Health Technology Assessment 2011; Vol. 15: No. 40
ISSN 1366-5278

A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

H Squires, E Simpson, Y Meng, S Harnan, JW Stevens, R Wong, S Thomas, J Michaels and G Stansby

December 2011
10.3310/hta15400

Health Technology Assessment
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Declared competing interests of authors: none

Published December 2011
DOI: 10.3310/hta15400

This report should be referenced as follows:

Squires H, Simpson E, Meng Y, Harnan S, Stevens JW, Wong R, *et al*. A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. *Health Technol Assess* 2011;**15**(40).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/ Clinical Medicine.

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The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 09/92/01. The protocol was agreed in April 2010. The assessment report began editorial review in November 2010 and was accepted for publication in May 2011. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

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Abstract

A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

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Background: Peripheral arterial disease (PAD) is a condition in which there is blockage or narrowing of the arteries that carry blood to the legs and arms. It is estimated to affect around 4.5% of people aged between 55 and 74 years within the UK. The most common symptom of PAD is intermittent claudication (IC), characterised by pain in the legs on walking that is relieved with rest.

Objective: To assess the effectiveness and cost-effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate, compared with no vasoactive drugs, for IC due to PAD in adults whose symptoms continue despite a period of conventional management.

Data source: Electronic bibliographic databases were searched during April to June 2010 (MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Conference Proceedings Citation Index, BIOSIS Previews).

Review methods: Effectiveness outcomes sought were maximal walking distance (MWD), pain-free walking distance (PFWD), ankle–brachial pressure index, cardiovascular events, mortality, adverse events (AEs) and health-related quality of life (HRQoL). A narrative synthesis was provided for all outcomes and a network meta-analysis was undertaken for the walking distance outcomes. A Markov model was developed to assess the relative cost-effectiveness of the interventions from a NHS perspective over a lifetime. The model has three states: vasoactive drug treatment, no vasoactive drug treatment and death. Each 1-week cycle, patients may continue with the drug, discontinue the drug or die. Regression analysis was undertaken to model the relationship between MWD and utility so that a cost per quality-adjusted life-year (QALY) outcome measure could be presented. Univariate and probabilistic sensitivity analyses were undertaken. All costs and outcomes were discounted at 3.5%.

Results: Twenty-six randomised controlled trials were identified that met the inclusion criteria for the clinical effectiveness review. There was evidence that walking distance outcomes were significantly improved by both cilostazol and naftidrofuryl oxalate; the 95% credible intervals for the difference from placebo in the logarithm mean change MWD from baseline were 0.108 to 0.337 and 0.181 to 0.762, respectively. It was not possible to

include inositol nicotinate within the meta-analysis of MWD and PFWD owing to the lack of 24-month data; however, the shorter-term data did not suggest a significant effect. AEs were minor for all drugs and included headaches and gastrointestinal difficulties. The incidence of serious adverse events (SAEs), including cardiovascular events and mortality, was not increased by the vasoactive drugs compared with placebo; however, most studies had a relatively short follow-up time to address this outcome. HRQoL data were limited. Two studies of limited quality were identified within the review of cost-effectiveness. The de novo model developed suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline and has a cost per QALY gained of around £6070 compared with no vasoactive drug. This result is reasonably robust to changes within the key model assumptions. Inositol nicotinate was not included within the main analysis owing to lack of data. However, it is unlikely to be considered to be cost-effective due to its high acquisition cost (£900 vs £100–500 per year for the other drugs).

Conclusions: Naftidrofuryl oxalate and cilostazol both appear to be effective treatments for this patient population, with minimal SAEs. However, naftidrofuryl oxalate is the only treatment that is likely to be considered cost-effective. The long-term effectiveness is uncertain and hence a trial comparing cilostazol, naftidrofuryl oxalate and placebo beyond 24 weeks would be beneficial. Outcomes associated with naftidrofuryl oxalate could also be compared with those associated with supervised exercise programmes and angioplasty.

Source of funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

Arithmetic mean A measure of central tendency calculated as the sum of all of the numbers in a series divided by the count of all numbers in the series.

Dominated (simple) Where an intervention is less effective and more expensive than its comparator.

Dominated (extended) Where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective comparator.

Geometric mean A measure of central tendency calculated by multiplying a series of numbers and taking the *n*th root of the product, where *n* is the number of items in the series.

Meta-analysis A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.

Posterior distribution A representation of the knowledge associated with the true value of a population parameter after combining the prior distribution with sample data.

Prior distribution A representation of the knowledge associated with the true value of a population parameter in addition to any sample data.

Relative risk Ratio of the probability of an event occurring in an exposed group relative to a non-exposed or control group.

List of abbreviations

ABPI	ankle–brachial pressure index
AE	adverse event
b.i.d.	twice a day
CEAC	cost-effectiveness acceptability curve
CHEC	Consensus on Health Economic Criteria
CHF	congestive heart failure
CI	confidence interval
COM	claudication outcome measure
CRD	Centre for Reviews and Dissemination
EMA	European Medicines Agency
HR	hazard ratio
HRQoL	health-related quality of life
IC	intermittent claudication
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
log	logarithm
MI	myocardial infarction
MWD	maximal walking distance
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
PAD	peripheral arterial disease
PFWD	pain-free walking distance
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SA	sensitivity analysis
SAE	serious adverse event
ScHARR	School of Health and Related Research
ScHARR-TAG	ScHARR Technology Assessment Group
SD	standard deviation
SF-36	Short Form questionnaire-36 items
t.i.d.	three times a day
VascuQoL	vascular quality of life
WHOQoL	World Health Organization Quality of Life
WIQ	Walking Impairment Questionnaire

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Peripheral arterial disease (PAD) is a condition in which there is blockage or narrowing of the arteries that carry blood to the legs and arms. It is estimated to affect around 4.5% of people between the age of 55 and 74 years within the UK. The most common symptom of PAD is intermittent claudication (IC), characterised by pain in the legs on walking that is relieved with rest. The treatment of IC is targeted at reducing the risk from cardiovascular events and includes smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Symptoms can be managed with exercise therapy and/or pharmacological therapies, including cilostazol (Pletal®, Otsuka Pharmaceuticals), naftidrofuryl oxalate (Praxilene®, Merk Serono), pentoxifylline (Trental 400®, Sanofi-aventis) and inositol nicotinate (Hexopal®, Genus Pharmaceuticals).

Objectives

To assess the effectiveness and cost-effectiveness of the following vasoactive drugs for IC due to PAD in adults whose symptoms continue despite a period of conservative management:

- cilostazol
- naftidrofuryl oxalate
- pentoxifylline
- inositol nicotinate.

Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of IC in people with PAD whose symptoms continue despite a period of conservative management. Electronic bibliographic databases were searched during April to June 2010 (MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Conference Proceedings Citation Index, BIOSIS Previews). The reference lists of relevant articles were also checked. Comparators were placebo, usual care of PAD without the vasoactive drugs assessed within this report and the vasoactive drugs for PAD compared with each other. Outcomes sought were maximal walking distance (MWD), pain-free walking distance (PFWD), ankle–brachial pressure index, cardiovascular events, mortality, adverse events (AEs) and health-related quality of life (HRQoL). A narrative synthesis was provided for all outcomes and a network meta-analysis was also undertaken for the MWD and PFWD outcomes.

A Markov model was developed to assess the cost-effectiveness of each vasoactive drug for PAD compared with no vasoactive drugs and with each other vasoactive drug from a NHS and PSS perspective. The model has three states: vasoactive drug treatment, no vasoactive drug treatment and death. Patients will start with one of the drugs under evaluation and after each weekly cycle may continue with the drug, discontinue with the drug or die. Patients may also start with no drug treatment. The time horizon of the model is the lifetime of the patients. Regression analysis

was undertaken to model the relationship between MWD and utility so that a cost per quality-adjusted life-year (QALY) outcome measure could be presented. Given the uncertainties around the quality-of-life evidence and the uncertain long-term outcomes, a threshold analysis was also undertaken. There was only one manufacturer submission (Otsuka) for this assessment and no economic model was provided.

Results

Twenty-six randomised controlled trials (RCTs) were identified that met the inclusion criteria for the clinical effectiveness review. These included trials comparing each of the vasoactive drugs for PAD with placebo, and also head-to-head comparisons of cilostazol and pentoxifylline, and cilostazol with usual care.

There was evidence to suggest that walking distance outcomes were statistically significantly improved by both cilostazol and naftidrofuryl oxalate; the 95% credible intervals for the difference from placebo in the logarithm mean change from baseline were 0.108 to 0.337 and 0.181 to 0.762, respectively. It was not possible to include inositol nicotinate within the meta-analysis of MWD and PFWD because of the lack of 24-week data. AEs were minor for all drugs and included headaches and gastrointestinal difficulties. The incidence of serious adverse events (SAEs), including cardiovascular events and mortality, was not increased by the vasoactive drugs compared with placebo. However, most studies had a relatively short follow-up time to address this outcome. HRQoL data are limited, as outcomes were often partially reported, not reported or not measured. There is some evidence that cilostazol improves physical function but does not affect mental health or overall quality of life. There are very limited data for naftidrofuryl oxalate and pentoxifylline. Naftidrofuryl oxalate may improve daily living, social life and mood, but not anxiety, and pentoxifylline has little effect on HRQoL. There was no HRQoL evidence for inositol nicotinate. Patient-level Short Form questionnaire-36 items HRQoL data were obtained from one RCT and these data were used within the economic evaluation.

The economic evaluation suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline, and has an incremental cost per QALY gained of around £6070 compared with no vasoactive drug. This result is reasonably robust to changes within the key model assumptions. The exception to this is the results of an exploratory subgroup analysis of patients with more severe IC, in whom successful vasoactive drug treatment may prevent the need for angioplasty. This is predicted to result in an incremental cost per QALY gained below £20,000 for no vasoactive drugs (all patients receive angioplasty) versus the vasoactive drugs. However, the assumptions within this subgroup analysis are largely based upon clinical advice owing to lack of evidence. This analysis is therefore highly uncertain, meaning that these results should be treated with caution. It was not possible to include inositol nicotinate within the base-case analysis owing to lack of 24-week data; however, because of its higher acquisition cost it would have to demonstrate considerably greater impacts upon quality of life than the other vasoactive drugs being assessed for it to have a cost per QALY gained below £20,000 compared with no vasoactive drug, and this is not suggested from the 12-week data.

Discussion

The main strengths of the review are that the literature search was comprehensive and that the included studies were of relevance to UK practice in terms of populations. In addition, all included trials prescribed medications in line with UK marketing authorisations. However, most of the trial data had follow-up periods of 24 weeks, which is relatively short term compared with clinical practice.

Within the meta-analysis of MWD and PFWD, several studies were excluded because the published reports did not provide data in a form that was suitable for inclusion in the meta-analysis. In the analysis, it was assumed that the data from the studies were missing at random and that the lack of usable data was not related to the observed treatment effect.

There is much uncertainty regarding the change in utility and discontinuation rate beyond 24 weeks because most RCTs do not have follow-up beyond this time point. Any additional effectiveness of naftidrofuryl oxalate beyond discontinuation would improve cost-effectiveness, and a sensitivity analysis was carried out to test alternative long-term discontinuation rates which did not have a substantial impact upon the results.

The regression model fitted to predict the change of utility from the change of MWD within the health economic model was based on patient-level data from a RCT of cilostazol of 106 patients in the UK. The underlying assumption of this analysis is that there is the same relationship for all drugs and no vasoactive drug between MWD and utilities. Direct long-term utility data associated with each of the drugs would provide less uncertain estimates of cost-effectiveness. A threshold analysis was undertaken to address this issue. A value-of-information analysis has not been undertaken because of the uncertainties associated with the long-term outcomes, which it was not possible to fully quantitate within the probabilistic sensitivity analysis.

Cardiovascular AEs are common for the patient population considered in the study. The long-term safety of cilostazol was tested in a good-quality trial, which suggests that there is very little difference between cardiovascular outcomes for cilostazol and placebo, and personal communication with the team of clinical advisors suggests that there is no clinical reason why these vasoactive drugs for PAD would impact upon the number of cardiovascular events. However, there are no long-term safety studies on naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, and if there was a small increase or reduction in the incidence of cardiovascular events when patients are on these drugs then the cost-effectiveness results could alter substantially because of the otherwise small impact on costs and quality of life associated with these drugs.

Conclusions

Naftidrofuryl oxalate and cilostazol are both effective treatments for this patient population, with minimal SAEs; however, naftidrofuryl oxalate is the only treatment with an incremental cost per QALY gained below £20,000 compared with no vasoactive drug. There is, however, uncertainty regarding long-term effectiveness, and hence a trial comparing the long-term effectiveness (beyond 24 weeks) of cilostazol, naftidrofuryl oxalate and placebo would be beneficial, which should collect utility data as well as walking distance outcomes. It would also be useful to compare the outcomes associated with naftidrofuryl oxalate with those associated with supervised exercise programmes and other treatments, such as angioplasty. Importantly, there are currently no long-term safety trials for naftidrofuryl oxalate; however, clinical experts suggest that the mechanism of the drugs is such that no long-term impacts on cardiovascular events or mortality would be expected.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Description of health problem

Peripheral arterial disease (PAD), also known as peripheral vascular disease, is a condition in which there is blockage of the arteries that carry blood to the legs and arms. The cause of PAD is atherosclerosis, which is the narrowing of the arteries (stenosis), caused by fatty deposits on the arterial walls.

There are four stages of PAD, as described by the Fontaine Classification scheme.[1] The disease can be asymptomatic (Fontaine Classification stage I) or symptomatic (Fontaine Classification stages II–IV).[1] The commonest symptom of PAD is intermittent claudication (IC) (stage II), characterised by pain in the legs on walking that is relieved with rest. People with severe PAD experience pain at rest (stage III), and this can then progress to necrosis and gangrene (stage IV).[1] Other symptoms of PAD include cold or numbness in the feet, hair loss and non-healing sores on the legs, feet or toes.[2]

Intermittent claudication is the consistent presence of muscle fatigue, cramping pain or aching experienced by patients when walking.[3] This pain results from the inadequate blood flow to leg muscles caused by PAD, limiting the increase in blood flow needed for muscle metabolism.[3] This pain is relieved with rest, as a result of normalisation of blood flow.[3] The restriction of mobility caused by IC can impair health-related quality of life (HRQoL).[2]

Aetiology, pathology and prognosis

Intermittent claudication is most commonly experienced in the calf and is often then associated with PAD of the femoropopliteal segment.[2] If PAD is present at the aortoiliac level, this can result in pain in the thigh, hip or buttock, rather than/or in addition to calf claudication.[2] Rarely, IC may be located in the foot.[3]

The major risk factors for developing PAD are similar to risk factors for coronary heart disease.[4] Up to 68% and 50% of patients with PAD will also have coronary and cerebrovascular disease, respectively, as these diseases have the same underlying pathology.[2,5] The major risk factors for PAD are smoking and diabetes mellitus.[3] Other risk factors are hypertension, hypercholesterolaemia, obesity, renal insufficiency, hyperhomocysteinaemia, raised C-reactive protein and a sedentary lifestyle.[3,4]

Intermittent claudication is not itself life-threatening, but it is estimated that 40–68% of affected individuals have coronary artery disease as well.[6] Patients with IC are at higher risk of cardiovascular mortality than patients with PAD who do not have claudication.[7] People with PAD are approximately two to three times more likely to suffer myocardial infarction (MI) or stroke than other people of their gender and age.[2,8] Risk of cardiovascular mortality is approximately the same in patients with PAD as for patients with coronary or cerebrovascular disease.[2] There is an increased risk of disease progression in patients with multilevel arterial involvement, low ankle–brachial pressure index (ABPI), chronic renal insufficiency or diabetes mellitus.[8] Few patients with IC progress to critical limb ischaemia.[3] Fewer than 5% of patients per 5 years deteriorate to a level requiring peripheral arterial endovascular treatments or surgery.[9]

Epidemiology and prevalence

The annual incidence of PAD is difficult to measure[3] and has not been quantitated in any documentation identified. It has been estimated (Edinburgh Artery Study[10]) that approximately 20% of people aged from 55 to 75 years have evidence of PAD in the legs, and the prevalence of IC in this age group has been estimated as 4.5%. Prevalence of PAD increases with age, from around 2% at age 55 years to around 7% at age 74 years.[3] In younger age groups, IC is more common in men than in women, but in older age groups prevalence of IC is similar in both genders.[3] The prevalence of IC also increases with lower social class[10] and PAD has a higher prevalence in people of black ethnicity than white ethnicity.[3]

Impact of health problem

Significance for patients in terms of ill health (burden of disease)

Patients with IC, by definition, suffer pain only during physical activity. However, this has wide-ranging effects on their health status, daily living and quality of life. Within studies of patients with IC whose health status was assessed with the Short Form questionnaire-36 items (SF-36), this population had significantly worse scores than published norms across all domains, i.e. physical and social function, physical and emotional role, vitality, bodily pain, general health and mental health.[11,12] This translates into quality-of-life detriments [as measured by the World Health Organization Quality of Life (WHOQoL) instrument], affecting overall health, social relationships, levels of independence, opportunities for acquiring new information and skills, and recreation and leisure.[12]

Significance for the NHS

Patients with IC may require treatment in primary or secondary care. It is estimated from population-based studies that around only 50–90% of patients with IC present for medical attention,[3] as a large proportion of people assume it is a natural part of ageing. Although PAD is a chronic disease, only around one-quarter of patients with IC will ever significantly deteriorate. Therefore, for the majority of patients, the burden on the NHS is in terms of the initial diagnosis and treatment aimed at reducing the risk from cardiovascular events. This includes smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Antiplatelet and statin therapy may be given as long-term prophylaxis against MI and stroke. The management of claudication symptoms includes the recommendation to exercise and may include vasoactive drugs. For patients with severe disability or deteriorating symptoms, further evaluation with imaging (with magnetic resonance angiography, computerised tomography angiography, duplex ultrasound or conventional arteriography) is required within secondary care to assess the potential for treatment with angioplasty or bypass surgery. Around 1–3.3% of patients with IC will need major amputation over a 5-year period.[3]

Measurement of disease

Not all patients with PAD will experience classic claudication symptoms and it is estimated that the ratio of symptomatic to asymptomatic patients is in the range of 1 : 3 to 1 : 4.[3] Often, patients will not know they have the disease until they have a heart attack or stroke. Equally, not all claudication pain is caused by PAD, and diseases such as deep vein thrombosis, hip, foot or ankle arthritis, sciatica and spinal stenosis (narrowing of the spinal canal) can cause similar symptoms.[3] Those with exercise-induced lower limb pain should undergo investigations to confirm that the cause is PAD. The patient's ABPI can be measured. This is done using a sphygmomanometer cuff and a Doppler (ultrasound) instrument to measure the pressure of arteries in the arm and ankle. Diagnostic criteria vary, but the recent UK primary care guidelines[13] consider a ABPI of 0.9 as confirmation of PAD. For those with ABPI between 0.91 and 1.30 and classic PAD symptoms, referral to hospital for exercise ABPI testing or other investigations is recommended. Although PAD is usually indicated by an ABPI below the normal value of 1, a high ABPI may also indicate

PAD because concomitant calcification of the vessels can elevate the ABPI. As such, patients with an ABPI of > 1.3 should be referred to a vascular specialist for assessment. When the ABPI indicates PAD, this does not rule out the possibility that coexisting conditions, such as arthritis and spinal stenosis, may be contributing to the patient's pain.

For the purposes of publications and clinical trials, claudication pain is often classified according to the Fontaine Classification,[1] as described above, or by the Rutherford Classification[14] (*Table 1*). Both of these classifications use pain-free walking distance (PFWD) to stage the disease. Maximal walking distance (MWD) and PFWD are usually assessed with the use of a graded treadmill test.[3] In primary care, the use of treadmills is not considered practical,[15] and, instead, a clinical diagnosis of IC (Fontaine stage II: mild, moderate or severe claudication by the Rutherford scale) may be simplified to the presence of pain upon exercise.[13] The Edinburgh Claudication Questionnaire[16] is a sensitive tool for identifying those with symptomatic IC. It asks patients to indicate the type, location and pattern of pain upon walking and during rest to assess whether or not their pain is consistent with a diagnosis of IC. Classical IC symptoms are the presence of reproducible leg muscle pain on exercise which is relieved by rest within 10 minutes.[17] Pain usually occurs in the calf, as the reduced blood supply is only adequate to serve the buttock and thigh, although, rarely, pain can occur in the buttocks and thigh and even more rarely in the foot. In those with no pain, walking impairment may still occur.[3]

To ensure that the pain is from claudication due to PAD, a PAD diagnosis should be confirmed by assessment of the patient's peripheral pulses and measuring the ABPIs at rest.

Maximal walking distance (also known as *absolute claudication distance*) is a measure of how far a patient can walk before IC no longer allows walking. PFWD (also known as *initial claudication distance*) is a measure of distance walked before IC causes pain. The European Medicines Agency (EMA) recommends treadmill tests to assess claudication distances.[18] The EMA specifies two internationally recognised treadmill protocols:[18] constant-workload treadmill protocols involve the treadmill being set at a fixed slope at a fixed speed;[18] graded test treadmill protocols (also known as variable load or progressive workloads) involve the treadmill being set at a fixed speed with the slope being increased by a pre-set amount at regular intervals.[18] Both of these types of test are valid but they are not interchangeable, i.e. trials should use the same protocol throughout.[18]

TABLE 1 The Fontaine Classification for chronic critical limb ischaemia[a]

Fontaine		Rutherford		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIa	IC, PFWD > 200 m	I	1	Mild claudication, completion of treadmill test, after-exercise ABPI > 50 mmHg and < 20 mmHg lower than resting value
IIb	IC, PFWD < 200 m		2	Moderate claudication, in between categories 1 and 3
			3	Severe claudication, cannot complete standard treadmill exercise, with after-exercise ABPI < 50 mmHg
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
			6	Major tissue loss

a Adapted from Norgren *et al.*[3]

Current service provision

Management of disease

Treatment within England and Wales is variable and there is limited published evidence of current practice. Patients may present with IC to primary or secondary care and a number of interventions are used for the conventional management of IC. Treatment is targeted at reducing the risk from cardiovascular events, such as smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Antiplatelet and statin therapy may be given as a long-term prophylaxis against MI and stroke. The management of claudication symptoms includes the recommendation to exercise. Supervised exercise programmes are the most effective form of exercise therapy,[19] but are not generally available across England and Wales. The vasoactive drugs being assessed within this report may also be used for the management of symptoms, although current usage is variable. For patients with severe disability or deteriorating symptoms, further evaluation with imaging is usually performed to assess the potential for treatment with angioplasty or bypass surgery.

Vasoactive drugs for PAD can be provided within both primary and secondary care. Provision does not usually require additional management, as these drugs would be provided alongside a range of other treatments for PAD. Their use is generally for symptom relief only and does not impact upon disease progression. Therefore, the burden upon the NHS is generally in terms of the drug acquisition cost only. Within England and Wales these drugs are generally available to be prescribed to patients with IC, although there may be restrictions to their use due to local policies (Steven Thomas, Jonathan Michaels and Gerard Stansby, University of Sheffield, September 2010, personal communication).

Clinical practice is variable between clinicians for prescribing vasoactive drugs for IC patients whose symptoms continue despite a period of conservative management. Some clinicians will assess whether or not angioplasty is appropriate within this patient group and, if so, undertake this immediately. If angioplasty either is not appropriate or fails, then those patients may receive vasoactive drugs. Alternative practice is for patients with IC to be offered vasoactive drugs whether or not they may be considered for angioplasty. If the drugs are unsuccessful, patients may then be considered for angioplasty if this is an appropriate option, but, if successful, vasoactive drugs for PAD may negate or delay the need for angioplasty.

Relevant national guidelines, including National Service Frameworks

Within England and Wales there is currently no guidance around the use of the vasoactive drugs considered in this report for PAD. The development of National Institute for Health and Clinical Excellence (NICE) guidance is currently under way regarding the diagnosis and management of lower limb PAD in adults; this is due to be published in October 2012.[20] NICE guidance has also been developed for clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal guidance No. 90),[21] within which patients with PAD are considered as a subgroup.

The Scottish Intercollegiate Guidelines Network (SIGN) has developed and published guidelines around the diagnosis and management of PAD within Scotland.[2] This recommends that patients with IC, in particular over a short distance, should be considered for treatment with cilostazol (Pletal®, Otsuka Pharmaceuticals). If cilostazol is ineffective after 3 months, or if adverse effects prevent compliance with therapy, the drug should be stopped. It also recommends that patients with IC and a poor quality of life may be considered for treatment with naftidrofuryl oxalate (Praxilene®, Merk Serono).

Description of technology under assessment

Summary of intervention

Four vasoactive drugs for IC are considered within this review. All are pharmacological agents for the symptomatic relief of IC secondary to PAD. Once a patient's diagnosis of both IC and PAD have been confirmed, treatment is twofold, namely management of associated cardiovascular risk factors and symptomatic relief. Symptomatic relief is addressed through exercise and lifestyle advice, and, where this is not effective, pharmacological agents may be used. Where pharmacological agents are effective, they are likely to be administered for the lifetime of the patient or until symptoms worsen and require surgery.

The four vasoactive drugs for PAD are as follows.

Cilostazol

- *Brand name, manufacturer* Pletal®, Otsuka Pharmaceuticals.[22]
- *Other manufacturers* None.
- *Therapeutic classification* Phosphodiesterase III inhibitor, which acts as a direct arterial vasodilator and also inhibits platelet aggregation.[23]
- *Dosage, length of treatment and route* Oral, at a dose of 100 mg twice daily (200 mg daily dose), 30 minutes before or 2 hours after food. Treatment for 16–24 weeks can result in a significant improvement in walking distance. Some benefit may be observed following treatment for 4–12 weeks.
- *Licensed indications* Cilostazol has a UK marketing authorisation for the improvement of the MWD and PFWD in patients with IC who do not have rest pain and who do not have evidence of peripheral tissue necrosis (PAD Fontaine stage II).[22]
- *Contraindications* Known hypersensitivity to cilostazol or to any of the excipients; severe renal impairment – creatinine clearance of 25 ml/minute; moderate or severe hepatic impairment; congestive heart failure (CHF); pregnancy; any known predisposition to bleeding [e.g. active peptic ulceration, recent (within 6 months) haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension]; with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and prolongation of the QTc interval.[22]
- *Warnings* Patients should be warned to report any episode of bleeding or easy bruising while on therapy. It is possible that an increased bleeding risk occurs in combination with surgery. There have been rare or very rare reports of haematological abnormalities. Caution is advised when cilostazol is co-administered with inhibitors or inducers of Cytochrom P enzymes CYP3A4 and CYP2C19 or with CYP3A4 substrates, when prescribing cilostazol along with any other agent that has the potential to reduce blood pressure for patients with atrial/ventricular ectopy and patients with atrial fibrillation or flutter or when co-administering cilostazol with any other agents that inhibit platelet aggregation. See the *Summary of Product Characteristics*[22] for further details.

Naftidrofuryl oxalate

- *Brand name, manufacturer* (Praxilene®, Merk Serono).[2]
- *Other manufacturers* Actavis UK, Kent Pharmaceuticals, Mylan, Teva UK.[24]
- *Therapeutic classification* Peripheral vasodilator that selectively blocks vascular and platelet 5-hydroxytryptamine (5-HT2) receptors.[23]
- *Dosage, length of treatment and route* Oral, one or two 100-mg capsules three times daily (300 mg or 600 mg daily dose) for a minimum of 3 months or at the discretion of the physician.[22]

- *Licensed indications* Naftidrofuryl oxalate has a UK marketing authorisation for peripheral vascular disorders including IC.[22]
- *Indications not included in this review* Peripheral vascular disorders – night cramps, rest pain, incipient gangrene, trophic ulcers, Raynaud's syndrome, diabetic arteriopathy and acrocyanosis; cerebral vascular disorders – cerebral insufficiency and cerebral atherosclerosis, particularly where these manifest themselves as mental deterioration and confusion in the elderly.[22]
- *Contraindications* Hypersensitivity to the drug. Patients with a history of hyperoxaluria or recurrent calcium-containing stones.[22]
- *Warnings* A sufficient amount of liquid should be taken during treatment to maintain an adequate level of diuresis.[22]

Pentoxifylline

- *Brand name, manufacturer* Trental 400®, Sanofi-aventis.[22]
- *Other manufacturers* Apotex UK.[24]
- *Therapeutic classification* Peripheral vasodilator, which is derived from methylxanthine.[23]
- *Dosage, length of treatment and route* Recommended initial dose, one tablet (400 mg) three times daily (1200 mg daily dose); two tablets daily may prove sufficient in some patients (800 mg daily dose), particularly for maintenance therapy. Tablets should be taken with or immediately after meals, and swallowed whole with plenty of water. In patients with impairment of renal function (creatinine clearance < 30 ml/minute), a dose reduction by approximately 30–50% may be necessary, guided by individual tolerance.[22]
- *Licensed indications* UK marketing authorisation for the treatment of PAD, including IC and rest pain.[22]
- *Contraindications:* Not suitable for children; known hypersensitivity to the active constituent, pentoxifylline other methylxanthines or any of the excipients; patients with cerebral haemorrhage, extensive retinal haemorrhage, acute MI and severe cardiac arrhythmias.[22]
- *Warnings* Use with caution in patients with hypotension or severe coronary artery disease, and particularly careful monitoring is required in patients with impaired renal function. See the *Summary of Product Characteristics*[22] for further details.

Inositol nicotinate

- *Brand name, manufacturer* Hexopal®, Genus Pharmaceuticals.[22]
- *Other manufacturers* Mylan.[24]
- *Therapeutic classification* Peripheral vasodilator thought to work by slowing the release of nicotinic acid.[23]
- *Dosage, length of treatment and route* The usual dose is two 500-mg tablets three times daily (3 g daily dose). The dose may be increased to 4 g daily if necessary.
- *Licensed indications* UK marketing authorisation for the symptomatic relief of severe IC.
- *Indications not included in the review* Raynaud's phenomenon.
- *Contraindications* Recent MI or acute phase of a cerebrovascular accident; hypersensitivity to ingredients.
- *Warnings* Use with caution in the presence of cerebrovascular insufficiency or unstable angina.

Identification of important subgroups

No specific subgroups have been identified for consideration within the effectiveness review. However, there is a subgroup of patients with more severe IC who may be more likely to be

offered angioplasty. If effective, these drugs may prevent the need for angioplasty for some patients within this small subgroup. This would impact upon cost-effectiveness and hence an exploratory subgroup analysis is undertaken within the cost-effectiveness analysis.

Current usage in the NHS

Within England and Wales the vasoactive drugs being assessed within this report are generally available for prescribing to patients with IC. However, there may be restrictions to their use due to local policies (Steven Thomas, Jonathan Michaels and Gerard Stansby, personal communication). The only evidence available around current usage of the vasoactive drugs for PAD within England and Wales is the *Prescription Costs Analysis England 2009*,[25] from which it is estimated that the proportionate market shares for cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate are 29%, 52%, 4% and 15%, respectively.

Anticipated costs associated with intervention

As described in *Current service provision*, the only additional costs associated with the vasoactive drugs compared with no vasoactive drugs for PAD are the acquisition costs. These are shown in *Table 2*.[26] Where there is more than one licensed dose available, the cost of the drug was based upon the doses used within the randomised controlled trials (RCTs) identified within the clinical effectiveness review. Naftidrofuryl oxalate is available both as a generic drug, at a lower price, and as Praxilene by the original patent-holder.

TABLE 2 Cost of drugs

Drug	Licensed dose	Dose used for estimating costs (mg/day)	Quantity	Drug specification (manufacturer)	Price (£)	Weekly costs (£)
Cilostazol	100 mg twice daily (30 minutes before or 2 hours after food), i.e. 200 mg per day	200	56	100-mg tablets (Pletal)	35.31	8.83
Naftidrofuryl oxalate	100–200 mg three times daily, i.e. 300 mg or 600 mg per day	600	84	100-mg capsules (generic)	4.52	2.26
			100	100-mg capsules (Praxilene)	9.83	4.13
Pentoxifylline	400 mg two to three times daily, i.e. 800 mg or 1200 mg per day	1200	90	400-mg tablets (Trental 400)	19.68	4.59
Inositol nicotinate	3 g daily in two or three divided doses; maximum 4 g daily (tablets 500 mg or 750 mg)	4000	100	500-mg tablets (Hexopal)	30.76	17.23

Chapter 2

Definition of the decision problem

This review will assess the clinical effectiveness and cost-effectiveness of vasoactive drugs for the treatment of IC due to PAD in adults whose symptoms continue despite a period of conservative management. Conventional management usually involves 3–6 months of conservative treatment that would consist of risk modification, usually with a statin, aspirin, smoking cessation advice and advice to exercise (Steven Thomas, Jonathan Michaels and Gerard Stansby, University of Sheffield, July 2010, personal communication).

Decision problem

The decision problem has been specified as follows.

Interventions

- Cilostazol (Pletal).
- Naftidrofuryl oxalate (Praxilene/generic).
- Pentoxifylline (Trental 400).
- Inositol nicotinate (Hexopal).

Population

The population will include people with IC due to PAD whose symptoms continue despite a period of conservative management. No relevant subgroups have been identified for consideration within the review; however, an exploratory analysis around a subgroup of patients with more severe IC who may receive angioplasty was carried out within the economic model. Subgroups of CVD risk factor would have been considered if data were available.

Relevant comparators

The vasoactive drugs will be compared with each other and with no vasoactive drugs.

Outcomes

- Maximal walking distance.
- Pain-free walking distance.
- Ankle–brachial pressure index.
- Vascular events (including interventions and requirement of hospitalisation).
- Mortality.
- Adverse effects of treatment.
- Health-related quality of life.

Overall aims and objectives of assessment

The review has the following aims:

1. to evaluate the clinical effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of IC due to PAD in adults whose symptoms continue despite a period of conservative management
2. to evaluate the adverse effect profile of the vasoactive drugs for PAD
3. to estimate the incremental cost-effectiveness of the vasoactive drugs for PAD
4. to identify key areas for primary research
5. to estimate the possible overall cost in England and Wales for vasoactive drugs for PAD.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of IC in people with PAD.

The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

The following databases were searched for published trials and systematic reviews:

- MEDLINE: Ovid, 1950 to present
- MEDLINE In-Process & Other Non-Indexed Citations: Ovid, 1950 to present
- EMBASE: Ovid, 1980 to present
- The Cochrane Library: Wiley Interscience
  - Cochrane Database of Systematic Reviews (CDSR), 1996 to present
  - Database of Abstracts of Reviews of Effects (DARE), 1995 to present
  - Cochrane Central Register of Controlled Trials (CCRCT), 1995 to present
  - Cochrane Methodology Register, 1904 to present
  - Health Technology Assessment Database (HTA), 1995 to present
  - NHS Economic Evaluation Database (NHS EED), 1995 to present
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): EBSCO, 1982 to present
- Web of Knowledge Science Citation Index, 1899 to present
- Conference Proceedings Citation Index (CPCI): Web of Knowledge, 1990 to present
- BIOSIS Previews: Web of Knowledge, 1969 to present.

Additional searches were carried out for unpublished studies (e.g. ongoing, completed):

- The National Research Register (NRR): NIHR, 2000–7
- The metaRegister of Controlled Trials (*m*RCT): Springer Science+Business Media, 2000 to present.

Industry submissions, as well as any relevant systematic reviews, were also hand searched in order to identify any further clinical trials.

The MEDLINE search strategy is presented in *Appendix 1*. The search strategies were translated across all databases. No date (from the start of database coverage date to present) or language restrictions were applied to all searches. Literature searches were conducted from

April to June 2010. References were collected in a bibliographic management database, and duplicates removed.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria were taken from the scope provided by NICE,[23] outlined below.

Interventions

The following vasoactive drugs were included if administered within their licensed indications:

- cilostazol
- naftidrofuryl oxalate
- pentoxifylline
- inositol nicotinate.

Population

- People with IC due to PAD, whose symptoms continue despite a period of conservative management.

Comparators

- Placebo.
- Usual care of PAD without vasoactive drugs.
- Vasoactive drugs compared with each other.

Outcomes

- Maximal walking distance.
- Pain-free walking distance.
- Ankle–brachial pressure index.
- Cardiovascular events (including interventions and requirement of hospitalisation).
- Mortality.
- Adverse effects of treatment.
- Health-related quality of life.

Study types

Randomised controlled trials were included. Data from non-randomised studies were not included, as evidence for relevant populations and outcomes was available from RCTs.

Systematic reviews were included if they provided additional data for RCTs meeting the inclusion criteria (i.e. unavailable from published trial reports). Other systematic reviews identified were not included but were checked for RCTs that met the inclusion criteria of this review.

Exclusion criteria

Studies based on animal models; preclinical and biological studies; editorials, opinion pieces; reports published as meeting abstracts only, where insufficient details were reported to allow inclusion; studies only published in languages other than English; studies with vasoactive drugs not within their licensed indications; studies in which the population was not restricted to Fontaine stage II, unless data for just this population were presented; and studies that did not present data for the included outcomes.

Studies retrieved for full-paper screening that were excluded are listed in *Appendix 2* with reasons for exclusion. Based on the above inclusion/exclusion criteria, study selection was conducted by one reviewer, with involvement of a clinical advisor when necessary.

Data abstraction and critical appraisal strategy

Data were extracted with no blinding to authors or journal. Quality relating to study design was assessed according to criteria based on NHS Centre for Reviews and Dissemination (CRD) Report No. 4,[27] and quality relating to studies of PAD was assessed according to criteria developed by EMA.[27] The quality assessment forms are shown in *Appendix 3*. The purpose of such quality assessment was to provide a narrative account of trial quality for the reader. Data were extracted by one reviewer using a standardised form, shown in *Appendix 4*, and checked by a second reviewer.

Data synthesis methods

Prespecified outcomes were tabulated and discussed within a descriptive synthesis. MWD and PFWD were synthesised across studies using meta-analysis models. Separate analyses were conducted for the evaluation of cilostazol on MWD, based on the studies described in the Cochrane review by Robless *et al.*,[28] and for MWD and PFWD for all studies that formed a network of evidence.

The analyses used a random effects model (to allow for heterogeneity in treatment effect across studies) implemented using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK);[29] details of the statistical model are described in *Appendix 5*. The summary statistics that were analysed were the absolute mean change from baseline in MWD compared with week 24 for studies included in the Cochrane review,[28] the logarithm (log) of the geometric mean change from baseline in MWD compared with week 24, and the log of the geometric mean change from baseline in PFWD compared with week 24.

Individual studies generally reported treatment effects in terms of the ratio of the geometric mean change from baseline. Taking the log of the geometric means meant that the transformed sample statistics were additive on the log scale. Studies that reported results only in terms of the arithmetic mean change from baseline were not transformed to the log scale because taking the log of arithmetic means does not produce additive results on the log scale.

Results were reported in terms of the mean difference and 95% credible interval for the mean difference for each intervention relative to placebo. Finally, a random effects model places a random component on the treatment by study interaction term in the model and acknowledges the fact that the effect of treatment varies across studies. Therefore, the posterior mean of the between-study standard deviation (SD) together with the 95% credible interval is also presented.

Results

Quantity and quality of research available

Quantity of research available

The search for clinical effectiveness literature yielded 1867 article citations after duplicates had been removed. *Figure 1* shows study selection. Citations presenting purely economic analyses were not included in this chapter. Trials excluded at full-paper screening stage (see *Figure 1*) are shown in *Appendix 2*.

Twenty-six RCTs were identified that met the inclusion criteria for this review. There were 36 published articles describing these 26 RCTs (*Table 3*).

Four published systematic reviews[28,31–33] were included in this review, as they provided additional data from the included RCTs that were unavailable from the published trial reports. In addition,

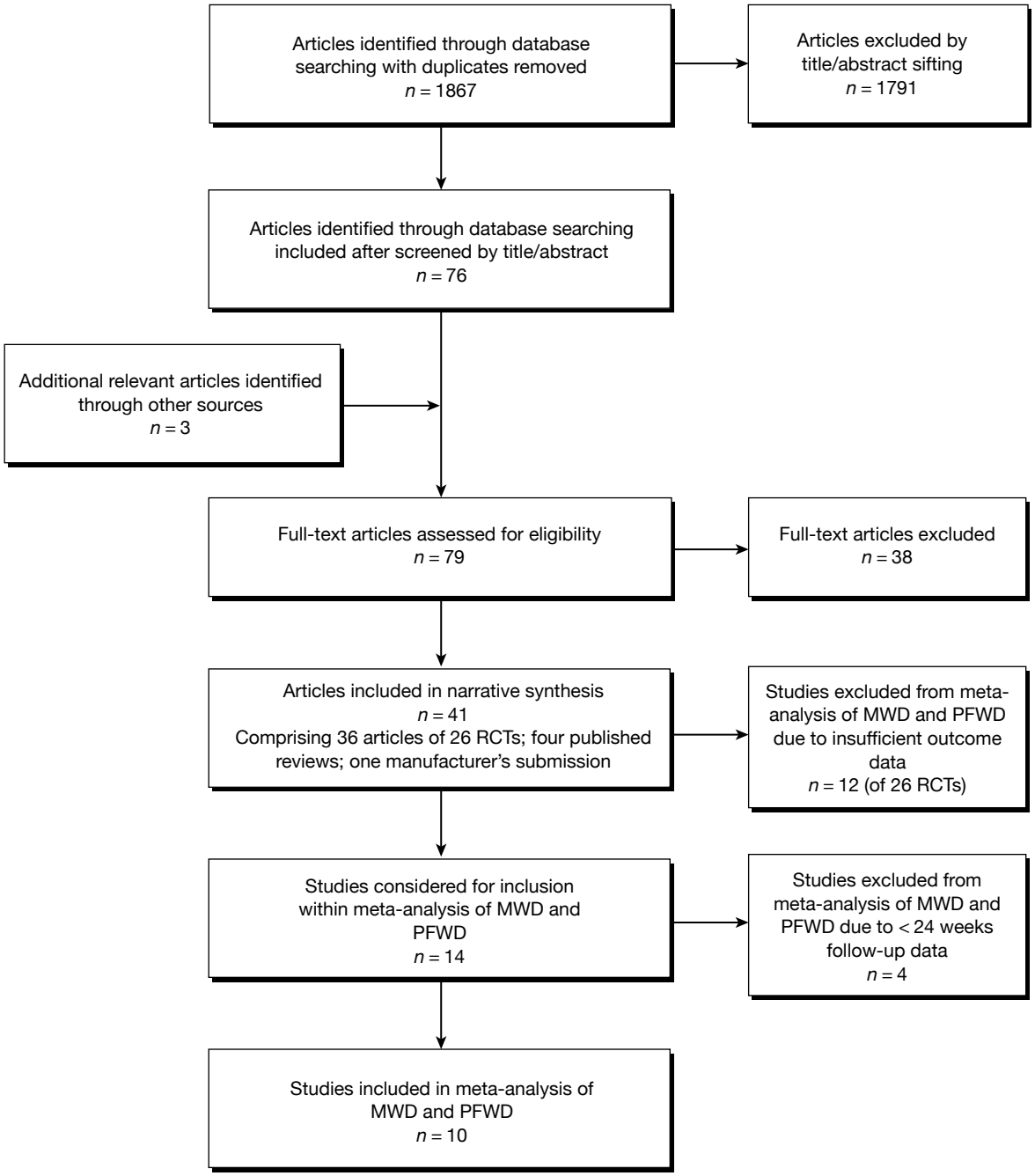

FIGURE 1 Flow diagram of study inclusion [adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[30])].

the manufacturer's submission to NICE of cilostazol[34] also provided additional data from the included RCTs which were not available in the trial reports.

Other published systematic reviews were not included in this review as they did not provide additional trial data, but they were checked for RCTs meeting the inclusion criteria of this review.[35–46] No additional RCTs were identified from these excluded reviews.

TABLE 3 Included studies

Trial name	Treatment group 1, daily dose	Treatment group 2, daily dose	Treatment group 3, daily dose	Treatment group 4	Groups not relevant to this review
CASTLE Hiatt 2008[48–50]	Cilostazol 200 mg	Placebo			
O'Donnell 2009[51,53–55,83]	Cilostazol 200 mg	Placebo			
Strandness 2002[56,57]	Cilostazol 200 mg	Placebo			Cilostazol 100-mg daily dose
Dawson 2000[58–60]	Cilostazol 200 mg	Placebo	Pentoxifylline 1200 mg		
Beebe 1999[61]	Cilostazol 200 mg	Placebo			Cilostazol 100-mg daily dose
Otsuka 21-94-301[34]	Cilostazol 200 mg	Placebo	Pentoxifylline 1200 mg		
Otsuka 21-98-213[34]	Cilostazol 200 mg	Placebo	Pentoxifylline 1200 mg		
Money 1998[62]	Cilostazol 200 mg	Placebo			
Dawson 1998[64]	Cilostazol 200 mg	Placebo			
Elam 1998[64]	Cilostazol 200 mg	Placebo			
Otsuka 21-95-201[34]	Cilostazol 200 mg	Placebo			Cilostazol 300 mg
Spengel 2002[47]	Naftidrofuryl oxalate 600 mg	Placebo			
Kieffer 2001[65]	Naftidrofuryl oxalate 600 mg	Placebo			
Adhoute 1986[66]	Naftidrofuryl oxalate 600 mg	Placebo			
Trubestein 1984[67]	Naftidrofuryl oxalate 600 mg	Placebo			
Ruckley 1978[68]	Naftidrofuryl oxalate 300 mg	Placebo			
Dettori 1989[69]	Pentoxifylline 1200 mg	Placebo			Acenocoumarol (dose adjusted according to INR) plus placebo; acenocoumarol plus pentoxifylline 1200 mg
Creager 2008[70]	Pentoxifylline 1200 mg	Placebo			Iloprost 100 µg plus placebo; iloprost 200 µg plus placebo; iloprost 300 µg plus placebo
Lindgarde 1989[71]	Pentoxifylline 1200 mg	Placebo			
Porter 1982, and Gillings 1987[72–75]	Pentoxifylline 1200 mg	Placebo			
Gallus 1985[76]	Pentoxifylline 1200 mg	Placebo			
Di Perri 1983[77]	Pentoxifylline 1200 mg	Placebo			
O'Hara 1988[78,79]	Inositol nicotinate 4 g	Placebo			
Kiff 1988[80]	Inositol nicotinate 4 g	Placebo			
Head 1986[81]	Inositol nicotinate 4 g	Placebo			
INEXACT Hobbs 2007[82]	Cilostazol 200 mg	Cilostazol 200 mg plus supervised exercise	Supervised exercise	Usual care	

INR, international normalised ratio.

Twenty-six RCTs[34,47–82] were included in this review. One of these was a pooled analysis of three RCTs, run as a study programme by Spengel *et al.*[47] The three individual RCTs were not considered separately. The included trials and their treatment groups are shown in *Table 3*. Eligibility criteria and baseline characteristics were similar across trials, with clinically diagnosed, stable IC, patients of both genders included, and age ranges within 35–86 years. Further details of these included trials, including baseline characteristics of the study population, outcome measures used, details of withdrawals and study results, are shown in *Appendix 4*.

Three of the included studies have not been published (to date) as trial reports: Otsuka 21-94-301; Otsuka 21-98-213; Otsuka 21-95-201. Information about these trials was available from three published reviews[28,31,33] and the manufacturer's submission to NICE.[34] Additional information on naftidrofuryl oxalate trials was available from one published systematic review.[32]

Placebo-controlled RCTs were available for all four of the vasoactive drugs for PAD assessed within this report. The only head-to-head comparison was that of cilostazol versus pentoxifylline. Studies with more than two trial arms provided data for more than one comparison.

The included studies provided data for the following comparisons:

- cilostazol 200 mg versus placebo (11 trials)
- naftidrofuryl oxalate 600 mg versus placebo (four trials)
- naftidrofuryl oxalate 300 mg versus placebo (one trial)
- pentoxifylline 1200 mg versus placebo (nine trials)
- inositol nicotinate 4 g versus placebo (three trials)
- cilostazol 200 mg versus pentoxifylline 1200 mg (three trials)
- cilostazol 200 mg (with or without supervised exercise) versus usual care (with or without supervised exercise) (one trial).

The number of patients and outcomes reported for these comparisons are shown in *Tables 4–10*. Treatment duration is also shown in these tables, and it can be seen that only two studies had a treatment duration of more than 24 weeks (CASTLE,[49] Dettori *et al.*[69]). The 11 trials comparing cilostazol versus placebo (see *Table 4*) were the same 11 trials included in the manufacturer's submission to NICE.[34]

The location of the trials and the number of participants from the UK are shown in *Table 11*. There are only six UK trials, including assessments of cilostazol (O'Donnell *et al.*[51,53–55,83] and Hobbs *et al.*[82]), naftidrofuryl oxalate (Ruckley *et al.*[68]) and inositol nicotinate (O'Hara *et al.*,[78,79] Kiff and Quick 1988[80] and Head 1986[81]). Most cilostazol studies took place in the USA, whereas studies of pentoxifylline and naftidrofuryl oxalate mostly took place in the USA and Europe.

Quality of research available

Details of the quality assessment scores for each trial are listed in *Appendix 3*. Across the four sets of studies, CRD items that relate to study quality (as listed in the tables in *Appendix 3*) were largely fulfilled. Treatment groups were generally comparable, blinding was usually maintained, intention-to-treat (ITT) analysis was usually undertaken, and at least 80% of participants were followed up in most cases. However, sequence generation and allocation concealment were poorly reported, and there may be some problems with imbalances between dropouts, as this was poorly reported. In some cases there is evidence of selective reporting of outcomes.

European Medicines Agency items were, however, less well adhered to. EMA items are specific to PAD and aim to minimise confounding factors. Criteria regarding diagnosis and length of having IC are included to avoid inclusion of patients who were misdiagnosed or have unstable

TABLE 4 Cilostazol 200 mg vs placebo

Trial	Treatment duration (weeks)	No. in analysis		Outcomes reported
		Cilostazol	Placebo	
CASTLE Hiatt 2008[49]	Up to 144	717	718	Mortality, cardiovascular events, AEs
O'Donnell 2009[51]	24	51	55	MWD, PFWD, AEs, HRQoL
Strandness 2002[56]	24	133	129	MWD, PFWD, mortality, cardiovascular events, AEs, HRQoL
Dawson 2000[58]	24	227	239	MWD, PFWD, ABPI, mortality, cardiovascular events, AEs, HRQoL
Beebe 1999[61]	24	175	170	MWD, PFWD, mortality, cardiovascular events, AEs, HRQoL
Otsuka 21-94-301[34]	24	123	124	MWD, PFWD, cardiovascular events, AEs
Otsuka 21-98-213[34]	24	260	260	MWD, PFWD, mortality, AEs
Money 1998[62]	16	119	120	MWD, PFWD, ABPI, mortality, cardiovascular events, AEs, HRQoL
Dawson 1998[63]	12	54	27	MWD, PFWD, mortality, cardiovascular events, AEs
Elam 1998[64]	12	95	94	MWD, PFWD, ABPI, mortality, cardiovascular events, AEs, HRQoL
Otsuka 21-95-201[34]	12	72	70	MWD, PFWD, mortality, AEs, HRQoL

AE, adverse event.

TABLE 5 Naftidrofuryl oxalate 600 mg vs placebo

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Naftidrofuryl oxalate	Placebo	
Spengel 2002[47]	24	382	372	PFWD, mortality, AEs, HRQoL
Kieffer 2001[65]	24	98	98	MWD, PFWD, ABPI, cardiovascular events, AEs
Adhoute 1986[66]	24	64	54	PFWD, ABPI, AEs
Trubestein 1984[67]	12	54	50	MWD, PFWD, AEs

AE, adverse event.

TABLE 6 Naftidrofuryl oxalate 300 mg vs placebo

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Naftidrofuryl oxalate	Placebo	
Ruckley 1978[68]	12	25	25	PFWD, AEs

AE, adverse event.

symptoms. These items were usually met, except in the case of inositol nicotinate. The EMA recommends that the treatment period should be a minimum of 24 weeks. Treatment period was a problem in some cases. The use of concomitant treatments was rarely reported and stratification for diabetes, as recommended by EMA, was rare. A placebo run-in period is also recommended, where all patients are given a placebo for between 2 and 6 weeks. The lack of placebo run-ins was an issue in studies of cilostazol and inositol nicotinate, but less problematic in studies of

TABLE 7 Pentoxifylline 1200 mg vs placebo

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Pentoxifylline	Placebo	
Dettori 1989[69]	52	37	37	PFW time, ABPI, mortality, cardiovascular events
Creager 2008[70]	24	86	84	MWD, PFWD, mortality, cardiovascular events, AEs, HRQoL
Dawson 2000[58]	24	232	239	MWD, PFWD, ABPI, mortality, cardiovascular events, AEs
Lindgarde 1989[71]	24	76	74	MWD, PFWD, AEs
Porter 1982[74]	24	67	61	MWD, PFWD, cardiovascular events that lead to withdrawal, AEs
Otsuka 21-94-301[34]	24	123	124	MWD, PFWD, cardiovascular events, AEs
Otsuka 21-98-213[34]	24	262	262	MWD, PFWD, mortality, AEs
Gallus 1985[76]	8	25	23	MWD, PFWD, mortality, cardiovascular events that lead to withdrawal
Di Perri 1983[77]	8	12	12	MWD

AE, adverse event; PFW, pain-free walking.

