Effect of Aficamten Compared with Metoprolol on Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy:

A prespecified analysis of MAPLE-HCM

Sheila M. Hegde, MD MPH[1,2], Xiaowen Wang, MD, MPH, Pablo Garcia-Pavia, MD, PhD, Stoyan Getchevski, MD, Ahmad Masri, MD, Bela Merkely, MD, Michael E. Nassif, MD, Maria Luisa Peña-Peña, MD, Roberto Barriales-Villa, MD, PhD, Ozlem Bilen, MD, Melissa Burroughs, MD, Brian Claggett, PhD, Juan Pablo Costabel, MD, Edileide de Barros Correia, MD, Anne M. Dybro, MD, PhD, Perry Elliott, MBBS, MD, Neal K. Lakdawala, MD, Amy Mann, BA, Martin S. Maron, MD, Ajith Nair, MD, Steen H. Poulsen, MD, Patricia Reant, MD, PhD, P. Christian Schulze, MD; Andrew Wang, MD, Regina Sohn, MD, PhD, Indrias Berhane, PhD, Stephen B. Heitner, MD, Daniel L. Jacoby, MD, Stuart Kupfer, MD, Fady I. Malik, MD, PhD, Amy Wohltman, ME, Michael A. Fifer, MD, Scott D. Solomon, MD, on behalf of the MAPLE-HCM Investigators

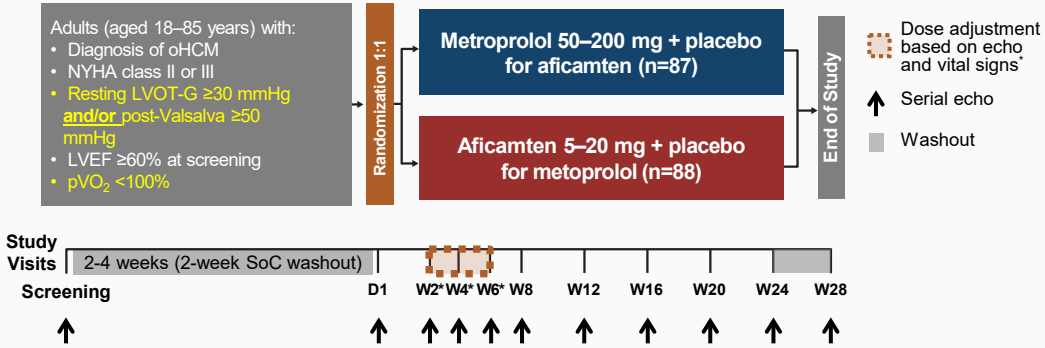
[1]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
[2]University of Texas Southwestern Medical Center, Dallas, TX, USA.

AUGUST 31, 2025

ESC Congress 2025 Madrid
TOGETHER WITH World Congress of Cardiology

Background

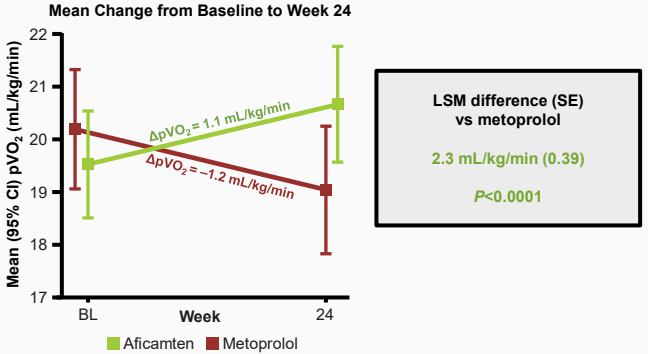
- Beta-blockers have served as the first-line therapy for symptomatic obstructive HCM (oHCM) for decades
- Aficamten is an investigational, next-in-class CMI, a small-molecule selective inhibitor of the cardiac myosin ATPase, that targets and reduces hypercontractility
- **MAPLE-HCM** is a phase 3 head-to-head comparative efficacy and safety study of monotherapy with aficamten vs metoprolol in adults with symptomatic oHCM



