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

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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.

-Approximately **two-thirds** of patients present with dynamic left ventricular outflow tract (LVOT) obstruction at rest and/or with provocation.

Echocardiography is essential for:

1) establishing the **diagnosis** of HCM

2) routine assessment of disease progression, including **degree of LVOT obstruction** and **severity of mitral regurgitation**

3) risk assessment of **sudden cardiac death** and **atrial fibrillation**

4) response to **therapy**

Recently updated guidelines for the management of obstructive hypertrophic cardiomyopathy (HOCM) 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

Class I recommendation:Mavacamten

symptoms 2

exercise capacity ١

measures of LV diastolic function ٤

LVOT gradients 3

Class II recommendation:Aficamten

half-life of ~3 days

echocardiography-based dose titration as early as 14 days after dose initiation

SEQUOIA-HCM

Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM

Demonstrated improvement in

1) peak oxygen uptake (pVO2)
2) symptoms by Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores (KCCQ-CSS)
3) resting and Valsalva LVOT gradients
4) New York Heart Association (NYHA) functional class
5) NT-proBNP

The objective of this prespecified analysis : **evaluate the effect of aficamten on echocardiographic measures of cardiac structure and function in SEQUOIA-HCM**

METHODS

EQUOIA-HCM

1-phase 3

2-multicenter

3-randomized

4-placebo-controlled trial

Inclusion criteria

1)18 to 85 years

2)confirmed clinical diagnosis of oHCM

3)LV wall thickness ≥15 mm with unexplained hypertrophy

4)left ventricular ejection fraction (LVEF) ≥60%

5)resting LVOT gradient ≥30 mm Hg

6)Valsalva LVOT gradient ≥50 mm Hg

7)predicted pVO2 ≤90%

8)on stable background medical therapy for >6 weeks

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 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).

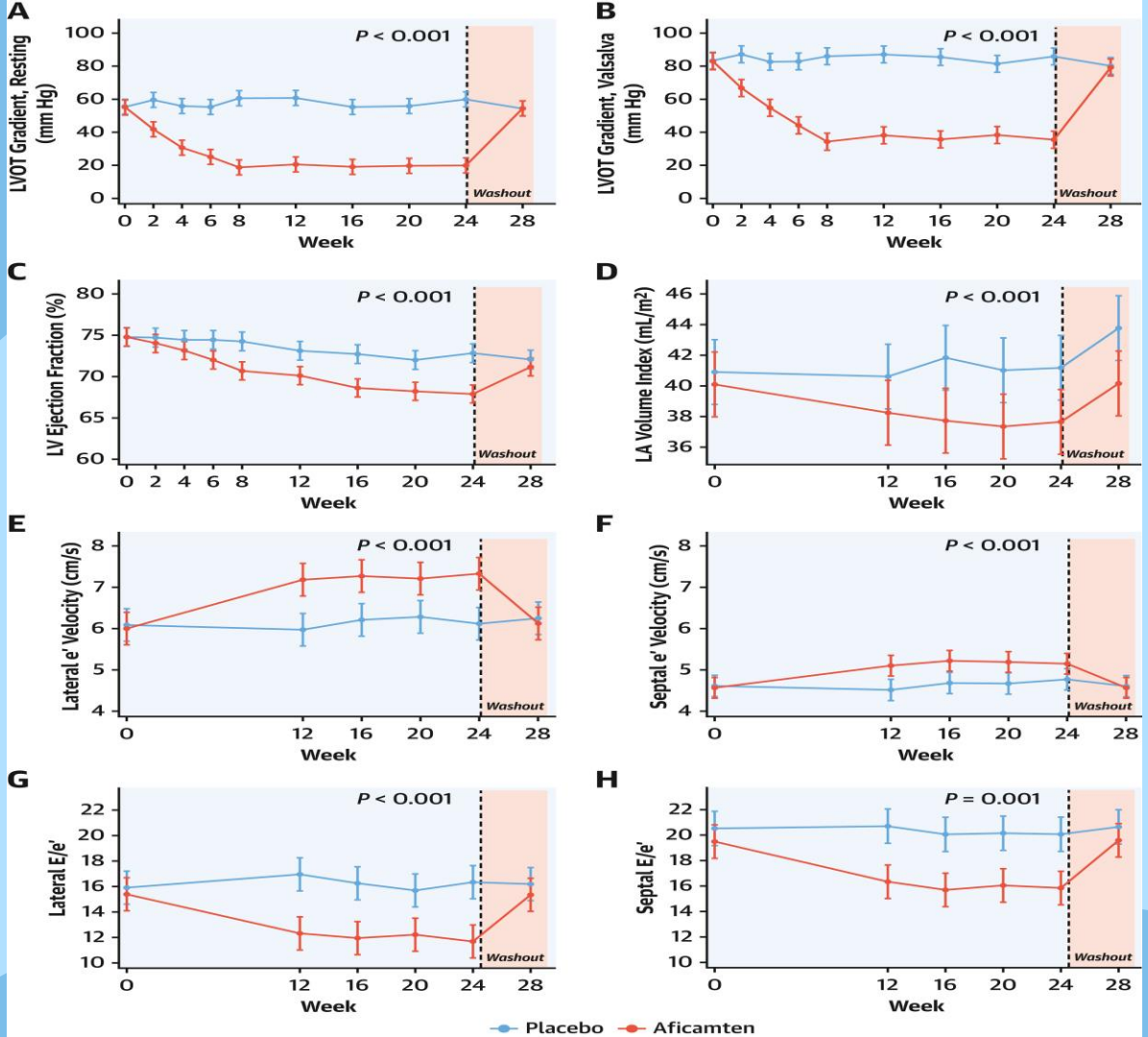
Site-read LVEF and Valsalva LVOT gradients were assessed by masked echocardiographers onsite and entered into the web-response system to determine dose titration.

