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RESEARCH HIGHLIGHT

Modulating energy metabolism to treat non-obstructive hypertrophic cardiomyopathy? Insights from IMPROVE-HCM

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease worldwide and may present with or without dynamic left ventricular outflow tract obstruction (LVOTO). Significant advances have been made in the management of obstructive HCM. On the other hand, despite their significant symptomatic burden, patients with non-obstructive HCM (nHCM) (i.e., without LVOTO) still do not have evidence-based therapeutical options. The recent IMPROVE-HCM study, a phase 2 randomized, double-blinded trial, aims to place a first step in filling this gap in knowledge. The study assessed the safety (primary endpoint) and efficacy (secondary endpoint) of ninerafaxstat, a novel cardiac mitotrope drug that increases adenosine triphosphate production. We highlighted the main findings of the trial, contextualizing these results within the larger landscape of completed and ongoing trials in nHCM.

Keywords Non-obstructive HCM · Ninerafaxstat · IMPROVE-HCM trial

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease worldwide with a prevalence ranging from 1:500 to 1:200 in the general population [1, 2]. Pharmacological and interventional therapeutic options for HCM with dynamic left ventricular outflow tract obstruction (LVOTO), referred to as obstructive HCM (oHCM), are now available: beta-blockers or calcium channel blockers (diltiazem or verapamil), disopyramide, mavacamten (a selective, allosteric, reversible cardiac myosin inhibitor), and myectomy or alcohol septal ablation [3–6]. Up to 40% of patients with non-obstructive HCM (nHCM) and preserved left ventricular ejection fraction (LVEF) have significant symptoms such as fatigue, angina, dyspnoea on exertion, or limitation of exercise capacity mainly attributed to microvascular ischemia or diastolic dysfunction [7]. Despite this, no evidence-based drugs have been demonstrated to improve symptoms, quality of life, or exercise capacity in symptomatic patients with nHCM. Possibly, this is because drugs tested so far do not directly act on the pathophysiological mechanisms of the disease [8], including the energy-deplete condition of the cardiomyocytes caused by alterations in sarcomeric function [9]. Metabolic derangements in the myocardium of patients with HCM have been well characterized. Myocardial contraction is critically dependent on energy metabolism, and cardiac diastolic function, particularly myocardial relaxation, can be adversely impacted as well. Impaired LV diastolic relaxation with the inability to increase stroke volume during exercise is a major determinant of heart failure (HF) symptoms and impaired functional capacity for HCM patients.

Thus, myocardial energetics are an attractive target for the treatment of nHCM. Mitotropes are positive inotropic drugs that can improve the efficiency of mitochondrial energy production by stabilizing the inner mitochondrial membrane or by shifting cardiac energy metabolism from free fatty acid oxidation to more efficient energy sources (e.g., glucose oxidation) [10]. In a randomized, double-blind, placebo-controlled, phase 2 trial (METAL-HCM trial, NCT00500552), enrolling a small cohort of patients with symptomatic exercise limitation caused by nHCM ($n=46$), the mitotrope perhexiline, a potent inhibitor of

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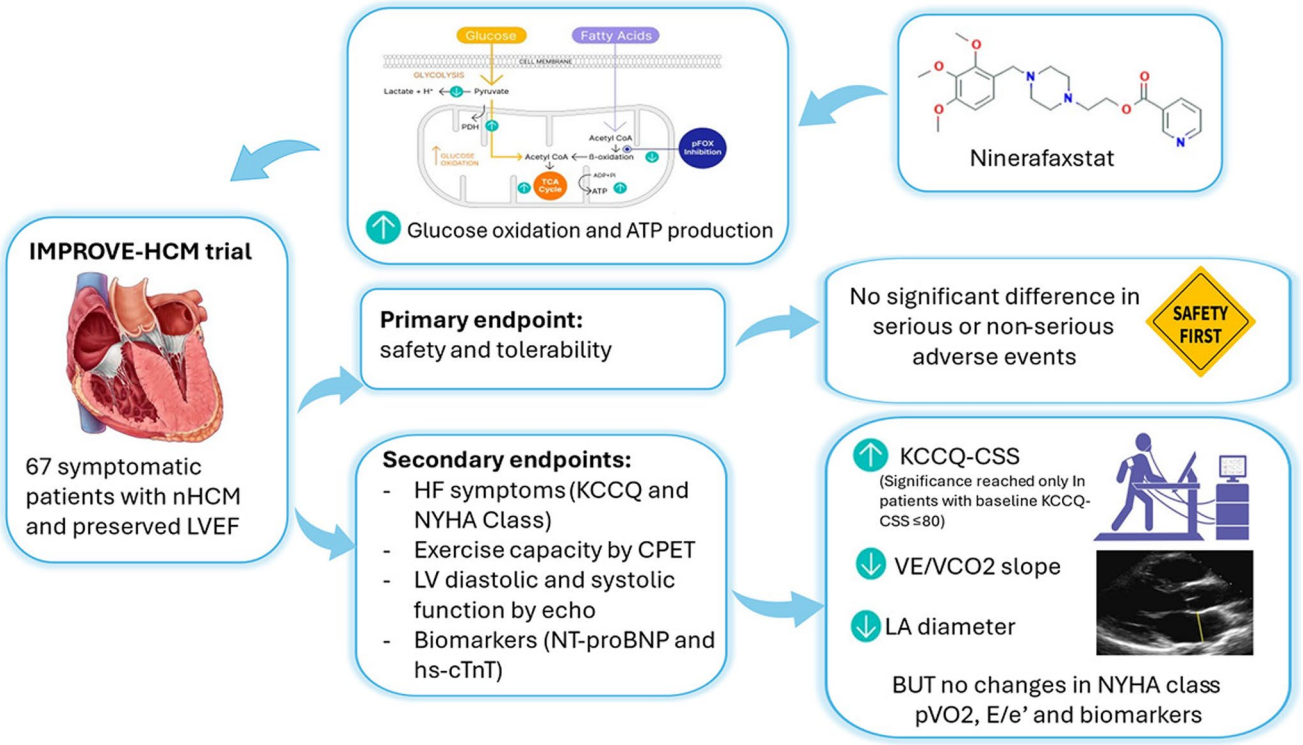

