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Perspective

Hypertrophic cardiomyopathy: current understanding and emerging therapeutics

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Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiovascular diseases, with a global prevalence estimated at 0.2% to 0.5%.[1] It is characterized by left ventricular hypertrophy which could not be explained by abnormal loading conditions, and a considerable proportion of patients were accompanied by either resting or inducible left ventricular outflow tract (LVOT) obstruction, leading to impaired cardiac function, mitral regurgitation due to systolic anterior motion (SAM) condition, with subsequent reduced quality of life, adverse clinical outcomes or even sudden death (Supplementary Text 1 online).[2] HCM was previously believed to exhibit an autosomal dominant inheritance pattern, typically caused by pathogenic mutations in genes encoding sarcomeric proteins, with *MYBPC3* and *MYH7* being the most commonly involved genes.[3] However, about 60% of all patients test negative for sarcomeric variants,[4] suggesting a possible polygenic inheritance pattern in these patients and the contribution of non-genetic factors on disease phenotype (Supplementary Text 2 online).[5] These missing causal genes may potentially be identified in the future with the assistance of rapidly advancing artificial intelligence models, such as AlphaFold 3.[6]

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Currently, the medical treatment of HCM is primarily limited to non-specific drugs, including heart rate-slowing and negatively inotropic agents such as β-blockers, non-dihydropyridine calcium channel blockers, and disopyramide, along with invasive septal reduction therapy (SRT), primarily in the form of surgical myectomy and transcatheter alcohol septal ablation.[7–9] β-blockers remain the cornerstone of HCM management, alleviating symptoms by reducing heart rate, myocardial oxygen demand, and contractility. Similarly, non-dihydropyridine calcium channel blockers enhance myocardial relaxation and improve exercise tolerance. However, neither class reverses myocardial hypertrophy or slows disease progression. Side effects, including fatigue, bradycardia, and hypotension, often impact patient adherence. Additionally, calcium channel blockers may worsen hemodynamics in patients with severe outflow tract obstruction, limiting their use in certain subgroups. Recently, several minimally invasive SRT procedures, such as the transapical beating-heart septal myectomy technique and percutaneous intramyocardial septal radiofrequency ablation, have been applied with promising initial results (Fig. 1).[10,11] While these treatments may alleviate symptoms in HCM patients to some extent, their impact on preventing the myocardial pathology and altering disease

