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REVIEW ARTICLE

Effects of cardiac myosin inhibitors on hemodynamic and functional outcomes in hypertrophic cardiomyopathy: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Cardiac myosin inhibitors are new medications found to change the course of hypertrophic cardiomyopathy (HCM) by altering cardiomyocyte contractility. This systematic review and meta-analysis aimed to investigate the hemodynamic and cardiac functional changes with mavacamten and aficamten in obstructive and nonobstructive HCM.

Methods: A meta-analysis of randomized controlled trials was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched PubMed, Scopus, and Cochrane CENTRAL from December 2025 to February 2026, assessed studies comparing cardiac myosin inhibitors with placebo, and analyzed results based on hemodynamic and cardiac functional changes, including left ventricular ejection fraction (LVEF), resting left ventricular outflow tract (LVOT) gradient, and post-Valsalva LVOT gradient. Other outcomes, such as New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, serious adverse events, pVO_2, and NT-proBNP, were evaluated. RevMan was used to perform statistical analyses.

Results: Seven Randomized controlled trials, including 883 patients, were analyzed. Treatment with myosin inhibitors demonstrated significant improvement in resting LVOT gradient mean difference [MD -59.38, 95% confidence interval (CI) -63.24 to -55.52] and post-Valsalva LVOT gradient (MD -58.05, 95% CI -67.28 to -48.81) compared with placebo. LVEF decreased significantly in the myosin inhibitor group (MD -4.38, 95% CI -6.71 to -2.06). Myosin inhibitors significantly improved NYHA class (risk ratio 2.15, 95% CI 1.80 to 2.57) and KCCQ scores (MD 7.36, 95% CI 4.71 to 10.01) versus placebo. NT-proBNP was significantly decreased in the myosin inhibitor group (MD -16.61%, 95% CI -26.85 to -6.38). pVO_2 and serious adverse events were similar between groups.

Conclusion: Our systematic review and meta-analysis found that myosin inhibitors significantly improved resting and post-Valsalva LVOT gradients, reduced LVEF, improved NYHA class and NT-proBNP, and had similar pVO_2 and serious adverse events compared with placebo.

Keywords: Myosin inhibitors, hypertrophic cardiomyopathy, mavacamten, aficamten.

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Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease characterized by unexplained hypertrophy of the left ventricular wall. Mutations in genes encoding sarcomere proteins are the primary pathophysiology associated with myocyte changes, such as fibrosis, myocyte disarray, and hypercontractility [1]. HCM affects approximately 1 in 500 adults (0.2%) globally, with large population-based imaging cohorts suggesting a prevalence as high as 1 in 200 when subclinical disease is included, corresponding to ~15 million individuals worldwide, highlighting the substantial disease burden and underdiagnosis of HCM [2]. Moreover, HCM is the most common inherited cardiomyopathy and a leading cause of sudden cardiac death in young individuals and competitive athletes [3]. HCM is associated with a wide range of complications, which include atrial fibrillation, left ventricular outflow tract (LVOT) obstruction, increased risk of thromboembolism, and heart failure [4,5]. However, no evidence suggests that medications reduce myocyte hypertrophy, modify disease progression, or improve cardiac function outcomes in patients with HCM [6].

Current HCM management focuses on controlling symptoms using β-blockers, calcium channel blockers, disopyramide, or invasive surgical procedures, such as septal reduction or myectomy, in advanced cases [7]. Although these therapies are effective in controlling symptoms, they do not target the molecular mechanisms responsible for sarcomere hypercontractility. Despite optimal treatment, patients often report significant symptoms [8]. Cardiac myosin inhibitors are novel small-molecule medications that have recently emerged as a class targeting the core pathophysiology in HCM; they specifically reduce cross-bridging between myosin and actin, which contributes to the disease's hypercontractility [9]. By modulating sarcomere function directly, these agents mark a significant shift from symptomatic management to mechanism-based treatment in HCM. Moreover, clinical trials have demonstrated significant improvements in LVOT gradients, functional parameters, cardiac biomarkers, and quality-of-life measures with mavacamten and aficamten, with safety profiles suggesting they may play a role in the management of HCM.

To date, seven randomized controlled trials (RCTs) have been published assessing the efficacy and safety of cardiac myosin inhibitors in HCM patients compared with placebo groups [8,10]. Despite the positive results obtained from the trials, it is unclear whether these advantages will be replicated on a larger scale for hemodynamic and functional cardiac changes. Moreover, the trials differ in study design, sample size, follow-up duration, and primary endpoints. In this systematic review and meta-analysis, we aim to combine and improve the statistical power of previous and up-to-date data to create an accurate summary of the clinical impact of myosin inhibitors on HCM patients.

Methods

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11] and in accordance with the Cochrane Handbook for Systematic Reviews and Meta-Analyses [12].

