, df = 6 (P = 0.50); I² = 0%								
Test for overall effect: Z = 7.00 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.14, df = 1 (P = 0.04), I² = 75.8%								



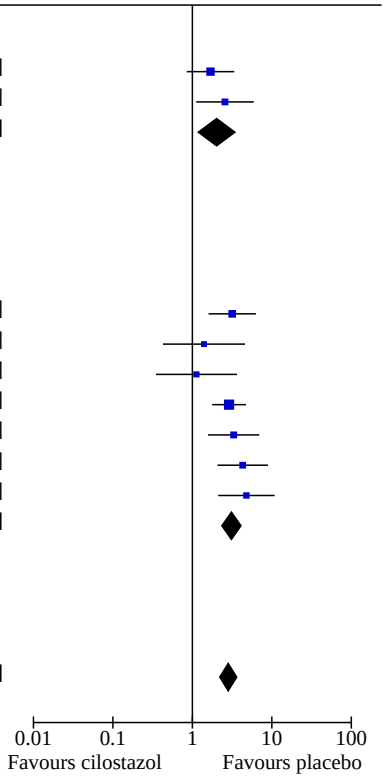
Analysis 1.15. Comparison 1: Cilostazol versus placebo, Outcome 15: Absolute claudication distance (ACD) sensitivity analysis

Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.15.1 Cilostazol 50 mg twice daily								
Beebe 1999	67.26	120.72	139	26.8	148.49	70	10.9%	40.46 [0.30 , 80.62]
Strandness 2002	49.9	111.17	128	23.2	72.75	63	22.3%	26.70 [0.36 , 53.04]
Subtotal (95% CI)			**267**			**133**	**33.2%**	**30.84 [8.81 , 52.86]**
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%								
Test for overall effect: Z = 2.74 (P = 0.006)								
1.15.2 Cilostazol 100 mg twice daily								
Beebe 1999	129.1	463.3	140	26.82	148.5	70	2.7%	102.28 [18.02 , 186.54]
Dawson 1998	84.6	144.94	52	4.56	61.5	25	8.4%	80.04 [33.85 , 126.23]
Dawson 2000	107.3	158.4	205	64.7	134.6	226	20.3%	42.60 [14.71 , 70.49]
Elam 1998	79.05	134.5	95	36.1	141.55	94	11.3%	42.95 [3.58 , 82.32]
Money 1998	101.1	154.9	119	47.1	124.88	120	13.4%	54.00 [18.31 , 89.69]
Strandness 2002	96.41	200.44	124	23.2	78.26	62	10.8%	73.21 [32.91 , 113.51]
Subtotal (95% CI)			**735**			**597**	**66.8%**	**56.30 [40.37 , 72.23]**
Heterogeneity: Tau² = 0.00; Chi² = 4.22, df = 5 (P = 0.52); I² = 0%								
Test for overall effect: Z = 6.93 (P < 0.00001)								
Total (95% CI)			**1002**			**730**	**100.0%**	**48.44 [34.49 , 62.39]**
Heterogeneity: Tau² = 46.74; Chi² = 7.91, df = 7 (P = 0.34); I² = 11%								
Test for overall effect: Z = 6.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.37, df = 1 (P = 0.07), I² = 70.3%								



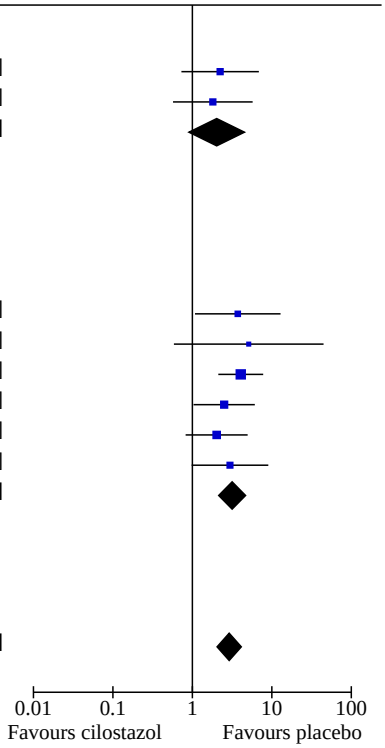
Analysis 1.16. Comparison 1: Cilostazol versus placebo, Outcome 16: Adverse event related to study medication - headache, sensitivity analysis

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.16.1 Cilostazol 50 mg twice daily						
Beebe 1999	40	171	13	85	15.9%	1.69 [0.85 , 3.37]
Strandness 2002	35	132	8	65	9.4%	2.57 [1.12 , 5.92]
Subtotal (95% CI)		**303**		**150**	**25.3%**	**2.02 [1.19 , 3.43]**
Total events:	75		21			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.16.2 Cilostazol 100 mg twice daily						
Beebe 1999	60	175	12	85	12.7%	3.17 [1.60 , 6.30]
Brass 2012	7	89	5	87	5.6%	1.40 [0.43 , 4.59]
Dawson 1998	11	54	5	27	6.3%	1.13 [0.35 , 3.65]
Dawson 2000	63	227	28	239	23.6%	2.89 [1.77 , 4.72]
Elam 1998	31	95	12	94	9.7%	3.31 [1.58 , 6.95]
Money 1998	36	119	11	120	9.1%	4.30 [2.06 , 8.95]
Strandness 2002	54	133	8	64	7.7%	4.78 [2.11 , 10.84]
Subtotal (95% CI)		**892**		**716**	**74.7%**	**3.10 [2.35 , 4.09]**
Total events:	262		81			
Heterogeneity: Chi² = 6.53, df = 6 (P = 0.37); I² = 8%						
Test for overall effect: Z = 8.03 (P < 0.00001)						
Total (95% CI)		**1195**		**866**	**100.0%**	**2.83 [2.21 , 3.61]**
Total events:	337		102			
Heterogeneity: Chi² = 9.03, df = 8 (P = 0.34); I² = 11%						
Test for overall effect: Z = 8.31 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.98, df = 1 (P = 0.16), I² = 49.6%						



