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REVIEW

Cardiac Myosin Inhibitors in Hypertrophic Cardiomyopathy: Clinical Advances and Therapeutic Prospects

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Abstract: Hypertrophic cardiomyopathy (HCM) is a common inherited disease with substantial residual morbidity despite established pharmacological and surgical therapies. We conducted a narrative review of the current evidence on cardiac myosin inhibitors, drawing on published studies up to July 2025, including pivotal clinical trials, real-world cohorts, and pharmacokinetic analyses. Mavacamten and Aficamten consistently reduced left ventricular outflow tract (LVOT) gradients, improved New York Heart Association class, and were generally well tolerated under echocardiography-guided titration. Long-term extensions and real-world registries confirmed sustained efficacy, while pharmacogenetic factors and monitoring strategies continue to shape individualized use. Comparative analyses suggest Aficamten offers more rapid pharmacokinetics and simplified dosing, though both require careful safety surveillance. Remaining challenges include limited data in non-obstructive HCM, uncertain antifibrotic and rhythm outcomes, high cost, and the burden of frequent imaging and genetic testing. Beyond HCM, early studies are exploring broader indications and next-generation modulators. Cardiac myosin inhibition is reshaping the therapeutic landscape of HCM, but cost-effective, precision-based implementation and long-term outcome studies remain critical priorities.

Keywords: cardiac myosin inhibitors, hypertrophic cardiomyopathy, heart failure, clinical studies

Introduction

Heart failure encompasses a spectrum of cardiac disorders, among which hypertrophic cardiomyopathy (HCM) represents a distinct and common inherited disease. Epidemiologic studies estimate that asymptomatic, unexplained HCM affects approximately 1 in 500 young adults in the United States, although the true prevalence is likely higher when unrecognized cases are considered.[1]

HCM is characterized by left ventricular hypertrophy, dynamic left ventricular outflow tract obstruction (LVOTO), diastolic dysfunction, myocardial fibrosis, and arrhythmias. These pathophysiological abnormalities translate into major clinical consequences such as exercise intolerance, atrial fibrillation, progressive heart failure, and sudden cardiac death. At the molecular level, many cases are linked to sarcomere gene mutations—for example, truncating variants in MYBPC3—which dysregulate myosin function and drive hypercontractility.[2]

Conventional therapies focus on symptom relief and prevention of complications. Non-vasodilating β-blockers and non-dihydropyridine calcium channel blockers remain first-line pharmacological options, but many patients remain symptomatic. Disopyramide can reduce obstruction but is limited by anticholinergic side effects. Septal myectomy and alcohol septal ablation are effective in experienced centers but invasive and not universally accessible. Implantable cardioverter-defibrillators reduce the risk of sudden cardiac death in high-risk patients but do not alter the disease substrate.[3]

These limitations highlight an urgent unmet need for therapies that directly target the hypercontractile mechanism of HCM. Small-molecule cardiac myosin inhibitors, represented by Mavacamten and Aficamten, have recently emerged as disease-specific agents capable of reducing LVOTO and improving functional status. This review summarizes the latest

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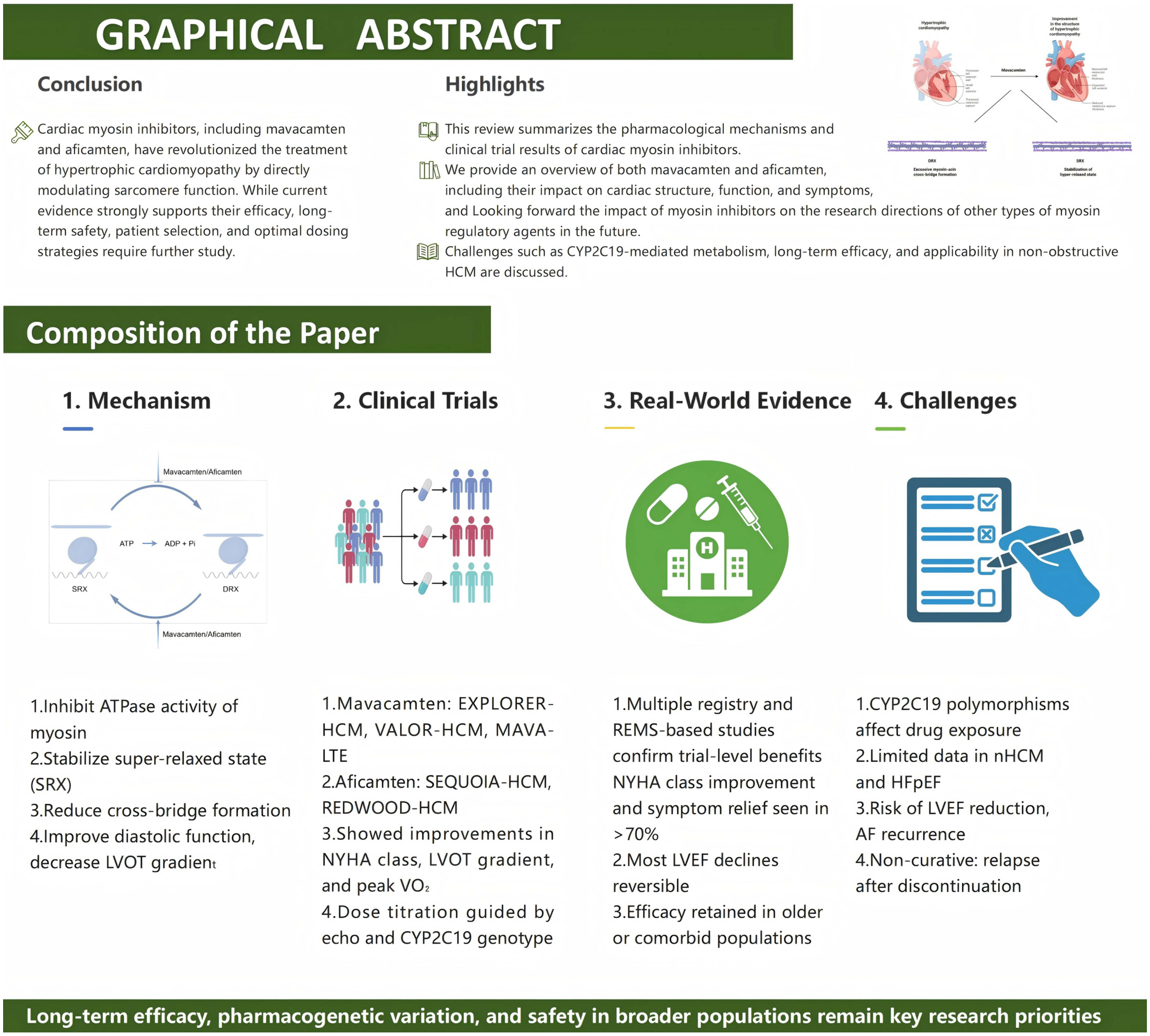
Graphical Abstract



clinical evidence, real-world data, and pharmacokinetic characteristics of these agents, and discusses their potential roles and challenges in the evolving management of HCM.[3]

Foundational Pre-Approval Studies of Mavacamten

As the only currently approved cardiac myosin inhibitor on the market, it is essential to review several of the early studies on this drug. As early as 2016, researchers developed a small molecule drug named "MYK-461". In murine and feline models, MYK-461 reduces myocardial contractility by inhibiting the ATPase activity of cardiac myosin, thereby reducing myocardial hypertrophy, This manifests as decreased myocardial contractility, suppression of ventricular hypertrophy, reduction of myocardial fibrosis, and even improvements in myocardial cell alignment and normalization of gene expression.[4] Subsequently, this compound was designated as "Mavacamten."

