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Efficacy and safety of mavacamten for the treatment of hypertrophic cardiomyopathy: an updated systematic review and meta-analysis of randomized controlled trials

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Abstract

The efficacy and safety profile of mavacamten, a cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy (HCM) is not well-established, prompting the need for an updated meta-analysis. The authors conducted an extensive search across multiple electronic databases, including Embase, MEDLINE (via Pubmed), and CENTRAL, to identify randomized controlled trials (RCTs) assessing the efficacy and safety of mavacamten in HCM. Review Manager 5.4 (Revman) was employed to pool risk ratios (RR) and mean differences (MD). Our literature search yielded 4 RCTs with a total of 503 patients. Mavacamten was found to be associated with higher rates of greater than or equal to 1 New York Heart Association (NYHA) class improvement (RR 2.20, 95% CI: 1.48–3.28; $I^2 = 51\%$) and change from baseline in the Kansas City Cardiomyopathy Questionnaire- Clinical Summary Score (KCCQ-CSS) (MD 7.50, 95% CI: 3.44–11.55; $I^2 = 50\%$). Mavacamten was also associated with improved resting left ventricular outflow tract (LVOT) gradient (MD – 38.33, 95% CI: – 49.38 to – 27.28; $I^2 = 75\%$), Valsalva LVOT gradient (MD – 48.08, 95% CI: – 62.21 to – 33.96; $I^2 = 78\%$), post-exercise LVOT gradient (MD – 37.1, 95% CI: – 44.37 to – 29.84; $I^2 = 0\%$), LVMI (MD – 16.91, 95% CI: – 28.29 to – 5.54; $I^2 = 88\%$), and lower rates of septal reduction therapy (SRT) (RR 0.30, 95% CI: 0.22–0.40; $I^2 = 0\%$). There were no significant differences between mavacamten and placebo regarding the composite functional outcome, greater than or equal to 1 treatment-emergent adverse event, greater than or equal to 1 serious adverse event, and atrial fibrillation. The authors; findings suggest that mavacamten contributes to improvements in NYHA class, KCCQ-CSS scores, and LVOT gradients while reducing the incidence of SRT in patients with HCM.

Keywords HOCM, hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, mavacamten

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder that affects the structure of the cardiac muscle, leading to impaired cardiac function. It is a relatively common condition. The disease is estimated to have a prevalence of 1 case per 500–1000 individuals, making it a significant threat, especially to

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young adults and athletes. HCM is characterized by a notable increase in left ventricular (LV) thickness, measuring greater than or equal to 15 mm in adults, accompanied by abnormal mitral valve, diminished compliance, myofibrillar disorganization, and cardiac fibrosis[1,2]. HCM is typically divided into two categories; obstructive and non-obstructive. Hypertrophic obstructive cardiomyopathy (HOCM) is a specific type characterized by the excessive thickening of the left ventricular myocardium. This thickening causes dynamic obstruction or blockage of the outflow tract of the left ventricle[3]. The presence of left ventricular outflow tract obstruction (LVOTO) is a prominent characteristic seen in several individuals diagnosed with HCM[4]. Significant LVOTO is not just related to symptoms such as chest pain, dyspnea, and fatigue. However, it also increases the risk for all-cause mortality, cardiovascular (CV) mortality, sudden cardiac death (SCD), and other cardiovascular complications[5].

In severe cases, treatment options such as surgical septal myectomy and alcohol septal ablations may be recommended as invasive procedures[6]. There are various therapeutic options available for treating HOCM. These options include β-blockers, non-dihydropyridine calcium-channel blockers, diuretics, and implantable cardioverter defibrillators (ICDs)[7,8]. However, these current agents are not entirely effective, and many patients continue to experience symptoms despite receiving treatment. Furthermore, no existing method has been successful in rectifying the genetic abnormalities. Therefore, there is a need for the development of a novel pharmacological approach[9].

Mavacamten (MYC-461 and camzyos) represents a novel and specific inhibitor of β-cardiac myosin ATPase[10]. Notably, in 2022, the US FDA approved this particular drug, which stands as the sole representative of its class, to serve as a targeted therapy for hypertrophic cardiomyopathy[11]. Mavacamten reduces the number of actin-myosin cross-bridges, thereby decreasing hypercontractility, a mechanism involved in HCM pathogenesis[12].