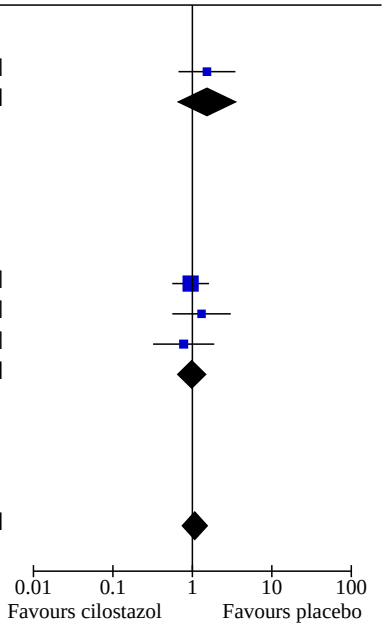
Analysis 1.17. Comparison 1: Cilostazol versus placebo, Outcome 17: Adverse event related to study medication - diarrhoea, sensitivity analysis

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.17.1 Cilostazol 50 mg twice daily						
Beebe 1999	17	171	4	85	11.4%	2.24 [0.73 , 6.86]
Strandness 2002	14	132	4	65	11.3%	1.81 [0.57 , 5.73]
Subtotal (95% CI)		**303**		**150**	**22.7%**	**2.02 [0.91 , 4.52]**
Total events:	31		8			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
1.17.2 Cilostazol 100 mg twice daily						
Beebe 1999	21	175	3	85	8.4%	3.73 [1.08 , 12.87]
Brass 2012	5	89	1	87	2.3%	5.12 [0.59 , 44.74]
Dawson 2000	43	227	13	239	24.2%	4.06 [2.12 , 7.78]
Elam 1998	18	95	8	94	15.4%	2.51 [1.03 , 6.11]
Money 1998	15	119	8	120	16.4%	2.02 [0.82 , 4.96]
Strandness 2002	22	133	4	64	10.6%	2.97 [0.98 , 9.03]
Subtotal (95% CI)		**838**		**689**	**77.3%**	**3.16 [2.15 , 4.67]**
Total events:	124		37			
Heterogeneity: Chi² = 2.05, df = 5 (P = 0.84); I² = 0%						
Test for overall effect: Z = 5.81 (P < 0.00001)						
Total (95% CI)		**1141**		**839**	**100.0%**	**2.91 [2.05 , 4.12]**
Total events:	155		45			
Heterogeneity: Chi² = 3.03, df = 7 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.97 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.97, df = 1 (P = 0.33), I² = 0%						



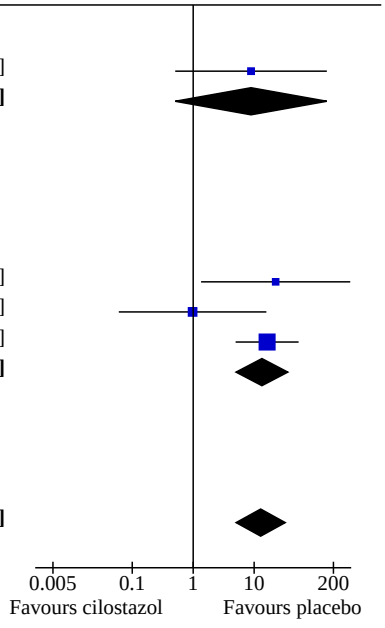
Analysis 1.18. Comparison 1: Cilostazol versus placebo, Outcome 18: Adverse event related to study medication - pain, sensitivity analysis

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 Cilostazol 50 mg twice daily						
Strandness 2002	26	132	9	65	16.8%	1.53 [0.67 , 3.48]
Subtotal (95% CI)		**132**		**65**	**16.8%**	**1.53 [0.67 , 3.48]**
Total events:	26		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.18.2 Cilostazol 100 mg twice daily						
Dawson 2000	30	227	33	239	48.3%	0.95 [0.56 , 1.62]
Elam 1998	14	95	11	94	16.3%	1.30 [0.56 , 3.04]
Strandness 2002	15	133	9	64	18.7%	0.78 [0.32 , 1.88]
Subtotal (95% CI)		**455**		**397**	**83.2%**	**0.98 [0.66 , 1.47]**
Total events:	59		53			
Heterogeneity: Chi² = 0.71, df = 2 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**587**		**462**	**100.0%**	**1.07 [0.75 , 1.54]**
Total events:	85		62			
Heterogeneity: Chi² = 1.62, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.70)						
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.34), I² = 0%						

