



# The Impact of Mavacamten on the Pathophysiology of Hypertrophic Cardiomyopathy: A Narrative Review

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## Abstract

Hypertrophic cardiomyopathy (HCM) is a chronic, progressive disease of the cardiomyocyte with a diverse and heterogeneous clinical presentation and course. This diversity and heterogeneity have added to the complexity of modeling the pathophysiological pathways that contribute to the disease burden. The development of novel therapeutic approaches targeting precise mechanisms within the underlying biology of HCM provides a tool to model and test these pathways. Here, we integrate the results of clinical observations with mavacamten, an allosteric, selective, and reversible inhibitor of cardiac myosin, the motor unit of the sarcomere, to develop an integrated pathophysiological pathway model of HCM, confirming the key role of excess sarcomeric activity. This model may serve as a foundation to understand the role of HCM pathophysiological pathways in the clinical presentation of the disease, and how a targeted therapeutic intervention capable of normalizing sarcomeric activity and repopulating low-energy utilization states may reduce the impact of these pathways in HCM and potentially related disease states.

## Key Points

The pathophysiology of hypertrophic cardiomyopathy (HCM) is complex and not yet fully understood.

Mavacamten is a first-in-class, selective, cardiac myosin inhibitor that improved function and symptoms in patients with HCM.

We used established biological pathways and the results of clinical observations with mavacamten to build an integrated pathophysiological pathway model of HCM.

## 1 Introduction

### 1.1 Genetics

Hypertrophic cardiomyopathy (HCM) is a chronic, progressive disease of the cardiomyocyte that leads to increased ventricular wall thickness, with a diverse and heterogeneous clinical presentation and course. Although the pathophysiology of HCM is complex and multifactorial [1], HCM is now generally recognized as a disease caused by dysfunction of the sarcomere, the basic contractile apparatus of the heart muscle. Indeed, approximately 40% of affected individuals, and a significant portion of those with a family history of clinical disease, have at least one mutation in one or more genes that encode sarcomere proteins [2–5]. Moreover, systolic hyperactivity and diastolic dysfunction in HCM have been reported regardless of etiology [6, 7], and often herald the clinical onset of the disease [8]. In most cases, myofibrillar dysfunction resulting from excess sarcomeric myosin–actin cross-bridge formation during systole and, more importantly, diastole, leads to hypertrophy, hypercontractility, and impaired relaxation as well as to myocardial inefficiency and unproductive energy consumption [9].

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## 1.2 Pathophysiology

In the healthy heart, 40–50% of the myosin heads are in the ‘off state’ with negligible energy consumption, whereas in HCM there is a shift in this ratio, with only 15–20% of the myosin heads being in this ‘off state’ [10–12]. The extra myosin heads in the ‘on state’ not only consume more adenosine triphosphate (ATP) (i.e., energy), but are also primed to interact with actin. These effects combine to cause excess myosin–actin cross-bridges during both systole and diastole, leading to inefficient hyperdynamic contraction and diastolic dysfunction [13]. This sustained sarcomeric hyperactivity activates pro-hypertrophic, pro-inflammatory, and pro-fibrotic pathways, resulting in progressive myocardial remodeling, characterized by fibrosis, myofilament disarray, and elevated stresses [13–15].

In a subset of patients with HCM, these functional derangements and their associated altered intraventricular hemodynamics can combine with septal hypertrophy, and/or morphological abnormalities of the mitral valvular apparatus, favoring anteriorly displacing forces which may lead to systolic anterior motion (SAM) of the mitral valve [16]. This combination triggers an obstruction to blood flow, creating a pressure gradient through the left ventricular outflow tract (LVOT), termed obstructive HCM (oHCM) [17]. In other cases, obstruction is due to dynamic narrowing within the left ventricular (LV) chamber driven by hypertrophy.

## 1.3 Current Management

Because the LVOT gradient is dynamic, reflecting increases in obstructing/anteriorly displacing forces that can occur with changes in heart rate, contractile force, and/or loading conditions, patients with oHCM are currently prescribed negative chronotropes and inotropes (non-vasodilating beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide). In cases refractory to pharmacological treatment, invasive therapies such as alcohol septal ablation or myectomy can relieve the structural obstruction. Conversely, in non-obstructive HCM (nHCM), the thickened heart muscle does not block blood outflow from the left ventricle, but does result in impaired relaxation and diastolic dysfunction, which is thought to play an important role in nHCM pathophysiology. Interestingly, impaired relaxation, associated with LV hypertrophy, is also observed in heart failure with preserved ejection fraction.

Responses to mavacamten, a first-in-class, precision intervention that directly targets the cardiac sarcomere and restores its organization and function to a natural state, allow us to confirm the role of the sarcomere and to refine our understanding of the pathology of HCM. Both preclinical (in vitro and in vivo) and clinical data begin to uncover the

potential inter-relationship between HCM’s impacts on systolic and diastolic function and, potentially, extend a framework for studying mechanistically related disease states.

## 1.4 Mavacamten: A Cardiac Myosin Inhibitor

Mavacamten is an allosteric, selective, and reversible inhibitor of cardiac myosin, the motor unit of the sarcomere [18]. Mavacamten decreases the number of myosin heads that can enter the on-actin (power-generating) state, thus reducing the probability of cross-bridge formation in HCM, and shifts the overall myosin population towards the energy-sparing ‘off state’ (see the Electronic Supplementary Material, Fig. S1) [12]. Consequently, and as observed in preclinical studies, mavacamten decreases overall ATP turnover (utilization) at the sarcomere level, reduces diastolic tensions, and promotes relaxation. As a result of these direct, salutary diastolic, systolic, and energy-sparing attributes, mavacamten increases the ventricular chamber size and reduces the velocity of myocardial contraction. This reduces anteriorly displacing forces that favor SAM and, therefore, creates an optimal intraventricular mechanical environment to reduce LVOT obstruction [12, 18, 19].

Because mavacamten has been studied in patients with oHCM and in patients with nHCM, we have aimed to map the related findings to pathophysiological pathways, examining the effects of pharmacological therapy that may be directly related to the impact of HCM on systolic and diastolic function [20–22]. In compiling the pathways, we aimed to describe a potential interdependent systolic and diastolic pathophysiology of HCM, and the resultant potential impact of cardiac myosin-directed intervention.