Early clinical data on the safety and efficacy of Mavacamten were derived from the PIONEER-HCM study, a Phase II clinical trial involving 21 symptomatic obstructive HCM patients classified as NYHA class II–III. The trial results demonstrated that Mavacamten significantly improved patients' exercise tolerance, alleviated dyspnea, and reduced left ventricular outflow tract (LVOT) obstruction. After 12 weeks of treatment, the LVOT gradient was markedly decreased from a baseline of 103 mmHg to 19 mmHg post-exercise, and peak oxygen consumption (Peak VO_2) increased by approximately 3.5 mL/kg/min.[5] The MAVERICK-HCM trial, a Phase II study targeting non-obstructive HCM patients and involving 59 participants, showed that Mavacamten significantly lowered levels of NT-proBNP and cardiac troponin I (cTnI), with favorable tolerability. These findings suggest its potential efficacy in treating non-obstructive cardiomyopathies.[6]

Subsequently, various research teams initiated Phase III clinical trials. Concurrently, due to the convenience of veterinary studies, veterinarians began exploring and attempting to apply Mavacamten in felines. The high genetic and pathophysiological similarities between feline and human HCM make novel cardiac myosin inhibitors like Mavacamten promising therapeutic options for feline hypertrophic cardiomyopathy, allowing veterinarians to become aware of the drug earlier than clinical physicians.[7]

The EXPLORER-HCM Phase III clinical trial, encompassing 251 symptomatic obstructive HCM patients, is one of the most renowned studies on Mavacamten. The trial results indicated that Mavacamten significantly reduced LVOT obstruction, improved exercise tolerance, and enhanced NYHA functional classification. Compared to the placebo group, patients treated with Mavacamten achieved significant improvements in primary endpoints, including Peak VO_2 and NYHA class. Mavacamten therapy enhanced functional capacity, symptom scores, and reduced LVOT gradients, along with lowering clinically significant biomarkers.[5] Subsequent studies further corroborated that Mavacamten not only significantly reduced LVOT pressure gradients but also improved diastolic function and cardiac structure. Compared to traditional pharmacotherapy, Mavacamten demonstrated more pronounced improvements in echocardiographically observable cardiac structure and function, particularly in alleviating mitral regurgitation and reducing cardiac volume.[8] Cardiac magnetic resonance imaging (CMR) showed improvements in left ventricular mass index (LVMI), left atrial volume index (LAVI), and maximal left ventricular wall thickness—predictors of poor prognosis in obstructive HCM patients.[9]

Another significant study, the VALOR-HCM trial, released in 2022, aimed to determine whether adding Mavacamten could obviate the need for septal reduction therapy (SRT) in severely symptomatic obstructive HCM patients. The results were impressive: the incidence of endpoint events was 17.9% (10/56) in the Mavacamten group compared to 76.8% (43/56) in the control group. Patients treated with Mavacamten exhibited significant improvements in NYHA functional class, resting or Valsalva-induced LVOT gradient, KCCQ-23 scores, NT-proBNP, and troponin I levels compared to the control group. After 16 weeks of treatment, only 17.9% of patients in the study group met the criteria for SRT, and the therapeutic effects became even more pronounced at 32 weeks. Mavacamten is the first drug capable of genuinely reducing the surgical demands in patients with obstructive HCM.[10,11] In 2023, the Week 56 Results from the VALOR-HCM Randomized Clinical Trial were published, showing that after 56 weeks, 5 out of 56 patients (8.9%) in the Mavacamten group met the SRT criteria or underwent SRT, compared to 10 out of 52 patients (19.2%) in the placebo cross-over group. These findings further demonstrate that Mavacamten can significantly reduce the long-term need for SRT in symptomatic obstructive HCM patients and improve symptoms and cardiac function parameters. However, the authors also noted that Mavacamten may lead to left ventricular systolic dysfunction, thus necessitating close monitoring of its safety.[12] Based on the results of Phase III clinical trials, Mavacamten was approved by the US Food and Drug Administration (FDA), and numerous additional clinical trials are underway. In the 2024 Guideline for the Management of Hypertrophic Cardiomyopathy, this drug also received high-level recommendations.[3]

Recent Advances in Mavacamten Research

New Evidence from Phase III Randomized Trials and Their Extensions

Following its regulatory approval, the clinical indications for Mavacamten have been progressively refined. A 2024 estimate by a French institution reported that approximately 40% of HCM patients exhibit LVOT obstruction, among whom nearly one-third meet the treatment criteria for cardiac myosin inhibitors. Notably, even under stricter criteria (LVOT gradient ≥50 mmHg), 24% of patients still qualify for therapy. Furthermore, approximately 4% of patients who

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initially do not meet treatment criteria may progress from asymptomatic to symptomatic stages, thereby becoming eligible for therapy.[13] A real-world study from Italy revealed notable differences between oHCM patients enrolled in clinical trials and those encountered in routine practice, including older age, a higher prevalence of atrial fibrillation, and more impaired left ventricular function. These findings suggest that real-world patients may present at a more advanced disease stage. Consequently, the number of patients eligible for Mavacamten therapy could be underestimated when solely relying on EXPLORER-HCM enrollment criteria.[14] Given these trends, Mavacamten is expected to see broader clinical use, reinforcing the need for ongoing, in-depth investigations.

The VALOR-HCM trial has spurred multiple subsequent analyses that provide deeper clinical insights. In one such study by Cremer et al, titled "Insights from the VALOR-HCM Trial", changes in diastolic function were evaluated before and after Mavacamten treatment, along with their association with secondary endpoints such as NYHA class, quality of life, and cardiac biomarkers. After 16 weeks, patients with obstructive HCM demonstrated significant diastolic improvement, closely linked to clinical and biomarker responses. The authors concluded that these benefits were independent of changes in LVOT obstruction and mitral regurgitation, reinforcing the drug's therapeutic potential.[15] Another sub-study by Desai et al, also titled "Insights from the VALOR-HCM Trial", evaluated Mavacamten's long-term impact on cardiac mechanics using global longitudinal strain (GLS). Patients receiving Mavacamten exhibited significant improvement in left ventricular GLS, indicating enhanced systolic function. Right ventricular strain, though subnormal at baseline, remained stable, suggesting preservation of right ventricular function.[16]

It is less well known that patients who completed the EXPLORER-HCM trial continued receiving Mavacamten, with 231 of them enrolling in the ongoing MAVA-LTE study, recently published in the European Heart Journal. After completing EXPLORER-HCM, patients remained on treatment for up to 252 weeks. The study aimed to evaluate the long-term effects of Mavacamten on LVOT gradients, cardiac function, symptom relief, and safety. The outcomes were highly favorable: from baseline to week 180, resting and Valsalva-induced LVOT gradients were reduced by 40.3 mmHg and 55.3 mmHg, respectively, confirming Mavacamten's efficacy in relieving LVOT obstruction. Left ventricular ejection fraction (LVEF) decreased markedly over 180 weeks, while plasma NT-proBNP levels were significantly reduced from baseline, reflecting marked symptomatic relief. However, 20 patients (8.7%) experienced a temporary drop in LVEF to below 50%, necessitating discontinuation of the drug; all cases recovered to above 50%. Five deaths occurred during the study period, but none were attributed to Mavacamten. This long-term extension study complements EXPLORER-HCM and provides robust support for the sustained clinical use of Mavacamten.[17] Enrico Ammirati et al also published insights related to the VALOR-HCM trial, discussing whether Mavacamten dose adjustments should be guided by echocardiographic parameters, pharmacokinetics, or CYP2C19 genotype. They further proposed that a decline in LVEF may not be the sole predictor of heart failure risk and called for future research to examine additional indicators, such as cardiac output and diastolic function.[18]

Additionally, a follow-up observational study to the PIONEER-HCM trial—PIONEER-OLE—was recently published by Ahmad Masri et al, offering long-term data on Mavacamten's sustained effects. This small-scale study tracked 13 HCM patients over a median follow-up of 201 weeks. Among them, nine patients improved from NYHA class II to I, and one from class III to II. The LVOT gradient decreased significantly at rest, post-Valsalva, and post-exercise (up to week 156). Serum NT-proBNP levels declined markedly from a baseline median of 594 ng/L to 155 ng/L at week 180. Echocardiographic measurements revealed improvements in left atrial volume index (LAVI) and left ventricular wall thickness, suggesting favorable cardiac remodeling.[19]

