ORIGINAL ARTICLE

# Mavacamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

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## ABSTRACT

### BACKGROUND

Mavacamten is approved to treat adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM). However, its effects in nonobstructive HCM remain uncertain.

### METHODS

We conducted a phase 3, international, double-blind, placebo-controlled, clinical trial to determine whether mavacamten improves functional capacity and patient-reported health status among adults with symptomatic nonobstructive HCM. Patients were randomly assigned in a 1:1 ratio to receive mavacamten (starting at 5 mg per day and adjusted up to a maximum of 15 mg per day on the basis of left ventricular ejection fraction) or placebo (with sham dose adjustment) for 48 weeks. The two primary end points were the change from baseline to week 48 in peak oxygen uptake and in the 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better health status).

### RESULTS

We randomly assigned 289 patients to receive mavacamten and 291 to receive placebo. The mean (±SD) age of the patients was 56±15 years, and 46% were women. From baseline to week 48, the least-squares mean change in peak oxygen uptake was 0.52 ml per kilogram of body weight per minute (95% confidence interval [CI], 0.09 to 0.95) in the mavacamten group and 0.05 ml per kilogram per minute (95% CI, −0.38 to 0.47) in the placebo group (between-group difference, 0.47 ml per kilogram per minute; 95% CI, −0.03 to 0.98; P=0.07). The least-squares mean change in the KCCQ-CSS was 13.1 points (95% CI, 10.7 to 15.5) in the mavacamten group and 10.4 points (95% CI, 8.0 to 12.8) in the placebo group (between-group difference, 2.7 points; 95% CI, −0.1 to 5.6; P=0.06). Reductions in ejection fraction and interruptions in the trial regimen were more common with mavacamten than with placebo.

### CONCLUSIONS

Among patients with nonobstructive HCM, mavacamten did not result in a significantly greater improvement in peak oxygen uptake or decrease in symptoms than placebo. (Funded by Bristol Myers Squibb; ODYSSEY-HCM ClinicalTrials.gov number, NCT05582395.)

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*A list of the ODYSSEY-HCM investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Hypertrophic cardiomyopathy (HCM) is a complex, often inherited myocardial disease with an estimated prevalence between 1 in 200 and 1 in 500 persons, with varying phenotypic characteristics. Dynamic left ventricular outflow tract obstruction is present in approximately 50 to 70% of patients and causes lifestyle-limiting symptoms.[1-3] Patients without left ventricular outflow tract obstruction may also have severe symptoms due to a combination of factors including a small hypercontractile left ventricular cavity, sometimes with midcavitary obstruction; a low stroke volume (the volume of blood pumped from the ventricle during each cardiac cycle); diastolic dysfunction; microvascular ischemia; pulmonary hypertension; arrhythmias; and chronotropic incompetence. Currently, there are no approved medical therapies for symptomatic nonobstructive HCM, and frequently used off-label pharmacotherapies, including diuretic agents, beta-blockers, verapamil, or diltiazem, have limited efficacy as well as side effects.[4,5] A previous study showed mixed results with ranolazine in patients with symptomatic HCM.[6] Accordingly, there is an unmet medical need for safe and more-effective treatments for patients with symptomatic nonobstructive HCM that increase functional capacity, reduce symptoms, and improve quality of life.[1,3]

In studies involving patients with symptomatic obstructive HCM, mavacamten decreased outflow tract obstruction, improved quality of life, reduced symptom burden, increased exercise capacity, and reduced eligibility for septal reduction therapy with favorable effects on short- and long-term cardiac remodeling.[7-19] On the basis of these findings, mavacamten is approved in multiple countries to treat adult patients with obstructive HCM who remain symptomatic despite treatment with beta-blockers or calcium-channel blockers. Mavacamten also has a class I recommendation for treatment of HCM in U.S. practice guidelines and a class IIa recommendation in European practice guidelines.[1,3] A small, phase 2, placebo-controlled trial involving patients with nonobstructive HCM showed improvements in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and troponin I levels with mavacamten.[20] We conducted a phase 3 trial (ODYSSEY-HCM) to assess whether mavacamten improves functional capacity and patient-reported health status in adult patients with symptomatic nonobstructive HCM.

## Methods

### Trial Organization and Oversight

This phase 3, double-blind, multicenter, parallel-group, randomized, placebo-controlled trial enrolled patients at 201 HCM referral centers in 22 countries from December 2022 through March 2024. The representativeness of the patient population is described in Table S1 in the Supplementary Appendix (available with the full text of this article at NEJM.org). The trial protocol, available at NEJM.org, was approved by an ethics committee at each participating site. The trial was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was provided by all the patients before any trial procedure.

The trial was sponsored by Bristol Myers Squibb and designed in collaboration with the Cleveland Clinic Coordinating Center for Clinical Research and an academic executive committee. The sponsor participated in the collection, analysis, and interpretation of the data. An independent data monitoring committee reviewed unblinded safety and efficacy data during the trial. Echocardiography data were analyzed by an imaging core laboratory at the Cleveland Clinic. The Cardiovascular and Metabolic Disease Research Institute was the core laboratory for analysis of data from cardiopulmonary exercise tests. The staff at both core laboratories and all trial personnel remained unaware of trial-group assignments and results of analyses until the database lock. Additional details of the trial protocol and trial organization have been published previously.[21] The first draft of the manuscript was written by the first author with input from coauthors, and the final version was approved by all the authors. Employees of the sponsor reviewed the manuscript and made suggestions, but the final decision on content was reserved for the first author, who vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

### Trial Design

The trial enrolled symptomatic patients who met established diagnostic criteria for nonobstructive HCM.[1,3] Full inclusion and exclusion criteria are provided in the Supplementary Appendix. Patients were at least 18 years of age and had a peak left ventricular outflow tract gradient of less than

30 mm Hg at rest and less than 50 mm Hg during provocation, New York Heart Association (NYHA) functional class II or III heart failure, a score of 85 or lower on the 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and better physical functioning), a left ventricular ejection fraction of at least 60% as measured by transthoracic echocardiography and assessed by the core laboratory, a respiratory exchange ratio of at least 1.0 during cardiopulmonary exercise testing, and a locally assessed NT-proBNP level above the upper limits of the normal range according to race, body-mass index, and the presence of atrial arrhythmias. Patients could be enrolled if they had left ventricular midcavitary obstruction in the absence of left ventricular outflow tract obstruction.

