

Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Aficamten, a next-in-class cardiac myosin inhibitor, improved peak oxygen uptake (pV_{O_2}) and lowered resting and Valsalva left ventricular outflow (LVOT) gradients in adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM), a phase 3, multicenter, randomized, double-blinded, placebo-controlled study.

OBJECTIVES The authors sought to evaluate the effect of aficamten on echocardiographic measures of cardiac structure and function in SEQUOIA-HCM.

METHODS Serial echocardiograms were performed over 28 weeks in patients randomized to receive placebo or aficamten in up to 4 individually titrated escalating doses (5-20 mg daily) over 24 weeks based on Valsalva LVOT gradients and left ventricular ejection fraction (LVEF).

RESULTS Among 282 patients (mean age 59 ± 13 years; 41% female, 79% White, 19% Asian), mean LVEF was $75\% \pm 6\%$ with resting and Valsalva LVOT gradients of 55 ± 30 mm Hg and 83 ± 32 mm Hg, respectively. Over 24 weeks, aficamten significantly lowered resting and Valsalva LVOT gradients, and improved left atrial volume index, lateral and septal e' velocities, and lateral and septal E/e' (all $P \leq 0.001$). LV end-systolic volume increased and wall thickness decreased (all $P \leq 0.003$). Aficamten resulted in a mild reversible decrease in LVEF (-4.8% [95% CI: -6.4 to -3.3]; $P < 0.001$) and absolute LV global circumferential strain (-3.7% [95% CI: 1.8 - 5.6]; $P < 0.0010$), whereas LV global longitudinal strain was unchanged. Several measures, including LVEF, LVOT gradients, and E/e' returned to baseline following washout. Among those treated with aficamten, improved pV_{O_2} and reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with improvement in lateral e' velocity and septal and lateral E/e' (all $P < 0.03$), whereas improvement in Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores (KCCQ-CSS) was associated with a decrease in both LVOT gradients (all $P < 0.001$).

CONCLUSIONS Compared with placebo, patients receiving aficamten demonstrated significant improvement in LVOT gradients and measures of LV diastolic function, and several of these measures were associated with improvements in pV_{O_2} , KCCQ-CSS, and NT-proBNP. A modest decrease in LVEF occurred yet remained within normal range. These findings suggest aficamten improved multiple structural and physiological parameters in oHCM without significant adverse changes in LV systolic function. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM [SEQUOIA-HCM]; [NCT05186818](https://clinicaltrials.gov/ct2/show/study/NCT05186818)) (JACC. 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**ABBREVIATIONS
AND ACRONYMS****CPET** = cardiopulmonary exercise testing**e'** = early diastolic mitral annular velocity**E/e'** = ratio between early mitral inflow velocity and early diastolic mitral annular velocity**GCS** = global circumferential strain**GLS** = global longitudinal strain**HCM** = hypertrophic cardiomyopathy**KCCQ-CSS** = Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores**LA** = left atrial**LV** = left ventricular**LVEF** = left ventricular ejection fraction**LVOT** = left ventricular outflow tract**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**oHCM** = obstructive hypertrophic cardiomyopathy**pVO₂** = peak oxygen consumption**RV** = right ventricular**SAM** = systolic anterior motion**TAPSE** = tricuspid annular plane systolic excursion

Hypertrophic cardiomyopathy (HCM), the most common inherited heart disease, is characterized by left ventricular (LV) hypertrophy not attributable to another cause and often associated with increased cardiac contractility and impaired LV diastolic function, leading to progressive symptoms, particularly with exercise.¹ Approximately two-thirds of patients present with dynamic left ventricular outflow tract (LVOT) obstruction at rest and/or with provocation, which when symptomatic, is the target of guideline-recommended therapies and associated with increased cardiac morbidity and mortality.¹⁻⁴ Echocardiography is essential for: establishing the diagnosis of HCM; routine assessment of disease progression, including degree of LVOT obstruction and severity of mitral regurgitation; risk assessment of sudden cardiac death and atrial fibrillation; and response to therapy.^{1,5,6}

Recently updated guidelines for the management of obstructive hypertrophic cardiomyopathy (oHCM) now include cardiac myosin inhibitors as second-line therapy in patients with persistent symptoms despite beta-blockers or non-dihydropyridine calcium-channel blockers as a Class I recommendation and alternative to disopyramide or septal reduction therapy.¹ Mavacamten, the recently approved first-in-class cardiac myosin inhibitor, improved exercise capacity, symptoms, and LVOT gradients in patients with oHCM.^{7,8} In addition, mavacamten therapy significantly improved measures of LV diastolic function.^{9,10} Aficamten, the next-in-class cardiac myosin inhibitor, has distinct pharmacologic properties allowing for echocardiography-based dose titration as early as 14 days after dose initiation as a result of a half-life of ~3 days.¹¹⁻¹³ In SEQUOIA-HCM

(Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM; [NCT05186818](#)), the phase 3 trial in patients with oHCM treated with aficamten, demonstrated rapid and significant improvement in peak oxygen uptake (pVO₂), symptoms by Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores (KCCQ-CSS), resting and Valsalva LVOT gradients, New York Heart Association (NYHA) functional class, and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

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METHODS

STUDY DESIGN. SEQUOIA-HCM was a phase 3, multicenter, randomized, double-blind, randomized, placebo-controlled trial in patients with symptomatic oHCM. As previously described, eligible individuals aged 18 to 85 years with a confirmed clinical diagnosis of oHCM (LV wall thickness ≥15 mm with unexplained hypertrophy), left ventricular ejection fraction (LVEF) ≥60%, resting LVOT gradient ≥30 mm Hg, Valsalva LVOT gradient ≥50 mm Hg, predicted pVO₂ ≤90%, and on stable background medical therapy for >6 weeks, received aficamten or placebo in a 1:1 ratio.^{14,15} Additional inclusion and exclusion criteria are available in [Supplemental Table 1](#). The protocol was reviewed and approved by an institutional review board at all sites, and all patients provided written informed consent.

