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Supplement

2 **The PRIZE Study Group**

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Supplementary Results

Exercise time according to the timepoint of the study

Treadmill exercise time differed during the trial period compared to before the trial (Supplementary Figure S3).

A statistically significant increase in overall exercise duration occurred during the trial, including by comparison at the end of Period 2 (Visit 5) versus baseline (Visit 3) (mean (SD) 29.5 (86.0), 95% CI 11.4, 47.6 seconds, n=89; p=0.0017) and at the end of Period 2 (Visit 5) versus the end of Period 1 (Visit 4) (mean (SD) 20.9 (74.2), 95% CI 5.3, 36.6 seconds, n=89, p=0.0092). By contrast, overall exercise duration did not change during sequential visits before the trial commenced i.e. exercise duration at baseline (Visit 3) was not different when compared to exercise duration at enrolment (Visit 1) (mean (SD) 2.2 (68.0), 95% CI -10.3, 14.7 seconds, n=117, p=0.7265).

18 **Supplementary Table S1.** Population characteristics.

	Screened population, n = 222	Trial population, n = 118	MRI population, n = 23
<i>Demographics</i>			
Age $\pm$ SD, years	64.0 (10.0)	63.5 (9.2)	67.9 (9.7)
Male sex, n (%)	90 (40.5)	47 (39.8)	13 (56.5)
Female sex, n (%)	132 (59.5)	71 (60.2)	10 (43.5)
<i>Ethnicity, n (%)</i>			
White	209 (94.6)	172 (1)	23 (100.0)
Asian Bangladeshi	1 (0.5)	1 (0.8)	0 (0.0)
Asian Indian	4 (1.8)	2 (1.7)	0 (0.0)
Asian Pakistani	1 (0.5)	1 (0.8)	0 (0.0)
Asian Other	2 (0.9)	1 (0.8)	0 (0.0)
Black African	1 (0.5)	0 (0.0)	0 (0.0)
Chinese	1 (0.5)	0 (0.0)	0 (0.0)
Other	2 (0.9)	0 (0.0)	0 (0.0)
Missing	1 (0.5)	0 (0.0)	0 (0.0)
<i>Medical history, n (%)</i>			
Hospitalization for chest pain	136 (61.5)	75 (63.6)	13 (56.5)
Vasospastic angina	56 (41.2)	30 (40.0)	12 (52.2)
Hypertension	29 (21.3)	17 (22.7)	14 (60.9)
Diabetes, treated	13 (9.6)	9 (12.0)	3 (13.0)
Percutaneous coronary intervention	38 (27.9)	19 (25.3)	3 (13.0)
Myocardial infarction	55 (24.9)	32 (27.1)	1 (4.3)
Atrial fibrillation or flutter	121 (54.8)	64 (54.2)	1 (4.3)
Hospitalization for chest pain	38 (17.2)	25 (21.2)	13 (56.5)
Any	41 (18.6)	21 (17.8)	6 (46.2)
≥ 3 hospitalizations for chest pain	28 (12.7)	13 (11.0)	2 (15.4)
History of two or more coronary angiograms	30 (13.6)	13 (11.0)	1 (7.7)
<i>Smoking status, n (%)</i>			
Every day smoker	5 (2.3)	5 (2.3)	5 (2.3)
Some days smoker (smokes but not every day)	3 (1.4)	3 (1.4)	3 (1.4)
Former smoker (quit at time of interview)	97 (44.1)	97 (44.1)	97 (44.1)
Never smoked	115 (52.3)	115 (52.3)	115 (52.3)

<i>Cardiac imaging</i>	182 (82.4)	94 (79.7)	18 (78.3)
Echocardiography	85 (46.7)	47 (50.0)	8 (44.4)
Cardiovascular magnetic resonance imaging	83 (45.6)	41 (43.6)	8 (44.4)
Computed tomography ventriculogram	0 (0.0)	0 (0.0)	0 (0.0)
Positron emission tomography	1 (0.5)	0 (0.0)	0 (0.0)
Single-photon emission computed tomography	10 (5.5)	5 (5.3)	2 (11.1)
Other	3 (1.6)	1 (1.1)	0 (0.0)
Left ventricular ejection fraction from cardiac imaging, mean (SD), %	62.0 (7.2)	62.5 (7.2)	63.4 (9.3)
<i>Presenting characteristics, mean (SD)</i>			
Body mass index, kg/m ²	29.6 (5.1)	29.0 (4.6)	27.1 (4.5)
Heart rate, mean (SD), bpm	72 (13)	73 (12)	69 (12)
Systolic blood pressure, mean (SD), mmHg	137 (19)	137 (18)	130 (16)
Diastolic blood pressure, mean (SD), mmHg	79 (12)	79 (12)	72 (11)
Canadian Cardiovascular Society angina class	219 (3)	118 (104)	23 (199)
I	40 (18.3)	14 (11.9)	2 (8.7)
II	133 (60.7)	79 (66.9)	18 (78.3)
III	45 (20.5)	24 (20.3)	3 (13.0)
IV	1 (0.5)	1 (0.8)	0 (0.0)
Not available	0 (0.0)	0 (0.0)	0 (0.0)
<i>Medication</i>			
Angina medication	205 (92.3)	109 (92.4)	23 (100.0)
0	17 (7.7%)	9 (7.6%)	0 (0.0%)
1	70 (31.5%)	30 (25.4%)	4 (17.4%)
2	78 (35.1%)	47 (39.8%)	10 (43.5%)
3	41 (18.5%)	20 (16.9%)	7 (30.4%)
4	14 (6.3%)	10 (8.5%)	1 (4.3%)
5	2 (0.9%)	2 (1.7%)	1 (4.3%)
Preventive medication	205 (92.3)	112 (94.9)	23 (100.0)
<i>Laboratory results at randomization</i>			
Hemoglobin, mean (SD), g/L	138 (13)	138 (12)	145 (11)
Minimum eGFR, ml/min/1.73m ²	71 (15)	72 (14)	70 (14)
HbA1c, mean mmol/mol Hb, %	40.9 (8.4)	41.3 (9.4)	37.7 (3.7)

