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Title: Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Hazel Squires was the Assessment Group lead, 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.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the nine departments that comprise 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 and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute of Health and Clinical Excellence. 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 Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

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.

DEFINITION OF TERMS

Arithmetic mean	A measure of central tendancy calculated as the sum of all 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 tendancy calculated by multiplying a series of numbers and taking the nth 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
Prior distribution	A representation of the knowledge associated with the true value of a population parameter in addition to any sample data.
Posterior distribution	A representation of the knowledge associated with the true value of a population parameter after combining the prior distribution with 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
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
ITT	Intention to treat
LOCF	Last observation carried forward
Log	Logarithm
LY G	Life years gained
MWD	Maximum walking distance
NICE	National Institute of Health and Clinical Excellence
NR	Not reported
PAD	Peripheral arterial disease
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PFWD	Pain-free walking distance
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	36-item short form
t.i.d.	Three times daily
USA	United States of America
UK	United Kingdom
WHOQoL	World Health Organization Quality of Life
WIQ	Walking Impairment Questionnaire

2 EXECUTIVE SUMMARY

2.1 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 age 55 and 74 years within the UK. The most common symptom of PAD is intermittent claudication (IC), characterized 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, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate.

2.2 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 conventional management:

- cilostazol;
- naftidrofuryl oxalate;
- pentoxifylline;
- inositol nicotinate.

2.3 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 conventional management. Electronic bibliographic databases were searched from April to June 2010 (MEDLINE, MEDLINE in-Process, EMBASE, Cochrane Library databases, CINAHL, Web of Science and 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 (ABPI), cardiovascular events, mortality, adverse events 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 for PAD from a NHS

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 time 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 to estimate the QALYs required in order for each of the drugs to be cost-effective at a range of willingness to pay thresholds. There was only one manufacturer submission (Otsuka) for this assessment and no economic model was provided.

2.4 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 comparison of cilostazol and pentoxifylline, and cilostazol with usual care.

There was evidence that walking distance outcomes were significantly improved by both cilostazol and naftidrofuryl oxalate. It was not possible to include inositol nicotinate within the meta-analysis of MWD and PFWD due to the lack of 24-month data, however the shorter term data did not suggest a significant effect. Adverse events were minor for all drugs and included headaches and gastro-intestinal difficulties. Incidence of serious adverse events, 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 is limited as outcomes were often partially reported, not reported or not measured. There is some evidence that cilostazol improves physical function, but does not effect mental health or overall quality of life. There is very limited data for naftidrofuryl and pentoxifylline. Naftidrofuryl 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 SF-36 HRQoL data were obtained from one RCT by contacting the leading author and the data were used in the economic evaluation.

The economic evaluation suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline and has a cost per QALY gained of around £6,070 compared with no vasoactive drug. This result is reasonably robust to changes within the key model assumptions. It was not possible to include inositol niotinate within the base case analysis due to lack of data; however it would have to demonstrate

considerably greater impacts upon quality of life than the other vasoactive drugs being assessed for it to be considered to be cost-effective, due to its more expensive acquisition cost.

The base case cost-effectiveness conclusions do not change for the majority of sensitivity analyses undertaken. The exception to this is the results of an exploratory subgroup analysis of patients with more severe IC for which successful vasoactive drug treatment may prevent the need for angioplasty. The comparator for this analysis is for angioplasty to be undertaken immediately. When it is assumed within this analysis that the the utility associated with angioplasty is higher than the utility associated with naftidrofuryl, no vasoactive drug would be considered to be the most cost-effective option at a willingness to pay threshold of £20,000 per QALY gained.

2.5 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, 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.

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 alter the conclusions.

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 with a sample size 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. 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 adverse events; 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. A value of information analysis has not been undertaken due to the uncertainties associated with the utility outcomes which it was not possible to fully quantify within the PSA.

Cardiovascular adverse events 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, the cost-effectiveness results could alter substantially due to the otherwise small impact on costs and quality of life associated with these drugs.

2.6 Conclusions

Naftidrofuryl and cilostazol are both effective treatments for this patient population, with minimal serious adverse events; however naftidrofuryl is the only treatment which is likely to be considered to be cost-effective. 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 with those associated with supervised exercise programs and other treatments such as angioplasty. Importantly, there are currently no long term safety trials for naftidrofuryl; 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.

3 BACKGROUND

3.1 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 to IV).[1] The commonest symptom of PAD is IC (stage II), characterized 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 produce necrosis and gangrene (stage IV).[1] Other symptoms of PAD include cold or numbness in the feet, hair-loss or non-healing sores on the legs, feet or toes.[2]

IC 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 of blood flow needed for muscle metabolism.[3] This pain is relieved with rest, due to 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

IC is most commonly experienced in the calf and is associated with PAD in the femoropopliteal segment.[2] If PAD is present at the aorto-iliac level, this can result in pain in the thigh, hip or buttock.[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, hyperhomocysteinemia, raised C-reactive protein and a sedentary lifestyle.[3,4]

IC is not itself life threatening, but it is estimated that 40% to 60% of claudicants have coronary artery disease as well[6] Patients with IC are at higher risk of cardiovascular mortality than PAD patients who do not have claudication.[7] People with PAD are approximately two to three times more likely to suffer myocardial infarction or stroke as other people of their sex and age.[2,8] Risk of cardiovascular mortality is approximately the same in 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 ABPI, chronic renal insufficiency or diabetes mellitus.[8] Few patients with IC progress to critical limb ischaemia.[3] Fewer than 5% of patients per five 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 quantified in any documentation identified. It has been estimated (Edinburgh Artery Study) 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%.[10] 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 women, but in older age groups prevalence of IC is similar in both sexes.[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 36 Item Short Form (SF-36), this population has 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 at primary or secondary care. It is estimated from population-based studies that only around 50% - 90% of patients with IC present for medical attention[3] since a large proportion of people assume it is a natural part of ageing. Although PAD is a chronic disease, only around a 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 intial 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 a long term prophylaxis of myocardial infarction 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 is may be 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.(Norgren et al[3])

Measurement of disease

Not all patients with PAD will experience claudication symptoms, and not all claudication symptoms are caused by PAD. As such, those with PAD should be assessed for claudication even if no pain is present, and patients with claudication should have a confirmation of PAD as the cause. Diagnosis and classification of chronic limb ischaemia involves an assessment of the presence, absence and type of pain the patient is experiencing, and measurement of a patient's ankle-brachial pressure index (ABPI).

Claudication pain is commonly classified according to the Fontaine scheme[1] as described above, or by the Rutherford scheme[13] (Table 1). MWD and PFWD can be assessed with the use of a graded treadmill test,[14] although in primary care this 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.[16]

Table 1: The Fontaine classification for chronic critical limb ischaemia (adapted from Norgren 2007[14])

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	IC, PFWD greater than 200 metres	I	1	Mild claudication, completion of treadmill test, after exercise ABPI >50mmHg and <20mmHg lower than resting value
IIb	IC, PFWD less than 200 metres	I	2	Moderate claudication, inbetween categories 1 and 3
		I	3	Severe claudication, cannot complete standard treadmill exercise with after exercise ABPI <50mmHg
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss
PFWD, pain free walking distance; ABPI, ankle-brachial pressure index				

For those with Fontaine stage II, to ensure that the claudication pain is not caused by another condition, a PAD diagnosis should be confirmed by measuring a patient's ankle-brachial pressure index (ABPI) at rest. 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[16] consider a ABPI of less than or equal to 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. Whilst 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 greater than 1.3 should be referred to a vascular specialist for assessment.

MWD (also known as absolute claudication distance) is a measure of how far a paient 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. EMA (European Medicines Agency) recommend treadmill tests to assess claudication distances.[17] EMA specify two internationally recognised treadmill protocols.[17] Constant workload treadmill protocols involve the treadmill being set at a fixed slope at a fixed speed.[17] 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.[17] Both these types of test are valid but they are not interchangeable, i.e. trials should employ the same protocol throughout the trial.[17]

3.2 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 of myocardial infarction and stroke. The management of claudication symptoms includes the recommendation to exercise. Supervised exercise programmes are the most effective form of exercise therapy[18] 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 since 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, particularly in secondary care (personal communication with team of clinical experts, September 2010).

Clinical practice is variable between clinicians for prescribing vasoactive drugs for IC patients whose symptoms continue despite a period of conventional management. Some clinicians will assess whether angioplasty is appropriate within this patient group and if so undertake this immediately. If angioplasty is either 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, vasoactive drugs for PAD may negate or delay the need for angioplasty.

There is thought to be some variability around treatment with these drugs according to geographical location. This is likely to be due to greater demand upon resources within regions with higher prevalence of the disease. Treatment may also vary depending upon whether it is provided within primary or secondary care.

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. NICE guidance is currently underway regarding the diagnosis and management of lower limb peripheral arterial disease in adults; this is due to be published in October 2012.[19] NICE Guidance is also being developed for Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90), due to be published in December 2010,[20] within which patients with PAD are considered as a subgroup within this guidance.

The Scottish Intercollegiate Guidelines Network (SIGN) have developed and published guidelines around the diagnosis and management of PAD within Scotland[2] This recommends that patients with intermittent claudication, in particular over a short distance, should be considered for treatment with cilostazol. If cilostazol is ineffective after three months, or if adverse effects prevent compliance with therapy, the drug should be stopped. It also recommends that patients with intermittent claudication and who have a poor quality of life may be considered for treatment with naftidrofuryl.

3.3 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 two-fold, 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 will 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[21]

Other manufacturers: None

Therapeutic classification: phosphodiesterase III inhibitor which acts as a direct arterial vasodilator and also inhibits platelet aggregation.[22]

Dosage, length of treatment and route: oral, at a dose of 100mg twice daily (200mg 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 maximal and pain-free walking distances in patients with IC, who do not have rest pain and who do not have evidence of peripheral tissue necrosis (PAD Fontaine stage II).[21]
Contraindications: Known hypersensitivity to cilostazol or to any of the excipients; Severe renal impairment: creatinine clearance of 25 ml/min; Moderate or severe hepatic impairment; Congestive heart failure; Pregnancy; Patients with any known predisposition to bleeding (e.g. active peptic ulceration, recent (within six months) haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension); Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and in patients with prolongation of the QTc interval.[21]
Warnings: Patients should be warned to report any episode of bleeding or easy bruising whilst 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 CYP3A4 and CYP2C19 or with CYP3A4 substrates, when prescribing cilostazol for patients with atrial or ventricular ectopy and patients with atrial fibrillation or flutter, with any other agent which has the potential to reduce blood pressure, or when when co-administering cilostazol with any other agents that inhibit platelet aggregation. Please see the Summary of Product Characteristics[21] for further details.

Naftidrofuryl oxalate
Brand name, manufacturer: (Praxilene, Merk Serono)[21]
Other manufacturers: Actavis UK, Kent Pharmaceuticals, Mylan, Teva.[23]
Therapeutic classification: peripheral vasodilator which selectively blocks vascular and platelet 5-hydroxytryptamine (5-HT2) receptors.[22]
Dosage, length of treatment and route: oral, one or two 100mg capsules three times daily (300mg or 600mg daily dose) for a minimum of three months, or at the discretion of the physician.[21]
Licensed indications: Naftidrofuryl oxalate has a UK marketing authorisation for peripheral vascular disorders in cluding IC.[21]
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.[21]
Contraindications: Hypersensitivity to the drug. Patients with a history of hyperoxaluria or recurrent calcium-containing stones.[21]

Warnings: A sufficient amount of liquid should be taken during treatment to maintain an adequate level of diuresis.[21]

Pentoxifylline

Brand name, manufacturer: (Trental 400, Sanofi-Aventis)[21]

Other manufacturers: Apotex UK.[23]

Therapeutic classification: peripheral vasodilator that is derived from methylxanthine[22]

Dosage, length of treatment and route: Recommended initial dose, 1 tablet (400 mg) three times daily (1200mg daily dose); two tablets daily may prove sufficient in some patients (800mg 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 below 30ml/min) a dose reduction by approximately 30% to 50% may be necessary, guided by individual tolerance.[21]

Licensed indications: UK marketing authorisation for the treatment of PAD, including IC and rest pain.[21]

Contraindications: not suitable for children. Known hypersensitivity to the active constituent, pentoxifylline other methyl xanthines or any of the excipients. Patients with cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction and severe cardiac arrhythmias.[21]

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. Please see the Summary of Product Characteristics[21] for further details.

Inositol nicotinate

Brand name, manufacturer: (Hepoxal, Genus Pharmaceuticals)[21]

Other manufacturers: Mylan.[23]

Therapeutic classification: peripheral vasodilator thought to work by slowing the release of nicotinic acid.[22]

Dosage, length of treatment and route: The usual dose is 2 x 500mg tablets three times daily (3g daily dose). The dose may be increased to 4g 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 myocardial infarction 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 sub-groups

No specific subgroups have been identified for consideration within the effectiveness review. However, there is a subgroup of patients who have 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, particularly in secondary care (personal communication with team of clinical experts, September 2010). The only evidence available around current usage of the vasoactive drugs for PAD within England and Wales is the Prescription Costs Analysis England 2009,[24] from which it is estimated that the proportionate market share for cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate is 29%, 52%, 4% and 15% respectively.

Anticipated costs associated with intervention

As described in Section 3.2, 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.[25] 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. Naftidrofuryl oxalate is available both as a generic drug, at a lower price, and produced by Praxilene, the original patent holder.

Table 2: Cost of drugs

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

4 DEFINITION OF THE DECISION PROBLEM

This review will assess the clinical and cost-effectiveness of vasoactive drugs for the treatment of IC due to PAD in adults whose symptoms continue despite a period of conventional management. Conventional management usually involves three to six months of conservative treatment that would consist of risk modification, usually with a statin, aspirin, smoking cessation advice and advice to exercise (personal communication with team of clinical experts, July 2010).

4.1 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 conventional 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 is considered 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 no vasoactive drugs.

Outcomes

- MWD
- PFWD
- ABPI
- Vascular events (including interventions and requirement of hospitalisation)
- Mortality
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

4.2 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 conventional 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.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 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-present

MEDLINE in-Process and Other Non-Indexed Citations: Ovid. 1950-present

EMBASE: Ovid. 1980-present

Cochrane Library: Wiley Interscience

Cochrane Database of Systematic Reviews (CDR). 1996-present

Database of Abstracts of Reviews of Effects (DARE). 1995-present

Cochrane Central Register of Controlled Trials (CCRT). 1995-present

Cochrane Methodology Register. 1904-present

Health Technology Assessment Database (HTA). 1995-present

NHS Economic Evaluation Database (NHS EED). 1995-present

CINAHL: EBSCO. 1982-present

Web of Science Citation Index: Web of Knowledge. 1899-present

Conference Proceedings Citation Index: Web of Knowledge. 1990-present

BIOSIS Previews: Web of Knowledge. 1969-present

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

The National Research Register: NIHR. 2000-2007

The MetaRegister of Controlled Trials: Springer Science + Business Media. 2000-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.

5.1.2 Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria were taken from the scope provided by NICE,[22] 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 conventional management

Comparators

- placebo
- usual care of PAD without vasoactive drugs
- vasoactive drugs compared with each other

Outcomes

- MWD
- PFWD
- ABPI
- cardiovascular events (including interventions and requirement of hospitalisation)
- mortality
- adverse effects of treatment

- health-related quality of life (HRQoL)

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 (that is, 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 was presented; studies that did not present data for the included outcomes.

Studies retrieved for full paper screening which were excluded were 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.

5.1.3 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 Report No.4,[26] and quality relating to studies of PAD was assessed according to criteria developed by EMA.[26] 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.

5.1.4 Data synthesis methods

Pre-specified outcomes were tabulated and discussed within a descriptive synthesis. MWD and PFWD was synthesised across studies using meta-analysis models. Separate analyses were conducted based on the evaluation of cilostazol on MWD based on the studies described in the Cochrane review (Robless *et al* 2008),[27] 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;(Lunn *et al*., 2000[28]) 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 to week 24 for studies included in the Cochrane review,[27] the logarithm of the geometric mean change from baseline in MWD compared to week 24, and the logarithm of the geometric mean change from baseline in PFWD compared to week 24.

Individual studies generally reported treatment effects in terms of the ratio of the geometric mean change from baseline. Taking the logarithm 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 logarithms of arithmetic means does not produce additive results on the log scale.

Results were reported in terms of the posterior mean difference between treatments and 95% credible interval. 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 together with the 95% credible interval is also presented.

5.2 Results

5.2.1 Quantity and quality of research available

5.2.1.1 Quantity of research available

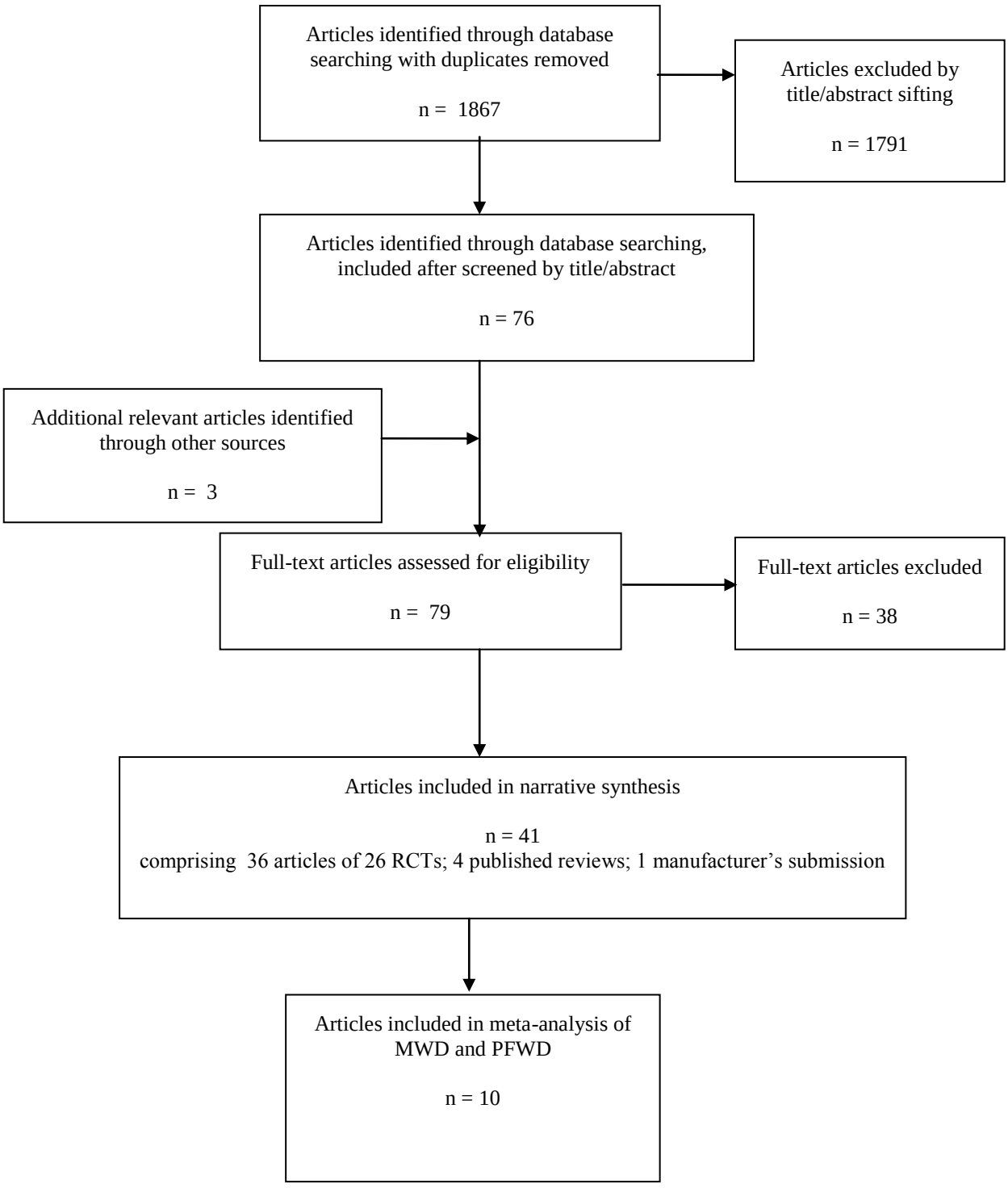
The search for clinical effectiveness literature yielded 1867 article citations after duplicates had been removed. Figure 1 shows study selection. Citations presenting purely economic analyses were not included in this chapter. Trials excluded at full paper screening stage (Figure 1) are in Appendix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

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

Four published systematic reviews[27,29,30,31] were included in this review as they provided additional data from the included RCTs which was unavailable from the published trial reports. In addition, the manufacturer's submission to NICE of cilostazol[32] also provided additional data from the included RCTs which was 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.[33,34,35,36,37,38,39,40,41,42,43,44] No additional RCTs were identified from these excluded reviews.

Figure 1: Flow diagram of study inclusion (adapted from PRISMA[45])



Twenty-six RCTs were included in this review. One of these was a pooled analysis of three RCTs run as a study programme (Spengel)[46] 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 sexes included, and age ranges within 35 to 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 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,[27,31,29] and the manufacturer's submission to NICE.[32] Additional information on naftidrofuryl oxalate trials was available from one published systematic review.[30]

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 Otsuka 21-98-214-01 Hiatt 2008[47,48,49]	Cilostazol 200mg	Placebo			
O'Donnell 2009[50,51,52,53,54]	Cilostazol 200mg	Placebo			
Strandness 2002. Otsuka 21-94-201[55,56]	Cilostazol 200mg	Placebo			Cilostazol 100mg daily dose
Dawson 2000. Otsuka 21-96-202[57,58,59]	Cilostazol 200mg	Placebo	Pentoxifylline 1200mg		
Beebe 1999. Otsuka 21-92-202[60]	Cilostazol 200mg	Placebo			Cilostazol 100mg daily dose
Otsuka 21-94-301[32]	Cilostazol 200mg	Placebo	Pentoxifylline 1200mg		
Otsuka 21-98-213[32]	Cilostazol 200mg	Placebo	Pentoxifylline 1200mg		
Money 1998. Otsuka 21-94-203[61]	Cilostazol 200mg	Placebo			
Dawson 1998. Otsuka 21-90-201[62]	Cilostazol 200mg	Placebo			
Elam 1998. Otsuka 21-93-201[63]	Cilostazol 200mg	Placebo			
Otsuka 21-95-201[32]	Cilostazol 200mg	Placebo			Cilostazol 300mg
Spengel 2002[46]	Naftidrofuryl 600mg	Placebo			
Kieffer 2001[64]	Naftidrofuryl 600mg	Placebo			
Adhoute 1986[65]	Naftidrofuryl 600mg	Placebo			
Trubestein 1984[66]	Naftidrofuryl 600mg	Placebo			
Ruckley 1978[67]	Naftidrofuryl 300mg	Placebo			
Dettori 1989[68]	Pentoxifylline 1200mg	Placebo			Acenocoumarol (dose adjusted according to INR) plus placebo; Acenocoumarol plus pentoxifylline 1200mg
Creager 2008[69]	Pentoxifylline 1200mg	Placebo			Iloprost 100micrograms plus placebo; iloprost 200micrograms plus placebo; iloprost 300micrograms plus placebo
Lindgarde 1989[70]	Pentoxifylline 1200mg	Placebo			
Porter 1982 and Gillings 1987[71,72,73,74]	Pentoxifylline 1200mg	Placebo			
Gallus 1985[75]	Pentoxifylline 1200mg	Placebo			
Di Perri 1983[76]	Pentoxifylline 1200mg	Placebo			
O'Hara 1988[77,78]	Inositol nicotinate 4g	Placebo			
Kiff 1988[79]	Inositol nicotinate 4g	Placebo			

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
Head 1986[80]	Inositol nicotinate 4g	Placebo			
INEXACT Hobbs 2005[81]	Cilostazol 200mg	Cilostazol 200mg plus supervised exercise	Supervised exercise	Usual care	

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 200mg versus placebo (11 trials);
Naftidrofuryl oxalate 600mg versus placebo (4 trials);
Naftidrofuryl oxalate 300mg versus placebo (1 trial);
Pentoxifylline 1200mg versus placebo (9 trials);
Inositol nicotinate 4g versus placebo (3 trials);
Cilostazol 200mg versus pentoxifylline 1200mg (3 trials);
Cilostazol 200mg (with or without supervised exercise) versus usual care (with or without supervised exercise) (1 trial).

The number of patients and outcomes reported for these comparisons are shown in Tables 4 to 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[48], Dettori[68]). The eleven trials comparing cilostazol versus placebo (Table 4) were the same eleven trials included in the manufacturer's submission to NICE.[32]

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 2009[50,51,52,53,54] and Hobbs 2005[81]), naftidrofuryl (Ruckley 1978[67]) and inositol nicotinate (O'Hara 1988[77,78], Kiff 1988[79] and Head 1986[80]). Most cilostazol studies took place in the USA, whilst studies of pentoxifylline and naftidrofuryl mostly took place in the USA and Europe.

Table 4: Cilostazol 200mg versus placebo

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Placebo	Outcomes reported
CASTLE study 21-98-214-01 Hiatt 2008[48]	up to 144	717	718	Mortality Cardiovascular events AEs
O'Donnell 2009[50]	24	51	55	MWD PFWD AEs HRQoL
Strandness 2002. Otsuka 21-94-201[55]	24	133	129	MWD PFWD Mortality Cardiovascular events AEs HRQoL
Dawson 2000. Otsuka 21-96-202[57]	24	227	239	MWD PFWD ABI Mortality Cardiovascular events AEs HRQoL
Beebe 1999. Otsuka 21-92-202[60]	24	175	170	MWD PFWD Mortality Cardiovascular events AEs HRQoL
Otsuka 21-94-301[32]	24	123	124	MWD PFWD Cardiovascular events AEs
Otsuka 21-98-213[32]	24	260	260	MWD PFWD Mortality AEs
Money 1998. Otsuka 21-94-203[61]	16	119	120	MWD PFWD ABI Mortality Cardiovascular events AEs HRQoL
Dawson 1998. Otsuka 21-90-201[62]	12	54	27	MWD PFWD Mortality Cardiovascular events AEs
Elam 1998. Otsuka 21-93-201[63]	12	95	94	MWD PFWD ABI Mortality Cardiovascular events AEs HRQoL
Otsuka 21-95-201[32]	12	72	70	MWD PFWD Mortality AEs HRQoL

Table 5: Naftidrofuryl 600mg versus placebo

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Outcomes
Spengel 2002[46]	24	382	372	PFWD Mortality AEs HRQoL
Kieffer 2001[64]	24	98	98	MWD PFWD ABI Cardiovascular events AEs
Adhoute 1986[65]	24	64	54	PFWD ABI AEs
Trubestein 1984[66]	12	54	50	MWD PFWD AEs

Table 6: Naftidrofuryl 300mg versus placebo

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Outcomes
Ruckley 1978[67]	12	25	25	PFWD AEs

Table 7: Pentoxifylline 1200mg versus placebo

Trial	Treatment duration (weeks)	Number in analysis Pentoxifylline	Number in analysis Placebo	Outcomes
Dettori 1989[68]	52	37	37	PFWtime ABI Mortality Cardiovascular events
Creager 2008[69]	24	86	84	MWD PFWD Mortality Cardiovascular events AEs HRQoL
Dawson 2000. 21-96-202[57]	24	232	239	MWD PFWD ABI Mortality Cardiovascular events AEs
Lindgarde 1989[70]	24	76	74	MWD PFWD AEs
Porter 1982[73]	24	67	61	MWD PFWD Cardiovascular events that lead to withdrawal AEs
Otsuka 21-94-301[32]	24	123	124	MWD PFWD Cardiovascular events AEs
Otsuka 21-98-213[32]	24	262	262	MWD PFWD Mortality AEs
Gallus 1985[75]	8	25	23	MWD PFWD Mortality Cardiovascular events that lead to withdrawal
Di Perri 1983[76]	8	12	12	MWD

Table 8: Inositol nicotinate 4g versus placebo

Trial	Treatment duration (weeks)	Number in analysis Inositol nicotinate	Number in analysis Placebo	Outcomes
O'Hara 1988[77]	12	62	58	PFWpaces Mortality Cardiovascular events that lead to withdrawal AEs that lead to withdrawal
Kiff 1988[79]	12	40	40	MWD ABI Cardiovascular events that lead to withdrawal AEs that lead to withdrawal
Head 1986[80]	12	51	62	Time to claudication Cardiovascular events that lead to withdrawal AEs that lead to withdrawal

Table 9: Cilostazol 200mg versus pentoxifylline 1200mg

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Pentoxifylline	Outcomes
Dawson 2000. 21-96-202[57]	24	227	232	MWD PFWD ABI Mortality Cardiovascular events AEs
Otsuka 21-94-301[32]	24	123	123	MWD PFWD Cardiovascular events AEs
Otsuka 21-98-213[32]	24	260	260	MWD PFWD Mortality AEs

Table 10: Cilostazol 200mg (with or without supervised exercise) versus usual care (with or without supervised exercise)

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Usual care	Outcomes
INEXACT Hobbs 2005[81]	24	16	18	MWD PFWD

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

Trial name	Treatment and dose	Location	Number participants from UK
CASTLE Otsuka 21-98-214-01 Hiatt 2008[47,48,49]	Cilostazol 200mg	USA	0
O'Donnell 2009[50,51,52,53,54]	Cilostazol 200mg	UK (Northern Ireland)	106
Strandness 2002. Otsuka 21-94-201[55,56]	Cilostazol 200mg	USA	0
Dawson 2000. Otsuka 21-96-202[57,58,59]	Cilostazol 200mg Pentoxifylline 1200mg	USA	0
Beebe 1999. Otsuka 21-92-202[60]	Cilostazol 200mg	USA	0
Otsuka 21-94-301[32]	Cilostazol 200mg Pentoxifylline 1200mg	USA	0
Otsuka 21-98-213[32]	Cilostazol 200mg Pentoxifylline 1200mg	USA	0
Money 1998. Otsuka 21-94-203[61]	Cilostazol 200mg	USA	0
Dawson 1998. Otsuka 21-90-201[62]	Cilostazol 200mg	USA	0
Elam 1998. Otsuka 21-93-201[63]	Cilostazol 200mg	USA	0
Otsuka 21-95-201[32]	Cilostazol 200mg	USA	0
Spengel 2002[46]	Naftidrofuryl 600mg	Germany, France, Belgium	0
INEXACT Hobbs 2005[81]	Cilostazol 200mg Cilostazol 200mg plus supervised exercise	UK	38
Kieffer 2001[64]	Naftidrofuryl 600mg	USA	0
Adhoute 1986[65,65]	Naftidrofuryl 600mg	France	0
Trubestein 1984[66]	Naftidrofuryl 600mg	Germany	0
Ruckley 1978[67]	Naftidrofuryl 300mg	UK	50
Dettori 1989[68]	Pentoxifylline 1200mg	Italy	0
Creager 2008[69]	Pentoxifylline 1200mg	USA	0
Lindgarde 1989[70]	Pentoxifylline 1200mg	Sweden, Denmark	0
Porter 1982 and Gillings 1987[71,72,73,74]	Pentoxifylline 1200mg	USA	0
Gallus 1985[75]	Pentoxifylline 1200mg	Australia	0
Di Perri 1983[76]	Pentoxifylline 1200mg	Italy	0
O'Hara 1988[77,78]	Inositol nicotinate 4g	UK	120
Kiff 1988[79]	Inositol nicotinate 4g	UK	80
Head 1986[80]	Inositol nicotinate 4g	UK	123

5.2.1.2 Quality of research available

Details of the quality assessment scores for each trial are listed in Appendix 3. Across the four sets of studies, Centre for Reviews and Dissemination (CRD) items which relate to study quality (as listed in 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 drop-outs as this was poorly reported. In some cases there is evidence of selective reporting of outcomes.