## 2 Data Source

### 2.1 Studies

Data from five phase 2/3 clinical trials of mavacamten were examined; these studies were as follows: PIONEER-HCM (NCT02842242) [20]; PIONEER-open-label extension (OLE) (NCT03496168; data cut-off June 4, 2020) [23]; MAVERICK-HCM (NCT03442764) [21]; EXPLORER-HCM (NCT03470545) [22] and its cardiac magnetic resonance (CMR) sub-study [24]; and MAVA-long-term extension (LTE) (NCT03723655; data cut-off October 30, 2020) [25]. Most patients enrolled in these studies were receiving background HCM treatments (beta-blockers and/or non-dihydropyridine calcium channel blockers). The designs and study populations are summarized in Table 1. Briefly, MAVA-LTE is an ongoing, extension study of mavacamten in patients who completed either EXPLORER-HCM or MAVERICK-HCM. Site personnel and patients remained

Table 1 Summary of study designs

Study	Phase Population			Design			Data included							
	Age, years	Condition	n	Blinding	Treatment duration	Allocation	LVOT gradient	Serial max. LVWT	E/e'	VE/VCO <sub>2</sub>	LAVI	NT-proBNP	cTnI <sup>a</sup>	ECV
PIONEER-HCM (NCT02842242)	2	18–70	21	Open-label	12 weeks	NA	√	-	√	√	√	√	-	-
PIONEER-OLE (NCT03496168)	2	≥ 18	13	Open-label	120 weeks <sup>b</sup>	NA	√	√	√	-	√	√	-	-
MAVERICK-HCM (NCT03442764)	2	≥ 18	59	Double-blind	16 weeks	Randomized	√	-	√	√	√	√	√	-
EXPLORER-HCM (NCT03470545)	3	≥ 18	251	Double-blind	30 weeks	Randomized	√	-	√	√	√	√	√	-
EXPLORER-HCM CMR sub-study <sup>c</sup> (NCT03470545)	NA	≥ 18	35	Double-blind	30 weeks	Randomized	√	√	-	-	√	√	√	√
MAVA-LTE <sup>d</sup> (NCT03723655)	2/3	≥ 18	267	Dose-blind	252 weeks <sup>e</sup>	NA	√	-	√	x	√	√	√	√

CMR cardiac magnetic resonance, cTnI cardiac troponin I, E/e' ratio between early mitral inflow velocity and early diastolic mitral annular velocity, ECV extracellular volume, HCM hypertrophic cardiomyopathy, LAVI left atrial volume index, LTE long-term extension, LVOT left ventricular outflow tract, LVWT left ventricular wall thickness, max. maximum, NA not applicable, nHCM non-obstructive hypertrophic cardiomyopathy, NT-proBNP N-terminal pro B-type natriuretic peptide, oHCM obstructive hypertrophic cardiomyopathy, OLE open-label extension, VE/VCO<sub>2</sub> minute ventilation to carbon dioxide production

<sup>a</sup>Different assays of varying sensitivities were used in the different studies

<sup>b</sup>The cut-off date for the interim analysis of PIONEER-OLE was June 4, 2020

<sup>c</sup>CMR data will still be collected for patients rolling over to MAVA-LTE; all patients will receive mavacamten

<sup>d</sup>Patients and investigators were blinded with respect to the mavacamten dose that was being administered and assigned treatment group in the parent study; all patients enrolled in MAVA-LTE received mavacamten

<sup>e</sup>The cut-off date for the interim analysis of MAVA-LTE was October 30, 2020, with a maximum treatment exposure of 72 weeks

blinded to treatment assignment and dosing in the respective parent studies.

## 2.2 Study Population

Overall, 331 unique patients were enrolled in the five clinical studies; the majority of patients participated in one of the extension studies. Each parent study included a post-treatment washout period of 4 weeks (PIONEER-HCM) or 8 weeks (MAVERICK-HCM and EXPLORER-HCM), and subsequent re-screening and enrolment into the respective extension studies. Eligible patients were 18 years old or older (and < 70 years for the PIONEER-HCM study only). All patients must have received a diagnosis of HCM (hypertrophied and non-dilated left ventricle in the absence of systemic or other known cause) with a maximum LV wall thickness of 15 mm or more at screening, or 13 mm or more with a positive family history of HCM. Patients in the MAVERICK-HCM study were required to have LVOT gradients under 30 mmHg at rest, during Valsalva maneuver, and post-exercise with no interventricular gradient (obstruction below the level of the LVOT [e.g., mid-cavity]). Eligible patients in the PIONEER-HCM study had a resting LVOT gradient of 30 mmHg or higher and a post-exercise LVOT gradient of 50 mmHg or higher, and these patients were eligible to enroll in the PIONEER-OLE study. Patients in the EXPLORER-HCM study had a Valsalva gradient of 30 mmHg or higher and at least one peak LVOT gradient of 50 mmHg or higher at rest, after Valsalva maneuver, or post-exercise. LV ejection fraction (LVEF) must have been 55% or more at baseline in all patients. The full eligibility criteria have been described previously [20–22]. Upon completion of the MAVERICK-HCM and EXPLORER-HCM studies, patients were eligible to enroll in the MAVA-LTE study.

## 2.3 Treatments

In total, 163 unique patients received mavacamten (PIONEER-HCM,  $n = 21$ ; PIONEER-OLE,  $n = 13$ ; MAVERICK-HCM,  $n = 40$ ; EXPLORER-HCM,  $n = 123$ ) and 147 received placebo (MAVERICK-HCM,  $n = 19$ ; EXPLORER-HCM,  $n = 128$ ). In addition, the 267 patients who enrolled in MAVA-LTE (data cut-off October 30, 2020) all received mavacamten. This includes 224 patients from EXPLORER-HCM (112 of whom previously received placebo) and 43 patients from MAVERICK-HCM (15 of whom previously received placebo). A summary of the dosage regimen used in each study is presented in the electronic supplementary material (Supplementary Table S1).

