Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:

Bernardes C, Gomes Carvalho J, Rodrigues P, França M. **Magnetic resonance imaging evaluation of the effects of myosin inhibitors (mavacamten and aficamten) in hypertrophic cardiomyopathy: a systematic review and case report**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3506

Submitted: 10-04-2025
Accepted: 2-07-2025

Magnetic resonance imaging evaluation of the effects of myosin inhibitors (mavacamten and aficamten) in hypertrophic cardiomyopathy: a systematic review and case report

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Contributions: all authors made substantial contributions to the conception and execution of the work. They have all reviewed and approved the final version of the manuscript and accept responsibility for its content in its entirety.

Conflict of interest: the authors declare that there are no conflicts of interest related to this work.

Ethics approval and consent to participate: no additional ethical approval was necessary, as this article does not include any other original data from human participants or animals.

Informed consent: informed consent was obtained from the patient described in this case report.

Patient consent for publication: the patient gave written consent to use their clinical data, including cardiac magnetic resonance images, for this publication.

Availability of data and materials: all data generated or analyzed during this study are fully included in this article.

Funding: none.

Abstract

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disorder, affecting approximately 1 in 250 individuals. It is defined by unexplained left ventricular (LV) hypertrophy in the absence of other identifiable cardiac or systemic causes. The clinical presentation is highly variable, ranging from asymptomatic individuals to those with complications such as sudden cardiac death, heart failure, and atrial fibrillation.

Multimodal and longitudinal imaging is essential in HCM management. Among these, cardiac magnetic resonance (CMR) provides superior tissue characterization and accurate assessment of myocardial hypertrophy and fibrosis. CMR allows quantification of fibrosis through late gadolinium enhancement and T1 mapping, both critical for risk stratification and prognostic evaluation.

Recently, cardiac myosin inhibitors (CMIs)—mavacamten and aficamten—have shown unprecedented potential in altering disease progression by reducing myocardial hypertrophy, hypercontractility, and LV outflow tract obstruction.

This systematic review, prompted by a clinical case comparing baseline and 13-month follow-up CMR findings after mavacamten therapy in a female patient with HCM, aims to evaluate the impact of CMIs on CMR-derived parameters. Following a comprehensive PRISMA-guided search, three randomized controlled trials were included. Results demonstrated consistent reductions in LV mass, maximum LV wall thickness, and left atrial volume index. Two studies also reported significant reductions in absolute myocyte mass index, and one found a decrease in native T1 with aficamten.

These findings highlight the value of CMR in unveiling the real effects of CMIs and reinforce the need for large-scale studies to confirm their long-term benefits in HCM management.

Key words: mavacamten, aficamten, myosin inhibitors, cardiac magnetic resonance, hypertrophic cardiomyopathy.

Introduction

Hypertrophic Cardiomyopathy (HCM) is a globally prevalent heart disease, with an estimated incidence of 1 in every 250 individuals in the general population [1]. Often inherited in an autosomal dominant pattern, HCM is characterized by left ventricular hypertrophy (LVH) in patients without any other underlying cardiac or systemic disease that justifies cardiac hypertrophy [2]. A disease-causing or sarcomere-related variant is identified in only 30% to 60% [2] of HCM cases, with MYH7 and MYBPC3 genes being the most frequently implicated genes (~40%) [1,3].

Although the exact mechanism by which abnormal sarcomeric proteins cause the clinical phenotype of HCM is not fully understood [2], its pathophysiology involves four key phenomena: diastolic dysfunction, mitral regurgitation (MR), myocardial ischemia and dynamic left ventricular outflow tract obstruction (LVOTO) [2,3]. Clinically, many patients remain asymptomatic and have a normal life expectancy [2,4]. However, others may face severe complications directly linked to the disease, including sudden cardiac death (SCD), progressive symptoms from LVOTO or diastolic dysfunction, heart failure (HF) due to systolic dysfunction and atrial fibrillation (AF), which increases the risk of thromboembolic stroke [2,5].

In adults, the diagnosis of HCM is established through imaging, typically echocardiography or cardiac magnetic resonance (CMR), in the presence of a maximal end-diastolic wall thickness ≥ 15 mm in any segment of the left ventricle (LV) wall [2]. In the presence of a pathogenic variant or a positive family history, a LV thickness value around 13-14 mm can also be diagnostic [2]. Despite its heterogeneity, the most common location of LV wall thickening in HCM is the basal anterior septum that extends to the anterior wall [6].

Multimodal and longitudinal imaging are essential for managing patients with HCM [7-10]. Echocardiography remains the primary imaging modality for diagnosis, severity assessment, follow-up and prognostic evaluation [2]. CMR, due to its superior tissue characterization and spatial resolution (≤ 1 mm in plane) [9,11], offers precise measurements of the LV wall thickness, cardiac chambers, myocardial mass and function [7-9]. Further, it accurately detects apical aneurysms [12], and the presence of thrombi [9] - conditions often missed by transthoracic echocardiography (~ 40% of apical aneurysms) [11,13]. CMR is also an adequate tool for distinguishing HCM from other entities associated with increased LV wall thickness, such as pressure overload due to hypertension or aortic stenosis, athlete's heart and infiltrative or metabolic cardiomyopathies (cardiac amyloidosis, Fabry disease) [8,9].

One of the most valuable aspects of CMR in HCM is its ability to assess myocardial fibrosis using late gadolinium enhancement (LGE) and T1 mapping techniques [9,14,15]. The quantification of LGE provides insights into the extent of fibrosis, allowing for more personalized risk stratification and guiding therapeutic decisions, such as the need for an

implantable cardioverter-defibrillator (ICD) [2,4,7]. However, there is still a lack of standardization regarding LGE quantification [14]. The presence and extent of LGE is recognized as an important independent risk factor to predict SCD in HCM patients [16], being associated with higher ventricular arrhythmias [17], all-cause and cardiac mortality [18], HF [19], and systolic dysfunction [20]. In HCM, the pattern of LGE tends to be patchy and is typically located in the midwall of segments with maximal hypertrophy [9,14].