Literature search and screening

We performed a comprehensive search of PubMed, Scopus, and Cochrane CENTRAL from December 2025 to February 2026 to identify all RCTs using the following search keywords*:* ("HCM" OR HCM OR hypertrophic obstructive cardiomyopathy OR HOCM) AND ("Myosin Inhibitors" OR "cardiac myosin inhibitor*" OR mavacamten OR aficamten OR MYK-461 OR CK-274). The detailed search strategy for each database is summarized in Supplementary Table S1. Following the electronic search, backward and forward citation analyses were conducted by screening the reference lists of all retrieved articles to ensure inclusion of all relevant studies. Titles and abstracts were screened initially, followed by full-text screening to identify eligible studies.

Eligibility criteria and endpoints

We included studies enrolling adult patients with obstructive or non-obstructive HCM receiving cardiac myosin inhibitors (intervention group) compared with placebo (control group) and reporting outcomes of interest. The primary outcomes were the mean change from baseline in resting and post-Valsalva LVOT gradient and changes in left ventricular ejection fraction (LVEF). Secondary outcomes included mean change in NT-proBNP levels, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [13], proportion of New York Heart Association (NYHA) class improvement [14], pVO_2, and serious adverse events.

Quality assessment

The risk of bias assessment of RCTs was performed using the Cochrane risk of bias assessment tool version 2 (ROB-2) [15]. The revised version of the ROB-2 tool assessed five main domains as follows: bias arising from the randomization process, bias arising from the deviation from the intended intervention, bias arising from missing outcome data, bias arising from the measurement of the outcome, and bias arising from the selection of the reported result. Each domain was judged as low risk, some concerns, or high risk of bias. Any disagreements between the authors were resolved via discussion with the corresponding author.

Data extraction and statistical analysis

We used a standardized Excel sheet to extract all relevant data from the studies included. The extracted data were as follows: (1) summary characteristics of the included studies, including country, study design, study duration, total number of included patients, patient characteristics, assessed outcomes, and key findings, with baseline characteristics of the patients included, such as sample size, age, males, NYHA Class, and dosing; (2) risk of bias domains; and (3) measured outcomes.

Dichotomous outcomes were extracted as the frequency of events with the total number of patients and were pooled as risk ratio (RR) with its 95% confidence interval (CI) using the DerSimonian–Laird random effects model [16]. Moreover, continuous outcomes were extracted as mean, standard deviations (SDs), and total number of patients and were pooled as mean difference (MD) with its 95% CI using the above-declared model, standard error for change in LVEF, and quality of life improvement measured via KCCQ. A significant heterogeneity among the studies was determined when a *p*-value was less than 0.1 and $I^2 \geq 50\%$ [17]. A leave-one-out sensitivity analysis and subgroup analysis were performed to rule out any significant heterogeneity between the studies. RevMan software was used to perform all the statistical analyses.

Results

Literature search and study selection

Our comprehensive search yielded 811 citations, of which 788 were excluded following title-abstract screening and duplicate removal, leaving 23 articles for full-text screening. We finally included seven RCTs in the meta-analysis. The selection process is shown in the PRISMA flow diagram Figure 1.

Study characteristics and quality assessment

The finally included RCTs were conducted across multiple countries between 2020 and 2025. The studies included a total of 883 patients; 57.8% (511 patients) were males, with a mean age of 57.05 ± 11.3 years. The patients were allocated to the myosin inhibitor group [486 (55%) patients] and to the control group [397 (45%) patients]. More detailed summary characteristics of the included studies and baseline data of the patients are stated in Table 1.

As shown in Figure 2, the seven included RCTs were assessed using the ROB-2 tool, and five studies had a low risk of bias, and only two studies had some concern of bias due to missing outcome dataClick or tap here to enter text..

