EFFECT OF AFICAMTEN ON CARDIAC STRUCTURE AND FUNCTION IN NONOBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: THE ACACIA-HCM CMR STUDY

Ahmad Masri[1], Maria Luisa Peña-Peña, Massimo Piepoli, Joseph Selvanayagam, Mark V. Sherrid, Caroline J. Coats, Brian L. Claggett, Carolyn Y. Ho, Zi Michael Miao, Punag H. Divanji, Stephen B. Heitner, Daniel L. Jacoby, Stuart Kupfer, Fady I. Malik, Joel Salazar-Mendiguchía, Amy Wohltman, Shu Zhuo, James Moon, Martin S. Maron, on behalf of the ACACIA-HCM Investigators

[1]Oregon Health and Science University, Portland, OR, USA

#ScientificSessions26

DISCLOSURES

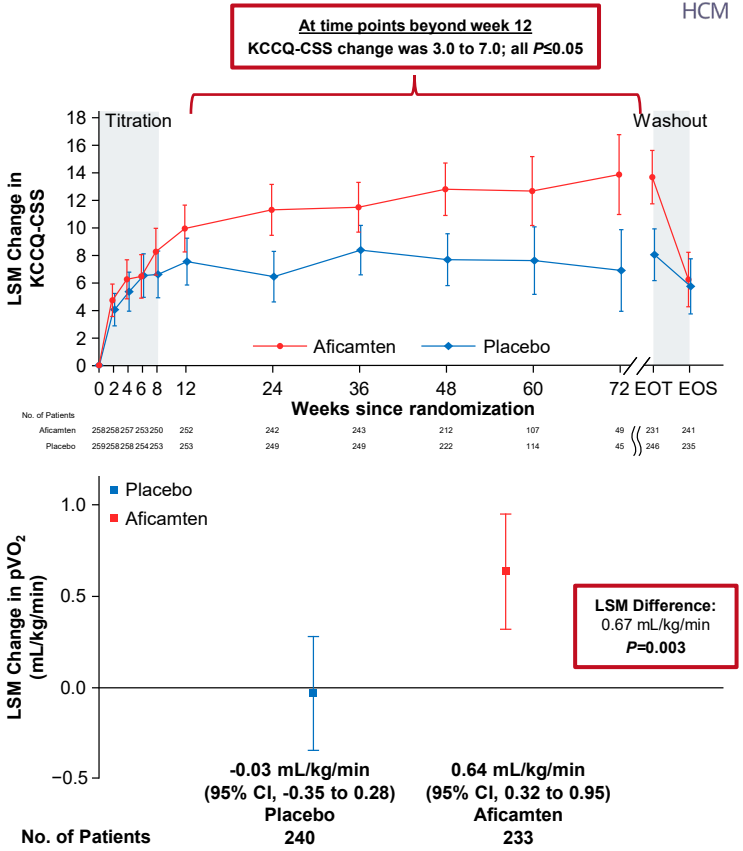
Ahmad Masri, MD

Research Grants from Attralus, Bayer, Cytokinetics and Janssen.

Fees from Cytokinetics, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Edgewise, Rocket, Lexeo, Bayer, Imbria, Braveheart, AstraZeneca, Avidity, and Neurimmune.

