Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients with Obstructive Hypertrophic Cardiomyopathy

Brief title: Echo Results From EXPLORER-HCM

Sheila M. Hegde, MD[a]; Steven J. Lester, MD[b]; Scott D. Solomon, MD[a]; Michelle Michels, MD[c]; Perry M. Elliott, MD[d]; Sherif F. Nagueh, MD[e]; Lubna Choudhury, MD[f]; David Zemanek, MD[g]; Donna R. Zwas, MD, MPH[h]; Daniel Jacoby, MD[i]; Andrew Wang, MD[j]; Carolyn Y. Ho, MD[a]; Wanying Li, PhD[k]; Amy J. Sehnert, MD[k]; Iacopo Olivotto, MD[l]; Theodore P. Abraham, MD[m]

From the [a]Division of Cardiovascular Medicine, Brigham and Wome n's Hospital, Boston, MA, USA; [b]Department of Cardiovascular Diseases, Mayo Clinic, Phoenix, AZ, USA; [c]Department of Cardiology, Thoraxcenter, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; [d]Institute of Cardiovascular Science, University College London, London, UK; [e]Methodist DeBakey Heart and Vascular Center, Houston, TX, USA; [f]Bluhm Cardiovascular Institute, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [g]2nd Department of Internal Medicine – Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [h]Heart Institute, Hadassah University Medical Center, Jerusalem, Israel; [i]Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University, New Haven, CT, USA; [j]Duke University School of Medicine, Durham, NC, USA; [k]MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, CA, USA; [l]Cardiomyopathy Unit, Azienda Ospedaliera Universitaria Careggi and the University of Florence, Florence, Italy; and the [m]UCSF HCM Center of Excellence, University of California San Francisco, San Francisco, CA, USA.

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Address for correspondence:
Sheila M. Hegde, MD
Division of Cardiovascular Medicine,
Brigham and Women's Hospital
75 Francis St.
Boston, MA 02115
Phone: 857-307-4000
shegde@bwh.harvard.edu

Tweet: Mavacamten therapy improves echocardiographic measures of cardiac structure and function in patients with obstructive HCM in the EXPLORER-HCM study.

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Abstract
Background: EXPLORER-HCM demonstrated that mavacamten, a cardiac myosin inhibitor, improves symptoms, exercise capacity, and left ventricular (LV) outflow tract (LVOT) obstruction in patients with obstructive hypertrophic cardiomyopathy (oHCM).
Objectives: To evaluate mavacamten's effect on measures of cardiac structure and function and its association with changes in other clinical measures.
Methods: Key echocardiographic parameters from serial echocardiograms over 30 weeks from 251 symptomatic oHCM patients (mavacamten [n=123], placebo [n=128]) were assessed in a core laboratory.
Results: More patients on mavacamten (80.9%; n=76/94) versus placebo (34.0%; n=33/97) showed complete resolution of mitral valve systolic anterior motion (SAM) after 30 weeks (difference, 46.8%; p<0.0001). Mavacamten also improved measures of diastolic function versus placebo, including left atrial volume index (LAVI; mean±standard deviation baseline, 40±12 vs 41±14 mL/m^2; mean [95% confidence interval] change from baseline of –7.5 [–9.0, –6.1] vs –0.09 [–1.6, 1.5] mL/m^2; p<0.0001) and lateral E/e' (baseline, 15±6 vs 15±8; change of –3.8 [–4.7, –2.8] vs 0.04 [–0.9, 1.0]; p<0.0001). Among mavacamten-treated patients, improvement in resting, Valsalva, and post-exercise LVOT gradients, LAVI, and lateral E/e' was associated with reduction in N-terminal pro B-type natriuretic peptide (NT-proBNP; p≤0.03 for all). Reduction in LAVI was associated with improved peak exercise oxygen consumption (p=0.04).
Conclusions: Mavacamten significantly improved measures of LV diastolic function and SAM. Improvement in LVOT obstruction, LAVI, and E/e'was associated with reduction in a biomarker of myocardial wall stress (NT-proBNP). These findings demonstrate improvement in important markers of the pathophysiology of oHCM with mavacamten.

Condensed abstract
The phase 3 EXPLORER-HCM study demonstrated the efficacy and safety of mavacamten, a cardiac myosin inhibitor, in symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Serial echocardiographic analyses investigated the effects of 30 weeks of mavacamten treatment on focused measures of cardiac structure and function. Compared with placebo, mavacamten significantly improved measures of left ventricular (LV) diastolic function (left atrial volume index, e', and E/e') and improved mitral valve systolic anterior motion (SAM). Changes in NT-proBNP were associated with changes in LV outflow tract gradients and other parameters over 30 weeks. These findings suggest mavacamten favorably impacts adverse pathophysiologic processes in oHCM.

Keywords
diastolic function, hypertrophic cardiomyopathy, mavacamten, N-terminal pro B-type natriuretic peptide

Abbreviations and acronyms
e' = early diastolic mitral annular velocity
E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity
HCM = hypertrophic cardiomyopathy
LA = left atrial
LAVI = left atrial volume index
LV = left ventricular

LVMI = left ventricular mass index
LVOT = left ventricular outflow tract
NT-proBNP = N-terminal pro B-type natriuretic peptide
SAM = systolic anterior motion

Clinical trial: NCT03470545

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction, and impaired relaxation leading to progressive symptoms (1,2). Many patients develop dynamic LV outflow tract (LVOT) obstruction (obstructive HCM), an important prognostic factor in these patients associated with an increased risk of disease progression, including heart failure, atrial fibrillation, and death (3,4). Echocardiography is essential to the diagnosis and monitoring of HCM (2,5). It is routinely used to assess structural and functional cardiac abnormalities, including LVOT gradient, degree of hypertrophy, systolic and diastolic function, as well as the response to therapy in this patient population. Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide for symptom relief; however, these recommendations are based on non-randomized studies and limited data (2,5). Furthermore, no available agent has been shown to improve the natural history of the disease or to convincingly improve diastolic function in HCM, and none target the underlying pathophysiology of the disease (6,7).

Mavacamten, a novel, small molecule inhibitor of cardiac myosin reduces excess actin–myosin cross-bridging by decreasing myosin adenosine triphosphatase activity of the cardiac myosin heavy chain, which results in decreased sarcomere power and force generation, or decreased contractility (8-10). Preclinical data have shown mavacamten reduced contractility, resolved mitral valve systolic anterior motion (SAM), and reduced LVOT gradients and if given earlier in life, there was attenuation of LV hypertrophy, cardiomyocyte disarray, and myocardial fibrosis (9,10). A phase 2 non-randomized clinical study demonstrated symptom improvement and LVOT gradient reduction in 21 symptomatic obstructive HCM patients treated with

mavacamten (11). These findings were confirmed in the randomized, double-blind, placebo-controlled, phase 3 EXPLORER-HCM study, which demonstrated significant reduction in LVOT gradients, improved exercise capacity, improved health status, and decreased symptom burden without clinically significant changes in LV ejection fraction after 30 weeks of mavacamten treatment (12,13). Significant reductions in LV mass index, absolute intracellular myocardial mass index, maximum LV wall thickness, and left atrial volume index (LAVI) with mavacamten were demonstrated in a cardiac magnetic resonance imaging substudy of 35 EXPLORER-HCM subjects (14).

The objective of this secondary analysis of EXPLORER-HCM was to evaluate the effect of mavacamten on key echocardiographic features of obstructive HCM and how these changes relate to its observed benefits in cardiac biomarkers and exercise capacity.

Methods

Study design and patient population

EXPLORER-HCM (ClinicalTrials.gov Identifier: NCT03470545) was a multicenter, double-blind, placebo-controlled, randomized, phase 3 study in patients with symptomatic obstructive HCM. Details of the study design and primary efficacy and safety results have been published previously (12,15). As described, eligible patients were at least 18 years old with obstructive HCM with unexplained LVH; peak LVOT gradient ≥ 50 mmHg at rest, with Valsalva maneuver, or during exercise; LV ejection fraction ≥ 55%; and New York Heart Association class II-III symptoms. Subjects were allowed to continue standard medical therapy except for disopyramide. The protocol was approved by institutional review boards at all sites, and all patients provided informed consent.

Procedures and assessments

Resting echocardiograms were performed at screening, day 1, and weeks 4, 6, 12, 18, 22, 26, 30 (end of treatment), and 38 (end of study). Post-exercise echocardiograms were performed at screening and week 30. All echocardiograms were acquired according to a detailed acquisition protocol by certified sonographers at each site. Images were assessed by the Cardiovascular Imaging Core Laboratory (Brigham and Women's Hospital, Boston, MA) according to American Society of Echocardiography recommendations (16). Core laboratory personnel performing the measurements were blinded to study treatment. Chamber dimensions included LV end systolic and end diastolic dimensions, LAVI, maximum LV wall thickness, interventricular septal wall thickness, and inferolateral wall thickness. LV ejection fraction was based on the modified Simpson's method. Maximum LV wall thickness at baseline was measured as the greatest wall thickness visualized in the parasternal long- and short-axis views. LV mass index (LVMI) was calculated from linear dimensions and indexed to height$^{2.7}$ per guidelines, though we acknowledge that accurate assessment of LVMI using echocardiography is limited by the atypical morphology seen in obstructive HCM (16). Markers related to ventricular filling included lateral and septal early diastolic mitral annular velocity (lateral e'and septal e', respectively), ratio between early mitral inflow velocity and lateral mitral annular early diastolic velocity (lateral E/e'), and ratio between early mitral inflow velocity and septal mitral annular early diastolic velocity (septal E/e'). LVOT gradient assessments included instantaneous peak LVOT gradient at rest, provoked peak LVOT gradient with the Valsalva maneuver, and instantaneous peak LVOT gradient immediately following exercise. Sonographers were instructed to sweep the angle of interrogation from the left atrium to the LVOT to aid the ability to distinguish between mitral regurgitation and LVOT Doppler profiles. The presence of mitral

valve SAM and mitral regurgitation was assessed as either present or absent. Complete resolution of SAM was defined as those who were identified with SAM present at baseline and absent at week 30. LVOT gradients and LV ejection fraction at rest were assessed at each study visit to allow for drug titration, whereas a more thorough echocardiographic assessment was performed at baseline, week 18, and week 30.

Statistical analyses

In this exploratory analysis, baseline values of the echocardiographic parameters, the last non-missing measurements prior to the first dose of the study drug, were summarized using descriptive statistics. For the analysis comparing the changes from baseline in continuous echocardiographic measurements (e.g., LAVI, e', and E/e') between treatment arms, least-squares means, 95% confidence intervals (CIs), and p-values were calculated using a mixed model for repeated measurements for data up to week 30, with treatment group (mavacamten vs placebo), time points, the interaction between treatment and time point, corresponding baseline value, and stratification factors (beta-blocker use, New York Heart Association class, and ergometer type) as fixed effects and patient as random effect. The categorical variables (absence of SAM or mitral regurgitation) were analyzed using the Cochran–Mantel–Haenszel test stratified by New York Heart Association class, beta-blocker use, and ergometer type.

Additional exploratory, post hoc analyses were conducted to assess the relationship between the baseline LVOT Valsalva gradients and mavacamten treatment effect on echocardiographic parameters (LAVI, e', and E/e'). The linear model was fitted on the change in echocardiographic parameter of interest with its baseline value, baseline LVOT Valsalva gradient, treatment, interaction between treatment, and those 2 baseline variables as explanatory variables.

The relationship between the changes from baseline to week 30 in echocardiographic parameters, LVOT gradients, and other clinical parameters was explored under the effect of mavacamten treatment. Simple linear regression was fitted by treatment group on the change in log-2 transformed cardiac biomarkers (N-terminal pro B-type natriuretic peptide [NT-proBNP] and high-sensitivity cardiac troponin I) and change in peak oxygen assumption, separately, with the change in each individual echocardiographic parameter (LVOT gradient, LAVI, E/e', e') as the explanatory variable. The fitted lines were overlaid with scatter plots. Note, the cardiac biomarker data were analyzed on log-2 scale as the biomarker data showed a log-normal-like distribution.

Missing data were not imputed. P-values <0.05 were considered statistically significant. P-values and 95% confidence intervals presented in this report have not been adjusted for multiplicity due to the exploratory nature of the analyses. SAS version 9.4 or higher was used for all statistical analyses.