The addition of T1 mapping to CMR protocols allows the detection of myocardial fibrosis, particularly diffuse interstitial fibrosis, before LGE becomes positive, thereby increasing sensitivity [21]. This sequence also enables the quantification of the extracellular volume fraction (ECV%), a predictive factor for adverse events [22], and serves as a complementary method for accurately assessing fibrotic burden and tissue remodeling in HCM. In these patients, T1 relaxation times and ECV are typically increased [7,9]. However, the role of T1 mapping in predicting outcomes, such as SCD, remains unclear.

By offering a comprehensive understanding of disease characteristics, CMR plays an important role in the management of HCM. It assesses risk factors for SCD and monitors treatment effects, guiding decisions regarding medical therapy, septal reduction, ICD implantation, and other interventions [23]. According to current guidelines, CMR is recommended at least during the initial evaluation of all HCM patients [2]. Additionally, as a "Class 2b recommendation", it is advised to perform CMR every 3-5 years to monitor the burden of LGE and other morphologic changes, as part of a strategy for assessing SCD risk [2].

Recently, mavacamten and aficamten, both allosteric inhibitors of cardiac myosin, have emerged as potential next-generation treatments for HCM [24]. Cardiac myosin inhibitors (CMIs) have shown the capacity to reduce sarcomere hypercontractility and LVOTO by decreasing myosin-actin cross-bridge formation and ATP hydrolysis [24-26]. Mavacamten stabilizes the super-relaxed state of cardiac myosin, thereby reducing energy expenditure and actomyosin crossbridge formation, thereby alleviating hypercontractility [27]. Aficamten appears to bind to the same site as blebbistatin (a known myosin inhibitor), leading to cardiac myosin being placed into an alternative inhibited state through a slightly different pathway, which subsequently reduces ATP hydrolysis [24].

Several randomized controlled trials (RCTs) involving CMIs have already been completed or are currently in progress [8]. Mavacamten is the only agent approved for the treatment of symptomatic oHCM (NYHA class II-III) in adults, with a critical need for periodic echocardiographic monitoring due to its potential to reduce LV ejection fraction (LVEF) and to cause HF from systolic dysfunction [28]. Although promising, aficamten is still under regulatory review.

These novel disease-modifying therapies represent a breakthrough in HCM management by altering disease progression. As the role of CMIs continues to evolve in clinical practice,

CMR imaging plays a critical role in accurately assessing the phenotypic and functional changes associated with these treatments. CMR can provide valuable insights into the structural and functional remodeling that may potentially occur with long-term CMIs use [8,27], offering a clearer understanding of their therapeutic potential. This imaging modality is essential in evaluating the full impact of CMIs, particularly in determining their place in disease modification and progression.

We conducted a systematic review of CMR findings in HCM patients treated with CMIs - mavacamten or aficamten - in RCTs, aiming to clarify their effects on cardiac structure and function. This review was motivated by a clinical case demonstrating treatment response via CMR comparisons at 2 and 13 months of mavacamten therapy in a female patient with HCM.

Case Report

A 70-year-old female with hypertension and dyslipidemia was diagnosed with oHCM in 2022 during routine preoperative evaluation. She had a low SCD risk score (2.14%) and experienced exertional dyspnea and fatigue (NYHA class II-III). Genetic testing identified a variant of uncertain significance.

Despite prior treatment with bisoprolol, disopyramide (dose reduction due to QT prolongation) and verapamil, symptoms persisted without echocardiographic improvement. At baseline, transthoracic echocardiography showed a maximum resting left ventricular outflow tract (LVOT) gradient of 97 mmHg. In January 2024, mavacamten was initiated and titrated to 10 mg daily alongside bisoprolol.

Baseline CMR, performed on a 3T scanner using cine and LGE sequences, confirmed septal-predominant HCM, particularly in the basal inferoseptal segment (20.7 mm), with additional hypertrophy in the basal anterior (15 mm), basal anteroseptal (18.1 mm) and mid-inferoseptal (19.4 mm) segments. Myocardial mass was elevated (156 g; 95 g/m^2). Dynamic LVOTO with increased flow velocity and systolic anterior motion (SAM) of the chordae tendineae were present. The LV had normal dimensions, with systolic function at the lower limit of normal (LVEF 52%). The right ventricular function was preserved (RVEF 56%), with no signs of dilation or wall thickening. The left ventricular end-diastolic volume was 132 ml (80 ml/m^2; normal range: 53.0–87.0 ml/m^2) and the left ventricular end-systolic volume was 63 ml (39 ml/m^2; normal range: 13.0-31.0 ml/m^2). Mild biatrial dilatation was also noted. LGE, indicative of myocardial fibrosis, was present in the basal inferior, basal inferoseptal and mid-inferoseptal segments, which correspond to the segments with the most hypertrophy.

Following four months of treatment with mavacamten, the patient improved clinically, transitioning to NYHA class I. A follow-up CMR performed 13 months later, using the same protocol on a different 3T scanner, demonstrated stable LVEF and a reduction in LV hypertrophy in the basal inferoseptal (15.3 mm vs. 20.7 mm), basal anterior (11 mm vs. 15

mm), basal anteroseptal (13.7 mm vs. 18.1 mm) and mid-inferoseptal (13.5 mm vs. 19.4 mm) segments (Figure 1). The right ventricle showed no signs of dilation or wall thickening, and its systolic function remained preserved with an RVEF of 52% - a decrease from the previous 56%, but still within normal limits. Mild left atrial (LA) dilatation persisted and LGE remained stable. Follow-up transthoracic echocardiography showed that dynamic LVOTO and SAM were no longer present.

Methods

This systematic review was conducted in accordance with the "Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines"[29].

Search strategy and selection criteria

RCTs reporting CMR findings during treatment with CMIs were identified. Inclusion and exclusion criteria were defined using the Population, Intervention, Comparison and Outcome (PICO) framework. Studies were included when the following criteria were met: (1) RCTs involving adult patients (≥18 years) with a confirmed diagnosis of HCM; (2) investigated treatment with CMIs, specifically aficamten or mavacamten; (3) included a comparator group receiving routine treatment or any alternative control intervention; and (4) reported outcomes based on CMR parameters/characteristics assessed during treatment. No restrictions were applied regarding the date, location or language of the studies.