BACKGROUND

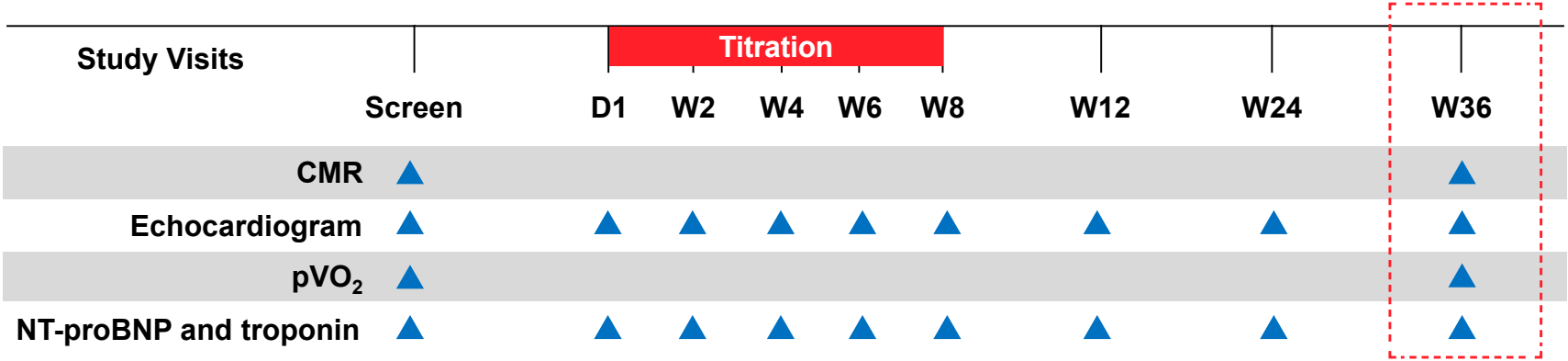
- In the pivotal phase 3, ACACIA-HCM trial in patients with symptomatic nHCM:
  - Aficamten yielded significantly greater improvements than placebo in exercise capacity and health status (**Figure**).[1]
  - Clinical benefits mirrored favorable effects on myocardial wall stress and diastolic function,[1-2] key pathophysiologic mechanisms of symptoms, and exercise intolerance in nHCM.[3]
- Heterogenous LV hypertrophy can limit geometric assumptions used in echocardiography.[4-5]
- Aficamten produced favorable myocardial remodeling in oHCM, with a larger and more precise effect of treatment on LVMI, wall thickness, and LAVI detected using CMR than echocardiography.[1]



CMR, cardiac magnetic resonance; EOS, end of strusy; EOT, end of treatment; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LSM, least squares mean; LV, left ventricular LVMI, left ventricular mass index; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake.

1. Masri A, et al. *N Engl J Med* 2026 Aug 28. doi: 10.1056/NEJMoa2603021. **2.** Hegde SM, et al. *Circulation* 2026 Aug 29. doi:10.1161/CIRCULATIONAHA.126.082343. **3.** Kawana M, et al. *Front Physiol* 2022;13:9750767. **4.** Ommen SR, et al. *Circulation* 2024;149:e1239-311. **5.** Myqorzo (aficamten) prescribing information. Cytokinetics; 2026.

METHODS: STUDY DESIGN



- A total of 69 patients were enrolled in the CMR substudy, and 61 (88.4%) completed both baseline and Week 36 CMR (n=25 aficamten, n=36 placebo).

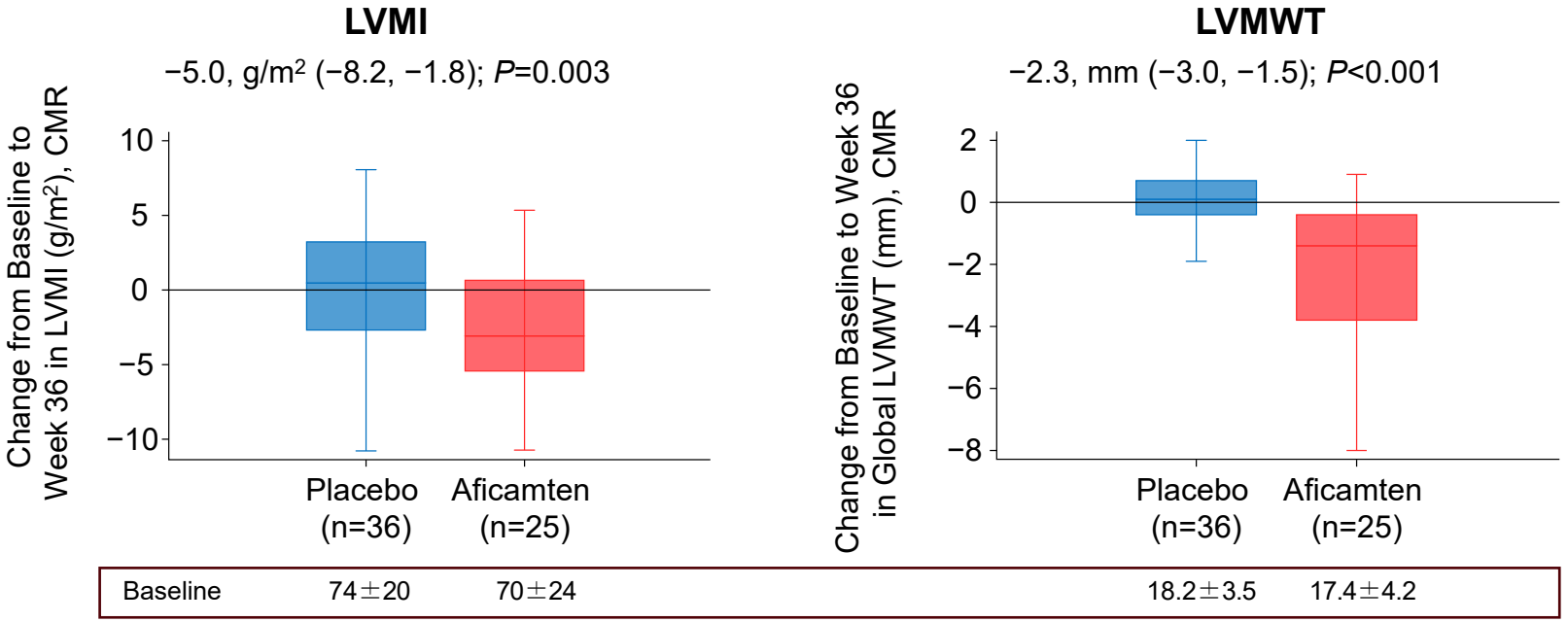
CMR, cardiac magnetic resonance; D, Day; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO_2, peak oxygen uptake; W, Week.

