


openheart Efficacy of cardiac myosin inhibitors mavacamten and aficamten in hypertrophic cardiomyopathy: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background Unlike other suggested therapies, myosin inhibitors have been shown to change the course of hypertrophic cardiomyopathy by altering the contractile mechanics of cardiomyocytes. This meta-analysis sought to determine the efficacy of mavacamten and aficamten in hypertrophic cardiomyopathy.

Methods The online databases were searched from inception to July 2024, including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ClinicalTrials.gov. The meta-analytical data were pooled using risk ratios (RRs) with 95% CI, standard mean difference (SMD) and SE.

Results A total of 6 randomised controlled trials with 826 hypertrophic cardiomyopathy patients (mean age±SD up to 59.8±14.2 years in intervention vs 60.9±10.5 years in placebo) were included in our study. Of these, 443 received a cardiac myosin inhibitor and 383 received a placebo. The resting left ventricular outflow tract (LVOT) gradient between the two groups was considerably improved by cardiac myosin inhibitors (MD −57.27; 95% CI −63.05 to −51.49). Significant differences were also observed in the post-Valsalva LVOT gradient between the two groups (MD −55.86; 95% CI −65.55 to −46.18). Significantly decreased left ventricle ejection fraction (LVEF) was also seen (MD −4.74; 95% CI −7.22 to −2.26). The New York Health Association (NYHA) class improvement between the two groups also changed significantly (RR 2.21; 95% CI 1.75 to 2.80). Cardiac myosin inhibitors also caused significant improvement in the Kansas City Cardiomyopathy Questionnaire in a Clinical Summary Score between the two groups (MD 7.71; 95% CI 5.37 to 10.05) and significant reduction in the N-terminal pro-B-type natriuretic peptide (SMD −13.27; 95% CI −17.51 to −9.03) and the cardiac troponin I (SMD −11.90; 95% CI −15.07 to −8.72).

Conclusion According to our meta-analysis, cardiac myosin inhibitors significantly improve the resting and post-Valsalva LVOT gradient, reduce the LVEF and improve the NYHA class and cardiac biomarkers when compared with the placebo.

PROSPERO registration number CRD52024586161.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ One in 500 members of the general public has hypertrophic cardiomyopathy (HCM).¹ While a number of therapies have proven safe and beneficial in managing HCM, no medication has been proven to alter the disease's course. Myosin inhibitors, however, have the ability to influence pathogenesis and alleviate symptoms related to HCM.

WHAT THIS STUDY ADDS

⇒ This study pools the data from randomised controlled trials and focuses on the role of mavacamten and aficamten in both HCM, showing improvement in resting and post-Valsalva left ventricular outflow tract gradients, New York Health Association functional class, cardiac biomarkers and quality of life. However, it also shows that the use of myosin inhibitors is associated with the risk of reduced left ventricle ejection fraction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The analysis shines light on the promising future of myosin inhibitors in HCM, both obstructive and non-obstructive, particularly with regard to the advantageous effects of aficamten, which will facilitate the drug's eventual FDA approval.

INTRODUCTION

One in 500 members of the general public has hypertrophic cardiomyopathy (HCM), a widespread inherited cardiovascular illness that is the leading cause of sudden mortality for young people, particularly athletes, and an annual mortality of 1% overall. Nonetheless, it is thought to be more common now according to modern diagnostic methods (such as genetic testing and imaging).^{1–3} HCM is histologically characterised by myocyte enlargement, disorganisation and myocardial fibrosis.⁴ While a number of therapies

have proven safe and beneficial in managing HCM, no medication has been proven to alter the disease's course or reduce the maximum wall thickness.³ Myosin inhibitors, however, have the ability to influence pathogenesis and alleviate symptoms related to HCM by modifying the contractile mechanics of the cardiomyocyte.⁵

Cardiac hypertrophy is caused by increased cardiac stress and afterload; the pathogenesis of the condition, however, is linked to myocardial remodelling.⁶ Patients with HCM are at risk for atrial fibrillation, heart failure and stroke.⁷ The most important predictor of heart failure in patients with HCM is left ventricular outflow tract (LVOT) obstruction, which is brought on by asymmetric hypertrophy of the cardiac septum.^{7,8} The various mechanisms that cause the left ventricular outflow obstruction include actin-myosin cross-bridging, which causes cardiac hypercontractility, prolonged mitral valve leaflets and protrusion of the hypertrophic ventricular

septum into the LVOT.⁹ A well-defined management approach is required due to the substantial morbidity and mortality associated with this illness. In contrast to other areas of cardiology, the care of patients with HCM is still inadequately addressed, despite modern therapies and techniques.¹⁰ The different treatment options include beta-blockers (BB), calcium channel blockers (CCB), antiarrhythmics, ACE inhibitors/angiotensin receptor blockers, diuretics and oral anticoagulants, and the surgical options are myomectomy or septal ablation.¹¹ Many patients experience insufficient relief of heart failure symptoms due to unsatisfactory gradient reduction or off-target adverse medication effects caused by the present pharmacological therapy.⁸ The sarcomere proteins are mutated genetically to produce structural abnormalities in cardiac myocytes and myofibrils, which causes aberrant force generation and electrical activity in the heart.⁸ Cardiac myosin inhibitors have lately surfaced

