Trials of pentoxifylline and placebo

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

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

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

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

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

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

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

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

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

BP, blood pressure; SE, standard error.

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

NR, not reported.

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

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

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

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

NR, not reported.

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

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

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

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

PFW, pain-free walking.

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

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

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

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

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

mph, miles per hour.

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

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

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

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