Title: A randomized, double blind, placebo-controlled trial of trimetazidine therapy in patients with non-obstructive hypertrophic cardiomyopathy

Authors: Caroline J Coats PhD[1,2], Menelaos Pavlou PhD[3], Oliver T Watkinson MD[1,4], Alexandros Protonotarios MD[4], Linda Moss BSc[4], Rebecca Hyland MSc[5], Khadija Rantell PhD[6], Antonis A Pantazis MD[7], Maite Tome PhD[8], William J McKenna MD[1], Michael P Frenneaux MD[9], Rumana Omar PhD[3], Perry M Elliott MD[1,4]

Affiliations: [1] UCL Institute of Cardiovascular Science, Gower Street, London, WC1E 6B1, UK, [2] Queen Elizabeth University Hospital, 1345 Govan Rd, Glasgow G51 4TF, UK, [3] Department of Statistical Science, University College London, WC1E 6BT London, UK, [4] Barts Heart Centre*, Barts Health NHS Trust, West Smithfield, London EC1A 7BE, UK, [5] Salisbury District Hospital, Odstock Rd, Salisbury SP2 8BJ, UK, [6] UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK, [7] Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK, [8] St George's Hospital, Blackshaw Rd, London SW17 0QT, UK, [9] University of East Anglia, Norwich Research Park, Norwich NR4 7UQ, UK, * St. Bartholomew's Hospital is a member of European Reference Network on Rare and Complex Diseases of the Heart (Guard-Heart; http://guard-heart.ern-net.eu).

Correspondence: UCL Institute for Cardiovascular Science, Paul O'Gorman Building room, University College London, 72 Huntley Street, London, WC1E 6DD, UK. perry.elliott@ucl.ac.uk

Revision dated 2nd December 2018

Manuscript word count: 1665

KEY POINTS

Question: Does trimetazidine improve exercise capacity in hypertrophic cardiomyopathy?

Findings: this single center, randomized, placebo-controlled, double-blind clinical trial found oxygen consumption at peak exercise was not improved by 3 months of oral trimetazidine therapy.

Meaning: In spite of early promise, metabolic modulators have limited application in HCM.

TWEET (71 characters)

Trimetazidine does not improve exercise capacity in non-obstructive HCM

ABSTRACT

Importance: Hypertrophic cardiomyopathy (HCM) causes limiting symptoms, mediated partly via inefficient myocardial energy utilisation. Inhibitors of myocardial fatty acid metabolism may improve exercise tolerance in patients with HCM.

Objective: To determine the effect of oral therapy with trimetazidine–a direct inhibitor of fatty acid beta-oxidation–on exercise capacity in patients with symptomatic non-obstructive HCM.

Design: A randomized, placebo-controlled, double-blind clinical trial.

Setting: Single tertiary center

Participants: 51 drug-refractory symptomatic (NYHA Class ≥ 2) patients aged 24 to 74 years with a maximum left ventricular outflow tract gradient < 50 mmHg and a peak oxygen consumption (peak VO_2) during exercise ≤ 80% predicted value for age and sex.

Intervention: Participants were randomly assigned to trimetazidine 20 mg three times daily (n=27) or placebo (n=24) therapy for 3 months.

Main outcome: The primary endpoint was peak VO_2 during upright bicycle ergometry. Secondary endpoints were: 6-minute walk distance, quality of life (Minnesota living with heart failure questionnaire), frequency of ventricular ectopics, diastolic function and serum NT-proBNP and troponin T.

Results: 49 participants (age 50 ± 13 years, 70 % male) who received trimetazidine (n=26) or placebo (n=23) completed the study. Trimetazidine therapy was not associated with improved exercise capacity. After adjusting for baseline values, peak VO_2 was 1.35 ml/kg/min lower (95% CI 2.58 to 0.11, p=0.033) in the intervention group after 3 months.

Conclusion and relevance: In symptomatic patients with non-obstructive HCM, trimetazidine therapy does not improve exercise capacity.