While the primary clinical trial data for Mavacamten have largely originated from studies in the United States and Europe, a substantial population of HCM patients resides in Asia. Initiated in January 2022, the EXPLORER-CN study is considered an extension of the global EXPLORER-HCM trial, specifically focusing on Chinese patients. This study enrolled 81 individuals who were randomized in a 2:1 ratio to receive either Mavacamten or placebo over a 30-week treatment period. The results demonstrated that Mavacamten significantly reduced Valsalva-induced LVOT gradients in Chinese patients with oHCM and improved all secondary endpoints. Regarding safety, the profile observed in Chinese patients was consistent with previous global trials, with no new safety concerns identified. Notably, despite a lower starting dose of 2.5 mg, meaningful clinical efficacy was observed as early as week 4 and was sustained through week 30.[20] This study affirms Mavacamten's therapeutic potential in Chinese patients and lays a foundation for its broader use in Asian populations. However, it is worth noting that the EXPLORER-CN trial did not adopt NYHA class improvement or pVO_2 as primary endpoints, nor did it evaluate SRT avoidance as seen in the VALOR-HCM trial. The use of LVOT gradient as the primary endpoint also presents certain limitations, given the dynamic nature of LVOT obstruction and the lack of standardized assessment protocols—particularly under Valsalva conditions.[21]

More recently, researchers at Kochi University in Japan extended the EXPLORER-HCM research framework through the HORIZON-HCM study, a Phase III, single-arm clinical trial evaluating Mavacamten in symptomatic Japanese oHCM patients. Of the 43 patients screened, 38 initiated Mavacamten treatment and 36 completed the 30-week regimen. After 30 weeks, the drug significantly reduced both post-exercise LVOT gradients and resting LVOT gradients. NT-proBNP levels declined substantially, and although LVEF decreased slightly, it remained above 74% throughout the treatment period. In addition, 63.2% of patients experienced an improvement of at least one NYHA functional class, and KCCQ-23 summary scores improved significantly. These findings reinforce Mavacamten's efficacy and safety in Japanese patients and are in line with the outcomes observed in the EXPLORER-HCM study.[22] Collectively, these two East Asian studies underscore the increasing feasibility of extending Mavacamten therapy to broader Asian patient populations.

Beyond structural and imaging benefits, Mavacamten also provides functional improvement in oHCM. In the pivotal EXPLORER-HCM trial, it significantly enhanced peak oxygen consumption (pVO_2) together with symptomatic and structural parameters.[5] Wheeler et al further showed that Mavacamten improves both maximal and submaximal exercise performance, reflected by better VE/VCO_2 slope and ventilatory efficiency, suggesting improved diastolic filling and ventilation-perfusion matching that supports daily exercise tolerance.[23]

In addition, exploratory analyses confirmed its effectiveness across subgroups and its impact on electromechanical properties. In a post-hoc EXPLORER-HCM analysis, Sikand and Sen demonstrated that even in patients with hypertension—who were older and had more obesity and diabetes—Mavacamten consistently improved pVO_2, LVOT gradients, and NYHA class, indicating robust efficacy irrespective of this common comorbidity.[24] Similarly, Del Franco et al investigated long-term electromechanical effects of Mavacamten in obstructive HCM patients, showing reductions in QT and mechanical dispersion and suggesting potential benefits on arrhythmogenic substrates beyond hemodynamics.[25]

Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy

While most published clinical trials have provided robust evidence for the use of Mavacamten in oHCM, clinical data for its application in nHCM remain limited. As noted earlier in this review, the MAVERICK-HCM study—a phase II clinical trial involving 59 nHCM patients—demonstrated that Mavacamten significantly reduced NT-proBNP and cTnI levels, with a favorable safety profile.[6] The ODYSSEY-HCM trial, the first phase III randomized study in nHCM, was launched in November 2022, with its design and baseline characteristics published in the European Heart Journal in February 2025. It plans to enroll ~160 symptomatic patients and evaluate once-daily Mavacamten over 36 weeks, with peak oxygen consumption as the primary endpoint and secondary outcomes including cardiac function, quality of life, and biomarkers. Results are pending, but this rigorous design is expected to provide critical evidence for the role of Mavacamten in nHCM.[26]

This review highlights Mavacamten, which has advanced to phase II and phase III clinical trials, with a summary of pivotal studies presented in Table 1.

Real-World Evidence and Observational Analyses

Although early clinical trials of Mavacamten—such as EXPLORER-HCM and VALOR-HCM—have consistently demonstrated its efficacy in improving LVOT gradients, symptoms, and functional capacity, real-world evidence has been eagerly awaited to confirm these findings in broader clinical settings. Desai et al recently reported the first large-scale real-world analysis of Mavacamten via the FDA's REMS program, involving over 6000 HCM patients who received treatment between April 2022 and February 2024. Data from healthcare providers, pharmacies, and echocardiographic monitoring revealed that 4.6% of Mavacamten-treated patients experienced reductions in LVEF to <50%, while 1.3% were hospitalized for heart failure. Among those treated for more than one year, these rates were 4.0% and 1.5%, respectively. Nearly all patients (97.2%) began treatment at 5 mg/day, and 74.1% remained on 5 mg or 10 mg at six months. Notably, 70.3% of patients treated for six

Table 1 Summary of Key Phase II and III Clinical Trials of Representative Myosin Modulators

Drug Name	Study Type	Conclusions (Defined Endpoints)	Year of Publication
Mavacamten	**Phase II Clinical Trial (PIONEER-HCM)**[5]	Showed improvements in exercise tolerance, relief of dyspnea, and reduction of left ventricular outflow tract (LVOT) gradient in patients with obstructive HCM	2019
	Phase II Clinical Trial (MAVERICK-HCM)[6]	In patients with non-obstructive HCM, significantly reduced NT-proBNP and cardiac troponin I (cTnI) levels with good tolerability.	2020
	Phase III Clinical Trial (EXPLORER-HCM)[8,9]	Significantly reduced LVOT gradient, improved patients' exercise tolerance, NYHA functional class, functional capacity, symptom scores, and clinical biomarkers.	2020
	Phase III clinical trial (VALOR-HCM)[10,11]	Significantly reduces the need for septal volume reduction therapy (SRT) in patients with obstructive HCM, and improves NYHA cardiac function classification, LVOT pressure gradient, quality of life scores, etc.	2022
	Phase III Clinical Trial (VALOR-HCM 56-Week Results)[12]	Significantly lowered the need for septal reduction therapy (SRT) in obstructive HCM patients, improved NYHA class, LVOT gradient, quality of life scores, etc.	2023
	Long-Term Study (MAVA-LTE)[17]	Long-term use (up to 252 weeks) continually reduced LVOT gradient, improved cardiac function and symptoms, and showed good safety.	2024
	Chinese Phase III Clinical Trial (EXPLORER-CN)[20,21]	In Chinese patients, significantly reduced LVOT gradient, improved NYHA class, health status, and cardiac structure. Safety consistent with global trials.	2023
	Japanese Phase III Clinical Trial (HORIZON-HCM)[22]	In Japanese symptomatic obstructive HCM patients, significantly reduced exercise-induced and resting LVOT gradients, improved NYHA class and health status, and maintained LVEF above 74% throughout.	2024
Aficamten	**Phase II Clinical Trial (REDWOOD-HCM)**[27]	Improved LVOT gradient, symptoms, NT-proBNP levels, and echocardiographic parameters, with good safety profile.	2021-2024
	Phase III Clinical Trial (SEQUOIA-HCM)[28–32]	Significantly reduced LVOT gradient, improved patient symptoms and NYHA class, and exhibited good safety compared to placebo.	2024-2025
	Large-Scale Clinical Study (FOREST-HCM)[33,34]	Under conditions where LVOT gradient remained low, allowed some patients to reduce or discontinue standard-of-care (SoC) medications. Monotherapy with Aficamten proved safe and effective.	2024
	Phase III Clinical Trial (MAPLE-HCM)[35]	a Phase 3, double-blind RCT enrolling ~400 symptomatic oHCM patients to compare Aficamten versus metoprolol, with peak VO_2 and KCCQ overall symptom score at week 24 as co-primary end points	2025-2026 (expected)
Omecamtiv Mecarbil	**Phase II Clinical Trial (COSMIC-HF)**[36]	In HFrEF patients, showed favorable remodeling, improved LV systolic function and volume regulation, and reduced heart size and NT-proBNP levels.	2016
	Phase III Clinical Trial (GALACTIC-HF)[37]	Reduced the composite endpoint of heart failure events or cardiovascular death in chronic HFrEF patients with EF ≤35%. Provided greater benefit in severe HF, but no significant difference in cardiovascular mortality alone and no major improvement in quality of life.	2020
	Phase III Clinical Trial (METEORIC-HF)[38]	Did not significantly improve exercise capacity (peak VO_2) in HFrEF patients; did not achieve the primary study endpoint.	2022

months achieved non-obstructive LVOT physiology (gradient <30 mmHg).[39] These findings affirm that Mavacamten's safety and efficacy extend beyond clinical trials into real-world practice.

