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Brief Report

Outcomes of cardiac myosin inhibitors in hypertrophic cardiomyopathy: an updated brief meta-analysis

Joud Fahed[1], Asad Ur Rab[2], Mohammad Hamza[3],Rehman Afraz[4], Ali Awad[5], Abdul Monem Al Riahi[6], Prakash Upreti[7]

[1]Department of Medicine, Ascension Saint Agnes Hospital, Baltimore, Maryland, USA

[2]Department of Medicine, Foundation University Medical College, Islamabad 44000, Pakistan

[3]Department of Hospital Medicine, Guthrie Cortland Regional Medical Center, Cortland, NY, USA

[4]Department of Medicine, HCA Los Robles Medical Center, CA, USA

[5]Department of Medicine, Detroit Medical Center/Wayne State University, Detroit, Michigan, USA

[6]William Carey University College of Osteopathic Medicine, Hattiesburg, MS, USA

[7]Department of Medicine, Sands Constellation Heart Institute, Rochester Regional Health, Rochester, New York, USA

*Author for correspondence: Email: joudf1997@gmail.com

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Introduction

Obstructive hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disease occurring in approximately 1 in 500 adults worldwide, characterized by left ventricular outflow tract (LVOT) obstruction, symptoms of heart failure, and increased risk of sudden cardiac death [1,2]. Conventional therapies; including beta-blockers, calcium channel blockers, and septal reduction, leave a significant proportion of patients symptomatic, necessitating investigation of novel management strategies [3].

Cardiac myosin inhibitors (CMIs) represent a novel mechanistic class targeting the underlying sarcomeric dysfunction in HCM. Recent phase 3 randomized controlled trials (RCTs) have demonstrated superiority over conventional therapy across functional, symptomatic, and hemodynamic endpoints[4–7]. While prior meta-analyses have evaluated CMI efficacy [8–10], we present an updated synthesis incorporating the most recent trial data, including the MAPLE-HCM trial (aficamten vs metoprolol, 2025), to provide a contemporary evidence base for clinical practice [11,12].

Methods

We conducted a systematic search of PubMed, Scopus, Embase, and Web of Science from inception through September 2025 using the terms: *"hypertrophic cardiomyopathy" AND ("cardiac myosin inhibitor" OR "mavacamten" OR "aficamten") AND "randomized controlled trial"*. Searches were limited to English-language publications in adult human populations. PubMed returned 84 results, Scopus 117, Embase 96, and Web of Science 71 (total 368 records; 112 duplicates removed). After title/abstract screening (n = 256), 31 full texts were assessed for eligibility, yielding 7 RCTs meeting inclusion criteria (see **Figure 1** for PRISMA flow diagram). Two independent reviewers (AR, JF) performed screening and data extraction; conflicts were resolved by a third reviewer (AS). Included studies compared CMIs versus placebo or active control in adult patients with HCM and reported patient level outcome data. Observational studies, non-English publications, and non-human studies were excluded.

Outcomes extracted included LVOT gradients (rest, exercise, Valsalva), LVEF, complete hemodynamic response, NYHA functional class, KCCQ clinical summary score (KCCQ-CSS), peak VO_2, and adverse events including atrial fibrillation. Categorical outcomes were pooled as risk ratios (RR) and continuous outcomes as standardized mean differences (SMD), both with 95% confidence intervals (CI), using random-effects models. Heterogeneity was quantified by I^2; leave-one-out sensitivity analyses were performed where I^2 >50%. Analyses used Microsoft Excel 16 and STATA v17.

