Supplemental material

Contents

Table S1. Primary (difference in delta in exercise time) and secondary (difference in delta in SAQ summary score) outcomes (intention-to-treat analysis).

	Amlodipine		Ranolazine	
	CMD	**Reference**	**CMD**	**Reference**
Exercise time (seconds)				
Increment	89 (95% CI 69 to 117)	13 (95% CI -14 to 40)	80 (95% CI 53 to 108)	5 (95% CI -27 to 37)
Difference in delta between groups	76 (95% CI 34 to 118)		75 (95% CI 31 to 120)	
P value	<0.001		0.001	
SAQ summary score				
Increment	7 (95% CI 3 to 11)	6 (95% CI 2 to 10)	11 (95% CI 6 to 16)	7 (95% CI 2 to 12)
Difference in delta between groups	1 (95% CI -5 to 7)		4 (95% CI -3 to 12)	
P value	0.768		0.254	

CMD: coronary microvascular disease; SAQ: Seattle Angina Questionnaire

Table S2. Exercise treadmill test parameters.

/	Baseline			Amlodipine			Ranolazine		
	CMD	Reference	P value	CMD	Reference	P value	CMD	Reference	P value
Frequency of angina, n (%)	44 (80)	23 (77)	0.710	30 (61)	15 (58)	0.766	25 (49)	14 (58)	0.451
Reason for stopping ETT, n (%)			0.459			0.198			0.433
Angina	29 (53)	17 (57)		16 (33)	8 (31)		16 (31)	12 (52)	
Dyspnea	15 (27)	4 (13)		7 (15)	8 (31)		17 (33)	7 (30)	
Fatigue	10 (18)	8 (27)		18 (38)	10 (38)		14 (28)	3 (13)	
Presyncope	1 (2)	1 (3)		3 (6)	0		3 (6)	1 (4)	
Musculoskeletal pain	0	0		4 (8)	0		1 (2)	0	
Time to angina, seconds	205±98	187±111	0.490	297±161	251±146	0.362	260±122	183±88	0.028

CMD: coronary microvascular disease; ETT: exercise treadmill test

Table S3. Within group differences in change in exercise time in patients with structural and functional CMD (intention-to-treat analysis).

	Structural CMD		Functional CMD	
	AML	**RNL**	**AML**	**RNL**
Exercise time (seconds)				
Mean increment	74 (95% CI 25 to 124)	42 (95% CI 8 to 76)	97 (95% CI 62 to 132)	101 (95% CI 63 to 139)
Difference in delta within group	39 (95% CI -1 to 79)		-2 (95% CI -29 to 25)	
P value	0.058		0.865	

CMD: coronary microvascular disease; AML: amlodipine; RNL: ranolazine

Table S4. Comparison of previous exemplar cardiovascular trials using exercise time as an outcome measure.

|	Study design	Baseline ET	Increment in ET
Obstructive CAD			
Fox KM et al[18] TIBET	Design: Double-blind parallel-group study Patient numbers: 319 Follow-up: Six weeks	417s (atenolol arm) 423s (nifedipine arm) 410 (combination arm)	91s (atenolol arm) 91s (nifedipine arm) 98s (combination arm)
Frischman WH et al[19]	Design: Double-blind, placebo controlled, RCT Patient numbers: 551 Follow-up: Four weeks	348s (verapamil) 360s (amlodipine) 348s (amlodipine and atenolol) 354s (placebo)	66s (verapamil) 60s (amlodipine) 72s (amlodipine and atenolol) 24s (placebo)
Chaitman BR et al[20] MARISA	Design: Double blinded placebo controlled RCT; Patient numbers: 191 Follow-up: One week of therapy at 3 sequentially doses	Baseline exercise times not reported	116s (Ranolazine 750mg) 70s (placebo)
Noman A et al[21]	Design: Double-blind, placebo-controlled, crossover RCT Patient numbers: 65 Follow-up: Six weeks	301s	6s (placebo) 93s (allopurinol)

Al-Lamee R et al[24] **ORBITA**	Design: Double-blinded sham procedure trial; Patient numbers: 230 Follow-up: Six weeks	528s (PCI group) 490s (sham group)	28s (PCI group) 12s (sham group)
Reynolds HR et al[26] **ISCHEMIA-CIAO**	Design: observational substudy Patient numbers: 116 Follow-up: One year	364s	46s
Heart failure with reduced ejection fraction			
Rouleau JL et al[22] **IMPRESS**	Design: Double-blinded parallel RCT Patient numbers: 573 Follow-up: 12 weeks	511s (omapatrilat arm) 500s (lisinopril arm)	24s (omapatrilat arm) 31s (lisinopril arm)
Australia/New Zealand Heart Failure Research Collaborative Group[23]	Design: Double-blind, placebo-controlled RCT Patient numbers: 415 Follow-up: One year	630s	7s 24s improvement) and placebo (roughly 17s improvement)

CAD: coronary artery disease; ET: exercise time

Table S5. Comparison of SAQ scores in other trials of patients with ischemic heart disease.