NT-proBNP, median [IQR], pg/mL	88 [50, 179]	86 [49, 163]	145 [55, 244]
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19 CI – confidence interval; estimated glomerular filtration rate; NT-proBNP - N-terminal pro-brain
20 natriuretic peptide; SD – standard deviation;

21 **Supplementary Table S2.** Drug treatments recorded at screening and at randomization.

	Screened population, n = 222	Trial population, n = 118	MRI population, n =23
<i>Cardiovascular medication, n (%)</i>			
Aldosterone receptor antagonist	6 (2.7)	4 (3.4)	1 (4.3)
Aspirin	128 (57.7)	73 (61.9)	19 (82.6)
Anti-Platelet medication	35 (15.8)	22 (18.6)	4 (17.4)
Statin	186 (83.8)	100 (84.7)	19 (82.6)
Other lipid lowering drug	15 (6.8)	11 (9.3)	1 (4.3)
Beta Blocker	100 (45.0)	51 (43.2)	11 (47.8)
Calcium Channel blocker	131 (59.0)	70 (59.3)	18 (78.3)
Long-acting nitrate	97 (43.7)	56 (47.5)	13 (56.5)
Nicorandil	40 (18.0)	26 (22.0)	7 (30.4)
ACE Inhibitor	69 (31.1)	36 (30.5)	8 (34.8)
Angiotensin receptor blocker	37 (16.7)	20 (16.9)	2 (8.7)
ACE Inhibitor or Angiotensin receptor blocker	106 (47.7)	56 (47.5)	10 (43.5)
Alpha blocker	10 (4.5)	4 (3.4)	2 (8.7)
Diuretic	18 (8.1)	6 (5.1)	1 (4.3)
Ranolazine	44 (19.8)	30 (25.4)	5 (21.7)
Ivabradine	3 (1.4)	1 (0.8)	0 (0.0)
Anticoagulant	25 (11.3)	9 (7.6)	1 (4.3)
<i>Other medication</i>			
Hormone replacement or oral contraceptive	15 (6.8)	9 (7.6)	0 (0.0)
Insulin	7 (3.2)	6 (5.1)	0 (0.0)
Antidepressant	45 (20.3)	22 (18.6)	4 (17.4)
Neuroleptic	11 (5.0)	7 (5.9)	0 (0.0)
Proton pump inhibitor	132 (59.5)	70 (59.3)	12 (52.2)
Oral analgesic	48 (21.6)	25 (21.2)	4 (17.4)

22 ACE – angiotensin converting enzyme.

23 **Supplementary Table S3.** Exercise test findings.

	Baseline, n	Baseline value	After placebo, n	After placebo value	After zibotentan, n	After zibotentan value	Effect estimate	95% CI	p- value
<i>Rest</i>									
Heart rate	117	73 (12)	98	72 (12)	94	72 (11)	-0.2	(-2.24, 1.84)	0.85
Sinus rhythm, n (%)	113	113 (96.6%)	91	91 (92.9%)	89	89 (94.7%)			
Atrial fibrillation, n (%)	1	1 (0.9%)	1	1 (1.0%)	2	2 (2.1%)			
Pacemaker	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)			
SBP, mean (SD), mmHg	117	135 (17)	98	134 (18)	94	128 (17)	-5.88	(-9.31, -2.45)	0.001
Rate pressure product, mean (SD), mmHg*bpm	117	160.2 (7.9)	98	160.1 (8.1)	94	159.3 (7.5)	0.01	(-0.32, 0.34)	0.96
Maximum predicted age-sex related heart rate, mean (SD),	117	1.7 (0.0)	98	1.7 (0.1)	94	1.7 (0.0)	0	(-0.01, 0.02)	0.47
Starting treadmill speed, mean (SD), mph	117	160.2 (7.9)	98	160.1 (8.1)	94	159.3 (7.5)	0.01	(-0.32, 0.34)	0.96
Starting treadmill slope, mean (SD), %	117	10.0 (0.0)	98	10.0 (0.0)	94				
<i>Exercise, peak</i>									
Heart rate at peak exercise, mean (SD)	117	125 (20)	98	125 (20)	94	124 (20)	-0.72	(-3.32, 1.89)	0.59
SBP at peak exercise, mean (SD), mmHg	116	163 (28)	98	167 (28)	94	162 (27)	-5.09	(-10.44, 0.22)	0.064
DBP at peak exercise, mean (SD), mmHg	116	80 (15)	98	83 (15)	94	76 (14)	-6.54	(-10.05, -3.05)	<0.001
Time to 0.1 mV ST depression from baseline, mean (SD), seconds	56	309 (137)	42	298 (107)	44	313 (113)	1.07	(0.66, 1.74)	0.79
Time to maximum ST depression, mean (SD), seconds	111	301 (143)	92	320 (124)	89	314 (132)	-5.92	(-25.22, 13.45)	0.55
Time to 75% maximum predicted heart rate, mean (SD), seconds	116	19881 (5306)	98	20201 (5521)	94	19317 (5487)	-692.3	(-1452.32, 61.89)	0.076
Rate pressure product, mean (SD), mmHg*bpm	117	303 (133)	98	330 (135)	94	326 (133)	-4.26	(-19.60, 11.06)	0.59
Exercise time, mean (SD), seconds	117	125 (20)	98	125 (20)	94	124 (20)	-0.72	(-3.32, 1.89)	0.59

