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Master's Thesis

Mavacamten治療肥厚型心肌病之療效與安全性的系統性文獻回顧與統合分析及臨床試驗計畫書

Efficacy and Safety of Mavacamten in the Treatment of Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis, A Clinical Study Protocol

呂紹瑀

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本論文係呂紹瑀 P11421408 在國立臺灣大學臨床醫學研究所完成之碩士學位論文，於民國 114 年 7 月 23 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Department / Graduate Institute of Clinical Medicine

On 23 /7 /2025, we have examined a Master's Thesis entitled above presented by Shao-Yu, Lu P11421408 candidate, and hereby certify that it is worthy of acceptance.

口試委員 Oral examination committee:

莊志明　　　　

（指導教授 Advisor）

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來到這裡，寫下這段話時差不多也到最後一站了，有一種如釋重負的感覺，身心靈都輕快許多!

我真的很感謝臺灣大學臨床醫學研究這些年給我的教導與指點，這一路也與大師們學習了許多。在大學時期，我也像一些同學一樣去找老師、教授們做專題研究，但總得來說那時候的學習都太片段了，大學時我去過生理學老師的實驗室學了西方墨點法（Western blot），也幫老師做了很多事，但都不知道為什麼要做這些，只知道跑電泳看蛋白質分析……。

來到臨床醫學研究所，我知道如何最有效率的收尋文獻、並且有效率的閱讀文獻、並再規定的時間內與大家分享文獻內容、瞭解文獻統計圖表的意涵、並會設計一個可靠的研究設計、自己獨力跑完統計....，應該算是一個初級合格的研究人員，但我知道這只是一個開始，我雖然已經學會一個研究人員基本該會的作法，但我深深地知道我還有許多要學習的、要精進的。就像陳培哲院士、臺大醫學院院長、臨床醫學研究所所長……等師長在畢業典禮上說的一樣:"畢業只是一個開始而已，未來的路還很長"。

最後要感謝莊志明教授收我為徒，願意當我的指導老師，每當我有困難都會輔導我，不論假日或是晚上。還要感謝邵文逸老師，雖然邵文逸老師不是我的指導老師，但我一路的研究提點與指教就像我的指導老師一樣，老師雖然很溫和，但在研究設計、統計學上的造詣有相當深厚的底蘊，可以一針見血的揪出我研究設計上的錯誤，雖然有時很痛，但更多時候我是佩服、崇拜老師的。最後還要感謝我們臺大醫院心臟科最年輕、漂亮的賀立婷醫師願意擔任我的口試委員，在口試當天的現場給我很多實質上的建議，讓我有如醍醐灌頂、獲益良多。此階段雖已告一段落，但人生如書，未完待續。他日重逢，願以更成熟之我，致敬今日所受之恩。

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中文摘要

背景：

肥厚型心肌病（HCM）是一種以心肌肥厚為特徵的遺傳性心肌疾病，常伴隨運動不耐與心臟衰竭症狀。Mavacamten（MYK-461）為一種新穎的小分子心肌肌球蛋白抑制劑，近期於多項隨機對照試驗中顯示其對有症狀 HCM 患者具臨床療效與安全性。

方法：

本研究包含兩部分：(1) 一篇針對 Mavacamten 治療 HCM 患者的系統性文獻回顧與統合分析（MA&SR），納入截至 2025 年 5 月之英語文獻資料庫（PubMed、EMBASE、Cochrane）中具隨機對照設計之臨床試驗，並以主要臨床療效指標（如 pVO_2、NYHA/KCCQ 分級、LAVI、LVOT 梗阻改善等）與安全性指標進行統合統計分析；(2) 一項自擬之亞洲族群中針對有症狀非阻塞型 HCM（nHCM）患者之前瞻性、隨機、雙盲、安慰劑對照臨床試驗，設計重點包含樣本數估計、給藥方案、影像與心臟功能指標監測週期，以及次族群分析策略。

結果：

統合分析結果顯示，Mavacamten 可顯著改善患者的 pVO_2（Mean Difference = 1.200, $p = 0.017$）、KCCQ 得分、左心房體積指數（LAVI），並降低左心室流出道壓差（LVOT gradient），整體安全性良好。根據本研究設計之 RCT 初步架構，預期將能提供亞洲族群中針對 nHCM 的補充證據。

結論：

Mavacamten 為一項對 HCM 患者具療效與安全性的創新治療選擇，未來針對 nHCM 及亞洲人群的臨床試驗將為其全球適應症拓展提供重要依據。

關鍵詞:Mavacamten、HCM、MYK-461、Placebo、Meta-analysis

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Abstract

Background:

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disorder characterized by myocardial hypertrophy, commonly associated with exercise intolerance and symptoms of heart failure. Mavacamten (MYK-461) is a novel small-molecule inhibitor of cardiac myosin that has recently demonstrated clinical efficacy and safety in multiple randomized controlled trials (RCTs) involving symptomatic HCM patients.

Methods:

This study comprises two components: (1) a systematic review and meta-analysis (SR&MA) of RCTs evaluating the efficacy and safety of mavacamten in HCM patients. Literature searches were conducted in English-language databases (PubMed, EMBASE, and Cochrane) up to May 2025. Key efficacy outcomes included peak oxygen consumption (pVO_2), NYHA/KCCQ classification, left atrial volume index (LAVI), and improvement in left ventricular outflow tract (LVOT) obstruction. Safety outcomes were also analyzed; (2) the design of a prospective, randomized, double-blind, placebo-controlled clinical trial targeting symptomatic non-obstructive HCM (nHCM) patients in an Asian population. The proposed protocol includes sample size estimation, dosing regimen, monitoring intervals for imaging and cardiac functional markers, and subgroup analysis strategies.

Results:

Meta-analysis results indicated that mavacamten significantly improved pVO_2 (Mean Difference = 1.200, p = 0.017), KCCQ scores, and LAVI, and reduced the LVOT gradient, with an overall favorable safety profile. The proposed RCT protocol is expected to provide supplementary evidence for the use of mavacamten in nHCM within Asian populations.

Conclusion:

Mavacamten represents an innovative and effective therapeutic option for patients with HCM. Future clinical trials focusing on nHCM and Asian cohorts will be critical for expanding its global indications.

Keyword : Mavacamten、HCM、MYK-461、Placebo、Meta-analysis

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1 Chapter 1: Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited myocardial disorder characterized by hypertrophy of cardiomyocytes, abnormal thickening of the left ventricular wall, and impaired diastolic function. The clinical manifestations of HCM are diverse, potentially leading to angina, dyspnea, arrhythmias, and even sudden cardiac death, significantly impacting patients' quality of life and long-term prognosis. Among these patients, approximately 70% present with dynamic left ventricular outflow tract obstruction (LVOTO), which represents a major mechanism underlying clinical symptoms and disease progression.

Mavacamten is the first small-molecule myosin inhibitor specifically designed to target the underlying mechanisms of myocardial hypertrophy. Its pharmacological action reduces the excessive interaction between actin and myosin filaments, thereby decreasing myocardial contractility and left ventricular outflow tract pressure, and ultimately alleviating hypercontractility and diastolic dysfunction. Clinical trials such as EXPLORER-HCM and VALOR-HCM have demonstrated that mavacamten can significantly improve symptoms, enhance exercise capacity, reduce LVOT gradients, and improve quality-of-life metrics. However, some limitations persist in the current

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literature, including small sample sizes, population heterogeneity, and reliance on singular clinical endpoints. Furthermore, safety outcomes have not been comprehensively synthesized across multiple domains.

Therefore, this study aims to conduct a systematic review and meta-analysis to integrate current evidence from randomized controlled trials (RCTs) regarding the efficacy and safety of mavacamten in the treatment of HCM. The analysis will be structured around four efficacy domains—exercise capacity, clinical symptoms, cardiac structure, and hemodynamics—as well as four safety domains—overall adverse events, neurological and systemic reactions, arrhythmias, and cardiac function deterioration. This comprehensive evaluation is expected to provide a more robust understanding of the clinical benefits and potential risks of mavacamten, thereby informing future clinical applications and the design of subsequent trials.

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2 Chapter 2: Methods

2.1 General Guidelines

This meta-analysis was conducted in accordance with the guidelines outlined in the most recent version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

2.2 Database Search

Independent electronic literature searches were conducted by the authors using the following databases: PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov. The search covered the period from each database's inception to the date of the final search (May 30, 2025). Literature was retrieved based on the PICO framework, and the search strategy employed the following keywords:

Patient: hypertrophic cardiomyopathy, obstructive hypertrophic cardiomyopathy, HCM

Intervention: mavacamten, MYK-461

Comparison: placebo, standard care, control group

Outcome: peak oxygen consumption, pVO_2, NYHA functional class, LVOT gradient reduction, KCCQ score, quality of life, HCMSQ-SoB, cardiac biomarkers, adverse

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events, safety outcomes, and deferral of septal reduction therapy.

2.3 Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review and meta-analysis were as follows:

(1). Randomized controlled trials (RCTs) involving human participants;

(2). Studies quantitatively assessing cardiac function before and after treatment with mavacamten;

(3). Placebo-controlled trials, regardless of participant age or treatment duration.

The exclusion criteria were:

(1). Non-randomized controlled trials (non-RCTs);

(2). Studies lacking a placebo control group;

(3). Studies without quantitative outcome assessments.

2.4 Methodological Quality Appraisal

To evaluate the methodological quality of the included studies, we applied the criteria described in the textbook:

Mark Elwood, Critical Appraisal of Epidemiological Studies and Clinical Trials, 3rd Edition, Oxford University Press Inc, New York, USA, 2007.

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This appraisal tool comprises five key domains:

A. Description of the evidence

B. Internal validity – consideration of non-causal explanations

C. Internal validity – consideration of positive features of causation

D. External validity – generalization of the results

E. Comparison of these results with other evidence

2.5 Primary Outcome (Efficacy)

The primary outcome of this study was to evaluate whether there is a statistically significant difference in cardiac functional improvement between HCM patients treated with mavacamten and those receiving placebo. The following indicators were analyzed: left ventricular ejection fraction (LVEF), left ventricular outflow tract (LVOT) gradient at rest, during Valsalva maneuver, and post-exercise, peak oxygen consumption (pVO_2), septal reduction therapy (SRT) eligibility rate, left atrial volume index (LAVI), New York Heart Association (NYHA) functional class, and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS).

Subsequent analyses further explored four domains of efficacy: improvement in exercise capacity and functional performance, alleviation of clinical symptoms,

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remodeling of cardiac structure, and enhancement in cardiac contractility and hemodynamics.

2.6 Secondary Outcome (Treatment-Associated Adverse Event Rates)

The secondary outcome of this study was to assess the incidence of treatment-associated adverse events. In addition to evaluating the overall rate of patients experiencing at least one adverse event and the incidence of serious adverse events (SAEs), specific adverse events were analyzed, including headache, palpitations, fatigue, dyspnea, nausea, atrial fibrillation (Afib), syncope, atrial flutter (AFL), coronary artery disease, and systolic dysfunction, among others.

These outcomes were also categorized into four domains for subgroup analysis: overall adverse events, neurological and systemic symptoms, arrhythmias, and deterioration in cardiac structure and function.

2.7 Statistical Analyses

Comprehensive Meta-Analysis (CMA) software was utilized to conduct the meta-analyses. For continuous variables (e.g., LVEF, LVOT gradient, peak VO_2, and KCCQ

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scores), Hedges' g was adopted as the effect size metric, along with 95% confidence intervals (CIs) to determine statistical significance. Hedges' g is a corrected version of the standardized mean difference (SMD), suitable for studies with small sample sizes. For binary outcomes (e.g., incidence of adverse events or arrhythmias), odds ratios (ORs) with corresponding 95% confidence intervals were calculated.

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3 Chapter 3: Results

3.1 Study Identification and Selection

The PRISMA flow diagram for the literature search process is presented in Figure 1. After removing duplicates and screening titles and abstracts for relevance, a total of four randomized controlled trials (RCTs) were included in the final analysis (Iacopo Olivotto, 2020; Milind Y. Desai, 2022; Carolyn Y. Ho, 2020; Zhuang Tian, 2023). Detailed information extracted from these RCTs is summarized in Table 1.

Collectively, the four eligible RCTs enrolled 504 participants, with a mean age of 56.1 ± 13.1 years, and 42.4% (n = 214) were male (see Table 2). All participants were diagnosed with hypertrophic cardiomyopathy (HCM), including both obstructive (oHCM) and non-obstructive (nHCM) phenotypes. The study populations were ethnically diverse, primarily comprising Asian and Caucasian individuals.

Regarding the overall methodological quality of the included studies, we found that nearly all studies exhibited a low risk of bias (see Figure 2).

3.2 Primary Outcomes: Efficacy of Mavacamten

1. Left Ventricular Ejection Fraction (LVEF)

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The meta-analysis revealed a statistically significant difference in LVEF between the mavacamten and placebo groups (Mean Difference = -3.317; 95% CI = -5.071 to -1.562; p <0.001), with moderate heterogeneity (I^2 = 43.89%) (see Figure 3).

Sensitivity analysis showed that the result remained significant after excluding the study by Carolyn Y. Ho (2020) (Mean Difference = -3.700, p < 0.001). However, excluding the study by Milind Y. Desai (2022) reduced the effect size to -1.780, which was not statistically significant (p = 0.374), suggesting that the Desai study may partially influence the overall effect (see Figure 4).

2. Resting Left Ventricular Outflow Tract (LVOT) Gradient

Compared with placebo, mavacamten significantly reduced the resting LVOT gradient (Mean Difference = -43.879; 95% CI = -63.887 to -23.871; p < 0.001), with low heterogeneity among studies (I^2 = 22.45%) (see Figure 5).

Sensitivity analyses further supported the robustness of the findings: excluding either Milind Y. Desai (2022) (Mean Difference = -54.990, p < 0.001) or Zhuang Tian (2023) (Mean Difference = -34.500, p < 0.001) did not alter the significance of the results, indicating strong consistency and stability of the evidence (see Figure 6).

3. LVOT Gradient During Valsalva Maneuver

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Mavacamten significantly reduced the LVOT gradient during the Valsalva maneuver compared with placebo (Mean Difference = -56.287; 95% CI = -80.255 to -32.319; $p < 0.001$) (see Figure 7).