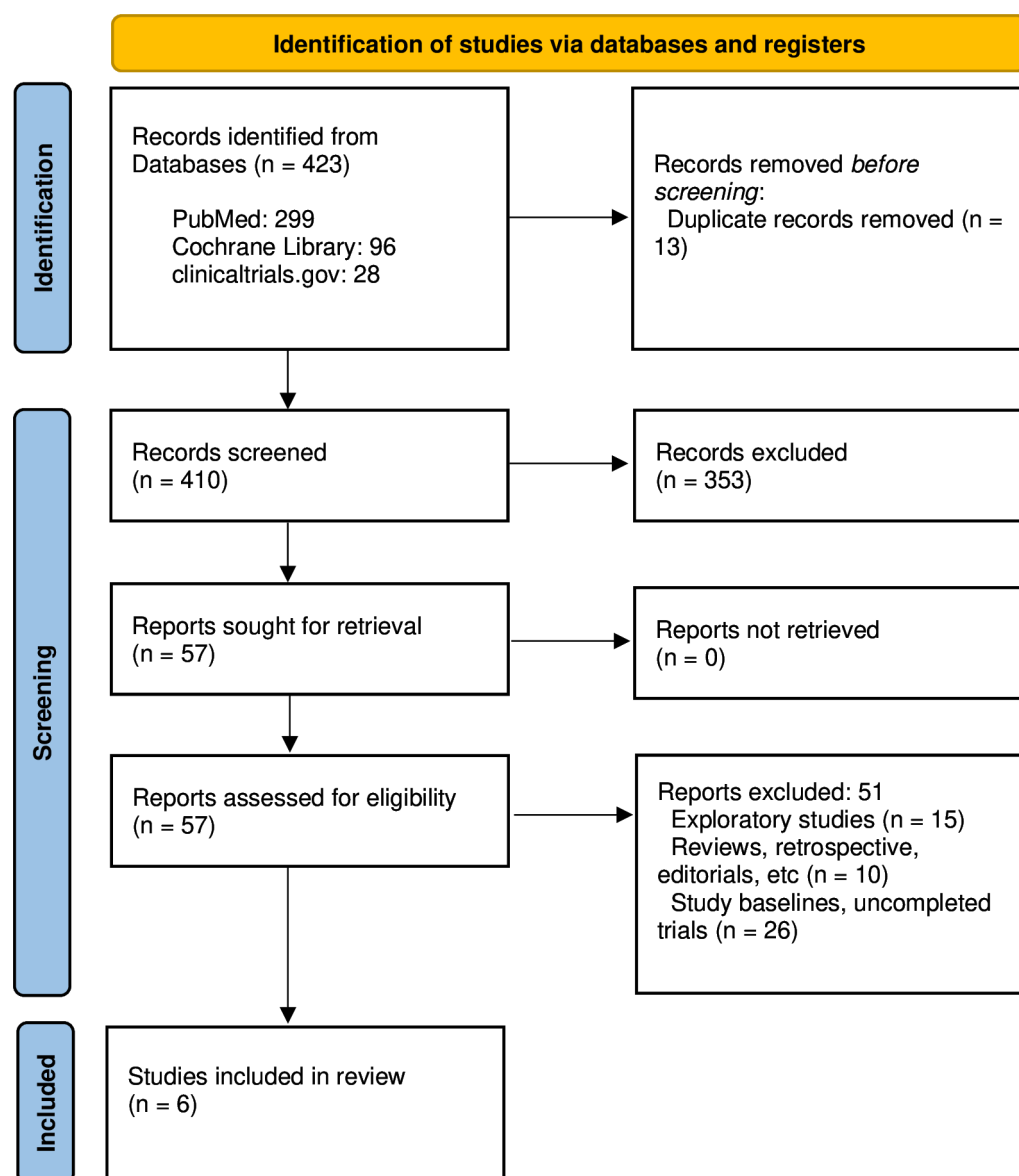


Figure 1 PRISMA flow diagram of included and excluded trials. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Baseline characteristics of included studies

Study ID	Trial name	Country	Design	Population (Intervention/ placebo)	Gender (male%)	Mean age±SD (Intervention/ placebo)	Study duration	Background HCM therapy (Intervention vs placebo)			NYHA functional class (Intervention vs placebo)			Medical history (Intervention vs placebo)			Peak LVOT gradient cut-off for inclusion in trials	Number of patients who discontinued
								Beta blocker	Calcium channel blocker	III	II	III	Family history of HCM	Hypertension	Atrial fibrillation			
Olivotto <i>et al.</i> , 2020 ¹³	EXPLORER-HCM	Multinational	Phase 3, double-blind RCT	Obstructive HCM 251 (123/128)	54/65	58.5±12.2/58.5±11.8	30 weeks	94 vs 95	25 vs 17	33 vs 36	88 vs 95	35 vs 33	57 vs 53	12 vs 23	Patients with peak LVOT gradient≥50 mm Hg at rest or post-Valsalva were included.	5 patients discontinued; 3 in mavacamten (due to adverse effects), 2 in placebo group (one due to sudden death and one withdrew)		
Ho <i>et al.</i> , 2020 ⁵	MAVERICK-HCM	Multicentre, USA	Phase 2, double-blinded RCT	Non-obstructive HCM 59 (40/19)	47.5/31.6	54±14.6/53.8±18.2	16 weeks	25 vs 12	10 vs 3	--	33 vs 13	7 vs 6	--	--	Patients with peak LVOT gradient≤30 mm Hg were excluded.	5 mavacamten-treated patients discontinued (due to decrease in LVEF<45%)		
Desai <i>et al.</i> , 2022 ²³	VALOR-HCM	Multicentre, USA	Phase 3, double-blind RCT	Obstructive HCM 112 (56/56)	51.8/50.0	59.8±14.2/60.9±10.5	16 weeks	26 vs 25	7 vs 10	17 vs 15	4 vs 4	52 vs 52	36 vs 34	11 vs 8	Patients with peak LVOT gradient≥50 mm Hg at rest or after Valsalva manoeuvre were included.	4 discontinued in placebo group (2 went for septal reduction therapy, 1 found ineligible post-enrolment, 1 withdrew); 2 discontinued in mavacamten group (went for septal reduction therapy)		
Tian <i>et al.</i> , 2023 ²⁴	EXPLORER-CN	Multicentre, China	Phase 3, double-blind RCT	Obstructive HCM 81 (54/27)	75.9/63.0	52.4±12.1/51.0±11.8	30 weeks	48 vs 24	4 vs 2	--	44 vs 18	10 vs 9	--	--	Patients with peak LVOT gradient≥50 mm Hg at rest or after Valsalva manoeuvre were included.	2 in the placebo group discontinued (one due to COVID-19 issues and one due to personal reasons)		
Maron <i>et al.</i> , 2023 ⁸	REDWOOD-HCM	Multicentre, North America and Europe	Phase 2, double-blind RCT	Obstructive HCM 41 (28/13)	46/38	57±25–32/59± (53–64)	10 weeks	21 vs 11	7 vs 2	--	17 vs 11	11 vs 2	--	--	Patients with peak LVOT gradient≥50 mm Hg at rest or after Valsalva manoeuvre; or resting LVOT gradient<50 mm Hg but>30 mm Hg were included.	No one discontinued.		
Maron <i>et al.</i> , 2024 ⁸	SEQUOIA-HCM	Multinational	Phase 3, double-blind RCT	Obstructive HCM 282 (142/140)	60.6/57.9	59.2±12.6/59.0±13.3	24 weeks	86 vs 87	45 vs 36	41 vs 34	108 vs 106	34 vs 33	75 vs 70	23 vs 21	Patients with resting LVOT gradient≥30 mm Hg and post-Valsalva LVOT gradient≥50 mm Hg were included.	9 patients discontinued (due to adverse effects or not meeting the cardiopulmonary exercise criteria)		
LVOT gradient, Left Ventricular Outflow Tract gradient; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; RCT, randomised controlled trial.																		