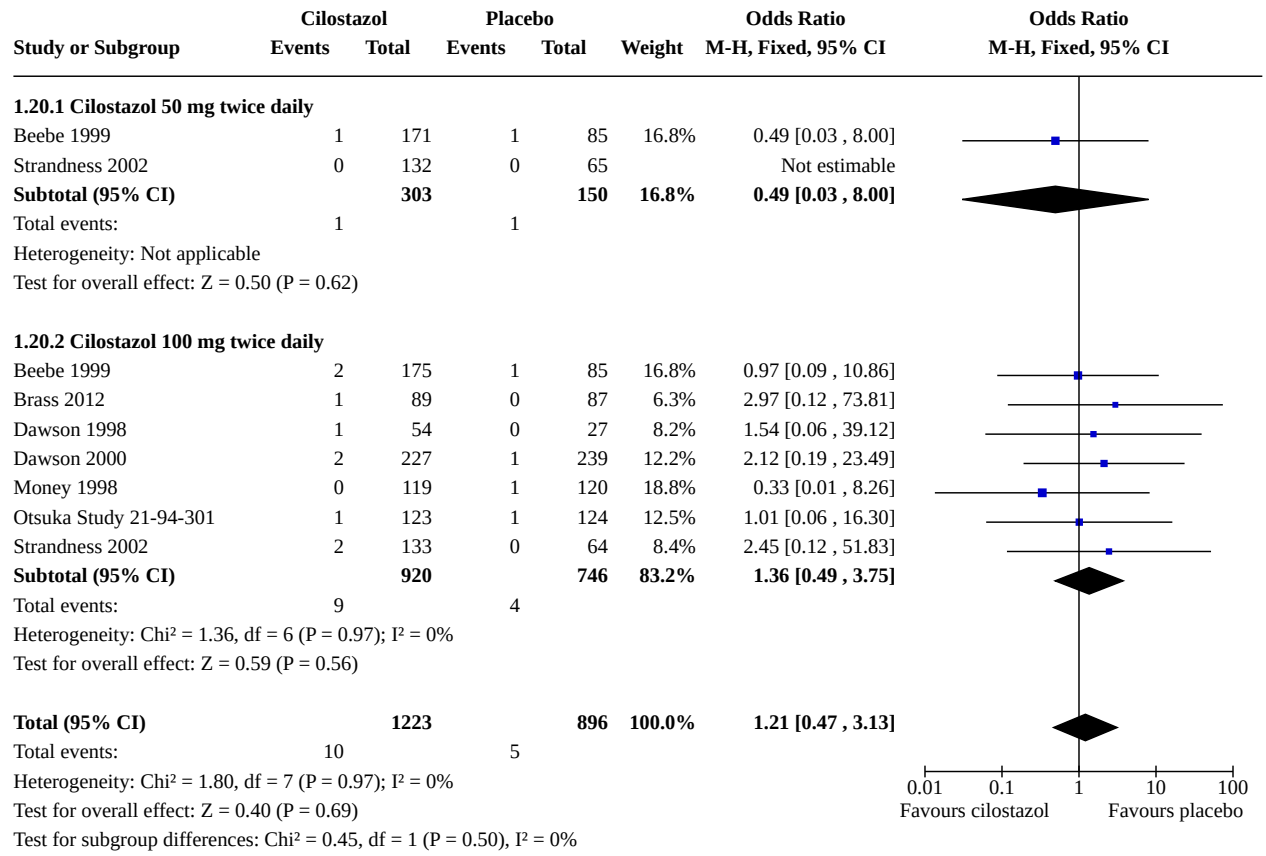


Analysis 1.19. Comparison 1: Cilostazol versus placebo, Outcome 19: Adverse event related to study medication - palpitations, sensitivity analysis

Study or Subgroup	Cilostazol Events	Cilostazol Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.19.1 Cilostazol 50 mg twice daily						
Beebe 1999	8	171	0	85	13.6%	8.89 [0.51 , 155.87]
Subtotal (95% CI)		**171**		**85**	**13.6%**	**8.89 [0.51 , 155.87]**
Total events:	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.19.2 Cilostazol 100 mg twice daily						
Beebe 1999	20	175	0	85	12.8%	22.54 [1.35 , 377.37]
Brass 2012	1	89	1	87	21.5%	0.98 [0.06 , 15.87]
Dawson 2000	39	227	3	239	52.1%	16.32 [4.97 , 53.63]
Subtotal (95% CI)		**491**		**411**	**86.4%**	**13.42 [5.05 , 35.68]**
Total events:	60		4			
Heterogeneity: Chi² = 3.63, df = 2 (P = 0.16); I² = 45%						
Test for overall effect: Z = 5.20 (P < 0.00001)						
Total (95% CI)		**662**		**496**	**100.0%**	**12.80 [5.06 , 32.36]**
Total events:	68		4			
Heterogeneity: Chi² = 3.65, df = 3 (P = 0.30); I² = 18%						
Test for overall effect: Z = 5.39 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



Analysis 1.20. Comparison 1: Cilostazol versus placebo, Outcome 20: All-cause mortality sensitivity analysis



Comparison 2. Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily

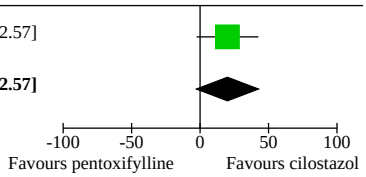
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Initial claudication distance (ICD)	1	417	Mean Difference (IV, Fixed, 95% CI)	20.00 [-2.57, 42.57]
2.2 Absolute claudication distance (ACD)	2	866	Mean Difference (IV, Random, 95% CI)	13.43 [-43.50, 70.36]
2.3 Adverse event related to study medication - headache	2	982	Odds Ratio (M-H, Random, 95% CI)	2.20 [1.16, 4.17]
2.4 Adverse event related to study medication - diarrhoea	2	982	Odds Ratio (M-H, Random, 95% CI)	1.80 [0.79, 4.12]
2.5 Adverse event related to study medication - abnormal stools	1	459	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [1.57, 6.21]
2.6 Adverse event related to study medication - pain	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
2.7 Adverse event related to study medication - palpitations	2	982	Odds Ratio (M-H, Fixed, 95% CI)	8.35 [4.11, 16.98]
2.8 All-cause mortality	3	1229	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.17, 1.98]
2.9 Ankle brachial index (ABI)	1	417	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.12, 0.10]