INTRODUCTION

Scientific background and explanation of rationale

Hypertrophic cardiomyopathy (HCM) is defined clinically by the presence of left ventricular hypertrophy unexplained by loading conditions; it predisposes to sudden cardiac death and progressive heart failure (1). In most patients, it is an autosomal dominant genetic trait caused by mutations cardiac sarcomere protein genes (2). Individuals with exertional symptoms caused by left ventricular outflow tract obstruction (LVOTO) can be treated with drugs or septal reduction therapy. Similar symptoms occur in the absence of LVOTO but medical treatment is often ineffective (1).

Many of the gene mutations that cause HCM increase the energetic cost of cardiomyocyte contraction and relaxation (3). Conventional therapies, such as beta-blockers and non-dihydropyridine calcium antagonists, reduce myocardial energy demands by decreasing heart rate and blood pressure, but their use is limited by side-effects or lack of clinical efficacy. An alternative approach is to stimulate glucose oxidation and reduce fatty acid oxidation through inhibition of fatty acid uptake into the mitochondrion and direct inhibition of β-oxidation (4). Compared to placebo, perhexiline (a carnitine palmitoyl transferase-1 (CPT-1) inhibitor) was shown to improve symptoms and exercise performance in HCM associated with improved myocardial energetics and diastolic filling (5). However, perhexiline is limited by its narrow therapeutic index and potential neuro- and hepatotoxicity when patients are exposed to sustained high plasma levels of the drug. We hypothesized that trimetazidine dihydrochloride, a safe and well tolerated direct inhibitor of β-oxidation, improves symptoms and exercise capacity in patients with non-obstructive HCM.

Specific objectives/hypothesis: To assess the effects of trimetazidine in medically refractory symptomatic patients with non-obstructive HCM.

METHODS:

Trial design: The study was a non-commercial, investigator led, single center randomized, double-blind, placebo-controlled, parallel-group design of 3 months duration (ClinicalTrials.gov Identifier: NCT01696370). The study was approved by the National Research Ethics Committee (11/AL/0161) and participants provided written informed consent prior to enrolment. Participants were allocated to placebo or intervention in a ratio of 1:1. The study was conducted according to the principles of the Declaration of Helsinki and monitored by an independent data and safety monitor.

Participants: Eligible participants were ≥ 18 years of age with a diagnosis of HCM on stable medical therapy. Participants were symptomatic (NYHA class ≥ 2) with reduced exercise capacity during symptom limited bicycle ergometry defined by peak oxygen consumption (peak VO_2) ≤ 80% of predicted values for age and sex. Individuals with diabetes mellitus, renal impairment (eGFR < 60 ml/min) or liver impairment were excluded. After trial commencement, eligibility criteria were amended to include patients with LVOTO < 50mmHg (instead of < 30 mmHg) and individuals with permanent atrial fibrillation and a ventricular rate (< 90 bpm). This was to improve recruitment of more symptomatic drug refractory patients.

Interventions: After baseline evaluation, patients were randomized in a double-blind fashion, to receive either trimetazidine 20 mg (n=27) or placebo (n=24) three times daily. No dose adjustments were made. Concomitant medications were continued for the trial duration.

Outcomes: The primary end-point was peak VO_2. Secondary end points were: a) symptom status assessed by the Minnesota living with heart failure questionnaire (MLHFQ) (6); b) exercise capacity assessed by 6-minute walk distance and the sub-maximal cardio-pulmonary exercise parameter VE/VCO_2 slope c) biomarkers: N-terminal pro brain natriuretic peptide (NT-proBNP), troponin T, insulin/glucose ratio and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance). d) systolic and diastolic function on echocardiography and e) ventricular ectopics on 24-hour ambulatory monitoring. Investigations were performed at baseline and 3 months. The study design is shown in

Supplementary Figure 1. No changes were made to primary or secondary endpoints after the trial commenced. Adverse events were assessed at the 4-week telephone call and 3-month follow-up visit.

Sample size: 72 patients (36 in each group) were required to detect a change in peak VO_2 of 2 ml/kg/min (power of 80% and significance level 5%) using a two-sample t-test. An estimated standard deviation (SD) of 3 ml/kg/min was used in the calculation (5).