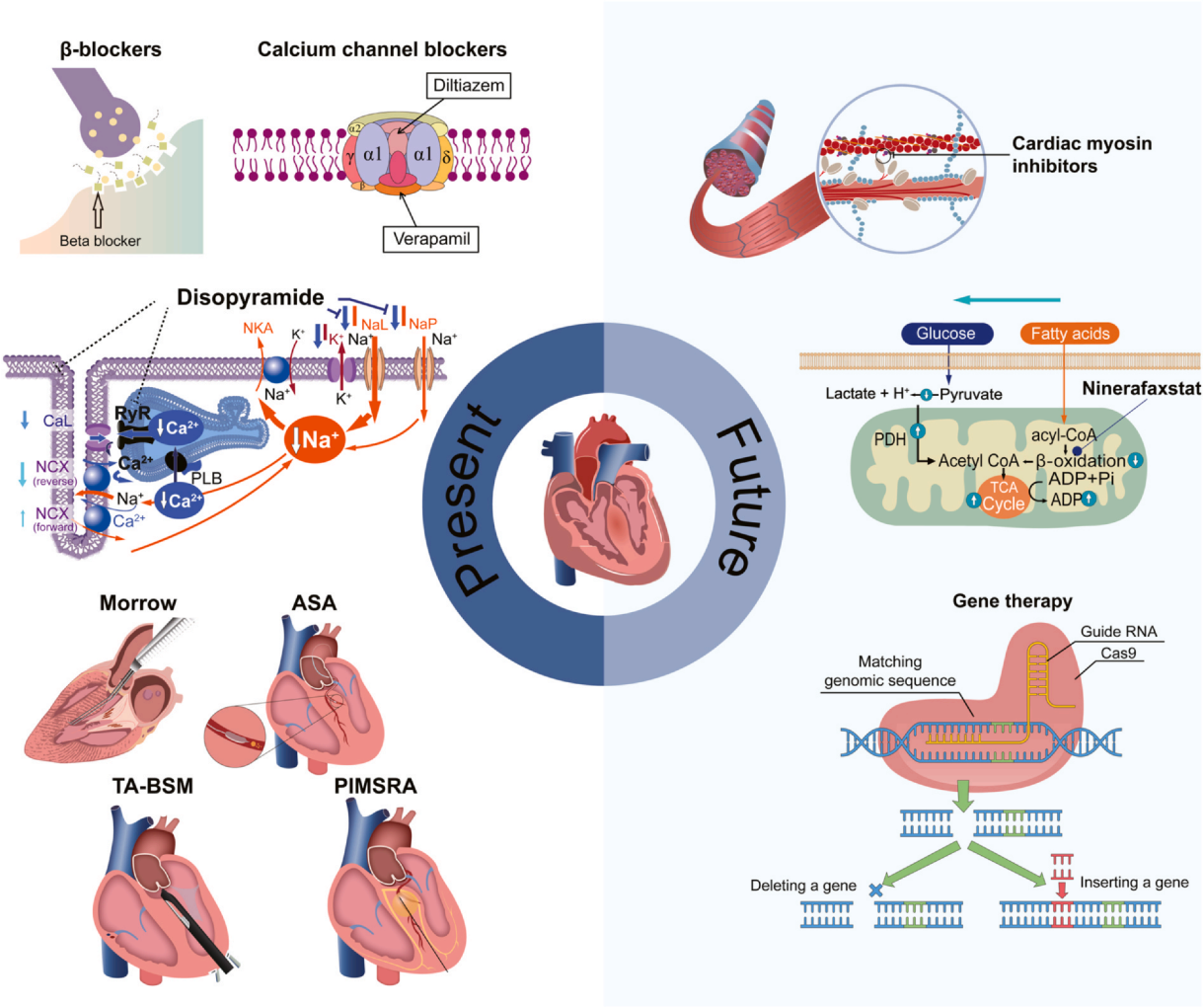

Fig. 1. Comparison of current and future treatment approaches for HCM. This figure illustrates the existing therapeutic strategies (labeled "Present") for HCM, including pharmacological treatments, interventional therapies, and surgical options. Future treatment modalities (labeled "Future") encompass emerging therapies, such as novel pharmacological agents and gene editing techniques. ASA: alcohol septal ablation; TA-BSM: transapical beating-heart septal myectomy; HCM: hypertrophic cardiomyopathy; PIMSRA: percutaneous intramyocardial septal radiofrequency ablation; TA-BSM: transapical beating-heart septal myectomy.

progression may still be limited. Additionally, the first-line treatments currently recommended by guidelines especially SRT are not supported by large-scale randomized clinical trials, and clinical practice recommendations are based on observational studies and expert opinion (Class I, Level B-NR) (Supplementary Text 3 online). Moreover, effective treatment options are lacking for approximately 30% of HCM patients with non-obstructive HCM (nHCM), and no approved therapies specifically target the underlying mechanisms of this subgroup. Invasive surgical myectomy also carries inherent risks of complications, and may not be suitable for patients with severe comorbidities or frailty. Minimally invasive SRT has limitations regarding myocardial regression after the procedure. Also, optimal procedural techniques are limited to a few centers of excellence, restricting widespread access to SRT for eligible oHCM patients (Supplementary Text 3 online).

Conventional therapies for HCM focus on symptom relief but fail to address the disease's underlying molecular causes, such as sarcomeric dysfunction and energy deficits. Emerging therapies, like myosin inhibitors and metabolic modulators, offer targeted mechanisms to alleviate hypercontractility and improve myocardial efficiency. This shift from symptom-based management to molecular precision represents a significant advancement, addressing the limitations of conventional treatments while potentially altering disease progression.