Results

Of the 251 patients with symptomatic obstructive HCM enrolled in EXPLORER-HCM, 123 (49%) received mavacamten and 128 (51%) received placebo. Baseline demographics have been described previously (12). The mean age was 58.5 years, 41% of patients were female, and 92% were on background beta-blocker or calcium channel blocker therapy. Nine subjects (7 mavacamten, 2 placebo) experienced a decline in LV ejection fraction (median 48%, [range 35-49%]), 7 subjects (4 mavacamten, 3 placebo) discontinued treatment, and no subjects were lost to follow-up in the first 30 weeks (**Supplemental Tables 1,2**). In those who experienced a LV ejection fraction decline, LV function recovered with protocol-driven temporary treatment

discontinuation; all subjects resumed mavacamten dosing at the same or lower dose per protocol and completed the study.

Baseline echocardiography demonstrated typical features of HCM with increased maximum LV wall thickness, reduced tissue Doppler indices of mitral annular e' velocities, elevated E/e', and mild LA enlargement (**Table 1**). Patients had elevated LVOT gradients (rest, Valsalva, and post-exercise), consistent with the study entry criteria.

Physiological changes

For patients with mitral valve SAM at baseline, treatment with mavacamten for 30 weeks led to complete resolution of SAM in 80.9% of patients (n = 76/94) compared with 34.0% of patients receiving placebo (n = 33/97), a difference (95% CI) of 46.8% (34.5 to 59.2); p <0.0001. For patients with mitral regurgitation at baseline, 9.0% (n = 10/111) of patients in the mavacamten group had complete resolution of mitral regurgitation compared with no patients in the placebo group (difference [95% CI] of 9.0% [3.7 to 14.3]; p <0.001). LV ejection fraction decreased compared with placebo (mean [standard deviation (SD)] baseline of 74 ± 6% vs 74 ± 6%; mean [95% CI] change from baseline of –3.9% [–5.3 to –2.5] vs –0.01% [–1.2 to 1.2]; p <0.0001) (12).

Patients treated with mavacamten also had significant improvement in markers of LV diastolic function compared with placebo (**Figures 1** and **2**; **Table 2**). The mean (95% CI) decrease from baseline in LAVI at week 30 was –7.5 (–9.0 to –6.1) mL/m^2 with mavacamten versus –0.1 (–1.6 to 1.5) mL/m^2 with placebo (p <0.0001). Mavacamten was also associated with improvement in septal e' (mean increase of 0.7 [0.4 to 1.0] vs –0.02 [–0.2 to 0.2] cm/s; p <0.0001), lateral e' (mean increase of 1.6 [1.2 to 1.9] vs 0.2 [–0.2 to 0.5] cm/s; p <0.0001), septal E/e' (mean decrease of –3.5 [–4.7 to –2.4] vs –0.3 [–1.1 to 0.6]; p <0.0001), and lateral E/e'

(mean decrease of –3.8 [–4.7 to –2.8] vs 0.04 [–0.9 to 1.0]; p <0.0001). Significant improvements were detectable as early as week 18 in LAVI, septal e', lateral e', septal E/e', and lateral E/e' and persisted through week 30 (**Figure 1**). No significant changes were seen in mitral inflow E and A velocities. Reduction in LVOT gradients (rest, Valsalva), LAVI, and E/e' were similar in subjects treated with mavacamten with and without complete resolution of mitral valve SAM (**Supplemental Table 3**).

Structural changes

The LV end diastolic dimension did not significantly change after 30 weeks with mavacamten compared with placebo (mean±SD baseline of 40 ± 5 vs 41 ± 5 mm; mean [95% CI] decrease from baseline of –1.0 [–1.5 to –0.4] vs –0.3 [–0.9 to 0.3] mm; p = 0.05), whereas the LV end systolic dimension increased marginally (mean baseline of 23 ± 3 vs 24 ± 4 mm; mean change of 1.0 [0.2 to 1.8] vs –0.3 [–0.9 to 0.3] mm; p = 0.02; **Table 2**). Inferolateral wall thickness decreased compared with placebo (mean baseline of 12 ± 2 vs 11 ± 2 mm; mean change of –0.6 [–0.9 to –0.3] vs 0.3 [0.0 to 0.6] mm; p <0.0001; **Figure 1**; **Table 2**). Mavacamten did not significantly change interventricular septal thickness, while the placebo group demonstrated a significant increase in interventricular septal thickness (mean baseline of 17 ± 3 vs 17 ± 3 mm; mean change of 0.1 [–0.2 to 0.4] vs 1.4 [1.0 to 1.7] mm; p <0.0001).

Relationship of baseline LVOT gradients with treatment effects on echocardiographic parameters

A significant interaction between baseline LVOT gradients and the treatment effect on LAVI was present (p=0.03) such that patients with higher baseline LVOT Valsalva gradients demonstrated greater reductions (placebo-corrected) in LAVI after adjusting for baseline LAVI

and baseline LVOT Valsalva gradients. No significant interactions were seen between baseline LVOT gradients and changes in e' velocities or E/e' ratios.

Relationship of changes to biomarkers and exercise capacity

Significant associations between reduction in serum NT-proBNP level and several echocardiographic parameters of cardiac structure and function, including LVOT gradients (rest, Valsalva, and post-exercise), LAVI, E/e', and e' (**Table 3, Figure 3**) were seen in the mavacamten group. The reduction in resting LVOT gradient demonstrated the strongest association with reduction in NT-proBNP (mavacamten, ß = 0.02, 95% CI: 0.01 to 0.03; p <0.0001); this association was present in subjects with resting LVOT gradients ≥ 30 mmHg or those with only provokable LVOT gradients ≥ 50 mmHg (i.e. subjects with resting LVOT gradient <50 mmHg) (**Supplemental Table 4**). Also, reduction in LAVI significantly but weakly associated with reduction in serum cardiac troponin I (mavacamten, ß = 0.02, 95% CI: 0.00 to 0.05; p = 0.048) and with reduction in pVO2 (mavacamten, ß = -0.08, 95% CI: -0.15 to 0.00; p = 0.041) in patients treated with mavacamten (**Table 3**). No significant association was noted between troponin I or pVO2 and other echocardiographic parameters (resting, Valsalva, and post-exercise LVOT gradients, lateral e', and lateral E/e') (**Table 3, Figures S1 and S2**).

Discussion

This analysis of EXPLORER-HCM represents the largest serial assessment of echocardiographic parameters in a prospective, double-blind, placebo-controlled study in patients with obstructive HCM. Mavacamten treatment improved several key pathophysiologic features associated with obstructive HCM, thereby providing additional mechanistic insights into the improvement in exercise capacity and LVOT obstruction previously described (12). After 30 weeks of mavacamten treatment, most patients had complete resolution of mitral valve SAM, an

important element in dynamic LVOT obstruction. Mavacamten also improved markers of diastolic function, including LAVI, e', and E/e' ratio, with only mild reduction in LV systolic function (**Central Illustration**). Notably, reductions in key echocardiographic parameters (LVOT gradients, LAVI, and E/e') were associated with reductions in NT-proBNP, an important marker of cardiac wall stress with strong prognostic value (17,18).

The dynamic LVOT gradient is a key feature of obstructive HCM and is attributed to the presence of septal hypertrophy and/or mitral valve SAM. Mavacamten decreased LVOT gradients, and there was complete resolution of SAM in a majority of patients. While similar reductions in LVOT gradients, LAVI, and E/e' were observed in those with and without complete resolution of SAM, the improvement also seen in those without complete resolution may reflect the response to partial improvement in SAM. To the extent that changes in SAM may reflect changes in mitral regurgitation, partial improvement in SAM may be sufficient to improve LVOT hemodynamics. A combination of factors may have contributed to improvement in SAM with mavacamten treatment, including reduction in hypercontractility. Early animal models attribute the reduction in contractility with mavacamten to decreased sarcomere power and force generation by decreasing myosin adenosine triphosphatase activity in a dose-dependent manner (9,19,20). The marked improvement in LVOT gradients and SAM was achieved with only a 4% mean decrease in LV ejection fraction and no significant change in heart rate, such that it appears that modifying contractility dynamics without a significant chronotropic effect with mavacamten is sufficient to relieve LVOT obstruction. (12). Further studies are needed to better understand the effect of mavacamten on contractility dynamics and correlates in echocardiography.

Consistent with pre-clinical findings (19,20), mavacamten was associated with improved measures of diastolic function, including myocardial relaxation and compliance. Increased e' velocities, a measure of early myocardial relaxation, with mavacamten are likely the mechanical consequence of direct effects on actin–myosin cross-bridges. One potential mechanism is that reduced cross-bridge formation reduces LV stiffness and conversely improves LV compliance, resulting in lower filling pressures. In biophysical models, mavacamten has been shown to improve cross-bridge detachment, thereby improving relaxation in diastole (21). In addition, improved hemodynamics with resolution of SAM and LVOT obstruction may also improve LV filling pressure simply by relief of the obstruction. Mitral E/e' ratios, which have been shown to correlate with instantaneous LV filling pressure (22) and predict long-term outcomes in HCM patients (23-27), also showed significant improvement with mavacamten. Given that there was no significant change in E velocities, this change in E/e' appears to be driven by improvement in e' velocities, or early myocardial relaxation.

In patients with obstructive HCM, elevated LA volumes, which are indicative of elevated LV filling pressures (28), may result from a combination of several possible mechanisms, including elevated LVOT gradients, mitral regurgitation secondary to SAM, and diastolic dysfunction. In this study, LAVI was mildly increased at baseline and decreased significantly in response to mavacamten. The mean reduction in LAVI of 7.5 mL/m^2 with only 30 weeks of therapy is consistent with the findings of a difference in LAVI reduction of 10.3 mL/m^2 between treatment and placebo in the cardiac magnetic resonance imaging substudy of EXPLORER-HCM (14) and reasonably comparable to the reduction in LAVI of ~10 mL/m^2 reported after septal reduction therapy (29,30). After accounting for baseline LAVI and baseline LVOT Valsalva gradients, those with higher baseline LVOT gradients experienced a greater decrease in

LA volume, which suggests that higher LVOT gradients contribute more significantly to LA size, likely due to a greater degree of associated mitral regurgitation. Septal reduction therapy has similarly shown that a change in LVOT gradients at peak exercise was the only echocardiographic parameter significantly associated with LAVI reverse remodeling (29). As there was a documented improvement in SAM and mitral regurgitation and a reduction in LV filling pressures, as suggested by a decrease in E/e', the mechanisms accounting for the reduction in LA size are likely multifactorial.

Echo-Doppler–based diastolic parameters, including LAVI and E/e', have been shown to be independent predictors of long-term outcomes, including atrial fibrillation, stroke, heart failure, cardiac transplantation, sudden cardiac death, cardiovascular mortality, and all-cause mortality in HCM patients (23-28,31-33). Notably, reductions in LVOT gradients at rest, with Valsalva, and post-exercise as well as LAVI, lateral e', and E/e' associated with reduction in serum NT-proBNP, a biomarker of cardiac wall stress that predicts morbidity and mortality in patients with HCM (17,18). Reduction in resting LVOT gradients was associated most strongly with reduction in NT-proBNP, particularly in those with resting LVOT gradients ≥ 30 mmHg or those with only provokable gradients ≥ 50 mmHg (i.e. subjects with resting LVOT gradient <50 mmHg). Additionally, the association of improvement in LAVI and E/e' with improvement in NT-proBNP supports the impact of mavacamten in reducing LV filling pressure with reduction in LVOT gradients. Patients with non-obstructive HCM treated with mavacamten in the MAVERICK-HCM trial also exhibited significant reductions in NT-proBNP, which suggests that mavacamten favorably impacts LV filling pressures by additional mechanisms apart from the observed improvement in LVOT gradients and SAM in obstructive HCM patients; this may be attributed to mavacamten's additional impact on diastolic function (34). Finally, reduction in

LAVI was the only echocardiographic parameter change that associated with improvement in functional capacity, suggesting that LA volume change in response to therapy may be more predictive of improvement in functional status compared to other echocardiographic measures, including LVOT gradient reduction. This is supported by data that have shown that increased LA volume is inversely associated with treadmill exercise capacity in HCM and further supports LAVI as a marker of HCM pathophysiology (33).