RESULTS: BASELINE CHARACTERISTICS BY TREATMENT GROUP

	Aficamten (n=31)	Placebo (n=38)
Age, y, mean (SD)	59.7 ± 15.1	56.3 ± 14.2
Female sex, n (%)	24 (77.4%)	21 (55.3%)
Race		
White, n (%)	26 (83.9%)	28 (73.7%)
Asian, n (%)	1 (3.2%)	3 (7.9%)
Other, n (%)	4 (12.9%)	7 (18.4%)
History of hypertension, n (%)	13 (41.9%)	15 (39.5%)
Family history of HCM, n (%)	9 (29.0%)	15 (39.5%)
Paroxysmal atrial fibrillation, n (%)	8 (25.8%)	8 (21.1%)
Permanent atrial fibrillation, n(%)	1 (3.2%)	1 (2.6%)
KCCQ Clinical Summary Score, mean (SD)	68.8 ± 15.0	69.7 ± 13.8
NYHA class III, n (%)	9 (29.0%)	5 (13.2%)
NT-proBNP, median [IQR], pg/mL	647 [359, 965]	884 [546, 1391]
hsTnI, median [IQR], ng/L	18 [7,45]	20 [15,50]
CMR		
LV mass index, g/m^2, mean (SD)	70 ± 24	74 ± 20
LV maximal wall thickness, mm, mean (SD)	17.4 ± 4.2	18.2 ± 3.5

CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

RESULTS: AFICAMTEN IMPROVED LV MASS AND WALL THICKNESS

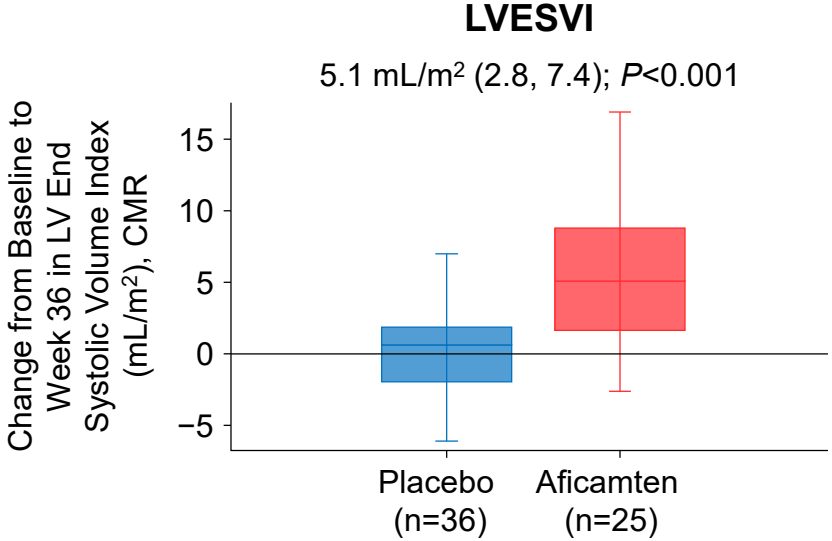


Baseline	74±20	70±24	18.2±3.5	17.4±4.2

- Reduction in LVMI was driven by regression of the cellular compartment (–5 g/m² [95% CI: –9 to –2 g/m²], *P*=0.002), while the interstitial mass remained stable (–0.6 g/m² [95% CI: –2.6 to 1.4 g/m²], *P*=0.57).

CMR, cardiac magnetic resonance; LV, left ventricular; LVMI, left ventricular mass index; Max, maximal; LVMWT, left ventricle maximal wall thickness.

RESULTS: AFICAMTEN INCREASED LV END-SYSTOLIC VOLUME

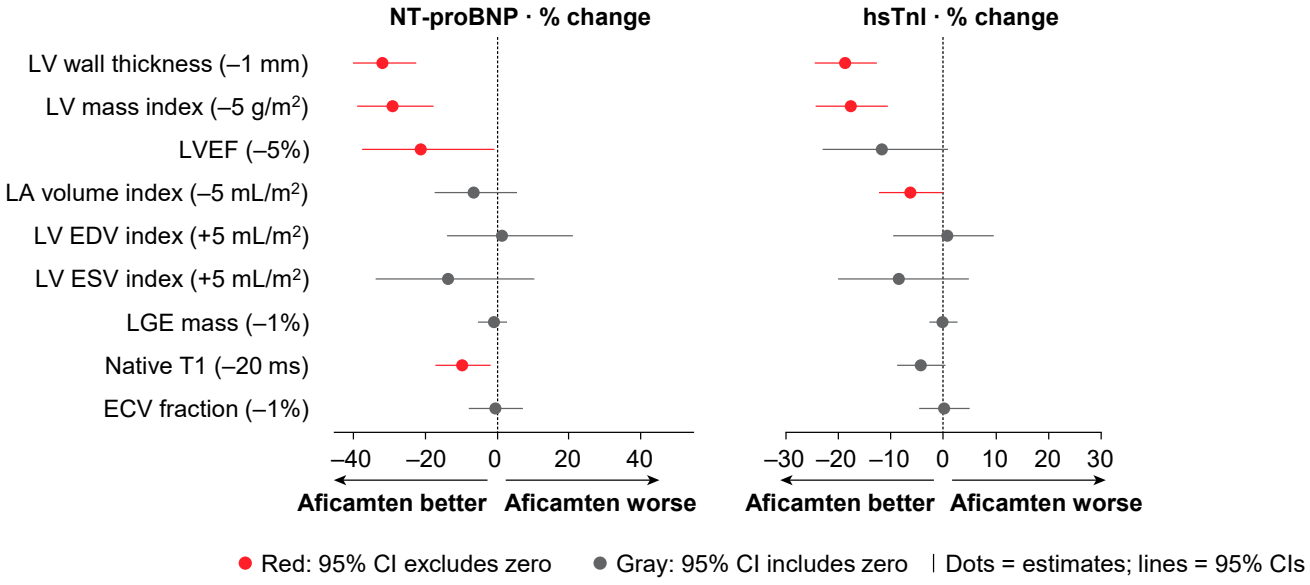


CMR Variable	Treatment Effect (95% CI)	*P* value
LV end diastolic volume index (mL/m²)	3 (−1, 6)	0.15
LAVI (mL/m²)	−1.1 (−6.4, 4.2)	0.69
LGE mass (g, 5SD)	2.8 (−1.2, 6.8)	0.16
LGE (% of LV mass)	2 (−1, 5)	0.25
LV native T1 (ms)	−4 (−35, 27)	0.80
LV ECV fraction (%)	1.0 (−1.1, 3.2)	0.34
LV ECV index (ml/m²)	−0.4 (−2.4, 1.6)	0.66

- Relative to placebo, aficamten significantly increased LV end-systolic volume index (**Figure**).
- There were no significant changes in LV end-diastolic volume index, LAVI, LGE, LV native T1, or ECV with aficamten (**Table**).