A deeper understanding of the key molecular pathways involved in the pathogenesis of HCM offers the opportunity to develop and test new therapies targeting genetic variants or downstream signaling pathways (Supplementary Text 4 online). Sarcomeres containing mutant proteins typically exhibit impaired calcium-dependent actin-myosin cross-bridge cycling, altered Ca^{2+} sensitivity of the troponin complex, and compromised force generation. Pathogenic mutations shift the balance of myosin molecules from the super-relaxed state to an actin-bound state, increasing the number of myosin molecules interacting with actin, thereby enhancing cardiomyocyte contractility and ATP utilization. Mutations in thin filament proteins increase the Ca^{2+} sensitivity of myofibrillar ATPase activity and enhance maximal force production. In HCM, the augmented ATPase activity and increased ATP utilization elevate adenosine diphosphate levels, which in turn reduce nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, leading to heightened oxidative stress and accumulation of reactive oxygen species (ROS). Additionally, the increased calcium sensitivity of the myofilaments reduces the availability of calcium for activating the Krebs cycle, thereby impairing nicotinamide adenine dinucleotide regeneration and contributing to the energy metabolism deficits observed in HCM patients (Supplementary Text 4 online).[12] These alterations in biological functions underlie the pathophysiological manifestations of hypercontractility, impaired relaxation, and increased energy consumption in the cardiomyocytes of HCM patients. This review will focus on recent advancements in disease-specific therapeutic agents targeting the pathophysiology of HCM, including the novel cardiac myosin inhibitor mavacamten, recently recommended as a second-line treatment for obstructive HCM (oHCM) patients by European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines,[13] the second-generation myosin inhibitor aficamten currently undergoing clinical trials,[14] and the novel cardiac mitotrope agent ninerafaxstat, which targets mitochondrial energy homeostasis (Fig. 1).[15]

Mavacamten: a first-in-class cardiac myosin inhibitor: Beta-cardiac myosin heavy chain (β-MHC) is the primary thick filament protein responsible for generating contractile force through cross-bridge formation with actin thin filaments.[3] Sarcomeric mutations disrupt the balance between the energy-saving super-relaxed (SRX) and disordered-relaxed (DRX) states, resulting in more myosin heads forming cross-bridges with actin and fewer myosin molecules in the energy-saving SRX state, leading to increased myocardial contractility with subsequent hypertrophy (Supplementary Text 5 online). Mavacamten is the first cardiac myosin adenosine triphosphatase (ATPase) inhibitor, which reduces actin-myosin cross-bridge formation, thereby decreasing myocardial contractility and improving myocardial energetics.[16] In preclinical mouse models, mavacamten was shown to reduce ATPase activity, myocardial tension, and fractional shortening in a dose-dependent manner.[13] Phase 1 trial results indicated that the drug is readily absorbed and extensively metabolized, primarily through cytochrome P450 enzymes CYP2C19 and CYP3A4, with a half-life of 7–9 d. The PIONEER-HCM (NCT02842242) Phase 2 open-label, proof-of-concept, and safety trial, which administered varying doses of mavacamten to two small cohorts of oHCM patients over 12 weeks, demonstrated a reduction in post-exercise LVOT gradient and improvements in exercise capacity and symptoms. Subsequently, the EXPLORER-HCM (NCT03470545) Phase 3

randomized, double-blind, placebo-controlled trial enrolled 251 symptomatic (New York Heart Association (NYHA) Class II/III) oHCM patients with left ventricular ejection fraction (LVEF) > 55%. After 30 weeks, mavacamten significantly reduced LVOT gradient, improved exercise capacity, and decreased serum NT-proBNP and troponin I levels compared to placebo. In 27% of mavacamten-treated patients, the LVOT gradient decreased to < 30 mmHg (1 mmHg = 0.133 kPa), with improvement to NYHA Class I. The incidence of treatment-related adverse events was similar between the mavacamten and placebo groups (8.1% vs. 8.6%), with transient left ventricular systolic dysfunction resolving after temporary drug discontinuation. The MAVA-LTE (NCT03723655) long-term extension study of 231 patients (95%) who completed EXPLORER-HCM showed that at 48 weeks, mavacamten demonstrated clinically meaningful and sustained improvements in LVOT gradient, NT-proBNP levels, and NYHA functional class, with good tolerability. The VALOR-HCM (NCT04349072) Phase 3 randomized, double-blind, placebo-controlled trial enrolled 112 oHCM patients referred for septal reduction therapy (SRT) due to refractory symptoms, showing that mavacamten significantly reduced the proportion of patients who underwent SRT or remained eligible according to guidelines at 16 and 32 weeks (Supplementary Text 5 online). These clinical trials demonstrated the efficacy and relative safety of mavacamten in oHCM patients receiving standard background therapy. Mavacamten improves exercise capacity, LVOT obstruction, NYHA functional class, and health status in symptomatic oHCM patients and reduces the need for SRT. Regarding safety, patients with LVEF < 50% during mavacamten treatment require temporary or permanent drug discontinuation. Based on these findings, the latest ESC and AHA/ACC guidelines recommend considering mavacamten as a second-line therapy for oHCM patients who are refractory or intolerant to first-line treatments such as β-blockers or non-dihydropyridine calcium channel blockers (Class I, Level B-R).[7,8]