TABLE 8 Inositol nicotinate 4 g vs placebo

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Inositol nicotinate	Placebo	
O'Hara 1988[78]	12	62	58	PFW paces, mortality, cardiovascular events that lead to withdrawal, AEs that lead to withdrawal
Kiff 1988[80]	12	40	40	MWD, ABPI, cardiovascular events that lead to withdrawal, AEs that lead to withdrawal
Head 1986[81]	12	51	62	Time to claudication, cardiovascular events that lead to withdrawal, AEs that lead to withdrawal

AE, adverse event; PFW, pain-free walking.

TABLE 9 Cilostazol 200 mg vs pentoxifylline 1200 mg

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Cilostazol	Pentoxifylline	
Dawson 2000[58]	24	227	232	MWD, PFWD, ABPI, mortality, cardiovascular events, AEs
Otsuka 21-94-301[34]	24	123	123	MWD, PFWD, cardiovascular events, AEs
Otsuka 21-98-213[34]	24	260	260	MWD, PFWD, mortality, AEs

AE, adverse event.

TABLE 10 Cilostazol 200 mg (with or without supervised exercise) vs usual care (with or without supervised exercise)

Trial	Treatment duration (weeks)	No. in analysis		Outcomes
		Cilostazol	Usual care	
INEXACT Hobbs 2007[82]	24	16	18	MWD, PFWD

TABLE 11 Included studies, study location and number of participants from the UK

Trial name	Treatment and dose	Location	No. of participants from UK
CASTLE Hiatt 2008[48–50]	Cilostazol 200 mg	USA	0
O'Donnell 2009[51,53–55,83]	Cilostazol 200 mg	UK (Northern Ireland)	106
Strandness 2002[56,57]	Cilostazol 200 mg	USA	0
Dawson 2000[58–60]	Cilostazol 200 mg, pentoxifylline 1200 mg	USA	0
Beebe 1999[61]	Cilostazol 200 mg	USA	0
Otsuka 21-94-301[34]	Cilostazol 200 mg, pentoxifylline 1200mg	USA	0
Otsuka 21-98-213[34]	Cilostazol 200 mg, pentoxifylline 1200 mg	USA	0
Money 1998[62]	Cilostazol 200 mg	USA	0
Dawson 1998[63]	Cilostazol 200 mg	USA	0
Elam 1998[64]	Cilostazol 200 mg	USA	0
Otsuka 21-95-201[34]	Cilostazol 200 mg	USA	0
Spengel 2002[47]	Naftidrofuryl oxalate 600 mg	Germany, France, Belgium	0
INEXACT Hobbs 2007[82]	Cilostazol 200 mg, cilostazol 200 mg plus supervised exercise	UK	38
Kieffer 2001[65]	Naftidrofuryl oxalate 600 mg	USA	0
Adhoute 1986[66]	Naftidrofuryl oxalate 600 mg	France	0
Trubestein 1984[67]	Naftidrofuryl oxalate 600 mg	Germany	0
Ruckley 1978[68]	Naftidrofuryl oxalate 300 mg	UK	50
Dettori 1989[69]	Pentoxifylline 1200 mg	Italy	0
Creager 2008[70]	Pentoxifylline 1200 mg	USA	0
Lindgarde 1989[71]	Pentoxifylline 1200 mg	Sweden, Denmark	0
Porter 1982, Gillings 1987[72–75]	Pentoxifylline 1200 mg	USA	0
Gallus 1985[76]	Pentoxifylline 1200 mg	Australia	0
Di Perri 1983[77]	Pentoxifylline 1200 mg	Italy	0
O'Hara 1988[78,79]	Inositol nicotinate 4 g	UK	120
Kiff 1988[80]	Inositol nicotinate 4 g	UK	80
Head 1986[81]	Inositol nicotinate 4 g	UK	123

naftidrofuryl oxalate and pentoxifylline. Treadmill testing is the preferred method of assessing walking distances and should follow a standardised protocol. Treadmill use was widespread and usually standardised (although different protocols were used), except in studies of inositol nicotinate. Some patients exhibit highly variable walking distances, which might introduce unwanted noise in these data. The use of two treadmill tests separated by at least a week at baseline and the selection of patients with < 25% change in baseline is recommended by EMA to minimise the effect these types of patients may have on results. These items were adhered to only sometimes and may therefore introduce variability to these data.

Cilostazol

For CRD quality assessment items, studies scored well in most cases and for most items, with some exceptions. Sequence generation and allocation concealment both scored poorly across studies, with most studies failing to report on these items. Imbalances between dropouts was poorly reported (Elam *et al.*,[64] Dawson *et al.*,[63] Money *et al.*,[62] Hiatt *et al.*,[49] Otsuka 21-95-201[34] and Otsuka 21-94-301[34]) and may be a source of bias. There was some evidence of selective reporting in the Strandness *et al.*,[56] Elam *et al.*[64] and Dawson *et al.*[58] trials, as additional data were found in published systematic reviews. These were mostly AE data and have been incorporated in this review, but they highlight the possibility that there are additional unreported data. It is unclear how this may affect current estimates of the study outcomes. For EMA items, quality

was largely good, although there is potential for some problems, mainly due to poor reporting. Treatment duration varied between studies, with only the Strandness *et al.*,[56] Beebe *et al.*,[61] Hiatt *et al.*,[64] O'Donnell *et al.*,[51] Dawson *et al.*,[58] Otsuka 21-94-301[34] and Otsuka 21-98-213[34] trials treating patients for at least 24 weeks (this will not affect the meta-analysis, which considers only studies that treated patients for 24 weeks). The use of concomitant treatment was poorly reported, and studies did not generally state that they had stratified for diabetes. Less than half of the studies stated that only patients with a < 25% change in baseline walking distances were selected, and this may introduce unwanted variability to the results. However, there does not appear to be clinical evidence to suggest that these patients respond differently to treatment. A placebo run-in period was reported only by Dawson *et al.*[63] and Hiatt *et al.*[49] – for between 2 and 6 weeks in both cases. All studies reporting walking distance outcomes used a standardised treadmill test. There was, however, heterogeneity in tests between protocols, which is discussed elsewhere in this report.

Naftidrofuryl oxalate

Studies of naftidrofuryl oxalate scored moderately well overall for both CRD and EMA items. Items that scored poorly were sequence generation and allocation concealment, as most studies scored unclear for these items. Baseline characteristics may influence results, as Trubestein *et al.*[67] and Ruckley *et al.*[68] did not score positively according to CRD criteria in that the former had more smokers in the intervention group and the latter did not report baseline characteristics. It is unclear what effects this would have on results. For EMA items, more specific problems with patient characteristics were identified as follows: concomitant treatment was unclear in every case; the distribution of diabetics was stratified only in the Kieffer *et al.*[65] trial and proportions of diabetics are unknown for the Adhoute *et al.*,[66] Trubestein *et al.*[67] and Ruckley *et al.*[68] trials; only Kieffer *et al.*[65] and Adhoute *et al.*[66] selected patients with a < 25% change at baseline measurements. Other EMA items were generally well addressed.

Pentoxifylline

Overall, studies were of mixed quality and some items may impact on estimates of treatment effect. Among the CRD quality items, sequence generation and allocation concealment may present problems, with two-thirds of studies scoring unclear. Items that were of mixed quality included the use of an ITT analysis, follow-up of at least 80% of participants, imbalances between dropouts and selective reporting of outcomes. EMA items were also only partially fulfilled. Although diagnosis, history of condition and treatment duration were mostly good, other items were mixed. Among items relating to patient characteristics, it was largely unclear whether or not concomitant treatment was comparable across groups; there may have been imbalances in the numbers of diabetics, and patients may not have always been selected on the basis of having a < 25% change in baseline assessments. Outcomes may also have been affected by the lack of a 2- to 6-week placebo run-in.[34,38,58]

Inositol nicotinate

Overall, studies of inositol nicotinate scored well for most CRD quality assessment items but very poorly for the EMA items. This reflects the age of the studies and is likely to introduce a considerable degree of inaccuracy to the study findings. Among the CRD quality assessment items, methods of randomisation and treatment allocation were poorly reported in every case. Baseline characteristics were not similar in the study by Head.[81] All studies stated that they were double blind. An ITT analysis was provided in every case, and at least 80% of participants were followed up in the final analysis. Imbalances in dropouts were not reported or did not occur, and this seems unlikely to affect results. There is no evidence of selective reporting within the studies. Several EMA items scored poorly or were unclear. Only Kiff and Quick[80] stated that IC was objectively diagnosed, and only this same study stated that patients had a 6-month history of the condition. None of the studies treated patients for 24 weeks or longer, and it was unclear

in every case whether or not concomitant treatments were comparable across groups. Kiff and Quick[80] and Head[81] did not stratify for diabetes, and did not report how many were diabetic in each group. Although MWD and/or PFWD were reported in O'Hara *et al.*[78] and Head,[81] neither of these studies used a treadmill test, although the alternative walking distance tests used did follow a standard protocol.

Assessment of effectiveness

Results of the clinical effectiveness review are presented for each outcome, organised by comparison.

Maximal walking distance

Maximal walking distance narrative summary

Details of MWD results, where reported, are shown in *Tables 12–17* (from published trial reports) and *Appendix 4* (which includes details from reviews and the manufacturer's submission). Across trials, there was a tendency for all groups, including placebo groups, to show improvement with time. Of the 10 studies of cilostazol 200 mg versus placebo comparison, seven significantly favoured cilostazol over placebo,[56,58,61–64,83] whereas three trials (the three unpublished Otsuka trials[34]) did not find any significant difference between groups. As patient populations were similar across trials, in terms of disease, diabetes, hypertension, smoking and age range, these characteristics cannot explain any significant differences between treatment groups. Other issues of trial design were similar across trials: all were blinded, randomised and presented ITT analyses, and all measured baseline walking distance with two treadmill tests. As the graded test encourages longer walking distances than the constant-load protocol, absolute mean walking distance in metres is not directly comparable between protocols (see *Chapter 3*, *Measurement of disease*).[28] The use of the treadmill protocol (see *Appendix 4*) may go some way to explaining the presence of heterogeneity across trials. All three trials using the graded test treadmill protocol reported a significantly greater improvement in the cilostazol group than in the placebo group: Dawson *et al.*[58] at 24 weeks' follow-up ($p = 0.0005$), Money *et al.*[62] at 16 weeks' follow-up ($p < 0.05$) and Elam *et al.*[64] at 12 weeks' follow-up ($p = 0.004$). However, treadmill protocol does not explain why some trials report significant differences and others do not, as this differs between trials using the same treadmill protocol (the constant treadmill protocol). Trials with non-significant results do not have shorter follow-up or smaller sample sizes than trials with significant results.

Of the seven trials using the constant-workload treadmill protocol, four[56,61,63,83] reported a significantly greater improvement in the cilostazol group than in the placebo group, although for one of these trials[83] significance was only borderline; three of these had follow-up time of 24 weeks [O'Donnell *et al.*[83] ($p = 0.048$), Strandness *et al.*[56] ($p = 0.0003$), Beebe *et al.*[61] ($p < 0.001$)], and the fourth trial, Dawson *et al.*,[63] had a follow-up time of 12 weeks ($p < 0.01$). The three trials[34] that did not find any significant difference between groups used the constant-workload treadmill protocol, and two of these trials had follow-up times of 24 weeks (Otsuka 21-94-301, $p = 0.06$;[34] Otsuka 21-98-213, $p = 0.91$[34]), and the other had a follow-up time of 12 weeks (Otsuka 21-95-201, $p = 0.90$[34]). Lack of significant treatment effect cannot be explained by sample size, as these three trials did not have smaller sample sizes than the other trials (see *Appendix 4*).

The review by Pande *et al.*[31] included nine industry-sponsored trials, of which six trials (Otsuka trials[56,57,61–64]) found a significant difference between treatment groups, and three trials (the three trials without published trial reports) found no significant difference between cilostazol 200 mg and placebo groups (Otsuka trials 21–94–301, 21–98–213, 21–95–201 *et al.*[34]).[31] The Pande *et al.* review[31] presented a pooled analysis of these nine trials as a ratio of geometric means, and calculated an estimate of treatment effect[31] of 1.15 95% [confidence interval (CI) 1.11 to 1.19], which significantly favoured cilostazol over placebo.[31] This analysis[31] did not include the O'Donnell *et al.* trial,[51] which found a borderline significant treatment effect for the

TABLE 12 Cilostazol 200 mg vs placebo MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD (%)		Comparison between groups
		Cilostazol	Placebo		Cilostazol group	Placebo group	
O'Donnell 2009[51]	24	51	55	Constant	161.7 mean improvement	79 mean improvement	$p=0.048$
Strandness 2002[57]	24	133	129	Constant	Mean difference (m): 76.2 improvement	Mean difference (m): 21.1 improvement	$p=0.0003$
Dawson 2000[58]	24	227	239	Graded	Mean difference (m): 107 (SD 158) improvement	Mean difference (m): 65 (SD 135) improvement	$p=0.0005$
Beebe 1999[61]	24	175	170	Constant	Mean difference (m): 129.1 improvement	Mean difference (m): 26.8 improvement	$p<0.001$
Money 1998[62]	16	119	120	Graded	Mean difference (m): 96.4 improvement	Mean difference (m): 31.4 improvement	$p<0.05$
Dawson 1998[63]	12	54	27	Constant	30.5 improvement	–9.3 change (worsening)	$p<0.01$
Elam 1998[64]	12	95	94	Graded	Mean difference (m): 72.7 improvement	Mean difference (m): 25.8 improvement	$p=0.004$

TABLE 13 Naftidrofuryl oxalate 600 mg vs placebo MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Naftidrofuryl oxalate	Placebo		Naftidrofuryl oxalate group	Placebo group	
Kieffer 2001[65]	24	98	98	Constant	Mean difference (m): 158.7 improvement	Mean difference (m): 28.1 improvement	$p<0.001$
Trubestein 1984[67]	12	54	50	Constant	Mean difference (m): 122 improvement	Mean difference (m): 90 improvement	Non-significant

TABLE 14 Pentoxifylline 1200 mg vs placebo MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Pentoxifylline	Placebo		Pentoxifylline group	Placebo group	
Creager 2008[70]	24	86	84	Graded	13.90% improvement	3.30% improvement	$p=0.039$
Dawson 2000[58]	24	232	239	Graded	Mean difference (m): 64 improvement	Mean difference (m): 65 improvement	$p= 0.82$
Lindgarde 1989[71]	24	76	74	Constant	Geometric mean 50% improvement (SE 9)	Geometric mean 29% improvement (SE 8)	$p=0.094$
Porter 1982[73]	24	67	61	Constant	Geometric mean 33% improvement (SE 8)	Geometric mean 20% improvement (SE 7)	Two-sided $p=0.316$, one-sided $p=0.049$
Gallus 1985[76]	8	25	23	Constant	Geometric mean 23% improvement	Geometric mean 17% improvement	Ratio of per cent change from baseline (pentoxifylline/placebo) 1.05 (95% CI 0.81 to 1.36), non-significant

TABLE 14 Pentoxifylline 1200 mg vs placebo MWD *(continued)*

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Pentoxifylline	Placebo		Pentoxifylline group	Placebo group	
Di Perri 1983[77]	8	12	12	Not treadmill, horizontal ground	Mean difference (m): 136 improvement	Mean difference (m): 6 improvement	$p < 0.01$

SE, standard error.

TABLE 15 Cilostazol 200 mg vs pentoxifylline 1200 mg MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Cilostazol	Pentoxifylline		Cilostazol group	Pentoxifylline group	
Dawson 2000[58]	24	227	232	Graded	Mean difference (m): 107 (SD 158) improvement	Mean difference (m): 64 (SD 127) improvement	$p = 0.0002$

TABLE 16 Inositol nicotinate 4 g vs placebo MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Inositol nicotinate	Placebo		Cilostazol group	Pentoxifylline group	
Kiff 1988	12	40	40	Patient walked at own pace on a constant slope	Mean difference (m): 65.4 improvement	Mean difference (m): 102.8 improvement	Non-significant

TABLE 17 Cilostazol 200 mg (with or without supervised exercise) vs usual care (with or without supervised exercise) MWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in MWD		Comparison between groups
		Cilostazol	Usual care		Cilostazol group	Usual care group	
INEXACT Hobbs 2007[82]	24	16 (seven with exercise, nine without)	18 (nine with exercise, nine without)	Constant	Plus exercise mean ratio 2.58 (SD 1.39), without exercise mean ratio 1.69 (SD 0.59) improvement	Plus exercise mean ratio 1.45 (SD 0.80), without exercise mean ratio 1.09 (SD 0.34) improvement	Difference in effect 1.64 ($p = 0.005$)

whole trial population ($p = 0.048$) but found no significant difference between treatment groups when considering the subgroups of patients with diabetes ($p = 0.09$, $n = 26$)[53] or without diabetes ($p = 0.27$, $n = 80$),[83] which may reflect the small sample sizes rather than lack of actual treatment effect. The cilostazol versus placebo comparison trials that reported significant treatment effect for MWD generally also reported significant treatment effect for PFWD (see *Chapter 5*, *Pain-free walking distance*) and vice versa; however, there were a couple of exceptions in that the O'Donnell *et al.*[83] and Elam *et al.*[64] trials, found a significant treatment effect for MWD but did not find a significant treatment effect for PFWD.

Two trials for the naftidrofuryl oxalate 600 mg versus placebo comparison reported MWD; Kieffer *et al.*[65] reported significantly greater improvement for naftidrofuryl oxalate 600 mg versus placebo ($p < 0.001$), and Trubestein *et al.*[67] found no significant difference between groups. It may be that this difference could be explained in terms of length of follow-up, in that Kieffer *et al.*[65] had a follow-up of 24 weeks, whereas Trubestein *et al.*[67] had a follow-up of 12 weeks. These trials both used the constant-workload treadmill protocol and designs were similar in terms of having a placebo run-in, being randomised, presenting ITT analyses, measuring baseline walking distance with two tests and being blinded. There was little difference between these two trials in baseline MWD (see *Appendix 4*). However, both naftidrofuryl oxalate trials (Kieffer *et al.*,[65] Trubestein *et al.*[67]) had higher baseline MWD than the cilostazol trials that used the constant workload treadmill protocol (Strandness *et al.*,[57] Beebe *et al.*,[61] Dawson *et al.*,[63] O'Donnell *et al.*,[51] Otuska trials 21–94–301, 21–98–213, 21–95–201) (see *Appendix 4*).[34,83] The Kieffer[65] trial found a significant treatment effect for PFWD (see *Chapter 5*, *Pain-free walking distance*) as well as for MWD. However, the Trubestein *et al.*[67] trial, which had not found a significant treatment effect for MWD, did report a significant effect for PFWD favouring naftidrofuryl oxalate (see *Chapter 5*, *Pain-free walking distance*).

Of the eight trials[34,58,70,71,73,76,77] comparing pentoxifylline versus placebo in terms of MWD, two trials significantly favoured pentoxifylline over placebo: Creager *et al.* ($p = 0.039$)[70] and Di Perri *et al.* ($p < 0.01$).[77] Of these, the Di Perri[77] trial did not use a treadmill protocol, instead measuring the distance that a patient could walk on a horizontal level at metronome controlled speed of 120 steps per minute, with a follow-up at 8 weeks. The Creager *et al.* [70] trial used a graded treadmill test protocol, and found a significant effect on MWD at 24 weeks. Of the six trials finding no significant difference between groups for MWD, one of these used the graded test (Dawson *et al.*;[58] $p = 0.82$) and had a follow-up of 24 weeks. The five trials using the constant-workload treadmill protocol all found no statistically significant difference between pentoxifylline and placebo groups (Gallus *et al.*,[76] Lindgarde *et al.*,[71] Porter *et al.*,[73] Otsuka 21-98-213[34] and Otsuka 21-94-301[34]). Of these, the Gallus *et al.*[76] study had a follow-up of only 8 weeks [ratio of percentage change from baseline 1.05 (95% CI 0.81 to 1.36), which was non-significant], and the other studies had follow-up of 24 weeks: Lindgarde *et al.*[71] ($p = 0.09$), Porter *et al.*[73] (two-sided $p = 0.32$), Otsuka 21-98-213[34] ($p = 0.24$) and Otsuka 21-94-301[34] ($p = 0.29$). The pentoxifylline-versus-placebo comparison trials that reported significant treatment effect for MWD generally also reported significant treatment effect for PFWD (see *Chapter 5*, *Pain-free walking distance*) and vice versa; however, there were a couple of exceptions in that the Creager *et al.*[70] trial, which found a significant treatment effect for MWD, did not find a significant treatment effect for PFWD, and the Dawson *et al.*[58] trial did not find an effect for MWD but did find a treatment effect for PFWD (see *Chapter 5*, *Pain-free walking distance*).

For the comparison of inositol nicotinate 4 g versus placebo, only the Kiff and Quick trial[80] reported MWD. This trial found no significant difference between inositol nicotinate and placebo groups at 12 weeks for MWD measured by patients walking at their most comfortable speed on a treadmill set at a 10% gradient.[80]

Three trials reported MWD for the comparison of cilostazol versus pentoxifylline, all with 24 weeks' follow-up (Dawson *et al.*,[58] Otsuka 21-98-213[34] and Otsuka 21-94-301[34]). Two trials found no significant difference between the cilostazol and pentoxifylline groups (Otsuka 21-98-213,[34] $p = 0.65$; Otsuka 21-94-301,[34] $p = 0.87$), both using the constant-workload treadmill protocol. One trial (Dawson *et al.*[58]), which used the graded test treadmill protocol, found a significantly greater improvement in MWD ($p = 0.0002$) in the cilostazol group than in the pentoxifylline group.[58]

In the one trial (Hobbs *et al.*[82]) comparing cilostazol (with or without supervised exercise) versus usual care (with or without supervised exercise), all treatment groups improved, but there was significantly more improvement for cilostazol added to supervised exercise or usual care ($p = 0.005$).[82] This trial used the constant workload treadmill protocol and measured MWD at 24 weeks.

Maximal walking distance meta-analysis

The reanalysis of the cilostazol trials included within the Cochrane review[28] is presented in *Table 18*, in terms of change from baseline in absolute mean walking distance.

The posterior distribution of a parameter is a weighted compromise between the prior information and the sample data. In particular, if for some value of the likelihood function (expressing what is known about a parameter based on the sample data) the likelihood of that value is small, so that these data suggest that this value is implausible, then the posterior distribution will also give small probability to this value. Similarly, if for some value of the prior distribution (expressing what is known about a parameter in addition to the sample data) the prior probability of that value is small, so that the prior information suggests that this value is implausible, then, again, the posterior distribution will also give small probability to this value. In general, the posterior probability will be high for some value only when *both* information sources support that value. The posterior mean treatment effect for the cilostazol studies, together with the 95% credible interval, is shown in *Table 19*. *Table 19* also shows the posterior mean of the between-study SD, together with the 95% credible interval.

The random effects meta-analysis of the change from baseline in absolute mean walking distance showed that treatment with cilostazol resulted in an increase of 57.27 m (95% credible interval 24.93 to 86.57 m) compared with placebo.

TABLE 18 Change from baseline in absolute mean walking distance (m)[a]

Study	Placebo: mean (SD), *n*	Cilostazol: mean (SD), *n*
Dawson 1998[63]	4.56 (61.5,) 25	84.6 (144.94), 52
Elam 1998[64]	36.1 (141.55), 94	79.05 (134.5), 95
Money 1998[62]	47.1 (124.88), 120	101.1 (154.9), 119
Beebe 1999[61]	26.82 (148.5), 140	129.1 (463.3), 140
Dawson 2000[58]	64.7 (134.61), 226	107.36 (158.4), 205
Strandness 2002[56]	23.2 (78.26), 125	96.41 (200.44), 124
Otsuka 21-95-201[34]	38.1 (69.7), 60	35.2 (72.05), 54

a Based on cilostazol studies used in the Cochrane review by Robless *et al.*[28]

For the overall comparison of the treatment options, of the 26 studies identified by the systematic literature review, 12 studies were excluded from the meta-analysis of MWD for the reasons provided within *Table 20*.

The evidence base for the log of the geometric mean change from baseline in MWD and PFWD generates a network of trials comparing different pairs or triplets of treatments, as shown in *Figure 2*. The numbers within *Figure 2* represent the number of times that specific treatment arms are compared within studies.

The 10 studies (leading to 16 comparisons) included within the meta-analysis of MWD, represented in *Figure 2*, are the seven two-arm and three three-arm 24-week studies that are described in *Table 21*. Three 12-week studies[34,63,64] and one 16-week study[62] in which there were data on MWD available, as described in *Table 21*, were excluded from this analysis as the outcomes from these studies with a shorter follow-up period are not directly comparable.

Table 22 also shows the estimated treatment effect of cilostazol relative to placebo in the study by Money *et al.*,[62] for which individual arm data were not available. This study was excluded from the meta-analysis because of the 16-week follow-up.

TABLE 19 Posterior distribution for the difference from placebo in change from baseline absolute mean walking distance[a]

Treatment effect	Mean (95% credible interval)
Cilostazol random effects	57.27 (24.93 to 86.57)
Cilostazol predictive distribution	57.28 (–16.40 to 127.40)
Between-study SD	25.16 (1.46 to 72.75)

a Based on cilostazol studies used in the Cochrane review by Robless *et al.*[28]

TABLE 20 Additional studies excluded from the analysis of the change from baseline in log MWD

Study	Drug assessed	Reason for exclusion
Di Perri 1983[77]	Pentoxifylline	This study was excluded because it was an 8-week study
Gallus 1985[76]	Pentoxifylline	This study was excluded because it was an 8-week study
Head 1986[81]	Inositol nicotinate	This study was excluded because it was a 12-week study and provided no information on percentage change from baseline
Kiff 1988[80]	Inositol nicotinate	This study was excluded because it was a 12-week study and provided no information on percentage change from baseline
O'Hara 1988[78]	Inositol nicotinate	This study was excluded because it was a 12-week study and provided no information on MWD or PFWD
Detorri 1989[69]	Pentoxifylline	This study was excluded because MWD or PFWD was not collected in the study
Otsuka 21–98–214[48–50]	Cilostazol	This study provided no information on MWD or PFWD
Adhoute 1986[66]	Naftidrofuryl oxalate	This study provided no information on MWD and no PFWD data suitable for inclusion in the network meta-analysis
Trubestein 1984[67]	Naftidrofuryl oxalate	This study provided no information on percentage change from baseline in MWD or PFWD
Ruckley 1978[68]	Naftidrofuryl oxalate	This study was excluded because it was a comparison of naftidrofuryl oxalate 300 mg daily and provided no information on percentage change from baseline in MWD or PFWD
Spengel 2002[47]	Naftidrofuryl oxalate	This study provided no information on MWD and no information on PFWD by treadmill test; PFWD was presented as patient estimates
Hobbs 2007[82]	Cilostazol	This study used Best Medical Treatment as the comparator (may be alongside supervised exercise)

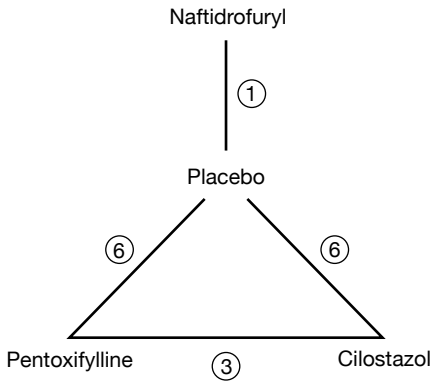

FIGURE 2 Network of evidence used in the analysis of the change from baseline in log mean walking distance (log m).

Goodness-of-fit was assessed by calculating the arm-specific and total residual deviance. The total residual deviance was 23.03, which compares favourably with the 23 data points being analysed. The arm-specific deviance terms were not indicative of any particular sample mean, being poorly represented by the model. The posterior mean treatment effect for these studies, together with the 95% credible interval, is shown in *Table 23*. *Table 23* also shows the posterior mean of the between-study SD, together with the 95% credible interval.

The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl oxalate had the greatest effect [60.3% = 1 – exp(0.472)] relative to placebo, followed by cilostazol (24.6%) and pentoxifylline (10.6%).

The 95% credible intervals suggest that treatment with naftidrofuryl oxalate and cilostazol produces real increases in the percentage change from baseline walking distance relative to placebo, although there was some uncertainty as to the true effect.

Table 24 gives a matrix of results from the network meta-analysis (see *Table 23*), where the upper right cells are the pair-wise posterior means (i.e. the direct effects) and the lower left cells are the network meta-analysis posterior means. Only four direct effects were estimable, and in three cases the mean results were essentially the same as the results from the network meta-analysis but with greater uncertainty, as expected. There was a greater difference in the results for the comparison between cilostazol and pentoxifylline, with the direct effect giving approximately 4% improvement in MWD in favour of cilostazol and the network meta-analysis result giving an approximately 11% improvement in favour of cilostazol, although there was considerable uncertainty as to the true effect based on the direct evidence alone.

There was moderate between-study variation, which suggests that the treatment effect varied depending on the characteristics of the study. The trial by Strandness *et al.*[56] had the largest observed effect of cilostazol compared with placebo (0.394) and the Otsuka 21-98-213[34] trial had the smallest observed cilostazol effect compared with placebo (0.016). The trial by Lindgarde *et al.*[71] had the largest observed pentoxifylline effect compared with placebo (0.190) and the trial by Dawson *et al.*[58] had the smallest observed pentoxifylline effect compared with placebo (–0.031).

Forest plots are shown in *Figure 3*.

Figure 3 suggests that the relative treatment effects are unrelated to the date of the study. Furthermore, of the trials used within the meta-analysis it is only some of the pentoxifylline trials

TABLE 21 Logarithm of the geometric mean change from baseline in MWD (log m)

Study	Placebo: mean (SD), *n*	Cilostazol: mean (SD), *n*	Pentoxifylline: mean (SD), *n*	Naftidrofuryl oxalate: mean (SD), *n*
[a,b]Dawson 1998[63]	–0.098 (0.847),[c] 25	0.266 (0.847),[c] 52		
[a,b]Elam 1998[64]	0.218 (0.438), 94	0.304 (0.438), 95		
[a,d]Money 1998[62]	NA[e] (0.358),[h] 120	NA[e] (0.358),[h] 119		
[a]Beebe 1999[61]	0.140 (0.464),[c] 140	0.412 (0.464),[c] 140		
[a]Strandness 2002[56]	0.184 (0.441), 125	0.578 (0.441), 124		
[a,b]Otsuka 21-95-201[34]	0.262 (0.396), 66	0.247 (0.396), 60		
[a]O'Donnell 2009[83]	0.582 (0.993),[f] 55	0.962 (0.993),[f] 51		
Porter 1982[72]	0.148 (NA), 61		0.285 (NA), 63	
Lindgarde 1989[71]	0.215 (0.608),[f] 74		0.405 (0.608),[f] 76	
Creager 2008[70]	0.032 (0.256),[f] 84		0.130 (0.256),[f] 86	
Kieffer 2001[65]	0.130 (NA), 92			0.603 (NA), 89
Dawson 2000[58]	0.293 (NA), 226	0.432 (NA), 205	0.262 (NA), 212	
[a]Otsuka 21-94-301[34]	0.351 (0.302),[g] 132	0.519 (0.302),[g] 123	0.501 (0.302), 118	
[a]Otsuka 21-98-213[34]	0.346 (0.226), 260	0.362 (0.226), 260	0.413 (0.226), 260	

NA, not available.
a Assumes common SD within study – SD derived from mean and CI for the difference between treatments in geometric mean change from baseline.
b Twelve-week study.
c Standard deviation derived from the mean and CI for the difference between treatments in geometric mean change from baseline taken from Pande 2010.[30]
d Sixteen-week study.
e Results available as a difference in treatment means (see *Table 22*).
f Standard deviation derived from the treatment mean changes from baseline and the *p*-value.
g Standard error derived from the mean and CI for the difference between treatments in geometric mean change from baseline – taken as the average of the estimates from the two comparisons.
h Standard error derived from the mean and CI for the difference between treatments in geometric mean change from baseline taken from Pande 2010.[31]

TABLE 22 Change from baseline in log mean walking distance (log m)

Study	Difference, cilostazol–placebo, mean (SE)
[a,b]Money 1998[62]	0.255 (0.045)[c]

SE, standard error.
a Assumes common SD within study – SD derived from mean and CI for the difference between treatments in geometric mean change from baseline.
b Sixteen-week study.
c Standard error derived from the mean and CI for the difference between treatments in geometric mean change from baseline, taken from Pande 2010.[31]

that pre-date the last 12 years. All trials of cilostazol and naftidrofuryl oxalate were published within the last 12 years.

The percentage change from baseline to 24 weeks in MWD, estimated by projecting the treatment effects from the network meta-analysis on to an estimated placebo response, is shown in *Table 25*.

Tables 26–28 give the results of five sensitivity analyses, which allow for more informative prior distributions for the between-study SD and treatment effects. *Tables 26* and *27* provide the results

TABLE 23 Posterior distribution for the difference from placebo in change from baseline log mean walking distance (log m)

Intervention	Treatment effect	Mean (95% credible interval)
Cilostazol	Random effects	0.220 (0.108 to 0.337)
	Predictive distribution	0.220 (–0.072 to 0.511)
Pentoxifylline	Random effects	0.101 (–0.016 to 0.217)
	Predictive distribution	0.101 (–0.195 to 0.383)
Naftidrofuryl oxalate	Random effects	0.472 (0.181 to 0.762)
	Predictive distribution	0.472 (0.087 to 0.865)
Between-study SD		0.125 (0.068 to 0.220)

TABLE 24 Matrix of results for the posterior distribution for the change from baseline in log mean walking distance (log m)

Intervention	Placebo (95% credible interval)	Cilostazol (95% credible interval)	Pentoxifylline (95% credible interval)	Naftidrofuryl oxalate (95% credible interval)
Placebo	–	0.222 (0.038 to 0.415)	0.096 (–0.001 to 0.195)	0.472[a] (–0.170 to 1.111)
Cilostazol	0.220 (0.108 to 0.337)	–	–0.045 (–0.889 to 0.790)	NA
Pentoxifylline	0.101 (–0.016 to 0.217)	–0.119 (–0.280 to 0.037)	–	NA
Naftidrofuryl oxalate	0.472 (0.181 to 0.762)	0.252 (–0.062 to 0.563)	0.371 (0.053 to 0.681)	–

NA, no direct estimate available.
a Based on one study; prior $\tau \sim U(0, 0.5)$; prior log(s) ~ $U(-1.0, -0.75)$ – no within-trial estimate of sampling variation available.
Default priors: $\mu_{\theta j} \sim N(0, 10{,}000)$; $\tau \sim U(0,10)$.

TABLE 25 Percentage change from baseline in MWD

Intervention	Mean (95% credible interval)
Placebo	27.6 (13.7 to 43.2)
Cilostazol	59.2 (35.4 to 87.1)
Pentoxifylline	41.4 (19.8 to 65.9)
Naftidrofuryl oxalate	106.7 (49.9 to 177.5)

of the sensitivity analyses for the placebo mean and the treatment effects relative to placebo, respectively, whereas *Table 28* provides the results for the between-study standard SD.

Table 26 shows that the placebo mean is insensitive to relatively informative prior distributions [i.e. sensitivity analysis 5 (SA5)] compared with the results based on weak prior distributions (i.e. SA1).

Table 27 shows that the treatment effects are insensitive to relatively informative prior distributions compared with the results based on weak prior distributions.

Table 28 shows that the between-study SD is relatively insensitive to more informative prior distributions than the results based on weak prior distributions, although the mean from SA5

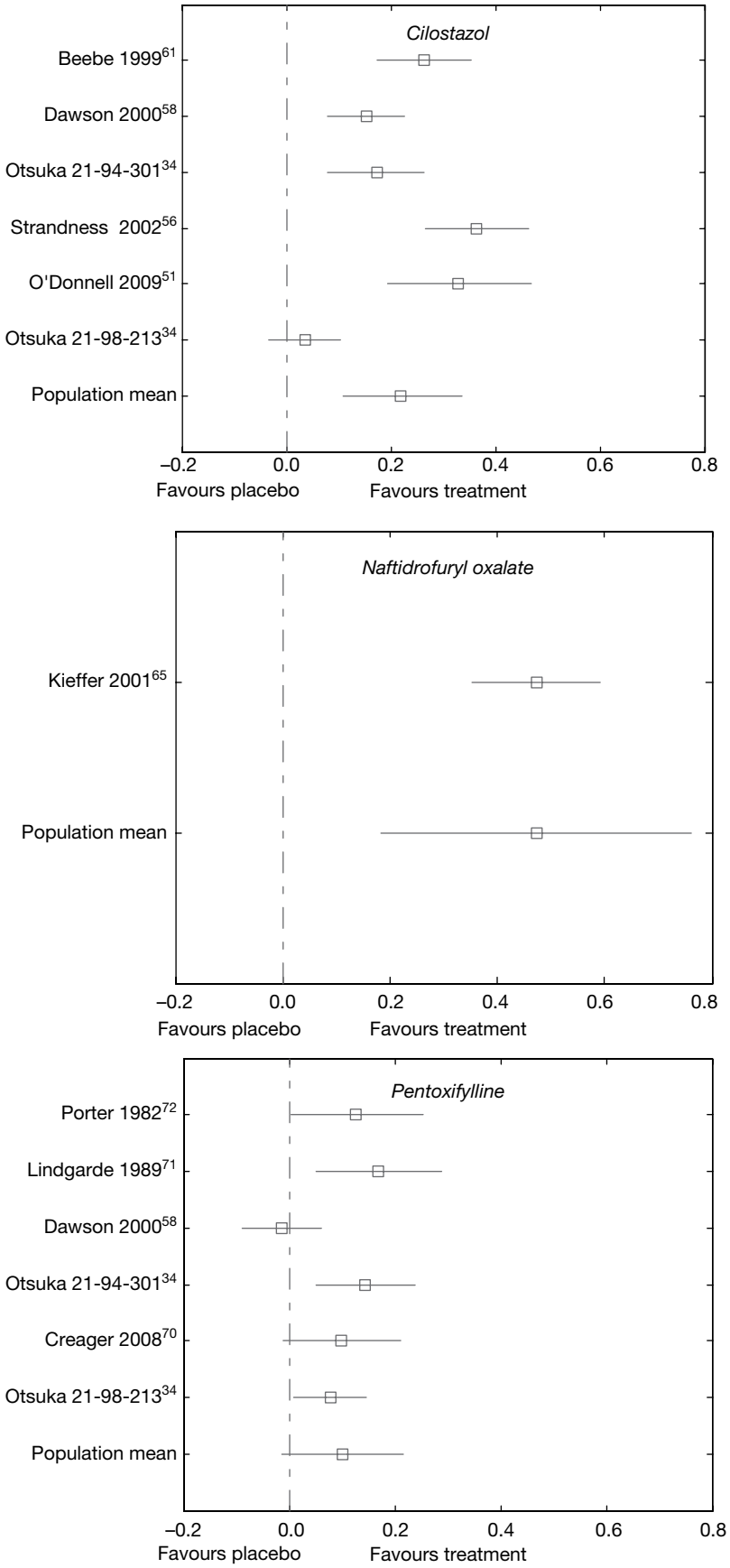

FIGURE 3 Posterior distribution for the change from baseline in log mean MWD for cilostazol, naftidrofuryl oxalate and pentoxifylline vs placebo.

TABLE 26 Placebo posterior results for the change from baseline in log mean walking distance (log m)

Prior distribution	Mean	SD	2.5 percentile	97.5 percentile
$\tau \sim U(0, 10)$, $\mu \sim N(10{,}000)$	0.242	0.0582	0.129	0.359
$\tau \sim U(0, 0.5)$, $\mu \sim N(10{,}000)$	0.242	0.0580	0.126	0.360
$\tau \sim U(0, 0.5)$, $\mu \sim N(1000)$	0.243	0.0591	0.125	0.361
$\tau \sim U(0, 0.25)$, $\mu \sim N(1000)$	0.242	0.0535	0.133	0.349
$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$	0.242	0.0490	0.143	0.341

τ, between-study SD for treatment effect and placebo effect; μ, baseline treatment, treatment effect, placebo effect.

TABLE 27 Posterior results for the change from baseline in log mean walking distance (log m) relative to placebo

	Mean	SD	2.5 percentile	97.5 percentile
Cilostazol				
$\tau \sim U(0, 10)$, $\mu \sim N(10{,}000)$	0.220	0.0576	0.108	0.337
$\tau \sim U(0, 0.5)$, $\mu \sim N(10{,}000)$	0.221	0.0577	0.109	0.340
$\tau \sim U(0, 0.5)$, $\mu \sim N(1000)$	0.220	0.0574	0.106	0.337
$\tau \sim U(0, 0.25)$, $\mu \sim N(1000)$	0.219	0.0569	0.108	0.335
$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$	0.220	0.0544	0.114	0.333
Pentoxifylline				
$\tau \sim U(0, 10)$, $\mu \sim N(10{,}000)$	0.101	0.0584	–0.016	0.217
$\tau \sim U(0, 0.5)$, $\mu \sim N(10{,}000)$	0.101	0.0576	–0.012	0.216
$\tau \sim U(0, 0.5)$, $\mu \sim N(1000)$	0.100	0.0580	–0.014	0.215
$\tau \sim U(0, 0.25)$, $\mu \sim N(1000)$	0.101	0.0579	–0.016	0.214
$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$	0.100	0.0559	–0.012	0.213
Naftidrofuryl oxalate				
$\tau \sim U(0, 10)$, $\mu \sim N(10{,}000)$	0.472	0.1464	0.181	0.762
$\tau \sim U(0, 0.5)$, $\mu \sim N(10{,}000)$	0.471	0.1422	0.188	0.751
$\tau \sim U(0, 0.5)$, $\mu \sim N(1000)$	0.472	0.1454	0.182	0.758
$\tau \sim U(0, 0.25)$, $\mu \sim N(1000)$	0.474	0.1441	0.187	0.759
$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$	0.472	0.1363	0.200	0.746

τ, between-study SD for treatment effect and placebo effect; μ, baseline treatment, treatment effect, placebo effect.

TABLE 28 Posterior results for the between-study SD of the change from baseline in log mean walking distance (log m) relative to placebo

	Between-study SD			
	Mean	SD	2.5 percentile	97.5 percentile
$\tau \sim U(0, 10)$, $\mu \sim N(10{,}000)$	0.125	0.0399	0.068	0.220
$\tau \sim U(0, 0.5)$, $\mu \sim N(10{,}000)$	0.125	0.0387	0.068	0.219
$\tau \sim U(0, 0.5)$, $\mu \sim N(1000)$	0.125	0.0392	0.070	0.220
$\tau \sim U(0, 0.25)$, $\mu \sim N(1000)$	0.124	0.0360	0.069	0.211
$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$	0.120	0.0305	0.068	0.185

τ, between-study SD for treatment effect and placebo effect; μ, baseline treatment, treatment effect, placebo effect.

is smaller than the results of the other analysis. This is a consequence of the prior distribution in SA5 excluding estimates considered plausible in the other sensitivity analyses, i.e. posterior estimates > 0.2.

Pain-free walking distance

Pain-free walking distance narrative summary

Tables 29–33 show PFWD results as reported by the trials. This may be reported as the difference in mean PFWD between baseline and final measurement, the change from baseline as a percentage or as an effect size. Details of treadmill protocols are shown in *Appendix 4*. As the graded test encourages longer walking distances than the constant-load protocol, absolute mean walking distance in metres is not directly comparable between protocols.[28]

For the 10 studies comparing cilostazol 200 mg with placebo, five did not find any significant difference between groups (O'Donnell *et al.*,[83] Otsuka trials 21–94–301, 21–98–213, 21–95–201,[34] Elam *et al.*[64]), and five significantly favoured cilostazol over placebo (Strandness *et al.*,[57] Dawson *et al.*,[58,63] Beebe *et al.*,[61] Money *et al.*[62]). *Table 29* shows the PFWD data from the published trial reports. The review by Pande *et al.*[31] included nine industry-sponsored trials, of which five trials (Strandness *et al.*,[57] Dawson *et al.*,[58,63] Beebe *et al.*,[61] Money *et al.*[62]) found a significant difference between treatment groups, and four trials (including the three trials without published trial reports) found no significant difference between cilostazol 200 mg and placebo groups (Otsuka

TABLE 29 Cilostazol 200 mg vs placebo PFWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in PFWD		Comparison between groups
		Cilostazol	Placebo		Cilostazol group	Placebo group	
O'Donnell 2009[51]	24	51	55	Constant	67% improvement	51.6% improvement	$p=0.63$
Strandness 2002[57]	24	133	129	Constant			22% (favours cilostazol)
Dawson 2000[58]	24	227	239	Graded	Mean difference (m): 94 (SD 127)	Mean difference (m): 57 (SD 93)	$p=0.0001$
Beebe 1999[61]	24	175	170	Constant	Mean difference (m): 67.5 59% improvement	Mean difference (m): 23.1 20% improvement	$p<0.001$
Money 1998[62]	16	119	120	Graded			$p<0.05$
Dawson 1998[63]	12	54	27	Constant	31.7% improvement	–2.5% change (worsening)	$p<0.01$

TABLE 30 Naftidrofuryl oxalate 600 mg vs placebo PFWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in PFWD		Comparison between groups
		Naftidrofuryl oxalate	Placebo		Naftidrofuryl oxalate group	Placebo group	
Spengel 2002[47]	24	382	372	Not treadmill – patient estimate only	Mean difference (m): 204 (SD 433)	Mean difference (m): 51 (SD 455)	$p<0.001$
Kieffer 2001[65]	24	98	98	Constant	Mean difference (m): 158.2	Mean difference (m): 29.9	$p<0.001$
Adhoute 1986[66]	24	64	54	Constant	Mean difference (m): 201.41	Mean difference (m): 98.03	$p<0.02$
Trubestein 1984[67]	12	54	50	Constant	Mean difference (m): 93	Mean difference (m): 36	$p<0.02$

TABLE 31 Pentoxifylline 1200 mg vs placebo PFWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in PFWD		Comparison between groups
		Pentoxifylline	Placebo		Pentoxifylline group	Placebo group	
Creager 2008[70]	24	86	84	Graded	34.30%	21.20%	Non-significant
Dawson 2000[58]	24	232	239	Graded	Mean difference (m): 74 (SD 106)	Mean difference (m): 57 (SD 93)	$p = 0.07$
Lindgarde 1989[71]	24	76	74	Constant	Geometric mean 80% improvement (SE 12)	Geometric mean 60% improvement (SE 11)	$p = 0.268$
Porter 1982[73]	24	67	61	Constant	47% (SE 10) by geometric mean	26% (SE 9) by geometric mean	Two-sided $p = 0.042$, one-sided $p = 0.01$
Gallus 1985[76]	8	25	23	Constant	55% improvement by geometric mean	26% improvement by geometric mean	Ratio of per cent change from baseline (pentoxifylline/placebo) 1.23 (95% CI 0.86 to 1.77); $p < 0.3$)

SE, standard error.

TABLE 32 Cilostazol 200 mg vs pentoxifylline 1200 mg PFWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in PFWD		Comparison between groups
		Cilostazol	Pentoxifylline		Cilostazol group	Pentoxifylline group	
Dawson 2000[58]	24	227	232	Graded	Mean difference (m): 94 (SD 127)	Mean difference (m): 74 (SD 106)	$p = 0.02$

TABLE 33 Cilostazol 200 mg (with or without supervised exercise) vs usual care (with or without supervised exercise) PFWD

Trial	Treatment duration (weeks)	No. in analysis		Treadmill protocol	Change in PFWD		Comparison between groups
		Cilostazol	Usual care		Cilostazol group	Usual care group	
INEXACT Hobbs 2007[82]	24	16 (seven with exercise, nine without)	18 (nine with exercise, nine without)	Constant	Mean ratio plus exercise 3.84 (SD 3.62) Without exercise, mean ratio 3.34 (SD 4.23)	Mean ratio plus exercise 2.22 (SD 2.71) Without exercise, mean ratio 1.23 (SD 0.73)	Difference in effect 2.07 $p = 0.090$

trials 21–94–301, 21–98–213, 21–95–201,[34] Elam *et al.*[64]). The five trials finding a significant difference between treatment groups reported this in published trial reports (see *Table 29*). The Pande *et al.* review[31] presented a pooled analysis of these nine trials as a ratio of geometric means, and calculated an estimate of treatment effect of 1.15 (95% CI 1.10 to 1.20), which significantly favoured cilostazol over placebo.[31] This analysis[31] did not include the O'Donnell *et al.* trial.[51] The O'Donnell *et al.* trial[51] did not find any significant treatment effect, with both the cilostazol and placebo groups showing improvement in PFWD (see *Table 29*). O'Donnell *et al.*[83] also found no significant difference between treatment groups when considering the subgroups of patients with diabetes ($p = 0.14$, $n = 26$)[53] or without diabetes ($p = 0.63$, $n = 80$), although, as described above (see *Maximum walking distance*), this may be due to the small sample sizes.

As patient populations were similar across trials, in terms of disease, diabetes, hypertension, smoking and age range, these characteristics do not appear to explain whether or not, significant differences between treatment groups were found and nor does sample size. Of the trials using the constant-workload treadmill protocol, three out of seven favoured cilostazol over placebo (Strandness *et al.*,[56] Beebe *et al.*,[61] Dawson *et al.*[63]), whereas four out of seven were non-significant (O'Donnell *et al.*,[83] Otsuka trials 21–94–301, 21–98–213, 21–95–201[34]). Of the trials using the graded test treadmill protocol, two out of three favoured cilostazol over placebo (Dawson *et al.*,[58] Money *et al.*[62]), whereas one was non-significant (Elam *et al.*[64]). For the graded test protocol trials, the trial with the non-significant result (Elam *et al.*[64]) was the trial with the shortest follow-up, at 12 weeks, whereas the trials with significant results had follow-up periods of 16 weeks (Money *et al.*[62]) and 24 weeks (Dawson *et al.*[58]). However, length of follow-up cannot explain the difference between significant and non-significant results in the constant-workload protocol trials. For the constant-workload protocol trials with 24 weeks' follow-up, three were non-significant in terms of PFWD comparing cilostazol versus placebo (O'Donnell *et al.*,[83] Otsuka trials 21–94–301, 21–98–213[34]), whereas two were significant (Strandness *et al.*,[56] Beebe *et al.*[61]). Two of the constant-workload protocol trials had follow-up of 12 weeks, and, of these, one produced significant results (Dawson *et al.*[63]), whereas the other one (Otsuka 21-95-201[34]) did not find any difference between treatment groups. Only Dawson *et al.*[63] specified administration of placebo during the run-in period of the study. These trials had similar designs: all were blinded, randomised and presented ITT analyses, and all measured baseline walking distance with two tests.

For the naftidrofuryl oxalate 600 mg versus placebo comparison (see *Table 30*), the three trials using constant-workload treadmill protocol – Kieffer *et al.*[65], Adhoute *et al.*[66] and Trubestein *et al.*[67] – all reported significantly greater improvement in PFWD in the naftidrofuryl oxalate group than in the placebo group. These trials had similar designs: all had placebo run-in, were randomised, presented ITT analyses, measured baseline walking distance with two tests, and were blinded with the exception that the clinicians in the Adhoute *et al.* trial[66] were not blinded to treatment group. The three naftidrofuryl oxalate 600 mg trials using constant-workload treadmill protocol – Kieffer *et al.*,[65] Adhoute *et al.*[66] and Trubestein *et al.*[67] – had some variation across trials in baseline PFWD; however, all had higher baseline PFWD (see *Appendix 4*) than the constant-workload cilostazol trials (Strandness *et al.*,[56] Beebe *et al.*,[61] Dawson 1998 *et al.*,[63] O'Donnell *et al.*,[83] Otsuka trials 21–94–301, 21–98–213, 21–95–201[34]). The Spengel *et al.* trial[47] reported significantly greater improvement in claudication distance in the naftidrofuryl oxalate 600 mg group than in the placebo group; however, this was based on patient estimates of PFWD at baseline and 24 weeks, not treadmill testing. The Ruckley *et al.* trial[68] of naftidrofuryl oxalate 300 mg versus placebo reported that there was no significant difference between groups for PFWD at 12 weeks' follow-up,[68] as measured by patients' normal walking pace on a level.

Of the seven trials comparing pentoxifylline 1200 mg versus placebo in terms of PFWD, five found no significant difference between treatment groups (Creager *et al.*,[70] Lindgarde *et*

al.,[71] Gallus *et al.*[76] and Otsuka 21-98-213, 21–94–301[34]), whereas two significantly favoured pentoxifylline over placebo for PFWD (Dawson *et al.*[58] and Porter *et al.*[73]). The Gallus *et al.*[76] study had a follow-up of only 8 weeks, whereas the other studies had a follow-up of 24 weeks. Three published trials (see *Table 31*) comparing pentoxifylline with placebo – Creager *et al.*,[70] Lindgarde *et al.*[71] and Gallus *et al.*[76] – reported no significant difference between treatment groups in PFWD. Two trials without published trial reports – Otsuka 21-98-213[34] and Otsuka 21-94-301[34] – also found no significant difference between the pentoxifylline and placebo groups in PFWD. Two trials (reported in *Table 31*) – Dawson *et al.*[58] and Porter *et al.*[73] – reported significantly greater improvement in PFWD for the pentoxifylline group than for the placebo group. Five of the trials comparing pentoxifylline with placebo used constant workload treadmill protocols, of which four found no significant treatment effect (Lindgarde *et al.*,[71] Gallus *et al.*,[76] Otsuka 21-98-213[34] and Otsuka 21-94-301[34]), and one favoured pentoxifylline (Porter *et al.*[73]). Of the two trials using a graded test protocol, one found a significant treatment effect (Dawson *et al.*[58]), whereas the other did not (Creager *et al.*[70]).