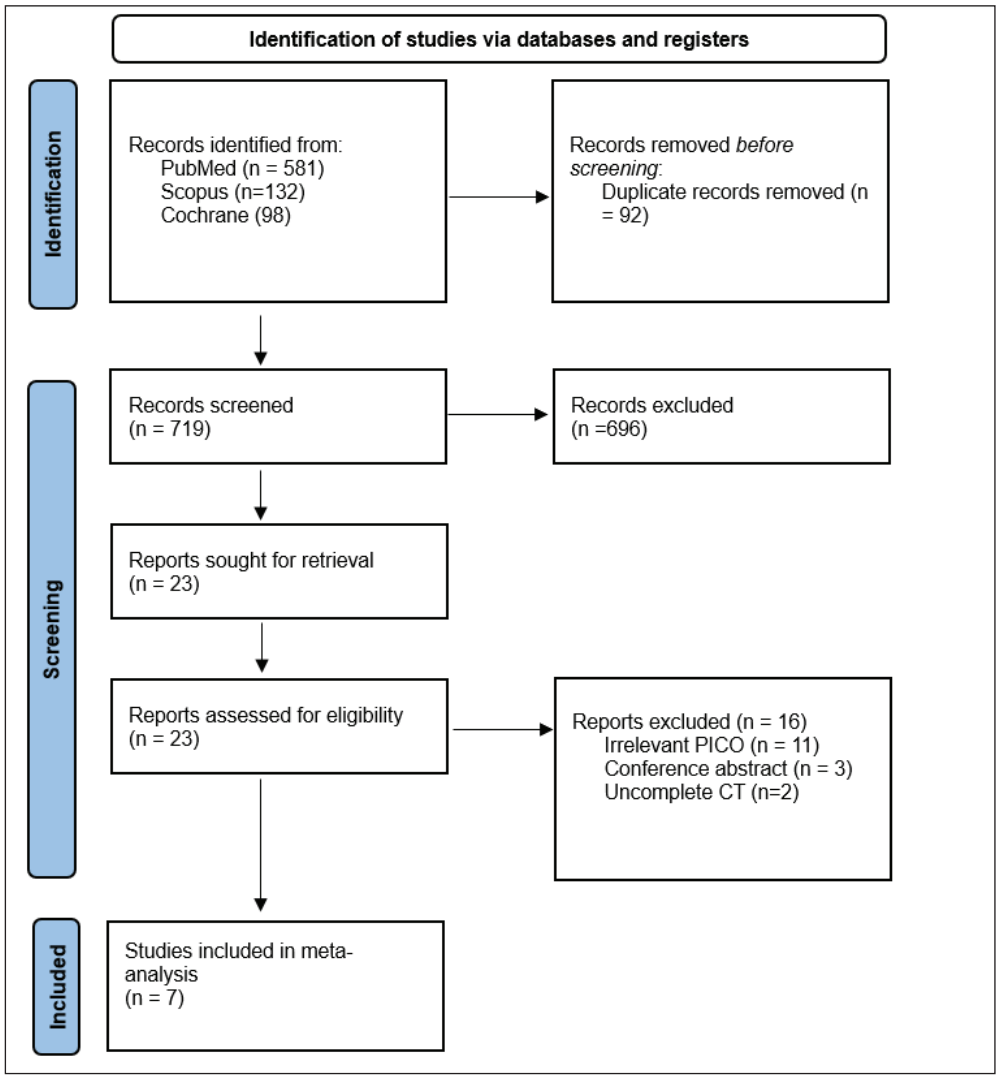

Figure 1. *The PRISMA flow diagram.*

Table 1. *Baseline demographic and clinical characteristics of patients with hypertrophic cardiomyopathy [8,10,18-21,29].*

					Age			Gender, Male (n, %)								
					Myosin inhibitor		Placebo	Myosin inhibitor		Placebo				NYHA class		
Study_ID	Country	Study type	Study duration	Total number of patients	Mean	SD	Mean	SD	*N*	%	N	%	Intervention	Control	II	III	Dose
Tian 2025	China	EXPLORER-CN RCT	30 weeks	81	52.4	± 12.1	51.0	±11.8	41	64.4%	17	38.4%	Mavacamten	Placebo	62	19	5 mg mavacamten
Desai 2022	US	VALOR-HCM RCT	16 weeks	112	59.8	±14.2	60.9	±10.5	29	51.7%	28	50%	Mavacamten	Placebo	8	104	5 mg mavacamten
HO CY 2020	US	MAVERICK-HCM RCT	16 weeks	59	54.0	±14.6	53.8	±18.2	19	47.5%	6	31.5%	Mavacamten	Placebo	46	13	5 mg mavacamten
Maron 2023	Europe and North America	REDWOOD-HCM RCT	10 weeks	41	57	±18.09	58.66	±8.14	13	46.4%	5	38.4%	Aficamten	Placebo	28	13	5-10 mg aficamten
Maron 2024	Multinational	SEQUOIA-HCM RCT	24 weeks	282	59.2	±12.6	59.0	±13.3	86	60.5%	81	57.8%	Aficamten	Placebo	214	67	5 mg aficamten
Masri 2024	Multinational	SEQUOIA-HCM CMR Sub study RCT	24 weeks	57	58.5 (±10.8)				37 (64.9%)				Aficamten	Placebo	39	18	5-20 mg aficamten
Olivotto 2020	Multinational	ECPLORER-HCM RCT	30 weeks	251	58·5	(±12·2)	58·5	±11·8	66	53.6%	83	64.8%	Mavacamten	Placebo	183	19	5 mg mavacamten

[a] Values are presented as mean ± SD or *n* (%) unless otherwise indicaed.

