

Hypertrophic cardiomyopathy: Perspectives of drug therapy

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Abstract

Background. Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease that affects approximately one in 500 people. HCM is a recognized genetic disorder most often caused by mutations involving myosin-binding protein C (MYBPC3) and β -myosin heavy chain (MYH7) which are responsible for approximately three-quarters of the identified mutations.

Aim. So far, no medical treatment has reliably shown to halt or reverse progression of HCM or to alleviate its symptoms. While the angiotensin receptor neprilysin inhibitor sacubitril/valsartan has shown to reduce mortality and hospitalization in heart failure with reduced ejection fraction, data on its effect on HCM are sparse. We sought to explore the effect of sacubitril/valsartan on exercise tolerance (ie, peak oxygen consumption) in patients with nonobstructive HCM compared to the optimal standard therapy (control group).

Methods. The study presented is a part of SILICOFCM - a prospective, multicenter, open-label, randomized, controlled, three-arm clinical trial (NCT03832660) that will recruit 240 adult patients with a confirmed diagnosis of nonobstructive HCM. However, this study included only 41 patients from a single center. Eligible patients are randomized to sacubitril/valsartan, or optimal standard therapy alone (control group). The primary endpoint is the change in functional capacity (ie, peak oxygen consumption).

Results. The study included 41 patients assigned to intervention group (29 patients) and control (12 patients). Mean age was 60.0 ± 10.4 years, and majority of patients were male (73.2%). Left ventricular wall thickness measured at interventricular septum and posterolateral wall was 17.3 ± 4.3 mm and 15.6 ± 3.5 mm, respectively. Baseline peak VO₂ was 14.0 ± 4.4 ml/kg/min and VE/VCO₂ 28.1 ± 6.4 . After 4 months follow-up, the intervention group expressed an increase in VO₂ from 14.4 ml/kg/min to 16.4 ml/kg/min ($p=0.016$). The value of VE/VCO₂ decreased from 26.6 to 25.8 in the intervention group, while in the control group it changed from 26.0 to 30.9. The value of VE/VCO₂ after 4 months follow-up was significantly lower in the intervention group (25.8 ± 5.3 vs 30.9 ± 4.9 ; $p=0.050$).

Conclusion. The results of the present study suggest that, despite the relatively short treatment period of 4 months, sacubitril/valsartan treatment can have positive effects functional capacity in patients with HCM. These results, together with the rest of the SILICOFCM study outcomes, will hopefully contribute to the optimization of the HCM management.

Key words hypertrophic cardiomyopathy, sacubitril/valsartan, exercise tolerance

Background

Hypertrophic cardiomyopathy (HCM) is the most frequent inherited disease of the myocardium, with a prevalence of approximately 0.2%^{1,2}. Despite the significant developments in diagnostic tools and genetic tests, the diagnosis of HCM is often delayed².

HCM is characterized by left ventricular (LV) hypertrophy without dilatation, in the absence of any other cardiac, systemic, metabolic, or syndromic disease that could explain myocardial hypertrophy²⁻⁵. Clinical presentation of HCM varies from completely asymptomatic with normal

life expectancy, to typical symptoms like chest pain, dyspnea, heart failure, palpitations, syncope, and in the worst case even sudden cardiac death^{2,6}. Complications of nonobstructive HCM include advanced myocardial fibrosis, microvascular ischemia, and deterioration of cardiac function⁷.

HCM is a recognized genetic disorder transmitted in an autosomal dominant fashion, caused by a single mutation in one of the sarcomeric protein genes, which can be present in either thick- or thin-filament genes^{8,9}. The two most common mutations involving thick filament are myosin-binding protein C (MYBPC3) and β -myosin heavy chain (MYH7) gene mutations, which are responsible for

approximately three-quarters of the identified mutations in HCM patients⁹⁻¹¹.