For the comparison of inositol nicotinate 4 g versus placebo, none of the trials reported PFWD. However, O'Hara *et al.*[78] measured pain-free walking paces and claudication time, and reported that there was no significant difference between groups in claudication time, and that pain-free walking paces improved significantly in both groups, with inositol nicotinate showing significantly greater improvement ($p < 0.05$) than the placebo group at 12 weeks.[78] The Head[81] trial reported improved claudication times for both treatment groups at 12 weeks, but there was a significant difference between treatment groups ($p < 0.001$) only for patients with moderate disease, among whom the inositol nicotinate group ($n = 24$) had a significantly greater improvement than the placebo group ($n = 28$).

For the comparison of cilostazol 200 mg versus pentoxifylline 1200 mg (see *Table 32*), Dawson *et al.*[58] found a significantly greater improvement in PFWD for the cilostazol group than for the pentoxifylline group. Two trials without published trial reports – Otsuka 21-98-213[34] and Otsuka 21-94-301[34] – found no significant difference between cilostazol and pentoxifylline groups in PFWD. The Dettori *et al.*[69] trial did not report PFWD, but did report pain-free walking time, which was statistically more improved for patients taking pentoxifylline ($p < 0.05$) in an analysis including all four trial arms of the study (see *Table 3* for summary table of included studies) at 1-year follow-up.

For the trial comparing cilostazol 200 mg (with or without supervised exercise) versus usual care (with or without supervised exercise) (see *Table 33*), all treatment groups improved but there was no significant effect of cilostazol added to supervised exercise or usual care.[82]

Pain-free walking distance meta-analysis

The 10 studies included within this analysis are the same as for those used in the meta-analysis of MWD, shown in *Table 21*. *Table 34* shows the change from baseline in log mean PFWD, including the three studies that are excluded from the meta-analysis because they had follow-up times of < 24 weeks.

Goodness-of-fit was assessed by calculating the arm-specific and total residual deviance. The total residual deviance was 23.07, which compares favourably with the 23 data points being analysed. The arm-specific deviance terms showed that the data from the Beebe *et al.*[61] and Strandness *et al.*[56] studies had the largest deviances.

The posterior mean treatment effects for these studies, together with the 95% credible intervals, are given in *Table 35*. *Table 35* also gives the posterior mean of the between-study SD, together with the 95% credible interval.

TABLE 34 Logarithm of the geometric mean change from baseline in PFWD (log m)

Study	Placebo: mean (SD), *N*	Cilostazol: mean (SD), *N*	Pentoxifylline: mean (SD), *N*	Naftidrofuryl oxalate: mean (SD), *N*
[a,b]Dawson 1998[63]	–0.025 (NA), 25	0.275 (NA), 52		
[a,b]Elam 1998[64]	0.322 (NA,) 94	0.513 (NA), 95		
[a]Beebe 1999[61]	0.182 (NA), 140	0.464 (NA), 140		
[a]Strandness 2002[56]	0.320 (NA), 125	0.611 (NA), 124		
[a,b]Otsuka 21-95-201[34]	0.419 (0.406), 66	0.457 (0.406), 60		
[a]O'Donnell 2009[83]	0.416 (0.581), 55	0.513 (0.581), 51		
Porter 1982[72]	0.166 (NA), 40		0.385 (NA), 42	
Lindgarde 1989[71]	0.470 (NA), 74		0.588 (NA), 76	
Creager 2008[70]	0.192 (NA), 84		0.295 (NA), 86	
Kieffer 2001[65]	0.155 (NA), 92			0.651 (NA), 89
Dawson 2000[58]	0.588 (0.602),[c] 226	0.663 (0.602),[c] 205	0.554 (0.602),[c] 212	
[a]Otsuka 21-94-301[34]	0.464 (0.474), 122	0.467 (0.474), 123	0.548 (0.474), 118	
[a]Otsuka 21-98-213[34]	0.501 (0.580), 260	0.521 (0.580), 260	0.578 (0.580), 260	

NA, not available.
a Assumes common SD within study – SD derived from mean and CI for the difference between treatments in geometric mean change from baseline.
b Twelve-week study.
c Standard deviation derived from the treatment mean changes from baseline and the *p*-value for the comparison of cilostazol vs pentoxifylline.

TABLE 35 Posterior distribution for the difference from placebo in change from baseline log mean PFWD (log m)

Intervention	Treatment effect	Mean (95% credible interval)
Cilostazol	Random effects	0.126 (0.024 to 0.226)
	Predictive distribution	0.126 (–0.107 to 0.359)
Pentoxifylline	Random effects	0.088 (–0.017 to 0.195)
	Predictive distribution	0.087 (–0.153 to 0.326)
Naftidrofuryl oxalate	Random effects	0.495 (0.231 to 0.764)
	Predictive distribution	0.496 (0.157 to 0.845)
Between-study SD		0.095 (0.032 to 0.184)

The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl oxalate had the greatest effect [64.2% = 1 – exp(0.496)] relative to placebo, followed by cilostazol (13.4%) and pentoxifylline (9.2%).

The 95% credible intervals suggest that treatment with naftidrofuryl oxalate and cilostazol produces real increases in the percentage change from baseline PFWD relative to placebo, although there was some uncertainty as to the true effect.

There was moderate between-study variation, which suggests that the treatment effect varied depending on the characteristics of the study. The trial by Strandness *et al.*[56] had the largest observed effect of cilostazol effect compared with placebo (0.291) and the Otsuka 21-94-301[34] trial had the smallest observed cilostazol effect compared with placebo (0.003). The trial by Porter *et al.*[72] had the largest observed pentoxifylline effect compared with placebo (0.219) and the trial by Dawson *et al.*[58] had the smallest observed pentoxifylline effect compared with placebo (–0.034).

Forest plots are shown in *Figure 4*.

The percentage change from baseline to 24 weeks in PFWD, estimated by projecting the treatment effects from the network meta-analysis on to a estimated placebo response, is shown in *Table 36*.

Ankle–brachial pressure index

Tables 37–40 show ABPI results as reported by the trials as difference in mean between baseline and final measurement or change from baseline as a percentage. Across all treatment groups in all trials, where reported, differences from baseline to final measurement were slight.

For the cilostazol 200 mg versus placebo comparison (see *Table 37*), only three trials reported ABPI, and these all reported significantly more improvement in the cilostazol treatment group than in the placebo group.[58,62,64] Only in the Dawson *et al.*[58] trial did the placebo group's ABPI slightly worsen, with the Money *et al.*[62] and Elam *et al.*[64] trials showing improvement in both groups.

For the naftidrofuryl oxalate 600 mg versus placebo comparison (see *Table 38*), the two trials[65,66] reporting ABPI found no significant difference between the naftidrofuryl oxalate and placebo groups, with both groups in both the Kieffer *et al.*[65] and Adhoute *et al.*[66] trials showing a small,

TABLE 36 Percentage change from baseline in PFWD

Intervention	Mean (95% credible interval)
Placebo	42.2 (25.1 to 60.7)
Cilostazol	61.4 (36.8 to 88.3)
Pentoxifylline	55.4 (31.6 to 82.8)
Naftidrofuryl oxalate	135.3 (74.9 to 212.6)

TABLE 37 Cilostazol 200 mg vs placebo ABPI

		No. of patients in analysis		Change in ABPI		
Trial	Follow-up	Cilostazol	Placebo	Cilostazol group	Placebo group	Comparison between groups
Dawson 2000[58]	24	205	226	Difference in means 0.04	Difference in means –0.01	$p<0.01$[a]
Money 1998[62]	16	119	120	9% increase	1% increase	$p=0.0125$[a]
Elam 1998[64]	12	95	94	9.03% increase	1.2% increase	$p<0.001$[a]

a Significantly more improvement in cilostazol than placebo.

TABLE 38 Naftidrofuryl oxalate 600 mg vs placebo ABPI

		No. of patients in analysis		Change in ABPI		
Trial	Follow-up	Naftidrofuryl oxalate	Placebo	Naftidrofuryl oxalate group	Placebo group	Comparison between groups
Kieffer 2001[65]	24	89	92	Difference in means 0.03	Difference in means 0.04	Non-significant
Adhoute 1986[66]	24	42	40	Difference in means 0.02	Difference in means 0.01	Non-significant

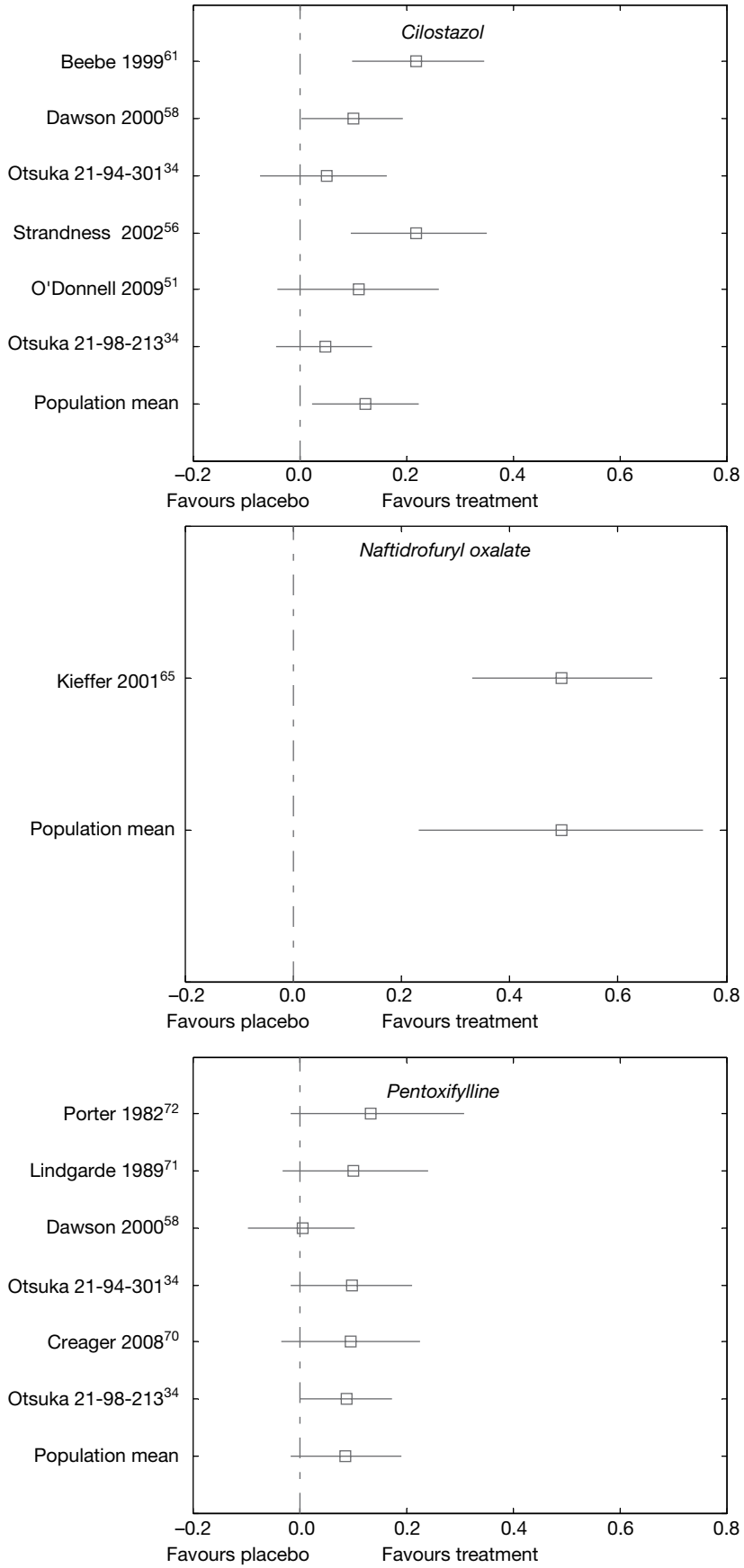

FIGURE 4 Posterior distribution for the difference from placebo in change from baseline log mean PFWD for cilostazol, naftidrofuryl oxalate and pentoxifylline vs placebo.

TABLE 39 Pentoxifylline 1200 mg vs placebo ABPI

Trial	Follow-up	No. of patients in analysis		Change in ABPI		Comparison between groups
		Pentoxifylline	Placebo	Pentoxifylline group	Placebo group	
Dettori 1989[69]	52	29	30	Post-exercise 8.3% At rest 2.5%	Post-exercise 9.4% At rest –3.1%	Post-exercise ABPI $p = 0.09$[a] At rest ABPI non-significant
Dawson 2000[58]	24	212	226	Difference in means 0.05	Difference in means –0.01	Non-significant

a Pentoxifylline significantly more improvement than placebo.

TABLE 40 Cilostazol 200 mg vs pentoxifylline 1200 mg ABPI

Trial	Follow-up	No. of patients in analysis		Change in ABPI		Comparison between groups
		Cilostazol group	Pentoxifylline group	Cilostazol group	Pentoxifylline group	
Dawson 2000[58]	24	205	212	Difference in means 0.04	Difference in means 0.05	Non-significant

non-significant improvement. Trubestein *et al.*[67] recorded ankle pressure and found no significant change for either treatment group.

For the pentoxifylline 1200 mg versus placebo comparison (see *Table 39*), Dawson *et al.*[58] did not find any significant difference between groups.[58] The Dettori *et al.* trial[69] with follow-up of 1 year found that, by geometric mean, there was no significant difference between pentoxifylline and placebo groups for ABPI measured at rest or post-exercise. For both of these trials,[58,69] there was a slight worsening of the placebo group and small improvement for the pentoxifylline group.

For the comparison of inositol nicotinate 4 g versus placebo, the Kiff and Quick[80] trial reported that there was no significant change, from baseline to final measurement at 12 weeks, in ABPI for either treatment group.

For the comparison of cilostazol 200 mg versus pentoxifylline 1200 mg (see *Table 40*), the Dawson *et al.*[58] study did not find any significant difference between groups for ABPI. The mean change was slightly larger in the pentoxifylline group than in the cilostazol group for this trial; however, there was greater variability in the pentoxifylline group. This resulted in a lack of significance in the comparison of pentoxifylline and placebo within this trial, but a significant difference between the cilostazol and placebo groups.

Mortality

Tables 41–45 show mortality results reported by trials. Across studies, there were no significant differences in mortality rates between treatment groups. No mortality was directly attributed to the vasoactive drugs. However, follow-up times were relatively short and hence very few deaths occurred. Only two studies had follow-up of over 24 weeks.[49,69] The CASTLE study[49] of cilostazol 200 mg versus placebo (which included some patients taking pentoxifylline in both groups) reported mortality of approximately 7% in both groups by ITT analysis at 144 weeks. The Dettori *et al.* study[69] of pentoxifylline 1200 mg versus placebo, at 1 year, found no mortality in the pentoxifylline group and a mortality rate of 5.4% in the placebo group, although this was based on only two deaths.

TABLE 41 Cilostazol 200 mg vs placebo, mortality

Trial	Treatment duration (weeks)	No. in analysis		Cilostazol group		Placebo group	
		Cilostazol	Placebo	Mortality (*n*)	Mortality (%)	Mortality (*n*)	Mortality (%)
CASTLE, Hiatt 2008[49]	Up to 144	717	718	49	6.8	52	7.2
Strandness 2002[56]	24	133	129	2	1.5	0	0
Dawson 2000[58]	24	227	239	2	0.8	1	0.4
Beebe 1999[61]	24	175	170	3	1.2	2	1.2
Otsuka 21-98-213[34]	24	260	260	0	0	2	0.8
Money 1998[62]	16	119	120	1	0.8	1	0.8
Dawson 1998[63]	12	54	27	0	0	1	3.7
Elam 1998[64]	12	95	94	1	1.1	1	1.1
Otsuka 21-95-201[34]	12	72	70	0	0	2	2.9

TABLE 42 Naftidrofuryl oxalate 600 mg vs placebo, mortality

Trial	Treatment duration (weeks)	No. in analysis		Naftidrofuryl oxalate group		Placebo group	
		Naftidrofuryl oxalate	Placebo	Mortality (*n*)	Mortality (%)	Mortality (*n*)	Mortality (%)
Spengel 2002[47]	24	382	372	1	0.26	5	1.30

TABLE 43 Pentoxifylline 1200 mg vs placebo, mortality

Trial	Treatment duration (weeks)	No. in analysis		Pentoxifylline group		Placebo group	
		Pentoxifylline	Placebo	Mortality (*n*)	Mortality (%)	Mortality (*n*)	Mortality (%)
Dettori 1989[69]	52	37	37	0	0	2	5.4
Creager 2008[70]	24	86	84	1	1.20	1	1.20
Dawson 2000[58]	24	232	239	3	1	1	0.4
Otsuka 21-98-213[34]	24	260	260	3	1.2	2	0.8
Gallus 1985[76]	8	25	23	0	0	1	4

Cardiovascular events

Across studies, there were no significant differences in cardiovascular event rates in between treatment groups within trials. Further details are provided in *Appendix 4*.

Only two studies had follow-up of over 24 weeks.[49,69] The CASTLE study of 144 weeks[49] of cilostazol versus placebo (which included some patients taking pentoxifylline in both groups) reported no significant difference in cardiovascular mortality between the cilostazol and placebo groups, with a hazard ratio (HR) for cilostazol of 0.852 (95% CI 0.515 to 1.410; $p = 0.533$) by ITT analysis. This was based on 28 events (3.9%) in the cilostazol group and 33 events (4.6%) in the placebo group.[49] The CASTLE study[49] also found no significant difference between groups when using on-treatment analysis, with 14 cardiovascular deaths in each treatment group. The Dettori *et al.* study[69] found one non-fatal cardiovascular event (2.7%) at 1-year follow-up in the

TABLE 44 Inositol nicotinate 4 g vs placebo, mortality

Trial	Treatment duration (weeks)	No. in analysis		Inositol nicotinate group		Placebo group	
		No. in analysis Inositol nicotinate	No. in analysis, placebo	Mortality (*n*)	Mortality (%)	Mortality (*n*)	Mortality (%)
O'Hara 1988[78]	12	62	58	0	0	1	1.70

TABLE 45 Cilostazol 200 mg vs pentoxifylline 1200 mg, mortality

Trial	Treatment duration (weeks)	No. in analysis		Cilostazol group		Pentoxifylline group	
		No. in analysis Cilostazol	No. in analysis, pentoxifylline	Mortality (*n*)	Mortality (%)	Mortality (*n*)	Mortality (%)
Dawson 2000[58]	24	227	232	2	0.8	3	1
Otsuka 21-98-213[34]	24	260	260	0	0	3	1.2

pentoxifylline group, and three cardiovascular events (of which one was fatal) in the placebo group (8.1%).

Eight of the cilostazol 200 mg versus placebo trials (Strandness *et al.*,[57] Dawson *et al.*[58,63] Beebe *et al.*,[61] Money *et al.*,[62] Elam *et al.*[64]) were included in an analysis by Pratt,[28,33] which reported a cardiovascular event rate of 6.5% (20/308) for the cilostazol 200 mg groups and 7.7% (23/299) for the placebo groups. This analysis also reported cardiovascular mortality within 30 days of drug administration as 0.67% (7/1048) for cilostazol 200 mg and 0.1% (1/973) for placebo.[33]

For the naftidrofuryl oxalate 600 mg versus placebo comparison, the Kieffer *et al.*[65] trial reported that 2% ($n = 2$) of the naftidrofuryl oxalate group and 3% ($n = 3$) of the placebo group were referred for vascular intervention with endovascular or surgical treatment.

For the pentoxifylline 1200 mg versus placebo comparison, Creager *et al.*[70] reported serious cardiovascular events for 7% ($n = 6$) of the pentoxifylline group and 12% ($n = 10$) of the placebo groups. The Porter and Bauer[74] and Gallus *et al.*[76] trials reported only cardiovascular events that led to withdrawal from the studies, with Porter and Bauer[74] reporting cardiovascular events for 1.5% ($n = 1$) of the pentoxifylline group and 4.8% ($n = 3$) of the placebo group, and Gallus *et al.*[76] reporting 12% ($n = 3$) for the placebo group but no events for the pentoxifylline group.

The inositol nicotinate 4 g trials reported only cardiovascular events that led to withdrawal from the studies. The O'Hara *et al.* trial[78] reported a 2% ($n = 1$) cardiovascular event rate in both the inositol nicotinate and placebo groups, Kiff and Quick[80] reported a 2.5% ($n = 1$) event rate for the inositol nicotinate group and no events for the placebo group, and Head[81] reported a 1.6% ($n = 1$) event rate for the placebo group and no events for the inositol nicotinate group.

Adverse events and serious adverse events

Tables 46–50 show numbers of patients experiencing at least one adverse event (AE) or serious adverse event (SAE) according to results reported by the trials. Further details, including types of AEs, are provided in *Appendix 4*. Differences in reporting across trials, including that some trials

TABLE 46 Cilostazol 200 mg vs placebo: SAE and AE

Trial	Treatment duration (weeks)	No. in analysis		Cilostazol group				Placebo group			
				Patients with one or more SAE		Patients with one or more AE		Patients with one or more SAE		Patients with one or more AE	
		Cilostazol	Placebo	*n*	%	*n*	%	*n*	%	*n*	%
Strandness 2002[56]	24	133	129	25	18.8	124	93.2	20	15.5	99	76.7
Dawson 2000[58]	24	227	239	27	11.9	201	88.5	31	13	188	78.7
Beebe 1999[61]	24	175	170	23	13.1	159	90.9	29	17.1	150	88.2
Otsuka 21-94-301[34]	24	123	124	16	13	116	94	11	9	103	83
Otsuka 21-98-213[34]	24	260	260	32	12.3	207	79.6	31	11.9	197	75.8
Money 1998[62]	16	119	120	14	11.8	98	82.4	11	9.2	90	75
Dawson 1998[63]	12	54	27	7	13	47	87	1	4	20	74
Elam 1998[64]	12	95	94	6	6.3	79	83.2	7	7.4	76	80.9
Otsuka 21-95-201[34]	12	72	70	4	5.6	60	83.3	10	14.3	52	74.3

TABLE 47 Naftidrofuryl oxalate 600mg vs placebo: SAE and AE

Trial	Treatment duration (weeks)	No. in analysis		Naftidrofuryl oxalate group				Placebo group			
				Patients with one or more SAE		Patients with one or more AE		Patients with one or more SAE		Patients with one or more AE	
		Naftidrofuryl oxalate	Placebo	*n*	%	*n*	%	*n*	%	*n*	%
Kieffer 2001[65]	24	98	98	12	12	18	18	13	13	21	21
Adhoute 1986[66]	24	64	54	NR	NR	5	7.80	NR	NR	4	7.80
Trubestein 1984[67]	12	54	50	NR	NR	2	4	NR	NR	2	4

NR, not reported.

TABLE 48 Naftidrofuryl oxalate 300 mg vs placebo: SAE and AE

Trial	Treatment duration (weeks)	No. in analysis		Naftidrofuryl oxalate group		Placebo group	
				Patients with one or more AE		Patients with one or more AE	
		Naftidrofuryl oxalate	Placebo	*n*	%	*n*	%
Ruckley 1978[68]	12	25	25	6	24	4	16

reported only AEs leading to discontinuation or had unclear clinical criteria for AEs, precluded meta-analysis.

Only two studies had follow-up of over 24 weeks.[49,69] The CASTLE study[49] of cilostazol versus placebo (which included some patients taking pentoxifylline in both groups), with a follow-up period of 144 weeks, reported higher frequency of headaches, diarrhoea and palpitations in

TABLE 49 Pentoxifylline 1200 mg vs placebo: SAE and AE

Trial	Treatment duration (weeks)	No. in analysis		Pentoxifylline group				Placebo group			
				Patients with one or more SAE		Patients with one or more AE		Patients with one or more SAE		Patients with one or more AE	
		Pentoxifylline	Placebo	*n*	%	*n*	%	*n*	%	*n*	%
Creager 2008[70]	24	86	84	12	14	59	69	14	17	49	58
Dawson 2000[58]	24	232	239	31	13.4	200	86.2	31	13	188	78.7
Lindgarde 1989[71]	24	76	74	NR	NR	17	22	NR	NR	10	14
Porter 1982[72]	24	63	61	NR	NR	37	55	NR	NR	24	39
Otsuka 21-94-301[34]	24	123	124	22	18	104	85	11	9	103	83
Otsuka 21-98-213[34]	24	260	260	NR	NR	208	80	31	11.9	197	75.8

NR, not reported.

TABLE 50 Cilostazol 200 mg vs pentoxifylline 1200 mg: SAE and AE

Trial	Treatment duration (weeks)	No. in analysis		Cilostazol group				Pentoxifylline group			
				Patients with one or more SAE		Patients with one or more AE		Patients with one or more SAE		Patients with one or more AE	
		Cilostazol	Pentoxifylline	*n*	%	*n*	%	*n*	%	*n*	%
Dawson 2000[58]	24	227	232	27	11.9	201	88.5	31	13.4	200	86.2
Otsuka 21-94-301[34]	24	123	123	16	13	116	94	22	18	104	85
Otsuka 21-98-213[34]	24	260	260	32	12.3	207	79.6	28	10.8	208	80

the cilostazol group, and a higher frequency of bronchitis in the placebo group than in the cilostazol group, although none of these events had a rate higher than 11%. Most SAEs reported by the CASTLE study were cardiovascular (see *Cardiovascular events*, above), but there was also dyspepsia occurring in 1% of the cilostazol group and 0.4% of the placebo group.[49] The Dettori *et al.*[69] study reported only SAEs leading to withdrawal from study drug, and these were all cardiovascular in nature (see *Cardiovascular events*, above).

Eight of the cilostazol 200 mg versus placebo trials (Strandness *et al.*,[57] Dawson *et al.*,[58,63] Beebe *et al.*,[61] Money *et al.*,[62] Elam *et al.*[64]) were included in an analysis by Pratt[33] that reported higher frequency of headaches, diarrhoea, peripheral oedema and palpitations in the cilostazol groups than in the placebo groups. Although this analysis[33] included cilostazol doses of 100 mg and 300 mg (excluded from the current report for not being the licensed dose), as well as the cilostazol 200 mg groups, this pattern is reflected in the published trial reports (see *Appendix 4*).

For both naftidrofuryl oxalate 600 mg and 300 mg compared with placebo, rates of AEs or SAEs were similar between treatment groups (see *Tables 47* and *48*). The Kieffer *et al.* trial[65] additionally reported SAEs, including cardiovascular and non-cardiovascular events, for 24 weeks following treatment cessation and again found no significant difference in rates between the naftidrofuryl

oxalate (6%) and placebo (7%) groups.[65] Non-SAEs were mostly gastrointestinal in nature (see *Appendix 4*).

For the pentoxifylline versus placebo trials (see *Table 49*) event rates were similar between treatment groups. Lower rates in the Lindgarde *et al.*[71] trial than in the Creager *et al.*,[70] Dawson *et al.*,[58] Porter *et al.*,[72] Otsuka 21-94-301[34] and Otsuka 21-98-213[34] trials are likely to be due to the patient self-reporting AEs, as populations were similar across trials. Non-SAEs were mostly headaches or gastrointestinal complaints (see *Appendix 4*).

The inositol nicotinate 4 g versus placebo trials reported only AEs that led to withdrawal from trials, and these were similar between treatment groups (see *Appendix 4*) and mostly related to difficulty swallowing or gastrointestinal problems.[79–81]

The cilostazol versus pentoxifylline trials reported similar rates of SAEs and AEs across treatment groups.[33,58]

Health-related quality of life

Several different outcome measures have been used to assess quality of life in study participants, and no single measure has been used to assess all four treatments. The most commonly used quality-of-life measure was the SF-36,[84] with data available for cilostazol and pentoxifylline. There are also data available for the Walking Impairment Questionnaire (WIQ[85]) for both cilostazol and pentoxifylline, although this measure aims to assess walking impairment and not quality of life. Other outcome measures used include the claudication outcome measure (COM –a measure developed by the funders but which had not undergone validation,[61] and does not appear to have been published), vascular quality of life (VascuQoL),[86] an independent measure that has been validated, and the Claudication Scale (CLAU-S), another independent, extensively validated tool.[87] *Tables 51–54* summarise the evidence around HRQoL.

Cilostazol

Table 51 summarises the HRQoL data for cilostazol, and *Table 52* further summarises SF-36 scales and subscales. Strandness *et al.*,[56,57] Beebe *et al.*,[61] Money *et al.*,[62] O'Donnell *et al.*,[53,83] (diabetics and non-diabetics), Dawson *et al.*,[58,63] and Otsuka 21-98-213[34] (diabetic and non-diabetic participants were reported separately by one author but are drawn from one study)[53,83] assessed the quality of life of study participants in trials of cilostazol using the SF-36. However, not all studies reported significance values for all summary measures and subscales, as can be seen from *Table 51*. It is likely that only scales that were significant were reported. Assuming this to be the case, no summary measure or subscale shows a consistent positive outcome for physical or mental health. The subscale physical function improved significantly in Strandness *et al.*,[56] Beebe *et al.*,[61] Money *et al.*[62] and O'Donnell *et al.*[83] (non-diabetics), although, of these, the magnitude of the change is only reported in Beebe *et al.*[61] and the effect does not seem to be strong enough to lead to significant changes in the summary physical function score. No study reported significant differences for between-group comparisons for any mental health component of the SF-36. COM was reported only by Beebe *et al.*,[61] and the results of this corresponded with the SF-36 results reported for the same trial.

VascuQoL was used in one study that reported diabetic (O'Donnell *et al.*[53]) and non-diabetic (O'Donnell *et al.*[83]) patients separately. VascuQoL scores did not correspond with SF-36 scores in either diabetic or non-diabetic patients. VascuQoL is a disease-specific measure designed for use with critical as well as chronic limb ischaemia,[87] and as such may have different psychometric properties. Across the five studies that used WIQ, results were conflicting, with some significant results reported in Beebe *et al.*[61] and Money *et al.*,[62] significant trends reported in Strandness *et*

TABLE 51 Cilostazol 200 mg vs placebo, HRQoL assessed using SF-36, WIQ, COM and/or VascuQoL

Trial	Duration (weeks)	No. of patients in analysis		Change in HRQoL		Comparison between groups
		Cilostazol	Placebo	Cilostazol group (0–100 scale)	Placebo group	
SF-36[a]						
Strandness 2002[56]	24	Unclear	Unclear	NR	NR	Physical health summary (physical function, bodily pain and role–physical), non-significant trend Physical function $p = 0.048$
				Mean change from baseline	Mean change from baseline	
Beebe 1999[61]	24	137	141	*Physical health*	*Physical health*	*Physical health*
				Physical function 7.1	Physical function 2.0	Physical function, significant
				Role–physical 5.3	Role–physical –2.8	Bodily pain, significant
				Bodily pain 7.2	Bodily pain –1.8	Role–physical, positive trend
				Mental health	*Mental health*	*Mental health*
				Social function 1.0	Social function 0.4	Non-significant
				Role–emotional 2.9	Role–emotional –1.66	
				Mental health 2.5	Mental health 0.9	
				Mean change from baseline	Mean change from baseline	
Money 1998[62]	16	Unclear, probably 119	Unclear, probably 120	Physical health summary 2.99	Physical health summary 0.12	Physical health summary $p = 0.0059$
				Physical function 8.3	Physical function 2.3	Physical function $p = 0.0024$
				Other subscales change NR	Other subscales change NR	Bodily pain $p = 0.0772$ General health $p = 0.436$ Role–physical $p = 0.061$ Mental components non-significant
				Difference between median at baseline and 24 weeks (calculated by reviewer)	Difference between median at baseline and 24 weeks (calculated by reviewer)	

continued

TABLE 51 Cilostazol 200 mg vs placebo, HRQoL assessed using SF-36, WIQ, COM and/or VascuQoL *(continued)*

		No. of patients in analysis		Change in HRQoL		
Trial	**Duration (weeks)**	**Cilostazol**	**Placebo**	**Cilostazol group (0–100 scale)**	**Placebo group**	**Comparison between groups**
O'Donnell 2009 (diabetics)[53]	24	12	14	Physical function 5.2	Physical function 0.5	Physical function $p=0.42$
				Role–physical 0	Role–physical 3.7	Role–physical $p=0.72$
				Body pain 3.4	Body pain 0	Body pain $p=0.31$
				General health 2.2	General health 0.2	General health $p=0.93$
				Total SF-36, 3.7	Total SF-36 1	Total SF-36 $p=0.40$
				Significance of change from baseline (unclear if median or mean)	Significance of change from baseline (unclear if median or mean)	
				Physical component $p=0.043$	No significant changes	
				Vitality $p=0.016$		
				Others NR		
				Mean change from baseline or significance of change from baseline NR	Mean change from baseline or significance of change from baseline NR	
O'Donnell 2009 (non-diabetics)[83]	24	39	41			Physical health summary $p=0.044$
						Physical function $p=0.013$
						Role–physical $p=0.62$
						Body pain, $p=0.21$
						General health $p=0.48$
						Other subsets and summary non-significant
						Total SF-36 $p=0.50$
Dawson 2000[58]	24	205	226	NR	NR	Mental health summary, general health perception, physical health summary, and vitality scores all non-significant
Otsuka 21-98-213[34]	24	NR	NR	NR	NR	Only week 12 statistics reported
						Physical health summary significant at 12 weeks
WIQ[b]						
Strandness 2002[56]	24	Unclear	Unclear	NR	NR	*Non-significant trends*
						General health perception
						Walking distance

Trial	Duration (weeks)	No. of patients in analysis		Change in HRQoL		Comparison between groups
		Cilostazol	Placebo	Cilostazol group (0–100 scale)	Placebo group	
Beebe 1999[61]	24	137	141	NR	NR	Walking speed and walking distance improved, unclear if significant
Money 1998[62]	16	Unclear, probably 119	Unclear, probably 120	NR	NR	Walking speed, $p=0.0331$ Walking distance, non-significant
O'Donnell 2009 (non-diabetics)[83]	24	12	14	Distance $p=0.014$ Speed $p=0.021$	Distance $p=0.81$ Speed $p=0.74$	Non-significant
Dawson 2000[58]	24	205	226	NR	NR	Non-significant
COM[c]						
				Mean change from baseline (0–4 scale)	Mean change from baseline (0–4 scale)	
Beebe 1999[61]	24	137	141	Change in pain/discomfort 2.8 Pain/discomfort daily activities 0.4 Pain/discomfort physical activities 0.5 Pain/discomfort social activities 0.3 Walking pain/discomfort 0.7 Worry/concern due to pain 0.8	Change in pain/discomfort 2.4 Pain/discomfort daily activities 0.2 Pain/discomfort physical activities 0.2 Pain/discomfort social activities 0.3 Walking pain/discomfort 0.4 Worry/concern due to pain 0.5	Statistically significant Walking pain/discomfort Change in walking pain/discomfort Walking pain/discomfort physical activities All other domains and subscales not significant
VascuQol[d]						
O'Donnell 2009 (diabetics)[53]	24	12	14	NR	NR	Activity $p=0.59$ Symptom $p=0.025$ (significantly more increase for placebo) Pain $p=0.08$ Emotion $p=0.013$ Social $p=0.06$ Total $p=0.04$

continued

TABLE 51 Cilostazol 200 mg vs placebo, HRQoL assessed using SF-36, WIQ, COM and/or VascuQoL *(continued)*

Trial	Duration (weeks)	No. of patients in analysis		Change in HRQoL		Comparison between groups
		Cilostazol	Placebo	Cilostazol group (0–100 scale)	Placebo group	
O'Donnell 2009 (non-diabetics)[83]	24	39	41	Significant improvement in pain ($p=0.005$) All others non-significant	No significant changes for placebo group	Activity $p=0.34$ Symptom $p=0.34$ Pain $p=0.89$ Emotion $p=0.63$ Social $p=0.67$ Total $p=0.78$

NR, not reported.

a The SF-36 comprises two main summary measures (physical health and mental health), which are composed of four subscales each. The four physical health subscales are physical functioning, role–physical, bodily pain and general health. The mental health summary measure subscales are vitality, social functioning, role–emotional and mental health.

b Walking Impairment Questionnaire self-rated measure of symptoms and walking impairment.[87]

c Claudication outcome measure funder-developed outcome measure that has not been independently validated. Measures walking pain, discomfort, physical limitations, daily and social functioning.[87]

d VascuQoL comprises five domains, namely pain, activity, symptoms, emotional and social. It is an independently constructed measure that has been validated but was developed for use with critical as well as chronic limb ischaemia.[87]

TABLE 52 Summary of between group comparisons of change from baseline in SF-36 scores, cilostazol 200 mg vs placebo

Trial	Duration (weeks)	No. of patients in analysis		Summary physical health	Physical function	Bodily pain	Role–physical	General health	Summary mental health	Vitality	Social functioning	Role–emotional	Mental health
		Cilostazol	Placebo										
SF-36[a]													
Strandness 2002[56]	24	Unclear	Unclear	Non-sig	Sig	Non-sig	Non-sig	Non-sig	NR	NR	NR	NR	NR
Beebe 1999[61]	24	137	141	NR	Sig	Sig	Non-sig	NR	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig
Money 1998[62]	16	Unclear, probably 119	Unclear, probably 120	Sig	Sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig
O'Donnell 2009 (diabetics)[53]	24	12	14	NR	Non-sig	Non-sig	Non-sig	Non-sig	NR	NR	NR	NR	NR
O'Donnell 2009 (non-diabetics)[83]	24	39	41	NR	Sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig
Dawson 2000[58]	24	205	226	Non-sig	NR	NR	NR	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig	Non-sig

NR, not reported; Non-sig, non-significant; Sig, significant.

a The SF-36 comprises two main summary measures (physical health and mental health), which are composed of four subscales each. The four physical health subscales are physical functioning, role–physical, bodily pain and general health. The mental health summary measure subscales are vitality, social functioning, role–emotional and mental health.

TABLE 53 Naftidrofuryl oxalate 600 mg vs placebo, HRQoL assessed using CLAU-S[a]

		No. of patients in analysis		Change in HRQoL		
Trial	Duration (weeks)	Naftidrofuryl oxalate	Naftidrofuryl oxalate group (0–100 scale)	Placebo	Placebo group	Comparison between groups
				Mean change from baseline read from graph/calculated from tables	Mean change from baseline read from graph/calculated from tables	
Spengel 2002[47]	24	358	351	Daily living 7.5/7.5	Daily living –1.3/–1.4	Daily living $p<0.001$
				Pain 8.4/6.4	Pain –0.4/–0.4	Pain $p<0.001$
				Social life 3.1/3.1	Social life –2.4/–2	Social life $p=0.001$
				Disease–specific anxiety 0.2/1.9	Disease specific anxiety 0.2/1.1	Disease-specific anxiety non-significant
				Mood 3.5/3.5	Mood –1.3/–1.2	Mood $p=0.03$

a CLAU-S, claudication scale. Internationally validated scale to measure quality of life in claudicants.[87]

TABLE 54 Pentoxifylline 1200 mg vs placebo, HRQoL assessed using SF-36 and/or WIQ

		No. of patients in analysis		Change in HRQoL		
Trial	Duration (weeks)	Pentoxifylline	Pentoxifylline group (0–100 scale)	Placebo	Placebo group	Comparison between groups
SF-36[a]						
Otsuka 21-98-213[34]				NR	NR	Physical health summary not significant
Creager 2008[70]	24	86	84	NR	NR	Non-significant in any component
WIQ[b]						
Creager 2008[70]	24	86	84	NR	NR	Non-significant

NR, not reported.

a The SF-36 comprises two main summary measures (physical health and mental health), which are composed of four subscales each. The four physical health subscales are physical functioning, role–physical, bodily pain and general health. The mental health summary measure subscales are vitality, social functioning, role–emotional and mental health.

b Walking Impairment Questionnaire self-rated measure of symptoms and walking impairment.[87]

al.[56] but no significant changes reported for the remaining two studies, O'Donnell *et al.*[83] (non-diabetics) and Dawson *et al.*[58]

Naftidrofuryl oxalate

- Only Spengel *et al.*[47] reported HRQoL for naftidrofuryl oxalate versus placebo. The outcome measure used was CLAU-S, and results were significant across four domains (daily living, pain, social life and mood) but not for the disease-specific anxiety domain.

Pentoxifylline

- Only Otsuka unpublished trial 21–98–213[34] and Creager *et al.*[70] reported HRQoL using the SF-36 for pentoxifylline versus placebo. Creager *et al.*[70] also reported WIQ.[70] No significant differences were reported.

Inositol nicotinate

- No studies reported HRQol data.

Summary

There is some evidence that cilostazol affects the physical function subscale of the SF-36, which suggests that there are some tangible improvements in physical function for the patient. This is somewhat supported by mixed evidence from WIQ, which suggests that patients perceive improvements in walking speed and distance in some cases. These health status improvements do not appear to translate into an overall improvement in HRQoL, with no changes in the mental health components, such as social functioning and the role–emotional subscale. The very limited evidence for naftidrofuryl oxalate suggests that improvements in pain are associated with improvements in daily living, social life and mood, but not with improvements in anxiety. The very limited evidence for pentoxifylline suggests that it does not improve HRQoL.

Discussion

Clinical effectiveness data were available from 26 RCTs. Blinded RCTs were available for all vasoactive drugs assessed within this report compared with placebo. The only vasoactive drugs for PAD compared head to head were cilostazol and pentoxifylline. Most of the trials were short term with follow-up of 24 weeks, with the exception of two trials. In practice most patients would take the vasoactive drugs for longer. Trial quality was generally good, with treatment groups within trials being comparable, blinding being maintained, and trials presenting ITT analysis.

The trial populations reported were relevant to UK practice. Populations across trials were very similar, having well-defined disease, with similar severity and duration of symptoms. Some trials specified that no specific advice was given about smoking cessation, diet and exercise, whereas others did not. Smoking tended to be balanced between treatment groups at baseline. Information about diet and exercise for participants was not reported, although there was no reason to believe that differences existed between treatment groups within trials.

For MWD and PFWD, all patients, including those in placebo groups, tended to show improvement on average. There was some evidence that walking distance outcomes were improved by cilostazol and naftidrofuryl oxalate to a significantly greater extent than improvement in placebo groups.

For walking distance data, most trials used standardised treadmill protocols, with the exception of RCTs of inositol nicotinate. Some trials used constant workload and others used graded test protocols, but treadmill protocols alone, across studies, do not seem to explain the difference between studies in whether or not a treatment effect was found. With a few exceptions, trials reporting a significant effect for MWD also reported a significant effect for PFWD.

Previously published Cochrane reviews found more improvement in MWD and PFWD compared with baseline for cilostazol than for placebo,[28] and in PFWD compared with baseline for naftidrofuryl oxalate than for placebo.[32] The Cochrane cilostazol review[28] included seven cilostazol versus placebo trials, all of which are included in this review. The Cochrane naftidrofuryl oxalate PFWD analysis[32] included six trials, of which three were excluded from this review because either the naftidrofuryl oxalate dose was not in line with UK marketing authorisation or the population included patients with Fontaine stage III.

The meta-analysis of MWD and PFWD included 10 studies. Several studies were excluded from the meta-analysis that had been included within the narrative synthesis because the published reports did not provide data in a form that was suitable for comparison across trials. In the analysis, it was assumed that data from the studies were missing at random and that the lack of usable data was not related to the observed treatment effect. Based upon evidence from the excluded studies, there is no evidence of publication bias for the naftidrofuryl oxalate trials. In addition, the studies that were excluded owing to short follow-up suggested a similar direction of effect.

Adverse events were minor and included headaches and gastrointestinal difficulties. Minor AEs were more frequent for cilostazol and pentoxifylline than for naftidrofuryl oxalate. Incidence of SAEs including cardiovascular events was not increased by the vasoactive drugs for PAD compared with placebo; however, most studies had relatively short follow-up time (up to 24 weeks) to address this outcome. Across studies, mortality rates had no significant differences between treatment groups; however, these were mostly based on relatively short follow-up times. Only two studies had follow-up of over 24 weeks:[49,69] the CASTLE study[49] of cilostazol versus placebo (which included some patients taking pentoxifylline in both groups) with a follow-up period of 3.5 years, and the Dettori *et al.* study[69] of pentoxifylline versus placebo with a follow-up period of 1 year. Neither of these trials reported treatment group differences for mortality or cardiovascular events. There were no trials of naftidrofuryl oxalate or inositol nicotinate with follow-up of over 24 weeks. ABPI was not reported by many trials, but mostly there was a non-significant trend to improve in both treatment groups, with some suggestion that cilostazol may improve ABPI more than placebo. HRQoL was measured in different ways across studies, making it difficult to compare treatments. There is some evidence that there are some tangible improvements in physical function for patients taking cilostazol, but these do not appear to translate into overal improvements in quality of life. Evidence for naftidrofuryl oxalate is very limited, but indicates that there may be improvements in both physical function and overall quality of life. Pentoxifylline does not seem to have HRQoL benefits but evidence is limited, and there was no evidence for inositol nicotinate.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Searches

A systematic literature search was undertaken to identify economic evaluations of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate compared with each other or no vasoactive drugs for the treatment of IC in people with PAD.

Appendix 1 reports details of the search strategy used and databases searched. None of the manufacturers submitted an economic model to evaluate the cost-effectiveness of the drugs.

Study selection, data extraction and quality assessment strategy

The inclusion and exclusion criteria applied to the searches are shown in *Table 55*. A health economic modeller applied the inclusion and exclusion criteria (YM), with checking by a second health economic modeller (HS). The quality of the economic evaluation studies that met the inclusion criteria was assessed using an adapted version of the Drummond and Jefferson *British Medical Journal* criteria for economic evaluation (Drummond *et al.*[88]) and the Consensus on Health Economic Criteria (CHEC)-list (Evers *et al.*[89]). Papers remaining in the review were read in detail and data extracted using a predesigned data extraction form (shown in *Appendix 6*). Data on the following were sought:

- study characteristics, such as the study question, study design, population, comparators, interventions, perspective, time horizon and type of modelling method used
- clinical effectiveness and cost parameters, such as effectiveness data, health-state utilities, cost and resource use data, discounting and other key assumptions
- baseline results and SA.

Results

The literature searches identified 187 potentially relevant citations. Only 25 of these appeared to relate to the economic evaluations of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate. From these, five full papers were reviewed, and two studies met the inclusion criteria: one is a published journal paper (Guest *et al.*[90]) and one is a conference poster presentation with only an abstract (Ratcliffe[91]). *Figure 5* shows the summary of the study selection and exclusion. The evaluation of the full paper met 9 out of the 10 Drummond and Jefferson quality assessment criteria and 15 out of the 19 CHEC-list criteria. The abstract met fewer assessment criteria due to limited information. Full details can be found in *Appendix 6*.

TABLE 55 Inclusion criteria for the systematic review of economic evaluations

Study design	Cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis or cost–utility analysis
Population	PAD patients with IC
Intervention	Cilostazol, naftidrofuryl oxalate, pentoxifylline and/or inositol nicotinate
Comparator	Placebo, exercise, surgical procedure and/or any vasoactive drug
Outcome	Cost-effectiveness

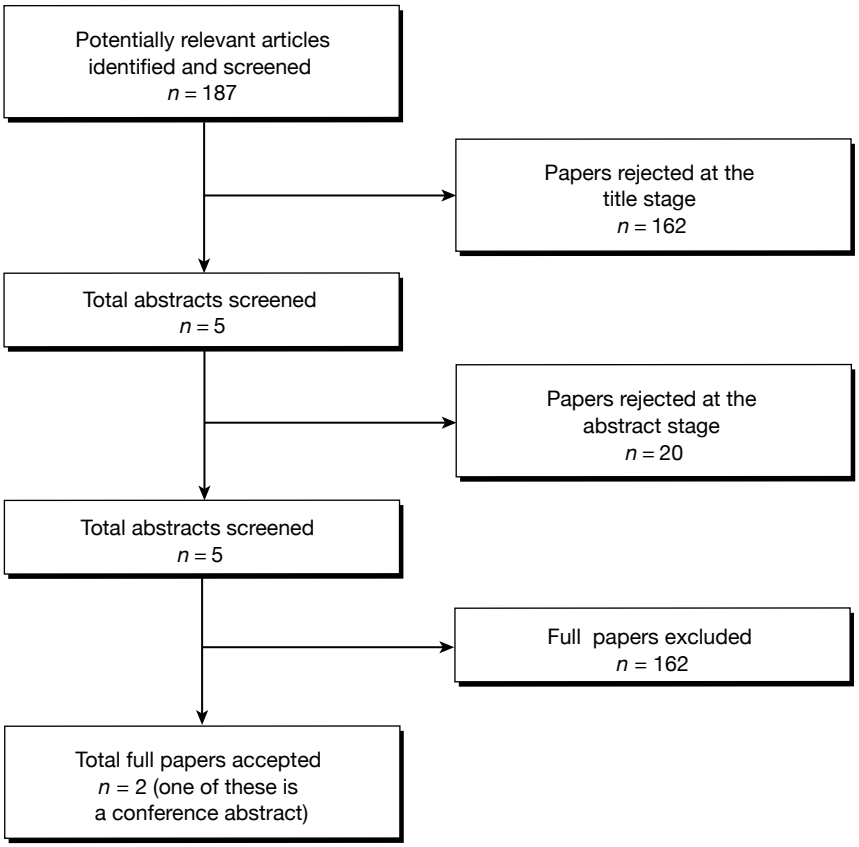

FIGURE 5 Summary of economic evaluation selection and exclusion.

The characteristics and the main results of the economic evaluations are summarised in *Table 56*.

Guest *et al.*[90] presented the methods and results of a cost-effectiveness analysis comparing cilostazol [100 mg twice daily (b.i.d.)], naftidrofuryl oxalate [300 mg b.i.d. or 200 mg three times daily (t.i.d.)] and pentoxifylline (400 mg t.i.d.) within UK patients who are 40 years of age and have had at least 6 months of IC. A decision tree model was developed in Data Professional (TreeAge Software Inc., Williamstown, MA, USA) to model the management of IC patients over a period of 24 weeks. The analysis was carried out from the UK NHS perspective and the outcome of the model was the change in the percentage improvement in MWD versus the change in costs. HRQoL was not considered within the model.

The decision tree model considered the decision by a vascular surgeon to initially treat a patient with either cilostazol, naftidrofuryl oxalate or pentoxifylline. Within the model, a patient may continue the initial treatment for 24 weeks or discontinue the initial treatment. Patients who do not continue with the initial treatment for 24 weeks may either switch to another drug or discontinue drug treatment. Additionally, patients may undergo an angioplasty or bypass surgery.

The effect of each drug in improving MWD for 24 weeks was derived from six published double-blind, placebo-controlled RCTs,[61,65,92–95] all of which were identified for inclusion within this clinical effectiveness review. RCTs that were not blinded or did not report treadmill speeds were excluded. Studies that used varying treadmill speeds or gradients were also excluded. The probabilities of continuing/discontinuing treatment were obtained from published studies. An assumption was made that patients who stop receiving treatment will achieve the same improvement of MWD as those patients on placebo. In the case of patients who switched drugs

TABLE 56 Summary of published economic analyses

	Author	
Study	**Guest *et al.*[90]**	**Ratcliffe (abstract)[91]**
Country and year of publication	UK, 2005	UK, 2005
Sponsor	Otsuka Pharmaceuticals	Unclear
Type of analysis	Cost-effectiveness (improvement in MWD at 24 weeks)	Cost–utility
Health economic perspective	NHS in the UK	NHS in Scotland
Model type	Decision tree	Unclear
Software used	DATA PROFESSIONAL (TreeAge Software, Inc., Williamstown, MA, USA) and CRYSTAL BALL (Oracle, Montreal, QC, Canada)	Unclear
Intervention(s)	Cilostazol	Cilostazol
Comparator(s)	Naftidrofuryl oxalate and pentoxifylline	Placebo
Population characteristics	Patients in the UK (aged 40 years) who have 24 weeks of symptomatic IC, secondary to PAD	Patients in Scotland with IC
Time horizon	24 weeks	24 weeks
Effectiveness data	Six published RCTs; panel of 12 vascular surgeons in the UK	Two published RCTs
Cost year and currency	2002–3, UK £	Unclear
Health economic outcomes	Change in the percentage improvement in MWD vs change in costs	Cost per QALY
Base-case results	*Cilostazol vs naftidrofuryl oxalate*: 32% increase in the percentage improvement in MWD for a 12% increase in costs	ICER: £12,500 per QALY
	Cilostazol vs pentoxifylline: 67% increase in the percentage improvement in MWD for a 2% decrease in costs	
	Naftidrofuryl oxalate vs pentoxifylline: 27% increase in the percentage improvement in MWD for a 14% decrease in costs	

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

and would have been on the new drug for 12 or 18 weeks, it was assumed that these patients would achieve the same improvement in MWD at these time points as the drug-treated patients in the trials.