Randomization: A blinded internet randomization service supplied by Sealed Envelope™ was used with linked randomization list for administrator un-blinding. Participants, researchers and clinicians were blinded to treatment.

Statistical methods: Data were analyzed with STATA (Version 14). Analyses were carried out by treatment allocated, using all available data (complete case) with intention to treat principles. Continuous variables were summarized using mean ± SD or median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages. A linear regression model, adjusting for baseline peak VO_2 was used to estimate the treatment effect on the primary outcome. Appropriate regression models were used for the secondary outcomes, adjusted for baselines values. A p-value < 0.05 was taken to indicate statistical significance.

RESULTS

Recruitment: All participants were recruited from cardiomyopathy clinics at The Heart Hospital, University College London Hospitals, London, UK between 31st May 2012 and 8th September 2014. A total of 51 patients were randomized: 24 in the intervention group and 27 in the control group. One patient withdrew from the study and another was excluded from final analysis because of poor compliance. Figure 1 summarizes participant flow through the study. Recruitment was incomplete at the end of the pre-specified enrolment period despite a 6-month extension and protocol amendments. With agreement from the sponsor and an independent advisor we undertook an interim

statistical analysis. The trial was terminated on 14th April 2015. Reasons for screen failure are summarized in Supplementary Table 1.

Baseline data: Patient demographics and baseline clinical variables are shown in Table 1. The trimetazidine and placebo groups were well matched.

Outcomes and estimation: The effects of placebo and trimetazidine on the primary and secondary outcomes are shown in Supplementary Table 2 and 3. Peak VO_2 increased from 17.36 ± 3.59 to 19.01 ± 4.68 ml/kg/min in the placebo group and from 17.35 ± 3.89 to 17.66 ± 3.53 ml/kg/min in the trimetazidine group. After adjusting for baseline peak VO_2, the trimetazidine group had a lower peak VO_2 by 1.35 ml/kg/min (95% CI -2.58 to -0.11, p = 0.033 (Table 2). Inspection of the distribution of residuals and residuals versus fitted values did not indicate a violation of the assumptions of linear regression. Figure 2 shows individual changes in peak VO_2.

Exercise capacity: On average, patients in the trimetazidine group walked 38 meters (95% CI -5 to -72) less than patients in the placebo group at 3 months after adjusting for their baseline walking distance measurements. The median VE/VCO_2 slope was higher by 0.13 (95% CI -1.52 to 1.77) (Table 2 and 3).

Symptom status: At 3 months, the adjusted MLHFQ score, adjusting for the baseline values, was lower in the trimetazidine group by 0.8 (95% CI -9.2 to 7.7)

Echocardiography: After adjusting for the baseline values, there was no change in adjusted diastolic function, LV ejection fraction, left atrial size or global LV longitudinal systolic strain.

Biomarkers: After adjusting for the baseline values, there was no change in adjusted log NTproBNP and Troponin T at 3 months in the trimetazidine group. The insulin/glucose ratio and HOMA-IR fell in the trimetazidine group indicating improved insulin sensitivity consistent with the known effects of trimetazidine (Table 2 and 3).

Arrhythmia: The odds of having more than 500 ventricular ectopics at 3 months in the Trimetazidine group was 0.5 times the odds in the placebo group (95% CI 0.04-6.96).

Adverse events: Two serious adverse events (SAEs) affecting a single patient in the placebo group) were recorded (chest pain and respiratory tract infection requiring hospital assessment). Non-serious adverse events are summarized in Supplementary Table 4.

DISCUSSION

The myocardium depends on oxygen for high-energy phosphate (adenosine triphosphate (ATP)) production by oxidative phosphorylation. In the normal heart, ATP is produced primarily by the metabolism of free fatty acids (FFAs) and carbohydrates, with FFAs accounting for approximately 70% of ATP production in the fasting state (4). In health, FFA oxidation is directly related to plasma FFA concentration, whereas glucose and lactate uptake are inversely related to plasma FFA levels via the Randle effect. Importantly, FFAs are less efficient as a source of myocardial energy as they require approximately 10% more oxygen than glucose in order to produce an equivalent amount of ATP (4). HCM is characterized by a reduction in the concentration of high-energy phosphates in the myocardium (4, 7) possibly due to myocardial ischemia or an energy wasting effect of sarcomere protein gene mutations (8, 9).

