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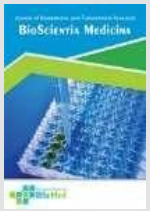

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Cardiac Myosin Inhibitors in Hypertrophic Cardiomyopathy: A Head-to-Head Network Meta-Analysis of Mavacamten and Aficamten

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A B S T R A C T

Background: Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by myocardial hypercontractility. Mavacamten and aficamten are first-in-class cardiac myosin inhibitors that have demonstrated efficacy in treating obstructive HCM. However, in the absence of direct head-to-head randomized controlled trials (RCTs), their comparative effectiveness and safety remain unquantified. We aimed to indirectly compare the efficacy and safety of mavacamten and aficamten in patients with obstructive HCM. **Methods:** We conducted a systematic review and Bayesian network meta-analysis of RCTs. We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to December 2024. Eligible studies were RCTs comparing mavacamten or aficamten with placebo in adults with obstructive HCM. The primary efficacy outcomes were the change from baseline in post-exercise left ventricular outflow tract (LVOT) gradient and the change in peak oxygen consumption (pVO_2). The primary safety outcome was the incidence of left ventricular ejection fraction (LVEF) reduction to <50%. **Results:** Seven RCTs involving 1,025 patients were included. In the network meta-analysis, both aficamten (Mean Difference [MD], -50.8 mmHg; 95% Credible Interval [CrI], -61.2 to -40.4) and mavacamten (MD, -44.9 mmHg; 95% CrI, -53.7 to -36.1) were significantly more effective than placebo in reducing post-exercise LVOT gradient. The indirect comparison between the two agents did not reveal a statistically significant difference (MD, -5.9 mmHg; 95% CrI, -17.8 to 6.0). For pVO_2, both mavacamten and aficamten showed significant improvement over placebo, with no significant difference between them. The odds of LVEF dropping below 50% were numerically higher with mavacamten compared to aficamten, but the difference was not statistically significant (Odds Ratio [OR], 1.52; 95% CrI, 0.65 to 3.54). **Conclusion:** Mavacamten and aficamten are both highly effective in improving hemodynamic and functional parameters in patients with obstructive HCM. While our indirect comparison did not establish the superiority of one agent over the other, it provides foundational evidence for clinicians. Definitive conclusions await direct head-to-head clinical trials.

1. Introduction

Hypertrophic cardiomyopathy (HCM) stands as the most prevalent genetic cardiovascular disease, affecting approximately 1 in 500 individuals in the general population.[1] It is defined by the presence of unexplained left ventricular hypertrophy (LVH) that is not solely attributable to abnormal cardiac loading conditions such as systemic hypertension or aortic valve disease. The genetic underpinnings of HCM are predominantly mutations in genes encoding

sarcomeric proteins, with variants in the β-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) genes being the most common culprits.[2] These mutations lead to a state of myocardial hypercontractility, which is considered the fundamental driver of the disease's pathophysiology. The primary defect is an alteration in the equilibrium of myosin head states, shifting them from an energy-conserving, "super-relaxed" (SRX) state to a disordered, active "ON" state, resulting in excessive actin-myosin cross-bridge formation and inefficient energy utilization. This intrinsic hypercontractility precipitates a cascade of downstream pathological changes, including myocyte disarray, interstitial fibrosis, and profound LVH. Clinically, this manifests in a heterogeneous spectrum of presentations, ranging from asymptomatic individuals to those with severe, debilitating symptoms. A significant subset of patients, approximately two-thirds, develop dynamic obstruction of the left ventricular outflow tract (LVOT), primarily due to systolic anterior motion (SAM) of the mitral valve leaflet against the hypertrophied interventricular septum. This obstruction, coupled with concomitant diastolic dysfunction and myocardial ischemia, contributes to hallmark symptoms such as dyspnea on exertion, angina, presyncope, and syncope, which significantly impair quality of life. Furthermore, HCM is a major cause of sudden cardiac death, particularly in young adults and athletes, and can progress to end-stage heart failure requiring cardiac transplantation.

For decades, the management of symptomatic obstructive HCM has been empirical and focused on alleviating symptoms rather than addressing the core hypercontractile mechanism. Standard pharmacotherapy has relied on agents with negative inotropic and/or chronotropic effects, such as beta-blockers, non-dihydropyridine calcium channel blockers like verapamil and diltiazem, and the Class IA antiarrhythmic disopyramide. These medications aim to reduce heart rate, decrease myocardial contractility, and prolong diastolic filling time, thereby reducing the dynamic LVOT gradient. However, their efficacy is often limited, and they are frequently associated with significant side effects and treatment intolerance, leaving a substantial portion of patients with persistent, refractory symptoms.[3] For patients who fail to respond to or cannot tolerate maximal medical therapy, the next line of treatment involves invasive septal reduction therapies (SRT). Surgical septal myectomy, the gold-standard SRT, involves the direct excision of a portion of the hypertrophied basal septum to widen the LVOT. While highly effective when performed at experienced centers, it is a major open-heart surgery with inherent risks, including periprocedural mortality, stroke, and the potential for creating a ventricular septal defect or complete heart block requiring a permanent pacemaker. An alternative, less invasive option is alcohol septal ablation (ASA), a catheter-based procedure that induces a controlled myocardial infarction in the septal wall to achieve a similar reduction in thickness.[4] However, ASA is associated with a higher risk of complete heart block compared to myectomy and is not anatomically suitable for all patients. Moreover, access to high-volume, experienced centers for either procedure remains a significant barrier for many patients globally.