Heterogeneity was 0% ($I^2 = 0\%$), indicating high consistency between the two contributing studies. Individually, both studies showed highly significant effects: Milind Y. Desai (2022) reported Mean Difference = -70.280 ($p < 0.001$), and Zhuang Tian (2023) reported Mean Difference = -45.600 ($p < 0.001$), strongly supporting mavacamten's efficacy in reducing Valsalva-induced LVOT gradient (see Figure 8).

4. Post-Exercise LVOT Gradient

Compared to placebo, mavacamten significantly improved the post-exercise LVOT gradient (Mean Difference = -37.109; 95% CI = -44.444 to -29.774; $p < 0.001$), with no heterogeneity between the two included studies ($I^2 = 0\%$), suggesting high consistency and reliability of the pooled result (see Figure 9).

Sensitivity analysis aligned with the main findings: excluding either Olivotto (2020) or Desai (2022) individually still resulted in significant effect sizes (Mean Difference = -37.300 and -37.000, respectively; $p < 0.001$ for both), demonstrating the robustness of the result and the absence of single-study dominance (see Figure 10).

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5. Change in Peak Oxygen Consumption (Peak VO_2)

Meta-analysis revealed that the mavacamten group showed a significantly greater improvement in peak oxygen consumption compared to the placebo group (Mean Difference = 1.200; 95% CI = 0.217 to 2.184; p = 0.017). Moderate heterogeneity was observed between the two included studies (I^2 = 35.1%), indicating an acceptable level of variability across trials (Figure 11).

Sensitivity analyses confirmed the robustness of this finding: after excluding either Olivotto (2020) or Ho (2020), the pooled effect size remained in the same direction and either retained statistical significance (Mean Difference = 1.500, p < 0.001) or trended in the same direction (Mean Difference = 0.360, p not significant), suggesting that the result is not driven by any single study (Figure 12).

6. Avoidance of Septal Reduction Therapy (SRT)

Pooled analysis demonstrated that mavacamten significantly increased the likelihood of avoiding septal reduction therapy in patients with HCM (pooled OR = 8.340; 95% CI = 3.736 to 18.617; p < 0.001), with moderate heterogeneity (I^2 = 53.96%). Individual studies also reported significant ORs: Olivotto (2020), OR =

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5.986 ($p < 0.001$); Desai (2022), OR = 13.765 ($p < 0.001$) (Figure 13).

Sensitivity analysis confirmed the robustness of this finding. The pooled OR remained highly significant when either Olivotto or Desai was excluded (OR = 13.765 or 5.966; both $p < 0.001$), suggesting that the result is stable and not dominated by a single study (Figure 14).

7. Change in Left Atrial Volume Index (LAVI)

Mavacamten significantly reduced the left atrial volume index in HCM patients compared to placebo (Mean Difference = -3.973; 95% CI = -6.452 to -1.495; $p = 0.002$). No heterogeneity was observed across studies ($I^2 = 0\%$), indicating strong consistency in results (Figure 15).

Sensitivity analyses showed mixed stability: after excluding Desai (2022), the effect was no longer statistically significant (Mean Difference = -2.210; $p = 0.345$), whereas excluding Ho (2020) preserved significance (Mean Difference = -4.700; $p = 0.002$). These findings suggest that the overall result may be predominantly influenced by the Desai study and should be discussed accordingly (Figure 16).

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8. Improvement in NYHA Functional Class

Mavacamten significantly increased the likelihood of improvement in NYHA functional class compared to placebo (pooled OR = 4.123; 95% CI = 2.177 to 7.810; $p < 0.001$), with moderate heterogeneity ($I^2 = 53.4\%$), indicating some variability across studies (Figure 17).

Sensitivity analyses revealed consistent results: after excluding any single study (Olivotto, Desai, Ho, or Zhuang), the pooled OR remained above 3, and p values remained < 0.05, suggesting high result stability not dependent on any one trial (Figure 18).

9. Change in KCCQ-CSS (Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score)

Mavacamten significantly improved patients' KCCQ-CSS scores, indicating enhanced symptom relief and quality of life (Mean Difference = 8.396; 95% CI = 5.859 to 10.932; $p < 0.001$). Moderate heterogeneity was present across studies ($I^2 = 57.9\%$) (Figure 19).

Sensitivity analyses supported the robustness of this effect: the result remained

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statistically significant even after excluding any individual study (Olivotto, Desai, Ho, or Zhuang). For instance, excluding Olivotto (2020) yielded a pooled Mean Difference of 7.629 (95% CI = 3.865 to 11.393; p <0.001). These findings indicate consistent and reliable benefits of mavacamten in improving patient-reported outcomes (Figure 20).

10. Improvement in NT-proBNP

According to the results of the present meta-analysis, Mavacamten treatment significantly reduced NT-proBNP levels compared to placebo (pooled rate ratio = 0.305; 95% CI: 0.128–0.730; p = 0.008), indicating a marked effect in alleviating cardiac stress and hemodynamic burden. The direction of effect was consistent across the two included studies (Ho et al., 2020; Tian et al., 2023), with low heterogeneity, supporting the stability and reliability of the pooled estimate (Figure 21).

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3.3 Secondary Outcomes: Incidence of Treatment-Related Adverse Events

1. Incidence of Treatment-Emergent Adverse Events (TEAEs)

Pooled analysis revealed that the risk of experiencing at least one treatment-emergent adverse event was slightly higher in the Mavacamten group compared to placebo (pooled OR = 1.752; 95% CI = 1.045 to 2.937; p = 0.033), reaching statistical significance. Although all included studies reported ORs greater than 1, individual results from Olivotto, Desai, and Ho did not reach statistical significance (p-values = 0.062, 0.201, and 0.053, respectively). Only the overall analysis demonstrated a consistent trend (see Figure 22).

These findings suggest that Mavacamten may be associated with a mildly increased risk of adverse events. However, the effect size remains modest, and the consistency across studies is limited. Further interpretation should consider clinical context and the nature of specific adverse events.

2. Dizziness During Treatment

Meta-analysis indicated a higher, but not statistically significant, risk of dizziness in the Mavacamten group (pooled OR = 1.897; 95% CI = 0.698 to 5.157; p = 0.209).

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Although all three studies reported ORs >1, none reached statistical significance (Desai p = 0.715; Ho p = 0.216; Zhuang p = 0.459) (see Figure 23).

These results imply a potential association between Mavacamten and dizziness, but current evidence is insufficient to confirm a significantly increased risk. Clinical monitoring is advised, but overinterpretation should be avoided.

3. Palpitations During Treatment

The pooled analysis showed no significant difference in the risk of palpitations between the Mavacamten and placebo groups (pooled OR = 0.896; 95% CI = 0.327 to 2.458; p = 0.831). None of the included studies (Desai, Ho, Zhuang) reached statistical significance (p-values = 0.985, 0.968, and 0.745, respectively), and all reported ORs were close to or below 1 (see Figure 24).

Overall, current evidence indicates that Mavacamten does not significantly increase the risk of palpitations, and its safety in this regard appears comparable to placebo.

4. Fatigue During Treatment

Meta-analysis showed no statistically significant difference in the risk of fatigue between the Mavacamten and placebo groups (pooled OR = 1.362; 95% CI = 0.423 to

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4.387; p = 0.605). The Desai (2022) study reported a higher OR (2.598), but it was not statistically significant (p = 0.267), and the confidence interval was wide. Conversely, Ho (2020) showed a trend in the opposite direction (OR = 0.784; p = 0.759) (see Figure 25).

Collectively, current evidence suggests that Mavacamten does not significantly increase the risk of fatigue during treatment and exhibits comparable safety to placebo in this aspect.

5. Dyspnea During Treatment

Pooled analysis revealed no significant difference in the risk of dyspnea between Mavacamten and placebo groups (pooled OR = 0.916; 95% CI = 0.300 to 2.793; p = 0.877). Individual studies by Desai (2022) and Ho (2020) reported ORs of 1.333 and 0.610 (p = 0.715 and 0.547, respectively), neither of which was statistically significant (see Figure 26).

Overall, current evidence does not indicate that Mavacamten significantly increases or decreases the risk of dyspnea during treatment, with safety in this domain appearing similar to placebo.

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6. Nausea During Treatment

The pooled analysis demonstrated no statistically significant difference in the risk of nausea between the Mavacamten and placebo groups (pooled OR = 1.722; 95% CI = 0.426 to 6.957; p = 0.445). In individual studies, Desai (2022) reported an OR of 4.154 (p = 0.210), while Ho (2020) reported an OR of 0.971 (p = 0.975), both non-significant and in opposite directions (see Figure 27).

Thus, current evidence does not support a significant increase in nausea risk with Mavacamten, though further research is warranted to clarify this outcome.

7. Incidence of Atrial Fibrillation (Afib) During Treatment

The meta-analysis showed no statistically significant difference in the risk of atrial fibrillation between the Mavacamten and placebo groups during treatment (pooled OR = 0.985; 95% CI = 0.278 to 3.486; p = 0.981). Among the three included studies, Olivotto (2020) reported an OR of 0.512 (p = 0.445), Desai (2022) reported an OR of 4.037 (p = 0.381), and Ho (2020) reported an OR of 1.500 (p = 0.733); none reached statistical significance, and effect directions varied (see Figure 28).

Overall, current evidence does not support a significant increase or decrease in the risk of atrial fibrillation associated with Mavacamten. Continued clinical monitoring

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is advised, though excessive concern is unwarranted.

8. Incidence of Syncope During Treatment

The pooled analysis revealed no statistically significant difference in the risk of syncope between the Mavacamten and placebo groups during treatment (pooled OR = 2.387; 95% CI = 0.346 to 16.469; p = 0.377). Individually, Olivotto (2020) reported an OR of 2.099 (p = 0.547) and Desai (2022) an OR of 3.000 (p = 0.504); both were non-significant with wide confidence intervals, indicating high uncertainty (see Figure 29).

Collectively, the current evidence does not support a significant change in syncope risk with Mavacamten. Given the limited sample sizes and imprecise estimates, further surveillance is recommended to monitor this potential safety signal.

9. Incidence of Multiple Serious Adverse Events (SAEs) During Treatment

The pooled analysis indicated no significant difference in the risk of experiencing more than one serious adverse event between the Mavacamten and placebo groups (pooled OR = 1.059; 95% CI = 0.443 to 2.527; p = 0.898). Among the four included studies, Desai (2022) and Zhuang (2023) reported higher ORs (4.154 and 4.240, respectively), but both had wide confidence intervals and were not statistically

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significant (p > 0.2). Ho (2020) and Olivotto (2020) reported ORs below 1 (see Figure 30).

Overall, the evidence does not support a significant difference in the risk of serious adverse events associated with Mavacamten. Ongoing safety monitoring and further large-scale studies are warranted.

10. Incidence of Atrial Fibrillation (Afib) – Expanded Analysis

In an expanded analysis including three studies, there remained no statistically significant difference in the risk of atrial fibrillation between Mavacamten and placebo groups (pooled OR = 1.773; 95% CI = 0.342 to 9.197; p = 0.496). Desai (2022) reported an OR of 4.037 (p = 0.381), Ho (2020) reported an OR of 0.973 (p = 0.983), and Zhuang (2023) reported an OR of 2.038 (p = 0.656); all were non-significant and inconsistent in direction (see Figure 31).

Overall, while current evidence suggests Mavacamten does not significantly increase the risk of Afib, the imprecision in pooled estimates warrants continued monitoring in future trials.

11. Incidence of Atrial Flutter During Treatment

The meta-analysis showed no statistically significant difference in the risk of atrial

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flutter between the Mavacamten and placebo groups (pooled OR = 0.485; 95% CI = 0.043 to 5.497; p = 0.559). Among the two included studies, Ho (2020) reported an OR of 0.234 (p = 0.408) and Zhuang (2023) an OR of 1.000 (p = 1.000); both were non-significant, and event counts were likely very low, contributing to unstable estimates (see Figure 32).

In summary, current data are insufficient to conclude a clear difference in risk of atrial flutter with Mavacamten. Future studies should collect additional data to determine the clinical implications.

12. Incidence of Coronary Artery Disease (CAD)-Related Adverse Events

The pooled analysis indicated no statistically significant difference in the risk of CAD-related adverse events between the Mavacamten and placebo groups (pooled OR = 0.435; 95% CI = 0.033 to 5.806; p = 0.529). Individually, Desai (2022) reported an OR of 0.982 (p = 0.993), and Ho (2020) an OR of 0.234 (p = 0.408); both were non-significant with very low event counts, leading to imprecise estimates (see Figure 33).

Taken together, there is currently no evidence supporting a significant effect of Mavacamten on CAD risk. Nevertheless, due to the rarity of these events, continued cardiovascular safety monitoring is recommended.

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13.Incidence of Systolic Dysfunction During Treatment

Meta-analysis showed no statistically significant difference in the risk of systolic dysfunction between the Mavacamten and placebo groups (pooled OR = 0.977; 95% CI = 0.073 to 13.035; p = 0.986). Desai (2022) reported an OR of 0.982 (p = 0.993) and Ho (2020) reported an OR of 0.974 (p = 0.988); both were non-significant, and the confidence intervals were extremely wide, indicating very few events and unstable estimates (see Figure 34).

In summary, Mavacamten does not appear to significantly increase the risk of systolic dysfunction; however, due to the rarity of such events, ongoing clinical vigilance and confirmation in future studies are advised.

3.4 Subgroup Analysis Results

1. Improvement in NYHA Functional Class: Subgroup Analysis by Disease Type (oHCM vs. nHCM)

Among patients with obstructive hypertrophic cardiomyopathy (oHCM), Mavacamten significantly increased the likelihood of improvement in NYHA functional class (pooled OR = 4.936, 95% CI = 3.252 to 7.492, p < 0.001), indicating

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robust and statistically significant efficacy. All three included oHCM studies (Olivotto, Desai, Zhuang) reached statistical significance, with ORs ranging from 4.093 to 8.364 (see Figure 35).

In contrast, among patients with non-obstructive HCM (nHCM), the effect was not statistically significant (pooled OR = 1.267, 95% CI = 0.412 to 3.896, p = 0.680), suggesting that the treatment effect of Mavacamten in this subgroup may be less evident.

Overall, Mavacamten demonstrated clearer efficacy in improving NYHA functional class among oHCM patients, while further research is warranted to confirm its effect in the nHCM population.