<i>Exercise, post</i>									
Ventricular ectopic beats during recovery, mean (SD), number per minute	104	1.0 (2.5)	87	0.9 (2.5)	80	2.1 (5.5)	1.18	(0.03, 2.34)	0.048
Maximum ST depression, mean (SD), mm	114	-0.9 (0.8)	92	-0.9 (0.8)	92	-0.9 (0.8)	-0.01	(-0.21, 0.19)	0.93
Maximum net ST segment deviation, mean (SD), mm	114	-0.4 (1.5)	93	-0.4 (1.4)	89	-0.1 (1.4)	0.29	(-0.08, 0.66)	0.12
ST/heart rate hysteresis, mean (SD), mV	76	0.0 (0.0)	67	0.0 (0.0)	62	0.0 (0.0)	0.01	(0.00, 0.01)	0.042
Heart rate reserve used, %	117	67.4 (19.6)	98	66.5 (21.3)	94	66.8 (21.1)	0.88	(-1.66, 3.44)	0.5
Maximum workload from ECG, mean (SD), METS	116	7.1 (2.2)	98	7.5 (2.1)	92	7.2 (2.1)	-0.27	(-0.58, 0.03)	0.082
Final treadmill speed, mean (SD), mph	117	2.7 (0.7)	98	2.8 (0.7)	94	2.8 (0.7)	-0.02	(-0.13, 0.08)	0.69
Final treadmill slope, mean (SD), %	117	12.4 (1.6)	98	12.7 (1.5)	94	12.7 (1.6)	-0.05	(-0.28, 0.18)	0.67
Stage of Bruce protocol at end of test	117	117 (1)	98	98 (2)					
1	23	23 (19.7%)	14	14 (14.3%)					
2	55	55 (47.0%)	39	39 (39.8%)					
3	34	34 (29.1%)	40	40 (40.8%)					
4	4	4 (3.4%)	5	5 (5.1%)					
5	1	1 (0.9%)	0	0 (0.0%)					
Exercise test stopped early, n (%)	78	78 (66.7%)	64	64 (65.3%)					
First reason for stopping	78	78 (0)	64	64 (0)					
Chest tightness	0	0 (0.0%)	0	0 (0.0%)					
Breathlessness	56	56 (71.8%)	34	34 (53.1%)					
Fatigue (exercise intolerance)	20	20 (25.6%)	26	26 (40.6%)					
Dizziness	1	1 (1.3%)	1	1 (1.6%)					
Palpitations	1	1 (1.3%)	1	1 (1.6%)					
Non-cardiac reason e.g. back pain	0	0 (0.0%)	0	0 (0.0%)					
Borg scale response	0	0 (0.0%)	2	2 (3.1%)					
6-12	117	117 (1)	98	98 (2)					
13	1	1 (0.9%)	2	2 (2.0%)					
14-20	98	98 (83.8%)	89	89 (90.8%)					

Angina scale for exercise tolerance test	18	18 (15.4%)	7	7 (7.1%)					
0	117	117 (1)	98	98 (2)					
1	18	18 (15.4%)	42	42 (42.9%)					
2	41	41 (35.0%)	17	17 (17.3%)					
3	29	29 (24.8%)	17	17 (17.3%)					
4	29	29 (24.8%)	22	22 (22.4%)					
Angina index for Duke score	0	0 (0.0%)	0	0 (0.0%)					
0	117	117 (1)	98	98 (2)					
1	19	19 (16.2%)	43	43 (43.9%)					
2	38	38 (32.5%)	19	19 (19.4%)					
Duke exercise score, mean (SD)	114	1.7 (8.9)	93	3.5 (7.8)	90	1.7 (8.7)	-1.78	(-3.59, 0.04)	0.059
VO2, mean (SD), METS	117	22.9 (6.1)	98	24.2 (5.8)	94	24.0 (6.1)	-0.18	(-1.08, 0.72)	0.7

24 CI – confidence interval; DBP - diastolic blood pressure; METS - metabolic equivalent; SBP - systolic blood pressure; SD – standard
25 deviation; VO2 - maximal rate of oxygen consumption;

26 **Supplementary Table S4.** Safety blood tests.

