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Abstract

Background and Aims

Pathophysiological features of hypertrophic cardiomyopathy include left ventricular hypertrophy, myocardial fibrosis, and myocardial energy deficiency. Depletion of cardiomyocyte copper I ions leads to impaired mitochondrial function, a state associated with left ventricular hypertrophy. Unbound or loosely bound copper II ions activate profibrotic pathways. Trientine dihydrochloride improves intracellular copper I ion trafficking and availability, and chelates copper II ions. In preclinical studies, trientine improved myocardial mitochondrial function and reduced left ventricular hypertrophy and fibrosis. The efficacy and safety of trientine in persons with hypertrophic cardiomyopathy are unknown.

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§ TEMPEST Investigators are listed in the supplemental file.

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Methods

In this multicentre, placebo-controlled phase 2 trial, adults with hypertrophic cardiomyopathy, a left ventricular wall thickness of 15 mm or greater, and who were in New York Heart Association class I to III were randomly assigned to receive trientine 400 mg twice daily or placebo for 52 weeks. Patients with any left ventricular outflow tract (LVOT) gradient were eligible. The primary endpoint was the change in left ventricular mass indexed to body surface area measured using cardiovascular magnetic resonance.

Results

A total of 154 patients underwent randomization. The mean age was 53.4 years, median maximum left ventricular wall thickness was 20.0 mm, median maximum LVOT gradient was 6.0 mmHg, 18.6% of patients had a resting LVOT gradient ≥ 30 mmHg, and 61.7% were in New York Heart Association class I. At 52 weeks, the mean change in the left ventricular mass indexed to body surface area was -4.4 ± 7.7 g/m² in the trientine group and -1.5 ± 6.1 g/m² in the placebo group (between-group difference -3.2 g/m²; 95% confidence interval -5.6 to -0.8 ; $P = .009$). The efficacy of trientine increased at higher levels of baseline left ventricular mass (baseline left ventricular mass indexed to body surface area by treatment allocation interaction $P = .015$). The effect of trientine was mediated via a reduction in myocardial cellular mass (average causal mediated effect -3.9 g/m²; 95% confidence interval -6.8 to -0.9). The incidence of adverse events was similar in the two groups.

Conclusions

Among patients with hypertrophic cardiomyopathy, treatment with trientine resulted in a significantly greater reduction in left ventricular mass indexed to body surface area than placebo. (Funded by NIH; TEMPEST ClinicalTrials.gov number, NCT04706429).

Structured Graphical Abstract

Key Question

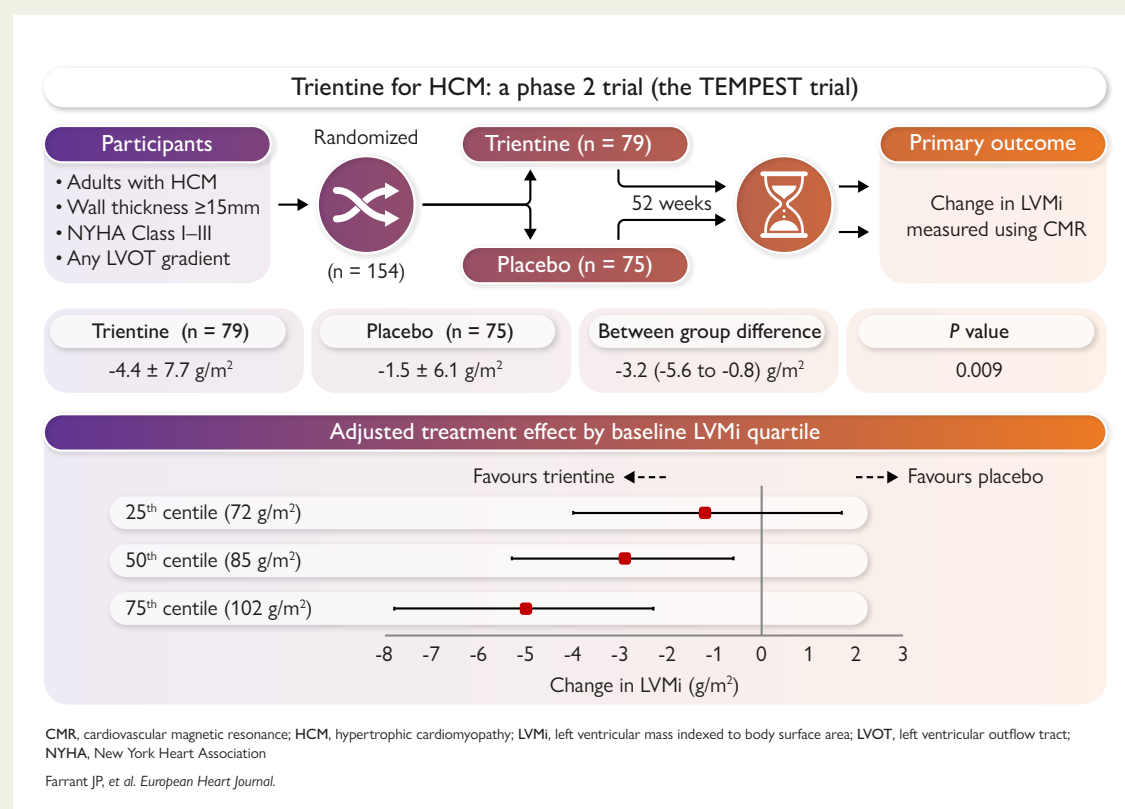
What are the efficacy, mechanism of action and safety of trientine in patients with hypertrophic cardiomyopathy (HCM)?

Key Finding

In a phase 2, multicenter, double-blind, randomized controlled trial in patients with HCM, treatment with trientine resulted in a significant reduction in left ventricular mass indexed to body surface area (LVMI). The efficacy of trientine increased with higher baseline LVMI. The effect of trientine was mediated via a reduction in myocardial cellular mass. Trientine was safe and well tolerated.

Take Home Message

Phase 3 trials are required to determine whether these favourable effects translate into clinical benefit.