Beyond left-ventricular outcomes, Wessly et al conducted an early real-world investigation of left atrial function in 15 consecutive Mavacamten-treated HCM patients, marking the first study to assess this parameter. Compared with baseline echocardiograms, patients showed a notable decline in left atrial systolic function, likely reflecting the drug's direct negative inotropic effect on atrial myocardium.[40] Although left ventricular diastolic improvements were also observed, the atrial effects raise questions about long-term atrial mechanics and warrant close monitoring in future studies.

In a UK multicentre cohort of 93 symptomatic oHCM patients (median follow-up ~24 weeks), 70% achieved a non-obstructive LVOT gradient (<30 mmHg) and 65% improved by at least one NYHA class, with overall LV function preserved. Transient LVEF reductions below 50% occurred in <5% of patients and resolved fully after dose adjustment.[41] A single-centre study from the University of Pennsylvania (n=96, 36-week follow-up) reported similar findings: 86% achieved a complete hemodynamic response (resting LVOT <30 mmHg and Valsalva <50 mmHg), and 77% improved by ≥1 NYHA class, with no patients remaining in class III at 36 weeks. Mean LVEF declined transiently by ~7.5% but stabilised after week 12, resolving after temporary discontinuation or dose reduction.[42] Together, these real-world studies across UK and US settings reinforce Mavacamten's robust effectiveness, tolerability, and the feasibility of safe dose management in routine multidisciplinary care.

Atrial fibrillation (AF) is four to six times more common in patients with HCM than in the general population, raising concerns about its interaction with disease-modifying therapies. In a single-center real-world study from Columbia University Irving Medical Center, researchers evaluated whether oHCM patients with coexisting AF respond differently to Mavacamten therapy. The study found that treatment with Mavacamten improved NYHA functional class and significantly reduced LVOT gradients in patients with AF, showing no meaningful difference in treatment response compared to oHCM patients without AF.[43] However, a separate observational study from Mayo Clinic yielded more cautionary findings. Among 63 oHCM patients treated with Mavacamten, new-onset AF occurred in 15% of those without prior AF, while 76% of those with a history of AF experienced symptomatic recurrence during follow-up, with some requiring multiple cardioversions. This reported AF incidence was higher than that observed in randomized clinical trials such as EXPLORER-HCM (2%) and VALOR-HCM (3.6%), in addition, Mavacamten did not significantly reduce the incidence of new-onset or recurrent AF.[44] While these two studies approached the question from different angles and featured small sample sizes, they collectively underscore the need for careful rhythm monitoring in oHCM patients treated with Mavacamten—particularly those with a prior history of AF. Further prospective studies are warranted to clarify its safety and rhythm-related outcomes in this subgroup.

Some HCM patients only develop LVOT obstruction under specific provocative conditions (eg, exercise or nitroglycerin use) and do not exhibit obstruction at rest. In a real-world study by Roehl et al, patients with obstructive HCM were stratified by the mode of LVOT obstruction induction—resting/Valsalva versus provocation-only (exercise or amyl nitrite). In the resting/Valsalva group, Mavacamten led to significant improvements in NYHA class, LVOT gradient, LVEF, and mitral regurgitation (MR). However, in patients with provoked-only obstruction, although LVOT gradients decreased, no NYHA class improvement was observed, and LVEF declined more notably. Furthermore, MR severity worsened in some patients, particularly those with non-SAM-type MR.[45] These results, albeit from a small cohort, highlight the need for individualized risk-benefit assessment and vigilant echocardiographic monitoring when initiating Mavacamten in this patient subset.

A concise summary of these real-world and observational studies—including study settings, major findings, and publication timelines—is provided in Table 2.

Comparative Efficacy and Combination Strategies of Mavacamten in HCM Management

Given the accumulating positive evidence from clinical studies on cardiac myosin inhibitors, a key question arises: Are these inhibitors groundbreaking cornerstone treatments, or merely adjunctive therapies complementing conventional medication? A recent network meta-analysis by Shang et al, incorporating data from 17 randomized controlled trials, provided comparative evidence on several drugs commonly used in HCM, including Mavacamten, Perhexiline, amlodipine, spironolactone, losartan, and candesartan. According to this analysis, both Mavacamten and Perhexiline significantly improved patients' exercise capacity and cardiac biomarkers. Mavacamten stood out for its notable effectiveness in reducing NT-proBNP, LVMI, and LAVI, whereas candesartan showed notable efficacy in reducing maximal wall thickness.[46] These findings suggest that Mavacamten possesses distinct advantages in certain therapeutic endpoints and holds potential as a cornerstone treatment in future HCM management. However, the absence of β-blockers in the included studies—a fundamental class of medications for HCM—limits the comprehensiveness of this meta-analysis.

Further exploring combination strategies, another meta-analysis conducted by Rehan et al examined the concurrent use of Mavacamten and β-blockers, demonstrating expected improvements in NYHA class, LVOT gradient, and LVEF.

Table 2 Summary of Real-World Studies Evaluating Mavacamten in Patients with Obstructive Hypertrophic Cardiomyopathy

Study Name	Summary (1–2 Sentences Including Findings)	Publication Date
US REMS Program Study[39]	Based on FDA's REMS program involving 6,299 oHCM patients (Apr 2022–Feb 2024): 4.6% had LVEF <50%, 1.3% hospitalized for heart failure. At 6 months, 70.3% achieved non-obstructive physiology (LVOT <30 mmHg), confirming real-world safety and efficacy comparable to clinical trials.	January 2025 (data until Feb 2024)
UK Multicenter Experience[41]	Across three NHS centers, 93 oHCM patients had ~24 weeks follow-up: 70% achieved non-obstructive LVOT, 65% improved ≥1 NYHA class. Temporary LVEF reductions (<5%) fully recovered with dose adjustment, showing effectiveness and manageable safety under structured care.	April 2025
University of Pennsylvania Cohort[42]	In a single-center US cohort (n=96, 36-week follow-up), 86% achieved complete hemodynamic response and 77% improved ≥1 NYHA class. LVEF declined ~7.5% early but stabilized by week 12; transient reductions resolved with temporary discontinuation or dose reduction.	March 2024
Columbia AF Subgroup Study[43]	A single-center study from Columbia University showed that oHCM patients with coexisting atrial fibrillation responded similarly to Mavacamten as those without AF, with significant improvements in LVOT gradient and NYHA class.	2024
Mayo Clinic AF Risk Study[44]	Among 63 oHCM patients, 15% developed new-onset AF and 76% of those with prior AF had symptomatic recurrences—higher than in EXPLORER-HCM and VALOR-HCM—raising concern about rhythm-related risks and emphasizing the need for monitoring.	2024
Provoked Obstruction Subtype Analysis[45]	Roehl et al stratified oHCM patients by mode of obstruction (resting/Valsalva vs provoked). Mavacamten improved LVOT, NYHA class, and LVEF in the resting group, but not in the provoked-only group, where MR worsened in some cases—highlighting the need for individualized risk-benefit assessment.	2024
COLLIGO-HCM (WAYFARER-HCM program)	Real-world registry (>3,000 oHCM); 59.9% NYHA class improvement at 24 w; ≥90% achieved resting LVOT ≤30 mmHg at 36 w; LVEF remained stable, rare reversible LVEF <50%.	2025-2026 (expected, ESC 2025 preliminary report)

Interestingly, the authors reported no significant additional benefit when combining β-blockers with Mavacamten compared to Mavacamten monotherapy.[47] Similar findings were observed in a subgroup analysis of patients from the EXPLORER-HCM and MAVA-LTE trials.[48] Nevertheless, due to the relatively small number of patients evaluated, further studies are warranted to validate these intriguing results.