## 2.4 Outcomes

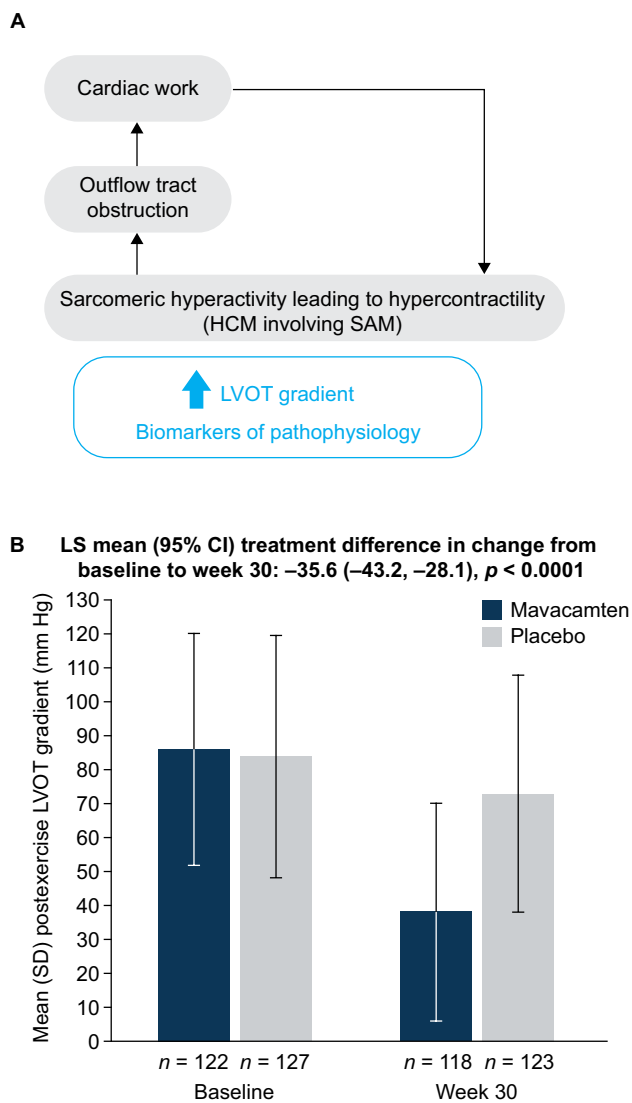
The outcomes of interest for the present article were as follows: LVOT gradient (for oHCM); maximum LV wall thickness; early diastolic mitral annular velocity ( $e'$ ) and the ratio between early mitral inflow velocity ( $E$ ) and  $e'$ ; minute ventilation to carbon dioxide production slope ( $VE/VCO_2$ ); left atrial (LA) volume index (LAVI); N-terminal pro B-type natriuretic peptide (NT-proBNP) level; and cardiac troponin I (cTnI) level (Table 1).

## 3 Observations/Findings

### 3.1 Sarcomeric Hyperactivity and LVOT Obstruction

In oHCM, the asymmetrically hypertrophied septum can lead to a dynamic systolic obstruction, commonly at the LVOT, that requires increased cardiac work to maintain cardiac output (Fig. 1A). Because the dynamic obstruction is the result of HCM-mediated hypertrophy, sarcomeric hyperactivity, and hypercontractility, the need to increase work (contractile force) to sustain cardiac output can result in a maladaptive positive feedback loop that may further increase sarcomeric overdrive and the obstruction (Fig. 1A) [26, 27]. Therefore, the reduction in sarcomeric hyperactivity and hypercontractility observed with mavacamten, measured by a normalization in LVEF, would be expected to lead to a decrease in peak LVOT gradients.

Indeed, mavacamten lowered the LVEF in patients with HCM, bringing it within the normal range in PIONEER, MAVERICK-HCM, EXPLORER-HCM, and MAVA-LTE (see the electronic supplementary material, Supplementary Table S2). Additionally, mavacamten was shown to decrease peak LVOT gradients in patients with oHCM [20, 22]. In the EXPLORER-HCM study, the mean (standard deviation) changes in post-exercise and Valsalva LVOT peak gradient from baseline to week 30 were  $-47$  (40) mmHg and  $-49$  (34) mmHg, respectively, in the mavacamten group and  $-10$  (30) mmHg and  $-12$  (31) mmHg, respectively, in the placebo group (Fig. 1B) [22]. These findings were confirmed in the MAVA-LTE study at week 48. In addition, in EXPLORER-HCM, more patients receiving mavacamten (80.9%;  $n = 76/94$ ) versus placebo (34.0%;  $n = 33/97$ ) showed complete resolution of mitral valve SAM after 30 weeks (difference, 46.8%;  $p < 0.0001$ ) [28]. The changes in LVOT peak gradients from baseline to end of treatment observed in the PIONEER-HCM, PIONEER-OLE, EXPLORER-HCM, and MAVA-LTE studies are presented in the electronic supplementary material (Supplementary Table S2). Notably and consistent with the normalization of sarcomeric activity, overall contractile state, and loading conditions, patients treated with mavacamten displayed



**Fig. 1** **A** The relationship between hypercontractility of the heart, LVOT obstruction, and cardiac work. **B** The effect of mavacamten on post-exercise LVOT peak gradient (EXPLORER-HCM). Data from Olivotto et al. *Lancet* 2020;396:759–69. *CI* confidence interval, *HCM* hypertrophic cardiomyopathy, *LVOT* left ventricular outflow tract, *LS* least-squares, *SAM* septal anterior motion, *SD* standard deviation

greater improvements in peak oxygen consumption ( $p\text{VO}_2$ ), a multidimensional index dependent on cardiac output, than those receiving placebo [22].

### 3.2 Sarcomeric Hyperactivity and LV Hypertrophy

The sarcomeric hyperactivity that occurs in HCM and that leads to hypercontractility of the heart has also been linked to an increase in pro-hypertrophic signaling [29], which in turn results in LV hypertrophy (Fig. 2A). Maximum LV wall thickness is a commonly accepted indicator of LV hypertrophy.

NT-proBNP, a biomarker of pro-hypertrophic signaling, is an inactive, stable peptide synthesized primarily in the left ventricle in response to increased wall tension, and plasma levels of NT-proBNP have been positively correlated with cardiac filling pressure [30, 31]. Owing to the mechanism of action of mavacamten and based on the relationships described above, a reduction in hypercontractility following treatment with mavacamten, as measured by change in LVEF, would be expected to lead to a decrease both in pro-hypertrophic signaling and in LV hypertrophy, as measured by plasma levels of NT-proBNP and maximal LV wall thickness, respectively.

Mavacamten treatment significantly reduced plasma NT-proBNP levels from baseline to end of treatment in both the oHCM and the nHCM studies, including PIONEER-HCM, PIONEER-OLE, MAVERICK-HCM, EXPLORER-HCM, and MAVA-LTE (Fig. 2B; Electronic Supplementary Material, Supplementary Table S2), and reductions in the cardiac gene expression of natriuretic peptide precursors following mavacamten treatment were observed in a mouse HCM model [19].