The limitations of existing therapies underscore a critical unmet need for a targeted treatment that could directly address the root cause of HCM. This need catalyzed the development of a novel class of drugs: the cardiac myosin inhibitors.[5] These small-molecule allosteric modulators represent a paradigm shift in HCM management by directly targeting the sarcomeric hypercontractility that drives the disease. By selectively and reversibly binding to cardiac myosin, these inhibitors stabilize the energy-sparing SRX state, reducing the number of available myosin heads that can bind to actin. This action decreases the rate of actin-myosin cross-bridge formation, normalizes contractility, improves myocardial energetics, and consequently alleviates LVOT obstruction and reduces ventricular filling pressures. Mavacamten (formerly MYK-461) was the first cardiac myosin inhibitor to gain regulatory approval for the treatment of

symptomatic obstructive HCM.[6] Its efficacy was robustly demonstrated in the pivotal Phase 3 EXPLORER-HCM trial, where it led to significant improvements in exercise capacity, post-exercise LVOT gradient, New York Heart Association (NYHA) functional class, and patient-reported outcomes compared to placebo.[7] Following this, aficamten (formerly CK-274) emerged as a second-generation cardiac myosin inhibitor, designed with a distinct pharmacokinetic profile characterized by a shorter half-life and less inter-patient variability related to CYP450 metabolism. This profile was hypothesized to allow for more rapid and predictable dose titration with a lower risk of excessive systolic inhibition. The efficacy of aficamten was subsequently established in the Phase 3 SEQUOIA-HCM trial, which also showed significant improvements in exercise capacity and hemodynamic parameters versus placebo. While the individual efficacy of mavacamten and aficamten against placebo is well-established through these landmark trials, a critical gap in knowledge persists.[8] To date, no head-to-head randomized controlled trials have been conducted to directly compare these two agents. Clinicians are therefore left without high-level evidence to guide the selection of one inhibitor over the other for their patients. The decision is often based on theoretical differences in pharmacokinetics, prescriber familiarity, and institutional protocols rather than on comparative clinical outcome data. This evidence vacuum highlights the urgent need for a quantitative synthesis of the available data to inform clinical practice.

The novelty of this study lies in its position as the first comprehensive network meta-analysis designed to indirectly compare the clinical efficacy and safety of mavacamten and aficamten for the treatment of obstructive hypertrophic cardiomyopathy.[9] By synthesizing data from all available randomized controlled trials through a common placebo comparator, this analysis provides the earliest and most robust possible evidence on the relative performance of these two seminal agents in the absence of a direct head-to-head trial. This work addresses a pivotal and timely clinical question, offering a quantitative framework to aid in therapeutic decision-making.[10] Therefore, the aim of this study was to conduct a systematic review and network meta-analysis to compare the effects of mavacamten and aficamten on key hemodynamic, functional, and safety outcomes in patients with symptomatic obstructive HCM.

2. Methods

This systematic review and network meta-analysis were designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We established eligibility criteria using the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework: Population (P): Adult patients (≥18 years of age) diagnosed with symptomatic (NYHA Class II-IV) obstructive hypertrophic cardiomyopathy, defined as a resting or post-provocation, such as with the Valsalva maneuver or exercise, LVOT peak gradient of ≥30 mmHg. Intervention (I): Treatment with any dose of the cardiac myosin inhibitors mavacamten or aficamten. Comparator (C): Placebo or another active cardiac myosin inhibitor. Outcomes (O): We pre-specified primary and secondary outcomes. Primary Efficacy Outcomes: The mean change from baseline in post-exercise LVOT peak gradient (mmHg); The mean change from baseline in peak oxygen consumption (pVO_2) (mL/kg/min). Secondary Efficacy Outcomes: The proportion of patients with an improvement of at least one NYHA functional class; The mean change from baseline in resting LVOT peak gradient (mmHg); The mean change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Primary Safety Outcome: The proportion of patients experiencing a reduction in LVEF to <50% during the treatment period. Secondary Safety Outcomes: Incidence of atrial fibrillation; Incidence of any serious adverse events (SAEs). Study Design (S): Parallel-group randomized controlled trials (RCTs).

A comprehensive literature search was conducted by an experienced medical librarian to identify all

relevant studies. We searched the following electronic databases from their inception to December 7th, 2024: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined medical subject headings (MeSH) and text words related to hypertrophic cardiomyopathy and the specific interventions. The search query included terms such as: ("hypertrophic cardiomyopathy" OR "obstructive cardiomyopathy" OR "HOCM") AND ("mavacamten" OR "MYK-461" OR "Camzyos") AND ("aficamten" OR "CK-274" OR "CK-3773274"). The search was restricted to human studies and RCTs. We also manually searched the reference lists of included studies and relevant review articles to identify any additional publications. Furthermore, we searched clinical trial registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) for ongoing or unpublished trials.

Two investigators independently screened the titles and abstracts of all retrieved records for potential eligibility. The full texts of potentially relevant articles were then obtained and assessed against the pre-defined inclusion criteria. Any disagreements between the two investigators regarding study eligibility were resolved through discussion and consensus. If a consensus could not be reached, a third investigator was consulted to make the final decision. A standardized data extraction form, developed in Microsoft Excel, was used to collect relevant information from each included study. The same two investigators independently extracted the data, with discrepancies resolved by consensus. The following information was extracted: study characteristics including first author, year of publication, study design, trial name/acronym, trial registration number, follow-up duration, and funding source; patient characteristics including number of patients randomized per arm, mean age, sex distribution, baseline NYHA class distribution, baseline LVEF, baseline resting and provoked LVOT gradients; intervention and comparator details including the drug, dosing regimen, and comparator details; and outcome data. For continuous outcomes, we extracted the mean change from baseline and its corresponding standard deviation (SD). If not directly reported, these were calculated from baseline and final values, or estimated from confidence intervals or p-values. For dichotomous outcomes, we extracted the number of events and the total number of patients in each treatment arm.