2. Improvement in KCCQ-CSS: Subgroup Analysis by Disease Type (oHCM vs. nHCM)

In patients with oHCM, Mavacamten significantly improved the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) (pooled Mean Difference = 9.245, 95% CI = 6.784 to 11.706, $p < 0.001$), indicating clear benefits in symptom burden and quality of life. All three oHCM studies (Olivotto, Desai, Zhuang) reported statistically significant results (see Figure 36).

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In contrast, for the nHCM subgroup, the treatment effect was not statistically significant (Mean Difference = 2.200, 95% CI = -4.918 to 9.318, p = 0.545), suggesting that improvements in subjective clinical symptoms and functional status may be less apparent in this group.

These results support the consistent and significant efficacy of Mavacamten in oHCM, especially in improving patient-reported symptoms and function, while additional evidence is needed to determine its efficacy in nHCM.

3. Improvement in NYHA Functional Class: Subgroup Analysis by Ethnicity (Asian vs. White)

Among Asian patients, Mavacamten significantly improved NYHA functional class (pooled OR = 8.364, 95% CI = 1.792 to 39.027, p = 0.007), with evidence drawn from a single study by Zhuang (2023) (see Figure 37).

In the White population, the pooled OR was 3.511 (95% CI = 1.691 to 7.292, p = 0.001), also indicating significant efficacy. All three included studies of White patients (Olivotto, Desai, Ho) achieved statistical significance, with ORs ranging from 1.267 to 6.111.

Overall, Mavacamten significantly improved NYHA functional class across both

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Asian and White populations, suggesting consistent efficacy across ethnic groups.

4. Improvement in KCCQ-CSS: Subgroup Analysis by Ethnicity (Asian vs. White)

In the Asian subgroup, Mavacamten significantly improved KCCQ-CSS scores, indicating notable improvements in symptoms and quality of life (Mean Difference = 9.500, 95% CI = 4.115 to 14.885, $p < 0.001$). This result was based on the study by Zhuang (2023), showing a large effect size and clear benefit.

Among White patients, the pooled Mean Difference was 7.538 (95% CI = 3.776 to 11.301, $p < 0.001$), also reflecting statistically significant improvements. All three included studies (Olivotto, Desai, Ho) demonstrated consistent and positive effects (see Figure 38).

Taken together, Mavacamten consistently improved KCCQ-CSS across ethnicities, with a larger effect size observed in the Asian population.

5. Incidence of ≥1 Treatment-Emergent Adverse Event (TEAE): Subgroup Analysis by Disease Type (nHCM vs. oHCM)

In patients with nHCM, the risk of experiencing at least one TEAE was higher in the Mavacamten group compared to placebo (pooled OR = 4.038, 95% CI = 0.975 to

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16.725, p = 0.054), which approached but did not reach conventional statistical significance. This result was derived from a single study (Ho, 2020).

Among patients with oHCM, the pooled OR was 1.594 (95% CI = 0.972 to 2.614, p = 0.065), also approaching the threshold for statistical significance. The three included studies (Olivotto, Desai, Zhuang) all demonstrated a consistent trend toward increased risk (see Figure 39).

Overall, Mavacamten may increase the risk of multiple TEAEs in both nHCM and oHCM populations; however, current evidence does not meet statistical significance, and further research is needed for confirmation.

6. Incidence of ≥1 Treatment-Emergent Adverse Event (TEAE): Subgroup Analysis by Ethnicity (Asian vs. White)

Among Asian patients, the risk of multiple TEAEs in the Mavacamten group did not differ significantly from the placebo group (pooled OR = 0.625, 95% CI = 0.155 to 2.528, p = 0.510), based on a single study (Zhuang, 2023), indicating limited data and imprecise estimates (see Figure 40).

In contrast, among White patients, the Mavacamten group exhibited a significantly higher risk of experiencing multiple TEAEs (pooled OR = 2.003, 95% CI = 1.227 to

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3.270, p = 0.005). All three studies (Olivotto, Desai, Ho) demonstrated a consistent trend of increased risk, with each reaching statistical significance.

Overall, Mavacamten may be associated with a greater risk of multiple TEAEs in the White population, while current evidence in Asian patients does not indicate a significant increase in risk.

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4 Chapter 4. Discussion

4.1 Four Dimensions of Efficacy

This study conducted a systematic review and meta-analysis on the efficacy and safety of Mavacamten in the treatment of hypertrophic cardiomyopathy (HCM). Based on clinically relevant disease indicators commonly used in practice, both efficacy and safety were evaluated across four core domains, allowing for a more granular understanding of the drug's effects on various pathophysiological mechanisms and clinical outcomes. This framework also facilitates stratified assessment and clinical decision-making by physicians in different scenarios.

In terms of efficacy, we explored four domains: exercise capacity (peak VO_2), clinical symptoms (NYHA class and KCCQ scores), cardiac structure (LAVI), and hemodynamics (LVOT gradient and LVEF). For safety, we analyzed overall adverse events (TEAEs/SAEs), neurologic and systemic reactions, arrhythmias, and deterioration of systolic function (decline in LVEF). The meta-analytic findings and heterogeneity assessments for each domain are detailed below, accompanied by clinical interpretations.

4.1.1 Improvement in Exercise Capacity and Functional Performance (pVO_2)

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This systematic review and meta-analysis incorporated data from two randomized controlled trials (RCTs) evaluating the effect of Mavacamten on peak oxygen consumption (pVO_2) in patients with HCM. The pooled effect size was Mean Difference = 1.200 (95% CI: 0.217 to 2.184, p = 0.017), indicating a statistically significant improvement in exercise capacity in the Mavacamten group compared to placebo.

Heterogeneity analysis yielded an I^2 of 35.1%, suggesting moderate heterogeneity and acceptable consistency across studies. As a standard indicator of cardiopulmonary fitness and exercise tolerance—and a crucial prognostic marker in HCM—improvement in pVO_2 further supports the clinical utility of Mavacamten in enhancing patient functional performance.

4.1.2 Improvement in Clinical Symptoms (NYHA Class and KCCQ Scores)

The meta-analysis demonstrated that Mavacamten significantly improved clinical symptoms in HCM patients, as evidenced by both objective (NYHA class) and subjective (KCCQ) assessments.

For NYHA functional class improvement, data from four RCTs were included. The

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pooled odds ratio (OR) was 4.123 (95% CI: 2.177–7.810, $p < 0.001$), indicating that patients in the Mavacamten group were approximately 4.1 times more likely to achieve NYHA class improvement compared to placebo. Heterogeneity was moderate ($I^2 = 53.4\%$), suggesting acceptable consistency across studies.

For the Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score (KCCQ-CSS), the pooled effect size was Mean Difference = 8.396 (95% CI: 5.859–10.932, $p < 0.001$), reflecting significant improvements in symptoms and quality of life post-treatment. Heterogeneity was moderate ($I^2 = 57.9\%$), indicating reasonable agreement across studies.

In summary, both objective and subjective symptom measures (NYHA and KCCQ) support the efficacy of Mavacamten in alleviating HCM-related symptoms, thereby enhancing patients' functional capacity and overall quality of life.

4.1.3 Improvement in Cardiac Structure (LAVI)

This analysis integrated data from two RCTs to evaluate the impact of Mavacamten on left atrial volume index (LAVI). The pooled effect size was Mean Difference = -3.973 (95% CI: -6.542 to -1.495, $p = 0.002$), indicating a statistically significant

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reduction in LAVI compared to placebo.

As a structural marker reflecting left atrial pressure load and diastolic compliance, elevated LAVI is closely associated with increased risk of atrial fibrillation and heart failure. Therefore, a reduction in LAVI suggests favorable cardiac remodeling and supports the hypothesis that Mavacamten offers not only functional benefits but also structural advantages.

Furthermore, heterogeneity was negligible ($I^2 = 0\%$), indicating excellent consistency between studies and reinforcing the robustness and clinical credibility of this finding.

4.1.4 Improvements in Cardiac Systolic Function and Hemodynamics (LVOT Obstruction and LVEF)

The meta-analysis of hemodynamic indicators following Mavacamten treatment revealed a highly consistent and significant improvement in left ventricular outflow tract (LVOT) obstruction across various physiological conditions (i.e., post-exercise, Valsalva maneuver, and resting states). Additionally, Mavacamten did not appear to cause clinically significant impairment of left ventricular systolic function (LVEF), supporting both its efficacy and safety profile.

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(1). Improvement in LVOT Obstruction Post-Exercise

Pooled results from two studies demonstrated that Mavacamten significantly reduced the LVOT pressure gradient post-exercise, with a combined effect size of Mean Difference = -37.109 (95% CI: -44.444 to -29.774, $p < 0.001$). Heterogeneity was negligible ($I^2 = 0\%$), indicating strong consistency across studies.

(2). Improvement in LVOT Obstruction During Valsalva Maneuver

The pooled effect size was Mean Difference = -56.287 (95% CI: -80.255 to -32.319, $p < 0.001$), with $I^2 = 0\%$, further supporting Mavacamten's consistent efficacy in relieving dynamic obstruction.

(3). Improvement in Resting LVOT Obstruction

For resting LVOT gradient, the pooled standardized mean difference was Mean Difference = -43.879 (95% CI: -63.887 to -23.871, $p < 0.001$), with moderate heterogeneity ($I^2 = 22.45\%$). These findings remain statistically and clinically significant.

(4). Impact on LVEF

The pooled effect size for changes in LVEF was Mean Difference = -3.317 (95% CI: -5.071 to -1.562, $p <0.001$), with moderate heterogeneity ($I^2 = 43.89\%$). This suggests that Mavacamten does not induce a clinically concerning decline in systolic function,

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thereby affirming its safety in this domain.

(5). Summary

Mavacamten consistently and significantly reduces LVOT obstruction across multiple physiological conditions without compromising left ventricular systolic function. These results affirm the drug's robust and stable hemodynamic efficacy and safety profile.

4.1.5 Summary of Efficacy Domains

This meta-analysis assessed the efficacy of Mavacamten in treating HCM across four major domains: exercise capacity, clinical symptoms, cardiac structure, and hemodynamics. The comparative findings are summarized as follows:

(1). Most Prominent and Consistent Efficacy: Hemodynamic Improvement

Mavacamten demonstrated the strongest and most consistent effects in reducing LVOT obstruction under resting, Valsalva, and post-exercise conditions (Mean Difference ranging from -37 to -56), with minimal heterogeneity ($I^2 = 0\%$). These results align with the drug's mechanism as a sarcomere inhibitor and carry substantial clinical implications.

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(2). Second Strongest Efficacy: Symptom Improvement

NYHA class improvement showed a pooled OR of 4.123 ($p < 0.001$), and the effect size for KCCQ-CSS was 0.653 ($p < 0.001$), reflecting moderate to large effects. Both physician-assessed and patient-reported outcomes showed consistent symptom relief, indicating significant clinical benefit.

(3). Moderate Efficacy: Cardiac Structural Improvement (LAVI)

The pooled effect size for LAVI reduction was Mean Difference = -3.973 ($p = 0.002$), indicating a moderate but consistent structural benefit ($I^2 = 0\%$), which may have prognostic implications for cardiac remodeling.

(4). Smallest but Statistically Significant Effect: Exercise Capacity (pVO_2)

The pooled effect size was Mean Difference = 1.200 ($p = 0.017$), representing the smallest of the four domains. Although statistically significant, the degree of improvement was modest, potentially influenced by baseline characteristics and measurement variability.

(5). Overall Conclusion

Among the four efficacy domains, hemodynamic improvement demonstrated the most robust and stable effect, followed by symptom relief and structural remodeling. Although exercise capacity showed improvement, its effect size was relatively

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limited. These findings may inform future clinical trial designs and aid in the selection of primary efficacy endpoints in subsequent studies.

4.2 Four Dimensions of Safety

The safety profile of Mavacamten can be examined through four core dimensions:

(1). General Adverse Events (AEs)

(2). Neurologic and Systemic Adverse Events

(3). Cardiac Arrhythmias

(4). Structural or Functional Cardiac Worsening

4.2.1 General Adverse Events

This meta-analysis synthesized data from four randomized controlled trials to evaluate the overall risk of adverse events in patients treated with Mavacamten, compared to placebo.

(1) Treatment-Emergent Adverse Events (TEAEs)

The pooled odds ratio for experiencing one or more TEAEs was OR = 1.752 (95% CI: 1.045–2.937, p = 0.033), indicating that patients in the Mavacamten group had a

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statistically higher risk of developing multiple adverse events compared to the placebo group. Although most events were mild to moderate in severity, the findings suggest a slightly increased likelihood of discomfort-related symptoms, underscoring the need for appropriate monitoring in clinical practice.

(2) Serious Adverse Events (SAEs)

The pooled odds ratio for experiencing at least one SAE was OR = 1.059 (95% CI: 0.443–2.579, p = 0.898), which did not reach statistical significance. This suggests that Mavacamten does not significantly increase the risk of serious adverse events and remains within an acceptable safety margin.

Summary

While there was a slight increase in the risk of TEAEs, no significant elevation in SAEs was observed. These findings indicate that Mavacamten is generally safe for clinical use, though clinicians should remain vigilant and consider dose adjustments as needed to maintain safety.

4.2.2 Neurologic and Systemic Adverse Events

This study conducted a meta-analysis on six commonly reported neurologic and

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systemic adverse events following Mavacamten treatment in HCM patients. Overall, the results showed that Mavacamten did not significantly increase the risk of most of these adverse events, indicating good tolerability.

(1) Dizziness

The pooled odds ratio was OR = 1.897 (95% CI: 0.698–5.157, p = 0.209), suggesting a potential upward trend but without statistical significance. Clinically, early monitoring is advisable, although treatment discontinuation is not necessary.

(2) Palpitations

The pooled OR was 0.896 (95% CI: 0.327–2.458, p = 0.831), showing no significant difference, indicating that palpitations were not notably increased in the Mavacamten group.

(3) Fatigue

The pooled odds ratio was OR = 1.362 (95% CI: 0.423–4.387, p = 0.605), which was not statistically significant, suggesting fatigue was not a predominant adverse event.

(4) Nausea

The odds ratio was OR = 1.722 (95% CI: 0.426–6.957, p = 0.445), indicating no clear difference and a low risk of gastrointestinal side effects.

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(5) Dyspnea

The pooled OR was 0.916 (95% CI: 0.300–2.793, p = 0.877), showing no statistically significant difference, implying limited impact on respiratory symptoms.

