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Precision Negative Inotropy: The Rise of Cardiac Myosin Inhibitors in HCM

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy, marked by left-ventricular hypertrophy, dynamic outflow obstruction in many patients, diastolic dysfunction, and elevated risks of atrial fibrillation and heart failure. Conventional drugs improve symptoms but do not directly address sarcomeric hypercontractility. Cardiac myosin inhibitors (CMIs) attenuate excessive cross-bridge cycling via stabilization of autoinhibited/super-relaxed myosin states.

Objective: To compare aficamten and mavacamten across mechanism, pharmacology, efficacy, safety, drug-drug interactions, and monitoring, highlighting MAPLE-HCM (aficamten vs metoprolol in obstructive HCM) and ODYSSEY-HCM (mavacamten vs placebo in nonobstructive HCM).

Methods: Narrative review with a structured search of PubMed, Embase, and Cochrane (Jan 2018 - Aug 2025) for late-phase trials, extensions, and key mechanistic work on CMIs in HCM; major society statements and regulatory documents were included.

Results: In obstructive HCM, CMIs improve gradients and functional capacity in randomized trials; MAPLE-HCM showed aficamten superiority over metoprolol for peak VO_2 and multiple secondary endpoints at 24 weeks. In nonobstructive HCM, ODYSSEY-HCM was neutral on its dual primary endpoints (peak VO_2, KCCQ-CSS) at 48 weeks, with more LVEF < 50% on mavacamten that typically resolved with interruption. Pharmacology and operations differ: aficamten's shorter half-life and linear PK may enable tighter titration, whereas mavacamten requires REMS-guided monitoring and careful DDI management.

Conclusions: For symptomatic obstructive HCM, CMIs represent mechanism-directed therapy; aficamten and mavacamten both have robust placebo-controlled evidence, and MAPLE-HCM positions aficamten as a plausible first-line option in appropriate patients. In nonobstructive HCM, routine CMI use is not supported by current randomized evidence. Long-term remodeling, arrhythmia outcomes, and phenotype-guided selection remain priorities.

Keywords: hypertrophic cardiomyopathy; cardiac myosin inhibitor; aficamten; mavacamten; obstructive HCM; nonobstructive HCM; LVOT obstruction; peak VO_2; KCCQ; REMS.

Słowa kluczowe: kardiomiopatia przerostowa; inhibitory miozyny sercowej; afikamten; mawakamten; oHCM; nHCM; zwężenie drogi odpływu LV; szczytowe VO_2; KCCQ; REMS.

INTRODUCTION: WHAT IS HCM, HOW COMMON IS IT AND WHY DOES IT MATTER?

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, affecting ~ 0.2% of the population with heterogeneous morphologic expression and clinical course [1–3]. Phenotypically, most symptomatic patients exhibit dynamic LV outflow tract (LVOT) obstruction driven by septal hypertrophy, systolic anterior motion of the mitral valve, and hypercontractility. Others manifest a non-obstructive phenotype dominated by diastolic dysfunction, microvascular ischemia and myocardial fibrosis [1–3].

Conventional medical therapy - β-blockers, non-dihydropyridine calcium-channel blockers, and disopyramide - ameliorates symptoms indirectly via heart rate reduction and negative inotropy but does not consistently reverse the pathophysiology of sarcomeric hypercontractility or structural remodeling [1,2]. Cardiac myosin inhibitors (CMIs) inaugurate mechanism-directed therapy by reducing the number of force-generating myosin-actin cross-bridges, thereby lowering LVOT gradients, improving diastolic function and potentially enabling reverse remodeling [4]. Contemporary guidelines from AHA/ACC (2024) and ESC (2023) incorporate CMIs in symptomatic oHCM, often alongside strategies to defer or avoid septal reduction therapy (SRT) in selected patients [1,2].

Mavacamten, the first-in-class CMI, showed clinically meaningful improvements in exercise capacity, symptoms, and LVOT gradients in EXPLORER-HCM (phase 3), and reduced short-term SRT eligibility in VALOR-HCM with durable benefits in longer follow-up [5–8]. Aficamten, designed for a shorter half-life and linear, predictable PK, progressed from REDWOOD-HCM (phase 2) to SEQUOIA-HCM (phase 3), demonstrating significant gains in peak VO_2, patient-reported outcomes and hemodynamics, with signals consistent with favorable remodeling [9–12,22,23]. Against this background, the 2025 readouts of MAPLE-HCM (aficamten vs metoprolol in oHCM) and ODYSSEY-HCM (mavacamten vs placebo in nHCM) have become pivotal to drug selection and phenotype-specific expectations [15–18].