In the EXPLORER-HCM CMR sub-study, mavacamten was associated with a greater reduction in maximal LV wall thickness measured by CMR than placebo (Fig. 2C; Supplementary Table S2), although the LV wall thickness remained in the hypertrophic range [24, 32]. It should be noted that only a small number of patients were enrolled in the CMR sub-study, and that although the change in LV wall thickness associated with mavacamten was statistically significant, it was small and should therefore be interpreted with caution. However, a reduction in LV wall thickness with mavacamten treatment was also observed in a model of HCM in heterozygous mice harboring a human mutation in the myosin heavy chain [19].

### 3.3 LV Hypertrophy and Relaxation

LV diastolic dysfunction is another hallmark of HCM that can be characterized by impaired relaxation [33–35]. LV hypertrophy has been shown to be a major contributing factor to impaired relaxation (Fig. 3A) [36–39]. Avegliano et al. reported an association between LV hypertrophy and the degree of diastolic dysfunction using tissue Doppler echocardiography methods [40]. Moreover, Wigle et al. showed a direct correlation between LV end-diastolic pressure and the extent of LV hypertrophy, and Chacko et al. reported a correlation between maximum LV wall thickness and diastolic function using CMR [41, 42]. Finally, Finocchiaro et al. also demonstrated a positive correlation between diastolic dysfunction and the degree of hypertrophy [43]. In addition, there is evidence that LV hypertrophy is associated with diastolic dysfunction and impaired relaxation (Fig. 3A) [44, 45]. However, it should be noted that other factors such

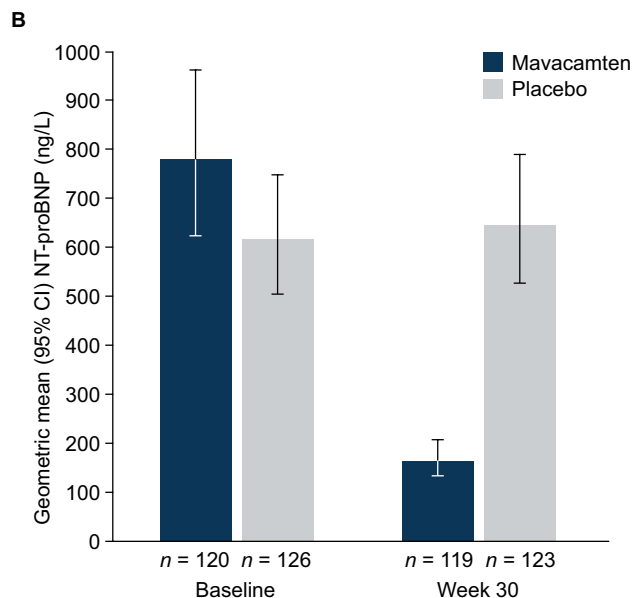
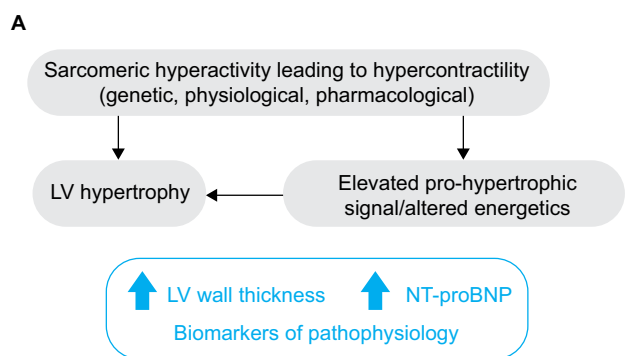
**Fig. 2** **A** The relationship between hypercontractility of the heart, LV hypertrophy, and elevated wall stress. **B** NT-proBNP plasma levels (EXPLORER-HCM). **(C)** The effect of mavacamten on maximal LV wall thickness (EXPLORER-HCM CMR sub-study). Reduction in NT-proBNP level after mavacamten treatment was 80% greater than for placebo (proportion of geometric mean ratio between the two groups, 0.202; 95% CI 0.169–0.241). The LV wall thickness after reduction following mavacamten treatment was still in the hypertrophic range. Data from Olivetto et al. *Lancet* 2020;396:759–69 and from Saberi et al. *Circulation* 2020;142:e470–500, abstract 18654. *CI* confidence interval, *CMR* cardiac magnetic resonance, *HCM* hypertrophic cardiomyopathy, *LV* left ventricular, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *SD* standard deviation

as abnormal calcium handling, structural remodeling, fibrosis, and/or inflammation can alter ventricular relaxation and filling.

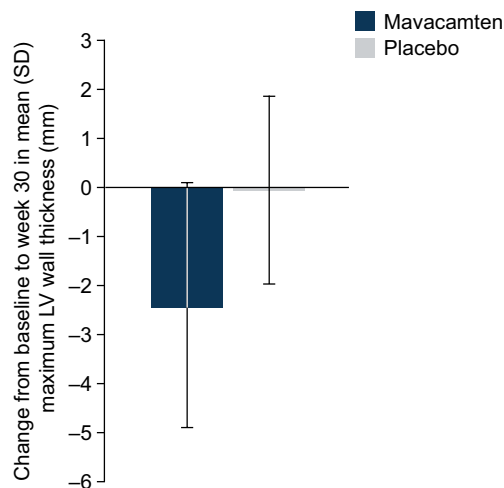
Reduced and delayed  $e'$  velocity is associated with impaired myocardial relaxation, while the  $E/e'$  ratio measured by echocardiography is a commonly used surrogate of LV filling pressure, and both are central to the evaluation of diastolic function [46–48]. As such, an elevated  $E/e'$  ratio is a good indicator of impaired relaxation of the heart, with healthy individuals presenting a ratio of less than 8, and a ratio over 14 suggesting elevated filling pressure and hindered relaxation [49]. Interestingly, Badran et al. demonstrated that the  $E/e'$  ratio was a powerful independent predictor of cardiac events in patients with HCM [50]. Overall, the ability of mavacamten to increase  $e'$  (Fig. 3B) and to reduce the  $E/e'$  ratio provides further evidence to support the interrelationship between LV hypertrophy on one hand and impaired relaxation of the heart on the other (see the Electronic Supplementary Material, Supplementary Table S2) [21, 22].