Costs included diagnosis of IC, drug costs, follow-up visits by the vascular surgeon and/or general practitioner (GP), supervised exercise, angioplasty and bypass surgery. The frequency of surgeon and GP visits and the probabilities of using different types of diagnostic techniques, switching to other drugs and undergoing supervised exercise, angioplasty or bypass surgery were based on interviews of 12 vascular surgeons in the UK. Unit resource costs were obtained from NHS reference costs, drug tariff and published studies. All costs were presented in 2002–3 UK pounds sterling. Costs and outcomes were not discounted due to the short period of modelled time.

Probabilistic sensitivity analyses (PSAs) were undertaken with uncertainty around parameters of percentage improvement in MWD, probabilities and resource use.

The results of the model suggested that starting treatment with cilostazol instead of naftidrofuryl oxalate increases the percentage improvement in MWD by 32% (from 57% to 75%) for a 12% increase in costs (from £801 to £895). Starting treatment with cilostazol instead of pentoxifylline was found to increase the percentage improvement of MWD by 67% (from 45% to 75%) and reduce costs by 2% (from £917 to £895). Starting treatment with naftidrofuryl oxalate instead of pentoxifylline was found to increase the percentage improvement in MWD by 27% (from 45% to 57%) and decrease costs by 13% (from £917 to £801). The sensitivity analyses suggest that

the variability around the incremental cost-effectiveness was driven by the uncertainty in the probabilities of continuing treatment for 24 weeks, the percentage improvement in MWD and the probability of having diagnostic tests among patients who complete 24 weeks of treatment.

The study has several limitations:

- There was not a 'no vasoactive drug' comparator.
- The time horizon was 24 weeks.
- Effectiveness was evaluated only in terms of improvement in MWD. HRQoL (utilities) was not evaluated.
- No model validation was reported.

Ratcliffe[91] presented a brief description of the methods and results of a cost–utility analysis of cilostazol (100 mg) versus placebo for Scottish patients with IC. The study was only available in an abstract as a conference poster and no full paper was available. The assessment group attempted to contact the author but this was unsuccessful. A decision analytical model (type of model was not specified) was built to evaluate the cost-effectiveness of cilostazol versus placebo over a period of 24 weeks. The analysis was carried out from the Scottish NHS perspective and the outcome of the model was the incremental cost per quality-adjusted life-year (QALY).

Effectiveness was based on two published 24-week RCTs of cilostazol versus placebo (not referenced in the abstract). HRQoL was measured in the trials using the SF-36. The scores were converted into utilities using a validated mapping algorithm (not referenced in the abstract). Costs included drug costs and treatment costs. Treatment costs were based on an independent survey of expert clinical opinion in Scotland. Both costs and QALYs were not discounted due to the short time horizon of the model.

The model results suggested that the incremental cost–utility ratio for cilostazol over placebo was estimated to be £12,500 per QALY gained. SA suggested that the results were most sensitive to the cost of an angiography, the utility values estimated and the price of cilostazol. Detailed evaluation of the model was not possible because there was no published full paper available.

Summary

There are currently no economic evaluations of cilostazol, naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, which consider long-term costs and outcomes. Only one economic evaluation of cilostazol considered outcomes in terms of a cost per QALY and this was reported in a non-peer-reviewed conference abstract only. A de novo economic evaluation is therefore required.

Independent economic assessment

Methods

This section provides details of a model developed by the assessment team and used to evaluate the cost-effectiveness of each vasoactive drug for PAD within its licensed indication compared with no vasoactive drug and with the remaining vasoactive drugs for PAD.

Model description

Patient population

A Markov model was developed in Excel® (Microsoft Corporation, Redmond, WA, USA) to determine the cost-effectiveness of each drug compared with no vasoactive drugs for PAD and with the remaining vasoactive drugs. The population considered was patients who have stable (at least for the past 3 months, which is the inclusion criterion for most of the RCTs identified)

and symptomatic IC, secondary to PAD. Furthermore, only patients whose symptoms continue despite a period of conservative management, such as advice to cease smoking or do more exercise, were considered by the model. The model did not distinguish between patients who are in primary care and secondary care, because no published evidence was identified to support this classification. The model also did not distinguish between patients with different severity of the disease, because the considered patient population was already narrowly defined (i.e. patients with stable IC who fail conservative management) and no published evidence was identified to support a subgroup analysis. However, an exploratory subgroup analysis was undertaken around patients with more severe IC who might receive angioplasty following drug discontinuation.

Interventions and comparators

The four drugs considered within their licensed indications for IC were cilostazol (200 mg per day), naftidrofuryl oxalate (600 mg per day), pentoxifylline (1200 mg per day) and inositol nicotinate (4 g per day). These were compared with each other and no vasoactive drugs for PAD. As it was not possible to include inositol nicotinate within the meta-analysis of MWD or PFWD, this drug has not been included within the main analysis. However, inositol nicotinate has been included within a threshold analysis to assess how many QALYs would be required for it to have a cost per QALY gained below £20,000 and £30,000 compared with no vasoactive drug.

Outcomes

The model outcome is the incremental cost per QALY gained. Owing to lack of evidence around the utilities of patients having naftidrofuryl oxalate, pentoxifylline and inositol nicotinate, change in MWD was used as a surrogate measure to estimate the change in utilities based on a regression model. MWD was selected as the surrogate because it is the primary outcome of most identified RCTs. More detail about this regression is provided below (see *Estimate of model parameters*). The life-years gained outcome is not presented within this analysis because the drugs are not expected to have an impact on life-years, only on patient quality of life.

Model structure

The structure of the decision model is presented in *Figure 6*. The model includes three main health states: vasoactive drug treatment (where patients receive one of the four drugs under evaluation); no vasoactive drug treatment (where patients receive none of the four drugs or have discontinued); and death. Patients begin in the vasoactive drug treatment state and have a weekly probability of moving to the no vasoactive drug treatment state by discontinuing. Patients also have a weekly probability of dying of any cause from both the vasoactive drug treatment state and the no vasoactive drug treatment state. Patients who do not receive any of the four drugs have

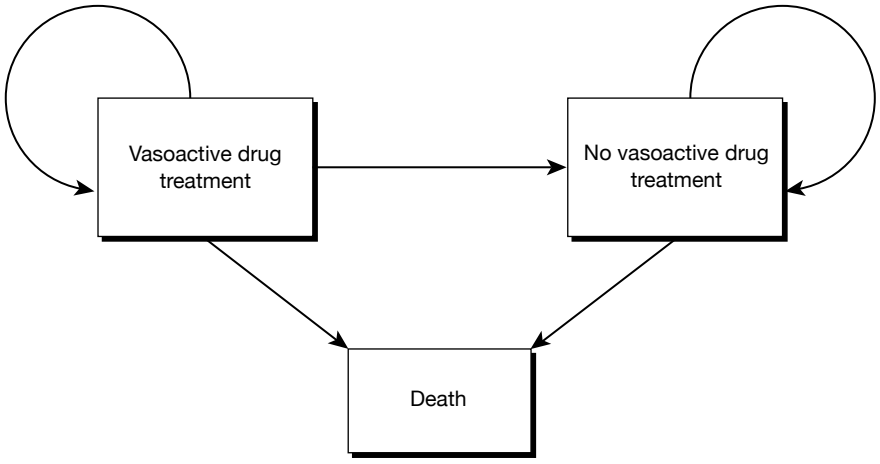

FIGURE 6 Diagram of the structure of the decision model.

zero time in the vasoactive drug treatment state. All patients are in Fontaine stage II and have had persistent IC symptoms despite a period of conservative management to be eligible to receive the vasoactive drugs for PAD. The health states are classified according to whether or not the patients are receiving vasoactive drugs for PAD rather than by progression through different disease stages (i.e. Fontaine stages II–IV), as the drugs are for symptom relief and it is assumed that they do not have an impact on disease progression.

Patients in the vasoactive drug treatment state could improve their quality of life as a result of the treatment effect. In the base-case analyses, the only extra cost for patients receiving the vasoactive drugs for PAD compared with no vasoactive drugs is the drug acquisition cost.

Patients may discontinue the drug because of AEs, death or other reasons of non-compliance. Switching to another vasoactive drug after discontinuation and returning to the same vasoactive drug after discontinuation were not considered within the model owing to lack of published evidence. In addition, expert clinical opinion suggested that this would not be standard practice within England and Wales (Steven Thomas, Jonathan Michaels and Gerard Stansby, personal communication).

Patients who have discontinued the drug therapy were assumed to incur no extra costs compared with those patients initially having no treatment. It was also assumed that the drugs are only effective while they are being given, as suggested by the study by Keiffer *et al.*,[65] which recorded MWD for 2 months beyond treatment discontinuation.[65] Therefore, patients discontinuing a vasoactive drug will have no extra health gains (regarding utility, walking distance or disease progression) compared with no vasoactive drug.

Time horizon

The time horizon of the model was 100 years to ensure that all differences in costs and benefits are captured within the model, and a starting age of 66 years was used to represent the average age of patients with IC. The starting age was based on the average age of patients within the CASTLE study,[49] which has the longest follow-up period and the largest sample size of all RCTs (Hiatt *et al.*[49]). A time cycle of 1 week was chosen as being sufficiently short to capture the effect of treatment, and the time period was in line with that used in the trials for measurement of walking distance and quality of life.

Discounting

All costs and QALYs were discounted at a rate of 3.5% per year.

Estimate of model parameters

Maximal walking distance and utilities

The majority of studies reported the change in MWD for the vasoactive drug and control arms, but only some stated that quality-of-life data were collected and only two RCTs (both for cilostazol)[61,83] reported quantitative data for SF-36 quality-of-life outcomes that can be converted to utilities using published algorithms.[96] No studies of naftidrofuryl oxalate, pentoxifylline or inositol nicotinate provided sufficient quality-of-life evidence to estimate utility outcomes associated with these drugs. However, in order to compare the cost-effectiveness of these vasoactive drugs with other interventions routinely funded by the NHS, quality-of-life estimates are required for all drugs being assessed so that an incremental cost per QALY can be calculated. Given the limited published data around quality-of-life outcomes, the authors of the identified RCTs were contacted to ask for the patient-level or summary SF-36 data if the paper mentioned that the SF-36 questionnaire was used within the RCT. The aim of this was to attempt to determine a relationship between the change in MWD and the change in utility scores that could be used to estimate the utility gains associated with the drugs being assessed for which there were

only MWD data and no utility data. MWD was chosen to be linked to utility because MWD is the primary outcome of most identified RCTs. Most of the authors responded (80%) but could not provide these data. One author (O'Donnell) provided a complete set of patient-level data ($N = 106$) for MWD and SF-36 scores based on a recent RCT in the UK comparing cilostazol and no vasoactive drug for PAD.[83]

The SF-36 conversion algorithm, as defined by Ara and Brazier,[96] was applied to the patient-level data from O'Donnell *et al.*[83] to calculate the utilities of each patient at week 0 and week 24 (the period of the RCT). These patient-level data were then used to test for a correlation between change in MWD and change in utilities from week 0 to week 24, which is the trial period of most identified RCTs. The correlation coefficient of the absolute difference in MWD on the log scale (log of MWD in week 24 minus log of MWD in week 0) and absolute difference in utilities (utility in week 24 minus utility in week 0) was 0.39 and the scatterplot is presented in *Figure 7*. A linear regression model was fitted to these data to predict the absolute change in utilities from the absolute change in MWD on the log scale during the RCT period. A linear relationship was assumed owing to lack of evidence of other types of underlying relationship. One regression model was fitted to the placebo and cilostazol data combined and this maximised the sample size for the regression analysis. The underlying assumption was that the relationship between MWD and utility is independent of treatment, such that the relationship can be applied to all of the vasoactive drugs being evaluated and the no vasoactive drug comparator. This was tested by including an additional term in the regression analysis representing the treatment effect which was not significant. The fitted regression based on the O'Donnell *et al.* patient-level data[83] and used in the economic model is:

$$\begin{aligned}\text{absolute change in utilities} = {} & -0.0076372417 \\ & + \text{absolute change in MWD on the log scale} \\ & \times 0.045770316 \end{aligned} \qquad \text{[Equation 1]}$$

It is reassuring that the constant within the regression model is very close to zero, which means that when there is no change in MWD, there is also no change in the utility score. The variance–covariance matrix of the slope and the intercept of the regression model is presented in *Table 57*. To represent the uncertainty of the regression model, the matrix was used to sample the two coefficients of the regression model in the PSA. By using the variance–covariance matrix within the PSA, the uncertainty around the relationship between MWD and utility is propagated through the model and represented within the model results. However, this uncertainty does not account for any differences in this relationship between the vasoactive drugs.

The estimate of treatment effect that is generally reported in the RCTs of the vasoactive drugs for PAD is the percentage change between treatments based on the geometric mean change from baseline. The reason for this is because the raw data are analysed on the log scale and anti-logging the sample means on the log scale produces sample geometric means. The motivation for transforming these data to the log scale is to produce a scale on which the treatment effects can be assumed to be linear. We use a similar rationale when relating the log of the difference in MWD to the absolute difference in utilities, with treatment effects in terms of utilities assumed to be linear on the absolute scale.

The regression model was applied to all four drugs and to no vasoactive drug treatment to estimate the absolute change in utilities given a certain change in MWD from week 0 to week 24 on the log scale. The baseline utilities, i.e. the utilities for patients at week 0, were also estimated from the patient-level data.[83] All estimated absolute changes in utilities were applied to the baseline utilities. The estimated mean of the baseline utilities was 0.4838 and the estimated SD was 0.1001. The patient-level data used for this analysis were collected within the latest reported

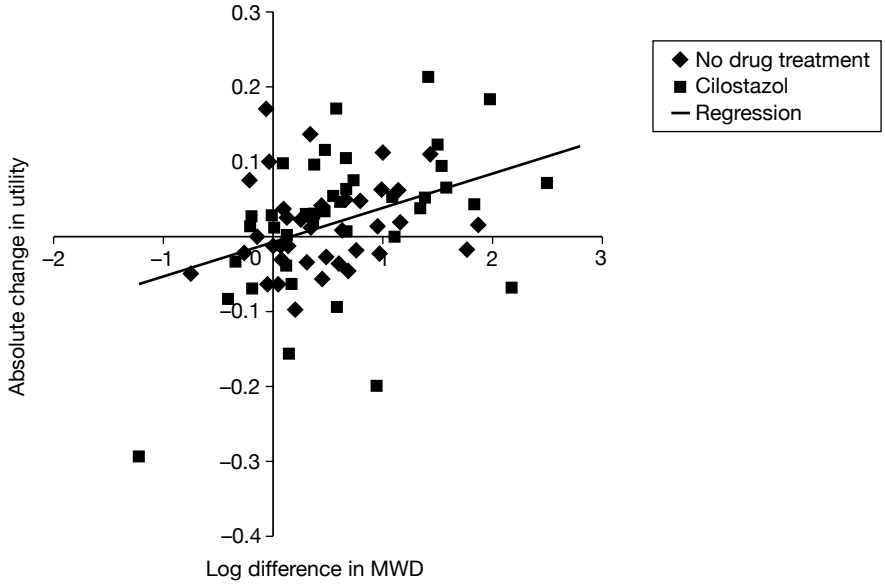

FIGURE 7 The relationship between the absolute change in utilities and the absolute change in MWD on log scale based on patient-level data (O'Donnell *et al.*[83]).

TABLE 57 Variance–covariance matrix of the slope and intercept of the regression model

	Slope	Intercept
Slope	0.00015001	
Intercept	–0.0000813	0.000111

clinical trial on cilostazol and were based on patients in the UK.[83] Therefore, the mean baseline utilities should reflect the quality of life of patients with stable IC in the UK NHS context. SA was performed to test alternative baseline utilities.

The SF-36 data were also available at week 6 for each patient; and the mean utility change over time (at weeks 0, 6 and 24) for all patients is presented in *Figure 8*. Several RCTs of cilostazol, naftidrofuryl oxalate and pentoxifylline reported the change in MWD over time, which also suggested a linear increase.[58,61,65,66] In the absence of any additional evidence, this suggests that a linear model may be appropriate when representing the increase in utilities over the first 24 weeks. For patients who receive a vasoactive drug beyond 24 weeks, it was assumed the utility remains constant from week 24 onwards, due to the lack of published evidence beyond this time point. For patients who discontinue treatment, it was assumed the utility returns to the level of the no vasoactive drug group at the time of discontinuation.

Given that the HRQoL of the general population is dependent upon age, it is important to take this into account in the model. General population utility estimates from Ara and Brazier[97] were applied using a regression analysis of utility versus age. The age-related utility was calculated by the following formula:

$$\text{utility} = A \times (\text{age}) + B \times (\text{age} \times \text{age}) + C \qquad \text{[Equation 2]}$$

where $A = -0.0001728$, $B = -0.000034$ and $C = 0.9584588$.

The ratio between the utility at age 66 years using this formula for the general population and the utility at age 66 years for IC patients estimated using the regression above was calculated. The age-related utility within the general population was then adjusted to account for the lower average utility associated with IC patients by multiplying it by this ratio for each age within the model.

Given the limited evidence in terms of utilities, a threshold analysis has also been undertaken to assess the QALY gain required for each of the drugs to be considered to be cost-effective compared with no vasoactive drug at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained. The threshold analysis is the only way in which the cost-effectiveness of inositol nicotinate is assessed owing to the lack of effectiveness data available for this drug.

Table 58 presents the predicted mean utility values for each vasoactive drug and no vasoactive drug treatment at week 24.

Adverse events

Within the trials identified within the systematic review, rates of SAEs were similar between the treatment groups and the placebo groups, and rates of minor AEs were similar between naftidrofuryl oxalate and placebo and inositol nicotinate and placebo. The trials of cilostazol and pentoxifylline reported higher rates of minor AEs within the treatment groups than the placebo groups, which were mainly headaches, diarrhoea, peripheral oedema and palpitations (see *Chapter 3*, *Adverse events and serious adverse events*, above, for further details). Clinical expert advice suggests that these patients are unlikely to require additional treatment as they would discontinue the vasoactive drugs, as suggested by the trials that demonstrate higher discontinuation rates for cilostazol and pentoxifylline. This means that there are unlikely to be any additional costs incurred as a result of these AEs. As these minor AEs would generally be experienced for a short time period, and, given that these patients already have a lower utility on

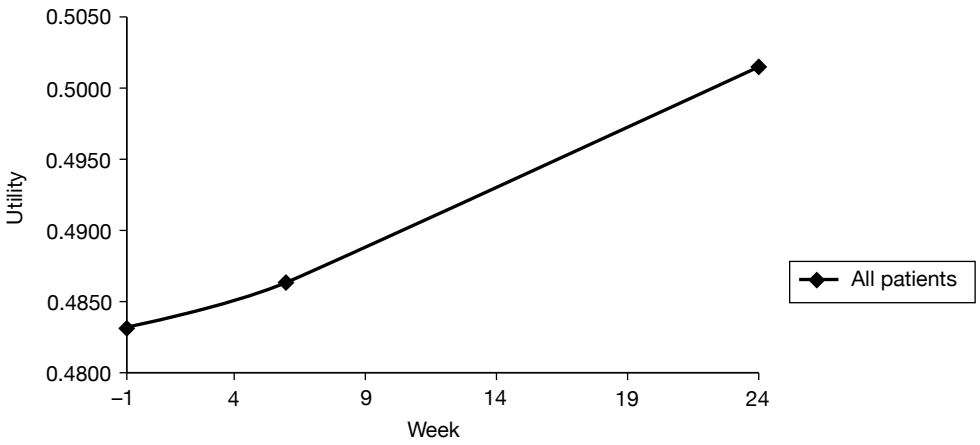

FIGURE 8 Mean utility change over time (at weeks 0, 6 and 24) based on patient-level data (O'Donnell *et al*.[83]).

TABLE 58 Mean utilities for each vasoactive drug and no vasoactive drug treatment at week 24

Drug	Mean utility at week 24
No vasoactive drug treatment	0.4873
Cilostazol	0.4973
Naftidrofuryl oxalate	0.5088
Pentoxifylline	0.4919

average than that experienced by the general population, the impact of these minor AEs upon utilities is expected to be minimal (i.e. unlikely to affect total QALYs to fewer than three decimal places). The quality of life of patients will therefore be affected within the model only by the patients discontinuing and hence having a lower quality of life than if they remain on treatment.

Discontinuation of treatment

The rates of discontinuation for the first 24 weeks were based on meta-analyses of all identified RCTs. The long-term discontinuation rate (i.e. beyond 24 weeks) was reported in only one study of cilostazol (Hiatt *et al.*[49]), which reported that 68% of patients in the cilostazol arm discontinued with the drug by 36 months. Expert clinical opinion suggests that many discontinuations beyond 24 weeks are likely to be due to the patients' condition improving or mortality and hence the patients no longer require the drug, rather than discontinuations being because of any AEs associated with the drugs. Therefore, given the lack of published evidence, the long-term discontinuation rates of the remaining three drugs were assumed to be the same as for cilostazol.

Mortality

It was assumed that all drugs are for symptomatic relief rather than having an impact on the progression of the disease (Steven Thomas, Jonathan Michaels and Gerard Stansby, personal communication). Therefore, all patients within the model have the same overall mortality rates. General population mortalities were based on the latest life tables of the general population in England and Wales [Office for National Statistics (ONS)].[98] The mortalities of the patient population in the model were calculated by multiplying the general population mortality by the relative risk of mortality of IC patients, which was assumed to be 1.6 based upon a study of the risk of mortality and cardiovascular disease associated with ABPI by Heald *et al.*[99]

Resource use and costs

The cost of each drug was based on the latest drug tariff updated in October 2010.[26] Where there is more than one licensed dose available, the cost of the drug was based upon the doses used within the RCTs identified within the clinical effectiveness review, which are also current practice in the UK. Inositol nicotinate is supplied in two packs: 100 tablets of 500 mg at a price of £30.76 (6.152p per 100 mg) and 112 tablets of 750 mg at a price of £51.03 (6.075p per 100 mg). The former pack was used for estimating costs as it has a higher unit price (in terms of 100 mg) and the identified inositol nicotinate RCTs used a dose of 4 g per day (which can not be divided by 750-mg tablets). Naftidrofuryl oxalate is available both as a generic drug at a price of 5.38p per 100 mg and produced by the manufacturer that held the original patent at a higher price of 9.83p per 100 mg. The former cost was used in the base-case model because this is expected to be the acquisition cost in practice. Drug costs included within the model are presented in *Table 59*.

Assessment of cost-effectiveness

The main results are an estimate of the total costs and total QALYs of each intervention and the comparator, and the incremental cost-effectiveness ratios (ICERs). In incremental analyses, one intervention may be dominated or extendedly dominated by the comparator. Dominance is defined as an intervention being less effective and more expensive than its comparator. Extended dominance is present if the ICER for a given treatment alternative is higher than that of the next more effective comparator. In total, 10,000 PSA runs were implemented to estimate the expected costs and QALYs. A cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness plane are included to give a measure of the uncertainty reflected by the model. A range of univariate sensitivity analyses were performed to explore the sensitivity of the model results to key parameters and assumptions.

TABLE 59 Resource use and costs model inputs

Drug	Licensed dose	Brand name	Dose used for estimating costs (mg/day)	Drug specification (manufacturer)	Quantity	Price (£)	Weekly costs (£)	Remarks
Cilostazol	100 mg twice daily (30 minutes before or 2 hours after food), i.e. 200 mg per day	Pletal	200	Cilostazol 100-mg tablets (Pletal)	56	35.31	8.83	
Naftidrofuryl oxalate	100–200 mg three times daily, i.e. 300 or 600 mg per day	Generic	600	Naftidrofuryl oxalate 100-mg capsules	84	4.52	2.26	
		Praxilene	600	Naftidrofuryl oxalate 100-mg capsules (Praxilene)	100	9.83	4.13	
Pentoxifylline	400 mg two or three times daily, i.e. 800 or 1200 mg per day	Trental 400, Pentofin, Oxpentifylline	1200	Pentoxifylline 400-mg modified-release tablets (Trental 400)	90	19.68	4.59	
Inositol nicotinate	3 g daily in two or three divided doses; maximum 4 g daily (tablets 500 mg or 750 mg)	Hexopal, Hexopal Forte, Hexanicotol	4000	Inositol nicotinate 500-mg tablets (Hexopal)	100	30.76	17.23	The drug is also supplied as 750-mg tablets in quantities of 112 at £51.03 (manufactured by Hexopal)

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was applied to the following input parameters to represent the uncertainty around the model inputs:

- discontinuation rates for the four drugs within 24 weeks
- discontinuation rates for cilostazol beyond 24 weeks (assumed to be equivalent for all other vasoactive drugs for PAD)
- change in MWD on the log scale for the vasoactive drugs and no vasoactive drug
- baseline utilities for patients at week 0
- coefficients (constant and slope) of the regression model to predict the change in utility from the change in MWD.

Table 60 summarises the input parameters and their base-case mean values and distributions (used for PSA) for the model.

Univariate sensitivity analysis

Univariate SA can be used to assess the impact of alternative assumptions upon the model results. This means that if there is uncertainty around any of the assumptions within the base-case model, it is possible to understand whether or not they are important in terms of the impact upon the results. The following univariate sensitivity analyses were performed to explore the uncertainty of model assumptions.

Sensitivity analysis 1: utility remains the same as when on the drug if discontinuation occurs after 24 weeks

Clinicians suggest that a proportion of patients discontinue with the drug after 24 weeks because their condition has improved. The SA assumes that if the patients discontinue the drug after 24 weeks, the utility remains the same over this subgroup of patients' remaining lifetime as when on the drug at the time of discontinuation.

Sensitivity analysis 2: alternative baseline utility

Two RCTs of cilostazol were identified within the clinical effectiveness review, which presented SF-36 data that could be converted to utilities.[61,83] The SF-36 data were converted into utilities for both studies and found to be very different from each other: a utility of 0.4838 versus 0.7562. The former utility was used within the base-case analysis, and the latter was tested within this SA. Utility would also be variable between patients in practice. The relationship between baseline utility and utility at 24 weeks is assumed to remain the same within this analysis.

Sensitivity analysis 3: alternative cost for naftidrofuryl oxalate

In the base-case model, the cost of generic naftidrofuryl oxalate is used. The drug is also produced by the manufacturer that held the patent (with a brand name of Praxilene), but at a higher cost of £4.13 per week compared with £2.26 per week in the base case. This SA was performed to test the impact on cost-effectiveness results using the alternative drug cost.

Sensitivity analysis 4: shorter time horizon

Most of the evidence on change in MWD, change in utility and discontinuation rates is based on RCTs that have a follow-up period of < 24 weeks. Beyond 24 weeks, a number of assumptions have been made within the model around the change in utilities and the drug discontinuation rates owing to a lack of published evidence. This SA tests a shorter time horizon of 24 weeks where data are most robust.

TABLE 60 Model input parameters for the base-case scenario

Parameters	Mean	Distribution (parameters)	Source
Age	66 years	Fixed	Hiatt *et al.* 2008[49]
Discount rate (costs and utilities)	3.5%		NICE 2008[100]
Relative risk of mortality for patients with IC	1.6		Heald *et al.* 2006[99]
Discontinuation rates (%)			
Proportion of patients discontinuing cilostazol within 24 weeks	27.8	Normal (27.8% to 1.5%)	Based on meta-analysis of RCTs reported in *Chapter 5*
Proportion of patients discontinuing naftidrofuryl oxalate within 24 weeks	11.1	Normal (11.1% to 2.5%)	
Proportion of patients discontinuing pentoxifylline within 24 weeks	29.1	Normal (29.1% to 1.8%)	
Proportion of patients discontinuing inositol nicotinate within 12 weeks[a]	20.0	Normal (20.0% to 6.3%)	
Proportion of patients discontinuing cilostazol (and other vasoactive drugs for PAD) within 36 months	68	Normal (68.0% to 1.7%)	Hiatt *et al.* 2008[49]
Drug costs (£)			
Weekly costs of cilostazol	8.83	Fixed	Drug Tariff, October 2010 (www.drugtariff.co.uk)[26]
Weekly costs of naftidrofuryl oxalate	2.26		
Weekly costs of pentoxifylline	4.59		
Weekly costs of inositol nicotinate	17.23		
Baseline utility			
Baseline utility	0.4838	Beta (11.58 to 12.36)	Based on patient-level data from O'Donnell *et al.*[83]
Change in MWD on the log scale			
Change in MWD on the log scale for no vasoactive drug (week 0 to week 24)	0.2419	The joint posterior distribution from the random effects network meta-analysis analysed in WinBUGS	Meta-analysis reported in *Chapter 5*
Change in MWD on the log scale for cilostazol (week 0 to week 24)	0.4615		
Change in MWD on the log scale for naftidrofuryl oxalate (week 0 to week 24)	0.7134		
Change in MWD on the log scale for pentoxifylline (week 0 to week 24)	0.3427		
Change in MWD on the log scale for inositol nicotinate (week 0 to week 24)[b]	NA		
Regression model			
Intercept of the regression model	–0.0283	Based on the variance–covariance matrix of the intercept and slope (see *Table 57*)	Based on patient-level data from O'Donnell *et al.*[83]
Slope of the regression model	0.0995		

NA, not available.

a There is no RCT reporting the discontinuation rate for inositol nicotinate for 24 weeks. Therefore, the discontinuation rate for 12 weeks was used.

b The change in MWD on the log scale can not be obtained for inositol nicotinate because no RCT provides sufficient data for the meta-analysis.

Sensitivity analysis 5: alternative starting age

The base-case model assumes that the cohort of patients within the model begin treatment at age 66 years. This SA assesses whether or not the age at which patients begin treatment affects the cost-effectiveness of the drugs. A starting age of 55 years (the age at which the disease begins being prevalent in the population) was applied to test the robustness of the results to starting age.

Sensitivity analysis 6: alternative long-term discontinuation rates

No evidence on the long-term discontinuation rates of pentoxifylline, naftidrofuryl oxalate or inositol nicotinate was identified. The base case assumes that the discontinuation rates of these vasoactive drugs beyond 24 weeks are the same as the discontinuation rates of cilostazol, as clinicians suggest that the reasons for discontinuation beyond 24 weeks would be more likely related to improvements in disease than to AEs, as for the first 24 weeks. However, in order to test the impact of alternative discontinuation rates beyond 24 weeks, the SA assumes that the long-term discontinuation rates of pentoxifylline and naftidrofuryl oxalate maintain the same relative ratios compared with cilostazol within the 24 weeks (i.e. as the discontinuation rate of pentoxifylline and naftidrofuryl oxalate are, respectively, 5% more and 60% less than that of cilostazol within the first 24 weeks. It is assumed that beyond 24 weeks the discontinuation rates of pentoxifylline and naftidrofuryl oxalate are also, respectively, 5% more and 60% less than the long-term discontinuation rate of cilostazol).

Sensitivity analysis 7: angioplasty procedure for patients discontinuing within 24 weeks

Clinical practice regarding prescribing of vasoactive drugs for IC patients whose symptoms continue despite a period of conservative management varies among clinicians. Some clinicians will assess whether angioplasty is appropriate within this patient group and if so undertake this immediately. If angioplasty either is not appropriate or fails then those patients may receive vasoactive drugs. Alternative practice is for IC patients to be offered vasoactive drugs whether or not they may be considered for angioplasty. If the drugs are unsuccessful, patients may then be considered for angioplasty if this is an appropriate option, but, if successful, these vasoactive drugs may negate or delay the need for angioplasty. The former clinical practice is considered within the base-case analysis. This SA concerns the latter of these two alternative clinical practices.

The subgroup of patients who would be potentially offered angioplasty may be prespecified as they tend to have a worse prognosis. It may be that the cost-effectiveness of the assessed drugs is different within this subgroup of patients and hence an exploratory analysis has been undertaken around this subgroup. The analysis is considered to be exploratory, as there is no published evidence reporting the costs and outcomes associated with this subgroup and hence it is mainly based upon personal communication with the team of clinical advisors (Steven Thomas, Jonathan Michaels and Gerard Stansby, personal communication). Those patients with a worse prognosis in whom angioplasty is potentially appropriate were estimated to represent around 15% of the overall patient group included within this assessment (Steven Thomas, Jonathan Michaels and Gerard Stansby, personal communication).

A set of simplified assumptions were made for this SA:

- Patients who discontinue the vasoactive drugs within 24 weeks will have angioplasty.
- Patients in the comparator group with no vasoactive drug treatment will have angioplasty at week 0.
- The costs of angioplasty include two hospital visits (£99.03 per visit),[90] one imaging (£189.90)[101] and the angioplasty procedure (£925.58).[90] All costs were adjusted to 2009–10 prices.[102]
- Owing to lack of comparative evidence around the utility associated with angioplasty, it will be varied over the largest plausible range within this analysis and will be related to the utility associated with naftidrofuryl oxalate (the drug associated with the highest utility). The lower bound of the utility increase due to angioplasty is assumed to be zero. The upper bound is assumed to be the same as the utility of the general population used in the model. The utility associated with angioplasty is therefore assumed to be:

  - equivalent to the utility associated with naftidrofuryl oxalate (the drug associated with the highest utility)
  - 20% higher than the utility associated with naftidrofuryl oxalate
  - 40% higher than the utility associated with naftidrofuryl oxalate
  - equivalent to the utility of the general population used in the model, which is around 60% higher than the utility associated with naftidrofuryl oxalate.
- Patients who have no vasoactive drugs and have angioplasty will have the utility described above for 1 year. The utility will then decrease to that associated with placebo.
- Patients who have angioplasty after discontinuation of the vasoactive drugs will have the utility described above until the end of the first year; it will then decrease to the level of utility associated with placebo.
- The baseline utility for these patients in practice will be lower, as they have a worse prognosis by definition within this subgroup analysis. However, the impact of baseline utility is tested within SA3 and hence is not altered here.

Sensitivity analysis 8: informative prior distributions within network meta-analysis

The impact of more informative prior distributions for the between-study SD and treatment effects within the network meta-analysis upon the results of the meta-analysis was tested and reported (see *Chapter 3*, *Maximal walking distance meta-analysis*). The results of the network meta-analysis when an informative prior distribution from SA5 was used [$\tau \sim U(0, 0.2)$, $\mu \sim N(100)$] and tested within the model.

Results

All results presented within this section are discounted.

Cost–utility analysis – base case

The total costs, the total QALYs and the ICERs associated with the base case are presented in *Table 61*.

The base-case results suggest that naftidrofuryl oxalate has the lowest additional costs (£298) compared with no vasoactive drug, and cilostazol has the highest additional costs (£964), whereas the additional cost of pentoxifylline is £493. In terms of total QALYs, naftidrofuryl oxalate is estimated to increase QALYs by 0.049 (from 4.975 to 5.024) compared with no vasoactive drug for PAD. Pentoxifylline is estimated to have the smallest QALY gains (0.009) compared with no vasoactive drug. Cilostazol increases QALYs by 0.019 compared with no vasoactive drug. Overall, the results show that both pentoxifylline and cilostazol are dominated by naftidrofuryl oxalate, which has both higher total QALYs and lower additional costs. The ICER associated with naftidrofuryl oxalate compared with no vasoactive drug is estimated to be £6070 in the base-case scenario, based upon the discounted expected values.

The CEAC is presented in *Figure 9*, which shows the probability of each vasoactive drug and the comparator being optimal given a range of willingness-to-pay thresholds (thresholds from £0 to £100,000 were tested). The probability of cilostazol or pentoxifylline being most cost-effective at any willingness-to-pay threshold is < 1%. Naftidrofuryl oxalate has the highest probability of being most cost-effective above willingness-to-pay thresholds of around £6000 per QALY gained.

To further demonstrate the cost-effectiveness of each drug compared with no vasoactive drug and the uncertainties around the cost-effectiveness results, the cost-effectiveness plane is presented in *Figure 10*, which shows the incremental effectiveness and incremental costs of each of the drugs versus no vasoactive drug for PAD. The willingness-to-pay thresholds of £10,000, £20,000 and £30,000 per QALY gained compared with no drug treatment are also shown on the

TABLE 61 Incremental discounted cost-effectiveness results (base case)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	4.975	–	
Pentoxifylline	493	4.984		Dominated by naftidrofuryl oxalate
Cilostazol	964	4.994		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	298	5.024	6070	

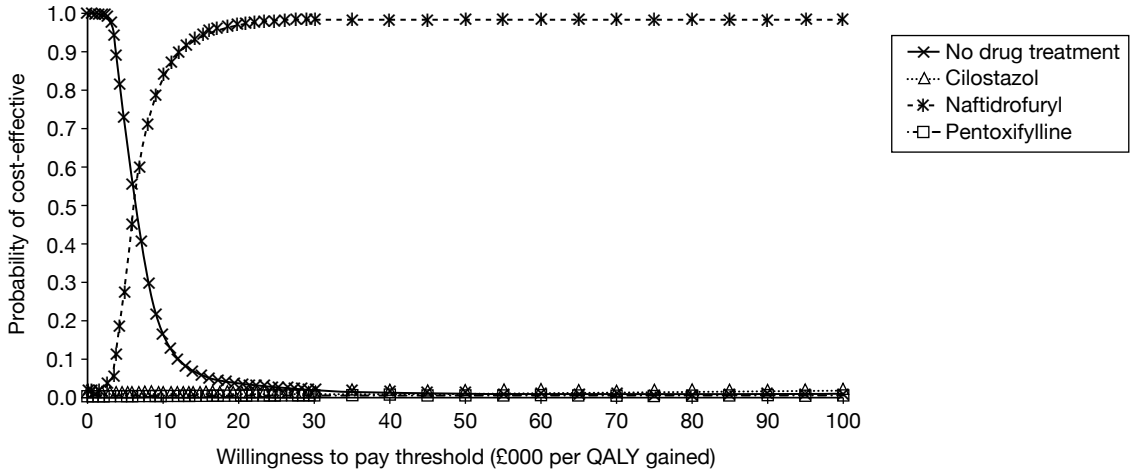

FIGURE 9 Cost-effectiveness acceptability curve for the base-case model results.

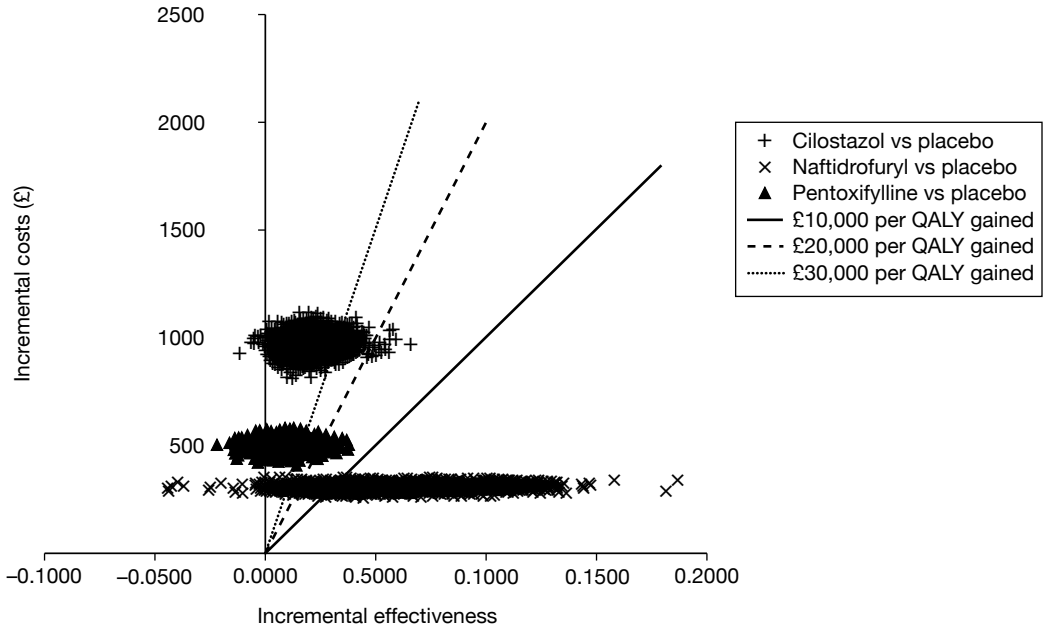

FIGURE 10 Cost-effectiveness plane showing incremental effectiveness and costs of the vasoactive drugs vs no vasoactive drug (base case).

plane. The figure shows why naftidrofuryl oxalate dominates both cilostazol and pentoxifylline, as the cluster representing naftidrofuryl oxalate is associated with higher incremental effectiveness and lower incremental costs. The figure also shows that naftidrofuryl oxalate has a cost per QALY gained below £10,000 compared with no vasoactive drug, as more points lie below the threshold line. However, naftidrofuryl oxalate is associated with the greatest uncertainty in terms of incremental effectiveness (from around –0.05 to around 0.2) and cilostazol is the least uncertain regarding incremental effectiveness. Therefore, based upon current evidence, it is possible for cilostazol to be more effective than naftidrofuryl oxalate; however, cilostazol is unlikely to have an incremental cost per QALY gained below £20,000 compared with no vasoactive drug due to the higher costs associated with this drug.

The figure also shows that all three drugs have a small probability of being more costly and less effective than no vasoactive drug (i.e. points located in the northwest quadrant), of which cilostazol has the smallest probability, of 0.11%, compared with 0.18% for naftidrofuryl oxalate and 4.05% for pentoxifylline.

Results of univariate sensitivity analyses

Sensitivity analysis 1: utility remains the same as when on the drug if discontinuation occurs after 24 weeks

The SA assumes the effectiveness of the vasoactive drug continues when patients discontinue the drug after 24 weeks. The incremental cost-effectiveness results of the SA are presented in *Table 62*. The results show that the effectiveness of all drugs increase significantly compared with no vasoactive drug. For example, the total QALYs of naftidrofuryl oxalate increase from 5.024 in the base case to 5.174. The base-case cost-effectiveness conclusions are not changed. Both pentoxifylline and cilostazol are dominated by naftidrofuryl oxalate. The ICER of naftidrofuryl oxalate compared with no vasoactive drug decreases from £6070 in the base case to £1538, which is more favourable to the intervention.

Sensitivity analysis 2: alternative baseline utility

This SA applies an increased baseline utility of 0.7562 compared with 0.4838. The incremental cost-effectiveness results of the SA are presented in *Table 63*. The base-case cost-effectiveness conclusions and the ICER of naftidrofuryl oxalate compared with no vasoactive drug are similar to the base-case results, which demonstrates that the model is not sensitive to different baseline utilities.

Sensitivity analysis 3: alternative cost for naftidrofuryl oxalate

This SA applies a higher cost for naftidrofuryl oxalate, which is £4.13 per week (using the cost of the brand name Praxilene), compared with £2.26 per week (generic) in the base case. The incremental cost-effectiveness results of the SA are presented in *Table 64*. The results show that cilostazol is dominated by naftidrofuryl oxalate, which has lower costs and higher total QALYs. Pentoxifylline is extendedly dominated by naftidrofuryl oxalate because the ICER associated with pentoxifylline is higher than that associated with naftidrofuryl oxalate. This is due to the drug acquisition cost of naftidrofuryl oxalate becoming substantially higher than that of pentoxifylline. The ICER of naftidrofuryl oxalate compared with no vasoactive drug is £11,058 per QALY gained, which is higher than the base case of £6070, because of the cost increase of naftidrofuryl oxalate.

Sensitivity analysis 4: shorter time horizon

This SA considers a time horizon of 24 weeks. The incremental cost-effectiveness results of the SA are presented in *Table 65*. The base-case cost-effectiveness conclusions are not changed. The ICER of naftidrofuryl oxalate compared with no vasoactive drug increases from £6070 in the base case to £10,733.

TABLE 62 Incremental discounted cost-effectiveness results (SA1)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	4.980	–	
Pentoxifylline	493	5.013		Dominated by naftidrofuryl oxalate
Cilostazol	963	5.053		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	298	5.174	1538	

TABLE 63 Incremental discounted cost-effectiveness results (SA2)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	7.764	–	
Pentoxifylline	493	7.773		Dominated by naftidrofuryl oxalate
Cilostazol	963	7.783		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	298	7.813	6053	

TABLE 64 Incremental discounted cost-effectiveness results (SA3)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	4.980	–	
Pentoxifylline	493	4.988		Extendedly dominated by naftidrofuryl oxalate
Cilostazol	963	4.999		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	545	5.029	11,058	

TABLE 65 Incremental discounted cost-effectiveness results (SA4)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	0.220	–	
Pentoxifylline	92	0.221		Dominated by naftidrofuryl oxalate
Cilostazol	178	0.222		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	51	0.225	10,733	

Sensitivity analysis 5: alternative starting age

This SA assumes that patients begin treatment with these drugs at age 55 years. The incremental cost-effectiveness results of the SA are presented in *Table 66*. The base-case cost-effectiveness conclusions and the ICER of naftidrofuryl oxalate compared with no vasoactive drug are similar to the base-case results, which demonstrates that the model is not sensitive to the starting age of patients.

Sensitivity analysis 6: alternative long-term discontinuation rates

This SA assumes that the long-term discontinuation rates of pentoxifylline and naftidrofuryl oxalate maintain the same relative ratios compared with cilostazol within the 24 weeks. The incremental cost-effectiveness results of the SA are presented in *Table 67*. The results show that cilostazol is dominated by naftidrofuryl oxalate, which has lower costs and higher total QALYs. Pentoxifylline is extendedly dominated by naftidrofuryl oxalate because the drug acquisition cost of naftidrofuryl oxalate becomes substantially higher than that of pentoxifylline, owing to the lower long-term discontinuation rate of naftidrofuryl oxalate compared with the base case. The ICER of naftidrofuryl oxalate compared with no vasoactive drug is £5899 per QALY gained, which is similar to the base case.

Sensitivity analysis 7: angioplasty procedure for patients discontinuing within 24 weeks

This subgroup analysis assumes that patients who have more severe IC and discontinue with the drugs within 24 weeks will receive an angioplasty procedure that will improve HRQoL of these patients on average. These patients who receive no vasoactive drug for PAD are assumed to have an angioplasty procedure at the start of the model and experience the improved

TABLE 66 Incremental discounted cost-effectiveness results (SA5)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	6.878	–	
Pentoxifylline	493	6.886		Dominated by naftidrofuryl oxalate
Cilostazol	963	6.897		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	298	6.927	6033	

TABLE 67 Incremental discounted cost-effectiveness results (SA5)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	4.980	–	
Pentoxifylline	473	4.988		Extendedly dominated by naftidrofuryl oxalate
Cilostazol	963	4.999		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	646	5.089	5899	

HRQoL immediately. Owing to lack of comparative evidence around the utility associated with angioplasty, four scenarios were tested: the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl oxalate, 20% and 40% higher than the utility associated with naftidrofuryl oxalate, and equivalent to the utility of general population used in the model.

The incremental cost-effectiveness results of the SA are presented in *Tables 68–71*. Unlike the base case and other sensitivity analyses, in which the cost of no vasoactive drug is zero, the comparator of no vasoactive drug is associated with a significant cost which is £1313, which represents the costs of angioplasty.

When it is assumed that the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl oxalate, naftidrofuryl oxalate dominates pentoxifylline, cilostazol and no vasoactive drug. When it is assumed that the utility associated with angioplasty is 20% and 40% higher than the utility associated with naftidrofuryl oxalate, no vasoactive drug (all patients receive angioplasty) is associated with the highest total QALYs. In both scenarios, pentoxifylline and cilostazol are dominated by naftidrofuryl oxalate and the ICERs of no vasoactive drug (all patients receive angioplasty) compared with naftidrofuryl oxalate are £17,992 and £6545 per QALY gained, respectively.

When it is assumed that the utility associated with angioplasty is equivalent to the utility of the general population within the model (around 60% higher than the utility associated with naftidrofuryl oxalate), no vasoactive drug (all patients receive angioplasty) is associated with the highest total QALYs. Naftidrofuryl oxalate is associated with fewer total QALYs than cilostazol because more patients discontinue with cilostazol and could therefore benefit from the angioplasty procedure. Pentoxifylline is dominated by naftidrofuryl oxalate and cilostazol is dominated by no vasoactive drug (all patients receive angioplasty). The ICER of no vasoactive drug (all patients receive angioplasty) compared with naftidrofuryl oxalate is £4094 per QALY gained.

Therefore, this exploratory analysis suggests that if angioplasty is associated with an increase in quality of life compared with the vasoactive drugs, vasoactive drugs are unlikely to be considered to be economically attractive at a willingness-to-pay threshold of £20,000 per QALY gained for this small subgroup of patients. However, this subgroup analysis is largely based upon clinical advice owing to lack of evidence. This is therefore an exploratory and highly uncertain analysis, and hence these results should be treated with caution.

Sensitivity analysis 8: informative prior distributions within network meta-analysis

This SA assesses the impact of allowing more informative prior distributions for the between-study SD and treatment effects within the network meta-analysis. The incremental cost-effectiveness results of the SA are presented in *Table 72*. The results suggest that changes to the prior distributions for the between-study SD and treatment effects have very little impact upon the model results.

Threshold analyses

Given the uncertainties around the quality-of-life evidence and the uncertain long-term outcomes, threshold analyses were carried out to determine the required QALYs gained for each drug for it to be associated with a cost per QALY gained below £20,000 and £30,000 compared with no vasoactive drug. The additional discounted costs for each drug compared with no vasoactive drug over the lifetime of the patients were based on the base-case PSA results of the economic model. The costs associated with the vasoactive drugs for PAD are associated with

TABLE 68 Incremental discounted cost-effectiveness results (SA7: same utility compared with naftidrofuryl oxalate)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained)	Dominance
Pentoxifylline	862	4.993		Dominated by naftidrofuryl oxalate
No vasoactive drug (baseline technology, all patients receive angioplasty)	1313	4.996		Dominated by naftidrofuryl oxalate
Cilostazol	1315	5.003		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	431	5.032	–	

TABLE 69 Incremental discounted cost-effectiveness results (SA7: 20% increased utility compared with naftidrofuryl oxalate)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
Pentoxifylline	862	5.019		Dominated by naftidrofuryl oxalate
Cilostazol	1315	5.028		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	431	5.044	–	
No vasoactive drug (baseline technology, all patients receive angioplasty)	1313	5.093	17,992	

TABLE 70 Incremental discounted cost-effectiveness results (SA7: 40% increased utility compared with naftidrofuryl oxalate)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained)	Dominance
Pentoxifylline	862	5.044		Dominated by naftidrofuryl oxalate
Cilostazol	1315	5.052		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	431	5.056	–	
No vasoactive drug (baseline technology, all patients receive angioplasty)	1313	5.191	6545	

much less uncertainty than the QALYs, with the biggest uncertainty relating to the costs being the long-term discontinuation rates. *Table 73* summarises the results of this analysis.

The threshold analysis suggests that for a willingness-to-pay threshold of £20,000 and £30,000 per QALY gained, naftidrofuryl oxalate requires a QALY gain of 0.015 and 0.010, respectively, as this is the cheapest vasoactive drug. Pentoxifylline requires QALY gains of 0.025 and 0.016, respectively, to make the drug cost-effective at willingness-to-pay thresholds of £20,000 and £30,000. The QALYs gained required for cilostazol to be cost-effective at willingness-to-pay

TABLE 71 Incremental discounted cost-effectiveness results (SA7: same utility compared with general population)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained)	Dominance
Pentoxifylline	862	5.066		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	431	5.067	–	
Cilostazol	1315	5.074		Dominated by no vasoactive drug
No vasoactive drug (baseline technology, all patients receive angioplasty)	1313	5.282	4094	

TABLE 72 Incremental discounted cost-effectiveness results (SA8)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (cost per QALY gained) (£)	Dominance
No vasoactive drug (baseline technology)	0	4.978	–	
Pentoxifylline	493	4.986		Dominated by naftidrofuryl oxalate
Cilostazol	964	4.996		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	298	5.027	6072	

TABLE 73 Threshold analyses for the cost-effectiveness of each vasoactive drug

Interventions and comparator	Additional costs compared with no vasoactive drug (95% CI) (£)	Required QALYs gained for threshold of:	
		£20,000 (95% CI)	£30,000 (95% CI)
No vasoactive drug (baseline technology)	0		
Cilostazol	964 (892 to 1040)	0.048 (0.045 to 0.052)	0.032 (0.030 to 0.035)
Naftidrofuryl oxalate	298 (273 to 325)	0.015 (0.014 to 0.016)	0.010 (0.009 to 0.011)
Pentoxifylline	493 (454 to 535)	0.025 (0.023 to 0.027)	0.016 (0.015 to 0.018)
Inositol nicotinate	1695 (1242 to 2200)	0.085 (0.062 to 0.110)	0.056 (0.041 to 0.073)

thresholds of £20,000 and £30,000 are 0.048 and 0.0322, respectively. Inositol nicotinate requires the biggest QALYs gained for it to be considered to be cost-effective. For willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, the required QALYs gained are 0.085 and 0.056, respectively.