The role of mavacamten in HCM is still unclear owing to the limited number of randomized controlled trials (RCTs)[13,14] possessing smaller sample sizes with significant heterogeneity among them. There is an increasing concern about potential variations in the safety and efficacy of mavacamten among patients with obstructive and non-obstructive hypertrophic cardiomyopathy. We conducted this updated systematic review and meta-analysis to consolidate the latest information regarding the efficacy and safety profile of mavacamten in obstructive and non-obstructive hypertrophic cardiomyopathy.

Material and methods

This systematic review and meta-analysis was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A587) statement[16]. We registered this review with The International Prospective Register of Systematic Reviews. We have also evaluated the quality of our systematic review through AMSTAR 2, Supplemental Digital Content 2, http://links.lww.com/MS9/A588 criteria[17].

HIGHLIGHTS

- Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder that affects the structure of the cardiac muscle, leading to impaired cardiac function.
- Current management strategies are not entirely effective, and many patients continue to experience symptoms despite receiving treatment. Therefore, there is a need for the development of a novel pharmacological approach.
- A total of 503 patients were included in our trial, 54.3% (273) were in the mavacamten group and 45.7% (230) were controls.
- Our findings suggest that mavacamten contributes to improvements in NYHA class, KCCQ-CSS scores, and LVOT gradients while reducing the incidence of SRT in patients with HCM.

Eligibility criteria

All RCTs that compared the use of mavacamten against placebo or standard care in patients with hypertrophic cardiomyopathy were included in the review. No language or geographical restrictions were applied. We excluded observational studies, literature and systematic reviews, case reports, editorials, and animal studies. Studies that did not evaluate our pre-specified clinical outcomes were also excluded from our review.

Information sources and search strategy

We conducted a thorough literature search from inception till October 2023 across multiple online databases including Embase (via Ovid), MEDLINE (via Pubmed), and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify RCTs assessing the efficacy and safety of mavacamten in HCM. Various International trial registers such as ClinicalTrials.gov. were also searched. We also screened reference lists of relevant systematic reviews and articles to retrieve pertinent studies.

Our literature search used terms related to “mavacamten”, “hypertrophic cardiomyopathy (HCM)”, and “hypertrophic obstructive cardiomyopathy (HOCM)”.

Study selection and data extraction

All literature search results were uploaded to Zotero 6.0.30 and duplicates were removed. Two researchers performed screening based on title and abstracts. The remaining articles were then subjected to full-text screening per our inclusion criteria. Any disputes between reviewers were settled through discussion.

After the study selection, a structured Excel spreadsheet was used to extract data from the included studies. The extracted data included patient characteristics (age, sex, duration of disease, type of hypertrophic cardiomyopathy), study characteristics (first author, year of publication, trial design), intervention details (dose, duration), comparator details, and outcome measures.

Outcome measures

Primary outcomes were: change from baseline in Kansa City Cardiomyopathy Questionnaire- clinical summary score

(KCCQ-CSS) and greater than or equal to 1 New York Heart Association (NYHA) class improvement. Secondary outcomes were analyzed amongst the following: Composite functional outcome; eligibility for septal reduction therapy (SRT); greater than or equal to 1 serious adverse event; greater than or equal to 1 treatment-emergent adverse event; atrial fibrillation; change from baseline in Valsalva LVOT peak gradient; change from baseline in resting LVOT peak gradient; change from baseline in LVMI and change from baseline in post-exercise LVOT peak gradient.

Risk of bias

The possibility of bias in the included studies was evaluated with the revised Cochrane 'Risk of bias' tool for randomized control trials (RoB 2.0)[18]. RoB 2.0 addresses five specific domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Two researchers independently applied the tool to every included study.

Data synthesis

Meta-analysis was done using Review Manager version 5.4 (Revman) provided that there was sufficient data present. A random-effects model with the DerSimonian variance estimator was used. χ^2 and I^2 statistics were assessed for every synthesis to evaluate the presence of heterogeneity and compute it, respectively. I^2 values were interpreted according to the Cochrane Handbook for Systematic Reviews of Interventions, section 10.10. Dichotomous data was analyzed utilizing risk ratios (RR) with a 95% CI. Continuous data were pooled using mean difference (MD) and 95% CI.

All the analyses were conducted as sub-group analyses based on the type of hypertrophic cardiomyopathy.