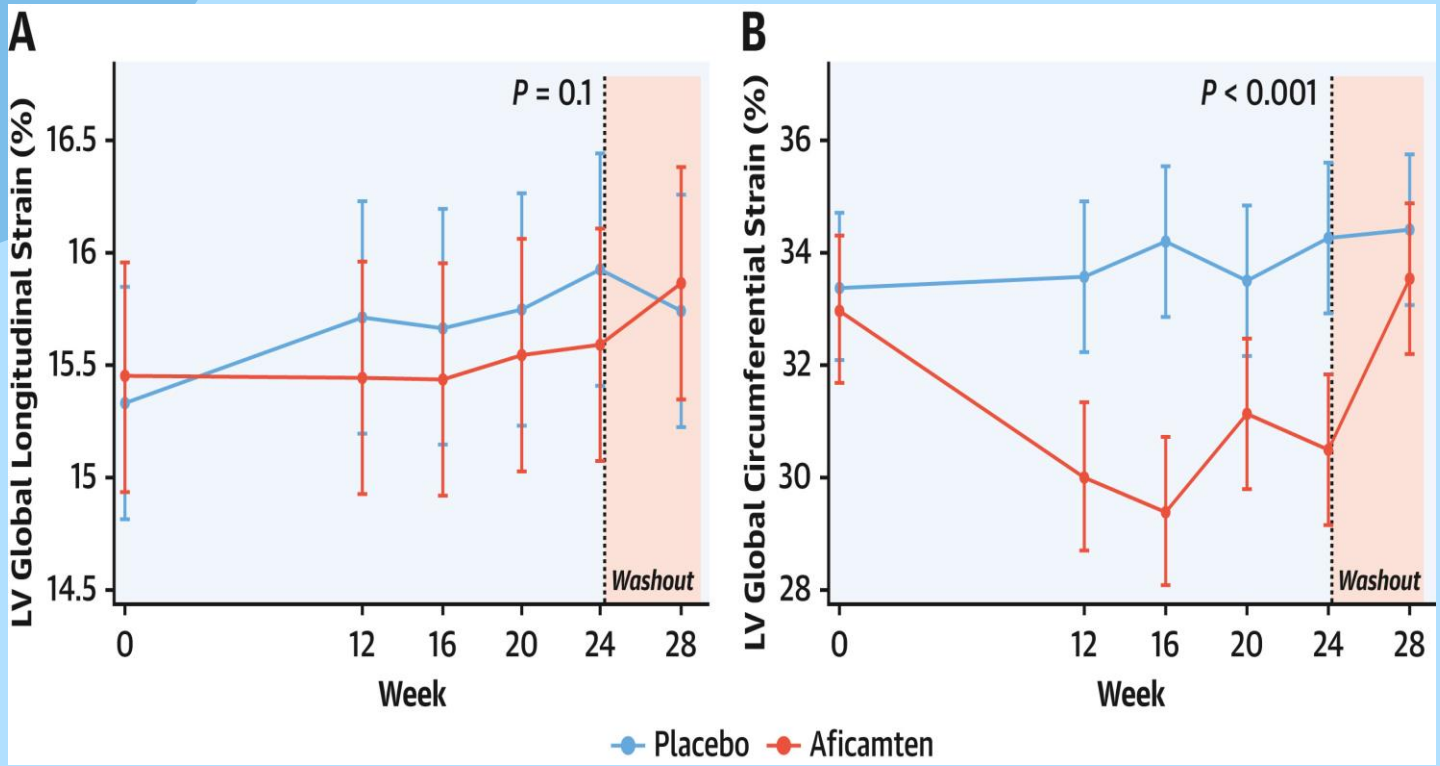
- Of the **282 subjects** enrolled in SEQUOIA-HCM, **142 received aficamten** and **140 received placebo**.
- Mean age **was 59.1 ± 12.9** years with **41% female** subjects.
- Background medical therapy included **beta-blockers (61%),** calcium channel blockers (29%), **disopyramide (13%),** and **no medical therapy (15%).**