Analysis 2.1. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 1: Initial claudication distance (ICD)

Study or Subgroup	Cilostazol Mean	SD	Total	Pentoxifylline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dawson 2000	93.6	127.4	205	73.6	106.4	212	100.0%	20.00 [-2.57 , 42.57]
Total (95% CI)			**205**			**212**	**100.0%**	**20.00 [-2.57 , 42.57]**

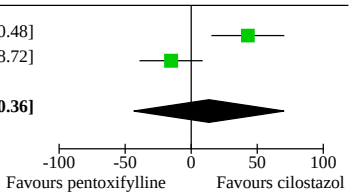
Heterogeneity: Not applicable
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 2: Absolute claudication distance (ACD)

Study or Subgroup	Cilostazol Mean	SD	Total	Pentoxifylline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dawson 2000	107.3	158.4	205	64.4	126.6	212	49.3%	42.90 [15.32 , 70.48]
Otsuka Study 21-98-213	60.4	108	218	75.6	148.5	231	50.7%	-15.20 [-39.12 , 8.72]
Total (95% CI)			**423**			**443**	**100.0%**	**13.43 [-43.50 , 70.36]**

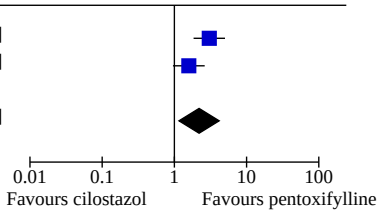
Heterogeneity: Tau² = 1514.32; Chi² = 9.73, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 3: Adverse event related to study medication - headache

Study or Subgroup	Cilostazol Events	Total	Pentoxifylline Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dawson 2000	63	227	26	232	50.2%	3.04 [1.84 , 5.02]
Otsuka Study 21-98-213	43	261	29	262	49.8%	1.58 [0.96 , 2.63]
Total (95% CI)		**488**		**494**	**100.0%**	**2.20 [1.16 , 4.17]**
Total events:	106		55			

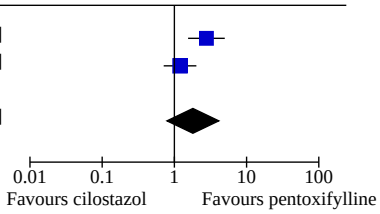
Heterogeneity: Tau² = 0.15; Chi² = 3.23, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 4: Adverse event related to study medication - diarrhoea

Study or Subgroup	Cilostazol Events	Cilostazol Total	Pentoxifylline Events	Pentoxifylline Total	Weight	Odds Ratio M-H, Random, 95% CI
Dawson 2000	43	227	18	232	48.7%	2.78 [1.55 , 4.98]
Otsuka Study 21-98-213	35	261	30	262	51.3%	1.20 [0.71 , 2.02]
Total (95% CI)		**488**		**494**	**100.0%**	**1.80 [0.79 , 4.12]**
Total events:	78		48			

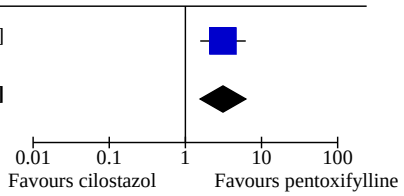
Heterogeneity: Tau² = 0.27; Chi² = 4.44, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 5: Adverse event related to study medication - abnormal stools

Study or Subgroup	Cilostazol Events	Cilostazol Total	Pentoxifylline Events	Pentoxifylline Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	33	227	12	232	100.0%	3.12 [1.57 , 6.21]
Total (95% CI)		**227**		**232**	**100.0%**	**3.12 [1.57 , 6.21]**
Total events:	33		12			

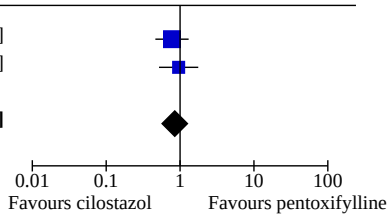
Heterogeneity: Not applicable
Test for overall effect: Z = 3.24 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 6: Adverse event related to study medication - pain

Study or Subgroup	Cilostazol Events	Cilostazol Total	Pentoxifylline Events	Pentoxifylline Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	30	227	38	232	60.8%	0.78 [0.46 , 1.31]
Otsuka Study 21-98-213	22	261	23	262	39.2%	0.96 [0.52 , 1.76]
Total (95% CI)		**488**		**494**	**100.0%**	**0.85 [0.57 , 1.26]**
Total events:	52		61			

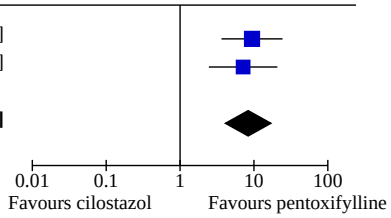
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 7: Adverse event related to study medication - palpitations