While there are known limitations to 2D measurement–derived LV mass calculations by echocardiography (35), particularly in the setting of asymmetric hypertrophy, our data suggest a statistically significant decline in wall thickness and LVMI with mavacamten versus placebo. These data are concordant with the recently published cardiac magnetic resonance imaging substudy of EXPLORER-HCM, wherein mean LVMI decreased by 15.8 g/m^2 and maximum wall thickness decreased by 2.4 mm in the mavacamten group compared with placebo (14) . These changes in wall thickness/mass are also in keeping with other small observational cohorts after septal reduction therapy in which reduction in lateral wall thickness accompanies reduction in septal wall thickness as soon as six months post procedure; this suggests that relief of LVOT obstruction and afterload reduction may contribute to reduction in LV wall thickness (29,30,36). Alternatively, reduction in wall thickness may be a direct result of fewer actin-myosin cross-bridges and/or reflect the associated mild decrease in contractility and LV function observed during the 30 weeks of study. The Mavacamten Long-Term Extension study (MAVA-LTE; NCT03723655) and other longitudinal studies will better clarify the impact of mavacamten therapy on cardiac hypertrophy.

The improvements in LV diastolic function, cardiac morphology, and biomarkers observed with mavacamten have not been reported in relation to contemporary pharmacologic

therapies for symptomatic obstructive HCM, such as beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide (37,38). In contrast, improvement in LA volumes, LV wall thickness, SAM, and NT-proBNP have been reported with successful septal reduction therapy, such as septal ablation and septal myectomy (29,30,36,39). Mavacamten appears to improve the underlying pathophysiology in HCM and may provide similar benefit without the need for invasive therapy and procedural risk. Further investigation of the effect of mavacamten on septal reduction therapy eligibility and the number of septal reduction therapy procedures performed in obstructive HCM patients is currently underway in the VALOR-HCM study (NCT04349072).

Study Limitations

The EXPLORER-HCM study design excluded patients with mild symptoms (New York Heart Association class I), those on disopyramide therapy, and those with LV ejection fraction <55%, and there was limited participation of ethnic minorities and younger patients (<50 years). Hence, our findings may not be generalizable to these subpopulations of obstructive HCM patients in the community. A small proportion of patients had a history of septal reduction therapy and atrial fibrillation, which may have impacted measures of diastolic function. SAM and mitral regurgitation were only semi-qualitatively assessed as present or absent in this study; the highly eccentric nature of the mitral regurgitation in obstructive HCM does not lend itself to accurate or reliable quantification. The protocol also precluded the use of ultrasound enhancing agents to avoid confounding effects on interpretations of adverse events. Lastly, EXPLORER-HCM was a relatively short duration study of 30 weeks. The ongoing long-term extension study (MAVA-LTE) will reveal whether these early benefits with mavacamten treatment persist beyond 30 weeks.

Conclusions

In this analysis of EXPLORER-HCM, mavacamten was associated with favorable changes in cardiac structure and function through 30 weeks of therapy, including improvement in echocardiographic markers of LV filling pressures (LAVI and E/e'), LVOT gradients, and SAM. Additionally, improvements in LVOT gradients, LAVI, and E/e' were associated with reductions in NT-proBNP.

Perspectives

Competency in Patient Care: In patients with obstructive hypertrophic cardiomyopathy (HCM), treatment with mavacamten, a cardiac myosin inhibitor, reduces systolic anterior motion (SAM) of the mitral valve and outflow tract (LVOT) gradient and improves echocardiographic markers of left ventricular (LV) diastolic function and exercise capacity.

Translational Outlook: Additional studies are needed to understand the mechanism by which mavacamten improves diastolic function and better characterize its long-term therapeutic effects in patients with obstructive HCM.

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Figure Legends

Figure 1. Echocardiographic Parameters Over Time

Mean (95% CI) LAVI over time (A), interventricular septal thickness (B), inferolateral wall thickness (C), septal e' (D), lateral e' (E), septal E/e' (F), and lateral E/e' (G).

Abbreviations as in Tables 1 and 2.

Figure 2. Change in Echocardiographic Parameters After 30 Weeks of Mavacamten in a Sample Patient

Treatment with mavacamten led to significant improvements in LV structure and function, including SAM, mitral regurgitation, LVOT gradients, lateral e', and septal e'.

Abbreviations as in Table 1.

Figure 3. Relationship of Log2 Change in NT-proBNP on Changes in Echocardiographic Parameters

Scatter plots show the linear regression of the week 30 to baseline log2 change in NT-proBNP on changes in resting LVOT gradient (A), Valsalva LVOT gradient (B), post-exercise LVOT gradient (C), LAVI (D), lateral E/e' (E), and lateral e' (F). Abbreviations as in Tables 1 and 2.

Central Illustration. Mechanism of Action of Mavacamten and Observed Changes

Reduction of actin–myosin cross-bridges with 30 weeks of mavacamten led to improvements in several echocardiographic parameters.

e' = early diastolic mitral annular velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HCM = hypertrophic cardiomyopathy; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; SAM = systolic anterior motion.

Table 1. Baseline Demographics and Characteristics

	Mavacamten (n = 123)	**Placebo (n = 128)**
Demographics		
Age, years	58.5 (12.2)	58.5 (11.8)
Female	57 (46%)	45 (35%)
HCM-related Characteristics		
Hypertension	57 (46%)	53 (41%)
Atrial fibrillation	12 (10%)	23 (18%)
Septal reduction therapy	11 (9%)	8 (6%)
Myectomy	1 (1%)	2 (2%)
Alcohol septal ablation	10 (8%)	6 (5%)
Family history of HCM*	33 (27%)	36 (28%)
%Pathogenic or likely pathogenic hypertrophic cardiomyopathy gene variant‡	28/90 (31%)	22/100 (22%)
Type 2 Diabetes	6 (5%)	7 (6%)
Body mass index, kg/m^2	29.7 (4.9)	29.2 (5.6)
Heart rate, beats/min	63 (10.1)	62 (10.6)
Systolic blood pressure, mmHg	128 (16.2)	128 (14.6)
Diastolic blood pressure, mmHg	75 (10.8)	76 (9.9)
NYHA class		
Class II	88 (72%)	95 (74%)
Class III	35 (29%)	33 (26%)

Baseline pharmacotherapy		
Beta-blocker	94 (76%)	95 (74%)
Calcium channel blocker	25 (20%)	17 (13%)
ACE-I/ARB	20 (16%)	26 (20%)
Mineralocorticoid receptor antagonists	7 (6%)	9 (7%)
Diuretics	22 (18%)	22 (17%)
NT-proBNP, geometric mean, ng/L (CV%)	777 (136) (n = 120)	616 (108) (n = 126)
hs-cTnI, geometric mean, ng/L (CV%)	12.5 (208) (n = 120)	12.5 (373) (n = 119)
Echocardiographic parameters		
LVEF, %	74 (6)	74 (6)
LVOT gradient, mm Hg		
Resting	52 (29)	51 (32)
Valsalva	72 (32)	74 (32)
Post-exercise	86 (34) (n = 122)	84 (36) (n = 127)
LV end diastolic dimension, mm	40 (5) (n = 117)	41 (5) (n = 124)
LV end systolic dimension, mm	23 (3) (n = 96)	24 (4) (n = 104)
Interventricular septal thickness, mm	17 (3) (n = 121)	17 (3) (n = 127)

Inferolateral wall thickness, mm	12 (2) (n = 118)	11 (2) (n = 124)
Max LV wall thickness, mm	20 (4)	20 (3)
LVMI, g/m^2	112 (27) (n = 117)	110 (26) (n = 123)
LAVI, mL/m^2	40 (12) (n = 122)	41 (14) (n = 128)
Lateral e', cm/s	6 (2) (n = 118)	7 (2) (n = 126)
Septal e', cm/s	5 (1) (n = 123)	5 (2) (n = 127)
E/e' lateral ratio	15 (6) (n = 118)	15 (8) (n = 122)
E/e' septal ratio	20 (7) (n = 123)	20 (9) (n = 127)
Peak E-wave velocity, cm/s	88 (25) (n = 123)	89 (28) (n = 128)
Peak A-wave velocity, cm/s	80 (26) (n = 121)	79 (26) (n = 123)
SAM	97 (82%) (n = 119)	102 (81%) (n = 126)
Mitral regurgitation	117 (98%) (n = 120)	124 (99%) (n = 125)

RVSP, mm Hg	29 (8) (n = 43)	27 (8) (n = 42)

Values are mean (SD) or n (%) unless otherwise indicated.

CV = coefficient of variation; e' = early diastolic mitral annular velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; ACE-I = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin II receptor blocker; RVSP = right ventricular systolic pressure; SAM = systolic anterior motion; SD = standard deviation.

*Family history of HCM was self-reported.

‡Denominator indicates number of subjects with gene testing performed.

Table 2. Changes From Baseline in Resting Echocardiographic Parameters

	Mavacamten		Placebo		LS mean difference (95% CI), mavacamten vs placebo at week 30	p-value*
	n	Change (95% CI) from baseline at week 30	n	Change (95% CI) from baseline at week 30		
LVEF, %	114	–3.9 (–5.3, –2.5)	119	–0.01 (–1.2, 1.2)	–4.0 (–5.5, –2.5)	<0.0001
LV end diastolic dimension, mm	108	–1.0 (–1.5, –0.4)	115	–0.3 (–0.9, 0.3)	–0.7 (–1.5, 0.0)	0.05
LV end systolic dimension, mm	82	1.0 (0.2, 1.8)	87	–0.3 (–0.9, 0.3)	1.0 (0.2, 1.9)	0.02
Interventricular septal thickness, mm	114	0.1 (–0.2, 0.4)	120	1.4 (1.0, 1.7)	–1.2 (–1.6, –0.9)	<0.0001
Inferolateral wall thickness, mm	110	–0.6 (–0.9, –0.3)	111	0.3 (0.0, 0.6)	–0.8 (–1.2, –0.4)	<0.0001
LVMI, g/m^2	108	–7.4	110	8.9	–15.5	<0.0001

		(–10.8, –3.9)		(6.0, 11.7)	(–19.0, –11.9)	
LAVI, mL/m^2	115	–7.5 (–9.0, –6.1)	123	–0.09 (–1.6, 1.5)	–7.5 (–9.4, –5.5)	<0.0001
Lateral e', cm/s	107	1.6 (1.2, 1.9)	116	0.2 (–0.2, 0.5)	1.3 (0.9, 1.8)	<0.0001
Septal e', cm/s	113	0.7 (0.4, 1.0)	119	–0.02 (–0.2, 0.2)	0.7 (0.4, 1.0)	<0.0001
E/e' lateral ratio	104	–3.8 (–4.7, –2.8)	112	0.04 (–0.9, 1.0)	–3.8 (–4.9, –2.6)	<0.0001
E/e' septal ratio	111	–3.5 (–4.7, –2.4)	117	–0.3 (–1.1, 0.6)	–3.4 (–4.7, –2.1)	<0.0001
Peak E-wave velocity, cm/s	111	–6.4 (–10.4, –2.5)	122	–2.9 (–6.1, 0.3)	–4.2 (–8.5, 0.1)	0.06
Peak A-wave velocity, cm/s	109	–1.2 (–4.0, 1.6)	115	0.8 (–2.3, 4.0)	–1.9 (–5.7, 1.8)	0.31

Values are mean (95% CI) unless otherwise indicated. No corrections for multiple testing were applied.

CI = confidence interval; LS = least squares; other abbreviations as in Table 1.