STUDY PROCEDURES. Patients were randomized to either placebo or aficamten with up to 4 escalating doses of aficamten (5-20 mg) within the first 6 weeks of the trial to achieve Valsalva LVOT <30 mm Hg while maintaining an LVEF ≥50%. Doses were then maintained until week 24, followed by a 4-week washout

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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period. Serial resting echocardiograms were performed at screening, day 1, and weeks 2, 4, 6, 8, 12, 16, 20, 24 (end of treatment), and 28 (end of study). Site-read LVEF and Valsalva LVOT gradients were assessed by masked echocardiographers onsite and entered into the web-response system to determine dose titration. Limited echocardiograms were performed for weeks 2, 4, 6, and 8 for titration purposes. Certified sonographers at each site performed all echocardiograms according to a prespecified protocol, and images were evaluated, blinded to treatment assignment, by the Cardiovascular Imaging Core Laboratory (Brigham and Women's Hospital) according to American Society of Echocardiography recommendations.¹⁶ Lab-wide reproducibility data have been published previously,¹⁷ and intraobserver variability for key echocardiographic measures for this study are included in [Supplemental Table 2](#). Maximum LV wall thickness was derived from the greatest wall thickness measured in the parasternal long- and short-axis views. Chamber dimensions included LV end-diastolic dimension, LV end-systolic dimension, LV end-diastolic volume index, LV end-systolic volume index, left atrial (LA) volume index, and left atrial width. The modified Simpson's method was used to estimate LVEF. LV mass index was derived from the linear dimensions and indexed to height^{2.7} per guidelines. Diastolic function parameters included early and late mitral inflow velocity (E-wave and A-wave velocity), septal and lateral early diastolic mitral annular velocity (septal e' and lateral e' velocity), and ratio between early mitral inflow velocity and septal and lateral mitral annular early diastolic velocity (septal E/e' and lateral E/e' ratio, respectively). As per updated LV diastolic function criteria, recommendations are for classification as either normal, indeterminate, or abnormal based on the presence or absence of abnormalities in: 1) average E/e' >14; 2) septal e' <7 cm/s or lateral e' <10 cm/s; 3) tricuspid regurgitation velocity <280 cm/s; and 4) LA volume index >34 mL/m².¹⁸ Due to a high degree of missingness (>50%), tricuspid regurgitation velocity was not used in the assessment of abnormal LV diastolic function measures.¹⁹ LVOT gradients were measured as the peak LVOT gradient at rest and following Valsalva maneuver. The imaging protocol instructed sonographers to sweep the angle of interrogation between the LVOT and LA to allow for better discrimination of LVOT gradients from mitral regurgitation Doppler profiles. The average of 3 peak resting LVOT gradients was measured in normal sinus rhythm and atrial fibrillation. The peak Valsalva gradient was measured as the peak value with attention to avoid

the measurement of ectopic beats or particularly abnormal R-R intervals. LV global longitudinal strain (GLS) and circumferential strain (GCS) were assessed with speckle tracking using vendor-independent software (TOMTEC); endocardial layer strain values are reported as absolute values. Analysis was performed on images with a frame rate of 50 to 80 frames/s. LV GLS was measured in the apical 4-chamber and apical 2-chamber views, whereas LV GCS was performed in the parasternal short-axis view at the level of the midpapillary muscle. Images with >1 segment dropout or significant foreshortening of the LV were not analyzed. The optimal cycle in normal sinus rhythm and atrial fibrillation was selected by the analyst. Mitral valve systolic anterior motion (SAM) was identified as present or absent. At the end of the study, those with absent SAM were defined as having complete resolution of SAM. Measures of right ventricular (RV) systolic function included tricuspid annular plane systolic excursion (TAPSE) and RV s' velocity.

STATISTICAL ANALYSES. Placebo-corrected treatment difference in echocardiographic parameters at 24 weeks and at 28 weeks (after 4 weeks of washout) compared with baseline was assessed using linear regression models adjusted for baseline echocardiographic parameter, treatment, and stratification by beta-blockers and exercise mode (bicycle vs treadmill). Linear regression models were used to assess the association between changes in pVO₂, the primary endpoint for SEQUOIA-HCM, and other clinical endpoints (NT-proBNP, KCCQ-CSS, NYHA functional class, high-sensitivity cardiac troponin I) and changes in echocardiographic measures, after adjusting for respective baseline values, beta-blocker use, and exercise mode with results presented as stratified by treatment. The model was fitted within each treatment group separately. Log₂ changes were evaluated for changes in NT-proBNP and high-sensitivity cardiac troponin I. The association between changes in LV GCS and changes in LVEF was assessed using a restricted cubic spline model. The number of knots that minimized model Akaike's information criterion (AIC) was selected (2 to 5 knots assessed), and 2 knots (a linear model) demonstrated the lowest AIC. The model was additionally adjusted for the following baseline values: LV GCS, LVEF, resting LVOT gradient, Valsalva LVOT gradient, average E/e', and the randomization stratification factors (beta-blocker use, cardiopulmonary exercise testing [CPET] modality). Missing data were not imputed. [Supplemental Table 3](#) demonstrates the number of echocardiographic observations by study week. All analyses

