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Research Paper

Efficacy and safety of cardiac myosin inhibitors in obstructive hypertrophic cardiomyopathy: Systematic review and comprehensive frequentist and Bayesian meta-analyses of Phase 3 randomized controlled trials

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ABSTRACT

Aims: Data on cardiac myosin inhibitors (CMIs) in obstructive hypertrophic cardiomyopathy (oHCM) are rapidly emerging. This systematic review and meta-analysis evaluated the efficacy and safety of CMIs in randomized placebo-controlled trials.

Methods: Phase 3 randomized placebo-controlled trials published up to 22-Apr-2025 were included. Outcomes extracted included symptoms, cardiopulmonary exercise testing (CPET), biomarkers, transthoracic echocardiography (TTE), cardiovascular magnetic resonance (CMR), and safety data. Frequentist (common/fixed effect, random) and Bayesian meta-analyses were performed using trial-level data to pool estimates of effects.

Results: Four randomized placebo-controlled trials involving 726 patients with oHCM were included (444 mavacamten/placebo, 282 aficamten/placebo). Trial follow-up durations ranged from 16 to 30 weeks. In common/fixed effects meta-analyses, CMIs were associated with a greater proportion achieving ≥1 NYHA improvement [difference 36 % (95 % CI 29, 43)] and an increase in KCCQ-CSS [8.4 (6.6, 10.2) points] versus placebo. CMIs significantly improved several CPET parameters including increased peak oxygen consumption [1.6 (1.0, 2.1) mL/kg/min] and reduced VE/VCO_2 [-2.0 (-2.7, -1.3)]. CMIs significantly reduced NT-proBNP [-79 % (-81 %, -77 %)] and hs-cTnI [-50 % (-54 %, -46 %)]. CMIs led to significant reductions in resting LVOT-G [-40 (-45, -35) mmHg] and favourable cardiac remodelling in other TTE and CMR parameters. Although CMIs increased the likelihood of LVEF <50 %, consistent with its known mechanism of action, none of these patients developed heart failure. No significant differences were seen in safety outcomes.

Conclusions: Mavacamten and aficamten significantly improve symptoms, enhance exercise performance, improve cardiac biomarkers, reduce LVOT obstruction, and promote favourable cardiac remodelling. These findings suggest a class effect of CMIs.

PROSPERO registration: CRD42024582096.

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited heart condition characterized by cardiac hypercontractility, which can promote left ventricular outflow tract (LVOT) obstruction, resulting in obstructive hypertrophic cardiomyopathy (oHCM). For several decades, the mainstay of medical therapy for symptomatic oHCM has included beta-blockers, non-dihydropyridine calcium-channel blockers, and

Abbreviation: CMI, cardiac myosin inhibitor; CMR, cardiovascular magnetic resonance; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; RCT, randomized controlled trial; SAE, serious adverse event.

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disopyramide. Cardiac myosin inhibitors (CMIs) have emerged as a new therapy to target hypercontractility in oHCM and are now incorporated into clinical practice guidelines.[1,2] Cardiac myosin modulation is a highly innovative and somewhat counterintuitive approach to cardiovascular disease, compared to "standard" treatments that either promote or do not interfere with cardiac contractility. Hence, broad confirmation of the efficacy and safety of CMIs as a therapeutic class is urgently needed.

New data on CMIs in oHCM are rapidly emerging. Using trial-level data, we aim to conduct a pre-specified meta-analysis to estimate the effect of CMIs on various clinical endpoints in Phase 3 randomized placebo-controlled clinical trials involving patients with oHCM. Prior meta-analyses of CMIs have predominantly focused on mavacamten trials,[3–14] with fewer including aficamten, a next-in-class CMI.[15–24] Moreover, these prior analyses often combined Phase 2 and Phase 3 trials, mixed observational studies with randomized trials, and included both oHCM and non-obstructive HCM, factors that may introduce heterogeneity and limit the validity and interpretability of the pooled results. Our updated meta-analysis addresses these limitations by incorporating aficamten, and offers a more comprehensive evaluation of novel outcomes not covered in previous meta-analyses.[15–24]

Methods

A systematic review (PROSPERO registration number CRD42024582096) was conducted to include relevant trials published up to 22 April 2025 (Supplementary Appendix). Two researchers (M.M.Y.L, F.C.G.) independently performed the literature search, data extraction, and risk of bias assessment, with any discrepancies resolved by consensus.

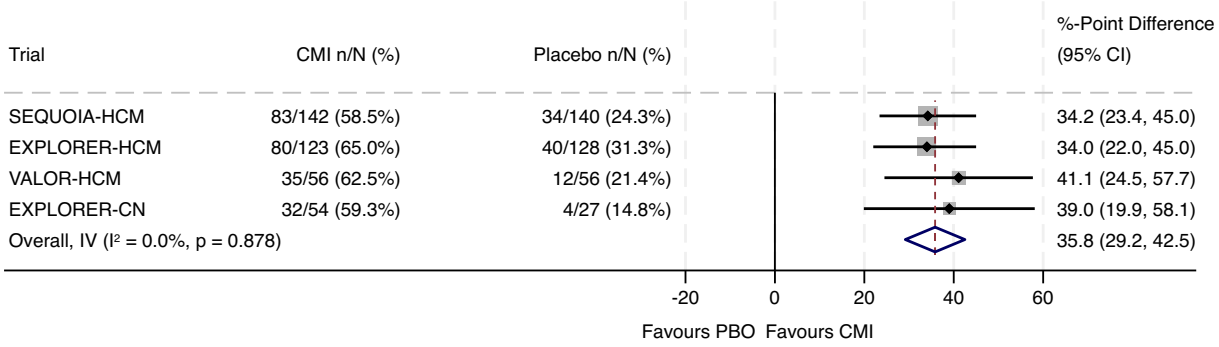
Data sources, search strategy and trial selection

The search was performed on PubMed, ClinicalTrials.gov, and relevant conference proceedings. The search strategy is detailed in Supplementary material online, Fig. S1 and Supplementary text. Inclusion criteria were randomized Phase 3 placebo-controlled trials enrolling patients aged ≥18 years with oHCM. Pre-specified and eligible post-hoc analyses were included. Observational studies and non-human clinical trials were excluded. There were no language restrictions, and trials of any sample size, follow-up duration, and from any country were included.

Data extraction and outcomes

Data were extracted on pre-specified efficacy outcomes across six main categories:

1. Symptoms and health-related quality of life (QoL): New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS), KCCQ Overall Summary Score (OSS), KCCQ Total Symptom Score (TSS), KCCQ Physical Limitation Score (PLS), KCCQ Social Limitation Score (SLS), KCCQ Quality of Life Score (QOL), EuroQol 5-Dimension 5-Level (EQ-5D-5L) index score, EuroQol visual analogue scale (EQ-VAS), Seattle Angina Questionnaire-7 (SAQ-7), Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ).
2. Cardiopulmonary exercise testing (CPET): peak oxygen uptake (pVO_2), peak workload, peak METS, peak circulatory power, peak exercise time/duration, heart rate reserve, peak respiratory exchange ratio (RER), peak partial pressure of end-tidal carbon dioxide ($PETCO_2$), ventilatory efficiency (VE/VCO_2) pre-ventilatory