5SD, 5 standard deviation above mean signal; BL, baseline; CMR, cardiac magnetic resonance; ECV, extracellular volume; LV, left ventricular; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LV, left ventricular; LVESVI, left ventrical end-systolic volume index.

RESULTS: PROPORTIONAL CHANGES IN CARDIAC BIOMARKERS AND CMR CHANGES



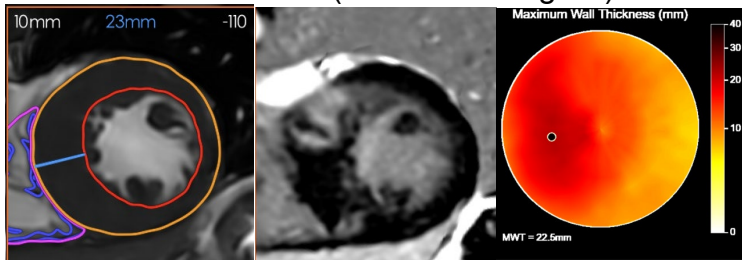
Reductions in LVMI and LV wall thickness were associated with reductions in NT-proBNP and hsTnI.

CMR, cardiac magnetic resonance; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; LGE, late gadolinium enhancement; LV, left ventricular; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B type natriuretic peptide.

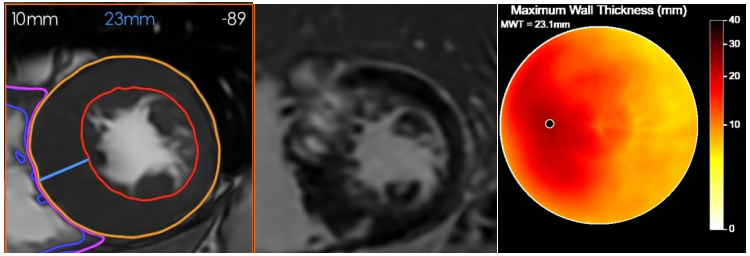
CMR AT BASELINE AND WEEK 36 IN AFICAMTEN VS PLACEBO TREATED PATIENTS

PLACEBO

Baseline (LVMI 74 ± 20 g/m^2)

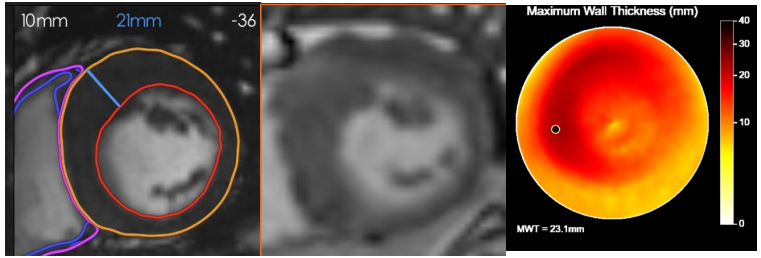


Week 36 (LVMI 74 ± 20 g/m^2)

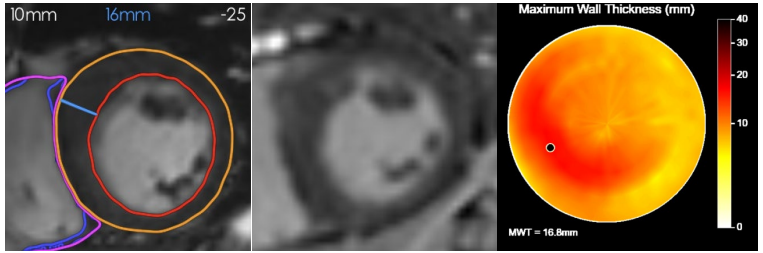


AFICAMTEN

Baseline (LVMI 70 ± 24 g/m^2)