Keywords

Hypertrophic cardiomyopathy • Copper chelation • Cardiac magnetic resonance • Indexed left ventricular mass • Efficacy • Mechanism of action • Safety • Phase 2 trial

Introduction

Hypertrophic cardiomyopathy is the most common inherited heart disease globally. Characterized by left ventricular hypertrophy, pathophysiological features include cardiomyocyte disarray, myocardial energy deficiency, oxidative stress and myocardial fibrosis.^{1,2} Cardiac myosin inhibitors improve heart failure symptoms and the functional capacity of patients with hypertrophic cardiomyopathy and left ventricular outflow tract (LVOT) obstruction by reducing hypercontractility.^{3,4} Cardiac myosin inhibitors have established that causal treatment of hypertrophic cardiomyopathy is achievable, but there remains a need for approaches that target additional mechanisms, particularly for patients without LVOT obstruction, which appear to comprise the majority of patients.^{5,6}

Copper is widely used as a catalytic or structural cofactor by enzymes and proteins involved in processes that are central to the pathophysiology of hypertrophic cardiomyopathy, including mitochondrial respiration, antioxidant defence, and extracellular matrix crosslinking.⁷ Depletion of cardiomyocyte copper I ions (Cu^+), which contribute ~95% of total body copper, leads to impaired mitochondrial function and dysregulated energy production and is associated with myocardial hypertrophy. In contrast, unbound or loosely bound copper II ions (Cu^{2+}), which are present extracellularly, powerfully catalyse oxidative stress, inhibit enzymatic antioxidants, and activate profibrotic pathways.⁷

Trientine dihydrochloride is a highly selective chelator of Cu^{2+} that also improves intracellular Cu^+ trafficking and availability through improved copper transporter and chaperone function.⁸ In preclinical models of increased cardiac afterload and diabetes, trientine was associated with improved myocardial mitochondrial function, reduced myocardial oxidative stress, improved organization of cardiomyocytes, reduced left ventricular hypertrophy, and reduced myocardial fibrosis.^{9,10} In patients with diabetic cardiomyopathy, trientine led to a reduction in left ventricular mass.¹¹ In a small, open-label trial in patients with hypertrophic cardiomyopathy, trientine was well tolerated.¹² The Efficacy and Mechanism of Trientine in Patients with Hypertrophic Cardiomyopathy (TEMPEST) trial was designed to evaluate the efficacy, mechanism of action, and safety of trientine in patients with hypertrophic cardiomyopathy.

Methods

Trial design and oversight

The TEMPEST trial was a phase 2, multicentre, parallel group, double-blind, randomized, placebo-controlled trial. The design of the trial has been described previously.¹³ The trial was designed by the research team with patient and public involvement, sponsored by Manchester University NHS Foundation Trust, and funded by the UK National Institute for Health and Care Research (funder reference NIHR127575). Trial management, independent data management, and independent statistical analysis were performed by Liverpool Clinical Trials Centre, a United Kingdom Clinical Research Collaboration fully registered Clinical Trials Unit. The study protocol was approved by a research ethics committee

(NHS Health Research Authority, reference 20/NW/0275), and trial conduct was overseen by a trial steering committee and an independent data and safety monitoring committee. The investigational medicinal product was provided in kind by Univar Solutions B.V. Univar Solutions B.V. had no role in trial design and was not involved in the preparation, drafting, or editing of this manuscript. Univar Solutions B.V. conducted a factual accuracy check of the manuscript, but any decisions to incorporate comments were made solely at the discretion of the authors. All patients provided written informed consent, and the trial was conducted in accordance with the principles of Good Clinical Practice and the World Medical Association Declaration of Helsinki. All authors reviewed and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available as [Supplementary data online, file](#).

Participants

Patients were eligible for enrolment if they were aged 18–75 years; had a confirmed clinical diagnosis of hypertrophic cardiomyopathy in keeping with the European Society of Cardiology guidelines with a left ventricular wall thickness of at least 15 mm in the absence of another cause of hypertrophy,¹⁴ and were in New York Heart Association class I, II, or III. Key exclusion criteria included a left ventricular ejection fraction of <50%; persistent atrial fibrillation; previous or planned septal reduction therapy; pacemaker or implantable cardioverter-defibrillator (ICD); anaemia; iron deficiency; copper deficiency; and contraindication to magnetic resonance imaging. No LVOT gradient threshold was specified in the recruitment criteria; patients with any LVOT gradient were eligible for inclusion. Detailed eligibility criteria are provided in [Supplementary data online, Table S1](#).

Procedures

Eligible patients were randomized in a 1:1 ratio to receive either trientine or placebo for 52 weeks using block randomization, stratified by site, with computer-generated randomization allocations and randomly varying block sizes. Randomization was done using web randomization software accessed using a secure website provided via the clinical trials unit. Trientine was taken orally as two Cufence 200 mg hard capsules two times per day (total daily dose of trientine was 800 mg, which is equivalent to 1200 mg of trientine dihydrochloride). An identical placebo was also taken orally as two capsules two times per day. All background medications were continued. Baseline assessments included laboratory investigations, electrocardiography, 24-h heart rhythm monitoring, cardiovascular magnetic resonance imaging and cardiopulmonary exercise testing, all of which were analysed in blinded core labs. Baseline assessments were repeated at the final visit (Week 52). A subgroup of participants ($n = 84$) additionally underwent 31-phosphorus magnetic resonance spectroscopy at baseline and the final visit, which was also analysed at a blinded core lab. All procedures, including core lab methods and cardiovascular magnetic resonance measurement reproducibility, have been described previously.^{13,15} The visit schedule including safety monitoring is detailed in [Supplementary data online, Table S2](#).