### 3.4 Impaired Relaxation, Increased Preload and LA Volume, and Risk of Atrial Fibrillation and Elevated Pulmonary Pressure

Impaired relaxation increases ventricular filling pressure, as seen by the elevated measures of  $E/e'$  described above and, therefore, diastolic stresses. Moreover, Appleton et al. have reported an association between increased LV filling pressure and LA enlargement in patients with cardiac disease [51]. It is well established that increased LAVI is associated with an increased risk of atrial fibrillation (AF) in patients with HCM (Fig. 4A) [52, 53]. Indeed, Tani et al. reported that LA volume was the most sensitive predictor for the occurrence of paroxysmal AF in patients with HCM [54]. In a retrospective longitudinal analysis, Debonnaire et al. showed that LA diameter and volume were positively correlated with new onset of AF in patients with HCM [55]. Interestingly, Costabel et al. demonstrated that the  $E/e'$  ratio as well as LA enlargement were strong, independent predictors of AF [56]. Both elevated  $E/e'$  and LA enlargement

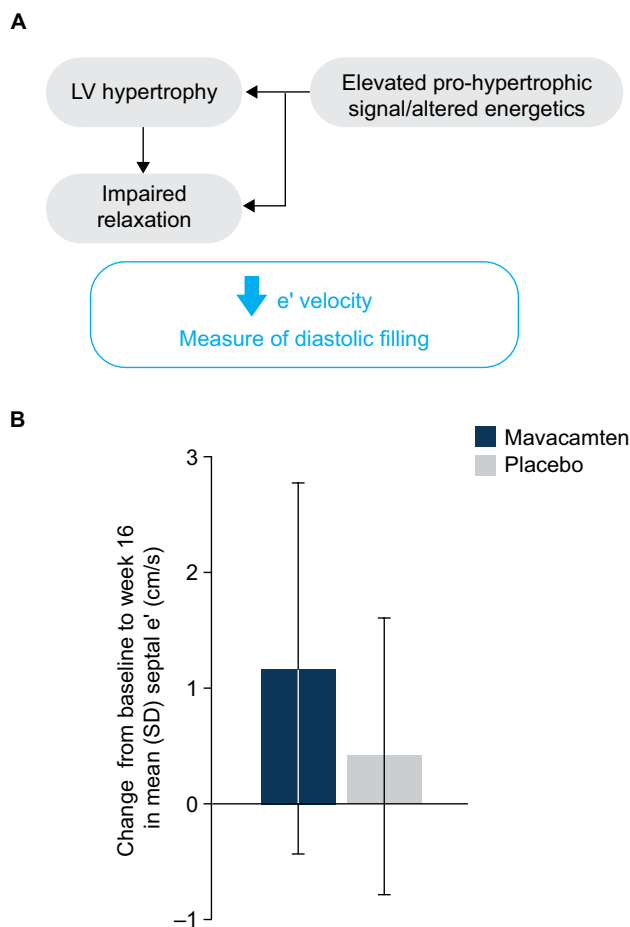


**C** Mean (95% CI) treatment difference in change from baseline to week 30:  $-2.4$  ( $-3.9$ ,  $-0.9$ ),  $p = 0.0079$



were observed at baseline in the patients with HCM enrolled in mavacamten clinical studies.

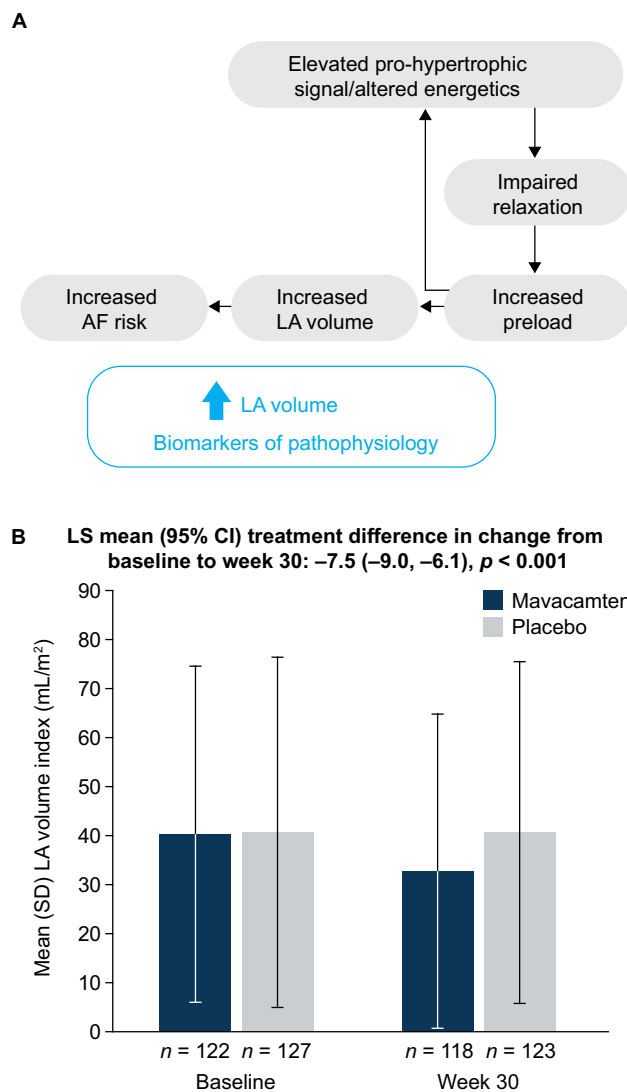
Consequently, mavacamten would be expected to decrease LA volume through its capacity to promote



**Fig. 3** **A** The relationship between elevated wall stress, LV hypertrophy, and impaired relaxation. **B** The effect of mavacamten on septal  $e'$  (MAVERICK-HCM). Data from Ho et al. *J Am Coll Cardiol* 2020;75:2649–60.  $e'$  early diastolic mitral annular velocity, HCM hypertrophic cardiomyopathy, LV left ventricular, SD standard deviation

relaxation, among other potential mechanisms. Indeed, results from PIONEER-OLE, EXPLORER-HCM, and the EXPLORER-HCM CMR sub-study showed reductions in LAVI in patients with oHCM (Fig. 4B; Electronic Supplementary Material, Supplementary Table S2) [24, 28]. The effect on LAVI was not observed during the 16-week MAVERICK-HCM study in nHCM, possibly owing to the short duration of the study, but reductions have been observed in the MAVA-LTE MAVERICK cohort over longer periods of treatment (Supplementary Table S2) [21, 57]. In EXPLORER-HCM, the rates of AF were similar between the mavacamten and placebo groups [22]. The impact of mavacamten on the occurrence of AF is being investigated through ongoing observation of AF events in the MAVA-LTE study.