Currently, research on other pharmacological combinations involving Mavacamten remains limited. A recent computational modeling study by Khalilimeybodi et al suggests promising therapeutic potential for a combination of Mavacamten and reactive oxygen species (ROS) inhibitors. This model predicted that simultaneous targeting of calcium sensitivity and ROS pathways could significantly inhibit cardiomyocyte hypertrophy and apoptosis, as well as reverse metabolic remodeling associated with HCM. Compared to other potential drug combinations, Mavacamten combined with ROS inhibitors exhibited superior efficacy.[49] While this study offers novel mechanistic insights, its conclusions are derived purely from computational predictions. The actual efficacy and safety of such a combination remain to be confirmed by real-world studies or experimental research involving human or animal subjects.

Beyond Efficacy: Adverse Effects and Research Gaps in Mavacamten Studies

Although pivotal clinical trials have provided safety data on Mavacamten, real-world evidence for adverse drug reactions (ADRs) remains limited. A recent pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) from January 2022 to September 2023 identified 1,004 Mavacamten-related ADRs. The known risks—including reduced LVEF, atrial fibrillation, dizziness, and syncope—were consistent with those reported in landmark trials such as EXPLORER-HCM and MAVA-LTE, while new potential safety signals were also noted, including urinary tract infections, gout, and peripheral edema.[50] These novel findings warrant further attention in real-world settings.

A single-center study conducted at Aurora Cardiovascular and Thoracic Services provided some degree of confirmation regarding Mavacamten's efficacy in reducing LVOT obstruction and improving symptoms, while also offering insights into its side effects. This study enrolled 31 adult patients and observed a significant decrease in LVOT gradient (LVOTG) as early as week 4 of treatment. By week 12, 83.8% (26/31) of patients reached the target LVOTG ≤30 mmHg, and 67% improved by at least two NYHA functional classes. Notably, no patient's LVEF dropped below 55%, and no dose adjustments were required.[51] Similar findings were reported by Morristown Medical Center, where six months of Mavacamten treatment led to significant reductions in both resting and Valsalva-induced LVOT gradients, accompanied by improvements in electrocardiographic and echocardiographic parameters, while LVEF remained consistently within the normal range.[52]

In the EXPLORER-HCM trial, approximately 10% of patients experienced transient reductions in LVEF, some as low as 35%, initially raising concerns about long-term safety and excessive wall thinning. However, follow-up reports noted that most LVEF reductions resolved with drug discontinuation or over time.[53] The aforementioned Aurora single-center study did not observe major adverse effects; two patients reported mild fatigue, which resolved spontaneously, and no significant ECG or Holter monitoring abnormalities were noted.[51] Additional reports include rare cases of elevated blood pressure following Mavacamten initiation.[54] To mitigate these risks, experts recommend prescribing Mavacamten under a REMS program with regular echocardiographic monitoring of LVEF and LVOT gradients, along with dose adjustments guided by clinical status.[55]

In addition, isolated case observations remind clinicians that Mavacamten is not universally effective. Desai and colleagues reported three patients who met guideline criteria yet exhibited atypical morphologies (extensive fibrosis, myocardial bridging, mixed phenotypes). Symptomatic or haemodynamic benefit was negligible, prompting drug discontinuation and alternative interventions. The authors advocate comprehensive multimodal imaging to refine patient selection and avoid futile exposure.[56]

Subsequent meta-analyses and systematic reviews (2024) have largely confirmed Mavacamten's favorable risk–benefit profile, while underscoring the need for continued large-scale safety assessment.[57–59] In the SEQUOIA-HCM and EXPLORER-HCM trials, a significant number of patients in the placebo group demonstrated improvement in many key endpoint, suggesting that placebo effects may account for part of the total observed benefit, the daily variability in HCM symptoms and outflow obstruction may contribute to baseline parameter instability, if screening and randomization capture data on patients' "worst days", improvements in both treatment and placebo arms might appear exaggerated. To address this, cross-over trial designs and repeated baseline measurements have been suggested to improve data reliability.[60]

Advances in the Pharmacological and Genetic Understanding of Mavacamten

Following its rapid market approval, the pharmacological investigation of Mavacamten continues, elucidating its molecular mechanisms and cardiac effects. At the molecular level, recent findings indicate that Mavacamten not only promotes the super-relaxed (SRX) state of myosin—thereby decreasing myosin-actin interactions—but also enhances myosin solubility within the thick filament, effectively reducing the number of available myosin heads for cross-bridge formation. In Figure 1, we have provided a summary illustration. This mechanism offers insight into how Mavacamten decreases myocardial contractility and ameliorates symptoms in hypertrophic cardiomyopathy (HCM) patients.[61]

Although Mavacamten reduces myocardial contractility, questions arise regarding the heart's ability to increase output during physiological stress. Recent work by Ma et al provided evidence that despite Mavacamten-induced inhibition of sarcomere activity, the heart maintains substantial functional reserve. Under conditions of increased calcium concentration, elevated heart rate, mechanical stretch, or β-adrenergic stimulation, myosin heads can still be recruited from the inhibited state to augment contractility.[62] This property likely improves cardiac mechanics during tachycardia, moderates excessive contractility, prolongs refractoriness, and potentially decreases the risk of ventricular tachyarrhythmias.[63] Pharmacological modeling based on studies such as MAVA-LTE and VALOR-HCM supports echocardiography-guided dose titration of Mavacamten, recommending monitoring Valsalva-induced LVOT gradients and LVEF to optimize individualized patient dosing.[64]

Mavacamten is primarily metabolized via CYP2C19, CYP3A4, and CYP2C9, leading to variable drug exposure across different CYP2C19 phenotypes. Patients classified as poor CYP2C19 metabolizers show higher drug