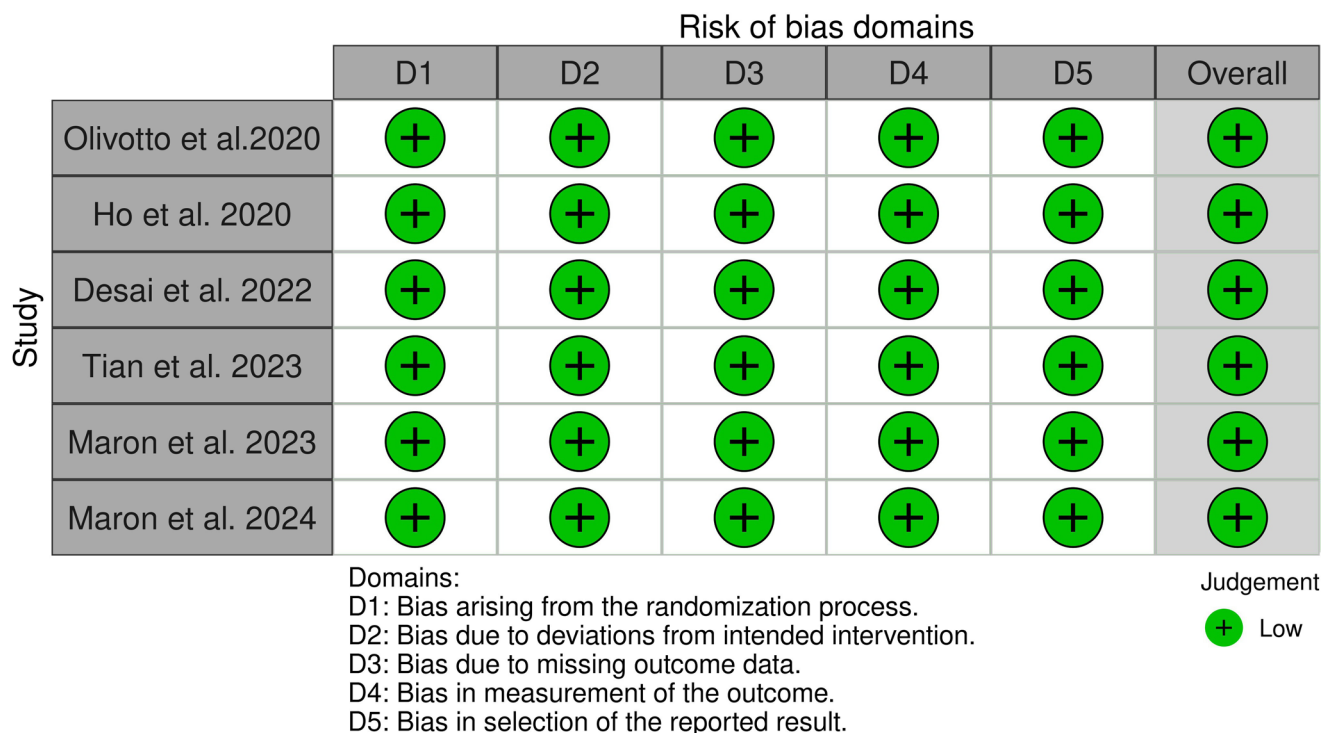


Figure 2 Quality assessment of the included randomised controlled trials.

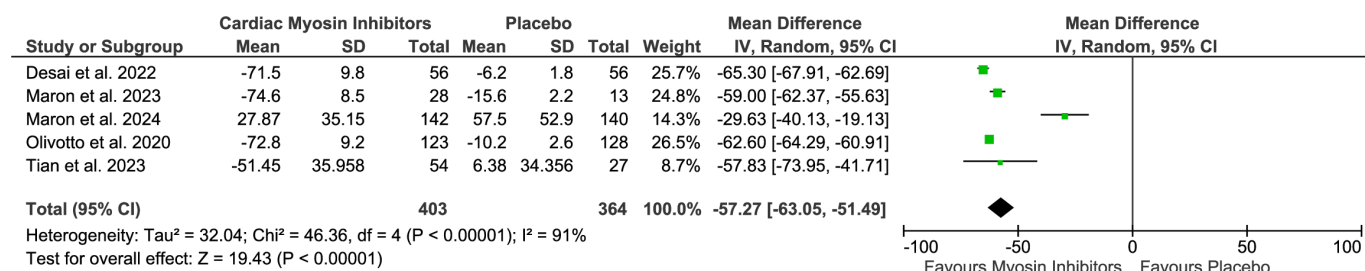


Figure 3 Forest plot of change in resting LVOT gradient. LVOT, left ventricular outflow tract.