Furthermore, increased LV filling pressure in HCM could lead to elevated pulmonary pressures, which can manifest by



**Fig. 4** **A** The relationship between elevated wall stress, impaired relaxation, increased preload, and LA volume, and the risk of AF. **B** The effect of mavacamten on LA volume index (EXPLORER-HCM). Data from Hegde et al. *J Am Coll Cardiol* 2021;78:2518–32. AF atrial fibrillation, CI confidence interval, HCM hypertrophic cardiomyopathy, LA left atrial, LS least-squares, SD standard deviation

an abnormal ventilatory response to exercise. The  $VE/VCO_2$  slope is a measure of ventilatory efficiency and can be used to identify an abnormal ventilatory response [58]. The reduction in  $VE/VCO_2$  slope observed in patients with symptomatic oHCM who were enrolled in the PIONEER-HCM and EXPLORER-HCM studies [20, 22] and who were treated with mavacamten may be indicative of reduced pulmonary congestion. However,  $VE/VCO_2$  slope is a complex biological parameter comprising several determinants which might also have influenced the improvements in ventilatory efficiency observed. Furthermore, improvements in the HCM Symptom Questionnaire (HCMSQ)-Shortness-of-Breath

sub-score and in the numerical rating scale (NRS) dyspnea score have been reported in the EXPLORER-HCM and PIO-NEER studies, respectively, reinforcing the potential for a mechanistic correlation [20, 22].

### 3.5 Hypertrophy, Myocardial Ischemia/injury, and Fibrosis

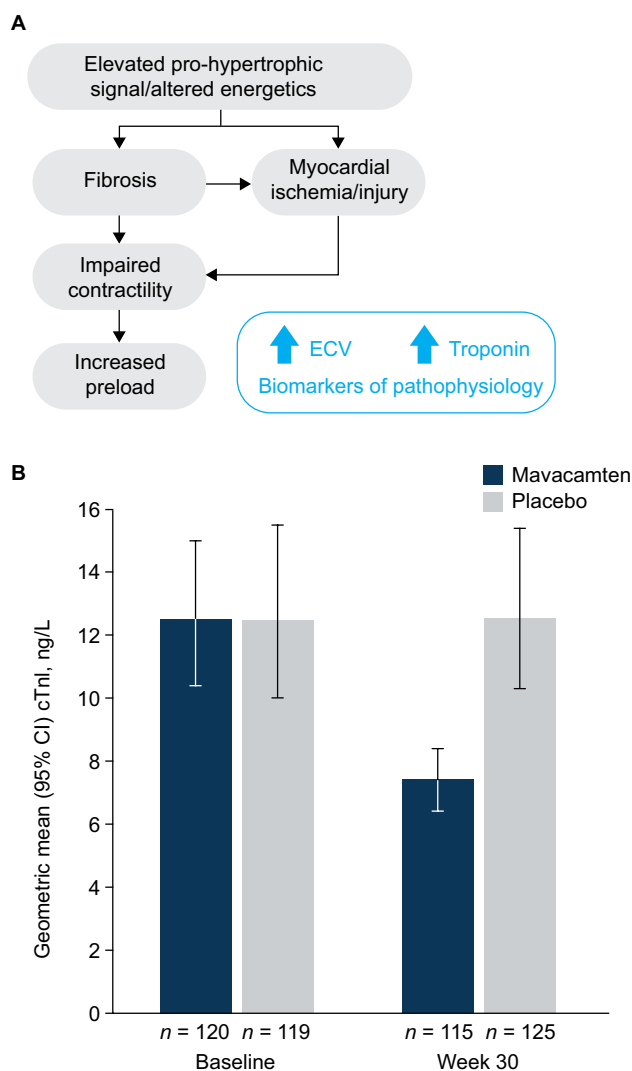
The hypertrophied ventricular myocardium has an increased myocardial oxygen demand leading to abnormal myocardial blood flow, which can be regarded as a surrogate for myocardial ischemia in patients with HCM [59]. Because increases in troponin levels show high specificity for myocyte cell death, cTnI and cardiac troponin T (cTnT) are strong and specific indicators of myocardial injury, and are well-established biomarkers of ischemia and cardiac injury [60, 61]. Additionally, altered energetics observed in HCM are characterized by an increase in glucose uptake, which reflects an impaired metabolism and has been linked to troponin release in HCM [62]. In patients with HCM, altered energetics have also been proposed as a potential mechanism driving fibrosis [63], which is a histopathological hallmark of HCM and is regarded as a consequence of ischemic and hemodynamic stressors [64]. The non-invasive assessment of myocardial extracellular volume (ECV) fraction by CMR is an established measure of interstitial fibrosis [65, 66].

Although the exact cause of troponin release in HCM is still unresolved, owing to its beneficial effect on hypertrophy and in accordance with the aforementioned relationships (Fig. 5A), mavacamten would be expected to reduce the level of myocardial ischemia/injury and fibrosis, and therefore the levels of injury biomarkers (such as cTnI and cTnT) and ECV observed in patients with HCM. Indeed, reductions in cTnI level have been reported in the MAVERICK-HCM and EXPLORER-HCM studies (Fig. 5B; Electronic Supplementary Material, Supplementary Table S2).

### 3.6 Proposed Integrated Model of HCM Clinical Pathophysiology

Because HCM has an impact on multiple pathophysiological pathways, we aimed to organize the learnings from the mavacamten studies into an integrated model (Fig. 6).