Discussion

Summary of key results

The economic evaluation suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline and has an incremental cost per QALY gained of around £6070 compared with no vasoactive drug. This result is reasonably robust to changes within the key model assumptions; however, the method for estimating utilities based upon MWD and long-term discontinuation

rates is uncertain. A threshold analysis was undertaken to assess the QALY gains required for naftidrofuryl oxalate to have an incremental cost per QALY gained of £20,000 compared with no vasoactive drug, which suggested that an estimated 0.015 QALYs gained would be required.

Sensitivity analyses suggest that the base-case ICER of naftidrofuryl oxalate compared with no vasoactive drug does not change substantially with alternative baseline utility (SA2), alternative starting age (SA5), alternative long-term discontinuation rates (SA6) and informative prior distributions within the network meta-analysis (SA8). When it is assumed that the effectiveness associated with the vasoactive drugs continues over a patient's lifetime when patients discontinue the drug after 24 weeks (SA1), the ICER of naftidrofuryl oxalate compared with no vasoactive drug decreases from £6070 in the base case to £1538 per QALY gained. When the patented manufacturer's cost for naftidrofuryl oxalate is used (SA3) and when a shorter time horizon of 24 weeks is used (SA4), the ICER of naftidrofuryl oxalate compared with no vasoactive drug increases to £11,058 and £10,733 per QALY gained, respectively. In all of these SAs, both cilostazol and pentoxifylline are dominated or extendedly dominated (for pentoxifylline in SA3 and SA6) by naftidrofuryl oxalate.

Exploratory subgroup analyses which assume that patients who discontinue with the drugs within 24 weeks will receive angioplasty (SA7) suggest that the effectiveness of the drugs depends on the assumed utility associated with angioplasty. When it is assumed that the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl oxalate, naftidrofuryl oxalate dominates pentoxifylline, no vasoactive drug and cilostazol. However, when it is assumed that the utility is higher than the utility associated with naftidrofuryl oxalate, no vasoactive drug is associated with the highest total QALYs, and the ICERs of no vasoactive drug compared with naftidrofuryl oxalate are < £20,000 per QALY gained. Cilostazol and pentoxifylline are dominated either by naftidrofuryl oxalate or by no vasoactive drug. However, this subgroup analysis is highly uncertain and hence these results should be treated with caution.

Given the current evidence around effectiveness, naftidrofuryl oxalate is estimated to dominate both cilostazol and pentoxifylline in the base case and in most sensitivity analyses. It was not possible to estimate the QALY gains associated with inositol nicotinate owing to lack of data around MWD at 24 weeks. Inositol nicotinate was therefore not included within the main analysis. However, the threshold analysis suggests that inositol nicotinate would have to demonstrate considerably greater impacts upon quality of life than the other vasoactive drugs being assessed for it to have an estimated incremental cost per QALY gained of < £20,000 compared with no vasoactive drug, because of its more expensive acquisition cost. An estimated QALY gain of 0.085 would be required using a willingness-to-pay threshold of £20,000 per QALY gained, compared with a 0.015 QALY gain required for naftidrofuryl oxalate. Therefore, it is unlikely that inositol nicotinate would be considered to be economically attractive compared with no vasoactive drug or with the other drugs being assessed, given the available effectiveness evidence.

Generalisability of results

There is no evidence to suggest that the results of the analysis cannot be generalised across all patients who have stable (at least for the past 3 months) and symptomatic IC, secondary to PAD, whose symptoms continue despite a period of conservative management. There may, however, be a subgroup of patients with more severe IC in whom treatment with these drugs may prevent the need for angioplasty. In this subgroup of patients, no vasoactive drug (all patients receive angioplasty) may have a favourable ICER compared with any of the vasoactive drugs; however, this analysis is highly uncertain owing to lack of evidence and hence further research is required around the effectiveness of angioplasty in these patients.

Strengths and limitations of analysis

The economic evaluation has several strengths compared with previous studies. To our knowledge, it is the first study to model the lifetime of the patients who take the drugs and it is also the first study to incorporate utility in the economic evaluation by predicting the change in utility from the change in MWD, based on patient-level data from a RCT.

There are several limitations of the study. There is uncertainty regarding the change in utility and discontinuation rate beyond 24 weeks because most RCTs do not have follow-up beyond this time point. In the base case, it was assumed that utility remains at the same level after 24 weeks if patients continue the drug or that it decreases to the level of no vasoactive drug if patients discontinue the drug. This was tested within a SA that did not alter the conclusions. Any additional effectiveness of naftidrofuryl oxalate beyond discontinuation would improve cost-effectiveness. It was also assumed that discontinuation rates of other drugs are the same as cilostazol beyond 24 weeks. There is evidence that once patients discontinue the drug, the MWD decreases to that of no vasoactive drug for PAD. A SA was carried out to test alternative long-term discontinuation rates, which did not alter the conclusions.

The regression model fitted to predict the change in utility from the change in MWD was based on patient-level data from a RCT of cilostazol with a sample size of 106 patients in the UK.[83] The underlying assumption of this analysis is that the same relationship applies for all drugs and no vasoactive drug between MWD and utilities. An analysis was undertaken using the patient-level data which suggested that there was no significant treatment effect for cilostazol versus placebo. However, this was based upon a relatively small sample of patients, and there may be some difference between treatment groups. Cilostazol is generally associated with more minor AEs; hence these may affect this relationship. Direct long-term utility data associated with each of the drugs would provide less uncertain estimates of cost-effectiveness. A value of information analysis has not been undertaken due to the uncertainties associated with the utility outcomes, which were not possible to fully quantitate within the PSA.

Cardiovascular AEs are common for the patient population considered in the study. The model assumes that the drugs are for symptom relief and have no impact on the progression of disease or serious cardiovascular events. The long-term safety of cilostazol was tested in a good-quality trial,[49] which suggests that there is very little difference between cardiovascular outcomes for cilostazol and placebo (for the 'on-treatment' group there was no difference in the number of cardiovascular mortalities and similar numbers of cardiovascular AEs). Personal communication with the team of clinical advisors (Steven Thomas, Jonathan Michaels and Gerard Stansby, University of Sheffield, August 2010, personal communication) suggests that there is no clinical reason why these vasoactive drugs for PAD would impact upon the number of cardiovascular events and hence this small difference in cardiovascular events is thought to be due to random variation. There are, however, no long-term safety studies on naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, and if there was a small increase or reduction in the incidence of cardiovascular events when patients are on these drugs, the results could alter substantially because of the otherwise small impact on costs and quality of life associated with these drugs.

The economic evaluation identified within the literature review by Guest *et al.*[90] included costs of diagnosis of IC, follow-up visits, supervised exercise, angioplasty and bypass surgery in addition to the drug acquisition costs. Within our model the cost of diagnosis and follow-up visits was assumed to be unchanged by the vasoactive drugs, as all patients will be diagnosed and patients will be followed up for other treatment they are receiving for PAD whether or not they are receiving vasoactive drugs. The team of clinical advisors (Steven Thomas, Jonathan Michaels and Gerard Stansby, University of Sheffield, July 2010, personal communication) suggested that in practice supervised exercise programmes are currently unavailable in many regions of

England and Wales and that the use of vasoactive drugs is unlikely to affect whether or not a patient requires bypass surgery. Vasoactive drugs may prevent the need for angioplasty in a small subgroup of patients who have more severe IC when clinical practice is to provide angioplasty following discontinuation of vasoactive drugs. Owing to the limited evidence base around the long-term comparative effectiveness of angioplasty in this patient population, this was treated as an exploratory subgroup analysis within this report, the results of which are described above.

The economic evaluation performed by Guest *et al.*[90] suggested that cilostazol is more cost-effective for improving MWD at 24 weeks than naftidrofuryl oxalate or pentoxifylline. The conclusion is different from this evaluation, which suggests that naftidrofuryl oxalate is most cost-effective compared with the other vasoactive drugs and no vasoactive drug. The main reason for the difference is the estimates of the changes in MWD for the vasoactive drugs. Guest *et al.*[90] estimated the mean percentage changes in MWD from baseline to be 82.6% and 59.9% for cilostazol and naftidrofuryl oxalate, respectively. The estimates were not based on a network meta-analysis, but were calculated independently for each drug as a weighted mean based on the sample size of the identified trials. Two trials of cilostazol[56,61] and three trials of naftidrofuryl oxalate[65,93,94] were included. The two included trials of cilostazol were the two trials demonstrating the greatest effectiveness of cilostazol at that time (see *Figure 3*), whereas two of the three trials of naftidrofuryl oxalate included within the analysis assess a dose that is not currently licensed within England and Wales. In comparison, this evaluation applied a random effects network meta-analysis, considering all trials identified by the systematic review, providing that they reported relevant outcomes and had a follow-up period of at least 24 weeks (see *Chapter 3, Maximal walking distance meta-analysis*, above). The estimated percentage changes from this analysis in terms of MWD from baseline for cilostazol and naftidrofuryl oxalate were 59.2% and 106.7%, respectively.

Chapter 5

Assessment of factors relevant to the NHS and other parties

The vasoactive drugs assessed within this report are generally currently available to be prescribed to patients with IC within England and Wales for symptom relief, although there may be restrictions to their use due to local policies. The only evidence available around current usage of the vasoactive drugs for PAD within England and Wales is the *Prescription costs analysis England 2009*.[25] Based upon this, assuming that all patients receive the licensed doses of the vasoactive drugs as outlined within this report for the whole year, 11,540 patients are currently estimated to be prescribed these vasoactive drugs for PAD within the community within England. The calculated proportional split of the usage of these vasoactive drugs based upon these data is shown in *Table 74*. However, it should be noted that these estimates are highly uncertain.

The costs associated with providing the vasoactive drugs for PAD are the acquisition costs of the drugs only; there are not expected to be any additional management costs due to the health-care requirements already incurred by this patient group. The estimated annual cost for each of the vasoactive drugs for PAD provided to this patient population is shown in *Table 75*. This is calculated using the graph of prevalence by age from the study by Norgren *et al.*[3] and England and Wales population statistics by age from the ONS.[98] This results in an estimated 703,403 prevalent cases of IC within England and Wales. Of these, it is assumed that 70% will seek medical help, based upon the mid-point of the range provided by Norgren *et al.*,[3] and that, of these, 20% would require the vasoactive drugs after a period of conservative management. This results in an estimated 98,476 people within England and Wales requiring treatment with a vasoactive drug.

TABLE 74 Current usage of the vasoactive drugs for PAD

Drug	Proportionate market share (from community prescriptions) (%)
Cilostazol	29
Naftidrofuryl oxalate	52
Pentoxifylline	4
Inositol nicotinate	15

TABLE 75 Annual cost of the vasoactive drugs for PAD within England and Wales

Drug	Annual cost (£)
Cilostazol	45,340,641
Naftidrofuryl oxalate (generic)	11,604,739
Naftidrofuryl oxalate (Praxilene)	21,206,891
Pentoxifylline	23,568,918
Inositol nicotinate	88,473,301

As some patients are already receiving these vasoactive drugs for PAD, the additional cost to the NHS of recommending one or more of these drugs is likely to be lower than predicted here. As an approximation, based upon the estimated current number of prescriptions dispensed within the community in England and the estimated proportionate market share of the vasoactive drugs for PAD shown in *Table 74*, the current cost of treatment in England is estimated to be just over £1.5M, although this estimate is highly uncertain.

Chapter 6

Discussion

Statement of principal findings

Clinical effectiveness data were available from 26 RCTs. There was some evidence that walking distance outcomes were improved by cilostazol and naftidrofuryl oxalate. The 95% credible intervals estimated from the network meta-analysis for the difference from placebo in the log mean change MWD from baseline were –0.016 to 0.217 for pentoxifylline, 0.108 to 0.337 for cilostazol and 0.181 to 0.762 for naftidrofuryl oxalate. Based upon this analysis, the percentage change in MWD from baseline to 24 weeks for placebo, pentoxifylline, cilostazol and naftidrofuryl oxalate can be estimated as 27.6%, 41.4%, 59.2% and 106.7%, respectively. It was not possible to include inositol nicotinate within the meta-analysis of MWD and PFWD owing to the lack of 24-week data; however, the shorter-term data did not suggest a significant effect. AEs were minor, and included headaches and gastrointestinal difficulties. The incidence of SAEs, including cardiovascular events and mortality, was not shown to be increased or decreased by the vasoactive drugs compared with placebo; however, most studies had relatively short follow-up time to address this outcome.

The economic evaluation suggests that it is unlikely that cilostazol, pentoxifylline or inositol nicotinate would have an incremental cost per QALY gained below £30,000 compared with no vasoactive drug. Naftidrofuryl oxalate is associated with an estimated incremental cost per QALY gained of around £6000 compared with no vasoactive drug. There are, however, uncertainties around the long-term effectiveness of the drugs. Naftidrofuryl oxalate would need to be associated with an estimated 0.0271 QALYs gained in order to have an estimated incremental cost per QALY gained of £20,000 compared with no vasoactive drug.

Strengths and limitations of the assessment

The main strengths of the review are that the literature search was comprehensive and that the included studies were of relevance to UK practice in terms of populations. In addition, all included trials prescribed medications in line with UK marketing authorisations. However, most of the trial data had follow-up of 24 weeks, which is relatively short-term compared with practice. Relevant trials that were not published in English may have been missed; however, methodology studies have indicated that language restrictions do not often influence the results of systematic reviews of conventional medicines.[103–105]

Within the meta-analysis of MWD and PFWD, several studies were excluded because the published reports did not provide data in a form that was suitable for inclusion. In the analysis, we assumed that the data from the studies were missing at random and that the lack of usable data was not related to the observed treatment effect. The existing evidence on naftidrofuryl oxalate which was excluded from the analysis does not suggest that publication bias is a problem. Furthermore, a review of existing trial databases was undertaken by De Backer *et al.*,[106] which suggests that there is no evidence of any publication bias. There are no head-to-head data comparing naftidrofuryl oxalate with any other vasoactive drug; the results of the analysis depended upon a network meta-analysis.

Within the health economic model, there is uncertainty regarding the utility estimates and discontinuation rate beyond 24 weeks because most RCTs do not have follow-up beyond this time point. The analysis takes the conservative assumption that there is no benefit of the vasoactive drugs following discontinuation. Therefore, any additional effectiveness of naftidrofuryl oxalate beyond discontinuation would improve cost-effectiveness of this drug. A SA was undertaken to test alternative long-term discontinuation rates, which did not alter the conclusions.

The regression model fitted to predict the change of utility from the change in MWD within the health economic model was based on patient-level data from a RCT of cilostazol with a sample size of 106 patients in the UK.[83] The underlying assumption of this analysis is that there is the same relationship for all drugs and no vasoactive drug between MWD and utilities. An analysis was undertaken using the patient-level data, which suggested that there was no significant treatment effect for cilostazol versus placebo. However, this was based upon a relatively small sample of patients, and there may be some difference between treatment groups. Cilostazol is generally associated with more minor AEs; hence, these may affect this relationship. Direct long-term utility data associated with each of the drugs would provide less uncertain estimates of cost-effectiveness. A threshold analysis was undertaken to address this issue. In addition, there was insufficient evidence around inositol nicotinate to assess this within the base-case analysis, hence, this was assessed only within a threshold analysis. A value of information analysis has not been undertaken owing to the uncertainties associated with the long-term outcomes, which were not possible to fully quantitate within the PSA.

Cardiovascular AEs are common among the patient population considered in the study. The model assumes that the drugs are prescribed for symptom relief and have no impact on the progression of disease or serious cardiovascular events. The long-term safety of cilostazol was tested in a good-quality trial[49] which found that there is very little difference in cardiovascular outcomes between cilostazol and placebo (among the 'on-treatment' group there was no difference in the number of cardiovascular mortalities and similar numbers of cardiovascular AEs). Personal communication with the team of clinical advisors (Steven Thomas, Jonathan Michaels and Gerard Stansby, August 2010) suggests that there is no clinical reason why these vasoactive drugs for PAD would impact upon the number of cardiovascular events and hence this small difference in cardiovascular events is thought to be due to random variation. There are, however, no long-term safety studies on naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, and if there was a small increase or reduction in the incidence of cardiovascular events when patients are on these drugs, the results could alter substantially due to the otherwise small impact on costs and quality of life associated with these drugs.

Uncertainties

The key uncertainties associated with this evaluation are:

- long-term quality-of-life impacts of the drugs
- long-term discontinuation rates
- the number of people using the drugs
- any long-term AEs or benefits associated with naftidrofuryl oxalate, pentoxifylline and inositol nicotinate.

Other relevant factors

Naftidrofuryl oxalate could potentially be prescribed to more patients than cilostazol, as CHF is not contraindicated for naftidrofuryl oxalate and it has fewer drug interactions.

Chapter 7

Conclusions

Naftidrofuryl oxalate and cilostazol are both effective treatments for this patient population, with minimal SAEs; however, naftidrofuryl oxalate is the only treatment with an incremental cost per QALY gained below £20,000 compared with no vasoactive drug, with an estimated incremental cost per QALY gained of £6070.

Implications for service provision

Provision of these drugs does not usually engender significant additional management costs, as these drugs would be provided alongside a range of other treatments for PAD and its risk factors and there is no evidence that they impact upon disease progression. Therefore, the burden upon the NHS is generally in terms of the drug acquisition cost only. Within England and Wales the vasoactive drugs assessed within this report are available to be prescribed to patients with IC, although there may be restrictions to their use due to local policies. Therefore, if these drugs were to be recommended, prescription rates of the drugs may rise considerably.

Suggested research priorities

A trial comparing the long-term effectiveness (beyond 24 weeks) of cilostazol, naftidrofuryl oxalate and placebo would be beneficial, which should collect utility data as well as walking distance outcomes. The health economic model currently assumes that the effectiveness of the vasoactive drugs is maintained while the patients are taking the drugs; however, this should be tested within a trial. It would also be useful to compare the outcomes associated with naftidrofuryl oxalate with those associated with supervised exercise programmes and other treatments, such as angioplasty. Importantly, there are currently no long-term safety trials for naftidrofuryl oxalate; however, clinical experts suggest that the mechanism of the drugs is such that no long-term impacts on cardiovascular events or mortality would be expected. Any such trials are likely to be costly due to the sample size and length of follow-up required to detect any differences between the two arms for these events.

Acknowledgements

The authors would like to thank Dr Mark O'Donnell for providing patient-level data from a trial of cilostazol. The authors would also like to thank Andrea Shippam for her help in preparing and formatting the report, and Dr Matt Stevenson and Dr Eva Kaltenthaler for peer reviewing the report.

Contributions of authors

Hazel Squires was the Assessment Group lead, who advised on the cost-effectiveness modelling and developed the budget impact model. Emma Simpson and Sue Harnan undertook the clinical effectiveness review. Yang Meng undertook the cost-effectiveness review and developed the cost-effectiveness model. John Stevens undertook the quantitative meta-analysis and Ruth Wong performed the literature searches. Steve Thomas, Jonathan Michaels and Gerard Stansby provided clinical advice throughout. All authors contributed to the report.

About the School of Health and Related Research

The School of Health and Related Research (ScHARR) is one of the nine departments that constitute the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of the public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the NIHR Health Technology Assessment programme on behalf of a range of policy-makers, including NICE. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS CRD, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

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Appendix 1

Literature search strategies

Search strategies were developed to retrieve both RCTs and systematic reviews.

Randomised controlled trials

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

1. Intermittent Claudication/
2. claudication.tw.
3. 1 or 2
4. exp Peripheral Vascular Diseases/
5. (peripheral adj arterial adj disease$).tw.
6. (peripheral adj vascular adj disease$).tw.
7. (atherosclero$ and (PAD or PVD)).tw.
8. ((arterial adj disease$) and (PAD or PVD)).tw.
9. or/4-8
10. Atherosclerosis/dt, th [Drug Therapy, Therapy]
11. Vascular Diseases/dt, th [Drug Therapy, Therapy]
12. Vasodilator Agents/
13. vasodilator$.tw.dh
14. Platelet Aggregation Inhibitors/
15. (platelet adj aggregation adj inhibitor$).tw.
16. Phosphodiesterase Inhibitors/
17. (phosphodiesterase adj inhibitor$).tw.
18. Tetrazoles/tu [Therapeutic Use]
19. or/10-18
20. 3 and 9 and 19
21. cilostazol$.tw.
22. (pletal or pletaal).tw.
23. OPC-13013.tw.
24. 73963-72-1.rn.
25. or/21-24
26. 3 and 25
27. 9 and 25
28. Nafronyl/
29. naftidrofuryl$.tw.
30. naphtidrofuryl.tw.
31. (nafronyl or naftifurin).tw.
32. praxilene.tw.
33. (dusodril or iridus).tw.
34. 3200-06-4.rn.
35. or/28-34
36. 3 and 35
37. 9 and 35
38. Pentoxifylline/

39. pentoxifylline.tw.
40. trental.tw.
41. oxpentifylline.tw.
42. (pentoxil or pentofin).tw.
43. bl-191.tw.
44. 6493-05-6.rn.
45. or/38-44
46. 3 and 45
47. 9 and 45
48. Nicotinic Acids/
49. (inositol adj (nicotinate or hexanicotinate)).tw.
50. (inositol adj niacinate).tw.
51. hexopal.tw.
52. (dilexpal or mesotal or palohex or hexanicotol or esantene or hexanicit or linodil or mesonex or dilcit).tw.
53. 6556-11-2.rn.
54. or/48-53
55. 3 and 54
56. 9 and 54
57. 26 or 36 or 46 or 55
58. 27 or 37 or 47 or 56
59. 57 or 58
60. 20 or 59
61. Randomized controlled trials as Topic/
62. Randomized controlled trial/
63. Random allocation/
64. randomized controlled trial.pt.
65. Double blind method/
66. Single blind method/
67. Clinical trial/
68. exp Clinical Trials as Topic/
69. controlled clinical trial.pt.
70. or/61-69
71. (clinic$ adj25 trial$).ti,ab.
72. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
73. Placebos/
74. Placebo$.tw.
75. (allocated adj2 random).tw.
76. or/71-75
77. 70 or 76
78. Case report.tw.
79. Letter/
80. Historical article/
81. 78 or 79 or 80
82. 77 not 81
83. 60 and 82
84. exp Animals/
85. Humans/
86. 84 not 85
87. 83 not 86

Broad drug class terms (10–18) were combined with both IC (1–2) and PAD statements (4-8). In addition, terms relating to the drug interventions (synonyms, alternative proprietary names, CAS registry numbers) were combined with either IC (1–2) or PAD terms (4–8). A RCT filter (61–86) was applied to retrieve the highest level of evidence.

Systematic reviews

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

61. meta-analysis as topic/
62. (meta analy$ or metaanaly$).tw.
63. Meta-Analysis/
64. (systematic adj (review$1 or overview$)).tw.
65. "Review Literature as Topic"/
66. or/61-65
67. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or b.i.ds or cancerlit).ab.
68. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
69. ((selection adj criteria) or (data adj extraction)).ab.
70. "review"/
71. 69 and 70
72. comment/ or editorial/ or letter/
73. Animals/
74. Humans/
75. 73 and 74
76. 73 not 75
77. 72 or 76
78. 66 or 67 or 68 or 71
79. 78 not 77
80. 60 and 79

Search statements 1–60 of the RCT search strategy above were combined with a systematic reviews methodology filter (statements 61–79).

Economic studies

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

61. exp "Costs and Cost Analysis"/
62. Economics/
63. exp Economics, Hospital/
64. exp Economics, Medical/
65. Economics, Nursing/
66. exp models, economic/
67. Economics, Pharmaceutical/
68. exp "Fees and Charges"/
69. exp Budgets/
70. budget$.tw.
71. ec.fs.

72. cost$.ti.
73. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
74. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
75. (price$ or pricing$).tw.
76. (financial or finance or finances or financed).tw.
77. (fee or fees).tw.
78. (value adj2 (money or monetary)).tw.
79. quality-adjusted life years/
80. (qaly or qalys).af.
81. (quality adjusted life year or quality adjusted life years).af.
82. or/61-81
83. 60 and 82

To retrieve evidence of cost-effectiveness studies, an economics filter was applied in place (61–82) of the RCT/SR search strategies above.

Adverse events

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

1. Nafronyl/ae, po, to
2. Pentoxifylline/ae, po, to
3. Nicotinic Acids/ae, po, to
4. or/1-3
5. cilostazol$.tw.
6. (pletal or pletaal).tw.
7. OPC-13013.tw.
8. 73963-72-1.rn.
9. naftidrofuryl$.tw.
10. naphtidrofuryl.tw.
11. (nafronyl or naftifurin).tw.
12. praxilene.tw.
13. (dusodril or iridus).tw.
14. 3200-06-4.rn.
15. pentoxifylline.tw.
16. trental.tw.
17. oxpentifylline.tw.
18. (pentoxil or pentofin).tw.
19. bl-191.tw.
20. 6493-05-6.rn.
21. (inositol adj (nicotinate or hexanicotinate)).tw.
22. (inositol adj niacinate).tw.
23. hexopal.tw.
24. (dilexpal or mesotal or palohex or hexanicotol or esantene or hexanicit or linodil or mesonex or dilcit).tw.
25. 6556-11-2.rn.
26. or/5-25
27. (adverse adj2 (event$ or effect$ or reaction$ or outcome$)).ti,ab.
28. (adrs or adr or complication$ or harm$ or harmful or risk$ or safe or safety or tolerability or tolerance or tolerate or toxic or toxicity).ti.
29. ((side or undesirable) adj2 effect$).ti,ab.

30. (treatment adj2 emergent).ti.
31. or/27-30
32. 26 and 31
33. 4 or 32
34. exp Animals/
35. Humans/
36. 34 not 35
37. 33 not 36

Two approaches were used in the search for AEs of the four interventions. First, the AE subheadings that are linked to indexed drug names (1–3) and second, free-text terms relating to AEs (27–31) were combined with the intervention terms (5–26).

Quality-of-life studies

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

61. "Quality of Life"/
62. (qol or (quality adj2 life)).ab,ti.
63. (value adj2 (money or monetary)).tw.
64. value of life/
65. quality adjusted life year/
66. quality adjusted life.tw.
67. (qaly$ or qald$ or qale$ or qtime$).tw.
68. disability adjusted life.tw.
69. daly$.tw.
70. health status indicators/
71. (SF-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
72. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
73. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
74. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
75. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
76. (euroqol or euro qol or eq5d or eq 5d).tw.
77. (hql or hqol or h qol or hrqol or hr qol).tw.
78. (hye or hyes).tw.
79. health$ year$ equivalent$.tw.
80. health utilit$.tw.
81. (hui or hui1 or hui2 or hui3).tw.
82. disutilit$.tw.
83. rosser.tw.
84. (quality adj2 wellbeing).tw.
85. qwb.tw.
86. (willingness adj2 pay).tw.
87. standard gamble$.tw.
88. time trade off.tw.
89. time tradeoff.tw.

90. tto.tw.
91. letter.pt.
92. editorial.pt.
93. comment.pt.
94. 91 or 92 or 93
95. or/61-90
96. 95 not 94
97. 60 and 96

Search statements 1–60 in the RCT search strategy were combined with the quality-of-life methodology filter (statements 61–96).

Quality-of-life of intermittent claudication

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

1. Intermittent Claudication/
2. claudication.tw.
3. 1 or 2
4. "Quality of Life"/
5. (qol or (quality adj2 life)).ab,ti.
6. (value adj2 (money or monetary)).tw.
7. value of life/
8. quality adjusted life year/
9. quality adjusted life.tw.
10. (qaly$ or qald$ or qale$ or qtime$).tw.
11. disability adjusted life.tw.
12. daly$.tw.
13. health status indicators/
14. (SF-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
15. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
16. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
17. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
18. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
19. (euroqol or euro qol or eq5d or eq 5d).tw.
20. (hql or hqol or h qol or hrqol or hr qol).tw.
21. (hye or hyes).tw.
22. health$ year$ equivalent$.tw.
23. health utilit$.tw.
24. (hui or hui1 or hui2 or hui3).tw.
25. disutilit$.tw.
26. rosser.tw.
27. (quality adj2 wellbeing).tw.
28. qwb.tw.
29. (willingness adj2 pay).tw.
30. standard gamble$.tw.

31. time trade off.tw.
32. time tradeoff.tw.
33. tto.tw.
34. letter.pt.
35. editorial.pt.
36. comment.pt.
37. 34 or 35 or 36
38. or/4-33
39. 38 not 37
40. 3 and 39

Searches for studies of patients with IC without treatment were carried out. Terms for IC (1–2) were combined with the quality-of-life filter as shown above (4–39). Records retrieved from the quality-of-life searches with interventions form a sub-set of the records retrieved from these searches.

Quality of life of advanced intermittent claudication

MEDLINE and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid, 1950 to present

1. Intermittent Claudication/
2. claudication.tw.
3. (advance$ or severe).tw.
4. (1 or 2) and 3
5. critical limb isch?emia.tw.
6. isch?emic rest pain.tw.
7. ((CLI or IRP) and (peripheral arterial disease or PAD)).tw.
8. advanced peripheral arterial disease.tw.
9. or/4-8
10. "Quality of Life"/
11. (qol or (quality adj2 life)).ab,ti.
12. (value adj2 (money or monetary)).tw.
13. value of life/
14. quality adjusted life year/
15. quality adjusted life.tw.
16. (qaly$ or qald$ or qale$ or qtime$).tw.
17. disability adjusted life.tw.
18. daly$.tw.
19. health status indicators/
20. (SF-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
24. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25. (euroqol or euro qol or eq5d or eq 5d).tw.
26. (hql or hqol or h qol or hrqol or hr qol).tw.

27. (hye or hyes).tw.
28. health$ year$ equivalent$.tw.
29. health utilit$.tw.
30. (hui or hui1 or hui2 or hui3).tw.
31. disutilit$.tw.
32. rosser.tw.
33. (quality adj2 wellbeing).tw.
34. qwb.tw.
35. (willingness adj2 pay).tw.
36. standard gamble$.tw.
37. time trade off.tw.
38. time tradeoff.tw.
39. tto.tw.
40. letter.pt.
41. editorial.pt.
42. comment.pt.
43. 40 or 41 or 42
44. or/10-39
45. 44 not 43
46. 9 and 45

Search terms for advanced IC (1–9) were combined with the quality-of-life methodology filter (9–45).

Appendix 2

Table of excluded studies with rationale

Trial	Comparison	Reason for exclusion
Adhoute 1990[93]	Naftidrofuryl fumarate vs placebo	Not licensed
Belcaro 2002[107]	Pentoxifylline 1600 mg vs placebo	Not licensed dose
Bieron 2005[108]	Intravenous pentoxifylline vs intravenous bencyclane	Not licensed
Boccalon 2001[109]	Naftidrofuryl oxalate 200 mg t.i.d. vs placebo	Population includes Fontaine stage III, non-English language
Bollinger 1977[110]	Pentoxifylline 600 mg vs placebo	Not licensed dose
Chacon-Quevedo 1994[111]	Pentoxifylline 1200 mg vs buflomedil 600 mg	Comparator not relevant
Ciocon 1997[112]	Pentoxifylline 400 mg t.i.d. vs aspirin 325 mg daily	Comparator not relevant
Clyne 1980[113]	Naftidrofuryl oxalate 400 mg vs placebo	Not licensed dose
de Albuquerque 2008[114]	Cilostazol 100 mg b.i.d. vs pentoxifylline 600 mg b.i.d. vs placebo	No comparative data between treatment groups for any of the outcomes included in this review
De Sanctis 2002[115]	Pentoxifylline 1600 mg vs placebo	Not licensed dose
Diehm 1989[116]	Intravenous naftidrofuryl oxalate 600 mg vs prostaglandins of the E1 type	Not licensed
Donaldson 1984[117]	Pentoxifylline 600 mg vs placebo	Not licensed dose
Hentzer 1965[118]	Inositol 1.8 g vs placebo	Not licensed dose
Jaffe 1975[119]	Inositol 3 g vs bradilan 1500 mg	Comparator not relevant
Karnik 1988[120]	Naftidrofuryl oxalate 400 mg b.i.d. vs placebo	Not licensed dose
Kriessman 1988[121]	Naftidrofuryl oxalate 400 mg vs placebo	Non-English language
Milio 2006[122]	Intravenous pentoxifylline and buflomedil vs postaglandins of the E1 type	Not licensed
Moody 1994[94]	Naftidrofuryl fumarate vs placebo	Not licensed
Reilly 1987[123]	Pentoxifylline 400 mg vs placebo	Not licensed dose
Roekaerts 1984[124]	Pentoxifylline 1200 mg vs placebo	Population includes Fontaine stage III
Rosas 1981[125]	Naftidrofuryl oxalate 300 mg vs buflomedil 500 mg	Comparator not relevant, population includes Fontaine stage III
Schubotz 1976[126]	Pentoxifylline 800 mg vs placebo	Population includes Fontaine stages I–III
Soga 2009[127]	Cilostazol 200 mg daily for 2 years vs oral ticlopidine for 4 weeks	Excluded population – all patients underwent endovascular therapy on day of starting study drug, some of patients in both groups had been taking cilostazol up to randomisation
Spitzer 1989[128]	Intravenous pentoxifylline vs placebo	Not licensed
Strano 1984[129]	Pentoxifylline 800 mg vs placebo	Population includes Fontaine stage III
Trubestein 1981[130]	Pentoxifylline 300 mg vs buflomedil 450 mg	Not licensed dose, comparator not relevant
Tyson 1979[131]	Inositol nicotinate vs placebo	Non-randomised study
Waters 1980[132]	Naftidrofuryl oxalate 200 mg t.i.d. vs placebo	No comparative data between treatment groups for any of the outcomes included in this review

Appendix 3

Quality assessment

TABLE 76 Quality assessment items adapted from criteria based on NHS CRD Report No.4:[27] cilostazol trials

Trial (first author, year, trial number if known)	Strandness 2002[56]	Beebe 1999[61]	Elam 1998[64]	Dawson 1998[63]	Money 1998[62]	CASTLE,[48–50] Stone 2008[48]	O'Donnell 2009[83]	Otsuka 21-95-201[34]	Hobbs 2007[82]	Dawson 2000[58]	Otsuka 21-94-301[34]	Otsuka 21-98-213[34]
Data from peer-reviewed journal(s)	Ref. no.s 56 and 57	Ref. no. 61	Ref. no. 64	Ref. no. 63	Ref. no. 62	Ref. no.s 48–50	Ref. no.s 51, 53, 55, 83 and 133	Unpublished trial from Otsuka[34]	Ref. no. 82	Ref. no. 58	Unpublished trial from Otsuka[34]	Unpublished trial from Otsuka[34]
Data from peer-reviewed systematic review(s)	Ref. no. 42		Ref. no. 42					Ref. no. 42		Ref. no. 42	Ref. no.s 35 and 42	
Data from industry submission	Ref. no. 34		Ref. no. 34	Ref. no. 34	Ref. no. 34		Ref. no. 34	Ref. no. 34			Ref. no. 34	Ref. no. 34
What method was used to generate the randomised allocation sequence?	U	a, b	U		U	U	U	U	b	c	U	U
Was the method used to generate the allocation sequence to treatment groups adequate?	U	Y	U	U	U	U	U	U	U	Y	U	U
What method was used to conceal treatment allocation?	U	c	U	U	U	U	d	U	U	e	U	U
Was the allocation of treatment concealed adequately?	U	Y	U	U	U	U	Y	U	U	Y	U	U
Were the treatment groups comparable at baseline?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were clinicians blind to treatment?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Were participants blind to treatment?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
If independent outcome assessors were used, were they blind to treatment?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Trial (first author, year, trial number if known)	Strandness 2002[56]	Beebe 1999[61]	Elam 1998[64]	Dawson 1998[63]	Money 1998[62]	CASTLE,[48–50] Stone 2008[48]	O'Donnell 2009[83]	Otsuka 21-95-201[34]	Hobbs 2007[82]	Dawson 2000[58]	Otsuka 21-94-301[34]	Otsuka 21-98-213[34]
Were participants analysed in their allocated treatment groups, in accordance with the ITT principle?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were at least 80% of the participants originally randomised followed up in the final analysis?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Were there any imbalances in dropouts between groups?	N	N	U	U	U	U	N	U	U	N	U	N
If so, were these imbalances in dropouts adjusted for in analyses?	NA	NA	NA	NA	NA	U	NA	U	NA	NA	U	NA
Is there any evidence of selective reporting of outcomes (i.e. that the authors measured more outcomes than reported)?	Y[f]	N	Y[f]	N	N	N	N	NA	N	Y[f]	NA	NA

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

a Master randomisation list.
b Permuted block design.
c Separate medication supply for each unique patient code, prepared remotely.
d By independent department, delivered by sealed envelopes.
e Interactive voice randomisation system.
f But missing data available from published reviews.

TABLE 77 Quality assessment items adapted from criteria developed by EMA:[18] cilostazol trials

Trial (first author, year, trial number if known)	Strandness 2002[56]	Beebe 1999[61]	Elam 1998[64]	Dawson 1998[63]	Money 1998[62]	CASTLE,[48–50] Stone 2008[48]	O'Donnell 2009[83]	Otsuka 21-95-201[34]	Hobbs 2007[82]	Dawson 2000[58]	Otsuka 21-94-301[34]	Otsuka 21-98-213[34]
Data from peer-reviewed journal(s)	Ref. no.s 56 and 57	Ref. no. 61	Ref. no. 64	Ref. no. 63	Ref. no. 62	Ref. no.s 48–50	Ref. no.s 51, 53, 55 and 133	Unpublished trial from Otsuka[34]	Ref. no. 82	Ref. no. 58	Unpublished trial from Otsuka[34]	Unpublished trial from Otsuka[34]
Data from peer-reviewed systematic review(s)	Ref. no. 42		Ref. no. 42					Ref. no. 42		Ref. no. 42	Ref. no.s 35 and 42	
Data from industry submission	Ref. no. 34		Ref. no. 34	Ref. no. 34	Ref. no. 34		Ref. no. 34	Ref. no. 34			Ref. no. 34	Ref. no. 34
Was IC diagnosed by objective evidence (e.g. reduced ankle systolic blood pressure)?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Did patients have a history of at least 6 months of IC?	Y	Y	Y	Y	Y	U	N	Y	N	Y	Y	Y
Was the treatment period at least 24 weeks' duration?	Y	Y	N	N	N	Y	Y	N	U	Y	Y	Y
Was concomitant treatment comparable across treatment groups?	U	U	Y	U	U	Y	Y	U	Y	U	U	U
If the study included diabetics and non-diabetics, was there stratification for diabetes?	U	N	U	N	U	U	Y	N	N	N	N	U
Was there a placebo run-in phase?	U	N	N	Y	N	Y	N	N	N	N	N	U
If so, did the placebo run-in phase last 2–6 weeks?	U	NA	NA	Y	NA	Y	NA	NA	NA	NA	NA	U
Did reported outcomes include MWD and/or PFWD?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Did the study use a clearly designed protocol for the treadmill test?	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y
If not a treadmill test, was there a clearly defined protocol for the walking distance test?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
For placebo run-in phase or baseline, were there at least two treadmill tests with an interval of at least 1 week?	U	Y	Y	U	U	NA	Y	Y	N	U	Y	U
If so, did patients have a baseline MWD with < 25% change?	U	Y	U	N	Y	NA	U	Y	NA	Y	Y	U

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

TABLE 78 Quality assessment items adapted from criteria based on NHS CRD Report No.4:[27] pentoxifylline trials

Trial (first author, year, trial number if known)	Dawson 2000[58]	Otsuka[34]	Otsuka 21-98-213[34]	Lindegarde 1989[71]	Porter 1982,[72] Gillings 1987[73]	Gallus 1985[76]	Di Perri 1983[77]	Dettori 1989[69]	Creager 2008[70]
Data from peer-reviewed journal	Ref. no. 58	Unpublished trial from Otsuka	Unpublished trial from Otsuka	Ref. no. 71	Ref. no.s 72–75	Ref. no. 76	Ref. no. 77	Ref. no. 69	Ref. no. 70
Data from peer-reviewed systematic review(s)	Ref. no. 42	Ref. no. 35							
Data from industry submission		Ref. no. 34	Ref. no. 34						
What method was used to generate the randomised allocation sequence?	Permuted block design	U	U	U	U	Random number sequence	U	Computer-generated random numbers	U
Was the method used to generate the allocation sequence to treatment groups adequate?	Y	U	U	U	U	Y	U	Y	U
What method was used to conceal treatment allocation?	a	U	U	U	U	b	U	c	U
Was the allocation of treatment concealed adequately?	Y	U	U	U	U	Y	U	Y	U
Were the treatment groups comparable at baseline?	Y	Y	Y	Y	Y	Y	U	Y	Y
Were clinicians blind to treatment?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were participants blind to treatment?	Y	Y	Y	Y	Y	Y	Y	N	Y
If independent outcome assessors were used, were they blind to treatment?	NA	NA	NA	NA	NA	NA	NA	Y	NA

continued

TABLE 78 Quality assessment items adapted from criteria based on NHS CRD Report No.4:[27] pentoxifylline trials *(continued)*

Trial (first author, year, trial number if known)	Dawson 2000[58]	Otsuka[34]	Otsuka 21-98-213[34]	Lindegarde 1989[71]	Porter 1982,[72] Gillings 1987[73]	Gallus 1985[76]	Di Perri 1983[77]	Dettori 1989[69]	Creager 2008[70]
Were participants analysed in their allocated treatment groups, in accordance with the ITT principle?	Y	Y	Y	Y	U	N	Y	N	Y
Were at least 80% of the participants originally randomised followed up in the final analysis?	Y	Y	Y	U	N	N	Y	Y	Y
Were there any imbalances in dropouts between groups?	N	U	N	U	U	N	N	N	U
If so, were these imbalances in dropouts adjusted for in analyses?	NA	U	NA	NA	U	NA	NA	NA	NA
Is there any evidence of selective reporting of outcomes (i.e. that the authors measured more outcomes than reported)?	Y[d]	NA	NA	Y	Y	N	N	Y	N

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

a Interactive voice randomisation system.

b Code held by pharmacist.

c Numbered bottles, blinded staff performed treadmill test, acenocoumarol was not blind to participants.

d But missing data available from published reviews.

TABLE 79 Quality assessment items adapted from criteria developed by EMA:[18] pentoxifylline trials

Trial (first author, year, trial number if known)	Dawson 2000[58]	Otsuka 21–94–301[34]	Otsuka 21–98–213[34]	Lindegarde 1989[71]	Porter 1982,[72] Gillings 1987[73]	Gallus 1985[76]	Di Perri 1983[77]	Dettori 1989[69]	Creager 2008[70]
Data from peer-reviewed journal	Ref. no. 58	Unpublished trial from Otsuka	Unpublished trial from Otsuka	Ref. no. 71	Ref. no.s 72–75	Ref. no. 76	Ref. no. 77	Ref. no. 69	Ref. no. 70
Data from peer-reviewed systematic review(s)	Ref. no. 42	Ref. no. 35							
Data from industry submission		Ref. no. 34	Ref. no. 34						
Was IC diagnosed by objective evidence (e.g. reduced ankle systolic blood pressure)?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did patients have a history of at least 6 months of IC?	Y	Y	Y	Y	Y	Y	Y	U	N
Was the treatment period at least 24 weeks' duration?	Y	Y	Y	Y	Y	N	N	Y	Y
Was concomitant treatment comparable across treatment groups?	U	U	U	U	Y	U	Y	U	U
If the study included diabetics and non-diabetics, was there stratification for diabetes?	N	N	U	NA	N	N	NA	N	N
Was there a placebo run-in phase?	N	N	U	Y	Y	Y	N	Y	Y
If so, did the placebo run-in phase last 2–6 weeks?	NA	NA	U	Y	Y	Y	NA	Y	Y
Did reported outcomes include MWD and/or PFWD?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the study use a clearly designed protocol for the treadmill test?	Y	Y	Y	Y	Y	Y	N	Y	Y
If not a treadmill test, was there a clearly defined protocol for the walking distance test?	NA	NA	NA	NA	NA	NA	Y	NA	NA
For placebo run-in phase or baseline, were there at least two treadmill tests with an interval of at least 1 week?	U	Y	U	Y	Y	Y	N	U	Y
If so, did patients have a baseline MWD with < 25% change?	Y	Y	U	N	Y	U	NA	U	Y

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

DOI: 10.3310/hta15400

TABLE 80 Quality assessment items adapted from criteria based on NHS CRD Report No.4:[27] naftidrofuryl oxalate trials

Trial (first author, year, trial number if known)	Kieffer 2001[65]	Adhoute 1986[66]	Trubestein 1984[67]	Ruckley 1978[68]	Spengel 2002[47]
Data from peer-reviewed journal(s)	Ref. no. 65	Ref. no. 66	Ref. no. 67	Ref. no. 68	Ref. no. 47
What method was used to generate the randomised allocation sequence?	Computer generated	U	NR	U	Computer-generated list
Was the method used to generate the allocation sequence to treatment groups adequate?	Y	U	U	U	Y
What method was used to conceal treatment allocation?	U	U	U	Coded container	U
Was the allocation of treatment concealed adequately?	U	U	U	U	U
Were the treatment groups comparable at baseline?	Y	Y	U	N	Y
Were clinicians blind to treatment?	Y	N	Y	Y	Y
Were participants blind to treatment?	Y	Y	Y	Y	Y
If independent outcome assessors were used, were they blind to treatment?	NA	NA	NA	NA	NA
Were participants analysed in their allocated treatment groups, in accordance with the ITT principle?	Y	Y	Y	U	Y
Were at least 80% of the participants originally randomised followed up in the final analysis?	Y	N	Y	Y	Y
Were there any imbalances in dropouts between groups?	N	N	N	U	N
If so, were these imbalances in dropouts adjusted for in analyses?	NA	NA	NA	NA	NA
Is there any evidence of selective reporting of outcomes?	Y	N	N	N	N

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

TABLE 81 Quality assessment items adapted from criteria developed by EMA:[18] naftidrofuryl oxalate trials

Trial (first author, year, trial number if known)	Kieffer 2001[65]	Adhoute 1986[66]	Trubestein 1984[67]	Ruckley 1978[68]	Spengel 2002[47]
Data from peer-reviewed journal(s)	Ref. no. 65	Ref. no. 66	Ref. no. 67	Ref. no. 68	Ref. no. 47
Was IC diagnosed by objective evidence (e.g. reduced ankle systolic blood pressure)?	Y	Y	Y	U	Y
Did patients have a history of at least 6 months of IC?	Y	Y	Y	U	N
Was the treatment period at least 24 weeks' duration?	Y	Y	N	N	Y
Was concomitant treatment comparable across treatment groups?	U	U	U	U	U
If the study included diabetics and non-diabetics, was there stratification for diabetes?	Y	U	U	N	N
Was there a placebo run-in phase?	Y	Y	Y	N	Y
If so, did the placebo run-in phase last 2–6 weeks?	Y	Y	Y	NA	Y
Did reported outcomes include MWD and/or PFWD?	Y	Y	Y	Y	Y
Did the study use a clearly designed protocol for the treadmill test?	Y	Y	Y	U	NA
If not a treadmill test, was there a clearly defined protocol for the walking distance test?	NA	NA	NA	NA	N
For placebo run-in phase or baseline, were there at least two treadmill tests with an interval of at least 1 week?	Y	Y	Y	N	N
If so, did patients have a baseline MWD with $<25\%$ change?	Y	Y	N	NA	NA

N, no; NA, not available; Ref. no., reference number; U, unclear; Y, yes.

TABLE 82 Quality assessment items adapted from criteria based on NHS CRD Report No.4:[27] inositol nicotinate trials

Trial (first author, year, trial number if known)	O'Hara 1988[78] (O'Hara 1985 same study)	Kiff 1988[80]	Head 1986[81]
Data from peer-reviewed journal(s)	Ref. no. 78	Ref. no. 80	Ref. no. 81
What method was used to generate the randomised allocation sequence?	U	U	U
Was the method used to generate the allocation sequence to treatment groups adequate?	U	U	U
What method was used to conceal treatment allocation?	U	U	U
Was the allocation of treatment concealed adequately?	U	U	U
Were the treatment groups comparable at baseline?	Y	Y	N
Were clinicians blind to treatment?	Y	Y	Y
Were participants blind to treatment?	Y	Y	Y
If independent outcome assessors were used, were they blind to treatment?	NA	NA	NA
Were participants analysed in their allocated treatment groups, in accordance with the ITT principle?	Y	Y	Y
Were at least 80% of the participants originally randomised followed up in the final analysis?	Y	Y	Y
Were there any imbalances in dropouts between groups?	N	N	U
If so, were these imbalances in dropouts adjusted for in analyses?	NA	NA	NA
Is there any evidence of selective reporting of outcomes?	Y	Y	Y

N, no; NA, not available; U, unclear; Y, yes.

TABLE 83 Quality assessment items adapted from criteria developed by EMA:[18] inositol nicotinate trials

Trial (first author, year, trial number if known)	O'Hara 1988[78] (O'Hara 1985 same study)	Kiff 1988[80]	Head 1986[81]
Data from peer-reviewed journal(s)	Ref. no. 78	Ref. no. 80	Ref. no. 81
Was IC diagnosed by objective evidence (e.g. reduced ankle systolic blood pressure)?	U	Y	U
Did patients have a history of at least 6 months of IC?	U	Y	U
Was the treatment period at least 24 weeks' duration?	N	N	N
Was concomitant treatment comparable across treatment groups?	U	U	U
If the study included diabetics and non-diabetics, was there stratification for diabetes?	U	N	N
Was there a placebo run-in phase?	N	N	N
If so, did the placebo run-in phase last 2–6 weeks?	NA	NA	NA
Did reported outcomes include MWD and/or PFWD?	Y	Y	N
Did the study use a clearly designed protocol for the treadmill test?	N	N	NA
If not a treadmill test, was there a clearly defined protocol for the walking distance test?	Y	NA	Y
For placebo run-in phase or baseline, were there at least two treadmill tests with an interval of at least 1 week?	N	N	N
If so, did patients have a baseline MWD with $< 25\%$ change?	NA	NA	NA

N, no; NA, not available; U, unclear; Y, yes.

Appendix 4

Data abstraction tables

Data are as reported in the primary publication listed in the 'publication type' row, unless indicated otherwise by square brackets [ ] . These data are taken from a secondary publication, as referenced.

Two-arm trials of cilostazol versus placebo

Strandness 2002[56]	
Study details	
Publication type	Strandness 2002,[56] full report in peer-reviewed journal
Additional sources of data	Strandness 1998,[57] Thompson 2002,[35] Cochrane review 2008,[28] Pande 2010,[31] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.) Placebo Cilostazol 100 mg (50 mg b.i.d.) – this dose is not licensed in the UK and has been excluded from analysis
Comparator	Placebo
Run-in phase	3 weeks, non-placebo
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 2 weeks, 4 weeks, then every 4 weeks until 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD AEs: patient self-report HRQoL: SF-36, WIQ, COM
Notes on statistics	Raw data: arithmetic mean, mean change and per cent change Analysis: last observation carried forward, analysis of variance of the log (distance at week 24/baseline). Between-group analysis by estimated treatment effect, calculated as ratio of geometric mean (antilog of the difference in mean of cilostazol change from baseline minus mean of placebo change from baseline)
Population	
Eligibility criteria	Age ≥ 40 years; stable, PAD-induced IC of at least 6 months' duration; no significant change in symptom severity for at least 3 months; diagnosis of PAD required Doppler measurement of an ABPI £ 0.90; resting ABPI < 0.90 and at least a 10 mmHg decrease in ankle systolic blood pressure in the reference leg at the completion of testing MWD on two consecutive prerandomisation treadmill tests varied by < 20%; walking distance 30–200 m. For subjects with equivalent bilateral disease, the limb with the lowest resting ABPI was analysed. Excluded if rest pain: Buerger's disease; ischaemic tissue necrosis; surgical or endovascular procedures within 3 months; unstable coronary artery disease or a coronary intervention within 6 months; deep vein thrombosis within 3 months; symptomatic cardiac arrhythmias; conditions other than claudication that limited exercise capacity, or other medical conditions likely to preclude completing the study; women of childbearing age not using a reliable birth control method; patients receiving anticoagulants or using > 81 mg/day aspirin or > 1200 mg/day ibuprofen; gross obesity; hypertension (> 200 mmHg systolic or > 100 mmHg diastolic supine resting pressures), malignancy or metastatic malignancy, exercise-limiting cardiac disease, history of bleeding tendencies, and concomitant use of antiplatelet, anticoagulant, haemorheological or non-steroidal anti-inflammatory agents
Concomitant interventions allowed or excluded	Allowed: occasional use of diclofenac sodium Disallowed: antiplatelet, anticoagulant, haemorheological or non-steroidal anti-inflammatory agents. No specific counselling regarding smoking cessation, diet or exercise was given
Power calculation	Powered at 90%, based on a 5% significance level (two-sided)
N randomised to treatments included in review	262

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	133	129
Baseline characteristics		
Age	Mean 63.1 years (SE 10.2 years)	Mean 64.4 years (SE 10.2 years)
Gender	M 76.7%; F 23.3%[a]	M 77.5%; F 22.5%
Smokers	50.4% current smokers	48.1% current smokers
Diabetics	23.3%	17.1%
Hypertension/blood pressure	NR	NR
Hyperlipidaemia	NR	NR
Obesity or weight	Mean weight 80.1 (SE 14.8) kg	Mean weight 80.1 (SE 15.1) kg
Angina	NR	NR
History of vascular therapy		
Other	Currently drinks alcohol 61.7%	Currently drinks alcohol 55.0%
Withdrawals		
Withdrawals/loss to follow-up	Nine did not have at least one post-randomisation treadmill test; 22.6% withdrew owing to AEs	Four did not have at least one post-randomisation treadmill test; 10.1% withdrew owing to AEs
Results		
MWD *n* in analysis	124 at 24 weeks	125 at 24 weeks
MWD baseline	Mean 119.4 m	Mean 120.1 m
MWD follow-up	Mean 195.6 m	Mean 141.2 m
MWD change	Mean 76.2 m (63.82%)	Mean 21.1 m (17.6%)
MWD between-group comparison	Estimated treatment effect 1.21 (95% CI 1.09 to 1.35) $p = 0.0003$	
PFWD *n* in analysis		
PFWD baseline	[Otsuka submission[34] arithmetic mean 63.6]	[Otsuka submission[34] arithmetic mean 67.5]
PFWD follow-up		
PFWD change	[Robless 2008:[28] mean 58.5 (SD 128.3)] [Otsuka submission[34] arithmetic mean 47.2 (84.3%)]	[Robless 2008:[28] mean 17.2 (SD 43.6)] [Otsuka submission[34] arithmetic mean 19.8 (37.7%)]
PFWD between-group comparison	[Strandness 1998:[57] 22% net improvement] [Otsuka submission[34] estimated treatment effect (geometric mean ratio) 1.22, $p = 0.0015$]	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	265	129
Vascular events follow-up	24 weeks	
Vascular events included	NR	
Vascular events reported	$n = 12$	$n = 5$
Vascular events between-group comparison	NR	

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
AEs *n* in analysis	133	129
AEs follow-up	24 weeks	
AEs included		
AEs reported	Headache 40.6%; infection 18%; leg pain 11.3%; diarrhoea 16.5%; abnormal stools 19.5%. Serious treatment-emergent AEs 18.8% Potentially cilostazol-related AEs ($n=7$) 5.3%	Headache 12.4%; infection 12.4%; leg pain 14.0%; diarrhoea 6.2%; abnormal stools 5.4% Serious treatment-emergent AEs 15.5%
AEs between-group comparison	NR	
Mortality reported	2	0
Mortality between-group comparison	Log-rank test on the Kaplan–Meier estimates of survival, no significant differences among treatment groups ($p=0.6723$) in the probability of having a cardiovascular event or dying throughout the course of the study	
HRQoL *n* in analysis	Unclear	Unclear
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison	Statistically significant improvement in the physical function scale at week 24 for the cilostazol group compared with placebo ($p=0.048$). Non-significant trend favouring cilostazol over placebo for physical health concept scales (physical function, bodily pain and role–physical), general health perception score and walking distance score on the WIQ	

F, female; M, male; NR, not reported; SE, standard error.
a Figures calculated by reviewer.