Mavacamten was added to usual-care background treatments, which could be continued for the duration of the trial. Patients were required to be clinically stable and could not initiate, discontinue, or adjust the dose of new cardiac medications within 2 weeks before screening and up to the day of randomization. Eligible patients were randomly assigned in a 1:1 ratio to receive mavacamten or placebo once daily for 48 weeks (Fig. S1). Randomization was stratified according to NYHA class (II or III), type of exercise testing (treadmill or exercise bicycle), and treatment with beta-blockers (yes or no) at baseline. The starting dose of mavacamten was 5 mg with the possibility of decreasing the dose at weeks 5 and 9 or increasing the dose at weeks 12, 24, and 36 on the basis of the left ventricular ejection fraction, which was analyzed in a blinded fashion by the core laboratory, typically within 1 to 2 business days after the echocardiogram was obtained. The possible doses were 1 mg, 2.5 mg, 5 mg, 10 mg, or 15 mg. Sham dose adjustment was performed for patients assigned to the placebo group. Full details are described in the protocol.[21]

Patients underwent echocardiography and cardiopulmonary exercise testing, and studies were analyzed at the respective core laboratories. Patient-reported health status was recorded during trial visits. Site investigators were instructed to interrupt the trial regimen for at least 4 weeks if the left ventricular ejection fraction was less than 50%. If the left ventricular ejection fraction increased to 50% or higher, patients resumed the trial regimen at the next dose below the dose that had been interrupted (patients who had been receiving the 1-mg dose resumed the same dose). If the trial regimen was interrupted twice on the basis of a left ventricular ejection fraction of less than 50% while the patient was receiving a 1-mg dose of mavacamten or placebo, then the regimen was permanently discontinued. Discontinuation of the regimen was required if a left ventricular ejection fraction of 30% or lower was reported either at the site or by the core laboratory. Additional criteria for discontinuation of the trial regimen are outlined in the trial protocol.[21]

### END POINTS

The two primary end points were the change from baseline to week 48 in peak oxygen consumption as determined by cardiopulmonary exercise testing and the change from baseline to week 48 in the KCCQ-CSS. The trial was designed such that the effect of treatment with mavacamten would be considered favorable if the results for at least one primary end point were statistically significant after adjustment for multiplicity. Secondary end points included changes from baseline to week 48 in the slope of minute ventilation divided by carbon dioxide production, NT-proBNP level, score on the shortness-of-breath domain of the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ, a disease-specific instrument developed to assess symptom burden in patients with HCM; shortness-of-breath scores range from 0 to 18, with higher scores indicating more frequent shortness of breath), and an improvement from baseline to week 48 of at least one NYHA class.

### STATISTICAL ANALYSIS

The sample size was estimated on the basis of the MAVERICK-HCM (Mavacamten in Adults with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy) trial,[20] under the assumption of a between-group difference (mavacamten vs. placebo) in the change from baseline to week 48 in mean peak oxygen uptake of at least 1.3 ml per kilogram of body weight per minute with a common standard deviation of 3.1 and in mean KCCQ-CSS of at least 5 points with a common standard deviation of 14. We estimated that a sample size of 420 patients would provide 95% power to reject the primary null hypothesis for KCCQ-CSS and 98% power for peak oxygen uptake.

All efficacy analyses were performed in the randomized population. Continuous outcomes were analyzed with the use of an analysis of covariance model, with trial group, stratification factors (NYHA class, type of exercise testing, and treatment with beta-blockers), and baseline value as covariates. The estimated least-squares mean between-group difference in change from baseline to week 48 and corresponding 95% two-sided confidence intervals were calculated. The estimands followed the treatment-policy approach, in which available end-point data were used regardless of discontinuation of the trial regimen. The number of patients with missing values for each end point are provided in Table S2, and the detailed imputation strategy for each end point is provided in the statistical analysis plan (available with the protocol), with additional details provided in the Supplementary Appendix. Multiplicity testing was conducted with the use of a graphical testing approach to control the overall type I error rate at 0.05. The initial step allocated an alpha level of 0.04 to the KCCQ-CSS end point and an alpha level of 0.01 to the peak oxygen uptake end point. Alpha allocation thereafter is described in Figures S2 and S3. Additional details are provided in the statistical analysis plan. Statistical analyses were performed with the use of SAS software, version 9.4, or R software.

## RESULTS

### PATIENTS

A total of 1043 patients were screened, and 580 underwent randomization (289 were assigned to mavacamten and 291 to placebo), with 569 (98.1%) completing the double-blind treatment period. The characteristics of the patients at baseline are summarized in Table 1 and Table S3 and have been described previously.[21] The mean (±SD) age of the patients was 56±15 years, 46% were women, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 28.2±5.0. The mean time from the initial HCM diagnosis to randomization was 10.3±9.3 years, 251 patients (43.3%) had a family history of HCM, 34 (5.9%) had a history of septal reduction therapy, and 453 (78.1%) were receiving beta-blockers. Among the patients who underwent randomization, 405 (69.8%) were classified by the investigators as having NYHA functional class II and 175 (30.2%) as having NYHA functional class III. The mean KCCQ-CSS was 56.9±19.9.