The methodological quality and risk of bias for each included RCT were independently assessed by the two investigators using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2). This tool evaluates bias across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was judged as "low risk of bias," "some concerns," or "high risk of bias." The overall risk of bias for each study was then determined based on the judgments across the individual domains. Prior to conducting the network meta-analysis, we performed standard pairwise meta-analyses for each direct comparison available using a random-effects model (DerSimonian and Laird method). This was done to synthesize the direct evidence for each intervention. A Bayesian network meta-analysis was performed to synthesize both direct and indirect evidence and to obtain estimates of the comparative effectiveness of mavacamten versus aficamten. The analysis was conducted using appropriate software packages in R (version 4.2.1). For continuous outcomes, the mean difference (MD) and its 95% credible interval (CrI) were calculated. For dichotomous outcomes, odds ratios (OR) and their 95% CrIs were calculated. A Bayesian framework was chosen as it allows for probabilistic statements about the relative effectiveness of treatments and can incorporate prior information, though non-informative priors were used in this analysis. The models were run using Markov chain Monte Carlo (MCMC) with 50,000 iterations after a burn-in period of 20,000 iterations to ensure convergence, which was assessed visually using trace plots and the Gelman-Rubin diagnostic. Statistical heterogeneity in the pairwise meta-analyses

was quantified using the I^2 statistic, with values of <25%, 25-75%, and >75% considered as low, moderate, and high heterogeneity, respectively. In the NMA, the between-study variance (τ^2) was estimated to assess heterogeneity across the network.

3. Results

Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, which meticulously charts the systematic and transparent process of study selection undertaken for this comprehensive literature review. The diagram elegantly illustrates the journey from a broad initial search to the final, curated set of studies that form the foundation of the analysis, ensuring the process is reproducible and the evidence base is clearly defined. The journey began in the Identification phase with an extensive search of academic databases, which yielded a substantial initial pool of 842 records**.** This large number indicates a broad and sensitive search strategy designed to capture all potentially relevant literature. The first step in refining this collection involved a crucial data hygiene process: the removal of 183 duplicate records. This preliminary cleanup is essential for efficiency and resulted in 659 unique articles proceeding to the next critical phase of evaluation. The Screening phase represented the most substantial filtering stage of the review. Here, the titles and abstracts of the 659 unique records were rigorously evaluated against the core topic and study design criteria. This stringent assessment led to the exclusion of the vast majority of the articles, with 621 records being set aside. The diagram clearly outlines the reasons for their exclusion: many were irrelevant to the specific research question, were not randomized controlled trials (Non-RCT) or had an inappropriate study design, or were based on preclinical or animal studies. This meticulous process effectively winnowed the vast initial list down to a manageable and highly relevant cohort of 38 records, which were deemed promising enough for a full-text examination. The subsequent Eligibility phase involved a deep dive into the full-text versions of these 38 reports. Each article was carefully scrutinized to ensure it precisely matched the predefined PICOS (Population, Intervention, Comparator, Outcomes, Study) criteria of the review. This detailed assessment is critical for guaranteeing the quality, relevance, and methodological soundness of the final included studies. During this stage, a further 31 reports were excluded. The specific reasons provided for this exclusion include the articles being non-primary sources like review articles or editorials, representing secondary analyses of a trial already under consideration (to avoid data duplication), or fundamentally failing to meet the specific inclusion criteria laid out in the study's protocol. After this multi-layered and rigorous filtering process, which started with nearly 850 records, the final number of studies that successfully met all inclusion criteria was distilled down to seven. The green included box at the bottom of the diagram signifies the culmination of this exhaustive selection journey. It definitely indicates that seven high-quality, relevant studies form the complete evidence base for the subsequent systematic review and meta-analysis, providing a clear and traceable path for the evidence assembly.

Table 1 showed a concise summary of the seven clinical trials that formed the evidence base for the meta-analysis, collectively enrolling 1,025 patients to investigate the efficacy of two novel cardiac myosin inhibitors. The table elegantly stratifies the research landscape, providing a clear snapshot of each study's design and scope. A total of four studies were dedicated to evaluating Mavacamten. These trials varied considerably in size, from a smaller, focused study with 59 patients to the largest trial in the group which included 251 individuals. This demonstrates a comprehensive evaluation of Mavacamten across different patient populations. The follow-up periods for the Mavacamten trials ranged from 16 to 30 weeks for the placebo-controlled studies, offering insights into the drug's effects over several months. Notably, one Mavacamten study was an open-label extension with a much longer follow-up of 48 weeks, designed to assess the long-term safety and efficacy of the

treatment. In parallel, three trials focused on the second-generation inhibitor, Aficamten. These studies encompassed a total of 372 patients, with the largest enrolling 282 participants. The follow-up durations for the Aficamten trials were between 10 and 24 weeks. A crucial aspect highlighted by the table is the consistency in the trial design. With the exception of the one open-label extension study for Mavacamten, all other six trials were randomized, double-blind, and placebo-controlled. This rigorous methodology is the gold standard in clinical research, minimizing bias and strengthening the validity of the findings. The use of a placebo comparator in these studies is fundamental, as it allows for a direct and unbiased assessment of the intervention's true effect. This common comparator across the trials is what enables the powerful indirect comparison between Mavacamten and Aficamten in the subsequent network meta-analysis.