Study or Subgroup	Cilostazol Events	Cilostazol Total	Pentoxifylline Events	Pentoxifylline Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	39	227	5	232	53.3%	9.42 [3.64 , 24.37]
Otsuka Study 21-98-213	26	261	4	262	46.7%	7.14 [2.45 , 20.75]
Total (95% CI)		**488**		**494**	**100.0%**	**8.35 [4.11 , 16.98]**
Total events:	65		9			

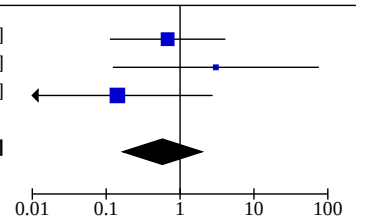
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 5.86 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 8: All-cause mortality

Study or Subgroup	Cilostazol Events	Cilostazol Total	Pentoxifylline Events	Pentoxifylline Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dawson 2000	2	227	3	232	42.5%	0.68 [0.11 , 4.10]
Otsuka Study 21-94-301	1	123	0	124	7.1%	3.05 [0.12 , 75.57]
Otsuka Study 21-98-213	0	261	3	262	50.4%	0.14 [0.01 , 2.76]
Total (95% CI)		**611**		**618**	**100.0%**	**0.58 [0.17 , 1.98]**
Total events:	3		6			

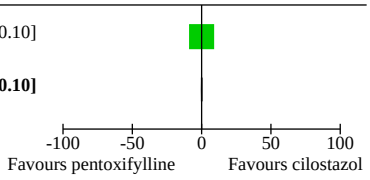
Heterogeneity: Chi² = 1.92, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily, Outcome 9: Ankle brachial index (ABI)

Study or Subgroup	Cilostazol Mean	Cilostazol SD	Cilostazol Total	Pentoxifylline Mean	Pentoxifylline SD	Pentoxifylline Total	Weight	Mean Difference IV, Fixed, 95% CI
Dawson 2000	0.04	0.57	205	0.05	0.58	212	100.0%	-0.01 [-0.12 , 0.10]
Total (95% CI)			**205**			**212**	**100.0%**	**-0.01 [-0.12 , 0.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Change in quality of life status (change in points or percentage from baseline)

		Beebe 1999			Dawson 2000			Money 1998		O'Donnell 2009	
Tool	**Domain**	**Cilostazol 100 mg (n = 137)**	**Cilostazol 50 mg (n = 135)**	**Placebo (n = 141)**	**Cilostazol 100 mg (n = 205)**	**Pentox 400 mg (n = 212)**	**Placebo (n = 226**	**Cilostazol 100 mg (n = 119)**	**Placebo (n = 120)**	**Cilostazol 100 mg (n = 39)**	**Placebo (n = 41)**
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 improv	no improv	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 Impairment Questionnaire (WIQ)	Walking speed	0.1	0.2	0.1	no diff	no diff	no diff	20.0%	0.0%	10%	4%
	Walking distance	0.2	0.2	0.1	no diff	no diff	no diff	-	-	-1%	3%
Claudication Outcome Measure (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	-	-	-	-	-	-	-
Vascular Quality of	Activity	-	-	-	-	-	-	-	-	7.3	1.8

Table 1. Change in quality of life status (change in points or percentage from baseline) *(Continued)*

Life (VascuQol)	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

Table 2. Adverse events related to study medication

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or pentoxifylline	Risk with cilostazol			
Cilostazol compared to placebo					
Diarrhoea 12 to 26 weeks follow-up	Study population 56 per 1000	140 per 1000 (108 to 181)	OR 2.73 (2.02 to 3.70)	2503 (7 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Abnormal stools 12 to 24 weeks follow-up	Study population 44 per 1000	143 per 1000 (101 to 198)	OR 3.63 (2.45 to 5.38)	1804 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Dizziness 12 to 26 weeks follow-up	Study population 42 per 1000	97 per 1000 (60 to 153)	OR 2.42 (1.43 to 4.08)	1120 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Pain 12 to 24 weeks follow-up	Study population 127 per 1000	123 per 1000 (94 to 159)	OR 0.96 (0.71 to 1.30)	1572 (4 RCTs)	⊕⊕⊖⊖ LOW [1, 2]
Palpitations 24 to 26 weeks follow-up	Study population 16 per 1000	103 per 1000 (60 to 173)	OR 7.16 (3.95 to 12.98)	1681 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1, 3]
Cilostazol compared to pentoxifylline					
Diarrhoea 24 weeks follow-up	Study population 97 per 1000	162 per 1000 (78 to 307)	OR 1.80 (0.79 to 4.12)	982 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1, 3, 4]
Abnormal stools 24 weeks follow-up	Study population 52 per 1000	145 per 1000 (79 to 253)	OR 3.12 (1.57 to 6.21)	459 (1 RCT)	⊕⊕⊖⊖ LOW [1, 5]
Pain 24 weeks follow-up	Study population 123 per 1000	107 per 1000 (74 to 151)	OR 0.85 (0.57 to 1.26)	982 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Palpitations 24 weeks follow-up	Study population 18 per 1000	134 per 1000 (71 to 240)	OR 8.35 (4.11 to 16.98)	982 (2 RCTs)	⊕⊕⊖⊖ LOW [1, 3]