The mean echocardiographic left ventricular ejection fraction was 65.8±4.0%. The mean left ventricular mass index was 122.3±30.8 kg per square meter, left atrial volume index was 43.5±15.7 ml per square meter, and ratio of the peak early mitral inflow velocity to the peak early diastolic mitral annular velocity was 13.3±5.5. With respect to cardiopulmonary exercise testing, 312 patients (53.8%) underwent bicycle ergometry testing and 268 (46.2%) underwent treadmill testing. The mean peak oxygen uptake was 18.2±5.7 ml per kilogram per minute (67.8±21.7% of the predicted value). The median NT-proBNP level was 917.5 ng per liter (interquartile range, 463.0 to 1725.0), and the median high-sensitivity troponin T level was 18.4 ng per liter (interquartile range, 12.4 to 27.0). Among the patients assigned to the mavacamten group, the final dose distribution at week 48 was 1 mg in 9 patients (3.1%), 2.5 mg in 18 (6.2%), 5 mg in 89 (30.8%), 10 mg in 80 (27.7%), and 15 mg in 62 (21.5%).

### PRIMARY EFFICACY ANALYSIS

The least-squares mean change from baseline to week 48 in peak oxygen uptake was 0.52 ml per kilogram per minute (95% CI, 0.09 to 0.95) in the mavacamten group and 0.05 ml per kilogram per minute (95% CI, −0.38 to 0.47) in the placebo group. The difference between groups in peak oxygen uptake was 0.47 ml per kilogram per minute (95% CI, −0.03 to 0.98; P=0.07). The least-squares mean change from baseline to week 48 in the KCCQ-CSS was 13.1 points (95% confidence interval [CI], 10.7 to 15.5) in the mavacamten group and 10.4 points (95% CI, 8.0 to 12.8) in the placebo group. The difference between groups in the KCCQ-CSS was 2.7 points (95% CI, −0.1 to 5.6; P=0.06). The results of the primary and secondary efficacy end points are shown in Table 2, Table S4, Figures 1 and 2, and Figure S4. Prespecified subgroup analyses are shown in Figure S5.

### SAFETY

The trial regimen was interrupted in 74 patients (25.7%) assigned to mavacamten and in 22 (7.6%) assigned to placebo. A total of 48 patients (8.3%) discontinued the assigned regimen permanently, 31 (10.7%) in the mavacamten group and 17 (5.8%) in the placebo group. Investigator-reported adverse

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Mavacamten (N=289) | Placebo (N=291) |
|---|---|---|
| Age — yr | 56.4±14.7 | 55.7±14.4 |
| Male sex — no. (%) | 148 (51.2) | 166 (57.0) |
| Race or ethnic group — no. (%)† | | |
| White | 195 (67.5) | 205 (70.4) |
| Black | 11 (3.8) | 14 (4.8) |
| Asian | 51 (17.6) | 39 (13.4) |
| Other | 32 (11.1) | 33 (11.3) |
| Hispanic | 40 (13.8) | 42 (14.4) |
| Body-mass index‡ | 27.9±4.9 | 28.6±5.2 |
| Duration of nonobstructive HCM — yr | 10.1±9.0 | 10.5±9.5 |
| Family history of HCM — no. (%) | 116 (40.1) | 135 (46.4) |
| Family history of sudden cardiac death — no. (%) | 46 (15.9) | 38 (13.1) |
| New York Heart Association functional class — no. (%) | | |
| II | 203 (70.2) | 202 (69.4) |
| III | 86 (29.8) | 89 (30.6) |
| Type of exercise testing — no. (%) | | |
| Treadmill | 139 (48.1) | 129 (44.3) |
| Exercise bicycle | 150 (51.9) | 162 (55.7) |
| History of atrial fibrillation — no. (%) | 97 (33.6) | 83 (28.5) |
| History of hypertension — no. (%) | 133 (46.0) | 127 (43.6) |
| History of septal reduction therapy — no. (%)§ | 16 (5.5) | 18 (6.2) |
| History of coronary artery disease — no. (%) | 24 (8.3) | 16 (5.5) |
| Background HCM therapy — no. (%) | | |
| Beta-blocker | 227 (78.5) | 226 (77.7) |
| Calcium-channel blocker | 34 (11.8) | 36 (12.4) |
| Disopyramide | 9 (3.1) | 8 (2.7) |
| Echocardiographic factors | | |
| Left ventricular ejection fraction — % | 65.8±4.0 | 65.7±4.0 |
| Left atrial volume index — ml/m$^2$ | 43.7±16.9 | 43.2±14.5 |
| Maximum left ventricular wall thickness — mm | 21.0±4.3 | 20.7±3.9 |
| Ratio of peak early mitral inflow velocity to peak early diastolic mitral annular velocity | 13.1±5.7 | 13.5±5.4 |
| Peak oxygen uptake — ml/kg/min | 18.4±5.9 | 17.9±5.5 |
| Predicted peak oxygen uptake — % | 69.0±20.6 | 66.7±22.7 |
| Slope of minute ventilation divided by carbon dioxide production | 36.8±8.6 | 37.1±8.6 |
| Kansas City Cardiomyopathy Questionnaire clinical summary score¶ | 56.3±20.7 | 57.5±19.1 |
| HCMSQ shortness-of-breath score‖ | 6.0±3.2 | 5.6±3.2 |

* Plus–minus values are means ±SD. HCM denotes hypertrophic cardiomyopathy, and HCMSQ Hypertrophic Cardiomyopathy Symptom Questionnaire.
† Race and ethnic group were reported by the patient. Collection of ethnic-group information was not allowed in all countries.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Patients who underwent myectomy or alcohol septal ablation were reported as having a history of septal reduction therapy.
¶ Scores range from 0 to 100, with higher scores indicating fewer symptoms and better physical functioning.
‖ Scores range from 0 to 18, with higher scores indicating more frequent shortness of breath.