Endpoints

The primary outcome measure was the change in left ventricular mass indexed to body surface area (LVMI ; g/m^2) from baseline to Week 52, measured using cardiovascular magnetic resonance. Pre-specified secondary outcomes included change, from baseline

to Week 52, in measurements of exercise capacity; left atrial volume and function; left ventricular mass, wall thickness, volumes and function; myocardial cellular mass; myocardial fibrosis; myocardial energetics; atrial and ventricular arrhythmia burden; high-sensitivity troponin; and urine copper excretion. Change in LVMI measured via artificial intelligence analysis of cardiovascular magnetic resonance images (MyCardium AI, 1CMR, version 010100zc) was included as an additional secondary outcome (replication analysis) following a trial steering committee meeting in May 2023 (included in the Statistical Analysis Plan in advance of database lock). Safety outcome measurements included adverse events and changes in vital signs, laboratory investigations, and electrocardiogram measurements. A complete list of pre-specified primary, secondary, and safety outcome measurements is provided in [Supplementary data online, Table S3](#).

Statistical analysis

We determined that 64 patients per group would provide the trial with 80% power to detect a minimum difference, between trientine and placebo groups, of 2.5 g/m² in terms of change in LVMI from baseline following 52 weeks of treatment, at a 5% significance level (two-sided), assuming a standard deviation of within-patient differences from baseline of 5 g/m². To allow for treatment discontinuation in up to 25% of patients, the number of patients was originally inflated to 86 per group (i.e. total $n = 172$); however, trial retention was found to be better than expected, therefore the protocol was modified to reduce the treatment discontinuation rate to 15%, meaning that 76 patients per group were required (i.e. total $n = 152$).

The trial was analysed and reported according to the Consolidated Standard of Reporting Trials (CONSORT) and International Conference on Harmonization E9 guidelines. The Statistical Analysis Plan, which prospectively detailed all analyses, and which was signed in advance of database lock, is available as [Supplementary data online, file](#). All analyses were performed according to the intention-to-treat principle, using complete case analysis. The primary and secondary outcomes were compared between treatment groups using analyses of covariance, adjusting for baseline values of the outcome variable, site, and treatment allocation. Including a baseline value by treatment allocation interaction term in the analyses of covariance models indicated that the homogeneity of regression slopes assumption was not met for the primary outcome, and some of the secondary outcomes were stated. Therefore, the 25th, 50th, and 75th quartiles of baseline values were computed, and three centred baseline variables were produced (quartile minus each baseline variable, in turn). The baseline variable in the analyses of covariance model (including the interaction) was then replaced by each centred baseline variable in turn. A sensitivity regression analysis, adjusting for baseline variables that predicted the primary outcome or missingness, was used to assess the robustness of the primary outcome results to missing data.¹⁶ An additional sensitivity analysis was performed to estimate the causal effect of treatment on the primary outcome by appropriately allowing for dose received using instrumental variable regression, thus accounting for informative premature treatment discontinuation. Potential mediators of the impact of trientine on LVMI were hypothesized to include myocardial fibrosis (myocardial extracellular mass), myocardial cellular mass, phosphocreatine to adenosine triphosphate ratio, and urine copper excretion. In order to test whether these variables predicted change in LVMI, mediation analysis was conducted, adjusting for baseline covariates that predicted both the mediator and LVMI. Sensitivity analyses were conducted to assess the potential impact of unmeasured confounding between mediator and outcome. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (version 27). The number and percentage of participants experiencing each safety outcome (from the period of informed consent to the final study visit) were reported, and

changes in safety outcomes were described using summary statistics. The conventional 5% significance level was used. Hypothesis testing on secondary outcomes was considered exploratory. All analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

Patients

From 17 February 2021 to 27 April 2023, 969 patients were pre-screened at six sites in the UK. One hundred ninety patients attended for a screening visit, of whom 154 patients were randomly assigned to receive trientine or placebo (see [Supplementary data online, Figure S1](#)). At the end of the trial, 2 patients were lost to follow-up, 11 had withdrawn from the trial, 2 were determined to have an exclusory cardiomyopathic cause of myocardial hypertrophy, and 3 had received an ICD, which precluded measurement of the primary outcome. A total of 136 patients were included in the final efficacy analysis.

The demographic and clinical characteristics of the two groups were well balanced at baseline ([Table 1](#) and [Supplementary data online, Table S4](#)). Mean age was 53.4 years, 23.4% were female, and 37% of patients who had undergone genetic testing had a confirmed pathogenic variant in a sarcomeric gene. Median LVMI was 85.8 g/m², median left ventricular maximum wall thickness was 20.0 mm, median maximum LVOT gradient was 6.0 mmHg, 61.7% of patients were in New York Heart Association class I, and estimated 5-year risk of sudden cardiac death was 2.0%.¹⁷ No patient received a cardiac myosin inhibitor during the trial.

Efficacy

The mean change in LVMI, measured using cardiovascular magnetic resonance, from baseline to Week 52 was -4.4 ± 7.7 g/m² among patients in the trientine group and -1.5 ± 6.1 g/m² among those in the placebo group. Mean between-group difference was -3.2 g/m² [95% confidence interval (CI) -5.6 to -0.8 ; $P = .009$]. As is evident from [Figure 1](#), the efficacy of trientine for reducing LVMI increased at higher levels of baseline LVMI (baseline LVMI by treatment allocation interaction $P = .015$), with the effect of trientine becoming significant at a minimum baseline LVMI of 81.6 g/m² (mean between-group difference in LVMI); at the 25th centile of baseline LVMI: -1.2 g/m² (95% CI -4.1 to 1.6 ; $P = .33$); at the 50th centile of baseline LVMI: -2.9 g/m² (95% CI -5.2 to -0.5 ; $P = .019$); and at the 75th centile of baseline LVMI: -5.0 g/m² (95% CI -7.7 to -2.2 ; $P < .001$) ([Table 2](#)). A sensitivity analysis adjusting for missing primary outcome data yielded consistent results ([Table 3](#)). The causal analysis was also consistent, demonstrating, for example, that for each additional 100 capsules of trientine taken (i.e. 25 days of treatment), there was a mean reduction in LVMI at 52 weeks of 0.5 g/m² (95% CI -0.7 to -0.3 ; $P < .001$) in patients with baseline LVMI at the 75th centile ([Table 3](#)). In a replication analysis, artificial intelligence measurement of LVMI yielded consistent results ([Table 3](#)). Baseline LVOT gradient did not have a significant impact on LVMI.