Fatty acid oxidation is regulated by the concentration of plasma FFAs, activity of CPT-1 and β-oxidation in the mitochondria. Drugs that inhibit cardiac fatty acid oxidation act in one of three ways: suppression of fatty acid release from adipocytes (e.g. beta-blockers); inhibition of CPT-I and fatty acid uptake into the mitochondria (e.g. perhexiline); and direct inhibition of β-oxidation (e.g. trimetazidine and ranolazine).

Trimetazidine, a reversible competitive inhibitor of 3-ketoacyl-coenzyme A thiolase has a good safety and tolerability profile and in placebo-controlled trials has been shown to improve exercise performance in patients with stable angina and ischemic cardiomyopathy (10-12). Trimetazidine appears to reduce free radical production and prevents accumulation of protons, sodium, and calcium in the myocyte (13).

In this study, we demonstrated no beneficial effect of trimetazidine on exercise capacity in patients with HCM. A negative result was also reported with ranolazine in HCM (14). This may reflect the weaker inhibition of fatty acid metabolism compared to CPT-1 inhibitors or that the 3-month duration of therapy was insufficient to improve symptoms. The fact that there was a 2 ml/kg/min increase in the placebo group could potentially represent a harmful effect of the drug but the change was within the 95% confidence interval of the study design.

Limitations: The study was stopped before the end of planned recruitment due to unanticipated reluctance for patients to participate because of travel distance and work commitments. The sample size in both arms was small so the power to examine the association between baseline characteristics and outcomes was limited. There was no measure of blood trimetazidine concentration, so compliance was assessed by diary card and pill counting.

Conclusions

Trimetazidine therapy does not improve exercise capacity in symptomatic patients with non-obstructive HCM.

OTHER INFORMATION

Trial registration: https://clinicaltrials.gov/ct2/show/NCT01696370

Protocol: The protocol is available from the sponsor. Biomedical Research Centre Research & Development, Maple House Suite A 1st floor, 149 Tottenham Court Road, London W1T 7DN

ACKNOWLEDGEMENTS

This was an investigator-led trial sponsored by University College London. We thank Bryan Mist and Kalaiarasi Janagarajan for their help with the CPET and echocardiography protocols. We thank all the participants who dedicated time to participate in the study.

Funding: The study was funded by a Clinical Research Training Fellowship from the British Heart Foundation awarded to CJC (FS/10/027/28248) and received additional support from a project grant awarded by UCLH/UCL NIHR Comprehensive Biomedical Research Centre. The funding organisations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Contributors: CJC, MPF and PME were responsible for the concept and design of the study. CJC, LM, RH led study recruitment. RO and KR were responsible for database design and management. OW and AP assisted with data collection and management. CJC and PME had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RO and MP conducted and are responsible for data analysis. CJC drafted the manuscript. AAP, MT, WJM, MPF assisted with interpretation of the data. All authors provided critical review of the manuscript and were responsible for the decision to submit the manuscript for publication.