So far, no medical treatment has reliably shown to prevent, halt, or reverse disease progression and targeted pharmacologic options are scarce¹². Clinical trials demonstrated limited or no effect of angiotensin receptor blockers or late sodium current inhibitor on disease progression, cardiac structure and function, exercise tolerance, and quality of life in patients with HCM¹³. Accordingly, treatment recommendations are focused on the alleviation of symptoms, prevention of thromboembolic events, and the prophylactic implantation of cardioverter-defibrillators in patients at high-risk of sudden cardiac death^{3,5}.

The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan is a novel treatment shown to reduce hospitalizations and mortality in heart failure with reduced ejection fraction¹⁴, while there was no significant benefit of sacubitril/valsartan on the rate of total hospitalizations for heart failure and cardiovascular death among patients with heart failure with preserved ejection fraction in the recently published PARAGON-HF trial¹⁵.

However, sacubitril/valsartan was shown to be more effective for the management of hypertensive patients, compared with an angiotensin receptor blocker¹⁶. Moreover, new preliminary data suggest that sacubitril/valsartan improves exercise tolerance and left ventricular wall motion, while reducing markers of left ventricular wall stress. As sacubitril/valsartan has not yet been evaluated in HCM, this is the first clinical trial to investigate its effects on cardiovascular performance in patients with HCM¹⁷.

Methods

SILICOFCM is a prospective, multicenter, open-label, randomized, three-arm, controlled phase II clinical trial that is designed to evaluate potential benefits of a 4-month pharmacological intervention (sacubitril/valsartan) vs lifestyle intervention in patients with nonobstructive HCM.

This trial has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement no. 777204.

This study included 41 patients with nonobstructive HCM from a single center that underwent 4 month pharmacological intervention (sacubitril/valsartan). We included stable outpatients with a history of nonobstructive HCM or borderline left ventricular hypertrophy are eligible if they have a left ventricular wall thickness of ≥ 15 mm or ≥ 13 mm in a first degree relative of someone with HCM and meet the inclusion and exclusion criteria.

Screening

After providing signed informed consent, participants undergo a screening visit to document age, weight/height, vital parameters, current symptoms, medical and family history, as well as prior, and concomitant medication. A physical examination, a 12-lead-electrocardiogram and a transthoracic echocardiography are performed. All participants undergo progressive cardiopulmonary exercise testing (CPET) using a cycle ergometer to evaluate

their exercise tolerance, that is, peak oxygen consumption, at baseline. At the time of enrolment, all participants must be on optimal standard therapy for HCM, conforming to contemporary guidelines such as the European Society of Cardiology guidelines. All cardiac medications must remain unchanged for at least 2 weeks before screening and randomization.

Randomization

Eligible participants with signed informed consent are randomly allocated to the study groups—receiving either treatment with sacubitril/valsartan—or the control group (optimal standard therapy) using consecutively numbered sealed envelopes.

Pharmacological intervention

Participants who are allocated to the pharmacological study group and have previously received an angiotensin-converting enzyme inhibitor- or angiotensin receptor blocker-therapy will require a 36-hour washout period before initiation of sacubitril/valsartan to reduce the risk of angioedema. The treatment period begins with the initial dosing of sacubitril/valsartan, followed by up-titration every 14 days to the target dose of 97/103 mg twice daily. The three doses of sacubitril/valsartan available throughout the study are 24/26 mg (dose level 1), 49/51 mg (dose level 2), and 97/103 mg (dose level 3), each taken by mouth twice daily.

Doses may be adjusted based on overall safety and tolerability. If necessary, dose adjustments or elimination of concomitant medications is made to alleviate adverse effects. If adverse effects are not alleviated or it is not possible to adjust concomitant medications, the study treatment may be down-titrated by one dose level—or, at the lowest dose, temporarily withdrawn—for 1 to 2 weeks. Participants may then be reassessed and the study treatment further down-titrated every 1 to 2 weeks until being deemed stable. Once stability is achieved, the participant is re-challenged with up-titration to the target dose. In case of discontinuation of the study medication, the participant is advised to return to the clinic for an end-of-study visit. Participants undergo treatment for 4 months. After enrollment into the study, all participants are instructed to notify the study site about any change or withdrawal of medication. Furthermore, all medication, medical procedures and significant nondrug therapies (eg, blood transfusions and physical therapy) administered after the patient has been enrolled into the study are recorded. tained from all eligible patients who are willing to participate in the study.