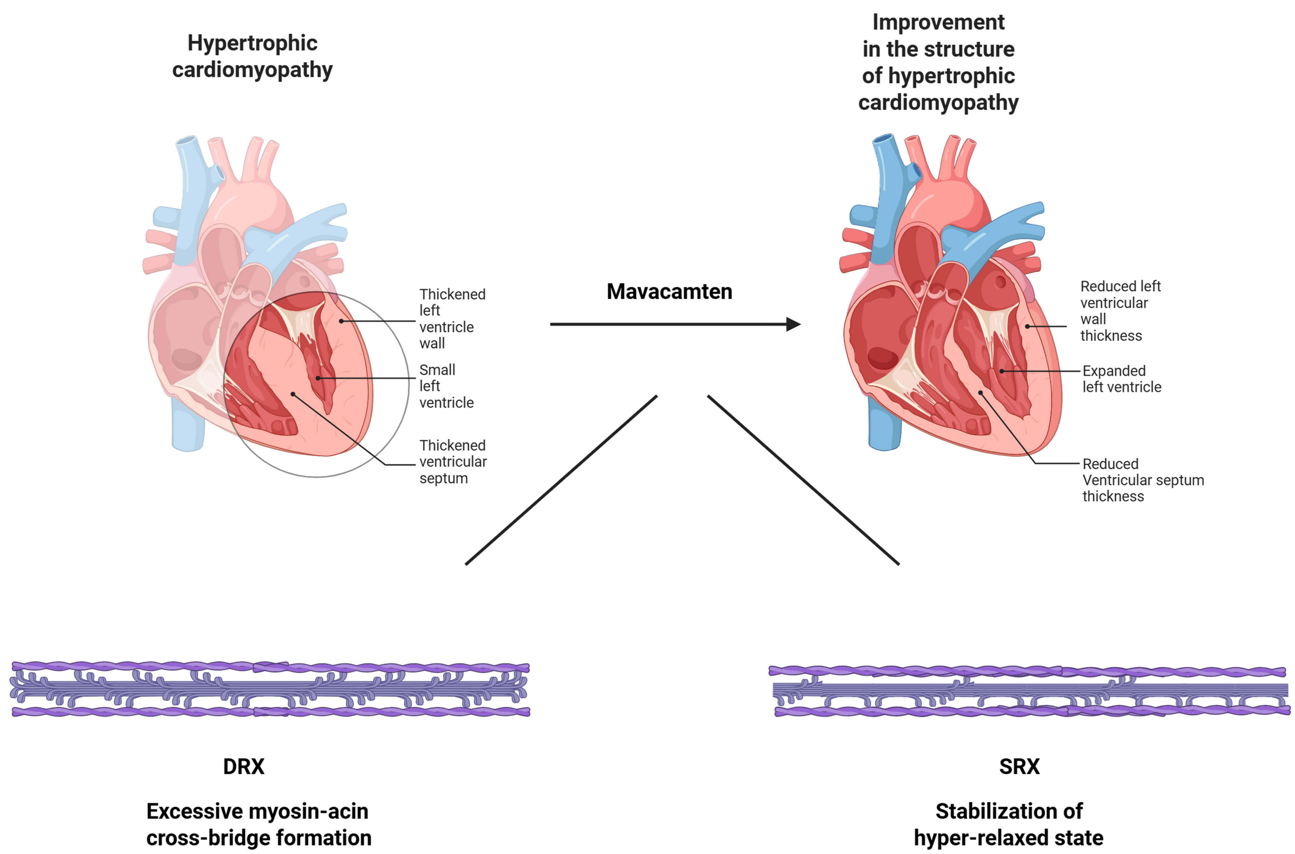

Figure 1 A brief explanation of the pharmacological effects of Mavacamten.

concentrations and require longer durations to achieve steady-state levels.[64] This pharmacogenetic interplay resembles that observed with clopidogrel, where CYP2C19 inhibitors (eg, omeprazole, fluconazole) notably affect drug efficacy.[65] Animal studies have confirmed significant impacts of CYP2C19 inhibitors like fluconazole on Mavacamten pharmacokinetics.[64] Furthermore, physiologically based pharmacokinetic (PBPK) modeling indicates that strong CYP inducers (eg, rifampin, carbamazepine) considerably reduce Mavacamten exposure, whereas inhibitors (eg, ticlopidine, itraconazole) significantly elevate its plasma concentrations.[66]

Both the FDA and EMA highlight CYP2C19 genotype as an important factor in Mavacamten dosing strategies, with the EMA explicitly incorporating genotyping requirements for poor metabolizers.[18,67] Recent long-term follow-up studies from Mayo Clinic suggest genetic backgrounds (eg, mutations in MYBPC3, MYH7, TNNT2) impact early responsiveness to Mavacamten treatment and long-term structural remodeling outcomes, reinforcing the potential necessity of genotype-guided dosing adjustments.[68] Complementing these findings, pharmacokinetic data from healthy Chinese volunteers also demonstrated similar genotype–exposure relationships, suggesting that CYP2C19-guided dosing is applicable across different ethnic populations.[69] Genotyping CYP2C19—already advised for some drugs like clopidogrel—might also prove beneficial with Mavacamten. Commentators suggest standardizing how CYP2C19 genotypes and predicted phenotypes are recorded, using uniform data standards (eg, SNOMED-CT), ensuring that patients receive their pharmacogenomic information and understand its implications for prescribing. Sharing pharmacogenomic data across different specialties and prescribers may improve therapeutic outcomes.[70]

In addition to its applications in HCM, Mavacamten has also demonstrated potential in other disease contexts. For example, João et al reported in a rat model of heart failure with preserved ejection fraction (HFpEF) that Mavacamten significantly reduced cardiomyocyte stiffness and improved diastolic compliance. The drug decreased Ca^{2+} sensitivity, lowered Ca^{2+}-activated tension, and accelerated the rate of force redevelopment, suggesting that it alleviates diastolic dysfunction by modulating the kinetics of cardiac myosin cross-bridge cycling. Although concerns remain about impairing systolic function, these findings support the hypothesis that, with careful dose titration, Mavacamten may offer a feasible therapeutic approach for HFpEF. Further validation in randomized controlled trials is warranted.[71]

Further Advances in Myosin Inhibition: Inheritance and Innovation of Aficamten

The development of treatment strategies for hypertrophic cardiomyopathy (HCM) has accelerated exploration into the functional and genetic relationships of sarcomeric proteins. While Mavacamten has spearheaded clinical applications among cardiac myosin inhibitors, it is not the only agent in this therapeutic class. Recently, Aficamten (CK-274), a next-generation cardiac myosin inhibitor developed by Cytokinetics, has emerged with promising therapeutic potential. Compared to Mavacamten, Aficamten offers notable pharmacological improvements in specificity, pharmacokinetics, and dosing, enabling more flexible administration and a lower risk of adverse effects.[72]

At the molecular level, Aficamten acts by significantly slowing phosphate release, thereby preventing cardiac myosin heads from entering a strongly bound state and effectively reducing myocardial contractility. Preclinical studies with animal models, including rats and beagle dogs, demonstrated that single oral doses of Aficamten markedly reduce cardiac contractility parameters, such as left ventricular ejection fraction (LVEF) and fractional shortening, closely correlating with plasma drug concentrations.[73]

Phase II and III Clinical Evidence: The REDWOOD-HCM and SEQUOIA-HCM Trials

Initial clinical evidence for Aficamten was provided by the Phase II REDWOOD-HCM trial (Cohorts 1 and 2), demonstrating that Aficamten significantly reduced left ventricular outflow tract gradients (LVOTG) and improved symptoms in obstructive hypertrophic cardiomyopathy (oHCM) patients, leading to the FDA granting it Breakthrough Therapy Designation in December 2021. Cohort 4 of the REDWOOD-HCM trial further supported its efficacy and safety, prompting progression to the Phase III ACACIA-HCM trial.[27]

The recent SEQUOIA-HCM Phase III trial (282 patients with symptomatic oHCM) provided comprehensive clinical evidence supporting Aficamten's efficacy and safety. This study demonstrated significant reductions in LVOT gradients, with average reductions of 21 mmHg at week 2 and 52 mmHg at week 8 compared with placebo. Hemodynamic parameters improved substantially, and the safety profile closely resembled Mavacamten, including transient LVEF reductions that resolved promptly upon temporary drug discontinuation.[28,29]

Notably, the SEQUOIA-HCM trial also highlighted substantial improvements in cardiac structure and function through echocardiography and cardiac magnetic resonance (CMR) assessments. Aficamten significantly reduced left ventricular wall thickness, LV mass index, and left atrial volume index (LAVI), correlating well with reductions in NT-proBNP and hsTnI levels.[28,30,31] CMR further revealed improved myocardial tissue characteristics, including reduced native T1 relaxation times. Additionally, SEQUOIA-HCM substudy analyses revealed marked improvements in peak oxygen consumption (VO_2max) and cardiopulmonary exercise test performance, aligning closely with the functional benefits observed with Mavacamten in EXPLORER-HCM.[32,74]

These benefits are consistent with preliminary evidence from non-obstructive HCM populations, where Aficamten also demonstrated reductions in NT-proBNP and improvements in functional status in a phase II open-label study.[75] Therefore, both Aficamten and Mavacamten currently have a small amount of evidence to prove their role in non-obstructive cardiomyopathy, and their indications will become broader in the future.

This review highlights Aficamten that have advanced to phase II and phase III clinical trials, with a summary of their pivotal studies presented in Table 1.

Potential for Reducing Standard-of-Care Medications

The FOREST-HCM study (145 patients, 36-week analysis) further enriched clinical insights, evaluating the potential for gradual reduction or withdrawal of standard-of-care (SoC) medications (eg, β-blockers, calcium-channel blockers) with stable Aficamten treatment. 64 of 136 patients (47.1%) successfully reduced or discontinued SoC medications without clinical deterioration or serious adverse events, and 59 of them (92.2%) succeeded in lowering at least one SoC agent. Although only

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about one-fourth achieved complete Aficamten monotherapy. While monotherapy is a promising goal, it remains achievable only in a subset of patients and requires cautious dose titration and personalized treatment planning.[33,34]

Complementing these findings, the MAPLE-HCM trial, a recent randomized study, directly compared Aficamten with metoprolol in oHCM. Aficamten produced greater reductions in LVOT gradients and improved exercise tolerance, while maintaining good tolerability, underscoring its advantage over conventional beta-blockers. Although the modest sample size calls for larger confirmatory trials, MAPLE-HCM offers important evidence for the efficacy of myosin inhibition relative to standard therapy.[35] The conclusions of this study are more conservative than the previous FOREST-HCM study. Although this new drug is superior to β-blockers in some cases, it is not recommended as a direct replacement.