Beebe 1999[61]	
Study details	
Publication type	Beebe 1999,[61] full report in peer-reviewed journal
Additional sources of data	Cochrane review 2008,[28] Uchiyama 2009,[42] Rowlands 2007,[41] industry submission[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.)
Comparator	Placebo
Run-in phase	3 weeks, non-placebo
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 4, 8, 12, 16, 20 and 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events: method NR AEs: patient self-report Mortality: method NR HRQoL: SF-36, WIQ, COM
Notes on statistics	Log transformation of the data was used for walking distances
Population	
Eligibility criteria	Age ≥ 40 years; stable, PAD-induced IC of at least 6 months' duration; no significant change in symptom severity for at least 3 months; diagnosis of PAD required Doppler measurement of an ABPI ≤ 0.90 and a ≥ 10 mmHg decrease in ankle artery blood pressure following the onset of MWD; PFWD 30–200 m on two consecutive pre-randomisation treadmill tests (12.5% incline, 3.2 km/hour) varied by < 20%. Excluded if rest pain; obesity; hypertension(> 200 mmHg systolic or > 100 mmHg diastolic supine resting blood pressure), current metastatic malignant neoplasm; conditions other than claudication that limited exercise capacity, or other medical conditions likely to preclude completing the study; women of childbearing age not using a reliable birth control method; history of bleeding tendencies
Concomitant interventions allowed or excluded	Allowed: [Otsuka submission,[34] diclofenac sodium as clinically indicated] Disallowed: anticoagulant, antiplatelet, vasoactive, haemorheological or non-steroidal anti-inflammatory agents
Power calculation	Powered at 80% to detect a doubling of the cardiovascular morbidity and all-cause mortality event rate, based on a 5% significance level (two-sided)
N randomised to treatments included in review	345

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	175	170
Baseline characteristics		
Age	Mean 64.3 years (SD 8.5 years)	Mean 65.1 years (SD 9.3 years)
Gender	M 74.3%; F 25.7%	M 77.1%; F 22.9%
Smokers	34.9%	44.1%
Diabetics	26.3%	28.2%
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight	Weight mean 78.6 (SD 16.1) kg range 41.8–115.0 kg	Weight mean 78.8 (SD 16.0) kg range 47.7–129.4 kg
Angina		
History of vascular therapy		
Other	Currently drinks alcohol 60.6%	Currently drinks alcohol 57.1%
Withdrawals		
Withdrawals/loss to follow-up	26 withdrew for AEs, 11 for other reasons	24 withdrew for AEs, five for other reasons
Results		
MWD *n* in analysis	140	140
MWD baseline	Geometric mean 129.7 m	Geometric mean 147.8 m
MWD follow-up	Geometric mean 258.8 at 24 weeks (at 16 weeks 216.0)	Geometric mean 174.6 at 24 weeks (at 16 weeks 161.9)
MWD change	Geometric mean change from baseline 1.51 at 24 weeks (at 16 weeks = 1.41); difference (258.8–129.7 = 129.1) [129.1 (463.3)][28] [Rowlands 2007:[41] mean change 51%]	Geometric mean change from baseline 1.15 at 24 weeks (at 16 weeks = 1.11); difference 26.82 [26.82 (148.5)][28] [Rowlands 2007:[41] mean change 15%]
MWD between-group comparison	$p < 0.001$ at 24 weeks ($p < 0.001$ at 16 weeks)	
PFWD *n* in analysis	140	140
PFWD baseline	Geometric mean 70.4 m	Geometric mean 72.4 m
PFWD follow-up	Geometric mean 137.9 at 24 weeks (at 16 weeks = 112.4)	Geometric mean 95.5 at 24 weeks (at 16 weeks = 91.9)
PFWD change	Geometric mean change from baseline 1.59 at 24 weeks (at 16 weeks = 1.43); difference 67.5 [Robless 2008:[28] 67.5 (130.4)] [Rowlands 2007:[41] mean change 59%]	Geometric mean change from baseline 1.20 at 24 weeks (at 16 weeks = 1.15); difference 23.04 [Robless 2008:[28] 23.04 (63.78) [Rowlands 2007:[41] mean change 20%]
PFWD between-group comparison	$p < 0.001$ at 24 weeks ($p < 0.001$ at 16 weeks)	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	175	170
Vascular events follow-up	24 weeks	

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
Vascular events included	1. MI verified by clinical symptoms, enzyme changes and electrocardiogram changes indicative of MI 2. Cerebrovascular infarct (stroke) verified by neurological deficit lasting > 24 hours confirmed by angiography, computerised tomography scan or magnetic resonance imaging 3. Arterial revascularisation, including angioplasty or surgical vascular reconstruction: a. Procedures for peripheral vascular disease, including lower extremity bypass[a] b. Other procedures, including CABG, carotid endarterectomy, and renal procedures[a] 4. Amputation for ischaemia	
Vascular events reported, *n* (%)	1. MI 2 (1.1) 2. Stroke 3 (1.7) 3. Arterial revascularisation CABG/carotid endarterectomy/renal procedure 0 (0); peripheral vascular procedure/lower extremity bypass 2 (1.1) 4. Amputation 0 (0) [Uchiyama 2008:[42] seven coronary vascular events, 2.0%; two cerebral vascular events 0.6%; one serious bleeding, 1.9%]	1. MI 2 (1.2) 2. Stroke 2 (1.2) 3. Arterial revascularisation CABG/carotid endarterectomy/renal procedure 1 (0.6); peripheral vascular procedure/lower extremity bypass 5 (2.9) 4. Amputation 1 (0.6) [Uchiyama 2008:[42] three coronary vascular events, 1.8%; three cerebral vascular events 1.8%; 0 serious bleeding]
Vascular events between-group comparison	No statistically significant differences between treatment groups in the probability of survival without cardiovascular morbidity or all-cause mortality during 24 weeks of therapy ($p = 0.71$)	
AEs *n* in analysis	175	170
AEs follow-up	24 weeks	
AEs included		
AEs reported	Headache 34.3%; abnormal stool samples 14.9%; diarrhoea 12.0%; dizziness 10.3%; palpitations 11.4% Withdrew due to headache $n = 4$; due to palpitations $n = 4$	Headache 14.7%; abnormal stool samples 3.5%; diarrhoea 4.1%; dizziness 4.7%; palpitations 0%
AEs between-group comparison		
Mortality reported	$n = 2$, 1.1%	$n = 2$, 1.2%
Mortality between-group comparison		
HRQoL *n* in analysis	137	141
HRQoL baseline		
HRQoL follow-up		
	Mean score (mean change from baseline)	Mean score (mean change from baseline)
HRQoL change	SF-36 physical health (score range 0–100): physical function 61.6 (7.1); role–physical 61.3 (5.3); bodily pain 62.9 (7.2); mental health (score range 0–100) social function 86.3 (1.0); role–emotional 91.7 (2.9); mental health 82.2 (2.5)	SF-36 physical health (score range 0–100): physical function 53.8 (2.0); role–physical 49.8 (–2.8); bodily pain 54.0 (–1.8); mental health (score range 0–100) social function 82.5 (0.4); role–emotional 84.2 (–1.66); mental health 79.6 (0.9)
HRQoL between-group comparison	For the physical health concepts domain of the SF-36, cilostazol was significantly superior to placebo at week 24 in the physical function and bodily pain scales. There was no significant difference between cilostazol and placebo for the mental health concepts domain. For the WIQ at week 24, both cilostazol groups were superior to placebo for walking speed and walking distance. Statistically significant improvements were seen in the following COM scales: walking pain/discomfort, change in walking pain/discomfort, and walking pain/discomfort related to ability to perform physical activities. For all other domains and subscales, the cilostazol groups were not significantly different from the placebo group	

CABG, coronary artery bypass graft; F, female; M, male.

a Classifications were defined by the executive committee of the study post hoc to clarify outcomes.

Elam 1998[64]	
Study details	
Publication type	Elam 1998,[64] full report in peer-reviewed journal
Additional sources of data	Thompson 2002,[35] Cochrane review 2008,[28] Uchiyama 2009,[42] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.)
Comparator	Placebo
Run-in phase	
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, then every 4 weeks until 12 weeks
Outcomes and measures	MWD: graded test, constant speed [Thompson 2002:[35] 2.0 mph (3.2 km/hour), at 0% grade with a 3.5% increase in grade every 3 minutes] ABPI: Doppler AEs: patient self-report
Notes on statistics	Arithmetic means used for MWD and PFWD
Population	
Eligibility criteria	Documented chronic, stable, symptomatic IC secondary to PAD. PAD was defined as an ABPI $\leq$ 0.90; termination of walking on a variable-load, constant-speed treadmill due to IC (between 54 and 805 m); and a Doppler-measured drop of $\geq$ 10 mmHg in blood pressure of one ankle after the treadmill test. For patients without a qualifying ABPI, a 20 mmHg drop in post-exercise ankle artery pressure was required for entry. Patients with documented IC underwent two fasting blood draws (at least 1 week apart) in which plasma triglyceride concentration (average of two determinations) was < 350 mg/dl, and plasma low-density lipoprotein cholesterol was between 100 and 190 mg/dl in all subjects. Women were not of child-bearing potential (either surgically sterilised or at least 1 year post-menopause). Exclusions: gross obesity (> 60% above ideal body weight), poorly controlled hypertension (systolic pressure > 200 mmHg; diastolic pressure > 100 mmHg), poorly controlled diabetes, a history of malignancy, current alcohol or drug abuse, renal disease (creatinine > 2.5 mg/dl), or bleeding tendencies; patients taking antiplatelet, anticoagulant, vasoactive, haemorheological or lipid-modifying medications
Concomitant interventions allowed or excluded	Allowed: therapy with beta-blockers and thiazide diuretics was allowed if held at a constant dose for 8 weeks before the trial and if the dosage was maintained during the 12-week treatment period Disallowed: specific counselling regarding smoking cessation, diet or exercise
Power calculation	Powered at 80%, based on a 5% significance level (two-sided)
N randomised to treatments included in review	

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	95	94
Baseline characteristics		
Age	Mean 66.7 years	Mean 65.8 years
Gender	M 87.4%; F 12.6%	M 80.9%; F 19.1%
Smokers		
Diabetics	18.9%	20.2%
Hypertension/blood pressure	55.8%	60.6%
Hyperlipidaemia		
Obesity or weight	Weight mean 81.7 kg	Weight mean 81.1 kg
Angina	8.4%	10.6%
History of vascular therapy	More CABG in placebo than cilostazol group, figures	
Other	NR Prior MI 10.6%	Prior MI 17.1%
Withdrawals		
Withdrawals/loss to follow-up	13.7% did not complete study. Four discontinued due to headache, one discontinued due to diarrhoea	6.4% did not complete study
Results		
MWD *n* in analysis	Unclear, could be all 95 with imputed data (as for lipid outcomes), 82 completed study	Unclear, could be all 94 with imputed data (as for lipid outcomes), 88 completed study
MWD baseline	Mean 262.3 m (SE 17 m)	Mean 278.2 m (SE 17 m)
MWD follow-up	335 (SE 24)	304 (SE 23)
MWD change	35.5% mean change; difference 72.7 [Robless 2008:[28] 79.05] [Otsuka submission[34] has 76.9 (35%)]	24.3% mean change; difference 25.8 [Robless 2008:[28] 36.1] [Otsuka submission[34] has 23.8 (18%)]
MWD between-group comparison	Cilostazol improved significance over placebo ($p = 0.004$)	
PFWD *n* in analysis		
PFWD baseline	Mean 122.2 m	Mean 142.3 m
PFWD follow-up		
PFWD change	[Otsuka submission[34] has 75.0 (67%)]	[Otsuka submission[34] has 48.8 (38%)]
PFWD between-group comparison	[Otsuka submission[34] has $p = 0.0035$]	
ABPI *n* in analysis	Unclear, could be all 95 with imputed data (as for lipid outcomes), 82 completed study	Unclear, could be all 94 with imputed data (as for lipid outcomes), 88 completed study
ABPI baseline	Mean 0.66 (SE 0.02)	Mean 0.65 (SE 0.02)
ABPI follow-up	0.73 (0.02)	0.65 (0.02)
ABPI change	Mean change 9.03% [difference mean 0.07]	Mean change 1.2% (as reported, even though baseline and final scores are the same) [difference mean 0.00]
ABPI between-group comparison	Cilostazol improved significance over placebo $p < 0.001$ [Otsuka submission:[34] has $p = 0.0008$)]	
Vascular events *n* in analysis	95	94
Vascular events follow-up		
Vascular events included		
Vascular events reported	[Uchiyama 2008:[42] no coronary vascular events; no cerebral vascular events; one serious bleeding, 1.1%]	[Uchiyama 2008:[42] no coronary vascular events; no cerebral vascular events; one serious bleeding, 1.1%]
Vascular events between-group comparison		

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
AEs *n* in analysis	95	94
AEs follow-up		
AEs included		
AEs reported	Headache 32.6%; diarrhoea 18.9%; musculoskeletal pain 14.7%; abnormal stools 13.7%; dizziness 12.6%; peripheral oedema 11.6%	Headache 12.8%; diarrhoea 8.5%; musculoskeletal pain 11.7%; abnormal stools 7.4%; dizziness 4.3%; peripheral oedema 5.3%
AEs between-group comparison	Headache $p<0.05$, all others non-significant	
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

CABG, coronary artery bypass graft; F, female; M, male; NR, not reported; SE, standard error; TIA, transient ischaemic attack.

Dawson 1998[63]	
Study details	
Publication type	Dawson 1998,[63] full report in peer-reviewed journal
Additional sources of data	Cochrane review 2008,[28] Uchiyama 2009,[42] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.)
Comparator	Placebo
Run-in phase	
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, then every 4 weeks until 12 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade
	PFWD: as MWD
	ABPI: continuous wave Doppler ultrasound and cuff occlusion
	AEs: patient self-report
Notes on statistics	Log transform for walking distances, last observation carried forward for missing data [Otsuka submission[34] states arithmetic mean used for MWD and PFWD]
Population	
Eligibility criteria	Stable symptoms of IC secondary to chronic occlusive arterial disease from atherosclerosis (symptoms present for at least 6 months and not significantly changed within the past 3 months). Clinical diagnoses of chronic occlusive arterial disease were supported with objective criteria from non-invasive vascular tests, including an PFWD on the treadmill between 30 and 200 m and a minimum post-exercise drop in Doppler-measured ankle systolic blood pressure of $\geq$ 20 mmHg. Exclusions: limb-threatening chronic limb ischaemia, manifested by ischaemic rest pain, ulceration or gangrene, lower-extremity surgical or endovascular arterial reconstructions or sympathectomy in the preceding 6 months, uncontrolled hypertension, inability to complete the treadmill walking test for reasons other than claudication, recent MI (within 6 months), recent deep vein thrombosis (within 3 months), severe concomitant diseases, substance abuse and gross obesity
Concomitant interventions allowed or excluded	Allowed: antihypertensive agents, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or calcium channel blockers, or the occasional use of nitroglycerin. Dosages of all concomitant medications were kept constant throughout the study when feasible. Acetaminophen and diclofenac sodium
	Disallowed: antiplatelet agents (including aspirin), anticoagulants, vasoactive agents (papaverine, isoxsuprine, nylidrin, cyclandelate, and niacin derivatives), haemorheological agents (pentoxifylline), and non-steroidal anti-inflammatory drugs. No specific counselling regarding smoking cessation, diet or exercise was provided
Power calculation	[Otsuka submission:[34] powered at 90%, based on a 5% significance level (two sided, assuming > 40% difference in MWD or PFWD)]
N randomised to treatments included in review	81

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	54	27
Baseline characteristics		
Age	Mean 66 years (SE 1.1 years)	Mean 67 years (SE 2.0 years)
Gender	M 70%; F 30%	M 89%; F 11%
Smokers	40.7%	55.6%
Diabetics	25.9%	14.8%
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight	Weight mean 79.1 (SE 2.3) kg	Weight mean 84.3 (SE 2.9) kg
Angina		
History of vascular therapy		
Other	Duration of symptomatic chronic arterial occlusive disease mean years 6.8 (SE 0.82) Current alcohol use 35.2%	Duration of symptomatic chronic arterial occlusive disease mean years 5.7 (SE 0.83) Current alcohol use 55.6%
Withdrawals		
Withdrawals/loss to follow-up	Total 18.5%, $n=10$. Five adverse drug reaction, two marked deterioration in clinical status, two ineligible for study, one laboratory abnormalities	Total 18.5%, $n=5$. One adverse drug reaction, one marked deterioration in clinical status, one ineligible for study, two other reasons
Results		
MWD *n* in analysis	52	25
MWD baseline	Mean 141.9 (SE 21.0) m	Mean 168.6 (SE 33.1) m
MWD follow-up	231.7 (SE 36.9)	152.1 (SE 23.9)
MWD change	Change from baseline least mean squares 88.9 (SE 22.7). Per cent change from baseline by geometric means 30.5%; difference 89.8 [Robless 2008:[28] 84.6] [Otsuka submission[34] has arithmetic mean change (per cent change) 88.9 (60%), geometric mean per cent change 30.5%]	Change from baseline least mean squares –16.9 (SE 32.6). Per cent change from baseline by geometric means –9.3%; difference –16.5% [Robless 2008:[28] 4.56] [Otsuka submission[34] has arithmetic mean change (per cent change) 168.6 (–16.9%), geometric mean per cent change –9.3%]
MWD between-group comparison	$p=0.002$. Per cent change from baseline by geometric means $p<0.01$ (at follow-ups prior to week 12 non-significant)	
PFWD *n* in analysis	52	25
PFWD baseline	Mean 71.2 (SE 6.0) m	Mean 77.7 (SE 8.4) m
PFWD follow-up	112.5 (SE 13.8)	84.6 (SE 13.7)
PFWD change	Change from baseline least mean squares 42.6 (SE 8.2). Per cent change from baseline by geometric means 31.7%; difference 41.3 [Robless 2008:[28] 38.9] [Otsuka submission[34] has arithmetic mean change per cent change) 42.6 (55%), geometric mean per cent change 31.7%]	Change from baseline least mean squares 3.5 (SE 11.7). Per cent change from baseline by geometric means –2.5%; difference 6.9 [Robless 2008:[28] 8.3] [Otsuka submission[34] has arithmetic mean change (per cent change) 3.5 (11%), geometric mean –2.5%]
PFWD between-group comparison	$p=0.007$. Per cent change from baseline by geometric means $p<0.01$	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison	There was no significant change in resting or post-exercise ABPI	

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
Vascular events *n* in analysis	54	27
Vascular events follow-up	12 weeks	
Vascular events included	NR	
Vascular events reported	One stenosis, one MI, one angina, one TIA (also in AEs) [Uchiyama 2008:[42] two coronary vascular events, 3.7%; one serious bleeding, 1.9%]	One death from MI (also in AEs) [Uchiyama 2008:[42] one coronary vascular event, 3.7%; one serious bleeding, 3.7%]
Vascular events between-group comparison		
AEs *n* in analysis		
AEs follow-up		
AEs included	(The US Food and Drug Administration defines a SAE as an occurrence that is fatal, life-threatening, disabling, or requires hospitalisation; or a drug overdose, congenital anomaly, or cancer)	
AEs reported	SAEs: *n* = 6 hospitalisations of cilostazol-treated patients [subclavian artery stenosis, unstable angina, pneumonia (*n* = 2), MI, and TIA] Non-SAEs: 44% gastrointestinal complaints, headaches 20%	SAEs: *n* = 1 death from MI in the placebo group Non-SAEs: 15% gastrointestinal complaints, headaches 15%
AEs between-group comparison		
Mortality reported		One death from MI
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; NR, not reported; SE, standard error; TIA, transient ischaemic attack.

Money 1998[62]	
Study details	
Publication type	Money 1998,[62] full report in peer-reviewed journal
Additional sources of data	Cochrane review 2008,[28] Uchiyama 2009,[42] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	NR, but one of the centres was Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 (100 b.i.d.) mg
Comparator	Placebo
Run-in phase	2-week screening, non-placebo
Treatment duration	16 weeks
Outcome(s)	
Follow-up	Baseline, then every 4 weeks until 16 weeks
Outcomes and measures	MWD: graded test, 2.0 mph (3.2 km/hour), at 0% grade with a 3.5% increase in grade every 3 minutes PFWD: as MWD ABPI: Doppler HRQoL: SF-36, WIQ
Notes on statistics	Log transform for walking distances, last observation carried forward [Otsuka submission[34] uses arithmetic mean and geometric mean comparison for MWD and PFWD]
Population	
Eligibility criteria	More than 40 years of age, PAD for at least 6 months with no change in symptoms in the previous 3 months. Diagnosis of PAD verified by a Doppler-measured ABPI of $\leq$0.90 after 10 minutes of rest and by a reduction in the blood pressure of at least one ankle artery by a minimum of 10 mmHg when measured 1 minute after claudication-limiting treadmill testing, or a decrease of at least one ankle artery blood pressure by a minimum of 20 mmHg when measured 1 minute after treadmill testing. Baseline initial claudication distance (PFWD) of at least 54 m (corresponding to 1 minute on the treadmill), a reproducible absolute claudication distance (MWD) (variance no greater than 20% between the two screening visits), and a maximum allowable absolute claudication distance of 805 m (corresponding to 15 minutes). Exclusion limb-threatening PAD, including gangrene or ischaemic rest pain; surgical or endovascular procedures in the preceding 3 months; gross obesity; hypertension, >200 systolic or >100 diastolic (mmHg); current malignancy (except basal cell carcinoma or in situ carcinoma); Buerger's disease or deep venous thrombosis in the previous 3 months; inability to complete treadmill testing for reasons unrelated to IC; or bleeding problems
Concomitant interventions allowed or excluded	Disallowed: warfarin, heparin and pentoxifylline, and antiplatelet agents, such as aspirin, persantine, ticlopidine, and non-steroidal anti-inflammatory agents
Power calculation	Powered at 80%, based on a 5% significance level (two-sided)
N randomised to treatments included in review	239

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	119	120
Baseline characteristics		
Age	Mean 64.8 years (SD 9.4 years)	Mean 64.5 years (SD 8.8 years)
Gender	M 75.6%; F 24.4%	M 75.0%; F 25.0%
Smokers	36.1%	40.0%
Diabetics	25.2%	30.8%
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight	Weight mean 82.5 (SD 16.6) kg, range 42–130 kg	Weight mean 79.6 (SD 14.9) kg, range 49–127 kg
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	(104 completed study) $n=2$ discontinued due to headaches, $n=1$ discontinued due to dizziness. 15 withdrawals, 12 of which for AEs	(108 completed study) $n=1$ discontinued due to headaches. 12 withdrawals, 10 of which for AEs
Results		
MWD *n* in analysis	119	120
MWD baseline	Mean trough 236.9 (SE 13.6) m; peak 211.4 (SE 12.4) m	Mean trough 244.3 (SE 13.7) m; peak 219.3 (SE 12.9) m
MWD follow-up	Trough 332.6 (SE 20.0) m; peak 306.9 (SE 19.1) m [at 12 weeks trough 313.4 (SE 19.9) m]	Trough 281.1 (SE 19.2) m; peak 267.5 (SE 18.5) m [at 12 weeks trough 279.2 (SE 18.3) m]
MWD change	At 16 weeks mean 96.4 m, $p<0.05$ [Robless 2008:[28] 101.1] [Otsuka submission[34] has arithmetic mean change (per cent change), trough 96.4 m (47.4%), peak 96.2 m (56.1%)]	At 16 weeks mean 31.4 m, $p<0.05$; [Robless 2008:[28] 47.1] [Otsuka submission:[34] has arithmetic mean change (per cent change), trough 31.4 m (12.9%), peak 44.4 m (25.4%)]
MWD between-group comparison	Difference between cilostazol and placebo, by geometric mean per cent change at 16 weeks, trough 32%, peak 27%, $p<0.05$ (at 12 weeks trough 21%, $p<0.05$ between groups). (The small subgroup size precluded the derivation of inferential statistics.) [Otsuka submission[34] has arithmetic mean change trough $p=0.0001$ and peak $p=0.0003$; ratio of geometric mean trough 1.29, $p=0.0001$, peak 1.21, $p=0.0005$]	
PFWD *n* in analysis	119	120
PFWD baseline	[Otsuka submission:[34] arithmetic mean trough 130.4, peak 118.5]	[Otsuka submission:[34] arithmetic mean trough 138.7, peak 129.9]
PFWD follow-up		
PFWD change	[Robless 2008:[28] 85.9] [Otsuka submission:[34] arithmetic mean change per cent change) trough 76.8 (68.3%), peak 80.7 (87.1%)]	[Robless 2008:[28] has 54.2] [Otsuka submission:[34] arithmetic mean change (per cent change) trough 47.6 (38.5%), peak 53.1 (49.7%)]
PFWD between-group comparison	Difference between cilostazol and placebo, by geometric mean per cent change, at 16 weeks, 27% trough, 32% peak, $p<0.05$ [Otsuka submission[34] has arithmetic mean change trough, $p=0.0019$, peak $p=0.0035$, ratio of geometric mean trough 1.2, $p=0.0049$, peak 1.2, $p=0.0074$]	
ABPI *n* in analysis	Unclear	Unclear
ABPI baseline	Mean 0.64 (SD 0.02)	Mean 0.68 (SD 0.02)
ABPI follow-up	0.70 (0.02)	0.69 (0.02)
ABPI change	9% increase [70/64 = 1.09375] [difference mean 0.06]	[69/68 = 1.01470, so 1% increase] [difference mean 0.01]
ABPI between-group comparison	$p=0.0125$	

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
Vascular events *n* in analysis	119	120
Vascular events follow-up		
Vascular events included		
Vascular events reported	One patient died of MI 6 days after stopping cilostazol [Uchiyama 2008:[42] one coronary vascular events, 0.8%; no cerebral vascular events; no serious bleeding]	[Uchiyama 2008:[42] one coronary vascular events, 0.8%; no cerebral vascular events; no serious bleeding]
Vascular events between-group comparison		
AEs *n* in analysis	119	120
AEs follow-up		
AEs included		
AEs reported	Headaches (30.3%), abnormal stools (16.0%), diarrhoea (12.6%) and dizziness (12.6%). SAEs 11.8% ($n=13$)	Headaches (9.2%), abnormal stools (5.0%), diarrhoea (6.7%) and dizziness (5.0%). SAEs 9.2% ($n=11$)
AEs between-group comparison		
Mortality reported	One patient died of MI 6 days after stopping cilostazol	One patient died while on placebo
Mortality between-group comparison		
HRQoL *n* in analysis	Unclear	Unclear
HRQoL baseline		
HRQoL follow-up		
HRQoL change	SF-36 physical component scale score increased by 2.99 points. WIQ improved 20%	
HRQoL between-group comparison	SF-36: cilostazol improved vs placebo physical component scale score, $p=0.0059$. Bodily pain ($p=0.0772$), general health ($p=0.436$), and role–physical ($p=0.061$). Non-significant for mental components. WIQ significantly better for cilostazol, $p=0.0331$ [Otsuka submission:[34] physical function score $p=0.0024$, WIQ significant improvements in walking speed and specific measures of walking difficulty]	

F, female; M, male; SE, standard error.

CASTLE, Hiatt 2007[49,50]/Stone 2008[48]	
Study details	
Publication type	Stone 2008,[48] Hiatt 2008 (RM22),[49] Hiatt 2007 (RM 2195).[50] Full reports in peer-reviewed journals
Additional sources of data	
Trial design	RCT, Phase IV (post-marketing), multicentre
Country	USA
Dates of participant recruitment	Up to November 2004
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 (100 b.i.d.) mg
Comparator	Placebo
Run-in phase	30 days, single blind
Treatment duration	Up to 36 months
Outcome(s)	
Follow-up	Every 26 weeks up to 3 years
Outcomes and measures	AEs: mortality, cardiovascular deaths. Categorisation of the event by the study sponsor according to standard definitions from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. All AEs were recorded when patients were on treatment through 14 days after discontinuation of treatment. Non-fatal AEs were not monitored after drug discontinuation. Serious adverse bleeding events were defined as haemorrhages that were fatal, life-threatening, required or prolonged hospitalisation, caused significant disability or were medically significant in the judgement of the site investigator
Notes on statistics	Given the high discontinuation rate of the study medication and that most deaths occurred 30 days after discontinuation of study drug, the committee determined that the original ITT analysis would not provide a full assessment of cilostazol safety or risk. Therefore, the committee used a primary analysis based on deaths that occurred while patients were taking the study medication plus a 30-day period designed to capture deaths that might have resulted from exposure to the study medication; hereafter, this is regarded as the 'on-treatment' period. The original, prospectively defined ITT population was also evaluated and defined as all randomised patients who received at least one dose of study medication. Also tabulated were deaths occurring in the ITT population during the entire study period, including those 30 days after study medication discontinuation
Population	
Eligibility criteria	Aged at least 17 years with a history of IC secondary to PAD as diagnosed by a physician (specific ABPI criteria for inclusion were not defined). Exclusion criteria included women who were pregnant or breastfeeding, patients currently or previously using of cilostazol, use of an investigational drug in the past 30 days, consumption of grapefruit juice, or patients found to be non-compliant during the 30-day single-blind, run-in phase. Patients with current CHF of any severity, as assessed by the site investigator, were excluded, but those with a history of heart failure who had recovered were eligible for enrolment. Subjects who failed to comply with at least 70% of placebo run-in prescribed regimen were withdrawn from the study
Concomitant interventions allowed or excluded	Allowed: patients taking aspirin, clopidogrel, pentoxifylline, or anticoagulants were eligible for participation
Power calculation	By 34 months after the first patient was randomised, less than half of the projected number of deaths had occurred and the discontinuation rate from study drug was high, which led to study termination in November 2004, as already described. As a result, the study was underpowered to meet its primary end point, but inferences with respect to cilostazol effects on mortality could be described by the 95% CI of the HR
N randomised to treatments included in review	1435

CHF, chronic heart failure.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	717	718
Baseline characteristics		
Age	Mean 66.5 years (SD 10.2 years)	Mean 65.9 years (SD 10.5 years)
Gender	M 65.6%	M 65.5%
Smokers	28.6%	31.3%
Diabetics	37.8%	33.7%
Hypertension/blood pressure	82.4%	81.1%
Hyperlipidaemia	(Hypercholesterolaemia 82.0%)	(Hypercholesterolaemia 78.0%)
Obesity or weight	Weight mean 84.6 (SD 19.5) kg	Weight mean 84.6 (SD 18.8) kg
Angina		
History of vascular therapy		
Other	MI 29.3%; stroke 10.3%; CHF 4.7%	MI 29.8%; stroke 10.6%; CHF 4.9%
Withdrawals		
Withdrawals/loss to follow-up	Probability of discontinuation from the study was 68% in the cilostazol group	Probability of discontinuation from the study was 64% in the placebo group
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	717	718
Vascular events follow-up	Up to 144 weeks	
Vascular events included		
Vascular events reported	ITT cardiovascular mortality $n=28$; event rate per person-year 1.89. On-treatment analysis $n=14$, event rate per person-year 1.34 [Uchiyama 2008:[42] 126 coronary vascular events, 17.6%; 18 cerebral vascular events 2.5%; 18 serious bleeding, 2.5%]	ITT cardiovascular mortality $n=33$; event rate per person-year 2.22. On-treatment analysis $n=14$, event rate per person-year 1.28 [Uchiyama 2008:[42] 132 coronary vascular events, 18.4%; 34 cerebral vascular events 4.7%; 22 serious bleeding, 3.1%]
Vascular events between-group comparison	HR for cardiovascular deaths was 1.054 (95% CI 0.502 to 2.210; $p=0.89$) in the on-treatment population and 0.852 (95% CI 0.515 to 1.410; $p=0.533$) in the ITT population	

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
AEs *n* in analysis	717	718
AEs follow-up	Up to 144 weeks	
AEs included		
AEs reported	*Minor events, n (%)*	*Minor events, n (%)*
	Headache 75 (10.5)	Headache 35 (4.9)
	Palpitations 38 (5.3)	Palpitations 18 (2.5)
	Diarrhoea 78 (10.9)	Diarrhoea 48 (6.7)
	Bronchitis 23 (3.2).	Bronchitis 37 (5.2)
	Serious events, n (%)	*Serious events, n (%)*
	Dyspnoea 7 (1.0)	Dyspnoea 3 (0.4)
	Cerebrovascular accident 7 (1.0)	Cerebrovascular accident 15 (2.1)
	Carotid artery stenosis 5 (0.7)	Carotid artery stenosis 11 (1.5)
	Femoral artery occlusion 3 (0.4)	Femoral artery occlusion 7 (1.0)
	Cardiac arrest 2 (0.3)	Cardiac arrest 7 (1.0)
	Events leading to discontinuation, n (%)	*Events leading to discontinuation, n (%)*
	Oedema 10 (1.4)	Oedema 0 (0)
	Headache 15 (2.1)	Headache 2 (0.3)
	Diarrhoea 20 (2.8)	Diarrhoea 5 (0.7)
	Serious bleeding events 18 (2.5)	Serious bleeding events 22 (3.1)
AEs between-group comparison		
Mortality reported	ITT all-cause mortality $n=49$; event rate per 100 person-years 3.31. On-treatment analysis $n=18$, event rate per person-year 1.72	On-treatment analysis mortality HR of 0.99 (95% CI 0.52 to 1.88, $p=0.97$). ITT all-cause mortality HR for cilostazol compared with placebo was 0.94 (95% CI 0.64 to 1.39, $p=0.77$)
Mortality between-group comparison	On-treatment analysis mortality HR of 0.99 (95% CI 0.52 to 1.88, $p=0.97$). ITT all-cause mortality HR for cilostazol compared with placebo was 0.94 (95% CI 0.64 to 1.39, $p=0.77$)	
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

O'Donnell 2009[51]	
Study details	
Publication type	O'Donnell 2009,[51] full report in peer-reviewed journal
Additional sources of data	O'Donnell 2009[83] (non-diabetic subgroup), O'Donnell 2008[55] (diabetic subgroup), O'Donnell 2009,[54] O'Donnell 2009 (RM2126)[53] (diabetic subgroup)
Trial design	RCT, single centre
Country	Northern Ireland
Dates of participant recruitment	2004–6
Sources of funding	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. Otsuka Pharmaceuticals provided the placebo for the study and have supported the corresponding author in presenting the results at research conferences
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 (100 b.i.d.) mg
Comparator	Placebo
Run-in phase	No, but two baseline assessments 4 weeks apart
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 6 and 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 3.2 km/hour (2 mph) 10% gradient
	PFWD: as MWD
	AEs: patient self-report
	HRQoL: SF-36, VascuQoL
Notes on statistics	[Otsuka submission:[34] The Mann–Whitney *U*-test was used for between-group differences. The Wilcoxon signed-rank test was used for within-group differences. All statistics were two sided and a *p*-value of <0.05 was considered significant]
Population	
Eligibility criteria	Male and female (non-pregnant) patients between the ages of 30 and 90 years, IC defined as reproducible muscle discomfort in the lower limb produced by exercise and relieved by rest, with an ABPI of <0.9, which had been stable on optimal medical therapy that included antiplatelet and lipid-lowering medication, cardiovascular risk assessment and treatment (e.g. hypertension) and smoking cessation therapy combined with the provision of exercise advice for a period of 3 months
	Exclusions current or previous acute or critical limb ischaemia, severe claudication that prohibited the use of treadmill testing as determined during pre-recruitment vascular assessments, an endovascular or surgical procedure within the preceding 6 months or a 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
Concomitant interventions allowed or excluded	Allowed: aspirin, clopidogrel, warfarin, statin, ACE inhibitors, ACE II antagonists, beta-blocker, calcium antagonist diuretic
	Disallowed: omeprazole and diltiazem
Power calculation	30 patients per treatment group completing the trial would have a 90% power to detect a statistically significant ($p<0.05$, two-tailed) difference in the change in MWD, between groups, of a magnitude of 45 m. assumed that approximately 20% of patients would withdraw from the study, a total of 144 patients were required
N randomised to treatments included in review	106

ACE, angiotensin-converting enzyme; mph, miles per hour.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	51	55
Baseline characteristics		
Age	Median 64.2 (range 37–86) years	Median 66.1 (range 39–80) years
Gender	M 67%	M 71%
Smokers	45%	55%
Diabetics	23.5%	25.5%
Hypertension/blood pressure	62.7%	67.3%
Hyperlipidaemia	Hypercholesterolaemia 76.5%	Hypercholesterolaemia 76.4%
Obesity or weight		
Angina	13.7	5.5
History of vascular therapy	CABG 5.9%, carotid endarterectomy 3.9%, vascular arterial bypass/endovascular intervention 7.8%	CABG 9.1%, carotid endarterectomy 5.5%, vascular arterial bypass/endovascular intervention 10.9%
Other	MI 17.6%, CVA 5.9%, abdominal aortic aneurysm 0%	MI 12.7%, CVA 5.5%, abdominal aortic aneurysm 1.8%
Withdrawals		
Withdrawals/loss to follow-up	$n=8$ (15.7%) owing to side effects $n=6$ [six non-diabetics withdrew, four due to AEs] [Otsuka submission[34] one withdrew due to non-compliance, six due to AEs, one due to other reasons]	$n=7$ (12.7%) owing to side effects $n=2$ [three non-diabetics withdrew] [Otsuka submission[34] two withdrew due to non-compliance, two due to AEs, three due to other reasons]
Results		
MWD *n* in analysis	51	55
MWD baseline	Median 144.4 (IQR 99.7 to 204.3) m; non-diabetics median 144.4 m, diabetics 118.5 m	Median 138.6 (IQR 101.7 to 193.8) m; non-diabetics median 138.6 m, diabetics 115.6 m
MWD follow-up	Non-diabetics median 286.1 m at 24 weeks, diabetics 158.3 m	Non-diabetics median 227.1 m at 24 weeks, diabetics 157.8 m
MWD change	161.7% mean change, non-diabetics median 173.1% change, diabetics 143.1%	79.0% mean change, non-diabetics median 92.1% change, diabetics 23.2%
MWD between-group comparison	$p=0.048$: non-diabetics non-significant, $p=0.27$; diabetics non-significant, $p=0.086$	
PFWD *n* in analysis	51	55
PFWD baseline	Median 69.7 (IQR 50.1 to 94.8) m; non-diabetics median 69.7 m, diabetics 69.3 m	Median 63.9 (IQR 45.2 to 85.8) m; non-diabetics median 63.5 m, diabetics 66.2 m
PFWD follow-up	Non-diabetics median 82.7 m at 24 weeks, diabetics 82.3 m	Non-diabetics median 85.0 m at 24 weeks, diabetics 55.9 m
PFWD change	67% mean change, non-diabetics median 84.8% change, diabetics 21.1%	51.6% mean change, non-diabetics median 66.5% change, diabetics –4.4% change
PFWD between-group comparison	$p=0.63$ non-significant: non-diabetics non-significant, $p=0.63$; diabetics non-significant, $p=0.14$	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		
AEs *n* in analysis	[O'Donnell 2009[83] diabetic subgroup 12]	[O'Donnell 2009[83] diabetic subgroup 14]
AEs follow-up	24 weeks	
AEs reported	[O'Donnell 2009:[83] diabetics 14 side effects (12 within first 6 weeks), this is number of events rather than number of patients with an event, events were headache, diarrhoea or palpitations]	[O'Donnell 2009:[83] diabetics seven side effects (all within first 6 weeks), this is number of events rather than number of patients with an event, events were headache, diarrhoea or palpitations]
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis	(O'Donnell 2009:[83] non-diabetics 39)	(O'Donnell 2009:[83] non-diabetics 41)
HRQoL baseline		
HRQoL follow-up	*Mean (SE)*	*Mean (SE)*
	SF-36 (%):	SF-36 (%):
	Physical function 11.0 (4.5)	Physical function –0.3 (3.1)
	Role–physical 7.8 (4.3)	Role–physical 5.4 (3.9)
	Body pain 3.7 (3.3)	Body pain 10.5 (3.5)
	General health 2.7 (3.5)	General health –1.0 (2.5)
	PCS 11.4 (3.2)	PCS 5.1 (3.4)
	Total 1.8 (3.2)	Total 1.4 (1.7)
	VascuQol activity 7.3 (4.6)	VascuQol activity 1.8 (2.9)
	Symptom 3.1 (3.0)	Symptom 3.2 (2.6)
	Pain 10.4 (5.1)	Pain 13.2 (4.3)
	Emotion 5.7 (4.1)	Emotion 1.8 (4.0)
	Social 1.1 (5.9)	Social 3.4 (5.2)
	Total 5.5 (3.5)	Total 3.0 (2.1)
	Diabetics [O'Donnell 2009[53]]: at 24 weeks median (IQR)	*Diabetics [O'Donnell 2009[53]]: at 24 weeks median (IQR)*
	SF-36 (%):	SF-36 (%):
	Physical function 38.1 (29.7 to 41.3)	Physical function 27.6 (24.5 to 40.2)
	Role–physical 34.8 (28.7 to 43.4)	Role–physical 37.3 (25.0 to 45.9)
	Body pain 46.1 (33.2 to 50.8)	Body pain 37.2 (33.0 to 43.8)
	General health 42.4 (31.7 to 45.8)	General health 41.0 (38.2 to 47.0)
	Total 42.5 (34.8 to 46.2)	Total 37.8 (31.2 to 46.3)
	VascuQol activity 3.9 (3.4 to 5.0)	VascuQol activity 4.4 (2.8 to 4.7)
	Symptom 5.5 (5.4 to 6.1)	Symptom 5.3 (3.9 to 5.4)
	Pain 5.0 (4.4 to 5.6)	Pain 4.3 (3.4 to 4.8)
	Emotion 5.6 (4.5 to 6.6)	Emotion 3.7 (3.0 to 5.0)
	Social 5.0 (4.5 to 6.5)	Social 4.0 (3.5 to 5.0)
	Total 5.2 (4.3 to 5.6)	Total 4.3 (3.2 to 4.9)

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
HRQoL change		
HRQoL between-group comparison	*Non-diabetics at 24 weeks mean (SE)*	
	SF-36 (%):	
	Physical function $p=0.013$ significantly more improvement for cilostazol	
	Role physical $p=0.62$	
	Body pain $p=0.21$	
	General health $p=0.48$	
	PCS $p=0.044$ significantly more improvement for cilostazol	
	Total $p=0.50$	
	VascuQol activity $p=0.34$	
	Symptom $p=0.34$	
	Pain $p=0.89$	
	Emotion $p=0.63$	
	Social $p=0.67$	
	Total $p=0.78$	
	WIQ – non-significant between-groups distance $p=0.41$, speed $p=0.88$ (even though cilostazol group had significantly improved and placebo group had non-significant improvement)	
	Diabetics [RM2126] at 24 weeks	
	SF-36 (%):	
	Physical function $p=0.42$	
	Role–physical $p=0.72$	
	Body pain $p=0.31$	
	General health $p=0.93$	
	Total $p=0.40$	
	VascuQol activity $p=0.59$	
	Symptom $p=0.025$ (significantly more increase for placebo, cilostazol more improved)	
	Pain $p=0.08$	
	Emotion $p=0.013$ (significantly more increase for cilostazol, cilostazol more improved)	
	Social $p=0.06$	
	Total $p=0.05$ (significantly more increase for cilostazol, cilostazol more improved)	

CABG, coronary artery bypass graft; CVA, cerebrovascular accident; IQR, interquartile range; M, male; PCS, physical component summary; SE, standard error.

Otsuka 21-95-201[34]	
Study details	
Publication type	Thompson 2002,[35] systematic review in peer-reviewed journal
Additional sources of data	Cochrane review 2008,[28] Uchiyama 2009,[42] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 (100 b.i.d.) mg
Comparator	Placebo
Run-in phase	No, but there was a screening phase
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, then every 4 weeks until 12 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events: unclear HRQoL: [Otsuka submission:[34] SF-36, WIQ]
Notes on statistics	
Population	
Eligibility criteria	Age ≥ 40 years; stable, PAD induced IC of at least 6 months' duration; no significant change in symptom severity for at least 3 months; diagnosis of PAD required Doppler measurement of an ABPI ≤ 0.90; MWD on two consecutive prerandomisation treadmill tests varied by < 20%. Excluded if rest pain: Buerger's disease; ischaemic tissue necrosis; surgical or endovascular procedures within 3 months; unstable coronary artery disease or a coronary intervention within 6 months; deep vein thrombosis within 3 months; symptomatic cardiac arrhythmias; conditions other than claudication that limited exercise capacity, or other medical conditions likely to preclude completing the study; women of childbearing age not using a reliable birth control method
Concomitant interventions allowed or excluded	Allowed: [Otsuka submission:[34] paracetamol] Disallowed: patients receiving anticoagulants or using > 81 mg/day of aspirin or > 1200 mg/day of ibuprofen. No specific counselling regarding smoking cessation, diet, or exercise was given
Power calculation	[Otsuka submission:[34] based on results from a previous study, 60 patients per group was calculated to provide > 90% power on the log and the raw scale, based on a 5% (two-sided) significance level]
N randomised to treatments included in review	142

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
N randomised to treatment	72	70
Baseline characteristics		
Age	[Robless 2008:[28] mean age 68 years] [Otsuka submission[34] has mean age 67.6 years (SD 8.8 years)]	[Robless 2008:[28] mean age 66 years] [Otsuka submission[34] has mean age 65.6 years (SD 7.4 years)]
Gender	[Robless 2008:[28] M 75%; F 25%]	[Robless 2008:[28] M 81%; F 19%]
Smokers	[Otsuka submission[34] has 38.1%]	[Otsuka submission[34] has 38.6%]
Diabetics	[Otsuka submission[34] has 30.6%]	[Otsuka submission[34] has 34.3%]
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight	[Otsuka submission[34] has weight 78.8 (SD 15.7) kg]	[Otsuka submission[34] has weight 84.3 (SD 16.8) kg]
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	[Otsuka submission[34] has 17 withdrawals: failed screening, one; marked deterioration, one; AE, 14; other, one]	[Otsuka submission[34] has eight withdrawals: lack of response, one; AE, six; other, one]
Results		
MWD *n* in analysis	[Otsuka submission[34] has 60]	[Otsuka submission[34] has 66]
MWD baseline	[Otsuka submission[34] has mean 121.9]	[Otsuka submission[34] has mean 123.4]
MWD follow-up		
MWD change	Approximately 28% (estimated from figure 1, Thompson 2002[35]) [Robless 2008:[28] mean 35.2 (SD 72.05)] [Otsuka submission[34] has arithmetic mean change 37.5 (59.4%)]	Approximately 30% (estimated from figure 1, Thompson 2002[35]) [Robless 2008:[28] mean 38.1 (SD 69.7)] [Otsuka submission[34] has arithmetic mean change 33.9 (59.6%)]
MWD between-group comparison	Non-significant [Otsuka submission[34] has 0.8585 ratio of geometric mean change 1.02 (CI 0.88 to 1.18), $p = 0.7925$]	
PFWD *n* in analysis	[Otsuka submission[34] has 60]	[Otsuka submission[34] has 66]
PFWD baseline	[Otsuka submission[34] has mean 65.7]	[Otsuka submission[34] has mean 67.4]
PFWD follow-up		
PFWD change	Approximately 58% (estimated from figure 2, Thompson 2002[35]) [Robless 2008:[28] mean 41.4 (SD 63.2)], [Otsuka submission[34] has arithmetic mean change 37.5 (59.4%)]	Approximately 52% (estimated from figure 2, Thompson 2002[35]) [Robless 2008:[28] mean 34.4 (SD 57.3)], [Otsuka submission[34] has arithmetic mean change 33.9 (59.6%)]
PFWD between-group comparison	Non-significant [Otsuka submission[34] has 0.4818 ratio of geometric mean change 1.18 (CI 1.02 to 1.37), $p = 0.0309$]	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		

Treatment group	Cilostazol 100 mg b.i.d.	Placebo
Vascular events *n* in analysis	145 (including 150-mg b.i.d. group, which was excluded from other analyses)	70
Vascular events follow-up		
Vascular events included		
Vascular events reported	[Uchiyama 2008:[42] three coronary vascular events, 2.1%; no cerebral vascular events; no serious bleeding]	[Uchiyama 2008:[42] one coronary vascular events, 1.4%; one cerebral vascular events 1.4%; no serious bleeding]
Vascular events between-group comparison		
AEs *n* in analysis		
AEs follow-up		
AEs reported		
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison	[Otsuka submission[34] has SF-36 positive trend in favour of cilostazol with regards to role–physical scores. WIQ showed a trend towards improvement with respect to walking difficulty secondary to pain]	

F, female; M, male.