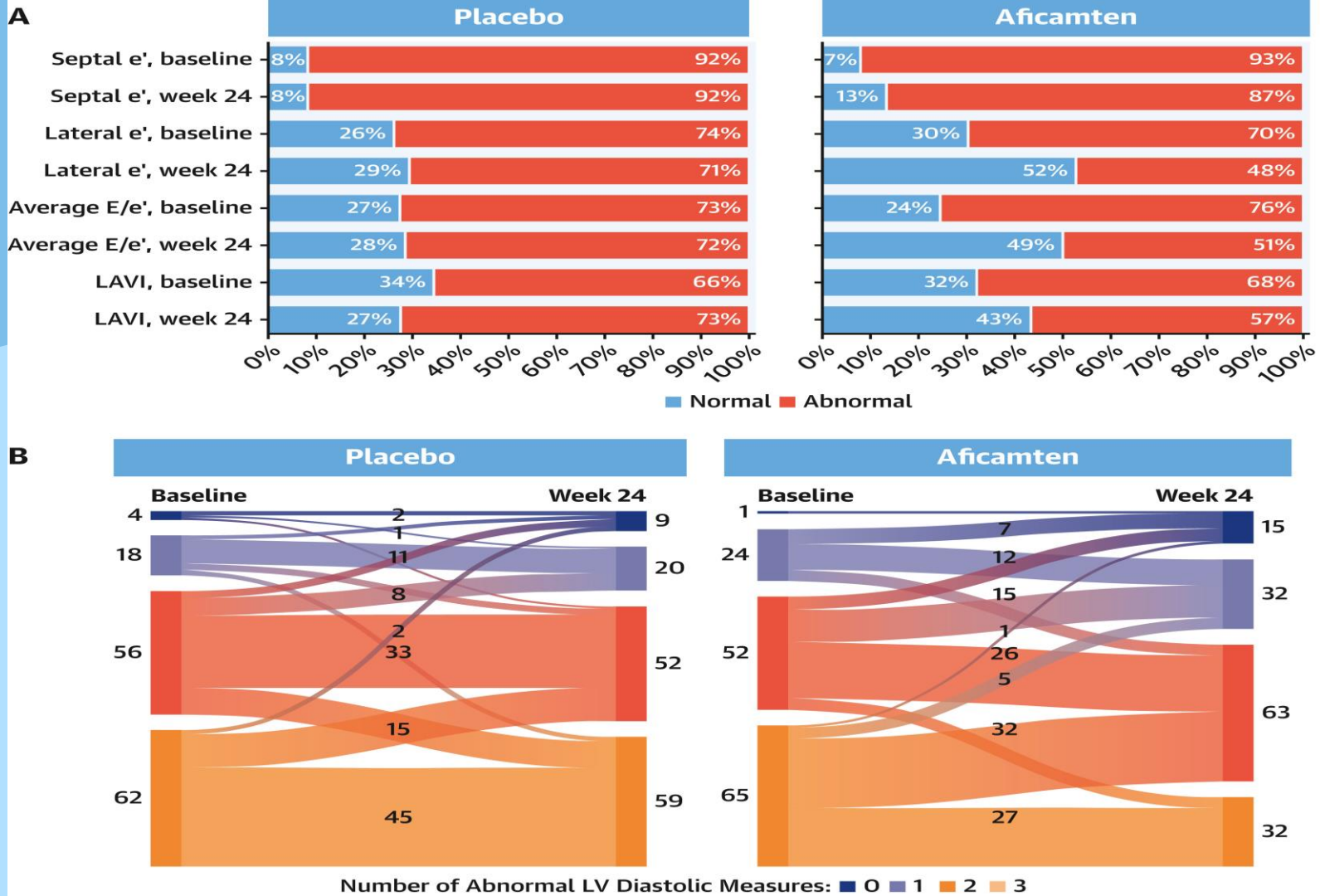
TABLE 1 Baseline and Change in Echocardiographic Parameters