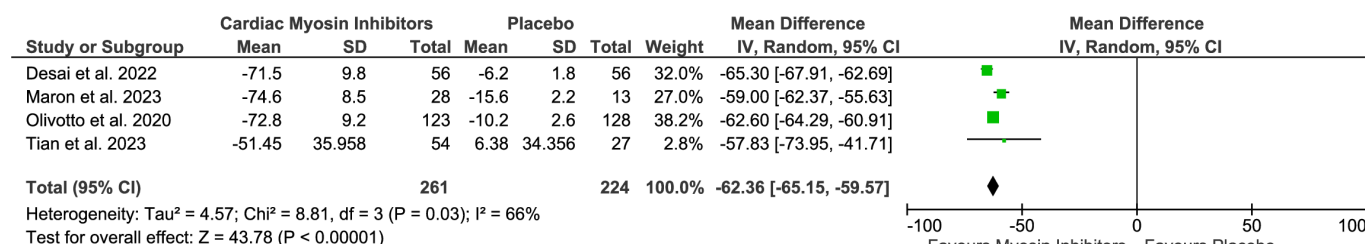


Figure 4 Forest plot of sensitivity analysis of change in resting LVOT gradient. LVOT, left ventricular outflow tract.

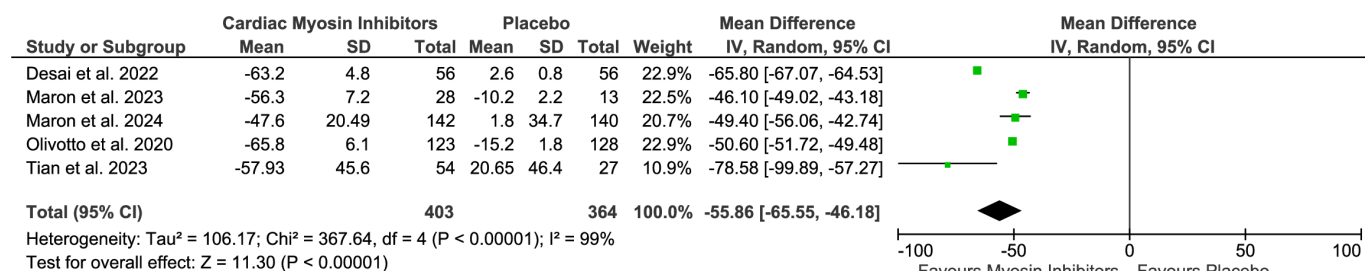


Figure 5 Forest plot of change in post-Valsalva LVOT gradient. LVOT, left ventricular outflow tract.

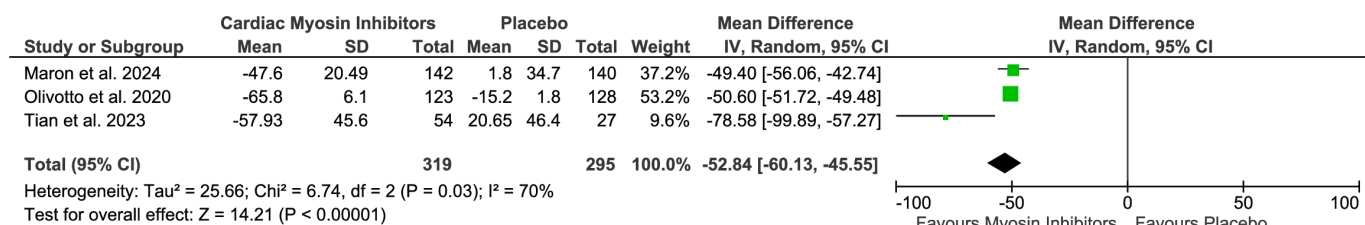


Figure 6 Forest plot of sensitivity analysis of change in post-Valsalva LVOT gradient. LVOT, left ventricular outflow tract.

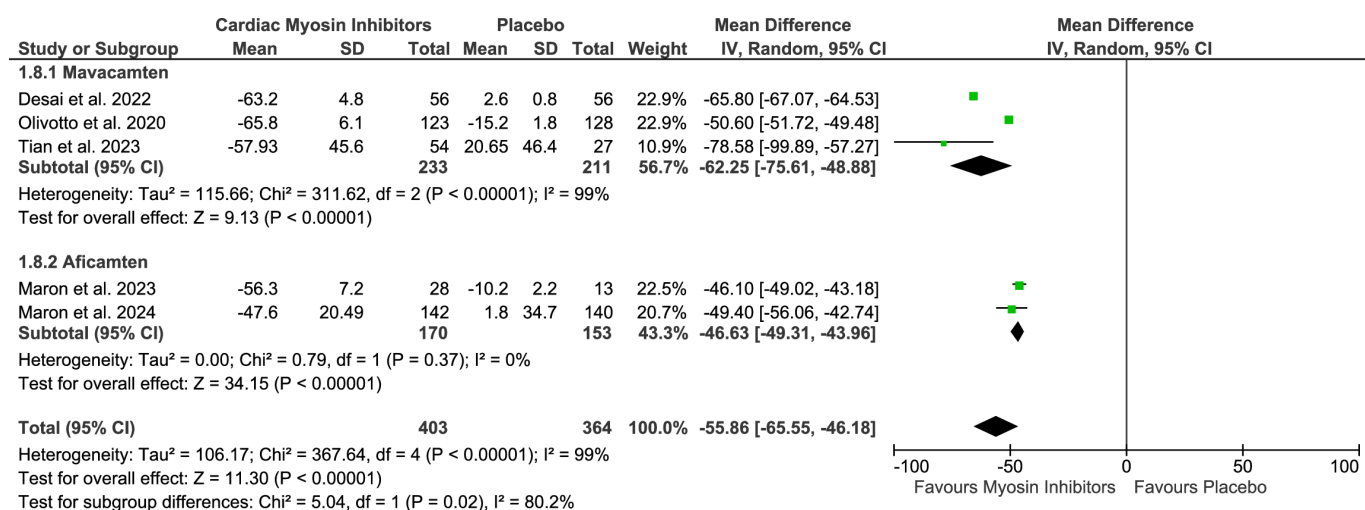


Figure 7 Forest plot of subgroup analysis of change in post-Valsalva LVOT gradient. LVOT, left ventricular outflow tract.