	Baseline, n	Baseline value	After placebo, n	After placebo value	After zibotentan, n	After zibotentan value	Effect estimate	95% CI	p- value
<i>Hematology</i>									
Hemoglobin, mean (SD), g/L	116	139 (13)	97	138 (12)	92	131 (12)	-7.73	(-9.43, -6.01)	<0.001
White cell count, mean (SD), x10⁹/L	116	7 (3)	97	7 (3)	92	7 (2)	-0.48	(-0.80, -0.16)	0.004
Platelet count, mean (SD), x10⁹/L	115	243 (61)	97	246 (63)	92	235 (63)	-9.67	(-16.62, -2.71)	0.008
<i>Renal function</i>									
Potassium, mean (SD), mmol/L	117	4.3 (0.4)	97	4.3 (0.3)	92	4.3 (0.3)	-0.05	(-0.12, 0.01)	0.098
Urea, mean (SD), mmol/L	113	5.6 (1.5)	94	5.9 (3.9)	91	5.6 (1.6)	-0.31	(-1.12, 0.50)	0.45
Creatinine, mean (SD), mean (SD), μmol/L	117	74 (17)	97	75 (17)	92	77 (21)	1.55	(-0.14, 3.23)	0.075
eGFR, ml/min/1.73m ²	117	72 (13)	97	70 (13)	92	70 (14)	-0.54	(-1.78, 0.69)	0.39
<i>Liver function</i>									
Alanine transaminase, mean (SD), U/L	117	27 (13)	97	27 (16)	92	25 (10)	-2.67	(-4.78, -0.55)	0.015
Aspartate transaminase, mean (SD), U/L	92	26 (11)	82	26 (11)	78	24 (8)	-1.58	(-3.35, 0.18)	0.084
Alkaline phosphatase, mean (SD), U/L	116	84 (21)	96	86 (26)	92	80 (21)	-5.57	(-8.37, -2.75)	<0.001
Albumin, mean (SD), g/L	117	42 (4)	97	42 (5)	92	41 (3)	-0.81	(-1.68, 0.05)	0.068
Bilirubin, mean (SD), μmol/L	117	11 (7)	97	11 (6)	92	10 (6)	-0.67	(-1.16, -0.18)	0.009
<i>Lipid profile</i>									
Total cholesterol, mean (SD), mmol/L	117	4.3 (1.0)	95	4.3 (1.2)	92	4.0 (1.1)	-0.33	(-0.46, -0.20)	<0.001
HDL, mean (SD), mmol/L	117	1.5 (0.6)	95	1.4 (0.4)	91	1.4 (0.4)	0	(-0.04, 0.04)	0.88
LDL cholesterol, mean (SD), mmol/L	111	2.1 (0.9)	91	2.1 (0.9)	88	1.9 (0.9)	-0.26	(-0.36, -0.16)	<0.001
VLDL cholesterol, mean (SD), mmol/L	46	0.7 (0.3)	42	0.7 (0.4)	36	0.7 (0.3)	-0.08	(-0.16, 0.01)	0.083
Cholesterol/HDL ratio, mean (SD), mmol/L	117	3.1 (0.9)	95	3.2 (1.3)	91	3.0 (1.2)	-0.26	(-0.38, -0.15)	<0.001
Triglycerides, mean (SD), mmol/L	117	1.7 (1.4)	95	1.8 (1.9)	92	1.8 (2.8)	-0.04	(-0.27, 0.20)	0.77
<i>Glucose metabolism</i>									
Glucose, mean (SD), mmol/L	84	6.1 (2.6)	81	6.2 (2.6)	73	5.7 (2.0)	-0.32	(-0.77, 0.13)	0.16
HbA1c, mean mmol/mol Hb, %	114	41.5 (9.6)	97	42.2 (10.5)	89	40.5 (9.9)	-1.85	(-2.67, -1.02)	<0.001

<i>Cardiac biomarkers</i>									
NT-proBNP, median [IQR], pg/mL	111	133 (139)	91	131 (138)	90	157 (225)	23.07	(-15.04, 61.16)	0.24
High sensitivity troponin I, median [IQR], ng/L	109	6.4 (16.8)	93	5.5 (13.4)	93	14.0 (78.3)	8.78	(-7.34, 24.89)	0.29

27 Hb – hemoglobin, SD – standard deviation; HDL - High-density lipoprotein; LDL - low-density lipoprotein; NT-proBNP - N-terminal

28 (NT)-pro hormone brain natriuretic peptide; VLDL - very-low density lipoprotein

29 **Supplementary Table S5.** Hemodynamics and biomarkers.