(6) Syncope

The pooled OR was 2.387 (95% CI: 0.346–16.469, p = 0.377), showing a trend toward increased risk; however, due to the small sample size and wide confidence interval, the inferential power is limited.

Summary

None of the six evaluated symptoms reached statistical significance, and most odds ratios were close to 1. These findings support the conclusion that Mavacamten is generally well tolerated, with an acceptable risk profile for neurologic and systemic adverse events.

4.2.3 Arrhythmias

This meta-analysis evaluated the risk of arrhythmias potentially induced by Mavacamten treatment, specifically focusing on atrial fibrillation (Afib) and atrial flutter. Overall findings indicate that Mavacamten does not significantly increase the risk of arrhythmias, supporting its electrophysiological safety.

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(1) Atrial Fibrillation

Based on data from three randomized controlled trials, the pooled odds ratio for atrial fibrillation was OR = 0.985 (95% CI: 0.278–3.486, p = 0.981), demonstrating no statistically significant difference between the treatment and placebo groups, with low heterogeneity (I^2 = 0%). An additional analysis of two other trials yielded consistent results: OR = 1.773 (95% CI: 0.342–9.197, p = 0.496), also not statistically significant.

(2) Atrial Flutter

The pooled odds ratio for atrial flutter was OR = 0.485 (95% CI: 0.043–5.497, p = 0.559). The wide confidence interval indicates a limited sample size and weaker inferential power, but there was no apparent increase in risk.

Summary

Although Mavacamten modulates cardiac contractility and may theoretically influence rhythm stability, current clinical trial data do not support an increased risk of arrhythmias. Its electrophysiological safety appears acceptable. Nevertheless, ECG monitoring is advisable for high-risk patients to ensure safe clinical application.

4.2.4 Structural or Cardiac Function Worsening

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To assess whether Mavacamten may lead to structural or functional deterioration of the heart, this study conducted meta-analyses on the risks of coronary artery disease (CAD) and systolic dysfunction (LVEF reduction) following treatment.

(1) Coronary Artery Disease

The pooled odds ratio was OR = 0.435 (95% CI: 0.033–5.806, p = 0.529), indicating no increase in CAD risk associated with Mavacamten. While the wide confidence interval reflects limited sample size and reduced inferential strength, there was no observable trend toward elevated risk.

(2) Systolic Dysfunction (LVEF Decline)

The pooled odds ratio for events where LVEF dropped below 50% during treatment was OR = 0.977 (95% CI: 0.073–13.055, p = 0.986), suggesting no significant increase in the risk of systolic function deterioration. Such events were rare and generally reversible.

Summary

Current clinical evidence does not indicate that Mavacamten causes structural cardiac damage or significant declines in systolic function. Nonetheless, it is recommended to monitor LVEF regularly, especially during the initiation phase or when adjusting dosage, to ensure ventricular function remains stable.

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4.2.5 Summary of Safety Findings

This meta-analysis systematically evaluated four core dimensions of safety following Mavacamten treatment in HCM patients:

General Adverse Events (AEs)

Neurologic and Systemic Adverse Events

Arrhythmias

Structural or Cardiac Function Worsening

1. Was the incidence of TEAEs statistically significant?

The pooled odds ratio for experiencing at least one treatment-emergent adverse event was:

• OR = 1.752 (95% CI: 1.054–2.937, p = 0.033)

This result is statistically significant, indicating a higher likelihood of experiencing one or more TEAEs in the Mavacamten group than in the placebo group. However, most events were mild to moderate and did not require treatment discontinuation.

2. Which events occurred most frequently?

Among specific adverse events, dizziness had the highest odds ratio (OR = 1.897, p

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= 0.209), although not statistically significant. It was the most frequently reported symptom and thus warrants clinical attention. Other symptoms such as fatigue, nausea, dyspnea, and palpitations were also reported but did not reach statistical significance.

3. Summary of the remaining three dimensions:

• Neurologic and Systemic AEs: None reached statistical significance, indicating good systemic tolerability.

• Arrhythmias (Afib, Atrial Flutter): All ORs were close to 1 with p-values > 0.4, suggesting no increased risk.

• LVEF Decline and CAD: These were rare events with pooled ORs ranging from ~0.4 to 0.9 and wide confidence intervals, showing no significant difference.

Conclusion:

Mavacamten demonstrates an overall favorable safety profile. Although the incidence of TEAEs was slightly elevated, most were mild and manageable. Clinicians should remain attentive to early symptoms such as dizziness and conduct close monitoring during dose adjustments or combination therapy to maintain safety.

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5 Chapter 5. Conclusion

Based on the findings from this systematic review and meta-analysis, Mavacamten demonstrates consistent and favorable effects across four major efficacy domains in the treatment of hypertrophic cardiomyopathy (HCM): exercise capacity, symptom relief, cardiac structural remodeling, and hemodynamic improvement. Among these, the reduction of left ventricular outflow tract (LVOT) obstruction emerged as the most prominent and consistent benefit.

Regarding safety, analysis across four key domains revealed that only the incidence of treatment-emergent adverse events (TEAEs) was significantly increased in the Mavacamten group, while no elevated risks were observed for neurological symptoms, arrhythmias, or reductions in left ventricular ejection fraction (LVEF), indicating an overall favorable safety profile.

However, several limitations were identified in the current body of evidence:

(1) Limited sample sizes in some studies led to insufficient statistical power to detect rare outcomes such as LVEF decline or syncope;

(2) The underrepresentation of Asian participants reduced the external validity of the findings for this population;

(3) Most clinical trials did not assess the integrated impact of Mavacamten on

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multiple clinical endpoints simultaneously;

(4) The efficacy of Mavacamten in patients with non-obstructive HCM remains unclear due to small sample sizes and limited data.

To address these evidence gaps, this study has further proposed a randomized controlled trial (RCT) specifically designed to evaluate the multidimensional clinical benefits of Mavacamten in Asian patients with non-obstructive HCM. This proposed trial aims to strengthen empirical support for this specific population and provide more comprehensive insight into diverse clinical outcomes.

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7 Appendices: Tables and figures

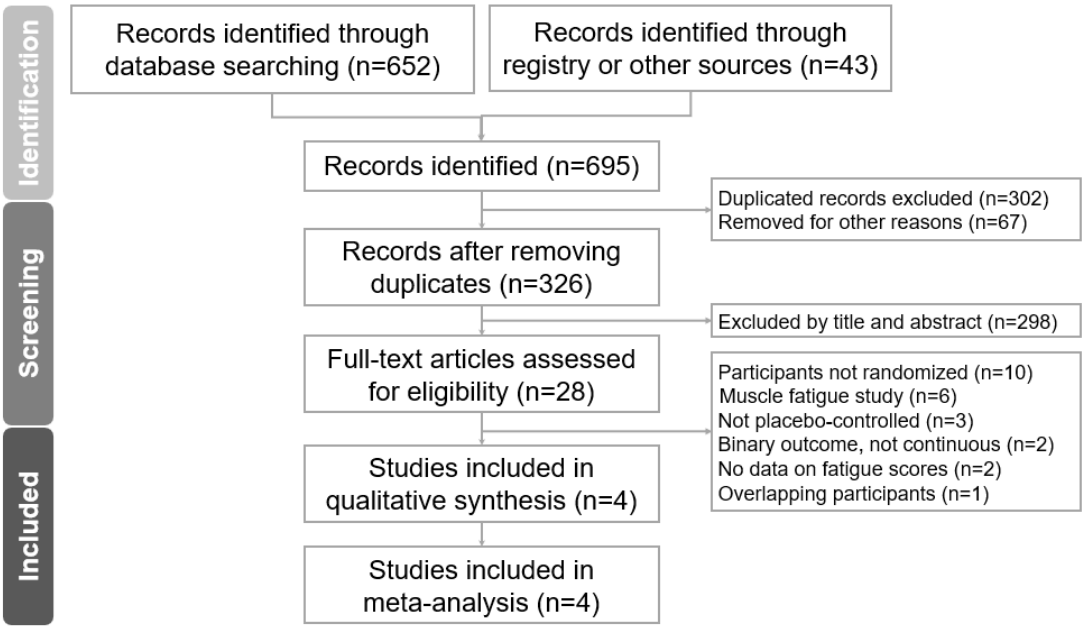

Figure 1 PRISMA 2020 flowchart of current meta-analysis.

Table 1 Baseline characteristics of the four randomized controlled trials (RCTs) included in this meta-analysis, including author, publication year, study design, participant age, disease type, and race.

	study		Author	year	Design	age	disease	Race
1	EXPLORER-HCM	Mavacamten	Iacopo Olivotto	2020	RCT	58.5±12.2	oHCM	White
		Placebo				58.5±11.8		
2	VALOR-HCM	Mavacamten	Milind Y. Desai	2022	RCT	59.8±14.2	oHCM	White
		Placebo				60.9±10.5		
3	MAVERICK-HCM	Mavacamten	Carolyn Y. Ho	2020	RCT	54.0±14.6	nHCM	White
		Placebo				53.8±18.2		
4	EXOLORER-CN	Mavacamten	Zhuang Tian	2023	RCT	52.4±12.1	oHCM	Asian
		Placebo				51.0±11.8		

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Table 2 Baseline demographic and clinical characteristics of patients from the four included RCTs, including sex, race, BMI, NYHA class, pVO_2, NT-proBNP, LVEF, maximal LV wall thickness, LVOT gradients, and left atrial volume index (LAVI).

	EXPLORER-HCM oHCM Iacopo Olivotto.2020		VALOR-HCM **oHCM** Milind Y. Desai.2022		MAVERICK-HCM **nHCM** Carolyn Y. Ho.2020		EXPLORER-CN **oHCM** Zhuang Tian.2023	
	Mavacamten	Placebo	Mavacamten	Placebo	Mavacamten	Placebo	Mavacamten	Placebo
Women (persons)	57	45	27	28	21	13	13	10
Men (persons)	66	83	29	28	19	7	41	17
White (persons)	115	114	48	52	35	17	0	0
Black (persons)	1	5	3	0	2	0	0	0
Native American (persons)	0	1					0	0
Asian (persons)	4	2	2	0	1	0	54	27
Unknown (persons)	3	6						
BMI (kg/m2)	29.7	29.2	29.3	31.9	29.3	31	25.2	26.1
NYHA II	88	95	4	4	33	13	44	18
NYHA III	35	33	52	52	7	6	10	9
pVO2 (mL/kg per min)	18.9	19.9			20.4	17.9		
NT-proBNP (ng/L)	777	616	724	743	821	914	810.5	1250.3
LVEF (%)	74	74	67.9	68.3	68.7	66.4	77.8	77
Maximum left ventricular wall thickness (mm)	20	20			20.6	18.8	22.9	24.3
LVOT gradient,rest (mmHg)	52	51	51.2	46.3			74.6	73.4
LVOT gradient,Valsalva (mmHg)	72	74	75.3	76.2			106.8	99.8
LVOT gradient,post-exercise (mmHg)	86	84	82.5	85.2				
LAVI (ml/m2)	40	41	41.3	40.9	37.3	40.8	43.3	47.5

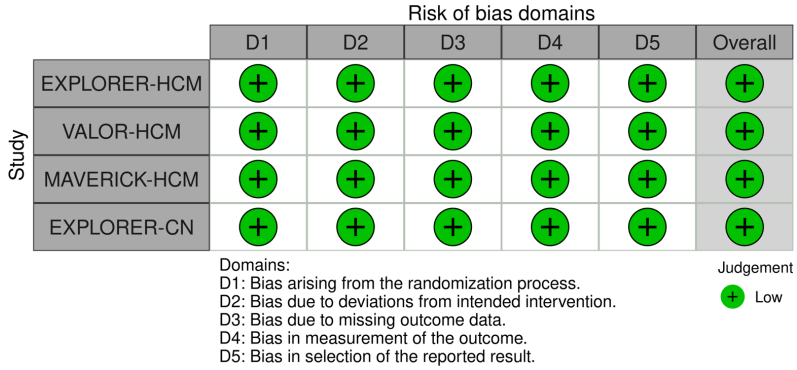

Figure 2 Summary of quality assessment of studies included in the meta-analysis using Cochrane risk of bias 2 tool.

doi:10.6342/NTU202502938

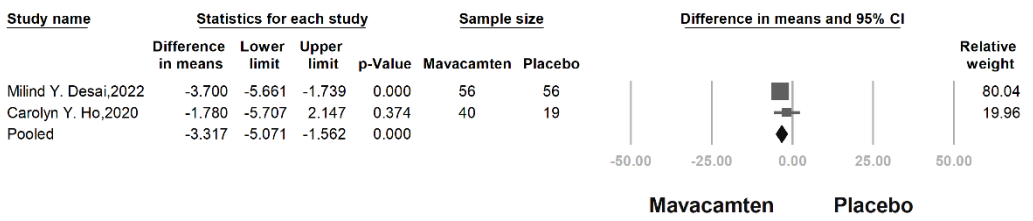

Figure 3. Forest plot of meta-analysis comparing the change in left ventricular ejection fraction (LVEF) between Mavacamten and placebo groups.

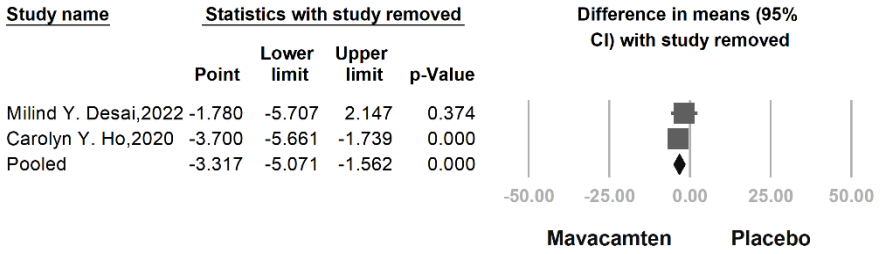

Figure 4. Leave-one-out sensitivity analysis (forest plot) of the effect of Mavacamten on change in left ventricular ejection fraction (LVEF).

doi:10.6342/NTU202502938

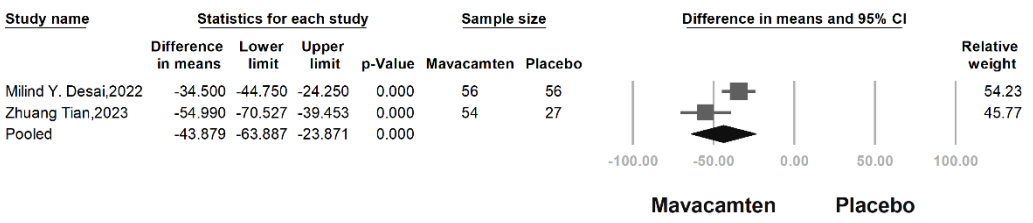

Figure 5 Forest plot of meta-analysis comparing changes in resting left ventricular outflow tract (LVOT) gradient between Mavacamten and placebo groups.