Baseline Characteristics

- 175 participants
- Mean age: 58 ± 13 years
- 42% Female
- 80% White, 14% Asian
- 70% prior B-blocker use
- 13% CCB use

Primary Endpoint (peak VO_2)

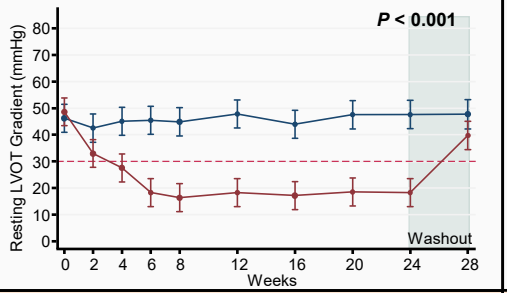


*Metoprolol doses were uptitrated in 50 mg increments from 50 to 200 mg. Aficamten doses were uptitrated in 5 mg increments from 5 to 20 mg.

CCB, calcium channel blocker; CMI, cardiac myosin inhibitor; D, day; echo, echocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSM, least squared mean; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract;; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake; SoC, standard of care; W, week.

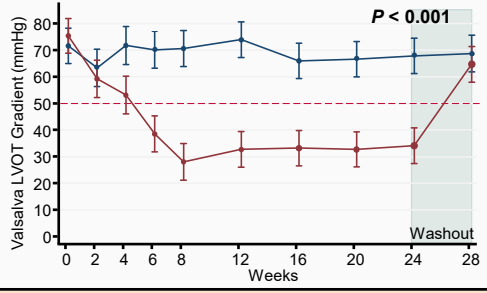
Systolic Function and Gradients

Resting LVOT Gradient



−30 mmHg (−37, −23)

Valsalva LVOT Gradient

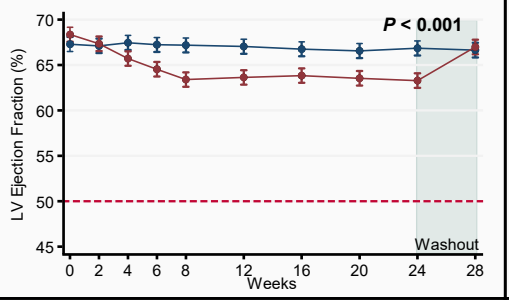


−35 mmHg (−44, −26)

Resting LVOT-G ↓
Valsalva LVOT-G ↓

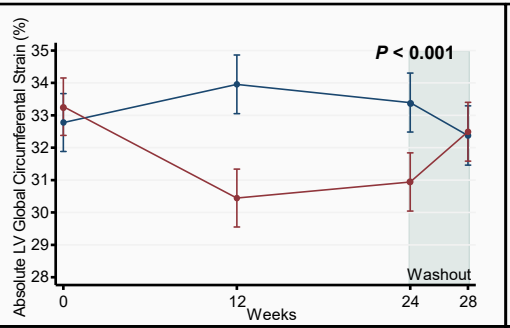
Metoprolol — Aficamten

LV Ejection Fraction



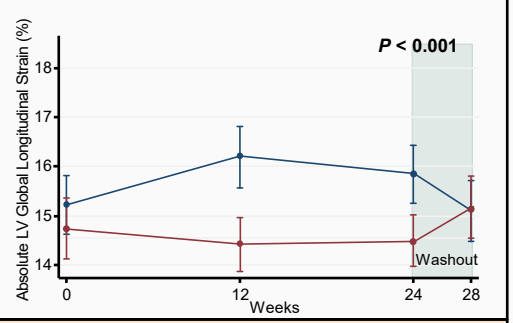
−5% (−5, −3)

Absolute LV GCS



−2.5% (−3.7, −1.3)

Absolute LV GLS



−1.8% (−1.8, −0.5)