TABLE 1 Baseline and Change in Echocardiographic Parameters

Echo Parameter	Placebo (n = 140)		Aficamten (n = 142)		Treatment (Week 24)		Washout (Week 28)	
	Baseline	Week 24	Baseline	Week 24	Placebo-Corrected Treatment Difference (95% CI)	P Value ^a	Placebo-Corrected Treatment Difference (95% CI)	P Value ^a
LVOT gradients								
LVOT gradient, rest, mm Hg	55 ± 32	60 ± 33	55 ± 27.0	20 ± 17	-40 (-46 to -34)	<0.001	-1 (-6 to 7)	0.83
LVOT gradient, Valsalva, mm Hg	83 ± 33	86 ± 33	83 ± 32	35 ± 25	-50 (-57 to -44)	<0.001	-1 (-8 to 6)	0.85
LV structure								
Max wall thickness, mm	21.0 ± 3.0	20.4 ± 3.0	20.7 ± 3.0	19.1 ± 3.2	-1.2 (-1.8 to -0.6)	<0.001	-	
Interventricular septal wall, mm	19.4 ± 3.3	20.0 ± 3.2	18.9 ± 2.9	18.7 ± 3.5	-1.0 (-1.6 to -0.3)	0.003	-0.3 (-1.0 to 0.4)	0.38
Inferolateral wall, mm	13.2 ± 2.9	13.5 ± 2.9	12.5 ± 2.6	12.3 ± 2.3	-0.8 (-1.3 to -0.3)	0.003	-0.2 (-0.8 to 0.3)	0.43
LV mass index, g/m ²	134.6 ± 36.6	141.5 ± 38.4	129.6 ± 31.0	124.6 ± 32.7	-12.2 (-18.0 to -6.5)	<0.001	-3.7 (-10.2 to 2.8)	0.27
LV end-diastolic dimension, mm	38.8 ± 5.9	38.9 ± 5.4	39.4 ± 5.1	39.0 ± 4.7	-0.3 (-1.1 to 0.5)	0.5	-0.7 (-1.6 to 0.2)	0.14
LV end-systolic dimension, mm	21.7 ± 4.1	21.0 ± 4.2	21.9 ± 3.8	22.5 ± 4.1	+1.6 (0.7 to 2.4)	0.001	-0.2 (-1.1 to 0.8)	0.72
LV end-diastolic volume index, mL/m ²	36.0 ± 9.2	36.4 ± 8.4	35.9 ± 7.8	36.2 ± 8.2	-0.2 (-1.5 to 1.2)	0.81	-1.2 (-2.5 to 0.1)	0.07
LV end-systolic volume index, mL/m ²	9.1 ± 3.8	10.0 ± 3.6	9.1 ± 2.9	11.7 ± 4.2	+1.7 (1.0 to 2.4)	<0.001	-0.1 (-0.7 to 0.5)	0.74
LV systolic function								
LV ejection fraction, %	75 ± 6	73 ± 7	75 ± 6	68 ± 7	-5 (-6 to -3)	<0.001	-1 (-2 to 1)	0.21
LV fractional shortening, %	44 ± 8	46 ± 9	45 ± 8	42 ± 9	-4 (-7 to -2)	<0.001	-1 (-3 to 2)	0.62
LV global longitudinal strain, ^b %	15.3 ± 3.3	-15.9 ± 3.4	15.4 ± 3.1	-15.6 ± 2.7	-0.4 (-0.9 to 0.1)	0.13	-0.1 (-0.6 to 0.5)	0.74
LV global circumferential strain, ^b %	33.4 ± 8.1	-34.3 ± 8.0	33.0 ± 7.1	-30.5 ± 8.4	-3.7 (-5.6 to -1.8)	<0.001	-0.8 (-2.5 to 0.9)	0.36
RV systolic function								
TAPSE, mm	21.0 ± 4.1	20.1 ± 5.0	21.4 ± 3.9	17.9 ± 4.0	-2.1 (-3.2 to -1.1)	<0.001	+0.8 (-0.3 to 1.9)	0.16
RV s' velocity, cm/s	13.2 ± 2.4	13.5 ± 2.6	12.7 ± 2.5	11.7 ± 2.5	-1.4 (-2.0 to -0.9)	<0.001	+0.3 (-0.2 to 0.9)	0.28
LV diastolic function								
LA volume index, mL/m ²	40.9 ± 15.1	41.2 ± 11.8	40.1 ± 12.7	37.6 ± 10.6	-3.8 (-5.5 to -2.2)	<0.001	-3.0 (-4.9 to -1.0)	0.003
LA width, mm	41.8 ± 6.0	42.7 ± 6.4	41.8 ± 5.9	40.2 ± 6.6	-2.7 (-3.8 to -1.7)	<0.001	-0.8 (-1.8 to 0.3)	0.14
Peak E-wave velocity, cm/s	87.4 ± 32.0	88.3 ± 29.1	82.2 ± 24.5	77.0 ± 20.8	-7.5 (-11.7 to -3.2)	0.001	-1.6 (-5.8 to 2.7)	0.47
Peak A-wave velocity, cm/s	83.6 ± 29.9	85.8 ± 28.3	81.7 ± 27.8	81.7 ± 25.5	-2.4 (-6.3 to 1.5)	0.22	+3.2 (-0.5 to 6.9)	0.09
Lateral e' velocity, cm/s	6.1 ± 2.2	6.1 ± 2.5	6.0 ± 2.0	7.3 ± 2.5	+1.2 (0.7 to 1.6)	<0.001	-0.2 (-0.6 to 0.3)	0.45
Septal e' velocity, cm/s	4.6 ± 1.6	4.8 ± 1.9	4.6 ± 1.4	5.2 ± 1.5	+0.5 (0.2 to 0.8)	0.001	-0.0 (-0.3 to 0.2)	0.96
Lateral E/e'	15.9 ± 7.8	16.3 ± 8.7	15.4 ± 7.3	11.7 ± 5.1	-3.9 (-5.0 to -2.8)	<0.001	-0.2 (-1.6 to 1.2)	0.78
Septal E/e'	20.5 ± 9.3	20.1 ± 8.5	19.5 ± 8.4	15.9 ± 5.5	-3.6 (-4.8 to -2.5)	<0.001	-0.6 (-1.7 to 0.6)	0.35

Values are mean ± SD or mean (95% CI). Placebo-corrected differences in echocardiographic parameters are adjusted for baseline echocardiographic parameter, treatment, and stratification by beta-blockers and exercise mode (bicycle vs treadmill). Maximum wall thickness was not measured at week 28. ^aP value for placebo-corrected treatment difference compared with baseline. ^bAbsolute strain values are presented.

e' = early diastolic mitral annular velocity; E wave = early mitral inflow velocity; E/e' = ratio between early mitral inflow velocity and early diastolic mitral annular velocity; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; RV = right ventricle; s' = peak systolic annular velocity; TAPSE = tricuspid annular plane systolic excursion.

were performed using STATA software version 16.1 (StataCorp). No adjustments were made for multiple comparisons. *P* values <0.05 were considered statistically significant.

RESULTS

Of the 282 subjects enrolled in SEQUOIA-HCM, 142 received aficamten and 140 received placebo. Baseline characteristics have previously been described (Supplemental Table 4).¹⁴ Mean age was 59.1 ± 12.9 years with 41% female subjects. Background medical therapy included beta-blockers (61%), calcium channel blockers (29%), disopyramide (13%), and no

medical therapy (15%). As per entry criteria, LVOT gradients at rest and with Valsalva were elevated (55 ± 30 mm Hg and 83 ± 32 mm Hg, respectively).

Baseline echocardiography demonstrated findings consistent with oHCM with a mean maximum LV wall thickness of 21 ± 3 mm with greater interventricular septal wall thickness compared to the inferolateral wall (Table 1). Abnormal mean measures of diastolic function included reduced e' velocities, elevated E/e', and mildly dilated LA. LV dimensions were within normal range with generally hyperdynamic LVEF (75% ± 6%). At baseline, the majority of patients (91% [228/250], missing data n = 32 patients) demonstrated mitral valve SAM. LV GLS was mildly

reduced, whereas LV GCS was normal to increased. Measures of RV systolic function (TAPSE, RV s' velocity) were within normal range (Table 1).

AFICAMTEN TREATMENT EFFECT. In addition to previously reported significant improvements in resting and Valsalva LVOT gradients (−40 mm Hg and −50 mm Hg, respectively), aficamten treatment for 24 weeks resulted in a decrease in LA volume index (−3.8 mL/m²) and improvements in lateral and septal e' velocities (+1.2 cm/s and +0.5 cm/s, respectively) and lateral and septal E/e' (−3.9 and −3.6, respectively) (all $P \leq 0.001$) (Table 1, Figure 1). The prevalence of abnormal measures of LV diastolic function decreased after 24 weeks of aficamten, particularly for lateral e' and average E/e' measures (Figure 2A). Many patients demonstrated improvement in the number of abnormal LV diastolic function measures after 24 weeks of aficamten (Figure 2B). LV end-systolic volume increased (+1.7 mL/m²) and all wall thickness measurements decreased (all $P \leq 0.003$) (Table 1). Aficamten resulted in a mild reversible decrease in LVEF (−4.8% [95% CI: −6.4 to −3.3]; $P < 0.001$) and absolute LV GCS (−3.7% [1.8–5.6]; $P < 0.001$), with LVEF and LV GCS approaching normal range, whereas absolute LV GLS was not changed (Table 1, Figure 3). Changes in LV GCS were associated with changes in LVEF in a linear regression model additionally adjusted for baseline LV GCS, LVEF, resting LVOT gradient, Valsalva LVOT gradient, average E/e', and the randomization stratification factors (beta-blocker use, CPET modality) as seen in Figure 4. There was also a mild decrease in RV systolic function (TAPSE and RV s'); however, these measures remained within normal range. Several measures, including LVEF, LVOT gradients, and E/e' returned to baseline following washout. Aficamten resulted in complete resolution of mitral valve SAM in approximately one-half of patients (52% [61/117], missing data n = 17 patients) with 82% (50/61) of this group reverting to baseline mitral valve SAM after washout.

