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RESEARCH ARTICLE

Sacubitril/valsartan for the treatment of non-obstructive hypertrophic cardiomyopathy: An open label randomized controlled trial (SILICOFCM)

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Aim Sacubitril/valsartan treatment reduces mortality and hospitalizations in heart failure with reduced ejection fraction but has limited application in hypertrophic cardiomyopathy (HCM). The aim of this study was to evaluate the effect of sacubitril/valsartan on peak oxygen consumption (VO_2) in patients with non-obstructive HCM.

Methods and results This is a phase II, randomized, open-label multicentre study that enrolled adult patients with symptomatic non-obstructive HCM (New York Heart Association class I–III) who were randomly assigned (2:1) to receive sacubitril/valsartan (target dose 97/103 mg) or control for 16 weeks. The primary endpoint was a change in peak VO_2. Secondary endpoints included echocardiographic measures of cardiac structure and function, natriuretic peptides and other cardiac biomarkers, and Minnesota Living with Heart Failure quality of life. Between May 2018 and October 2021, 354 patients were screened for eligibility, 115 patients (mean age 58 years, 37% female) met the study inclusion criteria and were randomly assigned to sacubitril/valsartan ($n = 79$) or control ($n = 36$). At 16 weeks, there was no significant change in peak VO_2 from baseline in the sacubitril/valsartan (15.3 [4.3] vs. 15.9 [4.3] ml/kg/min, $p = 0.13$) or control group ($p = 0.47$). No clinically significant changes were found in blood pressure, cardiac structure and function, plasma biomarkers, or quality of life.

Conclusion In patients with HCM, a 16-week treatment with sacubitril/valsartan was well tolerated but had no effect on exercise capacity, cardiac structure, or function.

Keywords Hypertrophic cardiomyopathy • Exercise capacity • Sacubitril/valsartan

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases characterized by left ventricular (LV) hypertrophy[1] with a prevalence ranging from 1:200 to 1:500.[2] It is caused by a pathological mutation of the cardiac sarcomeric protein genes and transmitted in an autosomal dominant manner.[3] Core pathophysiological features of HCM include increase in myocardial wall thickness, diastolic abnormalities, and dynamic LV outflow tract obstruction.[4–6]

There is limited evidence on the reliability of pharmacological treatments to alter disease progression in HCM. The VANISH trial showed significant improvements in cardiac structure and function in early stage HCM after 24-month administration of the angiotensin II receptor blocker valsartan, indicating an opportunity to attenuate disease progression.[7] However, most therapies focus on symptoms relief and the prophylactic implantation of cardioverter-defibrillators to reduce the risk of sudden cardiac death.[6,8] Moreover, hypotension and a reduction in LV ejection fraction (LVEF) associated with some therapies undermine the benefits of continued administration.[9]

Sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor, was approved for the treatment of heart failure with reduced ejection fraction based on its superiority over angiotensin-converting enzyme inhibitors (ACEi) in reducing cardiovascular mortality and heart failure hospitalizations.[10] Neprilysin degrades biologically active atrial and B-type natriuretic peptides, secreted by cardiomyocytes in response to increased myocardial wall tension and thus may play a cardio-protective role from volume and pressure overload.[11] Neprilysin inhibition increases generation of myocardial cyclic guanosine monophosphate, which improves myocardial relaxation and reduces hypertrophy.[11] There is evidence that sacubitril/valsartan improves myocardial morphology and physiology in heart failure[12–15] and can enhance exercise capacity.[16] However, the effects of sacubitril/valsartan on clinical and physiological phenotype in patients with HCM have not yet been evaluated. The aim of the present study was to determine the effect of sacubitril/valsartan on functional capacity, cardiac structure and function, cardiac biomarkers, and quality of life in patients with non-obstructive HCM. To the best of our knowledge this is the first study in human participants to report on the effect of sacubitril/valsartan on clinical phenotype in HCM.