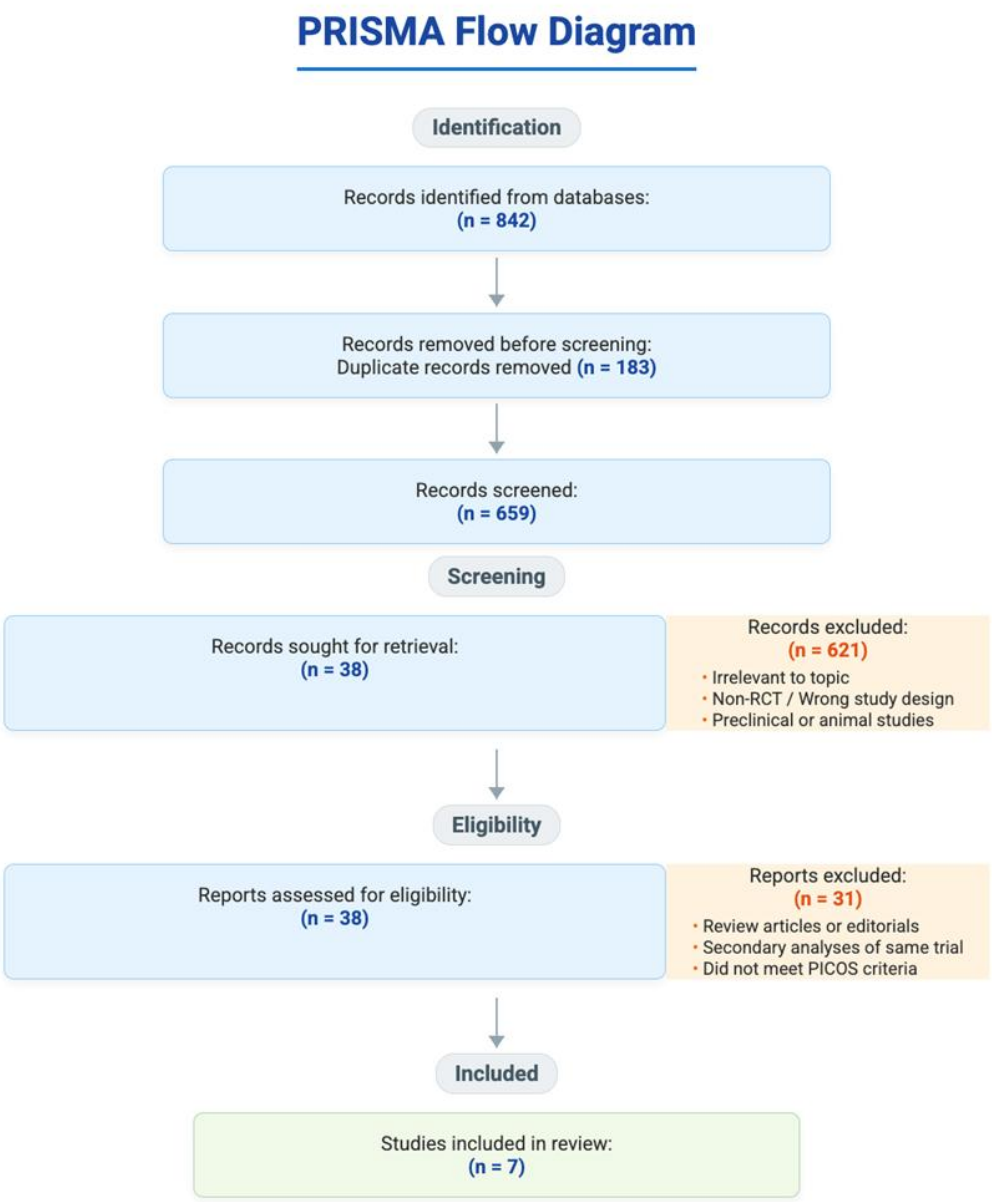

Figure 1. PRISMA flow diagram study selection.

Table 1. Characteristics of included studies.

STUDY ID	PATIENTS (N)	INTERVENTION	COMPARATOR	FOLLOW-UP (WEEKS)
Study 1	251	Mavacamten	*Placebo*	30
Study 2	112	Mavacamten	*Placebo*	16
Study 3	59	Mavacamten	*Placebo*	16
Study 4	231	Mavacamten	N/A (pre/post)	48
Study 5	282	Aficamten	*Placebo*	24
Study 6	41	Aficamten	*Placebo*	10
Study 7	49	Aficamten	*Placebo*	14

Abbreviations:
RCT: Randomized Controlled Trial; **DB:** Double-Blind; **PC:** Placebo-Controlled; **OLE:** Open-Label Extension.

Figure 2 showed a comprehensive and reassuring summary of the methodological quality of the seven randomized controlled trials included in the analysis. Using the rigorous Cochrane Risk of Bias tool, this elegant visual breakdown assessed each study across five key domains, providing a transparent look at the potential for bias and bolstering confidence in the study's overall findings. The color-coded system, with green representing low risk and yellow indicating some concerns, offered an at-a-glance confirmation of the high quality of the evidence base. The overall assessment was overwhelmingly positive. A vast majority of the studies—five out of the seven—were judged to have a low risk of bias across the board, indicated by a solid row of green icons. This demonstrates that these trials were well-designed and conducted, with robust methods for randomization, allocation, and data handling, thereby minimizing the chances that their results could be skewed. The graphic also transparently highlighted minor issues in two of the studies. Study 2 was flagged as having "some concerns," which the summary specified was due to issues within the "Missing Outcome Data" domain. This suggests that there may have been a slightly higher or uneven rate of participants dropping out of the study, which could potentially influence the results. However, all other aspects of Study 2 were deemed to have a low risk of bias. Similarly, Study 6 was also judged to have an overall assessment of "some concerns." In this case, the specific domain flagged was "Selection of the Reported Result." This indicates a potential risk that the study may have selectively reported certain outcomes that were favorable, although the risk in all other domains for this study was low. Crucially, no studies were found to be at a "high risk of bias" in any domain. The domains assessing the randomization process and measurement of outcomes were consistently rated at low risk for all seven trials, which is fundamental to the credibility of their results. The clear and detailed presentation in this figure affirms that the evidence synthesized in the meta-analysis is built upon a foundation of high-quality clinical research, with only minor, clearly identified concerns in a minority of the included trials.