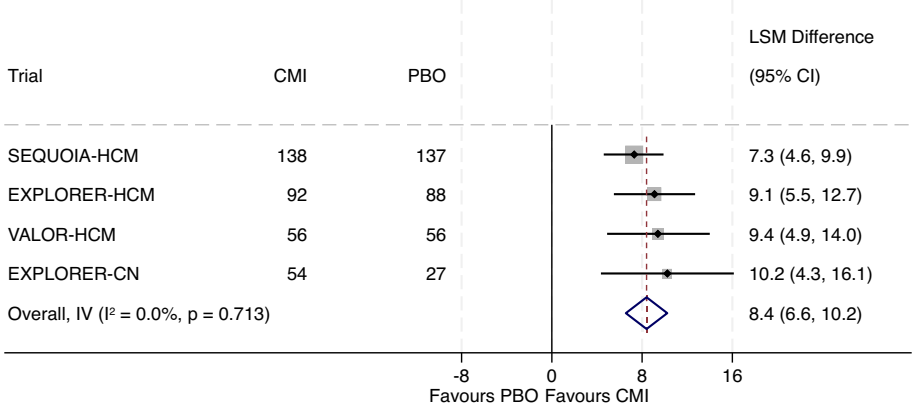


Fig. 1. a. Symptoms (≥1 NYHA improvement).
CMI, cardiac myosin inhibitor; IV, inverse variance; NYHA, New York Heart Association functional class; PBO, placebo.
b. Symptoms (KCCQ-CSS).
CMI, cardiac myosin inhibitor; CSS, Clinical Summary Score; IV, inverse variance; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSM, least squares mean; PBO, placebo.

anaerobic threshold, VE/VCO_2 throughout all of exercise, ventilatory power, ventilatory anaerobic threshold, rest $PETCO_2$, VO_2/workload slope.
3. Biomarkers: N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin I (hs-cTnI).
4. Transthoracic echocardiography (TTE): left ventricular outflow tract gradient (LVOT-G) at rest, LVOT-G with Valsalva, LVOT-G on exercise, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum (IVS) thickness, inferolateral wall thickness, left ventricular (LV) maximal wall thickness (MWT), left ventricular mass index (LVMI), left atrial volume index (LAVI), lateral E', septal E', E/e' lateral ratio, E/e' septal ratio, peak E wave velocity, peak A wave velocity, mitral regurgitation.
5. Cardiovascular magnetic resonance (CMR): LVEF, LAVI, LV MWT, LVM, LVMI, late gadolinium enhancement (LGE).
6. Septal reduction therapy (SRT): presence and duration of eligibility for SRT.

Safety outcomes assessed included:

7. Cardiac: LVEF <50 %, heart failure or cardiac failure congestive, atrial fibrillation, ventricular tachycardia, palpitations, chest pain or chest discomfort or angina pectoris, dizziness, hypertension, stress cardiomyopathy, corrected QT interval change, non-sustained ventricular tachycardia (NSVT) on 48-h Holter monitoring.
8. Non-cardiac: any adverse event (AE), any serious adverse event (SAE).

Data analysis and risk of bias assessment

Measures of effect included mean differences (95 % confidence intervals), percentage differences (95 % confidence intervals), and geometric mean proportion changes (95 % confidence intervals). Statistical analyses were conducted using StataSE version 18.0 (StataCorp). For efficacy outcomes, common/fixed effects meta-analyses were conducted using the inverse variance weighted method for outcomes reported in two or more trials. Outcomes reported in only one trial were not included in the meta-analysis. For safety outcomes, odds ratios (OR) with 95 % confidence intervals were calculated using the chi-squared test, with forest plots displaying a log-transformed OR on the X-axis. Between-trial heterogeneity of treatment effects was assessed using the chi squared test (Q test). Studies with zero-count events were excluded. Additional subgroup analyses of key outcomes were conducted to compare mavacamten and aficamten.

Sensitivity analyses were conducted to compare common/fixed and random effects meta-analyses, both of which are based on frequentist statistical methods. Random effects meta-analyses were performed using the DerSimonian and Laird method with Hartung-Knapp-Sidik-Jonkman adjustment, chosen due to the limited number of studies and its more conservative nature, which reduces the risk of Type 1 error.[25–27] A Bayesian meta-analysis was also performed for all key endpoints. Bayesian analysis combines the observed data with prior beliefs to generate a *posterior* distribution for the average treatment effect which is especially useful in analyses with limited data available.[28] A vague (flat) prior was used for the average treatment effect and a weakly informative half-normal prior (scale 0.5) was applied for between-study heterogeneity, reflecting an expectation of moderate heterogeneity between trial results.[29] A Bayesian random-effects meta-analysis was conducted using the *brms* package in R, assuming normally distributed effect sizes with known standard errors and accounting for between-study heterogeneity via a random intercept for trial.[30] The estimated average treatment effect was presented as the median and 95 % credible intervals (CrI) of the posterior distribution. No *p*-values or null hypothesis significant testing were used with Bayesian analyses. Model convergence was assessed using R-hat statistics (with all values near ≈1.0 indicating good convergence).

Risk of bias was independently assessed by two researchers (M.M.Y. L., F.C.G.) using the Risk of Bias 2 (RoB 2) tool.[31]

Results

A total of four randomized placebo-controlled clinical trials, including 726 patients with oHCM, were included, 444 investigating

Table 1
Baseline characteristics of randomized placebo-controlled trials in patients with obstructive hypertrophic cardiomyopathy.

Baseline characteristics	EXPLORER-HCM[32,36]	VALOR-HCM[33]	EXPLORER-CN[34]	SEQUOIA-HCM[35,39]
Year	2020	2022	2023	2024
Phase	3	3	3	3
Drug	Mavacamten	Mavacamten	Mavacamten	Aficamten
Sample size	251	112	81	282
Follow-up (weeks)	30	16	30	24
Age (years)	58.5	60	51.9	59.1
Female (%)	41	49	28	41
Asian (%)	2.4	1.8	NR[a]	19.1
Black or African American (%)	2.4	2.7	NR	1.1
Native American or Alaskan Native (%)	0.4	NR	NR	NR
White (%)	91.2	89.3	NR	79.1
AF (%)	13.9	17.0	NR[b]	1.1 (persistent)
NYHA II / III (%)	73 / 27	7.1 (+ exertional syncope) / 92.9 (III or higher)	76.5 / 23.5	76 / 24
Mean KCCQ-CSS	70.9 CMI / 70.3 PBO	69.5 CMI / 65.6 PBO	82.4 CMI / 84.4 PBO	76 CMI / 74 PBO
Mean pVO_2, mL/kg/min	18.9 CMI / 19.9 PBO	NR	NR	18.4 CMI / 18.6 PBO
LVOT-G rest, mmHg	52 CMI / 51 PBO	49	74.6 CMI / 73.4 PBO	55.1
LVEF (%)	74	67.9 CMI / 68.3 PBO	77.8 CMI / 77.0 PBO	74.8
NT-proBNP, pg/mL or ng/L[c]	777 CMI / 616 PBO	724 CMI / 743 PBO	810.5 CMI / 1250.3 PBO	818 CMI / 692 PBO
Beta-blocker (%)	75.3	75.0	88.9	61.3
Calcium-channel blocker (%)	16.7	34.8	7.4	28.7
Disopyramide (%)	0 (excluded)	19.6	0 (excluded)	12.8
No background HCM therapy (%)	8.0	5.4	NR	14.5

AF, atrial fibrillation; CMI; cardiac myosin inhibitor; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PBO, placebo; pVO_2, peak oxygen uptake.
Dosing of mavacamten differed in EXPLORER-HCM (2.5 to 15 mg), VALOR-HCM (2.5 to 15 mg), and EXPLORER-CN (1 to 15 mg).
VALOR-HCM data included only the 16-week treatment period, excluding crossover data from the open-label extension that started after 16 weeks.
[a] Conducted in China, where most of the population is of Asian descent.
[b] Included participants with persistent or permanent AF who were anticoagulated and adequately rate-controlled. Excluded paroxysmal AF.
[c] Geometric mean in EXPLORER-HCM and EXPLORER-CN, median in VALOR-HCM and SEQUOIA-HCM.

mavacamten and 282 investigating aficamten, with trial follow-up duration ranging from 16 to 30 weeks (Table 1; Supplementary material online, Fig. S1 CONSORT diagram). Fifteen papers (5 EXPLORER-HCM, 1 VALOR-HCM, 1 EXPLORER-CN, 8 SEQUOIA-HCM) were included in both the qualitative and quantitative analyses.[32–46] Six papers (5 VALOR-HCM, 1 EXPLORER-CN) were included in the qualitative analysis only.[47–52] Some trials had multiple companion post-hoc analyses used for different outcomes. The risk of bias was low across all four trials (Supplementary material online, Fig. S2).