Fig. 1 Mechanism of action and potential benefits of ninerafaxstat in patients with nHCM. ATP, adenosine triphosphate production; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; hs-cTnT, high-sensitivity cardiac troponin test; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; nHCM, non-obstructive hypertrophic cardiomyopathy; NYHA Class, New York Heart Association Class; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO_2, peak oxygen consumption; VE/VCO_2, ventilation/carbon dioxide production slope

carnitine palmitoyltransferase-1 enzyme which controls access of long chain fatty acids to the mitochondrial site of beta-oxidation, improved exercise capacity and diastolic function [11]. The metabolic modulator trimetazidine dihydrochloride (TMZ) was tested in a further study but did not result in significant improvement in exercise capacity [12].

Ninerafaxstat is a novel cardiac mitotrope pro-drug that partially inhibits fatty acid oxidation through direct competitive inhibition of 3-ketoacyl-CoA thiolase. This induces an increase in adenosine triphosphate production through increased glucose oxidation, as demonstrated in phase 2a trial using magnetic resonance imaging spectroscopy (Fig. 1) [13]. Maron and colleagues have recently reported the results of the IMPROVE-HCM trial, a phase 2 randomized, double-blinded, multicenter, placebo-controlled trial enrolling 67 patients with nHCM, preserved LVEF, and exercise limitation (i.e., defined as peak oxygen consumption [pVO2] < 80% than predicted based on age and gender) [14]. Patients were randomized in a 1:1 ratio to receive ninerafaxstat or placebo and underwent assessment by Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), cardiopulmonary exercise testing (CPET), echocardiography, and biomarkers at baseline and after a treatment period of 12 weeks. Patients had a mean age of 57 years. There was an underrepresentation of Asian and Black race (only 10.5%). Interestingly, many patients were overweight or obese (mean body mass index [BMI] 32.1 ± 6.1 kg/m^2). Overall, 91% of the patients were already on calcium channel blockers or beta-blockers. The primary endpoint was the incidence and severity of adverse events (AEs), and the secondary endpoints were changes in CPET and echocardiography parameters, symptoms, KCCQ-CSS score, and biomarkers. There was no significant difference in serious or non-serious AEs between the two arms, although the rate of non-serious AEs (such as nausea, headache, hypokalemia, chest discomfort, and fatigue) was numerically higher in the ninerafaxstat arm. No significant differences were found in symptoms (New York Heart Association (NYHA) class), and KCCQ-CSS score changes. Notably, a slight improvement in KCCQ-CSS was observed in both study arms. This is in line with previous studies and may be related to the closer follow-up and placebo effect [15, 16]. Importantly, in a post hoc analysis considering only patients most limited by heart failure symptoms (baseline KCCQ-CSS ≤ 80), patients on the ninerafaxstat arm showed a significantly greater mean improvement in KCCQ-CSS as compared to placebo (9.3 points; 95% CI, 0.2 to 18.5; $p = 0.04$) [14]. In the whole population, the ventilation/carbon dioxide production slope showed a statistically significant improvement with ninerafaxstat as compared to placebo; these results were confirmed in the subgroup of patients