**Table 2. Primary and Secondary Efficacy End Points at Week 48 in the Randomized Population.**

| End Point | Mavacamten (N=289) | Placebo (N=291) | Difference (95% CI)* |
|---|---|---|---|
| **Primary efficacy end points†** | | | |
| Change in peak oxygen uptake — ml/kg/min§ | | | |
| Least-squares mean (95% CI) | 0.52 (0.09 to 0.95) | 0.05 (–0.38 to 0.47) | 0.47 (–0.03 to 0.98)‡ |
| Change in KCCQ-CSS | | | |
| Least-squares mean (95% CI) | 13.1 (10.7 to 15.5) | 10.4 (8.0 to 12.8) | 2.7 (–0.1 to 5.6)‡ |
| **Secondary efficacy end points** | | | |
| Change in the slope of minute ventilation divided by carbon dioxide production¶ | | | |
| Least-squares mean (95% CI) | –0.64 (–1.84 to 0.55) | 0.16 (–1.02 to 1.34) | –0.81 (–2.21 to 0.60) |
| Change in NT-proBNP level‖ | | | |
| Geometric mean ratio of level at wk 48 to level at baseline (% coefficient of variation) | 0.42 (5.84) | 1.02 (5.66) | 0.41 (0.36 to 0.47) |
| 95% CI | 0.37 to 0.47 | 0.91 to 1.13 | |
| Improvement of at least one NYHA functional class level | | | |
| No. of patients (%) | 105 (36.3) | 92 (31.6) | 5.0 (–2.3 to 12.2)** |
| Change in HCMSQ shortness-of-breath score | | | |
| Least-squares mean (95% CI) | –1.8 (–2.2 to –1.4) | –1.1 (–1.5 to –0.7) | –0.7 (–1.2 to –0.2) |

* Values are the between-group difference in least-squares means for all end points except for change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, which is shown as the geometric mean ratio of the mavacamten group as compared with the placebo group, and improvement of at least one New York Heart Association (NYHA) functional class level, which is shown as the risk difference.

† Missing values for the two primary efficacy end points at week 48 were imputed with the use of the multiple imputation approach outlined in the statistical analysis plan and in the Supplementary Appendix. The estimated least-squares means and differences with 95% confidence intervals were derived from an analysis of covariance model, with trial group, stratification factors (NYHA class [II or III], type of exercise testing [treadmill or exercise bicycle], and treatment with beta-blockers [yes or no] at baseline), and baseline value as covariates.

‡ P=0.06 for the change in the 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and P=0.07 for the change in peak oxygen uptake. To show statistical significance, a P value of less than 0.04 was required for the change in KCCQ-CSS and a P value of less than 0.01 was required for peak oxygen uptake. Neither objective was met, and the graphical testing plan was stopped. No further P values are provided. The graphical testing plan is shown in Figure S2.

§ Peak oxygen uptake was measured during cardiopulmonary exercise testing, and higher numbers represent better functional capacity.

¶ The slope of minute ventilation divided by carbon dioxide production is a measure of ventilatory efficiency. A higher slope value indicates poorer outcomes.

‖ NT-proBNP level has a right-skewed distribution and is summarized with the use of the ratio of the geometric mean at week 48 to the geometric mean at baseline. Values above 1.0 indicate an increase from baseline, and values below 1.0 indicate a decrease from baseline. Elevated levels indicate a worsening condition.

** The risk difference and 95% confidence interval were calculated on the basis of the Miettinen–Nurminen method and stratified according to NYHA class (II or III), type of exercise testing (treadmill or exercise bicycle), and treatment with beta-blockers (yes or no) at baseline.

events and other safety data are shown in Table 3 and Table S5. A total of 42 patients (14.6%) in the mavacamten group and 15 (5.2%) in the placebo group had adverse events that occurred during treatment and resulted in interruption of the regimen, and 15 patients (5.2%) and 8 patients (2.8%), respectively, had adverse events that resulted in permanent discontinuation of the regimen. Serious adverse events involving congestive heart failure and atrial tachyarrhythmias (fibrillation or flutter) occurred in 19 patients (6.6%) and 12 patients (4.2%), respectively, in the mavacamten group and in 5 patients (1.7%) and 10 patients (3.4%), respectively, in the placebo group.

A left ventricular ejection fraction of less than 50% occurred in 62 patients (21.5%) assigned to receive mavacamten and 5 patients (1.7%) assigned to receive placebo, whereas a left ventricular ejection fraction of 30% or lower was observed in 7 patients (2.4%) in the mavacamten group and none in the placebo group. During the placebo-controlled period, the left ventricular ejection fraction returned to 50% or higher after interruption

