Trials of inositol nicotinate and placebo

O'Hara 1988[78]	
Study details	
Publication type	O'Hara 1988,[78] full report in peer-reviewed journal
Additional sources of data	O'Hara 1985[79]
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	NR
Sources of funding	Winthrop Laboratories, for drugs and statistical analysis
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (4 × 500-mg tablets b.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	PFWD: training device (pair of stirrups which moved in opposition in a near vertical plane by means of an interconnecting belt and pulley mechanism in a supporting metal frame), which simulated box-stepping. Elapsed time and number of steps to claudication were recorded. (Some information from O'Hara 1985.[79]) Time to recovery from claudication pain was recorded. Waist-band pedometer to record 'similar weekly walks' Vascular events: not systematically reported. Some given in withdrawals AEs: Subjective complaints were sought by the question 'How did the medication suit you?'
Notes on statistics	Wilcoxon matched pairs signed-rank and two-sample tests, Student's *t*-tests (paired and unpaired), or chi-squared test as appropriate
Population	
Eligibility criteria	Male or female with clinical diagnosis of IC, which limited walking to 500 yards (457 m). Aged 50–75 years. Weighing 40–100 kg. Exclusions: insulin-dependent diabetes, severe angina, rest pain or gangrene, non-vascular causes of IC, symptomatic treatment for claudication pain within the month preceding entry to the study, malignant diseases, gross renal or hepatic impairment and arterial surgery for claudication within previous 3 years
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	120

NR, not reported.

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
N randomised to treatment	62	58
Baseline characteristics		
Age	Mean 66.2 (SE 0.7) years	Mean 65.6 (SE 1.0) years
Gender	M 64.5%; F 35.5%	M 72.4%; F 27.6%
Smokers	64.5%	50%
Diabetics	4.8%	5.2%
Hypertension/blood pressure	Mean 161.4 (SE 2.4)/87.6 (SE 1.4)	Mean 152.7 (SE 2.5)/84.7 (SE 1.2)
Hyperlipidaemia		
Obesity or weight	Weight mean 69.3 (SE 1.3) kg	Weight mean 71.8 (SE 1.0) kg
Angina		
History of vascular therapy		
Other	Duration mean 2.3 (SE 0.4) years VAS pain score mean 62.1 (SE 2.1) mm No. of cigarettes smoked per day mean 16.1 (SE 1.2)	Duration mean 2.8 (SE 0.5) years VAS pain score mean 56.7 (SE 2.4) mm No. of cigarettes smoked per day mean 18.3 (SE 1.6)
Withdrawals		
Withdrawals/loss to follow-up	{O'Hara 1985:[79] five withdrawals [personal choice (two), stroke (one), gastrointestinal complaints (one), and 'too many tablets' (one)]}	{O'Hara 1985:[79] seven withdrawals [personal choice (two), persistent illness (one), death (O'Hara 1988[78] suggests this was unrelated to IC) (one), MI (one), general malaise (one), rash (one)]}
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		
PFWD *n* in analysis	57	51
PFWD baseline	Free walking paces (weekly): mean 455.2 (SE 78.5) Claudication time (s): mean 129.2 (SE 16)	Free walking paces (weekly): mean 617.2 (131.3) Claudication time (s): mean 102.4 (SE 12.2)
PFWD follow-up	(Only reported as change from baseline – see below)	(Only reported as change from baseline – see below)
PFWD change	Free walking paces (weekly): mean 469.6 (SE 183.7) Claudication time (s): mean 43.3 (SE 21)	Free walking paces (weekly): mean 325.4 (SE 220.6) Claudication time (s): mean 28.6 (SE 17.9)
PFWD between-group comparison	Free walking paces: within group comparisons significant for both T1 and T2. Between-group comparisons only significant for T1. Claudication time: between-group comparisons of change from baseline were not significant at $p = 0.05$. Within group comparisons of change from baseline were significant for inositol at 3 months, but not for placebo	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
Vascular events *n* in analysis	62	58
Vascular events follow-up		
Vascular events included		
Vascular events reported	Stroke, one – also reported in withdrawals	MI, one – also reported in withdrawals
Vascular events between-group comparison		
AEs *n* in analysis	62	58
AEs follow-up		
AEs reported	[O'Hara 1985:[79] 16.1% patients reported minor side effects, mostly related to difficulty in swallowing tablets]	[O'Hara 1985:[79] 19.0% patients reported minor side effects, mostly related to difficulty in swallowing tablets]
AEs between-group comparison		
Mortality reported	Zero	One – also reported in withdrawals
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; SE, standard error; VAS, visual analogue scale.