Secondary outcomes are presented in [Tables 3, S5, and S6](#). Treatment with trientine led to a significant increase in urine copper-creatinine ratio compared to placebo (mean difference 165.0 nmol/mM creatinine; 95% CI 132.6–197.4), with the effect seen by Week 13 and persisting throughout the treatment period (see [Supplementary data online, Figure S2](#)). Compared

Table 1 Demographic and clinical characteristics of the participants at baseline

Characteristic	Trientine (n = 79)	Placebo (n = 75)
Age, years	55 (48–63)	56 (45–63)
Female sex, n (%)	23 (29.1)	13 (17.3)
Medical history, n (%)		
Hypertension	31 (39.2)	21 (28.0)
Systolic blood pressure, mmHg	137 (123–153)	135 (123–152)
Paroxysmal atrial fibrillation	11 (13.9)	5 (6.7)
Transient ischaemic attack	1 (1.3)	5 (6.7)
Diabetes mellitus	5 (6.3)	3 (4.0)
Genetic testing, n (%)		
Did participant have genetic testing?	51 (64.6)	51 (68.0)
No pathogenic variant or variant of uncertain significance identified	28 (58.3)	30 (60.0)
Pathogenic variant in MYPBC3	12 (25.0)	10 (20.0)
Pathogenic variant in MYH7	4 (8.3)	6 (12.0)
Other pathogenic variant	4 (8.3)	4 (8.0)
Concomitant medications, n (%)		
Beta blockers	45 (57.0)	37 (49.3)
Cholesterol-lowering medications	25 (31.6)	27 (36)
Calcium channel blockers	12 (15.2)	17 (22.7)
Angiotensin-converting enzyme inhibitors	9 (11.4)	11 (14.7)
Cardiac myosin inhibitor	0 (0.0)	0 (0.0)
New York Heart Association functional class, n (%) ^a		
I	48 (60.8)	47 (62.7)
II	21 (26.6)	23 (30.7)
III	10 (12.7)	5 (6.7)
IV	0 (0)	0 (0)
Calculated risk of sudden cardiac death at 5 years, % ¹⁷	2.1 (1.5–2.7)	2.0 (1.6–2.6)
Maximum resting left ventricular outflow tract gradient, mmHg	7.0 (4.0–26.0)	5.0 (4.0–14.0)
Maximum resting left ventricular outflow tract gradient <30 mmHg, n (%)	45 (76.3)	51 (86.4)
Maximum resting left ventricular outflow tract gradient >30 mmHg, n (%)	14 (23.7)	8 (13.6)
Maximum valsalva left ventricular outflow tract gradient, mmHg	8.5 (4.0–48.0)	9.0 (4.0–33.0)
Laboratory investigations		
Serum iron, µmol/L	18.4 (14.1–22.6)	18.5 (14.5–22.1)
Serum copper, µmol/L	15.1 (13.4–17.5)	14.5 (13.5–16.6)
Serum caeruloplasmin, g/L	0.3 (0.2–0.3)	0.3 (0.2–0.3)
Urine copper–creatinine ratio, nmol/mM Cr	12.8 (9.9–17.2)	11.7 (9.7–14.1)
High sensitivity troponin, ng/L	10.0 (8.0–14.0)	11.0 (7.0–18.0)
Cardiovascular magnetic resonance variables		
Left ventricular mass indexed to body surface area, g/m ²	84.2 (69.6–99.7)	86.8 (74.5–112.0)
Left ventricular maximal wall thickness, mm	20 (18–23)	20 (18–22)

Continued

Table 1 Continued

Characteristic	Trientine (n = 79)	Placebo (n = 75)
Left ventricular ejection fraction, %	75.5 (72.0–80.0)	74.0 (70.0–78.0)
Left atrial volume indexed to body surface area, mL/m ²	59.1 (48.2–74.9)	57.8 (47.6–67.9)
Left ventricular cellular mass indexed to body surface area, g/m ²	125.4 (98.0–146.7)	130.7 (109.6–161.1)
Left ventricular extracellular mass indexed to body surface area, g/m ²	21.6 (18.1–27.5)	23.6 (20.2–28.8)
Magnetic resonance spectroscopy variable ^b		
Phosphocreatine to adenosine triphosphate ratio	1.6 (1.4–2.0)	1.5 (1.3–1.9)
Exercise capacity variables		
Peak oxygen uptake, mL/min/kg	19.9 (15.1–25.0)	20.8 (16.0–26.1)
Ventilatory efficiency ^c	27.2 (23.5–30.6)	27.1 (24.3–30.2)

Values are median (interquartile range) or n (%). Percentages may not total 100 because of rounding.

^aNew York Heart Association functional classes range from I to IV, with higher values indicating greater disability.

^bA subgroup of 84 participants underwent 31-phosphorus magnetic resonance spectroscopy for measurement of myocardial phosphocreatine to adenosine triphosphate ratio.

^cVentilatory efficiency is measured as minute ventilation/carbon dioxide production (VE/CO₂ slope).

with placebo, trientine led to a significant reduction in left ventricular maximum wall thickness (−0.6 mm; 95% CI −1.2 to −0.1) and left ventricular myocardial cellular mass (−3.7 g/m²; 95% CI −6.4 to −1.1). The impact of trientine on myocardial extracellular mass was dependent on baseline myocardial extracellular mass, with a numerically greater reduction in extracellular mass with trientine compared to placebo as baseline extracellular mass increased (e.g. −1.0 g/m²; 95% CI −1.9 to 0.0 at the 75th centile of baseline extracellular mass), but the difference was not significant. There were no between-group differences in atrial volumes and function, exercise capacity, circulating high-sensitivity troponin, or myocardial phosphocreatine to adenosine triphosphate ratio.

Mechanism of action

The trientine-induced reduction in LVMI was mediated via a reduction in myocardial cellular mass (average causal mediated effect −3.9 g/m²; 95% CI −6.8 to −0.9). It was not mediated via changes in urine copper excretion, systolic blood pressure, myocardial extracellular mass or myocardial phosphocreatine to adenosine triphosphate ratio (see [Supplementary data online, Table S7](#)).