Results

Study selection

A total of 387 articles were identified after searching multiple databases. Following the removal of duplicate records and initial screening of studies, 28 full-length articles were reviewed for eligibility as illustrated in the PRISMA diagram given in Figure 1. A total of four randomized control trials were included in our meta-analysis[19–22].

Study characteristics

Table 1 illustrates the study characteristics of all four included trials. A total of 503 patients were included in our trial, 54.3% (273) were in the mavacamten group and 45.7% (230) were controls. A double-blinded approach was employed across all four trials that were conducted in numerous medical facilities and clinics, taking place in a diverse range of countries, including the United States, Spain, Poland, and China. Follow-up period ranged from 2-4 weeks to up to 30 weeks. 3 out of the 4 included trials employed patients with hypertrophic obstructive cardiomyopathy, only the Maverick HCM trial had patients with hypertrophic non-obstructive cardiomyopathy[20].

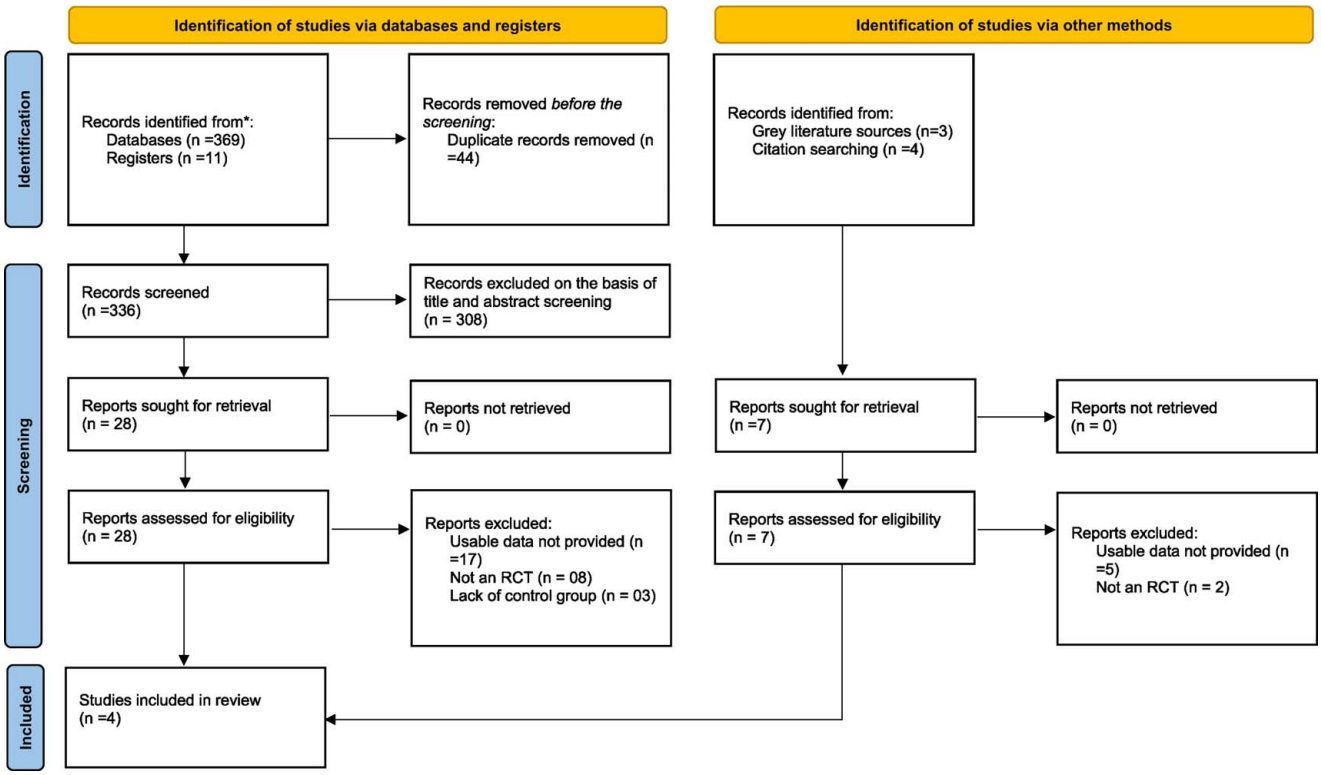

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. RCT, randomized controlled trial.