	Baseline, n	Baseline	After placebo, n	After placebo	After zibotentan, n	After zibotentan	Effect estimate	95% CI	p- value
<i>Blood pressure</i>									
Systolic blood pressure, mean (SD), mmHg	117	135 (18)	98	135 (16)	95	129 (17)	-5.49	(-8.49, -2.50)	<0.001
Diastolic blood pressure, mean (SD), mmHg	117	77 (12)	98	78 (11)	95	72 (11)	-6.19	(-8.41, -3.97)	<0.001
Heart rate	103	73 (12)	98	72 (12)	94	72 (11)	-0.20	(-2.24, 1.84)	0.85
<i>Endothelial function</i>									
Big endothelin-1, pmol/L	108	0.39 (0.14)	93	0.40 (0.23)	94	0.56 (0.21)	0.16	(0.11, 0.21)	<0.001
Endothelin-1, pg/ml	112	1.8 (0.8)	95	1.6 (0.6)	94	2.7 (1.3)	1.17	(0.91, 1.42)	<0.001
Mid regional pro-adrenomedullin, nmol/L	110	0.6 (0.2)	92	0.6 (0.2)	90	0.6 (0.2)	0.02	(-0.01, 0.06)	0.15
<i>Cardiac biomarkers</i>									
NT-proBNP, median [IQR], pg/mL	111	133 (139)	91	131 (138)	90	157 (225)	23.07	(-15.04, 61.16)	0.24
High sensitivity troponin I, median [IQR], ng/L	109	6.4 (16.8)	93	5.5 (13.4)	93	14.0 (78.3)	8.78	(-7.34, 24.89)	0.29
<i>Inflammation</i>									
Peak C-reactive protein, median (IQR), mg/L	110	1.9 (2.5)	94	2.3 (4.2)	90	1.8 (2.3)	-0.59	(-1.45, 0.27)	0.18
ICAM-1, median (IQR), ng/mL	114	599.9 (217.5)	96	595.1 (214.9)	95	581.0 (206.3)	-0.5	(-40.85, 39.63)	0.98
VCAM-1, median (IQR), ng/mL	114	1168.5 (428.7)	96	1115.3 (400.4)	95	1158.8 (466.5)	46.12	(-41.22, 133.95)	0.3
Interleukin-6, median [IQR], pg/mL	114	3.6 (2.8)	96	3.8 (2.6)	93	3.5 (2.4)	-0.28	(-0.83, 0.26)	0.31
<i>Metabolism</i>									
Glucose, mean (SD), mmol/L	115	5.6 (2.2)	96	5.6 (2.3)	95	5.3 (1.7)	-0.37	(-0.74, 0.00)	0.054
Total cholesterol, mean (SD), mmol/L	114	3.9 (1.1)	96	3.8 (1.3)	93	3.5 (1.1)	-0.36	(-0.52, -0.21)	<0.001
High-density lipoprotein, mean (SD), mmol/L	114	1.3 (0.3)	96	1.3 (0.4)	93	1.2 (0.4)	-0.02	(-0.07, 0.03)	0.39
Triglyceride, mean (SD), mmol/L	113	1.7 (1.0)	96	1.6 (1.1)	92	1.5 (0.9)	-0.2	(-0.36, -0.04)	0.018
Uric acid, mean (SD), mmol/L	114	4.8 (1.3)	96	4.6 (1.3)	92	4.5 (1.4)	-0.1	(-0.29, 0.08)	0.27

<i>Collagen turnover</i>									
PIIINP, mean (SD), µg/L	114	7.9 (2.6)	96	7.7 (2.2)	94	8.2 (2.3)	0.53	(0.14, 0.92)	0.009
<i>Fluid homeostasis</i>									
Copeptin, mean (SD), pmol/L	112	5.4 (3.9)	93	5.2 (3.7)	90	5.5 (4.5)	0.46	(-0.14, 1.07)	0.14
<i>Renal function</i>									
Cystatin C, mean (SD), mg/L	114	0.9 (0.2)	96	0.8 (0.2)	93	0.8 (0.2)	0.02	(-0.01, 0.05)	0.23

30 ICAM-1 - Intercellular adhesion molecule-1; Hb – hemoglobin; HDL - High-density lipoprotein; LDL - low-density lipoprotein; NT-
31 proBNP - N-terminal (NT)-pro hormone brain natriuretic peptide; PIIINP - amino terminal peptide of type III procollagen; SD –
32 standard deviation; VLDL - very-low density lipoprotein; VCAM-1 - vascular cell adhesion protein-1.

33 **Supplementary Table S6.** Cardiovascular MRI.