EMA 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 symptoms. These items were usually met, except in the case of inositol nicotinate. 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 were an issue in studies of cilostazol and inositol nicotinate, but less problematic in studies of 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 the data. The use of two treadmill tests separated by at least a week at baseline and the selection of patients with less than a 25% change in baseline is recommended by EMA to minimise the effect these types of patients may have on results. These items were only adhered to sometimes and may therefore introduce variability to the 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 drop-outs was poorly reported in Elam 1998, Dawson 1998, Money 1998, Hiatt 2008, Otsuka study 21-95-201, Hobbs 2005 and Otsuka 21-94-301,[63,62,61,32,81,48,32] and may be a source of bias. There was some evidence of selective reporting in Strandness 2002, Elam 1998 and Dawson 2000,[55,63,57] as data was found in published systematic reviews. For EMA items, quality was largely good, though there is potential for some problems, mainly due to poor reporting. Treatment duration varied between studies, with only Strandness 2002, Beebe 1999, Hiatt 2008, O'Donnell 2009, Dawson 2000, and Otsuka unpublished studies 21-94-301 and 21-98-213[55,60,50,57,32,32] treating patients for at least 24 weeks (this will not affect

the meta analysis which only considers studies which 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. However, as baseline characteristics were largely similar for diabetes, this is unlikely to present a source of bias. Less than half of the studies stated that only patients with less than 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 these patients respond differently to treatment. A placebo run-in period was only reported by Dawson 1998 and Hiatt 2008,[62,48] for between two and six weeks in both cases. All studies reporting walking distance outcomes used a standardised treadmill test. There was, however, heterogeneity between the protocol of the tests 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 1984 and Ruckley 1978[66,67] did not score positively according to CRD criteria. 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 only stratified in Kieffer 2001[64] and proportions of diabetics are unknown for Adhoute 1986, Tubestein 1984 and Ruckley 1978;[65,66,67] only Kieffer 2001 and Adhoute 1986[64,65] selected patients with less than 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. Amongst 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 include the use of an ITT analysis, follow-up of at least 80% of participants, imbalances between drop-outs, and selective reporting of outcomes. EMA items were also only partially fulfilled. Whilst diagnosis, history of condition and treatment duration were mostly good, other items were mixed. Amongst items relating to patient characteristics, it was largely unclear whether 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 less than a 25% change in baseline assessments. Outcomes may also have been affected by the lack of a 2 to 6 week placebo run-in for Dawson 2000, Otsuka 21-94-301, Otsuka 21-98-213 and Di Perri 1983.[57,32,32,76]

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. Amongst the CRD quality assessment items, methods of randomisation and treatment allocation were poorly reported in every

case. Baseline characteristics were not similar in Head 1986.[80] 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 drop outs 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 1988 stated that IC was objectively diagnosed,[79] and only this same study stated patients had a six month history of the condition. None of the studies treated patients for 24 weeks or longer, and it was unclear in every case whether concomitant treatments were comparable across groups. Kiff 1988 and Head 1986 did not stratify for diabetes, and did not report how many were diabetic in each group.[79,80] Whilst MWD and/or PFWD were reported in O'Hara 1988 and Head 1986, neither of these studies used a treadmill test, although the alternative walking distance tests used did follow a standard protocol.[77,80]

5.2.2 Assessment of effectiveness

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

5.2.2.1 Maximum walking distance (MWD)

5.2.2.1.1 MWD narrative summary

Details of MWD results, where reported, are in Tables 12 to 17 below (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. For the ten studies of cilostazol 200mg versus placebo comparison, seven favoured cilostazol over placebo (O'Donnell[82], Strandness 21-94-201[55], Beebe 21-92-202[60], Dawson 1998 21-90-201[62], Dawson 2000 21-92-202[57], Money 21-94-203[61], Elam 21-93-201[63]), whereas three trials (the three unpublished trials) did not find any significant difference between groups (Otsuka trials 21-94-301, 21-98-213, 21-95-201[32]). As patient populations were similar across trials, in terms of disease, diabetes, hypertension, smoking and age range, the trial populations 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 section 3.1 Measurement of disease).[27] The use of the treadmill protocol (see Appendix 4) may go some way to explaining heterogeneity across trials. All three trials employing the graded test treadmill protocol reported a significantly greater improvement in the cilostazol group than in the placebo group; Dawson 2000 21-92-202[57] at 24 weeks follow-up ($p=0.0005$), Money 21-94-203[61] at 16 weeks follow-up ($p<0.05$), Elam 21-93-201[63] at 12 weeks follow-up ($p=0.004$). However,

treadmill protocol cannot explain the difference across the constant workload protocol trials, and length of follow-up cannot explain the difference between significant and non-significant results in the constant workload protocol trials.

Of the seven trials using the constant workload treadmill protocol, four reported a significantly greater improvement in the cilostazol group than in the placebo group, although for one of these trials significance was only borderline (O'Donnell)[82]; three of these had follow-up time of 24 weeks O'Donnell (p=0.048), Strandness 21-94-201[55] (p=0.0003), Beebe 21-92-202[60] (p<0.001); and the fourth trial, Dawson 1998[62] 21-90-201, had a follow-up time of 12 weeks (p<0.01). The three trials that did not find any significant difference between groups employed the constant workload treadmill protocol, and two of these trials had follow-ups of 24 weeks (trials 21-94-301 p=0.06, 21-98-213 p=0.91[32]), and the other a follow-up time of 12 weeks (21-95-201 p=0.90[32]). 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[29] included nine industry sponsored trials, of which six trials (Otsuka trials Strandness 21-94-201,[55] Dawson 2000[57] 21-96-202, Beebe[60] 21-92-202, Money[61] 21-94-203, Dawson 1998[62] 21-90-201, Elam[63] 21-93-201) found a significant difference between treatment groups, and three trials (the three trials without published trial reports) found no significant difference between cilostazol 200mg and placebo groups (Otsuka trials 21-94-301, 21-98-213, 21-95-201).[29] The Pande review presented a pooled analysis of these nine trials as a ratio of geometric means, and calculated an estimate of treatment effect[29] of 1.15 (95%CI 1.11-1.19), which significantly favoured cilostazol over placebo.[29] This analysis[29] did not include the O'Donnell trial[50] that found a borderline significant treatment effect for the 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)[52] or without diabetes (p=0.27, n=80)[82] which may reflect the small sample sizes rather than lack of actual treatment effect. The cilostazol versus placebo comparison trials which reported significant treatment effect for MWD generally also reported significant treatment effect for PFWD (section 5.2.2.2) and vice versa, however there were a couple of exceptions in that the O'Donnell[82] and Elam[63] trials which found a significant treatment effect for MWD but did not find a significant treatment effect for PFWD.

Two trials for the naftidrofuryl oxalate 600mg versus placebo comparison reported MWD; Kieffer *et al.* reported significantly greater improvement for naftidrofuryl oxalate 600mg versus placebo[64] (p<0.001), and Trubestein *et al* found no significant difference between groups.[66] It may be that this difference could be explained in terms of length of follow-up, in that Kieffer[64] had a follow-up of 24 weeks, whereas Trubestein[66] had a follow-up of 12 weeks. These trials both employed 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 (Appendix 4), however both naftidrofuryl oxalate trials (Kieffer[64], Trubestein[66]) had higher baseline MWD than the cilostazol trials that employed the constant workload treadmill protocol (Strandness 21-94-201, Beebe 21-92-202, Dawson 1998 21-90-201, O'Donnell, 21-94-301, 21-98-213, 21-95-201) (Appendix 4).[32,82] The Kieffer[64] trial found a significant treatment for PFWD (section 5.2.2.2) as well as for MWD, however the Trubestein[66] trial which had not found a significant treatment effect for MWD, did report a significant effect for PFWD favouring naftidrofuryl oxalate (section 5.2.2.2).

Of the eight trials comparing pentoxifylline versus placebo in terms of MWD, two trials significantly favoured pentoxifylline over placebo, Creager ($p=0.039$)[69] and DiPerri ($p<0.01$).[76] Of these, the DiPerri trial[76] did not use a treadmill protocol instead measuring the distance a patient could walk on a horizontal level at metronome controlled speed of 120 steps per minute, with a follow-up at eight weeks. The Creager trial[69] employed 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 2000 ($p=0.82$)[57] which 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[75], Lindgarde[70], Porter[72], Otsuka 21-98-213[32] and Otsuka 21-94-301[32]). Of these, the Gallus[75] study had a follow-up of only eight weeks (ratio of percentage change from baseline 1.05 (95%CI 0.81-1.36) which was non-significant), and the other studies had follow-up of 24 weeks, Lindgarde ($p=0.09$)[70], Porter (2-sided $p=0.32$, borderline significance if measured by 1-sided $p=0.05$)[72], Otsuka 21-98-213 ($p=0.24$)[32] and Otsuka 21-94-301 ($p=0.29$).[32] The pentoxifylline versus placebo comparison trials which reported significant treatment effect for MWD generally also reported significant treatment effect for PFWD (section 5.2.2.2) and vice versa, however there were a couple of exceptions in that the Creager trial[69] which found a significant treatment effect for MWD did not find a significant treatment effect for PFWD, and the Dawson 2000 trial did not find an effect for MWD but did find a treatment effect for PFWD (section 5.2.2.2).

For the comparison of inositol nicotinate 4g versus placebo, only the Kiff trial[79] 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.[79]

Three trials reported MWD for the comparison of cilostazol versus pentoxifylline, all with 24 weeks follow-up (Dawson 2000[57], Otsuka 21-98-213[32] and Otsuka 21-94-301[32]). Two trials found no

significant difference between the cilostazol and pentoxifylline groups, Otsuka 21-98-213 (p=0.65)[32] and Otsuka 21-94-301 (p=0.87)[32], both using the constant workload treadmill protocol. One trial, that used the graded test treadmill protocol, Dawson 2000[57] found a significantly greater improvement in MWD (p=0.0002) for the cilostazol group than for the pentoxifylline group.[57]

For the one trial, Hobbs[81], 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.[81] This trial employed the constant workload treadmill protocol and measured MWD at 24 weeks.

Table 12: Cilostazol 200mg versus placebo MWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Placebo	Treadmill protocol	Cilostazol group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
O'Donnell 2009[50]	24	51	55	Constant	161.7% mean improvement	79% mean improvement	p=0.048
Strandness 2002. Otsuka 21-94-201[56]	24	133	129	Constant	mean difference in metres 76.2 improvement	mean difference in metres 21.1 improvement	p=0.0003
Dawson 2000. Otsuka 21-96-202[57]	24	227	239	Graded	mean difference in metres 107 (SD 158) improvement	mean difference in metres 65 (SD 135) improvement	p=0.0005
Beebe 1999. Otsuka 21-92-202[60]	24	175	170	Constant	mean difference in metres 129.1 improvement	mean difference in metres 26.8 improvement	p<0.001
Money 1998. Otsuka 21-94-203[61]	16	119	120	Graded	mean difference in metres 96.4 improvement	mean difference in metres 31.4 improvement	p<0.05
Dawson 1998. Otsuka 21-90-201[62]	12	54	27	Constant	30.5% improvement	-9.3% change (worsening)	p<0.01
Elam 1998. Otsuka 21-93-201[63]	12	95	94	Graded	mean difference in metres 72.7 improvement	mean difference in metres 25.8 improvement	p=0.004

Table 13: Naftidrofuryl 600mg versus placebo MWD

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Treadmill protocol	Naftidrofuryl group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
Kieffer 2001[64]	24	98	98	Constant	mean difference in metres 158.7 improvement	mean difference in metres 28.1 improvement	p<0.001
Trubestein 1984[66]	12	54	50	Constant	mean difference in metres 122 improvement	mean difference in metres 90 improvement	non-significant

Table 14: Pentoxifylline 1200mg versus placebo MWD

Trial	Treatment duration (weeks)	Number in analysis Pentoxifylline	Number in analysis Placebo	Treadmill protocol	Pentoxifylline group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
Creager 2008[69]	24	86	84	Graded	13.90% improvement	3.30% improvement	p=0.039
Dawson 2000. 21-96-202[57]	24	232	239	Graded	mean difference in metres 64 improvement	mean difference in metres 65 improvement	p= 0.82
Lindgarde 1989[70]	24	76	74	Constant	geometric mean 50% improvement (SE 9)	geometric mean 29% improvement (SE 8)	p=0.094
Porter 1982[72]	24	67	61	Constant	geometric mean 33% improvement (SE 8)	geometric mean 20% improvement (SE 7)	2-sided p=0.316, 1-sided p=0.049
Gallus 1985[75]	8	25	23	Constant	geometric mean 23% improvement	geometric mean 17% improvement	Ratio of % change from baseline (pent/placebo) 1.05 (95%CI 0.81-1.36) non-significant
Di Perri 1983[76]	8	12	12	Not treadmill, horizontal ground	mean difference in metres 136 improvement	mean difference in metres 6 improvement	p<0.01

Table 15: Cilostazol 200mg versus pentoxifylline 1200mg MWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Pentoxifylline	Treadmill protocol	Cilostazol group Change in PFWD	Pentoxifylline group Change in PFWD	Comparison between groups
Dawson 2000. 21-96-202[57]	24	227	232	Graded	mean difference in metres 107 (SD 158) improvement	mean difference in metres 64 (SD 127) improvement	p=0.0002

Table 16: Inositol nicotinate 4g versus placebo MWD

Trial	Treatment duration (weeks)	Number in analysis Inositol nicotinate	Number in analysis Placebo	Treadmill protocol	Cilostazol group Change in PFWD	Pentoxifylline group Change in PFWD	Comparison between groups
Kiff 1998	12	40	40	Patient walked at own pace on a constant slope	mean difference in metres 65.4 improvement	mean difference in metres 102.8 improvement	non-significant

Table 17: Cilostazol 200mg (with or without supervised exercise) versus usual care (with or without supervised exercise) MWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Usual care	Treadmill protocol	Cilostazol group Change in PFWD	Usual care group Change in PFWD	Comparison between groups
INEXACT Hobbs 2005[81]	24	16 (7 with exercise, 9 without)	18 (9 with exercise, 9 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

5.2.2.1.2 MWD meta-analysis

The re-analysis of the cilostazol trials included within the Cochrane review[27] is presented in Table 18, in terms of change from baseline in absolute mean walking distance.

Table 18: Change from baseline in absolute mean walking distance (metres)[a]

Study	**Placebo** **Mean (SD)** **N**	**Cilostazol** **Mean (SD)** **N**
1. Dawson 1998[62]	4.56 (61.5) 25	84.6 (144.94) 52
2. Elam 1998[63]	36.1 (141.55) 94	79.05 (134.5) 95
3. Money 1998[61]	47.1 (124.88) 120	101.1 (154.9) 119
4. Beebe 1999[60]	26.82 (148.5) 140	129.1 (463.3) 140
5. Dawson 2000[57]	64.7 (134.61) 226	107.36 (158.4) 205
6. Strandness 2002[55]	23.2 (78.26) 125	96.41 (200.44) 124
7. Otsuka 21-95-201[32]	38.1 (69.7) 60	35.2 (72.05) 54

[a]: Cilostazol studies used in the Cochrane review (Robless *et al* 2008)

The posterior mean treatment effect for these cilostazol studies, together with the 95% credible interval, is shown in Table 19. Table 19 also shows the posterior mean of the between study standard deviation, together with the 95% credible interval.

Table 19: Posterior distribution for the change from baseline in absolute mean walking distance[a]

	Mean **95% Credible Interval**
Cilostazol random effects	57.27 (24.93, 86.57)
Cilostazol predictive distribution	57.28 (-16.40, 127.40)
Between-study SD	25.16 (1.46, 72.75)

[a]: Based on cilostazol studies used in the Cochrane review (Robless *et al* 2008)

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

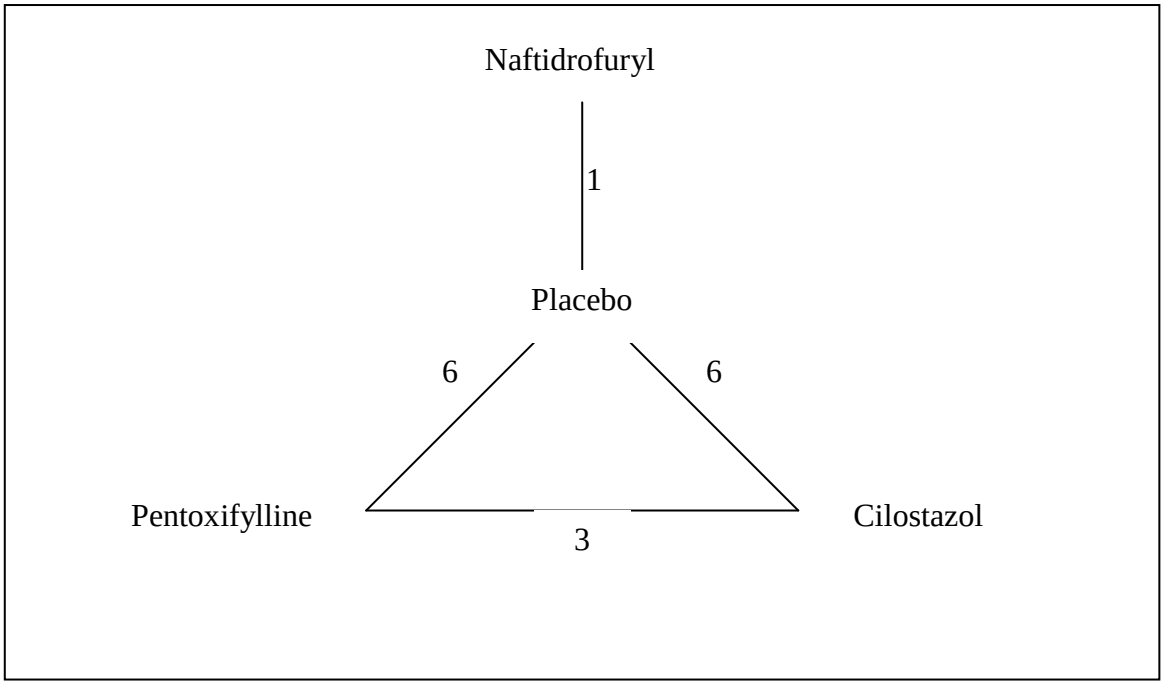
For the overall comparison of the treatment options, of the 26 studies identified by the systematic literature review, twelve studies were excluded from the meta-analysis of MWD for the reasons provided within Table 20.

Table 20: Additional studies excluded from the analysis of the change from baseline in log mean walking distance

Study, year	Drug assessed	Reason For Exclusion
Di Perri, 1983[76]	Pentoxifylline	This study was excluded because it was an 8 week study.
Gallus, 1985[75]	Pentoxifylline	This study was excluded because it was an 8 week study.
Head, 1986[80]	Inositol nicotinate	This study was excluded because it was a 12 week study and provided no information on percentage change from baseline.
Kiff, 1988[79]	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[77]	Inositol nicotinate	This study was excluded because it was a 12 week study and provided no information on MWD or PFWD.
Detorri, 1989[68]	Pentoxifylline	This study was excluded because MWD or PFWD was not collected in the study.
Otsuka, 21-98-214[47,48,49]	Cilostazol	This study provided no information on MWD or PFWD.
Adhoute, 1986[65]	Naftidrofuryl oxalate	This study provided no information on MWD or PFWD.
Trubestein, 1984[66]	Naftidrofuryl oxalate	This study provided no information on percentage change from baseline in MWD or PFWD.
Ruckley, 1978[67]	Naftidrofuryl oxalate	This study was excluded because it was a comparison of naftidrofuryl oxalate 300mg daily and provided no information on percentage change from baseline in MWD or PFWD.
Hobbs, 2005[81]	Cilostazol	This study used Best Medical Treatment as the comparator (may be alongside supervised exercise).
Thompson, 2002[33]	Cilostazol	This report is a meta-analysis of eight trials and was excluded to avoid double-counting studies.

The evidence base for the logarithm 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.

Figure 2: Network of evidence used in the analysis of the change from baseline in log mean walking distance (log metres)



The 10 studies (leading to 16 comparisons) included within the meta-analysis of MWD, represented in Figure 2, are the seven 2-arm and three 3-arm 24 week studies that are described in Table 21. Three 12-week studies[62,63,32] and one 16-week study (Money, 1998[61]) in which there was data on MWD available as described in Table 21 were excluded from this analysis since the outcomes from these studies with a shorter follow up period are not directly comparable.

Table 21: Logarithm of the geometric mean change from baseline in MWD (log metres)

Study	Placebo Mean (SD) N	Cilostazol Mean (SD) N	Pentoxifylline Mean (SD) N	Naftidrofuryl Mean (SD) N
1. Dawson 1998[62 a,g]	-0.098 (0.847)[b] 25	0.266 (0.847)[b] 52		
2. Elam 1998[63 a,g]	0.218 (0.438) 94	0.304 (0.438) 95		
3. Money 1998[61 a,h]	NA[f] (0.358) 120	NA[f] (0.358) 119		
4. Beebe 1999[60a]	0.140 (0.464)[b] 140	0.412 (0.464)[b] 140		
5. Strandness 2002[55a]	0.184 (0.441) 125	0.578 (0.441) 124		
6. Otsuka 21-95-201[32a,g]	0.262 (0.396) 66	0.247 (0.396) 60		
7. O'Donnell 2009[82a]	0.582 (0.993)[d] 55	0.962 (0.993)[d] 51		
8. Porter 1982[71]	0.148 (NA) 61		0.285 (NA) 63	
9. Lindgarde 1989[70]	0.215 (0.608)[d] 74		0.405 (0.608)[d] 76	
10. Creager 2008[69]	0.032 (0.256)[d] 84		0.130 (0.256)[d] 86	
11. Kieffer 2001[64]	0.130 (NA) 92			0.603 (NA) 89
12. Dawson 2000[57]	0.293 (NA) 226	0.432 (NA) 205	0.262 (NA) 212	
13. Otsuka 21-94-301[32a]	0.351 (0.302)[e] 132	0.519 (0.302)[e] 123	0.501 (0.302) 118	
14. Otsuka 21-98-213[32a]	0.346 (0.226) 260	0.362 (0.226) 260	0.413 (0.226) 260	

a: Assumes common standard deviation within study – standard deviation derived from mean and confidence interval for the difference between treatments in geometric mean change from baseline

b: Standard deviation derived from the mean and confidence interval for the difference between treatments in geometric mean change from baseline taken from Pande 2010.[29]

c: Standard error derived from the mean and confidence interval for the difference between treatments in geometric mean change from baseline taken from Pande 2010.[29]

d: Standard deviation derived from the treatment mean changes from baseline and the p-value

e: Standard error derived from the mean and confidence interval for the difference between treatments in geometric mean change from baseline – taken as the average of the estimates from the two comparisons

f: Results available as a difference in treatment means – Table 22

g: 12 week study

h: 16 week study

Table 22 also shows the estimated treatment effect of cilostazol relative to placebo in the study by Money *et al.*[61] for which individual arm data was not available. This study was excluded from the meta-analysis due to the 16-week follow up.

Table 22: Change from baseline in log mean walking distance (log metres)

Study	Difference Cilostazol-Placebo Mean (SE)
Money 1998[61a.c]	0.255 (0.045)[b]

a: Assumes common standard deviation within study – standard deviation derived from mean and confidence interval for the difference between treatments in geometric mean change from baseline

b: Standard error derived from the mean and confidence interval for the difference between treatments in geometric mean change from baseline taken from Pande 2010.[29]

c: 16 week study

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 standard deviation, together with the 95% credible interval.

Table 23: Posterior distribution for the change from baseline in log mean walking distance (log metres)

	Mean 95% Credible Interval
Cilostazol random effects	0.220 (0.108, 0.337)
Cilostazol predictive distribution	0.220 (-0.072, 0.511)
Pentoxifylline random effects	0.101 (-0.016, 0.217)
Pentoxifylline predictive distribution	0.101 (-0.195, 0.383)
Naftidrofuryl oxalate random effects	0.472 (0.181, 0.762)
Naftidrofuryl oxalate predictive distribution	0.472 (0.087, 0.865)
Between-study SD	0.125 (0.068, 0.220)

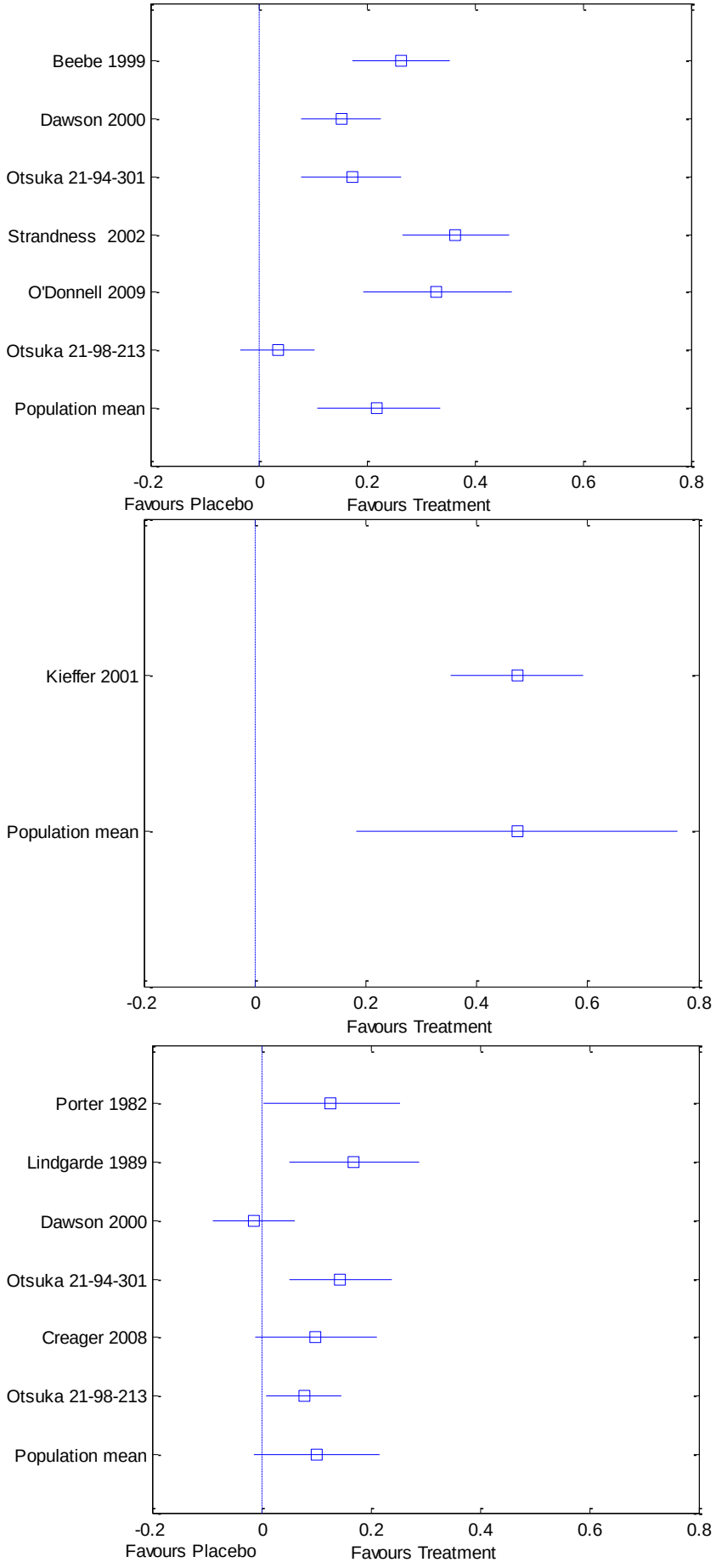
The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl oxalate had the greatest effect (60.3% = 1- exp(0.472) relative to placebo, followed by cilostazol (24.6%) and pentoxifylline (10.6%).

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.

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*.[55] had the largest observed effect of cilostazol compared to placebo (0.394) and the Otsuka 21-98-213[32] trial had the smallest observed cilostazol effect compared to placebo (0.016). The trial by Lindgarde *et al*.[70] had the largest observed pentoxifylline effect compared to placebo (0.190) and the trial by Dawson *et al*.[57] had the smallest observed pentoxifylline effect compared to placebo (-0.031).

Forest plots of this analysis are shown in Figure 3 below. The uncertainty within the population mean is based upon the between-study variation from the mixed treatment comparison.

Figure 3: Posterior distribution for the change from baseline in log mean MWD for cilostazol, naftidrofuryl oxalate and pentoxifylline versus placebo



5.2.2.2 Pain-free walking distance (PFWD)

5.2.2.2.1 PFWD narrative summary

Tables 24 to 28 show PFWD results as reported by the trials. This may be reported as the difference in mean PFWD between baseline and final measurement, or as 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.[27]

For the ten studies comparing cilostazol 200mg with placebo, five did not find any significant difference between groups (O'Donnell[82], Otsuka trials 21-94-301, 21-98-213, 21-95-201, Elam 21-93-201), and five significantly favoured cilostazol over placebo (Otsuka trials Strandness 21-94-201, Dawson 2000 21-96-202, Beebe 21-92-202, Money 21-94-203, Dawson 1998 21-90-201[32]). Table 24 shows the PFWD data from the published trial reports. The review by Pande[29] included nine industry sponsored trials, of which five trials (Otsuka trials Strandness 21-94-201, Dawson 2000 21-96-202, Beebe 21-92-202, Money 21-94-203, Dawson 1998 21-90-201[32]) found a significant difference between treatment groups, and four trials (including the three trials without published trial reports) found no significant difference between cilostazol 200mg and placebo groups (Otsuka trials 21-94-301, 21-98-213, 21-95-201, Elam 21-93-201[32]). The five trials finding a significant difference between treatment groups reported this in published trial reports (Table 24). The Pande review presented a pooled analysis of these nine trials as a ratio of geometric means, and calculated an estimate of treatment effect[29] of 1.15 (95% CI 1.10-1.20), which significantly favoured cilostazol over placebo.[29] This analysis[29] did not include the O'Donnell trial.[50] The O'Donnell trial did not find any significant treatment effect, with both the cilostazol and placebo groups showing improvement in PFWD (Table 24).[50] O'Donnell also found no significant difference between treatment groups when considering the subgroups of patients with diabetes (p=0.14, n=26)[52] or without diabetes (p=0.63, n=80),[82] although as described in Section 5.2.2.1 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, the trial populations do not appear to explain whether significant differences between treatment groups were found or not, and nor does sample size. Of the trials using the constant workload treadmill protocol, three out of seven favoured cilostazol over placebo (Strandness 21-94-201[55], Beebe 21-92-202[60], Dawson 1998 21-90-201[62]), whereas four out of seven were non-significant (O'Donnell, 21-94-301, 21-98-213, 21-95-201[32,82]). Of the trials using the graded test treadmill protocol, two out of three favoured cilostazol over placebo (Dawson 2000[57], Money[61]), whereas one out of three was non-significant (Elam[63]). For the graded test protocol trials, the trial with the non-significant result (Elam[63]) 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) and 24 weeks (Dawson 2000). 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, 21-94-301, 21-98-213[82]), whereas two were significant (Strandness 21-94-201[55], Beebe 21-92-202[60]). Two of the constant workload protocol trials had follow-up of 12 weeks, and of these, one produced significant results (Dawson 1998[62]), whereas the other one (21-95-201[57]) did not find any difference between treatment groups. Only Dawson 1998[62] 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 600mg versus placebo comparison (Table 25), the three trials using constant workload treadmill protocol, Kieffer[64], Adhoute[65] and Trubestein,[66] all reported significantly greater improvement in PFWD for the naftidrofuryl oxalate group than 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 Adhoute[65] were not blinded to treatment group. The three naftidrofuryl oxalate 600mg trials using constant workload treadmill protocol, Kieffer[64], Adhoute[65] and Trubestein[66], had some variation across trials in baseline PFWD, however all had higher baseline PFWD (Appendix 4) than the constant workload cilostazol trials (Strandness 21-94-201[55], Beebe 21-92-202[60], Dawson 1998 21-90-201)[62], O'Donnell, 21-94-301, 21-98-213, 21-95-201[82]). The Spengel trial[46] reported significantly greater improvement in claudication distance for the naftidrofuryl oxalate 600mg group than the placebo group, however this was based on patient estimates of PFWD at baseline and 24 weeks, not treadmill testing. The Ruckley trial[67] of naftidrofuryl oxalate 300mg versus placebo reported that there was no significant difference between groups for PFWD at 12 weeks follow-up,[67] as measured by patients' normal walking pace on a level.

Of the seven trials comparing pentoxifylline 1200mg versus placebo in terms of PFWD, five found no significant difference between treatment groups (Creager[69], Lindgarde[70] and Gallus[75], Otsuka 21-98-213[32] and Otsuka 21-94-301,[32]) whereas two significantly favoured pentoxifylline over placebo for PFWD (Dawson[57] and Porter[72]). The Gallus[75] study had a follow-up of only eight weeks, whereas the other studies had a follow-up of 24 weeks. Three published trials (Table 26) comparing pentoxifylline with placebo, Creager[69], Lindgarde[70] and Gallus[75], reported no significant difference between treatment groups in PFWD. Two trials without published trial reports, Otsuka 21-98-213[32] and Otsuka 21-94-301[32], also found no significant difference between the pentoxifylline and placebo groups in PFWD. Two trials (reported in Table 26), Dawson[57] and Porter[72], 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 treatment effect (Lindgarde[70], Gallus[75], Otsuka 21-98-213[32] and Otsuka 21-94-301[32]), and one favoured pentoxifylline (Porter[72]). Of the two trials using a graded test protocol, one found a significant effect (Dawson[57]) whereas the other did not (Creager[69]) .

For the comparison of inositol nicotinate 4g versus placebo, none of the trials reported PFWD. However, O'Hara[77] 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.[77] The Head trial[80] reported improved claudication times for both treatment groups at 12 weeks, but there was only a significant difference between treatment groups ($p<0.001$) for patients with moderate disease for whom the inositol nicontinate group (n=24) had a significantly greater improvement than the placebo group (n=28).

For the comparison of cilostazol 200mg versus pentoxifylline 1200mg (Table 27), Dawson[57] 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[32] and Otsuka 21-94-301[32], found no significant difference between cilostazol and pentoxifylline groups in PFWD. The Dettori trial[68] 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 one year follow-up.

For the trial comparing cilostazol 200mg (with or without supervised exercise) versus usual care (with or without supervised exercise) (Table 28) all treatment groups improved, but there was no significant effect of cilostazol added to supervised exercise or usual care.[81]

Table 24: Cilostazol 200mg versus placebo PFWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Placebo	Treadmill protocol	Cilostazol group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
O'Donnell 2009[50]	24	51	55	Constant	67% improvement	51.6% improvement	p=0.63
Strandness 2002. Otsuka 21-94-201[56]	24	133	129	Constant			22% (favours cilostazol)
Dawson 2000. Otsuka 21-96-202[57]	24	227	239	Graded	mean difference in metres 94 (SD 127)	mean difference in metres 57 (SD 93)	p=0.0001
Beebe 1999. Otsuka 21-92-202[60]	24	175	170	Constant	mean difference in metres 67.5 59% improvement	mean difference in metres 23.1 20% improvement	p<0.001
Money 1998. Otsuka 21-94-203[61]	16	119	120	Graded			p<0.05
Dawson 1998. Otsuka 21-90-201[62]	12	54	27	Constant	31.7% improvement	-2.5% change (worsening)	p<0.01

Table 25: Naftidrofuryl 600mg versus placebo PFWD

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Treadmill protocol	Naftidrofuryl group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
Spengel 2002[46]	24	382	372	Not treadmill – patient estimate only	mean difference in metres 204 (433)	mean difference in metres 51 (455)	p<0.001
Kieffer 2001[64]	24	98	98	Constant	mean difference in metres 158.2	mean difference in metres 29.9	p<0.001
Adhoute 1986[65]	24	64	54	Constant	mean difference in metres 201.41	mean difference in metres 98.03	p<0.02
Trubestein 1984[66]	12	54	50	Constant	mean difference in metres 93	mean difference in metres 36	p<0.02

Table 26: Pentoxifylline 1200mg versus placebo PFWD

Trial	Treatment duration (weeks)	Number in analysis Pentoxifylline	Number in analysis Placebo	Treadmill protocol	Pentoxifylline group Change in PFWD	Placebo group Change in PFWD	Comparison between groups
Creager 2008[69]	24	86	84	Graded	34.30%	21.20%	non-significant
Dawson 2000. 21-96-202[57]	24	232	239	Graded	mean difference in metres 74 (SD 106)	mean difference in metres 57 (SD 93)	p= 0.07
Lindgarde 1989[70]	24	76	74	Constant	geometric mean 80% improvement (SE 12)	geometric mean 60% improvement (SE 11)	p=0.268
Porter 1982[72]	24	67	61	Constant	47% (SE 10) by geometric mean	26% (SE 9) by geometric mean	2-sided p=0.042, 1-sided p=0.01
Gallus 1985[75]	8	25	23	Constant	55% improvement by geometric mean	26% improvement by geometric mean	Ratio of % change from baseline (pent/placebo) 1.23 (95%CI 0.86-1.77) p<0.3

Table 27: Cilostazol 200mg versus pentoxifylline 1200mg PFWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Pentoxifylline	Treadmill protocol	Cilostazol group Change in PFWD	Pentoxifylline group Change in PFWD	Comparison between groups
Dawson 2000. 21-96-202[57]	24	227	232	Graded	mean difference in metres 94 (SD 127)	mean difference in metres 74 (SD 106)	p=0.02

Table 28: Cilostazol 200mg (with or without supervised exercise) versus usual care (with or without supervised exercise) PFWD

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Usual care	Treadmill protocol	Cilostazol group Change in PFWD	Usual care group Change in PFWD	Comparison between groups
INEXACT Hobbs 2005[81]	24	16 (7 with exercise, 9 without)	18 (9 with exercise, 9 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

5.2.2.2.2 PFWD meta-analysis

The ten studies included within this analysis are the same as for those used in the meta-analysis of MWD, shown in Table 21.