Symptoms and health-related QoL

In four trials involving 726 patients, CMI treatment was associated with a greater proportion achieving ≥1 NYHA improvement [percentage-point difference 36 % (95 % CI 29, 43); I^2 = 0.0 %] compared to placebo over 16 to 30 weeks (Fig. 1a).[32–35] Additionally, in four trials with 648 patients, CMI treatment was associated with an increase in KCCQ-CSS [8.4 (95 % CI 6.6, 10.2) points; I^2 = 0.0 %] compared to placebo over 16 to 30 weeks (Fig. 1b).[32–34,37] In two trials involving up to 455 patients, CMI treatment was associated with significant increases in KCCQ-OSS [8.4 (95 % CI 6.0, 10.8); I^2 = 0.0 %], KCCQ-TSS [6.9 (95 % CI 4.5, 9.2); I^2 = 0.0 %], KCCQ-PLS [9.1 (95 % CI 6.6, 11.6); I^2 = 0.0 %], KCCQ-SLS [8.3 (95 % CI 5.1, 11.4); I^2 = 0.0 %], and KCCQ-QOL [9.8 (95 % CI 6.5, 13.1); I^2 = 0.0 %] compared to placebo over 24 to 30 weeks (Supplementary material online, Fig. S3).[36,37]

CPET

In two trials involving up to 508 patients, CMI treatment was associated with statistically significant increases compared to placebo in pVO_2 [1.56 (95 % CI 1.05, 2.07) mL/kg/min; I^2 = 0.0 %], peak METs [0.45 (95 % CI 0.30, 0.59); I^2 = 0.0 %], ventilatory power [0.8 (95 % CI 0.6, 1.0) mmHg; I^2 = 55.0 %], and circulatory power [486 (95 % CI 335, 636) mmHg x mL/kg/min; I^2 = 47.8 %], and a reduction (improvement) in VE/VCO_2 (nonpeak or pre-AT) [-2.0 (95 % CI -2.7, -1.3); I^2 = 57.8 %] over 24 to 30 weeks (Fig. 2; Supplementary material online, Figs. S4–S5).[32,35,38,39] No significant between-group differences were observed in exercise duration, peak RER, or aerobic efficiency.

Biomarkers

In four trials involving 701 patients, CMI treatment was associated with a significant reduction in NT-proBNP [-79 % (95 % CI -81 %, -77 %); I^2 = 70.8 %] compared to placebo over 16 to 30 weeks (Fig. 3).[32–35] Similarly, in four trials, CMI treatment was associated with a significant reduction in hs-cTnI [-50 % (95 % CI -54 %, -46 %); I^2 = 88.2 %] compared to placebo over 16 to 30 weeks.[32–34,40]

TTE

In three trials involving up to 475 patients, CMI treatment was associated with a significant reduction in LVOT-G at rest [-40 (95 % CI -45, -35) mmHg; I^2 = 69.0 %] and LVOT-G with Valsalva [-51 (95 % CI -56, -46) mmHg; I^2 = 53.6 %] compared to placebo over 16 to 30 weeks (Fig. 4a).[33–35,42] In two trials with 351 patients, CMI treatment was associated with a significant reduction in LVOT-G with exercise [-36 (95 % CI -42, -30) mmHg; I^2 = 0.0 %] compared to placebo over 16 to 30 weeks (Supplementary material online, Fig. S6).[32,33] Additionally, in two trials involving 363 patients, CMI treatment was associated with a higher proportion of patients achieving LVOT-G with Valsalva of <30 mmHg [percentage difference 45 % (95 % CI 37, 52); I^2 = 0.0 %] compared to placebo over 24 to 30 weeks (Supplementary material online, Fig. S7).[34,35]

Regarding cardiac dimensions and systolic function, in three trials with up to 632 patients, CMI treatment was associated with reductions in LVMI [-13.2 (95 % CI -16.0, -10.5) g/m^2; I^2 = 64.4 %], LAVI [-5.2 (95 % CI -6.3, -4.0) mL/m^2; I^2 = 76.3 %], and LVEF [-4.3 (95 % CI -5.2, -3.5) %, I^2 = 0.0 %] compared to placebo over 16 to 30 weeks (Fig. 4b; Supplementary material online, Fig. S8).[33,41,42] In two trials with up to 516 patients, CMI treatment was associated with a decrease in IVS [-1.2 (95 % CI -1.5, -0.8) mm; I^2 = 0.0 %] and inferolateral wall thickness [-0.8 (95 % CI -1.1, -0.5) mm; I^2 = 0.0 %], and an increase in LVESD [1.3 (95 % CI 0.7, 1.9) mm; I^2 = 0.0 %] and LVESVI [1.6 (95 % CI 1.0, 2.2) mL/m^2; I^2 = 0.0 %], compared to placebo over 24 to 30 weeks.[41,42] No significant between-group changes were observed in LVEDD, or LVEDVI.

Regarding LV diastolic function, in two trials involving up to 515 patients, CMI treatment was associated with a significant reduction in peak E wave velocity [-5.9 (95 % CI -8.9, -2.8) cm/s; I^2 = 12.6 %), lateral E/e' [-3.9 (95 % CI -4.6, -3.1); I^2 = 0.0 %], and septal E/e' [-3.5 (95 % CI

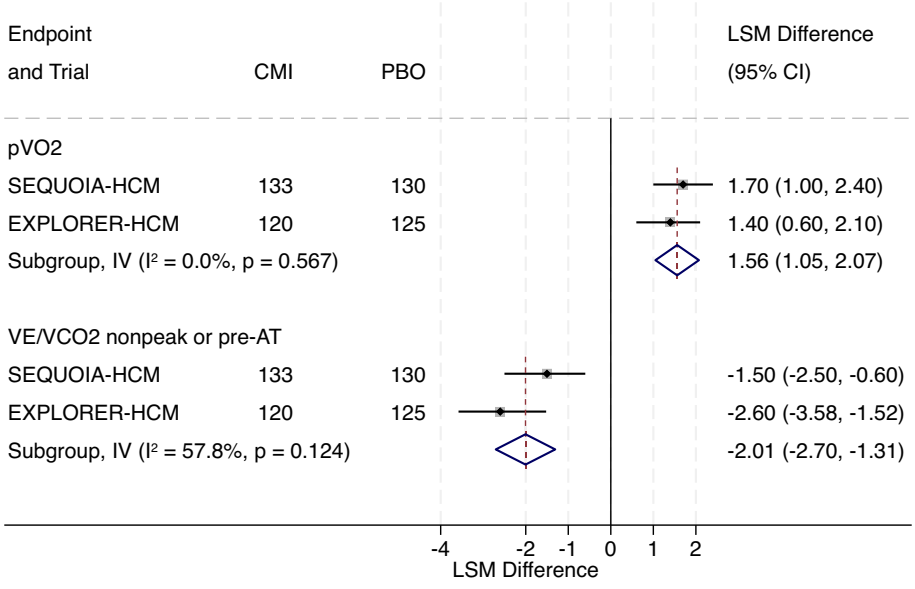


Fig. 2. Cardiopulmonary exercise test.
AT, anaerobic threshold; CMI, cardiac myosin inhibitor; IV, inverse variance; LSM, least squares mean; PBO, placebo; pVO2, peak oxygen uptake; VCO2, carbon dioxide output; VE, minute ventilation.