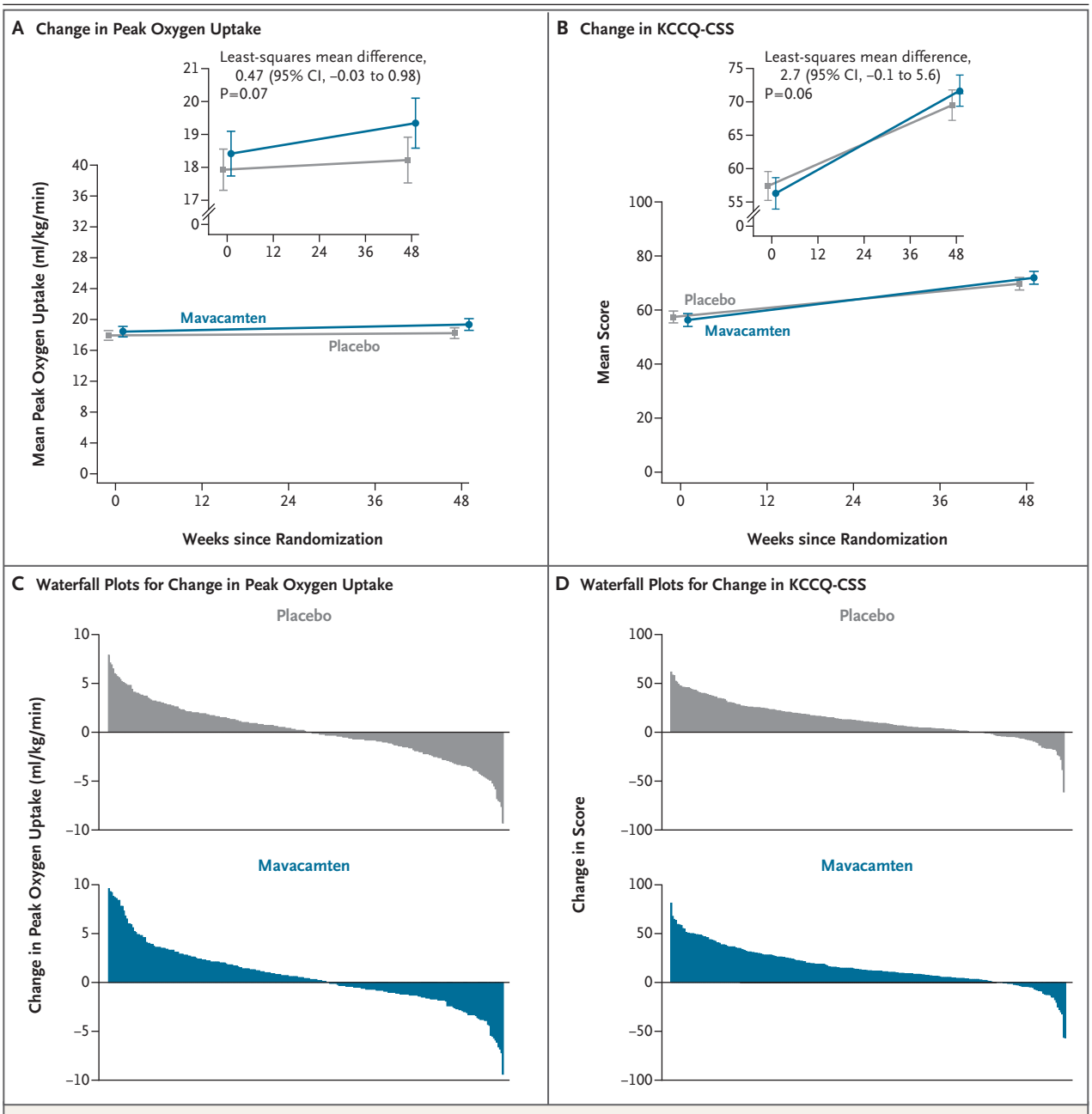


**Figure 1. Primary End Points.**

Panels A and B show the change from baseline to week 48 in the mean peak oxygen uptake and the mean 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), respectively. The KCCQ-CSS ranges from 0 to 100, with higher scores indicating better health status. Estimates were derived with an analysis of covariance model, with trial group, stratification factors (New York Heart Association functional class [II or III], type of exercise testing [treadmill or exercise bicycle], and beta-blocker treatment [yes or no]), and baseline value as covariates. I bars denote 95% confidence intervals. The insets show the same data on an expanded y axis. Panels C and D show waterfall plots of the change from baseline to week 48 in the peak oxygen uptake and the KCCQ-CSS, respectively, for each patient.

of the trial regimen in all but 3 patients (1 patient withdrew consent after the week 16 visit when the left ventricular ejection fraction was 45% with no follow-up echocardiography, and 2 patients had values of 42% and 46% at week 48 with no additional follow-up). A total of 5 of 19 patients (26%)

in the mavacamten group had congestive heart failure close to the time when the left ventricular ejection fraction was less than 50%, which returned to 50% or higher after interruption of mavacamten. In the mavacamten group, patients whose left ventricular ejection fraction decreased to less than 50% had a baseline value (65.2±4.9%) similar to those with a preserved ejection fraction during follow-up (65.9±3.7%).

## DISCUSSION

The ODYSSEY-HCM trial was an international trial conducted at 201 HCM centers and was designed