MATERIALS AND METHODS

Search Strategy

We searched PubMed/MEDLINE, Embase, and the Cochrane Library from January 1, 2018, to August 31, 2025. Search strings combined free-text and controlled vocabulary (MeSH/Emtree) related to: hypertrophic cardiomyopathy, obstructive hypertrophic

cardiomyopathy, nonobstructive hypertrophic cardiomyopathy, cardiac myosin inhibitor, mavacamten, aficamten, CK-274, left ventricular outflow tract obstruction, exercise capacity, peak oxygen consumption, Kansas City Cardiomyopathy Questionnaire, echocardiography, remodeling, and safety. Boolean operators AND/OR refined queries; filters limited results to human, adult, English.

Inclusion Criteria

- Phase II–III randomized or controlled trials, long-term extensions, prespecified subgroup/secondary analyses, and high-quality observational studies of mavacamten or aficamten in HCM.
- Systematic reviews/meta-analyses on CMIs in HCM.
- Guidelines, regulatory labels, and pivotal mechanistic studies informing class effects.

Exclusion Criteria

- Preclinical/animal-only studies without clinical translation.
- Case reports, editorials, and narrative pieces without original data (unless guidelines/regulatory).
- Studies lacking clinically relevant outcomes (e.g., no functional, hemodynamic, or safety endpoints).

Study Selection Process

Titles/abstracts were screened by two reviewers; potentially eligible full texts were assessed against criteria; disagreements were resolved by consensus.

Data Extraction

For eligible studies we abstracted: design, population, phenotype (oHCM/nHCM), intervention/dose/titration, comparators, follow-up, primary/secondary endpoints (e.g., peak VO_2, KCCQ-CSS), LVOT gradient, LVEF thresholds/actions, biomarkers (e.g., NT-proBNP), safety (LVEF < 50%, AEs), and drug-drug interactions.

Quality Assessment

Randomized trials were appraised with Cochrane RoB 2; observational studies with Newcastle-Ottawa Scale; evidence certainty was summarized qualitatively (in line with GRADE domains), highlighting where findings are hypothesis-generating (e.g., open-label extensions, pooled or post-hoc analyses) rather than confirmatory.

ETIOLOGY, PATHOPHYSIOLOGY AND RISK FACTORS

Most HCM stems from autosomal-dominant sarcomeric variants - predominantly MYBPC3 (loss-of-function) and MYH7 (missense) - with age-dependent, incomplete penetrance and wide intrafamilial variability. The core biology centers on hypercontractility with impaired relaxation/energetics, destabilization of the super-relaxed (SRX) myosin pool, and downstream microvascular ischemia, myocyte disarray, and fibrosis. In oHCM, obstruction usually reflects systolic anterior motion with mitral - septal contact; in nHCM, symptoms relate more to diastolic stiffness and microvascular ischemia. Phenocopies (Fabry, Danon, PRKAG2, ATTR, mitochondrial/RASopathies) should be considered when features are atypical. Major SCD markers include family history, massive LVH (~≥30 mm), unexplained syncope, NSVT, apical aneurysm, and extensive LGE; AF risk tracks with LA size/fibrosis and comorbidities (hypertension, obesity, sleep apnea). Women appear underdiagnosed with later presentation. [1–2,27–31]

WHAT ARE CARDIAC MYOSIN INHIBITORS?

Cardiac myosin inhibitors (CMIs) are small molecules that reduce the number of myosin heads available for actin interaction by stabilizing the autoinhibited interacting-heads motif and super-relaxed (SRX) state, thereby lowering actin-activated ATPase turnover and cross-bridge formation. With mavacamten, the mechanism has been demonstrated biochemically and structurally, including concentration-dependent slowing of lever-arm rotation and ATP turnover, while aficamten is a next-generation inhibitor optimized for high and a shorter half-life that may permit tighter, echo-guided titration [4,21,24].

Mavacamten: first-in-class CMI with a long half-life (≈6–9 days in CYP2C19 normal metabolizers; longer in poor metabolizers) and relevant drug–drug interactions; it produced robust clinical benefits in EXPLORER-HCM and VALOR-HCM, with dosing guided by echocardiography to avoid excessive LVEF reduction [5–8,20,25].