Methods

Study design

This was a prospective, multicentre, open-label, randomized, controlled phase II clinical trial which was registered with ClinicalTrials.gov (NCT03832660), and protocol published previously.[17] Data were collected between May 2018 and February 2022. The inclusion and exclusion criteria prioritized safety and included a patient population which was reflective of real-world non-obstructive HCM. Eligible patients were aged ≥18 years with a diagnosis of non-obstructive HCM (LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm if familial HCM]); LVEF ≥55%; and New York Heart Association (NYHA) class I–III. Patients had to be able to safely perform maximal cardiopulmonary exercise testing (CPET) and be willing/able to return for follow-up visit. Key exclusion criteria included less than 3 months post-septal reduction therapy (surgery or catheter-based intervention); resting LV outflow tract gradient >30 mmHg; renal insufficiency with a glomerular filtration rate <30 ml/min/1.73 m^2; life expectancy <12 months; history of exercise-induced syncope or sustained ventricular arrhythmias; concomitant treatment with aliskiren-containing drugs; history of ACEi- or angiotensin receptor blocker (ARB)-induced angioedema or history of hereditary or idiopathic angioedema; evidence of hepatic disease; history of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 2 years, regardless of whether there was evidence of local recurrence or metastases; life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 bpm. The study was in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Research Ethics Committees and/or Institutional Review Boards of the study sites. All patients provided written informed consent.

Study procedures

All patients underwent baseline assessments which included medical history, physical examination and anthropometrics, serum biomarker analysis, genetic testing (if not performed earlier), 12-lead electrocardiogram, transthoracic echocardiography, quality of life assessment and CPET. Biomarkers of cardio-metabolic function were evaluated using venous blood. Echocardiographic images were acquired in the standard parasternal (long-axis, short-axix) and apical (apical 4-chamber, apical 2-chamber, and apical long-axis) views, for which three cardiac cycles were recorded. Parasternal short-axis views were acquired at three levels: basal (at mitral valve level), mid-papillary, and apical (minimum cavity distal to papillary muscle level). LV diameter and fractional shortening, interventricular septum, and LV posterior wall thickness, and left atrial dimensions were measured using M-mode and two-dimensional echocardiography according to current recommendations.[18] Peak velocity of the LV outflow tract was recorded from the apical 5-chamber view by pulse Doppler, and pressure gradient was calculated. The sites and maximal extent of ventricular hypertrophy were assessed and measured in end-diastole. LV volumes and LVEF and right ventricular systolic function were assessed from the apical 4-chamber view, using the biplane method of discs. Left atrial volumes were measured in systole just before the mitral valve opening, using a monoplane area–length method. Transmitral Doppler imaging was used to assess diastolic function.

Patients completed an individualized symptom-limited graded CPET using cycle ergometer, according to established guidelines.[19] Pharmacologic therapy was maintained during CPET. Exercise commenced with 3 min of unloaded cycling followed by increased workloads of 10 W/min until maximum exertion was achieved. Bike cadence was maintained at 60–70 rpm throughout the test.

Simultaneous 12-lead electrocardiography and an automated blood pressure were recorded. Oxygen consumption (VO_2), minute ventilation (VE), carbon dioxide production (VCO_2), and other CPET variables were acquired breath by breath, and expressed in 10 s intervals. Peak VO_2 and peak respiratory exchange ratio (RER) were expressed as the highest 10 s averaged sample obtained during the last 20 s of testing. VE and VCO_2 values, acquired from the beginning of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft

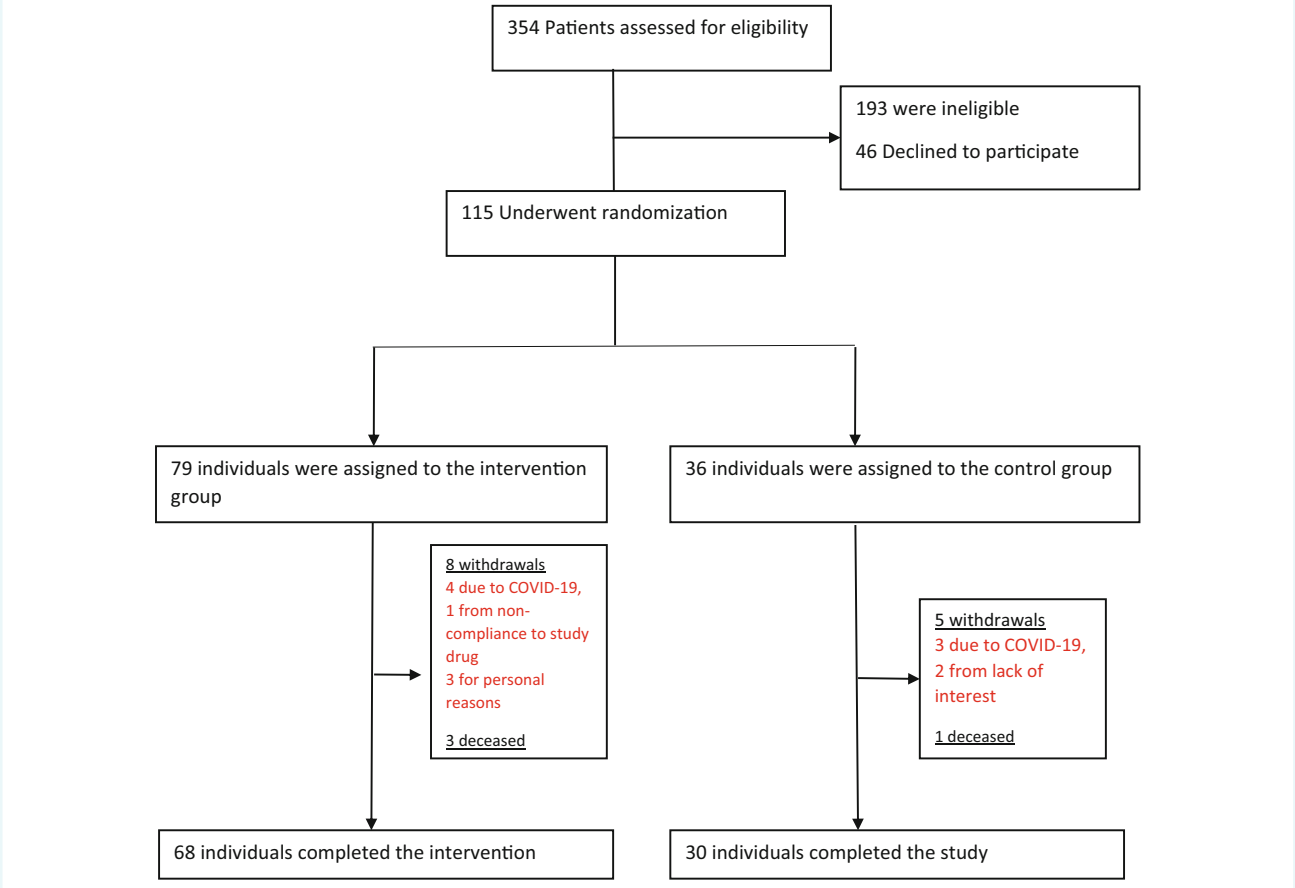

Figure 1 Flow of participants through the study (screening, randomization and follow-up).

Corp., Bellevue, WA, USA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). Test termination criteria consisted of symptoms (i.e. dyspnoea and/or fatigue), ventricular tachycardia, >2 mm of horizontal or downsloping ST-segment depression, a drop of systolic blood pressure >20 mmHg during progressive exercise, or RER ≥1.10.

Randomization

Patients were randomly assigned (2:1) using computer-generated numbers to receive orally administered sacubitril/valsartan or control group (optimal standard therapy). Randomization was stratified by functional capacity, NYHA class, current beta-blocker use (yes or no).