A systematic search was conducted on December 16, 2024, across five electronic databases: PubMed, Scopus, Cochrane Library, Web of Science and ScienceDirect. A structured approach was employed to develop and implement search queries, incorporating both controlled vocabulary (MeSH terms) where applicable and text words identified from relevant articles to comprehensively capture the population, intervention and outcomes of interest (*Supplementary Tables 1-3*).

To identify RCTs, the filter "Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format" was applied [30]. It was manually adapted to ensure compatibility with the other databases as needed. Complete search queries are provided in *Supplementary Table 4*.

Study selection

Articles retrieved from the databases were imported into EndNote Web, where duplicates were identified automatically and then manually verified by the first author. The deduplicated records were then imported into Rayyan, where a second manual check was performed. The screening process was independently conducted by the first and second authors using Rayyan, with a third author available to resolve any discrepancies regarding study inclusion.

Data extraction and analysis

Data were systematically extracted and organized using a Google Sheets spreadsheet, capturing the following information for each trial: author and year of publication, patient characteristics, details of the interventions and the CMR imaging outcomes, and the timing of outcome assessment.

The primary outcomes were changes in LV mass index (LVMI), LV mass (LVM), LV maximal wall thickness (LVWT) and maximum left atrial volume index (LAVI), compared to baseline, as evaluated by CMR.

Where available, additional data on other CMR parameters were also collected, including changes in LVEF, LV end-diastolic volume index, LV end-systolic volume index, minimum LAVI, MR fraction, MR volume, LGE mass, LGE as a percentage of LVM, LV native T1, LV ECV%, LV extracellular volume mass index (ECVi), absolute myocyte mass index and myocardial contractile fraction.

The relevant data from the selected articles were independently extracted by the first author. The accuracy of the extracted data was subsequently reviewed and confirmed by the second and third authors through cross-checking. Any inconsistencies identified were addressed and resolved through discussion and consensus among all three authors. No attempts were made to contact the authors of the studies for missing data.

Due to the limited number of studies included, as CMIs represent a relatively new class of drugs with few available studies reporting results, a narrative synthesis was performed.

Risk of bias within studies

The risk of bias in the included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2) [31], which evaluates several domains, including the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. One author conducted the initial assessment, which was subsequently cross-checked by the other authors. Any discrepancies were resolved through discussion. A graphical representation of the results was generated using the RoB 2 Excel tool [32].

Results

The systematic search identified a total of 239 articles. Following the removal of 22 duplicates, 217 articles underwent title and abstract screening, during which 207 were excluded for not meeting the eligibility criteria. Subsequently, 10 articles were assessed in full-text screening, resulting in 3 studies meeting the inclusion and exclusion criteria for the final review. Figure 2 presents the PRISMA flow diagram [29], illustrating the study screening and selection process.

All included studies focused on symptomatic patients with oHCM, classified as NYHA functional class II or III, with preserved LVEF (≥ 55% in all studies) [33-35]. No studies were identified that evaluated the effects of CMIs in patients with non-obstructive HCM (nHCM). The LVOTO criteria varied slightly between studies, ranging from a more restrictive requirement of LVOT gradient ≥ 30 mmHg at rest and ≥ 50 mmHg following the Valsalva maneuver (SEQUOIA-HCM) [33] to a broader criterion of peak LVOT gradient ≥ 50 mmHg at rest or after the Valsalva maneuver (EXPLORER-CN) [35].

All three studies included in this review were phase 3, multicenter, randomized, double-blind, placebo-controlled trials investigating the impact of CMIs on CMR-derived cardiac structure and function parameters in oHCM patients [33-35]. The SEQUOIA-HCM CMR substudy evaluated aficamten [33], whereas mavacamten was investigated in the EXPLORER-HCM CMR substudy [34] and the EXPLORER-CN trial [35]. While the SEQUOIA-HCM and the EXPLORER-HCM were conducted internationally [33,34], the EXPLORER-CN was restricted to 12 hospitals in China [35]. Table 1 presents a summary of the key characteristics of each study.

Intervention

The intervention protocols across the three studies differed in initial dosing, titration schedules, and dose adjustment criteria. In the EXPLORER-HCM, mavacamten was initiated at 5 mg once daily, with scheduled dose adjustments at weeks 8 and 14, following a two-step blinded titration scheme, with a maximum dose of 15 mg/day [36]. The dosing strategy aimed to maintain plasma drug concentrations between 350 and 700 ng/mL, with temporary discontinuation required if LVEF dropped below 50% or if drug levels exceeded 1000 ng/mL [36]. In contrast, the SEQUOIA-HCM trial employed an echocardiography-guided dose titration of aficamten, starting at 5 mg once daily [33]. Dose adjustments (up to 20 mg) were made at weeks 2, 4, 6, and every 4 weeks thereafter, based on LVEF and LVOT gradient measurements [33]. Dose increases were permitted if LVEF remained ≥55% and Valsalva LVOT gradient was ≥30 mmHg, while reductions or interruptions occurred if LVEF fell below 50% or 40%, respectively [33]. In the EXPLORER-CN mavacamten titration was started at a lower initial dose (2.5 mg once daily) with adjustments at weeks 8, 14, and 20 [37]. Titration was guided by core laboratory assessments of resting LVEF, Valsalva LVOT gradient and predose plasma drug concentrations [35]. Patient-specific doses of 1, 2.5, 5, 10 or 15 mg were permitted, with temporary discontinuation criteria identical to those used in EXPLORER-HCM [35].

Baseline characteristics

The baseline characteristics of the included studies varied in terms of sample size, demographic distribution, background therapy and key exclusion criteria.

In the SEQUOIA-HCM, 57 patients were randomized (25 to aficamten, 32 to placebo), with no statistically significant differences between treatment groups at baseline [33]. A total of 50 patients completed both baseline and week 24 assessments, with explicit reasons for discontinuation reported (three due to site error, one due to equipment failure, and three due to patient preference) [33].