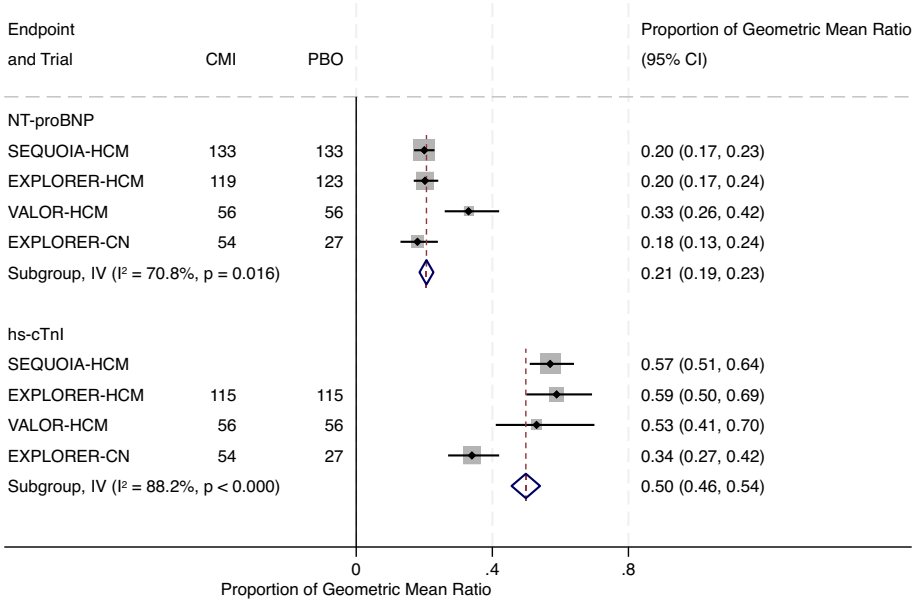


Fig. 3. Biomarkers.
CMI, cardiac myosin inhibitor; hs-cTnI, high-sensitivity cardiac troponin I; IV, inverse variance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PBO, placebo. SEQUOIA-HCM: hs-cTnI data were available for CMI (n = 139) and PBO (n = 131) at week 0, and for CMI (n = 136) and PBO (n = 134) at week 24.

-4.4, -2.7); I^2 = 0.0 %], along with increases in lateral E' velocity [1.2 (95 % CI 0.9, 1.6) cm/s; I^2 = 0.0 %] and septal E' velocity [0.6 (95 % CI 0.4, 0.8) cm/s, I^2 = 0.0 %] compared to placebo over 24 to 30 weeks (Fig. 4b; Supplementary material online, Fig. S8).[41,42] There were no significant between-group differences in peak A wave velocity.

CMR

In three trials involving 150 patients, CMI treatment was associated with a significant reduction in LVMI [-18.7 (95 % CI -23.6, -13.8) g/m^2; I^2 = 67.5 %] and LV MWT [-2.7 (95 % CI -3.3, -2.0) mm; I^2 = 43.3 %] compared to placebo over 24 to 30 weeks (Fig. 5; Supplementary material online, Fig. S9).[34,43,44] In two trials with 115 patients, CMI treatment was associated with a significant reduction in LVM [-43 (95 % CI -54, -32) g; I^2 = 71.0 %] compared to placebo over 24 to 30 weeks.[34,44] In two trials involving 92 patients, CMI treatment was associated with significant reductions in LVEF [-4.2 (95 % CI -6.7, -1.6) %; I^2 = 52.2 %], LAVI [-11.6 (95 % CI -15.7, -7.4) mL/m^2; I^2 = 0.0 %], and absolute myocyte mass index [-13.3 (95 % CI -18.2, -8.5) g/m^2; I^2 = 0.0 %] compared to placebo over 24 to 30 weeks.[43,44] No significant differences were observed in LGE mass.

SRT

In two trials with 173 patients eligible for SRT at baseline, those treated with CMI were significantly less likely to remain eligible at follow-up [OR 0.09 (95 % CI 0.04, 0.20); I^2 = 0.0 %] compared to placebo over 16 to 24 weeks (Supplementary material online, Fig. S10).[33,46]

Safety endpoints

Cardiac safety outcomes were assessed across three trials involving up to 614 patients (Fig. 6). In two trials, the CMI treatment group had a greater likelihood of LVEF <50 % [OR 4.21 (95 % CI 1.17, 15.15); I^2 = 0.0 %] compared to placebo over 24 to 30 weeks.[32,35,45] No significant differences were observed for atrial fibrillation, ventricular tachycardia, palpitations, chest pain/discomfort/angina pectoris, dizziness, or corrected QT interval change. In two trials (EXPLORER-HCM and EXPLORER-CN) that assessed NSVT using 48-h Holter monitoring, no significant differences were observed between the CMI and placebo group regarding the likelihood of this outcome at 0, 12, or 26 weeks (Supplementary material online, Fig. S11).[32,34]

Regarding non-cardiac safety outcomes, in three trials involving up to 614 patients, there were no significant differences between groups in terms of any AE, or any SAE (Supplementary material online, Fig. S12).[32,34,35]

Sensitivity analyses

Sensitivity analyses using random effects models, instead of common/fixed effects models, revealed broadly similar results for most efficacy outcomes relating to symptoms and health-related QoL, CPET, TTE, biomarkers, and CMR (Table 2). However, more conservative estimates were observed with random effects models for KCCQ-TSS, KCCQ-PLS, KCCQ-SLS, pVO_2, peak METS, ventilatory power, circulatory power, VE/VCO_2 nonpeak or pre-AT, exercise duration, TTE LVESD, TTE LVESVI, peak E velocity, septal E' velocity, CMR LVMI, CMR LVM, CMR LVEF, CMR LAVI, and the proportion with LVEF <50 %.

The 95 % Bayesian credible interval estimates were slightly more conservative (wider) than 95 % confidence intervals common/fixed effects models but more precise (narrower) than random-effects models (Table 2). Bayesian estimates can be interpreted as probability intervals, for example that there is a 95 % probability that CMI treatment causes an improvement in NYHA of at least one class of between 30 % and 42 % of patients, with the most probable improvement in 36 % of patients. While most parameters demonstrated good convergence and adequate ESS, a minority showed reduced ESS due to correlated samples, leading to wider credible intervals.