Pharmacological intervention

Patients allocated to the pharmacological intervention group began an initial dose of 24/26 mg or 49/51 mg sacubitril/valsartan, followed by up-titration every 14 days until the target dose of 97/103 mg twice daily was reached. Sacubitril/valsartan was administered orally for 16 weeks. Patients previously on ACEi or ARB therapy had a 36 h washout period before initiation of sacubitril/valsartan to reduce the risk of angioedema. Doses were adjusted based on overall safety and tolerability. Hypotension was defined as investigator-reported hypotension with a systolic blood pressure <100 mmHg. Pre-specified criteria for temporary discontinuation of study drug, including LVEF <50%, have been previously described.[17]

Optimal standard therapy (control group)

Patients in the control group received optimal standard therapy for HCM according to current guidelines.[8] All patients were asked to return for re-evaluation 16 weeks after enrolment and underwent the same procedures and assessments as at the baseline visit.

Outcomes

The primary study endpoint was a between-group change in exercise tolerance (i.e. peak VO_2) from baseline to week 16. Secondary endpoints were between-group change from baseline to follow-up visit in (a) indices of cardiorespiratory fitness, (b) quality of life measures (i.e. Minnesota Living with Heart Failure Questionnaire [MLHFQ] [range, 0–105; higher scores indicate worse quality of life; minimal clinically important difference, 5 points]), (c) cardiac remodelling measures from echocardiography (i.e. magnitude or distribution of cardiac hypertrophy, degree of LV outflow obstruction, LV chamber dimensions, systolic and diastolic function, and LV wall motion), (d) serum concentrations of creatine kinase, creatine kinase-myocardial band, and N-terminal pro-B-type natriuretic peptide (NT-proBNP), low-density lipoprotein,

high-density lipoprotein, total cholesterol, electrolytes. All assessments for secondary endpoints were controlled for type I error in hierarchical order upon achieving significance in the primary endpoint (with two-tailed $p < 0.05$ required to proceed). Pre-specified safety endpoints included frequency and severity of treatment-emergent adverse events and serious adverse events.

Statistical analysis

Existing literature suggests that between-group change of 1.27 ml/kg/min in peak VO_2 is clinically significant.[20] Assuming similar effects, 120 patients were required on a 2:1 randomization basis, to achieve 90% power to detect a significant difference in peak VO_2 between groups, at a two-tailed significance level of ≤0.05.

Statistical analysis was performed using SPSS (version 28 IBM). Data are presented as mean and standard deviation. Individual changes in outcome measures from baseline to follow-up were determined by either a paired *t*-test for normally distributed data or a Wilcoxon signed-rank test for non-normally distributed data. Between-group differences from baseline to follow-up were assessed by independent *t*-test for normally distributed data or a Mann–Whitney U test for non-normally distributed data. A two-sided *p*-value <0.05 was considered as statistically significant difference. All analyses were done on data from the modified intention to-treat population. Missing data occurred at random and were replaced with the mean for the sample at either baseline or follow-up.[21]

Results

From May 2018 to October 2021, 354 adults with non-obstructive HCM were screened for eligibility and 115 patients met the study inclusion criteria who were randomized into sacubitril/valsartan ($n = 79$) or control ($n = 36$) (*Figure 1*). Before randomization, 43 patients (37%) were taking ACEi and 17 patients (15%) were taking ARBs. We recruited a typical population of HCM patients from an outpatient HCM clinic. Our sample was diverse with 43% testing genotype-positive for HCM mutation and 10% having implanted cardioverter-defibrillators. No patient was treated via surgical or interventional septal reduction therapy. Baseline demographic characteristics were not significantly different between sacubitril/valsartan and control groups (*Table 1*).