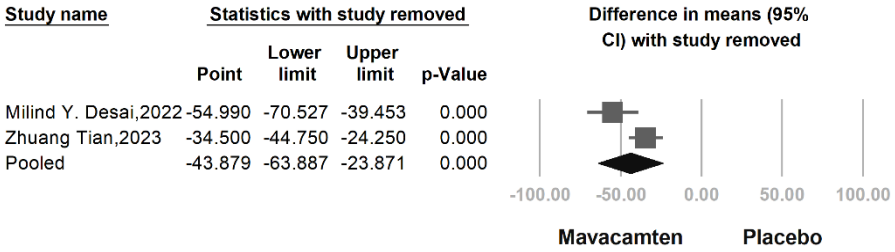

Figure 6 Sensitivity analysis of Mavacamten's effect on resting left ventricular outflow tract (LVOT) gradient reduction in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

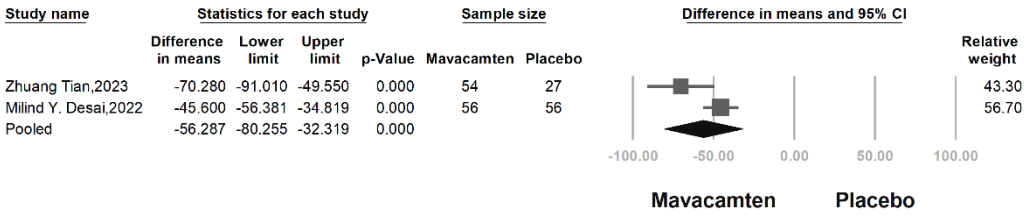

Figure 7. Meta-analysis of the effect of Mavacamten on LVOT gradient reduction during Valsalva in patients with hypertrophic cardiomyopathy (HCM).

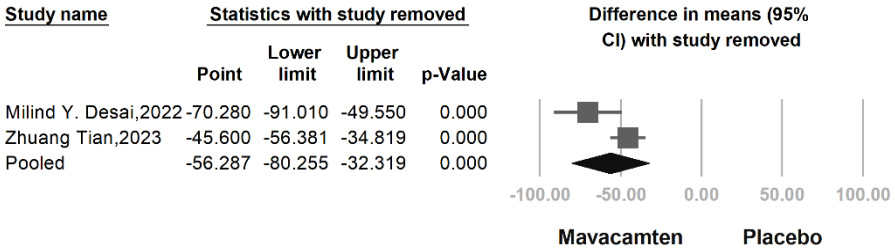

Figure 8. Sensitivity analysis of Mavacamten's effect on LVOT gradient reduction during Valsalva in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

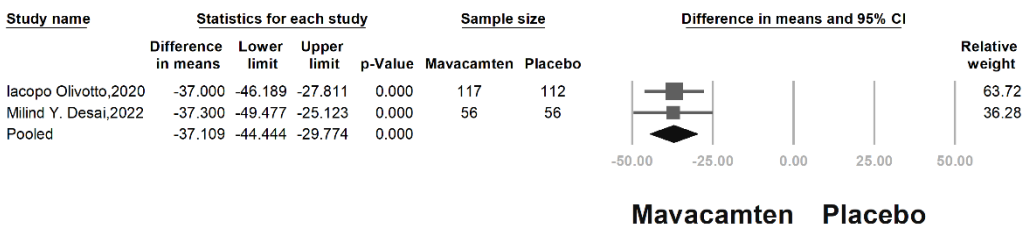

Figure 9. Forest plot of meta-analysis showing the effect of Mavacamten on change in post-exercise left ventricular outflow tract (LVOT) gradient.

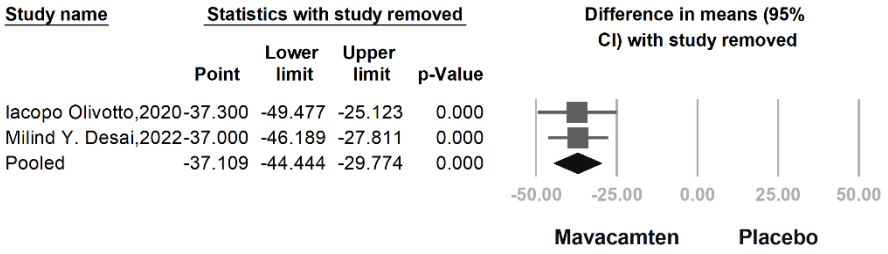

Figure 10. Sensitivity analysis of the effect of Mavacamten on post-exercise left ventricular outflow tract (LVOT) gradient change in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

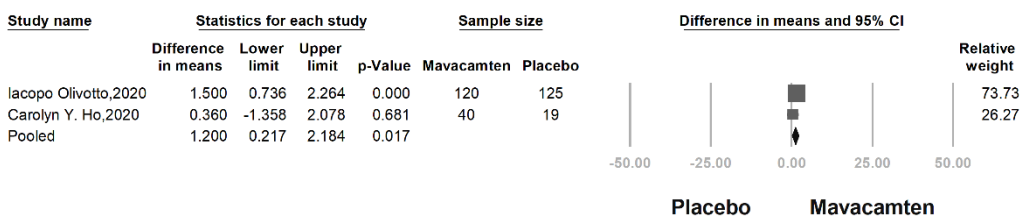

Figure 11. Forest plot of meta-analysis showing the effect of Mavacamten on change in peak oxygen consumption (VO_2) in patients with hypertrophic cardiomyopathy (HCM).

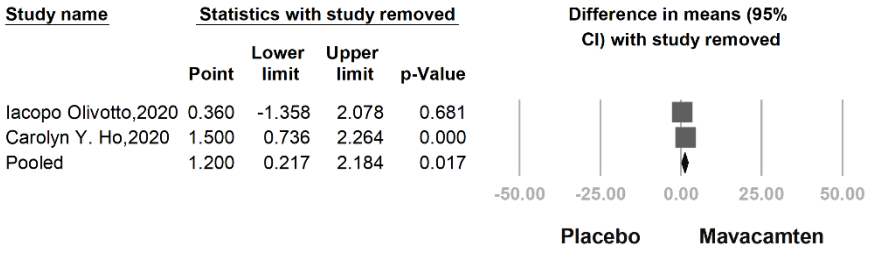

Figure 12. Sensitivity analysis of the effect of Mavacamten on change in peak oxygen consumption (VO_2) in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

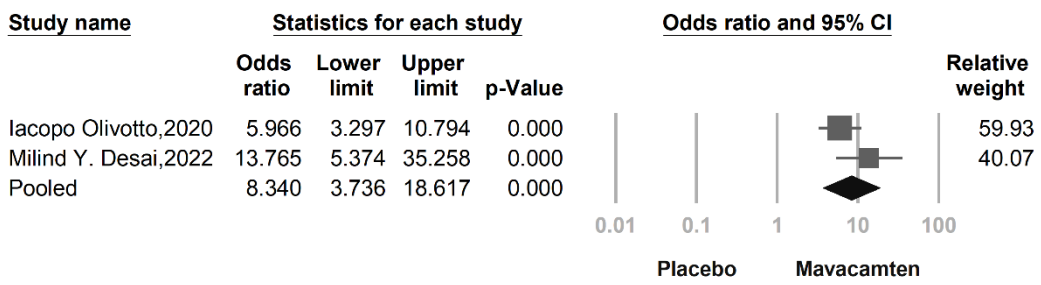

Figure 13. Forest plot of meta-analysis assessing the effect of Mavacamten on avoidance of septal reduction therapy (SRT) in patients with hypertrophic cardiomyopathy (HCM).

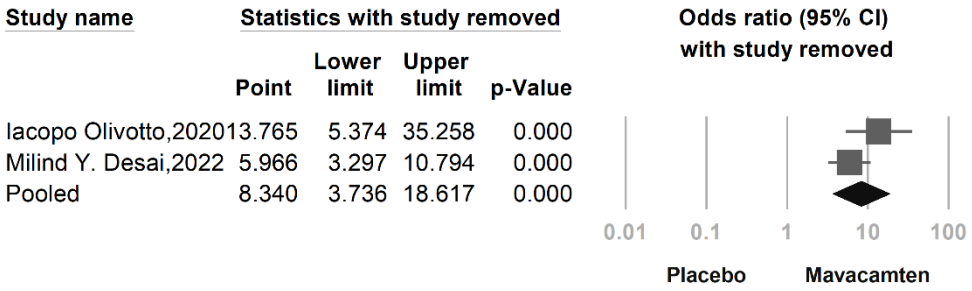

Figure 14. Sensitivity analysis of the effect of Mavacamten on avoidance of septal reduction therapy (SRT) in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

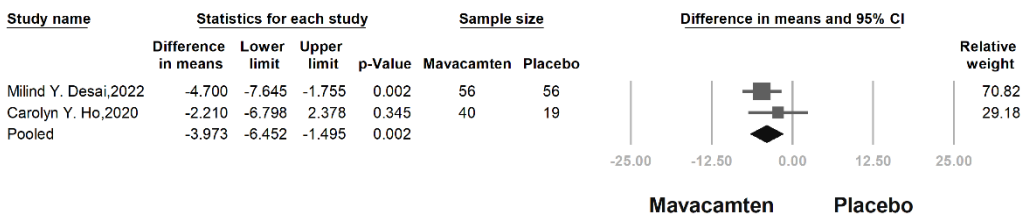

Figure 15. Forest plot of meta-analysis showing the effect of Mavacamten on left atrial volume index (LAVI) reduction in patients with hypertrophic cardiomyopathy (HCM).

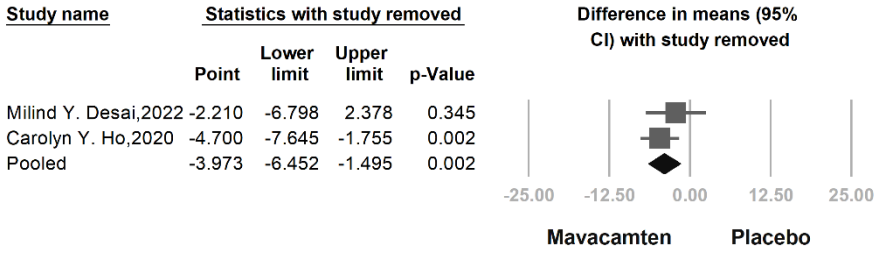

Figure 16. Sensitivity analysis of the effect of Mavacamten on left atrial volume index (LAVI) reduction in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

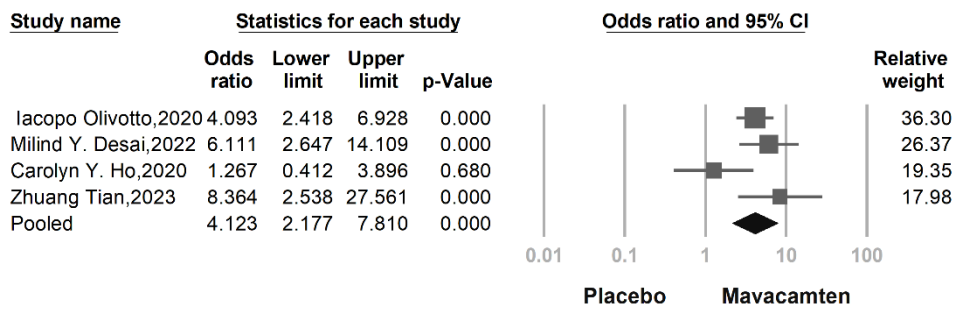

Figure 17. Forest plot of meta-analysis assessing the effect of Mavacamten on improvement in NYHA functional class in patients with hypertrophic cardiomyopathy (HCM).

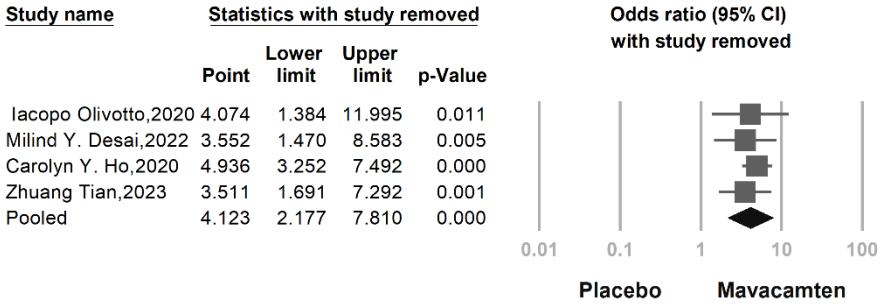

Figure 18. Sensitivity analysis of the effect of Mavacamten on improvement in NYHA functional class in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

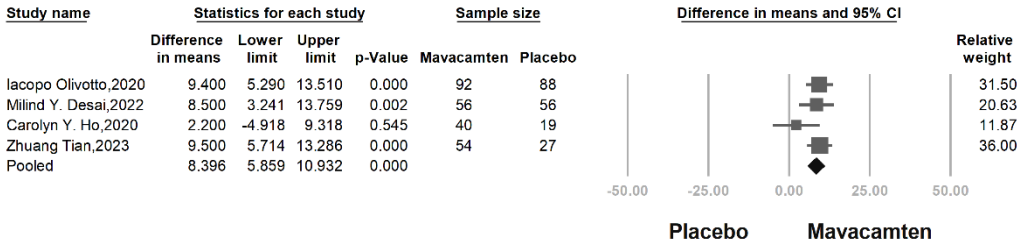

Figure 19. Forest plot of meta-analysis showing the effect of Mavacamten on change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) in patients with hypertrophic cardiomyopathy (HCM).