Kiff 1988[80]	
Study details	
Publication type	Kiff 1988,[80] full report in peer-reviewed journal
Additional sources of data	Unclear whether or not the patients are the same as some patients in O'Hara 1988[78] and O'Hara 1985.[79] Different outcomes reported using different techniques
Trial design	RCT
Country	UK
Dates of participant recruitment	March 1984 to January 1986
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (2 g b.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	MWD: treadmill with constant workload, 10% gradient
	ABPI: Doppler ultrasound flow detector and sphygmomanometer at rest
Notes on statistics	Wilcoxon matched pairs signed-rank test or student's paired *t*-tests as appropriate
Population	
Eligibility criteria	*Inclusion*: stable IC (duration of symptoms of at least 6 months), PAD confirmed by resting ankle pressure index of < 0.9 or a drop in ankle pressure with exercise of > 30 mmHg. All patients had palpable femoral pulses and could walk between 35 and 500 m on a treadmill. Any medication for IC stopped 1 month before trial
	Exclusion: walking distance on treadmill > 500 m, serious medical disease, rest pain or gangrene, treatment with beta-blockers which was not stabilised or arterial surgery for claudication within the previous 3 months
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	80

NR, not reported.

Treatment group	Inositol nicotinate 4-g daily dose (2-g b.i.d.)	Placebo
N randomised to treatment	40	40
Baseline characteristics		
Age	Mean 61.5 (SD 9.3) years	Mean 62.8 (SD 7.3) years
Gender	M 82.5%; F 17.5%	M 77.5%; F 22.5%
Smokers	57.5%	72.5%
Diabetics		
Hypertension/blood pressure	Mean 153.6 (SD 23.9) mmHg/87.5 (SD 10.6) mmHg	Mean 152.9 (SD 24.1) mmHg/88.3 (SD 10.5) mmHg
Hyperlipidaemia		
Obesity or weight		
Angina		
History of vascular therapy		
Other	Duration mean 2.5 (SD 1.8) years VAS pain score mean 49.1 (SD 22.6) mm Estimate of free walking mean 330.6 (SD 219) yards	Duration mean 1.6 (SD 1.1) years VAS pain score mean 53.4 (SD 17.8) mm Estimate of free walking mean 309.1 (SD 239.7) yards
Withdrawals		
Withdrawals/loss to follow-up	Eight withdrawals [reasons were eight out of: moved from district (three), family problems (two), felt unwell taking tablets (two), personal choice (four), referred for surgery (one), hospitalised for an unrelated condition (one)]	Seven withdrawals [reasons were nausea and vomiting (one), constipation (one) and five out of: moved from district (three), family problems (two), felt unwell taking tablets (two), personal choice (four), referred for surgery (one), hospitalised for an unrelated condition (one)]
Results		
MWD *n* in analysis	Initially 40 – assume 12 weeks minus withdrawals (32)	Initially 40 – assume 12 weeks minus withdrawals (33)
MWD baseline	Mean 131.7 (SD 80.4) ($n=40$)	Mean 118.4 (SD 70.9) ($n=40$)
MWD follow-up	Mean 197.1 (SD 125.7) (assume $n=32$)	Mean 221.2 (SD 154.2) (assume $n=33$)
MWD change	Calculated: 65.4, $p<0.05$	102.8, $p<0.05$
MWD between-group comparison	No statistically significant difference between the groups	
PFWD *n* in analysis		
PFWD baseline		
PFWD follow-up		
PFWD change		
PFWD between-group comparison		
ABPI *n* in analysis	Initially 40 – assume minus withdrawals (32) at 12 weeks	Initially 40 – assume minus withdrawals (33) at 12 weeks
ABPI baseline	Mean 0.718 (SD 0.144) m	Mean 0.694 (SD 0.215) m
ABPI follow-up	NR	NR
ABPI change	Not significant	Not significant
ABPI between-group comparison	Not significant	

Treatment group	Inositol nicotinate 4-g daily dose (2-g 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	As for withdrawals	As for withdrawals
AEs follow-up		
AEs reported		
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; NR, not reported; VAS, visual analogue scale.