Primary outcomes

The LVEF was assessed by seven studies, of which the pooled estimate showed a significant effect of decreasing LVEF of the myosin inhibitor group compared to the placebo group (MD -4.38, 95% CI: -6.71 to -2.06, p = 0.00001; I^2 = 97%, p < 0.0002), Figure 3. We performed sensitivity analysis; removing Tian 2025, Maron 2023, and HO CY 2020 decreased the heterogeneity to I^2 = 41, Suppl ementary Figure S1.

Resting LVOT was reported by six studies, of which the pooled estimate showed significant improvement for the myosin inhibitor group compared to placebo (MD -59.38, 95% CI: -63.24 to -55.52, p = 0.00001; I^2 = 89%, p < 0.00001), Figure 4A. The leave-one-out sensitivity test showed that removing Maron2024 decreased the heterogeneity to I^2 = 22, Supplementary Figure S2.

Post-Valsalva LVOT was reported by six studies, of which the pooled estimate showed significant improvement for the myosin inhibitor group compared to placebo (MD -58.05, 95% CI: -67.28 to -48.81, p = 0.00001; I^2 = 99%, p < 0.00001), Figure 4B. The sensitivity test showed that removing Desai 2022 decreased the heterogeneity to I^2 = 81, Supplementary Figure S3. Subgroup analysis was also performed. Two subgroups were based on the intervention: mavacamten and aficamten, which decreased heterogeneity to I^2 = 40.2%, Supplementary Figure S4.

Secondary outcomes

The improvement of NYHA classification was assessed by six studies, of which the rate was 59.2% (245 of 414 patients) in the myosin inhibitor group and 27.84% (108 of 388 patients) in the control group. The pooled analysis showed a significant difference between the myosin inhibitor and the placebo to improve the NYHA class (RR 2.15, 95% CI: 1.80 to 2.57, p = 0.35; I^2 = 10%, p < 0.00001), Figure 5.

KCCQ was reported by four studies, of which the pooled estimate showed a significant effect for improving the myosin inhibitor group over the placebo group (MD 7.36, 95% CI: 4.71 to 10.01, p = 0.15; I^2 = 44%, p < 0.00001), Figure 6.

The incidence of serious adverse events was reported by six studies. The rates were closely similar between the two groups: 7.69% (34 of 442 patients) in the myosin inhibitor group and 8.9% (34 of 382 patients) in the placebo group. The pooled estimate showed no significant difference between the two strategies (RR 0.80, 95% CI: 0.51 to 1.26, p = 0.17; I^2 = 35%, p = 0.34), Figure 7.

The NT-proBNP was assessed by six studies, of which the pooled estimate showed a significant effect of decreasing NT-proBNP for the myosin inhibitor group compared to the placebo group (MD -16.61%, CI: -26.85 to -6.38, p = 0.00001; I^2 = 99%, p < 0.001), Figure 8. We performed sensitivity analysis; removing Maron 2024, Maron 2023, and Desai 2022 decreased the heterogeneity to I^2 = 7%, Supplementary Figure S5.

The pVO_2 was assessed by three studies, of which the pooled estimate showed no significant difference between