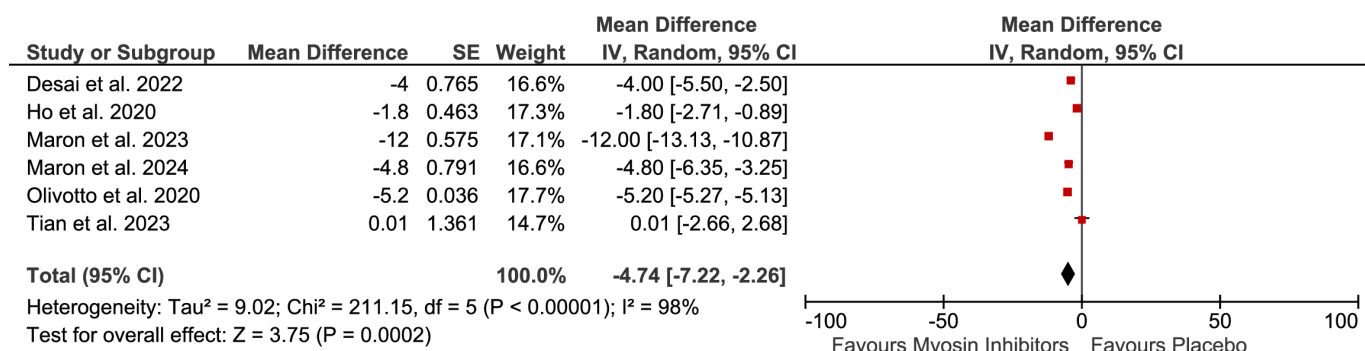


Figure 8 Forest plot of change in LVEF.

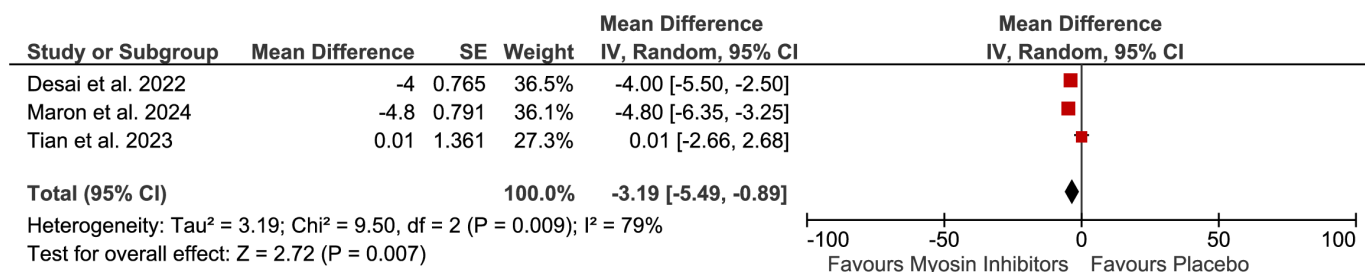


Figure 9 Forest plot of sensitivity analysis of change in LVEF.

as a potentially ground-breaking therapeutic option intended to improve heart failure symptoms in patients with obstructive HCM. They do this by reducing LVOT gradients and heart contractility.^{12–15} Because these medications, mavacamten and aficamten, inhibit the formation of actin-myosin cross-bridges, they improve symptoms, quality of life, LVOT gradients and biomarkers,

suggesting the potential for sarcomere-targeted therapy in the treatment of obstructive HCM.^{8 16}

The goal of this systematic review and meta-analysis is to emphasise the function of cardiac myosin inhibitors in the management of HCM. These medications are undergoing several clinical studies, and by compiling the data into one comprehensive analysis, we want to provide a

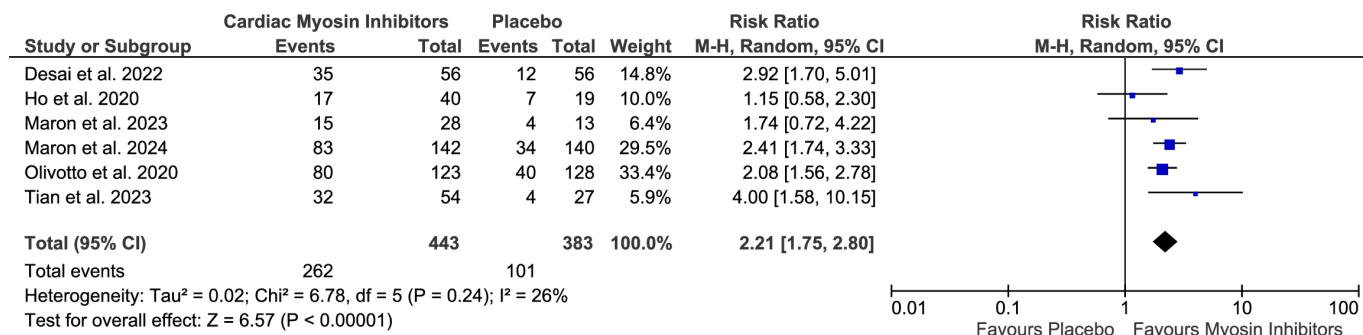


Figure 10 Forest plot of NYHA class improvement.

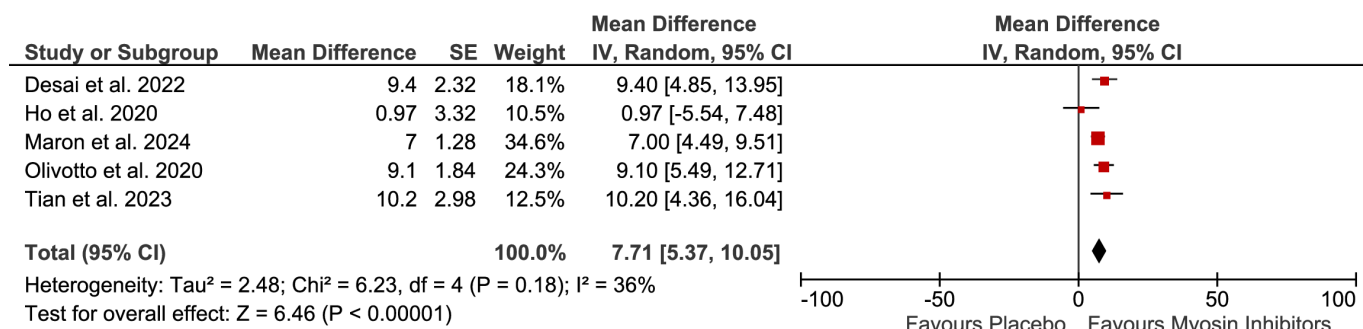


Figure 11 Forest plot of change in KCCQ-CSS.