Table 29: Change from baseline in log mean PFWD (log metres)

Study	Placebo Mean (SD) N	Cilostazol Mean (SD) N	Pentoxifylline Mean (SD) N	Naftidrofuryl Mean (SD) N
1. Dawson 1998[62a,c]	-0.025 (NA) 25	0.275 (NA) 52		
2. Elam 1998[63a,c]	0.322 (NA) 94	0.513 (NA) 95		
3. Beebe 1999[60a]	0.182 (NA) 140	0.464 (NA) 140		
4. Strandness 2002[55a]	0.320 (NA) 125	0.611 (NA) 124		
5. Otsuka 21-95-201[32a,c]	0.419 (0.406) 66	0.457 (0.406) 60		
6. O'Donnell 2009[82a]	0.416 (0.581) 55	0.513 (0.581) 51		
7. Porter 1982[71]	0.166 (NA) 40		0.385 (NA) 42	
8. Lindgarde 1989[70]	0.470 (NA) 74		0.588 (NA) 76	
9. Creager 2008[69]	0.192 (NA) 84		0.295 (NA) 86	
10. Kieffer 2001[64]	0.155 (NA) 92			0.651 (NA) 89
11. Dawson 2000[57]	0.588 (0.602)[b] 226	0.663 (0.602)[b] 205	0.554 (0.602)[b] 212	
12. Otsuka 21-94-301[32a]	0.464 (0.474) 122	0.467 (0.474) 123	0.548 (0.474) 118	
13. Otsuka 21-98-213[32a]	0.501 (0.580) 260	0.521 (0.580) 260	0.578 (0.580) 260	

a: Assumes common standard deviation within study – standard deviation derived from mean and confidence interval for the difference between treatments in geometric mean change from baseline

b: Standard deviation derived from the treatment mean changes from baseline and the p-value for the comparison of cilostazol versus pentoxifylline

c: 12 week study

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 and Strandness studies had the largest deviances.

The posterior mean treatment effect for these studies, together with the 95% credible interval, is shown in Table 30. Table 30 also shows the posterior mean of the between study standard deviation, together with the 95% credible interval.

Table 30: Posterior distribution for the change from baseline in log mean PFWD (log metres)

	Mean **95% Credible Interval**
Cilostazol random effects	0.126 (0.024, 0.226)
Cilostazol predictive distribution	0.126 (-0.107, 0.359)
Pentoxifylline random effects	0.088 (-0.017, 0.195)
Pentoxifylline predictive distribution	0.087 (-0.153, 0.326)
Naftidrofuryl oxalate random effects	0.495 (0.231, 0.764)
Naftidrofuryl oxalate predictive distribution	0.496 (0.157, 0.845)
Between-study SD	0.095 (0.032, 0.184)

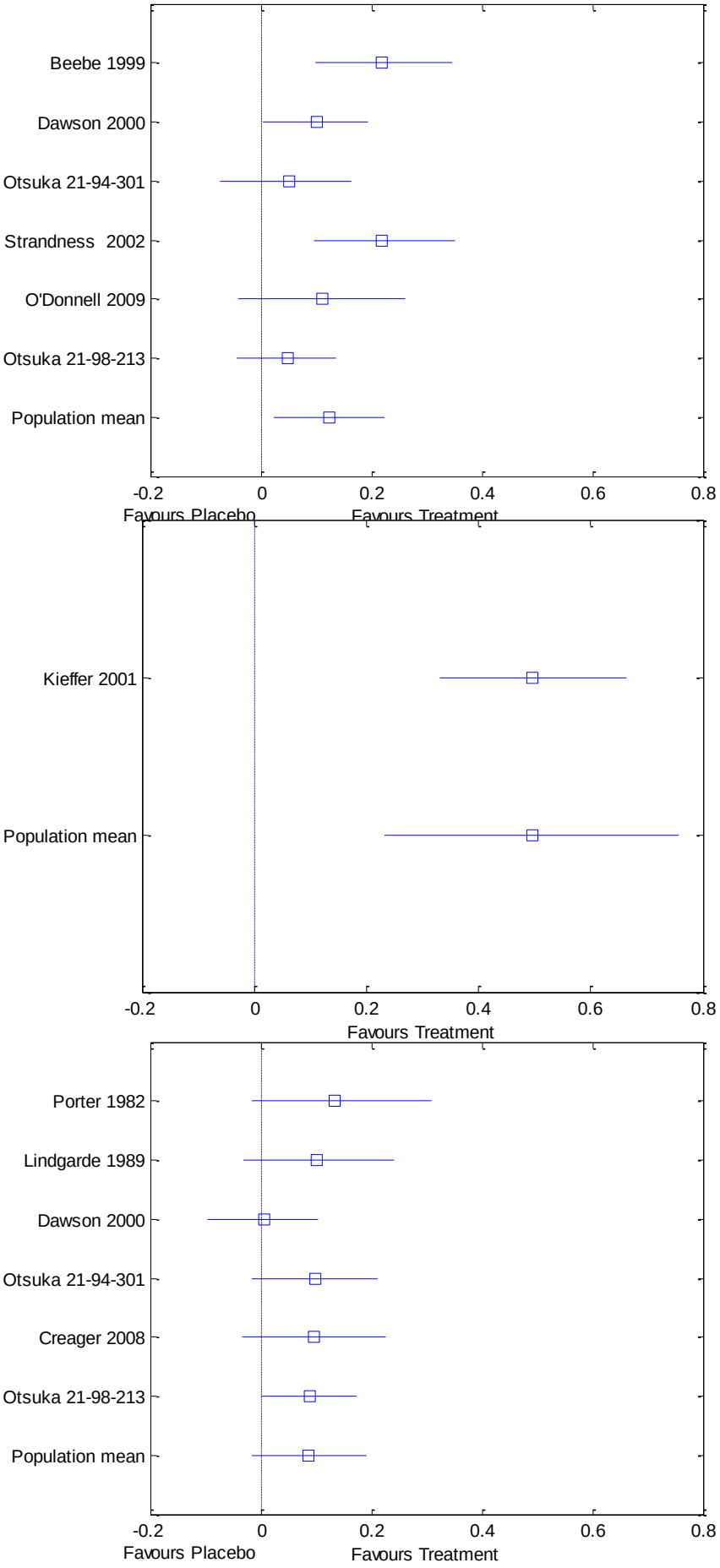
The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl oxalate had the greatest effect (64.2% = 1- exp(0.496) relative to placebo, followed by cilostazol (13.4%) and pentoxifylline (9.2%).

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*.[55] had the largest observed effect of cilostazol effect compared to placebo (0.291) and the Otsuka 21-94-301[32] trial had the smallest observed cilostazol effect compared to placebo (0.003). The trial by Porter *et al*.[71] had the largest observed pentoxifylline effect compared to placebo (0.219) and the trial by Dawson *et al*.[57] had the smallest observed pentoxifylline effect compared to placebo (-0.034).

The forest plots for this analysis are shown in Figure 4 below. The uncertainty within the population mean is based upon the between-study variation from the mixed treatment comparison.

Figure 4: **Posterior distribution for the change from baseline in log mean PFWD for cilostazol, naftidrofuryl oxalate and pentoxifylline versus placebo**



5.2.2.3 Ankle-brachial pressure index (ABPI)

Tables 31 to 34 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 200mg versus placebo comparison (Table 31), only three trials reported ABPI, and these all reported significantly more improvement in the cilostazol treatment group than in the placebo group.[57,61,63] Only in the Dawson 2000 trial[57] did the placebo group's ABPI slightly worsen, with the Money[61] and Elam[63] trials showing improvement in both groups.

For the naftidrofuryl oxalate 600mg versus placebo comparison (Table 32), the two trials[64,65] reporting ABI found no significant difference between the naftidrofuryl oxalate and placebo groups, with both groups in both the Kieffer[64] and Adhoute[65] trials showing a small, non-significant improvement. Trubestein[66] recorded ankle pressure and found no significant change for either treatment group.

For the pentoxifylline 1200mg versus placebo comparison (Table 33), Dawson[57] did not find any significant difference between groups.[57] The Dettori trial[68] with longer follow-up found that, by geometric mean, for post-exercise ABI the pentoxifylline group had significantly more improvement than the placebo group, but that there was no significant difference for ABI measured at rest. For both of these trials,[57,68] there was a slight worsening of the placebo group, and small improvement for the pentoxifylline group.

For the comparison of inositol nicotinate 4g versus placebo, the Kiff trial[79] reported that there was no significant change, from baseline to final measurement at 12 weeks, in ABI for either treatment group.

For the comparison of cilostazol 200mg versus pentoxifylline 1200mg (Table 34), the Dawson study[57] did not find any significant difference between groups for ABI. 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.

Table 31: Cilostazol 200mg versus placebo ABI

Trial	Follow-up	Cilostazol number of patients in analysis	Placebo number of patients in analysis	Cilostazol group change in ABI	Placebo group change in ABI	Comparison between groups
Dawson 2000. 21-96-202[57]	24	205	226	difference in means 0.04	difference in means -0.01	p<0.01 *
Money 1998. 21-94-203[61]	16	119	120	9% increase	1% increase	p=0.0125 *
Elam 1998[63]	12	95	94	9.03% increase	1.2% increase	p<0.001 *

*significantly more improvement in cilostazol than placebo

Table 32: Naftidrofuryl 600mg versus placebo ABI

Trial	Follow-up	Naftidrofuryl number of patients in analysis	Placebo number of patients in analysis	Naftidrofuryl group change in ABI	Placebo group change in ABI	Comparison between groups
Kieffer 2001[64]	24	89	92	difference in means 0.03	difference in means 0.04	non-significant
Adhoute 1986[65]	24	42	40	difference in means 0.02	difference in means 0.01	non-significant

Table 33: Pentoxifylline 1200mg versus placebo ABI

Trial	Follow-up	Pentoxifylline number of patients in analysis	Placebo number of patients in analysis	Pentoxifylline group change in ABI	Placebo group change in ABI	Comparison between groups
Dettori 1989[68]	52	29	30	Post-exercise 8.3% At rest 2.5%	Post-exercise -9.4% At rest - 3.1%	Post-exercise ABI p=0.09 * At rest ABI non-significant
Dawson 2000. 21-96-202[57]	24	212	226	difference in means 0.05	difference in means -0.01	non-significant

*pentoxifylline significantly more improvement than placebo

Table 34: Cilostazol 200mg versus pentoxifylline 1200mg ABI

Trial	Follow-up	Cilostazol group number of patients in analysis	Pentoxifylline group number of patients in analysis	Cilostazol group change in ABI	Pentoxifylline group change in ABI	Comparison between groups
Dawson 2000. 21-96-202[57]	24	205	212	difference in means 0.04	difference in means 0.05	non-significant

5.2.2.4 Mortality

Tables 35 to 39 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 intervention drugs. However, follow-up times were relatively short and hence very few deaths occurred. Only two studies had follow-up of over 24 weeks.[48,68] The CASTLE study[48] of cilostazol 200mg versus placebo (which included some patients taking pentoxifylline in both groups), reported mortality of approximately 7% in both groups by intention to treat analysis at 144 weeks. The Dettori study of pentoxifylline 1200mg versus placebo, at one year,[68] 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 35: Cilostazol 200mg versus placebo Mortality

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Placebo	Cilostazol group	Cilostazol group	Placebo group	Placebo group
				mortality n	mortality %	mortality n	mortality %
Otsuka 21-98-214-01. CASTLE. Hiatt 2008[48]	up to 144	717	718	49	6.8	52	7.2
Strandness 2002. 21-94-201[55]	24	133	129	2	1.5	0	0
Dawson 2000. 21-96-202[57]	24	227	239	2	0.8	1	0.4
Beebe 1999. 21-92-202[60]	24	175	170	3	1.2	2	1.2
Otsuka 21-98-213[32]	24	260	260	0	0	2	0.8
Money 1998. 21-94-203[61]	16	119	120	1	0.8	1	0.8
Dawson 1998. 21-90-201[62]	12	54	27	0	0	1	3.7
Elam 1998. 21-93-201[63]	12	95	94	1	1.1	1	1.1
Otsuka 21-95-201[32]	12	72	70	0	0	2	2.9

Table 36: Naftidrofuryl 600mg versus placebo Mortality

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Naftidrofuryl group	Naftidrofuryl group	Placebo group	Placebo group
				mortality n	mortality %	mortality n	mortality %
Spengel 2002[46]	24	382	372	1	0.26	5	1.30

Table 37: Pentoxifylline 1200mg versus placebo Mortality

Trial	Treatment duration (weeks)	Number in analysis Pentoxifylline	Number in analysis Placebo	Pentoxifylline group	Pentoxifylline group	Placebo group	Placebo group
				mortality n	mortality %	mortality n	mortality %
Dettori 1989[68]	52	37	37	0	0	2	5.4
Creager 2008[69]	24	86	84	1	1.20	1	1.20
Dawson 2000. 21-96-202[57]	24	232	239	3	1	1	0.4
Otsuka 21-98-213[32]	24	260	260	3	1.2	2	0.8
Gallus 1985[75]	8	25	23	0	0	1	4

Table 38: Inositol nicotinate 4g versus placebo Mortality

Trial	Treatment duration (weeks)	Number in analysis Inositol nicotinate	Number in analysis Placebo	Inositol nicotinate group	Inositol nicotinate group	Placebo group	Placebo group
				mortality n	mortality %	mortality n	mortality %
O'Hara 1988[77]	12	62	58	0	0	1	1.70

Table 39: Cilostazol 200mg versus pentoxifylline 1200mg Mortality

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Pentoxifylline	Cilostazol group	Cilostazol group	Pentoxifylline group	Pentoxifylline group
				mortality n	mortality %	mortality n	mortality %
Dawson 2000. 21-96-202[57]	24	227	232	2	0.8	3	1
Otsuka 21-98-213[32]	24	260	260	0	0	3	1.2

5.2.2.5 Cardiovascular events

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

Only two studies had follow-up of over 24 weeks.[48,68] The CASTLE study of 144 weeks[48] 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 for cilostazol of 0.852 (95% CI, 0.515-1.410; p=0.533) by intention to treat analysis This was based on 28 events (3.9%) in the cilostazol group, and 33 events (4.6%) in the placebo group.[48] The CASTLE study also found no significant difference between groups when using on treatment analysis, with 14 cardiovascular deaths in each treatment group. The Dettori study found at one year follow-up one non-fatal cardiovascular event (2.7%) in the pentoxifylline group, and three cardiovascular events (of which, one was fatal) in the placebo group (8.1%).[68]

Eight of the cilostazol 200mg versus placebo trials (Otsuka trials Strandness 21-94-201, Dawson 2000 21-96-202, Beebe 21-92-202, 21-94-301, Money 21-94-203, Dawson 1998 21-90-201, Elam 21-93-201, 21-95-201[32]) were included in an analysis by Pratt[31,27] that reported a cardiovascular event rate of 6.5% (20/308) for the cilostazol 200mg 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 200mg and 0.1% (1/973) for placebo.[31]

For the naftidrofuryl oxalate 600mg versus placebo comparison, the Kieffer trial[64] 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 1200mg versus placebo comparison, Creager[69] reported serious cardiovascular events for 7% (n=6) of the pentoxifylline group and 12% (n=10) of the placebo groups. The Porter[73] and Gallus[75] trials only reported cardiovascular events that led to withdrawal from the studies, with Porter[73] reporting cardiovascular events for 1.5% (n=1) of the pentoxifylline group and 4.8% (n=3) of the placebo group, and Gallus reporting 12% (n=3) for the placebo group but no events for the pentoxifylline group.[75]

The inositol nicotinate 4g trials only reported cardiovascular event that led to withdrawal from the studies. The O'Hara trial[77] reported a 2% (n=1) cardiovascular event rate in both the inositol nicotinate and placebo groups, Kiff[79] reported a 2.5% (n=1) event rate for the inositol nicotinate group and no events for the placebo group, and Head[80] reported a 1.6% (n=1) event rate for the placebo group and no events for the inositol nicotinate group.

5.2.2.6 Adverse events (AEs) and serious adverse events (SAEs)

Tables 40 to 44 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 AE, are provided in Appendix 4. Differences in reporting across trials, including that some trials only

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

Only two studies had follow-up of over 24 weeks.[48,68] The CASTLE study of 144 weeks[48] of cilostazol versus placebo (which included some patients taking pentoxifylline in both groups), reported higher frequency of headaches, diarrhoea, and palpitations in 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%.[48] Most SAEs reported by the CASTLE study were cardiovascular (see section 5.2.2.5), but there was also dyspnea occurring in 1% of the cilostazol group and 0.4% of the placebo group.[48] The Dettori study[68] only reported SAEs leading to withdrawal from study drug, and these were all cardiovascular in nature (see section 5.2.2.5).

Eight of the cilostazol 200mg versus placebo trials (Otsuka trials Strandness 21-94-201, Dawson 2000 21-96-202, Beebe 21-92-202, 21-94-301, Money 21-94-203, Dawson 1998 21-90-201, Elam 21-93-201, 21-95-201[32]) were included in an analysis by Pratt[31] that reported higher frequency of headaches, diarrhoea, peripheral oedema and palpitations in the cilostazol groups than in the placebo groups. Although this analysis[31] included cilostazol doses of 100mg and 300mg (excluded from the current report for not being the licensed dose) as well as the cilostazol 200mg groups, this pattern is reflected in the published trial reports (see Appendix 4).

For both naftidrofuryl oxalate 600mg and 300mg compared with placebo, rates of AEs or SAEs were similar between treatment groups (Tables 41 and 42). The Kieffer trial[64] 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.[64] Non-serious AEs were mostly gastro-intestinal in nature (Appendix 4).

For the pentoxifylline versus placebo trials (Table 43) event rates were similar between treatment groups. Lower rates in the Lindgarde[70]trial than in the Creager[69], Dawson 2000[57], Porter[71], Otsuka 21-94-301[32] and Otsuka 21-98-213[32] trials, are likely to be due to the patient self reporting of AE recording, as populations were similar across trials. Non-serious AEs were mostly headaches or gastro-intestinal complaints (Appendix 4).

The inositol nicotinate 4g versus placebo trials reported only AEs that lead to withdrawal from trials, and these were similar between treatment groups (see Appendix 4) and mostly related to difficulty swallowing or gastro-intestinal problems.[78,79,80]

The cilostazol versus pentoxifylline trials reported similar rates of SAEs and AEs across treatment groups.[31,32,57]

Table 40: Cilostazol 200mg versus placebo SAE and AE

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Placebo	Cilostazol group Patients with 1 or more SAE (n)	Cilostazol group Patients with 1 or more SAE (%)	Cilostazol group Patients with 1 or more AE (n)	Cilostazol group Patients with 1 or more AE (%)	Placebo group Patients with 1 or more SAE (n)	Placebo group Patients with 1 or more SAE (%)	Placebo group Patients with 1 or more AE (n)	Placebo group Patients with 1 or more AE (%)
Strandness 2002. 21-94-201[55]	24	133	129	25	18.8	124	93.2	20	15.5	99	76.7
Dawson 2000. 21-96-202[57]	24	227	239	27	11.9	201	88.5	31	13	188	78.7
Beebe 1999. 21-92-202[60]	24	175	170	23	13.1	159	90.9	29	17.1	150	88.2
Otsuka 21-94-301[32]	24	123	124	16	13	116	94	11	9	103	83
Otsuka 21-98-213[32]	24	260	260	32	12.3	207	79.6	31	11.9	197	75.8
Money 1998. 21-94-203[61]	16	119	120	14	11.8	98	82.4	11	9.2	90	75
Dawson 1998. 21-90-201[62]	12	54	27	7	13	47	87	1	4	20	74
Elam 1998. 21-93-201[63]	12	95	94	6	6.3	79	83.2	7	7.4	76	80.9
Otsuka 21-95-201[32]	12	72	70	4	5.6	60	83.3	10	14.3	52	74.3

Table 41: Naftidrofuryl 600mg versus placebo SAE and AE

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Naftidrofuryl group Patients with 1 or more SAE (n)	Naftidrofuryl group Patients with 1 or more SAE (%)	Naftidrofuryl group Patients with 1 or more AE (n)	Naftidrofuryl group Patients with 1 or more AE (%)	Placebo group Patients with 1 or more SAE (n)	Placebo group Patients with 1 or more SAE (%)	Placebo group Patients with 1 or more AE (n)	Placebo group Patients with 1 or more AE (%)
Kieffer 2001[64]	24	98	98	12	12	18	18	13	13	21	21
Adhoute 1986[65]	24	64	54	NR	NR	5	7.80%	NR	NR	4	7.80%
Trubestein 1984[66]	12	54	50	NR	NR	2	4%	NR	NR	2	4

Table 42: Naftidrofuryl 300mg versus placebo SAE and AE

Trial	Treatment duration (weeks)	Number in analysis Naftidrofuryl	Number in analysis Placebo	Naftidrofuryl group Patients with 1 or more AE (n)	Naftidrofuryl group Patients with 1 or more AE (%)	Placebo group Patients with 1 or more AE (n)	Placebo group Patients with 1 or more AE (%)
Ruckley 1978[67]	12	25	25	6	24%	4	16%

Table 43: Pentoxifylline 1200mg versus placebo SAE and AE

Trial	Treatment duration (weeks)	Number in analysis Pentoxifylline	Number in analysis Placebo	Pentoxifylline group Patients with 1 or more SAE (n)	Pentoxifylline group Patients with 1 or more SAE (%)	Pentoxifylline group Patients with 1 or more AE (n)	Pentoxifylline group Patients with 1 or more AE (%)	Placebo group Patients with 1 or more SAE (n)	Placebo group Patients with 1 or more SAE (%)	Placebo group Patients with 1 or more AE (n)	Placebo group Patients with 1 or more AE (%)
Creager 2008[69]	24	86	84	12	14	59	69	14	17	49	58
Dawson 2000. 21-96-202[57]	24	232	239	31	13.4	200	86.2	31	13	188	78.7
Lindgarde 1989[70]	24	76	74	NR	NR	17	22	NR	NR	10	14
Porter 1982[71]	24	63	61	NR	NR	37	55	NR	NR	24	39
Otsuka 21-94-301[32]	24	123	124	22	18	104	85	11	9	103	83
Otsuka 21-98-213[32]	24	260	260	NR	NR	208	80	31	11.9	197	75.8

Table 44: Cilostazol 200mg versus pentoxifylline 1200mg SAE and AE

Trial	Treatment duration (weeks)	Number in analysis Cilostazol	Number in analysis Pentoxifylline	Cilostazol group Patients with 1 or more SAE (n)	Cilostazol group Patients with 1 or more SAE (%)	Cilostazol group Patients with 1 or more AE (n)	Cilostazol group Patients with 1 or more AE (%)	Pentoxifylline group Patients with 1 or more SAE (n)	Pentoxifylline group Patients with 1 or more SAE (%)	Pentoxifylline group Patients with 1 or more AE (n)	Pentoxifylline group Patients with 1 or more AE (%)
Dawson 2000. 21-96-202[57]	24	227	232	27	11.9	201	88.5	31	13.4	200	86.2
Otsuka 21-94-301[32]	24	123	123	16	13	116	94	22	18	104	85
Otsuka 21-98-213[32]	24	260	260	32	12.3	207	79.6	28	10.8	208	80

5.2.2.7 Health-related quality of life (HRQoL)

Several different outcome measures have been used to assess quality of life in study participants, and no one measure has been used to assess all four treatments. The most commonly used quality of life measure was the SF-36[83], with data available for cilostazol and pentoxifylline. There is also data available for the Walking Impairment Questionnaire (WIQ[84]) for both cilostazol and pentoxifylline, though 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 that had not undergone validation[60], and does not appear to have been published, the VascuQoL[85], an independent measure which has been validated, and CLAU-S, another independent, extensively validated tool.[86] Tables 45 to 48 summarise the evidence around health-related quality of life.

Cilostazol: Table 45 summaries the HRQoL data for cilostazol, and Table 46 further summarises SF-36 scales and subscales. Strandness 2002, Beebe 1999, Money 1998, O'Donnell 2009(diabetics), O'Donnell 2009 (non-diabetics), Dawson 2000 and Otsuka unpublished trial 21-98-213[55,60,61,52,82,57,32] (diabetic and non-diabetic participants were reported separately by one author but are drawn from one study)[52,82] 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 45. 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 2002, Beebe 1999, Money 1998 and O'Donnell 2009 (non-diabetics),,[55,60,61,82] though of these, the magnitude of the change is only reported in Beebe 1999[60] 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 in between group comparisons for any mental health component of the SF-36. COM was reported in Beebe 1999 only,[60] and the results of this corresponded with the SF-36 results reported for the same trial.

VascuQoL was used in one study which reported diabetic (O'Donnell 2009[52]) and non-diabetic (O'Donnell 2009[82]) 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 ischemia,[86] and as such may have different psychometric properties. Across the five studies which used WIQ, results were conflicting, with some significant results reported in Beebe 1999 and Money 1998,[60,61]

significant trends reported in Strandness 2002[55] but no significant changes reported for the remaining two studies, O'Donnell 2009 (non-diabetics) and Dawson 2000.[82,57]

Naftidrofuryl oxalate: Only Spengel 2002 reported HRQoL of naftidrofuryl oxalate versus placebo.[46] 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 and Creager 2008 reported HRQoL using the SF-36 for pentoxifylline versus placebo.[32,69] Creager 2008 also reported WIQ.[69] No significant differences were reported.

Inositol nicotinate: No studies reported HRQol data.

In summary, there is some evidence that cilostazol affects the physical function subscale of the SF-36, which suggests there are some tangible improvements in physical function for the patient. This is somewhat supported by mixed evidence from WIQ which suggests 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 it does not improve HRQoL.

Table 45: Cilostazol 200mg versus placebo, HRQoL assessed using SF-36, WIQ, COM and/or VascuQoL

Trial	Duration	Cilostazol number of patients in analysis	Placebo number of patients in analysis	Cilostazol group change in HRQoL (0-100 scale)	Placebo group change in HRQoL	Comparison between groups
SF-36*						
Strandness 2002. 21-94-201[55]	24 weeks	Unclear	Unclear	NR	NR	Physical health summary (physical function, bodily pain, and role-physical), non-significant trend. Physical function P=0.048
Beebe 1999. 21-92-202[60]	24 weeks	137	141	Mean change from baseline Physical health: Physical function 7.1; Role–physical 5.3; Bodily pain 7.2. Mental health: Social function 1.0; Role–emotional 2.9; Mental health 2.5	Mean change from baseline Physical health: Physical function 2.0; Role–physical - 2.8; Bodily pain -1.8; Mental health: Social function 0.4; Role–emotional - 1.66; Mental health 0.9	 Physical health: physical function, significant bodily pain, significant role physical, positive trend Mental health : Non significant
Money 1998. 21-94-203[61]	16 weeks	Unclear, probably 119	Unclear, probably 120	Mean change from baseline Physical health summary 2.99 Physical function 8.3 Other subscales change NR	Mean change from baseline physical health summary 0.12 Physical function 2.3 Other subscales change NR	 Physical health summary p=0.0059. Physical function P=0.0024 bodily pain p =0.0772 general health p = 0.436 role-physical p = 0.061

						Mental components non-significant.
O'Donnell 2009 (diabetics)[52]	24 weeks	12	14	Difference between median at baseline and 24 weeks (calculated by reviewer) Physical Function, 5.2; Role Physical, 0 ; Body Pain, 3.4; General Health, 2.2; Total SF-36, 3.7 Significance of change from baseline (unclear if median or mean) Physical component P=0.043 vitality P =0.016 others NR	Difference between median at baseline and 24 weeks (calculated by reviewer) Physical Function,0.5; Role Physical, 3.7; Body Pain, 0 ; General Health, 0.2; Total SF-36, 1 Significance of change from baseline(unclear if median or mean) no significant changes	Physical Function p=0.42; Role Physical p=0.72 ; Body Pain, p=0.31 ; General Health p=0.93 ; Total SF-36 p=0.40
O'Donnell 2009 (nondiabetics)[82]	24 weeks	39	41	Mean change from baseline or significance of change from baseline NR	Mean change from baseline or significance of change from baseline NR	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. 21-96-202[57]	24 weeks	205	226	NR	NR	Mental health summary, General health perception, Physical health summary, and Vitality Scores all non-significant
OTSUKA 21-98-213[32]	24 weeks	NR	NR	NR	NR	Only week 12 statistics reported. Physical Health summary significant at 12 weeks
WIQ**						
Strandness 2002. 21-94-201[55]	24 weeks	Unclear	Unclear	NR	NR	non-significant trends: General health perception Walking distance
Beebe 1999. 21-92-202[60]	24 weeks	137	141	NR	NR	Walking speed and walking distance improved, unclear if significant.
Money 1998. 21-94-203[61]	16 weeks	Unclear, probably 119	Unclear, probably 120	NR	NR	Walking speed, p=0.0331, Walking distance, non significant
O'Donnell 2009 (nondiabetics)[82]	24 weeks	12	14	Distance P=0.014 Speed P=0.021	Distance p=0.81, Speed P=0.74	non significant
Dawson 2000. 21-96-202[57]	24 weeks	205	226	NR	NR	Non significant
COM***						
Beebe 1999.	24 weeks	137	141	mean change from baseline	mean change from baseline	Statistically significant

21-92-202[60]				(0 to 4 scale) 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	(0 to 4 scale) 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	Walking pain/discomfort Change in walking pain/discomfort Walking pain/discomfort physical activities. All other domains and subscales not significant.
VascuQol****						
O'Donnell 2009 (diabetics)[52]	24 weeks	12	14	NR	NR	Activity p=0.59 ; Symptom p=0.025 (sig more increase for placebo) ; Pain p=0.08 ; Emotion p=0.013; Social p=0.06 ; Total p=0.04
O'Donnell 2009 (nondiabetics)[82]	24 weeks	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.
*The SF-36 is comprised of two main summary measures (physical health and mental health) which are composed of four sub- scales each. The four physical health sub-scales 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.
**WIQ, walking impairment questionnaire, self-rated measure of symptoms and walking impairment.[86]
***COM, claudication outcome measure, funder-developed outcome measure that has not been independently validated. Measures walking pain, discomfort, physical limitations, daily and social functioning[86]
***VascuQoL is comprised of 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 ischemia.[86]

Table 46: Summary of between group comparisons of change from baseline in SF-36 scores, Cilostazol 200mg versus placebo.

Trial	Duration	Cilostazol number of patients in analysis	Placebo number 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
SF-36*													
Strandness 2002. 21-94-201[55]	24 weeks	Unclear	Unclear	Non sig	Sig	Non sig	Non sig	Non sig	NR	NR	NR	NR	NR
Beebe 1999. 21-92-202[60]	24 weeks	137	141	NR	Sig	Sig	Non sig	NR	Non sig	Non sig	Non sig	Non sig	Non sig
Money 1998. 21-94-203[61]	16 weeks	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)[52]	24 weeks	12	14	NR	Non sig	Non sig	Non sig	Non sig	NR	NR	NR	NR	NR
O'Donnell 2009 (nondiabetics)[82]	24 weeks	39	41	NR	Sig	Non sig	Non sig	Non sig	Non sig	Non sig	Non sig	Non sig	Non sig
Dawson 2000. 21-96-202[57]	24 weeks	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

*The SF-36 is comprised of two main summary measures (physical health and mental health) which are composed of four sub- scales each. The four physical health sub-scales 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 47: Naftidrofuryl 600mg versus placebo, HRQoL assessed using CLAU-S

Trial	Duration	Naftidrofuryl number of patients in analysis	Placebo number of patients in analysis	Naftidrofuryl group change in HRQoL (0-100 scale)	Placebo group change in HRQoL	Comparison between groups
CLAU-S*						
Spengel 2002[46]	24 weeks	358	351	mean change from baseline 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	mean change from baseline 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	 Daily living, p<0.001; Pain, p<0.001; Social life, p=0.001, Disease specific anxiety, non-significant; Mood, p=0.03

NR, Not reported
*CLAU-S, claudication scale. Internationally validated scale to measure quality of life in claudicants.[86]

Table 48: Pentoxifylline 1200mg versus placebo, HRQoL assessed using SF-36 and/or WIQ

Trial	Duration	Pentoxifylline number of patients in analysis	Placebo number of patients in analysis	Pentoxifylline group change in HRQoL (0-100 scale)	Placebo group change in HRQoL	Comparison between groups
SF-36*						
OTSUKA 21-98-213[32]				NR	NR	Physical health summary not signficant
Creager 2008[69]	24 weeks	86	84	NR	NR	Non-significant in any component.
WIQ**						
Creager 2008[69]	24 weeks	86	84	NR	NR	non-significant

NR, not reported.
*The SF-36 is comprised of two main summary measures (physical health and mental health) which are composed of four sub- scales each. The four physical health sub-scales 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.
**WIQ, walking impairment questionnaire, self-rated measure of symptoms and walking impairment.[86]

5.2.3 Discussion

Clinical effectiveness data were available from twenty-six randomised controlled trials. 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, it was uncertain if these were similar across 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 to baseline for cilostazol than placebo,[27] and in PFWD compared to baseline for naftidrofuryl oxalate than placebo.[30] The Cochrane cilostazol review[27] included seven cilostazol versus placebo trials, all of which are included in this review. The Cochrane naftidrofuryl oxalate PFWD analysis[30] included six trials of which three were excluded from

this review because 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 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. Based upon evidence from the excluded studies, there is no evidence of publication bias.