Pharmacokinetic Insights in Special Populations

Understanding Aficamten's pharmacokinetics in special patient populations is crucial for broad clinical applicability. A recent dedicated pharmacokinetic study investigated the effects of hepatic impairment and renal dysfunction on Aficamten exposure. Results indicated that mild-to-moderate hepatic impairment and renal dysfunction had minimal effects on Aficamten pharmacokinetics, suggesting that standard dosing can be maintained safely in these patient groups without significant adjustment. However, severe impairment was associated with notable increases in exposure, emphasizing the importance of careful monitoring and potential dose adjustment in severely impaired individuals.[76]

In addition, comprehensive QT/QTc studies in healthy volunteers found no clinically significant prolongation of QT intervals at therapeutic and supratherapeutic doses of Aficamten, providing reassuring cardiac safety evidence and supporting its overall favorable safety profile.[77]

Safety Profile and Practical Considerations in Aficamten Use

Despite generally positive results, clinicians should note that Aficamten's clinical benefits depend on ongoing treatment; SEQUOIA-HCM health status scores markedly deteriorated after discontinuation, underscoring its non-curative but symptom-relieving nature.[28,78,79] Safety has been favorable across trials. In FOREST-HCM, treatment was well tolerated with durable symptom relief; transient LVEF declines occurred but resolved after dose interruption or adjustment. Dose–exposure analyses support an echo-guided titration strategy (typically 5–20 mg), as higher exposure correlated with small, reversible reductions in LVEF.[80] Similarly, MAPLE-HCM reported safety outcomes comparable to metoprolol while confirming superior efficacy.[35] Collectively, these findings indicate that Aficamten can be dosed safely with structured echocardiographic surveillance, and that occasional declines in LVEF are generally manageable and reversible.

Discussion and Future Perspectives

Precision Myosin Inhibition: From Concept to Clinical Benefit

Reviewing the evolution of therapies for cardiomyopathies and heart failure, we observe a paradigm shift from conventional treatments, such as diuretics, β-blockers, and ACE inhibitors, toward targeted molecular interventions. Over recent decades, novel therapeutic agents including angiotensin receptor–neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors have significantly reshaped heart failure management by addressing fundamental molecular and metabolic abnormalities. Most recently, the emergence of cardiac myosin modulators—especially selective myosin inhibitors such as Mavacamten and Aficamten—has ushered in an era of precision medicine specifically tailored for hypertrophic cardiomyopathy (HCM).[53,56]

Mavacamten and Aficamten exemplify this new therapeutic approach by directly modulating cardiac myosin function. These agents effectively stabilize the super-relaxed (SRX) state of cardiac myosin, thereby reducing excessive myocardial contractility, a fundamental pathological hallmark of hypertrophic cardiomyopathy.[54,56] Clinical trials such as EXPLORER-HCM and SEQUOIA-HCM have demonstrated their capability to markedly lower left ventricular outflow tract (LVOT) gradients, alleviate heart failure symptoms, and improve echocardiographic parameters including left ventricular mass index (LVMI), left atrial volume index (LAVI), and left ventricular wall thickness.[53] These structural improvements correlate closely with substantial reductions in biomarkers indicative of myocardial stress, such as NT-proBNP and hs-TnI, suggesting beneficial cardiac remodeling and improved myocardial energetics.[52,53,56] The two agents also differ in several important aspects, including pharmacokinetic properties, dosing flexibility, and monitoring requirements. For example, Mavacamten has a longer half-life and requires REMS-based titration with close echocardiographic surveillance, whereas Aficamten has a shorter half-life with faster on/off dynamics and is currently supported mainly by clinical trial data.[39] A concise summary of their shared features and key distinctions is presented in Table 3.

Remaining Challenges and Individualized Management

Nevertheless, translating these promising clinical outcomes into widespread clinical practice raises several critical issues that remain incompletely addressed. One important concern is the long-term sustainability of therapeutic effects; emerging data suggest symptom relapse and worsening of clinical status upon drug discontinuation, highlighting that current myosin inhibitors manage symptoms rather than providing a curative effect[53,54]. Furthermore, although preliminary evidence indicates improvements in myocardial tissue characteristics and reductions in native T1 relaxation

Table 3 Comparison of Key Characteristics Between Mavacamten and Aficamten

	Mavacamten	Aficamten
Shared characteristics and clinical evidence	Both are selective cardiac myosin inhibitors. In pivotal trials, both reduced LVOT gradient, improved NYHA class, exercise tolerance, and quality of life. Transient, reversible LVEF reductions were observed; all trials mandated echocardiographic monitoring to guide safe dosing.	
Mechanism	Stabilizes myosin heads in the super-relaxed (SRX) state, reducing available actin–myosin cross-bridges.	Inhibits transition from weak- to strong-binding by slowing phosphate release, selectively suppressing contractility.
Pharmacokinetics and monitoring	Half-life ~6–9 d (normal CYP2C19) and ~23 d (poor metabolizers). Strongly influenced by CYP2C19 genotype and DDIs. Long half-life necessitates REMS and echo-guided titration in the US.	Half-life ~75–85 h (≈3–3.5 d); steady state in 10–12 d. Effects reversible within 24–48 h, enabling more flexible titration. Not yet under regulatory monitoring requirements.
Dosing strategy	Initial 5 mg QD; titrated (2.5–15 mg) every ≥4 weeks under REMS with echo monitoring; slower on/off due to long half-life.	Initial 5 mg QD; titrated (5–20 mg) every ~2 weeks under trial protocols with echo guidance; faster reversibility allows more flexible adjustment.
Efficacy—pivotal trials	**EXPLORER-HCM (phase III)**: Improved exercise capacity, LVOT gradient, NYHA class, and health status.[8,9] **VALOR-HCM**: Reduced eligibility/need for SRT, benefits sustained to 56 and 128 weeks.[10–12] **MAVERICK-HCM (nHCM)**: Established dosing and safety signals in non-obstructive HCM.[17]	**REDWOOD-HCM (phase II)**: Marked reduction in LVOT gradient and symptomatic improvement.[27] **SEQUOIA-HCM (phase III)**: Met all primary and secondary endpoints, with consistent improvement in peak VO_2, symptoms, and functional measures.[28–32] **FOREST-HCM (open-label extension)**: At 48 weeks, 82% achieved ≥1 NYHA class improvement, with significant gains in KCCQ and favorable structural/diastolic remodeling.[33,34]
Head-to-head trial	No direct randomized head-to-head trial against standard medical therapy (eg, beta-blockers or calcium channel blockers)	First head-to-head trial vs metoprolol; preliminary report from 2025 ESC superiority in reducing exercise-induced LVOT gradient and improving symptoms, with an overall acceptable safety profile.
Safety	RCTs, extensions, and real-world studies show need for continuous monitoring to avoid excessive systolic suppression. REMS program implemented in the US.	SEQUOIA and FOREST: LVEF <50% in ~4%, all asymptomatic and reversible. Overall well tolerated; monitoring advised to mitigate risk.
Impact on care pathway / need for SRT	VALOR-HCM: significantly reduced eligibility/need for SRT; sustained up to 128.[10–12]	SEQUOIA and FOREST: consistent gradient and symptom reduction; some patients reduced concomitant therapy; potential to defer/reduce SRT.[28–34]
Regulatory / guideline status	FDA approved for obstructive HCM; prescribing restricted under REMS with mandatory echo monitoring.[12]	Not yet approved; after positive SEQUOIA-HCM (III), granted FDA Breakthrough Therapy Designation (BTD); regulatory submission ongoing.[52,56]

Abbreviations: LVOT, left ventricular outflow tract; NYHA, New York Heart Association functional class; QoL, quality of life; LVEF, left ventricular ejection fraction; SRT, septal reduction therapy; REMS, Risk Evaluation and Mitigation Strategy; BTD, Breakthrough Therapy Designation; OLE, open-label extension; DDIs, drug–drug interactions.