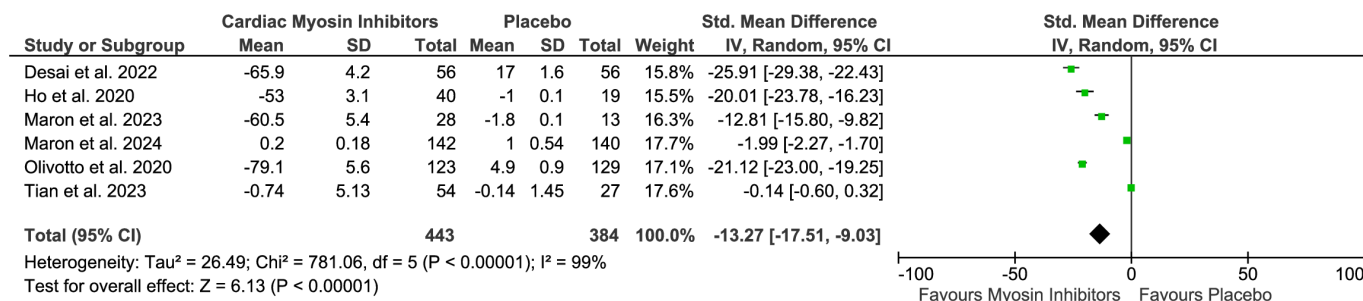


Figure 12 Forest plot of change in NT-proBNP.

certain assessment of their effectiveness in treating HCM and further update the evidence. Future studies on mavacamten and aficamten and their roles in HCM will benefit from the direction and guidance this review offers.

METHODS

This systematic review and meta-analysis was conducted following the guidelines recommended by the Cochrane Handbook for Systematic Reviews¹⁷ and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.¹⁸ The protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) and available as CRD52024586161.

Data sources and search strategy

The following databases, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ClinicalTrials.gov, were searched in a systematic manner to retrieve all the relevant articles from inception to July 2024. The following MeSH terms were used: 'Hypertrophic cardiomyopathy', 'cardiac myosin inhibitors', 'Mavacamten'

and 'Aficamten'. The reference lists of all the included studies were also screened to identify any potential articles. The detailed search strategy is given in online supplemental table S1.

Study selection and eligibility criteria

After importing the studies into Endnote software, we removed the duplicates. Titles and abstracts were screened by two reviewers (ArA and BA) independently. Full-text screening was performed according to the eligibility criteria and any conflicts were resolved by a third reviewer (AyA). The inclusion criteria were as follows (online supplemental table S2) (1) Population: Patients having HCM whether obstructive or non-obstructive; (2) Intervention: Cardiac myosin inhibitors either mavacamten or aficamten; (3) Control: Placebo and (4) Outcomes: Primary outcomes were change in resting and post-Valsalva left ventricle outflow tract (LVOT) gradient, change in left ventricle ejection fraction (LVEF) and secondary outcomes were change in N-terminal pro-B-type natriuretic peptide (NT-pro-BNP),

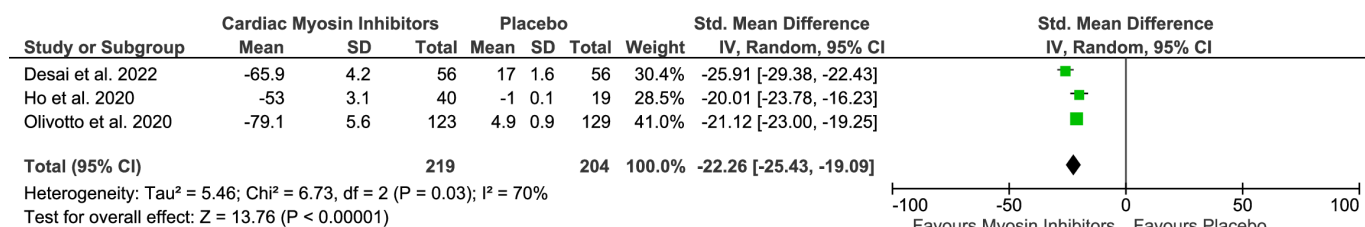


Figure 13 Forest plot of sensitivity analysis of change in NT-proBNP.

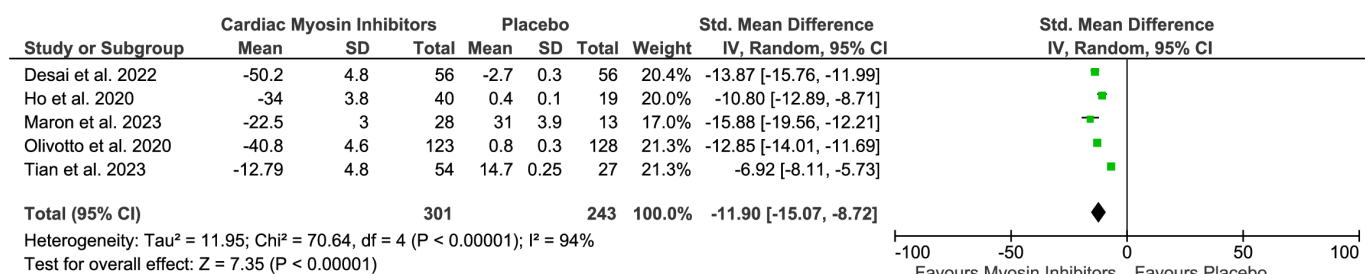


Figure 14 Forest plot of change in cTnI.