	Baseline, n	Baseline	After placebo, n	After placebo	After zibotentan, n	After zibotentan	Effect estimate	95% CI	p-value
<i>Cardiac dimensions</i>									
<i>Atria</i>									
RA area, end-diastole, cm ²	23	39.57 (25.02)	19	41.29 (15.87)	17	42.74 (17.22)	1.01	(-6.00, 8.00)	0.79
LA area, end-diastole, cm ²	23	33.66 (16.88)	19	31.95 (9.80)	17	37.19 (10.98)	5.07	(-0.15, 10.40)	0.079
<i>Ventricles</i>									
LV EDVi mean (SD), mL/m²	23	72.44 (13.86)	19	75.48 (11.08)	17	84.63 (14.52)	9.4	(4.80, 13.97)	<0.001
LV ESVi, mean (SD), mL/m²	23	25.84 (7.67)	19	26.02 (6.82)	17	29.67 (9.29)	3.73	(1.65, 5.82)	0.003
LV mass (diastole), mean (SD), g	23	93.26 (20.95)	19	96.51 (16.60)	17	102.86 (17.34)	5.23	(0.86, 9.61)	0.03
RV EDVi, mean (SD), mL/m²	23	77.35 (17.90)	19	82.55 (14.92)	17	88.66 (13.92)	7.17	(1.19, 12.92)	0.03
RV ESVi, mean (SD), mL/m ²	23	44.27 (11.81)	19	49.30 (10.13)	17	51.55 (9.21)	2.38	(-2.89, 7.51)	0.39
<i>Left ventricular function</i>									
LV ejection fraction, mean (SD), %	23	64.62 (6.36)	19	65.73 (6.01)	17	65.43 (6.26)	-0.3	(-2.39, 1.77)	0.78
Global circumferential strain	23	-19.43 (2.89)	19	-19.21 (2.42)	17	-20.10 (2.82)	-0.85	(-1.95, 0.24)	0.15
Mean circumferential strain, Ecc	23	-19.83 (2.49)	19	-19.31 (2.24)	17	-20.01 (3.43)	-0.65	(-2.15, 0.85)	0.41
Mean longitudinal strain, Ell	23	-13.42 (8.80)	19	-14.97 (2.12)	17	-14.49 (3.77)	0.66	(-0.91, 2.27)	0.43
Mean radial strain, Err	23	38.10 (7.48)	19	36.88 (6.96)	17	39.49 (8.84)	2.63	(-0.62, 5.81)	0.13
<i>Myocardial tissue characteristics</i>									
Global native T1 relaxation time, ms	23	1143.50 (122.02)	18	1128.44 (117.55)	17	1155.65 (133.04)	30.72	(16.30, 45.50)	<0.001
Global extracellular volume	20	25.67 (3.28)	12	27.43 (3.13)	12	28.58 (3.08)	2.01	(0.65, 3.16)	0.016
<i>Hemodynamics, rest</i>									
Heart rate, /min	16	62.00 (9.87)	15	60.73 (8.33)	13	60.69 (12.43)	-2.82	(-5.93, 0.39)	0.11

Stroke volume index, ml/m²	23	46.61 (9.08)	19	49.46 (7.29)	17	54.97 (7.98)	5.56	(1.89, 9.18)	0.009
<i>Hemodynamics, adenosine stress</i>									
Heart rate, stress, /min	16	85.12 (9.86)	15	81.53 (5.64)	13	76.46 (10.80)	-6.62	(-10.28, -2.76)	0.005
Heart rate increase (stress vs. rest), /min	16	38.84 (16.60)	15	35.77 (14.63)	13	28.40 (18.32)	-4.63	(-12.26, 2.94)	0.26
Systolic blood pressure, mmHg	18	139.22 (18.18)	16	144.12 (17.42)	15	130.93 (16.64)	-11.8	(-15.99, -7.71)	<0.001
Diastolic blood pressure, mmHg	18	72.44 (9.49)	16	78.62 (12.10)	15	72.47 (14.24)	-5.94	(-10.69, -1.23)	0.03
<i>Myocardial blood flow, rest</i>									
Global, ml/min/g	23	0.75 (0.26)	17	0.67 (0.18)	16	0.78 (0.20)	0.14	(0.07, 0.20)	<0.001
Subendocardium, ml/min/g	18	0.73 (0.20)	14	0.67 (0.18)	13	0.83 (0.21)	0.12	(0.05, 0.19)	0.006
Subepicardium, ml/min/g	18	0.69 (0.22)	14	0.62 (0.18)	13	0.78 (0.22)	0.12	(0.06, 0.19)	0.004
Endocardial: epicardial ratio	18	1.08 (0.09)	14	1.08 (0.04)	13	1.07 (0.07)	0	(-0.03, 0.02)	0.87
<i>Myocardial blood flow, stress</i>									
Global, ml/min/g	20	2.00 (0.42)	17	2.01 (0.51)	17	1.96 (0.38)	0.01	(-0.19, 0.21)	0.92
Subendocardium, ml/min/g	16	1.94 (0.37)	14	1.87 (0.41)	14	1.82 (0.38)	-0.02	(-0.18, 0.16)	0.85
Subepicardium, ml/min/g	16	2.18 (0.46)	14	2.13 (0.49)	14	2.06 (0.45)	0.01	(-0.15, 0.18)	0.91
Endocardial: epicardial ratio	16	0.90 (0.08)	14	0.88 (0.07)	14	0.88 (0.05)	-0.01	(-0.04, 0.03)	0.71
<i>Myocardial perfusion reserve</i>									
Global	15	3.15 (0.63)	13	3.31 (0.56)	12	2.50 (0.78)	-0.67	(-1.06, -0.30)	0.005
Subendocardium	15	2.80 (0.57)	13	2.98 (0.54)	12	2.23 (0.68)	-0.64	(-0.99, -0.28)	0.003
Subepicardium	15	3.44 (0.72)	13	3.59 (0.63)	12	2.73 (0.88)	-0.71	(-1.13, -0.32)	0.005

34 EDVi – end-diastolic volume index, ESVi – end-systolic volume index

35 **Supplementary Table S7.** Sites, participants enrolled and randomized.

