Two-arm trials of naftidrofuryl oxalate and placebo

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

NR, not reported.

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

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

a Figures calculated by reviewer.

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

BMI, body mass index; NR, not reported.

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

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

NR, not reported.

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

NR, not reported.

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

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

NR, not reported.

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

NR, not reported.

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

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

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

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

NR, not reported.

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

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

NR, not reported.