Table 3. Linear Regression of Log2 Changes in Biomarkers and Changes in Exercise Capacity on the Changes in Echocardiographic Parameters

	Mavacamten				Placebo			
	n	**Intercept**	**Slope (95% CI)**	**p-value**	**n**	**Intercept**	**Slope (95% CI)**	**p-value**
Log2 change in NT-proBNP, ng/L								
Resting LVOT gradient, mmHg	114	−1.60	0.02 (0.01, 0.03)	<0.0001	120	0.03	−0.001 (−0.006, 0.003)	0.63
Valsalva LVOT gradient, mmHg	114	−1.81	0.01 (0.00, 0.02)	0.005	121	0.06	0.002 (−0.002, 0.006)	0.35
Post-exercise LVOT gradient, mmHg	112	−1.96	0.007 (0.001, 0.013)	0.035	118	0.03	−0.001 (−0.005, 0.003)	0.64
LAVI, mL/m^2	112	−2.02	0.04 (0.01, 0.07)	0.015	120	0.04	−0.002 (−0.017, 0.013)	0.79
Lateral E/e'	101	−2.00	0.08 (0.02, 0.13)	0.007	109	0.07	0.01 (−0.02, 0.04)	0.39
Lateral e', cm/s	104	−2.05	−0.18 (−0.32, −0.04)	0.011	113	0.06	0.01 (−0.06, 0.09)	0.74
Log2 change in hs-cTnI, ng/L								

Resting LVOT gradient, mmHg	112	−0.60	0.005 (−0.001, 0.011)	0.12	110	−0.01	0.001 (−0.006, 0.008)	0.83
Valsalva LVOT gradient, mmHg	112	−0.67	0.002 (−0.003, 0.007)	0.40	111	0.02	0.003 (−0.003, 0.009)	0.36
Post-exercise LVOT gradient, mmHg	110	−0.79	0.000 (−0.004, 0.004)	0.99	108	−0.06	−0.005 (−0.012, 0.002)	0.17
LAVI, mL/m^2	111	−0.61	0.02 (0.00, 0.05)	0.048	110	−0.01	0.005 (−0.018, 0.028)	0.68
Lateral E/e'	100	−0.78	−0.003 (−0.040, 0.034)	0.87	99	−0.05	−0.01 (−0.05, 0.04)	0.76
Lateral e', cm/s	102	−0.69	−0.05 (−0.14, 0.05)	0.32	103	−0.06	0.06 (−0.06, 0.17)	0.32

Change in pVO_2. mL/kg/min								
Resting LVOT gradient, mmHg	116	1.17	−0.01 (−0.03, 0.01)	0.53	123	−0.13	−0.01 (−0.03, 0.01)	0.46
Valsalva LVOT gradient, mmHg	116	1.71	0.01 (−0.01, 0.02)	0.46	124	−0.01	0.01 (−0.01, 0.02)	0.41
Post-exercise LVOT	117	1.85	0.01	0.25	122	−0.14	−0.01	0.15

gradient, mmHg			(−0.01, 0.02),				(−0.03, 0.00)	
LAVI, mL/m^2	114	0.86	−0.08 (−0.15, 0.00)	0.041	123	−0.04	0.03 (−0.03, 0.09)	0.40
Lateral E/e'	103	1.12	−0.02 (−0.15, 0.11)	0.73	112	−0.05	−0.06 (−0.17, 0.06)	0.32
Lateral e', cm/s	106	0.92	0.20 (−0.12, 0.52)	0.22	116	−0.11	−0.08 (−0.40, 0.23)	0.59

No corrections for multiple testing were applied.

pVO_2 = peak oxygen consumption; other abbreviations as in Tables 1 and 2.

n = Number of patients with non-missing change from baseline values for the pair of corresponding parameters.

The results are based on a linear regression model with Log2 change in NT-proBNP or Log2 change in hs-cTnI or change in pVO2 as the dependent variable and echocardiographic parameters as the independent variables.

Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients with Obstructive Hypertrophic Cardiomyopathy

Deleted: Effect of Mavacamten on Key Echocardiographic Features in Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results From EXPLORER-HCM ¶

Brief title: Echo Results From EXPLORER-HCM

Sheila M. Hegde, MD[a]; Steven J. Lester, MD[b]; Scott D. Solomon, MD[a]; Michelle Michels, MD[c]; Perry M. Elliott, MD[d]; Sherif F. Nagueh, MD[e]; Lubna Choudhury, MD[f]; David Zemanek, MD[g]; Donna R. Zwas, MD, MPH[h]; Daniel Jacoby, MD[i]; Andrew Wang, MD[j]; Carolyn Y. Ho, MD[a]; Wanying Li, PhD[k]; Amy J. Sehnert, MD[k]; Iacopo Olivotto, MD[l]; Theodore P. Abraham, MD[m]

From the [a]Division of Cardiovascular Medicine, Brigham and Wome n's Hospital, Boston, MA, USA; [b]Department of Cardiovascular Diseases, Mayo Clinic, Phoenix, AZ, USA; [c]Department of Cardiology, Thoraxcenter, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; [d]Institute of Cardiovascular Science, University College London, London, UK; [e]Methodist DeBakey Heart and Vascular Center, Houston, TX, USA; [f]Bluhm Cardiovascular Institute, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [g]2nd Department of Internal Medicine – Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [h]Heart Institute, Hadassah University Medical Center, Jerusalem, Israel; [i]Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University, New Haven, CT, USA; [j]Duke University School of Medicine, Durham, NC, USA; [k]MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, CA, USA; [l]Cardiomyopathy Unit, Azienda Ospedaliera Universitaria Careggi and the University of Florence, Florence, Italy; and the [m]UCSF HCM Center of Excellence, University of California San Francisco, San Francisco, CA, USA.

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Address for correspondence:
Sheila M. Hegde, MD
Division of Cardiovascular Medicine,
Brigham and Women's Hospital
75 Francis St.
Boston, MA 02115
Phone: 857-307-4000
shegde@bwh.harvard.edu

Tweet: Mavacamten therapy improves echocardiographic measures of cardiac structure and function in patients with obstructive HCM in the EXPLORER-HCM study.

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Abstract

Background: EXPLORER-HCM demonstrated that mavacamten, a cardiac myosin inhibitor, improves symptoms, exercise capacity, and left ventricular (LV) outflow tract (LVOT) obstruction in patients with obstructive hypertrophic cardiomyopathy (oHCM).

Objectives: To evaluate mavacamten's effect on measures of cardiac structure and function and its association with changes in other clinical measures.

Methods: Key echocardiographic parameters from serial echocardiograms over 30 weeks from 251 symptomatic oHCM patients (mavacamten [n=123], placebo [n=128]) were assessed in a core laboratory.

Results: More patients on mavacamten (80.9%; n=76/94) versus placebo (34.0%; n=33/97) showed complete resolution of mitral valve systolic anterior motion (SAM) after 30 weeks (difference, 46.8%; p<0.0001). Mavacamten also improved measures of diastolic function versus placebo, including left atrial volume index (LAVI; mean±standard deviation baseline, 40±12 vs 41±14 mL/m^2; mean [95% confidence interval] change from baseline of –7.5 [–9.0, –6.1] vs –0.09 [–1.6, 1.5] mL/m^2; p<0.0001) and lateral E/e' (baseline, 15±6 vs 15±8; change of –3.8 [–4.7, –2.8] vs 0.04 [–0.9, 1.0]; p<0.0001). Among mavacamten-treated patients, improvement in resting, Valsalva, and post-exercise LVOT gradients, LAVI, and lateral E/e' was associated with reduction in N-terminal pro B-type natriuretic peptide (NT-proBNP; p≤0.03 for all). Reduction in LAVI was associated with improved peak exercise oxygen consumption (p=0.04).

Conclusions: Mavacamten significantly improved measures of LV diastolic function and SAM. Improvement in LVOT obstruction, LAVI, and E/e' was associated with reduction in a biomarker of myocardial wall stress (NT-proBNP). These findings demonstrate improvement in important markers of the pathophysiology of oHCM with mavacamten.

Condensed abstract

The phase 3 EXPLORER-HCM study demonstrated the efficacy and safety of mavacamten, a cardiac myosin inhibitor, in symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Serial echocardiographic analyses investigated the effects of 30 weeks of mavacamten treatment on focused measures of cardiac structure and function. Compared with placebo, mavacamten significantly improved measures of left ventricular (LV) diastolic function (left atrial volume index, e', and E/e') and improved mitral valve systolic anterior motion (SAM). Changes in NT-proBNP were associated with changes in LV outflow tract gradients and other parameters over 30 weeks. These findings suggest mavacamten favorably impacts adverse pathophysiologic processes in oHCM.

Keywords

diastolic function, hypertrophic cardiomyopathy, mavacamten, N-terminal pro B-type natriuretic peptide

Abbreviations and acronyms

e' = early diastolic mitral annular velocity
E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity
HCM = hypertrophic cardiomyopathy
LA = left atrial
LAVI = left atrial volume index
LV = left ventricular

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LVMI = left ventricular mass index
LVOT = left ventricular outflow tract
NT-proBNP = N-terminal pro B-type natriuretic peptide
SAM = systolic anterior motion

Clinical trial: NCT03470545

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction, and impaired relaxation leading to progressive symptoms (1,2). Many patients develop dynamic LV outflow tract (LVOT) obstruction (obstructive HCM), an important prognostic factor in these patients associated with an increased risk of disease progression, including heart failure, atrial fibrillation, and death (3,4). Echocardiography is essential to the diagnosis and monitoring of HCM (2,5). It is routinely used to assess structural and functional cardiac abnormalities, including LVOT gradient, degree of hypertrophy, systolic and diastolic function, as well as the response to therapy in this patient population. Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide for symptom relief; however, these recommendations are based on non-randomized studies and limited data (2,5). Furthermore, no available agent has been shown to improve the natural history of the disease or to convincingly improve diastolic function in HCM, and none target the underlying pathophysiology of the disease (6,7).

Mavacamten, a novel, small molecule inhibitor of cardiac myosin reduces excess actin–myosin cross-bridging by decreasing myosin adenosine triphosphatase activity of the cardiac myosin heavy chain, which results in decreased sarcomere power and force generation, or decreased contractility (8-10). Preclinical data have shown mavacamten reduced contractility, resolved mitral valve systolic anterior motion (SAM), and reduced LVOT gradients and if given earlier in life, there was attenuation of LV hypertrophy, cardiomyocyte disarray, and myocardial fibrosis (9,10). A phase 2 non-randomized clinical study demonstrated symptom improvement and LVOT gradient reduction in 21 symptomatic obstructive HCM patients treated with

mavacamten (11). These findings were confirmed in the randomized, double-blind, placebo-controlled, phase 3 EXPLORER-HCM study, which demonstrated significant reduction in LVOT gradients, improved exercise capacity, improved health status, and decreased symptom burden without clinically significant changes in LV ejection fraction after 30 weeks of mavacamten treatment (12,13). Significant reductions in LV mass index, absolute intracellular myocardial mass index, maximum LV wall thickness, and left atrial volume index (LAVI) with mavacamten were demonstrated in a cardiac magnetic resonance imaging substudy of 35 EXPLORER-HCM subjects (14).

The objective of this secondary analysis of EXPLORER-HCM was to evaluate the effect of mavacamten on key echocardiographic features of obstructive HCM and how these changes relate to its observed benefits in cardiac biomarkers and exercise capacity.

Methods

Study design and patient population

EXPLORER-HCM (ClinicalTrials.gov Identifier: NCT03470545) was a multicenter, double-blind, placebo-controlled, randomized, phase 3 study in patients with symptomatic obstructive HCM. Details of the study design and primary efficacy and safety results have been published previously (12,15). As described, eligible patients were at least 18 years old with obstructive HCM with unexplained LVH; peak LVOT gradient ≥ 50 mmHg at rest, with Valsalva maneuver, or during exercise; LV ejection fraction ≥ 55%; and New York Heart Association class II-III symptoms. Subjects were allowed to continue standard medical therapy except for disopyramide. The protocol was approved by institutional review boards at all sites, and all patients provided informed consent.

Procedures and assessments

Resting echocardiograms were performed at screening, day 1, and weeks 4, 6, 12, 18, 22, 26, 30 (end of treatment), and 38 (end of study). Post-exercise echocardiograms were performed at screening and week 30. All echocardiograms were acquired according to a detailed acquisition protocol by certified sonographers at each site. Images were assessed by the Cardiovascular Imaging Core Laboratory (Brigham and Women's Hospital, Boston, MA) according to American Society of Echocardiography recommendations (16). Core laboratory personnel performing the measurements were blinded to study treatment. Chamber dimensions included LV end systolic and end diastolic dimensions, LAVI, maximum LV wall thickness, interventricular septal wall thickness, and inferolateral wall thickness. LV ejection fraction was based on the modified Simpson's method. Maximum LV wall thickness at baseline was measured as the greatest wall thickness visualized in the parasternal long- and short-axis views. LV mass index (LVMI) was calculated from linear dimensions and indexed to height$^{2.7}$ per guidelines, though we acknowledge that accurate assessment of LVMI using echocardiography is limited by the atypical morphology seen in obstructive HCM (16). Markers related to ventricular filling included lateral and septal early diastolic mitral annular velocity (lateral e'and septal e', respectively), ratio between early mitral inflow velocity and lateral mitral annular early diastolic velocity (lateral E/e'), and ratio between early mitral inflow velocity and septal mitral annular early diastolic velocity (septal E/e'). LVOT gradient assessments included instantaneous peak LVOT gradient at rest, provoked peak LVOT gradient with the Valsalva maneuver, and instantaneous peak LVOT gradient immediately following exercise. Sonographers were instructed to sweep the angle of interrogation from the left atrium to the LVOT to aid the ability to distinguish between mitral regurgitation and LVOT Doppler profiles. The presence of mitral

valve SAM and mitral regurgitation was assessed as either present or absent. Complete resolution of SAM was defined as those who were identified with SAM present at baseline and absent at week 30. LVOT gradients and LV ejection fraction at rest were assessed at each study visit to allow for drug titration, whereas a more thorough echocardiographic assessment was performed at baseline, week 18, and week 30.