The proposed model places sarcomeric hyperactivity and hypercontractility at the center of the anatomical and pathophysiological pathways of HCM (Fig. 6A). By design, mavacamten is able to normalize the sarcomeric hyperactivity observed in HCM, and provides a mechanistically targeted therapeutic approach with downstream improvement in several of the various pathophysiological manifestations of HCM that extend well beyond LVOT obstruction relieve and negative inotropy. The proposed pathophysiological model of HCM suggests a unifying mechanism for structural



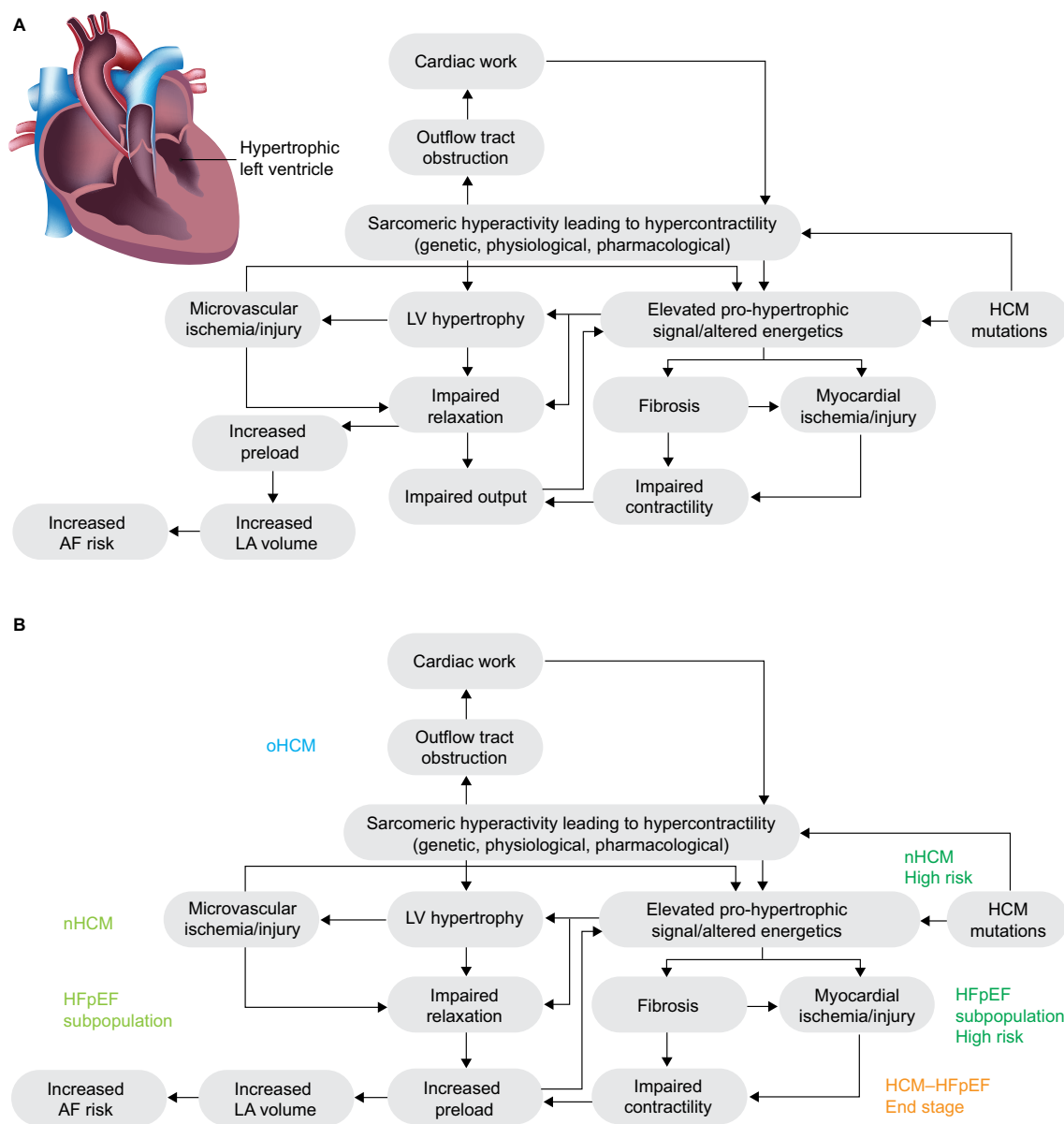
**Fig. 5** **A** The relationship between elevated wall stress, myocardial ischemia/injury, fibrosis, impaired contractility, and increased preload. **B** The effect of mavacamten on cTnI levels (EXPLORER-HCM). Data from Olivotto et al. *Lancet* 2020;396:759–69. *CI* confidence interval, *cTnI* cardiac troponin I, *ECV* extracellular volume, *HCM* hypertrophic cardiomyopathy

changes associated with HCM and other diseases of pathogenic hypertrophy such as heart failure with preserved ejection fraction (Fig. 6B) [67–69]. Figure 7 shows the various biomarkers used to assess the clinical course of the disease, and the effect of mavacamten on those biomarkers.

## 4 Discussion

The pathophysiology of HCM is complex, multifactorial, and not fully understood. Here, we propose an integrated model of HCM clinical pathophysiology based on established pathways of the disease and on the effect of





