Two-arm trials of cilostazol versus placebo

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

mph, miles per hour; NR, not reported.

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

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

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

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

mph, miles per hour; NR, not reported.

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

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

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

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

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

mph, miles per hour; NR, not reported.

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

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

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

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

mph, miles per hour; NR, not reported.

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

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

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

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

mph, miles per hour; NR, not reported.

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

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

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

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

CHF, chronic heart failure.

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

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

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

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

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

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

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

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

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

mph, miles per hour; NR, not reported.

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

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

F, female; M, male.