Table 1

Study characteristics of individual studies

	EXPLORER HCM (2020)		MAVERICK HCM (2020)		VALOR HCM (2022)		EXPLORER-CN (2023)	
Study (year)	**Mavacamten**	**Placebo**	**Mavacamten**	**Placebo**	**Mavacamten**	**Placebo**	**Mavacamten**	**Placebo**
Sample size	123 (251)	128 (251)	40 (59)	19 (59)	112 (56)	112 (56)	81 (54)	81 (27)
Mavacamten (dose, mg)	Starting dose at 2.5 mg		Starting dose at 5 mg		Starting dose at 5 mg		Starting dose at 5 mg; titrated to 15 mg	
Follow-up duration, weeks	2–4		16		16		30	
Mean age, years	58.5 ± 12.2	58.5 ± 11.8	54.0 ± 14.6	53.8 ± 18.2	59.8 ± 14.2	60.9 ± 10.5	52.4 ± 12	51.0 ± 11.8
Sex male	66 (54)	83 (65)	—		29 (51.8)	28 (50.0)	41	17
Female	57 (46)	45 (35)	21 (52.5)	13 (68.4)	27 (48.2)	28 (50.0)	13	10
Duration of HCM, years	—		—		7.5 ± 9.4	6.7 ± 7.4	—	
Medical History Family history of HCM	33	36	—		17	15	—	
A fib	12	23	—		11	8	—	
Hypertension	57	53	—		36	34	—	
Syncope or Pre-syncope	—		—		29	30	—	
SRT	11	8	—		56	56	—	
Hyperlipidemia	27	39	—		—		—	
CAD	12	6	—		—		—	
Obesity	15	14	—		—		—	
Type2 diabetes	6	7	—		—		—	
Asthma	17	11	—		—		—	
COPD	2	3	—		—		—	
ICD	27	29	—		9	10	—	
NYHA Classification Class II	88	95	33	13	4	4	44	18
Class III or higher	35	33	7	6	52	52	10	9
Background HCM therapy β-blockers	94	95	25	12	26	25	48	24
Calcium channel blockers	25	17	10	3	7	10	4	2
Echocardiographic parameters LVOT gradient, mmHg								
LVOT gradient, Rest, mm Hg	52 ± 29	51 ± 32	—		51.2 ± 31.4	46.3 ± 30.5	46.3 ± 30.5	73.4 ± 32.2
LVOT gradient, Valsalva, mm Hg	72 ± 32	74 ± 32	—		75.3 ± 30.8	76.2 ± 29.9	106.8 ± 43.2	99.8 ± 41.1
LVOT gradient, Post-exercise mmHg	86 ± 34	84 ± 36	—		82.5 ± 34.7	85.2 ± 37.0	—	
LVEF, %	74 ± 6	74 ± 6	68.7 ± 5.5	66.4 ± 7.7	67.9 ± 3.7	68.3 ± 3.2	77.8 ± 6.9	77.0 ± 6.7
Left atrial diameter, mm	42 ± 5	42 ± 6	—		—		—	
Maximum left ventricular wall thickness, mm	20 ± 4	20 ± 3	20.6 ± 4.0	18.8 ± 3.5	—		22.9 ± 4.9	24.3 ± 6.4
Left atrial volume index, ml/m^2	40 ± 12	41 ± 14	37.3 ± 13.0	40.8 ± 15.2	41.3 ± 16.5	40.9 ± 15.2	43.3 ± 12.1	47.5 ± 14.7
Pathogenic or likely pathogenic HCM gene variant/HCM genetic testing consented to or performed	28/90 ± 31	22/100 ± 22	14 (50.0)	8 (66.7)	—		—	
Laboratory measurements (drug/control)								
NT-proBNP, ng/l	777	616	821 (790–1293)	914 (770–1558)	724	743	810.5	1250.3
Cardiac troponin I, ng/l	12.5	12.5	0.023 (0–0.253)	0.020 (0.013–0.119)	17.3	12.9	33.5	38.7
Cardiac troponin T, μg/l	—		—		0.014	0.011	—	

CAD, Coronary artery disease; COPD, Chronic Obstructive Pulmonary Disease; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, Left Ventricular Ejection Fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SRT, septal reduction therapy.

Risk of bias in included studies

Three of the four included studies had a low risk of bias. The Maverick HCM trial reported some concerns showing bias in the selection of reported results and bias arising during the randomization process[20]. [Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A589].