REFERENCES

1. Authors/Task Force m, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79.
2. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circulation research. 2017;121(7):749-70.
3. Ashrafian H, Watkins H. Myocardial dysfunction in hypertrophic cardiomyopathy. Circulation. 2001;104(25):E165.
4. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev. 2005;85(3):1093-129.
5. Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, et al. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. Circulation. 2010;122(16):1562-9.
6. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J. 1992;124(4):1017-25.
7. Crilley JG, Boehm EA, Blair E, Rajagopalan B, Blamire AM, Styles P, et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. J Am Coll Cardiol. 2003;41(10):1776-82.
8. Olivotto I, Girolami F, Sciagra R, Ackerman MJ, Sotgia B, Bos JM, et al. Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. Journal of the American College of Cardiology. 2011;58(8):839-48.
9. Timmer SA, Knaapen P. Coronary microvascular function, myocardial metabolism, and energetics in hypertrophic cardiomyopathy: insights from positron emission tomography. Eur Heart J Cardiovasc Imaging. 2013;14(2):95-101.
10. Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. J Am Coll Cardiol. 2006;48(5):992-8.
11. Vitale C, Wajngaten M, Sposato B, Gebara O, Rossini P, Fini M, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. Eur Heart J. 2004;25(20):1814-21.
12. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. Cochrane Database Syst Rev. 2005(4):CD003614.
13. Stanley WC, Marzilli M. Metabolic therapy in the treatment of ischaemic heart disease: the pharmacology of trimetazidine. Fundam Clin Pharmacol. 2003;17(2):133-45.
14. Olivotto I, Camici PG, Merlini PA, Rapezzi C, Patten M, Climent V, et al. Efficacy of Ranolazine in Patients With Symptomatic Hypertrophic Cardiomyopathy: The RESTYLE-HCM Randomized, Double-Blind, Placebo-Controlled Study. Circ Heart Fail. 2018;11(1):e004124.