Three-arm trials of cilostazol, pentoxifylline and placebo

Dawson 2000[58]	
Study details	
Publication type	Dawson 2000,[58] full report in peer-reviewed journal
Additional sources of data	Cochrane review 2008,[28] Uchiyama 2009[42]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.) plus placebo
	Pentoxifylline 1200 mg daily dose (400 mg t.i.d.) plus placebo
Comparator	Placebo
Run-in phase	No, but 2- to 3-week baseline assessment period
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 2 weeks, 4 weeks, then every 4 weeks until 24 weeks
Outcomes and measures	MWD: treadmill with graded test, 2.0 mph (3.2 km/hour), at 0% gradient with a 3.5% increase in gradient every 3 minutes
	PFWD: as MWD
	ABPI: Doppler
	AEs: patient self-report
	HRQoL: SF-36, WIQ
Notes on statistics	Geometric mean change in MWD was determined. This change was expressed as a log of the quotient of the post-treatment MWD divided by the baseline MWD value
Population	
Eligibility criteria	Stable, PAD-induced IC of at least 6 months' duration; no significant change in symptom severity for at least 3 months; diagnosis of PAD required Doppler measurement of an ABPI ≤ 0.90; MWD on two consecutive pre-randomisation treadmill tests varied by $< 20\%$; baseline PFWD more than or equal to 53.6 m; MWD ≤ 537.6 m. Excluded if rest pain; Buerger's disease; lower extremity arterial reconstruction (surgical or endovascular) or sympathectomy within the previous 3 months, exercise capacity limited by conditions other than IC
Concomitant interventions allowed or excluded	Allowed: aspirin at a dose of no more than 81 mg per day, up to 1200 mg per day of ibuprofen
	Disallowed: anticoagulants or other antiplatelet agents, non-steroidal anti-inflammatory drugs
Power calculation	Two hundred patients per treatment group would provide $> 95\%$ power at a 5% significance level to detect a difference between cilostazol and pentoxifylline, based on these values and a SD of 68%
N randomised to treatments included in review	698

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
N randomised to treatment	227	232	239
Baseline characteristics			
Age	Mean 66 years (SD 9 years)	Mean 66 years (SD 9 years)	Mean 66 years (SD 9 years)
Gender	M 76%	M 78%	M 74%
Smokers	41%	33%	38%
Diabetics	32%	28%	31%
Hypertension/blood pressure	73%	69%	72%
Hyperlipidaemia	Hypercholesterolaemia 65%	Hypercholesterolaemia 67%	Hypercholesterolaemia 67%
Obesity or weight	Weight 81 (SD 16) kg	Weight 82 (SD 15) kg	Weight 81 (SD 15) kg
Angina			
History of vascular therapy			
Other			
Withdrawals			
Withdrawals/loss to follow-up	$n=39$ (no significant differences in the baseline demographic or clinical features of patients who withdrew from the study before completion compared with those who completed the study) due to AEs 16%	$n=40$ due to AEs 19%	$n=25$ due to AEs 9%
Results			
MWD *n* in analysis	205	212	226
MWD baseline	Mean 241 (SD 123) m	Mean 238 (SD 119) m	Mean 234 (SD 119) m
MWD follow-up	Mean 350 (SD 209) m	Mean 308 (SD 183) m	Mean 300 (SD 180) m
MWD change	Mean 107 (SD 158) m [Robless 2008:[28] 107.36 (158.4) m]	Mean 64 (SD 127) m [Robless 2008:[28] 64.7 (134.61) m]	Mean 65 (SD 135) m [Robless 2008:[28] 64.4 (126.6) m]
MWD between-group comparison	Cilostazol vs placebo $p=0.0005$; pentoxifylline vs placebo 0.82; cilostazol vs pentoxifylline $p=0.0002$		
PFWD *n* in analysis	205	212	226
PFWD baseline	Mean 124 (SD 81) m	Mean 126 (SD 79) m	Mean 122 (SD 69) m
PFWD follow-up	Mean 218 (SD 149) m	Mean 202 (SD 139) m	Mean 180 (SD 115) m
PFWD change	Mean 94 (SD 127) m [Robless 2008:[28] 93.6 (127.4) m]	Mean 74 (SD 106) m [Robless 2008:[28] 56.5 (93.1) m]	Mean 57 (SD 93) m [Robless 2008:[28] 73.6 (93.1) m]
PFWD between-group comparison	Cilostazol vs placebo $p=0.0001$; pentoxifylline vs placebo 0.07; cilostazol vs pentoxifylline $p=0.02$		
ABPI *n* in analysis	205	212	226
ABPI baseline	Mean 0.66 (SD 0.18)	Mean 0.66 (SD 0.21)	Mean 0.68 (SD 0.42)
ABPI follow-up	Mean 0.70 (SD 0.18)	Mean 0.71 (SD 0.24)	Mean 0.67 (SD 0.19)
ABPI change	[Difference in means 0.04]	[Difference in means 0.05]	[Difference in means –0.01]
ABPI between-group comparison	Significantly more improvement in cilostazol than placebo $p<0.01$. Non-significant between other groups		

Treatment group	Cilostazol 100 mg b.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
Vascular events *n* in analysis			
Vascular events follow-up			
Vascular events included			
Vascular events reported	[Uchiyama 2008:[42] two coronary vascular events, 0.9%; three cerebral vascular events 1.3%; no serious bleeding]	[Uchiyama 2008:[42] two coronary vascular events, 0.8%; no cerebral vascular events; no serious bleeding]	
Vascular events between-group comparison			
AEs *n* in analysis	227	232	239
AEs follow-up			
AEs reported	*n* (%)	*n* (%)	*n* (%)
	Patients with at least one event 201 (86)	Patients with at least one event 200 (86)	Patients with at least one event 188 (79)
	Headache 63 (28)	Headache 26 (11)	Headache 28 (12)
	Pain 30 (13)	Pain 38 (16)	Pain 33 (14)
	Diarrhoea 43 (19)	Diarrhoea 18 (8)	Diarrhoea 13 (5)
	Pharyngitis 22 (10)	Pharyngitis 32 (14)	Pharyngitis 17 (7)
	Peripheral vascular disorder 13 (6)	Peripheral vascular disorder 22 (10)	Peripheral vascular disorder 26 (11)
	Abnormal stools 33 (15)	Abnormal stools 12 (5)	Abnormal stools 7 (3)
	Palpitation 39 (17)	Palpitation 5 (2)	Palpitation 3 (1)
	SAEs 27 (12)	SAEs 31 (13)	SAEs 31 (13)
AEs between-group comparison	Withdrawal due to AEs similar in cilostazol (16%) and pentoxifylline (19%), significantly less in placebo (9%). Headache, diarrhoea and abnormal stools were significantly more common in cilostazol than other groups		
Mortality reported	0.8%, $n=2$	1%, $n=3$	0.4%, $n=1$
Mortality between-group comparison	NR		
HRQoL *n* in analysis			
HRQoL baseline			
HRQoL follow-up			
HRQoL change			
HRQoL between-group comparison	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 WIQ		

M, male; NR, not reported.

Otsuka 21-94-301[34]	
Study details	
Publication type	Thompson 2002,[35] systematic review in peer-reviewed journal
Additional sources of data	Uchiyama 2009,[42] Otsuka Pharmaceuticals submission to NICE[34]
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	NR
Sources of funding	Otsuka
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 (100 b.i.d.) mg, pentoxifylline 1200 (400 t.i.d.) mg
Comparator	Placebo
Run-in phase	
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 2 weeks, 4 weeks, then every 4 weeks until 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events
Notes on statistics	[Otsuka submission:[34] to reduce the impact of variability in walking distances, log transformation was employed. Treatment differences were assessed in the efficacy ITT population as the estimated treatment effect of cilostazol 100 mg b.i.d. vs placebo and cilostazol 100 mg b.i.d. vs pentoxifylline 400 mg t.i.d. Secondary analyses were performed for absolute claudication distance and PFWD with last visit and time point analyses using last observation carried forward, completers, and categorical analysis. Continuous efficacy measures: analysis of variance and the Wilcoxon rank-sum test. Categorical efficacy measures: van Elteren test and Cochran–Mantel–Haenszel test. For the primary and secondary efficacy analyses, values of test statistics were considered statistically significant if $p < 0.025$ and $p < 0.05$, respectively]
Population	
Eligibility criteria	Age ≥ 40 years; stable, PAD-induced IC of at least 6 months' duration; no significant change in symptom severity for at least 3 months; diagnosis of PAD required Doppler measurement of an ABPI ≤ 0.90; MWD on two consecutive prerandomisation treadmill tests varied by < 20%. Excluded if rest pain; Buerger's disease; ischaemic tissue necrosis; surgical or endovascular procedures within 3 months; unstable coronary artery disease or a coronary intervention within 6 months; deep vein thrombosis within 3 months; symptomatic cardiac arrhythmias; conditions other than claudication that limited exercise capacity; or other medical conditions likely to preclude completing the study; women of childbearing age not using a reliable birth control method
Concomitant interventions allowed or excluded	Allowed: 81 mg/day aspirin, 1200 mg/day ibuprofen Disallowed: anticoagulants, no specific counselling regarding smoking cessation, diet or exercise was provided
Power calculation	[Otsuka submission:[34] sample size was based on the results of previous studies of cilostazol and placebo. Estimating mean walking distances (percentage increase from baseline) as 35% for cilostazol, 25% for pentoxifylline and 15% for placebo, with a SD of about 37, it was originally estimated that 100 patients per group would provide approximately 90% power to detect the above-mentioned differences, based on a 5% two-sided significance level. Based on 100 completed patients, the actual power to detect differences is 91% for the cilostazol vs placebo comparison and is 34% for the cilostazol vs pentoxifylline comparison]
N randomised to treatments included in review	370

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 100 mg b.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
N randomised to treatment	123	123	124
Baseline characteristics			
Age	[Otsuka submission[34] has mean 66 (SD 8.3) years]	[Otsuka submission[34] has mean 66.4 (SD 8.2) years]	[Otsuka submission[34] has mean 65.9 (SD 8.8) years]
Gender	[Otsuka submission[34] has M 69.9%; F 30.1%]	[Otsuka submission[34] has M 72.4%; F 27.6%]	[Otsuka submission[34] has M 73.4%; F 26.6%]
Smokers	[Otsuka submission[34] has 29%]	[Otsuka submission[34] has 32.5%]	[Otsuka submission[34] has 35.5%]
Diabetics	[Otsuka submission[34] has12.2%]	[Otsuka submission[34] has10.6%]	[Otsuka submission[34] has 12.1%]
Hypertension/blood pressure			
Hyperlipidaemia			
Obesity or weight	[Otsuka submission[34] has weight (*n* = 121) 73.9 (SD 13.6) kg]	[Otsuka submission[34] has weight 73.1 kg (SD 11.7) kg]	[Otsuka submission[34] has weight 72.4 (SD 11.5) kg]
Angina			
History of vascular therapy			
Other			
Withdrawals			
Withdrawals/loss to follow-up	[Otsuka submission[34] has 34 withdrew. Non-compliance, one; marked deterioration, one; AE, 30; death, one; other, one]	[Otsuka submission[34] has 37 withdrew. Non-compliance, two; marked deterioration, zero; AE, 33; death, zero; other, two]	[Otsuka submission[34] has 19 withdrew. Non-compliance, two; marked deterioration, zero; AE, 14; death, one; other, two]
Results			
MWD *n* in analysis	[Otsuka submission[34] has *n* = 123]	[Otsuka submission[34] has *n* = 118]	[Otsuka submission[34] has *n* = 122]
MWD baseline	[Otsuka submission[34] has mean 128.1]	[Otsuka submission[34] has mean 135.4]	[Otsuka submission[34] has mean 128.1]
MWD follow-up			
MWD change	Approximately 68% (estimated from Figure 1 Thompson 2002[35]) [Otsuka submission:[34] arithmetic mean change 86.3 (54.9%)]	Approximately 65% (estimated from Figure 1 Thompson 2002[35]) [Otsuka submission:[34] arithmetic mean change 86.7 (64.0%)]	Approximately 42% (estimated from Figure 1 Thompson 2002[35]) [Otsuka submission:[34] arithmetic mean change 52.7 (46.1%)]
MWD between-group comparison	Non-significant. [Otsuka submission[34] has arithmetic mean change, cilostazol vs pentoxifylline $p = 0.4827$, cilostazol vs placebo $p = 0.4382$, pentoxifylline vs placebo $p = 0.1421$; ratio of geometric mean, cilostazol vs pentoxifylline 0.99 (CI 0.88 to 1.11) $p = 0.8700$, cilostazol vs placebo 1.06 (CI 0.94 to 1.18) $p = 0.3616$, pentoxifylline vs placebo 1.07 (CI 0.95 to 1.20) $p = 0.2876$]		
PFWD *n* in analysis	[Otsuka submission[34] has *n* = 123]	[Otsuka submission[34] has *n* = 118]	[Otsuka submission[34] has *n* = 122]
PFWD baseline	[Otsuka submission[34] has mean 77.7]	[Otsuka submission[34] has mean 81.4]	[Otsuka submission[34] has mean 74.3]
PFWD follow-up			
PFWD change	Approximately 68% (estimated from Figure 2, Thompson 2002[35]) [Otsuka submission[34] has arithmetic mean change 52.3 (59.5%)]	Approximately 59% (estimated from Figure 2, Thompson 2002[35]) [Otsuka submission[34] has arithmetic mean change 46.6 (72.9%)]	Approximately 50% (estimated from Figure 2, Thompson 2002[35]) [Otsuka submission[34] has arithmetic mean change 36.5 (59.1%)]
PFWD between-group comparison	Non-significant. [Otsuka submission[34] has arithmetic mean change, cilostazol vs pentoxifylline $p = 0.3017$, cilostazol vs placebo $p = 0.8528$, pentoxifylline vs placebo $p = 0.2245$; ratio of geometric mean, cilostazol vs pentoxifylline 0.98 (CI 0.87 to 1.11), $p = 0.7217$, cilostazol vs placebo 1.01 (CI 0.90 to 1.14), $p = 0.0.8258$, pentoxifylline vs placebo 1.04 (CI 0.92 to 1.17), $p = 0.5678$]		

Treatment group	Cilostazol 100 mg b.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
ABPI *n* in analysis			
ABPI baseline			
ABPI follow-up			
ABPI change			
ABPI between-group comparison			
Vascular events *n* in analysis	123		124
Vascular events follow-up			
Vascular events included			
Vascular events reported	[Uchiyama 2008:[42] two coronary vascular events, 1.6%; two cerebral vascular events 1.6%; one serious bleeding, 0.8%]		[Uchiyama 2008:[42] three coronary vascular events, 2.4%; no cerebral vascular events; no serious bleeding]
Vascular events between-group comparison			
AEs *n* in analysis	[Otsuka submission[34] has *n*=123]	[Otsuka submission[34] has *n*=123]	[Otsuka submission[34] has *n*=124]
AEs follow-up			
AEs reported	[Otsuka submission[34] has one or more AEs, 116. *AEs that occurred in >10% patients:* headache 47 (38.2%), abnormal stools 17 (13.8%), diarrhoea 33 (26.8%), dyspepsia 12 (9.8%), nausea 14 (11.4%) pain 10 (8.1%), pharyngitis 12 (9.8%)]	[Otsuka submission[34] has one or more AEs, 104. *AEs that occurred in >10% patients*: headache 14 (11.4%), abnormal stools 7 (5.7%), diarrhoea 11 (8.9%), dyspepsia 14 (11.4%), nausea 20 (16.3%), pain 10 (8.1%), pharyngitis 14 (11.4%)]	[Otsuka submission[34] has one or more AEs, 103. *AEs that occurred in >10% patients*: headache 19 (15.3%), abnormal stools 3 (2.4%), diarrhoea 8 (6.5%), dyspepsia 11 (8.9%), nausea 14 (11.3%), pain 18 (14.5%), pharyngitis 6 (4.8%)]
AEs between-group comparison	There was a greater number of withdrawals due to AEs in the two active treatment groups than in the placebo group ($p=0.0061$)		
Mortality reported	1	0	1
Mortality between-group comparison			
HRQoL *n* in analysis			
HRQoL baseline			
HRQoL follow-up			
HRQoL change			
HRQoL between-group comparison			

F, female; M, male.

Otsuka 21-98-213[34]	
Study details	
Publication type	Pande 2010,[31] systematic review in peer-reviewed journal
Additional sources of data	Otsuka industry submission[34]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	1. Cilostazol 200-mg daily dose (100 mg b.i.d.)
	2. [Otsuka submission[34] has pentoxifylline 1200-mg daily dose (400 mg t.i.d.)]
Comparator	Placebo
Run-in phase	NR
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, every 4 weeks until 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2.0 mph (3.2 km/hour) at a constant 12.5% grade
	PFWD: as MWD
	Vascular events:
	AEs: patient self-report
	Mortality:
	HRQoL: SF-36, WIQ, COM
Notes on statistics	[Otsuka submission:[34] for the primary efficacy analyses, values of test statistics were considered statistically significant if $p \leq 0.05$. Continuous efficacy measures were analysed by analysis of variance and the Wilcoxon rank-sum test. Categorical efficacy measures were analysed by the van Elteren test and the Cochran–Mantel–Haenszel test. Centre 138 data were excluded from all efficacy analyses due to their unreliability based on the results of a site audit]
Population	
Eligibility criteria	40 years or older, with PAD and IC with stable symptoms for the preceding 3 months. PAD diagnosed as an abnormal resting ABPI [Otsuka submission:[34] ABPI ≥ 0.4 and ≤ 0.9 in the reference leg], with addition decline in postexercise ABPI ≥ 10 mmHg as confirmation. Symptomatic patients with normal resting ABPI but with pressure drop of > 20 mmHg were also eligible. MWD varied by no more than 20% on two or three consecutive treadmill tests
	Exclusion: limb-threatening ischaemia, limb revascularisation within 3 months, unstable coronary artery disease, coronary revascularisation within 6 months, thromboangiitis obliterans, deep vein thrombosis within 3 months, symptomatic arrhythmia and conditions other than PAD that might limit exercise ability or preclude completion of the study. CHF
Concomitant interventions allowed or excluded	Allowed: aspirin at up to 81 mg/day
	Disallowed: aspirin > 81 mg/day, high-dose ibuprofen (> 1200 mg/day)
Power calculation	[Otsuka submission:[34] based on the results of study 21–96–202, the between-group difference in the change from baseline in the log (absolute claudication distance) was expected to be 0.14, with a SD of 0.45. In order to detect this difference with 90% power at a 5% significance level (two sided), at least 218 patients were required per treatment arm. Therefore, a recruitment target was set at 260 patients per treatment arm or a total of 780 patients
N randomised to treatments included in review	[Otsuka submission:[34] 785]

mph, miles per hour; NR, not reported.

Treatment group	Cilostazol 200 mg t.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
N randomised to treatment	[Otsuka submission:[34] 261]	[Otsuka submission:[34] 262]	[Otsuka submission:[34] 262]
Baseline characteristics			
Age (years)	[Otsuka submission:[34] 66.7 ± 9.9	[Otsuka submission:[34] 67.4 ± 9.4	[Otsuka submission:[34] 67.1 ± 10.0]
Gender	[Otsuka submission:[34] M 75.4%; F 24.6%]	[Otsuka submission:[34] M 76.9%; F 23.1%]	[Otsuka submission:[34] M 75.4%; F 24.6%]
Smokers	[Otsuka submission:[34] 31.5%]	[Otsuka submission:[34] 33.8%]	[Otsuka submission:[34] 31.9%]
Diabetics			
Hypertension/blood pressure			
Hyperlipidaemia			
Obesity or weight	[Otsuka submission:[34] (*n* = 258) mean 83.2 (SD 15.2) kg]	[Otsuka submission:[34] (*n* = 260) mean 79.6 (SD 15.3) kg]	[Otsuka submission:[34] (*n* = 260) mean 82.9 (SD 15.8) kg]
Angina			
History of vascular therapy			
Other			
Withdrawals			
Withdrawals/loss to follow-up	[Otsuka submission:[34] 35.4% overall. Non-compliance, 2.7%; AEs, 24.6%; other, 8.1%]	[Otsuka submission:[34] 31.5% overall. Non-compliance, 3.5%; AEs, 18.8%; other, 9.2%]	[Otsuka submission:[34] 26.9% overall. Non-compliance, 4.2%; AEs, 12.7%; other, 10%]
Results			
MWD *n* in analysis	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]
MWD baseline	[Otsuka submission:[34] arithmetic mean 138.2]	[Otsuka submission:[34] arithmetic mean 148.0]	[Otsuka submission:[34] arithmetic mean 141.4]
MWD follow-up			
MWD change	[Otsuka submission:[34] arithmetic mean 60.4 (43.6%)]	[Otsuka submission:[34] arithmetic mean 75.6 (51.2%)]	[Otsuka submission:[34] arithmetic mean 59.0 (41.4%)]
MWD between-group comparison	Cilostazol vs placebo mean difference 1.3 (SE 11.7) m, $p = 0.910$. Estimated treatment effect 1.03 (95% CI 0.95 to 1.12)		
	[Otsuka submission:[34] *arithmetic means*: cilostazol vs placebo $p = 0.7502$; pentoxifylline vs placebo $p = 0.2774$, cilostazol vs pentoxifylline $p = 0.4490$; *estimated treatment effects*: cilostazol vs placebo 1.03 (95% CI 0.95 to 1.12), $p = 0.4749$; pentoxifylline vs placebo 1.05 (95% CI 0.97 to 1.14), $p = 0.2385$, cilostazol vs pentoxifylline 0.98 (95% CI 0.90 to 1.07), $p = 0.6491$]		
PFWD *n* in analysis	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]
PFWD baseline	[Otsuka submission:[34] arithmetic mean 74.9]	[Otsuka submission:[34] arithmetic mean 77.1]	[Otsuka submission:[34] arithmetic mean 75.5]
PFWD follow-up			
PFWD change	[Otsuka submission:[34] arithmetic mean 47.3 (62.6%)]	[Otsuka submission:[34] arithmetic mean 62.6 (86.0%)]	[Otsuka submission:[34] arithmetic mean 45.3 (65.0%)]
PFWD between-group comparison	Cilostazol vs placebo 1.02 (95% CI 0.92 to 1.13)		
	[Otsuka submission:[34] *arithmetic means*: cilostazol vs placebo $p = 0.8322$; pentoxifylline vs placebo $p = 0.1363$, cilostazol vs pentoxifylline $p = 0.0923$; *estimated treatment effects*: cilostazol vs placebo 1.02 (95% CI 0.92 to 1.13), $p = 0.7692$; pentoxifylline vs placebo 1.08 (95% CI 0.97 to 1.19), $p = 0.1517$; cilostazol vs pentoxifylline 0.94 (95% CI 0.85 to 1.05), $p = 0.2602$]		
ABPI *n* in analysis			
ABPI baseline			
ABPI follow-up			
ABPI change			
ABPI between-group comparison			

Treatment group	Cilostazol 200 mg t.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
Vascular events *n* in analysis			
Vascular events follow-up			
Vascular events included			
Vascular events reported			
Vascular events between-group comparison			
AEs *n* in analysis	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]	[Otsuka submission:[34] 260]
AEs follow-up	24 weeks		
AEs reported	[Otsuka submission:[34] 79.6% patients had one or less AE	[Otsuka submission:[34] 80% patients had one or less AE	[Otsuka submission:[34] 75.8% patients had one or less AE
	AEs occurring in > 10% of patients	*AEs occurring in > 10% of patients*	*AEs occurring in > 10% of patients*
	Pharyngitis 9.6%	Pharyngitis 15%	Pharyngitis 11.2%
	Headache 16.5%	Headache 10.8%	Headache 6.2%
	Diarrhoea 13.1%	Diarrhoea 11.2%	Diarrhoea 6.2%
	Pain 8.1%	Pain 8.8%	Pain 11.5%
	Palpitation 10%]	Palpitation 1.5%]	Palpitation 2.7%]
AEs between-group comparison			
Mortality reported	0	3	2
Mortality between-group comparison			
HRQoL *n* in analysis			
HRQoL baseline			
HRQoL follow-up			
HRQoL change			
HRQoL between-group comparison	[Otsuka submission:[34] the physical component score of the SF-36 was statistically significantly better with cilostazol 100 mg than with placebo (at week 12). Pentoxifylline was not significantly different from placebo with respect to the SF-36 physical component score]		

F, female; M, male; SE, standard error.

Two-arm trials of naftidrofuryl oxalate and placebo

Kieffer 2001[65]	
Study details	
Publication type	Kieffer 2001,[65] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	France
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl oxalate 600 (200 t.i.d.) mg
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks, 16 weeks, 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 3.2 km/hour, 10% incline PFWD: as MWD ABPI: mode of measurement NR Vascular events AEs: recorded whether or not considered treatment related
Notes on statistics	Log transform for walking distances
Population	
Eligibility criteria	Outpatients of both genders, aged 35–85 years, with moderately severe chronic, stable IC of at least 6 months and which had been clinically stable during the last 3 months and the diagnosis of which was confirmed by arteriography or duplex scan. All patients had already undergone a course of exercise therapy. PFWD and MWD between 100 and 300 m (treadmill 3.2 km/hour, 10% slope), did not vary by more than 25% during placebo run-in phase. Exclude Fontaine stage I, III or IV; non-vascular leg pain; revascularisation within last 6 months or likely to be needed within 6 months; severe or unstable hypertension; exercise-limiting condition or medication; pregnancy or childbearing potential; poor (< 70%) compliance with medication during placebo run-in
Concomitant interventions allowed or excluded	Allowed: NR Disallowed: NR
Power calculation	Minimum 100 patients per group required to detect difference of 20% (alpha error 0.5, beta error 0.1) in treadmill walking distance
N randomised to treatments included in review	196

NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	98	98
Baseline characteristics		
Age	Mean 67.5 (SD 10.1) years	Mean 66.3 (SD 10.9) years
Gender	M 78.7%; F 21.3%[a]	M 81.5%; F 18.5%
Smokers	83.1%	89.1%
Diabetics	19.1%	20.6%
Hypertension/blood pressure	51.7%	42.4%
Hyperlipidaemia	35.2%	37.0%
Obesity or weight	BMI mean 25.9 (SD 4.3)	BMI mean 24.5 (SD 3.4)
Angina		
History of vascular therapy	Prior vascular surgery 25.8%	Prior vascular surgery 22.8%
Other	Hypercholesterolaemia 36.4%	Hypercholesterolaemia 37.0%
Withdrawals		
Withdrawals/loss to follow-up	Nine randomised to naftidrofuryl oxalate did not supply any more data (five patient refusals, two reported AE, two lost to follow-up). A further 13 withdrew during 6-month study (six patient refusals, four lost to follow-up, three not specified)	Six randomised to placebo did not supply any more data (four patient refusals, one reported AE, one did not meet eligibility criteria). A further 16 withdrew during 6-month study (five patient refusals, six lost to follow-up, five not specified)
Results		
MWD *n* in analysis	89	92
MWD baseline	Geometric mean 191.9 m, arithmetic mean 202 (SD 62) m	Geometric mean 203.0 m, arithmetic mean 213 (SD 63) m
MWD follow-up	At 24 weeks, geometric mean 350.6. Arithmetic means: 16 weeks 322, 24 weeks 385, 32 weeks (2 months without treatment) 296	At 24 weeks, geometric mean 231.1. Arithmetic means: 16 weeks 266, 24 weeks 259, 32 weeks (2 months without treatment) 265
MWD change	At 24 weeks by geometric mean 82.7%. Subgroup geometric means: diabetics 87.2% change, non-diabetics 81.6% change	At 24 weeks by geometric mean 13.9%. Subgroup geometric means: diabetics 9.5% change, non-diabetics 15.0% change
MWD between-group comparison	At 24 weeks by geometric mean $p<0.001$. Arithmetic means 16 weeks $p<0.01$, 24 weeks $p<0.001$ (at 8 weeks non-significant)	
PFWD *n* in analysis	89	92
PFWD baseline	Geometric mean 172.3, arithmetic mean 182 (SD 64) m	Geometric mean 177.9, arithmetic mean 189 (SD 63) m
PFWD follow-up	At 24 weeks, geometric mean 330.5. arithmetic means 16 weeks 298, 24 weeks 367, 32 weeks (2 months without treatment) 281	At 24 weeks, geometric mean 207.8. arithmetic means 16 weeks 244, 24 weeks 237, 32 weeks (2 months without treatment) 240
PFWD change	At 24 weeks by geometric mean 91.8%. Subgroup geometric means diabetics 103.0% change, non-diabetics 89.2% change [RM1987 has mean 156.35 (SD 104.88)]	At 24 weeks by geometric mean 16.8%. Subgroup geometric means diabetics 17.3% change, non-diabetics 16.7% change [RM1987 has mean 39.67 (SD 83.84)]
PFWD between-group comparison	At 24 weeks by geometric mean $p<0.001$. arithmetic means 16 weeks $p<0.01$, 24 weeks $p<0.001$, 32 weeks (2 months without treatment) $p<0.05$ (at 8 weeks non-significant)	
ABPI *n* in analysis	89	92
ABPI baseline	Mean 0.55 (SD 0.35)	Mean 0.55 (SD 0.37)
ABPI follow-up	Mean 0.58 (SD 0.33)	Mean 0.59 (SD 0.33)
ABPI change	Difference 0.03	Difference 0.04
ABPI between-group comparison	Non-significant	

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported	(Two vascular surgery, also listed in AEs)	(Three vascular surgery, also listed in AEs)
Vascular events between-group comparison		
AEs *n* in analysis	98	98
AEs follow-up		
AEs reported	Number of patients with at least one AE 18. Number of AEs 21 (of which 12 serious: two vascular surgery and two hospitalisation for other diseases and two surgery for other condition). Non-serious possibly treatment-related one mild digestive disorder	Number of patients with at least one AE 21. Number of AEs 25 (of which 13 serious: three vascular surgery and six hospitalisation for other diseases and one surgery for other condition). Non-serious possibly treatment-related – three
AEs between-group comparison	Non-significant	
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

a Figures calculated by reviewer.

Adhoute 1986[66]	
Study details	
Publication type	Adhoute 1986,[66] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	France
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl oxalate 600 (200 t.i.d.) mg
Comparator	Placebo
Run-in phase	
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline after 4-week run-in, 3 months, 6 months
Outcomes and measures	PFWD: treadmill with constant workload 3 km/hour, 10% slope
	ABPI: ultra sonographic measure
	AEs: patient self-report
Notes on statistics	No adjustment due to homogeneity of groups
Population	
Eligibility criteria	Patients of both genders between 40 and 70 years with Fontaine stage II PAD, IC for at least 6 months, diagnosis confirmed by angiography or Doppler velocimetry examination, PFWD (at 3 km/hour, 10% slope) 150–300 m and after a wash-out period of 1 month up to 20% variation in PFWD. Exclude vascular surgery or specific physical training within 6 months, recent MI, angina pectoris, myocardial/renal/hepatic insufficiency, labile diabetes, non-treated arterial hypertension
Concomitant interventions allowed or excluded	Allowed: patients given rules about smoking and physical training
	Disallowed: all other treatments for arterial disease
Power calculation	NR
N randomised to treatments included in review	154

BMI, body mass index; NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	NR. 64 remained at end of study	NR. 54 remained at end of study
Baseline characteristics		
Age	Mean 58.53 (± 8.35) years	Mean 59.62 (± 8.35) years
Genders	M 86%; F 14%	M 93%; F 7%
Smokers	63%	63%
Diabetics		
Hypertension/blood pressure		
Hyperlipidaemia	31%	33%
Obesity or weight		
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	(Whole study 118 remained of 154 randomised) Naftidrofuryl oxalate group reasons for withdrawal included surgery ($n=2$), pathology, patient refusal or treatment intolerance ($n=3$, gastralgia) Placebo group reasons for withdrawal included surgery ($n=3$), pathology, patient refusal or treatment intolerance ($n=2$, nausea or cutaneous rash)	
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		
PFWD *n* in analysis	64	54
PFWD baseline	214.95 m mean (SD 58.33 m)	214.98 m mean (SD 57.92 m)
PFWD follow-up	335.21 m mean (SD 193.11 m) at 12 weeks; at 24 weeks 416.36 (SD 273.58) m	274.24 m mean (SD 124.55 m) at 12 weeks; at 24 weeks 313.01 (SD 169.56) m
PFWD change	At 24 weeks 201.37 (SD 254.80) significantly improved $p<0.02$; [RM1987 has mean 199.63 (SD 247.91)]	At 24 weeks 98.33 (SD 145.65) significantly improved $p<0.02$; [RM1987 has mean 106.54 (SD 182.66)]
PFWD between-group comparison	At 12 weeks naftidrofuryl oxalate significantly more improved than placebo $p<0.05$; at 24 weeks naftidrofuryl oxalate significantly more improved than placebo $p<0.02$	
ABPI *n* in analysis		
ABPI baseline	0.65 (SD 0.24)	0.61 (SD 0.20)
ABPI follow-up	0.67 (SD 0.23)	0.62 (SD 0.17)
ABPI change	Non-significant	Non-significant
ABPI between-group comparison	Non-significant	
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
AEs *n* in analysis	64	54
AEs follow-up		
AEs reported	Gastric, 5	Gastric, 6
AEs between-group comparison		
Mortality reported	One death due to MI. Does not specify if during run-in period, or, if randomised, to which group	
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

NR, not reported.

Trubestein 1984[67]	
Study details	
Publication type	Trubestein 1984,[67] full report in peer-reviewed journal
Additional sources of data	de Backer-Tine 2008 (RM1987)[32]
Trial design	RCT, multicentre
Country	Germany
Dates of participant recruitment	1981–3
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl oxalate 600 (200 t.i.d.) mg
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 8 and 12 weeks
Outcomes and measures	MWD: treadmill with constant workload 5 km/hour, 10% slope. Performed twice with at least 20 minutes interval PFWD: as MWD ABPI: Doppler ultrasound (venous occlusion plethysmography) AEs: method of data collection not reported
Notes on statistics	Log transform for MWD and PFWD
Population	
Eligibility criteria	IC patients between 40 and 65 years, PAD of femoral artery, with IC for at least 6 months and maximum 5 years, no physical training for at least 6 months, diagnosis confirmed with angiography, baseline PFWD (at 5 km/hour, 10% slope) of 100–300 m, after 4-week run-in no more than 30% change. Exclude beta-blockers, defibrinogenating enzymes, antiplatelets, anticoagulants; non-vascular exercise limiting diseases, coronary heart disease within 6 months, myocardial/respiratory/renal insufficiency, severe hypertension systolic 180 mmHg, diastolic 110 mmHg, vascular surgery within 6 months
Concomitant interventions allowed or excluded	Allowed: therapy allowed Disallowed: beta-blockers, defibrinogenating enzymes, antiplatelets, anticoagulants
Power calculation	
N randomised to treatments included in review	104

NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	54	50
Baseline characteristics		
Age		
Gender		
Smokers	63%	44%
Diabetics		
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up		
Results		
MWD *n* in analysis	54	50
MWD baseline	220 m	224 m
MWD follow-up	342 m	314 m
MWD change		
MWD between-group comparison	Non-significant between groups. For subgroup stenosis femoral artery, naftidrofuryl oxalate group significantly more improvement than placebo $p < 0.02$; non-significant between groups for occlusion femoral or tibial arteries	
PFWD *n* in analysis	54	50
PFWD baseline	137 m	135 m
PFWD follow-up	230 m	171 m
PFWD change	Difference 93 m [de Backer-Tine[32] mean 82.2 (SD 144.39)]	Difference 36 m [de Backer-Tine[32] mean 32.48 (SD 68.49)]
PFWD between-group comparison	$p < 0.02$. For subgroups stenosis femoral artery and occlusion tibial arteries, naftidrofuryl oxalate group significantly more improvement than placebo $p < 0.01$; non-significant between-groups for occlusion femoral artery; tibial arteries	
ABPI *n* in analysis	54	50
ABPI baseline	98 (SD 3.7) mmHg [unclear if mean and SD]	93 (SD 3.2) mmHg
ABPI follow-up	101 (SD 3.98) mmHg (non-significant)	92 (SD 3.9) mmHg (non-significant)
ABPI change		
ABPI between-group comparison	Non-significant change for either group	
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
AEs *n* in analysis	54	50
AEs follow-up		
AEs reported	*n* = 2 gastric disorders or erythema	*n* = 2 gastric disorders or erythema
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

NR, not reported.

Spengel 2002[47]	
Study details	
Publication type	Spengel 2002,[47] full report in peer-reviewed journal
Additional sources of data	
Trial design	Meta-analysis of three multicentre RCTs (Liard 1997, Spengel 1999 and D'Hooge 2001)
Country	Germany, France, Belgium
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl oxalate 600 (200 t.i.d.) mg
Comparator	Placebo
Run-in phase	1 month
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 12 and 24 weeks
Outcomes and measures	PFWD: Claudication distance as estimated by patient at baseline and at the end of the study
	AEs: AEs were reported by the patients, in response to indirect questions from the investigator, who assessed their relationship to treatment. Reported as death, serious, minor
	HRQoL: CLAU-S (five dimensions – daily living, pain, social life, disease-specific anxiety, mood)
Notes on statistics	Individual patient data meta analysis, study block factor added. Many other technical details reported
	CLAU-S multivariate analysis of covariance using the five dimensions at baseline as the multivariate covariate. If this showed effect, univariate analysis of covariance conducted. Multivariate analysis of covariance adjusted for baseline values, study effect and first order study treatment interaction
Population	
Eligibility criteria	IC (Fontaine stage II), age 40–80 years, history of IC > 3 months, stable over the previous 3 months, subjective PFWD of 50–500 m, ABPI of ≤ 0.85. In addition, it is not clear if only patients who completed the 1-month run-in (included those who had not undergone any surgical intervention during the previous 3 months nor was any surgical intervention planned and that they did not have any difficulty in understanding, or completing the questionnaire) and patients whose ABPI remained ≤ 0.85 and whose tablet compliance was > 70% were randomised
Concomitant interventions allowed or excluded	NR for trial, though some patients excluded for taking non-permitted concomitant medication. For run-in period, no concomitant treatment with vasoactive or rheologically active substances was permitted, basic rules pertaining to hygiene, diet, tobacco consumption and physical exercise were explained to the patients
Power calculation	NR
N randomised to treatments included in review	754

NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	382	372
Baseline characteristics		
Age (years)	Mean 66.2 ± 9.5	Mean 65.7 ± 9.1
Gender	M, 70.4%; F, 29.6%	M, 73.8%; F, 26.2%
Smokers	Ex and current 72.3%	Ex and current 70.9%
Diabetics	17.9% (of 510 cases for whom information available)	15.3% (of 510 cases for whom information available)
Hypertension/blood pressure		
Hyperlipidaemia	36%	32.8%
Obesity or weight	23.7%, BMI (mean ± SD) 26.1 ± 3.8	19.1%, BMI (mean ± SD) 25.9 ± 3.9
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	24 – baseline data only – excluded from analysis	21 – baseline data only – excluded from analysis (two further not analysed, for PFWD, but HRQoL data available)
	16 – lost to follow-up	14 – lost to follow-up
	Nine – did not comply with treatment protocol/had concomitant medication	12 – did not comply with treatment protocol/had concomitant medication
	Four – referral to hospital	Six – referral to hospital
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		
PFWD *n* in analysis	358	349
PFWD baseline	Mean 389 (SD 389) m	Mean 424 (SD 432) m
PFWD follow-up	Mean 593 (SD 500) m	Mean 476 (SD 476) m
PFWD change	Mean 204 (SD 443) m	Mean 51 (SD 455) m
PFWD between-group comparison	Final absolute value $p = 0.002$	
	Difference $p < 0.001$	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported	One death from MI	Unclear
Vascular events between-group comparison		

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
AEs *n* in analysis	Unclear (states 'whole study population' for deaths, but not clear if withdrawals were followed up for AEs, and presumably those lost to follow-up would not have been included)	Unclear (states 'whole study population' for deaths, but not clear if withdrawals were followed up for AEs, and presumably those lost to follow-up would not have been included)
AEs follow-up	Assume 6 months	
AEs reported	One death	Five deaths
	33 serious (one considered to be in relation to the treatment)	34 serious [two considered to be in relation to the treatment (assume assessor was blinded)]
	11 minor (11 gastrointestinal, five skin reactions)	12 minor (eight gastrointestinal, four skin events)
AEs between-group comparison		
Mortality reported	One also reported in AEs	Five also reported in AEs
Mortality between-group comparison		
HRQoL *n* in analysis	358	351
HRQoL baseline	Daily living, 65.8 (SD 23.7); pain, 65.6 (SD 18.9); social life, 86.9 (SD 19.8); disease-specific anxiety, 81.1 (SD 20.3); mood, 79.3 (SD 20.1)	Daily living, 66.9 (SD 23); pain, 65 (SD 19.2); social life, 86.1 (SD 20.2); disease-specific anxiety, 80.9 (SD 20.2); mood, 80.7 (SD 18.5)
HRQoL follow-up	Daily living, 73.3 (SD 25); pain, 72 (SD 19.2); social life, 90.0 (SD 16.9); disease-specific anxiety, 83 (SD 20.3); mood, 82.8 (SD 18.5)	Daily living, 65.5 (SD 26.2); Pain, 64.6 (SD 23.1); social life, 84.1 (SD 24.6); disease-specific anxiety, 82 (SD 19.3); mood, 79.5 (SD 22.4)
HRQoL change	(Read from graph/calculated from tables): daily living, 7.5/7.5; pain, 8.4/6.4; social life, 3.1/3.1; disease-specific anxiety, 0.2/1.9; mood, 3.5/3.5	(Read from graph/calculated from tables): daily living,–1.3/–1.4; pain, –0.4/–0.4; social life, –2.4/–2; disease-specific anxiety, 0.2/1.1; mood, –1.3/–1.2
HRQoL between-group comparison	ANCOVA: daily living, $p<0.001$; pain, $p<0.001$; social life, $p=0.001$; disease-specific anxiety, non-significant; mood, $p=0.03$	

ANCOVA, analysis of covariance; BMI, body mass index; F, female; M, male.

Ruckley 1978[68]	
Study details	
Publication type	Ruckley 1978,[68] short report in peer-reviewed journal
Additional sources of data	
Trial design	Unclear if RCT or clinical trial
Country	UK
Dates of participant recruitment	NR
Sources of funding	Lipha Pharmaceuticals UK
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl oxalate 300 (100 t.i.d.) mg
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 2 weeks, 4 weeks, then every 4 weeks until 24 weeks
Outcomes and measures	PFWD: not explicit that treadmill was used, but likely that it was. Categorised as < 100 yards = severe, 100–200 yards = moderate, > 200 yards = mild
	AEs: patient self-report
Notes on statistics	Wilcoxon rank-sum test
Population	
Eligibility criteria	Consecutive patients attending a peripheral vascular clinic with stable claudication
Concomitant interventions allowed or excluded	Allowed: all patients asked to take regular exercise
Power calculation	NR
N randomised to treatments included in review	50

NR, not reported.

Treatment group	Naftidrofuryl oxalate 100 mg t.i.d.	Placebo
N randomised to treatment		
Baseline characteristics		
Age		
Gender		
Smokers		
Diabetics		
Hypertension/blood pressure		
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other	Severity: 15 mild, three moderate, seven severe	Severity: nine mild, six moderate, 10 severe
Withdrawals		
Withdrawals/loss to follow-up	One patient failed to attend final test, NR which group	
Results		
MWD *n* in analysis		
MWD baseline	Severity: 15 mild, three moderate, seven severe	Severity: nine mild, six moderate, 10 severe
MWD follow-up		
MWD change		
MWD between-group comparison	Not significant at $p = 0.05$	
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Naftidrofuryl oxalate 100 mg t.i.d.	Placebo
AEs *n* in analysis	25	25
AEs follow-up	12 weeks	
AEs reported	Vertigo 8%	Epigastric pain 4%
	Nausea 8%	Indigestion 4%
	Slight insomnia 8%	Constipation 4%
		Headache and nausea 4%
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

NR, not reported.

Trials of pentoxifylline and placebo

Lindgarde 1989[71]	
Study details	
Publication type	Lindgarde 1989,[71] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre (two Sweden, one Denmark)
Country	Sweden, Denmark
Dates of participant recruitment	NR
Sources of funding	Drugs supplied by Hoechst AG Werk Albert
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)
Comparator	Placebo
Run-in phase	4–6 weeks
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline (after run-in) then every 4 weeks until 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 2 mph (3.2 km/hour), 12.5% inclination PFWD: as MWD AEs: recorded at each follow-up
Notes on statistics	Efficacy results reported after adjustment for study site. Comparison of treatment effects was performed with the extended Mantel–Haenszel test with stratification adjustment for site and standardised rank scores. Geometric means of per cent change from baseline and CI calculated. ANOVA to test treatment groups and background variables, Wilcoxon signed-rank test for changes in normal/abnormal lab tests, chi-squared test for side effects. All tests two sided, $p < 0.05$ significance
Population	
Eligibility criteria	At least 40 years of age, suffering from moderately severe chronic obstructive pulmonary airways disease with a PFWD of between 50 and 200 m, as tested on a treadmill set at a speed of 2 mph (3.2 km/hour) and an inclination of 12.5% (7.1°). History of IC of at least 6 months in duration. The diagnosis of chronic obstructive pulmonary disease was established by clinical examination and by Doppler pressure assessment at rest and after exercise. Diagnosis confirmed by angiography. PFWD stable for the last two visits of run-in phase (difference of < 35% in patients with baseline PFWD up to 100 m, < 25% in patients with baseline PFWD 101–200 m. Excluded if: complete occlusion of the aortoiliac segment, femoral bifurcation, or popliteal artery without angiographically proven distal refilling of the segment; vascular reconstruction or sympathectomy within the last 12 months; peripheral neuropathy; Buerger's disease; marked postphlebotic syndrome; diabetes; cardiac failure or sever rhythm disorders; major infections; abnormal values for platelets; prothrombin index or partial thromboplastin time; history of xanthine hypersensitivity; addiction to analgesics; malignant disease, or any other condition that limits walking ability or full understanding of study procedure
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	

ANOVA, analysis of variance; mph, miles per hour; NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	76	74
Baseline characteristics		
Age	Mean 65 (SD 7) years	Mean 64 (SD 8) years
Gender	M 79%; F 21%	M 80%; F20%
Smokers	63%	59%
Diabetics	0%	0%
Hypertension/blood pressure	37%	35%
Hyperlipidaemia	26%	30%
Obesity or weight	1.03 (SD 0.1) (as reported, note that value is not within standard BMI range)	1.05 (SD 0.2) (as reported, note that value is not within standard BMI range)
Angina	26%	24%
History of vascular therapy		
Other	MI, 24%; isolated iliac or iliofemoropopliteal lesions, 17%; isolated femoropopliteal or femoropopliteal/ lower leg lesions, 72%	MI, 18%; isolated iliac or iliofemoropopliteal lesions, 12%; isolated femoropopliteal or femoropopliteal/ lower leg lesions, 68%
Withdrawals		
Withdrawals/loss to follow-up	NR	NR
Results		
MWD *n* in analysis	76	74
MWD baseline	Geometric mean 132 (SEM 9) m	Geometric mean 155 (SEM 11) m
MWD follow-up	50% improvement (SEM 9%) (crude calculation, 198 m)	24% improvement (SEM 7%) (crude calculation, 192.2 m)
MWD change	Crude calculation, 66 m	Crude calculation, 37.2 m
MWD between-group comparison	Non-significant, $p = 0.094$	
PFWD *n* in analysis	76	74
PFWD baseline	Geometric mean 77 (SEM 4) m	Geometric mean 79 (SEM 4) m
PFWD follow-up	80% improvement (SEM 12%) (crude calculation, 138.6 m)	60% improvement (SEM 11%) (crude calculation, 126.4 m)
PFWD change	Crude calculation, 61.6 m	Crude calculation, 47.4 m
PFWD between-group comparison		
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
AEs *n* in analysis		
AEs follow-up		
AEs reported	22% (13 reported gastrointestinal complaints, other mild events were not defined)	14% (seven reported gastrointestinal complaints, other mild events were not defined)
AEs between-group comparison	Gastrointestinal complaints non-significant	
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

BMI, body mass index; F, female; M, male; NR, not reported; SEM, standard error of mean.

Porter 1982[72]	
Study details	
Publication type	Porter 1982,[72] full report in peer-reviewed journal
Additional sources of data	Gillings 1987 (RM265),[73] post hoc ITT analysis Porter 1982 (RM294),[74] Reich 1984 (RM287)[75]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	NR
Sources of funding	Drugs supplied by Hoechst–Roussel Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 600-mg daily dose (200 mg t.i.d.) for first week, increased in a stepped manner to 1200-mg daily dose (assume 400 mg t.i.d.) by fourth week
Comparator	Placebo
Run-in phase	4–6 weeks
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 2, 4, 6, 8, 12, 16, 20 and 24 weeks
Outcomes and measures	MWD: [Porter 1982:[74] at each visit two treadmill tests were performed at 30- to 60-minute intervals and the mean of the two tests used. Treadmill set to 1.5 mph, 7°] PFWD: as MWD AEs: brief physical examination and careful monitoring of observed and reported unwanted effects. ECG and routine blood analysis performed once or more during the trial and again at the end. Audiograms and ophthalmic examinations were only repeated at the final visit Vascular events: reported as part of AE analysis
Notes on statistics	PFWD and MWD analysed with repeat measures two way analysis of variance with interaction (investigator, intervention, investigator and intervention). Transformed into per cent change (= geometric mean of response value/baseline value -1×100) to limit undue influence of outlying values. After 24 weeks were analysed by the extended Mantel–Haenszel procedure for ordered contingency tables by classifying patients into one of four categories (< 25% change, 25–49% change, 50–100% change, > 100% change). Mantel–Haenszel results not extracted [RM 265: as above for log of (distance/baseline) ratios. Gives equations in statistical appendix. ITT analysis was of all patients who completed at least one follow-up. Extended Mantel–Haenszel procedure with log-rank scores, provides a two-sided non-parametric test. Fisher procedure also with log-rank scores gives one-sided test]
Population	
Eligibility criteria	*Included*: patients with IC secondary to chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease diagnosed by arteriography or by the absence of diminution of one or more lower limb pulses as determined by palpation. IC must have been experienced for at least 6 months prior to a patient's enrolment. IC characterised by pain, muscular ache, cramps or severe fatigue involving one or both lower limbs when walking. Patients had to be able to walk on the treadmill for at least 50 m at a speed of 1.5 mph and a grade of 7º without experiencing claudication, but not for > 510 m in 9.5 minutes at a speed of 2 mph before claudication. MWD had to be stable in last two visits during placebo run-in, i.e. within 20% of one another. [Reich 1984:[75] patients had to demonstrate compliance with protocol] *Excluded*: patients with severe chronic obstructive pulmonary disease (pain at rest, ulceration, gangrene), sympathectomy within previous 6 months, severe peripheral neuropathy, chronic infection or any hypersensitivity to methylxanthines (caffeine, theophylline, theobromine) and women who were pregnant/of childbearing potential/using oral contraceptives
Concomitant interventions allowed or excluded	Allowed: NR Disallowed: all current treatment for peripheral vascular disease was stopped for 2 weeks before placebo run-in phase
Power calculation	NR
N randomised to treatments included in review	127 (one randomised twice, therefore authors treat total number as 128)

ECG, electrocardiogram; mph, miles per hour; NR, not reported.

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
N randomised to treatment	66 (67 if include placebo patient randomised a second time)	61
Baseline characteristics		
Age (years)	Mean 62	Mean 63.5
Gender	M 82.1%; F 17.9%	M 82%; F 18%
	[Gillings 1987:[73] *n* = 124, M 81%; F 19%]	[Gillings 1987:[73] *n* = 124, M 82%; F 18%]
Smokers	67.2%	68.9%
	[Gillings 1987:[73] *n* = 124, 67%]	[Gillings 1987:[73] *n* = 124, 69%]
Diabetics	22.4%	24.6%
	[Gillings 1987:[73] *n* = 124, 22%]	[Gillings 1987:[73] *n* = 124, 25%]
Hypertension/blood pressure	[Gillings 1987:[73] mean diastolic BP 81 mmHg]	[Gillings 1987:[73] mean diastolic BP 82 mmHg]
Hyperlipidaemia		
Obesity or weight		
Angina	[Reich 1984:[75] 10/63 (15.9%)]	[Reich 1984:[75] 6/61 (9.8%)]
History of vascular therapy		
Other	Mean duration of chronic obstructive airways disease, 3.0 years	Mean duration of chronic obstructive airways disease, 2.8 years
	[Gillings 1987:[73] mean duration of chronic obstructive pulmonary disease, 3.4 years]	[Gillings 1987:[73] mean duration of chronic obstructive pulmonary disease 4.3 years]
	[Reich 1984:[75] occasional exercise, 29/63 (46.0%), regular exercise 25/63 (39.7%)]	[Reich 1984:[75] occasional exercise, 28/61 (45.9%), regular exercise 19/61 (31.1%)]
Withdrawals		
Withdrawals/loss to follow-up	Patients excluded from non-ITT analysis (25/67): already randomised, 1; did not keep visit schedule, 8; prescribed improper medication, 2; trial closed before patient completed 24 weeks, 4; intercurrent medical problem, 5	Patients excluded from non-ITT analysis (21/61): treadmill entry criteria violated, 2; did not keep visit schedule, 7; refused medication, 2; prescribed improper medication, 2; trial closed before patient completed 24 weeks, 1; intercurrent medical problem, 4
	[Gillings 1987:[73] ITT analysis: only four excluded: discontinued study before first follow-up, 3; previously randomised to placebo, 1]	[Gillings 1987:[73] ITT analysis: no withdrawals]
Results		
MWD *n* in analysis	42	40
	[Gillings 1987:[73] 63]	[Gillings 1987:[73] 61]
MWD baseline	172 m [Gillings 1987:[73] 147 (SE 9 m)]	181 [Gillings 1987:[73] 161(SE 10 m)]
MWD follow-up	268 m	250 m
MWD change	38% (calculated: 96 m) [Gillings 1987:[73] 33 (SE 8 m)]	25% (calculated: 69 m) [Gillings 1987:[73] 16 (SE 5 m)]
MWD between-group comparison	$p = 0.035$ by repeat measures two-way analysis of variance with interaction of the study data	
	[Gillings 1987:[73] extended Mantel–Haenszel $p = 0.316$, one-sided $p = 0.049$]	
PFWD *n* in analysis	42	40
PFWD baseline	111 m [Gillings 1987:[73] 95 (SE 6 m)]	117 m [Gillings 1987:[73] 102 (SE 6 m)]
PFWD follow-up	195 m	180 m [RM265: 147 (SE 9 m)]
PFWD change	59% (calculated: 84 m) [Gillings 1987:[73] 47 (SE 10 m)]	36% (calculated: 63 m) [Gillings 1987:[73] 18 (SE 6 m)]
PFWD between-group comparison	$p = 0.016$ by repeat measures two-way analysis of variance with interaction of the study data. [Gillings 1987:[73] extended Mantel–Haenszel $p = 0.042$, one-sided $p = 0.1$]	

Treatment group	Naftidrofuryl oxalate 200 mg t.i.d.	Placebo
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	66 (67)	61
Vascular events follow-up		
Vascular events included		
Vascular events reported	One angina	One MI, one cerebrovascular accident, one cardiac surgery
Vascular events between-group comparison		
AEs *n* in analysis		
AEs follow-up		
AEs reported	(Also listed in withdrawals): 37 (55%) experienced some AEs including: nausea, 24 (35.8%); depression of the central nervous system symptoms, 15 (22.4%). Other AEs not detailed	(Also listed in withdrawals): 24 (39%) experienced some AEs including: nausea, 3; depression of the central nervous system symptoms, 7; blurred vision, 1; weakness, 1. Other AEs not detailed
AEs between-group comparison	Nausea $p < 0.05$, depression of the central nervous system and others not significant	
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

BP, blood pressure; SE, standard error.