Adverse events were minor and included headaches and gastro-intestinal difficulties. Incidence of serious adverse events 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.[48,68] The CASTLE study[48] of cilostazol versus placebo (which included some patients taking pentoxifylline in both groups) at up to three and a half years, and the Dettori study[68] of pentoxifylline versus placebo at one 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. ABI 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 ABI 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 the patient 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 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.

6 ASSESSMENT OF COST-EFFECTIVENESS

6.1 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 manufactuers 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 49. 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 which met the inclusion criteria was assessed using an adapted version of the Drummond and Jefferson BMJ criteria for economic evaluation (Drummond *et al* 2005[87]) and the Consensus on Health Economic Criteria (CHEC)-list (Evers *et al.* 2005[88]). 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 sensitivity analysis.

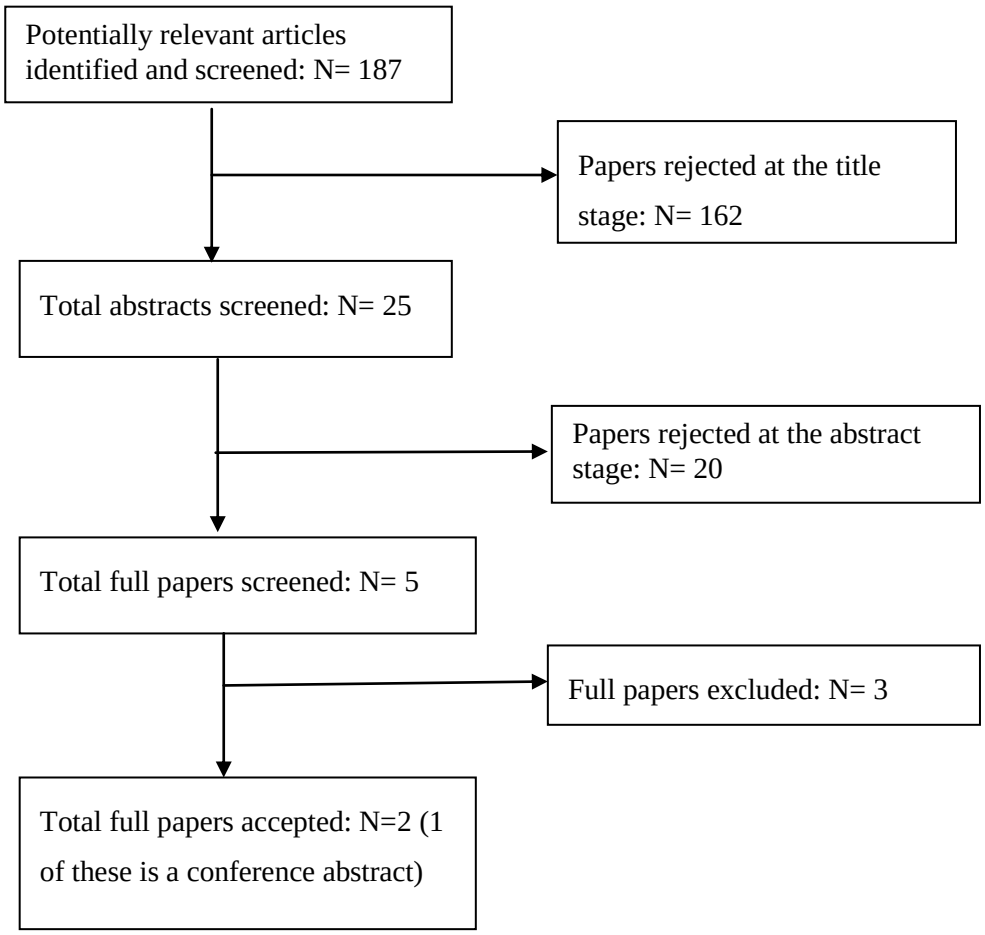
Table 49: Inclusion criteria for the systematic review of economic evaluations

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

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* 2005[89]) and one is a conference poster presentation with only an abstract (Ratcliffe 2005[90]). Figure 5 shows the summary of the study selection and exclusion. The evaluation of the full paper met nine of the ten Drummond and Jefferson quality assessment criteria and 15 of the 19 CHEC-list criteria. The abstract met fewer assessment criteria due to limited information. Full details can be found in Appendix 6.

Figure 5: Summary of economic evaluation selection and exclusion



The characteristics and the main results of the economic evaluations are summarised in Table 50.

Table 50: Summary of published economic analyses

Author	Guest *et al.*[89]	Ratcliffe (abstract) [90]
Country & 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) and Crystal Ball	Unclear
Intervention(s)	Cilostazol	Cilostazol
Comparator(s)	Naftifrofuryl and pentoxifylline	Placebo
Population characteristics	Patients in the UK (>=40) who have >=24 weeks of symptomatic IC , secondary to PAD	Patients in Scotland with IC
Time horizon	24 weeks	24 weeks
Effectiveness data	6 published RCTs; panel of 12 vascular surgeons in the UK	2 published RCTs
Cost year and currency	2002/2003, 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: 32% increase in the percentage improvement in MWD for a 12% increase in costs; cilostazol vs pentoxifylline: 67% increase in the percentage improvement in MWD for a 2% decrease in costs; naftidrofuryl vs pentoxifylline: 27% increase in the percentage improvement in MWD for a 14% decrease in costs.	ICER: £12,500 per QALY

Guest *et al.* present the methods and results of a cost-effectiveness analysis comparing cilostazol (100mg b.i.d), naftidrofuryl oxalate (300mg b.i.d or 200mg t.i.d) and pentoxifylline (400mg t.i.d) within UK patients who are 40 years of age or above and have had at least six months of IC.[89] A decision tree model was developed in DATA Professional (Treeage, 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. Health-related quality of life 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 6 published double-blind, placebo-controlled RCTs[60,91,92,93,64,94] 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. For patients who switched drugs 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 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 studied. All costs were presented in 2002/2003 UK pounds. Costs and outcomes were not discounted due to the short period of modelled time.

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

The results of the model suggest 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 14% (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 treatment.

The study has several limitations:

- There is not a no vasoactive drug comparator;
- The time horizon was 24 weeks;
- Effectiveness is only evaluated in terms of improvement in MWD. Health-related quality of life (utilities) was not evaluated;
- No model validation was reported.

Ratcliffe presents a brief description of the methods and results of a cost-utility analysis of cilostzol (100mg) versus placebo for Scottish patients with IC.[90] 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 uwas unsuccessful. A decision analytical model (type of model is not specified) was built to evaluate the cost-effectiveness of cilostazol verus 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 QALY.

Effectiveness was based on two published 24-week RCTs of cilostazol versus placebo (not referenced in the abstract). Health-related quality of life 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 suggest that the incremental cost-utility ratio for cilostazol over placebo was estimated to be £12,500 per QALY gained. Sensitivity analysis 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 considers 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.

6.2 Independent economic assessment

6.2.1 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® 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 conventional 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 conventional management) and no published evidence was identified to support a subgroup analyses. 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 (200mg per day), naftidrofuryl oxalate (600mg per day), pentoxifylline (1200mg per day) and inositol nicotinate (4g per day). These are compared with each other and no vasoactive drugs for PAD. Since 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 be considered to be cost-effective.

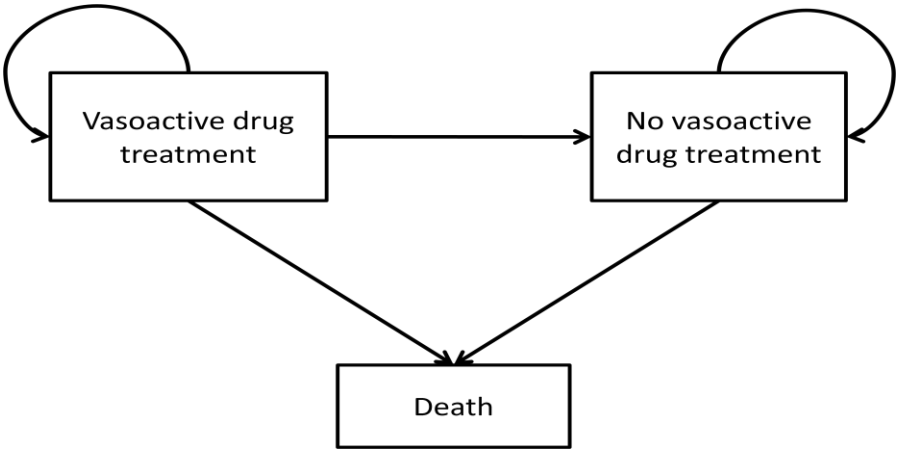
Outcomes

The model outcome is the cost per QALY gained. Due 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. 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 who do not receive any of the four drugs have 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 conventional management to be eligible to receive the vasoactive drugs for PAD. The health states are classified according to whether the patients are receiving vasoactive drugs for PAD or not rather than by progression through different disease stages (i.e. Fontaine stage II, III and IV) since the drugs are for symptom relief and it is assumed that they do not have an impact on disease progression.

Figure 6: Diagram of the structure of the decision model



Patients in the vasoactive drug treatment state could improve their quality of life due to 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 with the drug due to adverse events, 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 due to lack of published evidence. In addition, expert clinical opinion suggested that this would not be standard practice with England and Wales (personal communication with clinical experts, July 2010).

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 whilst they are being given, as suggested by the study by Keiffer *et al*. which recorded MWD for two months beyond treatment discontinuation.[64] Therefore, patients discontinuing with 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 the lifetime of patients (up to age 100 years), 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 which has the longest follow-up period and largest sample size of all RCTs. (Hiatt et al 2008[48]) A time cycle of 1 week was chosen as being sufficiently short enough 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 are discounted at a rate of 3.5% per year.

Estimate of model parameters

MWD 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)[82,60] reported quantitative data for SF-36 quality of life outcomes which can be converted to utilities using published algorithms.[95] No studies of naftidrofuryl oxalate, pentoxifylline or inositol nicotinate provided sufficient quality of life evidence to estimate utility outcomes associated with these drugs. 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 which could be used to estimate the utility gains associated with the drugs being assessed for which there was no utility data. Most of the authors responded (80%) but could not provide the data. One author provided us with 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.[82]

The SF-36 conversion algorithm, as defined by Ara and Brazier[95] was applied to calculate the utilities of each patient at week 0 and week 24 (the period of the RCT). The 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. The correlation coefficient of the absolute difference in MWD on the logarithm scale (logarithm of MWD in week 24 minus logarithm of MWD in week 0) and absolute difference in utilities (utility in week 24 minus utility in week 0) was 0.39 and the scatter plot is presented in Figure 7. A linear regression model was fitted to the data to predict the absolute change in utilities from the absolute change in MWD on the logarithm scale during the RCT period. 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 indepedant of treatment. This was tested by including an additional term in the regression analysis representing the

treatment effect which was not significant. The fitted regression used in the economic model is:

*absolute change in utilities = -0.0076372417 +absolute change in MWD on the log scale * 0.045770316*

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 51. To represent the uncertainty of the regression model, the matrix was used to sample the two coefficients of the regression model in the probabilistic sensitivity analysis (PSA).

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 logarithm scale and anti-logging the sample means on the logarithm scale produces sample geometric means. The motivation for transforming that data to the logarithm 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 logarithm 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.

Figure 7: The relationship between the absolute change in utilities and the absolute change in MWD on logarithm scale based on patient-level data (O'Donnell et al 2009)[82]

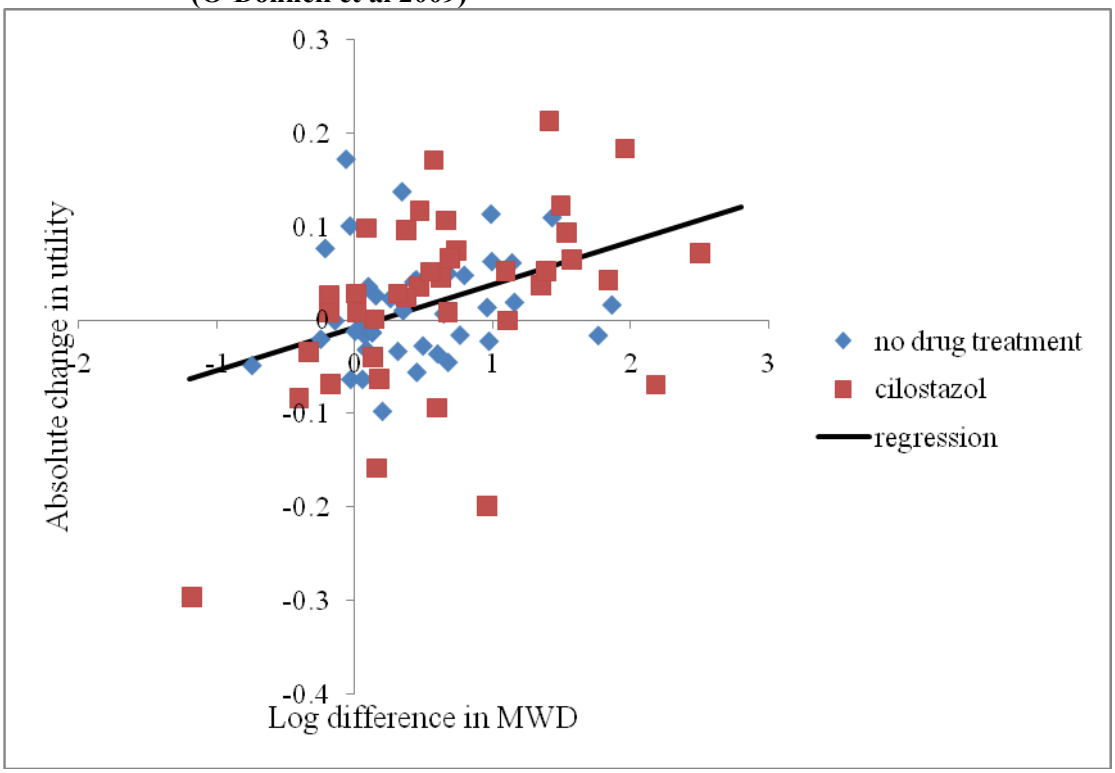


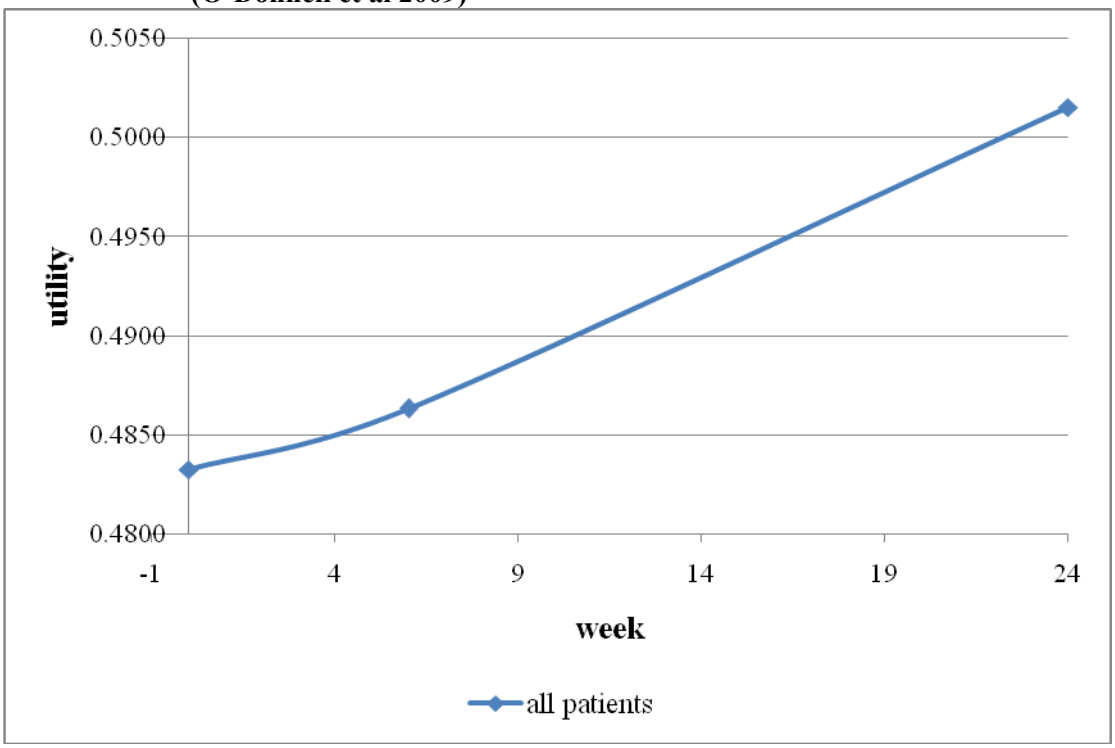
Table 51: Variance-covariance matrix of the slope and intercept of the regression model

	Slope	Intercept
Slope	0.00015001	
Intercept	-0.0000813	0.000111

The regression model was applied to all four drugs and to no vasoactive drug to estimate the absolute change in utilities given a certain change in MWD from week 0 to week 24 on the logarithm scale. The baseline utilities, i.e. the utilities for patients at week 0, were also estimated from the patient-level data. All estimated absolute change in utilities will be applied to the baseline utilities. The estimated mean of the baseline utilities was 0.4838 and the estimated standard deviation was 0.1001. The patient-level data used for this analysis was collected within the latest reported clinical trial on cilostazol and was based on patients in the UK.[82] Therefore the mean baseline utilities should reflect the quality of life of patients with stable IC in the UK NHS context. Sensitivity analysis 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 week 0, 6 and 24) for all patients is presented in Figure 8. Several RCTs reported the change in MWD over time which also suggested a linear increase.[60,57,65,64] 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.

Figure 8: Utility change over time (at week 0, 6 and 24) based on patient-level data (O'Donnell et al 2009)



Given that the health-related quality of life 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[96] were applied using a regression analysis of utility versus age. The age-related utility was calculated by the following formula:

$$Utility = A \times (Age) + B \times (Age \times Age) + C$$

where A = -0.0001728, B = -0.000034, C = 0.9584588

The ratio between the utility at age 66 using this formula for the general population and the utility at age 66 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 due to the lack of effectiveness data available for this drug.

Table 52 presents the predicted mean utilities values for each vasoactive drug and no vasoactive drug treatment at week 24.

Table 52: 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

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 nitrate 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 Section 5.2.2.6 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 which demonstrate higher discontinuation rates for cilostazol and pentoxifylline. This means that there is unlikely to be any additional costs incurred as a result of these adverse events. Since these minor adverse events would generally be experienced for a short time period, and given that these patients already have a lower utility on average than

that experienced by the general population, the impact of these minor adverse events upon utilities is expected to minimal (i.e. unlikely to affect total QALYs to less than three decimal places).

Discontinuation of treatment

The rate of discontinuation for the first 24 weeks were based on meta-analyses of all identified RCTs (see Table 54 for each drug). The long term discontinuation rate (i.e. beyond 24 weeks) was only reported in one study of cilostazol (Hiatt *et al.* 2008[48]) which shows 68% of patients in the cilostazol arm discontinue 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 adverse events 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 cilostazol.

Mortality

It was assumed that all drugs are for symptomatic relief rather than having an impact on the progression of the disease (personal communication with team of clinical advisors, July 2010). 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 (ONS 2008[97]). 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*.[98]

Resource use and costs

The cost of each drug was based on the latest drug tariff updated in October 2010.[25] 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 500mg at a price of £30.76 (6.152p per 100mg) and 112 tablets of 750mg at a price of £51.03 (6.075p per 100mg). The former pack was used for estimating costs since it has a higher unit price (in terms of 100mg) and the identified inositol nicotinate RCTs used a dose of 4g per day (which can not be divided by 750mg tablets). Naftidrofuryl oxalate is available both as a generic drug at a price of 5.38p per 100mg and produced by the manufacturer that held the original patent at a higher price of 9.83p per 100mg. 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 53.

Table 53: Resource use and costs model inputs

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

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 dominiated or extendedly dominated by the comparator. Dominance is defined as where an intervention is less effective and more expensive than its comparator. Extend dominance is defined as where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective comparator. 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 uncertainly 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.

Probabilistic sensitivity analysis

PSA 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 in the logarithm scale for the vasoactive drugs and no vasoactive drug;
- baseline utilities for patients at week 0; and
- coefficients (constant and slope) of the regression model to predict the change in utility from the change in MWD.

Table 54 summarises the input parameters and their base case mean values and distributions (used for PSA) for the model.

Table 54: Model input parameters for the base case scenario

Parameters	Mean	Distribution (parameters)	Source
Age	66	Fixed	Hiatt *et al* 2008[48]
Discount rate (costs and utilities)	3.5%	Fixed	NICE 2008[99]
Relative risk of mortality for patients with IC	1.6	Fixed	Heald *et al* 2006[98]
Discontinuation rates			
Proportion of patients discontinuing cilostazol within 24 weeks	27.8%	Normal (27.8%, 1.5%)	Based on meta-analysis of RCTs reported in Section 5
Proportion of patients discontinuing naftidrofuryl oxalate within 24 weeks	11.1%	Normal (11.1%, 2.5%)	
Proportion of patients discontinuing pentoxifylline within 24 weeks	29.1%	Normal (29.1%, 1.8%)	
Proportion of patients discontinuing inositol nicotinate within 12 weeks[a]	20.0%	Normal (20.0%, 6.3%)	
Proportion of patients discontinuing cilostazol (and other vasoactive drugs for PAD) within 36 months	68%	Normal (68.0%, 1.7%)	Hiatt *et al* 2008[48]
Drug costs			
Weekly costs of cilostazol	£8.83	Fixed	Drug Tariff, October 2010 (www.drugtariff.co.uk)[25]
Weekly costs of naftidrofuryl oxalate	£2.26	Fixed	
Weekly costs of pentoxifylline	£4.59	Fixed	
Weekly costs of inositol nicotinate	£17.23	Fixed	
Baseline utility			
Baseline utility	0.4838	Beta (11.58, 12.36)	Based on patient-level data from O'Donnell *et al.*[82]
Change in MWD on the logarithm scale			
Change in MWD on the logarithm 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 Section 5
Change in MWD on the logarithm scale for cilostazol (week 0 to week 24)	0.4615		
Change in MWD on the logarithm scale for naftidrofuryl oxalate (week 0 to week 24)	0.7134		
Change in MWD on the logarithm scale for pentoxifylline (week 0 to week 24)	0.3427		
Change in MWD on the logarithm scale for inositol nicotinate (week 0 to week 24)[b]	n/a		
Regression model			
Intercept of the regression model	-0.0283	Based on the variance-covariance matrix of the intercept and slope (see Table 51)	Based on patient-level data from O'Donnell *et al.*[82]
Slope of the regression model	0.0995		

[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 logarithm scale can not be obtained for inositol nicotinate because no RCT provides sufficient data for the meta-analysis.

Univariate sensitivity analysis

The following univariate sensitivity analyses were performed to explore the uncertainty of model assumptions:

SA1: 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 sensitivity analysis assumes that if the patients discontinue the drug after 24 weeks, the utility remains the same over this subgroup of patient's remaining lifetime as when on the drug at the time of discontinuation.

SA2: Alternative baseline utility

The baseline utility varied between the two RCTs identified within the clinical effectiveness review which presented SF-36 data which can be converted to utilities.[60,82] It would also be variable between patients in practice. Therefore, an assessment of the impact of an alternative baseline utility was estimated from a study of cilostazol which reported SF-36 summary statistics.[60] The data were converted into utilities using the same algorithm as the base case.[95] The alternative baseline utility estimated from the study is 0.7562. The relationship between baseline utility and utility at 24 weeks is assumed to remain the same within this analysis.

SA3: 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 (Praxilene), but at a higher cost of £4.13 per week compared with £2.26 per week in the base case. The sensitivity analysis is performed to test the impact on cost-effectiveness results using the alternative drug cost.

SA4: Shorter time horizon

Most of the evidence on change in MWD, change in utility and discontinuation rates are based on RCTs which have a follow up period of less than 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 due to lack of published evidence. This sensitivity analysis tests a shorter time horizon of 24 weeks where data are most robust.

SA5: Alternative starting age

The base case assumes that the cohort of patients within the model will begin treatment at age 66. This sensitivity analysis assesses whether 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) is applied to test the robustness of the results to starting age.

SA6: 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 since clinicians suggest that the reasons for discontinuation beyond 24 weeks would be more likely related to improvements in disease rather than due to adverse events, as for the first 24 weeks. However, in order to test the impact of alternative discontinuation rates beyond 24 weeks, the sensitivity analysis 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. since the discontinuation rate of pentoxifylline and naftidrofuryl oxalate respectively is 5% more and 60% less than that of cilotazol within the first 24 weeks, it is assumed that beyond 24 weeks the discontinuation rate of pentoxifylline and naftidrofuryl oxalate is also respectively 5% more and 60% less than the long term disconinuation rate of cilotazol).. However, given the limited evidence available, this alternative assumption on long term discontinuation rates would be reasonable.

SA7: Angioplasty procedure for patients discontinuing within 24 weeks

Clinical practice is variable between clinicians for prescribing vasoactive drugs for IC patients whose symptoms continue despite a period of conventional management. Some clinicians will assess whether angioplasty is appropriate within this patient group and if so undertake this immediately. If angioplasty is either 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. This sensitivity analysis concerns the latter of these two alternative clinical practices.

The subgroup of patients who would be potentially offered angioplasty may be pre-specified 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 since 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 (September, 2010). These patients with a worse prognosis in which angioplasty is potentially appropriate are estimated to represent around 15% of the overall patient group included within this assessment (personal communication with team of clinical advisors, September 2010).

A set of simplified assumptions were made for this sensitivity analysis:

- Patients who discontinue with 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),[89] one MRI imaging (£189.90),[100] and the angioplasty procedure (£925.58).[89] All costs were adjusted to 2009-10 prices[101];
- Due to lack of comparative evidence around the utility associated with angioplasty, it will be varied within this analysis and will be related to the utility associated with naftidrofuryl (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 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 (the drug associated with the highest quality of life)
    - 20% higher than the utility associated with naftidrofuryl
    - 40% higher than the utility associated with naftidrofuryl
    - equivalent to the utility of general population used in the model, which is around 60% higher than the utiity associated with naftidrofuryl
- Patients who have no vasoactive drugs and have angioplasty will have the utility described above for one 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 since they have a worse prognosis by definition within this subgroup analysis. However, the impact of baseline utility is tested within sensitivity analysis 3 and hence is not altered here.

6.2.2 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 55.

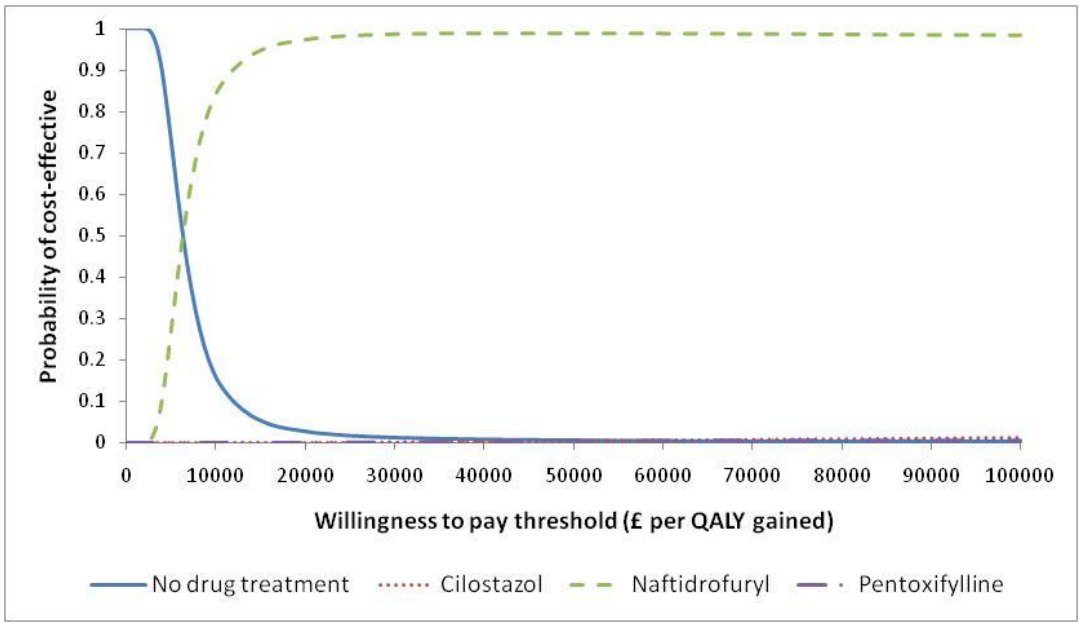
The base case results suggest that naftidrofuryl oxalate has the lowest additional costs (£298) compared with no vasoactive drug and cilostazol has the highest additional costs (£964); while the additional costs of pentoxifylline is £493. In terms of total QALYs, naftidrofuryl oxalate is estimated to 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 £6,070 in the base case scenario based upon the discounted expected values.

Table 55: Incremental discounted cost-effectiveness results (base case)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	£6,070	

The cost-effectiveness acceptability curve (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 less than 1%. Naftidrofuryl oxalate has the highest probability of being most cost-effective above willingness to pay thresholds of around £6,000 per QALY gained.

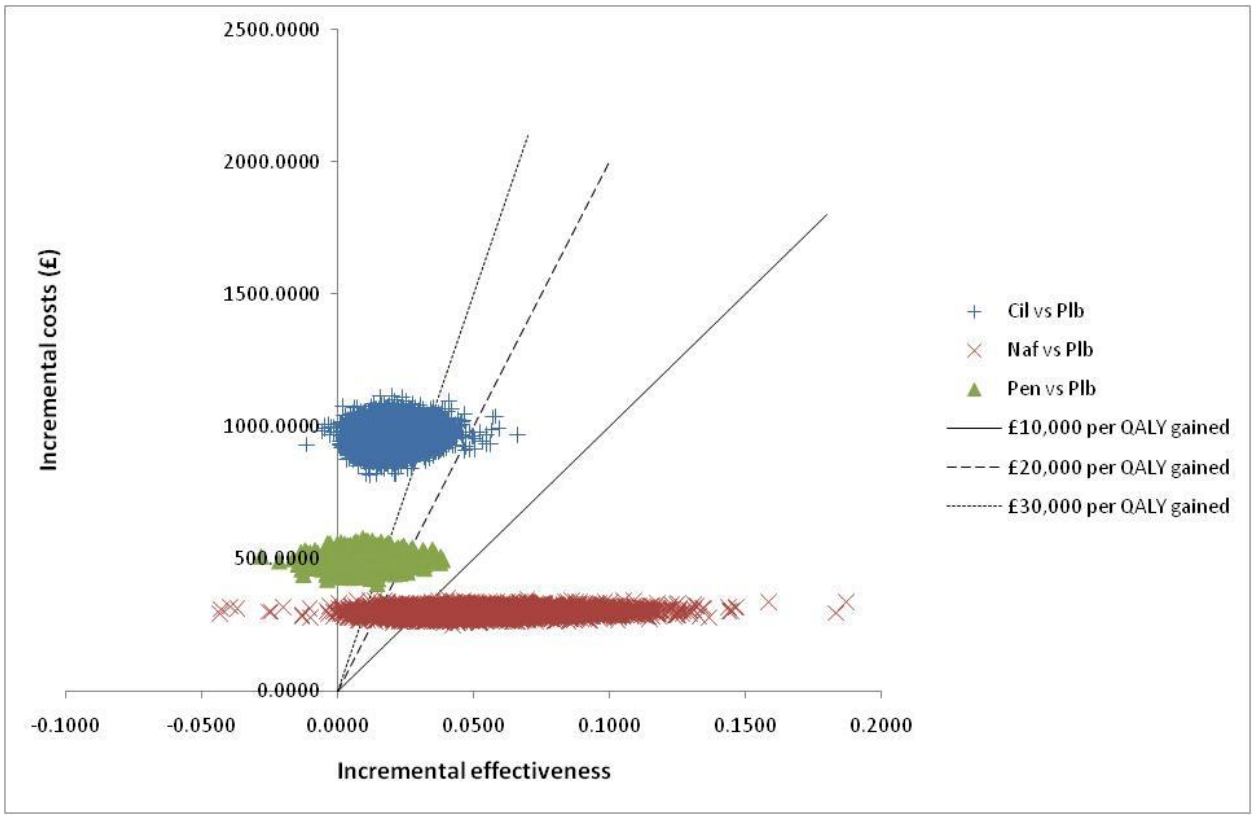
Figure 9: Cost-effectiveness acceptance curve for the base case model results



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 treamtent are also shown on the plane. The figure shows why naftidrofuryl oxalate dominates both cilostazol and pentoxifylline since the cluster representing naftidrofuryl oxalate is associated with higher incremental effectiveness and lower incremental costs. The figure also shows that naftidrofuryl oxalate is cost-effective compared with no vasoactive drug using the thresholds of £10,000, £20,000 and £30,000 per QALY gained since more points lie below the threshold lines. 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 most robust regarding incremental effectiveness, with the smallest range of uncertainty. Therefore, based upon current evidence, it is possible for cilostazol to be more effective than naftidrofuryl; however cilostazol is unlikely to be considered to be cost-effective 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 compared with 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.