Head 1986[81]	
Study details	
Publication type	Head 1986,[81] full report in peer-reviewed journal
Additional sources of data	
Trial design	RCT, multicentre
Country	UK
Dates of participant recruitment	NR
Sources of funding	NR
Intervention(s) and comparator	
Treatment groups	Inositol nicotinate 4-g daily dose (1-g q.i.d.)
Comparator	Placebo
Run-in phase	No
Treatment duration	12 weeks
Outcome(s)	
Follow-up	Baseline, 12 weeks
Outcomes and measures	PFWD: time to claudication was recorded: a metronome was set at 80 beats/minute and each patient was instructed to climb up and down the first two steps of a standard ladder with a rung interval of 19 cm. Patients climbed one step at a time to the beat of the metronome, leading with the worse leg and bringing the other leg up before proceeding to the next step and then returning to the ground in a similar fashion. The time to onset of calf pain was recorded using a stopwatch, and pressure readings repeated AEs: elicited by question 'How did the tablets suit you?'
Notes on statistics	NR
Population	
Eligibility criteria	Patients with clinical diagnosis of IC due to vascular insufficiency. Male or female, aged between 18 and 80 years, weigh between 40 and 100 kg and be judged suitable to receive a 3-month course of inositol nicotinate 1-g q.d. or matching placebo
Concomitant interventions allowed or excluded	NR
Power calculation	NR
N randomised to treatments included in review	123

NR, not reported; q.d., once a day; q.i.d., four times a day.

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
N randomised to treatment	51 (plus unspecified number who withdrew)	62 (plus unspecified number who withdrew)
Baseline characteristics		
Age	Severe (IC < 60 seconds): mean 68.6 (SD 7.7)	Severe (IC < 60 seconds): mean 64.3 (SD 7.6)
	Moderate (IC 60–120 seconds): mean 67.0 (SD 6.7)	Moderate (IC 60–120 seconds): mean 64.8 (SD 7.7)
	Mild (IC > 120 seconds): mean 65.0 (SD 14.4)	Mild (IC > 120 seconds): mean 61.6 (SD 13.4)
Gender	Severe (IC < 60 seconds): M 78.9%; F 21.1%	Severe (IC < 60 seconds): M 66.7%; F 33.3%
	Moderate (IC 60–120 seconds): M 84.6%; F 15.4%	Moderate (IC 60–120 seconds): M 81.3%; F 18.7%
	Mild (IC > 120 seconds): M 66.7%; F 33.3%	Mild (IC > 120 seconds): M 55.6%; F 44.4%
Smokers	Severe (IC < 60 seconds): 57.9%	Severe (IC < 60 seconds): 47.6%
	Moderate (IC 60–120 seconds): 73.1%	Moderate (IC 60–120 seconds): 46.9%
	Mild (IC > 120 seconds): 33.3%	Mild (IC > 120 seconds): 44.4%
Diabetics	Severe (IC < 60 seconds): 15.8%	Severe (IC < 60 seconds): 4.8%
	Moderate (IC 60–120 seconds): 0%	Moderate (IC 60–120 seconds): 3.1%
	Mild (IC > 120 seconds): 0%	Mild (IC > 120 seconds): 0%
Hypertension/blood pressure	All in mmHg:	All in mmHg:
	Severe (IC < 60 seconds): mean 162.1 (SD 23.3)/85.7 (SD 8.2)	SEVERE (IC < 60 seconds): mean 164.3 (SD 19.9)/92.6 (SD 10.1)
	Moderate (IC 60–120 seconds): mean 159.4 (SD 21.1)/88.6 (SD 12.3)	Moderate (IC 60–120 seconds): mean 163.3 (SD 29.8)/89.7 (SD 16.6)
	Mild (IC > 120 seconds): mean 160 (SD24.5)/83.0 (SD 12.2)	Mild (IC > 120 seconds): mean 155.7 (SD 13.2)/85.3 (SD 8.5)
Hyperlipidaemia		
Obesity or weight	Severe (IC < 60 seconds): mean 69.3 (SD 13.4) kg	Severe (IC < 60 seconds): mean 68.0 (SD 11.3) kg
	Moderate (IC 60–120 seconds): mean 72.0 (SD 11.7) kg	Moderate (IC 60–120 seconds): mean 73.4 (SD 11.7) kg
	Mild (IC > 120 seconds): mean 69.6 (SD 4.8) kg	Mild (IC > 120 seconds): mean 72.3 (9.7) kg
Angina		
History of vascular therapy		
Other		
Withdrawals		
Withdrawals/loss to follow-up	Broken ankle, one; inability to swallow, one; constipation, one; non-compliance, one	Cerebrovascular accident, one; thrombophlebitis, one; gastrointestinal upset, two; personal reasons, one
	Also, 10 patients were excluded from analysis, unclear which groups they were from	Also, 10 patients were excluded from analysis, unclear which groups they were from
	Reasons were: congestive cardiac failure, three; osteoarthritis, two; severe leg pain at rest, one; carcinoma of the stomach with secondaries in the liver, one; failure to return, one; leukaemia, one; rheumatoid arthritis, one	Reasons were: congestive cardiac failure, three; osteoarthritis, two; severe leg pain at rest, one; carcinoma of the stomach with secondaries in the liver, one; failure to return, one; leukaemia, one; rheumatoid arthritis, one
Results		
MWD *n* in analysis		
MWD baseline		
MWD follow-up		
MWD change		
MWD between-group comparison		