	SAQ scores at baseline	SAQ scores with treatment
CorMicA[7]	Summary score 51 Angina frequency score 59	Summary score 52 (control arm) Summary score 68 (intervention arm) Angina frequency score 56 (control arm) Angina frequency score 75 (intervention arm) <u>Follow-up:</u> 6 months
ORBITA[24]	Angina frequency score 63 (PCI group) Angina frequency score 60 (sham group)	Angina frequency score 74 (PCI group) Angina frequency score 68 (sham group) <u>Follow-up:</u> 6 weeks
Spertus JA et al[25] ISCHEMIA	Summary score 73 (invasive arm) Summary score 75 (conservative arm) Angina frequency score 81 (invasive arm) Angina frequency score 82 (conservative arm)	Summary score 89 (invasive arm) Summary score 83 (conservative arm) <u>Follow-up:</u> 3 years
ISCHEMIA-CIAO[26]	Summary score 83 Angina frequency score 90	Summary score 92 Angina frequency score 100 <u>Follow-up:</u> 6 months

Figure S1. A comparison of exercise time between first and fourth ETTs.
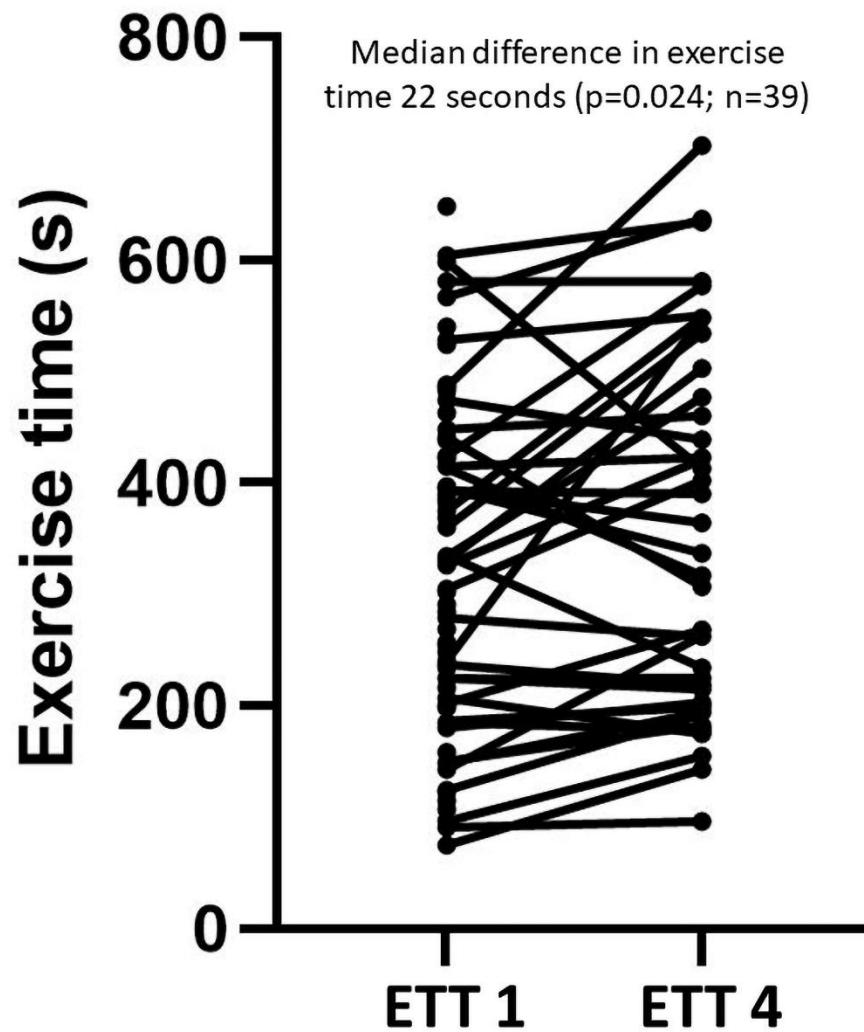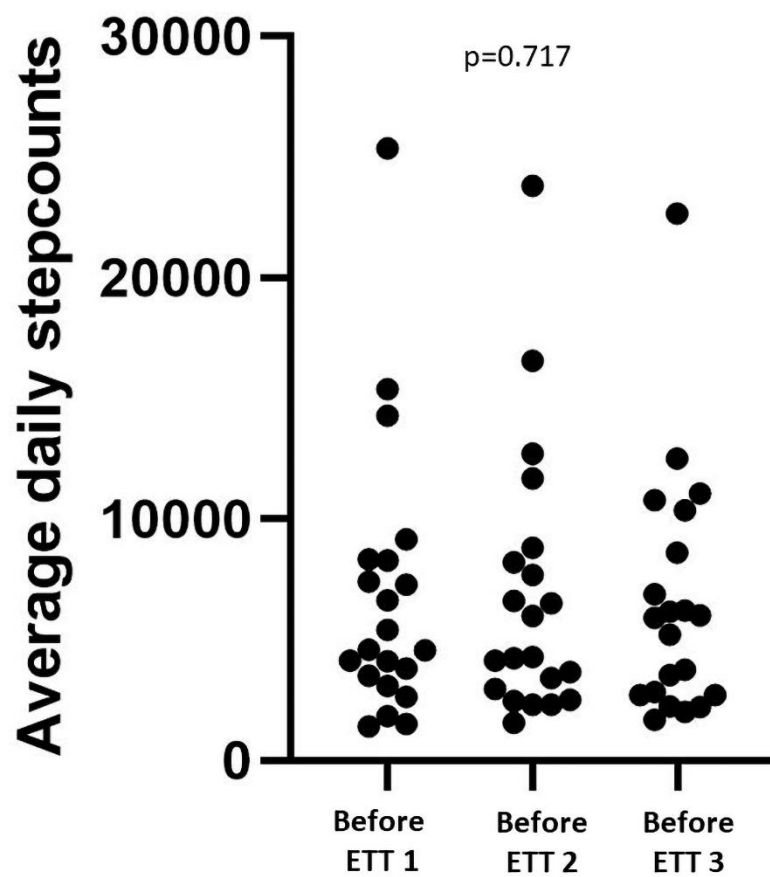