Figure 1. Flow diagram of the study cohort

Abbreviations: N/A not applicable

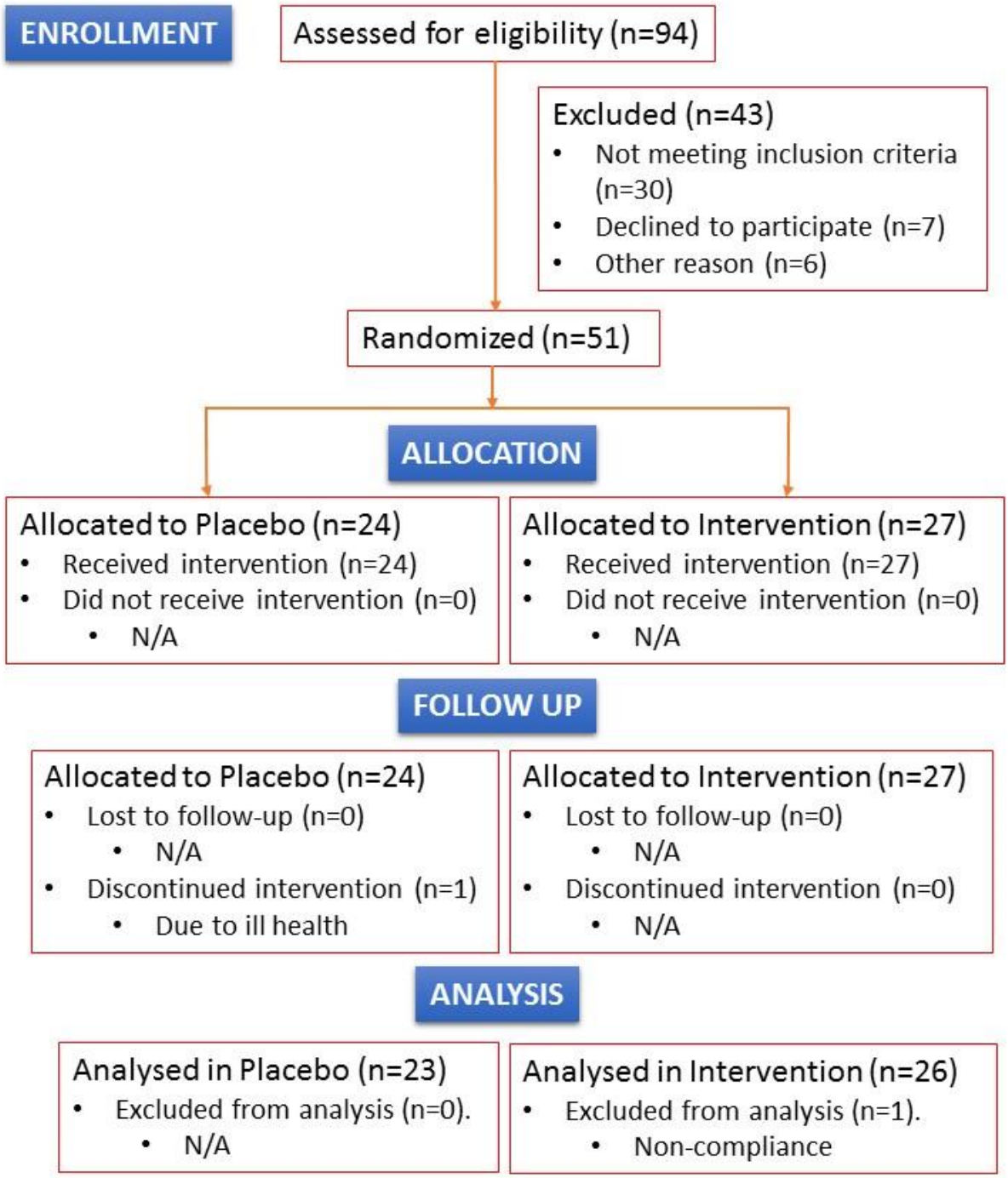

Figure 2. Study primary outcome. The effects of placebo and trimetazidine on exercise capacity. Peak VO_2 increased from 17.36 ± 3.59 to 19.01 ± 4.68 ml/kg/min in the Placebo group and from 17.35 ± 3.89 to 17.65 ± 3.53 ml/kg/min in the Trimetazidine group.

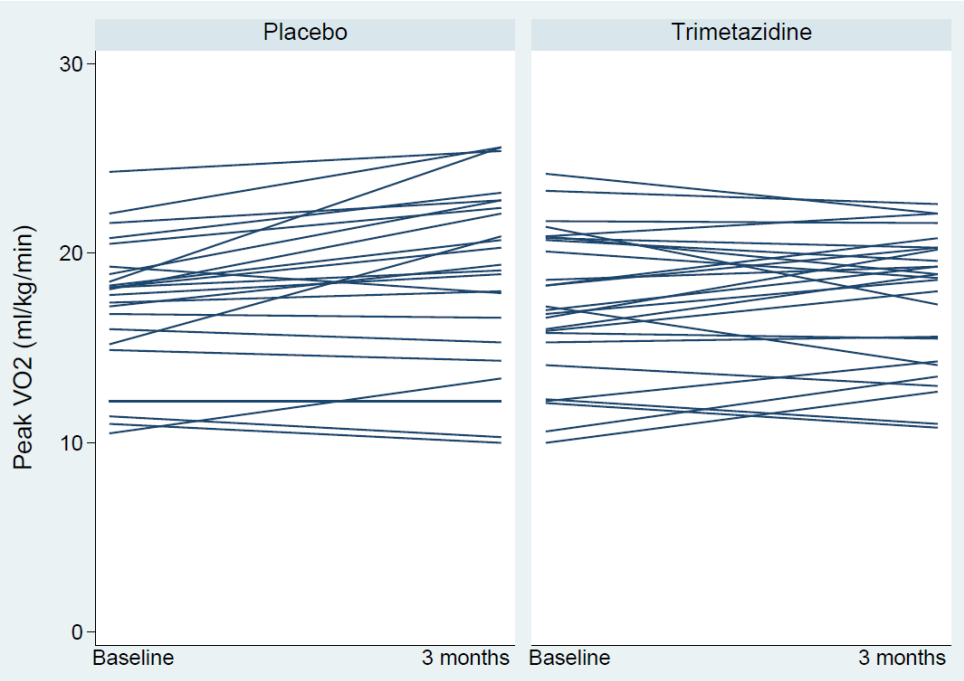

Table 1. Descriptive statistics for baseline variables in 51 patients. Categorical variables are described as number (%) and continuous variables as median (IQR, interquartile range) or mean ± standard deviation (range).