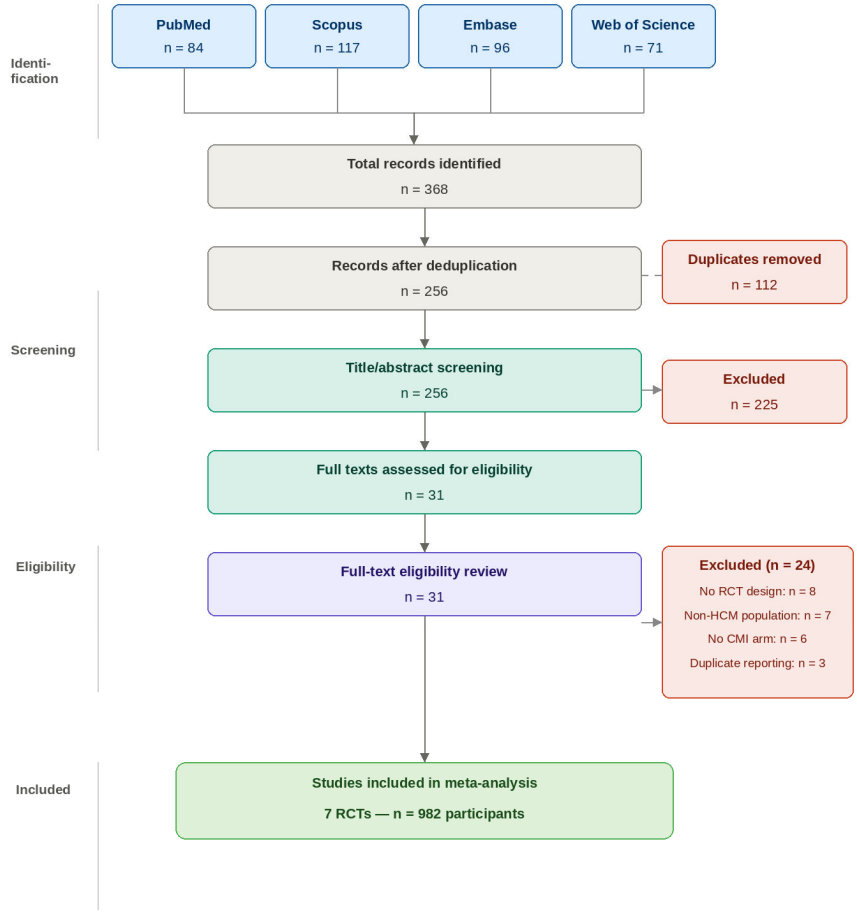

Figure 1. PRISMA 2020 flow diagram. CMI = cardiac myosin inhibitor; HCM = hypertrophic cardiomyopathy; RCT = randomised controlled trial.

Figure 1. PRISMA flow diagram. Records identified: PubMed (n=84), Scopus (n=117), Embase (n=96), Web of Science (n=71). After removal of duplicates (n=112): 256 records screened. Records excluded at title/abstract level (n=225). Full texts assessed (n=31). Studies excluded at full-text review (n=24; reasons: no RCT design, n=8; non-HCM population, n=7; no CMI arm, n=6; duplicate reporting, n=3). Studies included in meta-analysis: n=7.

Results

Seven RCTs comprising 982 participants were included [1–7]: 531 received CMI and 451 received placebo or active control. Study characteristics are presented in **Table 1** and pooled meta-analysis results in **Table 2**.

Safety

There was no statistically significant difference in overall adverse events (RR 1.05, 95% CI 0.98–1.13; I^2 = 15.1%; P = 0.315), serious adverse events (RR 0.87, 95% CI 0.55–1.36; I^2 = 0%; P = 0.647), or atrial fibrillation (RR 0.94, 95% CI 0.38–2.37; I^2 = 0%; P = 0.589) between CMIs and controls (**Table 2**). Prespecified subgroup analyses by drug type, comparator, and HCM phenotype were not significant for any safety endpoint.

Hemodynamic outcomes

CMIs significantly reduced LVOT gradients at rest (SMD −5.76, 95% CI −10.35 to −1.17; I^2 = 98.9%) and during Valsalva (SMD −5.83, 95% CI −10.74 to −0.91; I^2 = 99.2%). Exercise LVOT reduction was directionally favorable but non-significant (SMD −0.65, 95% CI −1.56 to 0.26). Complete hemodynamic response strongly favored CMIs (RR 6.50, 95% CI 1.47–28.78; I^2 = 76.7%), with heterogeneity eliminated on leave-one-out sensitivity analysis. CMIs were associated with greater LVEF reduction (SMD −2.33, 95% CI −4.01 to −0.65; I^2 = 96%), attenuated and non-significant in mavacamten-only analysis (SMD −1.99, 95% CI −4.56 to 0.58) (**Table 2**).

Functional and quality-of-life outcomes

NYHA class improvement by ≥1 class strongly favored CMIs (RR 2.17, 95% CI 1.84–2.55; I^2 = 13.8%). Quality of life (KCCQ-CSS) was significantly better with CMIs (SMD 2.90, 95% CI 1.06–4.74; I^2 = 98.9%). Peak VO_2 was directionally favorable (SMD 4.99, 95% CI −0.01 to 9.98) but characterized by very high heterogeneity (I^2 = 99.6%) (**Table 2**).