Primary outcomes

Greater than or equal to 1 NYHA class improvement

Mavacamten was associated with higher rates of greater than or equal to 1 NYHA functional class improvement (RR 2.20, 95% CI: 1.48, 3.28; Fig. 2). A moderate level of heterogeneity was reported among studies for this outcome ($I^2 = 51\%$). In sub-group

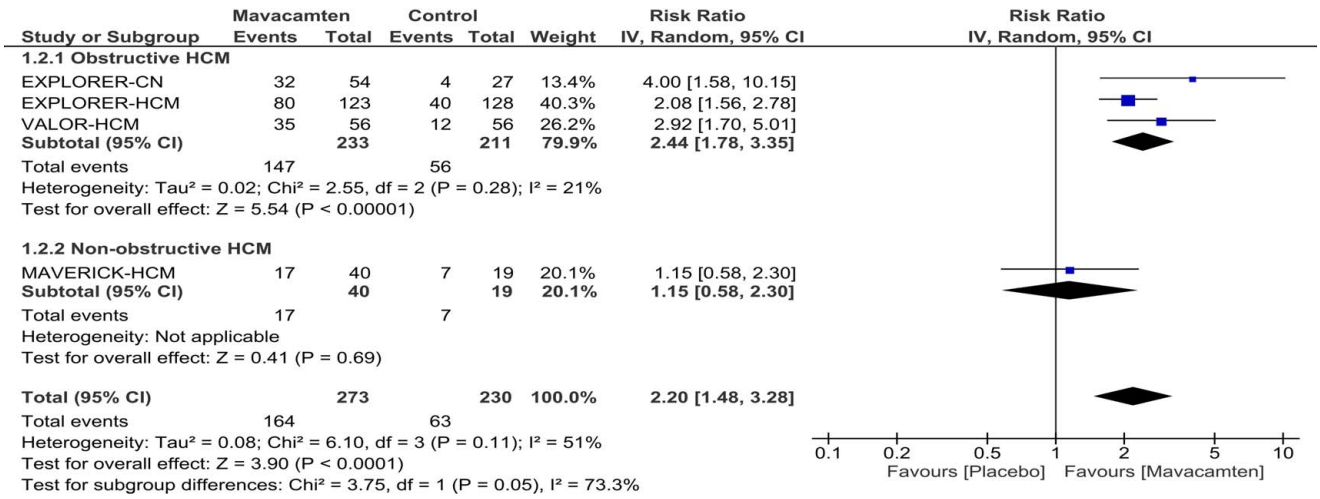

Figure 2. Forest plot of the effect of mavacamten vs placebo on ≥ 1 New York Heart Association (NYHA) class improvement. HCM, hypertrophic cardiomyopathy.

analysis, patients with obstructive HCM achieved greater rates of greater than or equal to 1 NYHA class improvement (RR 2.44 vs. 1.15; $P = 0.05$) compared to non-obstructive HCM patients.

Change from baseline in KCCQ-CSS score

Mavacamten was associated with higher KCCQ-CSS (MD 7.50, 95% CI: 3.44, 11.55; Fig. 3). A moderate level of heterogeneity was reported among studies for this outcome ($I^2 = 50\%$). In sub-group analysis, patients with obstructive HCM achieved greater rates of improvement in KCCQ-CSS scores (MD 9.28 vs. -0.97; $P = 0.02$) compared to non-obstructive HCM patients.

Secondary outcomes

Positive composite endpoint

There was no significant difference between the mavacamten and control group regarding number of patients achieving composite functional endpoint (RR 1.78, 95% CI: 0.99, 3.22; Supplementary Figure 2, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). The heterogeneity reported between studies for this outcome was low ($I^2 = 29\%$). When sub-group analysis was performed based on the type of hypertrophic cardiomyopathy, no significant difference was observed between the two groups ($P = 0.23$).

Eligibility for SRT

Mavacamten was associated with decreased number of patients that were eligible for SRT compared to the control group (RR 0.30, 95% CI: 0.22, 0.40; Supplementary Figure 3, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). No significant heterogeneity was found among the studies ($I^2 = 0\%$).