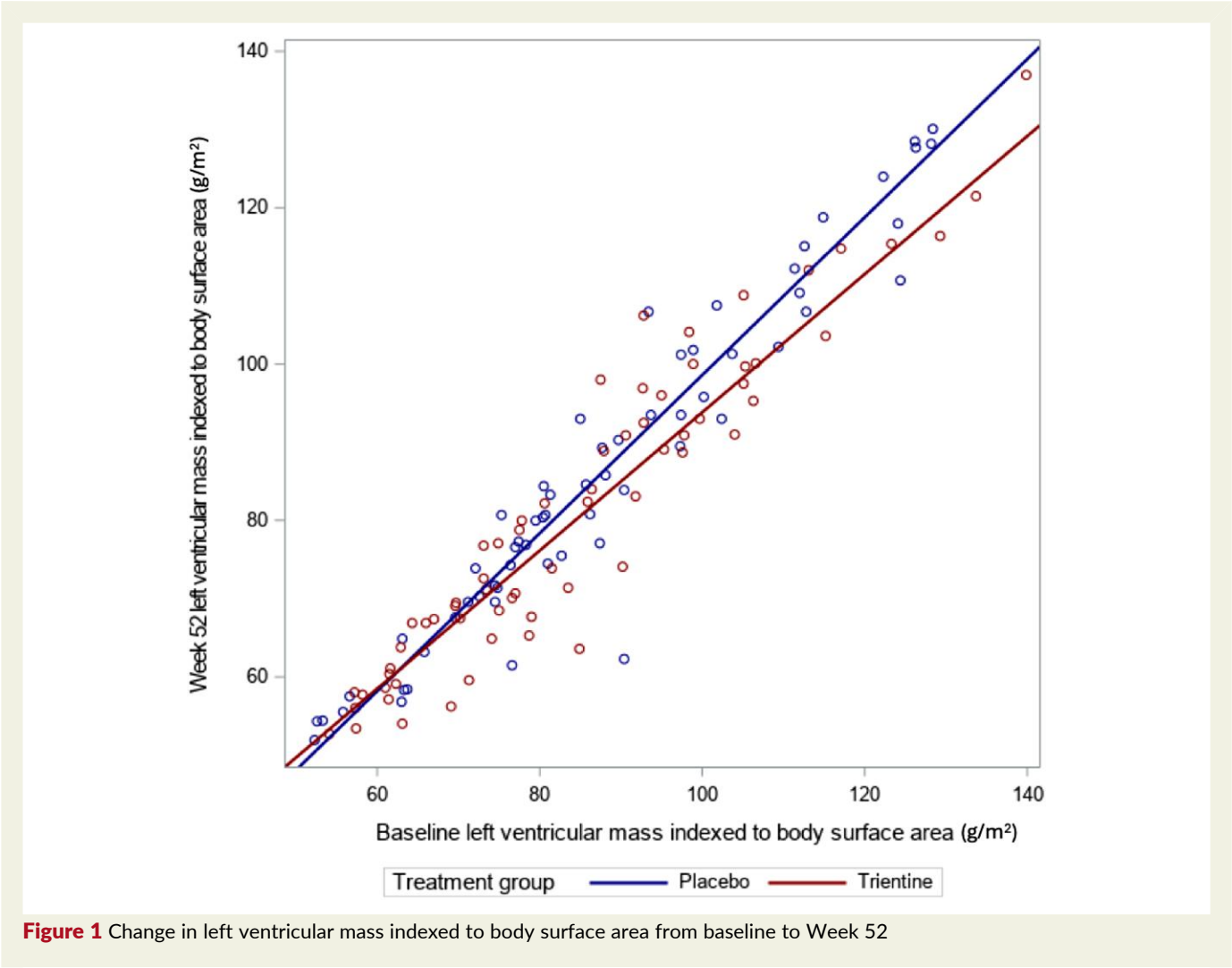
Safety

Trientine was well tolerated. Of the 11 patients who withdrew from the trial, including 8 in the trientine group and 3 in the placebo group, only 1 patient, who was in the trientine group, did so because of a possible trial mediation-related adverse event (nausea and dizziness) (see [Supplementary data online, Table S8](#)). Adverse events resulted in two patients in the trientine group (psoriasis skin flare, anaemia), and two patients in the placebo group (nausea, anxiety), discontinuing treatment early (see [Supplementary data online, Table S9](#)). No deaths occurred during the trial. Four patients (5%) in the trientine group, and seven patients (10%) in the placebo group, experienced one or more serious adverse events, none of which were related to

trientine or placebo ([Table 4](#) and [S10](#)). Overall, 56 (72%) patients receiving trientine and 49 (67%) patients receiving placebo reported an adverse event ([Table 4](#) and [S11](#)). Ninety-three per cent of adverse events reported by patients receiving trientine, and 91% of adverse events reported by patients receiving placebo, were mild. The number of cardiovascular adverse events was low and did not differ between groups. Gastrointestinal adverse events were more common in the trientine group. Trientine was not associated with a change in left ventricular ejection fraction, systolic blood pressure, or electrocardiogram measurements ([Table 3](#)). The number of ventricular ectopic beats declined among patients in both treatment groups (trientine: −0.6 ± 4.1 ventricular ectopic beats per 1000 beats; placebo: −1.5 ± 17.9 ventricular ectopic beats per 1000 beats), and there was no change in the number of episodes of non-sustained ventricular tachycardia in either group and no difference between groups (see [Supplementary data online, Table S6](#)). The number of atrial ectopic beats increased slightly among patients in the trientine group compared to patients in the placebo group (2.1 additional atrial ectopic beats per 1000 beats; 95% CI 1.2–3.7), but there was no change in the number of episodes of atrial fibrillation in either group, and no difference between groups (see [Supplementary data online, Table S6](#)). Anaemia was more common among patients receiving trientine compared to placebo (6.4% vs 2.7%; mean between-group difference in haemoglobin −5.6 g/L; 95% CI −8.0 to −3.3), as was hypocupraemia (10.3% vs 1.4%; mean between-group difference in serum copper −0.79 g/L; 95% CI −1.4 to −0.2), but there were no differences in serum caeruloplasmin or iron ([Table 3](#) and [S12](#)). There was no clinically relevant difference in the utilisation of concomitant medications between baseline and week 52. ([Table S13](#)).