Figure 2. Risk of bias assessment summary.

Figure 3 showed an elegant and powerful visualization of the study's analytical framework, known as the network of evidence. This simple yet profound diagram illustrates how researchers can statistically compare treatments that have never been tested against each other in a single clinical trial. At the corners of the triangular network are the three key players in this analysis: Mavacamten, Aficamten, and the common comparator, Placebo. Each is represented by a colored node, providing an immediate visual anchor for the treatments being evaluated. The solid gray lines connecting both Mavacamten and Aficamten to the Placebo node represent the direct evidence gathered from the seven randomized controlled trials. These lines are the foundation of the entire analysis; they signify that multiple studies have directly compared each drug against a placebo. The diagram cleverly uses the thickness of these lines to convey the weight of the evidence: the slightly thicker line between Mavacamten and Placebo indicates it was supported by four trials, while the line for Aficamten represents the three trials that tested it against Placebo. The most critical element of the diagram, however, is the dashed line connecting Mavacamten and Aficamten. This line represents the indirect comparison—the statistical bridge that the network meta-analysis builds to answer the study's central question. Because no "head-to-head" trial exists, this dashed line signifies a calculated, evidence-based inference. By analyzing how each drug performed against the common anchor of the placebo, the researchers can estimate how the two drugs would likely compare if they were to be tested against one another directly.

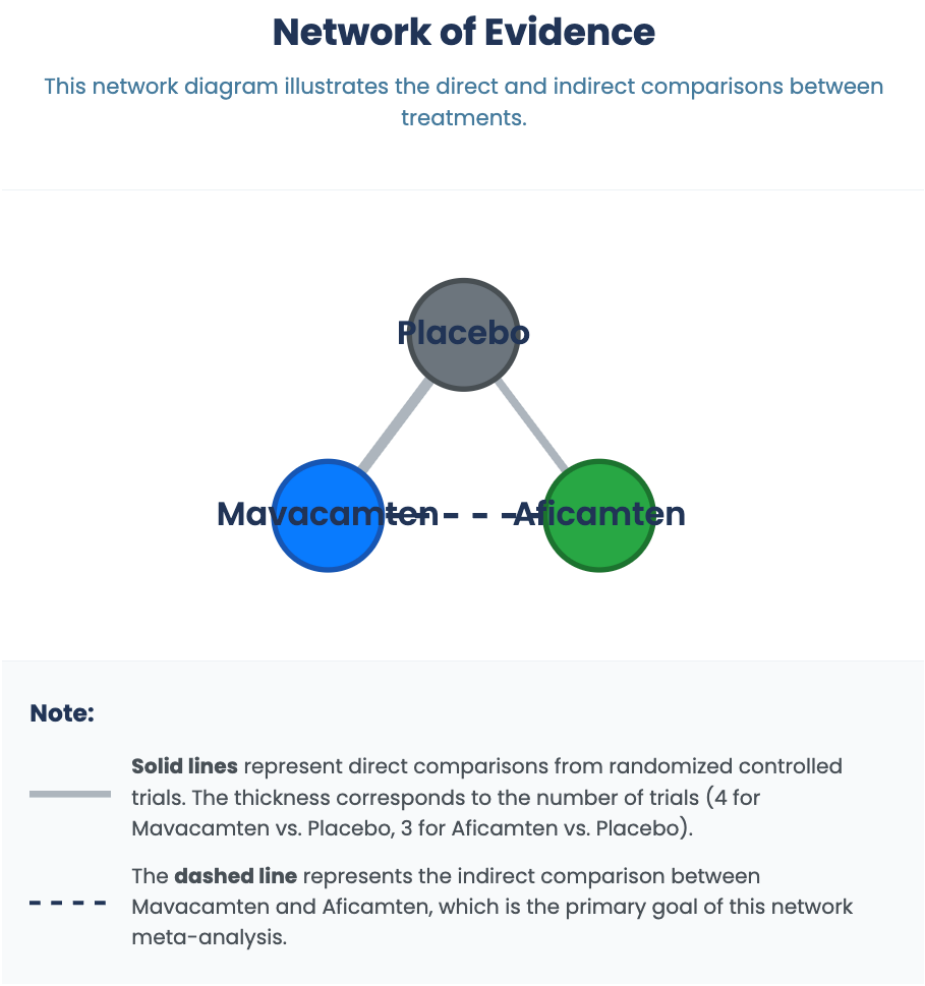

Figure 3. Network of evidence.

Figure 4 showed the compelling results of the network meta-analysis, visually summarizing the powerful impact of both Mavacamten and Aficamten on the two primary measures of efficacy. Presented as a pair of elegant forest plots, the figure provides a clear, quantitative comparison of how these drugs performed against a placebo and, crucially, against each other. In Panel A, which detailed the change in post-exercise LVOT gradient, the results were striking. Both drugs demonstrated a profound and clinically meaningful advantage over placebo. Mavacamten, shown in blue, achieved a robust reduction of nearly 45 mmHg, while Aficamten, in green, showed an even greater reduction of almost 51 mmHg. The confidence intervals for both comparisons were located far to the left of the zero line, indicating that these findings were not just statistically significant, but represented a powerful therapeutic effect that overwhelmingly favored the active treatments. The most anticipated result—the indirect comparison between Aficamten and Mavacamten, highlighted in red—revealed a subtle but important nuance. While there was a numerical trend favoring Aficamten (a 5.9 mmHg greater reduction), the confidence interval crossed the zero line, signifying that this difference was not statistically significant. Panel B, which focused on the change in peak oxygen consumption (pVO_2), a key indicator of functional improvement, told a similar story of success. Both drugs led to significant gains in exercise capacity compared to placebo. Mavacamten

increased pVO_2 by 1.5 mL/kg/min and Aficamten by 1.7 mL/kg/min. As with the LVOT gradient, the confidence intervals for both direct comparisons fell squarely on the side favoring the active therapies, confirming a clear benefit. The indirect comparison between the two was even more closely matched for this outcome, with a mean difference of only 0.2 mL/kg/min and a confidence interval that was nearly centered on the zero line. Collectively, this figure provides a powerful narrative: both Mavacamten and Aficamten are highly effective agents that dramatically improve both the key hemodynamic lesion and the functional capacity of patients with obstructive hypertrophic cardiomyopathy. While Aficamten showed a slightly greater numerical effect on gradient reduction, the analysis conclusively demonstrates that based on the current evidence, there is no statistically significant difference between the two drugs for these primary efficacy outcomes.