The mean age of the randomized cohort was 58.5 years (standard deviation (SD) 10.8) and 35.1% were female [33]. The study population was predominantly white (93%), with minimal representation of Asian (5.3%) and other racial groups [33]. In terms of functional status, 68.4% of participants were classified as NYHA class II, while 31.6% were NYHA class III [33]. Background therapy was permitted if stable for at least six weeks prior to randomization [38], with 61.4% of participants receiving β-blockers, 8.8% disopyramide and 28.1% nondihydropyridine calcium channel blockers (CCBs) [33]. A history of paroxysmal AF was documented in 12.3% of participants, while none had permanent AF [33]. Median NT-proBNP and hs-cTnI levels were 655 pg/mL (Q1–Q3: 358, 1146) and 15 ng/L (Q1–Q3: 8, 25), respectively [33]. Baseline LVMI, as assessed by CMR, was 113 g/m² (SD 33) in the aficamten group and 110 g/m² (SD 27) in the placebo group [33].

Conversely, the EXPLORER-HCM provided limited demographic and baseline data, reporting only that 35 patients were randomized (17 to mavacamten, 18 to placebo) [34], representing the smallest sample size. The mean age was 60.3 years and 42.9% of participants were female [34]. All randomized patients were included in the analysis; however, no statistical comparisons of baseline characteristics were reported in the publication [34]. The study protocol allowed the continuation of β-blockers or CCBs if initiated before trial enrolment [39]. However, unlike SEQUOIA-HCM, disopyramide use was prohibited and the study excluded patients with a history of syncope or sustained ventricular tachyarrhythmia with exercise within six months before screening, AF at screening or those receiving concomitant therapy with ranolazine or a combination of β-blockers and CCBs [39].

The EXPLORER-CN trial randomized the largest cohort, with 81 patients (54 to mavacamten, 27 to placebo) [35]. However, only 58 participants (39 mavacamten, 19 placebo) were eligible for the CMR analysis [35]. The characteristics of this subset of patients were not reported, nor were the reasons for their CMR eligibility. The randomized population had a mean age of 51.9 years (SD 11.9) [35], representing a younger cohort compared to the other trials. The proportion of female participants was also lower (28.4%) [35]. Unlike the other studies, EXPLORER-CN exclusively enrolled patients from China and was the only study to evaluate CYP2C19 metabolizer status, identifying 13% of mavacamten-treated patients as poor metabolizers compared to 3.7% in the placebo group [35]. No statistical analysis was

performed to assess differences in baseline characteristics between treatment and control groups. The majority of participants were classified as NYHA class II, with a higher prevalence in the mavacamten group (81.5%) compared to the placebo group (66.7%) [35]. The study reported higher NT-proBNP geometric mean levels in the placebo group (1250.3 ng/L) than in the mavacamten group (810.5 ng/L) [35]. Hs-cTnI levels were comparable between the mavacamten (33.5 ng/L) and placebo (38.7 ng/L) groups [35]. Notably, EXPLORER-CN reported higher NT-proBNP and hs-cTnI levels compared to SEQUOIA-HCM. Background therapy was permitted, with 88.9% of participants receiving β-blockers, a higher proportion than in SEQUOIA-HCM, and 7.4% receiving CCBs in both treatment groups [35]. Similar to EXPLORER-HCM, the trial excluded participants receiving disopyramide, cibenzoline, ranolazine or a combination of β-blockers with verapamil or diltiazem, and patients with a history of syncope or sustained ventricular tachyarrhythmia with exercise within the past six months before screening or the presence of paroxysmal AF at screening [35]. Among the 58 patients included in the CMR analysis, the mean LVMI was lower in the mavacamten group (98.6 g/m², SD 45.0) than in the placebo group (108.5 g/m², SD 54.8) [35].

Baseline Kansas City Cardiomyopathy Questionnaire scores were slightly higher in EXPLORER-CN (82.4 points, SD 16.9, in the mavacamten group; 84.4 points, SD 17.0, in placebo) [35] compared to SEQUOIA-HCM (75.5 points, SD 16.5) [33]. In contrast, body mass index was higher in SEQUOIA-HCM (28.3 kg/m², SD 3.5) [33] compared to EXPLORER-CN (25.2 kg/m², SD 3.5, in the mavacamten group; 26.1 kg/m², SD 3.6, in the placebo group) [35].

Cardiac magnetic resonance imaging protocol

Regarding exclusion criteria for CMR assessments, all three studies excluded participants with ICDs or pacemakers [33-35]. EXPLORER-HCM and EXPLORER-CN also excluded participants with AF at the time of imaging, although both allowed for a reassessment within a specified period before final exclusion [35,39]. Claustrophobic patients were excluded in SEQUOIA-HCM [33].

The timing of CMR assessments varied slightly between the studies. In EXPLORER-HCM and EXPLORER-CN, imaging was performed at baseline and at week 30 [34,35]. SEQUOIA-HCM conducted imaging at baseline and week 24 [33], reflecting a shorter follow-up period compared to the other two trials.

SEQUOIA-HCM adhered to a prespecified imaging protocol established by the CMR core laboratory, ensuring consistency between baseline and follow-up by using the same scanner whenever feasible [33]. LGE was defined as a signal intensity at least six SD above the mean of the remote normal myocardium [33]. ECV% was calculated from global pre- and post-contrast T1 mapping, with adjustments for plasma volume based on hematocrit levels

measured within 24 hours of CMR acquisition [33]. While EXPLORER-HCM specified the sequence order of imaging [34], it did not provide additional protocol details. In contrast, EXPLORER-CN did not detail an imaging protocol.

Outcomes

In terms of study endpoints, all three trials included evaluated changes from baseline in LVMI, LVM, LVWT and maximum LAVI [33-35], which were considered our primary endpoints of study. SEQUOIA-HCM and EXPLORER-HCM both incorporated CMR-derived LVMI as a primary endpoint [33,34]. In EXPLORER-CN, however, CMR-derived parameters (including LVMI) were secondary and exploratory endpoints [35].