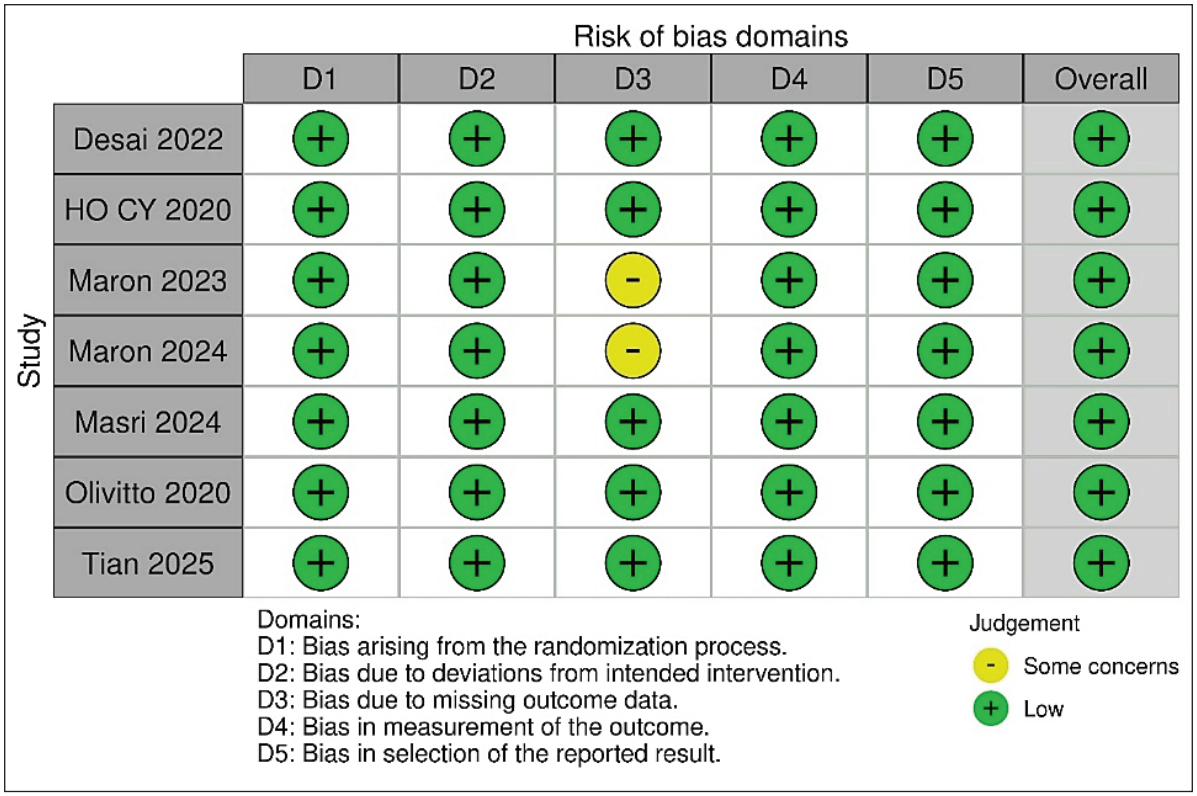

Figure 2. *ROB assessment (ROB-2) of the included RCTs.*

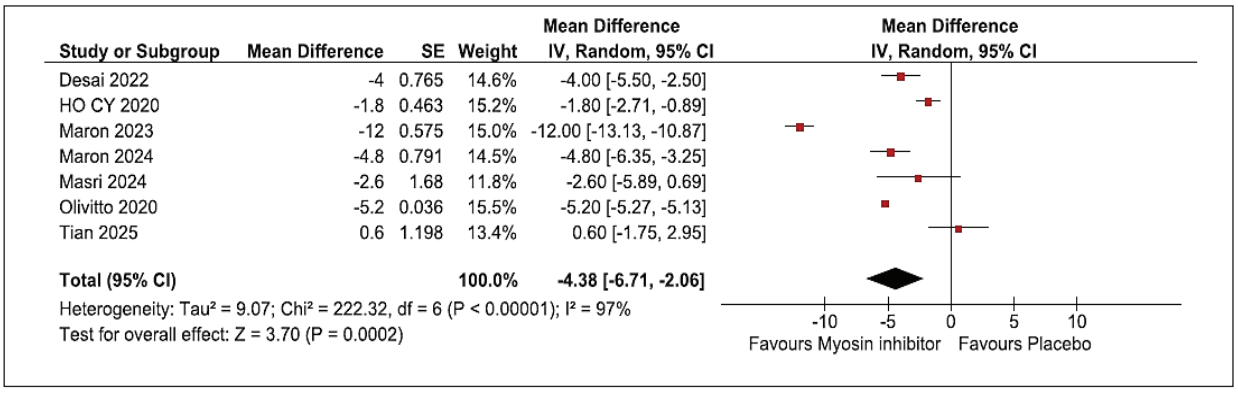

Figure 3. *Random-effect model of LVEF.*

groups (MD 0.78, 95% CI: -0.75 to 2.12, $p = 0.10$; $I^2 = 56\%$, $p = 0.26$), Figure 9. We performed leave-one-out sensitivity analysis; removing HO CY 2020 decreased heterogenicity to $I^2 = 0\%$, Supplementary Figure S6.