Statistical analyses

In this exploratory analysis, baseline values of the echocardiographic parameters, the last non-missing measurements prior to the first dose of the study drug, were summarized using descriptive statistics. For the analysis comparing the changes from baseline in continuous echocardiographic measurements (e.g., LAVI, e', and E/e') between treatment arms, least-squares means, 95% confidence intervals (CIs), and p-values were calculated using a mixed model for repeated measurements for data up to week 30, with treatment group (mavacamten vs placebo), time points, the interaction between treatment and time point, corresponding baseline value, and stratification factors (beta-blocker use, New York Heart Association class, and ergometer type) as fixed effects and patient as random effect. The categorical variables (absence of SAM or mitral regurgitation) were analyzed using the Cochran–Mantel–Haenszel test stratified by New York Heart Association class, beta-blocker use, and ergometer type.

Additional exploratory, post hoc analyses were conducted to assess the relationship between the baseline LVOT Valsalva gradients and mavacamten treatment effect on echocardiographic parameters (LAVI, e', and E/e'). The linear model was fitted on the change in echocardiographic parameter of interest with its baseline value, baseline LVOT Valsalva gradient, treatment, interaction between treatment, and those 2 baseline variables as explanatory variables.

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The relationship between the changes from baseline to week 30 in echocardiographic parameters, LVOT gradients, and other clinical parameters was explored under the effect of mavacamten treatment. Simple linear regression was fitted by treatment group on the change in log-2 transformed cardiac biomarkers (N-terminal pro B-type natriuretic peptide [NT-proBNP] and high-sensitivity cardiac troponin I) and change in peak oxygen assumption, separately, with the change in each individual echocardiographic parameter (LVOT gradient, LAVI, E/e', e') as the explanatory variable. The fitted lines were overlaid with scatter plots. Note, the cardiac biomarker data were analyzed on log-2 scale as the biomarker data showed a log-normal-like distribution.

Missing data were not imputed. P-values <0.05 were considered statistically significant. P-values and 95% confidence intervals presented in this report have not been adjusted for multiplicity due to the exploratory nature of the analyses. SAS version 9.4 or higher was used for all statistical analyses.

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Results

Of the 251 patients with symptomatic obstructive HCM enrolled in EXPLORER-HCM, 123 (49%) received mavacamten and 128 (51%) received placebo. Baseline demographics have been described previously (12). The mean age was 58.5 years, 41% of patients were female, and 92% were on background beta-blocker or calcium channel blocker therapy. Nine subjects (7 mavacamten, 2 placebo) experienced a decline in LV ejection fraction (median 48%, [range 35-49%]), 7 subjects (4 mavacamten, 3 placebo) discontinued treatment, and no subjects were lost to follow-up in the first 30 weeks (**Supplemental Tables 1,2**). In those who experienced a LV ejection fraction decline, LV function recovered with protocol-driven temporary treatment

discontinuation; all subjects resumed mavacamten dosing at the same or lower dose per protocol and completed the study.

Baseline echocardiography demonstrated typical features of HCM with increased maximum LV wall thickness, reduced tissue Doppler indices of mitral annular e' velocities, elevated E/e', and mild LA enlargement (**Table 1**). Patients had elevated LVOT gradients (rest, Valsalva, and post-exercise), consistent with the study entry criteria.

Physiological changes

For patients with mitral valve SAM at baseline, treatment with mavacamten for 30 weeks led to complete resolution of SAM in 80.9% of patients (n = 76/94) compared with 34.0% of patients receiving placebo (n = 33/97), a difference (95% CI) of 46.8% (34.5 to 59.2); p <0.0001. For patients with mitral regurgitation at baseline, 9.0% (n = 10/111) of patients in the mavacamten group had complete resolution of mitral regurgitation compared with no patients in the placebo group (difference [95% CI] of 9.0% [3.7 to 14.3]; p <0.001). LV ejection fraction decreased compared with placebo (mean [standard deviation (SD)] baseline of 74 ± 6% vs 74 ± 6%; mean [95% CI] change from baseline of –3.9% [–5.3 to –2.5] vs –0.01% [–1.2 to 1.2]; p <0.0001) (12).

Patients treated with mavacamten also had significant improvement in markers of LV diastolic function compared with placebo (**Figures 1** and **2**; **Table 2**). The mean (95% CI) decrease from baseline in LAVI at week 30 was –7.5 (–9.0 to –6.1) mL/m^2 with mavacamten versus –0.1 (–1.6 to 1.5) mL/m^2 with placebo (p <0.0001). Mavacamten was also associated with improvement in septal e' (mean increase of 0.7 [0.4 to 1.0] vs –0.02 [–0.2 to 0.2] cm/s; p <0.0001), lateral e' (mean increase of 1.6 [1.2 to 1.9] vs 0.2 [–0.2 to 0.5] cm/s; p <0.0001), septal E/e' (mean decrease of –3.5 [–4.7 to –2.4] vs –0.3 [–1.1 to 0.6]; p <0.0001), and lateral E/e'

(mean decrease of –3.8 [–4.7 to –2.8] vs 0.04 [–0.9 to 1.0]; p <0.0001). Significant improvements were detectable as early as week 18 in LAVI, septal e', lateral e', septal E/e', and lateral E/e' and persisted through week 30 (**Figure 1**). No significant changes were seen in mitral inflow E and A velocities. Reduction in LVOT gradients (rest, Valsalva), LAVI, and E/e' were similar in subjects treated with mavacamten with and without complete resolution of mitral valve SAM (**Supplemental Table 3**).

Structural changes

The LV end diastolic dimension did not significantly change after 30 weeks with mavacamten compared with placebo (mean±SD baseline of 40 ± 5 vs 41 ± 5 mm; mean [95% CI] decrease from baseline of –1.0 [–1.5 to –0.4] vs –0.3 [–0.9 to 0.3] mm; p = 0.05), whereas the LV end systolic dimension increased marginally (mean baseline of 23 ± 3 vs 24 ± 4 mm; mean change of 1.0 [0.2 to 1.8] vs –0.3 [–0.9 to 0.3] mm; p = 0.02; **Table 2**). Inferolateral wall thickness decreased compared with placebo (mean baseline of 12 ± 2 vs 11 ± 2 mm; mean change of –0.6 [–0.9 to –0.3] vs 0.3 [0.0 to 0.6] mm; p <0.0001; **Figure 1**; **Table 2**). Mavacamten did not significantly change interventricular septal thickness, while the placebo group demonstrated a significant increase in interventricular septal thickness (mean baseline of 17 ± 3 vs 17 ± 3 mm; mean change of 0.1 [–0.2 to 0.4] vs 1.4 [1.0 to 1.7] mm; p <0.0001).

Relationship of baseline LVOT gradients with treatment effects on echocardiographic parameters

A significant interaction between baseline LVOT gradients and the treatment effect on LAVI was present (p=0.03) such that patients with higher baseline LVOT Valsalva gradients demonstrated greater reductions (placebo-corrected) in LAVI after adjusting for baseline LAVI

and baseline LVOT Valsalva gradients. No significant interactions were seen between baseline LVOT gradients and changes in e' velocities or E/e' ratios.

Relationship of changes to biomarkers and exercise capacity

Significant associations between reduction in serum NT-proBNP level and several echocardiographic parameters of cardiac structure and function, including LVOT gradients (rest, Valsalva, and post-exercise), LAVI, E/e', and e' (**Table 3, Figure 3**) were seen in the mavacamten group. The reduction in resting LVOT gradient demonstrated the strongest association with reduction in NT-proBNP (mavacamten, ß = 0.02, 95% CI: 0.01 to 0.03; p <0.0001); this association was present in subjects with resting LVOT gradients ≥ 30 mmHg or those with only provokable LVOT gradients ≥ 50 mmHg (i.e. subjects with resting LVOT gradient <50 mmHg) (**Supplemental Table 4**). Also, reduction in LAVI significantly but weakly associated with reduction in serum cardiac troponin I (mavacamten, ß = 0.02, 95% CI: 0.00 to 0.05; p = 0.048) and with reduction in pVO2 (mavacamten, ß = -0.08, 95% CI: -0.15 to 0.00; p = 0.041) in patients treated with mavacamten (**Table 3**). No significant association was noted between troponin I or pVO2 and other echocardiographic parameters (resting, Valsalva, and post-exercise LVOT gradients, lateral e', and lateral E/e') (**Table 3, Figures S1 and S2**).

Discussion

This analysis of EXPLORER-HCM represents the largest serial assessment of echocardiographic parameters in a prospective, double-blind, placebo-controlled study in patients with obstructive HCM. Mavacamten treatment improved several key pathophysiologic features associated with obstructive HCM, thereby providing additional mechanistic insights into the improvement in exercise capacity and LVOT obstruction previously described (12). After 30 weeks of mavacamten treatment, most patients had complete resolution of mitral valve SAM, an

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important element in dynamic LVOT obstruction. Mavacamten also improved markers of diastolic function, including LAVI, e', and E/e' ratio, with only mild reduction in LV systolic function (**Central Illustration**). Notably, reductions in key echocardiographic parameters (LVOT gradients, LAVI, and E/e') were associated with reductions in NT-proBNP, an important marker of cardiac wall stress with strong prognostic value (17,18).

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The dynamic LVOT gradient is a key feature of obstructive HCM and is attributed to the presence of septal hypertrophy and/or mitral valve SAM. Mavacamten decreased LVOT gradients, and there was complete resolution of SAM in a majority of patients. While similar reductions in LVOT gradients, LAVI, and E/e' were observed in those with and without complete resolution of SAM, the improvement also seen in those without complete resolution may reflect the response to partial improvement in SAM. To the extent that changes in SAM may reflect changes in mitral regurgitation, partial improvement in SAM may be sufficient to improve LVOT hemodynamics. A combination of factors may have contributed to improvement in SAM with mavacamten treatment, including reduction in hypercontractility. Early animal models attribute the reduction in contractility with mavacamten to decreased sarcomere power and force generation by decreasing myosin adenosine triphosphatase activity in a dose-dependent manner (9,19,20). The marked improvement in LVOT gradients and SAM was achieved with only a 4% mean decrease in LV ejection fraction and no significant change in heart rate, such that it appears that modifying contractility dynamics without a significant chronotropic effect with mavacamten is sufficient to relieve LVOT obstruction. (12). Further studies are needed to better understand the effect of mavacamten on contractility dynamics and correlates in echocardiography.

Consistent with pre-clinical findings (19,20), mavacamten was associated with improved measures of diastolic function, including myocardial relaxation and compliance. Increased e' velocities, a measure of early myocardial relaxation, with mavacamten are likely the mechanical consequence of direct effects on actin–myosin cross-bridges. One potential mechanism is that reduced cross-bridge formation reduces LV stiffness and conversely improves LV compliance, resulting in lower filling pressures. In biophysical models, mavacamten has been shown to improve cross-bridge detachment, thereby improving relaxation in diastole (21). In addition, improved hemodynamics with resolution of SAM and LVOT obstruction may also improve LV filling pressure simply by relief of the obstruction. Mitral E/e' ratios, which have been shown to correlate with instantaneous LV filling pressure (22) and predict long-term outcomes in HCM patients (23-27), also showed significant improvement with mavacamten. Given that there was no significant change in E velocities, this change in E/e' appears to be driven by improvement in e' velocities, or early myocardial relaxation.