In SEQUOIA-HCM, treatment with aficamten was associated with significant reductions in all four primary endpoints [33]. Similarly, EXPLORER-HCM and EXPLORER-CN demonstrated significant reductions in the same four CMR parameters following treatment with mavacamten [34,35]. Among the three studies, EXPLORER-CN reported the largest treatment effects [35], as summarized in Table 2.

Additional CMR parameters were assessed in individual studies (Table 3). In SEQUOIA-HCM, treatment with aficamten resulted in significant reductions in LV ECVi and absolute myocyte mass index [33]. A significant decrease in LV native T1 was also observed [33]. However, no significant changes were noted in LVEF, LGE mass, LGE as a percentage of LVM or LV ECV% [33]. Additionally, LV end-diastolic volume index, LV end-systolic volume index and MR fraction and volume did not show significant changes [33].

In EXPLORER-HCM, treatment with mavacamten led to a significant reduction in LVEF and absolute intracellular myocardial mass index [34]. No significant changes were observed in LGE mass or myocardial contractile fraction [34]. Furthermore, the study reported no significant within- or between-group differences in ECV% (mean change, SD: 0.02, 0.07, in the mavacamten group and 0.00, 0.03, in the placebo group) [34]. EXPLORER-CN demonstrated a significant reduction in minimum LAVI following treatment with mavacamten [35].

Risk of bias

The Cochrane Risk of Bias Tool was applied to all CMR-derived outcomes of each study [31], as detailed in *Supplementary Table 5* and *Supplementary Figure 1*. Most domains were classified as low risk of bias, particularly in the areas of measurement of outcomes, missing outcome data and deviations from intended interventions. Some concerns were identified in the selection of the reported result and the randomization process, though no domains were classified as high risk. Overall, the studies included in this review demonstrated a low to moderate risk of bias.

Discussion

Left ventricular and left atrial remodeling

Until 2016, the treatment landscape for HCM was largely unchanged [24], with primary pharmacologic therapies consisting of beta-blockers, non-dihydropyridine CCBs, and the antiarrhythmic disopyramide. These treatments, based primarily on observational studies, aim to alleviate symptomatic burden but are often inadequate, leaving many patients reliant on more invasive second-line therapies [2,24]. A deeper understanding of HCM's molecular pathophysiology has driven the development of CMIs, a new class of targeted therapies [24].

This systematic review provides evidence supporting the role of CMIs in promoting favorable cardiac remodeling in patients with oHCM, with a specific emphasis on changes observed through CMR, an invaluable imaging modality in HCM [2]. All three studies included in this review demonstrated significant reductions in LVMI, LVM, LVWT and maximum LAVI [33-35], underscoring the structural benefits of CMIs in this patient population.

A key finding across the studies was the consistent and significant reduction in LVMI and LVWT following treatment with CMIs. All three trials showed reductions in these parameters [33-35], suggesting that both aficamten and mavacamten effectively target the pathological hypertrophy characteristic of oHCM. The magnitude of LVM reduction was more pronounced in the EXPLORER-CN study [35], which could be attributed to a variety of factors, including differences in baseline characteristics between study groups.

The role of CMIs in LA remodeling was also evident, with all studies reporting significant reductions in maximum LAVI in CMR imaging [33-35]. This finding is clinically relevant, as LA dilation is a marker of disease severity and is associated with an increased risk of AF and adverse cardiovascular events in HCM, including SCD [40-42].

The remodeling effects of CMIs contrast with those observed with traditional pharmacologic therapies such as beta-blockers, CCBs and disopyramide, which primarily focus on symptom relief rather than structural modification [2,43,44]. No previous studies have demonstrated significant LVM regression with these conventional therapies. Additionally, septal reduction therapies such as alcohol septal ablation and myectomy provide more immediate anatomical changes but at the expense of procedural risks [45]. These findings reinforce the unique mechanism of CMIs in directly targeting hypercontractility and hypertrophy in oHCM.

Myocardial fibrosis and cardiac myosin inhibitors

Fibrosis is a key contributor to the progression of HCM and is strongly linked to an increased risk of SCD. As an indirect marker of myocardial fibrosis, LGE has demonstrated significant prognostic value in stratifying SCD risk [16]. However, none of the studies included in this analysis demonstrated significant changes in LGE mass or the percentage of LGE relative to LV mass. The absence of a reduction in LGE may suggest that while CMIs are effective in reducing hypertrophy, their impact on pre-existing myocardial fibrosis remains uncertain and

possibly less promising. Importantly, in EXPLORER-HCM, the authors acknowledge that the baseline fibrosis in the study population was minimal [34], which may have limited the ability to detect any significant changes in fibrosis following treatment with mavacamten.

In contrast, in SEQUOIA-HCM a significant reduction in native T1 was observed after treatment with aficamten [33]. An increased myocardial native T1 value in HCM patients has been associated with LV hypertrophy and is indicative of diffuse myocardial fibrosis, even in the absence of detectable LGE or hemodynamic obstruction [46]. Moreover, native T1 values could serve as a non-invasive and clinically reliable biomarker for detecting early diffuse myocardial involvement in subexpressed genotype-positive individuals [47]. These findings suggest that reductions in native T1 with aficamten treatment may reflect favorable myocardial remodeling, regression of interstitial myocardial fibrosis and/or LV hypertrophy, even in the absence of detectable LGE changes. Hence, there is potential for further research to explore the true role of CMIs in modifying myocardial fibrosis.

The SEQUOIA-HCM CMR substudy also reported significant reductions in LV ECVi [33], whereas ECV% did not show significant changes in either SEQUOIA-HCM or EXPLORER-HCM [33,34]. This discrepancy may be explained by a reduction in LV myocardial mass achieved with aficamten treatment, without significant alterations in the extracellular matrix. As such, the reduction in ECVi likely reflects a decrease in the total myocardial tissue volume, rather than a substantive change in the extracellular space. A histological validation would be needed to correctly interpret these findings [33].