Site	Date first recruited	Participants enrolled, n	Participants randomized, n
All	28 October 2019	222	118 (53.2%)
Queen Elizabeth University Hospital, NHS Greater Glasgow & Clyde Health Board	28 October 2019	82	46 (56.1%)
Royal Papworth Hospital NHS Foundation Trust	16 November 2020	50	21 (42%)
Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust	18 January 2021	16	13 (81.2%)
Glenfield Hospital, University Hospitals of Leicester NHS Trust	24 September 2020	15	11 (73.3%)
John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust	28 October 2020	14	4 (28.6%)
Royal Free London NHS Foundation Trust	22 April 2021	11	5 (45.5%)
Blackpool Victoria Hospital, Blackpool Teaching Hospitals NHS Foundation Trust	17 November 2020	10	8 (80%)
Guy's and St Thomas' NHS Foundation Trust	07 April 2021	10	4 (40%)
Hammersmith Hospital, Imperial College Healthcare NHS Trust	01 June 2021	7	3 (42.9%)
Newcastle Hospitals NHS Foundation Trust	23 March 2022	4	1 (25%)
Royal Devon University Healthcare NHS Foundation Trust	16 February 2022	2	1 (50%)

Basildon University Hospital, Mid and South Essex NHS Foundation Trust	27 April 2022	1	1 (100%)

37 **Supplementary Table S8.** Since participating in the cardiovascular MRI study and scanner types.

Site	MRI scanner	Field strength	Coils
All			
Queen Elizabeth University Hospital, NHS Greater Glasgow & Clyde Health Board	MAGNETOM PRISMA, Siemens	3.0 Tesla	Anterior - x2 18-channel surface coils Spine - 32-channel coil
John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust	Magnetom Siemens Avanto fit	1.5 Tesla	Anterior 18 channel surface coil
Royal Papworth Hospital NHS Foundation Trust	MAGNETOM PRISMA, Siemens	3.0 Tesla	Body coil, 32 channel
Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust	MAGNETOM PRISMA, Siemens	3.0 Tesla	Anterior - x2 18-channel surface coils Posterior - Spine 32-channel coil
Royal Free London NHS Foundation Trust	Siemens Aera	1.5 Tesla	Body Matrix

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39 **Supplementary Table S9.** COVADIS criteria for microvascular angina.³³

Criterion	Definition
1. Symptoms of myocardial ischemia	Effort and/or rest angina Angina equivalents (i.e. shortness of breath)
2. Absence of obstructive CAD (>50% diameter reduction and/or FFR <0.80) by either:	CT coronary angiography Invasive coronary angiography
3. Objective evidence of myocardial ischemia	Ischemic ECG changes during an episode of chest pain Stress-induced chest pain and/or ischemic ECG changes in the presence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off values depending on methodology use between ≤ 2.0 and ≤ 2.5) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing. Abnormal coronary microvascular resistance indices (e.g. index of microvascular resistance >25 , hyperaemic microvascular resistance ≥ 2.5 mm Hg·cm ⁻¹ ·s) Coronary slow flow phenomenon

41 **Supplementary Table S9.** COVID-19 timeline for healthcare restrictions in NHS Scotland,
 42 United Kingdom.

16 March 2020	Suspension of clinical research Deployment of medical research staff to clinical service Non-essential social contact prohibited, and stay-at-home policy implemented
1 June 2020	Clinical research restarted. In-person site visits prohibited
5 November 2020	Second national lockdown
4 January 2021	Third national lockdown
29 March 2021	Stay-at-home order ends
1 July 2021	In-person visits for clinical research restarted