In patients with obstructive HCM, elevated LA volumes, which are indicative of elevated LV filling pressures (28), may result from a combination of several possible mechanisms, including elevated LVOT gradients, mitral regurgitation secondary to SAM, and diastolic dysfunction. In this study, LAVI was mildly increased at baseline and decreased significantly in response to mavacamten. The mean reduction in LAVI of 7.5 mL/m^2 with only 30 weeks of therapy is consistent with the findings of a difference in LAVI reduction of 10.3 mL/m^2 between treatment and placebo in the cardiac magnetic resonance imaging substudy of EXPLORER-HCM (14) and reasonably comparable to the reduction in LAVI of ~10 mL/m^2 reported after septal reduction therapy (29,30). After accounting for baseline LAVI and baseline LVOT Valsalva gradients, those with higher baseline LVOT gradients experienced a greater decrease in

LA volume, which suggests that higher LVOT gradients contribute more significantly to LA size, likely due to a greater degree of associated mitral regurgitation. Septal reduction therapy has similarly shown that a change in LVOT gradients at peak exercise was the only echocardiographic parameter significantly associated with LAVI reverse remodeling (29). As there was a documented improvement in SAM and mitral regurgitation and a reduction in LV filling pressures, as suggested by a decrease in E/e', the mechanisms accounting for the reduction in LA size are likely multifactorial.

Echo-Doppler–based diastolic parameters, including LAVI and E/e', have been shown to be independent predictors of long-term outcomes, including atrial fibrillation, stroke, heart failure, cardiac transplantation, sudden cardiac death, cardiovascular mortality, and all-cause mortality in HCM patients (23-28,31-33). Notably, reductions in LVOT gradients at rest, with Valsalva, and post-exercise as well as LAVI, lateral e', and E/e' associated with reduction in serum NT-proBNP, a biomarker of cardiac wall stress that predicts morbidity and mortality in patients with HCM (17,18). Reduction in resting LVOT gradients was associated most strongly with reduction in NT-proBNP, particularly in those with resting LVOT gradients ≥ 30 mmHg or those with only provokable gradients ≥ 50 mmHg (i.e. subjects with resting LVOT gradient <50 mmHg). Additionally, the association of improvement in LAVI and E/e' with improvement in NT-proBNP supports the impact of mavacamten in reducing LV filling pressure with reduction in LVOT gradients. Patients with non-obstructive HCM treated with mavacamten in the MAVERICK-HCM trial also exhibited significant reductions in NT-proBNP, which suggests that mavacamten favorably impacts LV filling pressures by additional mechanisms apart from the observed improvement in LVOT gradients and SAM in obstructive HCM patients; this may be attributed to mavacamten's additional impact on diastolic function (34). Finally, reduction in

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LAVI was the only echocardiographic parameter change that associated with improvement in functional capacity, suggesting that LA volume change in response to therapy may be more predictive of improvement in functional status compared to other echocardiographic measures, including LVOT gradient reduction. This is supported by data that have shown that increased LA volume is inversely associated with treadmill exercise capacity in HCM and further supports LAVI as a marker of HCM pathophysiology (33).

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While there are known limitations to 2D measurement–derived LV mass calculations by echocardiography (35), particularly in the setting of asymmetric hypertrophy, our data suggest a statistically significant decline in wall thickness and LVMI with mavacamten versus placebo. These data are concordant with the recently published cardiac magnetic resonance imaging substudy of EXPLORER-HCM, wherein mean LVMI decreased by 15.8 g/m^2 and maximum wall thickness decreased by 2.4 mm in the mavacamten group compared with placebo (14) . These changes in wall thickness/mass are also in keeping with other small observational cohorts after septal reduction therapy in which reduction in lateral wall thickness accompanies reduction in septal wall thickness as soon as six months post procedure; this suggests that relief of LVOT obstruction and afterload reduction may contribute to reduction in LV wall thickness (29,30,36). Alternatively, reduction in wall thickness may be a direct result of fewer actin-myosin cross-bridges and/or reflect the associated mild decrease in contractility and LV function observed during the 30 weeks of study. The Mavacamten Long-Term Extension study (MAVA-LTE; NCT03723655) and other longitudinal studies will better clarify the impact of mavacamten therapy on cardiac hypertrophy.

The improvements in LV diastolic function, cardiac morphology, and biomarkers observed with mavacamten have not been reported in relation to contemporary pharmacologic

therapies for symptomatic obstructive HCM, such as beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide (37,38). In contrast, improvement in LA volumes, LV wall thickness, SAM, and NT-proBNP have been reported with successful septal reduction therapy, such as septal ablation and septal myectomy (29,30,36,39). Mavacamten appears to improve the underlying pathophysiology in HCM and may provide similar benefit without the need for invasive therapy and procedural risk. Further investigation of the effect of mavacamten on septal reduction therapy eligibility and the number of septal reduction therapy procedures performed in obstructive HCM patients is currently underway in the VALOR-HCM study (NCT04349072).

Study Limitations

The EXPLORER-HCM study design excluded patients with mild symptoms (New York Heart Association class I), those on disopyramide therapy, and those with LV ejection fraction <55%, and there was limited participation of ethnic minorities and younger patients (<50 years). Hence, our findings may not be generalizable to these subpopulations of obstructive HCM patients in the community. A small proportion of patients had a history of septal reduction therapy and atrial fibrillation, which may have impacted measures of diastolic function. SAM and mitral regurgitation were only semi-qualitatively assessed as present or absent in this study; the highly eccentric nature of the mitral regurgitation in obstructive HCM does not lend itself to accurate or reliable quantification. The protocol also precluded the use of ultrasound enhancing agents to avoid confounding effects on interpretations of adverse events. Lastly, EXPLORER-HCM was a relatively short duration study of 30 weeks. The ongoing long-term extension study (MAVA-LTE) will reveal whether these early benefits with mavacamten treatment persist beyond 30 weeks.

Conclusions

In this analysis of EXPLORER-HCM, mavacamten was associated with favorable changes in cardiac structure and function through 30 weeks of therapy, including improvement in echocardiographic markers of LV filling pressures (LAVI and E/e'), LVOT gradients, and SAM. Additionally, improvements in LVOT gradients, LAVI, and E/e' were associated with reductions in NT-proBNP.

Perspectives

Competency in Patient Care: In patients with obstructive hypertrophic cardiomyopathy (HCM), treatment with mavacamten, a cardiac myosin inhibitor, reduces systolic anterior motion (SAM) of the mitral valve and outflow tract (LVOT) gradient and improves echocardiographic markers of left ventricular (LV) diastolic function and exercise capacity.

Translational Outlook: Additional studies are needed to understand the mechanism by which mavacamten improves diastolic function and better characterize its long-term therapeutic effects in patients with obstructive HCM.

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Figure Legends

Figure 1. Echocardiographic Parameters Over Time

Mean (95% CI) LAVI over time (A), interventricular septal thickness (B), inferolateral wall thickness (C), septal e' (D), lateral e' (E), septal E/e' (F), and lateral E/e' (G).

Abbreviations as in Tables 1 and 2.

Figure 2. Change in Echocardiographic Parameters After 30 Weeks of Mavacamten in a Sample Patient

Treatment with mavacamten led to significant improvements in LV structure and function, including SAM, mitral regurgitation, LVOT gradients, lateral e', and septal e'.

Abbreviations as in Table 1.

Figure 3. Relationship of Log2 Change in NT-proBNP on Changes in Echocardiographic Parameters

Scatter plots show the linear regression of the week 30 to baseline log2 change in NT-proBNP on changes in resting LVOT gradient (A), Valsalva LVOT gradient (B), post-exercise LVOT gradient (C), LAVI (D), lateral E/e' (E), and lateral e' (F). Abbreviations as in Tables 1 and 2.

Central Illustration. Mechanism of Action of Mavacamten and Observed Changes

Reduction of actin–myosin cross-bridges with 30 weeks of mavacamten led to improvements in several echocardiographic parameters.

e' = early diastolic mitral annular velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HCM = hypertrophic cardiomyopathy; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; SAM = systolic anterior motion.

Deleted: **Correlation Between Changes in Echocardiographic Parameters From Baseline and Ratio of NT-proBNP to Baseline**

Deleted: Scatter plots show correlation between change from baseline to week 30 in resting LVOT gradient (A), Valsalva LVOT gradient (B), post-exercise LVOT gradient (C), LAVI (D), and lateral E/e' with ratio of week 30 to baseline NT-proBNP.¶

Deleted: The correlation between change from baseline to week 30 in lateral e' with week 30 to baseline NT-proBNP ratio was not significant.¶
Abbreviations as in Tables 1 and 2.¶

Table 1. Baseline Demographics and Characteristics

	Mavacamten (n = 123)	**Placebo (n = 128)**
Demographics		
Age, years	58.5 (12.2)	58.5 (11.8)
Female	57 (46%)	45 (35%)
HCM-related Characteristics		
Hypertension	57 (46%)	53 (41%)
Atrial fibrillation	12 (10%)	23 (18%)
Septal reduction therapy	11 (9%)	8 (6%)
Myectomy	1 (1%)	2 (2%)
Alcohol septal ablation	10 (8%)	6 (5%)
Family history of HCM*	33 (27%)	36 (28%)
%Pathogenic or likely pathogenic hypertrophic cardiomyopathy gene variant‡	28/90 (31%)	22/100 (22%)
Type 2 Diabetes	6 (5%)	7 (6%)
Body mass index, kg/m^2	29.7 (4.9)	29.2 (5.6)
Heart rate, beats/min	63 (10.1)	62 (10.6)
Systolic blood pressure, mmHg	128 (16.2)	128 (14.6)
Diastolic blood pressure, mmHg	75 (10.8)	76 (9.9)
NYHA class		
Class II	88 (72%)	95 (74%)
Class III	35 (29%)	33 (26%)

Baseline pharmacotherapy		
Beta-blocker	94 (76%)	95 (74%)
Calcium channel blocker	25 (20%)	17 (13%)
ACE-I/ARB	20 (16%)	26 (20%)
Mineralocorticoid receptor antagonists	7 (6%)	9 (7%)
Diuretics	22 (18%)	22 (17%)
NT-proBNP, geometric mean, ng/L (CV%)	777 (136) (n = 120)	616 (108) (n = 126)
hs-cTnI, geometric mean, ng/L (CV%)	12.5 (208) (n = 120)	12.5 (373) (n = 119)
Echocardiographic parameters		
LVEF, %	74 (6)	74 (6)
LVOT gradient, mm Hg		
Resting	52 (29)	51 (32)
Valsalva	72 (32)	74 (32)
Post-exercise	86 (34) (n = 122)	84 (36) (n = 127)
LV end diastolic dimension, mm	40 (5) (n = 117)	41 (5) (n = 124)
LV end systolic dimension, mm	23 (3) (n = 96)	24 (4) (n = 104)
Interventricular septal thickness, mm	17 (3) (n = 121)	17 (3) (n = 127)

Inferolateral wall thickness, mm	12 (2) (n = 118)	11 (2) (n = 124)
Max LV wall thickness, mm	20 (4)	20 (3)
LVMI, g/m^2	112 (27) (n = 117)	110 (26) (n = 123)
LAVI, mL/m^2	40 (12) (n = 122)	41 (14) (n = 128)
Lateral e', cm/s	6 (2) (n = 118)	7 (2) (n = 126)
Septal e', cm/s	5 (1) (n = 123)	5 (2) (n = 127)
E/e' lateral ratio	15 (6) (n = 118)	15 (8) (n = 122)
E/e' septal ratio	20 (7) (n = 123)	20 (9) (n = 127)
Peak E-wave velocity, cm/s	88 (25) (n = 123)	89 (28) (n = 128)
Peak A-wave velocity, cm/s	80 (26) (n = 121)	79 (26) (n = 123)
SAM	97 (82%) (n = 119)	102 (81%) (n = 126)
Mitral regurgitation	117 (98%) (n = 120)	124 (99%) (n = 125)

RVSP, mm Hg	29 (8) (n = 43)	27 (8) (n = 42)

Values are mean (SD) or n (%) unless otherwise indicated.

CV = coefficient of variation; e' = early diastolic mitral annular velocity; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; ACE-I = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin II receptor blocker; RVSP = right ventricular systolic pressure; SAM = systolic anterior motion; SD = standard deviation.

*Family history of HCM was self-reported.

‡Denominator indicates number of subjects with gene testing performed.