Primary outcome

All patients achieved peak level of exertion at baseline and follow-up demonstrated by mean RER of 1.08 both in sacubitril/valsartan and control groups. At 16 weeks, there was no significant change in peak VO_2 from baseline in the sacubitril/valsartan (15.3 [4.3] vs. 15.9 [4.3] ml/kg/min, $p = 0.13$), or control group (15.2 [3.8] vs. 15.6 [3.9] ml/kg/min, $p = 0.47$) (*Table 2*).

Secondary outcomes

There were no significant changes from baseline in anaerobic threshold or peak heart rate in sacubitril/valsartan (9.9 [3.5] vs. 10.7 [3.1] ml/kg/min, $p = 0.12$; 118 [19] vs. 115 [18] bpm, $p = 0.09$) or control group (11.1 [2.9] vs. 11.2 [3.4] ml/kg/min, $p = 0.90$; 120 [18] vs. 118 [16] bpm, $p = 0.53$) (*Table 2*). There were no

Table 1 Baseline characteristics of the study population

Variables	Sacubitril/valsartan ($n = 79$)	Control ($n = 36$)
Demographic characteristics		
Age (years)	59 (10)	57 (12)
Female sex, *n* (%)	29 (37)	14 (39)
Body weight (kg)	84.8 (17.4)	80.9 (15.1)
BMI (kg/m^2)	28.1 (5)	26.8 (4)
NYHA functional class, *n* (%)		
I	28 (35)	21 (55)
II	43 (55)	14 (39)
III	7 (10)	1 (6)
Systolic blood pressure (mmHg)	137 (21)	131 (18)
Diastolic blood pressure (mmHg)	82 (11)	77 (10)
LA dimension (mm)	42.6 (5.6)	41.5 (5.4)
LA volume (ml)	42.6 (11.9)	37.7 (10.3)
Atrial fibrillation, *n* (%)	7 (9)	1 (3)
ICD, *n* (%)	8 (10)	4 (11)
Genetic mutation[a], *n* (%)		
MYBPC3	34 (43)	15 (42)
MYH7	15 (18)	5 (14)
MYL3	1 (1)	0 (0)
TNNT2	12 (15)	6 (17)
TNNI3	10 (13)	2 (6)
TPM1	1 (1)	0 (0)
Negative	26 (33)	9 (25)
N/A	8 (10)	5 (14)
Medications, *n* (%)		
Angiotensin-converting enzyme inhibitors	5 (6)	2 (6)
Angiotensin receptor blockers	2 (3)	1 (3)
Beta-adrenergic blocking agent	61 (77)	29 (81)
Calcium channel blocking agent	25 (32)	12 (33)
Diuretics	28 (35)	13 (36)
Diabetes	6 (8)	1 (3)
Anti-inflammatory	32 (41)	13 (36)
Statins	31 (39)	15 (42)
Anticoagulants	19 (24)	10 (28)
Family history, *n* (%)		
Hypertrophic cardiomyopathy	14 (18)	5 (14)
Dilated cardiomyopathy	2 (3)	2 (6)
Sudden cardiac death	27 (34)	12 (33)
Comorbidities, *n* (%)		
Diabetes	7 (9)	2 (6)
Thyroid disease	4 (5)	3 (8)
Renal dysfunction	2 (3)	0 (0)
Hepatic dysfunction	1 (1)	2 (6)
Chronic obstructive pulmonary disease	4 (5)	2 (6)
Anaemia	2 (3)	0 (0)

Values are given as mean (standard deviation), unless otherwise indicated.
BMI, body mass index; ICD, implantable cardioverter-defibrillator; LA, left atrial; MYBPC, myosin-binding protein C; MYH, β-myosin heavy chain; MYL, myosin light chain; N/A, not available; NYHA, New York Heart Association; TNNT, troponin T; TNNI, troponin I; TPM, tropomyosin.
[a]Some patients express more than one gene mutation.