Beyond oHCM, two other populations under investigation are HCM patients without resting or provocable LVOT obstruction (nHCM) and those with heart failure with preserved ejection fraction (HFpEF). MAVERICK-HCM (NCT03442764), a Phase 2 randomized, dose-ranging trial in symptomatic (NYHA Class II/III) nHCM patients, showed that 16 weeks of mavacamten treatment was associated with significant reductions in NT-proBNP and cTnI levels compared to placebo, with most subjects tolerating the drug well, suggesting potential benefits for nHCM patients. These findings establish a foundation for subsequent research on mavacamten within this patient population (Supplementary Text 5 online). EMBARK-HFpEF (NCT04766892), an exploratory, open-label, proof-of-concept Phase 2 trial, assessed the effects of mavacamten in patients with HFpEF and LVEF of 60% or more. After 26 weeks, mavacamten reduced heart stress and injury markers like NTproBNP, hsTnT, and hsTnI, with no sustained reductions in LVEF observed. About 42% showed improved symptoms, and heart function markers improved, indicating potential benefits of mavacamten for HFpEF patients (Supplementary Text 6 online).

Aficamten: a second-generation myosin inhibitor: Aficamten is a next-generation small molecule selective cardiac myosin inhibitor with a shorter half-life (3–4 d) compared to mavacamten, allowing for more rapid dose titration and drug washout, and with fewer interactions with cytochrome P450 isoenzymes.[14] A Phase 1 dose-escalation study in healthy subjects demonstrated that aficamten was well tolerated with LVEF reduction in a concentration-dependent manner. REDWOOD-HCM (NCT04219826) is a Phase 2 randomized, dose-finding trial that includes four different patient cohorts. The first two cohorts (n = 41) randomized patients receiving background first-line therapy (beta-blocker or calcium-channel blocker) to low- and high-dose aficamten groups, showing significant dose-dependent reductions in resting and Valsalva-provoked LVOT gradients after 10 weeks of treatment, with improvements in biomarkers and symptoms, and the drug appeared safe and well-tolerated. The third cohort included patients receiving background first-line therapy with disopyramide (n = 13), where adding aficamten showed significant benefits in reducing LVOT gradients and improving NYHA functional class. The final cohort included non-obstructive HCM patients (n = 41), where after 10 weeks of aficamten treatment, patients showed improvements in functional class, symptoms, and NT-proBNP and high-sensitivity cardiac troponin I levels, with apparent good safety. Thirty-four patients who completed REDWOOD-HCM Cohort 4 participated in FOREST-HCM (NCT04848506), an ongoing open-label extension trial, where after 36 weeks of aficamten treatment, most patients demonstrated sustained improvements in functional class, health status, and NT-proBNP levels, with apparent good safety and tolerability. In the large-scale SEQUOIA-HCM (NCT05186818) Phase 3 trial, 282 symptomatic oHCM patients were

randomized to aficamten or placebo, and aficamten improved exercise capacity (peak oxygen uptake) over 24 weeks compared to placebo. By Week 12, improvements in LVOT pressure gradient, health status, and symptoms were significantly greater, with similar rates of adverse events (Supplementary Text 7 online).