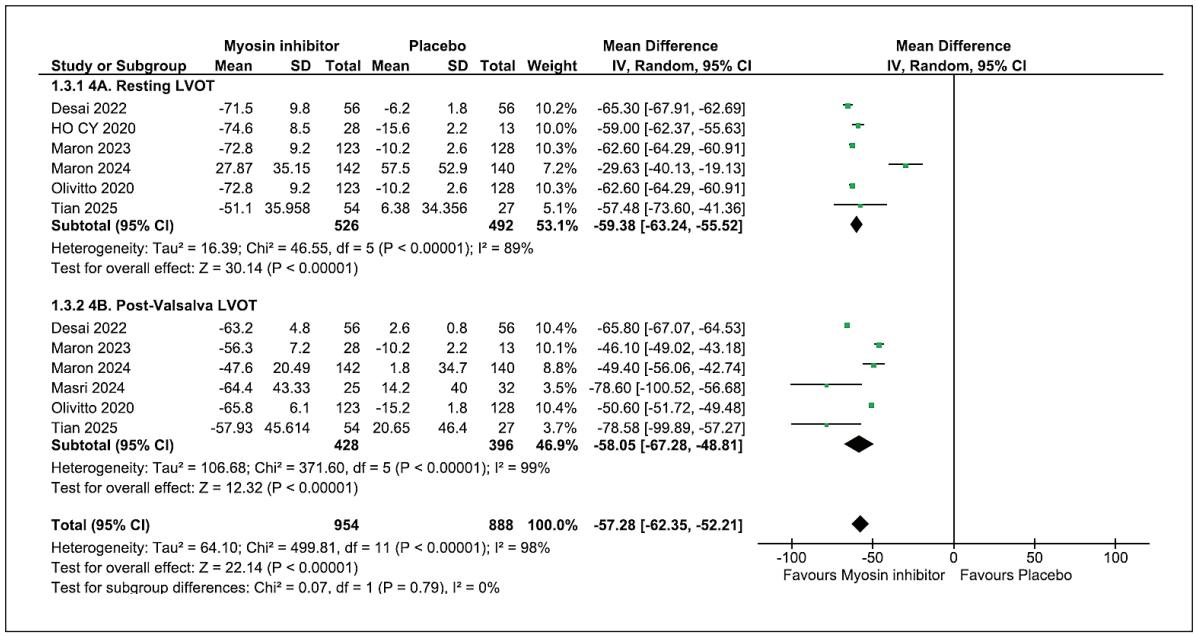

Figure 4. *Random-effect model of LVOT. LVOT. A) Resting LVOT, and B) Post-Valsalva LVOT.*

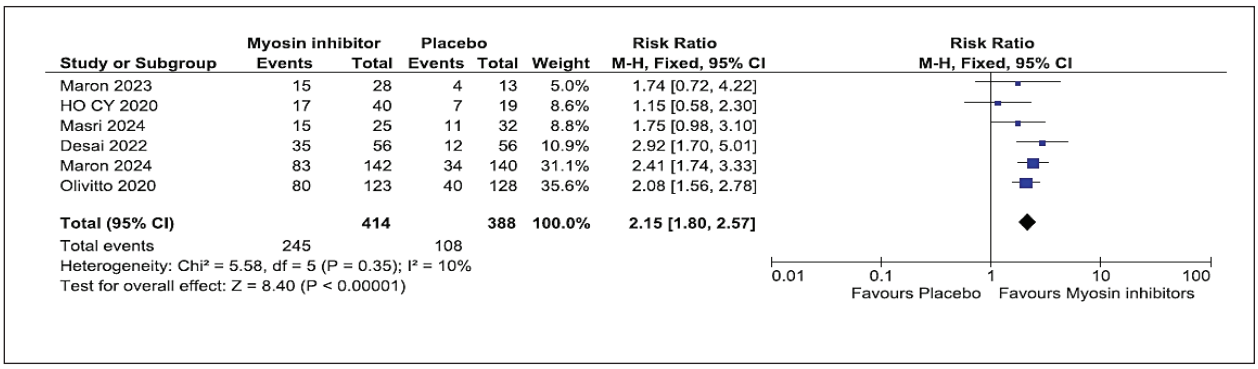

Figure 5. *Random-effect model of NYHA classification.*

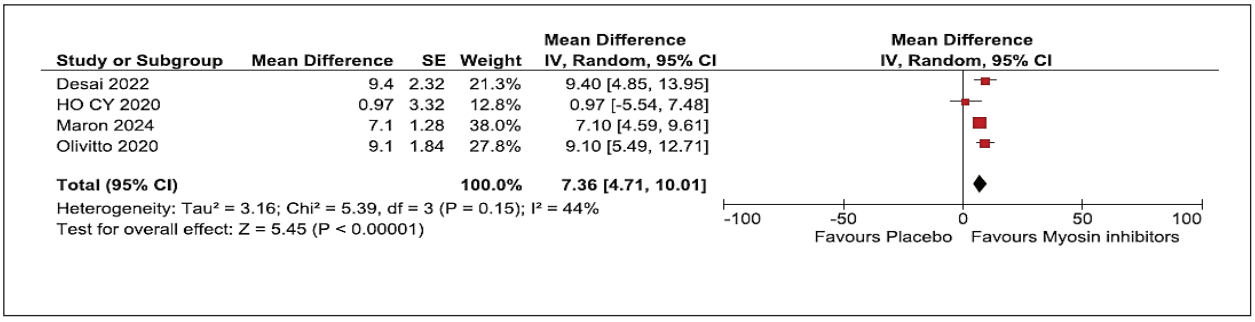

Figure 6. *Random-effect model of KCCQ.*

Discussion

This systematic review and meta-analysis evaluate the effect of myosin inhibitors on cardiac function in patients with HCM, including seven RCTs with 883 patients. This review reports that cardiac myosin inhibitors significantly reduced both resting and post-Valsalva LVOT gradients, decreased LVEF, and improved NYHA class, NT-proBNP levels, and KCCQ scores, while showing no significant differences in serious adverse events or pVO_2 between the two groups. These findings support the role of cardiac myosin inhibitors as effective therapies that improve hemodynamic and symptomatic outcomes in HCM.