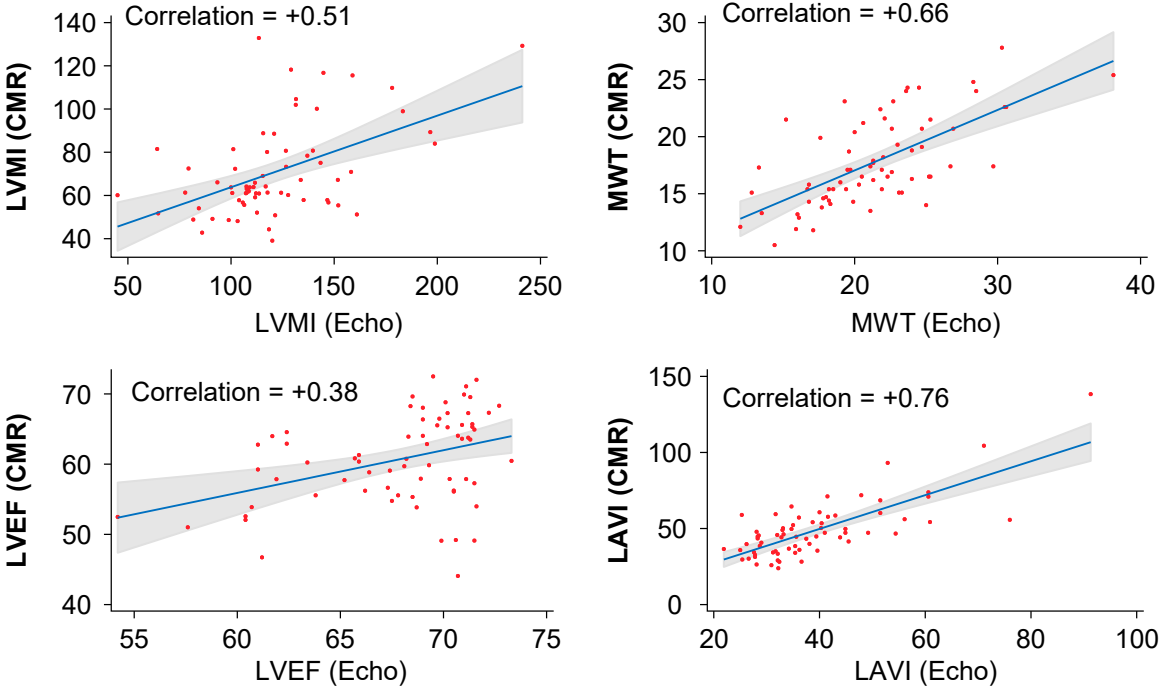


Week 36 (LVMI 65 ± 18 g/m^2)



CMR, cardiac magnetic resonance, LVMI, left ventricular mass index.