Discussion

In this phase 2 randomized, placebo-controlled trial involving patients with hypertrophic cardiomyopathy, trientine reduced



Variable	Trientine (n = 79)		Placebo (n = 75)		Between-group difference (95% CI)	P-value
	Patients no.	Mean change (± SD)	Patients no.	Mean change (± SD)		
Change in LVMI from baseline to Week 52, g/m ²	68	−4.4 ± 7.7	68	−1.5 ± 6.1	−3.2 (−5.6 to −0.8)	.009
Effect by baseline LVMI quartile ^a						
25th centile					−1.2 (−4.1 to 1.6)	.40
50th centile					−2.9 (−5.2 to −0.5)	.02
75th centile					−5.0 (−7.7 to −2.2)	<.001

LVMI, left ventricular mass indexed to body surface area; SD, standard deviation.

^aThe effect of trientine on LVMI increased with higher baseline LVMI (baseline LVMI by treatment allocation interaction *P* = .015). Therefore, the overall between-group difference is presented, and the between-group differences after replacing baseline LVMI with 25th, 50th, and 75th quartile centred baseline LVMI in the analysis of covariance models in turn are presented. See Methods and Discussion for details.

left ventricular hypertrophy. The effect of trientine was greater at higher levels of baseline left ventricular mass. The reduction in left ventricular hypertrophy was mediated by a reduction in myocardial cellular mass. Trientine was safe

and well-tolerated. The findings provide initial evidence for a novel approach to the treatment of hypertrophic cardiomyopathy targeting copper metabolism ([Structured Graphical Abstract](#)).

Table 3 Key secondary endpoints

Variable	Trientine (n = 79)		Placebo (n = 75)		Between-group difference (95% CI)	P-value
	Patients no.	Mean change (± SD)	Patients no.	Mean change (± SD)		
Secondary analyses of the primary outcome						
Replication analysis: change in LVMI measured using AI image analysis ^a —g/m ²	66	−2.5 ± 9.2	66	1.5 ± 6.1	3.5 (−5.7 to −1.2)	.003
Effect by baseline LVMI quartile ^b						
25th centile					0.1 (−2.9 to 3.1)	.95
50th centile					−3.2 (−5.7 to −0.7)	.01
75th centile					−7.7 (−10.6 to −4.8)	<.001
Sensitivity analysis: change in LVMI adjusted for missing data, g/m ²	68	−4.4 ± 7.7	68	−1.5 ± 6.1	−2.8 (−5.1, −0.5)	.02
Effect by baseline LVMI quartile ^b						
25th centile					−1.1 (−3.9 to 1.7)	.44
50th centile					−2.4 (−4.8 to −0.1)	.04
75th centile					−4.2 (−6.8 to −1.6)	.002
Causal analysis: change in LVMI for each additional 100 capsules of trientine taken ^c , g/m ²	53	-	68	-	−0.4 (−0.6, −0.2)	<.001
Effect by baseline LVMI quartile ^b						
25th centile					−0.2 (−0.4 to 0.05)	.12
50th centile					−0.3 (−0.5 to −0.1)	.001
75th centile					−0.5 (−0.7 to −0.3)	<.001
Key secondary outcomes						
Urine copper/creatinine ratio	64	177.7 (106.0)	44	5.1 (23.0)	165.0 (132.6–197.4)	-
Left ventricular maximal wall thickness, mm	68	−0.6 ± 1.8	68	0.04 ± 1.6	−0.6 (−1.2 to −0.1)	-
Indexed LV myocardial cellular mass, g/m ²	67	−2.7 ± 7.4	63	0.1 ± 8.6	−3.7 (−6.4 to −1.1)	-
Indexed LV myocardial extracellular mass, g/m ²	67	−0.9 ± 2.3	63	−0.5 ± 2.6	−0.4 (−1.3 to 0.5)	-
Effect by baseline extracellular mass quartile ^b						
25th centile					0.2 (−0.8 to 1.2)	-
50th centile					−0.3 (−1.2 to 0.6)	-
75th centile					−1.0 (−1.9 to 0.0)	-
Indexed LA volume, mL/m ²	65	−0.3 ± 8.0	68	1.2 ± 8.1	−1.0 (−3.7 to 1.7)	-
Peak oxygen uptake, mL/min/kg	60	−0.9 ± 4.4	61	−0.1 ± 4.1	−1.2 (−2.7 to 0.3)	-
Ventilatory efficiency ^d	59	0.5 ± 6.3	60	−0.7 ± 4.5	1.1 (−0.6 to 2.8)	-
High-sensitivity troponin, ng/L	69	−0.8 ± 8.7	69	0.7 ± 13.6	−0.9 (−4.6 to 2.9)	-
Phosphocreatine to adenosine triphosphate ratio ^e	27	0.1 ± 0.5	33	0.1 ± 0.4	0.1 (−0.1 to 0.3)	-
Left ventricular ejection fraction, %	68	−0.1 ± 5.1	68	−0.1 ± 4.5	0.2 (−1.4 to 1.7)	-
No. non-sinus supraventricular beats per 1000 beats	69	3.1 ± 24.0	67	0.1 ± 3.6	2.1 (1.2 to 3.7)	-
No. ventricular-origin beats per 1000 beats	69	−0.6 ± 4.1	67	−1.5 ± 17.9	0.5 (0.3 to 0.9)	-
No. episodes of NSVT	69	1.8 ± 0.8	67	0.8 ± 3.6	0.9 (0.5 to 1.7)	-