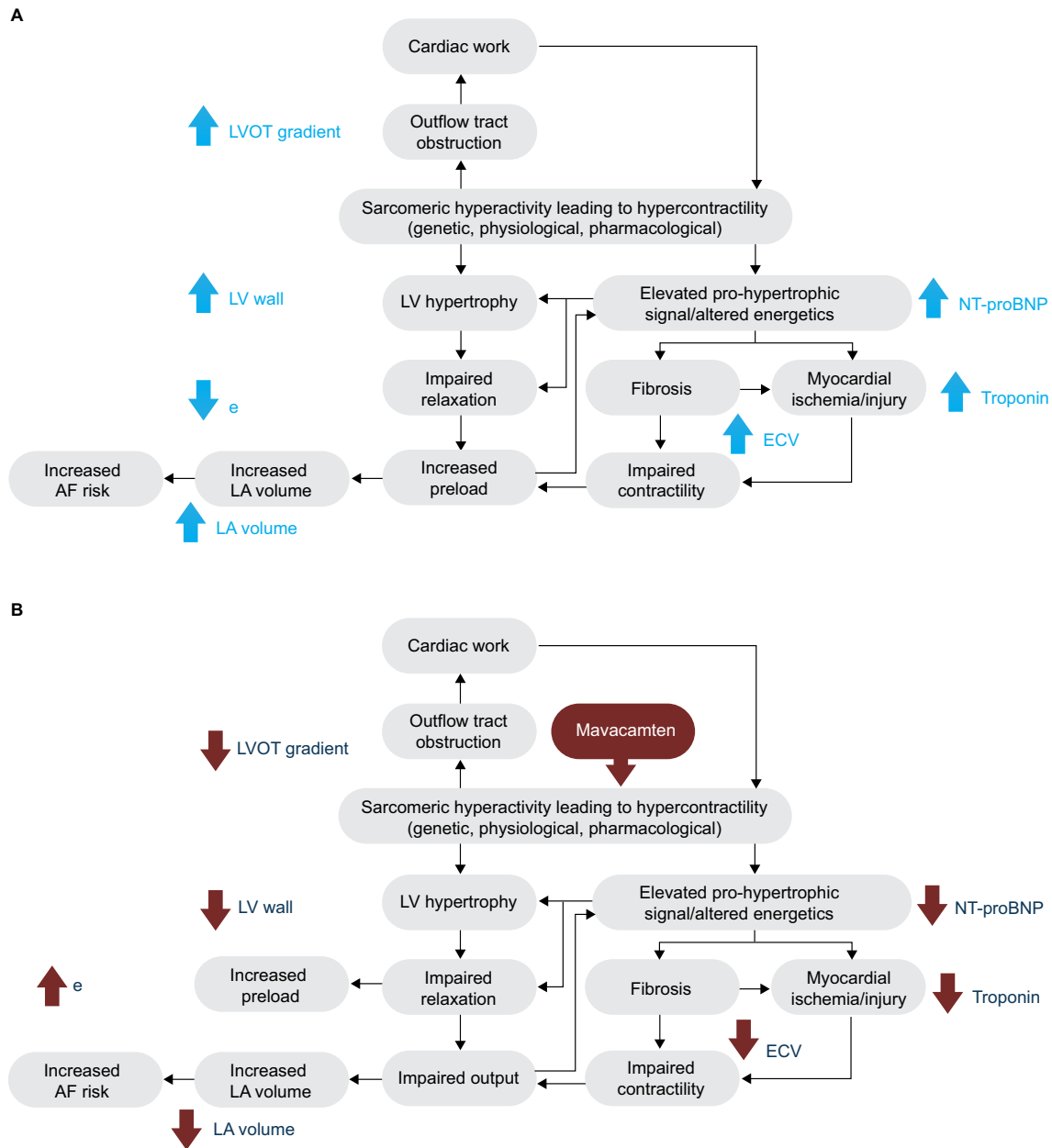
**Fig. 6** **A** Proposed integrated model of HCM clinical pathophysiology. **B** The common mechanism with HFpEF. *AF* atrial fibrillation, *HCM* hypertrophic cardiomyopathy, *HFpEF* heart failure with pre-

served ejection fraction, *LA* left atrial, *LV* left ventricular, *nHCM* non-obstructive hypertrophic cardiomyopathy, *oHCM* obstructive hypertrophic cardiomyopathy

mavacamten, the first-in-class, selective inhibitor of cardiac myosin. The pathway model highlights the proposed positive feedback loop in *oHCM*, placing sarcomeric overactivity as its main effector, and emphasizing the connection of this loop to the broader pathways impacted in *HCM*. It is not anticipated that all pathways are equal nor that the pathways are similarly induced in all patients with *HCM* at all times. Indeed, it is well established that the presentations of *HCM* are diverse with temporal variability. The results with mavacamten serve as a means to better understand *HCM* pathophysiology, the relationship between *HCM*'s impacts on systolic and diastolic function, and improvements that

could address the underlying biology of *HCM*. The lack of effect in patients with *nHCM* on exercise performance, NT-proBNP levels, diastolic function or quality of life observed with ranolazine, a late sodium inhibitor, illustrates the specific action of mavacamten and strengthen the model hypothesized here [70].

Owing to its mechanism of action, mavacamten reduces hypercontractility by returning more myosin heads to the 'off state.' Multiple *ex vivo* and *in vivo* studies support the clinical observations summarized in this article. For instance, *in vivo*, mavacamten has been shown to blunt cardiac hypercontractility, alleviating *LVOT* obstruction and improving



**Fig. 7** **A** The biomarkers of HCM. **B** The overall effect of mavacamten. AF atrial fibrillation, ECV extracellular volume,  $e'$  early diastolic mitral annular velocity, HCM hypertrophic cardiomyopathy, LA

left atrial, LV left ventricular, LVOT left ventricular outflow tract, nHCM non-obstructive hypertrophic cardiomyopathy, NT-proBNP N-terminal pro B-type natriuretic peptide

systemic hemodynamic. In cats with naturally occurring HCM [71] and in mice harboring HCM pathogenic mutation in myosin, mavacamten has been shown to not only prevent hypertrophy (i.e., reduce hypertrophic wall thickness), but also to prevent the activation of pro-inflammatory, pro-fibrotic, and pro-hypertrophic pathways, including the normalization of natriuretic peptide gene expressions [19]. Results from the studies of mavacamten enabled the development of the proposed model of HCM pathophysiology that is generalizable to both oHCM and nHCM, and illustrate

the impact of normalizing the ratio of 'on' and 'off' myosin heads on the HCM heart. The model allows the integration of the diverse results of mavacamten treatment in oHCM and nHCM studies to illustrate the potential relationship between obstruction, LV hypertrophy, myocardial ischemia/injury and LA volume, and diastolic filling. This integrated model links the ability of mavacamten to reverse the pathophysiology of HCM to resolve clinical presentations and suggests possible extensions to other diseases caused by a similar underlying pathophysiology.

It should be noted that, although based on pre-clinical and clinical evidence, our model remains hypothetical and has the potential to serve as a blueprint for future studies. This model will most certainly require refinement as more evidence emerges from other studies. For instance, pre-clinical and clinical evidence from other cardiac myosin inhibitors such as aficamten, which has been reported to reduce LVOT gradients in a phase 2 trial, would help in refining and strengthening our model [72]. Additionally, it would be of great interest to assess the effect of cardiac myosin inhibitors in patients with heart failure with preserved ejection fraction. Another area of potential future research is the investigation of the pathophysiology of HCM and of the effects of cardiac myosin inhibitors in a pediatric patient population.

## 5 Conclusions

Building from well-known pathophysiological pathways of HCM and previously published data on the effects of mavacamten on accepted HCM biomarkers, we constructed an integrated model of HCM clinical pathophysiology that identifies sarcomeric hyperactivity as a key driver of disease.

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## Declarations

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**Conflict of interest** AJS and RM are employees of MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb. JME, MEM, and CLdR were employees of MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb.

**Ethical approval** This article does not contain any previously unpublished studies with human participants or animals performed by any of the authors.

**Availability of data** The data underlying this article will be shared on reasonable request to the corresponding author.

**Code availability** Not applicable.

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