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

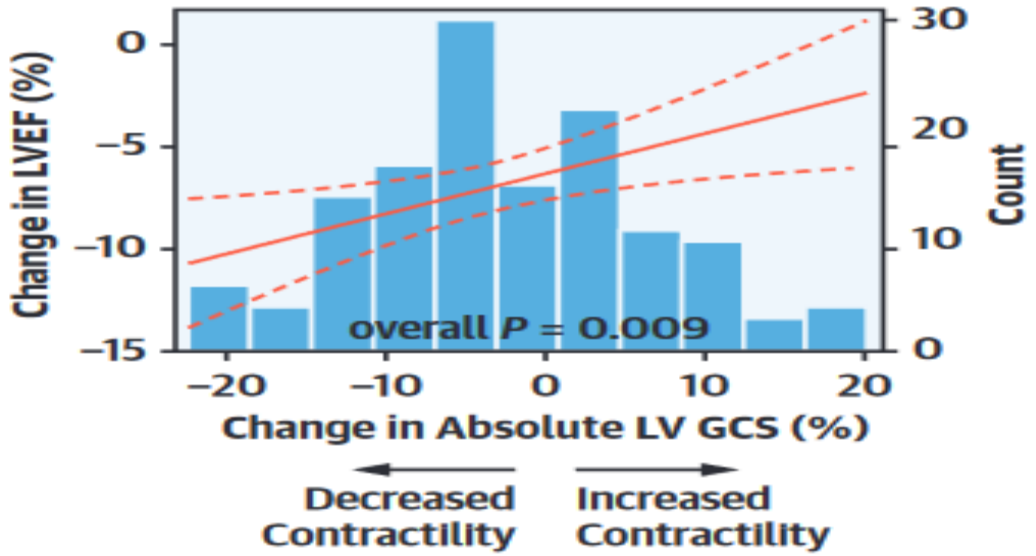
RV systolic function								
TAPSE, mm	21.0 ± 4.1	20.1 ± 5.0	21.4 ± 3.9	17.9 ± 4.0	−2.1 (−3.2 to −1.1)	<0.001	+0.8 (−0.3 to 1.9)	0.16
RV s' velocity, cm/s	13.2 ± 2.4	13.5 ± 2.6	12.7 ± 2.5	11.7 ± 2.5	−1.4 (−2.0 to −0.9)	<0.001	+0.3 (−0.2 to 0.9)	0.28
LV diastolic function								
LA volume index, mL/m^2	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


