Three-arm trials of cilostazol, pentoxifylline and placebo

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

mph, miles per hour; NR, not reported.

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

Treatment group	Cilostazol 100 mg b.i.d.	Pentoxifylline 400 mg t.i.d.	Placebo
Vascular events *n* in analysis			
Vascular events follow-up			
Vascular events included			
Vascular events reported	[Uchiyama 2008:[42] two coronary vascular events, 0.9%; three cerebral vascular events 1.3%; no serious bleeding]	[Uchiyama 2008:[42] two coronary vascular events, 0.8%; no cerebral vascular events; no serious bleeding]	
Vascular events between-group comparison			
AEs *n* in analysis	227	232	239
AEs follow-up			
AEs reported	*n* (%)	*n* (%)	*n* (%)
	Patients with at least one event 201 (86)	Patients with at least one event 200 (86)	Patients with at least one event 188 (79)
	Headache 63 (28)	Headache 26 (11)	Headache 28 (12)
	Pain 30 (13)	Pain 38 (16)	Pain 33 (14)
	Diarrhoea 43 (19)	Diarrhoea 18 (8)	Diarrhoea 13 (5)
	Pharyngitis 22 (10)	Pharyngitis 32 (14)	Pharyngitis 17 (7)
	Peripheral vascular disorder 13 (6)	Peripheral vascular disorder 22 (10)	Peripheral vascular disorder 26 (11)
	Abnormal stools 33 (15)	Abnormal stools 12 (5)	Abnormal stools 7 (3)
	Palpitation 39 (17)	Palpitation 5 (2)	Palpitation 3 (1)
	SAEs 27 (12)	SAEs 31 (13)	SAEs 31 (13)
AEs between-group comparison	Withdrawal due to AEs similar in cilostazol (16%) and pentoxifylline (19%), significantly less in placebo (9%). Headache, diarrhoea and abnormal stools were significantly more common in cilostazol than other groups		
Mortality reported	0.8%, $n=2$	1%, $n=3$	0.4%, $n=1$
Mortality between-group comparison	NR		
HRQoL *n* in analysis			
HRQoL baseline			
HRQoL follow-up			
HRQoL change			
HRQoL between-group comparison	None of the treatments significantly affected the Medical Outcomes Scale Short Form-36 scores on Mental Health Concepts, General Health Perception, Physical Health Concepts or Vitality Scores. There were also no significant differences in patient-reported walking distance or speed as determined by the WIQ		

M, male; NR, not reported.

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

mph, miles per hour; NR, not reported.

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

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

F, female; M, male.

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

mph, miles per hour; NR, not reported.

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

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

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

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