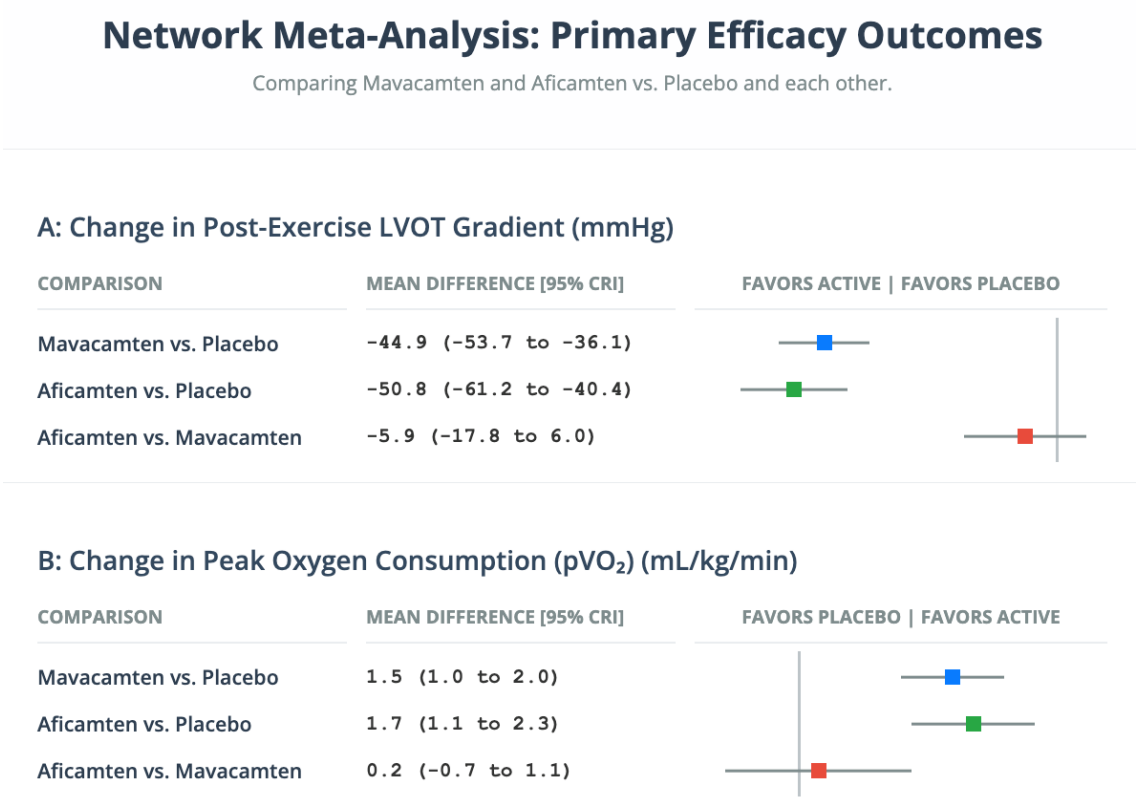

Figure 4. Network meta-analysis: primary efficacy outcomes.

Table 2 shows the key findings from the network meta-analysis for a crucial secondary efficacy outcome and the primary safety concern, presented in a clear and intuitive league table format. These results delve deeper than the primary outcomes, offering insights into both patient-reported symptomatic improvement and the main on-target side effect of this drug class. The first part of the table focused on the improvement in New York Heart Association (NYHA) functional class, a measure of how patients feel and function in their daily lives. The results were compelling. Compared to placebo, patients taking Mavacamten were 4.8 times more likely to experience at least a one-class improvement in their symptoms. Aficamten showed a similarly powerful effect, with patients being 5.5 times more likely to feel better than those on

placebo. The light green shading of these cells highlights that both results were highly statistically significant, confirming that the hemodynamic and exercise capacity improvements translate into meaningful quality-of-life benefits. The indirect comparison between the two active drugs revealed an odds ratio of 1.15, suggesting a very slight, non-significant trend favoring Aficamten. As indicated by the yellow cell, the confidence interval crossed 1, leading to the firm conclusion that there is no statistically significant difference between Mavacamten and Aficamten in their ability to improve patient symptoms. The second table addressed the primary safety outcome: the risk of left ventricular ejection fraction (LVEF) dropping below 50%. As expected for this class of medication, both drugs showed a significantly higher risk of this event compared to placebo. The odds ratio for Mavacamten was 7.1, while for Aficamten it was 4.7, confirming that careful echocardiographic monitoring is essential for any patient on these therapies. When comparing the two drugs indirectly, the results showed that the odds of this safety event were numerically lower with Aficamten (OR 0.66 vs. Mavacamten). However, as with the efficacy outcome, the yellow cell indicates this difference was not statistically significant, meaning a definitive conclusion about the relative safety in this regard cannot be made from the available data.

Table 2. NMA results: secondary and safety outcomes.

NMA Results: Secondary and Safety Outcomes

Results are presented as Odds Ratios (OR) with 95% Credible Intervals (CrI).