A
LVOT Gradient, Resting (mm Hg)
P < 0.001
Washout
Week
B
LVOT Gradient, Valsalva (mm Hg)
P < 0.001
Washout
Week
C
LV Ejection Fraction (%)
P < 0.001
Washout
Week
D
LA Volume Index (mL/m²)
P < 0.001
Washout
Week
E
Lateral e' Velocity (cm/s)
P < 0.001
Washout
Week
F
Septal e' Velocity (cm/s)
P < 0.001
Washout
Week
G
Lateral E/e'
P < 0.001
Washout
Week
H
Septal E/e'
P = 0.001
Washout
Week
Placebo
Aficamten


A
LV Global Longitudinal Strain (%)
16.5
16
15.5
15
14.5
P = 0.1
Washout
0
12
16
20
24
28
Week
B
LV Global Circumferential Strain (%)
36
34
32
30
28
P < 0.001
Washout
0
12
16
20
24
28
Week
Placebo
Aficamten


A
Placebo
Aficamten
Septal e', baseline
Septal e', week 24
Lateral e', baseline
Lateral e', week 24
Average E/e', baseline
Average E/e', week 24
LAVI, baseline
LAVI, week 24
8%
92%
8%
92%
26%
74%
29%
71%
27%
73%
28%
72%
34%
66%
27%
73%
7%
93%
13%
87%
30%
70%
52%
48%
24%
76%
49%
51%
32%
68%
43%
57%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Normal
Abnormal
B
Placebo
Aficamten
Baseline
Week 24
4
18
56
62
9
20
52
59
2
1
11
8
2
33
15
45
1
24
52
65
15
32
63
32
7
12
15
1
26
5
32
27
Number of Abnormal LV Diastolic Measures: 0 1 2 3

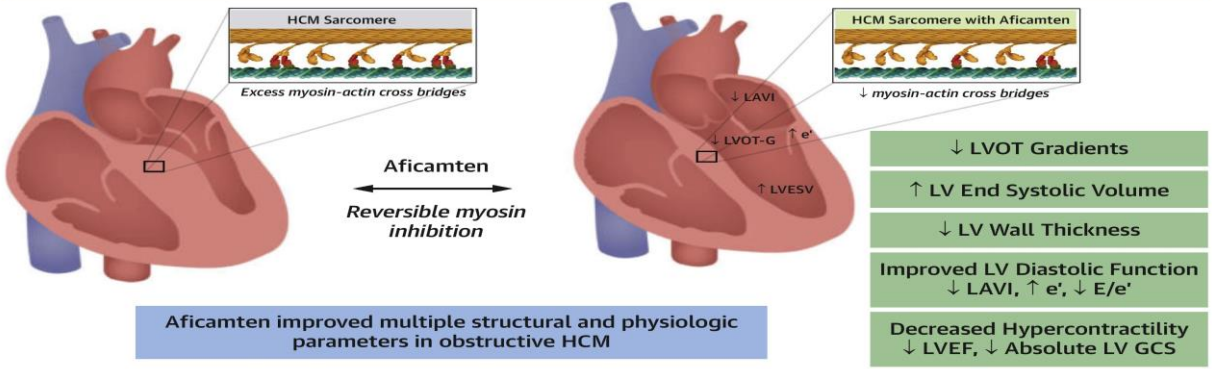
Systolic Function



The change in LV global circumferential strain (GCS) is associated with change in LVEF in a 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, cardiopulmonary exercise testing modality). Abbreviations as in Figure 1.