Myosin inhibitors offer a promising addition to the therapeutic options for HCM. For oHCM, therapies such as mavacamten and aficamten effectively reduce LVOT gradients and improve symptoms like dyspnea and fatigue. Clinical trials such as EXPLORER-HCM and SEQUOIA-HCM support these findings. However, in nHCM, evidence is limited. The MAVERICK-HCM trial showed that mavacamten reduced biomarkers like NT-proBNP but had a less pronounced impact on clinical symptoms. And a small cohort of the REDWOOD-HCM trial showed that aficamten improved both clinical symptoms and biomarkers in nHCM patients. Despite these benefits, myosin inhibitors carry the risk of inducing systolic dysfunction and reducing LVEF, necessitating frequent echocardiographic monitoring. The long-term safety and efficacy of these drugs remain undetermined on a large scale, and a diminished treatment response has been observed in some patients. Furthermore, their safety and effectiveness in non-Caucasian populations and children are yet to be established. These issues represent key areas for future research. Additionally, the cost of these agents is significantly higher compared to current first-line treatments (Supplementary Text 8 online). Mavacamten is currently priced at around $75,000 per year, which exceeds the typical cost-effectiveness threshold of $150,000 per quality-adjusted life year (QALY) suggested by the Institute for Clinical and Economic Review (ICER). In low-income regions, the high cost, along with the need for specialized monitoring, may limit accessibility (Supplementary Table 1 online). To address these challenges, there is a call for price reductions, generic options, or subsidized models to make the treatment more affordable and available globally.

Ninerafaxstat: a novel cardiac mitotrope agent: Ninerafaxstat is a novel cardiac mitotrope agent targeting mitochondrial energy homeostasis. It specifically targets 3-KAT, the last enzyme in the mitochondrial long-chain fatty acid beta-oxidation pathway. This inhibition redirects the heart's energy metabolism from fatty acid oxidation to glucose oxidation, which is more efficient and consumes less oxygen per mole of adenosine triphosphate (ATP) produced. Specifically, ninerafaxstat helps to restore a more efficient metabolic state by decreasing oxidative stress and ROS, which are elevated in HCM due to mitochondrial dysfunction. By improving the energy-deficient state in HCM patients, ninerafaxstat can improve symptoms such as exercise intolerance, fatigue, and heart failure, especially in those with nHCM (Supplementary Text 9 online). In the IMPROVE-HCM (NCT04826185) Phase 2 proof-of-concept study, 67 patients with nHCM were randomized to receive either ninerafaxstat (200 mg twice daily) or placebo for 12 weeks. Ninerafaxstat was associated with improved exercise capacity, ventilatory efficiency, health status in subgroups with baseline abnormalities, and reduced left atrial size, with good safety and tolerability.[15] Compared to myosin inhibitors, treatment with ninerafaxstat can improve the functional capacity of nHCM patients and appears not to affect LVEF, thereby avoiding adverse hemodynamic effects. More extensive clinical trials are needed to further evaluate its safety and efficacy specifically in HCM patients.

Patients with certain genetic backgrounds, particularly those with mutations in *MYBPC3* or *MYH7*, often experience more severe disease and may benefit most from targeted therapies like mavacamten or aficamten. Additionally, patients with advanced symptoms (NYHA Class II/III) and those with nHCM may also be prioritized for molecular therapies, including metabolic modulators like ninerafaxstat. The integration of polygenic risk scores and clinical factors such as atrial fibrillation or increased LV stiffness can further guide therapy selection.

Recent advancements in understanding the pathophysiology of HCM have paved the way for novel therapies targeting the underlying mechanisms of the disease. Mavacamten, the first approved cardiac myosin inhibitor, has demonstrated significant efficacy in reducing LVOT obstruction and improving symptoms in oHCM patients. Aficamten, a next-generation myosin inhibitor, offers additional benefits with a shorter half-life and fewer drug interactions. Ninerafaxstat, a novel cardiac mitotrope agent, presents a promising new approach to enhancing cardiac mitochondrial function in HCM patients. These

emerging therapeutics represent a significant step forward in the management of HCM, offering new hope for patients and potentially altering the course of the disease. Multidisciplinary treatment, combining novel pharmacotherapies with SRT, represents the future direction in managing HCM. Further research and clinical trials are needed to fully establish their long-term efficacy and safety in diverse patient populations.

CRediT authorship contribution statement

Jia-Qi Dai: Writing original draft, Funding acquisition, Data curation. **Da Zhu:** Writing review & editing, Visualization, Supervision, Funding acquisition. **Maurizio Taramasso:** Visualization, Writing review & editing. **Xiang-Bin Pan:** Writing review & editing, Validation, Funding acquisition, Conceptualization. **Dao-Wen Wang:** Writing review & editing, Validation, Conceptualization.

Declaration of competing interest

Xiang-Bin Pan is an editorial board member for *Medicine Plus* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.medp.2025.100073.

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