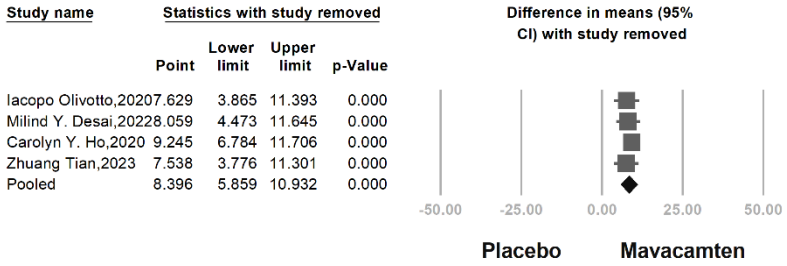

Figure 20. Sensitivity analysis of the effect of Mavacamten on change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) in patients with hypertrophic cardiomyopathy (HCM).

doi:10.6342/NTU202502938

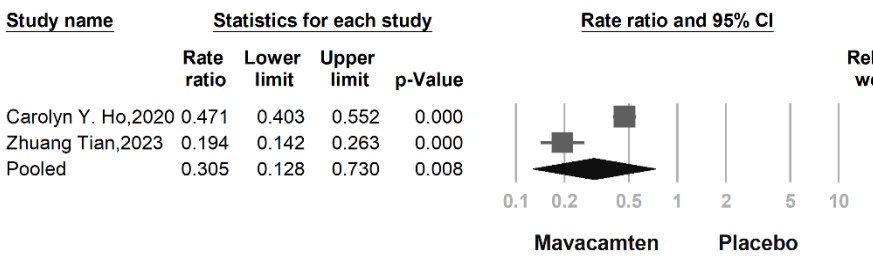

Figure 21. Forest plot of meta-analysis comparing the change in NT-proBNP between Mavacamten and placebo groups.

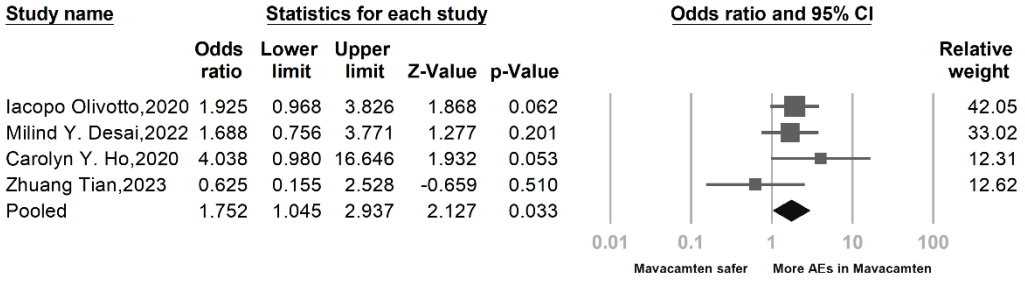

Figure 22. Forest plot of meta-analysis comparing the odds of experiencing more than one treatment-emergent adverse event (TEAE) between Mavacamten and placebo groups.

doi:10.6342/NTU202502938

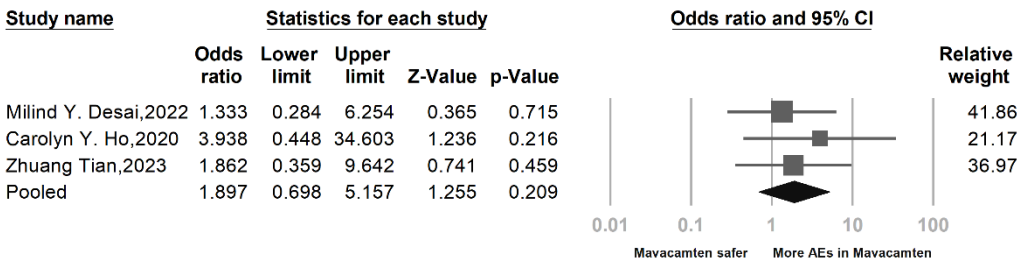

Figure 23. Forest plot of meta-analysis comparing the odds of treatment-emergent dizziness in Mavacamten-treated versus placebo-treated patients.

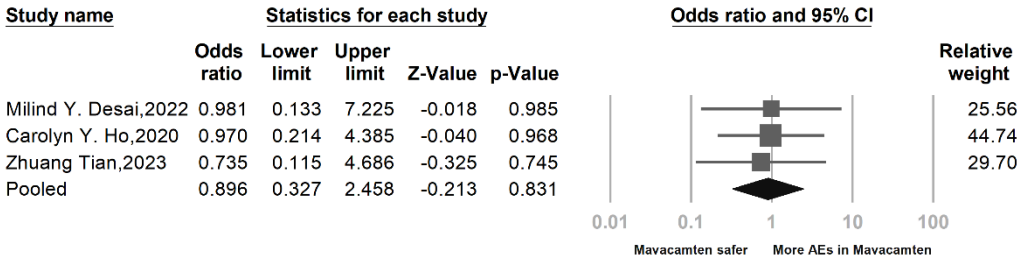

Figure 24. Forest plot of meta-analysis comparing the odds of treatment-emergent palpitations in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

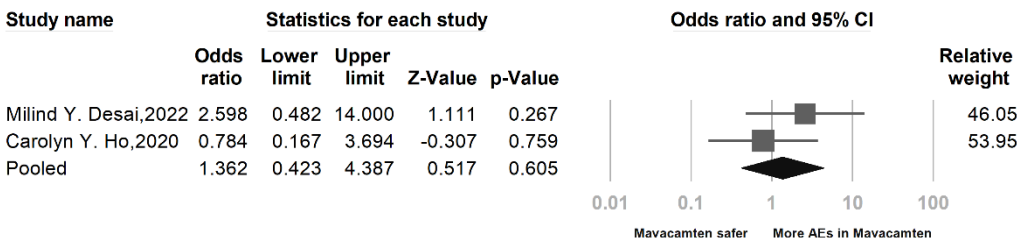

Figure 25. Forest plot of meta-analysis comparing the odds of treatment-emergent fatigue in Mavacamten-treated versus placebo-treated patients.

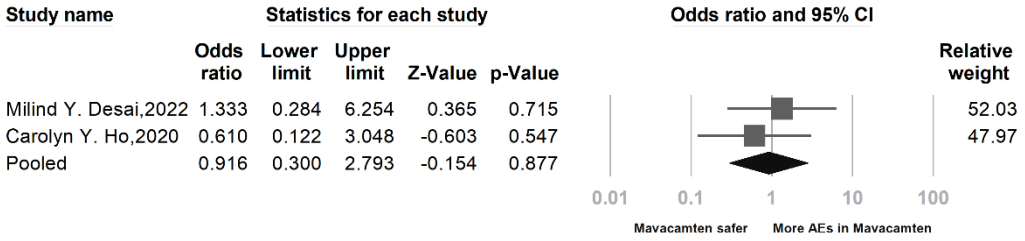

Figure 26. Forest plot of meta-analysis comparing the odds of treatment-emergent dyspnea in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

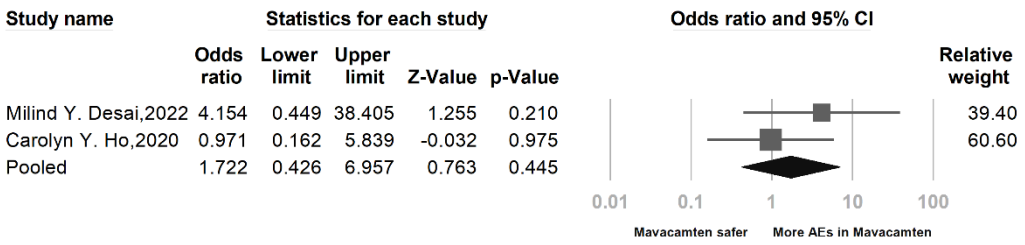

Figure 27. Forest plot of meta-analysis comparing the odds of treatment-emergent nausea in Mavacamten-treated versus placebo-treated patients.

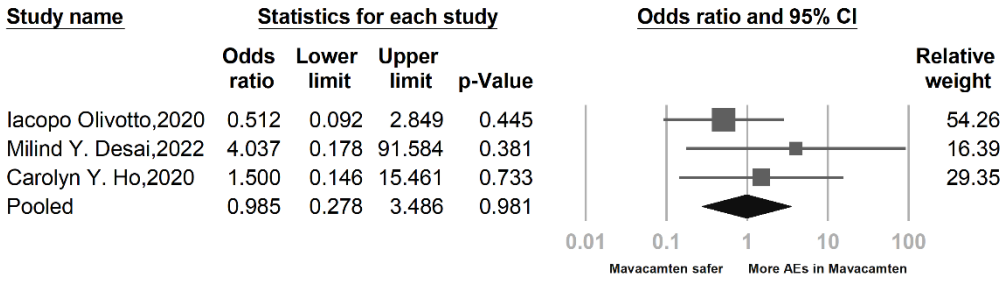

Figure 28. Forest plot of meta-analysis comparing the odds of treatment-emergent atrial fibrillation (Afib) in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

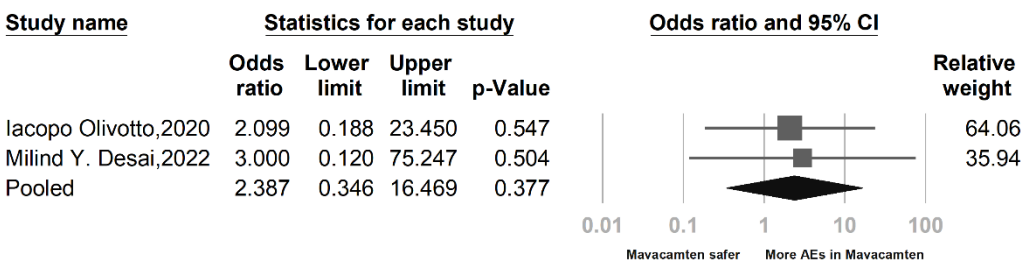

Figure 29. Forest plot of meta-analysis comparing the odds of treatment-emergent syncope in Mavacamten-treated versus placebo-treated patients.

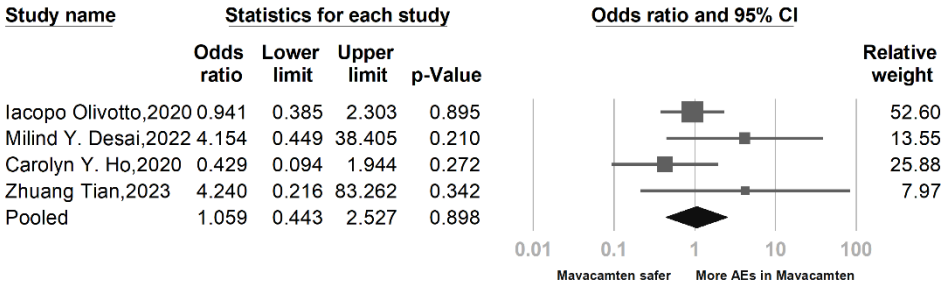

Figure 30. Forest plot of meta-analysis comparing the odds of experiencing more than one serious adverse event (SAE) in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

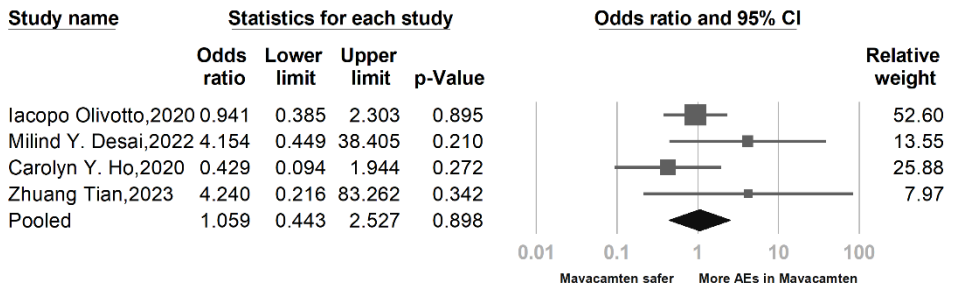

Figure 31. Forest plot of meta-analysis comparing the odds of treatment-emergent atrial fibrillation (Afib) in Mavacamten-treated versus placebo-treated patients.

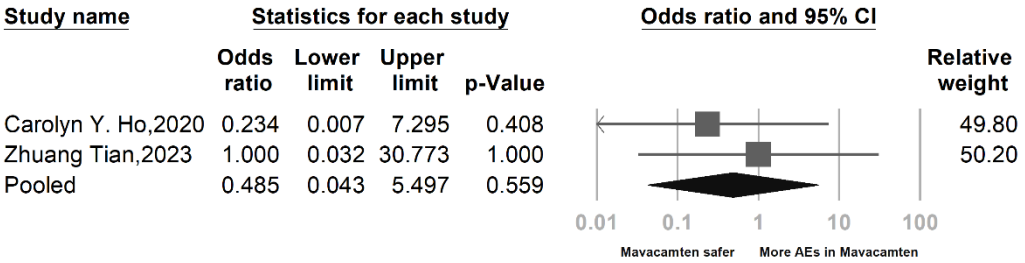

Figure 32. Forest plot of meta-analysis comparing the odds of treatment-emergent atrial flutter in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

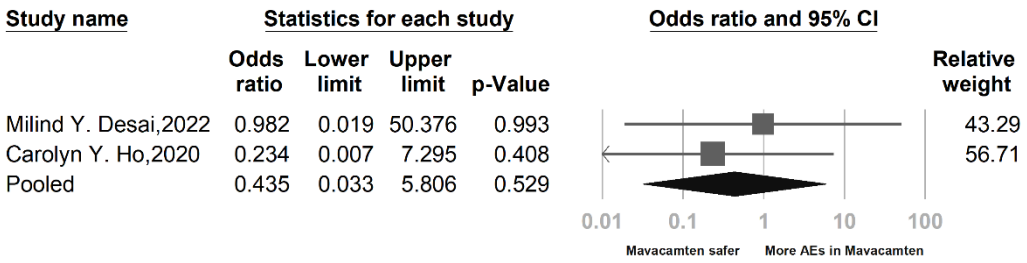

Figure 33. Forest plot of meta-analysis comparing the odds of treatment-emergent coronary artery disease in Mavacamten-treated versus placebo-treated patients.