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

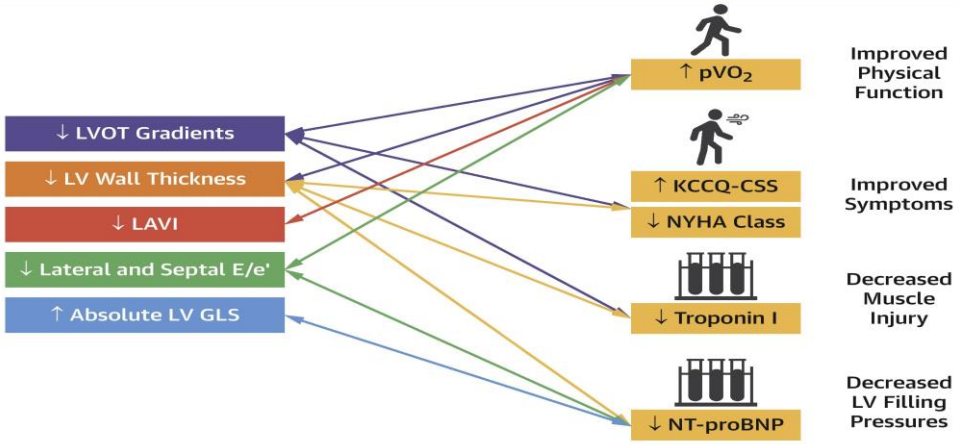
Effect of Aficamten on Cardiac Structure and Function



- ↓ LVOT Gradients
- ↑ LV End Systolic Volume
- ↓ LV Wall Thickness
- Improved LV Diastolic Function ↓ LAVI, ↑ e', ↓ E/e'
- Decreased Hypercontractility ↓ LVEF, ↓ Absolute LV GCS

Aficamten improved multiple structural and physiologic parameters in obstructive HCM

Changes in Echocardiographic Measures are Associated With Changes in pVO_2 and Other Outcomes in Aficamten-Treated Patients



Hegde SM, et al. *JACC*. 2024;10.1016/j.jacc.2024.08.002

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
- significant improvements in LVOT gradients
- 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
- improvement in several outcome measures, including pVO2, NT-proBNP, KCCQ-CSS, and high-sensitivity cardiac troponin I

Aficamten Treatment Effect

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.

myosin inhibition may in parallel directly contribute to reduction in wall thickness in addition to the secondary effects of decreased afterload.

Aficamten Treatment Effect

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.

Aficamten Treatment Effect

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'.

Aficamten Treatment Effect

With aficamten, LV GLS was unchanged and remained mildly impaired.

A similar response in absolute LV GLS and LV GCS has been observed with septal myectomy

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.

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

After 4 weeks of washout following aficamten treatment, **nearly all measures of cardiac structure and function returned to baseline values**.

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.

The reversal of the noted drug effects within 4 weeks to baseline values, including LVEF, is of particular importance to **safety**.

Aficamten Treatment Effect

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.

Aficamten Treatment Effect

Aficamten significantly improved the primary outcome of pVO2 compared with placebo in patients with oHCM.

Abnormal diastolic function has been associated with impaired exercise capacity in HCM

In this analysis, reduction in LA size is uniquely associated with improvement in functional status compared with the other outcomes.

Aficamten Treatment Effect

- Aficamten decreased both cardiac biomarkers, NT-proBNP and high-sensitivity cardiac troponin I
- **Reductions in NT-proBNP** ⇒ 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** ⇒ significant reduction in Valsalva LVOT gradients and interventricular septal wall thickness, and increase in septal e' velocity

Aficamten Treatment Effect

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

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.