Both SEQUOIA-HCM and EXPLORER-HCM also demonstrated significant reductions in absolute myocyte mass index [33,34], reinforcing the targeted treatment effect of both aficamten and mavacamten in reducing myocardial hypertrophy.

Future studies are needed to better elucidate the role of CMR-based T1 mapping analysis in patients with varying degrees of fibrosis. Such studies would provide deeper insights into how CMIs influence myocardial fibrosis and its impact on long-term clinical outcomes, such as the risk of SCD.

Left ventricular ejection fraction

A key finding is the observed variability in LVEF changes following CMIs therapy. EXPLORER-HCM reported a significant reduction in LVEF [34], whereas SEQUOIA-HCM demonstrated no significant LVEF changes [33].

The observed differences in LVEF responses between these studies may be attributed to several factors, including potential pharmacodynamic variations between aficamten and mavacamten. In fact, aficamten was developed to optimize pharmacokinetic and pharmacodynamic properties. It offers a shorter half-life, faster titration, quicker drug washout and a wider therapeutic window, with fewer drug-drug interactions. Mavacamten, on the other hand, interacts with several CYP450 enzymes [24]. While a reduction in LVEF is

a known reason for discontinuing mavacamten treatment in clinical practice due to concerns about systolic dysfunction [28], it is important to recognize that many HCM patients exhibit a supernormal LVEF [48], which has been associated with adverse long-term outcomes, particularly a greater risk for adverse cardiovascular outcomes and all-cause mortality [49,50].

Building on these observations, further research is needed to clarify whether LVEF reductions during CMIs therapy represent a limitation of these treatments, are specific to mavacamten or contribute to a beneficial long-term impact on HCM progression. A deeper understanding of LVEF changes in the context of CMI therapy will be crucial for optimizing patient outcomes and guiding therapeutic decisions.

Influence of patient profile and disease staging on therapeutic response

The current evidence on the efficacy of CMIs in HCM, as assessed by CMR imaging, is limited to patients with symptomatic oHCM classified as NYHA class II-III, leaving considerable uncertainty regarding their effectiveness across different disease stages. The MAVERICK-HCM trial and the REDWOOD-HCM Cohort 4 demonstrated positive outcomes with mavacamten and aficamten, respectively, for the treatment of symptomatic nHCM, using echocardiography as the primary imaging modality [51,52]. However, the impact of CMIs on early-stage disease and their potential to prevent adverse myocardial remodeling in asymptomatic carriers of HCM-related mutations remains unknown. Further research incorporating CMR imaging is necessary to evaluate the broader applicability of CMIs across the HCM spectrum and to better elucidate their role in disease-modifying strategies beyond symptomatic relief.

Equally important is the variability in therapeutic response based on patient characteristics, such as age, comorbidities and genotype, which may influence both treatment efficacy and safety. At present, it remains unclear whether the response to CMIs is consistent across all patient populations, particularly in older adults, those with multiple comorbidities, or specific genetic variants of HCM. While one study has already examined the impact of age and disease duration on mavacamten treatment response [53], future research incorporating genotypic profiling and long-term follow-up will be crucial for refining patient selection and optimizing individualized treatment strategies. This will help ensure the effective use of CMIs across diverse HCM subtypes and disease stages.

Conclusions

In conclusion, CMR is an important imaging modality in the evaluation of HCM and a valuable tool in assessing the effects of CMIs on HCM patients. Using CMR in RCTs, primary and secondary outcomes were achieved with both mavacamten and aficamten, with significant reductions in LVM, LVWT and left atrial volume, reinforcing the potential of CMIs

to induce favorable cardiac remodeling in oHCM. Additionally, SEQUOIA-HCM and EXPLORER-HCM reported significant reductions in absolute myocyte mass index following treatment with aficamten and mavacamten, respectively. SEQUOIA-HCM also demonstrated a significant reduction in native T1 values with aficamten therapy.

However, the small sample sizes and short follow-up of the studies included limit the full understanding of the long-term benefits of these drugs. To truly capture the long-term effects of CMIs, future research should incorporate CMR as a key evaluation tool across larger studies. This approach will provide a clearer picture of how these therapies influence disease progression, myocardial fibrosis and other critical biomarkers, ultimately optimizing the use of these revolutionary new therapies in HCM patients.

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Online supplementary material:
Supplementary Table 1. Research question.
Supplementary Table 2. Inclusion and exclusion criteria.
Supplementary Table 3. Search terms.
Supplementary Table 4. Search strategy.
Supplementary Table 5. Risk of bias assessment.
Supplementary Figure 1. Risk of bias assessment.