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times, the drugs' long-term antifibrotic effects remain uncertain, warranting additional longitudinal imaging studies, particularly cardiac magnetic resonance (CMR)-based evaluations.[52]

Pharmacokinetic variability also presents substantial clinical implications. The metabolism of Mavacamten and Aficamten involves pathways heavily influenced by genetic polymorphisms, particularly in the CYP2C19 enzyme system, necessitating personalized dose adjustments, careful monitoring of drug plasma levels, and regular echocardiographic surveillance to prevent adverse events such as excessive reduction in LVEF.[53,56] Such pharmacogenetic considerations will be crucial for optimizing therapeutic efficacy and safety in clinical practice.

Moreover, the integration of these novel myosin inhibitors into current therapeutic algorithms, which include β-blockers, calcium channel blockers, and emerging therapies such as ARNIs and SGLT2 inhibitors, is not fully understood. Recent studies, such as FOREST-HCM and MAPLE-HCM, have shown that while Aficamten may allow for reduction or withdrawal of traditional medications in selected patients, complete monotherapy is achievable only in a limited subset, and dose adjustments remain frequently necessary during follow-up.[52] Hence, clinicians must cautiously interpret these results and adopt individualized therapeutic strategies, emphasizing ongoing monitoring and dynamic dose titration according to each patient's clinical status and echocardiographic parameters.[52,56]

Finally, the economic and monitoring burden represents a major barrier to broader implementation. Annual treatment costs of myosin inhibitors are expected to exceed those of conventional medical therapy and approach or surpass the expense of septal reduction procedures in some settings. Early cost-effectiveness models, including a 2025 French evaluation, demonstrate that Mavacamten combined with standard of care may be cost-effective versus standard therapy alone, with incremental cost-utility ratios in the order of €80,000-€90,000 per QALY,[81] so potential value when reductions in invasive interventions are considered, but the real-world balance will heavily depend on pricing negotiations, reimbursement policies, and health system resources. In parallel, frequent echocardiographic surveillance—mandated by the REMS program for Mavacamten and similarly embedded in Aficamten trial protocols—adds substantial logistical and financial strain. Although regulatory updates have permitted less intensive monitoring in selected maintenance-phase patients, early initiation still requires repeated imaging, and pharmacogenetic testing (eg, CYP2C19 status) may further increase up-front costs. Together, these issues highlight that affordability and accessibility remain central challenges, particularly in low- and middle-income health systems. Future research should therefore integrate robust cost-effectiveness analyses, explore streamlined monitoring schedules, and develop strategies to minimize financial barriers, which will be critical to ensure sustainable and equitable adoption of myosin inhibitors.

Indication Expansion Beyond HCM

As research on myosin inhibitors advances, efforts have also been made to explore their utility beyond HCM. The Phase 2a EMBARK-HFpEF trial evaluated Mavacamten in patients with HFpEF (LVEF ≥60%) while explicitly excluding those with diagnosed HCM or LVOT obstruction. The study aimed to assess whether sarcomere unloading could improve diastolic compliance and myocardial stress in non-HCM patients, with preliminary findings showing biomarker improvement and functional gains in some participants.[82]

Building on this approach, the AURORA-HFpEF trial is currently evaluating the next-generation myosin inhibitor MYK-224 in a larger, randomized controlled setting.

Beyond Inhibition: Emerging Modulators and Future Directions

The clinical advances of myosin inhibitors like Mavacamten and Aficamten have revitalized the field of myosin-targeted therapeutics, prompting the development of diverse classes of myosin modulators with distinct mechanisms of action. In contrast to myosin inhibitors utilized primarily for hypertrophic cardiomyopathy, myosin activators have emerged as promising therapeutic strategies for conditions characterized by impaired myocardial systolic function, particularly HFrEF. Among these, Omecamtiv Mecarbil is the most extensively studied and clinically advanced agent. By selectively enhancing the ATPase activity of cardiac myosin and prolonging the duration of myocardial systole without increasing intracellular calcium, Omecamtiv Mecarbil improves cardiac function through a fundamentally distinct and calcium-independent mechanism.[36,83,84] In the pivotal phase III GALACTIC-HF trial involving over 8,000 patients with HFrEF, Omecamtiv Mecarbil significantly reduced the composite endpoint of cardiovascular death and heart failure

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hospitalization, particularly benefiting patients with severely impaired systolic function (LVEF <28%).[37,83] Despite these encouraging results, the subsequent METEORIC-HF trial found no significant improvement in functional capacity, measured by cardiopulmonary exercise testing, raising important questions regarding the overall clinical impact and optimal patient selection criteria for this agent.[38,84]

Danicamtiv, another myosin activator currently in early-to-mid-phase clinical development, similarly aims to improve myocardial systolic performance through direct enhancement of myosin ATPase activity. Recent phase II trials demonstrated favorable hemodynamic effects, characterized by increased stroke volume and improved cardiac output, accompanied by a reassuring safety profile without significant proarrhythmic effects.[85] Ongoing larger-scale trials are essential to determine whether Danicamtiv could provide clinically meaningful benefits in broader heart failure populations and define its therapeutic positioning relative to Omecamtiv Mecarbil and standard heart failure therapies.

Beyond direct myosin activators, other novel agents modulating myocardial calcium handling and relaxation mechanisms are also progressing. Istaroxime, a dual-action agent that inhibits the Na^+/K^+-ATPase and activates sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a), represents a distinctive approach to improving systolic and diastolic performance. Ongoing clinical evaluation in the SEISMiC study for acute heart failure has demonstrated promising early results, including enhanced cardiac function without increased arrhythmic risk compared to traditional inotropes.[86]

The therapeutic concept of myosin modulation has also inspired exploration beyond cardiology. MYK-581, a structural analog of Mavacamten, is under preclinical investigation for hypercontractile skeletal muscle disorders linked to sarcomeric mutations (eg, TNNI1), highlighting the broader translational potential of sarcomere-directed therapies.[87]

Collectively, emerging research into diverse myosin modulators across cardiac and skeletal conditions underscores the extensive therapeutic potential of sarcomere modulation. Future studies should focus on refining patient selection, optimizing pharmacologic profiles, and assessing long-term safety and efficacy to integrate these innovative agents into personalized therapeutic strategies.

From a broader perspective, advancing myosin-targeted therapy will benefit significantly from interdisciplinary innovations, incorporating structural biology, computational modeling, multi-omics analytics, and big-data-driven artificial intelligence (AI) algorithms. Such technological advancements promise next-generation myosin modulators with superior specificity and improved safety profiles, potentially expanding indications beyond obstructive HCM to include non-obstructive phenotypes and even HFpEF, a condition sharing pathophysiological similarities.[56] Precision medicine approaches utilizing genetic profiling, metabolic phenotyping, and advanced multimodal imaging are expected to play increasingly critical roles in refining patient selection, predicting therapeutic response, and personalizing dosing regimens to maximize therapeutic benefits and minimize adverse events.

Ultimately, the comprehensive integration of rigorous basic research, well-designed clinical trials, and real-world observational studies remains essential. Ensuring robust validation of novel therapeutic strategies through evidence-based practice is critical for delivering precise, sustainable, and effective treatments for cardiomyopathies and heart failure, ultimately translating into meaningful improvements in patient outcomes and quality of life.

Conclusion

Myosin inhibitors have reshaped the treatment landscape of hypertrophic cardiomyopathy by moving beyond symptomatic relief to disease modification at its molecular root. Mavacamten and Aficamten have consistently lowered LVOT gradients, improved symptoms and quality of life, and reduced the need for septal reduction procedures, establishing themselves as the first pharmacological alternative to surgery in this field. Despite these advances, key limitations remain, including the need for regular echocardiographic monitoring, uncertainty about long-term safety, and the economic burden associated with chronic therapy. The most critical research priorities are to define the durability of benefit and safety over extended follow-up, evaluate cost-effectiveness and access across diverse healthcare settings, and determine their role in broader phenotypes of heart failure, can myosin inhibition be extended to other heart failure phenotypes, such as non-obstructive HCM or HFpEF, where sarcomeric dysfunction also plays a role? Addressing these challenges—long-term safety, monitoring strategies, cost-effectiveness, and broader applicability—will determine whether myosin modulation evolves into a sustainable cornerstone of cardiovascular medicine.

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