Subgroup analyses

Using common/fixed effects models, no statistically significant heterogeneity by drug (mavacamten versus aficamten) was observed for key outcomes: NYHA (*P-interaction* = 0.71), KCCQ-CSS (*P-interaction* = 0.26), pVO_2 (*P-interaction* = 0.57), VE/VCO_2 (nonpeak or pre-AT) (*P-interaction* = 0.12), NT-proBNP (*P-interaction* = 0.56), resting LVOT-G (*P-interaction* = 0.93), lateral E/e' (*P-interaction* = 0.90), CMR LVMI

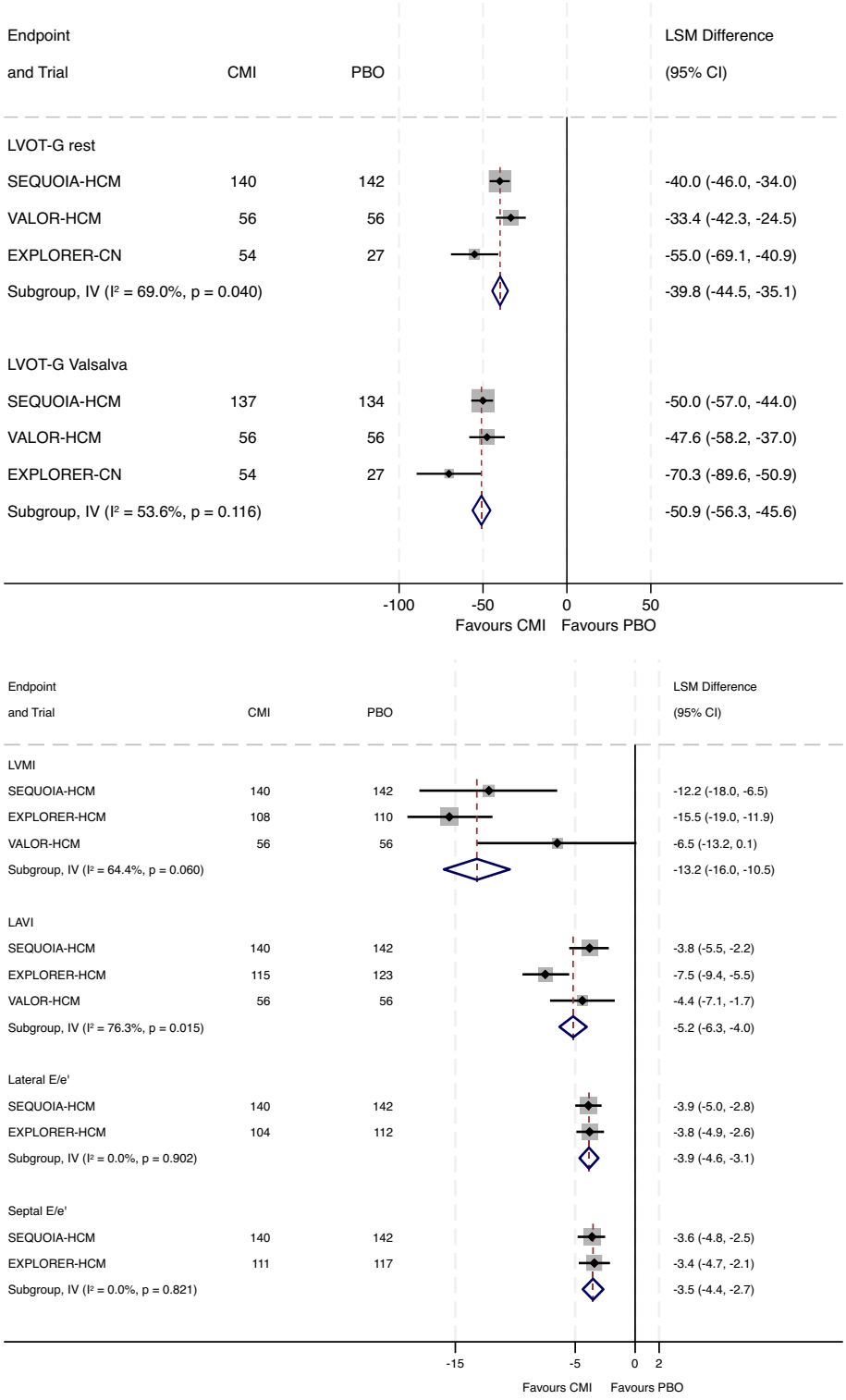


Fig. 4. a. Echocardiography (LVOT-G).
CMI, cardiac myosin inhibitor; IV, inverse variance; LSM, least squares mean; LVOT-G, left ventricular outflow tract gradient; PBO, placebo.
b. Echocardiography.
CMI, cardiac myosin inhibitor; IV, inverse variance; LAVI, left atrial volume index; LSM, least squares mean; LVMI, left ventricular mass index; PBO, placebo.

(*P-interaction* = 0.37), CMR LAVI (*P-interaction* = 0.52), LVEF <50 % (*P-interaction* = 0.83), and any SAE (*P-interaction* = 0.46). In contrast, significant heterogeneity was seen for hs-cTnI, with reductions of -43 % (95 % CI -36 %, -50 %) for aficamten versus -55 % (95 % CI -61 %, -50 %) for mavacamten (*P-interaction* = 0.005).

Some outcomes were reported in only one trial and thus were not included in the meta-analysis. The EuroQol 5-dimension 5-level index score, EuroQol visual analogue scale score, and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB) were reported solely in EXPLORER-HCM.[36,47] The SAQ-7 and total workload were only reported in SEQUOIA-HCM.[35,37,39] SEQUOIA-HCM provided two VE/VCO_2 slopes, one pre-anaerobic

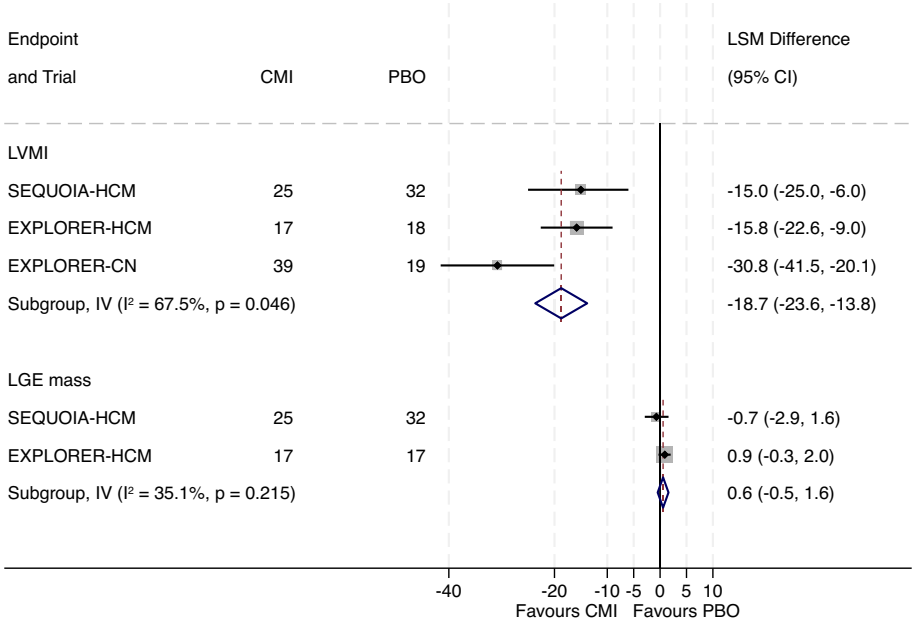


Fig. 5. Cardiovascular magnetic resonance.
CMI, cardiac myosin inhibitor; IV, inverse variance; LGE, late gadolinium enhancement; LSM, least squares mean; LVMI, left ventricular mass index; PBO, placebo. LGE was defined as signal intensity ≥6 SD above the mean signal intensity of the remote normal myocardium.

threshold and one throughout exercise; this approach was not used in EXPLORER-HCM.[38,39] Additionally, ventilatory anaerobic threshold units was reported differently in EXPLORER-HCM (mL/kg/min) and SEQUOIA-HCM (mL/min), so it was not meta-analyzed.[38,39] EXPLORER-HCM was the only trial to report the proportion achieving LVOT-G exercise <50 mmHg, whilst EXPLORER-CN was the only trial to report the proportion achieving LVOT-G Valsalva <50 mmHg, representing the threshold for SRT eligibility.[32,34] VALOR-HCM did not report between-treatment group differences (95 % CI) for several health status (KCCQ scores other than CSS) and TTE outcomes (ventricular strain, LA function, and diastolic function variables, including average E/e' and maximum mitral E wave velocity), and these were therefore not included in the meta-analysis.[48,50–52] SEQUOIA-HCM was the only trial to report TTE LV global longitudinal strain and LV global circumferential strain.[42] Regarding CMR outcomes, EXPLORER-HCM was the only trial to report myocardial contractile function, while SEQUOIA-HCM was the only trial to report mitral regurgitation fraction and mitral regurgitation volume.[43,44] Safety outcomes reported in only one trial or with zero-count events - such as heart failure, hypertension, and stress cardiomyopathy – were not included in the meta-analysis.