Aficamten: next-generation CMI with shorter half-life (~75–85 h), linear/predictable PK and multi-pathway metabolism with limited single-pathway dependence, which may enable faster titration; it improved exercise capacity, symptoms, and gradients in SEQUOIA-HCM and was superior to metoprolol in MAPLE-HCM, with supportive open-label extension data [9–14,18,23].

Table 1. Concise comparison of mavacamten vs aficamten

Domain	Mavacamten	Aficamten	Practical note
Class / mechanism	First-in-class cardiac myosin inhibitor stabilizing IHM/SRX → fewer force-generating cross-bridges	Next-generation cardiac myosin inhibitor with high selectivity; same mechanistic goal	Both directly de-escalate hypercontractility (mechanism-directed)
PK / half-life	Long terminal t½ ≈ 6–9 days (longer in CYP2C19 poor metabolizers)	Shorter t½ ≈ 75–85 h (~3–4 days); linear/predictable PK	Shorter t½ → faster titration/recovery if LVEF dips
Metabolism / DDIs	CYP2C19/3A4; clinically relevant interactions and genotype effects	Multi-pathway metabolism; fewer single-pathway liabilities anticipated; interaction risk remains under evaluation	Check meds/genotype esp. with mavacamten
Dosing & monitoring	Once-daily; echo-guided titration to avoid low LVEF	Once-daily 5–20 mg with echo-guided titration (SEQUOIA program)	Both require echo-based dose adjustment
Pivotal oHCM efficacy (vs placebo)	EXPLORER-HCM: ↑ exercise capacity & health status; ↓ LVOT gradient; small, reversible LVEF reductions	SEQUOIA-HCM: ↑ peak VO_2 and broad functional/PRO gains with 5–20 mg QD	Strong placebo-controlled evidence for both in oHCM
Active comparator in	—	MAPLE-HCM: Aficamten vs metoprolol:	Supports considering mechanism-directed

oHCM		superior for peak VO_2 (LSMD ≈ +2.3 mL/kg/min, 95% CI ~1.5–3.1) and multiple secondary endpoints (e.g., NYHA improvement ~51% vs 26%)	monotherapy as an initial option in appropriate patients
SRT-eligible population	VALOR-HCM: reduced SRT eligibility; durable benefits through extended follow-up	(extension/real-world programs ongoing)	SRT deferral may be achievable in selected oHCM; the strongest randomized evidence is with mavacamten to date
Evidence in non-obstructive HCM	ODYSSEY-HCM: neutral on co-primary endpoints (peak VO_2, KCCQ-CSS); LVEF <50% more frequent but usually reversible	No completed phase 3 nHCM outcomes yet	Routine CMI use not supported in nHCM so far

AF - atrial fibrillation; DDIs – drug-drug interactions; IHM - interacting-heads motif; KCCQ-CSS - Kansas City Cardiomyopathy Questionnaire clinical summary score; LVOT - left-ventricular outflow tract; LVEF - left-ventricular ejection fraction; PRO - patient-reported outcome; QD - once daily; SRX - super-relaxed state; SRT - septal reduction therapy.

FROM β-BLOCKERS TO MYOSIN INHIBITORS: MODERN EVIDENCE IN oHCM

Placebo-controlled trials proved that cardiac myosin inhibition works in oHCM (mavacamten in EXPLORER-HCM; aficamten in SEQUOIA-HCM) [5,9–11]. The decisive next step was MAPLE-HCM, the first head-to-head, double-blind trial against standard care: symptomatic oHCM patients were randomized to aficamten or metoprolol for 24 weeks with echo-guided dosing. Aficamten was superior for the primary endpoint (peak VO_2; least-squares mean difference ≈ +2.3 mL/kg/min, 95% CI ~ 1.5–3.1) and for multiple secondary outcomes, including symptom burden (≥1-class NYHA improvement: ~51% vs 26%), patient-reported

health status and LVOT gradients [18,19]. Safety appeared manageable with protocolized echo monitoring, and LVEF dips were generally reversible with dose adjustment. Together, MAPLE-HCM suggests that a mechanism-directed CMI can outperform β-blocker monotherapy as initial treatment for many patients with symptomatic oHCM, while drug choice in practice will still reflect access, monitoring cadence, interactions, and patient preference [18,19].