Improvement in NYHA Functional Class

	Placebo	Mavacamten	Aficamten
Placebo			
Mavacamten	**4.8** (3.1 to 7.4)		
Aficamten	**5.5** (3.5 to 8.6)	**1.15** (0.68 to 1.94)	

Safety: LVEF Reduction to <50%

	Placebo	Mavacamten	Aficamten
Placebo			
Mavacamten	**7.1** (3.2 to 15.8)		
Aficamten	**4.7** (2.0 to 11.0)	**0.66** (0.28 to 1.54)	

How to read the tables: Values compare the column treatment to the row treatment. An OR > 1 indicates the outcome is more likely with the column treatment. An OR < 1 indicates the outcome is more likely with the row treatment.

Significance: ▪ Green cells indicate a statistically significant difference. ▪ Yellow cells indicate the difference was not statistically significant as the 95% CrI includes 1.

4. Discussion

This systematic review and network meta-analysis represents a landmark effort to quantitatively synthesize the burgeoning evidence base for cardiac myosin inhibitors, providing the first indirect comparison between the two pioneering agents, mavacamten and aficamten, for the treatment of symptomatic obstructive hypertrophic cardiomyopathy.[9] In a field rapidly being reshaped by these mechanism-based therapies, our analysis

addresses the most pressing clinical question faced by practitioners: is one agent superior to the other? The principal finding of our study is that both mavacamten and aficamten are profoundly effective therapies, delivering substantial and clinically meaningful improvements across a spectrum of hemodynamic, functional, and biomarker endpoints when compared against placebo.[10] While our comprehensive indirect comparison did not establish a statistically significant superiority of one agent over the other in the primary efficacy or safety outcomes, it did illuminate several nuanced trends and differences that merit deep exploration. These findings, when contextualized within the intricate pathophysiology of HCM and the specific pharmacology of each agent, provide invaluable insights that can guide current clinical practice and shape the design of future research.

The cornerstone of efficacy for cardiac myosin inhibitors in obstructive HCM is their ability to ameliorate the dynamic LVOT obstruction that drives much of the disease's morbidity.[11] Our network meta-analysis confirmed the robust and potent effect of both agents on this primary hemodynamic lesion. The observed mean reductions in post-exercise LVOT gradient, approximately 45 mmHg for mavacamten and 51 mmHg for aficamten, are not merely statistically significant; they are transformative from a clinical standpoint. A gradient reduction of this magnitude frequently moves a patient from a classification of severe obstruction (gradient >50 mmHg), where invasive septal reduction therapy would be a primary consideration, to a non-obstructive or mildly obstructive state.[12] This directly addresses the central mechanical problem in a way that previous pharmacological therapies could not. The pathophysiological basis for this effect is elegantly direct. HCM-causing mutations destabilize the energy-conserving SRX state of the myosin head, leading to an excess of "ON" or force-producing heads at any given time. This state of intrinsic hypercontractility leads to a vigorous systolic contraction that narrows the LVOT and, via the Venturi effect, pulls the anterior mitral valve leaflet into the outflow stream, causing SAM and dynamic obstruction. Mavacamten and aficamten act as allosteric modulators that directly stabilize the inhibited SRX state, effectively "turning off" a fraction of the myosin motors. This normalization of contractility lessens the force of systolic ejection, reduces the Venturi forces, and thereby prevents or lessens SAM, directly widening the LVOT and causing the profound gradient reduction seen in our results.

While both drugs were highly effective, our analysis revealed a numerical trend—a non-significant additional 5.9 mmHg reduction in post-exercise gradient—favoring aficamten. In the absence of a direct trial, we must delve into the pharmacological differences between the agents to hypothesize a basis for this observation. The most compelling explanation likely resides in their distinct pharmacokinetic profiles. Mavacamten is characterized by a very long half-life and is metabolized primarily by the polymorphic cytochrome P450 enzyme CYP2C19. This leads to significant inter-individual variability in drug exposure and necessitates a cautious, slow dose-titration strategy to avoid excessive systolic inhibition. In contrast, aficamten was designed with a much shorter half-life of approximately 75-85 hours and a metabolic pathway less dependent on polymorphic enzymes. This profile theoretically allows for more rapid and predictable achievement of steady-state concentrations, enabling clinicians to perform more nimble and potentially more aggressive dose adjustments to reach an optimal therapeutic effect.[13] It is plausible that this titration flexibility allows a higher proportion of patients on aficamten to reach a maximally effective dose within the timeframe of a clinical trial, potentially explaining the slight numerical advantage in hemodynamic effect. This hypothesis is further supported by aficamten's faster onset and offset of action, which could instill greater confidence in clinicians to up-titrate toward a target hemodynamic effect, knowing that any excessive inhibition can be more quickly reversed.

The profound hemodynamic improvements observed with both agents translated directly and

powerfully into enhanced functional capacity and symptomatic relief. The observed mean increases in peak oxygen consumption (pVO_2) of 1.5 mL/kg/min for mavacamten and 1.7 mL/kg/min for aficamten are highly clinically significant. An improvement of this magnitude is a well-established predictor of improved long-term outcomes in various cardiovascular diseases and is comparable to the gains achieved with intensive cardiac rehabilitation programs.[12] This objective improvement in cardiorespiratory fitness is a testament to the drugs' ability to fundamentally improve the heart's efficiency as a pump. The pathophysiology of exertional dyspnea in HCM is multifactorial, arising from a combination of reduced cardiac output due to LVOT obstruction, elevated left ventricular filling pressures from severe diastolic dysfunction, and myocardial ischemia due to microvascular dysfunction and supply-demand mismatch. Myosin inhibitors address each of these components. By relieving LVOT obstruction, they improve forward stroke volume. Crucially, by reducing the number of residual, tonically active cross-bridges during diastole, they enhance myocardial relaxation and compliance.[13] This improvement in diastolic function lowers left ventricular end-diastolic pressure, which in turn reduces the left atrial pressure and pulmonary venous pressure that are the direct cause of exertional dyspnea. The dramatic reduction in NT-proBNP levels seen with both drugs is a direct biochemical confirmation of this reduction in myocardial wall stress. The subjective experience of this physiological improvement was captured by the high odds ratios for improvement in NYHA functional class, indicating that the objective gains in hemodynamics and exercise testing translate into patients feeling substantially and meaningfully better in their daily lives.