Figure 10: Cost-effectiveness plane showing incremental effectiveness and costs of the vasoactive drugs versus no vasoactive drug (base case)



Results of univariate sensitivity analyses

SA1: Utility remains the same as when on the drug if discontinuation occurs after 24 weeks

The sensitivity analysis assumes the effectiveness of the vasoactive drug continues when patients discontinue the drug after 24 weeks. The incremental cost-effectiveness results of the sensitivity analysis are presented in Table 56. 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 vascoactive drug decreases from £6,070 in the base case to £1,538, which makes the drug more cost-effective.

Table 56: Incremental discounted cost-effectiveness results (SA1)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	£1,538	

SA2: Alternative baseline utility

This sensitivity analysis applies an increased baseline utility of 0.7562 compared with 0.4838. The incremental cost-effectiveness results of the sensitivity analysis are presented in Table 57. 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 demonstrate that the model is not sensitive to different baseline utilities.

Table 57: Incremental discounted cost-effectiveness results (SA2)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	£6,053	

SA3: Alternative cost for naftidrofuryl oxalate

This sensitivity analysis applies a higher cost for naftidrofuryl oxalate which is £4.13 per week (manufactured by Praxilene) compared with £2.26 per week (generic) in the base case. The incremental cost-effectiveness results of the sensitivity analysis are presented in Table 58. The results show that cilostazol is dominated by naftidrofuryl oxalate which has lower costs and higher total QALYs. Pentoxifylline is extendely 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 £6,070, because of the cost increase of naftidrofuryl oxalate.

Table 58: Incremental discounted cost-effectiveness results (SA3)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	

SA4: Shorter time horizon

This sensitivity analysis considers a time horizon of 24 weeks. The incremental cost-effectiveness results of the sensitivity analysis are presented in Table 59. The base case cost-effectiveness

conclusions are not changed. The ICER of naftidrofuryl oxalate compared with no vasoactive drug increases from £6,070 in the base case to £10,733.

Table 59: Incremental discounted cost-effectiveness results (SA4)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	

SA5: Alternative starting age

The sensitivity analysis assumes that patients begin treatment with these drugs at age 55. The incremental cost-effectiveness results of the sensitivity analysis are presented in Table 60. 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 demonstrate that the model is not sensitive to the starting age of patients.

Table 60: Incremental discounted cost-effectiveness results (SA5)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	£6,033	

SA6: Alternative long term discontinuation rates

The sensitivity analysis 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 sensitivity analysis are presented in Table 61. The results show that cilostazol is dominated by naftidrofuryl oxalate which has lower costs and higher total QALYs. Pentoxifylline is extendely dominated by naftidrofuryl oxalate because the drug

acquisition cost of naftidrofuryl oxalate becomes substantially higher than that of pentoxifylline due 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 £5,899 per QALY gained which is similar to the base case.

Table 61: Incremental discounted cost-effectiveness results (SA5)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ 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	£5,899	

SA7: 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 which 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 HRQoL immediately. Due to lack of comparative evidence around the utility associated with angioplasty, four scenarios are 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 sensitivity analysis are presented in Tables 62-65. Unlike the base case and other sensitivity analyses where the cost of no vasoactive drug is zero, the comparator of no vasoactive drug is associated with a significant cost which is £1,313 which represents the costs of angioplasty. In the sensitivity analysis, the total QALYs assoaciated with no vasoactive drug also increase with increased assumed utility associated with angioplasty procedure because all patients with no vasoactive drug are assumed to receive angioplasty at the beginning and can benefit improved HRQoL immediately.

When it is assumed that the 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 the utility associated with angioplasty is 20% and 40% higher than the utility associated with naftidrofuryl oxalate, no vasoactive drug 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 compared with naftidrofuryl oxalate are £17,992 and £6,545 per QALY gained respectively.

When it is assumed that the the utility associated with angioplasty is equivalent to the utility of general population used in the model (around 60% higher than the utility associated with naftidrofuryl oxalate), no vasoactive drug is associated with the highest total QALYs. Naftidrofuryl oxalate is associated with less total QALYs than cilostazol because more patients discontinue with cilostazol and could therefore benefit from the angioplasty procedure. In terms of cost-effectiveness conclusions, pentoxifylline is dominated by naftidrofuryl oxalate and cilostazol is dominated by no vasoactive drug. The ICER of no vasoactive drug compared with naftidrofuryl oxalate is £4,094 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 willingness to pay thresholds of £20,000 per QALY gained for this small subgroup of patients.

Table 62: 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	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
Pentoxifylline	£862	4.993		Dominated by naftidrofuryl oxalate
No vasoactive drug (baseline technology)	£1,313	4.996		Dominated by naftidrofuryl oxalate
Cilostazol	£1,315	5.003		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£431	5.032	-	

Table 63: 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	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
Pentoxifylline	£862	5.019		Dominated by naftidrofuryl oxalate
Cilostazol	£1,315	5.028		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£431	5.044	-	
No vasoactive drug (baseline technology)	£1,313	5.093	£17,992	

Table 64: 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	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
Pentoxifylline	£862	5.044		Dominated by naftidrofuryl oxalate
Cilostazol	£1,315	5.052		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£431	5.056	-	
No vasoactive drug (baseline technology)	£1,313	5.191	£6,545	

Table 65: Incremental discounted cost-effectiveness results (SA7 – same compared with general population)

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
Pentoxifylline	£862	5.066		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£431	5.067	-	
Cilostazol	£1,315	5.074		Dominated by no vasoactive drug
No vasoactive drug (baseline technology)	£1,313	5.282	£4,094	

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 considered cost-effective 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 much less uncertainty than the QALYs; with the biggest uncertainty relating to the costs being the long term discontinuation rates. Willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained were used for this threshold analysis. Table 66 summarises the results of this analysis.

Table 66: 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)	Required QALYs gained for threshold of £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 (£1,242 to £2,200)	0.085 (0.062 to 0.110)	0.056 (0.041 to 0.073)

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 since this is the cheapest vasoactive drug. Pentoxifylline requires a QALY gain of 0.025 and 0.016 respectively to make the drug cost-effective at a willingness to pay threshold of £20,000 and £30,000. The QALYs gained required for cilostazol to be cost effective at a willingness to pay threshold 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 a willingness to pay threshold of £20,000 and £30,000 per QALY gained, the required QALYs gained are 0.085 and 0.056 respectively.

6.2.3 Discussion

Summary of key results

The economic evaluation suggests that naftidrofuryl oxalate dominates cilostazol and pentoxifylline and has a cost per QALY gained of around £6,070 compared with no vasoactive drug, and hence is

estimated to be the most cost-effective treatment option assessed at a willingness to pay threshold of £20,000 per QALY gained. 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 are uncertain. A threshold analysis was therefore undertaken to assess the QALY gains required for naftidrofuryl oxalate to be considered to be cost-effective at a willingness to pay threshold of £20,000. This suggested that an estimated 0.015 QALYs gained would be required compared with no vasoactive drug.

Sensitivity analyses suggest that base case cost-effectiveness conclusions and the ICERs of naftidrofuryl oxalate compared with no vasoactive drug are not changed with alternative baseline utility (SA2), alternative starting age (SA5) and alternative long term discontinuation rates (SA6). When it is assumed that the effectiveness associated with the vasoactive drugs continue 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 £6,070 in the base case to £1,538 per QALY gained, making the drug more cost-effective. 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 repectively, making the drug less cost-effective but still below the £20,000 threshold. In all of these sensitivity analyses, both cilostazol and pentoxifylline are dominated or extendedly dominated (for pentoxifylline in SA3 and SA6) by naftidrofuryl oxalate.

Sensitivity analyses which assume that patient who discontinue with the drugs within 24 weeks will receive angioplasty (SA7) suggest that the effectiveness of the drugs depend on the assumed utility associated with angioplasty. When it is assumed that the the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl, naftidrofuryl dominates pentoxifylline, no vasoactive drug and cilostazol. However, when it is assumed that the the utility is higher than the utility associated with naftidrofuryl, no vasoactive drug is associated with the highest total QALYs and the ICERs of no vasoactive drug compared with naftidrofuryl oxalate are less than £20,000 per QALY gained. Cilostazol and pentoxifylline are either dominated by naftidrofuryl oxalate or by no vasoactive drug.

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 due 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 be considered to be cost-

effective, due to 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 cost-effective 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 conventional management. There may, however, be a subgroup of patients with more severe IC in which treatment with these drugs may prevent the need for angioplasty. In this subgroup of patients, naftidrofuryl is unlikely to be cost-effective compared with no vasoactive drug for PAD, however further research is required around the effectiveness of angioplasty in these patients.

Strengths and limitations of analysis

The economic evaluation has several strengths compared to 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 an 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 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 sensitivity analysis which 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.[64] A sensitivity analysis was carried out 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 of MWD was based on patient-level data from a RCT of cilostazol with a sample size of 106 patients in the UK.[82] 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 adverse events; 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 it was not possible to fully quantify within the PSA.

Cardiovascular adverse events 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[48] 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 adverse events). Personal communication with the team of clinical advisors (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.

The economic evaluation identified within the literature review by Guest *et al.*[89] 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, since 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 (July, 2010) suggested that in practice supervised exercise programs are currently unavailable in many regions of England and Wales and that the use of vasoactive drugs is unlikely to affect whether 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. Due 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.

7 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, particularly in secondary care. The only evidence available around current usage of the vasoactive drugs for PAD within England and Wales is the Prescription Costs Analysis England 2009.[24] 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 this data is shown in Table 67.

Table 67: 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%

The costs associated with providing the vasoactive drugs for PAD are the acquisition costs of the drugs only, and are not expected to require any additional management costs due to the healthcare 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 68. This is calculated using the graph of prevalence by age from the study by Norgren *et al*. (2007[3]) and England and Wales population statistics by age from the Office for National Statistics.[97] This results in 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*. (2007[3]), and that of these, 20% would require the vasoactive drugs after a period of conventional management. This results in an estimated 98,476 people within England and Wales requiring treatment with a vasoactive drug.

Table 68: 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

Since 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 67, the current cost of treatment in England is estimated to be just over £1.5 million.

8. DISCUSSION

8.1 Statement of principle findings

Clinical effectiveness data were available from twenty-six randomised controlled trials. There was some evidence that walking distance outcomes were improved by cilostazol and naftidrofuryl oxalate. Adverse events were minor and included headaches and gastro-intestinal difficulties. Incidence of serious adverse events 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 be considered to be cost-effective at a willingness to pay threshold of £30,000 per QALY gained. Naftidrofuryl oxalate is associated with an estimated cost per QALY gained of around £6,000 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 be considered to be cost-effective at a willingness to pay threshold of £20,000.

8.2 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.[102,103,104]

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[105] which suggests that there is no evidence of

any publication bias. There is no head-to-head data comparing naftidrofuryl oxalate with any other vasoactive drug; the results of the analysis depended upon a mixed treatment comparison.

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 sensitivity analysis was underaken 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 of 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.[82] 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 adverse events; 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 only assessed within a threshold analysis. A value of information analysis has not been undertaken due to the uncertainties associated with the long term outcomes which it was not possible to fully quantify within the PSA.

Cardiovascular adverse events 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[48] 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 adverse events). Personal communication with the team of clinical advisors (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.

8.3 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 adverse events or benefits associated with the naftidrofuryl oxalate, pentoxifylline and inositol nicotinate.

8.4 Other relevant factors

Naftidrofuryl could potentially be prescribed to more patients than cilostazol since congestive heart failure is not contraindicated for naftidrofuryl and it has fewer drug interactions.

9 CONCLUSIONS

Naftidrofuryl and cilostazol are both effective treatments for this patient population, with minimal serious adverse events; however naftidrofuryl is the only treatment which is likely to be considered to be cost-effective at a willingness to pay threshold of £20,000 per QALY gained, with an estimated cost per QALY of £6,070 compared with no vasoactive drugs for PAD.

9.1 Implications for service provision

Provision of these drugs does not usually engender significant additional management costs since 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, particularly in secondary care. Therefore, if these drugs were to be recommended, prescription rates of the drugs may rise considerably.

9.2 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 whilst 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 with those associated with supervised exercise programs and other treatments such as angioplasty. Importantly, there are currently no long term safety trials for naftidrofuryl; 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.

10 APPENDICES

Appendix 1: Literature Search Strategies

Search strategies were developed to retrieve both randomised controlled trials and systematic reviews.

Randomised controlled trials

Medline and MEDLINE(R) In-Process & Other Non-Indexed Citations: Ovid. 1950 -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.
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 intermittent claudication (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 intermittent claudication (1-2) or PAD terms (4-8). A randomised controlled trial 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 -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 -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 -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 adverse events of the four interventions. First, the adverse event subheadings that are linked to indexed drug names (1-3) and second, free-text terms relating to adverse events (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 -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 -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 intermittent claudication without treatment were carried out. Terms for intermittent claudication (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 -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 intermittent claudication (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[92]	naftidrofuryl fumarate vs. placebo	Not licensed
Belcaro 2002[106]	pentoxifylline 1600mg vs. Placebo	Not licensed dose
Bieron 2005[107]	intra-venous pentoxifylline vs intra-venous bencyclane	Not licensed
Boccalon 2001[108]	naftidrofuryl 200 mg tid vs. Placebo	Population includes Fontaine stage III, non-English language
Bollinger 1977[109]	pentoxifylline 600mg vs. placebo	Not licensed dose
Chacon-Quevedo 1994[110]	pentoxifylline 1200mg vs. buflomedil 600mg	Comparator not relevant
Ciocon 1997[111]	pentoxifylline 400mg tid vs. aspirin 325mg daily	Comparator not relevant
Clyne 1980[112]	naftidrofuryl 400mg vs. placebo	Not licensed dose
de Albuquerque2008[113]	cilostazol 100mg b.i.d vs. pentoxifylline 600mg b.i.d vs. Placebo	No comparative data between treatment groups for any of the outcomes included in this review
de Sanctis 2002[114]	pentoxifylline 1600mg vs. Placebo	Not licensed dose
Diehm 1989[115]	intra-venous naftidrofuryl 600mg vs. PGE1	Not licensed
Donaldson 1984[116]	pentoxifylline 600mg vs. placebo	Not licensed dose
Hentzer 1965[117]	inositol 1.8g vs. Placebo	Not licensed dose
Jaffe 1975[118]	inositol 3g vs. bradilan 1500mg	Comparator not relevant
Karnik 1988[119]	naftidrofuryl 400mg b.i.d vs. Placebo	Not licensed dose
Kriessman 1988[120]	naftidrofuryl 400mg vs. placebo	Non-English language
Milio 2006[121]	intra-venous pentoxifylline and buflomedil vs. PGE1	Not licensed
Moody 1994[93]	naftidrofuryl fumarate vs. placebo	Not licensed
Reilly 1987[122]	pentoxifylline 400mg vs. placebo	Not licensed dose
Roekaerts 1984[123]	pentoxifylline 1200mg vs. Placebo	Population includes Fontaine stage III
Rosas 1981[124]	naftidrofuryl 300mg vs. buflomedil 500mg	Comparator not relevant, population includes Fontaine stage III
Schubotz 1976[125]	pentoxifylline 800mg vs. placebo	Population includes Fontaine stages I to III
Soga 2009[126]	cilostazol 200mg 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[127]	intra-venous pentoxifylline vs. Placebo	Not licensed
Strano 1984 [128]	pentoxifylline 800mg vs. placebo	Population includes Fontaine stage III
Trubestein 1981[129]	pentoxifylline 300mg vs. buflomedil 450mg	Not licensed dose, comparator not relevant
Tyson 1979[130]	inositol nicotinate vs. placebo	Non-randomised study
Waters 1980[131]	naftidrofuryl 200mg tid vs. Placebo	No comparative data between treatment groups for any of the outcomes included in this review

Appendix 3: Quality assessment

Table 69: Quality assessment items adapted from criteria based on NHS CRD Report No.4 [26]; Cilostazol trials

Trial (first author, year, trial number if known)	Strandness 2002. 21-94-201 106[55]	Beebe 1999. 21-92-202[60]	Elam 1998. 21-93-201[63]	Dawson 1998. 21-90-201[62]	Money 1998. 21-94-203[61]	Otsuka 21-98-214-01. CASTLE.[47,48];	O'Donnell 2009	Otsuka 21-95-201	Hobbs 2005.	Dawson 2000. 21-96-202	Otsuka 21-94-301	Otsuka 21-98-213
Data from peer reviewed journal(s)	[55,56]	[60]	[63]	[62]	[61]	[47,48,49]	[50,82,54,132,52]	Unpublished trial from Otsuka [32]	[81]	[57]	Unpublished trial from Otsuka [32]	Unpublished trial from Otsuka [32]
Data from peer reviewed systematic review(s)	[40]		[40]					[40]		[40]	[33,40]	
Data from Industry submission	[32]		[32]	[32]	[32]		[32]	[32]			[32]	[32]
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
Were participants analysed in their allocated treatment groups, in accordance with the intention-to-treat 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 drop-outs between groups?	N	N	U	U	U	U	N	U	U	N	U	N
If so, were these imbalances in drop-outs 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*	N	Y*	N	N	N	N	NA	N	Y*	NA	NA

Y, yes; N, no; U, unclear; NA, not applicable.
a, master randomization 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.
*but missing data available from published reviews.

Table 70: Quality assessment items adapted from criteria developed by EMA:[17] Cilostazol trials

Trial (first author, year, trial number if known)	Strandness 2002. 21-94-201 106[55]	Beebe 1999. 21-92-202[60]	Elam 1998. 21-93-201[63]	Dawson 1998. 21-90-201[62]	Money 1998. 21-94-203[61]	Otsuka 21-98-214-01. CASTLE.[47,48,]	O'Donnell 2009	Otsuka 21-95-201	Hobbs 2005.	Dawson 2000. 21-96-202	Otsuka 21-94-301	Otsuka 21-98-213
Data from peer reviewed journal(s)	[55,56]	[60]	[63]	[62]	[61]	[47,48,49]	[50,82,54,132,52]	Unpublished trial from Otsuka[32]	[81]	[57]	Unpublished trial from Otsuka[32]	Unpublished trial from Otsuka[32]
Data from peer reviewed systematic review(s)	[40]		[40]					[40]		[40]	[33,40]	
Data from Industry submission	[32]		[32]	[32]	[32]		[32]	[32]			[32]	[32]
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 one week?	U	Y	Y	U	U	NA	Y	Y	N	U	Y	U
If so, did patients have a baseline MWD with less than 25% change?	U	Y	U	N	Y	NA	U	Y	NA	Y	Y	U
Y, yes; N, no; U, unclear; NA, not applicable.												

Table 71: Quality assessment items adapted from criteria based on NHS CRD Report No.4 [26]; Pentoxifylline trials

Trial (first author, year, trial number if known)	Dawson 2000. 21-96-202	Otsuka 21-94-301	Otsuka 21-98-213	Lindegarde 1989	Porter 1982a, Gillings 1987	Gallus 1985	Di Perri 1983	Dettori 1989	Creager 2008
Data from peer reviewed journal	[57]	Unpublished trial from Otsuka	Unpublished trial from Otsuka	[70]	[71,72 73 74]	[75]	[76]	[68]	[69]
Data from peer reviewed systematic review(s)	[40]	[33]							
Data from Industry submission		[32]	[32]						
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
Were participants analysed in their allocated treatment groups, in accordance with the intention-to-treat 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 drop-outs between groups?	N	U	N	U	U	N	N	N	U
If so, were these imbalances in drop-outs 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*	NA	NA	Y	Y	N	N	Y	N

Y, yes; N, no; U, unclear; NA, not applicable.
a, interactive voice randomisation system; b, Code held by pharmacist; c, numbered bottles, blinded staff performed treadmill test, acenocoumarol was not blind to participants.
*but missing data available from published reviews.

Table 72: Quality assessment items adapted from criteria developed by EMA:[17] Pentoxifylline trials

Trial (first author, year, trial number if known)	Dawson 2000. 21-96-202	Otsuka 21-94-301	Otsuka 21-98-213	Lindegarde 1989	Porter 1982a, Gillings 1987	Gallus 1985	Di Perri 1983	Dettori 1989	Creager 2008
Data from peer reviewed journal	[57]	Unpublished trial from Otsuka	Unpublished trial from Otsuka	[70]	[71,72 73 74]	[75]	[76]	[68]	[69]
Data from peer reviewed systematic review(s)	[40]	[33]							
Data from Industry submission		[32]	[32]						
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 one week?	U	Y	U	Y	Y	Y	N	U	Y
If so, did patients have a baseline MWD with less than 25% change?	Y	Y	U	N	Y	U	NA	U	Y

Table 73: Quality assessment items adapted from criteria based on NHS CRD Report No.4 [26]; Naftidrofuryl trials

Trial (first author, year, trial number if known)	Kieffer 2001	Adhoute 1986	Trubestein 1984	Ruckley 1978	Spengel 2001
Data from peer reviewed journal(s)	[64]	[65]	[66]	[67]	[46]
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 intention-to-treat 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 drop-outs between groups?	N	N	N	U	N
If so, were these imbalances in drop-outs adjusted for in analyses?	NA	NA	NA	NA	NA
Is there any evidence of selective reporting of outcomes?	Y	N	N	N	N

Table 74. Quality assessment items adapted from criteria developed by EMA:[17] Naftidrofuryl trials

Trial (first author, year, trial number if known)	Kieffer 2001	Adhoute 1986	Trubestein 1984	Ruckley 1978	Spengel 2001
Data from peer reviewed journal(s)	[64]	[65]	[66]	[67]	[46]
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 one week?	Y	Y	Y	N	N
If so, did patients have a baseline MWD with less than 25% change?	Y	Y	N	NA	NA

Table 75: Quality assessment items adapted from criteria based on NHS CRD Report No.4 [26]; Inositol nicotinate trials

Trial (first author, year, trial number if known)	O'Hara 1988 (O'Hara 1985 same study)	Kiff 1988	Head 1986
Data from peer reviewed journal(s)	[77]	[79]	[80]
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 intention-to-treat 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 drop-outs between groups?	N	N	U
If so, were these imbalances in drop-outs adjusted for in analyses?	NA	NA	NA
Is there any evidence of selective reporting of outcomes?	Y	Y	Y
Y, yes; N, no; U, unclear; NA, not applicable.			

Table 76: Quality assessment items adapted from criteria developed by EMA:[17] Inositol nicotinate trials

Trial (first author, year, trial number if known)	O'Hara 1988 (O'Hara 1985 same study)	Kiff 1988	Head 1986
Data from peer reviewed journal(s)	[77]	[79]	[80]
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 one week?	N	N	N
If so, did patients have a baseline MWD with less than 25% change?	NA	NA	NA
Y, yes; N, no; U, unclear; NA, not applicable.			

Appendix 4: Data abstraction tables

Data is as reported in the primary publication listed in the "publication type" row, unless indicated otherwise by [ ]. This data is taken from a secondary publication, as referenced.

Two arm trials of Cilostazol versus placebo

	Strandness 2002. 21-94-201
Study details	
Publication type	Strandness 2002,[55] full report in peer reviewed journal
Additional sources of data	Strandness 1998,[56] Thompson 2002,[33] Cochrane review 2008,[27] Pande 2010,[29] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d) Placebo Cilostazol 100mg (50mg 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 & measures	MWD: treadmill with constant workload, 2.0 miles per hour (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 % change. Analysis: LOCF, 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 or older; stable, PAD induced IC of at least 6 months duration; no significant change in symptom severity for at least 3 months; diagnosis of peripheral arterial disease required Doppler measurement of an ankle– brachial index less than or equal to 0.90; resting ABI less than 0.90 and at least a 10-mm Hg decrease in ankle systolic blood pressure in the reference leg at the completion of testing maximal walking distance (MWD) on 2 consecutive prerandomisation treadmill tests varied by less than 20%; walking distance 30-200m; For subjects with equivalent bilateral disease, the limb with the lowest resting ABI 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 more than 81 mg/day of aspirin or more than 1,200 mg/day of ibuprofen; gross obesity; hypertension (> 200 mm Hg systolic or > 100 mm Hg diastolic supine resting pressures), malignancy or metastatic malignancy, exercise limiting cardiac disease, history of bleeding tendencies, and concomitant use of antiplatelet, anticoagulant, hemorheologic, or nonsteroidal antiinflammatory agents.
Concomitant interventions allowed or excluded	Allowed: Occasional use of Diclofenac sodium Disallowed: antiplatelet, anticoagulant, haemorheologic, or nonsteroidal antiinflammatory 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

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	133	129
Baseline characteristics		
Age	Mean 63.1 (SE10.2)	Mean 64.4 (SE10.2)
Sex	M 76.7%; F 23.7%	M 77.5%; F 22.5%
Smokers	50.4% current smokers	48.1% current smokers
Diabetics	23.3%	17.1%
Hypertension/ blood pressure	Not reported	Not reported
Hyperlipidaemia	Not reported	Not reported
Obesity or weight	Mean weight 80.1kg (SE14.8)	Mean weight 80.1kg (SE15.1)
Angina	Not reported	Not reported
History of vascular therapy		
Other	Currently drinks alcohol 61.7%	Currently drinks alcohol 55.0%
Withdrawals		
Withdrawals/loss to follow-up	9 didn't have at least one post randomisation treadmill test. 22.6% withdrew due to AEs	4 didn't have at least one post-randomisation treadmill test. 10.1% withdrew due to AEs
Results		
MWD n in analysis	124 at 24weeks	125 at 24weeks
MWD baseline	Mean 119.4m	
MWD follow-up	Mean 195.6m	
MWD change	Mean 76.2m (63.82%)	Mean 23.0m (20.8%)
MWD between group comparison	Estimated treatment effect 1.21, 95%CI 1.09-1.35 P=0.0003	
PFWD n in analysis		
PFWD baseline	[Otsuka submission[32] arithmetic mean 63.6]	[Otsuka submission[32] arithmetic mean 67.5]
PFWD follow-up		
PFWD change	[Robless 2008:[27]mean 58.5 (SD	[Robless 2008:[27] mean 17.2 (SD

	128.3)] [Otsuka submission[32] arithmetic mean 47.2 (84.3%)]	43.6)] [Otsuka submission[32] arithmetic mean 19.8 (37.7%)]
PFWD between group comparison	[Strandness 1998[56]: 22% net improvement] [Otsuka submission[32] estimated treatment effect (geometric mean ratio) 1.22, P=0.0015]	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI 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	
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). Nonsig 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	

	Beebe 1999. 21-92-202
Study details	
Publication type	Beebe 1999,[60] full report in peer reviewed journal
Additional sources of data	Cochrane review 2008,[27] Uchiyama 2009,[40] Rowlands 2007,[39] Industry submission[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg 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, 24 weeks.
Outcomes & Measures	MWD: treadmill with constant workload, 2.0 miles per hour (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events: method not reported AEs: patient self-report Mortality: method not reported HRQoL: SF-36, WIQ, COM
Notes on statistics	Log transformation of the data was used for walking distances
Population	
Eligibility criteria	Age 40 years or older; stable, PAD induced IC of at least 6 months duration; no significant change in symptom severity for at least 3 months; diagnosis of peripheral arterial disease required Doppler measurement of an ankle– brachial index less than or equal to 0.90 and a 10 mm Hg or more; decrease in ankle artery blood pressure following the onset of maximal walking distance; PFWD 30-200m on 2 consecutive pre-randomisation treadmill tests (12.5% incline, 3.2km/hour) varied by less than 20%. Excluded if rest pain; obesity; hypertension(>200 mm Hg systolic or >100 mm Hg 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[32] Dicolfenac sodium as clinically indicated] Disallowed: anticoagulants, antiplatelets, vasoactive, hemorrheologic, or nonsteroidal anti-inflammatory agents
Power calculation	Powered at 80% to detect a doubling of the cardiovascular morb.i.dity and all-cause mortality event rate, based on a 5% significance level (two-sided)
N randomised to treatments included in review	345

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	175	170
Baseline characteristics		
Age	Mean 64.3 (SD 8.5)	Mean 65.1 (SD 9.3)
Sex	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) range 41.8-115.0	Weight mean 78.8 (SD 16.0) range 47.7-129.4
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, 5 for other reasons
Results		
MWD n in analysis	140	140
MWD baseline	Geometric mean 129.7m	Geometric mean 147.8m
MWD follow-up	Geometric mean 258.8 at 24weeks (at 16weeks 216.0)	Geometric mean 174.6 at 24weeks (at 16weeks 161.9)
MWD change	Geometric mean change from baseline 1.51 at 24weeks (at 16 weeks 1.41); difference (258.8-129.7 = 129.1) [129.1 (463.3)][27] [Rowlands 2007:[39] mean change 51%]	Geometric mean change from baseline 1.15 at 24weeks (at 16weeks 1.11); difference 26.82 [26.82 (148.5)][27] [Rowlands 2007:[39] mean change 15%]
MWD between group comparison	p<0.001 at 24 weeks (p<0.001 at 16weeks)	
PFWD n in analysis	140	140
PFWD baseline	Geometric mean 70.4m	Geometric mean 72.4m
PFWD follow-up	Geometric mean 137.9 at 24weeks (at 16weeks 112.4)	Geometric mean 95.5 at 24weeks (at 16weeks 91.9)
PFWD change	Geometric mean change from baseline 1.59 at 24weeks (at 16weeks 1.43); difference 67.5 [Robless 2008:[27] 67.5 (130.4)] [Rowlands 2007:[39] mean change 59%]	Geometric mean change from baseline 1.20 at 24weeks (at 16weeks 1.15); difference 23.04 [Robless 2008:[27] 23.04 (63.78) [Rowlands 2007:[39] mean change 20%]
PFWD between group comparison	p<0.001 at 24weeks (p<0.001 at 16weeks)	
ABI n in analysis		
ABI baseline		
ABI follow-up		

ABI change		
ABI between group comparison		
Vascular events n in analysis	175	170
Vascular events follow up	24 weeks	
Vascular events included	1. Myocardial infarction verified by clinical symptoms, enzyme changes, and electrocardiogram changes indicative of myocardial infarction 2. Cerebrovascular infarct (stroke) verified by neurologic deficit lasting longer than 24 hours confirmed by angiography, computed tomographic scan, or magnetic resonance imaging 3. Arterial revascularization, including angioplasty or surgical vascular reconstruction: a. Procedures for peripheral vascular disease, including lower extremity bypass* b. Other procedures, including coronary artery bypass graft, carotid endarterectomy, and renal procedures* 4. Amputation for ischemia	
Vascular events reported	1. Number (%) myocardial infarction 2 (1.1) 2. Stroke 3 (1.7) 3. Arterial revascularization CABG/carotid endartectomy/renal procedure 0 (0) ; Peripheral vascular procedure/lower extremity bypass 2 (1.1) 4. Amputation 0 (0) [Uchiyama 2008:[40] 7 coronary vascular events, 2.0%; 2 cerebral vascular events 0.6%; 1 serious bleeding, 1.9%]	1. Number (%) Myocardial infarction 2 (1.2) 2. Stroke 2 (1.2) 3. Arterial revascularization CABG/carotid endartectomy/renal procedure 1 (0.6) ; Peripheral vascular procedure/lower extremity bypass 5 (2.9) 4. Amputation 1 (0.6) [Uchiyama 2008:[40] 3 coronary vascular events, 1.8%; 3 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 morb.i.dity 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.	Headache14.7%; 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		

HRQoL change	Mean score (mean change from baseline) 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)	Mean score (mean change from baseline) SF-36 Physical health (score range 0-100) Physical function 53.8 (2.0); Role–physical 49.8 (minus 2.8); Bodily pain 54.0 (minus1.8) ; Mental health (score range 0-100) Social function 82.5 (0.4); Role–emotional 84.2 (minus 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.	