Discussion

This up-to-date meta-analysis of Phase 3 randomized controlled trials (RCTs) provides a holistic understanding of the global effects of CMIs in oHCM beyond LVOT-G reduction as well as providing valuable insights on symptom improvement, biomarker and mechanistic data on cardiac remodelling. This meta-analysis includes trials of both available CMIs, mavacamten and aficamten, and, for the first time, reports comprehensive novel outcomes which were not covered in prior meta-analyses. These include symptoms and health-related QoL (e.g. KCCQ subscores), CPET (e.g. peak METS, exercise duration, ventilatory efficiency), TTE (e.g. LV MWT, LV diastolic function), CMR (e.g. LGE mass, absolute myocyte mass index), septal reduction eligibility, and safety outcomes (e.g. ventricular tachycardia, palpitations, NSVT). These outcomes are essential to fully characterise the efficacy of CMIs with regard to cardiac remodelling and patient-reported symptoms, and to inform their clinical implementation with respect to safety.

The summary statistics derived from these meta-analyses are valuable for several reasons. First, they represent the most comprehensive synthesis to date across diverse and clinically meaningfully outcome domains, including symptoms, CPET, TTE, biomarkers, CMR, and safety. Second, they provide clinicians with quantifiable evidence of CMI benefits, relevant to patient selection and setting realistic outcome expectations. Third, they enable comparisons of mavacamten and aficamten in the absence of head-to-head trials. Fourth, they inform guideline updates by emphasizing the efficacy and safety of both CMIs, while illustrating the need for monitoring, due to increased likelihood of LVEF <50 % (OR 4.21). Fifth, the analysis highlights knowledge gaps in long-term outcomes. Finally, integrating both frequentist (common/fixed and random effects) and Bayesian meta-analytic methods offers complementary insights and enhances the statistical rigour and robustness of the findings, and offers simple probabilistic interpretations of the average CMI treatment effects with Bayesian estimates.

Robust randomized double-blind placebo-controlled trials were included with a low risk of bias (Supplemental Fig. S2). Core labs were used for CPET, biomarker, echocardiography, and CMR. Both peak and non-peak CPET variables were studied. Patients who were on disopyramide therapy were included in SEQUOIA-HCM, but not in EXPLORER-HCM or EXPLORER-CN.

Significant heterogeneity was observed among trials for several outcomes, including NT-proBNP ($I^2 = 70.8$ %, $P = 0.016$), hs-cTnI ($I^2 = 88.2$ %, $P < 0.000$), LVOT-G rest ($I^2 = 69.0$ %, $P = 0.040$), TTE LAVI ($I^2 = 76.3$ %, $P = 0.015$), and CMR LVMI ($I^2 = 67.5$ %, $P = 0.046$), which might impact interpretation.

Subgroup analyses showed no evidence of heterogeneity between mavacamten and aficamten across key outcomes, except for hs-cTnI, where greater reductions were observed with mavacamten, though this finding should be interpreted cautiously given it derives from a single aficamten trial and trial-level rather than individual participant data.

Several key differences between mavacamten and aficamten should be noted. The compounds have different binding sites on the myosin S1 domain, and whilst both inhibit actin-activated phosphate release, they differ in pharmacological properties.[53] Aficamten has faster binding kinetics, a shorter half-life, and more predictable dose–response

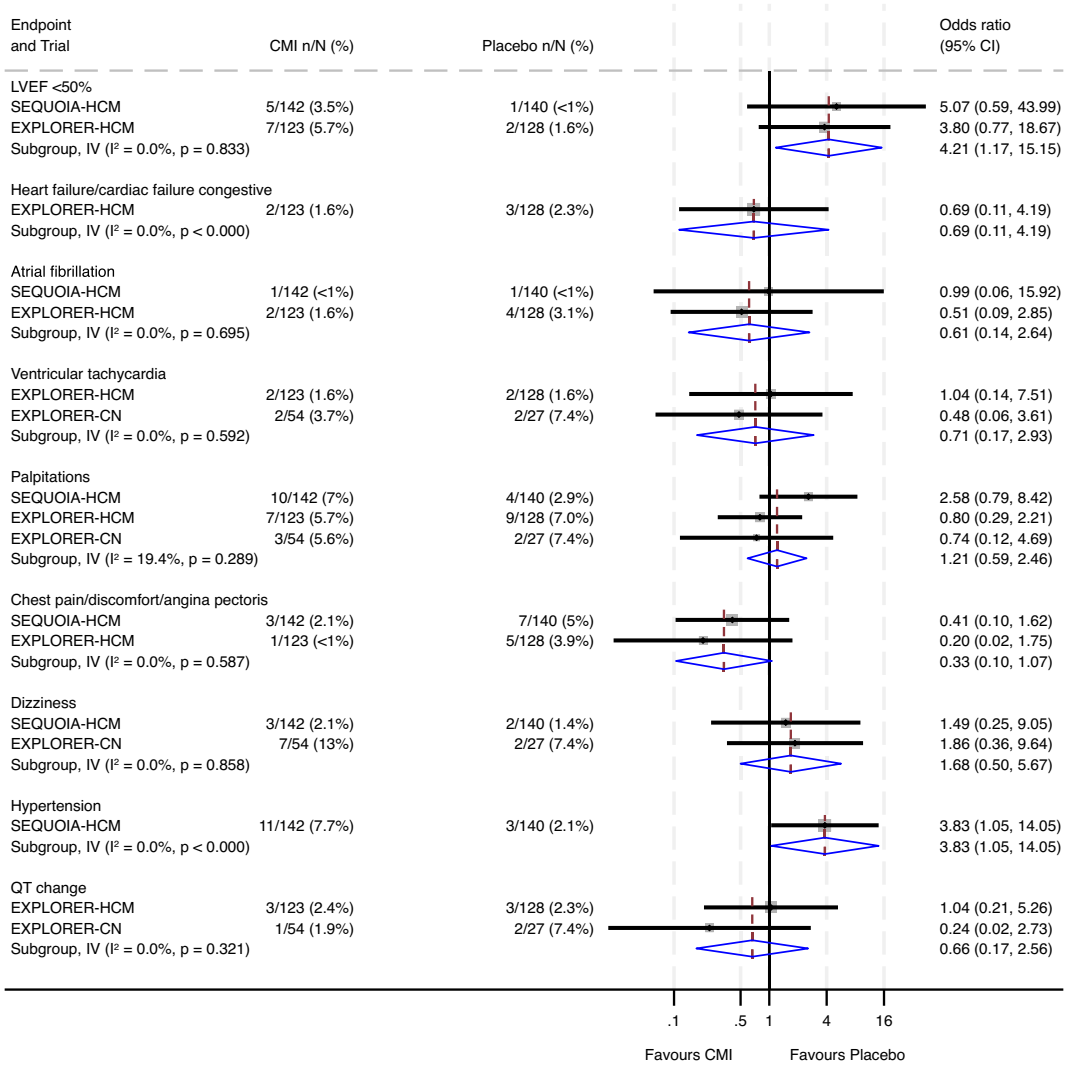


Fig. 6. Safety outcomes (cardiac).
CMI, cardiac myosin inhibitor; IV, inverse variance; LVEF, left ventricular ejection fraction; QTc, corrected QT interval.
Zero-count events were excluded from the meta-analysis for HF in SEQUOIA-HCM (CMI $n = 0$, PBO $n = 1$) and EXPLORER-CN (CMI $n = 0$, PBO $n = 0$); chest pain/discomfort/angina pectoris in EXPLORER-CN (CMI $n = 3$, PBO $n = 0$); hypertension in EXPLORER-CN (CMI $n = 3$, PBO $n = 0$); stress cardiomyopathy in EXPLORER-HCM (CMI $n = 2$, PBO $n = 0$). QT change was defined as 'QTc changes (Fridericia's formula)' in EXPLORER-HCM and as 'electrocardiogram QT prolonged' in EXPLORER-CN.

behaviour, allowing quicker titration and reversibility compared with the slower, longer-acting mavacamten. Aficamten is primarily metabolized by CYP3A4 and has fewer clinically significant drug–drug interactions, whereas mavacamten is metabolized by both CYP2C19 and CYP3A4, making it more susceptible to variability and interactions with inhibitors or inducers of these enzymes.