Table 2. Adverse events related to study medication *(Continued)*

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] downgraded one level for publication bias because pharmaceutical sponsors involvement raises questions of whether unpublished studies that suggest no benefit exist
[2] downgraded one level for risk of bias because 2 studies (Elam 1998; Strandness 2002) rated at high risk for selective reporting
3 downgraded one level for imprecision due to wide CIs
4 downgraded one level for inconsistency because of heterogeneity: $I^2 = 77\%$
[5] downgraded one level for imprecision due to data from 1 RCT with wide CIs (Dawson 2000)

Table 3. Reasons 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 SDs, but the treadmill method was 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 do offer graphical information on the mean change in maximal walking distances, 'expressed as percent of control'.
Lee 2001	For ACD and ABI, mean baseline and follow-up values with SD were given; we can calculate mean change but for the imputation of SD we need the SDs associated with the change and the baseline and the post-intervention mean, for at least one similar length study, which we do not have. Mean changes in ACD without SD or other variance were also reported in the text.
O'Donnell 2009	For ICD and ACD, mean baseline and follow-up values were given, but no SDs 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 SD.
Otsuka Study 21-86-101	Placebo-corrected mean change from baseline was provided for the treatment group, with no SDs. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but these data could not be recalculated to mean change and SD.
Otsuka Study 21-86-103	Raw mean change from baseline was provided for the cilostazol and placebo groups, with no SDs. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but these data could not be recalculated to mean change and SD.
Otsuka Study 21-87-101	Placebo-corrected mean change from baseline was provided for the treatment group, with no SDs. Also, a ratio of the geometric means of change was calculated between cilostazol and placebo, but these data could not be recalculated to mean change and SD.
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 these data could not be recalculated to mean change and SD.

Table 3. Reasons for study not being included in meta-analyses of initial claudication distance (ICD), absolute claudication distance (ACD) and ankle brachial index (ABI) *(Continued)*

Otsuka Study 21-98-213	For ICD, raw mean change from baseline was provided for the cilostazol and comparison groups, with no SDs. Also, a ratio of the geometric means of change was calculated between cilostazol and comparisons, but these data could not be recalculated to mean change and SD. Mean change data with SDs were available for the ACD outcome.

ACD: absolute claudication distance
ABI: ankle brachial index
ICD: initial claudication distance
SD: standard deviation

APPENDICES

Appendix 1. Database search strategies

Source	Search strategy	Hits retrieved
CENTRAL via CRSO	#1 MESH DESCRIPTOR Arteriosclerosis 1010 #2 MESH DESCRIPTOR Arteriolosclerosis 0 #3 MESH DESCRIPTOR Arteriosclerosis Obliterans 88 #4 MESH DESCRIPTOR Atherosclerosis 1362 #5 MESH DESCRIPTOR Arterial Occlusive Diseases 882 #6 MESH DESCRIPTOR Intermittent Claudication 916 #7 MESH DESCRIPTOR Ischemia 2071 #8 MESH DESCRIPTOR Vascular Diseases 814 #9 MESH DESCRIPTOR intermittent claudication EXPLODE ALL TREES 916 #10 MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES 3193 #11 (atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY 16562 #12 ((arter*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 5893 #13 ((vascular) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 683 #14 ((vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 439 #15 ((veno*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 313 #16 ((peripher*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 1683 #17 (peripheral near/3 dis*):TI,AB,KY 0	Nov 2020: **2477**

(Continued)

#18 arteriopathic:TI,AB,KY 6

#19 ((claudic* or hinken*)):TI,AB,KY 2452

#20 ((isch* or CLI)):TI,AB,KY 43328

#21 dysvascular*:TI,AB,KY 28

#22 (leg near (obstruct*or steno* or block* or obliter*)):TI,AB,KY 122

#23 (limb near (obstruct*or steno* or block* or obliter*)):TI,AB,KY 309

#24 ((lower extrem*) near (obstruct* or occlus* or steno* or block* or obliter*)):TI,AB,KY 179

#25 ((aort* or iliac or femoral or popliteal or femoropop* or fempop* or crural) near (obstruct* or occlus*)):TI,AB,KY 649

#26 MESH DESCRIPTOR Femoral Artery EXPLODE ALL TREES 979

#27 MESH DESCRIPTOR Popliteal Artery EXPLODE ALL TREES 350

#28 MESH DESCRIPTOR Iliac Artery EXPLODE ALL TREES 162

#29 MESH DESCRIPTOR Iliac Vein EXPLODE ALL TREES 46

#30 MESH DESCRIPTOR Popliteal Vein EXPLODE ALL TREES 65

#31 MESH DESCRIPTOR Femoral Vein EXPLODE ALL TREES 233

#32 Fontaine:TI,AB,KY 365

#33 #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 OR #32 68856

#34 MESH DESCRIPTOR Vasodilator Agents EXPLODE ALL TREES 25529

#35 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES 11085

#36 MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES 7118

#37 MESH DESCRIPTOR Tetrazoles EXPLODE ALL TREES 3581

#38 vasodilator*:TI,AB,KY 6961

#39 Cilostazol:TI,AB,KY 815

#40 OPC-13013:TI,AB,KY 6

#41 (platelet near3 inhibitor*):TI,AB,KY 4290

#42 (phosphodiesterase inhibitor*):TI,AB,KY 1041

#43 pletal:TI,AB,KY 26

#44 pletaal:TI,AB,KY 12

#45 73963-72-1:TI,AB,KY 3

#46 #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 42222

(Continued)