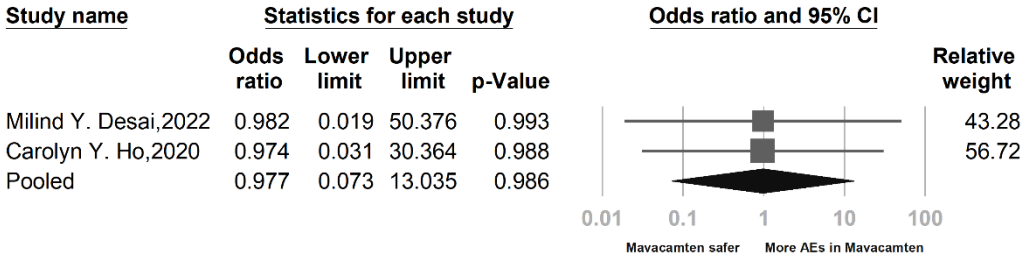

Figure 34. Forest plot of meta-analysis comparing the odds of treatment-emergent systolic dysfunction in Mavacamten-treated versus placebo-treated patients.

doi:10.6342/NTU202502938

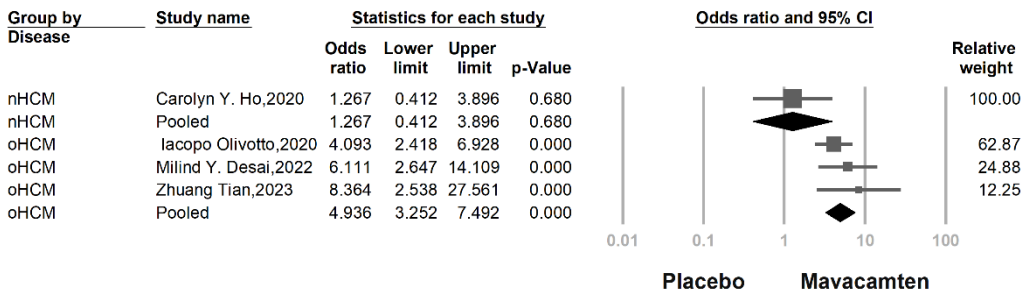

Figure 35. Forest plot of subgroup meta-analysis showing the odds ratio for NYHA functional class improvement with Mavacamten in obstructive (oHCM) and non-obstructive (nHCM) hypertrophic cardiomyopathy.

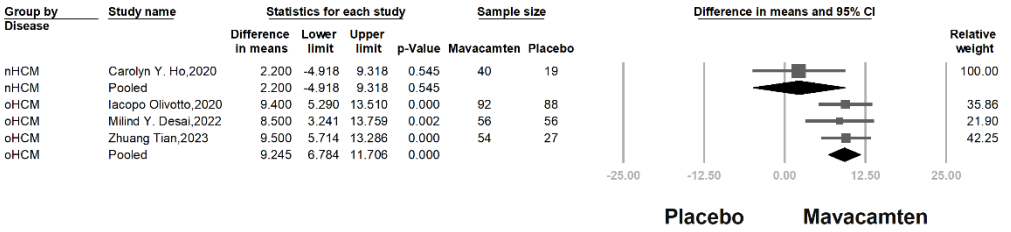

Figure 36. Subgroup meta-analysis forest plot of the effect of Mavacamten on KCCQ Clinical Summary Score (KCCQ-CSS) by disease type (oHCM vs nHCM) in patients with hypertrophic cardiomyopathy.

doi:10.6342/NTU202502938

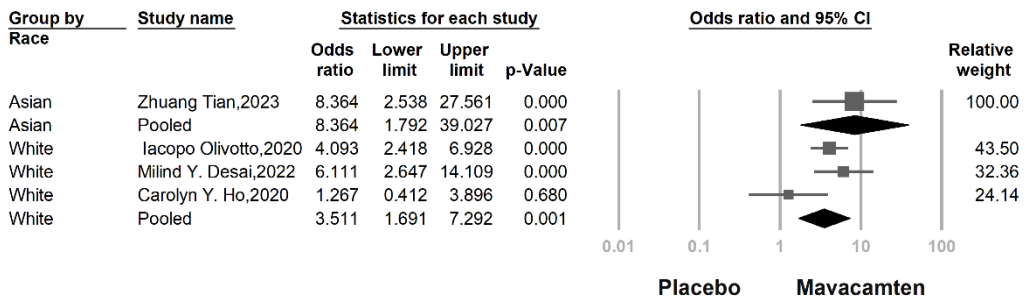

Figure 37. Forest plot of subgroup meta-analysis comparing the odds ratio for NYHA functional class improvement with Mavacamten by race (Asian vs White) in patients with hypertrophic cardiomyopathy.

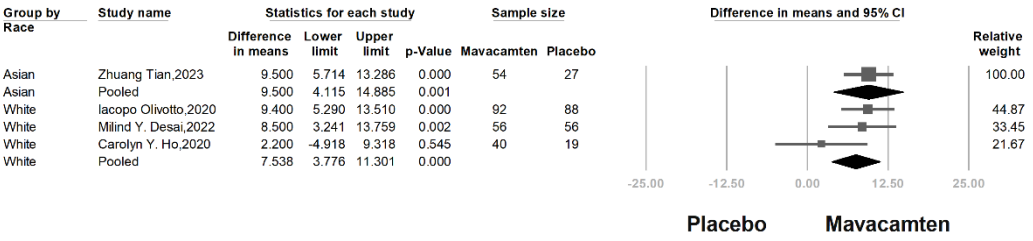

Figure 38. Forest plot of subgroup meta-analysis of pooled effect size (Mean Difference) for KCCQ-CSS improvement with Mavacamten by race (Asian vs White) in patients with hypertrophic cardiomyopathy.

doi:10.6342/NTU202502938

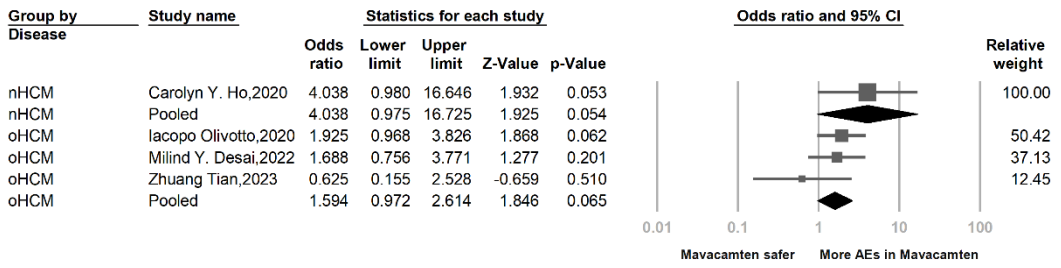

Figure 39. Forest plot of subgroup meta-analysis of the odds ratio for experiencing more than one treatment-emergent adverse event (TEAE) with Mavacamten, comparing non-obstructive (nHCM) and obstructive (oHCM) hypertrophic cardiomyopathy.

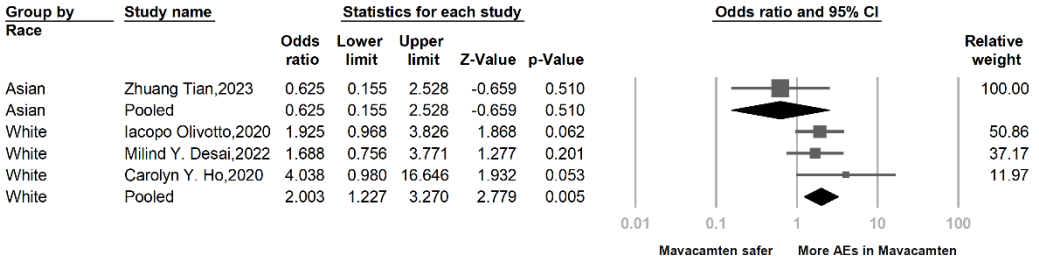

Figure 40. Forest plot of subgroup meta-analysis of the odds ratio for experiencing more than one treatment-emergent adverse event (TEAE) with Mavacamten, comparing Asian and White patients.

doi:10.6342/NTU202502938

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event(s)
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BID	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CrCl	Creatinine Clearance
CT	Computed Tomography
CTCAE	Common Terminology Criteria for

doi:10.6342/NTU202502938

	Adverse Events
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ECV	Extracellular Volume
EF	Ejection Fraction
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLS	Global Longitudinal Strain
HBV	Hepatitis B Virus
HCM	Hypertrophic Cardiomyopathy
HCU	Healthcare Utilization
HCV	Hepatitis C Virus
HR	Hazard Ratio
hs-cTnI	High-sensitivity Cardiac Troponin I
IDMC	Independent Data Monitoring

doi:10.6342/NTU202502938

	Committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ITT	Intention-To-Treat
I^2	I-squared Statistic (Heterogeneity)
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left Atrial Volume Index
LGE	Late Gadolinium Enhancement
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MA	Meta-analysis
nHCM	Non-obstructive Hypertrophic Cardiomyopathy
NYHA	New York Heart Association
OR	Odds Ratio
PBO	Placebo
pVO_2	Peak Oxygen Consumption

doi:10.6342/NTU202502938

QD	Once Daily
QTc	Corrected QT Interval
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SRT	Septal Reduction Therapy
TEAE	Treatment-Emergent Adverse Event
T1	Native T1 Mapping
Valsalva	Valsalva Maneuver

doi:10.6342/NTU202502938

Protocol Synopsis

Study Title	A Multicenter, Double-Blind, Placebo-Controlled, Exploratory Phase 2b Trial of Mavacamten (MYK-461) in East Asian Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (nHCM)
Background and Objective	Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disorder often associated with diastolic dysfunction. While Mavacamten has demonstrated efficacy in obstructive HCM (oHCM), evidence in non-obstructive HCM (nHCM), especially among East Asians, remains limited. This trial aims to evaluate the preliminary efficacy and safety of Mavacamten in East Asian patients with nHCM and to explore the

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	role of cardiac MRI-based imaging biomarkers.
Study Design	Phase 2b, randomized, double-blind, placebo-controlled, multicenter trial. A total of 38 patients will be recruited across five medical centers in northern Taiwan and randomized (1:1) using block randomization. The treatment period is 16 weeks, followed by an 8-week off-treatment observation.
Population	Patients aged 20–80 years with nHCM (LVOT gradient <30 mmHg at rest and Valsalva), NT-proBNP ≥300 pg/mL, and abnormal CMR findings (GLS >–16%, native T1 ≥1000 ms, or ECV >28%). Key exclusions: prior septal reduction, LVEF <50%, significant comorbidities.

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Primary Endpoint	Percent change in plasma NT-proBNP from baseline to Week 24 (geometric mean)
Secondary Endpoints	Imaging (CMR): LVEF, GLS, native T1, ECV, LGE area Clinical: NYHA class improvement, KCCQ-CSS, peak VO_2, hs-cTnI
Intervention	Mavacamten 5 mg QD or matching placebo for 16 weeks 8-week follow-up period without treatment Concomitant use of stable β-blockers or calcium channel blockers allowed
Blinding & Randomization	Double-blind with centralized randomization. Investigators, participants, and evaluators are blinded

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	to group assignment.
Sample Size and Statistics	Estimated effect size (Cohen's d) = 1.25 based on prior NT-proBNP data. With α = 0.05, power = 90%, and 25% dropout rate, 38 subjects (19 per group) are required. Primary analysis via ANCOVA; other endpoints via t-tests, chi-square, or regression models.
Safety Monitoring	An Independent Data Monitoring Committee (IDMC) will oversee safety. A ≥10% decrease in LVEF to <50% will trigger evaluation. All AEs and SAEs will be recorded.
Study Timeline	Each subject will participate for ~28 weeks. Total study duration: 12–18 months.

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Title:

A Randomized, Double-Blind, Placebo-Controlled Trial of Mavacamten (MYK-461) in Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (nHCM) Patients Across Five Medical Centers in Taiwan

1 Background

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disorder characterized by abnormal thickening of the myocardium, particularly in the left ventricular wall. This hypertrophy may reduce myocardial efficiency and impair blood outflow from the heart. Patients with HCM often present with symptoms such as chest pain, dyspnea, or syncope, while some may remain asymptomatic.

Mavacamten is a novel cardiac myosin inhibitor developed for the treatment of HCM. By selectively inhibiting β-cardiac myosin, a key protein involved in sarcomere contraction, Mavacamten reduces hypercontractility and alleviates left ventricular outflow tract (LVOT) obstruction. Clinical trials have demonstrated that Mavacamten improves symptoms, exercise capacity, and quality of life in patients with obstructive HCM.

However, most clinical trials to date have focused on Western populations and

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primarily on obstructive HCM (oHCM). Evidence for Mavacamten in non-obstructive HCM (nHCM), particularly among East Asian patients, remains limited. Although the early MAVERICK-HCM study by Ho et al. (2020) in nHCM did not reach statistical significance, a trend toward improvement in left atrial volume index (LAVI) was consistent with results from the larger VALOR-HCM trial (Desai, 2022). Our meta-analysis also demonstrated a significant pooled effect (Hedges' $g = -0.48$, $p = 0.002$, $I^2 = 0\%$), with no heterogeneity, supporting the potential efficacy of Mavacamten in nHCM.

We therefore propose a randomized controlled trial (RCT) targeting East Asian populations, incorporating cardiac magnetic resonance (CMR) imaging for phenotypic stratification. This study aims to identify responders and refine patient selection, thereby addressing a major evidence gap and advancing the application of Mavacamten in the context of precision medicine. This trial is both necessary and clinically valuable.

2 Objective

This study aims to evaluate the therapeutic efficacy of Mavacamten in East Asian patients with symptomatic non-obstructive HCM, with patient stratification based on cardiac magnetic resonance imaging (CMR). Specifically, the study will assess

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structural and functional cardiac changes and identify clinical and imaging predictors of treatment response.

3 Study Design

This is an exploratory, multicenter, Phase 2b randomized controlled trial (RCT) designed to evaluate the preliminary efficacy and safety of Mavacamten in East Asian patients with non-obstructive hypertrophic cardiomyopathy (nHCM). A total of 38 participants will be enrolled across five medical centers in northern Taiwan. Patients will be randomized in a 1:1 ratio using block randomization to receive either Mavacamten or placebo for a treatment duration of 24 weeks. The trial will be conducted with an open recruitment approach under a double-blind design and in accordance with Good Clinical Practice (GCP) guidelines.

The primary efficacy endpoint is the percent change from baseline in plasma NT-proBNP levels, which serves as a biomarker reflecting left ventricular wall stress and pressure load.