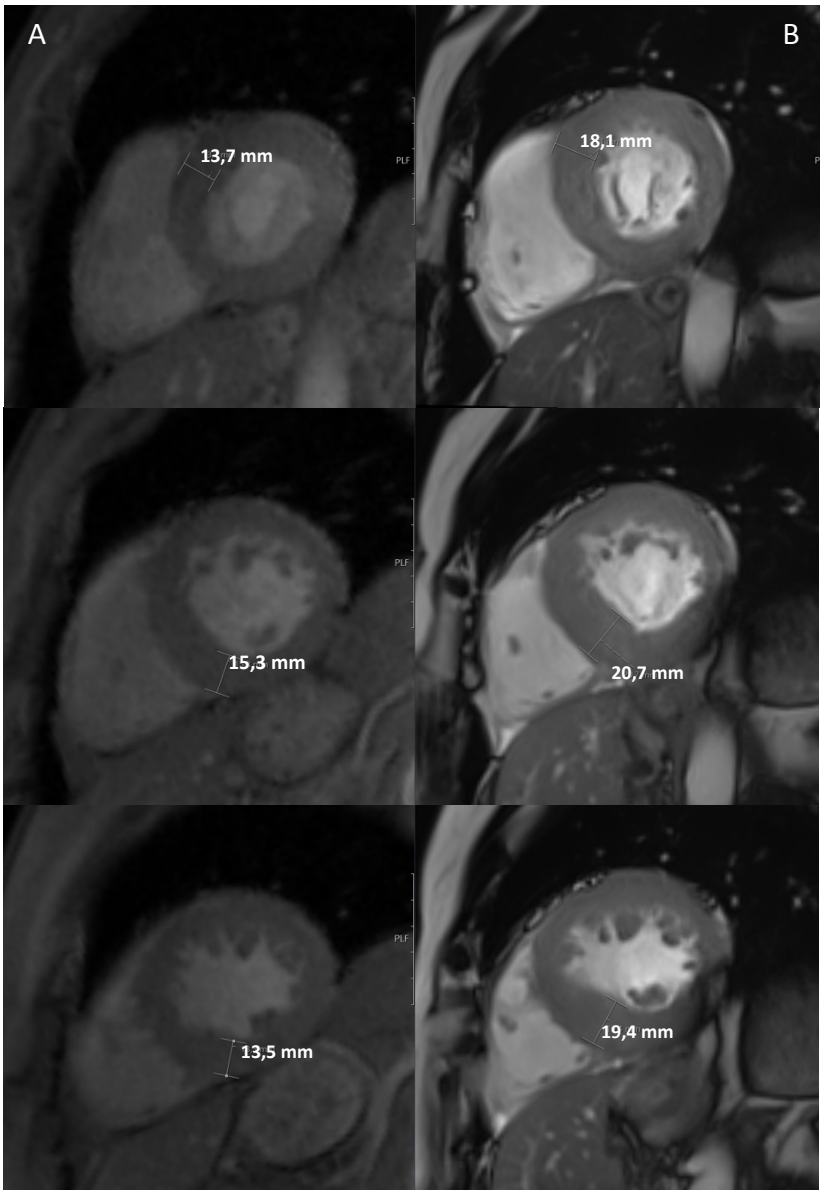

Figure 1. LV short-axis end-diastolic cine images (basal do apical) depicting the reduction in LV hypertrophy. Panel A – follow-up CMR performed 13 months after the first examination (Panel B).

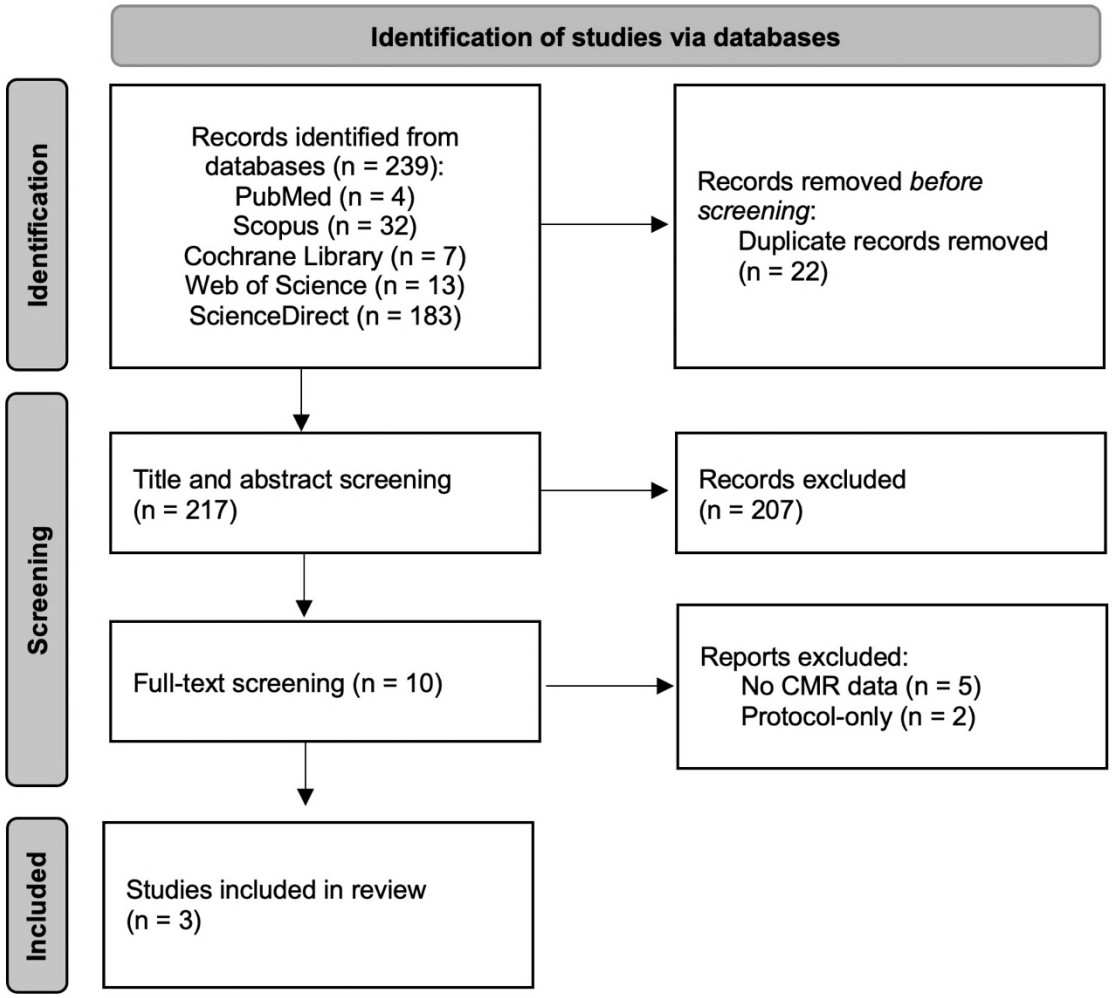

Figure 2 - Search results (adapted from PRISMA[29] 2020 Flow Diagram). CMR, cardiac magnetic resonance.

Table 1. Characteristics of included studies.