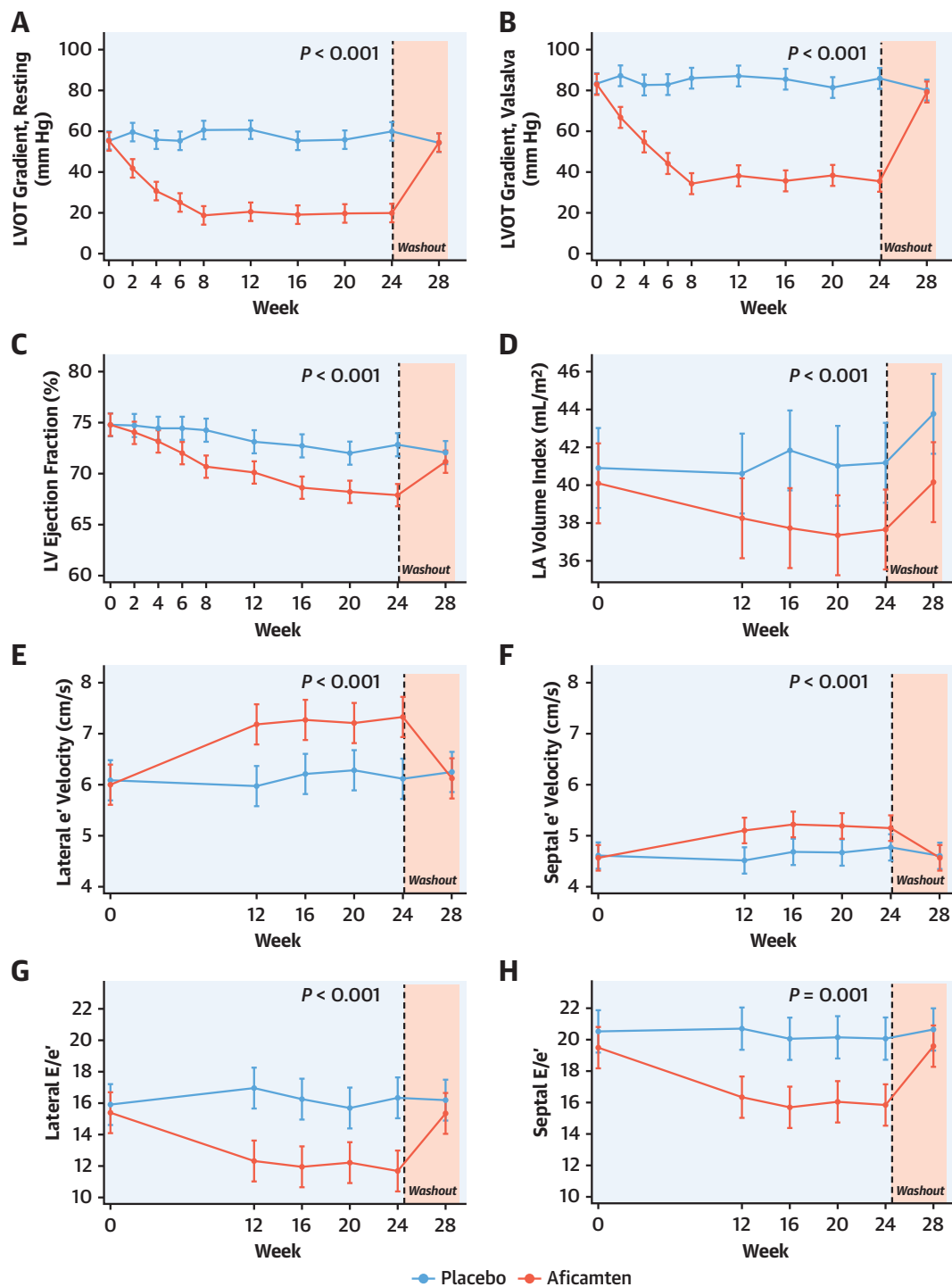
RELATIONSHIP BETWEEN CHANGES IN pVO₂ AND OTHER ENDPOINTS WITH CHANGES IN ECHOCARDIOGRAPHIC MEASURES. Among those treated with aficamten, improvement in pVO₂ (per 1 mL/kg/min) over 24 weeks was associated with improvement in LA volume index (−0.46 mL/m²), peak A velocity (−1.17 cm/s), lateral e' velocity (+0.16 cm/s), lateral E/e' (−0.29), and septal E/e' (−0.26) (all $P < 0.05$) (Supplemental Table 5). A reduction in NT-proBNP (per $-\log_2$ change, or 50% reduction) was significantly associated with reduction in resting and Valsalva LVOT gradients (−5.6 mm Hg and −7.4 mm Hg, respectively), reduction in maximum wall thickness

and interventricular septal wall thickness (−0.50 mm and −0.06 mm, respectively), increase in lateral and septal e' velocities (+0.53 cm/s and +0.26 cm/s, respectively), decrease in lateral and septal E/e' (−1.1 and −1.0, respectively), and increase in absolute LV GLS (0.43%) (all $P < 0.05$) (Supplemental Table 5). Improvement in KCCQ-CSS (per 5-point increase) was significantly associated with reduction in resting and Valsalva LVOT gradients (−2.7 mm Hg and −3.8 mm Hg, respectively), reduction in inferolateral wall thickness (−0.19 mm), and increase in LV end-systolic dimension (+0.34 mm) (all $P < 0.05$) (Supplemental Table 5). A reduction in high-sensitivity cardiac troponin I (per $-\log_2$ change, or 50% reduction) was significantly associated with reduction in the Valsalva LVOT gradient (−6.6 mm Hg), reduction in maximum wall thickness and interventricular septal wall thickness (−1.2 mm and −1.0 mm, respectively), and increase in septal e' velocity (+0.39 cm/s) (all $P < 0.05$) (Supplemental Table 5). A 1-class improvement in NYHA functional class, only in aficamten-treated patients, was associated with reduction in the Valsalva LVOT gradient (−8.21 mm Hg) and reduction in inferolateral wall thickness (−0.63 mm) (all $P < 0.05$) (Supplemental Table 5). Changes in pVO₂, NT-proBNP, KCCQ-CSS, and high-sensitivity cardiac troponin I were not significantly associated with change in LVEF.