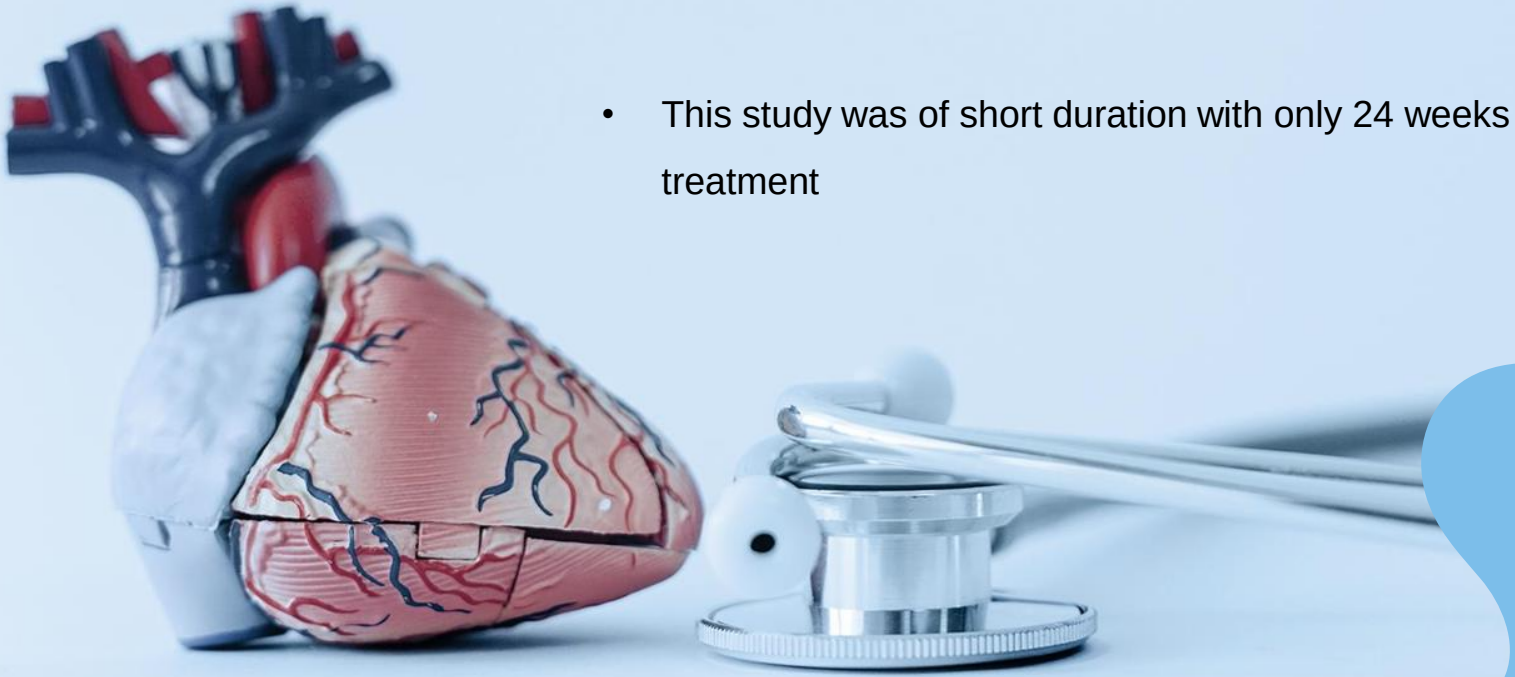
In the recent randomized placebo-controlled trial of **metoprolol** vs placebo, metoprolol decreased LVOT obstruction and improved LV GLS without effect on E/e', invasively measured filling pressures, or symptoms.

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.***

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.

Study Limitations

- Ultrasound-enhancing agents were not approved for use in this study
- Mitral valve SAM and mitral regurgitation were assessed qualitatively as present or absent
- This study was of short duration with only 24 weeks of treatment

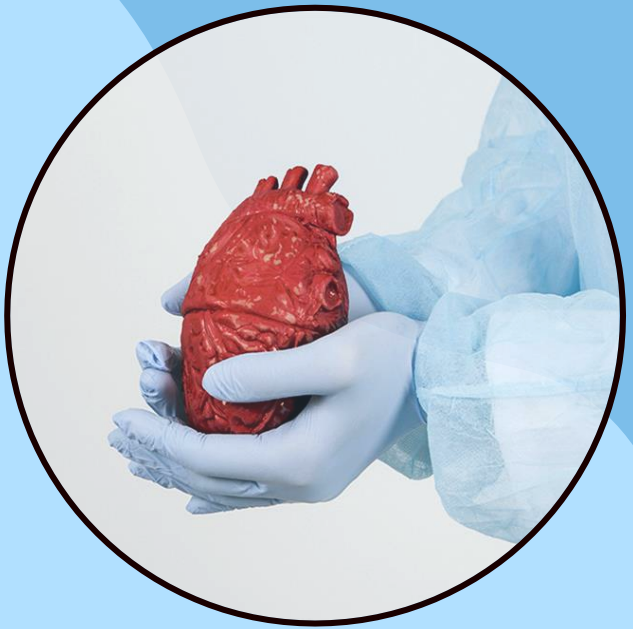


Conclusions

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.

Thanks for your attention