	#47 #33 AND #46 7069 #48 01/01/2013 TO 09/11/2020:CD 1027175 #49 #47 AND #48 2477	
Clinicaltrials.gov	**intermittent claudication OR Peripheral Vascular Diseases | Cilostazol OR Tetrazoles OR phosphodiesterase inhibitorS OR pletal OR Vasodilator Agents OR Aggregation Inhibitors**	Nov 2020: 61
ICTRP Search Portal		Nov 2020:
Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present	1 Arterial Occlusive Diseases/ 2 Arteriolosclerosis/ 3 Arteriosclerosis/ 4 Arteriosclerosis Obliterans/ 5 Femoral Artery/ 6 Iliac Artery/ 7 Intermittent Claudication/ 8 Ischemia/dt, et, mo, su, th [Drug Therapy, Etiology, Mortality, Surgery, Therapy] 9 Leg/bs [Blood Supply] 10 exp Peripheral Vascular Diseases/ 11 Popliteal Artery/ 12 Tibial Arteries/ 13 arteriosclero*.ti,ab. 14 arteriopathic.ti,ab. 15 claudic*.ti,ab. 16 CLI.ti,ab. 17 dysvascular*.ti,ab. 18 ischemi*.ti,ab. 19 PVD.ti,ab. 20 PAOD.ti,ab. 21 (peripheral adj3 dis*).ti,ab. 22 (("lower extrem*" or arter* or crural or femdist* or femoral or fempop* or iliac or infrainquinal or infrapopliteal or inguinal or limb or peripher* or popliteal or tibial or vascular or vein* or veno*) adj3 (block* or harden* or lesio* or obliter* or obstruct* or occlus* or reocclus* or re-occlus* or restenos* or steno* or stiffen*)).ti,ab. 23 or/1-22 24 Cilostazol/ 25 Vasodilator Agents/	Nov 2020: 2771

(Continued)

	26 Platelet Aggregation Inhibitors/	
	27 Phosphodiesterase Inhibitors/	
	28 Tetrazoles/	
	29 vasodilator*.ti,ab.	
	30 Cilostazol.ti,ab.	
	31 OPC-13013.ti,ab.	
	32 (platelet adj3 inhibitor*).ti,ab.	
	33 "phosphodiesterase inhibitor*".ti,ab.	
	34 pletal.ti,ab.	
	35 pletaal.ti,ab.	
	36 73963-72-1.ti,ab.	
	37 or/24-36	
	38 23 and 37	
	39 randomized controlled trial.pt.	
	40 controlled clinical trial.pt.	
	41 randomized.ab.	
	42 placebo.ab.	
	43 drug therapy.fs.	
	44 randomly.ab.	
	45 trial.ab.	
	46 groups.ab.	
	47 or/39-46	
	48 exp animals/ not humans.sh.	
	49 47 not 48	
	50 38 and 49	
	51 (2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).ed.	
	52 50 and 51	
Embase	1 peripheral occlusive artery disease/	Nov 2020: 2218
	2 arteriolosclerosis/	
	3 arteriosclerosis/	
	4 femoral artery/	
	5 iliac artery/	
	6 intermittent claudication/	
	7 ischemia/dt, et, su, th [Drug Therapy, Etiology, Surgery, Therapy]	

(Continued)

8 exp peripheral vascular disease/

9 popliteal artery/

10 tibial artery/

11 arteriosclero*.ti,ab.

12 arteriopathic.ti,ab.

13 claudic*.ti,ab.

14 CLI.ti,ab.

15 dysvascular*.ti,ab.

16 PVD.ti,ab.

17 PAOD.ti,ab.

18 (peripheral adj3 dis*).ti,ab.

19 (("lower extrem*" or arter* or crural or femdist* or femoral or fempop* or iliac or infrainquinal or infrapopliteal or inguinal or limb or peripher* or popliteal or tibial or vascular or vein* or veno*) adj3 (block* or harden* or lesio* or obliter* or obstruct* or occlus* or reocclus* or re-occlus* or restenos* or steno* or stiffen*)).ti,ab.

20 or/1-19

21 cilostazol/

22 vasodilator agent/

23 phosphodiesterase inhibitor/

24 vasodilator*.ti,ab.

25 Cilostazol.ti,ab.

26 OPC-13013.ti,ab.

27 (platelet adj3 inhibitor*).ti,ab.

28 "phosphodiesterase inhibitor*".ti,ab.

29 pletal.ti,ab.

30 pletaal.ti,ab.

31 73963-72-1.ti,ab.

32 or/21-31

33 20 and 32

34 randomized controlled trial/

35 controlled clinical trial/

36 random$.ti,ab.

37 randomization/

38 intermethod comparison/

39 placebo.ti,ab.