Change from baseline in Valsalva LVOT peak gradient

Mavacamten was associated with improved Valsalva LVOT peak gradient (MD – 48.08, 95% CI: – 62.21, – 33.96; Supplementary

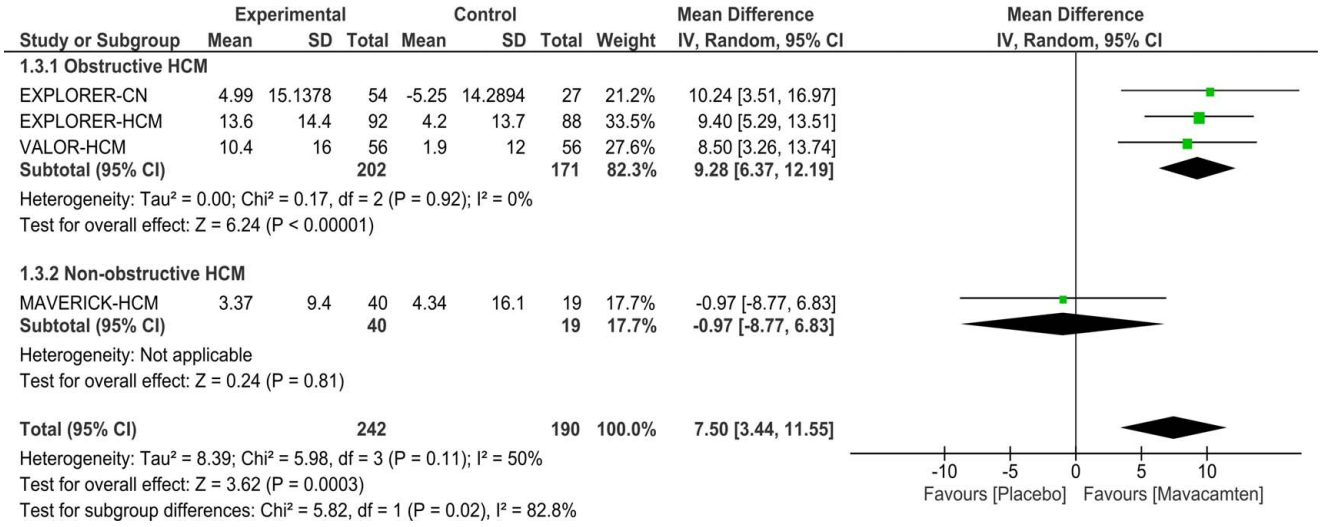

Figure 3. Forest plot of the effect of mavacamten vs placebo on change from baseline in Kansa City Cardiomyopathy Questionnaire Score (KCCQ-CSS). HCM, hypertrophic cardiomyopathy.

Figure 4, Supplemental Digital Content 3, http://links.lww.com/MS9/A589) with substantial heterogeneity ($I^2 = 78\%$).

Change from baseline in post-exercise LVOT gradient

Mavacamten was associated with improved post-exercise LVOT gradient (MD – 37.10, 95% CI: – 44.37, – 29.84; Supplementary Figure 5, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). Heterogeneity was found to be minimal ($I^2 = 0\%$).

Change from baseline in resting LVOT peak gradient

Mavacamten was associated with improved resting LVOT peak gradient (MD – 38.33, 95% CI: – 49.38, – 27.28; Supplementary Figure 6, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). Heterogeneity was found to be high ($I^2 = 75\%$).

Change from baseline in LVMI

Mavacamten was associated with improved LVMI (MD – 16.91, 95% CI: – 28.29, – 5.54; Supplementary Figure 7, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). Interstudy heterogeneity was substantial ($I^2 = 88\%$).

≥ 1 serious adverse event

No statistically significant difference was found between the two groups regarding greater than or equal to 1 serious adverse event (RR 0.96, 95% CI: 0.48, 1.91; Supplementary Figure 8, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). The heterogeneity for this outcome was very low ($I^2 = 6\%$). When sub-group analysis was performed based on the type of hypertrophic cardiomyopathy, no significant difference was observed between the two groups ($P = 0.23$).

Greater than or equal to1 treatment-emergent adverse event

No statistically significant difference was found between the two groups in greater than or equal to 1 treatment-emergent adverse event (RR 1.09, 95% CI: 0.97, 1.23; Supplementary Figure 9, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). Mild statistical heterogeneity was found ($I^2 = 33\%$). When sub-group analysis was performed based on the type of hypertrophic cardiomyopathy, no significant difference was observed between the two groups ($P = 0.21$).