	Elam 1998. 21-93-201
Study details	
Publication type	Elam 1998,[63] full report in peer reviewed journal
Additional sources of data	Thompson 2002,[33] Cochrane review 2008,[27] Uchiyama 2009,[40] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg 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 & Measures	MWD: graded test, constant speed, [Thompson 2002[33]: 2.0 miles per hour (3.2 km/hour), at 0% grade with a 3.5% increase in grade every 3 minutes] ABI: Doppler AEs: patient self-report
Notes on statistics	Unclear if LOCF as used for lipid outcomes was used for walking distance and ABI. Arithmetic means used for MWD and PFWD.
Population	
Eligibility criteria	Documented chronic, stable, symptomatic IC secondary to peripheral arterial disease (PAD). PAD was defined as an ankle-brachial index (ABI) less than or equal to 0.90; termination of walking on a variable-load, constant-speed treadmill due to IC (between 54-805 m); and a Doppler-measured drop of more than or equal to 10 mm Hg in blood pressure of 1 ankle after the treadmill test. For patients without a qualifying ABI, a 20mm Hg 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 2 determinations) was <350 mg/dL, and plasma LDL-C was between 100 and 190 mg/dL in all subjects. Women were not of child-bearing potential (either surgically sterilized or at least 1 year postmenopausal). Exclusions: gross obesity (>60% above ideal body weight), poorly controlled hypertension (systolic pressure >200 mm Hg; diastolic pressure >100 mm Hg), 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, hemorheologic, 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	

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	95	94
Baseline characteristics		
Age	Mean 66.7	Mean 65.8
Sex	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 81.7kg	Weight mean 81.1kg
Angina	8.4%	10.6%
History of vascular therapy	More CABG in placebo than Cilostazol group, figures NR	
Other	Prior myocardial infarction 10.6%	Prior myocardial infarction 17.1%
Withdrawals		
Withdrawals/loss to follow-up	13.7% did not complete study. 4 discontinued due to headache, 1 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 262.3m (SE 17)	Mean 278.2m (SE 17)
MWD follow-up	335 (SE 24)	304 (SE23)
MWD change	35.5% mean change; difference 72.7 [Robless 2008:[27] 79.05] [Otsuka submission[32] has 76.9 (35%)]	24.3% mean change; difference 25.8 [Robless 2008:[27] 36.1] [Otsuka submission[32] has 23.8 (18%)]
MWD between group comparison	Cilostazol improved sig over placebo p=0.004	
PFWD n in analysis		
PFWD baseline	Mean 122.2m	Mean 142.3m
PFWD follow-up		
PFWD change	[Otsuka submission[32] has 75.0 (67%)]	[Otsuka submission[32] has 48.8 (38%)]
PFWD between group comparison	[Otsuka submission[32] has p=0.0035]	
ABI 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
ABI baseline	Mean 0.66 (SE0.02)	Mean 0.65 (SE 0.02)
ABI follow-up	0.73 (0.02)	0.65 (0.02)
ABI change	Mean change 9.03% difference mean 0.07]	Mean change 1.2% (as reported, even though baseline and final

		scores aree the same) [difference mean 0.00]
ABI between group comparison	Cilostazol improved sig over placebo p<0.001 [Otsuka submission:[32] has p=0.0008)]	
Vascular events n in analysis	95	94
Vascular events follow up		
Vascular events included		
Vascular events reported	[Uchiyama 2008:[40] 0 coronary vascular events, ; 0 cerebral vascular events ; 1 serious bleeding, 1.1%]	[Uchiyama 2008:[40] 0 coronary vascular events, ; 0 cerebral vascular events ; 1 serious bleeding, 1.1%]
Vascular events between group comparison		
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		

	Dawson 1998. 21-90-201
Study details	
Publication type	Dawson 1998,[62] full report in peer reviewed journal
Additional sources of data	Cochrane review 2008,[27] Uchiyama 2009,[40] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg 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 & Measures	MWD: treadmill with constant workload, 2.0 miles per hour (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD ABI: continuous wave Doppler ultrasound and cuff occlusion AEs: patient self-report
Notes on statistics	log transform for walking distances, LOCF for missing data [Otsuka submission[32] states arithmetic mean used for MWD and PFWD]
Population	
Eligibility criteria	Stable symptoms of intermittent claudication 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 noninvasive vascular tests, including an ICD on the treadmill between 30 and 200 m and a minimum postexercise drop in Doppler-measured ankle systolic blood pressure of more than or equal to 20 mm Hg. Exclusions: limb-threatening chronic limb ischemia, manifested by ischemic 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 myocardial infarction (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 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), hemorheological agents (pentoxifylline), and

	nonsteroidal anti-inflammatory drugs. No specific counselling regarding smoking cessation, diet, or exercise was provided.
Power calculation	[Otsuka submission:[32] 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

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	54	27
Baseline characteristics		
Age	Mean 66 (SE1.1)	Mean 67 (SE2.0)
Sex	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 kg 79.1 (SE 2.3)	Weight mean kg 84.3 (SE 2.9)
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. 5 adverse drug reaction, 2 marked deterioration in clinical status, 2 ineligible for study, 1 laboratory abnormalities	total 18.5%, n=5. 1 adverse drug reaction, 1 marked deterioration in clinical status, 1 ineligible for study, 2 other reasons
Results		
MWD n in analysis	52	25
MWD baseline	mean m 141.9 (SE21.0)	mean m 168.6 (SE 33.1)
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). Percent change from baseline by geometric means 30.5%; difference 89.8 [Robless 2008:[27] 84.6] [Otsuka submission[32] has arithmetic mean change (% change) 88.9 (60%), geometric mean % change 30.5%]]	change from baseline least mean squares minus 16.9 (SE 32.6). Percent change from baseline by geometric means minus9.3%; difference minus16.5 [Robless 2008:[27] 4.56] [Otsuka submission[32] has arithmetic mean change (% change) 168.6 (minus16.9%), geometric mean % change minus9.3%]
MWD between group comparison	p=0.002. Percent change from baseline by geometric means p<0.01 (at follow-ups prior to week 12 nonsig)	
PFWD n in analysis	52	25
PFWD baseline	Mean m 71.2 (SE 6.0)	Mean m 77.7 (SE 8.4)
PFWD follow-up	112.5 (se 13.8)	84.6 (se 13.7)
PFWD change	Change from baseline least mean	Change from baseline least mean

	squares 42.6 (SE 8.2). Percent change from baseline by geometric means 31.7%; difference 41.3 [Robless 2008:[27] 38.9] [Otsuka submission[32] has arithmetic mean change (% change) 42.6 (55%), geometric mean % change 31.7%]	squares 3.5 (SE 11.7). Percent change from baseline by geometric means minus2.5%; difference 6.9 [Robless 2008:[27] 8.3] [Otsuka submission[32] has arithmetic mean change (% change) 3.5 (11%), geometric mean minus2.5%]
PFWD between group comparison	p=0.007. Percent change from baseline by geometric means p<0.01	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison	There was no significant change in resting or postexercise ABI	
Vascular events n in analysis	54	27
Vascular events follow up	12 weeks	
Vascular events included	Not reported	
Vascular events reported	1 stenosis, 1MI, 1 angina, 1 TIA (also in AEs)[Uchiyama 2008:[40] 2 coronary vascular events, 3.7%; 1 serious bleeding, 1.9%]	1 death from MI (also in AEs) [Uchiyama 2008:[40] 1 coronary vascular event, 3.7%; 1 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 serious adverse event as an occurrence that is fatal, life-threatening, disabling, or requires hospitalization; or a drug overdose, congenital anomaly, or cancer.)	
AEs reported	Serious AEs n=6 hospitalisations of cilostazol-treated patients (subclavian artery stenosis, unstable angina, pneumonia (n=2), myocardial infarction, and transient ischemic attack). Non-serious AEs 44% gastrointestinal complaints, headaches 20%	Serious AEs n=1 death from myocardial infarction in the placebo group. Non-serious AEs 15% gastrointestinal complaints, headaches 15%
AEs between group comparison		
Mortality reported		1 death from myocardial infarction
Mortality between group comparison		
HRQoL n in analysis		
HRQoL baseline		

HRQoL follow-up		
HRQoL change		
HRQoL between group comparison		

	Money 1998. 21-94-203
Study details	
Publication type	Money 1998,[61] full report in peer reviewed journal
Additional sources of data	Cochrane review 2008,[27] Uchiyama 2009,[40] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Not reported, but one of the centres was Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d)
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 & Measures	MWD: graded test, 2.0 miles per hour (3.2 km/hour), at 0% grade with a 3.5% increase in grade every 3 minutes PFWD: as MWD ABI: Doppler HRQoL: SF-36, WIQ
Notes on statistics	log transform for walking distances, LOCF [Otsuka submission[32] uses arithmetic mean and geometric mean comparison for MWD and PFWD]
Population	
Eligibility criteria	More than 40 years of age, PAOD for at least 6 months with no change in symptoms in the previous 3 months. Diagnosis of PAOD verified by a Doppler-measured ABI of 0.90 or lower after 10 minutes of rest and by a reduction in the blood pressure of at least one ankle artery by a minimum of 10 mm Hg 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 mm Hg when measured 1 minute after treadmill testing. baseline initial claudication distance (ICD) of at least 54 meters (corresponding to 1 minute on the treadmill), a reproducible absolute claudication distance (ACD; variance no greater than 20% between the two screening visits), and a maximum allowable ACD of 805 meters (corresponding to 15 minutes). Exclusion limb-threatening PAOD, including gangrene or ischemic rest pain; surgical or endovascular procedures in the preceding 3 months; gross obesity; hypertension, >200 systolic or >100 diastolic (mm Hg); 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	Allowed: Disallowed: warfarin, heparin, and pentoxifylline, and Antiplatelet agents, such as aspirin, persantine, and ticlopidine, and nonsteroidal anti-inflammatory agents
Power calculation	Powered at 80%, based on a 5% significance level (two-sided)

N randomised to treatments included in review	239

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	119	120
Baseline characteristics		
Age	Mean 64.8 (SD 9.4)	Mean 64.5 (SD 8.8)
Sex	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) range 42-130	weight mean 79.6 (SD 14.9) range 49-127
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 m trough 236.9 (SE 13.6); peak 211.4 (SE 12.4)	mean m trough 244.3 (SE 13.7); peak 219.3 (SE 12.9)
MWD follow-up	trough 332.6 (SE 20.0); peak 306.9 (SE 19.1) (at 12weeks trough 313.4 (SE 19.9);	trough 281.1 (SE 19.2); peak 267.5 (SE 18.5) (at 12weeks trough 279.2 (SE 18.3)
MWD change	at 16 weeks mean m 96.4 $p<0.05$ [Robless 2008:[27] 101.1] [Otsuka submission[32] has arithmetic mean change (% change), trough 96.4 (47.4%), peak 96.2 (56.1%)]	at 16 weeks mean m 31.4 $p<0.05$; [Robless 2008:[27] 47.1] [Otsuka submission:[32] has arithmetic mean change (% change), trough 31.4 (12.9%), peak 44.4 (25.4%)]
MWD between group comparison	Difference between Cilostazol and placebo, by geometric mean % 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[32] 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:[32] arithmetic mean trough 130.4, peak 118.5]	[Otsuka submission:[32] arithmetic mean trough 138.7, peak 129.9]
PFWD follow-up		
PFWD change	[Robless 2008:[27] 85.9] [Otsuka submission:[32] arithmetic mean change (% change) trough 76.8 (68.3%), peak 80.7 (87.1%)]	[Robless 2008:[27] has 54.2] [Otsuka submission:[32] arithmetic mean change (% change) trough 47.6 (38.5%), peak 53.1 (49.7%)]

PFWD between group comparison	difference between Cilostazol and placebo, by geometric mean % change, at 16 weeks, 27% trough, 32% peak, p<0.05 [Otsuka submission[32] 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]	
ABI n in analysis	Unclear	unclear
ABI baseline	Mean 0.64 (SD 0.02)	Mean 0.68 (SD 0.02)
ABI follow-up	0.70 (0.02)	0.69 (0.02)
ABI change	9% increase [70/64= 1.09375] [difference mean 0.06]	[69/68= 1.01470, so 1% increase] difference mean 0.01]
ABI between group comparison	p=0.0125	
Vascular events n in analysis	119	120
Vascular events follow up		
Vascular events included		
Vascular events reported	1 patient died of myocardial infarction 6 days after stopping cilostazol [Uchiyama 2008:[40] 1coronary vascular events, 0.8%; 0 cerebral vascular events ; 0 serious bleeding,]	[Uchiyama 2008:[40] 1coronary vascular events, 0.8%; 0 cerebral vascular events ; 0 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%). Serious AEs 11.8% (n=13)	headaches (9.2%), abnormal stools (5.0%), diarrhoea (6.7%), and dizziness (5.0%). Serious AEs 9.2% (n=11)
AEs between group comparison		
Mortality reported	1 patient died of myocardial infarction 6 days after stopping cilostazol	1 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 sig better for Cilostazol p=0.0331 [Otsuka submission[32] Physical function score p=0.0024, WIQ significant improvements in walking speed and specific measures of walking difficulty]	

	Otsuka 21-98-214-01. CASTLE. Hiatt / Stone 2008
Study details	
Publication type	Stone 2008,[47] Hiatt 2008 (RM22),[48] Hiatt 2007 (RM 2195).[49] Full reports in peer reviewed journals.
Additional sources of data	
Trial design	RCT, phase 4 (postmarketing), multicentre
Country	USA
Dates of participant recruitment	Up to Nov 2004
Sources of funding	Otsuka America Pharmaceuticals, Inc.
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d)
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 & Measures	AEs: mortality, cardiovascular deaths. Categorization of the event by the study sponsor according to standard definitions from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. All adverse events were recorded when patients were on-treatment through 14 days after discontinuation of treatment. Nonfatal adverse events were not monitored after drug discontinuation. Serious adverse bleeding events were defined as haemorrhages that were fatal, life-threatening, required or prolonged hospitalization, caused significant disability, or were medically significant in the judgment 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 intent-to-treat (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 randomized 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 old with a history of intermittent claudication secondary to PAD as diagnosed by a physician (specific ABI 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 noncompliant during the 30-day single-blind, run-in phase. Patients with current congestive heart

	failure 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 randomized, 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 hazard ratio.
N randomised to treatments included in review	1435

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	717	718
Baseline characteristics		
Age	Mean 66.5 (SD 10.2)	Mean 65.9 (SD 10.5)
Sex	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		
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI 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:[40] 126 coronary vascular events, 17.6%; 18 cerebral vascular events 2.5% ; 18serious 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:[40] 132 coronary vascular events, 18.4%; 34 cerebral vascular events 4.7% ; 22serious bleeding,3.1%]
Vascular events between group comparison	hazard ratio for cardiovascular deaths was 1.054 (95% CI,0.502-2.210; P=0.89) in the on-treatment population and 0.852 (95% CI, 0.515-1.410; P =0.533) in the ITT population	
AEs n in analysis	717	718
AEs follow up	Up to 144 weeks	
AEs included		
AEs reported	Minor events, No (%) Headache 75 (10.5) ;Palpitations 38 (5.3) ;Diarrhoea 78 (10.9) Bronchitis 23 (3.2). Serious events, No (%) Dyspnea 7 (1.0) ; Cerebrovascular accident 7 (1.0) ; Carotid artery stenosis 5 (0.7) ; Femoral artery occlusion 3 (0.4) ; Cardiac arrest 2 (0.3) ; Events leading to discontinuation, No. (%) Oedema 10 (1.4) ; Headache 15 (2.1) ; Diarrhoea 20 (2.8) . Serious bleeding events 18 (2.5%)	Minor events, No (%) Headache 35 (4.9) Palpitations 18 (2.5) Diarrhoea 48 (6.7) Bronchitis 37 (5.2) Serious events, No (%) Dyspnea 3 (0.4) Cerebrovascular accident 15 (2.1) Carotid artery stenosis 11 (1.5) Femoral artery occlusion 7 (1.0) Cardiac arrest 7 (1.0) Events leading to discontinuation, No. (%) Oedema 0 (0) Headache 2 (0.3) Diarrhoea 5 (0.7). 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	on-treatment analysis mortality hazard ratio of 0.99 (95% CI, 0.52-1.88, P=0.97). ITT all-cause mortality hazard ratio for cilostazol

	1.72	compared with placebo was 0.94 (95% CI, 0.64-1.39, P=0.77).
Mortality between group comparison	on-treatment analysis mortality hazard ratio of 0.99 (95% CI, 0.52-1.88, P=0.97). ITT all-cause mortality hazard ratio for cilostazol compared with placebo was 0.94 (95% CI, 0.64-1.39, P=0.77).	
HRQoL n in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between group comparison		

	O'Donnell 2009
Study details	
Publication type	O'Donnell 2009a,[50] full report in peer reviewed journal
Additional sources of data	O'Donnell 2009b,[82] (nondiabetic subgroup), O'Donnell 2008[54] (diabetic subgroup), O'Donnell 2009c,[53] O'Donnell 2009d (RM2126),[52] (diabetic subgroup).
Trial design	RCT, single centre
Country	Northern Ireland
Dates of participant recruitment	2004-2006
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 200mg (100mg b.i.d)
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 & Measures	MWD: treadmill with constant workload, 3.2km/hour (2 miles per hour) 10% gradient PFWD: as MWD AEs: patient self-report HRQoL: SF-36, VascuQoL
Notes on statistics	[Otsuka submission[32] The Mann Whitney U test was used for between-group differences. The Wilcoxon signed-rank test (WSR) was used for within-group differences. All Statistics were two sided and a –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 ABI less than 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 co-morb.i.dity 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	Allowed: Aspirin, Clopidogrel, Warfarin, Statin, ACE inhibitors, ACE II antagonists, B-blocker, Calcium antagonist diuretic

excluded	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 maximal walking distance, 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

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	51	55
Baseline characteristics		
Age	median 64.2 (range 37-86)	median 66.1(range 39-80)
Sex	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 endartectomy 3.9%, vascular arterial bypass/endovascular intervention 7.8%	CABG 9.1%, carotid endartectomy 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%), due to side effects n=6 [6 nondiabetics withdrew, 4 due to AEs] [Otsuka submission[32] 1 withdrew due to non-compliance, 6 due to adverse events, 1 due to other reasons]	n=7 (12.7%)due to side effects n=2 [3 nondiabetics withdrew] [Otsuka submission[32] 2 withdrew due to non-compliance, 2 due to adverse events, 3 due to other reasons]
Results		
MWD n in analysis	51	55
MWD baseline	median 144.4 m (IQR 99.7-204.3); nondiabetics median 144.4m, diabetics 118.5 m	median 138.6 m (IQR 101.7-193.8); nondiabetics median 138.6m, diabetics 115.6m
MWD follow-up	nondiabetics median 286.1m at 24 weeks, diabetics 158.3	nondiabetics median 227.1m at 24 weeks, diabetics 157.8m
MWD change	161.7% mean change, nondiabetics median 173.1% change, diabetics143.1%	79.0% mean change, nondiabetics median 92.1% change, diabetics 23.2%
MWD between group comparison	p=0.048, nondiabetics nonsig p=0.27, diabetics nonsig p=0.086	
PFWD n in analysis	51	55
PFWD baseline	median 69.7 m (IQR 50.1-94.8); nondiabetics median 69.7m,	median 63.9 m (IQR 45.2-85.8); nondiabetics median 63.5m,

	diabetics 69.3m	diabetics 66.2m
PFWD follow-up	nondiabetics median 82.7m at 24 weeks, diabetics 82.3m	nondiabetics median 85.0m at 24 weeks, diabetics 55.9m
PFWD change	67% mean change, nondiabetics median 84.8% change, diabetics 21.1%	51.6% mean change, nondiabetics median 66.5% change, diabetics minus4.4% change
PFWD between group comparison	p=0.63 nonsig, nondiabetics nonsig p=0.63, diabetics nonsig p=0.14	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
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 2009b[82] diabetic subgroup 12]	[O'Donnell 2009b[82] diabetic subgroup 14]
AEs follow up	24 weeks	
AEs reported	[O'Donnell 2009b[82] 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 2009b[82] Diabetics 7 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 2009b[82]: nondiabetics 39)	(O'Donnell 2009b[82]: nondiabetics 41)
HRQoL baseline		
HRQoL follow-up	mean (SE) Short-Form 36 % Physical Function 11.0 (4.5); Role Physical 7.8 (4.3) ; Body Pain, 3.7 (3.3) ; General Health 2.7 (3.5) ; PCS (physical component summary) 11.4 (3.2); Total 1.8 (3.2) ; VascuQol Activity 7.3 (4.6) ;	mean (SE): Short-Form 36 % Physical Function minus0.3 (3.1); Role Physical 5.4 (3.9) ; Body Pain, 10.5 (3.5) ; General Health minus1.0 (2.5) ; PCS (physical component summary) 5.1 (3.4); Total 1.4 (1.7) ; VascuQol Activity 1.8 (2.9) ;

	Symptom 3.1 (3.0) ; Pain 10.4 (5.1); Emotion 5.7 (4.1) ; Social 1.1 (5.9) ; Total 5.5 (3.5) diabetics [O'Donnell 2009d[52]]: at 24 weeks median (interquartile range): Short-Form 36% Physical Function 38.1 (29.7-41.3); Role Physical 34.8 (28.7-43.4) ; Body Pain, 46.1 (33.2-50.8) ; General Health 42.4 (31.7-45.8) ; Total 42.5 (34.8-46.2) ; VascuQol Activity 3.9 (3.4-5.0) ; Symptom 5.5 (5.4-6.1) ; Pain 5.0 (4.4-5.6); Emotion 5.6 (4.5-6.6) ; Social 5.0 (4.5-6.5) ; Total 5.2 (4.3-5.6)	Symptom 3.2 (2.6) ; Pain 13.2 (4.3); Emotion 1.8 (4.0) ; Social 3.4 (5.2) ; Total 3.0 (2.1) diabetics [O'Donnell 2009d[52]]: at 24 weeks median (interquartile range): Short-Form 36% Physical Function 27.6 (24.5-40.2); Role Physical 37.3 (25.0-45.9) ; Body Pain, 37.2 (33.0-43.8) ; General Health 41.0 (38.2-47.0) ; Total 37.8 (31.2-46.3) ; VascuQol Activity 4.4 (2.8-4.7) ; Symptom 5.3 (3.9-5.4) ; Pain 4.3 (3.4-4.8); Emotion 3.7 (3.0-5.0) ; Social 4.0 (3.5-5.0) ; Total 4.3 (3.2-4.9)
HRQoL change		
HRQoL between group comparison	nondiabetics at 24 weeks mean (SE): Short-Form 36 % Physical Function p=0.013 sig more improvement for cilostazol; Role Physical p=0.62 ; Body Pain, p=0.21 ; General Health p=0.48 ; PCS (physical component summary) p=0.044 sig 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 Walking impairment questionnaire - nonsig between groups distance p=0.41, speed p=0.88 (even though cilostazol group had significantly improved and placebo group had nonsig improvement). diabetics [RM2126] at 24 weeks Short-Form 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 (sig more increase for placebo, cilostazol more improved) ; Pain p=0.08 ; Emotion p=0.013(sig more increase for cilostazol, cilostazol more improved) ; Social p=0.06 ; Total p=0.05 (sig more increase for cilostazol, cilostazol more improved)	

	Otsuka 21-95-201
Study details	
Publication type	Thompson 2002,[33] systematic review in peer reviewed journal
Additional sources of data	Cochrane review 2008,[27] Uchiyama 2009,[40] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d)
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 & Measures	MWD: treadmill with constant workload, 2.0 miles per hour (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events: unclear HRQoL: [Otsuka submission[32]: SF-36, WIQ]
Notes on statistics	
Population	
Eligibility criteria	age 40 years or older; stable, PAD induced IC of at least 6 months duration; no significant change in symptom severity for at least 3 months; diagnosis of peripheral arterial disease required Doppler measurement of an ankle– brachial index less than or equal to 0.90; maximal walking distance (MWD) on 2 consecutive prerandomisation treadmill tests varied by less than 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:[32] acetaminophen] Disallowed: patients receiving anticoagulants or using more than 81 mg/day of aspirin or more than 1,200 mg/day of ibuprofen. No specific counselling regarding smoking cessation, diet, or exercise was given
Power calculation	[Otsuka submission[32]: based on results from a previous study, 60 patients per group was calculated to provide greater than 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

Treatment group	**Cilostazol 100mg bid**	**Placebo**
N randomised to treatment	72	70
Baseline characteristics		
Age	[Robless 2008:[27] mean age 68] [Otsuka submission[32]has mean age 67.6 (SD8.8)]	[Robless 2008:[27] mean age 66] [Otsuka submission[32] has mean age 65.6 (SD 7.4)]
Sex	[Robless 2008:[27] M 75%; F 25%]	[Robless 2008:[27] M 81%; F 19%]
Smokers	[Otsuka submission[32] has 38.1%]	[Otsuka submission[32] has 38.6%]
Diabetics	[Otsuka submission[32] has 30.6%]	[Otsuka submission[32] has 34.3%]
Hypertension/ blood pressure		
Hyperlipidaemia		
Obesity or weight	[Otsuka submission[32] has weight 78.8Kg (SD 15.7)]	[Otsuka submission[32] has weight 84.3 (SD16.8)]
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	[Otsuka submission[32] has 17 withdrawals. Failed screening, 1; marked deterioration, 1; adverse event, 14; other, 1.]	[Otsuka submission[32] has 8 withdrawals. Lack of response, 1; adverse event, 6; other, 1]
Results		
MWD n in analysis	[Otsuka submission[32] has 60]	[Otsuka submission[32] has 66]
MWD baseline	[Otsuka submission[32] has mean 121.9]	[Otsuka submission[32] has mean 123.4]
MWD follow-up		
MWD change	approx 28% (estimated from figure 1 Thompson 2002[33]) [Robless 2008:[27] mean 35.2 (SD 72.05)] [Otsuka submission[32] has arithmetic mean change 37.5 (59.4%),]	approx 30% (estimated from figure 1 Thompson 2002[33]) [Robless 2008:[27] mean 38.1 (SD 69.7)] [Otsuka submission[32] has arithmetic mean change 33.9 (59.6%)]
MWD between group comparison	Nonsig [Otsuka submission[32] has 0.8585 ratio of geometric mean change 1.02 (CI 0.88-1.18), P=0.7925]	
PFWD n in analysis	[Otsuka submission[32] has 60]	[Otsuka submission[32] has 66]
PFWD baseline	[Otsuka submission[32] has mean 65.7]	[Otsuka submission[32] has mean 67.4]
PFWD follow-up		
PFWD change	approx 58% (estimated from figure 2 Thompson 2002[33]) [Robless 2008:[27] mean 41.4 (SD 63.2)] [Otsuka submission[32] has arithmetic mean change 37.5 (59.4%)]	approx 52% (estimated from figure2 Thompson 2002[33]) [Robless 2008:[27]mean 34.4 (SD 57.3)] [Otsuka submission[32] has arithmetic mean change 33.9 (59.6%)]
PFWD between group comparison	Nonsig [Otsuka submission[32] has 0.4818 ratio of geometric mean change 1.18 (CI 1.02 – 1.37), P=0.0309]	
ABI n in analysis		

ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis	145 (including 150mg b.i.d group which was excluded from other analyses)	70
Vascular events follow up		
Vascular events included		
Vascular events reported	[Uchiyama 2008:[40] 3 coronary vascular events, 2.1%; 0 cerebral vascular events ; 0 serious bleeding,]	[Uchiyama 2008:[40] 1coronary vascular events, 1.4%; 1cerebral vascular events 1.4% ; 0 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[32] 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.]	

Three arm trials of Cilistazol, pentoxifylline and placebo.

	Dawson 2000. 21-96-202
Study details	
Publication type	Dawson 2000,[57] full report in peer reviewed journal
Additional sources of data	Cochrane review 2008,[27] Uchiyama 2009,[40]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals, Inc
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d) plus placebo Pentoxifylline 1200mg daily dose (400mg tid) plus placebo
Comparator	Placebo
Run-in phase	No, but 2-3 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 & Measures	MWD: treadmill with graded test, 2.0 miles per hour (3.2 km/hour), at 0% grade with a 3.5% increase in grade every 3 minutes PFWD: as MWD ABI: Doppler AEs: patient self-report Mortality HRQoL: SF-36, WIQ
Notes on statistics	Geometric mean change in maximal walking distance was determined. This change was expressed as a logarithm of the quotient of the posttreatment maximal walking distance divided by the baseline maximal walking distance 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 peripheral arterial disease required Doppler measurement of an ankle– brachial index less than or equal to 0.90; maximal walking distance (MWD) on 2 consecutive prerandomisation treadmill tests varied by less than 20%; baseline PFWD more than or equal to 53.6 m; MWD less than or equal to 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 1,200 mg per day of ibuprofen Disallowed: anticoagulants or other antiplatelet agents, NSAIDs
Power calculation	Two hundred patients per treatment group would provide greater than 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	698

review	

Treatment group	**Cilostazol 100mg bid**	**Pentoxifylline 400mg tid**	**Placebo**
N randomised to treatment	227	232	239
Baseline characteristics			
Age	mean 66 (SD 9)	mean 66 (SD 9)	mean 66 (SD 9)
Sex	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 81kg (AD 16)	weight 82kg (AD 15)	weight 81kg (AD 15)
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 m 241 (SD 123)	mean m 238 (SD 119)	mean m 234 (SD 119)
MWD follow-up	mean m 350 (SD 209)	mean m 308 (SD183)	mean m 300 (SD 180)
MWD change	mean m 107 (SD 158) [Robless 2008:[27] 107.36 (158.4)]	mean m 64 (SD 127) [Robless 2008:[27] 64.7 (134.61)]	mean m 65 (SD 135) [Robless 2008:[27] 64.4 (126.6)]
MWD between group comparison	cilostazol vs placebo p=0.0005 ; pentoxifyllinevs placebo 0.82 ; cilostazol vs pentoxifyllinep=0.0002		
PFWD n in analysis	205	212	226
PFWD baseline	mean m 124 (SD 81)	mean m 126 (SD 79)	mean m 122 (SD 69)
PFWD follow-up	mean m 218 (SD 149)	mean m 202 (SD139)	mean m 180 (SD 115)
PFWD change	mean m 94 (SD 127) [Robless 2008:[27] 93.6 (127.4)]	mean m 74 (SD 106) [Robless 2008:[27] 56.5 (93.1)]	mean m 57 (SD 93) [Robless 2008:[27] 73.6 (93.1)]
PFWD between group comparison	cilostazol vs placebo p=0.0001 ; pentoxifylline vs placebo 0.07 ; cilostazol vs pentoxifylline p=0.02		

ABI n in analysis	205	212	226
ABI baseline	mean 0.66 (SD0.18)	mean 0.66 (SD0.21)	mean 0.68 (SD0.42)
ABI follow-up	mean 0.70 (SD0.18)	mean 0.71 (SD0.24)	mean 0.67 (SD0.19)
ABI change	[difference in means 0.04]	[difference in means 0.05]	[difference in means minus0.01]
ABI between group comparison	sig more improvement in cilostazol than placebo p<0.01. nonsig between other groups		
Vascular events n in analysis			
Vascular events follow up			
Vascular events included			
Vascular events reported	[Uchiyama 2008:[40] 2 coronary vascular events, 0.9%; 3cerebral vascular events 1.3% ; 0 serious bleeding,]	[Uchiyama 2008:[40] 2 coronary vascular events, 0.8%; 0 cerebral vascular events ; 0 serious bleeding,]	
Vascular events between group comparison			
AEs n in analysis	227	232	239
AEs follow up			
AEs reported	n (%) Patients with at least one event 201 (86) ; Headache 63 (28) ; Pain 30 (13) ; Diarrhoea 43 (19) ; Pharyngitis 22 (10) ; Peripheral vascular disorder 13 (6) ; Abnormal stools 33 (15) ; Palpitation 39 (17) ; Serious adverse events 27 (12)	n (%) Patients with at least one event 200 (86) ; Headache 26 (11) ; Pain 38 (16) ; Diarrhoea 18 (8) ; Pharyngitis 32 (14) ; Peripheral vascular disorder 22 (10) ; Abnormal stools 12 (5) ; Palpitation 5 (2) ; Serious adverse events 31 (13)	n (%) Patients with at least one event 188 (79) ; Headache 28 (12) ; Pain 33 (14) ; Diarrhoea 13 (5) ; Pharyngitis 17 (7) ; Peripheral vascular disorder 26 (11) ; Abnormal stools 7 (3) ; Palpitation 3 (1) ; Serious adverse events 31 (13)
AEs between group comparison	withdrawal due to AEs similar in cilostazol (16%) and pentoxifylline (19%), sig 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	Not reported		
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 Walking Impairment Questionnaire.