Table 2. Changes From Baseline in Resting Echocardiographic Parameters

	Mavacamten		Placebo		LS mean difference (95% CI), mavacamten vs placebo at week 30	p-value*
	n	Change (95% CI) from baseline at week 30	n	Change (95% CI) from baseline at week 30		
LVEF, %	114	–3.9 (–5.3, –2.5)	119	–0.01 (–1.2, 1.2)	–4.0 (–5.5, –2.5)	<0.0001
LV end diastolic dimension, mm	108	–1.0 (–1.5, –0.4)	115	–0.3 (–0.9, 0.3)	–0.7 (–1.5, 0.0)	0.05
LV end systolic dimension, mm	82	1.0 (0.2, 1.8)	87	–0.3 (–0.9, 0.3)	1.0 (0.2, 1.9)	0.02
Interventricular septal thickness, mm	114	0.1 (–0.2, 0.4)	120	1.4 (1.0, 1.7)	–1.2 (–1.6, –0.9)	<0.0001
Inferolateral wall thickness, mm	110	–0.6 (–0.9, –0.3)	111	0.3 (0.0, 0.6)	–0.8 (–1.2, –0.4)	<0.0001
LVMI, g/m^2	108	–7.4	110	8.9	–15.5	<0.0001

		(–10.8, –3.9)		(6.0, 11.7)	(–19.0, –11.9)	
LAVI, mL/m^2	115	–7.5 (–9.0, –6.1)	123	–0.09 (–1.6, 1.5)	–7.5 (–9.4, –5.5)	<0.0001
Lateral e', cm/s	107	1.6 (1.2, 1.9)	116	0.2 (–0.2, 0.5)	1.3 (0.9, 1.8)	<0.0001
Septal e', cm/s	113	0.7 (0.4, 1.0)	119	–0.02 (–0.2, 0.2)	0.7 (0.4, 1.0)	<0.0001
E/e' lateral ratio	104	–3.8 (–4.7, –2.8)	112	0.04 (–0.9, 1.0)	–3.8 (–4.9, –2.6)	<0.0001
E/e' septal ratio	111	–3.5 (–4.7, –2.4)	117	–0.3 (–1.1, 0.6)	–3.4 (–4.7, –2.1)	<0.0001
Peak E-wave velocity, cm/s	111	–6.4 (–10.4, –2.5)	122	–2.9 (–6.1, 0.3)	–4.2 (–8.5, 0.1)	0.06
Peak A-wave velocity, cm/s	109	–1.2 (–4.0, 1.6)	115	0.8 (–2.3, 4.0)	–1.9 (–5.7, 1.8)	0.31

Values are mean (95% CI) unless otherwise indicated. No corrections for multiple testing were applied.

CI = confidence interval; LS = least squares; other abbreviations as in Table 1.

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Table 3. Linear Regression of Log2 Changes in Biomarkers and Changes in Exercise Capacity on the Changes in Echocardiographic Parameters

	Mavacamten				Placebo			
	n	Intercept	Slope (95% CI)	p-value	n	Intercept	Slope (95% CI)	p-value
Log2 change in NT-proBNP, ng/L								
Resting LVOT gradient, mmHg	114	−1.60	0.02 (0.01, 0.03)	<0.0001	120	0.03	−0.001 (−0.006, 0.003)	0.63
Valsalva LVOT gradient, mmHg	114	−1.81	0.01 (0.00, 0.02)	0.005	121	0.06	0.002 (−0.002, 0.006)	0.35
Post-exercise LVOT gradient, mmHg	112	−1.96	0.007 (0.001, 0.013)	0.035	118	0.03	−0.001 (−0.005, 0.003)	0.64
LAVI, mL/m^2	112	−2.02	0.04 (0.01, 0.07)	0.015	120	0.04	−0.002 (−0.017, 0.013)	0.79
Lateral E/e'	101	−2.00	0.08 (0.02, 0.13)	0.007	109	0.07	0.01 (−0.02, 0.04)	0.39
Lateral e', cm/s	104	−2.05	−0.18 (−0.32, −0.04)	0.011	113	0.06	0.01 (−0.06, 0.09)	0.74
Log2 change in hs-cTnI, ng/L								

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pVO$_2$, mL/kg/min ... [2]

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Resting LVOT gradient, mmHg	112	−0.60	0.005 (−0.001, 0.011)	0.12	110	−0.01	0.001 (−0.006, 0.008)	0.83
Valsalva LVOT gradient, mmHg	112	−0.67	0.002 (−0.003, 0.007)	0.40	111	0.02	0.003 (−0.003, 0.009)	0.36
Post-exercise LVOT gradient, mmHg	110	−0.79	0.000 (−0.004, 0.004)	0.99	108	−0.06	−0.005 (−0.012, 0.002)	0.17
LAVI, mL/m²	111	−0.61	0.02 (0.00, 0.05)	0.048	110	−0.01	0.005 (−0.018, 0.028)	0.68
Lateral E/e'	100	−0.78	−0.003 (−0.040, 0.034)	0.87	99	−0.05	−0.01 (−0.05, 0.04)	0.76
Lateral e', cm/s	102	−0.69	−0.05 (−0.14, 0.05)	0.32	103	−0.06	0.06 (−0.06, 0.17)	0.32

Change in pVO_2. mL/kg/min								
Resting LVOT gradient, mmHg	116	1.17	−0.01 (−0.03, 0.01)	0.53	123	−0.13	−0.01 (−0.03, 0.01)	0.46
Valsalva LVOT gradient, mmHg	116	1.71	0.01 (−0.01, 0.02)	0.46	124	−0.01	0.01 (−0.01, 0.02)	0.41

Post-exercise LVOT gradient, mmHg	117	1.85	0.01 (−0.01, 0.02),	0.25	122	−0.14	−0.01 (−0.03, 0.00)	0.15
LAVI, mL/m²	114	0.86	−0.08 (−0.15, 0.00)	0.041	123	−0.04	0.03 (−0.03, 0.09)	0.40
Lateral E/e'	103	1.12	−0.02 (−0.15, 0.11)	0.73	112	−0.05	−0.06 (−0.17, 0.06)	0.32
Lateral e', cm/s	106	0.92	0.20 (−0.12, 0.52)	0.22	116	−0.11	−0.08 (−0.40, 0.23)	0.59

No corrections for multiple testing were applied.

pVO_2 = peak oxygen consumption; other abbreviations as in Tables 1 and 2.

n = Number of patients with non-missing change from baseline values for the pair of corresponding parameters.

The results are based on a linear regression model with Log2 change in NT-proBNP or Log2 change in hs-cTnI or change in pVO2 as the dependent variable and echocardiographic parameters as the independent variables.

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¶
The following variables were not significantly correlated with change in hs-cTnI: Valsalva and post-exercise LVOT gradients, lateral e', and lateral E/e'.¶

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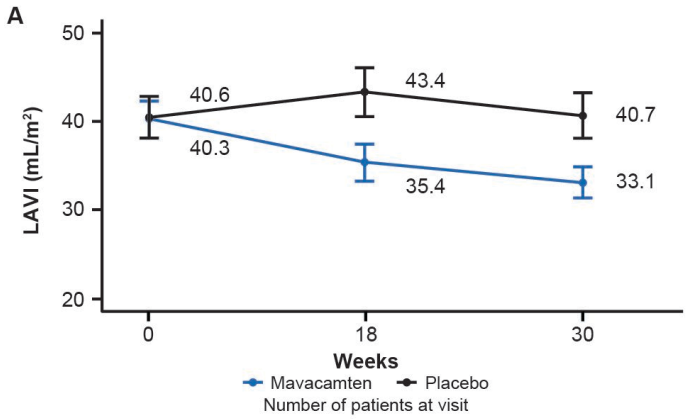
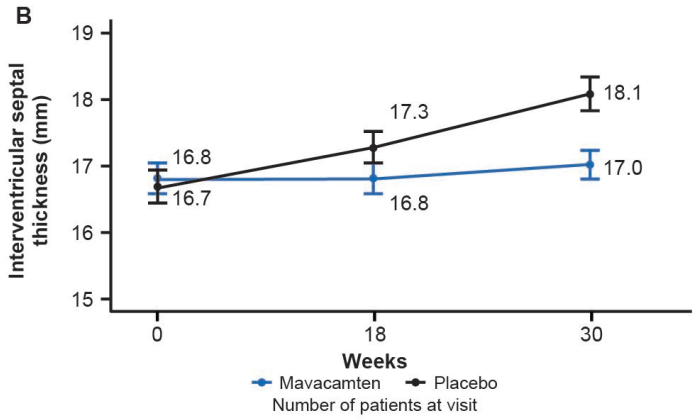