Our review results are consistent with the major randomized trials (EXPLORER-HCM, REDWOOD-HCM, SEQUOIA-HCM) and their extension studies, which demonstrated significant reductions in LVOT

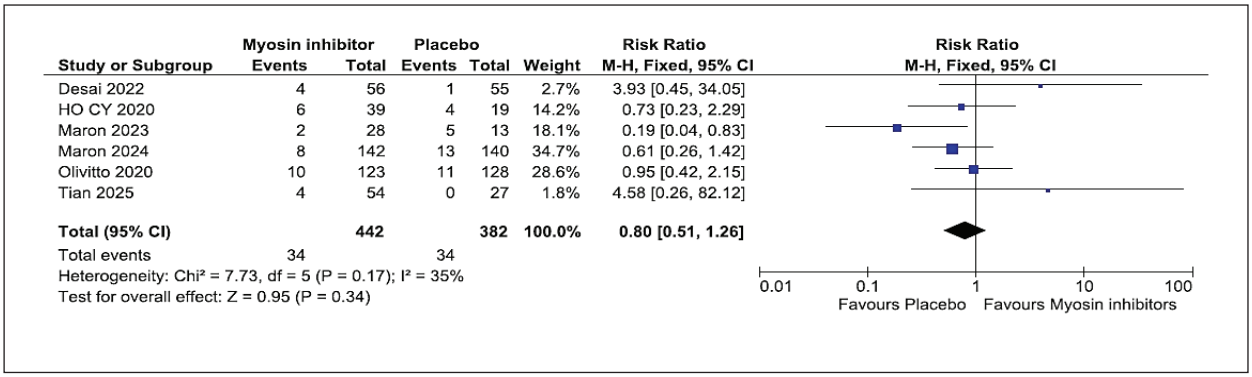

Figure 7. *Random-effect model of serious adverse events.*

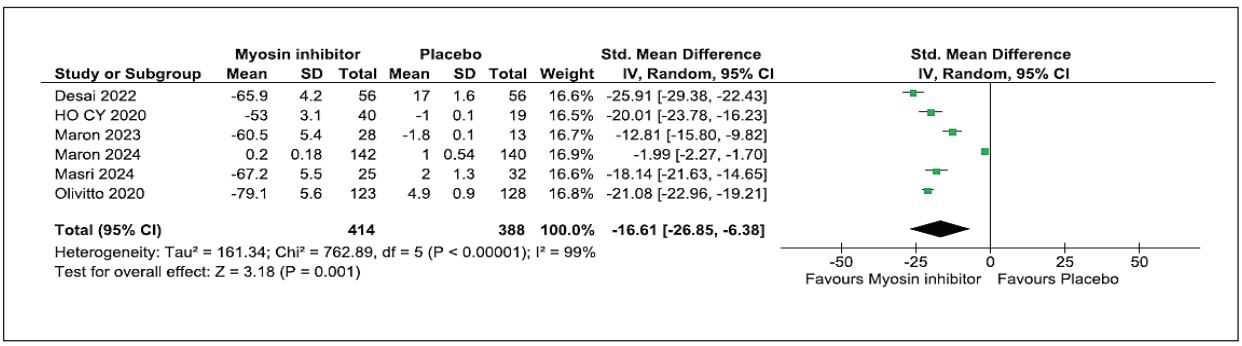

Figure 8. *Random-effect model of NT-proBNP.*

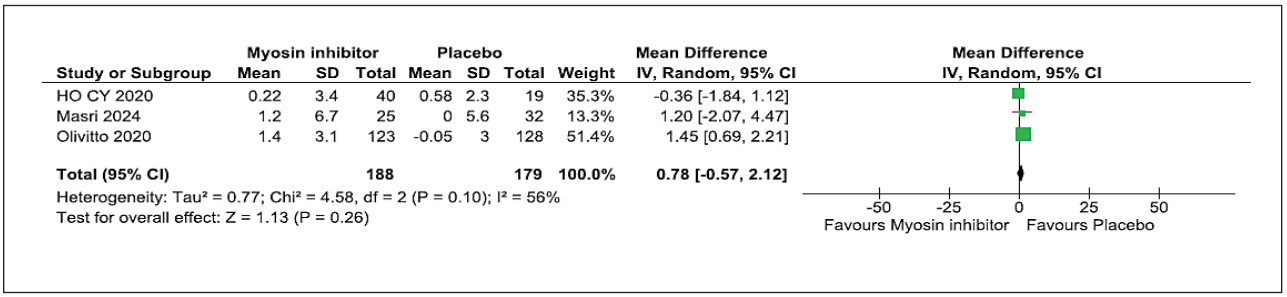

Figure 9. *Random-effect model of pVO_2.*

gradients and improvements in functional status with cardiac myosin inhibition [10,18,19]. Previous individual trials and observational studies have similarly reported improvements in biomarkers and patient-reported outcomes without significant serious adverse events [20,21]. By pooling data across multiple RCTs with varying study designs and populations, this meta-analysis enhances statistical power and provides a more accurate estimate of treatment effects, strengthening the evidence that the benefits seen in previous studies are reliable and consistent across trials.