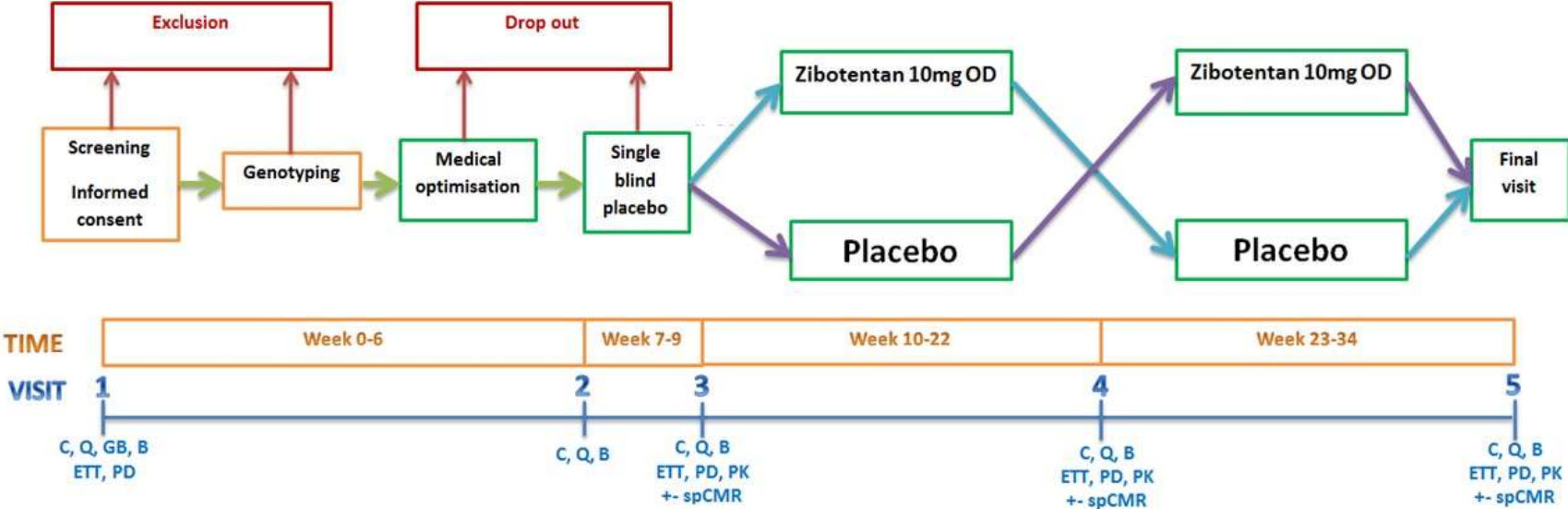
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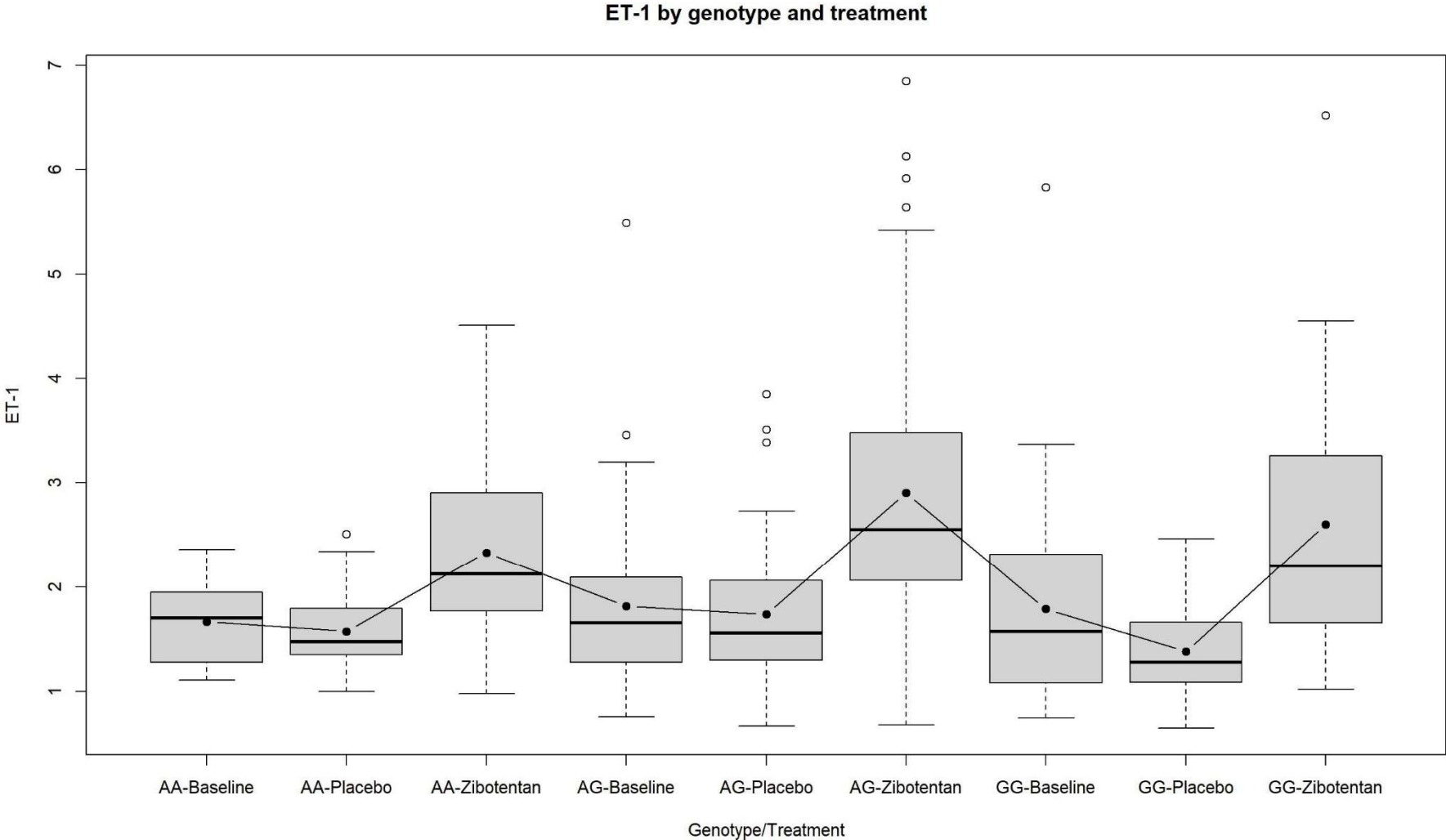
Supplementary figure legends

Figure S1. Study design: a prospective, randomized, double-blind, placebo-controlled, sequential crossover design to assess the effects of zibotentan 10 mg or matched placebo, once daily for 12 weeks.

Figure S2. Plasma endothelin-1 concentration (pg/mL) by genotype alleles for rs9349379 single nucleotide polymorphism and treatment: n=122 at baseline, n=95 placebo, n=94 zibotentan, and n=87 zibotentan - placebo. Compared to placebo, plasma endothelin-1 concentration increased with zibotentan, but plasma endothelin-1 concentration did not associate with genotype (p=0.1366).

Figure S3. Exercise test duration (seconds) by visit: baseline n=117; visit 3 vs. visit 4, n=103; visit 4 vs. visit 5, n=89; visit 5 vs. visit 3, n=103. The increase in exercise duration during the trial compared to before the trial reflects the subjective response (motivation) of the trial participants.





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61 **Supplementary Figure S3.**