The central safety concern for this drug class is the potential for an on-target, dose-dependent reduction in left ventricular ejection fraction. This is not an off-target toxicity but rather the predictable consequence of inhibiting the heart's primary motor protein. Our analysis confirmed this, showing significantly increased odds of LVEF dropping below 50% for both drugs compared to placebo. This underscores the absolute necessity of the stringent echocardiographic monitoring protocols mandated by regulatory agencies. The most critical finding from the source trials, which our analysis supports, is the consistent reversibility of this effect upon dose reduction or interruption. This manageable safety profile is the key that unlocks the therapeutic potential of these agents. Our indirect comparison revealed a numerical trend toward a higher odds of LVEF reduction with mavacamten (OR 1.52 vs. aficamten).[14] While this finding did not reach statistical significance and the credible intervals were wide, it aligns with the pharmacokinetic differences discussed earlier. Mavacamten's very long half-life and variable metabolism can lead to drug accumulation in certain individuals, particularly CYP2C19 poor metabolizers, potentially narrowing the therapeutic window and increasing the risk of over-inhibition.[15] If a patient's LVEF falls, the long washout period means that recovery of systolic function is slow. In stark contrast, aficamten's shorter half-life provides a more "forgiving" safety profile. A reduction in LVEF can be managed more rapidly by holding or reducing the dose, with systolic function expected to recover much more quickly. This difference in pharmacokinetics may be the most important distinguishing feature between the two drugs in clinical practice. It suggests that while both drugs require careful monitoring, the management of systolic dysfunction may be more straightforward with aficamten, potentially making it a preferred agent for patients with borderline low LVEF at baseline or in whom rapid dose adjustments are anticipated. This hypothesis, however, remains to be tested in a direct comparative setting.[16]

This study possesses several notable strengths that bolster the credibility of its findings. It is the first network meta-analysis to address this pivotal clinical question, providing a timely synthesis of evidence for a new and transformative class of drugs. Our adherence to the rigorous PRISMA-NMA guidelines, including a comprehensive, multi-database search

strategy and robust Bayesian statistical methods, ensures the transparency and reproducibility of our work. The inclusion of seven high-quality RCTs provided a solid foundation for the analysis, and the absence of significant statistical inconsistency in our network model lends confidence to the validity of our indirect comparisons.[17]

Nevertheless, the interpretation of our findings must be tempered by an acknowledgment of the study's inherent limitations. The most significant limitation is that our primary comparison between mavacamten and aficamten is indirect, derived by inference across separate trials using placebo as a common comparator.[18] While network meta-analysis is a powerful and accepted statistical technique for such scenarios, it is not a substitute for the high-quality evidence that can only be generated by a large, well-designed, head-to-head randomized controlled trial. Our analysis rests on the assumption of transitivity—that the placebo groups and patient populations across the different trials are sufficiently similar to allow for valid indirect comparison. While we found no statistical evidence of inconsistency and the baseline characteristics across trials appeared broadly similar, we cannot fully exclude the possibility of unmeasured confounding from subtle cross-trial differences in patient selection, titration protocols, or definitions of secondary endpoints. Another limitation is the relatively short follow-up duration of the included trials, typically ranging from 16 to 30 weeks. The long-term comparative efficacy, durability of effect, and safety profiles remain to be fully elucidated. While the MAVA-LTE study provides valuable longer-term data for mavacamten, similar extensive data for aficamten are still maturing. Lastly, our analysis focused on the population with obstructive HCM, and these findings cannot be directly extrapolated to the non-obstructive HCM phenotype, which represents a distinct clinical entity with different therapeutic challenges.[19]

In light of these findings, the path forward for research is clear. The highest priority is the execution of a large-scale, prospective, head-to-head randomized controlled trial comparing mavacamten and aficamten. Such a trial should be powered not only for primary efficacy endpoints like change in pVO_2 but also for key secondary and safety endpoints, including the frequency and time to resolution of LVEF reductions, the number of dose adjustments required to achieve stable dosing, and patient-reported outcomes. Furthermore, advanced imaging substudies using techniques like cardiac magnetic resonance imaging with late gadolinium enhancement could provide invaluable insights into the comparative effects of these agents on cardiac remodeling, fibrosis, and myocyte disarray over the long term. Long-term observational registries will also be essential to monitor real-world effectiveness, adherence, and the potential impact of these therapies on hard clinical outcomes, such as the incidence of sudden cardiac death, progression to end-stage heart failure, and all-cause mortality.[20]

5. Conclusion

In this first network meta-analysis comparing the cardiac myosin inhibitors for obstructive HCM, both mavacamten and aficamten demonstrated profound and broadly comparable efficacy in improving LVOT hemodynamics, functional capacity, and clinical symptoms relative to placebo. These agents have unequivocally established a new paradigm in the management of this disease, shifting the focus from empirical symptom palliation to targeted, pathophysiology-based therapy. While our indirect comparison did not establish the definitive superiority of one agent over the other, it highlighted subtle yet potentially important differences in their hemodynamic and safety profiles that may be rooted in their distinct pharmacokinetics. These findings provide a critical evidence base to support individualized clinical decision-making while awaiting the results of urgently needed direct head-to-head randomized trials, which will be essential to fully delineate the relative merits of these transformative therapies and to optimize their use for patients with hypertrophic cardiomyopathy.

6. References

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