Atrial fibrillation

No statistically significant association was found between the two groups regarding atrial fibrillation (RR 0.91, 95% CI: 0.26, 3.15; Supplementary Figure 10, Supplemental Digital Content 3, http://links.lww.com/MS9/A589). Heterogeneity was found to be minimal ($I^2 = 0\%$). When sub-group analysis was performed based on the type of hypertrophic cardiomyopathy, no significant difference was observed between the two groups ($P = 0.93$).

We were unable to create a funnel plot to assess publication bias because studies included in our meta-analysis were less than ten[19–22].

Discussion

This meta-analysis represents an updated analysis of the efficacy and safety of mavacamten for treating HCM. We analyzed data from four RCTs, involving a total of 503 participants diagnosed with HCM. A predetermined sub-group analysis categorized patients into obstructive and non-obstructive HCM, facilitating assessment of mavacamten's role in two different types of HCM. Our findings suggest that mavacamten significantly improves clinical and functional outcomes compared to placebo in patients with HCM. Mavacamten was associated with marked improvement in NYHA classification and elevated KCCQ-CSS scores, suggesting a positive impact on quality of life. Patients receiving mavacamten had improved LVMI and significantly lower rates of eligibility for SRT. Additionally, the analysis reported improvement in peak gradients for post-exercise LVOT, Valsalva LVOT, and resting LVOT, demonstrating improved cardiac function. The overall incidence of treatment-emergent adverse events, severe adverse events, and atrial fibrillation in the mavacamten cohort did not significantly differ from placebo, indicating good tolerance. No significant correlation was observed between the number of participants who achieved the composite functional endpoint when comparing mavacamten to placebo.

In our sub-group analyses, significant improvement in KCCQ-CSS scores and greater than or equal to 1 NYHA class in obstructive compared to non-obstructive HCM patients was observed in our analyses. This difference could be attributed to the difference in patients' selection criteria with the exclusion of patients with an LVOT gradient of more than 30 mmHg and variability in dosage and disease duration in MAVERICK trial, which is the only trial evaluating outcomes in non-obstructive HCM[20].

Scientific progress in recent years has enhanced our comprehension of HCM pathogenesis, reshaping treatment strategies toward effective pharmacological interventions over invasive techniques[23]. The role of mavacamten does not fit into the classification of conventional drugs, it is uniquely designed to reduce contractility and enhance energy utilization in myocytes[24]. One notable discovery is the remarkable effectiveness of mavacamten in diminishing the need for SRT, an invasive procedure frequently recommended for individuals with severe HCM[25]. This implies that mavacamten may provide a promising approach for alleviating symptoms in people with HCM, perhaps circumventing the need for costly and intrusive treatments that are linked to various problems[26].

Many similarities were found between the previous study conducted by Memon *et al.*[13], and this meta-analysis. Both studies arrived at the same conclusion, confirming positive outcomes and impressive adherence to mavacamten. Both analyses reported improvement of at least one category in NYHA classification, and the patients receiving mavacamten had significantly lower rates of eligibility for SRT compared to the placebo group. Furthermore, the positive impact of mavacamten on a patient's functional limitations, quality of life, and symptom burden was reflected in an improved KCCQ-CSS score in both analyses[13]. Meanwhile, there were significant distinctions between the two analyses. We included the latest RCT, namely EXPLORER-CN, thus increasing the power of our analysis. The sample size in our analysis was larger, with a total of 503 compared to 422. Our study provides additional details on innovative outcome measures including positive changes in peak gradients for Valsalva LVOT and resting LVOT, as well as change from baseline in LVMI[13].

Ismayl *et al.*[14] reported findings in congruence with our meta-analysis. However, significantly higher rates of primary composite endpoint and treatment-emergent adverse effects associated

with mavacamten were reported by this study, which is in contrast to our findings. The differences in the primary composite endpoint between the two meta-analyses might be influenced by factors such as characteristics of the patient population and the criteria used to define composite endpoints in included studies, this disparity emphasizes the complexity of assessing composite outcomes[14]. Additionally, we used the random-effects model to perform the meta-analyses compared to the fixed-effect model used by previous reviews. In contradiction to our findings, this study reported that patients receiving mavacamten were more likely to experience treatment-emergent adverse events; specific adverse events contributing to this were not reported; however, there is mention of them being generally mild including dizziness, palpitations, and fatigue[14,21].