Abbreviations: BP blood pressure, CRT cardiac resynchronisation therapy,

	Trimetazidine (n=27)	**Placebo (n=24)**
Male	18 (67%)	18 (75%)
Caucasian	17 (63%)	19 (79%)
Age (years)	49 ± 13 (25 - 69)	51 ± 14 (24 - 74)
Weight (kg)	87 ± 23 (47 - 132)	87 ± 18 (49 - 133)
Height (cm)	171 ± 10 (155 - 191)	175 ± 10 (153 - 192)
Body Mass Index (kg/m^2)	29 ± 6 (18 - 42)	28 ± 5 (21-38)
Pulse (beats per minute)	69 ± 11 (50 - 88)	69 ± 10 (51 - 85)
Systolic BP (mmHg)	118 ± 15 (90 - 151)	120 ± 19 (92 - 173)
Diastolic BP (mm Hg)	73 ± 9 (56 - 87)	72 ± 6 (62 - 89)
Creatinine (µmol/L)	90 ± 18 (50 - 131)	83 ± 13 (60 - 105)
Haemoglobin (g/L)	14.7 (IQR 13.7 - 15.4)	14.7 (IQR 13.9 – 15.5)
Current or ex-smoker	19 (70%)	14 (58%)
Alcohol (units per week)	5 ± 8 (0 - 30)	8 ± 9 (0 - 40)
Electrocardiogram		
Sinus rhythm	18 (69%)	17 (71%)
Atrial Fibrillation	2 (8%)	4 (17%)
Paced rhythm	6 (22%)	3 (12%)
QRS interval (msec)	122 ± 34 (82 - 212)	126 ± 35 (80 - 194)
Medical History		
Hypertension	5 (19%)	0 (0%)
Paroxysmal atrial fibrillation	1 (4%)	1 (4%)
Implantable Cardioverter Defibrillator	11 (41%)	12 (50%)
Septal myectomy	5 (19%)	8 (33%)
Alcohol septal ablation	1 (4%)	2 (8%)
CRT device	1 (4%)	0 (0%)
Concomitant Medication		
Bisoprolol	12 (44%)	10 (42%)
Verapamil	9 (33%)	5 (21%)
Disopyramide	1 (4%)	3 (13%)
Aspirin	12 (44%)	5 (21%)
Clopidogrel	1 (4%)	1 (4%)
Warfarin	10 (37%)	13 (54%)
Spironolactone	8 (30%)	11 (46%)
Simvastatin	5 (19%)	3 (13%)

Table 2. Mean difference (95%CI) in outcome comparing TMZ and Placebo after adjustment for baseline outcome value (unless otherwise stated)

Abbreviations: LVOT left ventricular outflow tract, NTproBNP N-terminal pro brain natriuretic peptide, VEs ventricular ectopics, VE ventilation, VCO_2 carbon dioxide production, VO_2 oxygen production.

Outcome at 3 months	Mean difference	(95%CI)	p-value
Primary outcome Peak VO_2 (ml/kg/min)	-1.35	(-2.58, -0.11)	0.033
6 min walking distance (metres)	-38.4	(-71.70, -5.13)	
VEs > 500 /24 hours	0.49*	(0.035-6.96)	
Minnesota heart failure score	-0.77	(-9.22, 7.68)	
Grade of diastolic function	0.89**	(0.15, 5.49)	
LV ejection fraction (%)	0.72	(-2.45,3.88)	
Left Atrial Area (cm sq.)	-0.95	(-3.16, 1.26)	
Global Systolic Strain	-0.07	(-1.40, 1.26)	
Left atrial volume index (mls/m^2)	−0.909	(−7.45, 5.64)	
Log NT pro BNP (pmol/L)	0.07	(-0.28,0.14)	
Troponin T (ng/L)	0.001	(-0.013,0.016)	
Insulin/Glucose ratio	0.14***	(0.77, 1.05)	
$VEVO_2$ Slope	-0.74	(-3.76, 2.28)	
VO_2 Work Slope	0.009	(-1.09, 1.11)	
$VEVCO_2$	0.13	(-1.52,1.78)	

*Odds Ratio comparing TMZ group to Placebo (based on logistic regression)
** Odds Ratio comparing TMZ group to Placebo (based on ordinal regression)
***Median difference after adjusting for baseline values (based on quantile regression)