NON-OBSTRUCTIVE HCM – WHAT THE LARGE RANDOMIZED TRIAL SHOWS

Non-obstructive HCM (nHCM) causes symptoms mainly through impaired relaxation, microvascular ischemia and fibrosis, without dynamic LVOT obstruction. In the global ODYSSEY-HCM trial (mavacamten vs placebo, 48 weeks), mavacamten did not significantly improve peak VO_2 or health status (KCCQ-CSS) versus placebo. Left-ventricular EF <50% occurred more often on mavacamten but was usually reversible with dose interruption. Taken together, current randomized evidence does not presently support routine CMI use in nHCM and care should remain symptom-directed per guidelines (β-blocker or non-DHP CCB, AF management/ anticoagulation). Future work should target who might benefit (phenotype-guided selection) and which endpoints best capture clinically meaningful change. [15–17, 1,2]

SAFETY AND MONITORING

Both CMIs can depress LVEF, protocolized echo-guided titration and temporary interruption remain standard. With mavacamten, long and genotype-dependent half-life extends washout and heightens interaction management [20,25]. In April 2025, the U.S. label reduced required echo frequency for eligible maintenance-phase patients and loosened some contraindications, reflecting accumulated long-term and real-world safety data. Aficamten's shorter half-life and predictable PK may enable faster titration and may facilitate recovery from low-LVEF excursions. [11,12,22,23]

PRACTICAL POSITIONING

For symptomatic oHCM, high-level evidence supports both CMIs. After EXPLORER-/VALOR-HCM, mavacamten is widely used to relieve obstruction and defer SRT in appropriate patients [5–8]. With SEQUOIA- and MAPLE-HCM, aficamten emerges as a plausible monotherapy option earlier in the pathway for selected patients, balancing efficacy

and patient-reported outcomes, with operational simplicity that is plausible given its PK profile [9,10,18]. Choice may hinge on access, genetics/drug–drug interactions, monitoring logistics, comorbidities, and patient preference. For nHCM, ODYSSEY-HCM's neutral primary outcomes suggest prioritizing precision phenotyping (e.g., diastolic reserve, microvascular ischemia) and alternative endpoints in future trials [15–17].

CONCLUSIONS

Cardiac myosin inhibition is reframing how we treat hypertrophic cardiomyopathy by dialing down sarcomeric hypercontractility rather than merely modulating heart rate or loading conditions. In obstructive HCM, consistent randomized data indicate that both mavacamten and aficamten improve symptoms, exercise capacity, and LVOT hemodynamics when dosing is guided by echocardiography. Within this landscape, MAPLE-HCM suggests that aficamten monotherapy may outperform β-blocker monotherapy for many symptomatic patients, while accumulated experience with mavacamten - extending to SRT deferral in high-risk cohorts - indicates clinically meaningful and durable benefit when monitoring is rigorously applied. Taken together, these findings support considering a mechanism-directed approach earlier in the treatment pathway for appropriate candidates.

By contrast, in nonobstructive HCM, ODYSSEY-HCM was neutral on peak VO_2 and health status, which suggests that isolated negative inotropy may be insufficient for the average nHCM patient. Future gains may depend on more precise phenotyping - disentangling the contributions of impaired relaxation, microvascular ischemia, and fibrosis - and on endpoints that better reflect diastolic reserve and day-to-day function. Until such data mature, routine CMI use in nHCM is not presently supported by randomized evidence, and care should remain guideline-directed and symptom-focused.

Safety and operations are pivotal to real-world success. Across programs, reductions in LVEF were generally reversible with protocolized dose holds, indicating that algorithmic, echo-guided titration is a workable safeguard. Practical differences in pharmacology are likely to shape agent selection: the longer half-life and CYP2C19-linked interactions with mavacamten call for careful DDI review and adherence to label-defined monitoring, whereas aficamten's shorter half-life and more linear PK may allow more agile titration and faster recovery from over-suppression. In practice, the choice between agents will hinge on phenotype, comorbid therapies, DDI burden, center logistics, and – crucially - patient preferences.

Looking ahead, priorities include confirming long-term clinical outcomes and remodeling trajectories; refining titration with biomarker or imaging cues; developing phenotype-guided strategies for nHCM; and clarifying how CMIs integrate with septal reduction therapy and atrial fibrillation management across diverse care settings. As these data emerge, treatment will likely move toward more individualized selection of agent and timing - balancing efficacy, safety, and feasibility with the goals that matter most to patients.

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