Optimal standard therapy (control group)

Participants in the control group receive optimal standard therapy for HCM as advocated in the current guideline of the European Society of Cardiology⁵. Optimal standard therapy may include an appropriate lifestyle, adequate management of heart failure symptoms and atrial fibrillation as well as risk stratification and preventive measures against sudden cardiac death.

Table 1. Various clinical parameters between the groups

	Grupa	N	Mean	Std. Deviation	P value
Age (years)	Intervention	29	57.3	10.4	0.007
	Control	12	66.7	7.4	
Weight [kg]	Intervention	29	91.3	15.4	0.973
	Control	12	91.5	17.9	
Weight 2 [kg]	Intervention	21	90.0	15.2	0.653
	Control	9	87.3	14.4	
Height [cm]	Intervention	29	176.6	8.8	0.262
	Control	12	172.8	11.9	
BMI 1	Intervention	29	29.2	4.3	0.407
	Control	12	30.4	3.6	
BMI 2	Intervention	21	28.9	4.3	0.704
	Control	9	29.5	1.6	
Systolic 1	Intervention	29	135.0	23.2	0.463
	Control	12	130.4	15.3	
Systolic 2	Intervention	20	140.8	22.3	0.592
	Control	8	145.6	19.2	
Diastolic 1	Intervention	29	77.4	9.7	0.106
	Control	12	71.7	11.1	
Diastolic 2	Intervention	20	77.8	10.9	0.332
	Control	8	82.5	12.8	
LVEF 1	Intervention	29	61.4	7.8	0.706
	Control	12	62.7	13.2	
LVEF 2	Intervention	21	62.5	5.2	0.074
	Control	9	67.2	8.5	
LVOT maxPG - VM 1	Intervention	12	52.3	45.3	0.190
	Control	11	29.8	32.8	
LVOT maxPG - VM 2	Intervention	12	34.4	44.2	0.841
	Control	8	38.2	36.5	
Peak VO2 1	Intervention	29	14.3	4.6	0.411
	Control	8	12.8	3.7	
Peak VO2 2	Intervention	17	16.4	6.4	0.124
	Control	6	12.0	3.2	
Peak HR 1	Intervention	29	115.7	21.3	0.620
	Control	8	120.0	23.2	
Peak HR 2	Intervention	17	120.6	19.9	0.678
	Control	6	124.2	9.2	
Peak RER 1	Intervention	29	1.1	0.1	0.352
	Control	8	1.1	0.1	
Peak RER 2	Intervention	17	1.1	0.1	0.711
	Control	6	1.1	0.0	
Peak VE/VCO2 1	Intervention	28	28.6	6.9	0.385
	Control	6	26.0	3.5	
Peak VE/VCO2 2	Intervention	17	25.8	5.3	0.050
	Control	6	30.9	4.9	

BMI – Body mass index, LVEF- left ventricular ejection fraction, LVOT – left ventricle outflow tract, HR – heart rate. Number 1 is the first value obtained during study commencement, number 2 is the value after 4 month period

Results

The study included 41 patients assigned to interventional group (29 patients) and control (12 patients). Mean age was 60.0±10.4 years, and majority of patients were male (73.2%). According to the body mass index (BMI), the patients were overweight with mean BMI 29.6±4.1 kg/m².

At baseline, the most frequent symptoms included fatigue (63.4%), dyspnea (36.6%), chest pain (34.1%), palpitations (29.3%) and syncope (9.8%). There was 41.5% patients without heart failure related symptoms who belonged to NYHA functional class I, whereas 48.8% and 9.7% belonged to NYHA functional call II and III, respectively. Baseline systolic and diastolic blood pressure was 133.7±21.1 mmHg and 75.7±10.3 mmHg, respectively.