Table 1. Characteristics of included randomized control trials.

Study (Trial)	Drug	N (CMI / Control)	Comparator	Follow-up	HCM Phenotype
Ho *et al.* 2020 (VALOR-HCM)	Mavacamten	112 / 56	Placebo	16 weeks	Obstructive
Olivotto *et al.* 2020 (EXPLORER-HCM)	Mavacamten	123 / 128	Placebo	30 weeks	Obstructive
Tian *et al.* 2023 (EXPLORER-CN)	Mavacamten	54 / 54	Placebo	30 weeks	Obstructive
Maron *et al.* 2023 (MAVERICK-HCM)	Mavacamten	40 / 19	Placebo	16 weeks	Non-obstructive
Maron *et al.* 2023 (SEQUOIA-HCM)	Aficamten	99 / 83	Placebo	24 weeks	Obstructive
Maron *et al.* 2024 (REDWOOD-HCM)	Aficamten	123 / 101	Placebo	10 weeks	Obstructive
Garcia-Pavia *et al.* 2025 (MAPLE-HCM)	Aficamten	87 / 86	Metoprolol	24 weeks	Obstructive

CMI: Cardiac Myosin Inhibitor; HCM: Hypertrophic Cardiomyopathy; LVOT: Left Ventricular Outflow Tract.

Table 2. Summary of meta-analysis results.

Outcome	Studies (n)	Measure	Pooled Estimate (95% CI)	I^2	P value	Interpretation
Safety Outcomes						
Any adverse events	7	RR	1.05 (0.98–1.13)	15.1%	0.315	No significant difference
Serious adverse events	5	RR	0.87 (0.55–1.36)	0%	0.647	No significant difference
Atrial fibrillation	5	RR	0.94 (0.38–2.37)	0%	0.589	No significant difference
Hemodynamic Outcomes						
LVOT gradient at rest	7	SMD	−5.76 (−10.35 to −1.17)	98.9%	<0.05	Significantly reduced with CMI
LVOT gradient (Valsalva)	7	SMD	−5.83 (−10.74 to −0.91)	99.2%	<0.05	Significantly reduced with CMI
LVOT gradient (exercise)	2	SMD	−0.65 (−1.56 to 0.26)	—	NS	Non-significant trend
Complete hemodynamic response	5	RR	6.50 (1.47–28.78)	76.7%	<0.05	Strongly favors CMI
Change in LVEF	4	SMD	−2.33 (−4.01 to −0.65)	96%	<0.05	Greater LVEF reduction with CMI; attenuated in mavacamten subgroup
Functional/QoL Outcomes						
NYHA class improvement ≥1	7	RR	2.17 (1.84–2.55)	13.8%	<0.001	Strongly favors CMI
KCCQ-CSS score	5	SMD	2.90 (1.06–4.74)	98.9%	<0.05	Significantly improved with CMI
Peak VO_2	4	SMD	4.99 (−0.01 to 9.98)	99.6%	0.050	Directionally favorable; high heterogeneity

CI: Confidence Interval; CMI: Cardiac Myosin Inhibitor; I^2: Heterogeneity Statistic; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF: Left Ventricular Ejection Fraction; LVOT: Left Ventricular Outflow Tract; NS: Not Significant; RR: Risk Ratio; SMD: Standardized Mean Difference; VO2: Oxygen uptake

Conclusion

This updated meta-analysis demonstrates that CMIs provide clinically meaningful and statistically significant improvements in functional status, quality of life, and LVOT hemodynamics in patients with HCM, without a significant increase in serious adverse events or atrial fibrillation. The observed LVEF reduction was heterogeneous, attenuated with mavacamten specifically, and supports structured echocardiographic monitoring rather than precluding use.

These findings, contextualized within the growing evidence base of over 1,600 recent publications [8–12], confirm CMIs as effective, targeted, disease-modifying therapy, particularly in obstructive HCM phenotypes. Ongoing trials evaluating class effects, non-obstructive phenotypes, and long-term outcomes will further refine patient selection and therapeutic strategy[11,12].

Disclosures

The authors report no conflicts of interest. No external funding was received for this study.

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