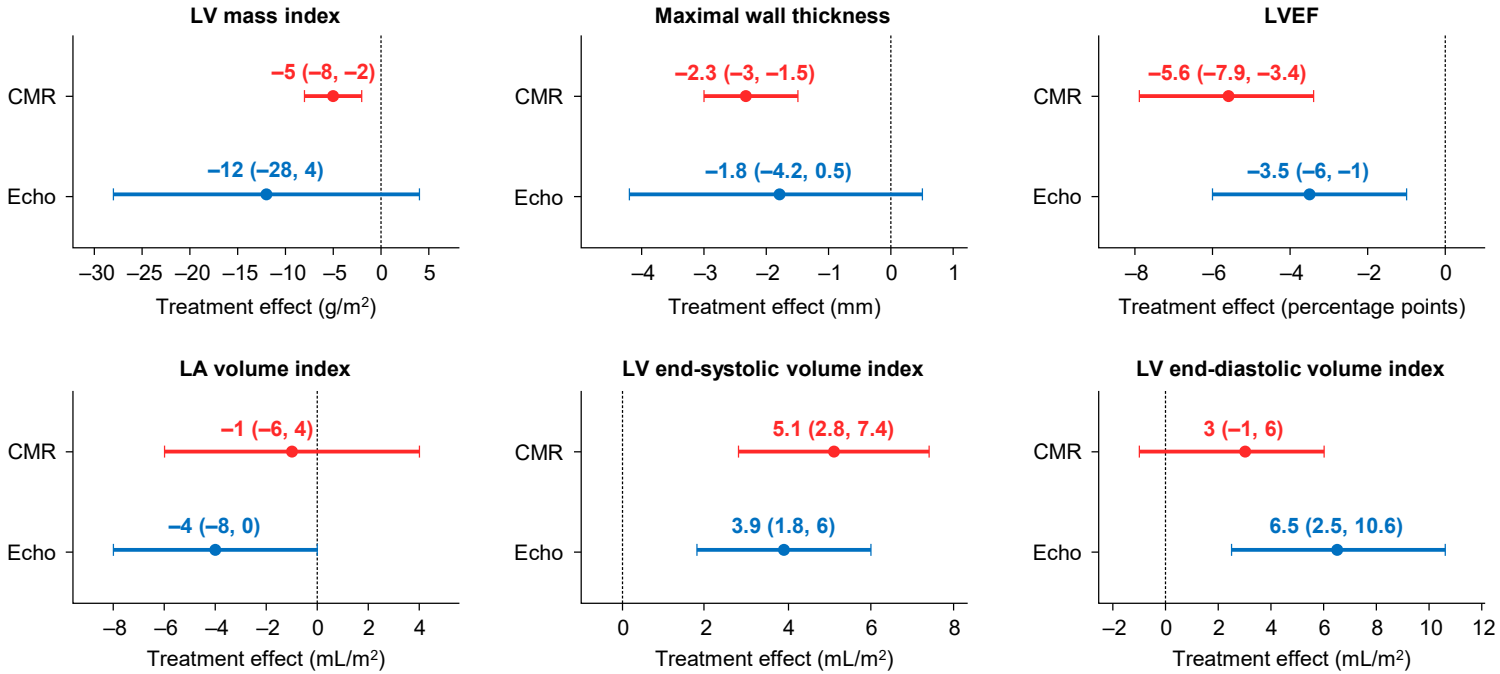
RESULTS: CORRELATION OF BL MEASUREMENTS ON CMR AND ECHOCARDIOGRAPHY



At baseline there was moderate correlation between CMR and echocardiographic measurements of LVMI, LVEF, and LV wall thickness, and a strong correlation of LAVI.

BL, baseline; CMR, cardiac magnetic resonance; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MWT, maximal wall thickness.

RESULTS: COMPARATIVE TREATMENT EFFECT BETWEEN CMR AND ECHOCARDIOGRAPHY



Echo data was restricted to those who also had CMR.
Data shown as mean ± SD, unless specified otherwise.
CMR, cardiac magnetic resonance; echo, echocardiogram; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

CONCLUSIONS

- In the ACACIA-HCM CMR substudy in patients with symptomatic nHCM, 36 weeks of aficamten treatment promoted favorable cardiac remodeling, including reduced LVMI and LV wall thickness.
  - Regression of hypertrophy reflected a reduction in cellular compartment, with no significant change in extracellular matrix or myocardial fibrosis measures
- Structural changes observed with CMR were associated with improvements in NT-proBNP and hsTnI.
- CMR identified changes in LV hypertrophy that were not clearly demonstrated by echocardiography, revealing the complexity in using geometric assumptions in nHCM.
- The ongoing long-term extension FOREST-HCM CMR substudy will characterize longer-term changes in cardiac structure and function in patients with nHCM.

CMR, cardiac magnetic resonance; hsTnI, high-sensitivity troponin I; LV, left ventricular; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B type natriuretic peptide.

ACKNOWLEDGMENTS

The ACACIA-HCM trial is sponsored by Cytokinetics, Incorporated. We thank the following individuals for their contributions to this clinical trial:

- Participants and their families.
- Investigators and study site staff.
- Data Monitoring Committee members.
- Clinical Event Adjudication Committee.
- Steering Committee members: Michael Arad, Roberto Barriales-Villa, Caroline J. Coats, Edileide de Barros Correia, Juan Pablo Costabel, Perry M. Elliott, Jorge E. Silva Enciso, Carolyn Y. Ho, Gregory D. Lewis, Matthew W. Martinez, Ahmad Masri, Mathew S. Maurer, Michelle Michels, Sumeet S. Mitter, Jesus E. Pino Moreno, Iacopo Olivotto, Anjali T. Owens, Steen H. Poulsen, Florian Rader, Ethan J. Rowin, Junbo Ge, P. Christian Schulze, Mark V. Sherrid, Scott D. Solomon, John A. Spertus, and Charles Teale Sr.
- Editorial support for the preparation of this presentation was provided by Elyse Smith, PhD, CMPP, on behalf of Envision Medical Communications, and was funded by Cytokinetics, Incorporated.

THANK YOU

Scientific Sessions

#ScientificSessions26

ACACIA HCM