Table 2. Clinical presentation

Cross-tabs (Chi square)	All pts N (%)	Intervention N (%)	Control N (%)	P value
Sex				
Male	30(73.2)	21(72.4)	9(75.0)	1.000
Female	11(26.8)	8(27.6)	3(25.0)	
ICD	6(14.6)	4(13.8)	2(16.7)	1.000
Fatigue 1	26(63.4)	17(58.6)	9(75.0)	0.480
Fatigue 2	15(50.0)	9(42.9)	6(66.7)	0.427
Dyspnoea 1	15(36.6)	10(34.5)	5(41.7)	0.730
Dyspnoea 2	9(30.0)	6(28.6)	3(33.3)	1.000
Chest pain 1	14(34.1)	10(34.5)	4(33.3)	1.000
Chest pain 2	8(19.5)	6(28.6)	2(22.2)	1.000
Palpitations 1	12(29.3)	9(31.0)	3(25.0)	1.000
Palpitations 2	9(30.0)	8(38.1)	1(11.1)	0.210
Syncope 1	4(9.8)	2(6.9)	2(16.7)	0.567
Syncope 2	1(3.3)	1(4.8)	0(0.0)	1.000
NYHA Class 1				
I	17(41.5)	13(44.8)	4(33.3)	0.106
II	20(48.8)	15(51.7)	5(41.7)	
III	4(9.7)	1(3.4)	3(25.0)	
NYHA Class 2				
I	15(51.7)	13(61.9)	2(25.0)	0.126
II	13(44.8)	7(33.3)	6(75.0)	
III	1(3.5)	1(4.8)	0(0.0)	
Heart murmur 1	11(26.8)	10(34.5)	1(8.3)	0.128
Heart murmur 2	9(30.0)	8(38.1)	1(11.1)	0.210
Pretibial edema 1	6(14.6)	5(17.2)	1(8.3)	0.651
Pretibial edema 2	2(6.7)	2(9.5)	0(0.0)	1.000
MR 1				
0	5(12.2)	2(6.9)	3(25.0)	0.197
0/1	10(24.4)	7(24.1)	3(25.0)	
1	11(26.8)	9(31.0)	2(16.7)	
1/2	4(9.8)	4(13.8)	0(0.0)	
2	5(12.2)	2(6.9)	3(25.0)	
2/3	6(14.6)	5(17.2)	1(8.3)	
3	0(0.0)	0(0.0)	0(0.0)	
MR 2				
0	3(10.0)	2(9.5)	1(11.1)	0.287
0/1	10(33.3)	5(23.8)	5(55.6)	
1	6(20.0)	5(23.8)	1(11.1)	
1/2	4(13.3)	3(14.3)	1(11.1)	
2	2(6.7)	2(9.5)	0(0.0)	
2/3	4(13.3)	4(19.0)	0(0.0)	
3	1(3.3)	0(0.0)	1(11.1)	
systolic anterior motion 1	6(14.6)	4(13.8)	2(16.7)	1.000
systolic anterior motion 2	6(18.8)	4(19.0)	2(18.2)	1.000

ICD – implantable cardioverter defibrillator, NYHA – New York Heart Association, MR – mitral regurgitation. Number 1 is the first value obtained during study commencement, number 2 is the value after 4 month period

Follow-up visit was performed 4 months after the enrollment, with escalating dose of sacubitril/valsartan to the maximal 97/103 mg taken twice daily in the intervention group, and with optimal standard therapy in the control group. No significant difference was noted in patients' subjective symptoms and NYHA function class distribution between the groups. Echocardiography parameters of the left atrium including left atrial diameter and volume, as well as the LV including systolic and diastolic diameters and volumes and wall thicknesses did not change significantly. LVEF also remained unchanged.