Table 2 Changes in exercise measures from baseline to follow-up

Variables	Sacubitril/valsartan			Control			Between group Δ (95% CI)	*p*-value
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ		
Peak VO_2 (ml/kg/min)	15.3 (4.3)	15.9 (4.3)	0.65 (3.6)	15.2 (3.8)	15.6 (3.9)	0.46 (3.8)	0.19 (−1.28–1.67)	0.80
VO_2AT (ml/kg/min)	9.90 (3.5)	10.7 (3.1)	0.80 (3.7)	11.1 (2.9)	11.2 (3.4)	0.09 (3.8)	0.71 (−1.00–2.43)	0.41
Peak HR (bpm)	118 (19)	115 (18)	−3.41 (17)	120 (18)	118 (16)	−1.97 (18.6)	−1.44 (−8.53–5.65)	0.69
Peak VE/VCO_2	30.1 (7.0)	28.4 (4.9)	−1.65 (6.4)	27.6 (3.5)	29.1 (4.7)	1.44 (4.8)	−3.10 (−5.61 to −0.58)	0.02

Data are given as mean (standard deviation).
AT, anaerobic threshold; CI, confidence interval; HR, heart rate; VE/VCO_2, minute ventilation to carbon dioxide output slope (ventilatory efficiency); VO_2, oxygen consumption.

Table 3 Changes in secondary outcomes from baseline to follow-up

Variables	Sacubitril/valsartan			Control			Between group Δ (95% CI)	*p*-value
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ		
Cardiac structure and function								
SBP (mmHg)	137 (21)	136 (20)	−1 (19)	131 (18)	129 (22)	−2 (21)	−1.12 (−9.4–7.2)	0.79
DBP (mmHg)	82 (11)	80 (12)	−2 (13)	77 (10)	79 (12)	−2 (12)	0.44 (−2.0–9.2)	0.20
LVOT gradient (rest) (mmHg)	12 (14)	12 (14)	0.08 (11)	12 (14)	14 (13)	2 (6)	−1.92 (−5.7–1.9)	0.191
IVSd (mm)	18.4 (3.5)	17.9 (3.2)	−0.46 (2.2)	18.7 (4.3)	18.5 (3.7)	−0.22 (2.5)	−0.25 (−1.2–0.7)	0.277
PLWd (mm)	12.9 (3.4)	12.7 (2.4)	−0.15 (2.5)	11.9 (3.0)	11.6 (2.2)	−0.27 (2.2)	0.12 (−0.8–1.1)	0.797
E/e'	12.2 (5.2)	12.7 (4.7)	0.54 (4.8)	11.7 (3.9)	11.0 (3.4)	−0.65 (3.2)	1.20 (−0.6–3.0)	0.143
LVEF (%)	64 (7)	64 (6)	−0.5 (4.5)	66 (8)	68 (7)	2.3 (8.4)	−2.79 (−5.2 to −0.4)	0.023
LVOT gradient (Valsalva) (mmHg)	23 (23)	21 (20)	−2.5 (18.6)	21 (25)	19.0 (17)	−2.05 (17)	−0.45 (−8.0–7.1)	0.41
LAVi (ml)	43 (12)	43 (12)	0.59 (10)	38 (10)	36 (8)	−1.49 (10)	2.08 (−2.3–6.5)	0.349
Blood biomarkers								
CK (μ/L)	120 (64)	107 (51)	−13 (60)	128 (53)	133 (54)	5 (59)	−18 (−43.0–6.5)	0.075
CK-MB (μ/L)	15 (5.5)	17 (7)	2.23 (5.8)	18 (4)	17 (5.7)	−1.33 (6)	3.6 (−0.9–8.0)	0.131
NT-proBNP (pg/ml)	779 (258–1285)	986 (300–1204)		951 (568–1428)	916 (315–1030)		0.02 (−0.2–0.2)[a]	0.841[a]
Sodium (mmol/L)	140 (2.5)	140 (2.7)	0.00 (3.30)	141 (1.8)	139 (2.5)	−1.67 (2.9)	1.67 (0.4–2.9)	0.015
Potassium (mmol/L)	4.6 (0.4)	4.5 (0.5)	−0.01 (0.6)	4.4 (0.3)	4.5 (0.5)	0.06 (0.5)	−0.07 (−0.3–0.1)	0.527
AST (μmol/L)	24 (7.7)	23 (6.2)	−1.23 (7.6)	25 (6.9)	25 (8.1)	0.13 (6.9)	−1.36 (−4.5–1.8)	0.525
Troponin (ng/L)	28 (27)	26 (25)	−2.51 (27)	23 (22)	(20) (14)	−2.43 (15)	−0.08 (−11.5–11.4)	0.47
Total protein (g/L)	73 (4.6)	72 (4.7)	−1.23 (5.0)	72 (5.8)	73 (4.9)	0.32 (5.3)	−1.55 (−3.6–0.5)	0.138
LDL (mmol/L)	3.0 (1.0)	2.7 (0.8)	−0.27 (0.9)	3.0 (1.0)	2.8 (1.0)	−0.2 (1.1)	−0.06 (−0.5–0.3)	0.752
HDL (mmol/L)	1.2 (0.4)	1.2 (0.3)	−0.01 (0.3)	1.4 (0.3)	1.3 (0.4)	−0.02 (0.3)	0.00 (−0.1–0.1)	0.955
Total cholesterol (mmol/L)	5.0 (1.3)	4.9 (1.1)	−0.15 (0.9)	5.0 (1.2)	4.8 (1.3)	−0.19 (1.5)	0.04 (−0.5–0.6)	0.896
Triglycerides (mmol/L)	1.7 (0.8)	1.6 (0.6)	−0.08 (0.8)	1.4 (0.9)	1.4 (0.4)	−0.07 (0.96)	−0.01 (−0.4–0.3)	0.441
Quality of life								
MLHFQ	27 (7–41)	22 (8–29)		27 (19–36)	24 (11–35)		−4.88 (−12–3)	0.2