Building on these pharmacological differences, it is important to consider the clinical trial landscape. No direct head-to-head trials comparing these two CMIs have been conducted. Key ongoing trials investigating mavacamten and aficamten in HCM include long-term extension studies (MAVA-LTE NCT03723655, VALOR-HCM LTE NCT04349072, FOREST-HCM NCT04848506), adolescent oHCM (CEDAR-HCM NCT06412666; SCOUT-HCM NCT06253221) and non-obstructive HCM (ACACIA-HCM NCT06081894). To date, two randomized trials of mavacamten in non-obstructive HCM, MAVERICK-HCM and ODYSSEY-HCM, have reported.[54,55] The MAPLE-HCM trial comparing aficamten monotherapy with metoprolol monotherapy in oHCM, met its primary endpoint, showing a statistically significant improvement in pVO_2 from baseline to week 24.[56]

Several limitations should be acknowledged. Trials included varied in duration but were relatively short (ranging from 16 to 30 weeks), and long-term extension data from these trials were not included due to lack of placebo controls. Similarly, non-randomized trials or those without placebo controls were not included. Real-world data, while offering larger sample sizes and longer follow-up–particularly for safety assessments–were also excluded due to lower methodological rigour, with limitations such as potential bias in data collection, non-standardised outcome reporting, greater reliance on statistical adjustments, and weaker causal inference compared to RCTs.

As only trial-level data, rather than individual participant data, were available, additional statistical analyses–including network meta-analysis, and meta-regression–were not performed due to the risks of ecological bias, unmeasured confounding, and limited ability to adjust for covariates, and this may impact extrapolation across diverse populations with oHCM. Moreover, patients with NYHA class I or IV, non-obstructive HCM, aged <18 years, or with prior successful SRT were not included limiting the generalisability of findings to these individuals.

Further limitations include the limited data on arrhythmia as only two studies included rhythm monitoring in the protocol. Low patient

Table 2
Summary of meta-analysis estimates: frequentist (common/fixed and random effects), Bayesian analyses, and sensitivity comparisons.