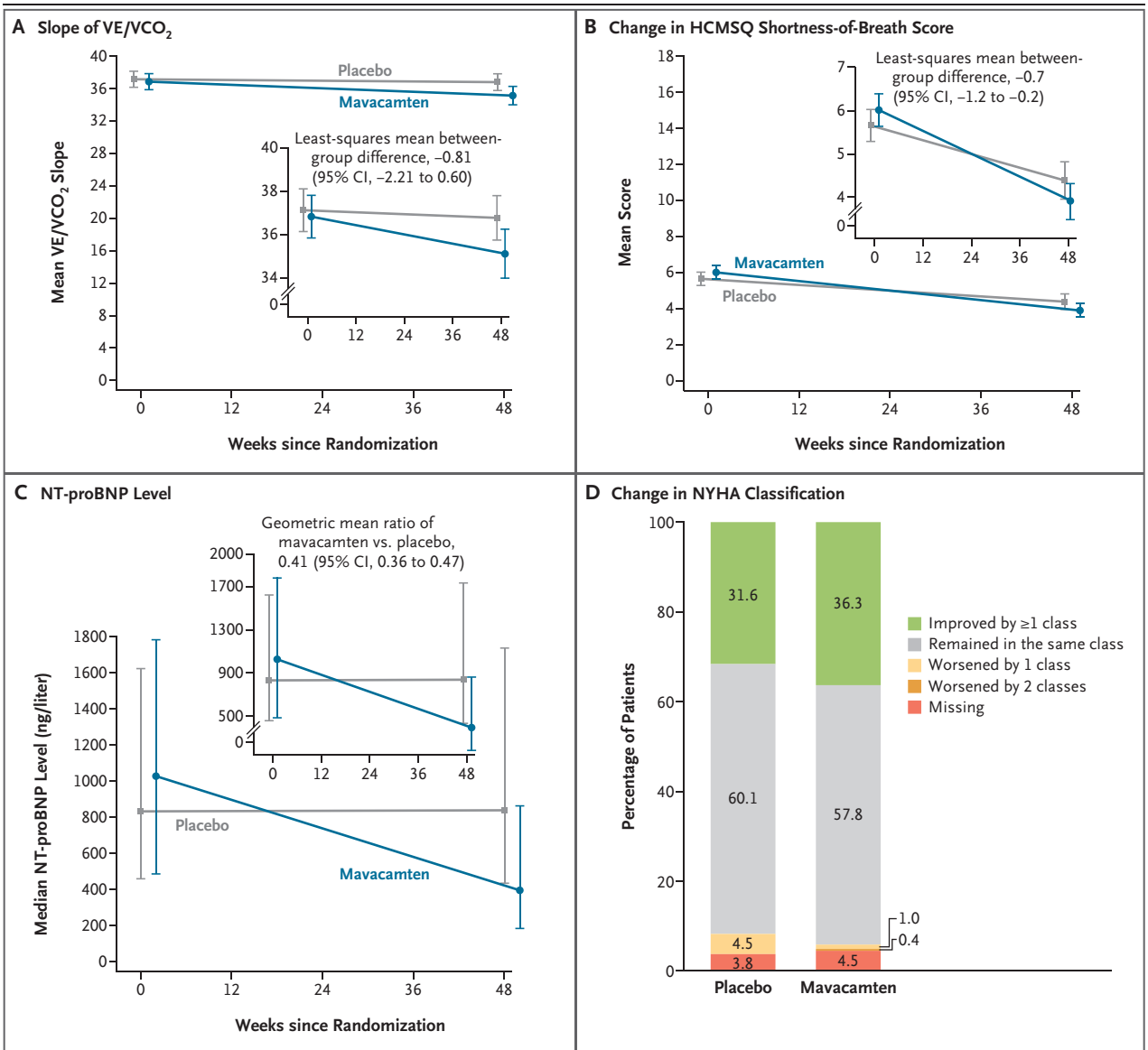


**Figure 2. Key Secondary End Points.**

Panels A and B show the change from baseline to week 48 in the mean slope of minute ventilation (VE) divided by carbon dioxide production ($VCO_2$) and the mean Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) score on the shortness-of-breath domain, respectively. HCMSQ shortness-of-breath scores range from 0 to 18, with higher scores indicating more frequent shortness of breath. I bars denote 95% confidence intervals. Panel C shows the change from baseline to week 48 in the median N-terminal pro–B-type natriuretic peptide (NT-proBNP) level. I bars denote interquartile ranges. Insets in Panels A, B, and C show the same data on an expanded y axis. Panel D shows the percentage of patients with a change from baseline to week 48 in New York Heart Association (NYHA) functional class.

**Table 3. Summary of Adverse Events.***

| Adverse Event | Mavacamten (N=288) | Placebo (N=290) |
|---|---|---|
| | *no. of patients (%)* | |
| **Adverse events during the treatment period** | | |
| Any adverse event | 250 (86.8) | 239 (82.4) |
| Adverse event leading to interruption of mavacamten or placebo | 42 (14.6) | 15 (5.2) |
| Adverse event leading to discontinuation of mavacamten or placebo | 15 (5.2) | 8 (2.8) |
| Adverse event leading to death | 1 (0.3) | 1 (0.3) |
| **Serious adverse events** | | |
| Any serious adverse event | 55 (19.1) | 44 (15.2) |
| Cardiac disorders | 31 (10.8) | 21 (7.2) |
| Congestive heart failure | 19 (6.6) | 5 (1.7) |
| Atrial tachyarrhythmia | 12 (4.2) | 10 (3.4) |
| Ventricular tachyarrhythmia | 3 (1.0) | 1 (0.3) |
| Coronary artery disease | 2 (0.7) | 2 (0.7) |
| Cardiac conduction disorder | 1 (0.3) | 3 (1.0) |
| Cardiac arrest | 1 (0.3)† | 0 |
| Cardiogenic shock | 1 (0.3)† | 0 |
| Palpitations | 0 | 2 (0.7) |
| Vascular disorder | 1 (0.3) | 3 (1.0) |
| Phlebitis | 1 (0.3) | 0 |
| Hypertension | 0 | 2 (0.7) |
| Raynaud's phenomenon | 0 | 1 (0.3) |
| Nervous system disorder | 9 (3.1) | 6 (2.1) |
| Cerebral infarction | 2 (0.7) | 0 |
| Stroke | 2 (0.7) | 1 (0.3) |
| Syncope | 2 (0.7) | 2 (0.7) |
| Cerebral hemorrhage | 1 (0.3) | 0 |
| Seizure | 1 (0.3) | 1 (0.3) |
| Transient ischemic attack | 1 (0.3) | 1 (0.3) |
| Ischemic stroke | 0 | 1 (0.3) |
| **Prespecified adverse events of clinical interest** | | |
| Permanent discontinuation of mavacamten or placebo owing to left ventricular ejection fraction ≤30% | 7 (2.4) | 0 |
| Left ventricular ejection fraction <50% | 62 (21.5) | 5 (1.7) |
| Major adverse cardiac events plus‡ | 27 (9.4) | 17 (5.9) |