	Otsuka 21-94-301
Study details	
Publication type	Thompson 2002,[33] systematic review in peer reviewed journal
Additional sources of data	Uchiyama 2009,[40] Otsuka Pharmaceuticals submission to NICE.[32]
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Otsuka
Intervention(s) and comparator	
Treatment groups	Cilostazol 200mg (100mg b.i.d) Pentoxifylline 1200mg (400mg tid)
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 & Measures	MWD: treadmill with constant workload, 2.0 miles per hour (3.2 km/hour) at a constant 12.5% grade PFWD: as MWD Vascular events
Notes on statistics	[Otsuka submission[32] 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 versus placebo and cilostazol 100 mg b.i.d versus pentoxifylline 400 mg tid. Secondary analyses were performed for ACD and ICD with last visit and time point analyses using LOCF, completers, and categorical analysis. Continuous efficacy measures: analysis of variance and the Wilcoxon rank sum test. Categorical efficacy measures: van Elteren test and CMH 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 or older; stable, PAD induced IC of at least 6 months duration; no significant change in symptom severity for at least 3 months; diagnosis of peripheral arterial disease required Doppler measurement of an ankle– brachial index less than or equal to 0.90; maximal walking distance (MWD) on 2 consecutive prerandomisation treadmill tests varied by less than 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	Allowed: 81 mg/day of aspirin, 1,200 mg/day of ibuprofen. Disallowed: Anticoagulants No specific counselling regarding smoking

excluded	cessation, diet, or exercise was provided
Power calculation	[Otsuka submission[32]: 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 standard deviation 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 versus placebo comparison and is 34% for the cilostazol versus pentoxifylline comparison.]
N randomised to treatments included in review	370

Treatment group	**Cilostazol 100mg bid**	**Pentoxifylline 400mg tid**	**Placebo**
N randomised to treatment	123	123	124
Baseline characteristics			
Age	[Otsuka submission[32] has mean 66 (SD 8.3)]	[Otsuka submission[32] has mean 66.4 (SD 8.2)]	[Otsuka submission[32] has mean 65.9 (SD 8.8)]
Sex	[Otsuka submission[32] has M69.9%; F30.1%]	[Otsuka submission[32] has M72.4%; F27.6%]	[Otsuka submission[32] has M73.4%; F26.6%]
Smokers	[Otsuka submission[32] has 29%]	[Otsuka submission[32] has 32.5%]	[Otsuka submission[32] has 35.5%]
Diabetics	[Otsuka submission[32] has12.2%]	[Otsuka submission[32] has10.6%]	[Otsuka submission[32] has 12.1%]
Hypertension/ blood pressure			
Hyperlipidaemia			
Obesity or weight	[Otsuka submission[32] has weight (n=121) 73.9Kg (SD13.6)]	[Otsuka submission[32] has weight 73.1 (SD11.7)]	[Otsuka submission[32] has weight 72.4 (SD11.5)]
Angina			
History of vascular therapy			
Other			
Withdrawals			
Withdrawals/loss to follow-up	[Otsuka submission[32] has 34 withdrew. Non-compliance, 1; marked deterioration, 1; adverse event, 30; Death, 1; other, 1.]	[Otsuka submission[32] has 37 withdrew. Non-compliance, 2; marked deterioration, 0; adverse event, 33; Death, 0; other, 2.]	[Otsuka submission[32] has 19 withdrew. Non-compliance, 2; marked deterioration, 0; adverse event, 14; Death, 1; other, 2.]
Results			
MWD n in analysis	[Otsuka submission[32] has n=123]	[Otsuka submission[32] has n=118]	[Otsuka submission[32] has n=122]
MWD baseline	[Otsuka submission[32] has mean 128.1]	[Otsuka submission[32] has mean 135.4]	[Otsuka submission[32] has mean 128.1]
MWD follow-up			
MWD change	approx 68% (estimated from figure 1 Thompson	approx 65% (estimated from figure 1 Thompson	approx 42% (estimated from figure 1 Thompson

	2002[33]) [Otsuka submission:[32] arithmetic mean change 86.3 (54.9%)]	2002[33]) [Otsuka submission:[32] arithmetic mean change 86.7 (64.0%)]	2002[33]) [Otsuka submission:[32] arithmetic mean change 52.7 (46.1%)]
MWD between group comparison	Nonsig. [Otsuka submission[32] 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 0.88-1.11), P=0.8700, Cilostazol vs Placebo 1.06 (CI 0.94-1.18) P=0.3616, Pentoxifylline vs Placebo 1.07 (CI 0.95-1.20) P=0.2876]		
PFWD n in analysis	[Otsuka submission[32] has n=123]	[Otsuka submission[32] has n=118]	[Otsuka submission[32] has n=122]
PFWD baseline	[Otsuka submission[32] has mean 77.7]	[Otsuka submission[32] has mean 81.4]	[Otsuka submission[32] has mean 74.3]
PFWD follow-up			
PFWD change	approx 68% (estimated from figure 2 Thompson 2002[33]) [Otsuka submission[32] has arithmetic mean change 52.3 (59.5%)]	approx 59% (estimated from figure 2 Thompson 2002[33]) [Otsuka submission[32] has arithmetic mean change 46.6 (72.9%)]	approx 50% (estimated from figure 2 Thompson 2002[33]) [Otsuka submission[32] has arithmetic mean change 36.5 (59.1%)]
PFWD between group comparison	Nonsig. [Otsuka submission[32] 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 0.87-1.11), P=0.7217, Cilostazol vs Placebo 1.01 (CI 0.90-1.14) P=0.0.8258, Pentoxifylline vs Placebo 1.04 (CI 0.92-1.17) P=0.5678]		
ABI n in analysis			
ABI baseline			
ABI follow-up			
ABI change			
ABI between group comparison			
Vascular events n in analysis	123		124
Vascular events follow up			
Vascular events included			
Vascular events reported	[Uchiyama 2008:[40] 2 coronary vascular events, 1.6%; 2 cerebral vascular events 1.6%; 1 serious bleeding,0.8%]		[Uchiyama 2008:[40] 3 coronary vascular events, 2.4%; 0 cerebral vascular events ; 0 serious bleeding,]
Vascular events between group comparison			
AEs n in analysis	[Otsuka submission[32] has n=123]	[Otsuka submission[32] has n=123]	[Otsuka submission[32] has n=124]
AEs follow up			
AEs reported	[Otsuka submission[32] has one or more adverse	[Otsuka submission[32] has one or more adverse	[Otsuka submission[32] has one or more adverse

	events, 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%).]	events, 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%).]	events, 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			

	OTSUKA 21-98-213
Study details	
Publication type	Pande 2010,[29] systematic review in peer reviewed journal
Additional sources of data	Otsuka industry submission[32]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Otsuka America Pharmaceuticals, Inc
Intervention(s) and comparator	
Treatment groups	1) Cilostazol 200mg daily dose (100mg b.i.d) 2) [Otsuka submission[32] has Pentoxifylline 1200mg daily dose (400mg t.i.d)]
Comparator	Placebo
Run-in phase	Not reported
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, every 4 weeks until 24 weeks
Outcomes & Measures	MWD: treadmill with constant workload, 2.0 miles per hour (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:[32] 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 CMH 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	$0 years or older, with PAD and intermittent claudication with stable symptoms for the preceding 3 months. PAD diagnosed as an abnormal resting ABI [Otsuka submission:[32] ABI≥0.4 and ≤0.9 in the reference leg], with addition decline in post-exercise ABI ≥10 mmHg as confirmation. Symptomatic patients with normal resting ABI but with pressure drop of >20mmHg were also eligible. MWD varied by no more than 20% on two to three consecutive treadmill tests. Exclusion: limb-threatening ischemia, limb revascularization within 3 months, unstable coronary artery disease, coronary revascularization 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. Congestive heart failure.
Concomitant	Allowed: aspirin <81mg/day

interventions allowed or excluded	Disallowed: aspirin >91mg/day, high dose ibuprophen (>1200 mg/day)
Power calculation	[Otsuka submission[32] has Based on the results of study 21-96-202, the between-group difference in the change from baseline in the log(ACD) was expected to be 0.14, with a standard deviation 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[32]: 785]

Treatment group	**Cilostazol 200mg tid**	**Pentoxifylline 400mg tid**	**Placebo**
N randomised to treatment	[Otsuka submission[32]: 261]	[Otsuka submission[32]: 262]	[Otsuka submission[32]: 262]
Baseline characteristics			
Age	[Otsuka submission[32]: 66.7 ± 9.9	[Otsuka submission[32]: 67.4 ± 9.4	[Otsuka submission[32]:
Sex	[Otsuka submission[32]: M75.4%; F24.6%]	[Otsuka submission[32]: M76.9%; F23.1%]	[Otsuka submission[32]: M75.4%; F24.6%]
Smokers	[Otsuka submission[32]: 31.5%]	[Otsuka submission[32]: 33.8%]	[Otsuka submission[32]: 31.9%]
Diabetics			
Hypertension/ blood pressure			
Hyperlipidaemia			
Obesity or weight	[Otsuka submission[32]: (n=258) mean 83.2 Kg (SD 15.2)	[Otsuka submission[32]: (n=260) mean 79.6Kg (SD 15.3)	[Otsuka submission[32]: (n=260) mean 82.9Kg (SD 15.8)
Angina			
History of vascular therapy			
Other			
Withdrawals			
Withdrawals/loss to follow-up	[Otsuka submission[32]: 35.4% overall. Non compliance, 2.7%; adverse events,24.6% ; other,8.1%.]	[Otsuka submission[32]: 31.5% overall. Non compliance, 3.5%; adverse events,18.8% ; other,9.2%.]	[Otsuka submission[32]: 26.9% overall. Non compliance, 4.2%; adverse events, 12.7%; other,10%.]
Results			
MWD n in analysis	[Otsuka submission[32]: 260]	[Otsuka submission[32]: 260]	[Otsuka submission[32]: 260]
MWD baseline	[Otsuka submission[32]: arithmetic mean 138.2]	[Otsuka submission[32]: arithmetic mean 148.0]	[Otsuka submission[32]: arithmetic mean 141.4]
MWD follow-up			
MWD change	[Otsuka submission[32]: arithmetic mean 60.4 (43.6%),]	[Otsuka submission[32]: arithmetic mean 75.6 (51.2%)]	[Otsuka submission[32]: arithmetic mean 59.0 (41.4%)]
MWD between group comparison	Cilostazol vs placebo mean difference 1.3 meters (SE 11.7), p=0.910. Estimated treatment effect 1.03 (95% CI 0.95-1.12) [Otsuka submission.[32] 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 0.95-1.12), P=0.4749; Pentoxifylline vs placebo 1.05 (95% CI 0.97 – 1.14), P=0.2385, Cilostazol vs Pentoxifylline 0.98 (95% CI 0.90 – 1.07), P=0.6491.]		
PFWD n in analysis	[Otsuka submission[32]: 260]	[Otsuka submission[32]: 260]	[Otsuka submission[32]: 260]
PFWD baseline	[Otsuka submission[32]: arithmetic mean 74.9]	[Otsuka submission[32]: arithmetic mean 77.1]	[Otsuka submission[32]: arithmetic mean 75.5]
PFWD follow-up			
PFWD change	[Otsuka submission[32]: arithmetic mean 47.3 (62.6%),]	[Otsuka submission[32]: arithmetic mean 62.6 (86.0%)]	[Otsuka submission[32]: arithmetic mean 45.3 (65.0%)]
PFWD between group comparison	Cilostazol vs placebo 1.02 (95% CI 0.92-1.13) [Otsuka submission.[32] 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 0.92-1.13), P=0.7692; Pentoxifylline vs placebo 1.08 (95% CI 0.97 – 1.19), P=0.1517, Cilostazol vs Pentoxifylline 0.94 (95% CI 0.85 – 1.05), P=0.2602.]		
ABI n in analysis			
ABI baseline			
ABI follow-up			
ABI change			
ABI between group comparison			
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[32]: 260]	[Otsuka submission[32]: 260]	[Otsuka submission[32]: 260]
AEs follow up	24 weeks		
AEs reported	[Otsuka submission[32]. 79.6% patients had ≥1 AE. AEs occurring in >10% of patients: pharyngitis, 9.6%; headache, 16.5%; diarrhoea, 13.1%; pain, 8.1%; palpitation, 10%.]	[Otsuka submission[32]. 80% patients had ≥1 AE. AEs occurring in >10% of patients: pharyngitis, 15%; headache, 10.8%; diarrhoea, 11.2%; pain, 8.8%; palpitation, 1.5%.]	[Otsuka submission[32]. 75.8% patients had ≥1 AE. AEs occurring in >10% of patients: pharyngitis, 11.2%; headache, 6.2%; diarrhoea, 6.2%; pain, 11.5%; 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[32] 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.]		

Two arm trials of naftidrofuryl and placebo

	Kieffer 2001
Study details	
Publication type	Kieffer 2001,[64] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	France
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl 600mg (200mg tid)
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks, 16 weeks, 24 weeks
Outcomes & Measures	MWD: treadmill with constant workload, 3.2km/hour, 10% incline PFWD: as MWD ABI: mode of measurement not reported Vascular events AEs: recorded whether or not considered treatment related
Notes on statistics	log transform for walking distances
Population	
Eligibility criteria	Outpatients of both sexes, aged 35 to 85 years, with moderately severe chronic, stable intermittent claudication 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 100-300m (treadmill 3.2km/hour, 10%slope), did not vary by more than 25% during placebo run-in phase. Exclude Fontaine stage 1, 3 or 4; nonvascular 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 (less than 70%) compliance with medication during placebo run-in
Concomitant interventions allowed or excluded	Allowed: Not reported Disallowed: Not reported
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

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to	98	98

treatment		
Baseline characteristics		
Age	Mean 67.5 (SD 10.1)	Mean 66.3 (SD 10.9)
Sex	M 78.6%; f 21.3%	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 (SD4.3)	BMI mean 24.5 (SD3.4)
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	9 randomised to naftidrofuryl didn't supply any more data (5 patient refusal, 2 reported AE, 2 lost to follow up). A further 13 withdrew during 6month study (6 patient refusal, 4 lost to follow-up, 3 not specified)	6 randomised to placebo didn't supply any more data (4 patient refusal, 1 reported AE, 1 didn't meet eligibility criteria). A further 16 withdrew during 6month study (5 patient refusal, 6 lost to follow-up, 5 not specified)
Results		
MWD n in analysis	89	92
MWD baseline	Geometric mean 191.9, arithmetic mean 202m (SD 62)	Geometric mean 203.0, arithmetic mean 213m (SD 63)
MWD follow-up	At 24 weeks, geometric mean 350.6. Arithmetic means 16weeks 322, 24 weeks 385, 32 weeks (2months without treatment) 296	At 24 weeks, geometric mean 231.1. Arithmetic means 16weeks 266, 24weeks 259, 32 weeks (2months without treatment) 265
MWD change	At 24 weeks by geometric mean 82.7%. Subgroup geometric means diabetics 87.2% change, nondiabetics 81.6% change	At 24 weeks by geometric mean 13.9%. Subgroup geometric means diabetics 9.5% change, nondiabetics 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 8weeks non-significant).	
PFWD n in analysis	89	92
PFWD baseline	geometric mean 172.3, arithmetic mean 182m (SD 64)	geometric mean 177.9, arithmetic mean 189m (SD 63)
PFWD follow-up	at 24 weeks, geometric mean 330.5. arithmetic means 16weeks 298, 24weeks 367, 32 weeks (2months without treatment) 281	at 24 weeks, geometric mean 207.8. arithmetic means 16weeks 244, 24weeks 237, 32 weeks (2months without treatment) 240
PFWD change	at 24 weeks by geometric mean 91.8%. Subgroup geometric means diabetics 103.0% change, nondiabetics 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, nondiabetics 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 16weeks $p<0.01$, 24weeks $p<0.001$, 32 weeks (2months without treatment) $p<0.05$ (at 8weeks nonsig)	

ABI n in analysis	89	92
ABI baseline	mean 0.55 (SD 0.35)	mean 0.55 (SD 0.37)
ABI follow-up	mean 0.58 (SD 0.33)	mean 0.59 (SD 0.33)
ABI change	difference 0.03	difference 0.04
ABI between group comparison	nonsig	
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported	(2 vascular surgery, also listed in AEs)	(3 vascular sugery, 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 n=18. number of AEs 21 (of which 12 serious of which 2 vascular surgery and 2 hospitalisation for other diseases and 2 surgery for other condition). Nonserious possibly treatment related 1 mild digestive disorder.	number of patients with at least one AE n=21. number of AEs 25 (of which 13 serious of which 3 vascular surgery and 6 hospitalisation for other diseases and 1 surgery for other condition). Nonserious possibly treatment related 3.
AEs between group comparison	nonsig	
Mortality reported		
Mortality between group comparison		
HRQoL n in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between group comparison		

	Adhoute 1986
Study details	
Publication type	Adhoute 1986,[65] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	France
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl 600mg (200mg tid)
Comparator	Placebo
Run-in phase	
Treatment duration	24 weeks
Outcome(s)	
Follow-up	baseline after 4 week run-in, 3 months, 6 months
Outcomes & Measures	PFWD: treadmill with constant workload 3km/hour 10% slope ABI: ultra-sonographic measure AEs: patient self-report
Notes on statistics	No adjustment due to homogeneity of groups
Population	
Eligibility criteria	Patients of both sexes between 40 and 70 years with Fontaine stage II PAOD, IC for at least 6months, diagnosis confirmed by angiography or Doppler velocimetry examination, PFWD (at 3km/hour 10% slope) 150-300m and after a wash-out period of 1month up to 20% variation in PFWD. Exclude vascular surgery or specific physical training within 6months, recent myocardial infarction, angina pectoris, myocardial/renal/hepatic insufficiency, labile diabetes, nontreated 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	Not reported
N randomised to treatments included in review	154

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	Not reported. 64 remained at end of study.	Not reported. 54 remained at end of study.
Baseline characteristics		
Age	mean 58.53 (+/- 8.35)	mean 59.62 (+/- 8.35)
Sex	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 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	214.95m mean (SD 58.33)	214.95m mean (SD 58.33)
PFWD follow-up	335.21m mean (SD 193.11) at 12weeks; at 24 weeks 416.36 (SD 273.58)	274.24m mean (SD 124.55) at 12weeks; at 24 weeks 313.01 (SD 169.56)
PFWD change	at 24 weeks 201.37 (SD 254.80) sig improved p<0.02; [RM1987 has mean 199.63 (SD 247.91)]	at 24 weeks 98.33 (SD 145.65) sig improved p<0.02 ; [RM1987 has mean 106.54 (SD 182.66)]
PFWD between group comparison	At 12 weeks naftidrofuryl sig more improved than placebo p<0.05; at 24 weeks naftidrofuryl sig more improved than placebo p<0.02	
ABI n in analysis		
ABI baseline	0.65 (SD 0.24)	0.61 (SD 0.20)
ABI follow-up	0.67 (SD 0.23)	0.62 (SD 0.17)
ABI change	nonsig	nonsig
ABI between group comparison	nonsig	
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
Vascular events between group comparison		
AEs n in analysis	64	54
AEs follow up		
AEs reported	Gastric, 5.	Gastric, 6.
AEs between group comparison		
Mortality reported	1 death due to myocardial infarction. Doesn't 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		

	Trubestein 1984
Study details	
Publication type	Trubestein 1984,[66] full report in peer reviewed journal
Additional sources of data	De Backer Tine 2008 (RM1987)[30]
Trial design	RCT, multicentre
Country	Germany
Dates of participant recruitment	1981-1983
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl 600mg (200mg tid)
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 8 and 12 weeks
Outcomes & Measures	MWD: treadmill with constant constant workload 5km/hour 10% slope. Performed twice with at least 20minutes interval. PFWD: as MWD ABI: Doppler ultrasound (venous occlusion plethysmography) AEs
Notes on statistics	Log transform for MWD and PFWD
Population	
Eligibility criteria	IC patients between 40 and 65years, PAD of femoral artery, with IC for at least 6 months and maximum 5 years, no physical training for at least 6months, diagnosis confirmed with angiography, baseline PFWD (at 5km/hour 10% slope) of 100-300m, after 4week run-in no more than 30% change. Exclude Beta-blockers, defibrinogenating enzymes, antiplatelets, anticoagulants; non-vascular exercise limiting diseases, coronary heart disease within 6months, myocardial/respiratory/renal insufficiency, severe hypertension systolic 180mmHG diastolic 110mmHg, 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

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	54	50
Baseline characteristics		
Age		
Sex		
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	220m	224m
MWD follow-up	342m	314m
MWD change		
MWD between group comparison	Nonsig between groups. For subgroup stenosis femoral artery, naftidrofuryl group sig more improvement than placebo p<0.02; nonsig between groups for occlusion femoral or tibial arteries	
PFWD n in analysis	54	50
PFWD baseline	137m	135m
PFWD follow-up	230m	171m
PFWD change	difference 93m [de Backer Tine: /id[30] mean 82.2 (SD 144.39)]	difference 36m [de Backer Tine: /id[30] mean 32.48 (SD 68.49)]
PFWD between group comparison	p<0.02. For subgroups stenosis femoral artery and occlusion tibial arteries, naftidrofuryl group sig more improvement than placebo p<0.01; nonsig between groups for occlusion femoral artery; tibial arteries	
ABI n in analysis	54	50
ABI baseline	98 (SD 3.7)mmHg [unclear if mean and SD]	93 (SD 3.2)mmHg
ABI follow-up	101 (SD 3.98)mmHg (nonsig)	92 (SD 3.9)mmHg (nonsig)
ABI change		
ABI between group comparison	nonsig change for either group	
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
Vascular events between group comparison		
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		

	Spengel 2001
Study details	
Publication type	Spengel 2001,[46] full report in peer reviewed journal
Additional sources of data	
Trial design	Meta analysis of 3 multicentre RCT (Liard 1997, Spengel 1999 and D'Hooge 2001)
Country	Germany, France, Belgium
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl 600mg (200mg tid)
Comparator	Placebo
Run-in phase	1 month
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 12 and 24 weeks
Outcomes & Measures	PFWD: Claudication distance as estimated by patient at baseline and at the end of the study. AEs: adverse events 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 (5 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 (ManCoVa) using the 5 dimensions at baseline as the multivariate covariate. If this showed effect, univariate analysis of covariance conducted. ManCoVa adjusted for baseline values, study effect and first order study treatment interaction
Population	
Eligibility criteria	IC (Fontaine Stage II), age 40-80, history of IC >3 months, stable over the previous 3 months, subjective PFWD of 50-500m, ankle brachial index 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 ABI 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	Not reported
N randomised to treatments included in review	754

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	382	372
Baseline characteristics		
Age	mean 66.2±9.5	mean 65.7±9.1
Sex	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) 26.125.9 ± 3.9
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	24 - baseline data only - excluded from analysis 16 - lost to follow-up 9 - did not comply with treatment protocol/had concomitant medication 4 - referral to hospital	21 - baseline data only - excluded from analysis (2 further not analysed, not accounted for) 14 - lost to follow-up 12 - did not comply with treatment protocol/had concomitant medication 6 - referral to hospital
Results		
MWD n in analysis	358	349
MWD baseline	mean 389 (SD 389) meters	mean 424 (SD 432) meters
MWD follow-up	mean 593 (SD 500) meters	mean 476 (SD 476) meters
MWD change	mean 204 (SD 443) meters	mean 51 (SD 455) meters
MWD between group comparison	Final absolute value P=0.002 Difference P<0.001	
PFWD n in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between group comparison		
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow		

up		
Vascular events included		
Vascular events reported	1 death from MI	unclear
Vascular events between group comparison		
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	1 death 33 serious (one considered to be in relation to the treatment), 11 minor (11 gastrointestinal, 5 skin reactions)	5 death 34 serious (2 considered to be in relation to the treatment (assume assessor was blinded)) 12 minor (8 gastrointestinal, 4 skin events)
AEs between group comparison		
Mortality reported	1 also reported in Aes	5 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, $p=0.03$	

	Ruckley 1978
Study details	
Publication type	Ruckly 1978,[67] short report in peer reviewed journal.
Additional sources of data	
Trial design	Unclear if RCT or clinical trial
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Lipha Pharmaceuticals UK
Intervention(s) and comparator	
Treatment groups	Naftidrofuryl 300mg (100mg tid)
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 & Measures	PFWD: Not explicit that treadmill was used, but likely that it was. Categorised as <100yards = severe, 100-200 yards = moderate, >200yards = mild. AEs: patient self-report
Notes on statistics	Wilcoxon's 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	Not reported
N randomised to treatments included in review	50

Treatment group	**Naftidrofuryl 100mg tid**	**Placebo**
N randomised to treatment		
Baseline characteristics		
Age		
Sex		
Smokers		
Diabetics		
Hypertension/ blood pressure		
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other	severity: 15 mild, 3 moderate, 7	severity: 9 mild, 6 moderate, 10

	severe	severe
Withdrawals		
Withdrawals/loss to follow-up	1 patient failed to attend final test, NR which group	
Results		
MWD n in analysis		
MWD baseline	severity: 15 mild, 3 moderate, 7 severe	severity: 9 mild, 6 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		
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
Vascular events between group comparison		
AEs n in analysis	25	25
AEs follow up	12 weeks	
AEs reported	Vertigo 8% Nausea 8% Slight insomnia 8%	epigastric pain 4% indigestion 4% 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		

Trials of pentoxifylline and placebo

	Lindgarde 1989
Study details	
Publication type	Lindgarde 1989,[70] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT, multicentre (2 Sweden, 1 Denmark)
Country	Sweden, Denmark
Dates of participant recruitment	Not reported
Sources of funding	Drugs supplied by Hoechst AG Werk Albert.
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200mg daily dose (400mg 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 & Measures	MWD: treadmill with constant workload, 2mph (3.2km/hr), 12.5% inclincation 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 perfomed with the extended Mantel-Haenszel test with stratification adjustment for site and standardized rank scores. Geometric means of % change from baseline and CI calculated. ANOVA to test treatment groups and background variables, Wilcoxons 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 COAD with an initial cludication distance (ICD) between 50 and 200m as tested on a treadmill set at a speed of 2mph (3.2Km/hr) and an inclination of 12.5%(7.1°). History of intermittent claudication of at least 6 months in duration. The diagnosis of COAD was established by clinical examination and by Doppler pressure assessment at rest and after exercise. Diagnosis confirmed by angiography. ICD stable for the last two visits of run-in phase (Difference of <35% in patients with baseline ICD up to 100m, <25% in patients with baseline ICD 101m-200m. Excluded if: complete occlusion of the aortoiliac segment, femoral bifurcation, or popliteal artery without angiographically proven distal refilling of the respective segment; vascualr reconstruction or sympathectomy within the last 12 months; peripheral neuropathy; Buerger's disease; marked postphelbotic syndrome; diabetes; cardiac failure or sever rhythm disorders; major infections; abnormal values for platelets; prothrombin index or partial thromboplastin time; history of zanthine 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	Not reported
Power calculation	Not reported
N randomised to treatments included in review	

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	76	74
Baseline characteristics		
Age	mean 65 (SD 7)	mean 64 (SD 8)
Sex	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	Myocardial infarction, 24%; isolated iliac or ilio/femoropopliteal lesions, 17%; isolated femoropopliteal or femoropopliteal/lower leg lesions, 72%.	Myocardial infarction, 18%; isolated iliac or ilio/femoropopliteal lesions, 12%; isolated femoropopliteal or femoropopliteal/lower leg lesions, 68%.
Withdrawals		
Withdrawals/loss to follow-up	Not reported	Not reported
Results		
MWD n in analysis	76	74
MWD baseline	Geometric mean 132m (SEM 9)	geometric mean 155m (SEM 11)
MWD follow-up	50% improvement (SEM 9) (crude calculation, 198m)	24% improvement (SEM 7) (crude calculation, 192.2m)
MWD change	crude calculation, 66m	crude calculation,37.2m
MWD between group comparison	Non significant, P= 0.094	
PFWD n in analysis	76	74
PFWD baseline	geometric mean 77m (SEM 4)	geometric mean 79m (SEM 4)
PFWD follow-up	80% improvement (SEM 12) (crude calculation, 138.6m)	60% improvement (SEM 11) (crude calculation, 126.4m)
PFWD change	crude calculation, 61.6m	crude calculation, 47.4m
PFWD between group comparison		
ABI n in analysis		

ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
Vascular events between group comparison		
AEs n in analysis		
AEs follow up		
AEs reported	22% (13 reported gastrointestinal complaints, other mild events were not defined)	14% (7 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		

	Porter 1982
Study details	
Publication type	Porter 1982,[71] full report in peer reviewed journal
Additional sources of data	Gillings 1987 (RM265),[72] post-hoc ITT analysis Porter 1982 (RM294),[73] Reich 1984 (RM 287)[74]
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Drugs supplied by Hoechst-Roussel Pharmaceuticals Inc
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 600mg daily dose (200mg t.i.d.) for first week, increased in a stepped manner to 1200mg daily dose (assume 400mg t.i.d.) by fourth week.
Comparator	Placebo
Run-in phase	4 to 6 weeks
Treatment duration	24 weeks
Outcome(s)	
Follow-up	Baseline, 2, 4,6,8, 12, 16, 20 and 24 weeks
Outcomes & Measures	MWD: [Porter 1982:[73] at each visit two treadmill tests were performed at 30 to 60 minute intervals and the mean of the two tests used. Treadmil set to 1.5mph, 7 degree angle] 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 % change (= geometric mean of response value/baseline value -1 *100) to limit undue influence of outlying values. after 24 weeks were analyzed by the extended Mantel-Haenszel procedure for ordered contingency tables by classifying patients into one of four categories (<25% change, 25 to 49% change, 50 to 100% change, greater than 100% change). Mantel-Haenszel results not extracted. [RM 265: As above for logarithms 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 logrank scores, provides a two-sided nonparametric test. Fisher procedure also with logrank scores gives one-sided test.]
Population	
Eligibility criteria	Included: patients with intermittent claudication secondary to COAD. COAD diagnosed by arteriography or by the absence of diminuation of one or more lower limb pulses as determined by palpation. Intermitted claudication must have been experienced for at least 6 months prior to a patient's enrollment. IC characterised by pain, muscualr 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 meters at a speed of 1.5mph and a grade of 7 degrees without experiencing claudication, but not for more than 510 meters in 9.5 minutes at a speed of 2mph before claudication. MWD had to be stable in last two visits during placebo run-in ie. within 20% of one another. [Reich 1984:[74] patients had to demonstrate compliance with protocol.] Excluded: patients with severe COAD (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/childbearing potential/using oral contraceptives.
Concomitant interventions allowed or excluded	Allowed: Not reported Disallowed: all current treatment for peripheral vascular disease was stopped for 2 weeks before placebo run-in phase.
Power calculation	Not reported
N randomised to treatments included in review	127 (one randomised twice, therefore authors treat total number as 128)

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	66 (67 if include placebo patient randomised a second time)	61
Baseline characteristics		
Age	mean 62	mean 63.5
Sex	M 82.1%; F 17.9% [Gillings 1987:[72] n=124, M 81%; F 19%]	M 82.0%; F 18% [Gillings 1987:[72] n=124, M 82%; F 18%]
Smokers	67.2% [Gillings 1987:[72] n=124, 67%]	68.9% [Gillings 1987:[72] n=124, 69%]
Diabetics	22.4% [Gillings 1987:[72] n=124, 22%]	24.6% [Gillings 1987:[72] n=124, 25%]
Hypertension/ blood pressure	[Gillings 1987:[72] mean diastolic BP: 81mmHg]	[Gillings 1987:[72] mean diastolic BP: 82mmHg]
Hyperlipidaemia		
Obesity or weight		
Angina	[Reich 1984:[74] 10/63 (15.9%)]	[Reich 1984:[74] 6/61 (9.8%)]
History of vascular therapy		
Other	Mean duration of COAD, 3.0 years [Gillings 1987:[72] Mean duration of COAD, 3.4 years] [Reich 1984:[74] occasional exercise, 29/63 (46.0%), regular exercise 25/63 (39.7%)]	Mean duration of COAD (#296): 2.8 years [Gillings 1987:[72] Mean duration of COAD 4.3 years] [Reich 1984:[74] 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;

	[Gillings 1987:[72] ITT analysis: only 4 excluded: discontinued study before first follow-up, 3; previously randomised to placebo, 1.]	intercurrent medical problem, 4. [Gillings 1987:[72] ITT analysis: no withdrawals.]
Results		
MWD n in analysis	42 [Gillings 1987:[72] 63]	40 [Gillings 1987:[72] 61]
MWD baseline	172m [Gillings 1987:[72] 147 (SE 9m)]	181 [Gillings 1987:[72] 161(SE 10m)]
MWD follow-up	268m	#296: 250
MWD change	38% (calculated: 96m) [Gillings 1987:[72] 33 (SE 8m)]	#296: 25% (calculated: 69m) [Gillings 1987:[72] 16 (SE 5m)]
MWD between group comparison	P=0.035 by repeat measures two-way analysis of variance with interaction of the study data. [Gillings 1987:[72] Extended Mantel-Haenszel P=0.316, one-sided p=0.049]	
PFWD n in analysis	42	40
PFWD baseline	111 [Gillings 1987:[72] 95 (SE 6m)]	117m [Gillings 1987:[72] 102 (SE 6m)]
PFWD follow-up	195m	180m [RM265: 147 (SE 9m)]
PFWD change	59% (calculated: 84m) [Gillings 1987:[72] 47 (SE 10m)]	36% (calculated: 63m) [Gillings 1987:[72] 18 (SE 6m)]
PFWD between group comparison	p=0.016 by repeat measures two-way analysis of variance with interaction of the study data. [Gillings 1987:[72] Extended Mantel-Haenszel p=0.042, one sided p=0.1]	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis	66 (67)	61
Vascular events follow up		
Vascular events included		
Vascular events reported	1 angina	1 myocardial infarction, 1 cerebrovascular accident, 1 cardiac surgery.
Vascular events between group comparison		
AEs n in analysis		
AEs follow up		
AEs reported	(also listed in withdrawals): 37 (55%) experienced some adverse events including: nausea, 24	(also listed in withdrawals): 24 (39%) experienced some adverse events including: nausea, 3; CNS

	(35.8%); CNS symptoms, 15 (22.4%). Other Aes not detailed.	symptoms, 7; blurred vision, 1; weakness, 1. Other Aes not detailed.
AEs between group comparison	Nausea $p<0.05$, CNS 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		

	Gallus 1985
Study details	
Publication type	Gallus 1985,[75] full report in peer reviewed journal.
Additional sources of data	
Trial design	RCT crossover (extract up to crossover)
Country	Australia
Dates of participant recruitment	Not reported
Sources of funding	Hoechst Australia supported trail.
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 800mg daily dose (400mg b.i.d) for first week, increased to 1200mg daily dose(400mg tid)
Comparator	Placebo
Run-in phase	4 weeks
Treatment duration	8 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks
Outcomes & Measures	MWD: treadmill with constant speed of 4Kph and a slope of 10 degrees. PFWD: as MWD Vascular events Mortality
Notes on statistics	Geometric means used. Logarithimic 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 "theraputic 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 less than 750 meteres before the onset of leg pain. Stable claudicationdistance for over six months, the presence of peripheral vascular disease documented through clinical examination by a vascular surgeon and supplemented by angiography or non-invasive testing, age over 50 years, a pledge not to change smoking habits during the trial and informed consent. Exclude: those with vascualr surgery or sympathectomy within the previous six months, ischemic leg ulcer or rest pain, exercise tolerance limieted by condidtions other than peripheral vascualr disease and treatment with lip 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	Not reported
N randomised to treatments included in review	47