LVOT obstruction is the central pathophysiological abnormality in obstructive HCM, driven by sarcomere hypercontractility, septal hypertrophy, and systolic anterior motion of the mitral valve, which eventually creates a dynamic gradient during systole [22,23]. Cardiac myosin inhibitors directly target the sarcomere by reducing the number of force-generating actin–myosin cross-bridges, thereby attenuating excessive contractility at the molecular level and decreasing the inotropic contribution to dynamic obstruction [8,24].

These effects decrease resting and post-Valsalva LVOT gradients, which improves intraventricular hemodynamics [10,25]. Clinically, this improvement in hemodynamics is associated with enhanced NYHA functional class and reductions in NT-proBNP, a biomarker of myocardial wall stress and adverse outcomes in HCM [26]. The observed decrease in LVEF with myosin inhibitors reflects attenuation of hypercontractility rather than intrinsic myocardial dysfunction [10]. However, a significant decrease in LVEF in some patients has been reported as a reason to adjust the dose or stop the medication, highlighting the importance of careful dose adjustments and echocardiographic monitoring [20].

Cardiac myosin inhibitors represent a substantial shift in the management of HCM by shifting the focus from symptom-based approaches to mechanism-targeted therapies [27]. Traditional treatments, including beta-blockers and calcium channel blockers, primarily alleviate symptoms through heart rate reduction and afterload modulation; however, they do not directly affect sarcomere dysfunction [8]. In contrast, myosin inhibitors target the molecular driver of disease and provide substantial improvements in hemodynamic obstruction, symptoms, and quality of life. The lack of a significant increase in serious adverse events implies that these agents are generally safe when appropriately monitored [28].

The absence of significant improvement in pVO_2 may indicate that maximal exercise capacity does not immediately reflect improvements in resting or provoked hemodynamics [10,29]. However, more trials are needed to address this outcome, as was reported in only three.

Strength

This systematic review and meta-analysis represent the most comprehensive study to date of RCTs evaluating cardiac myosin inhibitors in HCM. Strengths include the inclusion of seven RCTs with the largest pooled patient population reported thus far (883 patients), enhancing statistical power and precision. The analysis incorporated both objective hemodynamic measures and patient-centered outcomes, including LVOT gradients, LVEF, NYHA class, KCCQ, NT-proBNP, pVO_2, and serious adverse events. Inclusion of both obstructive and non-obstructive HCM populations, as well as evaluation of two pharmacologically distinct agents, improves heterogeneity. Rigorous methodology, sensitivity analyses, and subgroup analyses further strengthen the reliability of the findings.

Limitations

This meta-analysis has several limitations. Long-term data on mortality, disease progression, ventricular remodeling, and safety outcomes remain limited, restricting conclusions regarding the long-term prognostic impact of cardiac myosin inhibitors. Significant heterogeneity was observed in several outcomes, driven by differences in trial design, pharmacokinetics of the studied agents (aficamten, mavacamten), duration of follow-up, and patient populations. Additionally, data on aficamten in non-obstructive HCM remain insufficient to draw conclusions regarding its efficacy.

Future research by clinical investigators and pharmaceutical developers should prioritize focusing on long-term randomized trials evaluating cardiac myosin inhibitors as disease-modifying therapies in HCM. These studies should evaluate the sustainability of treatment benefits, the impact on disease progression, changes in cardiac structure, and effects on survival. Comparative trials with standard therapies, such as beta-blockers and calcium channel blockers, are needed to determine the optimal sequence for using these treatments. Studies evaluating transition strategies from conventional therapy to myosin inhibitors and head-to-head comparisons among different agents within this class would further clarify class-specific differences and optimize patient selection for treatment.

Conclusion

This meta-analysis concludes that cardiac myosin inhibitors, including mavacamten and aficamten, are a useful treatment option for HCM, as they successfully lower the LVOT gradient, which significantly improves symptoms and overall quality of life. Furthermore, some medications are linked to positive modifications to KCCQ and NYHA class, along with a decrease in cardiac NT-proBNP. However, these advantages are offset by a lower LVEF with no changes in serious adverse events and pVO_2.

List of Abbreviations

HCM	Hypertrophic cardiomyopathy
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
NYHA	New York Heart Association

Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

Finding
None.

Consent to participate
Not applicable.

Ethical approval
Not applicable.

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Supplementary content (If any) is available online.

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