Continued

Table 3 Continued

Variable	Trientine (n = 79)		Placebo (n = 75)		Between-group difference (95% CI)	P-value
	Patients no.	Mean change (± SD)	Patients no.	Mean change (± SD)		
No. episodes of atrial fibrillation ^f	69	1.0 ± 0.0	67	1.0 ± 0.0	-	-
Serum haemoglobin, g/L	70	-5.0 ± 8.3	68	-0.5 ± 6.8	-5.6 (-8.0 to -3.3)	-
Serum copper, µmol/L	70	-0.9 ± 2.2	68	0.1 ± 1.5	-0.8 (-1.4 to -0.2)	-
Serum ceruloplasmin, g/L	68	0 ± 0.13	66	-0.01 ± 0.07	0.02 (-0.02 to 0.05)	-
Serum iron, µmol/L	70	-0.9 ± 7.2	68	-0.8 ± 8.3	-0.01 (-2.1 to 2.1)	-
Systolic blood pressure, mmHg	70	-7.1 ± 18.0	68	-0.9 ± 16.5	-3.2 (-8.2 to 1.8)	-

LA, left atrial; LV, left ventricular; LVMi, left ventricular mass indexed to body surface area; NSVT, non-sustained ventricular tachycardia.

All indexation is to body surface area.

^aAll image analysis was not possible on images from two participants in each group.

^bThe effect of trientine on LVMi and indexed LV myocardial extracellular mass increased with higher baseline LVMi (baseline LVMi by treatment allocation interaction $P = .015$). Therefore, the overall between-group difference is presented, and the between-group differences after replacing baseline LVMi with 25th, 50th, and 75th quartile centred baseline LVMi in the analysis of covariance models in turn are presented. See Methods and Discussion for details.

^cCoefficient of trientine use.

^dVentilatory efficiency is measured as minute ventilation/carbon dioxide production (VE/CO₂ slope).

^eA subgroup of participants underwent 31-phosphorus magnetic resonance spectroscopy for measurement of myocardial phosphocreatine to adenosine triphosphate ratio.

^fInsufficient events to run an ANCOVA model.

Trials of cardiac myosin inhibitors reporting improvements in heart failure symptoms and functional capacity have included symptomatic patients with obstructive hypertrophic cardiomyopathy (mean resting LVOT peak gradient over 50 mmHg).^{3,4} Early or asymptomatic hypertrophic cardiomyopathy represents a substantial unmet need for disease-modifying therapies. In the present trial, most patients reported no symptoms with ordinary physical activity, did not have LVOT obstruction, and were at low risk of sudden cardiac death, suggesting trientine may have a role in this group. At the same time, the observation that the effect of trientine on left ventricular mass increased with higher baseline mass suggests that patients with more advanced phenotypes may derive greater benefit. Further work is required to define the optimal target population for trientine therapy. The monitoring requirements for trientine are straightforward, comprising periodic (e.g. haematological indices and copper parameters) blood tests, without the need for surveillance imaging. This approach is consistent with maintaining copper homeostasis and identifying potential deficiency, which is a principal safety consideration with longer-term therapy.

We did not specify an LVOT gradient in the recruitment criteria; patients with any LVOT gradient were eligible. We suspect the low median LVOT gradient reflects the nature of patients with hypertrophic cardiomyopathy seen in UK clinical practice, and the requirement for participants to undergo cardiovascular magnetic resonance. Patients with ICDs at baseline were excluded, which likely excluded patients with more advanced phenotypes, including LVOT obstruction. This is in keeping with the NHLBI HCMR Registry ($n = 2762$), in which only 18% of patients had a LVOT gradient above 30 mmHg.⁵

Left ventricular mass and wall thickness are both central to the pathogenesis of hypertrophic cardiomyopathy and independently predictive of adverse outcomes, suggesting that a reduction in left ventricular mass and wall thickness may be

clinically relevant.¹⁸⁻²¹ Trientine became more efficacious at reducing left ventricular mass at higher levels of baseline left ventricular mass; indeed, patients with LVMi <81.6 g/m² did not derive benefit. It is important to note that the use of centred baseline variables derived from the 25th, 50th, and 75th quartiles does not represent a *post hoc* or responder analysis. Rather, it reflects the statistically appropriate approach following identification of a baseline left ventricular mass-treatment interaction, as demonstrated by the diverging treatment group regression slopes with increasing baseline mass.

The reduction in LVMi observed with trientine was modest (-3.2 g/m²) but similar in magnitude to that reported with mavacamten in non-obstructive hypertrophic cardiomyopathy in ODYSSEY-HCM (-3.8 g/m²),^{22,23} in contrast to the larger reductions observed with myosin inhibitors in obstructive HCM, where relief of LVOT obstruction likely contributes substantially to left ventricular mass regression.^{24,25} Baseline LVMi was substantially higher in ODYSSEY-HCM than in the present study. Taken together with the observation that baseline left ventricular mass may be an important determinant of the magnitude of response to trientine, we hypothesize that the effect size of trientine may have been larger in a population with a higher baseline LVMi, although this requires further investigation. More generally, LVMi is associated with adverse outcomes in HCM, including arrhythmia and appropriate ICD therapy.¹⁸

Several randomized trials have targeted alternative mechanisms in hypertrophic cardiomyopathy, including metabolic modulation (e.g. perhexiline, ranolazine, N-acetylcysteine, nifedipine)²⁶⁻²⁹ and renin-angiotensin-aldosterone system inhibition (e.g. spironolactone, losartan, valsartan).³⁰⁻³² To our knowledge, the present trial is the first to report a significant reduction in left ventricular mass with a non-sarcomere-targeted therapy. Our data indicate that the mechanism of action of trientine was a reduction in myocardial cellular mass rather than