* Data are shown for all patients who underwent randomization and received at least one dose of the trial regimen.
† Additional details are provided in the Supplementary Appendix.
‡ Major adverse cardiac events plus include death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, hospitalization for arrhythmias, or appropriate implantable cardioverter–defibrillator therapy.

to determine whether mavacamten improves functional capacity and patient-reported health status in patients with symptomatic nonobstructive HCM. The trial showed that mavacamten did not lead to a significantly greater improvement in exercise capacity (as assessed by peak oxygen uptake) or a significantly greater decrease in symptoms (as assessed by the KCCQ-CSS) than placebo at 48 weeks. Interruptions and discontinuations in the trial regimen along with reductions in left ventricular ejection fraction to levels below prespecified thresholds occurred more frequently among patients assigned to the mavacamten group than those assigned to the placebo group.

Patient age, body-mass index, and background HCM therapy in this trial were broadly similar to those in previous phase 3 trials involving patients with obstructive HCM.[7-9,22] However, patients enrolled in the current trial had a higher incidence of familial HCM, a longer duration of symptomatic HCM, a higher prevalence of atrial fibrillation, and a lower KCCQ-CSS. Before randomization, all the patients had a preserved left ventricular ejection fraction with no resting or latent dynamic left ventricular outflow tract obstruction. Because of the advanced disease burden, patients also had diastolic dysfunction as evidenced by an increased left atrial volume index and ratio of the peak early mitral inflow velocity to the peak early diastolic mitral annular velocity and elevated NT-proBNP and troponin I levels.

Among all patients with HCM, the prevalence of nonobstructive HCM is 30 to 50%, with current pharmacotherapies showing variable efficacy and adverse effects.[1,2,23,24] In previous studies involving patients with symptomatic obstructive HCM, mavacamten decreased left ventricular outflow tract obstruction, improved exercise capacity, reduced eligibility for septal reduction therapy, and was associated with favorable effects on short- and long-term cardiac remodeling.[7-19] By targeting sarcomeric dysfunction, mavacamten was hypothesized to mitigate hypercontractility and improve left ventricular efficiency, thus extending the benefits beyond relief of left ventricular outflow tract obstruction. The MAVERICK-HCM trial showed significant improvements in NT-proBNP and troponin I levels, with a post hoc analysis identifying a subpopulation of patients with nonobstructive HCM who had a more favorable change from baseline in peak oxygen uptake and KCCQ-CSS with mavacamten than with placebo.[20] These results provided the rationale for conducting the current phase 3 ODYSSEY-HCM trial.

The lack of a difference between the mavacamten and placebo groups in peak oxygen uptake or KCCQ-CSS in the current trial differs from what has been reported in previous studies involving patients with obstructive HCM. This difference in study findings suggests that dynamic left ventricular outflow tract obstruction may have a greater effect on exercise capacity and patient-reported health status in patients with obstructive HCM than in patients with nonobstructive HCM. In patients with nonobstructive HCM without left ventricular outflow obstruction, the plausible dominant contributors to symptoms and impaired exercise capacity are the presence of subendocardial ischemia, diastolic dysfunction, left ventricular noncompliance, and aberrant cellular energetics. In that context, cardiac myosin inhibitors may have a limited effect on improving hemodynamics or energy efficiency, thereby reducing the likelihood of clinically meaningful improvements in exercise capacity or patient-reported health status. Furthermore, treatment with cardiac myosin inhibitors could result in the inhibition of an overactive sarcomere without the compensatory benefit of alleviating left ventricular outflow obstruction. In addition, the results of the current trial suggest that favorable changes in biomarkers may not reliably predict clinical efficacy in patients with nonobstructive HCM.

Patient-reported outcomes are increasingly recommended by professional medical society guidelines and major health authorities (the Food and Drug Administration and the European Medicines Agency) in evaluating therapies in the management of HCM.[1,3,25] In the current trial, patient-reported outcomes (the KCCQ-CSS and the HCMSQ) improved not only in the mavacamten group but also in the placebo group, which may reflect improved and intensified background HCM care during the clinical trial, including recognition and treatment of arrhythmias.

The trial required echocardiographic assessment of left ventricular ejection fraction by a core laboratory to guide trial-participation eligibility, dose adjustment, and decisions regarding interruption and discontinuation of the trial regimen. Because left ventricular outflow tract obstruction is often latent, provocative maneuvers performed during resting and stress echocardiography were used to identify patients with truly nonobstructive

HCM,[26-28] and patients who underwent randomization in the trial met rigorous clinical criteria for the diagnosis of nonobstructive HCM.[1-3] As a result, the current trial population was similar to those reported in other HCM trials and dissimilar to patients with heart failure with preserved ejection fraction.[7-9,22]

The dose administration of mavacamten was developed to provide an effective balance between efficacy and safety. This approach was based on pharmacokinetic and pharmacodynamic modeling that used left ventricular ejection fraction measurements obtained monthly to determine the appropriate dose. At week 48, the percentage of patients with an interruption of the trial regimen owing to a left ventricular ejection fraction of less than 50% or a discontinuation of the trial regimen owing to a left ventricular ejection fraction of 30% or less was higher in the mavacamten group than in the placebo group, which is consistent with the inhibitory effect of mavacamten on cardiac myosin. In the current trial, almost half the patients (49.1%) in the mavacamten group were receiving the higher doses (10 mg and 15 mg) of the drug, which is a higher percentage of patients than in the previous obstructive HCM trials.[7-9] Whether this aggressive dose-adjustment scheme affected the incidence of reductions in left ventricular ejection fraction is uncertain. In all but three patients with an interruption of the trial regimen, the left ventricular ejection fraction returned to 50% or higher. The percentage of patients with atrial fibrillation or atrial flutter appeared to be similar in the mavacamten and placebo groups.