Table 1 Major completed or ongoing trials in symptomatic nHCM patients

Name (ID)	Intervention/treatment	Population	Study type	Primary endpoint	Results
MAVERICK-HCM (NCT03442764)	Mavacamten vs. placebo	59 patients	Phase 2; multicenter, double-blind, randomized, dose-ranging, placebo-controlled	Safety and tolerability	Safe; significant reduction in NT-proBNP and troponin
ODYSSEY-HCM (NCT05582395)	Mavacamten vs. placebo	420 patients	Phase 3; randomized, double-blind, placebo-controlled	Change in KCCQ-23 CSS and VO_2 max from baseline to week 48	Recruiting
ACACIA-HCM (NCT06081894)	Aficamten vs. placebo	420 patients	Phase 3; randomized, double-blind, placebo-controlled	Change in KCCQ-CSS from baseline to week 36	Recruiting
FORTITUDE-HCM	Ninerafaxstat	–	Phase 3	–	Future study
TEMPO II (NCT05569382)	Bisoprolol vs. verapamil vs. placebo	100 patients	Phase 4; multicenter, double-blinded, randomized, placebo-controlled, cross-over	Change in NSVT, LVEDV and VO_2 max	Recruiting
MyPEAK-1 (NCT05836259)	Genetic TN-201, a recombinant adeno-associated virus serotype 9 (AAV9) containing myosin binding protein C transgene	6-15 patients with MYBPC3 mutation-associated nHCM	Phase 1; first-in-human, non-randomized, open-label	Safety, tolerability and dose-finding	Recruiting
EXCITE-HCM (NCT05818605)	Moderate intensity exercise training vs. usual physical activity	70 patients	Randomized, controlled, blinded	Change VO_2 max from baseline to week 24	Recruiting
NCT04164732	Sacubitril/valsartan vs. placebo	46 patients	Phase 2; multicenter, randomized, double-blinded, placebo-controlled	VO_2 max from baseline to week 50	Completed (no results posted)
NCT06401343	Empagliflozin vs. placebo	94 patients	Phase 4; a prospective, multicenter, open-label, randomized, controlled	VO_2 max from baseline to 12 months	Recruiting

LVEDV left ventricular end-diastolic volume, *NSVT* non-sustained ventricular tachycardia, nHCM non-obstructive hypertrophic cardiomyopathy, *VO_2 max* maximal oxygen consumption

with more advanced symptoms (NYHA class III at baseline or baseline KCCQ-CSS ≤ 80). On the other hand, no significant difference was found in peak oxygen consumption. Even though it was not statistically significant, a decrease in LVEF was observed. As for parameters related to diastolic dysfunction, a significant reduction of 2 mm (95% CI − 3 to + 1; $p = 0.01$) in LA diameter was reported, while no significant difference was found between the two groups in the *E*/*e*′ ratio (with just a trend towards reduction in the ninerafaxstat arm). No significant reduction was found for both troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values.

Overall, this small study showed the safety and tolerability of this new mitotrope drug ninerafaxstat over the short term, paving the way to larger phase 3 studies. The efficacy results, particularly in the subgroups with more advanced symptoms, seem promising but should be interpreted with caution. Indeed, ninerafaxstat therapy was associated with positive changes in quality of life and exercise capacity. However, other objective markers of HF severity like NT-proBNP did not improve significantly. Furthermore, no improvement in *E*/*e*′ was found, while it was expected based on the mechanism of action and as the first step toward improvement in exercise capacity or symptoms. A potential extracardiac effect of the intervention that primarily drives improvement in functional capacity cannot be excluded. Also, the trend toward the reduction of LVEF requires further investigation. Finally, given the lack of heterogeneity in the sample, it will be interesting to see in phase 3 studies how ninerafaxstat behaves in patients with normal/low BMI or with different ethnicities. Further studies are also needed to explore if the modulation of disease mechanisms translates into positive effects on wall thickness and ventricular fibrosis. We may also consider that ninerafaxstat is a positive inotropic drug and might therefore increase the risk of developing LVOTO. Despite these possible study limitations, ninerafaxstat has the potential to emerge as a new safe and well-tolerated second-line option to improve HF symptoms and functional capacity in patients affected by nHCM and with preserved LVEF.

In conclusion, the results of the IMPROVE-HCM study support the initiation of the phase 3 FORTITUDE-HCM clinical trial of ninerafaxstat in patients with symptomatic nHCM. Several studies with further drugs (i.e., mavacamten and aficamten) are ongoing (Table 1) and might support, in the future, the efficacy of drugs that act directly on pathophysiological mechanisms in this population. The efficacy of drugs approved for the treatment of HF in patients with nHCM is currently scarce, being nHCM often among the exclusion criteria of major HF trials. Both sacubitril/valsartan and sodium-glucose co-transporter 2 inhibitors are being studied in dedicated trials for nHCM (Table 1). Also, genetic therapy may represent an opportunity in the next years.

A few considerations for the design of future trials should be included. Most of the trials leading to changes in guidelines have been based on the composite primary endpoint of cardiovascular (CV) death and hospitalization for HF and have enrolled thousands of patients, which is not achievable in nHCM trials. This endpoint now can be expanded to include outpatient worsening HF events [17]. More recently, patient-related outcome measures (PROMs) have been included to boost the number of events and the power to detect differences. Importantly, the improvement in quality of life, assessed by KCCQ, needs to be correlated with the objective improvements in functional capacity, by means of VO_2, which has been traditionally used as an endpoint in HCM. Other surrogate endpoints, like biomarkers, may be included as well. Repeated assessment with cardiac magnetic resonance imaging could allow the identification of structural and functional changes (i.e., the degree of myocardial fibrosis, LV systolic and diastolic function) following treatment with disease-modifying drugs in nHCM.

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Declarations

Conflict of interest D.T. received speaker fees from Alnylam, AstraZeneca, Boehringer Ingelheim, Pfizer and Roche Diagnostics, outside the present work. A.A. received grants from Pfizer and Eidos, outside the present work. Other authors have nothing to declare.

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