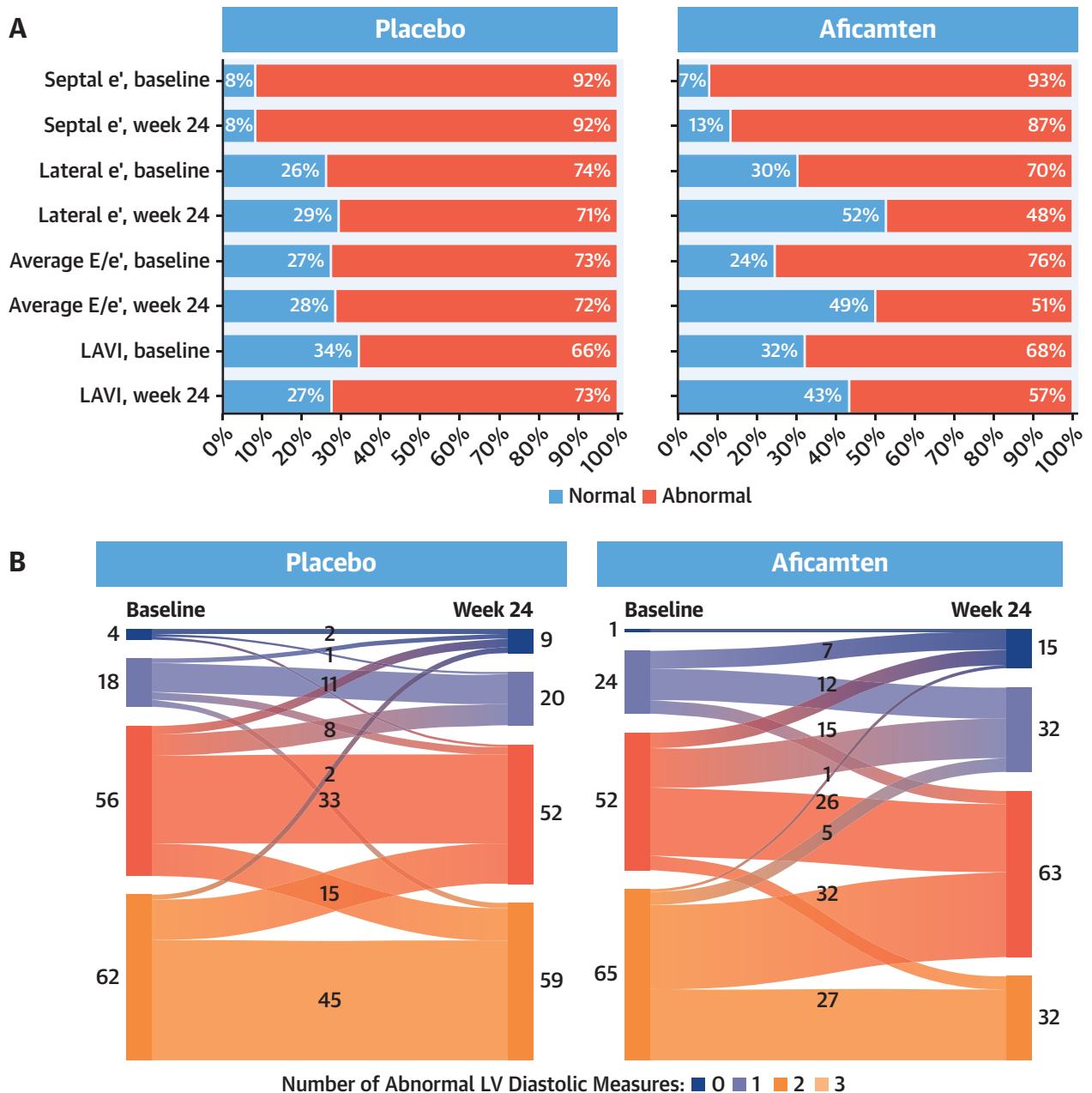
DISCUSSION

In this prespecified analysis of patients with oHCM, treatment with aficamten for 24 weeks resulted in significant improvement relative to placebo in important measures of cardiac structure and function. In addition to previously reported significant improvements in LVOT gradients, aficamten improved measures of LV diastolic function, including LA size, e' velocities, and E/e'. LV systolic function by LVEF also changed from a generally hyperdynamic to a more normal range. Aficamten-associated improvement in several outcome measures, including pVO₂, NT-proBNP, KCCQ-CSS, and high-sensitivity cardiac troponin I, was associated with improvement in multiple measures of cardiac structure and function. Together, these findings demonstrate the effect of aficamten on cardiac structure and function, and provide some insight into the mechanism of action underlying the demonstrated clinical benefits (Central Illustration).

At baseline, echocardiographic measures were typical of patients with symptomatic, oHCM with mean LVEFs in the hyperdynamic range. Maximum wall thickness on average exceeded 2.0 cm,