Category	Outcome	Common/fixed effects (IV)	Random effects (DL + HKSJ)	Bayesian	Effect (units)
Symptoms and health-related QoL	≥1 NYHA improvement	36 % (29, 43)	36 % (31, 41)	36 % (30, 42)	Percentage-point difference
	KCCQ-CSS	8.4 (6.6, 10.2)	8.4 (6.4, 10.4)	8.4 (6.5, 10.3)	LSM difference (points)
	KCCQ-OSS	8.4 (6.0, 10.8)	8.4 (0.9, 15.9)	8.4 (6.0, 10.8)	LSM difference (points)
	KCCQ-TSS	6.9 (4.5, 9.2)	6.9 (-1.0, 14.8)	6.8 (4.4, 9.2)	LSM difference (points)
	KCCQ-PLS	9.1 (6.6, 11.6)	9.1 (-4.8, 22.9)	9.1 (6.6, 11.7)	LSM difference (points)
	KCCQ-SLS	8.3 (5.1, 11.4)	8.3 (-3.0, 19.6)	8.3 (5.1, 11.6)	LSM difference (points)
	KCCQ-QOL	9.8 (6.5, 13.1)	9.8 (7.9, 11.7)	9.7 (6.3, 13.2)	LSM difference (points)
CPET	pVO_2	1.56 (1.05, 2.07)	1.56 (-0.34, 3.46)	1.56 (0.79, 2.35)	LSM difference (mL/kg/min)
	Peak METS	0.45 (0.30, 0.59)	0.45 (-0.12, 1.02)	0.45 (-0.04, 0.99)	LSM difference
	Ventilatory power	0.8 (0.6, 1.0)	0.8 (-1.1, 2.7)	0.76 (0.11, 1.35)	LSM difference (mmHg)
	Circulatory power	486 (335, 636)	483 (-870, 1836)	481 (325, 637)	LSM difference (mmHg x mL/kg/min)
	VE/VCO_2 nonpeak or pre-AT	-2.0 (-2.7, -1.3)	-2.0 (-9.0, 5.0)	-2.0 (-3.0, -1.0)	LSM difference
	Exercise duration	0.88 (0.53, 1.23)	0.88 (-0.98, 2.75)	0.87 (0.13, 1.49)	LSM difference (min)
	Peak RER	0.01 (-0.01, 0.02)	0.01 (-0.12, 0.14)	0.01 (-0.31, 0.41)	LSM difference
	Aerobic efficiency	0.04 (-0.00, 0.08)	0.04 (-0.17, 0.25)	0.07 (-0.48, 0.67)	LSM difference (mL/min/W)
Biomarkers	NT-proBNP	0.21 (0.19, 0.23)	0.22 (0.12, 0.31)	0.22 (0.11, 0.36)	Proportion of geometric mean ratio
	hs-cTnI	0.50 (0.46, 0.54)	0.51 (0.32, 0.69)	0.50 (0.28, 0.73)	Proportion of geometric mean ratio
TTE (LVOT-G)	LVOT-G (rest)	-40 (-45, -35)	-41 (-66, -16)	-40 (-44, -35)	LSM difference (mmHg)
	LVOT-G (Valsalva)	-51 (-56, -46)	-53 (-77, -28)	-51 (-56, -46)	LSM difference (mmHg)
	LVOT-G (exercise)	-36 (-42, -30)	-36 (-46, -27)	-36 (-42, -30)	LSM difference (mmHg)
	LVOT-G (Valsalva) <30 mmHg	45 % (37, 52)	45 % (19, 70)	45 % (37, 53)	Percentage difference
TTE (cardiac dimensions and systolic function)	LVMI	-13.2 (-16.0, -10.5)	-12.0 (-23.1, -0.9)	-13.1 (-15.9, -10.2)	LSM difference (g/m^2)
	LAVI	-5.2 (-6.3, -4.0)	-5.2 (-10.3, -0.2)	-5.2 (-6.7, -3.8)	LSM difference (mL/m^2)
	LVEF	-4.3 (-5.2, -3.5)	-4.3 (-5.8, -2.9)	-4.3 (-5.3, -3.4)	LSM difference (%)
	IVS thickness	-1.2 (-1.5, -0.8)	-1.2 (-2.2, -0.1)	-1.1 (-1.8, -0.5)	LSM difference (mm)
	Inferolateral wall thickness	-0.8 (-1.1, -0.5)	-0.8 (-0.8, -0.8)	-0.8 (-1.4, -0.1)	LSM difference (mm)
	LVEDD	-0.5 (-1.1, 0.0)	-0.5 (-3.0, 2.0)	-0.5 (-1.3, 0.3)	LSM difference (mm)
	LVESD	1.3 (0.7, 1.9)	1.3 (-2.5, 5.1)	1.3 (0.4, 2.1)	LSM difference (mm)
	LVEDVI	-0.3 (-1.5, 1.0)	-0.3 (-2.5, 2.0)	-0.3 (-1.8, 1.2)	LSM difference (mL/m^2)
	LVESVI	1.6 (1.0, 2.2)	1.6 (-1.4, 4.6)	1.5 (0.5, 2.5)	LSM difference (mL/m^2)
TTE (LV diastolic function)	Peak E wave velocity	-5.9 (-8.9, -2.8)	-5.9 (-26.8, 15.1)	-5.9 (-8.9, -2.7)	LSM difference (cm/s)
	Lateral E/e'	-3.9 (-4.6, -3.1)	-3.9 (-4.5, -3.2)	-3.9 (-4.9, -2.9)	LSM difference
	Septal E/e'	-3.5 (-4.4, -2.7)	-3.5 (-4.8, -2.3)	-3.5 (-4.6, -2.4)	LSM difference
	Lateral E' velocity	1.2 (0.9, 1.6)	1.2 (0.6, 1.9)	1.3 (0.7, 1.9)	LSM difference (cm/s)
	Septal E' velocity	0.6 (0.4, 0.8)	0.6 (-0.7, 1.9)	0.6 (-0.05, 1.2)	LSM difference (cm/s)
	Peak A wave velocity	-2.1 (-4.8, 0.6)	-2.1 (-5.3, 1.0)	-2.2 (-4.9, 0.7)	LSM difference
CMR	LVMI	-18.7 (-23.6, -13.8)	-19.9 (-41.2, 1.3)	-18.7 (-23.8, -13.8)	LSM difference (g/m^2)
	LV MWT	-2.7 (-3.3, -2.0)	-2.7 (-4.6, -0.7)	-2.7 (-3.5, -1.7)	LSM difference (mm)
	LVM	-43 (-54, -32)	-42 (-180, 95)	-43 (-55, -32)	LSM difference (g)
	LVEF	-4.2 (-6.7, -1.6)	-4.3 (-28.4, 19.7)	-4.2 (-6.8, -1.5)	LSM difference (%)
	LAVI	-11.6 (-15.7, -7.4)	-11.6 (-28.7, 5.6)	-11.6 (-15.7, -7.4)	LSM difference (mL/m^2)
	Absolute myocyte mass index	-13.3 (-18.2, -8.5)	-13.3 (-18.3, -8.3)	-13.4 (-18.3, -8.4)	LSM difference (g/m^2)
	LGE mass	0.6 (-0.5, 1.6)	0.4 (-9.0, 9.8)	0.5 (-0.9, 1.8)	LSM difference (g)
SRT	SRT eligibility	0.09 (0.04, 0.20)	0.09 (0.00, 8.69)	0.10 (0.04, 0.27)	Odds ratio
Safety outcomes (cardiac)	LVEF <50 %	4.21 (1.17, 15.15)	4.21 (0.73, 24.23)	4.23 (1.03, 17.43)	Odds ratio
	Atrial fibrillation	0.61 (0.14, 2.64)	0.61 (0.01, 25.20)	0.62 (0.11, 3.33)	Odds ratio
	Ventricular tachycardia	0.71 (0.17, 2.93)	0.71 (0.01, 96.65)	0.70 (0.15, 3.34)	Odds ratio
	Palpitations	1.21 (0.59, 2.46)	1.21 (0.21, 6.99)	1.21 (0.49, 3.03)	Odds ratio
	Chest pain/discomfort/angina pectoris	0.33 (0.10, 1.07)	0.33 (0.01, 19.82)	0.33 (0.09, 1.24)	Odds ratio
	Dizziness	1.68 (0.50, 5.67)	1.68 (0.41, 6.91)	1.68 (0.41, 6.36)	Odds ratio
	QT change	0.66 (0.17, 2.56)	0.66 (0.00, 3924.88)	0.64 (0.14, 2.86)	Odds ratio
	NSVT at 0 weeks	1.22 (0.74, 2.03)	1.22 (0.07, 21.51)	1.28 (0.57, 3.35)	Odds ratio
	NSVT at 12 weeks	0.79 (0.45, 1.38)	0.85 (0.01, 115.60)	0.84 (0.35, 2.32)	Odds ratio
	NSVT at 26 weeks	0.95 (0.57, 1.57)	0.95 (0.46, 1.94)	0.94 (0.40, 2.23)	Odds ratio
Safety outcomes (non-cardiac)	Any adverse event	1.32 (0.88, 1.96)	1.31 (0.47, 3.71)	1.30 (0.64, 2.41)	Odds ratio
	Any serious adverse event	0.74 (0.39, 1.41)	0.74 (0.04, 15.57)	0.74 (0.31, 1.76)	Odds ratio

AT, anaerobic threshold; CMR, cardiovascular magnetic resonance; CSS, Clinical Summary Score; DL, DerSimonian and Laird; HKSJ, Hartung-Knapp-Sidik-Jonkman; hs-cTnI, high-sensitivity cardiac troponin I; IV, inverse variance; IVS, interventricular septum; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LSM, least squares mean; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMI, left ventricular mass index; LVOT-G, left ventricular outflow tract gradient; METS, metabolic equivalents; MWT, maximal wall thickness; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; PLS, Physical Limitation Score; pVO_2, peak oxygen uptake; QOL, Quality of Life Score; RER, respiratory exchange ratio; SLS, Social Limitation Score; SRT, septal reduction therapy; TSS, Total Symptom Score; TTE, transthoracic echocardiography; VCO_2, carbon dioxide output; VE, minute ventilation.
Frequentist: Common/fixed effects and random effects (95 % CI) shown.
Bayesian: Median (95 % credible intervals) shown. R-hat 1.00 for all (except 1.01 for Peak RER).

numbers for CMR data limits generalizability. Dosing of mavacamten differed in EXPLORER-HCM (2.5 to 15 mg), VALOR-HCM (2.5 to 15 mg), and EXPLORER-CN (1 to 15 mg). VALOR-HCM data included only the 16-week treatment period, excluding crossover data from the open-label extension that started after 16 weeks.[49–52] There is a lack of data on hard endpoints such as death or hospitalizations due to trial duration. Washout period data were not studied in this meta-analysis. A funnel plot for publication bias was not performed due to the small number of trials.

Finally, SRT eligibility is an endpoint driven by guideline criteria rather than patient choice, based on both subjective (e.g. NYHA class) and objective (e.g. LVOT-G) criteria, which may introduce bias or inconsistency in assessment. In real-world practice, SRT decisions are complex and individualised, factoring in patient preference and institutional expertise. Since not all patients with oHCM meet SRT eligibility criteria at baseline, and SRT may not be appropriate or available for all, its applicability as a universal endpoint is limited.

Conclusion

Mavacamten and aficamten significantly improve symptoms (NYHA, KCCQ-CSS), enhance exercise performance (CPET), reduce LVOT-G, lower biomarkers associated with cardiac wall stress (NT-proBNP) and myocyte injury (troponin), and promote beneficial cardiac reverse remodelling (TTE and CMR). This up-to-date comprehensive meta-analysis suggests a class effect of CMIs in oHCM with consistent therapeutic benefits and safety profile.

CRediT authorship contribution statement

Matthew M.Y. Lee: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Fraser C. Goldie:** Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Alasdair D. Henderson:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Ahmad Masri:** Writing – review & editing. **Iacopo Olivotto:** Writing – review & editing. **Caroline J. Coats:** Writing – original draft, Visualization, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

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Data availability

All supporting data are available within the article and its online supplementary files.

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