Values are given as mean (standard deviation, or median (interquartile range)).
AST, aspartate transaminase; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase myocardial band; DBP, diastolic blood pressure; E/e', ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; HDL, high-density lipoprotein; IVSd, interventricular septal diameter; LAVi, left atrial volume index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PLWd, posterior left ventricular wall diameter; SBP, systolic blood pressure.
[a]Calculated from log transformed data.

clinically relevant changes in other outcome measures including ventilatory efficiency, systolic or diastolic function, cardiac chamber dimensions and thickness, NT-proBNP and quality of life (*Table 3*).

Adverse events

Treatment with sacubitril/valsartan was generally well tolerated and there were no observations of hypotension, non-sustained ventricular arrhythmias, atrial fibrillation, or other arrythmias suggesting that it could be used for relevant indications in patients with HCM. All patients reached the target dose of 97/103 mg. The use of sacubitril/valsartan was not associated with any serious adverse events. During the study period, three patients in the sacubitril/valsartan group died from sudden cardiac death, ischaemic stroke, and decompensated heart failure due to infective endocarditis, whilst one patient in the control group died from sudden cardiac death.

Discussion

This is the first study to evaluate the effect of sacubitril/valsartan in patients with non-obstructive HCM. Our results show that

treatment with sacubitril/valsartan for 16 weeks was well tolerated, but had no significant effect on exercise capacity, cardiac structure or function. Analyses of other outcomes of exercise performance and cardiac remodelling revealed no significant differences between baseline and follow-up for either sacubitril/valsartan or control group. Our results are significant as this is the first study to report findings on the effects of angiotensin receptor–neprilysin inhibitor in HCM patients.