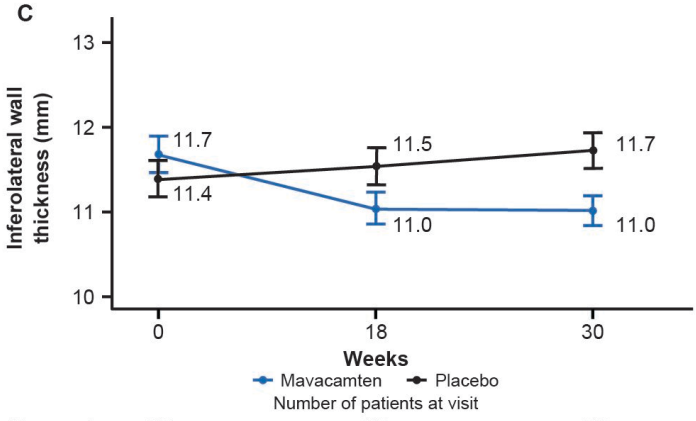
Number of patients at visit

Mavacamten	122	116	116
Placebo	128	118	123



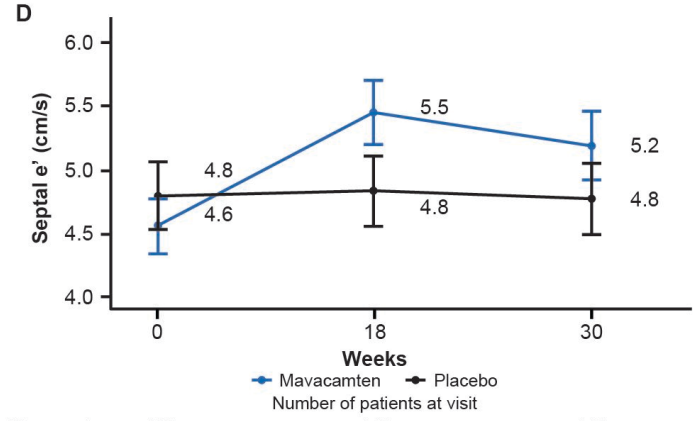
Number of patients at visit

Mavacamten	121	116	116
Placebo	127	121	121



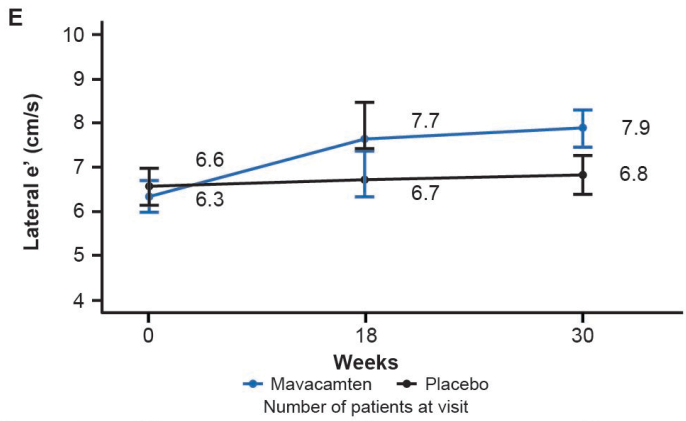
Number of patients at visit

Mavacamten	118	113	113
Placebo	124	117	115



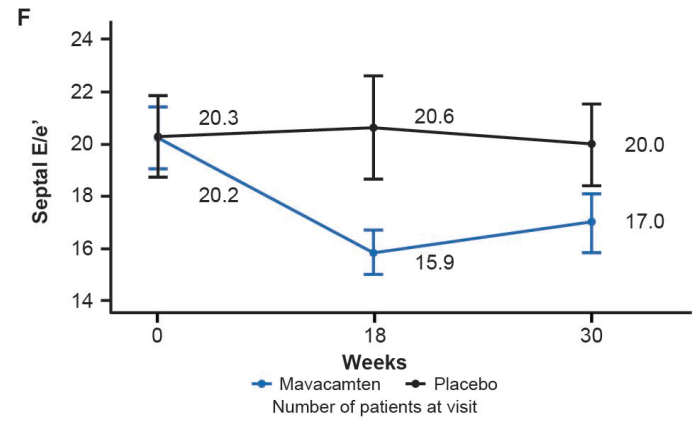
Number of patients at visit

Mavacamten	123	112	113
Placebo	127	118	120



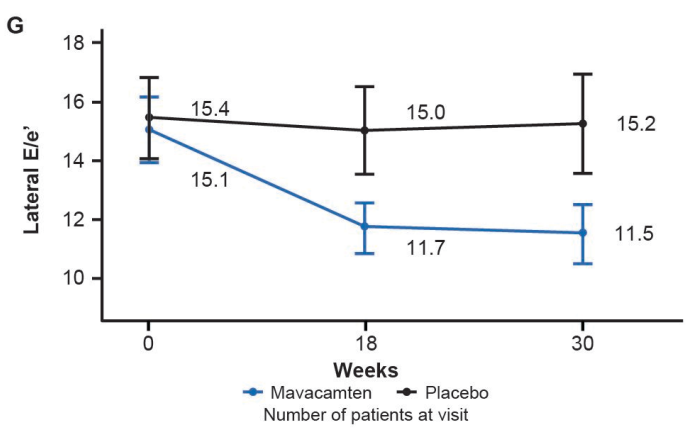
Number of patients at visit

Mavacamten	118	110	111
Placebo	126	113	118



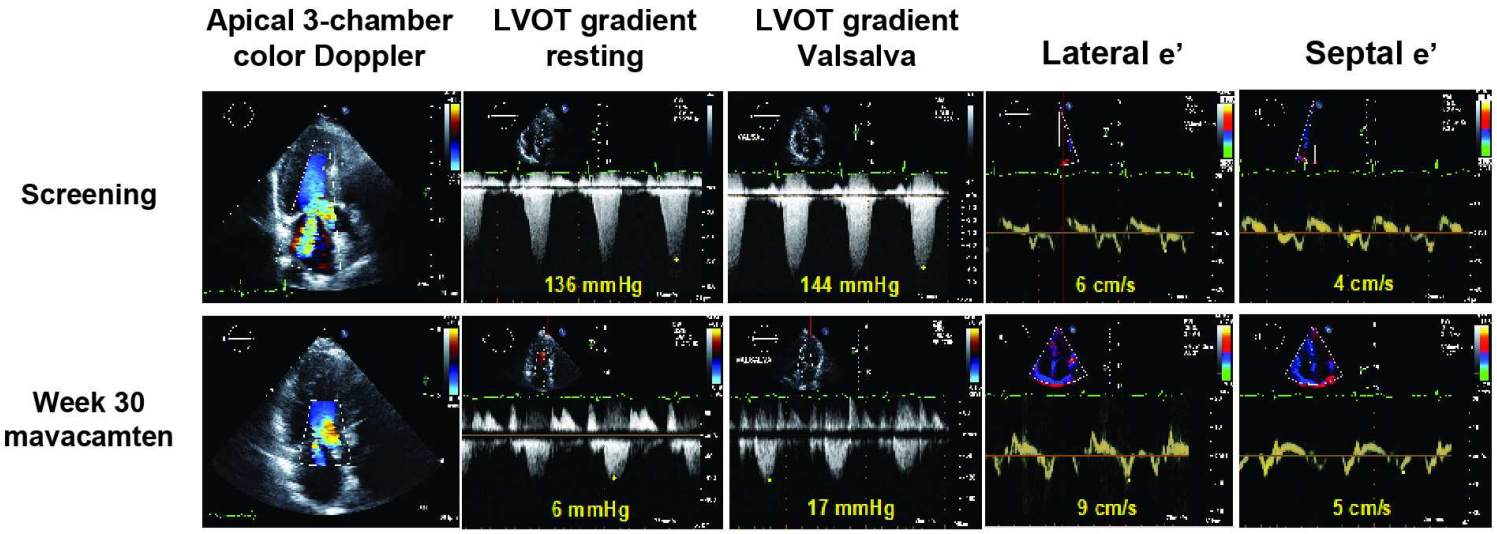
Number of patients at visit

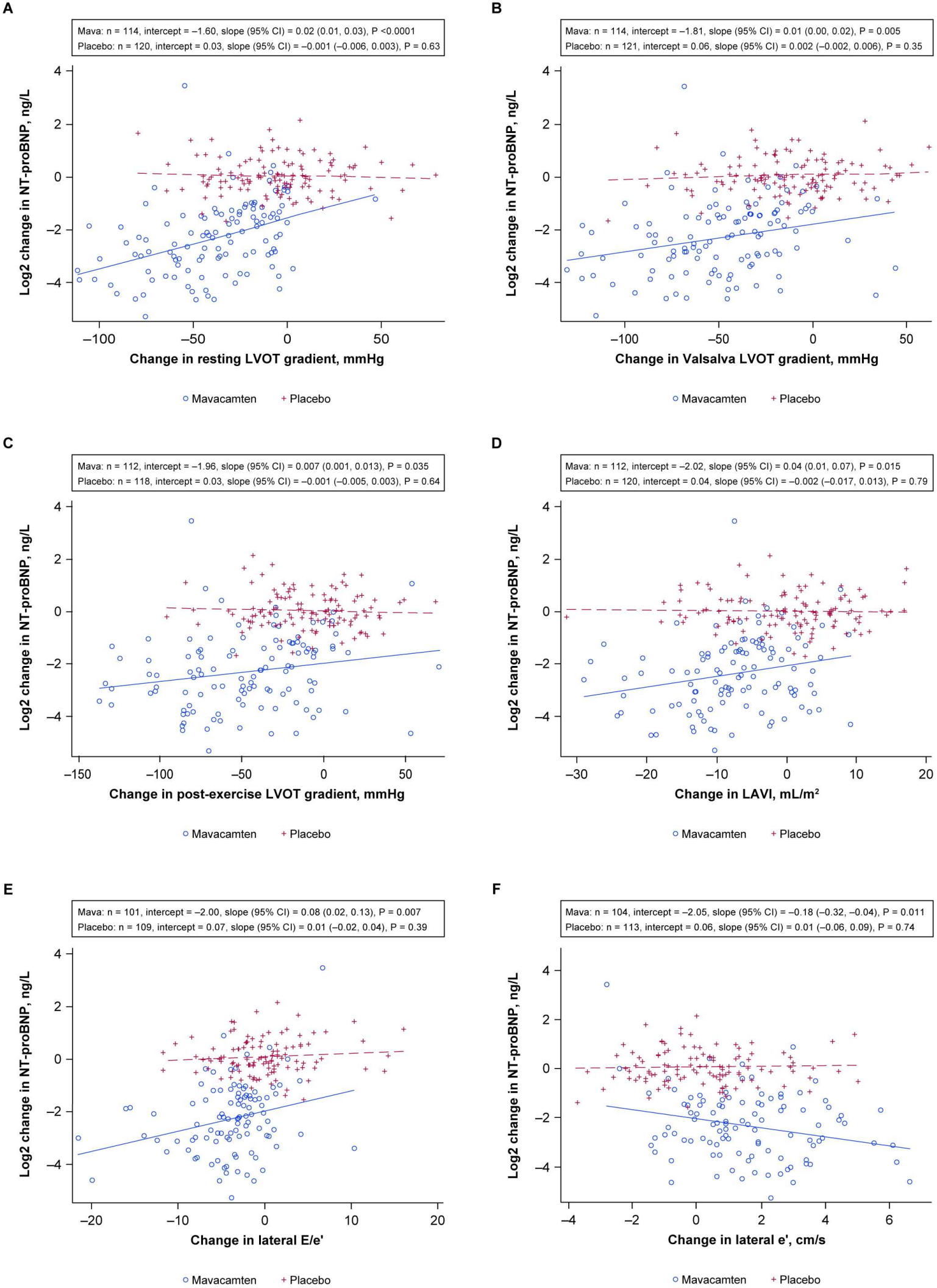
Mavacamten	123	112	111
Placebo	127	116	118



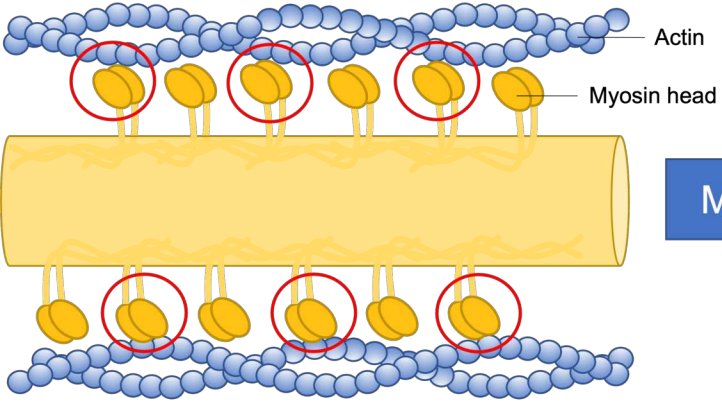
Number of patients at visit

Mavacamten	118	110	108
Placebo	122	112	117


Apical 3-chamber color Doppler
LVOT gradient resting
LVOT gradient Valsalva
Lateral e'
Septal e'
Screening
136 mmHg
144 mmHg
6 cm/s
4 cm/s
Week 30 mavacamten
6 mmHg
17 mmHg
9 cm/s
5 cm/s


A
Mava: n = 114, intercept = –1.60, slope (95% CI) = 0.02 (0.01, 0.03), P <0.0001
Placebo: n = 120, intercept = 0.03, slope (95% CI) = –0.001 (–0.006, 0.003), P = 0.63
Log2 change in NT-proBNP, ng/L
Change in resting LVOT gradient, mmHg
Mavacamten
Placebo
B
Mava: n = 114, intercept = –1.81, slope (95% CI) = 0.01 (0.00, 0.02), P = 0.005
Placebo: n = 121, intercept = 0.06, slope (95% CI) = 0.002 (–0.002, 0.006), P = 0.35
Log2 change in NT-proBNP, ng/L
Change in Valsalva LVOT gradient, mmHg
Mavacamten
Placebo
C
Mava: n = 112, intercept = –1.96, slope (95% CI) = 0.007 (0.001, 0.013), P = 0.035
Placebo: n = 118, intercept = 0.03, slope (95% CI) = –0.001 (–0.005, 0.003), P = 0.64
Log2 change in NT-proBNP, ng/L
Change in post-exercise LVOT gradient, mmHg
Mavacamten
Placebo
D
Mava: n = 112, intercept = –2.02, slope (95% CI) = 0.04 (0.01, 0.07), P = 0.015
Placebo: n = 120, intercept = 0.04, slope (95% CI) = –0.002 (–0.017, 0.013), P = 0.79
Log2 change in NT-proBNP, ng/L
Change in LAVI, mL/m²
Mavacamten
Placebo
E
Mava: n = 101, intercept = –2.00, slope (95% CI) = 0.08 (0.02, 0.13), P = 0.007
Placebo: n = 109, intercept = 0.07, slope (95% CI) = 0.01 (–0.02, 0.04), P = 0.39
Log2 change in NT-proBNP, ng/L
Change in lateral E/e'
Mavacamten
Placebo
F
Mava: n = 104, intercept = –2.05, slope (95% CI) = –0.18 (–0.32, –0.04), P = 0.011
Placebo: n = 113, intercept = 0.06, slope (95% CI) = 0.01 (–0.06, 0.09), P = 0.74
Log2 change in NT-proBNP, ng/L
Change in lateral e', cm/s
Mavacamten
Placebo

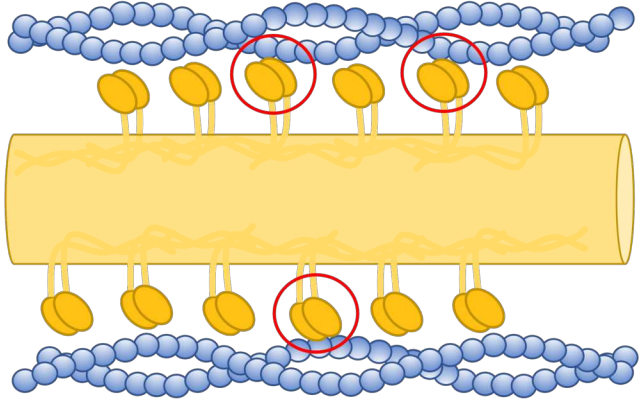
HCM Sarcomere



Too many myosin-actin cross-bridges

Mavacamten

HCM Sarcomere after Mavacamten



Fewer myosin-actin cross-bridges

- ↓ LVEF
- ↓ SAM
- ↓ LVOT gradients
- ↑ e' velocity
- ↓ E/e'
- ↓ LAVI