LVEF ↓
Absolute LV GCS ↓
Absolute LV GLS ↓

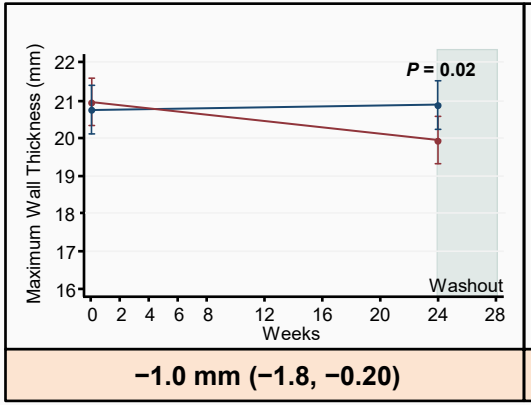
Treatment-corrected difference (95% CI) is adjusted for baseline echo measure, treatment, exercise mode (bicycle vs treadmill) and stratification by time of diagnosis (recent [Group 1] vs chronic [Group 2]) with corresponding *P* values at 24 weeks.

Horizontal dashed lines represent thresholds for gradients and normal values for LVEF.

GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient.

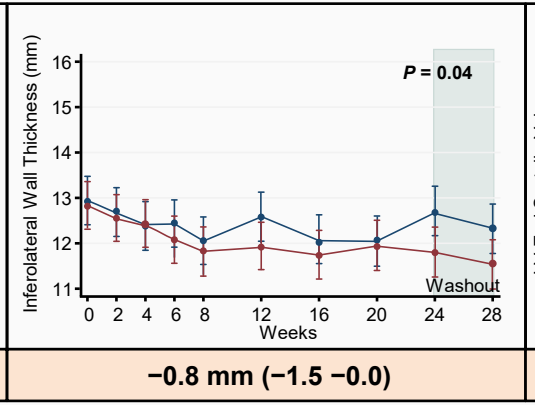
Cardiac Structure

Maximal Wall Thickness



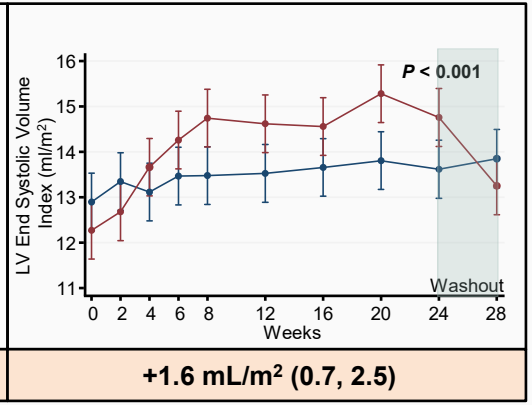
−1.0 mm (−1.8, −0.20)

Inferolateral Wall Thickness



−0.8 mm (−1.5 −0.0)

LV ESVi



+1.6 mL/m² (0.7, 2.5)

Metoprolol — Aficamten

Maximal Wall Thickness ↓

Inferolateral Wall ↓

LV ESVi ↑

Not Shown:

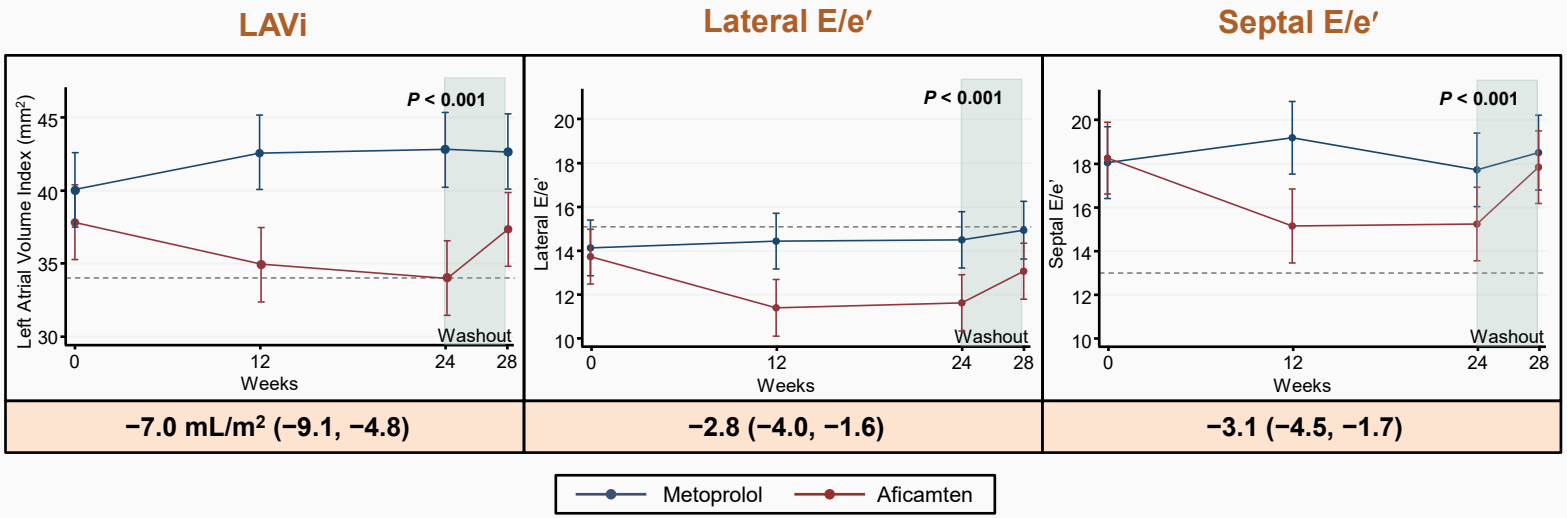
Interventricular Septal Wall ↔

LV Mass Index ↔

Treatment-corrected difference (95% CI) is adjusted for baseline echo measure, treatment, exercise mode (bicycle vs treadmill) and stratification by time of diagnosis (recent [Group 1] vs chronic [Group 2]) with corresponding *P* values at 24 weeks.

LV, left ventricular; LV; ESVi, left ventricular end systolic volume index.

Diastolic Function



LAVi ↓
Lateral e′ ↑
Septal e′ ↑
Lateral E/e′ ↓
Septal E/e′ ↓

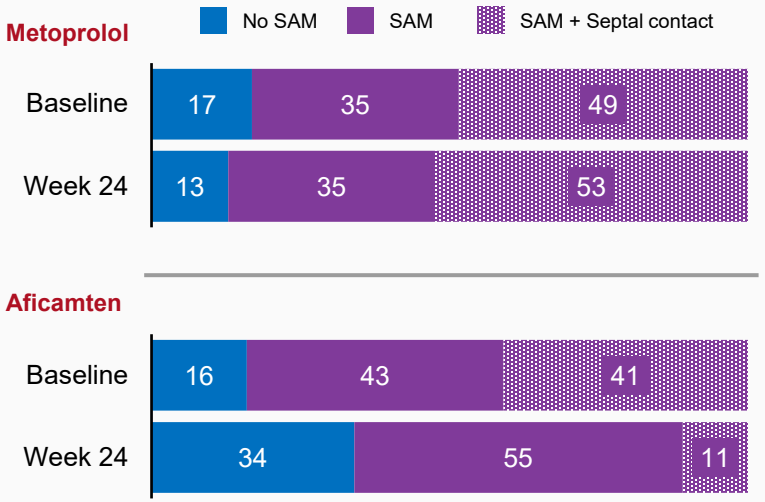
Treatment-corrected difference (95% CI) is adjusted for baseline echo measure, treatment, exercise mode (bicycle vs treadmill) and stratification by time of diagnosis (recent [Group 1] vs chronic [Group 2]) with corresponding *P* values at 24 weeks.

Horizontal dashed lines represent normal values left atrial volume index, lateral E/e' , and septal E/e'.