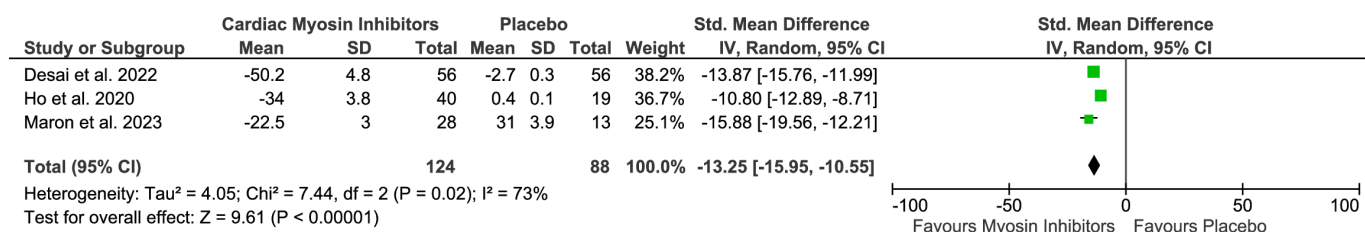


Figure 15 Forest plot of sensitivity analysis of change in cTnI.

cardiac troponin I (cTnI) and improvement in the form of change in Kansas City Cardiomyopathy Questionnaire in a Clinical Summary Score (KCCQ-CSS), proportion of patients achieving at least one New York Health Association (NYHA) class improvement. (5) Study design: Only randomised controlled trials (RCTs). If studies included interventions other than cardiac myosin inhibitors or were animal studies or any other study design, they were excluded.

Data synthesis and extraction

Two independent reviewers (BA and MM) carried out data extraction using an Excel spreadsheet. Data regarding study characteristics (study identification, affiliation, trial name, study design, total participants, intervention dosage and duration in weeks, age, percentage of male population, peak LVOT gradient cut-off values for inclusion in trials, number of patients who discontinued intervention, medical history and background therapy as well as NYHA functional class) were extracted. Any confusion was resolved through discussion with a third reviewer (AyA). Data for the outcomes were extracted as follows: mean and SD for change from baseline in both resting and post-Valsalva LVOT gradients, change from baseline in levels of NT-proBNP and cTnI; mean difference (MD) and SE for change in LVEF and quality of life improvement measured via KCCQ-CSS. The outcome data were

also extracted from figures if values were not mentioned directly.

Risk of bias and quality assessment

The quality of the included trials was assessed using the revised Cochrane Risk of Bias Tool for RCTs (ROB 2.0).¹⁹ Following domains were assessed: Bias arising from the randomisation process, deviation from the intended intervention, missing outcome data, measurement of outcome and selective reporting of results. Overall risk of bias was identified as 'high', 'low' or 'some concerns'.²⁰ The studies were assessed individually by two reviewers (AlA and SA) and if needed, a third reviewer (ArA) was consulted. Publication bias was assessed only if the number of studies was found to be more than 10.²¹

Statistical analysis

We conducted statistical analysis using the Review Manager software (RevMan V.5.4). Study-specific effect sizes were compared via pooled risk ratios (RRs) and 95% CIs for binary outcomes. For continuous outcomes, MD and SD were used. A random effects model was employed using the DerSimonian and Laird variance estimator.²² Using I^2 and χ^2 values, heterogeneity was assessed. A $p < 0.1$ was considered to be statistically significant. If heterogeneity was found to be high, leave-out analysis was performed to identify any outliers. Subgroup analysis was

performed; subgroups being made on the basis of intervention (either mavacamten or aficamten).

RESULTS

Search results and study selection

A total of 423 studies were identified from various databases (Cochrane, PubMed and ClinicalTrials.gov). After duplicates removal and primary screening, 57 articles were identified. Full texts of those 57 articles were assessed for eligibility. A total of six RCTs were included in our meta-analysis. The screening process is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (figure 1).

Characteristics of included studies

We included six RCTs in our meta-analysis. A total of 826 HCM patients were included with a mean age \pm SD up to 59.8 \pm 14.2 years in intervention vs 60.9 \pm 10.5 years in placebo, of which 443 received cardiac myosin inhibitor and 383 received placebo. All studies had patients having background BB or CCB therapy.

The REDWOOD-HCM⁸ had a study duration of 10 weeks, MAVERICK-HCM⁵ and VALOR-HCM²³ had 16 weeks, SEQUOIA-HCM⁹ had 24 weeks and EXPLORER-HCM¹³ and EXPLORER-CN²⁴ had a duration of 30 weeks. Detailed characteristics of included studies are shown in table 1.

Risk of bias and quality of evidence

The Cochrane ROB2 tool was used to assess the risk of bias in the included studies. All the included studies were found to have a low risk of bias (figure 2).

Primary outcomes

Change in resting LVOT gradient

The data for the resting LVOT gradient were reported by five studies. Cardiac myosin inhibitors significantly improved the resting LVOT gradient between the two groups (MD -57.27; 95% CI -63.05 to -51.49) (figure 3). There was high interstudy heterogeneity ($I^2=91\%$). The study by Maron *et al* was removed during sensitivity analysis and the heterogeneity decreased to $I^2=66\%$ (figure 4). Subgroup analysis yielded insignificant results.

Change in post-Valsalva LVOT gradient

Five studies reported the data for the post-Valsalva LVOT gradient. Cardiac myosin inhibitors caused a significant decrease in the post-Valsalva LVOT gradient between the two groups (MD -55.86; 95% CI -65.55 to -46.18) (figure 5). There was a high statistical heterogeneity between the studies ($I^2=99\%$). The sensitivity analysis was performed and studies by Desai *et al* and Maron *et al* were removed, reducing the heterogeneity to $I^2=70\%$ (figure 6). Subgroup analysis was also performed. Two subgroups were made based on the intervention: mavacamten and aficamten. This decreased the heterogeneity to $I^2=80.2\%$ (figure 7).

Change in LVEF

All the six studies reported the data for the LVEF. Our meta-analysis indicated that cardiac myosin inhibitors significantly decreased the LVEF (MD -4.74; 95% CI -7.22 to -2.26) (figure 8). The statistical heterogeneity was estimated to be high ($I^2=98\%$). During sensitivity analysis, studies by Ho *et al*, Olivotto *et al* and Maron *et al* were removed. The heterogeneity decreased to $I^2=79\%$ (figure 9). Subgroup analysis yielded insignificant results.

Secondary outcomes

NYHA class improvement

The data for NYHA class improvement was reported by all the six studies. The meta-analysis showed that cardiac myosin inhibitors produced a significant change in the NYHA class improvement between the two groups (RR 2.21; 95% CI 1.75 to 2.80) (figure 10) with statistically insignificant heterogeneity.