ETT: exercise treadmill test

Data are presented as individual plots; p value is calculated using the Wilcoxon matched pairs signed rank test.
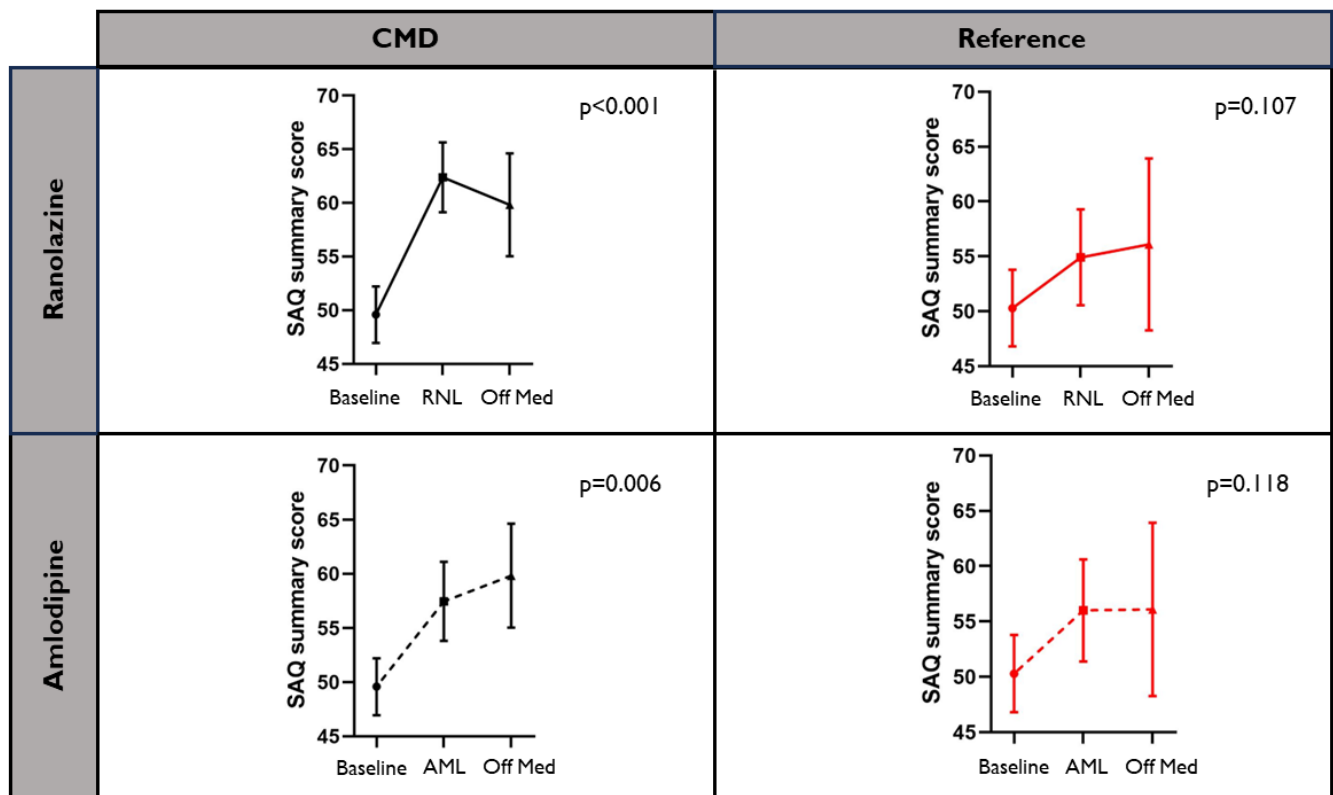
Figure S2. A comparison of average daily step counts in the four-week period preceding ETTs.

ETT: exercise treadmill test

Data are presented as individual plots; p value is calculated using the Friedman test.

Figure S3. Change in SAQ summary score between baseline, with anti-ischemic medication and without anti-ischemic medication.

CMD: coronary microvascular disease; RNL: ranolazine; AML: amlodipine; Off Med: after cessation of study medications

Data are presented as mean±SEM; p values are for repeated measures ANOVA