FIGURE 1 Effect of Aficamten on Cardiac Structure and Function Over Time

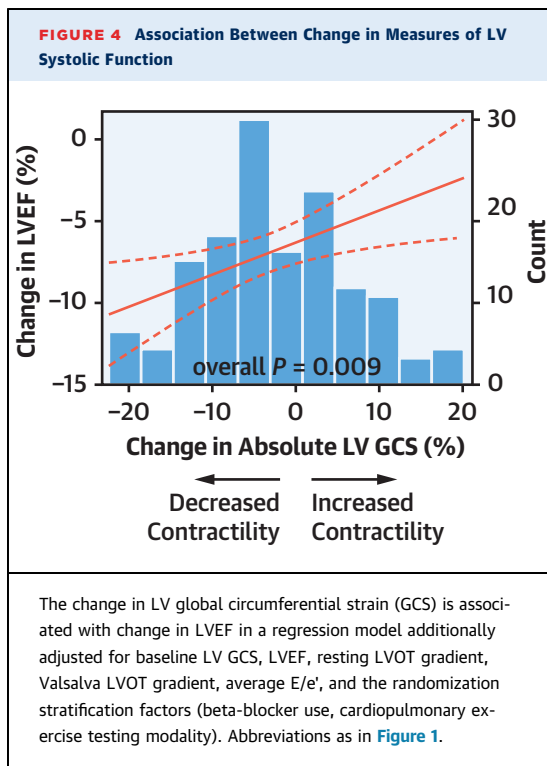
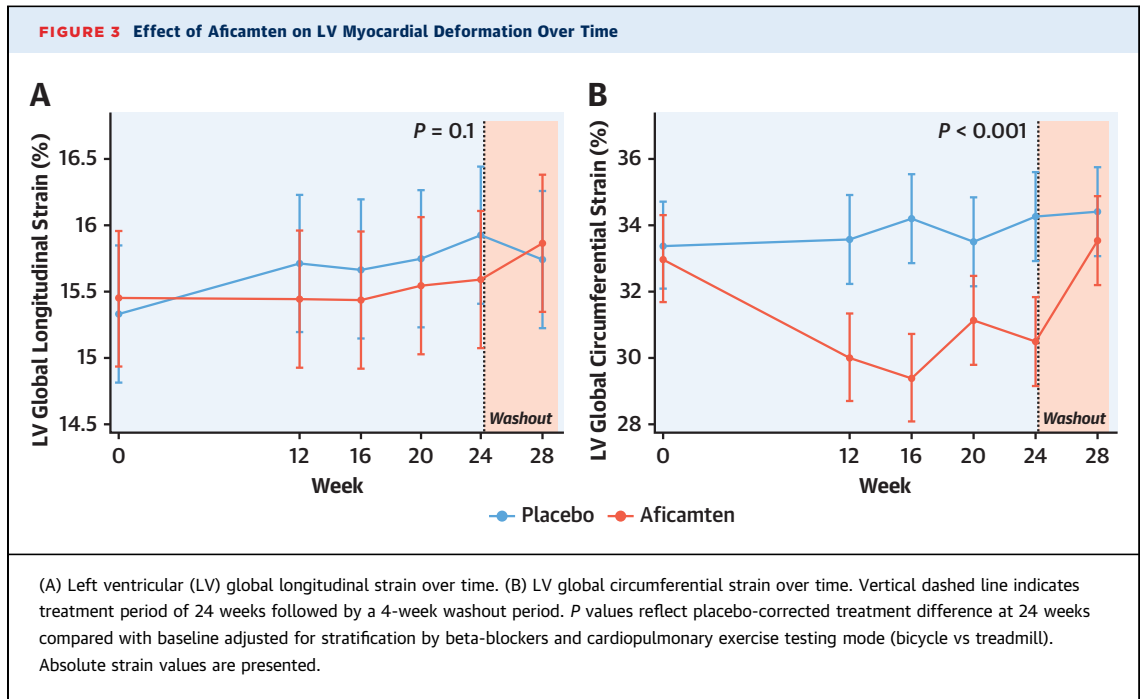
(A) Left ventricular outflow tract (LVOT) gradient at rest over time. (B) LVOT gradient with Valsalva over time. (C) Left ventricular ejection fraction (LVEF) over time. (D) Left atrial (LA) volume index over time. (E) LVOT gradient at rest over time. (F) LVOT gradient with Valsalva over time. (G) Lateral early diastolic mitral annular velocity (e') over time. (H) Septal e' velocity over time. (G) Lateral ratio between early mitral inflow velocity and early diastolic mitral annular velocity (E/e') over time. (H) Lateral E/e' over time. Vertical dashed line indicates treatment period of 24 weeks followed by a 4-week washout period. P values reflect placebo-corrected treatment difference at 24 weeks compared with baseline adjusted for stratification by beta-blockers and cardiopulmonary exercise testing mode (bicycle vs treadmill). Panels A and B adapted with permission from Massachusetts Medical Society from Maron et al.¹⁴

FIGURE 2 Prevalence of Abnormal LV Diastolic Function Measures and Change Over Time

(A) Prevalence of abnormal LV diastolic function measures (septal e' or lateral e', average E/e', left atrial volume index [LAVI]) at baseline and 24 weeks by treatment group. (B) Change in number of patients and number of abnormal LV diastolic function measures by treatment group. Abbreviations as in Figure 1.

consistent with severe LV hypertrophy. LVOT gradients at rest and with Valsalva were markedly elevated above entry criteria requirements with mean resting and Valsalva gradients >50 mm Hg, the threshold generally considered associated with symptoms and

for considering advanced pharmacologic or invasive therapies.¹ LVOT obstruction is primarily due to the presence of mitral valve SAM, which was present in the majority of these patients at baseline. Furthermore, these patients demonstrated evidence of

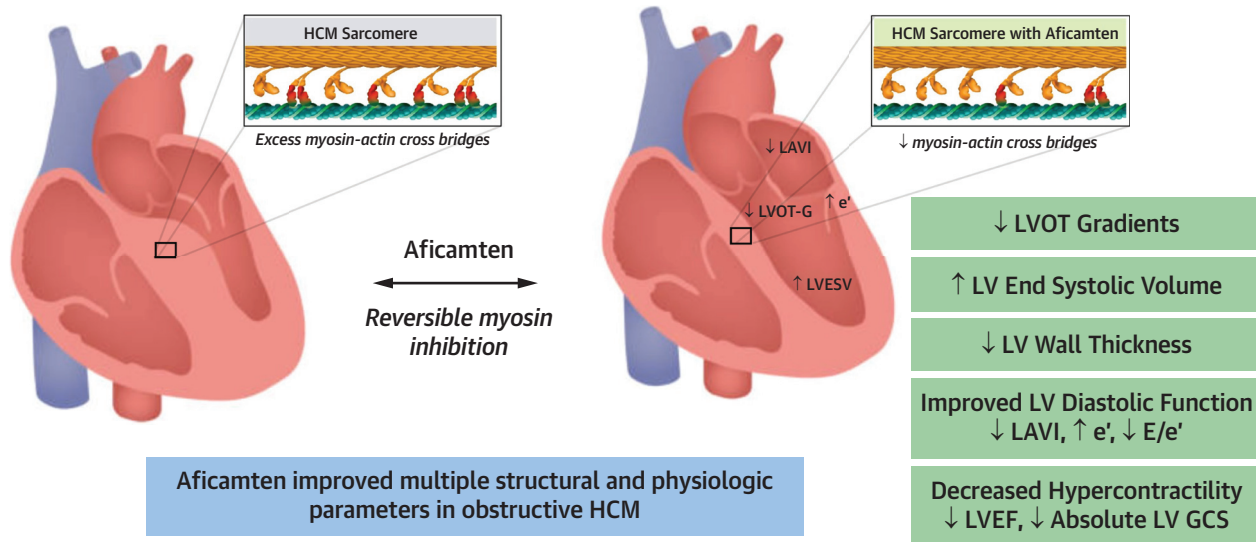


abnormal LV diastolic function with mildly dilated LA volumes, reduced tissue Doppler indices, and elevated E/e' values.