The measurement of cardiac troponin concentration has proven to be valuable not only in diagnosing acute cardiovascular disease but also as an indicator of subclinical cardiovascular dysfunction[27]. Further research evaluating post-treatment cardiac troponin levels is necessary to enhance our ability to predict the outcomes on a molecular level when using mavacamten for HCM. This will provide a deeper understanding of how mavacamten influences cardiac health and potentially improve patient management and prognostic assessment in HCM.

Our meta-analysis stands out from previous studies, by inclusion of a larger pool of patients and additionally includes the most recent RCT published[13,14]. The trials under consideration were conducted in different countries with distinctive populations and research settings strengthening our study by implying generalizability. The addition of innovative measures of outcome, namely changes in peak gradients for Valsalva LVOT and resting LVOT also sets it apart from previous research[9,13,14]. The robustness of our review was further supported by the involvement of high-quality studies with a low risk of bias. The use of the random-effects model for meta-analyses to incorporate heterogeneity instead of the fixed-effect model used in prior systematic reviews enhanced the validity of our findings.

Acknowledging the limitations of our study is crucial for its evaluation as a valuable tool. The sample size in each trial was small which makes it challenging to generalize our results. Significant improvement in KCCQ-CSS scores and greater than or equal to 1 NYHA class in obstructive compared to non-obstructive HCM patients was observed in our data, this may be due to a higher representation of obstructive trials than non-obstructive trials in our meta-analyses. There is a substantial degree of heterogeneity among the included trials. Potential sources of this heterogeneity include variations in patient characteristics, such as variable duration of HCM, varying background HCM therapies, and comorbid conditions. Three trials included patients with New York Heart Association (NYHA) functional classes II and III, whereas the VALOR HCM trial primarily included patients with NYHA classes III and IV[19]. The dosage of mavacamten also varied across the trials, with the majority (75%) starting at 5 mg, while the most recent EXPLORER-CN trial began with a 2.5 mg dose[22]. Due to the limited number of studies (fewer than ten), we could not assess publication bias using a funnel plot. Additionally, the follow-up periods among the trials ranged from 16 to 30 weeks. Limited follow-up periods further constrict our postulation regarding assessment of improvement in outcomes. The safety profile of mavacamten for a longer period is still questionable due to the short follow-up duration of all trials. Another limitation of our study was the absence of data for every outcome across all included studies, compromising the power of our analyses. We were also unable to evaluate the effects of different doses of mavacamten due to insufficient data and uniformity of dosages amongst trials. One of the included RCTs showed some concerns of bias in the process of randomization, adding to the limitations of our study[20]. We could not assess the impact of potential confounders such as the use of background medical therapy due to insufficient evidence.

Restricted available therapeutic modalities for hypertrophic cardiomyopathy impose a great burden on cardiovascular-related morbidity and mortality worldwide, which needs to draw more attention toward advanced therapeutics[28]. Researchers are highlighting mavacamten as a newer drug and evaluating its effect among target patients, further primary research and trials are required to solidify and establish conclusive findings about this drug. The need for expanded large-scale trials involving patients of different regions, races, and severity must be executed with high-quality study settings. It is crucial to conduct trials to evaluate the efficacy of mavacamten in patients with non-obstructive HCM. The safety profile of mavacamten must be evaluated among high-risk patients and patients with co-morbidities. Limited follow-up periods limit the ability to make conclusions about the long-term safety of the drug, extended follow-up duration across trials is required. Economic issues must also be addressed before its approval by the FDA for low and middle-income countries.

Conclusion

Our findings suggest that mavacamten contributes to improvements in NYHA class, KCCQ-CSS scores, and LVOT gradients while reducing the incidence of SRT in patients with HCM. Further large-scale randomized controlled trials are required to provide definite conclusions.

Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent

Informed consent was not required for this review.

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Author contribution

N.E.A., M.E., H.A.C., and M.A. contributed to the conception and design of the study. N.E.A., S.A.U.N.B., M.H.Q., M.I., C.Z.R., A.R.A., A.H. and J.I. contributed to the analysis, interpretation and writing of the original draft. M.E., W.U.R., H.A.C., M.A., K.K., S.I., A.P., K.P., and M.A.S. contributed to the interpretation and critical revision of the draft. All authors have agreed on the journal to which the article will be submitted and have given the final approval for the version to be published. All

authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

Research registration unique identifying number (UIN)

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Guarantor

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Data availability statement

Data will be provided on reasonable request from the corresponding author.

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