Table 4 Adverse events

Event	Trientine (n = 78)	Placebo (n = 73)
Any adverse event	56 (71.8)	49 (67.1)
Any serious adverse event	4 (5.1)	7 (9.6)
Cardiovascular		
Palpitations	8 (10.3)	10 (13.7)
Atrial fibrillation	2 (2.6)	2 (2.7)
Chest pain	0 (0)	3 (4.1)
First-degree atrioventricular block	1 (1.3)	1 (1.4)
Bradycardia	1 (1.3)	0 (0)
Peripheral oedema	1 (1.3)	0 (0)
Pre-syncope	0 (0)	1 (1.4)
Gastrointestinal		
Nausea	7 (9.0)	6 (8.2)
Abdominal pain upper	4 (5.1)	1 (1.4)
Diarrhoea	7 (9.0)	1 (1.4)
Gastro-oesophageal reflux	4 (5.1)	1 (1.4)
Other		
Dizziness	11 (14.1)	13 (17.8)
Headache	3 (3.8)	4 (5.5)
Lower respiratory tract infection	2 (2.6)	4 (5.5)
SARS-CoV-2 test positive	7 (9.0)	6 (8.2)
Blood tests		
Anaemia	5 (6.4)	2 (2.7)
Copper decreased	8 (10.3)	1 (1.4)
Ceruloplasmin decreased	5 (6.4)	5 (6.8)
Iron decreased	1 (1.3)	2 (2.7)

changes in myocardial fibrosis, blood pressure, or myocardial energetics. In this paucisymptomatic population, trientine did not improve exercise capacity. Further work is needed to determine the effect of trientine in more symptomatic patients with hypertrophic cardiomyopathy.

Unbound or loosely bound Cu^{2+} is known to activate profibrotic pathways, and preclinical studies have demonstrated that trientine can reduce myocardial fibrosis.^{7,9–11} We therefore hypothesized that trientine would reduce myocardial extracellular mass. However, no significant between-group difference was observed. There was, however, a numerically greater reduction in extracellular mass with trientine compared with placebo at higher baseline levels of extracellular mass, suggesting that any antifibrotic effect of trientine may be more pronounced, or more readily detectable, in patients with more advanced disease and greater baseline fibrosis.

Trientine was well tolerated, with a low discontinuation rate. Adverse event rates were low, and no unexpected safety issues were identified. There was a modest reduction in haemoglobin

and serum copper, with no corresponding reduction in serum caeruloplasmin or iron. Anaemia is a recognized potential side effect of trientine. Although haemoglobin declined modestly with trientine as expected, such a reduction would typically be associated with an increase rather than a decrease in left ventricular mass. This suggests that the observed reduction in LVMI is unlikely to be explained by haemoglobin-related effects.

Future studies should evaluate trientine in cohorts with more advanced hypertrophic cardiomyopathy, where the potential for treatment response may be greater. Such studies would benefit from incorporating endpoints that capture patient-centred outcomes, including health status, and relevant circulating biomarkers, to better define the clinical impact of treatment.

A limitation of this trial was that we did not measure health status or natriuretic peptides. This was an academic-funded trial, originally designed in a funding application submitted in 2018, which predated regulatory guidance emphasizing patient-reported outcomes and 'feel and function' endpoints in drug development, and at a time when the role of natriuretic peptides in hypertrophic cardiomyopathy trials was not yet well established.³³ Excluding patients with ICDs, to enable cardiovascular magnetic resonance, is likely to have disproportionately excluded patients with more advanced disease; our results indicate that patients with more advanced disease may have derived greater benefit from trientine. The limited number of genotyped patients precluded meaningful analysis of treatment effect according to genotype. Another limitation is the lower proportion of female participants, which should be interpreted in the context of well-described sex differences in hypertrophic cardiomyopathy diagnosis and trial enrolment, including the use of absolute wall thickness thresholds that do not account for sex-related differences and lower rates of incidental diagnosis in women. Female representation is often particularly low in early-phase or mechanistic hypertrophic cardiomyopathy studies, especially when first-in-class therapies are evaluated. In this study, most participants were in New York Heart Association class I, and this represented the first evaluation of trientine in hypertrophic cardiomyopathy. Notably, fewer than one-third of participants in the HCMR Registry are female, indicating that the sex distribution observed here is consistent with broader patterns in hypertrophic cardiomyopathy research.⁵

In this phase 2 trial in patients with hypertrophic cardiomyopathy, treatment with trientine resulted in a significantly greater reduction in left ventricular hypertrophy than placebo. These results warrant further investigation.

Supplementary data

Supplementary data are available at [European Heart Journal](https://eurheartj/advance-article/doi/10.1093/eurheartj/ehag512/6734889) online.

Declarations

Disclosure of interest

J.C.M. has received honoraria from BMS and Cytokinetics, and is a shareholder in MyCardium AI Ltd and Guilford Street Laboratories. S.G. has received consultancy fees from Biosensors. C.B. is employed by the University of Glasgow, which holds consultancy and research agreements for his work with Abbott Vascular, AskBio, AstraZeneca, Boehringer

Ingelheim, Causeway Therapeutics, Corvoentis, HeartFlow, Menarini, Novartis, Siemens Healthcare, Zoll Medical, and Valo Health. C.A.M. has participated on advisory boards/consulted for AstraZeneca, Boehringer Ingelheim, Lilly Alliance, Novartis, and PureTech Health, serves as an advisor for HAYA Therapeutics, has received speaker fees from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk, conference attendance support from AstraZeneca, and research support from Amicus Therapeutics, AstraZeneca, Guerbet Laboratories Limited, and Roche.

Data availability

De-identified participant data will be made available on reasonable request 1 year after the date of publication, with no end date to availability, and may be used for any purpose. Requests should be directed to the corresponding author. Requestors will be required to sign a data access agreement.

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Ethical Approval

The trial was designed by the research team with patient and public involvement, sponsored by Manchester University NHS Foundation Trust, and funded by the UK National Institute for Health and Care Research (funder reference NIHR127575). Trial management, independent data management, and independent statistical analysis were performed by Liverpool Clinical Trials Centre, a United Kingdom Clinical Research Collaboration fully registered Clinical Trials Unit. The study

protocol was approved by a research ethics committee (NHS Health Research Authority, reference 20/NW/0275), and trial conduct was overseen by a trial steering committee and an independent data and safety monitoring committee.

Pre-registered Clinical Trial Number

TEMPEST ClinicalTrials.gov number, NCT04706429.

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