Changes in KCCQ-CSS

The data for the changes in KCCQ-CSS were reported by five studies. Cardiac myosin inhibitors significantly improved the KCCQ-CSS between the two groups (MD 7.71; 95% CI 5.37 to 10.05) (figure 11). Heterogeneity was found to be statistically insignificant.

Changes in NT-proBNP

The data for the changes in NT-proBNP were reported by all the studies. Cardiac myosin inhibitors significantly decreased the NT-proBNP (standardised MD (SMD) -13.27; 95% CI -17.51 to -9.03) (figure 12). The heterogeneity reported between studies for this outcome was high ($I^2=99\%$). Studies by Tian *et al*, Maron *et al* and Maron *et al* were removed during sensitivity analysis, decreasing the heterogeneity to $I^2=70\%$ (figure 13). Subgroup analysis showed statistically insignificant results.

Change in cardiac troponin I

Five studies reported the data for the cardiac troponin I. The meta-analysis indicated that myosin inhibitors caused a significant decrease in the cardiac troponin I between the two groups (SMD -11.90; 95% CI -15.07 to -8.72) (figure 14) with high interstudy heterogeneity ($I^2=94\%$). During sensitivity analysis, studies by Olivotto *et al* and Tian *et al* were removed. As a result, the heterogeneity decreased to $I^2=73\%$ (figure 15). Subgroup analysis did not yield any significant results.

DISCUSSION

This meta-analysis summarises the findings of six RCTs. It shows that cardiac myosin inhibitors are associated with a decrease in resting as well as post-Valsalva LVOT gradient, decrease in LVEF, improvement in NYHA class and KCCQ-CSS. They also decrease the levels of NT-proBNP and cardiac troponin I.

LVOT obstruction is one of the critical components of HCM,²⁵ caused by septal hypertrophy, systolic anterior motion of mitral valve leaflet and dynamic conditions

that increase catecholamines in blood like exercise.²⁶ Cardiac myosin inhibitors decrease LVOT obstruction by decreasing cardiac contractility,²⁷ leading to decrease in both resting as well as post-Valsalva LVOT gradient. Thus, myosin inhibitors provide relief to patients by decreasing chest pain, dyspnoea, improved exercise tolerance and better health status.^{28–30} They decrease the need for septal reduction therapies like surgical myectomy and other invasive procedures for reducing LVOT obstruction.³¹ RCTs included in this analysis show that myosin inhibitors are generally well tolerated with a safety profile similar to placebo, with most adverse effects being mild.

But the advantage of reduced LVOT gradient comes at the cost of reduced LVEF,³² which is reported by all six trials included in the meta-analysis. Reduced LVEF in HCM patients is associated with worse outcomes, including higher risks of sudden cardiac death, heart failure hospitalisation and cardiovascular death.³³ Some of the patients included in the trials had to discontinue the drug due to significant drop in LVEF (<50%). But reduction in LVEF resolved after either drug discontinuation or dosage adjustment, showing reversible and dosage-dependent effect of myosin inhibitors on LVEF. High heterogeneity observed in the analysis of LVOT gradient and LVEF resolved after performing sensitivity analysis showing that heterogeneity was due to study characteristics like population demographics, disease severity, presence of comorbidities, differences in dosage or duration of treatment.

Patients with intense symptoms have higher NYHA classification which shows inverse correlation with health-related quality of life quantified by KCCQ-CSS.³⁴ The NYHA class is improved by myosin inhibitors, especially in symptomatic obstructive disease as they enhance cardiac performance, as demonstrated by all of the RCTs in this analysis, and five of them also demonstrated improvements in quality of life.

The biomarkers of the severity and prognosis of HCM are released into the serum as a consequence of the pathophysiological alterations in myocytes. These include pro-BNP and troponin I.³⁵ When compared with placebo, mavacamten and aficamten were both found to lower serum cardiac markers by reducing sarcomere force generation.

The strength of this study lies in a strong foundation thorough compilation of previously published research data in the form of high-quality RCTs that not only reduce the possibility of bias but also increase the power of the study. The accuracy and depth of this meta-analysis were improved by the extensive research done on several databases for this study. Rigid inclusion and exclusion criteria were followed. The results were more plausible since standard protocols were used for data extraction, assessment and analysis, further adding to the evidence. The analysis shines light on the promising future of myosin inhibitors, particularly with regard to the advantageous effects of aficamten, which will facilitate the drug's eventual FDA (Food and Drug Administration) approval.

Despite its positive aspects, the meta-analysis has some limitations. The outcomes of cardiac myosin inhibitors have not been studied in pregnant patients with HCM, thereby excluding a significant population. The drugs need to be studied in conjunction with multitudes of existing treatment for heart failure and over-the-counter medications to furnish details regarding drug interactions. Isolating the effects on the heart obscures the interconnectedness of the cardiovascular and renal systems, making it necessary to investigate the overall effect when several comorbidities are present. The findings of this analysis require confirmation by other randomised investigations to substantiate their reliability.

In conclusion, this meta-analysis shows that cardiac myosin inhibitors, such as mavacamten and aficamten, represent a promising therapeutic option for HCM, effectively reducing LVOT gradient leading to significant improvements in symptoms and overall quality of life. Additionally, these drugs are associated with favourable changes in NYHA class and KCCQ-CSS as well as a reduction in cardiac biomarkers. However, these benefits are counterbalanced by decreased LVEF.

Contributors AyA: writing—original draft, supervision, software, methodology, formal analysis, data curation, conceptualisation, screening. (This author is the guarantor and takes full responsibility for the work's integrity.) ArA: writing—original draft, methodology, formal analysis, data curation, screening. BA: writing—review and editing, software, writing—original draft, data curation, screening. MM: writing—review and editing, writing—original draft, software, formal analysis. MZB: writing—original draft, software, methodology, formal analysis. AIA: writing—original draft, software, risk of bias assessment, methodology. SA: writing—review and editing, risk of bias assessment, formal analysis. FY: writing—review and editing, writing—original draft.

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Patient consent for publication Not applicable.

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