CPET results at 4 months follow-up did not show significant difference in VO₂ between the groups. However, the intervention group expressed an increase in VO₂ from 14.4 ml/kg/min at baseline to 16.4 ml/kg/min at follow-up ($p=0.016$). Although most of the parameters did not significantly differ between the groups nor pre- and postintervention, one has to notice a significant difference in peak VE/VCO₂ after the intervention. The value of VE/VCO₂ decreased from 26.6 to 25.8 in the intervention group, while in the control group it changed from 26.0 to 30.9. The value of VE/VCO₂ after 4 months follow-up was significantly lower in the intervention group (25.8 ± 5.3 vs 30.9 ± 4.9 ; $p=0.050$).

Mean left ventricular ejection fraction (LVEF) was $61.8\pm9.8\%$. Left ventricular wall thickness measured at interventricular septum (IVS) and posterolateral wall (PLW) was 17.3 ± 4.3 mm and 15.6 ± 3.5 mm, respectively. Systolic anterior motion was present in 14.6% patients. CPET results showed peak VO₂ 14.0 ± 4.4 ml/kg/min and VE/VCO₂ 28.1 ± 6.4 .

The most important findings of the study are presented in the following tables.

Discussion

The present study explored the effects of ARNI sacubitril/valsartan in patients with nonobstructive HCM compared to the optimal standard therapy. Despite the comprehensive research and promising results of the sacubitril/valsartan treatment in heart failure with both reduced¹⁴ and preserved ejection fraction¹⁵, this therapy has not yet been investigated in patients with HCM.

The presented results are only a part of the multicenter SILICOFCM trial¹⁷, which seeks to provide novel data on whether the complementary addition of either sacubitril/valsartan or lifestyle intervention to the optimal standard therapy improves cardiovascular performance in patients with nonobstructive HCM as well as their clinical phenotypic characteristics, injury and stretch activation markers, habitual physical activity, and quality of life. A comprehensive genetic analysis for the majority of known mutations responsible for HCM, as well as their connection to the clinical phenotype is being investigated as well¹¹. Hence, the presented results are preliminary estimates from a single center, and the complete comprehensive analysis of the joint results from all centers is yet to come.

HCM is a disease of a younger age, as it is often first diagnosed before the age of 40¹⁸. In our study, the patients were older with mean age of 60 years. Patients in our study were predominantly male, which is consistent with gender distribution across literature, where about two-thirds of HCM patients are male¹⁹.

The majority of patients included in the study belonged to NYHA functional class II, with most common symptoms being fatigue, dyspnea, chest pain and palpitations. These patients' characteristics are consistent with generally determined outlines of the common HCM presentation².

Although morphological characteristics of the LV determined by echocardiography did not change after 4 months of follow-up in both intervention and control

group, some interesting changes in exercise capacity measured by CPET were recorded. Peak oxygen consumption increased significantly from 14.4 to 16.4 ml/kg/min in the intervention group. This result is similar to the effect of sacubitril/valsartan treatment in patients heart failure, where VO₂ increased by 2.4 ml/kg/min after 6 months of follow-up²⁰. Ventilatory efficiency was estimated using the relationship between minute ventilation and carbon dioxide production (VE/VCO₂). This index has proven to be a reliable predictor of cardiac mortality and cardiac-related hospitalizations in patients with heart failure, with particularly elevated risk in patients with VE/VCO₂ value ≥ 34 ²¹. In our population the mean VE/VCO₂ was below 34 in both groups, however the interesting finding is the significant difference in this parameter established after 4 months of sacubitril/valsartan treatment compared to the control group.

The design of the study has a few limitations to be considered, in particular the short treatment period. Preliminary data about expectable treatment effects of sacubitril/valsartan in patients with nonobstructive HCM is missing to date. The sample size of this trial was considered sufficient to get robust effect estimates in regard to the efficacy and safety of the study treatments. Participants undergo study treatment for 4 months, which was deemed sufficient to observe potentially beneficial effects of the complementary addition of sacubitril/valsartan to the optimal standard therapy of HCM. Comparable treatment durations with sacubitril/valsartan were previously shown to significantly reduce NT-proBNP in patients with heart failure with preserved ejection fraction²² and to improve cardiac function in the case report of a patient with HCM [23]. Due to the above-mentioned limitations, the results of our trial may have to be interpreted with caution. However, they may pave the way for future clinical trials on patients with nonobstructive HCM.