Reduced peak VO_2 has been shown to correlate with clinical decompensation and mortality in HCM.[22,23] As disease progresses, the majority of HCM patients develop dyspnoea on exertion, thus limiting exercise capacity, an important predictor of mortality.[24] Heart failure symptoms are frequently experienced despite normal ejection fraction due to LV outflow obstruction or diastolic dysfunction[25] caused by impaired cardiac energetics which can manifest in genotype-positive individuals before the development of hypertrophy.[26] Whilst pilot studies have shown that sacubitril/valsartan can improve exercise capacity in heart failure patients,[16,27] our results, like several randomized controlled trials including the PARALLAX[28] and ACTIVITY-HF[29] studies, failed to show significant benefits of sacubitril/valsartan over placebo or control in improving exercise capacity.[28–31] One study suggested that patients with limited exercise capacity could exhibit early resistance to treatment, thus improvements may only occur with longer treatment.[29]

The present trial did not find any significant echocardiographic evidence of improvement or deterioration in hypertrophy, LV geometry, systolic or diastolic function in the intervention or control group. Whilst findings from a few trials agree with our results,[32,33] the VANISH trial showed improvement in myocardial structure and function after treatment with ARBs.[7] Improved diastolic function and reduced LV mass was also reported in pilot studies.[34–36] Evidence from pre-clinical[37,38] and clinical studies[7] suggests that calcium channel blocker or ARB treatment may not only attenuate disease progression but might also promote improvement. However, these benefits were seen prior to or in early phase of LV hypertrophy.

Elevated natriuretic peptide concentrations are associated with adverse outcomes in patients with heart failure irrespective of LVEF.[39] The present study did not show any benefit of sacubitril/valsartan administration on NT-proBNP. We report slightly reduced NT-proBNP levels in the control group, which may not be unusual considering that patients were on optimum dose of recommended medication and were managed according to current guidelines. A previous report based on the PARADIGM-HF trial suggested that treatment with sacubitril/valsartan was almost twice as likely as enalapril to reduce NT-proBNP to values below 1000 pg/ml.[39] Furthermore, the PARAMOUNT heart failure preserved ejection fraction study showed that these effects could be seen as early as 4 weeks with benefits sustained for 36 weeks.[11]

Patient-reported assessments using the MLHFQ showed that sacubitril/valsartan did not impact quality of life unlike reports presented previously.[28,40] Patients in the present study had a median quality-of-life score of 27 with a range between 7 and 41 points out of a possible 105 points, which seems to suggest quality of life is not severely compromised. This is unsurprising considering over 90% of patients were in NYHA class I and II heart failure categories. However, relatively low functional capacity observed in the present study suggests that quality of life may be independent of peak exercise capacity unlike previously reported in heart failure patients.[41]

Limitations

In the present study, the following limitations should be considered. Due to the COVID-19 pandemic, recruitment was halted, and number of patients recruited into the study was reduced. Interpretation of the main findings should be considered with caution due to the following limitations. Firstly, the study design was not double-blind, placebo-controlled and thus may lead to bias and limit generalizability of findings. Secondly, our initial power calculation suggested the need of 120 patients to be recruited but the study randomized 115 patients and report missing follow-up data for selected variables in 15–20% of cases. Thirdly, drug titration up to maximum dose was at the discretion of each clinical centre, thus modality of medication administration could have impacted some results, e.g. quality of life. Moreover, prior treatment with ACEi or ARB may have affected our results. Fourthly, echocardiography and CPET analyses was not centralized but performed and interpreted by experts at each centre. Lastly, duration of the intervention of 16 weeks may not be sufficient to allow adaptations that may occur at the cellular and molecular level, further leading to changes in clinical and physiological phenotype.

Conclusions

This is the first study to evaluate the effect of sacubitril/valsartan on clinical phenotype in non-obstructive HCM in humans. Based on the major findings of the present study, it can be concluded that among patients with non-obstructive HCM, sacubitril/valsartan was well tolerated. It did not however lead to a significant improvement in functional capacity, cardiac function and structure.

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Conflict of interest: none declared.

Appendix A

SILICOFCM Study Centres and Investigators

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[Correction added on 11 June 2024, after first online publication: The appendix section containing the name of the investigators has been added in this version]

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