LAVi, left atrial volume index; e', mitral annular early diastolic velocity; E/e', ratio between early mitral inflow velocity and septal and lateral mitral annular early diastolic velocity

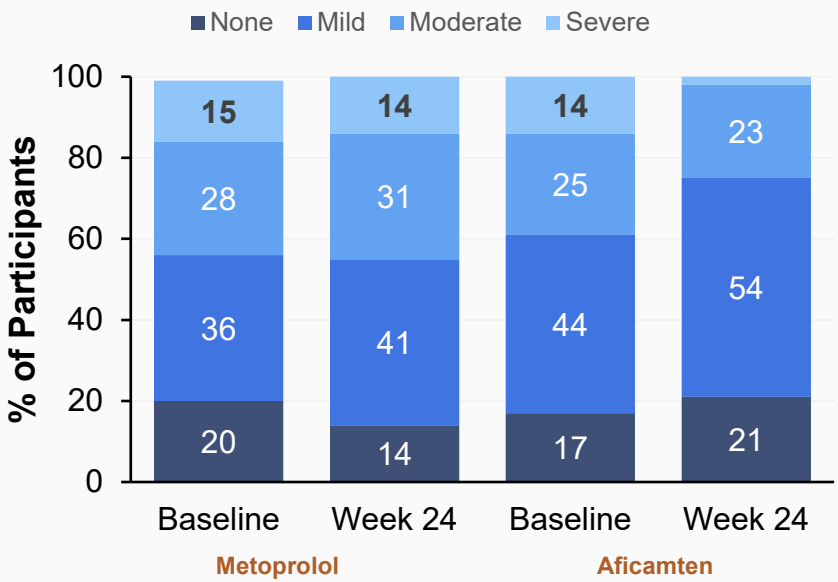
Results: Change in Mitral Valve Function

Systolic Anterior Motion



Aficamten decreased SAM with and without contact
- SAM: OR 0.20 [0.08, 0.52], *P* = 0.001
- SAM + contact: OR 0.09 [0.04, 0.24], *P* < 0.001

Mitral Regurgitation



Aficamten improved MR severity
- OR 2.49 [1.38, 4.51], *P* = 0.002

MR, mitral regurgitation; OR, odds ratio; SAM, systolic anterior motion.

Conclusions

- Compared with metoprolol, aficamten demonstrated significant improvement in multiple measures of cardiac structure and function
- A modest decline in measures of LV systolic function occurred (LVEF, LV GCS), yet they remained within normal range, reflecting less hypercontractility
- Surprisingly, LVOT gradients were not effectively lowered with metoprolol despite physiologic evidence of adequate beta-blockade

These findings further support the overall superiority of therapy with aficamten over metoprolol demonstrated in MAPLE-HCM with evidence of favorable changes in multiple echocardiographic measures of cardiac structure and function in patients with symptomatic oHCM

GCS, global circumferential strain; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MR, mitral regurgitation; oHCM, obstructive hypertrophic cardiomyopathy; SAM, systolic anterior motion; e′, mitral annular early diastolic velocity; E/e′, ratio between early mitral inflow velocity and septal and lateral mitral annular early diastolic velocity.

Acknowledgments

The MAPLE-HCM trial is funded by Cytokinetics, Incorporated.

We thank the following individuals for their contributions to this clinical trial:

- Participants and their families.
- Investigators and study site staff
- Brigham and Women's Hospital Cardiovascular Core Imaging Laboratory
- Data Monitoring Committee members
- Steering Committee Members: Pablo Garcia-Pavia (**Co-PI**), Michael Fifer (**Co-PI**), Edileide Correra de Barros, Ozlem Bilen, Melissa Burroughs, Juan Pablo Costabel, Anne Dybro, Perry Elliott, Neal Lakdawala, Amy Mann, Ajith Nair, Michael Nassif, Steen Poulsen, Patricia Reant, Christian Schulze, Andrew Wang

Simultaneously published in

JACC