(Continued)

	40 (compare or compared or comparison).ti. 41 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 42 (open adj label).ti,ab. 43 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 44 double blind procedure/ 45 parallel group$1.ti,ab. 46 (crossover or cross over).ti,ab. 47 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 48 (assigned or allocated).ti,ab. 49 (controlled adj7 (study or design or trial)).ti,ab. 50 (volunteer or volunteers).ti,ab. 51 trial.ti. 52 or/34-51 53 33 and 52 54 (2013* or 2014* or 2015* or 2016* or 2017* or 2016* or 2017* or 2018* or 2019* or 2020*).dc. 55 53 and 54	
CINAHL	S54 S52 AND S53 S53 EM 2013 OR EM 2014 OR EM 2015 OR EM 2016 OR EM 2017 OR EM 2018 OR EM 2019 OR EM 2020 S52 S36 AND S51 S51 S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 S50 MH "Random Assignment" S49 MH "Triple-Blind Studies" S48 MH "Double-Blind Studies" S47 MH "Single-Blind Studies" S46 MH "Crossover Design" S45 MH "Factorial Design" S44 MH "Placebos" S43 MH "Clinical Trials" S42 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" S41 TX crossover OR "cross-over" S40 AB placebo*	Nov 2020: 782

(Continued)

S39 TX random*

S38 TX trial*

S37 TX "latin square"

S36 S22 AND S35

S35 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34

S34 TX 73963-72-1

S33 TX pletaal

S32 TX pletal

S31 TX "phosphodiesterase inhibitor*"

S30 TX platelet N3 inhibitor*

S29 TX OPC-13013

S28 TX Cilostazol

S27 TX vasodilator*

S26 (MH "Phosphodiesterase Inhibitors")

S25 (MH "Platelet Aggregation Inhibitors")

S24 (MH "Vasodilator Agents")

S23 (MH "Cilostazol")

S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

S21 TX ("lower extrem*" or arter* or crural or femdist* or femoral or fempop* or iliac or infrainquinal or infrapopliteal or inguinal or limb or peripher* or popliteal or tibial or vascular or vein* or veno*) N3 (block* or harden* or lesio* or obliter* or obstruct* or occlus* or reocclus* or re-occlus* or restenos* or steno* or stiffen*)

S20 TX peripheral N3 dis*

S19 TX PAOD

S18 TX PVD

S17 TX ischemi*

S16 TX dysvascular*

S15 TX CLI

S14 TX claudic*

S13 TX arteriopathic

S12 TX arteriosclero*

S11 (MH "Tibial Arteries")

S10 Tibial Arteries

S9 (MH "Popliteal Artery")

(Continued)

S8 (MH "Peripheral Vascular Diseases+")

S7 (MH "Leg/BS")

S6 (MH "Ischemia/DT/ET/MO/SU")

S5 (MH "Intermittent Claudication")

S4 (MH "Iliac Artery")

S3 (MH "Femoral Artery")

S2 (MH "Arteriosclerosis")

S1 (MH "Arterial Occlusive Diseases")

F E E D B A C K

Unpublished trials (Feedback and response added 11 September 2007),

Summary

The Cochrane review of cilostazol (1/2007) included only one study of cilostazol (CLZ) and pentoxifylline (PTX, TRENTAL), (Dawson DL 2000), and stated: "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 had been 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 (= pentoxyfylline). A second study comparing cilostazol with pentoxifylline was the Dawson DL 2000 (trial 21-96-202). The FDA stated (p.231): "There is not yet a convincing basis with which to conclude that CLZ is more efficious 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 the 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 are 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 does 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
31 March 2021	New citation required but conclusions have not changed	New author joined review team. One author left review team. GRADE and Summary of Findings incorporated. Conclusions not changed.
31 March 2021	New search has been performed	Searches rerun. One new included study, 23 new excluded studies identified.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 1, 2007

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
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

TB: assessed references from the updated search, assessed risk of bias, extracted data, undertook meta-analyses, added summary of findings tables and applied GRADE criteria, and drafted the review.

RBF: assessed risk of bias, extracted data, and assisted in drafting the review.

MC: provided clinical support, contributed to the discussion and conclusion and checked the draft review.

DPM: provided clinical support, contributed to the discussion and conclusion and checked the draft review.

GS: provided clinical support, contributed to the discussion and conclusion and checked the draft review.

MS: assessed references from the updated search, checked data analysis and assisted in drafting the review.

DECLARATIONS OF INTEREST

TB: none.

RBF: none.

MC: none.

DPM: declared that he received payment to attend meetings (Amgen, Novo Nordisk), advisory boards (Novo Nordisk), and present lectures on lipids and cilostazol (Amgen, Novo Nordisk and Libytec). It is five years since his last lecture on cilostazol (Libytec). As Editor-in-Chief; royalties were paid to him (Informa, SAGE and Bentham publications). He has published peer-reviewed material regarding cilostazol.

GS: none.

MS: MS is a member of the Cochrane Vascular editorial base. In order to maintain integrity, editorial tasks for this review have been carried out by other members of the editorial team.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

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

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2021 update

We restructured the review text and meta-analyses so that the outcomes are presented according to the comparisons 'cilostazol versus placebo' and 'cilostazol versus pentoxifylline' with the cilostazol doses subgrouped. We revised the outcomes (but not the other components of the PICO) to reflect current clinical practice and clinical importance: health-related quality of life is now a primary outcome (was a secondary outcome); we changed ‘progression to surgery’ to specifically relate to ‘revascularisation'; we added ‘amputation’ and 'major adverse limb event' (MALE); finally, we renamed ‘adverse events’ to be clearly related to study medication. Lastly, we added summary of findings tables and assessed the outcomes presented in the tables using GRADE criteria.

2014 update

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)".

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; participants had been 'patients with intermittent claudication or patients undergoing bypass surgery for peripheral arterial disease' and this was changed to only '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 had 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)

Bias; Cilostazol [*therapeutic use]; Intermittent Claudication [*drug therapy] [etiology]; Myocardial Infarction [prevention & control]; Pentoxifylline [therapeutic use]; Peripheral Vascular Diseases [complications] [drug therapy]; Placebos [therapeutic use]; 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