This trial had limitations. The majority of the patients were White, and the results may not be generalizable to other populations. Some patients with heart failure with preserved ejection fraction may have been included in the trial because of overlapping features with nonobstructive HCM despite stringent entry criteria. A total of 8.3% of the patients discontinued the assigned trial regimen, which may have affected the trial outcome. In addition, the current trial was conducted for 48 weeks and did not evaluate longer-term outcomes.

Among patients with nonobstructive HCM, mavacamten did not result in a significantly greater improvement in exercise capacity measured by peak oxygen uptake or a significantly greater decrease in symptoms as assessed by the KCCQ-CSS than placebo.

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## REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503-626.
2. Maron BJ, Desai MY, Nishimura RA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2022;79:372-89.
3. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2024;149(23):e1239-e1311.
4. Hutt E, Desai MY. Medical treatment strategies for hypertrophic cardiomyopathy. Am J Cardiol 2024;212S:S33-S41.
5. Desai MY, Owens A, Wang A. Medical therapies for hypertrophic cardiomyopathy: current state of the art. Prog Cardiovasc Dis 2023;80:32-7.
6. Gentry JL III, Mentz RJ, Hurdle M, Wang A. Ranolazine for treatment of angina or dyspnea in hypertrophic cardiomy-

opathy patients (RHYME). J Am Coll Cardiol 2016;68:1815-7.
**7.** Desai MY, Owens A, Geske JB, et al. Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol 2022;80:95-108.
**8.** Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69.
**9.** Tian Z, Li L, Li X, et al. Effect of mavacamten on Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy: the EXPLORER-CN randomized clinical trial. JAMA Cardiol 2023;8:957-65.
**10.** Cremer PC, Geske JB, Owens A, et al. Myosin inhibition and left ventricular diastolic function in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: insights from the VALOR-HCM study. Circ Cardiovasc Imaging 2022;15(12):e014986.
**11.** Desai MY, Owens A, Geske JB, et al. Dose-blinded myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: outcomes through 32 weeks. Circulation 2023;147:850-63.
**12.** Desai MY, Owens A, Wolski K, et al. Mavacamten in patients with hypertrophic cardiomyopathy referred for septal reduction: week 56 results from the VALOR-HCM Randomized Clinical Trial. JAMA Cardiol 2023;8:968-77.
**13.** Hegde SM, Lester SJ, Solomon SD, et al. Effect of mavacamten on echocardiographic features in symptomatic patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2021;78:2518-32.
**14.** Rader F, Oręziak A, Choudhury L, et al. Mavacamten treatment for symptomatic obstructive hypertrophic cardiomyopathy: interim results from the MAVA-LTE study, EXPLORER-LTE cohort. JACC Heart Fail 2024;12:164-77.
**15.** Spertus JA, Fine JT, Elliott P, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2467-75.
**16.** Desai MY, Okushi Y, Gaballa A, et al. Serial changes in ventricular strain in symptomatic obstructive hypertrophic cardiomyopathy treated with mavacamten: insights from the VALOR-HCM trial. Circ Cardiovasc Imaging 2024(9);17:e017185.
**17.** Desai MY, Owens A, Wolski K, et al. Mavacamten in obstructive hypertrophic cardiomyopathy patients referred for septal reduction: health status analysis through week 56 in VALOR-HCM Trial. J Am Coll Cardiol 2024;84:1041-5.
**18.** Desai MY, Okushi Y, Wolski K, et al. Mavacamten-associated temporal changes in left atrial function in obstructive HCM: insights from the VALOR-HCM trial. JACC Cardiovasc Imaging 2025;18:251-62.
**19.** Garcia-Pavia P, Oręziak A, Masri A, et al. Long-term effect of mavacamten in obstructive hypertrophic cardiomyopathy. Eur Heart J 2024;45:5071-83.
**20.** Ho CY, Mealiffe ME, Bach RG, et al. Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2020;75:2649-60 .
**21.** Desai MY, Nissen SE, Abraham T, et al. Mavacamten in symptomatic nonobstructive hypertrophic cardiomyopathy: design, rationale, and baseline characteristics of ODYSSEY-HCM. JACC Heart Fail 2025;13:358-70.
**22.** Maron MS, Masri A, Nassif ME, et al. Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. N Engl J Med 2024;390:1849-61.
**23.** Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2020; 76(25):e159-e240.
**24.** Stern JA, Markova S, Ueda Y, et al. A small molecule inhibitor of sarcomere contractility acutely relieves left ventricular outflow tract obstruction in feline hypertrophic cardiomyopathy. PLoS One 2016; 11(12):e0168407.
**25.** Maron BJ, Desai MY, Nishimura RA, et al. Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2022;79:390-414.
**26.** Desai MY, Bhonsale A, Patel P, et al. Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. JACC Cardiovasc Imaging 2014;7:26-36.
**27.** Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006; 114:2232-9.
**28.** Cui H, Schaff HV, Nishimura RA, Dearani JA, Geske JB, Ommen SR. Latent outflow tract obstruction in hypertrophic cardiomyopathy: clinical characteristics and outcomes of septal myectomy. J Thorac Cardiovasc Surg 2022;164(6):1863-1869.e1.