Treatment group	**Pentoxifylline 800mg daily dose (400mg bid) for first week, increased to 1200mg daily dose(400mg tid)**	**Placebo**
N randomised to treatment	25	23
Baseline characteristics		
Age	Not including 5 withdrawals: mean 68 years (S.D.6)	Not including 4 withdrawals: mean 66 years (S.D.6)
Sex	not including 5 withdrawals: M 89.5%; F 10.5%	not including 4 withdrawals: M 73.7%; F 26.3%
Smokers	not including 5 withdrawals: 52.6%	not including 4 withdrawals: 36.8%
Diabetics	not including 5 withdrawals: 15.8%	not including 4 withdrawals: 10.5%
Hypertension/ blood pressure	not including 5 withdrawals, Supine BP (mmHg): mean systolic 167 (s.d. 30); mean diastolic 88 (s.d.12)	not including 4 withdrawals, Supine BP (mmHg): mean systolic 165 (s.d. 27); mean diastolic 90 (s.d.12)
Hyperlipidaemia		
Obesity or weight	NR, weight mean 76 Kg (s.d.11)	NR, weight mean 74 Kg (s.d.12)
Angina	not including 5 withdrawals: 26.3%	not including 4 withdrawals: 26.3%
History of vascular therapy	not including 5 withdrawals: vascular reconstruction 31.6%; sympathectomy 15.8%	not including 4 withdrawals: vascular reconstruction 31.6%; sympathectomy26.3%
Other	not including 5 withdrawals: myocardial infarction 21.1%,cerebral ischemia 10.5%; symptom duration (geometric mean ±1 SD) 53 ± 23-122 months.	not including 4 withdrawals: myocardial infarction 10.5%, cerebral ischemia 26.3%; symptom duration (geometric mean ±1 SD) 24 ± 9-59 months.
Withdrawals		
Withdrawals/loss to follow-up	5 withdrawals, only 2 before crossover: nausea and vomiting, 1; Breathless with effort, 1. (3 who withdrew after crossover: R on T extrasystoles with effort (as reported), 1; uninterpretable exercise ECG,1; onset of effort angina, 1.) Missing data in results (table 3) not explained, though probably due to exclusion of patients with <10 meter baseline claudication distance.	4 withdrawals, all before crossover: Death (myocardial infarction), 1; myocardial infarct/stroke, 1; angina with exercise, 1; technical, 1. Missing data in results (table 3) not explained, though probably due to exclusion of patients with <10 meter 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 meters	geometric mean 99.8 meters
MWD follow-up		
MWD change	% change from baseline (x 100) 1.23	% change from baseline (x 100) 1.17
MWD between group comparison	Ratio of % change from baseline (pent/placebo) 1.05 (95%CI 0.81-1.36)	
PFWD n in analysis	18 at baseline, 16 at 8 weeks	19 at baseline, 16 at 8 weeks
PFWD baseline	geometric mean 47.7 meters	geometric mean 48.3 meters
PFWD follow-up		
PFWD change	% change from baseline (x 100)	% change from baseline (x 100)

	1.55	1.26
PFWD between group comparison	Ratio of % change from baseline (pent/placebo) 1.23 (95%CI 0.86-1.77)	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported	0 withdrawals due to vascular events	3 withdrawals due to vascular events (1 fatal MI, 1 MI, 1 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		

	Di Perri 1983
Study details	
Publication type	Di Perri 1983,[76] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT crossover (extract up to crossover)
Country	Italy
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200mg daily dose (400mg t.i.d)
Comparator	Placebo
Run-in phase	No
Treatment duration	8 weeks
Outcome(s)	
Follow-up	Baseline, 8 weeks
Outcomes & Measures	MWD: measured absolute walking distance in meters, i.c. 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 timepoint the walking test was performed three times and a mean taken. AEs: unclear how recorded
Notes on statistics	Student's t-test and two ways analysis of variance were used
Population	
Eligibility criteria	Outpatients suffering from peripheral arterial occlusive disease with intermittent claudication. Fontaine's classification stage II severity. Walking capacity between 100 meters and 400 meters. Free from pain at rest and skin lesions. Excluded diabetes mellitus, severe hypertension (>180/110 mmHg) and congestive heart failure.
Concomitant interventions allowed or excluded	None allowed
Power calculation	Not reported
N randomised to treatments included in review	24

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	12	12
Baseline characteristics		
Age	mean 59.3 years	mean 59.3 years
Sex	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 gropus 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±20m (sd or se NR). Also reported as ±29m	mean 208±24.6m
MWD follow-up	mean 359±29m (sd or se NR)	mean 215±25m
MWD change	136m (reported)	6m (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		
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
Vascular events between group comparison		
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		

	Dettori 1989
Study details	
Publication type	Dettori 1989,[68] 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 1200mg daily dose (400mg t.i.d)
Comparators	1) Acenocoumarol 4 mg tablets (adjusted to patient) 2) 1200mg pentoxyfilline daily dose (400mg 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 & Measures	PFWTime: Speed of 3KM per hour, 10% elevation. Pain-free walking time recorded. For those who could walk for 30 minutes without experiencing pain, a higher speed was used in the second test (5Km/hr). ABI: Doppler ultrasound. Measured on both lower limbs, highest value measure used as denominator. Vascular events: AEs: Mortality:
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. ABI 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

Treatment group	**Pentoxifylline 1200mg daily dose (400mg tid)**	**Acenocoumarol 4 mg tablets (adjusted to patient)**	**1200mg pentoxyfilline daily dose (400mg tid.) 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
Sex	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, 1; unrelated diseases, 3; intolerance, 2; Refusal, 2. Total = 8	Nonfatal bleeding, 2; Angina, 1; unrelated diseases, 3. Total = 6	Fatal bleeding, 2; nonfatal bleeding, 1; angina, 1; unrelated diseases, 1; intolerance, 2. Total = 7	fatal myocardial infarction, 2; reversible ischemic neurologic deficit, 1; unrelated diseases, 1; refusal, 3. Total = 7
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 to 660) secs	geometric mean 121 (range 13 - 395) secs	geometric mean 138 (range 45 - 480) secs	geometric mean 144 (range 45 - 758) secs
PFWD follow-up	geometric mean 324 (range 50 - 1800) secs	geometric mean 406 (range 115 - 1800) secs	geometric mean 468 (range 118 - 1800) secs	geometric mean 349 (range 60 - 1800) secs
PFWD change	+189% categorisation: improved, 25; unchanged, 3; worse, 1.	+236% categorisation: improved, 26; unchanged, 4; worse, 0.	+239% categorisation: improved, 28; unchanged, 0; worse, 1.	+149% categorisation: improved, 20; unchanged, 7; worse, 3.
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 v not improved (worse + unchanged) for Pentoxifylline (chi square 4.73, P <0.05) and aceno (chi square 5.08, P <0.05). Analysis of variance for repeated measures was non-significant.			
ABI n in analysis	29	30	29	30
ABI 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)
ABI 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)
ABI 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%
ABI between group comparison	At rest: T2 compared to placebo significant (P=0.04), T3 compared to placebo boarderline (P=0.07) After exercise: T1 v placebo P=0.09, T2 v placebo P=0.05, T3 v 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, nonfatal bleeding, angina, reversible ischemic neurologic deficit.			
Vascular events reported	1	3	4	1 (plus 2 deaths from MI, not included in statistical comparison between groups)
Vascular events between group comparison	Only compared acenocoumarol to non-aceoncoumarol groups (T2, T3 v T4, T1): non-significant difference			
AEs n in analysis	37	36	36	37
AEs follow up	negative end points were defined as death, acute myocardial infarction, onset of angina pectoris, stroke or transient ischemic attack, cerebral hemorrhage. Other side effects (such as epigastric pain) were all recorded			
AEs reported	Angina, 1; unrelated diseases, 3; intolerance, 2; Refusal, 2. Total = 8	Nonfatal bleeding, 2; Angina, 1; unrelated diseases, 3. Total = 6	Fatal bleeding, 2; nonfatal bleeding, 1; angina, 1; unrelated diseases, 1; intolerance, 2. Total = 7	fatal myocardial infarction, 2; reversible ischemic neurologic deficit, 1; unrelated diseases, 1; refusal, 3. Total = 7
AEs between group comparison	Not reported for pentoxifylline.			
Mortality reported	0	0	2	2
Mortality between group comparison	Not reported			
HRQoL n in analysis				
HRQoL baseline				
HRQoL follow-up				
HRQoL change				
HRQoL between group comparison				

	Creager 2008
Study details	
Publication type	Creager 2008,[69] full report in peer reviewed journal.
Additional sources of data	
Trial design	RCT, multicentre
Country	USA
Dates of participant recruitment	Feb 1998 to Oct 1999
Sources of funding	Berlex Pharmaceuticals, Inc.
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200mg daily dose (400mg t.i.d)
Comparator	1) Placebo 2) iloprost 50µg twice daily plus placebos to make up to 3 capsules tid 3) iloprost 100µg twice daily (increased in second week from 50µg twice daily) plus placebos to make up to 3 capsules tid 4) iloprost 150µg twice daily (increased to 150µg by 50µg/week from 50µg twice daily in first week) plus placebos to make up to 3 capsules tid
Run-in phase	4-6 weeks
Treatment duration	26 weeks
Outcome(s)	
Follow-up	Baseline, 26 weeks
Outcomes & Measures	MWD: Graded treadmill, speed at a constant 2mph. 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 to placebo. Serious adverse events reported (death, permanent substantial disability, inpatient hospitalization or prolongation of existing inpatient hospitalisation, or an adverse event that was lifethreatening or was a congenital anomaly, cancer or overdose) are those that affected >1%. Mortality: HRQoL: WIQ and SF-36.
Notes on statistics	Primary analysis: mean % 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. Pairwise testing of placebo versus drug and pentoxifylline versus iloprost. Subgroup analysis included age, sex, race, smoking status, duration of PAD, prior intervention, antiplatelet medication, ACD at baseline and diabetic status.

Population	
Eligibility criteria	Men and women 40 years of age or greater, with PAD and intermittent claudication (Fontaine Stage II) were eligible for participation. Stable claudication for at least 3 months prior to entry, despite standard care, which included cardiovascualr risk factor modification and exercise training. Absolute claudication distance between 50 and 800 meters on a baseline eligibility exercise test. Ankle Brachial index (ABI) of ≤ 0.9 in the symptomatic leg. In addition, a greater than 20% fall in ABI within 1 minute following cessation of exercise served as confirmation of a diagnosis of PAD. In patients with non-compressible vessels (ABI >1.50), the toe-brachial index (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: ischemic rest pain, ulcers, gangrene (Fontaine Stage III or IV), evidence of non-atherosclerotic PAD, and peripheral neuropathy that impaired walking ability, revascularization for PAD within the preceding 3 months, sympathectomy within 6 months, type 1 diabetes mellitus, myocardial infarction or major cardiac surgery within 3 months, unstable angina, and heart failure.
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 100µg tid, 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

Treatment group	**Pentoxifylline 1200mg daily dose (400mg t.i.d)**	**Placebo**	**Iloprost 50µg twice daily plus placebos to make up to 3 capsules tid**	**Iloprost 100µg twice daily (increased in second week from 50µg twice daily) plus placebos to make up to 3 capsules tid**	**Iloprost 150µg twice daily (increased to 150µg by 50µg/week from 50µg twice daily in first week) plus placebos to make up to 3 capsules tid**
N randomised to treatment	86	84	87	86	87
Baseline characteristics					
Age	67.2	66.5	67.1	66.6	67.3
Sex	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 myocardial infarction: 30.2%; aspirin use: 75.6%; mean duration of claudication: 65.9 months	history of myocardial infarction: 34.5%; aspirin use: 72.6%; mean duration of claudication: 80.4 months	history of myocardial infarction: 29.9%; aspirin use: 71.3%; mean duration of claudication: 61.4 months	history of myocardial infarction: 27.9%; aspirin use: 74.4% mean duration of claudication: 65.5 months	history of myocardial infarction: 36.8%; aspirin use: 70.1%; mean duration of claudication: 74.6 months
Withdrawals					
Withdrawals/loss to follow-up	Serious adverse events leading to discontinuation,	Serious adverse events leading to	Serious adverse events leading to	Serious adverse events leading to	Serious adverse events leading to

	15% (headache, 2%; pain in extremity, 0%; vasodilation, 0%, dyspepsia, 1%)	discontinuation, 14% (headache, 1%; pain in extremity, 1%; vasodilation, 0%, dyspepsia, 1%)	discontinuation, 31% (headache, 14%; pain in extremity, 6%; vasodilation, 1%, dyspepsia, 0%)	discontinuation, 57% (headache, 36%; pain in extremity, 6%; vasodilation, 2%, dyspepsia, 0%)	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) metres	mean 292 (SD 161) meters	mean 244 (SD 164) meters	mean 312 (SD 193) meters	mean 289 (SD 171) meters
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.				
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) meters	mean 120 (SD 88) meters	mean 105 (SD 81) meters	mean 124 (SD 96) meters	mean 129 (SD 88) meters
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				
ABI n in analysis					
ABI baseline					
ABI follow-up					
ABI change					
ABI 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 to 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 not reported. 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 occured more frequently in pentoxifylline group. No meaningful numerical differences among groups in any specific cardiovascular events (angina, congestive heart failure, myocardial infarction)				
Mortality reported	1 (1.2%)	1 (1.2%)	0	0	0
Mortality between group comparison	not numerically different				
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 to placebo	NA	Only differences seen in stair climbing ability. 11% improvement compared to placebo	NR	Only differences seen in stair climbing ability. 16% improvement compared to 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				

Trials of Inositol nicotinate and placebo

	O'Hara 1988
Study details	
Publication type	O'Hara 1988,[77] full report in peer reviewed journal
Additional sources of data	O'Hara 1985[78]
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Winthrop Laboratories, for drugs and statistical analysis
Intervention(s) and comparator	
Treatment groups	inositol nicotinate 4g daily dose (4 x 500mg tablets tid)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes & 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 #278). 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 intermittent claudication, which limited walking to 500 yards (457 meters). Aged 50 to 75 years. Weighing 40 to 100kg. Exclusions: insulin dependent diabetes, severe angina, rest pain or gangrene, non-vascular causes of intermittent claudication, symptomatic treatment for claudication pain within the month preceding entry to the study, malignant diseases, gross renal or hepatic impairment and arterial surgery for claudicaiton within previous three years.
Concomitant interventions allowed or excluded	Not reported
Power calculation	Not reported
N randomised to treatments included in review	120

Treatment group	**Inositol nicotinate 4g 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
Sex	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 69.3Kg (SE 1.3)	weight mean 71.8Kg (SE 1.0)
Angina		
History of vascular therapy		
Other	duration mean 2.3 years (SE 0.4) VAS pain score mean 62.1mm (SE 2.1) number of cigarettes smoked per day mean 16.1 (SE 1.2)	duration mean 2.8 years (SE 0.5) VAS pain score mean 56.7mm (SE 2.4) number of cigarettes smoked per day mean 18.3 (SE 1.6)
Withdrawals		
Withdrawals/loss to follow-up	[O'Hara 1985:[78] 5 withdrawals (personal choice (2), stroke (1), gastrointestinal complaints (1), and "too many tablets" (1))]	[O'Hara 1985:[78] 7 withdrawals (personal choice (2), persistent illness (1), death (#251 suggests this was unrealted to IC) (1), myocardial infarction (1), general malaise (1), rash (1))]
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 (secs): mean 129.2 (SE 16)	Free walking paces (weekly): mean 617.2 claudication time (secs): mean 102.4 (SE 12.2)
PFWD follow-up		
PFWD change	Free walking paces (weekly): mean 469.6 (SE183.7) claudication time (secs): mean 43.3 (SE 21)	Free walking paces (weekly): mean 325.4 (SE 220.6) claudication time (secs): 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 p0.05. Within group comparisons of change from baseline were significant for inositol at 3 months, but not for placebo.	
ABI n in analysis		
ABI baseline		

ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis	62	58
Vascular events follow up		
Vascular events included		
Vascular events reported	stroke, 1 - also reported in withdrawals	myocardial infarction, 1 - also reported in withdrawals
Vascular events between group comparison		
AEs n in analysis	62	58
AEs follow up		
AEs reported	[O'Hara 1985:[78] 16.1% patients reported minor side effects, mostly related to difficulty in swallowing tablets.]	[O'Hara 1985:[78] 19.0% patients reported minor side effects, mostly related to difficulty in swallowing tablets.]
AEs between group comparison		
Mortality reported	0	1 – also reported in withdrawals
Mortality between group comparison		
HRQoL n in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between group comparison		

	Kiff 1988
Study details	
Publication type	Kiff 1988,[79] full report in peer reviewed journal
Additional sources of data	Unclear whether the patients are the same as some patients in O'Hara 1988[77]and O'Hara 1985.[78] Different outcomes reported using different techniques.
Trial design	RCT.
Country	UK
Dates of participant recruitment	March 1984 to January 1986
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4g daily dose (2g bd)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes & Measures	MWD: treadmill with constant workload, 10% gradient. ABI: Doppler ultrasound flow detector and sphygmomanometer at rest. AE's:
Notes on statistics	Wilcoxon matched pairs signed rank test or student's paired t tests as appropriate.
Population	
Eligibility criteria	Stable IC (duration of symptoms of at least six months), PAD confirmed by resting ankle pressure index of <0.9 or a drop in ankle pressure with exercise of more than 30mmHg. All patients had palpable femoral pulses and could walk between 35 and 500 meters on a treadmill. Any medication for IC stopped 1 month before trial. Exclusion: walking distance on treadmill >500m, serious medical disease, rest pain or gangrene, treatment with beta blockers which was not stabilised or arterial surgery for claudication within the previous three months.
Concomitant interventions allowed or excluded	Not reported
Power calculation	Not reported
N randomised to treatments included in review	80

Treatment group	**Inositol nicotinate 4g daily dose (2g bd)**	**Placebo**
N randomised to treatment	40	40
Baseline characteristics		
Age	mean 61.5 (SD 9.3) years	mean 62.8 (SD 7.3) years
Sex	M 82.5%; F 17.5%	M 77.5%; F 22.5%
Smokers	57.5%	72.5%
Diabetics		
Hypertension/ blood pressure	mean 153.6 (SD23.9)/87.5 (SD10.6) mmHg	mean 152.9 (SD 24.1)/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	8 withdrawals (reasons were 8 out of: moved from district (3), family problems (2), felt unwell taking tablets (2), personal choice (4), referred for surgery (1), hospitalised for an unrelated condition (1))	7 withdrawals (reasons were nausea and vomiting (1), constipation (1) and 5 out of: moved from district (3), family problems (2), felt unwell taking tablets (2), personal choice (4), referred for surgery (1), hospitalised for an unrelated condition (1)
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	calcualted: 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		
ABI n in analysis	initially 40 - assume minus withdrawals (32) at 12 weeks	initially 40 - assume minus withdrawals (33) at 12 weeks
ABI baseline	mean 0.718 (SD 0.144) meters	mean 0.694 (SD 0.215) meters
ABI follow-up	NR	NR
ABI change	not significant	not significant

ABI between group comparison	not significant	
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		

	Head 1986
Study details	
Publication type	Head 1986,[80] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4g daily dose (1g qid)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes & Measures	PFWD: Time to claudication was recorded: a metronome was set at 80 beats per 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:
Notes on statistics	Not reported
Population	
Eligibility criteria	patients with clinical diagnosis of intermittent claudication due to vascular insufficiency. Male or female, aged between 18 and 80 years, weigh between 40 and 100kg and be judged suitable to receive a three month course of inositol nicotinate 1g qds or matching placebo.
Concomitant interventions allowed or excluded	Allowed: Disallowed:
Power calculation	Not reported
N randomised to treatments included in review	123

Treatment group	**Inositol nicotinate 4g 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 secs):mean 68.6 (SD 7.7) moderate (IC 60-120 secs): mean 67.0 (SD 6.7) mild (IC >120 secs):mean 65.0 (SD 14.4)	Severe (IC <60 secs): mean 64.3 (SD7.6) moderate (IC 60-120 secs): mean 64.8 (SD 7.7) mild (IC >120 secs): mean 61.6 (SD 13.4)
Sex	Severe (IC <60 secs): M 78.9%; F 21.1% moderate (IC 60-120 secs): M 84.6%; F 15.4% mild (IC >120 secs): M66.7%; F 33.3%	Severe (IC <60 secs): M 66.7%; F 33.3% moderate (IC 60-120 secs): 81.3%; F 18.7% mild (IC >120 secs): M 55.6%; F 44.4%
Smokers	Severe (IC <60 secs): 57.9% moderate (IC 60-120 secs): 73.1% mild (IC >120 secs): 33.3%	Severe (IC <60 secs):47.6% moderate (IC 60-120 secs): 46.9% mild (IC >120 secs): 44.4%
Diabetics	Severe (IC <60 secs): 15.8% moderate (IC 60-120 secs):0% mild (IC >120 secs): 0%	Severe (IC <60 secs): 4.8% moderate (IC 60-120 secs): 3.1% mild (IC >120 secs): 0%
Hypertension/ blood pressure	All in mmHg Severe (IC <60 secs): mean 162.1 (SD 23.3)/ 85.7 SD(8.2) moderate (IC 60-120 secs): mean 159.4 (SD 21.1)/88.6 (SD 12.3) mild (IC >120 secs): mean 160 (SD24.5)/83.0 (SD 12.2)	All in mmHg Severe (IC <60 secs): mean 164.3 (SD19.9)/92.6 (10.1) moderate (IC 60-120 secs): mean 163.3 (SD 29.8)/89.7 (SD 16.6) mild (IC >120 secs): mean 155.7 (SD 13.2)/ 85.3 (SD8.5)
Hyperlipidaemia		
Obesity or weight	Severe (IC <60 secs): mean 69.3 (SD13.4)kg moderate (IC 60-120 secs): mean 72.0 (SD 11.7)kg mild (IC >120 secs): mean 69.6 (SD 4.8)kg	Severe (IC <60 secs): mean 68.0 (SD11.3)kg moderate (IC 60-120 secs): mean 73.4 (11.7)kg mild (IC >120 secs): mean 72.3 (9.7) kg
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	broken ankle, 1; inability to swallow, 1; constipation, 1; non-compliance, 1. Also, 10 patients were excluded from analysis, unclear which groups they were from. Reasons were: congestive cardiac failure, 3; osteoarthritis, 2; severe leg pain at rest, 1; carcinoma of the stomach with secondaries in the liver, 1; failure to return, 1; lukaemia, 1; rheumatoid arthritis, 1.	cerebrovascular accident, 1; thrombophlebitis, 1; gastro-intestinal upset, 2; personal reasons, 1. Also, 10 patients were excluded from analysis, unclear which groups they were from. Reasons were: congestive cardiac failure, 3; osteoarthritis, 2; severe leg pain at rest, 1; carcinoma of the stomach with secondaries in the liver, 1; failure to return, 1; lukaemia, 1; rheumatoid arthritis, 1.

Results		
MWD n in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between group comparison		
PFWD n in analysis	47	57
PFWD baseline	PFW Time (seconds) Severe: mean 44.42 (SD 14.78) Moderate: mean 85.23 (SD 15.96) Mild: mean 183.5 (SD 66.67)	PFW Time (seconds) Severe: mean 44.33 (SD 14.81) Moderate: mean 88.53 (SD 17.21) Mild: mean 156.9 (SD 19.71)
PFWD follow-up	PFW Time Severe: mean 59.59 (SD 28.08) Moderate: mean 105.50 (SD 36.71) Mild: mean 156.2 (SD 40.87)	PFW Time Severe: mean 64.86 (SD 36.70) Moderate: mean 97.11 (SD 36.25) Mild: mean 194.6 (SD 93.49)
PFWD change	PFW Time (seconds) Severe: $p<0.05$ Moderate: $p<0.01$ Mild: non sig	PFW Time (seconds) Severe: $p<0.01$ Moderate: $p<0.01$ Mild: non sig
PFWD between group comparison	PFW Time (seconds) Severe: non sig Moderate: significant between group comparison $p<0.001$ Mild: non sig	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis	51	62
Vascular events follow up		
Vascular events included	Taken from adverse events	
Vascular events reported	0	cerebrovascular accident, 1; thrombophlebitis, 1. - also reported in AE's
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, 1 (2%); inability to swallow, (2%); constipation, (2%); non-compliance, (2%).	5/62 (8.1%). cerebrovascular accident, 1 (1.6%); thrombophlebitis, 1 (1.6%); gastro-intestinal upset, 2 (3.2%); personal reasons, 1 (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		

Trials testing intervention against other treatments

	Hobbs 2005. "INEXACT"
Study details	
Publication type	Hobbs 2005,[81] full report in peer reviewed journal
Additional sources of data	None
Trial design	RCT, single centre
Country	UK
Dates of participant recruitment	Not reported
Sources of funding	Mr 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 200mg (100mg b.i.d). If side effects, dosing halved for 1 week
Comparator	usual care,
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 & Measures	MWD: treadmill with constant workload, 3 km/h at a 10% incline PFWD: as MWD ABI: 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; max walking distance 20-500 m. Excluded Significant aortoiliac disease, Unable to complete treadmill assessment to ACD, MI, TIA, CVA, or PTCA in past 3 mo, GFR 20 mL/min, Congestive heart failure, 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 TAT in the treatment groups with 80% power and a P value of <0.05
N randomised to treatments included in review	18

Treatment group	**Cilostazol 100mg bid**	**Usual Care**
N randomised to treatment	9	9
Baseline characteristics		
Age	mean 58 (52-71)	Mean 67 (63.5-74)

Sex	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	(Not reported 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	9	9
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		
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow up		
Vascular events included		
Vascular events reported		
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		

	Ciocon 1997
Study details	
Publication type	Ciocon 1997,[111] full report in peer reviewed journal
Additional sources of data	
Trial design	RCT
Country	USA
Dates of participant recruitment	Not reported
Sources of funding	Not reported
Intervention(s) and comparator	
Treatment groups	Pentoxifylline 1200mg daily dose (400mg t.i.d)
Comparator	325mg Aspirin daily dose
Run-in phase	no
Treatment duration	6 weeks
Outcome(s)	
Follow-up	Baseline, 2 weeks, 4 weeks, then every 4 weeks until 24 weeks
Outcomes & Measures	MWD: maximum distance walked to point of absolute claudication with use of a regular treadmill was noted. Participants walked at own pace. ABI:
Notes on statistics	Student's t-test. Not stated if means report SD or SE. Not stated if arithmetic or geometric means used. Unclear in some cases whether average is mean.
Population	
Eligibility criteria	65 years and older who were ambulatory, had not taken aspirin or pentoxifylline during the past six months, experienced leg claudication and were clinically proven to have PVD with an ankle to arm pressure ratio less than 0.8. No patients had leg rest pain. Excluded: patients who had taken aspirin or pentoxifylline within the last six months or had vascular surgery , an ankle to arm pressure ratio greater than 0.8, coexisting stable angina, sever osteoarthritis, peripheral neuropathy or leg surgery within the past six months.
Concomitant interventions allowed or excluded	Not reported
Power calculation	Not reported
N randomised to treatments included in review	90

Treatment group	**Naftidrofuryl 200mg tid**	**Placebo**
N randomised to treatment	45 reported, though might be 44 (10 males, 34 females)	45 reported, though might be 46 (12 males, 34 females)
Baseline characteristics		
Age	mean 78±3 years	mean 80±5 years
Sex	Unclear - states 10 males and 34 females, which disagrees with total of 45. Assuming these numbers to be correct: M 22.7%; F 77.3%	Unclear - states 12 males and 34 females, which disagrees with total of 45. Assuming these numbers to be correct: M 26%; F74%
Smokers		
Diabetics	6.7% (or 6.8% if asume 44 pts)	8.9% (or 8.7% if assume 46pts)
Hypertension/ blood pressure	17.8% (18.2% if assume 44 pts)	22.2% (21.7% if assume 44 pts)
Hyperlipidaemia		
Obesity or weight		
Angina	0%	0%
History of vascular therapy		
Other	COPD 4.4% (4.5% if assume 44 pts), level of pain (visual analogue scale 0 (no pain) to 5 (severe pain)): 2 of 5, scored level of activity on 0 to 100 scale: mean 40±6	COPD 8.9% (8.7% if assume 44 pts), level of pain (visual analogue scale 0 (no pain) to 5(severe pain)): 2 of 5, scored level of activity on 0 to 100 scale: mean 44±5
Withdrawals		
Withdrawals/loss to follow-up	Not reported	Not reported
Results		
MWD n in analysis	45 or 44	45 or 46
MWD baseline	1 mile (assume mean)	0.8 miles (assume mean)
MWD follow-up	2 miles (assume mean)	1.2 miles (assume mean)
MWD change	1 mile (calculated, assume mean)	0.4 miles (calculated, assume mean)
MWD between group comparison	student t-test <0.05	
PFWD n in analysis	45 or 44	45 or 46
PFWD baseline	0.6±0.1 (assume mean)	0.6±0.3 (assume mean)
PFWD follow-up	0.7±0.2 (assume mean)	0.6±0.5 (assume mean)
PFWD change	0.1 (calculated, assume mean)	0 (calculated, assume mean)
PFWD between group comparison	non-significant difference	
ABI n in analysis		
ABI baseline		
ABI follow-up		
ABI change		
ABI between group comparison		
Vascular events n in analysis		
Vascular events follow		

up		
Vascular events included		
Vascular events reported		
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		

Table 77: 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 Otsuka 21-98-214-01 Hiatt 2008[47,48,49]	Cilostazol 200mg		
O'Donnell 2009[50,51,52,53,54]	Cilostazol 200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 10% gradient	SF-36 VascuQoL
Strandness 2002. Otsuka 21-94-201[55,56]	Cilostazol 200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	SF-36 WIQ COM
Dawson 2000. Otsuka 21-96-202[57,58,59]	Cilostazol 200mg Pentoxifylline 1200mg	Treadmill with graded test: 3.2km/hour (2 miles per hour) 0% gradient with a 3.5% increase in gradient every 3 minutes	SF-36 WIQ

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
Beebe 1999. Otsuka 21-92-202[60]	Cilostazol 200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	SF-36 WIQ COM
Otsuka 21-94-301[32]	Cilostazol 200mg Pentoxifylline 1200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	
Otsuka 21-98-213[32]	Cilostazol 200mg Pentoxifylline 1200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	SF-36 WIQ COM
Money 1998. Otsuka 21-94-203[61]	Cilostazol 200mg	Treadmill with graded test: 3.2km/hour (2 miles per hour) 0% gradient with a 3.5% increase in gradient every 3 minutes	SF-36 WIQ
Dawson 1998. Otsuka 21-90-201[62]	Cilostazol 200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	
Elam 1998. Otsuka 21-93-201[63]	Cilostazol 200mg	Treadmill with graded test: 3.2km/hour (2 miles per hour) 0% gradient with a 3.5% increase in gradient every 3 minutes	
Otsuka 21-95-201[32]	Cilostazol 200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	SF-36 WIQ
INEXACT Hobbs 2005[81]	Cilostazol 200mg , Cilostazol 200mg plus supervised exercise	Treadmill with constant workload: 3km/hour 10% gradient	
Spengel 2002[46]	Naftidrofuryl 600mg	Estimated by patient	CLAU-S

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
Kieffer 2001[64]	Naftidrofuryl 600mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 10% gradient	
Adhoute 1986[65,65]	Naftidrofuryl 600mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 10% gradient	
Trubestein 1984[66]	Naftidrofuryl 600mg	Treadmill with constant workload: 5km/hour 10% gradient, performed twice with at least 20minutes interval.	
Ruckley 1978[67]	Naftidrofuryl 300mg	Unclear if treadmill used <100yards = severe 100-200 yards = moderate >200yards = mild.	
Dettori 1989[68]	Pentoxifylline 1200mg	Treadmill with varied workload: 3km/hour. If pain free walking time >30mins, higher speed was used in the second test (5km/hour). 10% gradient.	
Creager 2008[69]	Pentoxifylline 1200mg	Treadmill with graded test: 3.2km/hour (2 miles per hour) 0% gradient, increased by 2% every 2 minutes.	SF-36 WIQ
Lindgarde 1989[70]	Pentoxifylline 1200mg	Treadmill with constant workload: 3.2km/hour (2 miles per hour) 12.5% gradient	

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
Porter 1982 and Gillings 1987[71,72,73,74]	Pentoxifylline 1200mg	Treadmill with constant workload: 1.5 miles per hour 7 degree gradient, two treadmill tests were performed at 30 to 60 minute intervals and the mean of the two tests used.	
Gallus 1985[75]	Pentoxifylline 1200mg	Treadmill with constant workload: 4km/hour 10 degree gradient	
Di Perri 1983[76]	Pentoxifylline 1200mg	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.	
O'Hara 1988[77,78]	Inositol nicotinate 4g	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".	
Kiff 1988[79]	Inositol nicotinate 4g	treadmill with constant workload: 10% gradient.	
Head 1986[80]	Inositol nicotinate 4g	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 per minute leading with the worse leg.	

Trial name	Treatment and dose	Outcome measures for PFWD and MWD	Outcome measures for HRQoL
PFWD, pain free walking distance; MWD, maximum walking distance; SF-36, short form 36; VascuQOL, vascular quality of life; WIQ, walking impairment questionnaire; COM, claudication outcome measure.			

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 $\mu_{ij} = \phi_i + \theta_{ij}$.

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 $\phi_i \sim N(0,10{,}000)$.

We assume a random (treatment) effects model in which the θ_{ij} are assumed to come from a common population distribution such that $\theta_{ij} \sim N(\mu_{\theta_j}, \tau^2)$. 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 μ_{θ_j} is the population mean effect of treatment *j* relative to treatment 1.

We give μ_{θ_j}, $j \neq 1$, a weak prior distribution such that $\mu_{\theta_j} \sim N(0,10{,}000)$.

τ represents the between-study standard deviation, which we give a prior uniform distribution, $\tau \sim U(0,200)$.

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 logarithm of the population standard deviation a prior uniform distribution such that:

$$\log(\sigma) \sim U(-10,10).$$

The model for the network meta-analyses differs from this basic model in two particular ways. Firstly, the estimates of treatment effect within each study are represented as functions of each treatment effect relative to placebo. Secondly, 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 standard deviations were the same in each treatment arm of the study within study.

Sample standard deviations on the logarithm scale generally had to be derived. In some cases, these were derived from the mean and confidence interval 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

Table78: Drummond adapted criteria (Drummond *et al.* 2005)

	Guest *et al.*	Ratcliffe
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 applicable	Not applicable
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

Table79: Consensus on Health Economic Criteria list (Evers *et al.* 2005)

	Guest *et al.*	Ratcliffe
1. Is the study population clearly described?	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes
3. Is a well-defined research question posed in answerable form?	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	Yes	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	Yes	Unclear
8. Are all costs measured appropriately in physical units?	Yes	Unclear
9. Are costs valued appropriately?	Yes	Unclear
10. Are all important and relevant outcomes for each alternative identified?	Yes	Unclear
11. Are all outcomes measured appropriately?	Yes	Yes
12. Are outcomes valued appropriately?	Not applicable	Yes
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes
14. Are all future costs and outcomes discounted appropriately?	Not applicable	Not applicable
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Unclear
16. Do the conclusions follow from the data reported?	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?	No	Unclear
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Unclear
19. Are ethical and distributional issues discussed appropriately?	No	Unclear

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