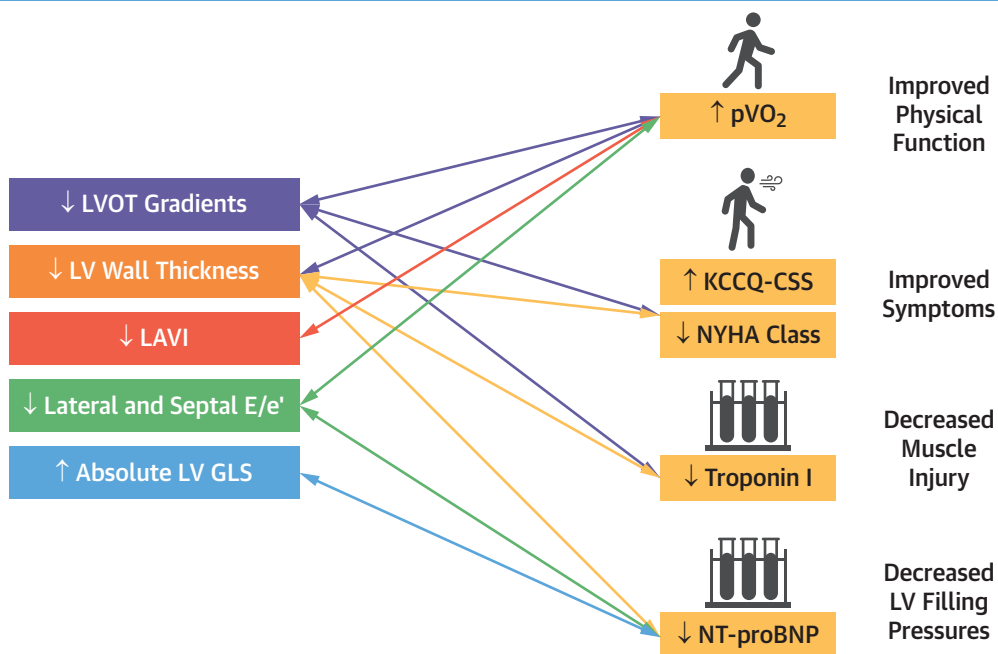
AFICAMTEN TREATMENT EFFECT. Treatment with aficamten resulted in significant improvements in multiple measures of cardiac structure and function. As previously described, both resting and Valsalva LVOT gradients significantly decreased.¹⁴ Approximately one-half of those treated with aficamten demonstrated complete resolution of mitral valve SAM. Maximal wall thickness, interventricular septal wall thickness, inferolateral wall thickness, and LV mass index significantly decreased with aficamten treatment. Although LV mass index estimation by echocardiography has limitations in HCM,^{20,21} the treatment effect appears to be consistent across all wall thickness measurements. Septal reduction therapy has also demonstrated regression of LV hypertrophy with reduction in wall thickness in segments other than the septum, suggesting that LV hypertrophy may be in part compensatory to the increased afterload associated with LVOT obstruction.²²⁻²⁵ With aficamten, myosin inhibition may in parallel directly contribute to reduction in wall thickness in addition

CENTRAL ILLUSTRATION Effect of Aficamten on Cardiac Structure and Function and Association With Outcomes

Effect of Aficamten on Cardiac Structure and Function



Changes in Echocardiographic Measures are Associated With Changes in pVO₂ and Other Outcomes in Aficamten-Treated Patients



Hegde SM, et al. JACC. 2024;■(■):■-■.

Aficamten is a next-in-class cardiac myosin inhibitor that results in reversible reduction of actin-myosin cross bridges with improvement in multiple measures of cardiac structure and function over 24 weeks. Improvement in peak oxygen uptake (pVO₂), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin I, New York Heart Association (NYHA) functional class, and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) was associated with improvement in several measures of cardiac structure and function. 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; LVESV = left ventricular end-systolic volume; LV GLS = left ventricular global longitudinal strain; LVOT-G = left ventricular outflow tract gradient.

to the secondary effects of decreased afterload. Longer-term changes will be important in understanding the extent of remodeling that occurs with aficamten.

Abnormal diastolic function in HCM has been attributed to elevated LV pressures, reduced LV compliance due to hypertrophy and/or fibrosis, microvascular ischemia, and abnormal energetics.^{1,26,27} LA volume index significantly decreased by a mean of 3.8 mL/m² with 24 weeks of aficamten. Septal reduction therapy, which targets reducing or eliminating LVOT obstruction, has also demonstrated significant reductions in LA volumes of ~8 to 10 mL/m² from baseline severely dilated LAs (48-64 mL/m²) as early as 6 months postprocedure.^{22-24,28} The reduction in LA size is likely multifactorial with multiple simultaneous changes, including LVOT gradient reduction, reduced LV filling pressures, and decrease in mitral valve SAM and related mitral regurgitation. In addition, aficamten was associated with an increase in lateral and septal *e'* velocities and a corresponding decrease in lateral and septal *E/e'* values, consistent with improvement in annular motion and reductions in a surrogate of LV filling pressure, respectively. Septal myectomy has demonstrated similar improvement in *E/e'*.^{24,29}

LV GLS has been established as a more sensitive marker of systolic function with prognostic value.³⁰ Patients with HCM demonstrate impaired LV GLS despite normal LVEF, and this abnormal LV GLS has been associated with adverse cardiovascular outcomes.^{31,32} Abnormal LV GLS in HCM may reflect the underlying abnormal histopathology of myocyte disarray and interstitial fibrosis.^{10,33} Reference ranges for strain vary by age and sex with normal values of absolute LV GLS approximately 20% ± 2%¹⁶ with greater variability in reported normal ranges for absolute LV GCS 23.3% (95% CI: 22.1% to 24.6%).^{24,34} With aficamten, LV GLS was unchanged and remained mildly impaired. Contractility, as measured by LVEF and absolute LV GCS, decreased modestly with both approaching a more normal, less hyperdynamic range. A similar response in absolute LV GLS and LV GCS (GLS 16% ± 4% to 16% ± 4% postmyectomy; *P* > 0.05; GCS 31% ± 5% to 25% ± 5% postmyectomy; *P* < 0.05) has been observed with septal myectomy in spite of focal decline at myectomy sites,²⁴ suggesting that alleviation of LVOT obstruction and unloading of the LV, either pharmacologically or invasively, is associated with a mild lowering or normalization of a hyperdynamic LV as measured by LVEF and LV GCS, whereas neither approach

appears to impact LV GLS.³⁵ At baseline, aortic stenosis is associated with similarly impaired LV GLS and higher GCS, which is thought to be a compensatory mechanism to preserve LV function in the setting of high LV afterload.²⁴ Unlike with HCM, unloading the LV in aortic stenosis with valve replacement has been associated with improved LV GLS although this may in part reflect opportunity for improvement in patients with less chronically elevated LV afterload and less fibrosis.³⁶⁻³⁸ Therefore, the absence of changes in LV GLS with unloading the LV may reflect irreversible abnormal histopathology after many years of obstructive physiology and chronic afterload and raises the question of whether earlier treatment before the development of significant fibrosis could normalize LV GLS. Alternatively, the absence of changes in LV GLS with aficamten treatment may represent a net neutral effect from some reduction in LV systolic function balancing improvement in diastolic function or it may represent a differential effect on myocardial fibers, where LV GLS tends to represent subendocardial function and LV GCS tends to represent mid-myocardial fibers.^{39,40} In contrast, a small study of 15 patients treated with mavacamten demonstrated a mild decline in absolute LV GLS from 14.2% ± 2.9% to 12.6% ± 3.1% after 30 days of treatment,⁴¹ suggesting that there may be some impact of myosin inhibitors on LV GLS. Whether LV GLS is modifiable remains unknown. Further investigation is needed into the long-term effect, regional and layer-specific changes in myocardial mechanics, and timing of initiation of aficamten.