Conclusion

The results of the present study suggest that, despite the relatively short treatment period of 4 months, sacubitril/valsartan treatment can have positive effects functional capacity in patients with HCM. These results, together with the rest of the SILICOFCM study outcomes, will hopefully contribute to the optimization of the HCM management.

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Sažetak

Hipertrofična miokardiopatija: mogućnosti novih lekova

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Uvod. Hipertrofična kardiomiopatija (HCM) je najčešća nasledna kardiovaskularna bolest koja pogađa približno jednog od 500 ljudi. HCM je genetski poremećaj koji je najčešće uzrokovan mutacijama koje uključuju protein C koji veže miozin (MIBPC3) i β -miozin teški lanac (MIH7), a koji su odgovorni za približno tri četvrtine identifikovanih mutacija.

Cilj. Do sada nije pouzdano pokazano da su bilo koji lekovi zaustavili ili preokrenuo napredovanje HCM-a ili ublažili njegove simptome. Iako se pokazalo da inhibitor neprilisin receptora za angiotenzin sakubitril / valsartan smanjuje smrtnost i hospitalizaciju kod srčane insuficijencije sa smanjenom ejekcionom frakcijom, podaci o njegovom uticaju na HCM su retki. Naš cilj je bio da istražimo efekat sakubitril / valsartana na toleranciju napora (tj. maksimalnu potrošnju kiseonika) kod pacijenata sa neopstruktivnom HCM u poređenju sa optimalnom standardnom terapijom (kontrolna grupa).

Metode. Prikazana studija deo je SILICOFCM - prospektivnog, multicentričnog, otvorenog, randomiziranog, kontrolisanog, kliničkog ispitivanja sa tri dela (NCT03832660) koje će regrutovati 240 odraslih pacijenata sa potvrđenom dijagnozom neopstruktivne HCM-a. Ova studija je obuhvatila 41 pacijenta iz jednog centra. Pacijenti koji ispunjavaju uslove randomizirani su na primenu sakubitril / valsartana ili same optimalne standardne terapije (kontrolna grupa). Primarni krajnji cilj je bila promena funkcionalnog kapaciteta (tj. maksimalna potrošnja kiseonika).

Rezultati. Studija je obuhvatila 41 pacijenta koji su bili podeljeni u interventnu (29 pacijenata) i kontrolnu grupu (12 pacijenata). Prosečna starost je iznosila 60.0 ± 10.4 godina, a većina pacijenata je bila muškog pola (73.2%). Debljina zida leve komore iznosila je 17.3 ± 4.3 mm na interventrikularnom septumu i 15.6 ± 3.5 mm na posterolateralnom zidu. Početni vršni VO_2 bio je 14.0 ± 4.4 ml/kg/min a VE/VCO_2 28.1 ± 6.4 . Nakon 4 meseca, u interventnoj grupi došlo je do porasta VO_2 sa 14.4 ml/kg/min na 16.4 ml/kg/min ($p=0.016$). Vrednost VE/VCO_2 smanjila se sa 26.6 na 25.8 u interventnoj grupi, dok se u kontrolnoj grupi promenila sa 26.0 na 30.9. Vrednost VE/VCO_2 nakon 4 meseca bila je značajno niža u interventnoj grupi (25.8 ± 5.3 vs 30.9 ± 4.9 ; $p=0.050$).

Zaključak. Rezultati ove studije sugerišu da, uprkos relativno kratkom periodu lečenja od 4 meseca, lečenje sakubitril / valsartanom može imati pozitivne efekte na funkcionalni kapacitet kod pacijenata sa HCM. Očekujemo da će ovi nalazi, zajedno sa ostalim SILICOFCM rezultatima, doprineti optimizaciji terapije HCM.

Key words: hipertrofična miokardiopatija, sakubitril/valsartan, tolerancija fizičkog napora