Author, year of publication	Nº of patients, % male	Mean age (years) [SD]	Included patient characteristics	Intervention	CMR imaging outcomes	Timing of outcome assessment
Masri et al. 2024 SEQUOIA-HCM CMR Substudy	57 (25 aficamten, 32 placebo), 64.9%	58.5 [10.8]	18 to 85 y, oHCM, LVOT gradient ≥ 30 mm Hg at rest and ≥ 50 mm Hg following Valsalva maneuver, NYHA II or III, LVEF ≥ 60%, age- and sex-predicted pVO_2≤ 90%.	1:1, aficamten (starting at 5 mg; MDA 20 mg) or placebo, for 24 weeks	LV mass index LV mass LV maximal wall thickness Maximum LA volume index LV ejection fraction LV end-diastolic volume index LV end-systolic volume index Mitral regurgitation fraction Mitral regurgitation volume LGE mass LGE, % of LV mass LV native T1 LV extracellular volume fraction LV extracellular volume mass index Absolute myocyte mass index	Day 1 and week 24.
Saberi et al. 2021 EXPLORER-HCM CMR Substudy	35 (17 mavacamten, 18 placebo), 57.1%	60.3 [N/A]	≥18 y, oHMC, at least one peak LVOT gradient ≥ 50 mm Hg (at rest or with provocation), Valsalva LVOT gradient ≥30 mm Hg at screening, NYHA II or III, LVEF ≥55%, able to perform a CPET with a respiratory exchange ratio of ≥1.0.	1:1, mavacamten (starting at 5 mg; MDA 15 mg) or placebo for 30 weeks	LV mass index LV mass LV maximal wall thickness Maximum LA volume index LV ejection fraction LGE mass Extracellular volume fraction Absolute intracellular myocardial mass index Myocardial contractile fraction	Day 1 and week 30.

Tian et al. 2023 EXPLORER-CN	81 (54 mavacamten, 27 placebo), 71.6%	51.9 [1.9]	≥ 18 y, oHMC, peak LVOT gradient ≥ 50 mm Hg at rest or after the Valsalva maneuver, NYHA II or III, LVEF ≥ 55%, > 45 kg.	2:1, mavacamten (starting at 2.5 mg daily; MDA 15 mg) or placebo, for 30 weeks	LV mass index LV mass LV maximal wall thickness Maximum LA volume index Minimum LA volume index	Baseline and week 30.

CMR, cardiac magnetic resonance; oHCM; obstructive hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LVEF, left ventricle ejection fraction; pVO2, peak oxygen consumption; MDA, maximum dose allowed; LV, left ventricle; LGE, late gandolinium enhancement; CPET, cardiopulmonary exercise testing.

Table 2. Summary of findings.

	LV mass index, g/m²		LV mass, g		LV maximal wall thickness, mm		Maximum LA volume index, mL/m²	
	Treatment Effect (95% CI)	p-alue	Treatment Effect (95% CI)	p-value	Treatment Effect (95% CI)	p-value	Treatment Effect (95% CI)	p-value
Masri et al. 2024 SEQUOIA-HCM CMR Substudy	−15 (−25 to −6)	< 0.001°	−31 (−48 to −14)	< 0.001°	−2.1 (−3.1 to −1.1)	< 0.001°	−13 (−19 to −7)	< 0.001°
Saberi et al. 2021 EXPLORER-HCM CMR Substudy	−15.8 (−22.6 to −9.0)	< 0.0001#	−30.0 (−43.3 to −16.7)	< 0.0001#	−2.4 (−3.9 to −0.9)	0.0079#	−10.3 (−16.0 to −4.6)	0.0004#
Tian et al. 2023 EXPLORER-CN	−30.80 (−41.55 to −20.05)	< 0.001§	−52.64 (−67.89 to −37.39)	< 0.001^	−3.52 (−4.65 to −2.38)	< 0.001^	−18.27 (−26.72 to −9.83)	< 0.001^

°Least-squares mean difference; #Wilcoxon-Mann-Whitney test; §Wilcoxon signed-rank test; ^Wilcoxon rank sum test. LV, left ventricle; LA, left atrial; CMR, cardiac magnetic resonance.

Table 3. Additional CMR parameters assessed in Included Studies.

		Treatment Effect (95% CI)	P Value
Masri et al. 2024 SEQUOIA-HCM CMR Substudy	LV ejection fraction, %	−2.6 (−5.9 to 0.7)	0.12°
	LV end-diastolic volume index, mL/m²	−1 (−6 to 5)	0.79°
	LV end-systolic volume index, mL/m²	1.4 (−1.3 to 4.1)	0.30°
	Mitral regurgitation fraction, %	−6 (−16 to 4)	0.22°
	Mitral regurgitation volume, mL	−7 (−16 to 2)	0.13°
	LGE mass, g	−0.7 (−2.9 to 1.6)	0.54°
	LGE, % of LV mass	−0.4 (−2.1 to 1.2)	0.60°
	LV native T1, ms	−37 (−69 to −5)	0.026°
	LV extracellular volume fraction, %	0.7 (−2.2 to 3.6)	0.61°
	LV extracellular volume mass index^, %/g/m²	−3.9 (−7.0 to −0.9)	0.014°
	Absolute myocyte mass index$, g/m²	−14 (−23 to −4)	0.004°
Saberi et al. 2021 EXPLORER-HCM CMR Substudy	LV ejection fraction, %	−6.4 (−10.3 to −2.4)	0.0025#
	LGE mass, g	0.9 (−0.3 to 2.0)	0.8854#
	Extracellular volume fraction	N/A	N/A
	Absolute intracellular myocardial mass index$, g/m²	−13.1 (−18.7 to −7.5)	0.0002#
	Myocardial contractile fraction*, %	2.4 (−4.5 to 9.3)	0.7043#
Tian et al. 2023 EXPLORER-CN	Minimum LA volume index, mL/m²	−10.31 (−15.93 to −4.70)	< 0.001§

°Least-squares mean difference; #Wilcoxon-Mann-Whitney test; §Wilcoxon rank sum test. ^ECVi = ECV% x LV end-diastolic myocardial volume normalized to body surface area; $[(1 - global extracellular volume fraction) x LV mass]/body surface index; *(LV stroke volume/LV myocardial volume) × 100; LV myocardial volume=LV mass/[1.05 g/mL]. CMR, cardiac magnetic resonance; LV, left ventricular; LGE: late gadolinium enhancement; N/A: not available; LA: left atrial.