Gallus 1985[76]	
Study details	
Publication type	Gallus 1985,[76] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT crossover (extract up to crossover)
Country	Australia
Dates of participant recruitment	NR
Sources of funding	Hoechst Australia supported trial
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 800-mg daily dose (400 mg b.i.d.) for first week, increased to 1200-mg daily dose (400 mg t.i.d.)
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	8 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks
Outcomes and measures	MWD: treadmill with constant speed of 4 km/hour and a slope of 10º
	PFWD: as MWD
	Vascular events
	Mortality
Notes on statistics	Geometric means used. Log transformation was used to normalise apparently log-normal distribution of several variables, including all treadmill distances. Student's *t*-test with confidence limits of 95% were calculated according to Armitage for the 'therapeutic effects ratio' obtained by dividing the observed pentoxifylline effect on treadmill claudication or walking distance by the observed placebo effect
Population	
Eligibility criteria	*Include*: patients who estimated they could walk < 750 m before the onset of leg pain. Stable claudication distance for over 6 months, the presence of peripheral vascular disease documented through clinical examination by a vascular surgeon and supplemented by angiography or non-invasive testing, age > 50 years, a pledge not to change smoking habits during the trial and informed consent
	Exclude: those with vascular surgery or sympathectomy within the previous 6 months, ischaemic leg ulcer or rest pain, exercise tolerance limited by conditions other than peripheral vascular disease and treatment with lipid-lowering or antiplatelet drugs
Concomitant interventions allowed or excluded	Allowed: unspecified non-trial drugs allowed
	Disallowed: lipid-lowering or antiplatelet drugs not allowed
Power calculation	NR
N randomised to treatments included in review	47

NR, not reported.

Treatment group	Pentoxifylline 800-mg daily dose (400 mg b.i.d.) for first week, increased to 1200-mg daily dose (400 mg t.i.d.)	Placebo
N randomised to treatment	25	23
Baseline characteristics		
Age	Not including five withdrawals: mean 68 (SD 6) years	Not including four withdrawals: mean 66 (SD 6) years
Gender	Not including five withdrawals: M 89.5%; F 10.5%	Not including four withdrawals: M 73.7%; F 26.3%
Smokers	Not including five withdrawals: 52.6%	Not including four withdrawals: 36.8%
Diabetics	Not including five withdrawals: 15.8%	Not including four withdrawals: 10.5%
Hypertension/blood pressure	Not including five withdrawals, supine BP (mmHg): mean systolic 167 (SD 30); mean diastolic 88 (SD 12)	Not including four withdrawals, supine BP (mmHg): mean systolic 165 (SD 27); mean diastolic 90 (SD 12)
Hyperlipidaemia		
Obesity or weight	NR, weight mean 76 (SD 11) kg	NR, weight mean 74 (SD 12) kg
Angina	Not including five withdrawals: 26.3%	Not including four withdrawals: 26.3%
History of vascular therapy	Not including five withdrawals: vascular reconstruction 31.6%; sympathectomy 15.8%	Not including four withdrawals: vascular reconstruction 31.6%; sympathectomy 26.3%
Other	Not including five withdrawals: MI 21.1% cerebral ischaemia 10.5%; symptom duration (geometric mean ± 1 SD) 53 ± 23–122 months	Not including four withdrawals: MI 10.5%, cerebral ischaemia 26.3%; symptom duration (geometric mean ± 1 SD) 24 ± 9–59 months
Withdrawals		
Withdrawals/loss to follow-up	Five withdrawals, only two before crossover: nausea and vomiting, one; breathless with effort, one. Three who withdrew after crossover: R on T extra systoles with effort (as reported), one; uninterpretable exercise ECG, one; onset of effort angina, one.) Missing data in results (Table 3) not explained, though probably due to exclusion of patients with < 10 m baseline claudication distance	Four withdrawals, all before crossover: death (MI), one; myocardial infarct/stroke, one; angina with exercise, one; technical, one. Missing data in results (Table 3) not explained, though probably due to exclusion of patients with < 10 m baseline claudication distance
Results		
MWD *n* in analysis	19 at baseline, 16 at 8 weeks	19 at baseline, 16 at 8 weeks
MWD baseline	Geometric mean 90.4 m	Geometric mean 99.8 m
MWD follow-up		
MWD change	Per cent change from baseline (× 100) 1.23	Per cent change from baseline (× 100) 1.17
MWD between-group comparison	Ratio of per cent change from baseline (pentoxifylline/placebo) 1.05 (95% CI 0.81 to 1.36)	
PFWD *n* in analysis	18 at baseline, 16 at 8 weeks	19 at baseline, 16 at 8 weeks
PFWD baseline	Geometric mean 47.7 m	Geometric mean 48.3 m
PFWD follow-up		
PFWD change	Per cent change from baseline (× 100) 1.55	Per cent change from baseline (× 100) 1.26
PFWD between-group comparison	Ratio of per cent change from baseline (pentoxifylline/placebo) 1.23 (95% CI 0.86 to 1.77)	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		

Treatment group	Pentoxifylline 800-mg daily dose (400 mg b.i.d.) for first week, increased to 1200-mg daily dose (400 mg t.i.d.)	Placebo
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported	No withdrawals due to vascular events	Three withdrawals due to vascular events (one fatal MI, one MI, one angina)
Vascular events between-group comparison		
AEs *n* in analysis		
AEs follow-up		
AEs reported		
AEs between-group comparison		
Mortality reported	0	1
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

BP, blood pressure; ECG, electrocardiogram; F, female; M, male; NR, not reported.

Di Perri 1983[77]	
Study details	
Publication type	Di Perri 1983,[77] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT crossover (extract up to crossover)
Country	Italy
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	8 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks
Outcomes and measures	MWD: measured absolute walking distance (m). The absolute distance which the individual patient was able to cover by walking on horizontal level at metronome-controlled speed of 120 steps/minute under supervision of a medical doctor. At each time point the walking test was performed three times and a mean taken AEs: unclear how recorded
Notes on statistics	Student's *t*-test and two-way analysis of variance were used
Population	
Eligibility criteria	Outpatients suffering from peripheral arterial occlusive disease with IC. Fontaine's classification stage II severity. Walking capacity between 100 m and 400 m. Free from pain at rest and skin lesions. Excluded diabetes mellitus, severe hypertension (> 180/110 mmHg) and CHF
Concomitant interventions allowed or excluded	None allowed
Power calculation	NR
N randomised to treatments included in review	24

NR, not reported.

Treatment group	Pentoxifylline 400 mg t.i.d.	Placebo
N randomised to treatment	12	12
Baseline characteristics		
Age	Mean 59.3 years	Mean 59.3 years
Gender	M 83.3%; F 16.7%	M 75%; F 25%
Smokers		
Diabetics	0%	0%
Hypertension/blood pressure	0%	0%
Hyperlipidaemia	0%	0%
Obesity or weight		
Angina		
History of vascular therapy		
Other	12 across the two groups displayed symptoms of moderate coronary heart disease and/or cerebrovascular disorders	
Withdrawals		
Withdrawals/loss to follow-up	0	0
Results		
MWD *n* in analysis	12	12
MWD baseline	Mean 223 ± 20 m (SD or SE NR). Also reported as ± 29 m	Mean 208 ± 24.6 m
MWD follow-up	Mean 359 ± 29 m (SD or SE NR)	Mean 215 ± 25 m
MWD change	136 m (reported)	6 m (reported)
MWD between-group comparison	Student's *t*-test of the individual increases discloses significant superiority in the pentoxifylline group ($p < 0.01$)	
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Pentoxifylline 400 mg t.i.d.	Placebo
AEs *n* in analysis	12	12
AEs follow-up		
AEs reported	0	0
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; NR, not reported; SE, standard error.

Dettori 1989[69]	
Study details	
Publication type	Dettori 1989,[69] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre, factorial
Country	Italy
Dates of participant recruitment	Between March 1983 and February 1985
Sources of funding	Hoechst Italia
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)
Comparators	1. acenocoumarol 4-mg tablets (adjusted to patient) 2. 1200 mg pentoxifylline daily dose (400 mg t.i.d.) plus acenocoumarol 4-mg tablets (adjusted to patient) 3. placebo
Run-in phase	4 weeks
Treatment duration	52 weeks
Outcome(s)	
Follow-up	Baseline, 13 weeks, 26 weeks, 39 weeks, 52 weeks
Outcomes and measures	PFW time: speed of 3 km/hour, 10% elevation. PFW time recorded. For those who could walk for 30 minutes without experiencing pain, a higher speed was used in the second test (5 km/hour) ABPI: Doppler ultrasound. Measured on both lower limbs, highest value measure used as denominator
Notes on statistics	Analysis of variance to compare baseline characteristics. Chi-squared test for PFWD, by categorising patients into improved (≥ 25% from baseline), not improved (–25% to +25% from baseline), deteriorated (> –25% from baseline). Also assessed by means of the analysis of variance for repeated measures. ABPI compared by means of Mann–Whitney test. Fisher's exact test used to compare frequency of relevant clinical events
Population	
Eligibility criteria	
Concomitant interventions allowed or excluded	Allowed: advice to quit smoking and to perform daily walks Disallowed: anticoagulants, other medications unless authorised by the physicians involved in the study
Power calculation	80%, $p < 0.05$
N randomised to treatments included in review	146

PFW, pain-free walking.

Treatment group	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)	Acenocoumarol 4-mg tablets (adjusted to patient)	1200-mg pentoxifylline daily dose (400 mg t.i.d.) plus acenocoumarol 4-mg tablets (adjusted to patient)	Placebo
N randomised to treatment	37	36	36	37
Baseline characteristics				
Age	(m bar = mean?) 62 ± SD 5 years	(m bar = mean?) 58 ± SD 7 years	(m bar = mean?) 60 ± SD 6 years	(m bar = mean?) 59 ± SD 8 years
Gender	M 89.2%; F 10.8%	M 91.7%; F 8.3%	M 91.7%; F 8.3%	M 94.6%; F 5.4%
Smokers				
Diabetics	10.8%	8.3%	13.9%	24.3%
Hypertension/blood pressure	32.4%	27.8%	36.1%	35.1%
Hyperlipidaemia				
Obesity or weight				
Angina				
History of vascular therapy	0%	0%	0%	0%
Other	Heart disease: 13.5%; median duration of symptoms, 8 months	Heart disease: 22.2%; median duration of symptoms, 7.5 months	Heart disease: 19.4%; median duration of symptoms, 12 months	Heart disease: 13.5%, median duration of symptoms, 12 months
Withdrawals				
Withdrawals/loss to follow-up	Angina, one; unrelated diseases, three; intolerance, two; refusal, two Total = eight	Non-fatal bleeding, two; angina, one; unrelated diseases, three Total = six	Fatal bleeding, two; non-fatal bleeding, one; angina, one; unrelated diseases, one; intolerance, two Total = seven	Fatal MI, two; reversible ischaemic neurological deficit, one; unrelated diseases, one; refusal, three Total = seven
Results				
MWD *n* in analysis				
MWD baseline				
MWD follow-up				
MWD change				
MWD between-group comparison				
PFWD *n* in analysis	29	30	29	30
PFWD baseline	Geometric mean 112 (range 25–660) seconds	Geometric mean 121 (range 13–395) seconds	Geometric mean 138 (range 45–480) seconds	Geometric mean 144 (range 45–758) seconds
PFWD follow-up	Geometric mean 324 (range 50–1800) seconds	Geometric mean 406 (range 115–1800) seconds	Geometric mean 468 (range 118–1800) seconds	Geometric mean 349 (range 60–1800) seconds
PFWD change	+189% categorisation: improved, 25; unchanged, three; worse, one	+236% categorisation: improved, 26; unchanged, four; worse, zero	+239% categorisation: improved, 28; unchanged, zero; worse, one	+149% categorisation: improved, 20; unchanged, seven; worse, three
PFWD between-group comparison	Two-way contingency, grouping T1 and T3 (pentoxifylline groups) together, and T2 and T4 (no pentoxifylline) together gave a statistically significant difference between improved vs not improved (worse + unchanged) for pentoxifylline ($\chi^2 = 4.73$, $p < 0.05$) and acenocoumarol ($\chi^2 = 5.08$, $p < 0.05$). Analysis of variance for repeated measures was non-significant			

Treatment group	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)	Acenocoumarol 4-mg tablets (adjusted to patient)	1200-mg pentoxifylline daily dose (400 mg t.i.d.) plus acenocoumarol 4-mg tablets (adjusted to patient)	Placebo
ABPI *n* in analysis	29	30	29	30
ABPI baseline	At rest: (m bar = mean?) 0.68 (SD 0.14) After exercise: (m bar = mean?) 0.57 (SD 0.22)	At rest: 0.68 (SD 0.18) After exercise:0.54 (SD 0.23)	At rest: 0.69 (SD 0.20) After exercise:0.56 (SD 0.27)	At rest: 0.67 (SD 0.14) After exercise: 0.57 (SD 0.19)
ABPI follow-up	At rest: (m bar = mean?)0.71 (SD 0.17) After exercise: 0.62 (SD 0.21)	At rest: 0.75 (SD 0.20) After exercise: 0.61 (SD 0.24)	At rest: 0.73 (SD 0.16) After exercise: 0.65 (SD 0.22)	At rest: 0.65 (SD 0.13) After exercise: 0.52 (SD 0.19)
ABPI change	At rest: +2.5% After exercise: +8.3%	At rest: +9.7% After exercise:+16.1%	At rest: +8.7% After exercise: +20.6%	At rest: –3.1% After exercise: –9.4%
ABPI between-group comparison	At rest: T2 compared with placebo significant ($p = 0.04$), T3 compared with placebo borderline ($p = 0.07$) After exercise: T1 vs placebo $p = 0.09$, T2 vs placebo $p = 0.05$, T3 vs placebo $p = 0.01$. Differences between active drugs non-significant			
Vascular events *n* in analysis	37	36	36	37
Vascular events follow-up				
Vascular events included	Fatal bleeding, non-fatal bleeding, angina, reversible ischaemic neurological deficit			
Vascular events reported	One	Three	Four	One (plus two deaths from MI, not included in statistical comparison between groups)
Vascular events between-group comparison	Only compared acenocoumarol with non-acenocoumarol groups (T2, T3 vs T4, T1): non-significant difference			
AEs *n* in analysis	37	36	36	37
AEs follow-up	Negative end points were defined as death, acute MI, onset of angina pectoris, stroke or TIA, cerebral haemorrhage. Other side effects (such as epigastric pain) were all recorded			
AEs reported	Angina, one; unrelated diseases, three; intolerance, two; refusal, two Total = eight	Non-fatal bleeding, two; angina, one; unrelated diseases, three Total = six	Fatal bleeding, two; non-fatal bleeding, one; angina, one; unrelated diseases, one; intolerance, two Total = seven	Fatal MI, two; reversible ischaemic neurological deficit, one; unrelated diseases, one; refusal, three Total = seven
AEs between-group comparison	NR for pentoxifylline			
Mortality reported	Zero	Zero	Two	Two
Mortality between-group comparison	NR			
HRQoL *n* in analysis				
HRQoL baseline				
HRQoL follow-up				
HRQoL change				
HRQoL between-group comparison				

F, female; M, male; NR, not reported; TIA, transient ischaemic attack.

Creager 2008[70]	
Study details	
Publication type	Creager 2008,[70] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	February 1998 to October 1999
Sources of funding	Berlex Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)
Comparator	1. Placebo 2. Iloprost 50 µg twice daily plus placebos to make up to three capsules t.i.d. 3. Iloprost 100 µg twice daily (increased in second week from 50 µg twice daily) plus placebos to make up to three capsules t.i.d. 4. Iloprost 150 µg twice daily (increased to 150 µg by 50 µg/week from 50 µg twice daily in first week) plus placebos to make up to three capsules t.i.d.
Run-in phase	4–6 weeks
Treatment duration	26 weeks
Outcome(s)	
Follow-up	Baseline, 26 weeks
Outcomes and measures	MWD: graded treadmill, speed at a constant 2 mph. Graduation started at 0% and increased by 2% every 2 minutes. Primary measure was walking time, converted to distance PFWD: as MWD AEs: reports those that affected > 5% of any group with a ratio > 2.0 or < 0.5 compared with placebo. SAEs reported (death, permanent substantial disability, inpatient hospitalisation or prolongation of existing inpatient hospitalisation, or an AE that was life-threatening or was a congenital anomaly, cancer or overdose) are those that affected > 1% HRQoL: WIQ and SF-36
Notes on statistics	*Primary analysis*: mean per cent change from baseline between T4 and T2. Efficacy analysis based on ITT (only those 370 participants with baseline treadmill, at least one dose after randomisation, and one follow-up treadmill assessment). Two-way analysis of covariance. Last observation carried forward *Secondary analysis*: individual comparisons between placebo and T1, T3, T4 and T5. No adjustment for multiple comparisons. Additional analyses used graded threshold criteria (25%, 25–50% and 50% from baseline). Cochran–Mantel–Haenszel method based on rank (Van Elteren) was applied, stratified by baseline diabetic status. Also done for secondary efficacy variables. All tests were two-tailed and performed at $p = 0.05$. Pair-wise testing of placebo vs drug and pentoxifylline vs iloprost. Subgroup analysis included age, gender, race, smoking status, duration of PAD, prior intervention, antiplatelet medication, absolute claudication distance at baseline and diabetic status
Population	
Eligibility criteria	Men and women aged ≥ 40 years, with PAD and IC (Fontaine stage II) were eligible for participation. Stable claudication for at least 3 months prior to entry, despite standard care, which included cardiovascular risk factor modification and exercise training. Absolute claudication distance between 50 and 800 m on a baseline eligibility exercise test. ABPI of ≤ 0.9 in the symptomatic leg. In addition, a > 20% fall in ABPI within 1 minute following cessation of exercise served as confirmation of a diagnosis of PAD. In patients with non-compressible vessels (ABPI > 1.50), the TBI at rest had to be < 0.70. Run-in phase requirements: MWD measured by exercise treadmill test on two to three occasions at an interval of 7–14 days had to be within 20% of the MWD measured at the previous test (up to three tests to meet this requirement), drug compliance had to be 80–120% Exclusions: ischaemic rest pain, ulcers, gangrene (Fontaine stage III or IV), evidence of non-atherosclerotic PAD, and peripheral neuropathy that impaired walking ability, revascularisation for PAD within the preceding 3 months, sympathectomy within 6 months, type 1 diabetes mellitus, MI or major cardiac surgery within 3 months, unstable angina and heart failure

Creager 2008[70]	
Concomitant interventions allowed or excluded	Allowed: aspirin alone or warfarin alone Disallowed: warfarin in combination with aspirin, or any drug specific to the treatment of IC, low molecular weight heparin
Power calculation	Based on comparison of placebo and iloprost 100 µg t.i.d., assuming 20% improvement of MWD in placebo group, and total 55% improvement for iloprost group; 80 patients per group would give 90% power at $p = 0.05$ level using two-tailed *t*-test
N randomised to treatments included in review	430

mph, miles per hour.

Treatment group	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)	Placebo	Iloprost 50 µg twice daily plus placebos to make up to three capsules t.i.d.	Iloprost 100 µg twice daily (increased in second week from 50 µg twice daily) plus placebos to make up to three capsules t.i.d.	Iloprost 150 µg twice daily (increased to 150 µg by 50 µg/ week from 50 µg twice daily in first week) plus placebos to make up to three capsules t.i.d.
N randomised to treatment	86	84	87	86	87
Baseline characteristics					
Age (years)	67.2	66.5	67.1	66.6	67.3
Gender	M 78%; F 22%	M 82%; F 18%	M 83%; F 17%	M 86%; F 14%	M 77%; F 23%
Smokers	Currently smoking 31.4%	Currently smoking 33.3%	Currently smoking 31%	Currently smoking 38.4%	Currently smoking 27.6%
Diabetics	24.4%	33.3%	31%	23.3%	29.9%
Hypertension/blood pressure	72.1%	71.4%	71.3%	68.6%	75.9%
Hyperlipidaemia	70.9%	70.2%	64.4%	73.3%	74.7%
Obesity or weight					
Angina	30.2%	31%	32.2%	32.6%	26.4%
History of vascular therapy	Previous intervention (not defined further): 32.6%	Previous intervention (not defined further): 32.1%	Previous intervention (not defined further): 31.0%	Previous intervention (not defined further): 32.6%	Previous intervention (not defined further): 32.2%
Other	History of MI: 30.2%	History of MI: 34.5%	History of MI: 29.9%	History of MI: 27.9%	History of MI: 36.8%
	Aspirin use: 75.6%	Aspirin use: 72.6%	Aspirin use: 71.3%	Aspirin use: 74.4%	Aspirin use: 70.1%
	Mean duration of claudication: 65.9 months	Mean duration of claudication: 80.4 months	Mean duration of claudication: 61.4 months	Mean duration of claudication: 65.5 months	Mean duration of claudication: 74.6 months
Withdrawals					
Withdrawals/loss to follow-up	SAEs leading to discontinuation, 15% (headache, 2%; pain in extremity, 0%; vasodilation, 0%; dyspepsia, 1%)	SAEs leading to discontinuation, 14% (headache, 1%; pain in extremity, 1%; vasodilation, 0%; dyspepsia, 1%)	SAEs leading to discontinuation, 31% (headache, 14%; pain in extremity, 6%; vasodilation, 1%; dyspepsia, 0%)	SAEs leading to discontinuation, 57% (headache, 36%; pain in extremity, 6%; vasodilation, 2%; dyspepsia, 0%)	SAEs leading to discontinuation, 53% (headache, 26%; pain in extremity, 6%; vasodilation, 2%; dyspepsia, 3%)
Results					
MWD *n* in analysis	NR (86 originally randomised, unclear how many dropped out of this group)	NR (84 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)	NR (86 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)
MWD baseline	Mean 316 (SD 191) m	Mean 292 (SD 161) m	Mean 244 (SD 164) m	Mean 312 (SD 193) m	Mean 289 (SD 171) m
MWD follow-up	NR	NR	NR	NR	NR
MWD change	13.9%	3.3%	7.7%	8.8%	11.2%
MWD between-group comparison	Statistically significant ($p = 0.039$) difference for pentoxifylline only				

Treatment group	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)	Placebo	Iloprost 50 µg twice daily plus placebos to make up to three capsules t.i.d.	Iloprost 100 µg twice daily (increased in second week from 50 µg twice daily) plus placebos to make up to three capsules t.i.d.	Iloprost 150 µg twice daily (increased to 150 µg by 50 µg/week from 50 µg twice daily in first week) plus placebos to make up to three capsules t.i.d.
PFWD *n* in analysis	NR (86 originally randomised, unclear how many dropped out of this group)	NR (84 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)	NR (86 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)
PFWD baseline	Mean 118 (SD 83) m	Mean 120 (SD 88) m	Mean 105 (SD 81) m	Mean 124 (SD 96) m	Mean 129 (SD 88) m
PFWD follow-up	NR	NR	NR	NR	NR
PFWD change	34.3%	21.2%	24%	28.9%	31.2%
PFWD between-group comparison	No significant difference				
ABPI *n* in analysis					
ABPI baseline					
ABPI follow-up					
ABPI change					
ABPI between-group comparison					
Vascular events *n* in analysis	NR (86 originally randomised, unclear how many dropped out of this group)	NR (84 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)	NR (86 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)
Vascular events follow-up	26 weeks				
Vascular events included	Cardiovascular events that affected >1% of any group with a ratio >2.0 or <0.5 in treatment groups compared with placebo				
Vascular events reported	7%	12%	8%	2%	2%
Vascular events between-group comparison	Not numerically different				
AEs *n* in analysis	NR (86 originally randomised, unclear how many dropped out of this group)	NR (84 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)	NR (86 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)
AEs follow-up	26 weeks (assumed)				
AEs reported	69%	59%	77%	88%	90%
AEs between-group comparison	Statistical significance NR. Dose–response-like results seen for iloprost and headache and flushing. Other AEs occurred more frequently in iloprost groups: pain in extremities, jaw pain, nausea, diarrhoea. Mild dyspepsia occurred more frequently in pentoxifylline group. No meaningful numerical differences among groups in any specific cardiovascular events (angina, CHF, MI)				
Mortality reported	One (1.2%)	One (1.2%)	Zero	Zero	Zero
Mortality between-group comparison	Not numerically different				

Treatment group	Pentoxifylline 1200-mg daily dose (400 mg t.i.d.)	Placebo	Iloprost 50 µg twice daily plus placebos to make up to three capsules t.i.d.	Iloprost 100 µg twice daily (increased in second week from 50 µg twice daily) plus placebos to make up to three capsules t.i.d.	Iloprost 150 µg twice daily (increased to 150 µg by 50 µg/ week from 50 µg twice daily in first week) plus placebos to make up to three capsules t.i.d.
HRQoL *n* in analysis	NR (86 originally randomised, unclear how many dropped out of this group)	NR (84 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)	NR (86 originally randomised, unclear how many dropped out of this group)	NR (87 originally randomised, unclear how many dropped out of this group)
HRQoL baseline	NR	NR	NR	NR	NR
HRQoL follow-up	NR	NR	NR	NR	NR
HRQoL change	Only differences seen in stair-climbing ability; 9% improvement compared with placebo	NA	Only differences seen in stair-climbing ability; 11% improvement compared with placebo	NR	Only differences seen in stair-climbing ability; 16% improvement compared with placebo
HRQoL between-group comparison	Stair-climbing ability statistically significant improvement for T1, T3 and T5. All other outcomes not statistically significant for WIQ and SF-36				

F, female; M, male; NA, not applicable; NR, not reported.

Trials of inositol nicotinate and placebo

O'Hara 1988[78]	
Study details	
Publication type	O'Hara 1988,[78] full report in peer-reviewed journal
Additional sources of data	O'Hara 1985[79]
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	NR
Sources of funding	Winthrop Laboratories, for drugs and statistical analysis
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (4 × 500-mg tablets b.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	PFWD: training device (pair of stirrups which moved in opposition in a near vertical plane by means of an interconnecting belt and pulley mechanism in a supporting metal frame), which simulated box-stepping. Elapsed time and number of steps to claudication were recorded. (Some information from O'Hara 1985.[79]) Time to recovery from claudication pain was recorded. Waist-band pedometer to record 'similar weekly walks' Vascular events: not systematically reported. Some given in withdrawals AEs: Subjective complaints were sought by the question 'How did the medication suit you?'
Notes on statistics	Wilcoxon matched pairs signed-rank and two-sample tests, Student's *t*-tests (paired and unpaired), or chi-squared test as appropriate
Population	
Eligibility criteria	Male or female with clinical diagnosis of IC, which limited walking to 500 yards (457 m). Aged 50–75 years. Weighing 40–100 kg. Exclusions: insulin-dependent diabetes, severe angina, rest pain or gangrene, non-vascular causes of IC, symptomatic treatment for claudication pain within the month preceding entry to the study, malignant diseases, gross renal or hepatic impairment and arterial surgery for claudication within previous 3 years
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	120

NR, not reported.

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
N randomised to treatment	62	58
Baseline characteristics		
Age	Mean 66.2 (SE 0.7) years	Mean 65.6 (SE 1.0) years
Gender	M 64.5%; F 35.5%	M 72.4%; F 27.6%
Smokers	64.5%	50%
Diabetics	4.8%	5.2%
Hypertension/blood pressure	Mean 161.4 (SE 2.4)/87.6 (SE 1.4)	Mean 152.7 (SE 2.5)/84.7 (SE 1.2)
Hyperlipidaemia		
Obesity or weight	Weight mean 69.3 (SE 1.3) kg	Weight mean 71.8 (SE 1.0) kg
Angina		
History of vascular therapy		
Other	Duration mean 2.3 (SE 0.4) years VAS pain score mean 62.1 (SE 2.1) mm No. of cigarettes smoked per day mean 16.1 (SE 1.2)	Duration mean 2.8 (SE 0.5) years VAS pain score mean 56.7 (SE 2.4) mm No. of cigarettes smoked per day mean 18.3 (SE 1.6)
Withdrawals		
Withdrawals/loss to follow-up	{O'Hara 1985:[79] five withdrawals [personal choice (two), stroke (one), gastrointestinal complaints (one), and 'too many tablets' (one)]}	{O'Hara 1985:[79] seven withdrawals [personal choice (two), persistent illness (one), death (O'Hara 1988[78] suggests this was unrelated to IC) (one), MI (one), general malaise (one), rash (one)]}
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		
PFWD *n* in analysis	57	51
PFWD baseline	Free walking paces (weekly): mean 455.2 (SE 78.5) Claudication time (s): mean 129.2 (SE 16)	Free walking paces (weekly): mean 617.2 (131.3) Claudication time (s): mean 102.4 (SE 12.2)
PFWD follow-up	(Only reported as change from baseline – see below)	(Only reported as change from baseline – see below)
PFWD change	Free walking paces (weekly): mean 469.6 (SE 183.7) Claudication time (s): mean 43.3 (SE 21)	Free walking paces (weekly): mean 325.4 (SE 220.6) Claudication time (s): mean 28.6 (SE 17.9)
PFWD between-group comparison	Free walking paces: within group comparisons significant for both T1 and T2. Between-group comparisons only significant for T1. Claudication time: between-group comparisons of change from baseline were not significant at $p = 0.05$. Within group comparisons of change from baseline were significant for inositol at 3 months, but not for placebo	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
Vascular events *n* in analysis	62	58
Vascular events follow-up		
Vascular events included		
Vascular events reported	Stroke, one – also reported in withdrawals	MI, one – also reported in withdrawals
Vascular events between-group comparison		
AEs *n* in analysis	62	58
AEs follow-up		
AEs reported	[O'Hara 1985:[79] 16.1% patients reported minor side effects, mostly related to difficulty in swallowing tablets]	[O'Hara 1985:[79] 19.0% patients reported minor side effects, mostly related to difficulty in swallowing tablets]
AEs between-group comparison		
Mortality reported	Zero	One – also reported in withdrawals
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; SE, standard error; VAS, visual analogue scale.

Kiff 1988[80]	
Study details	
Publication type	Kiff 1988,[80] full report in peer-reviewed journal
Additional sources of data	Unclear whether or not the patients are the same as some patients in O'Hara 1988[78] and O'Hara 1985.[79] Different outcomes reported using different techniques
Trial design	RCT
Country	UK
Dates of participant recruitment	March 1984 to January 1986
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (2 g b.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	MWD: treadmill with constant workload, 10% gradient
	ABPI: Doppler ultrasound flow detector and sphygmomanometer at rest
Notes on statistics	Wilcoxon matched pairs signed-rank test or student's paired *t*-tests as appropriate
Population	
Eligibility criteria	*Inclusion*: stable IC (duration of symptoms of at least 6 months), PAD confirmed by resting ankle pressure index of < 0.9 or a drop in ankle pressure with exercise of > 30 mmHg. All patients had palpable femoral pulses and could walk between 35 and 500 m on a treadmill. Any medication for IC stopped 1 month before trial
	Exclusion: walking distance on treadmill > 500 m, serious medical disease, rest pain or gangrene, treatment with beta-blockers which was not stabilised or arterial surgery for claudication within the previous 3 months
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	80

NR, not reported.

Treatment group	Inositol nicotinate 4-g daily dose (2-g b.i.d.)	Placebo
N randomised to treatment	40	40
Baseline characteristics		
Age	Mean 61.5 (SD 9.3) years	Mean 62.8 (SD 7.3) years
Gender	M 82.5%; F 17.5%	M 77.5%; F 22.5%
Smokers	57.5%	72.5%
Diabetics		
Hypertension/blood pressure	Mean 153.6 (SD 23.9) mmHg/87.5 (SD 10.6) mmHg	Mean 152.9 (SD 24.1) mmHg/88.3 (SD 10.5) mmHg
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other	Duration mean 2.5 (SD 1.8) years VAS pain score mean 49.1 (SD 22.6) mm Estimate of free walking mean 330.6 (SD 219) yards	Duration mean 1.6 (SD 1.1) years VAS pain score mean 53.4 (SD 17.8) mm Estimate of free walking mean 309.1 (SD 239.7) yards
Withdrawals		
Withdrawals/loss to follow-up	Eight withdrawals [reasons were eight out of: moved from district (three), family problems (two), felt unwell taking tablets (two), personal choice (four), referred for surgery (one), hospitalised for an unrelated condition (one)]	Seven withdrawals [reasons were nausea and vomiting (one), constipation (one) and five out of: moved from district (three), family problems (two), felt unwell taking tablets (two), personal choice (four), referred for surgery (one), hospitalised for an unrelated condition (one)]
Results		
MWD *n* in analysis	Initially 40 – assume 12 weeks minus withdrawals (32)	Initially 40 – assume 12 weeks minus withdrawals (33)
MWD baseline	Mean 131.7 (SD 80.4) ($n=40$)	Mean 118.4 (SD 70.9) ($n=40$)
MWD follow-up	Mean 197.1 (SD 125.7) (assume $n=32$)	Mean 221.2 (SD 154.2) (assume $n=33$)
MWD change	Calculated: 65.4, $p<0.05$	102.8, $p<0.05$
MWD between-group comparison	No statistically significant difference between the groups	
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis	Initially 40 – assume minus withdrawals (32) at 12 weeks	Initially 40 – assume minus withdrawals (33) at 12 weeks
ABPI baseline	Mean 0.718 (SD 0.144) m	Mean 0.694 (SD 0.215) m
ABPI follow-up	NR	NR
ABPI change	Not significant	Not significant
ABPI between-group comparison	Not significant	

Treatment group	Inositol nicotinate 4-g daily dose (2-g b.i.d.)	Placebo
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		
AEs *n* in analysis	As for withdrawals	As for withdrawals
AEs follow-up		
AEs reported		
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; NR, not reported; VAS, visual analogue scale.

Head 1986[81]	
Study details	
Publication type	Head 1986,[81] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (1-g q.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	PFWD: time to claudication was recorded: a metronome was set at 80 beats/minute and each patient was instructed to climb up and down the first two steps of a standard ladder with a rung interval of 19 cm. Patients climbed one step at a time to the beat of the metronome, leading with the worse leg and bringing the other leg up before proceeding to the next step and then returning to the ground in a similar fashion. The time to onset of calf pain was recorded using a stopwatch, and pressure readings repeated AEs: elicited by question 'How did the tablets suit you?'
Notes on statistics	NR
Population	
Eligibility criteria	Patients with clinical diagnosis of IC due to vascular insufficiency. Male or female, aged between 18 and 80 years, weigh between 40 and 100 kg and be judged suitable to receive a 3-month course of inositol nicotinate 1-g q.d. or matching placebo
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	123

NR, not reported; q.d., once a day; q.i.d., four times a day.

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
N randomised to treatment	51 (plus unspecified number who withdrew)	62 (plus unspecified number who withdrew)
Baseline characteristics		
Age	Severe (IC < 60 seconds): mean 68.6 (SD 7.7)	Severe (IC < 60 seconds): mean 64.3 (SD 7.6)
	Moderate (IC 60–120 seconds): mean 67.0 (SD 6.7)	Moderate (IC 60–120 seconds): mean 64.8 (SD 7.7)
	Mild (IC > 120 seconds): mean 65.0 (SD 14.4)	Mild (IC > 120 seconds): mean 61.6 (SD 13.4)
Gender	Severe (IC < 60 seconds): M 78.9%; F 21.1%	Severe (IC < 60 seconds): M 66.7%; F 33.3%
	Moderate (IC 60–120 seconds): M 84.6%; F 15.4%	Moderate (IC 60–120 seconds): M 81.3%; F 18.7%
	Mild (IC > 120 seconds): M 66.7%; F 33.3%	Mild (IC > 120 seconds): M 55.6%; F 44.4%
Smokers	Severe (IC < 60 seconds): 57.9%	Severe (IC < 60 seconds): 47.6%
	Moderate (IC 60–120 seconds): 73.1%	Moderate (IC 60–120 seconds): 46.9%
	Mild (IC > 120 seconds): 33.3%	Mild (IC > 120 seconds): 44.4%
Diabetics	Severe (IC < 60 seconds): 15.8%	Severe (IC < 60 seconds): 4.8%
	Moderate (IC 60–120 seconds): 0%	Moderate (IC 60–120 seconds): 3.1%
	Mild (IC > 120 seconds): 0%	Mild (IC > 120 seconds): 0%
Hypertension/blood pressure	All in mmHg:	All in mmHg:
	Severe (IC < 60 seconds): mean 162.1 (SD 23.3)/85.7 (SD 8.2)	SEVERE (IC < 60 seconds): mean 164.3 (SD 19.9)/92.6 (SD 10.1)
	Moderate (IC 60–120 seconds): mean 159.4 (SD 21.1)/88.6 (SD 12.3)	Moderate (IC 60–120 seconds): mean 163.3 (SD 29.8)/89.7 (SD 16.6)
	Mild (IC > 120 seconds): mean 160 (SD24.5)/83.0 (SD 12.2)	Mild (IC > 120 seconds): mean 155.7 (SD 13.2)/85.3 (SD 8.5)
Hyperlipidaemia		
Obesity or weight	Severe (IC < 60 seconds): mean 69.3 (SD 13.4) kg	Severe (IC < 60 seconds): mean 68.0 (SD 11.3) kg
	Moderate (IC 60–120 seconds): mean 72.0 (SD 11.7) kg	Moderate (IC 60–120 seconds): mean 73.4 (SD 11.7) kg
	Mild (IC > 120 seconds): mean 69.6 (SD 4.8) kg	Mild (IC > 120 seconds): mean 72.3 (9.7) kg
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	Broken ankle, one; inability to swallow, one; constipation, one; non-compliance, one	Cerebrovascular accident, one; thrombophlebitis, one; gastrointestinal upset, two; personal reasons, one
	Also, 10 patients were excluded from analysis, unclear which groups they were from	Also, 10 patients were excluded from analysis, unclear which groups they were from
	Reasons were: congestive cardiac failure, three; osteoarthritis, two; severe leg pain at rest, one; carcinoma of the stomach with secondaries in the liver, one; failure to return, one; leukaemia, one; rheumatoid arthritis, one	Reasons were: congestive cardiac failure, three; osteoarthritis, two; severe leg pain at rest, one; carcinoma of the stomach with secondaries in the liver, one; failure to return, one; leukaemia, one; rheumatoid arthritis, one
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
PFWD *n* in analysis	47	57
PFWD baseline	*PFW time (s)*:	*PFW time (s)*:
	Severe: mean 44.42 (SD 14.78)	Severe: mean 44.33 (SD 14.81)
	Moderate: mean 85.23 (SD 15.96)	Moderate: mean 88.53 (SD 17.21)
	Mild: mean 183.5 (SD 66.67)	Mild: mean 156.9 (SD 19.71)
PFWD follow-up	*PFW time (s)*:	*PFW time (s)*:
	Severe: mean 59.59 (SD 28.08)	Severe: mean 64.86 (SD 36.70)
	Moderate: mean 105.50 (SD 36.71)	Moderate: mean 97.11 (SD 36.25)
	Mild: mean 156.2 (SD 40.87)	Mild: mean 194.6 (SD 93.49)
PFWD change	*PFW time (s)*:	*PFW time (s)*:
	Severe: $p < 0.05$	Severe: $p < 0.01$
	Moderate: $p < 0.01$	Moderate: $p < 0.01$
	Mild: non-significant	Mild: non-significant
PFWD between-group comparison	*PFW time (s)*:	
	Severe: non-significant	
	Moderate: significant between-group comparison $p < 0.001$	
	Mild: non-significant	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	51	62
Vascular events follow-up		
Vascular events included	Taken from AEs	
Vascular events reported	Zero	Cerebrovascular accident, one; thrombophlebitis, one – also reported in AEs
Vascular events between-group comparison		
AEs *n* in analysis	Baseline, 51; 12 weeks, 47	Baseline, 62; 12 weeks 57
AEs follow-up		
AEs reported	4/51 (7.8%). Broken ankle, one (2%); inability to swallow, one (2%); constipation, one (2%); non-compliance, one (2%)	5/62 (8.1%). Cerebrovascular accident, one (1.6%); thrombophlebitis, one (1.6%); gastrointestinal upset, two (3.2%); personal reasons, one (1.6%)
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; PFW, pain-free walking.

Trials testing intervention against other treatments

Hobbs 2007,[82] INEXACT	
Study details	
Publication type	Hobbs 2007,[82] full report in peer-reviewed journal
Additional sources of data	None
Trial design	RCT, single centre
Country	UK
Dates of participant recruitment	NR
Sources of funding	S Hobbs is supported by a British Heart Foundation Junior Research Fellowship and the Royal College of Surgeons of England 'Lea Thomas' Research Fellowship
Intervention(s) and comparator	
Treatment groups	Cilostazol 200 mg (100 mg b.i.d.). If side effects, dosing halved for 1 week, with or without exercise
Comparator	Usual care, with or without exercise
Run-in phase	No
Treatment duration	Unclear: 3 or 6 months. Follow-up 24 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks, 24 weeks
Outcomes and measures	MWD: treadmill with constant workload, 3 km/hour at a 10% incline PFWD: as MWD AEs: patient self-report
Notes on statistics	None
Population	
Eligibility criteria	IC diagnosed by Edinburgh claudication questionnaire and reduced ABPI < 0.9, reviewed after 3–6 months; MWD 20–500 m. Excluded: significant aortoiliac disease; unable to complete treadmill assessment to absolute claudication distance; MI, TIA, CVA or PTCA in past 3 months; GFR 20 ml/minute, CHF, known predisposition for bleeding
Concomitant interventions allowed or excluded	Allowed: antiplatelets, statins, antihypertensives, ACE inhibitor Disallowed: CYP3A4 or CYP2C19 inhibitors (cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole and human immunodeficiency virus 1 protease inhibitors)
Power calculation	32 subjects were required to detect a 50% reduction in thrombin–antithrombin complex (outcome NR in this review) in the treatment groups with 80% power and a *p*-value of < 0.05
N randomised to treatments included in review	34

ACE, angiotensin-converting enzyme; CVA, cardiovascular accident; GFR, glomerular filtration rate; NR, not reported; PTCA, percutaneous transluminal coronary angioplasty.

Treatment group	Cilostazol 100 mg b.i.d.	Usual care
N randomised to treatment	16 (nine cilostazol alone, seven cilostazol plus exercise)	18 (seven usual care alone, nine usual care plus exercise)
Baseline characteristics		
Age	Mean 58 (52 to 71) years	Mean 67 (63.5 to 74) years
Gender	M 89%	M 78%
Smokers	33%	22%
Diabetics		
Hypertension/blood pressure	(*n* = 6 on antihypertensives)	(*n* = 8 on antihypertensives)
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	[NR by group. Of 38 participants recruited, four subjects withdrew after randomisation (three no longer wished to continue to participate in the trial, and one subject sustained a fractured ankle unrelated to trial participation)]	
Results		
MWD *n* in analysis	16	18
MWD baseline		
MWD follow-up		
MWD change	$p = 0.008$ mean ratio 1.69 (SD 0.59)	$p = 0.635$ mean ratio 1.09 (SD 0.34)
MWD between-group comparison	Cilostazol vs no cilostazol (combined groups, not just usual care group) effect 1.64, $p = 0.005$	
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis		
Vascular events follow-up		
Vascular events included		
Vascular events reported		
Vascular events between-group comparison		

Treatment group	Cilostazol 100 mg b.i.d.	Usual care
AEs *n* in analysis		
AEs follow-up		
AEs reported		
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

M, male; NR, not reported.

Walking distance and HRQoL outcome measures used in included studies

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
CASTLE, Hiatt 2008[48–50]	Cilostazol 200 mg	NR	NR
O'Donnell 2009[51,53–55,83]	Cilostazol 200 mg	*Treadmill with constant workload*:	SF-36
		3.2 km/hour (2 mph)	VascuQoL
		10% gradient	
Strandness 2002[56,57]	Cilostazol 200 mg	*Treadmill with constant workload*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		12.5% gradient	COM
Dawson 2000[58–60]	Cilostazol 200 mg, pentoxifylline 1200 mg	*Treadmill with graded test*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		0% gradient with a 3.5% increase in gradient every 3 minutes	
Beebe 1999[61]	Cilostazol 200 mg	*Treadmill with constant workload*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		12.5% gradient	COM
Otsuka 21-94-301[34]	Cilostazol 200 mg, pentoxifylline 1200 mg	*Treadmill with constant workload*:	NR
		3.2 km/hour (2 mph)	
		12.5% gradient	
Otsuka 21-98-213[34]	Cilostazol 200 mg, pentoxifylline 1200 mg	*Treadmill with constant workload*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		12.5% gradient	COM
Money 1998[62]	Cilostazol 200 mg	*Treadmill with graded test*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		0% gradient with a 3.5% increase in gradient every 3 minutes	
Dawson 1998[63]	Cilostazol 200 mg	*Treadmill with constant workload*:	NR
		3.2 km/hour (2 mph)	
		12.5% gradient	
Elam 1998[64]	Cilostazol 200 mg	*Treadmill with graded test*:	NR
		3.2 km/hour (2 mph)	
		0% gradient with a 3.5% increase in gradient every 3 minutes	
Otsuka 21-95-201[34]	Cilostazol 200 mg	*Treadmill with constant workload*:	SF-36
		3.2 km/hour (2 mph)	WIQ
		12.5% gradient	
INEXACT, Hobbs 2007[82]	Cilostazol 200 mg, cilostazol 200 mg plus supervised exercise	*Treadmill with constant workload*:	NR
		3 km/hour	
		10% gradient	
Spengel 2002[47]	Naftidrofuryl oxalate 600 mg	Estimated by patient	CLAU-S
Kieffer 2001[65]	Naftidrofuryl oxalate 600 mg	*Treadmill with constant workload*:	NR
		3.2 km/hour (2 mph)	
		10% gradient	
Adhoute 1986[66]	Naftidrofuryl oxalate 600 mg	*Treadmill with constant workload*:	NR
		3.2 km/hour (2 mph)	
		10% gradient	

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
Trubestein 1984[67]	Naftidrofuryl oxalate 600 mg	*Treadmill with constant workload*: 5 km/hour 10% gradient, performed twice with at least 20 minutes interval	NR
Ruckley 1978[68]	Naftidrofuryl oxalate 300 mg	Unclear if treadmill used < 100 yards = severe 100–200 yards = moderate > 200 yards = mild	NR
Dettori 1989[69]	Pentoxifylline 1200 mg	*Treadmill with varied workload*: 3 km/hour. If PFW > 30 minutes, higher speed was used in the second test (5 km/hour) 10% gradient	NR
Creager 2008[70]	Pentoxifylline 1200 mg	*Treadmill with graded test*: 3.2 km/hour (2 mph) 0% gradient, increased by 2% every 2 minutes	SF-36 WIQ
Lindgarde 1989[71]	Pentoxifylline 1200 mg	*Treadmill with constant workload*: 3.2 km/hour (2 mph) 12.5% gradient	NR
Porter 1982[72,74] and Gillings 1987[73,75]	Pentoxifylline 1200 mg	*Treadmill with constant workload*: 1.5 mph 7° gradient, two treadmill tests were performed at 30- to 60-minute intervals and the mean of the two tests used	NR
Gallus 1985[76]	Pentoxifylline 1200 mg	*Treadmill with constant workload*: 4 km/hour 10° gradient	NR
Di Perri 1983[77]	Pentoxifylline 1200 mg	Absolute distance covered by walking on horizontal level at metronome controlled speed of 120 steps/minute. Walking test was performed three times and a mean taken	NR
O'Hara 1988[78,79]	Inositol nicotinate 4 g	Training device (pair of stirrups in a metal frame), which simulated box-stepping. Elapsed time and number of steps to claudication and time to recovery were recorded. Waist-band pedometer to record 'similar weekly walks'	NR
Kiff 1988[80]	Inositol nicotinate 4 g	*Treadmill with constant workload*: 10% gradient	NR
Head 1986[81]	Inositol nicotinate 4 g	Time to claudication. Patients climbed up and down the first two steps of a standard ladder in time with a metronome set at 80 beats/minute leading with the worse leg	NR

mph, miles per hour; NR, not reported.

Appendix 5

Statistical methods used within meta-analysis

We present the basic details for the meta-analysis of the data described in this report.

For treatment j in study i, we have an observation vector, y_{ij}, such that:

$$y_{ij} = \left(\bar{x}_{ij}, \frac{s_{ij}^2}{n_{ij}} \right),$$

where $\bar{x}_{ij}$ is the sample mean for treatment j in study i, and $s_{ij}/\sqrt{n_{ij}}$ is the standard error for treatment j in study i.

We assume that the sample means, $\bar{x}_{ij}$, are normally distributed such that:

$$\bar{x}_{ij} \sim N\left(\mu_{ij}, \frac{\sigma^2}{n_{ij}} \right),$$

and that $\mu_{ij} = \phi_1 + \theta_{ij}$.

ϕ_i is the effect of study i, and θ_{ij} is the effect of treatment j in study i.

We treat the ϕ_i as nuisance parameters with fixed (but unknown) study effects and give them weak prior distributions such that $\phi_1 \sim N(0,10{,}000)$.

We assume a random (treatment) effects model in which the θ_{ij} are assumed to come from a common population distribution such that $\theta_{ij} \sim N(\mu_{\theta 1}, \tau^2)$. To make the parameters identifiable, we set $\mu_{\theta 1} = 0$ so that ϕ_i is the effect of the control group in study i, and $\mu_{\theta 1}$ is the population mean effect of treatment j relative to treatment 1.

We give $\mu_{\theta 1}, j \neq 1$ a weak prior distribution such that $\theta_{ij} \sim N\left(\mu_{\theta 1}, \tau^2\right)$.

τ represents the between-study SD, which we give a prior uniform distribution, $\tau \sim U(0,10)$.

We assume that the sample variances, s_{ij}^2, are gamma distributed such that:

$$s_{ij}^2 \sim Gamma\left(\frac{n_{ij}-1}{2}, \frac{n_{ij}-1}{2\sigma^2} \right)$$

The model is completed by giving the log of the population SD a prior uniform distribution such that $\log(\sigma) \sim U(0,10)$.

The model for the network meta-analyses differs from this basic model in two particular ways. First, the estimates of treatment effect within each study are represented as functions of each treatment effect relative to placebo. Second, it is acknowledged that three of the studies are multi-arm studies in which there will be correlation between treatment effects.

For each study it was assumed that the sample SDs were the same in each treatment arm of the study within study.

Sample SDs on the log scale generally had to be derived. In some cases, these were derived from the mean and CI for the difference between treatments in geometric mean change from baseline; in others it was derived from the treatment mean changes from baseline and the *p*-value for the comparison between treatments.

Appendix 6

Economic evaluation checklist

Drummond adapted criteria

For details see Drummond and Jefferson.[133]

Criteria	Guest 2005[90]	Ratcliffe 2005[91]
1. Was a well-defined question posed in answerable form?	Yes	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes	Unclear
3. Was the effectiveness of the programme or services established?	Yes	Yes
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes	Unclear
5. Were costs and consequences measured accurately in appropriate physical units?	Yes	Unclear
6. Were the cost and consequences valued credibly?	Yes	Unclear
7. Were costs and consequences adjusted for differential timing?	Not available	Not available
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Unclear
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	Unclear
Consensus on Health Economic Criteria list (Evers 2005[134])		
11. Is the study population clearly described?	Yes	Yes
12. Are competing alternatives clearly described?	Yes	Yes
13. Is a well-defined research question posed in answerable form?	Yes	Yes
14. Is the economic study design appropriate to the stated objective?	Yes	Yes
15. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes
16. Is the actual perspective chosen appropriate?	Yes	Yes
17. Are all important and relevant costs for each alternative identified?	Yes	Unclear
18. Are all costs measured appropriately in physical units?	Yes	Unclear
19. Are costs valued appropriately?	Yes	Unclear
20. Are all important and relevant outcomes for each alternative identified?	Yes	Unclear
21. Are all outcomes measured appropriately?	Yes	Yes
22. Are outcomes valued appropriately?	Not available	Yes
23. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes
24. Are all future costs and outcomes discounted appropriately?	Not available	Not available
25. Are all important variables, whose values are uncertain, appropriately subjected to SA?	Yes	Unclear
26. Do the conclusions follow from the data reported?	Yes	Yes
27. Does the study discuss the generalisability of the results to other settings and patient/client groups?	No	Unclear
28. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Unclear
29. Are ethical and distributional issues discussed appropriately?	No	Unclear

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We look forward to hearing from you.

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ISSN 1366-5278