Treatment group	Inositol nicotinate 4-g daily dose	Placebo
PFWD *n* in analysis	47	57
PFWD baseline	*PFW time (s)*:	*PFW time (s)*:
	Severe: mean 44.42 (SD 14.78)	Severe: mean 44.33 (SD 14.81)
	Moderate: mean 85.23 (SD 15.96)	Moderate: mean 88.53 (SD 17.21)
	Mild: mean 183.5 (SD 66.67)	Mild: mean 156.9 (SD 19.71)
PFWD follow-up	*PFW time (s)*:	*PFW time (s)*:
	Severe: mean 59.59 (SD 28.08)	Severe: mean 64.86 (SD 36.70)
	Moderate: mean 105.50 (SD 36.71)	Moderate: mean 97.11 (SD 36.25)
	Mild: mean 156.2 (SD 40.87)	Mild: mean 194.6 (SD 93.49)
PFWD change	*PFW time (s)*:	*PFW time (s)*:
	Severe: $p < 0.05$	Severe: $p < 0.01$
	Moderate: $p < 0.01$	Moderate: $p < 0.01$
	Mild: non-significant	Mild: non-significant
PFWD between-group comparison	*PFW time (s)*:	
	Severe: non-significant	
	Moderate: significant between-group comparison $p < 0.001$	
	Mild: non-significant	
ABPI *n* in analysis		
ABPI baseline		
ABPI follow-up		
ABPI change		
ABPI between-group comparison		
Vascular events *n* in analysis	51	62
Vascular events follow-up		
Vascular events included	Taken from AEs	
Vascular events reported	Zero	Cerebrovascular accident, one; thrombophlebitis, one – also reported in AEs
Vascular events between-group comparison		
AEs *n* in analysis	Baseline, 51; 12 weeks, 47	Baseline, 62; 12 weeks 57
AEs follow-up		
AEs reported	4/51 (7.8%). Broken ankle, one (2%); inability to swallow, one (2%); constipation, one (2%); non-compliance, one (2%)	5/62 (8.1%). Cerebrovascular accident, one (1.6%); thrombophlebitis, one (1.6%); gastrointestinal upset, two (3.2%); personal reasons, one (1.6%)
AEs between-group comparison		
Mortality reported		
Mortality between-group comparison		
HRQoL *n* in analysis		
HRQoL baseline		
HRQoL follow-up		
HRQoL change		
HRQoL between-group comparison		

F, female; M, male; PFW, pain-free walking.