The observed mild decline in LVEF and absolute LV GCS is important to place in a clinical context. Over 24 weeks of aficamten therapy, patients demonstrate a mean reduction in LVEF of 5% (LVEF = 67.9% ± 7.4% at 24 weeks) and in absolute LV GCS of 4% (LV GCS = -30.5% ± 8.4% at 24 weeks); LVEF and LV GCS remain in normal range despite a mild decline from baseline hyperdynamic values. This effect is seen as an intended drug effect to improve and normalize the adverse effects of hyperdynamic LV systolic function and LVOT obstruction in this population. In the context of other potentially cardiotoxic drugs such as chemotherapy, strain measures (LV GLS) also demonstrate a mild decline; however, these are absolute decreases to below normal ranges and are typically associated with other adverse markers of cardiotoxicity, including elevation in NT-proBNP levels.^{42,43} In the case of aficamten, the modest decline in LVEF and LV GCS is associated with significant decline in NT-proBNP levels and improved *E/e'* values, suggesting a more favorable and intended

drug response. Longer-term studies will demonstrate whether the effects of aficamten are sustained.

After 4 weeks of washout following aficamten treatment, nearly all measures of cardiac structure and function returned to baseline values (Table 1). Resting and Valsalva LVOT gradients were no longer significantly different from baseline. LVEF, wall thickness measurements, tissue Doppler indices, and E/e' also returned to baseline. The only exception was the LA volume index, which remained significantly smaller compared with placebo at 28 weeks due to a rise in LA volume index in both groups, but LA volume index did return to baseline values with washout (Figure 1). This may in part be due to the limitations of measurement of LA volumes by echocardiography, which is also reflected by the larger SDs for this measurement. The reversal of the noted drug effects within 4 weeks to baseline values, including LVEF, is of particular importance to safety. Of the 142 patients treated with aficamten, 5 (3.5%) experienced a transient reduction in LVEF <50% without developing clinical heart failure. By comparison, surgical myectomy has been associated with a modest reduction in LVEF of ~3% in observational studies.^{24,28} Because changes in LV GCS parallel changes in LVEF, both measures may be assessed to monitor for possible further decline in LV systolic function, which can be further assessed with longer-term data.

RELATIONSHIP BETWEEN CHANGES IN pVO₂ AND OTHER ENDPOINTS WITH CHANGES IN ECHOCARDIOGRAPHIC MEASURES. Aficamten significantly improved the primary outcome of pVO₂ compared with placebo in patients with oHCM. This improvement in functional capacity was associated with improvement in LA volume index, decrease in peak A-wave velocity, increase in lateral e' velocity, and reduction in lateral and septal E/e'. Abnormal diastolic function has been associated with impaired exercise capacity in HCM.^{1,44} In this analysis, reduction in LA size is uniquely associated with improvement in functional status compared with the other outcomes. Other studies support the LA as a marker of HCM pathophysiology, including LA myopathy, as measured by strain, which has been associated with impaired exercise capacity in patients with both obstructive and nonobstructive HCM.⁴⁵⁻⁴⁸ Together, these findings support the close relationship between the left atrium and LV diastolic function with functional capacity.

Aficamten also resulted in improvement in the exploratory endpoints, NT-proBNP and high-sensitivity cardiac troponin I, and secondary endpoint KCCQ-CSS. Aficamten decreased both

cardiac biomarkers, NT-proBNP¹⁴ and high-sensitivity cardiac troponin I, measured in SEQUOIA-HCM. Reductions in NT-proBNP were associated with significant reduction in resting and Valsalva LVOT gradients and interventricular septal wall thickness, as well as improvement in lateral and septal e' velocities, lateral and septal E/e', and LV GLS. Reduction in high-sensitivity cardiac troponin I was associated with significant reduction in Valsalva LVOT gradients and interventricular septal wall thickness, and increase in septal e' velocity. Improvement in both biomarkers was associated with improvement in LVOT gradients, septal wall thickness, and indices of diastolic function, likely representing global cardiac structure and function improvement in response to therapy. With aficamten treatment, improvement in symptoms by NYHA functional class and KCCQ-CSS was associated with improvement in Valsalva LVOT gradients and reduction in inferolateral wall thickness, but not measures of LV diastolic function, suggesting that changes in LVOT gradients contribute more to symptom relief.

COMPARATIVE THERAPIES. Until recently, pharmacologic therapy for oHCM has primarily targeted relief of LVOT obstruction to improve symptoms. Traditional therapies (beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide) lower LVOT gradients but have not been reported to improve LV diastolic function or cardiac structure in randomized controlled trials.⁴⁹⁻⁵¹ In the recent randomized placebo-controlled trial of metoprolol vs placebo, metoprolol decreased LVOT obstruction and improved LV GLS without effect on E/e', invasively measured filling pressures, or symptoms.^{52,53} Cardiac myosin inhibitors present a new targeted approach; decreasing the number of actin-myosin cross-bridges at the level of the cardiac sarcomere results in normalization of contractility and relief of LVOT obstruction, enabling improvement in functional capacity and symptoms. This has now been demonstrated with both mavacamten and aficamten.^{7,14} Aficamten demonstrated similar improvements in LVOT gradients, wall thickness measurements, LA volumes, tissue Doppler indices, and E/e' over 24 weeks as those demonstrated with mavacamten.⁹ Although septal reduction therapy has been associated with similar improvements in cardiac structure and function, including LV diastolic function, cardiac myosin inhibitors provide an alternative therapy to those who may prefer to avoid invasive therapies with procedural risk as reflected in the recently updated HCM guidelines.^{1,23-25,29}

STUDY LIMITATIONS. Ultrasound-enhancing agents were not approved for use in this study, which may have influenced measurements of LV volumes. Mitral valve SAM and mitral regurgitation were assessed qualitatively as present or absent, so further characterization is limited. The highly eccentric nature of mitral regurgitation in this population limits quantitative assessment by echocardiography. This study was of short duration with only 24 weeks of treatment. Further analysis of the ongoing FOREST-HCM (Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults With HCM; [NCT04848506](#)) long-term extension study will help demonstrate the nature of more long-term changes in cardiac structure and function.

CONCLUSIONS

Compared with placebo, patients receiving aficamten demonstrated significant improvement in LVOT gradients, wall thickness, and measures of LV diastolic function indices, and several of these measures were associated with improvements in pVO₂, KCCQ-CSS, and NT-proBNP. A modest reduction in LVEF occurred from generally hypercontractile function at baseline, resulting in more normal range LV systolic function. Furthermore, reversal of the noted aficamten-related changes in cardiac structure and function occurred within 4 weeks of cessation of therapy. These findings suggest aficamten improved multiple structural and physiological parameters in oHCM without significant adverse changes in LV systolic function.

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a data-sharing request for this study. Requests may be submitted to medicalaffairs@cytokinetics.com.

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KEY WORDS aficamten, diastolic function, hypertrophic cardiomyopathy, LVOT gradient

APPENDIX For supplemental tables, please see the online version of this paper.