To further explore the structural and functional myocardial effects of Mavacamten, all participants will undergo cardiac magnetic resonance imaging (CMR) at baseline and at week 24. Key secondary imaging endpoints include:

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(1). Left ventricular ejection fraction (LVEF)

(2). Global longitudinal strain (GLS)

(3). Native T1 relaxation time and extracellular volume fraction (ECV)

(4). Changes in late gadolinium enhancement (LGE) area

Additional secondary clinical endpoints will include:

NYHA functional class

Kansas City Cardiomyopathy Questionnaire (KCCQ) score

Peak oxygen consumption (peak VO_2)

High-sensitivity cardiac troponin I (hs-cTnI) concentration

4 Inclusion Criteria

Participants must meet all of the following criteria to be eligible for the study:

1. Aged 20 to 80 years, male or female
2. Diagnosis of non-obstructive HCM (nHCM) according to the 2020 AHA/ESC criteria:

   Left ventricular wall thickness ≥15 mm

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Resting and provoked LVOT gradient <30 mmHg (including during Valsalva)

3. NT-proBNP ≥300 pg/mL (recommended to be at least twice the upper limit of normal)
4. At least one abnormal CMR finding:

   GLS > -16%

   Native T1 mapping ≥1000 ms or ECV >28%
5. Peak VO_2 <80% of predicted value (based on age- and sex-matched norms)
6. Ability and willingness to comply with 24-week treatment and imaging protocols, with written informed consent provided

5 Exclusion Criteria

Participants will be excluded if any of the following conditions apply:

1. LVOT gradient ≥30 mmHg at rest or with provocation
2. Prior septal reduction therapy (surgical myectomy or alcohol septal ablation)
3. LVEF <50%
4. Renal impairment (eGFR <30 mL/min/1.73m²)
5. Pregnancy, lactation, or plans to become pregnant during the study period

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6. History of other major comorbidities or malignancies that may interfere with treatment efficacy evaluation

6 Blinding

Blinding Methodology

This study adopts a double-blind design, in which both the participants and study personnel (including investigators and healthcare providers) are unaware of treatment allocation—whether the participant is receiving Mavacamten or placebo.

Blinding Applied to the Following Individuals

Participants: Subjects enrolled in the study will not know whether they are receiving Mavacamten or placebo, minimizing bias from patient expectations.

Physicians and Investigators: Physicians administering treatment and investigators responsible for outcome assessment and data analysis will be blinded to group allocation to reduce assessment bias.

Other Personnel: Pharmacists and clinical trial monitors involved in study operations will also remain blinded to the treatment assignments, thereby reinforcing the integrity of the blinding process.

Measures to Maintain Blinding

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1. Identical Appearance: Mavacamten and placebo capsules are visually indistinguishable.
2. Central Randomization: A centralized system manages randomization, assigning each participant a unique code, which determines the dispensation of either the active drug or placebo without revealing group identity.

7 Study Intervention

This trial is a double-blind, randomized controlled study, in which participants will be randomly assigned in a 1:1 ratio to one of the following two groups:

1. Mavacamten Group: Oral administration of Mavacamten 5 mg once daily (QD) in capsule form
2. Placebo Group: Oral administration of a matching placebo capsule once daily (QD)

Treatment Duration

The intervention period is 16 weeks. Participants will begin medication on Day 1 and continue until Day 112 (end of Week 16). This will be followed by an 8-week treatment-free follow-up period, concluding on Day 168 (Week 24) with a final assessment.

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Dosing Protocol

To simplify the trial and ensure drug safety, Mavacamten is administered as a fixed dose of 5 mg QD. No therapeutic drug monitoring or dose titration will be performed. However, for participants weighing less than 50 kg, investigators may initiate treatment at 2.5 mg QD based on clinical judgment.

Concomitant Medication Control

Participants already taking HCM-related medications such as beta-blockers (e.g., metoprolol), calcium channel blockers (e.g., verapamil), or other agents must maintain a stable dose for at least two weeks prior to randomization and continue at consistent doses throughout the study. Any changes in these medications during the trial must be documented as adverse events.

Drug Formulation and Administration

Both Mavacamten and placebo will be provided as once-daily oral capsules, taken at a consistent time each day, either with or without food. Study medications will be dispensed by the site pharmacy according to participant codes, and adherence will be tracked.

Safety Monitoring

To monitor for potential declines in left ventricular ejection fraction (LVEF), all

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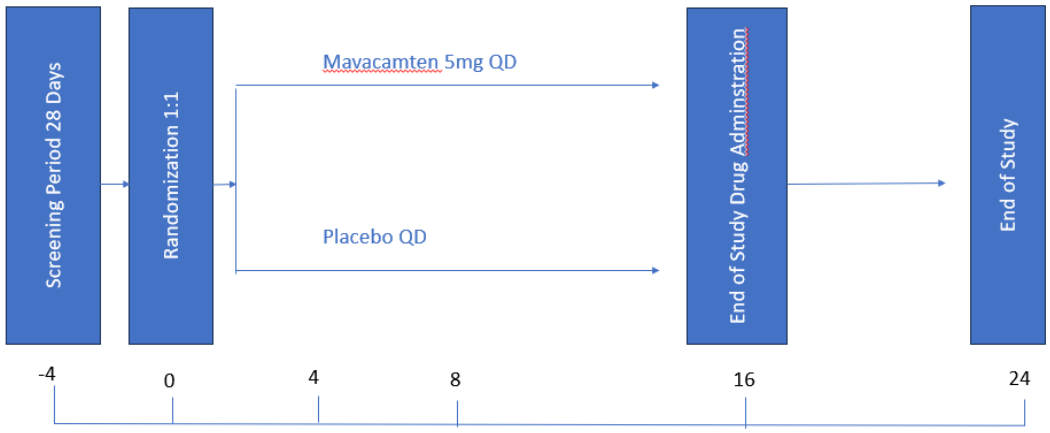
participants will undergo CMR imaging at baseline and Week 16. A decline in LVEF of >10% from baseline resulting in an absolute LVEF <50% will be considered a potential drug-related adverse event. The investigator will assess the need for temporary discontinuation or permanent withdrawal of the study drug in such cases. Any symptoms of discomfort, arrhythmia, or heart failure must prompt immediate medical attention and notification of the study team.



Assessment item	baseline	4 week	8 week	16 week	24 week
Informed Consent	*				
Liver function	*	*	*	*	*
eGFR	*	*	*	*	*
Echocardiography	*	*	*	*	*
peak VO2	*	*	*	*	*
hs-cTnI	*	*	*	*	*
NT-proBNP	*	*	*	*	*
NYHA Class	*			*	*
KCCQ	*			*	*
CMR	*				*

8 Study Duration

The total participation period for each subject in this study is expected to be up to 28 weeks, consisting of the following phases:

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1. Screening Period (up to 4 weeks / 28 days):

   To confirm diagnosis, ensure stable concomitant medication, and complete baseline evaluations including NT-proBNP measurement, cardiac magnetic resonance imaging (CMR), and Kansas City Cardiomyopathy Questionnaire (KCCQ).

2. Treatment Period (16 weeks):

   Subjects will receive daily oral administration of either Mavacamten or placebo. During this phase, blood tests, symptom assessments, and monitoring of efficacy endpoints will be performed.

3. Follow-up Period (8 weeks):

   A treatment-free observation period to evaluate post-discontinuation changes in clinical status and monitor safety. Optional imaging assessments may be conducted after treatment cessation.

The overall study duration, including participant recruitment and data collection across the five participating centers, is estimated to span 12 to 18 months, depending on enrollment pace and imaging schedules.

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9 Primary and Secondary Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

Percent change from baseline in plasma NT-proBNP levels at Week 24, expressed as the geometric mean.

NT-proBNP is a widely used biomarker for heart failure that reflects left ventricular pressure overload and myocardial wall stress. Its use as the primary endpoint allows for an objective evaluation of the potential effect of Mavacamten on ventricular pressure and diastolic function in patients with non-obstructive hypertrophic cardiomyopathy (nHCM).

Secondary Efficacy Endpoints

To comprehensively assess the potential effects of Mavacamten on myocardial structure, function, symptoms, and quality of life, the following secondary endpoints have been defined:

- **Imaging-Based Secondary Endpoints (assessed via cardiac magnetic resonance imaging at baseline and Week 24):**

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1. Change in left ventricular ejection fraction (LVEF)
2. Change in global longitudinal strain (GLS)
3. Change in native T1 values and extracellular volume (ECV)
4. Change in total area of late gadolinium enhancement (LGE)

- **Clinical and Functional Secondary Endpoints:**

5. Proportion of improvement in New York Heart Association (NYHA) functional class
6. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS)
7. Change in peak oxygen consumption (peak VO_2)
8. Change in high-sensitivity cardiac troponin I (hs-cTnI) concentrations

Each endpoint will be assessed at baseline and Week 24 to provide a multi-dimensional understanding of the therapeutic effects and underlying mechanisms of Mavacamten in the East Asian nHCM population.

10 Sample Size and Statistical Considerations

Sample size calculation was based on NT-proBNP, a well-recognized biomarker for ventricular wall stress and pressure, which reflects cardiac filling pressure and

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symptom severity. In previous studies involving nHCM patients, treatment with Mavacamten resulted in a 53.2% reduction in NT-proBNP levels compared to only 0.7% in the placebo group ($p = 0.0005$). Given its international recognition and routine use in heart failure and cardiomyopathy trials, NT-proBNP is considered a robust and clinically relevant primary endpoint.

The geometric means of NT-proBNP were transformed into ratios and subsequently log-transformed to calculate the effect size. Based on this transformation, Cohen's d was estimated at 1.25.

With a two-tailed test at $\alpha = 0.05$, power = 90%, and assuming a 25% dropout rate, the required sample size was calculated to be 19 participants per group, yielding a total of 38 subjects for this randomized controlled trial.

11 Statistical Analysis Principles

(1) Descriptive Statistics

At the initial stage, descriptive statistics (mean, median, standard deviation, etc.) will be computed to summarize baseline characteristics and measurement indicators of the study population.

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(2) t-Tests

Used to compare continuous variables (e.g., peak VO_2) between treatment groups at baseline and follow-up time points.

(3) Chi-square Tests

Applied to categorical variables (e.g., incidence of adverse events or proportion of patients meeting a clinical endpoint).

(4) Linear Regression

When multiple covariates (e.g., age, sex, disease duration) may influence outcomes, regression analysis will be used to adjust for these potential confounders.

(5) Intention-to-Treat (ITT) Analysis

All randomized participants will be included in the final analysis, regardless of adherence or dropout, to preserve the integrity of randomization.

Required Data for Analysis

(1). Baseline data: Patient demographics (age, sex), clinical history, ECG findings, and CMR parameters.

(2). Follow-up data: All key clinical indicators during treatment and observation

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periods, including NYHA class, KCCQ scores, lab values, and CMR findings.

(3). Safety data: All reported adverse events, especially serious adverse events (SAEs) and those suspected to be drug-related.

(4). Endpoint events: All predefined primary and secondary endpoint occurrences will be documented for analysis.

These statistical methodologies and systematic data handling will ensure a comprehensive and reliable evaluation of the efficacy and safety of Mavacamten in comparison to placebo, thereby enhancing the credibility and scientific rigor of the study findings.

12 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established and will convene regularly to review accumulating study data. The primary responsibilities of the IDMC are to safeguard participant welfare, monitor interim safety data, and provide expert recommendations to the sponsor and investigators on any emerging concerns or protocol-related issues.

The IDMC may also propose modifications to evaluation procedures or analytical

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methods in order to detect and investigate potential safety signals. Their independent oversight ensures the ethical integrity and scientific validity of the trial.

13 Monitoring of Serious Adverse Events (SAEs)

Throughout the trial, all participants will be closely monitored for any potential serious adverse events (SAEs), including cardiac-related events, hypersensitivity reactions, and other health complications potentially associated with Mavacamten treatment.

Routine clinical evaluations—including echocardiography, electrocardiograms (ECG), and laboratory tests—will be performed to assess the safety profile of the investigational drug.

Management Strategies for Serious Adverse Events

(1) Treatment Interruption or Discontinuation

If a participant experiences an SAE, investigators may decide to temporarily interrupt or permanently discontinue Mavacamten treatment. For example, if the participant's left ventricular ejection fraction (LVEF) falls significantly below 50%, treatment will be paused until clinical stabilization or recovery.

(2) Symptom Management and Supportive Care:

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Appropriate symptomatic and supportive interventions will be provided for drug-related adverse events. This may include pharmacologic therapy or other necessary medical procedures.

(3) Event Documentation and Reporting:

All SAEs must be thoroughly documented and reported to relevant regulatory authorities and the institutional review board (IRB) for further evaluation and risk assessment.

(4) Ongoing Monitoring and Evaluation:

Even after the resolution of an SAE, the affected participant will undergo enhanced clinical surveillance and regular follow-up assessments to ensure long-term health status and safety.

Collection and Analysis of Safety Data

Safety data collected during the trial will be analyzed to build a comprehensive safety profile for Mavacamten and inform its future clinical application.

These data will contribute to assessing the drug's overall risk-benefit ratio across diverse patient populations.

These rigorous monitoring and management protocols are designed to ensure timely and appropriate medical responses to any SAEs, thereby maximizing the protection of

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participant safety and well-being.

14 Informed Consent Process

(1) Information Provision

Potential participants will be provided with a detailed informed consent document outlining the purpose of the trial, study procedures, potential risks and benefits, participants' rights, and the option to withdraw at any time.

(2) Explanation and Discussion

Study personnel will engage in face-to-face discussions with prospective participants to ensure full comprehension of the information presented and to address any questions. This step is crucial in supporting an informed and voluntary decision.

(3) Signing the Consent Form

If a participant agrees to enroll, they will sign the informed consent form. It must be ensured that the decision is made freely, without coercion, and with a clear understanding of the trial.

(4) Ongoing Information Access

Participants will have continuous access to relevant information throughout the

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study and retain the right to withdraw consent and discontinue participation at any time.

Regulatory Compliance:

Ethics Review:

The informed consent process and documentation must be approved by an Institutional Review Board (IRB) or relevant ethics committee to ensure compliance with ethical standards and participant rights protection.

Language and Clarity:

The informed consent document must be written in clear, understandable language tailored to the participant population, avoiding medical jargon that could cause confusion.

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