Divergent Effect of Aficamten Versus Metoprolol on Exercise Performance in Obstructive Hypertrophic Cardiomyopathy: A Prespecified Analysis of MAPLE-HCM

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

[1]Mass General Brigham Heart and Vascular Institute, Massachusetts General Hospital, Boston, MA, USA

Background:
Obstructive Hypertrophic Cardiomyopathy (oHCM)

Exercise intolerance is an important clinical feature of oHCM

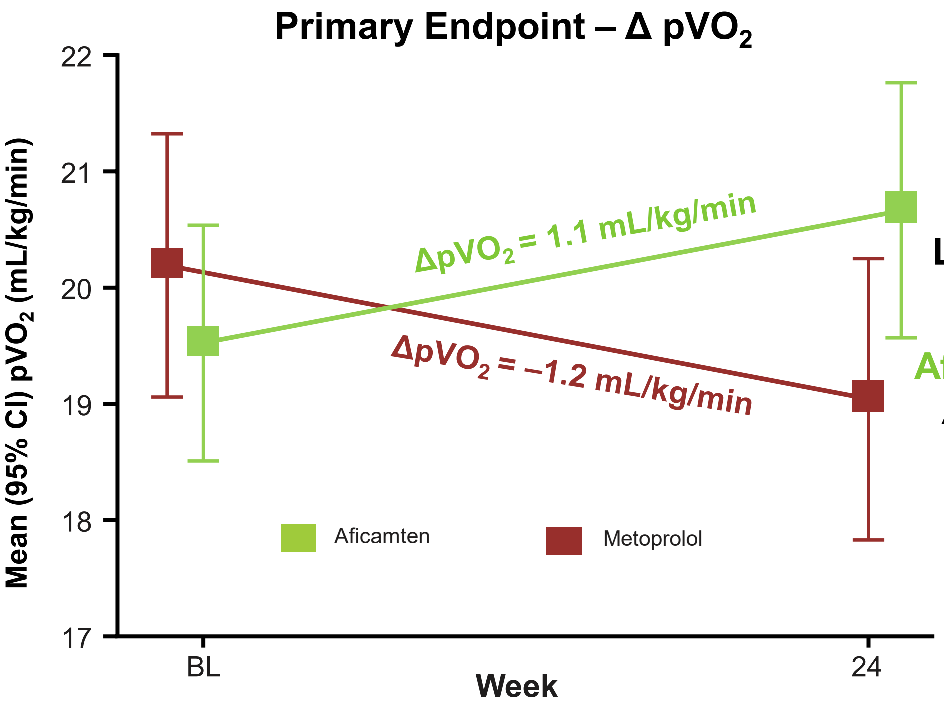
With aficamten

↓ Left Ventricular Outflow Tract Gradient → **↑ Exercise Tolerance (peak oxygen uptake)**

LVOT, left ventricular outflow tract; pVO_2, peak oxygen uptake; SAM, systolic anterior motion.

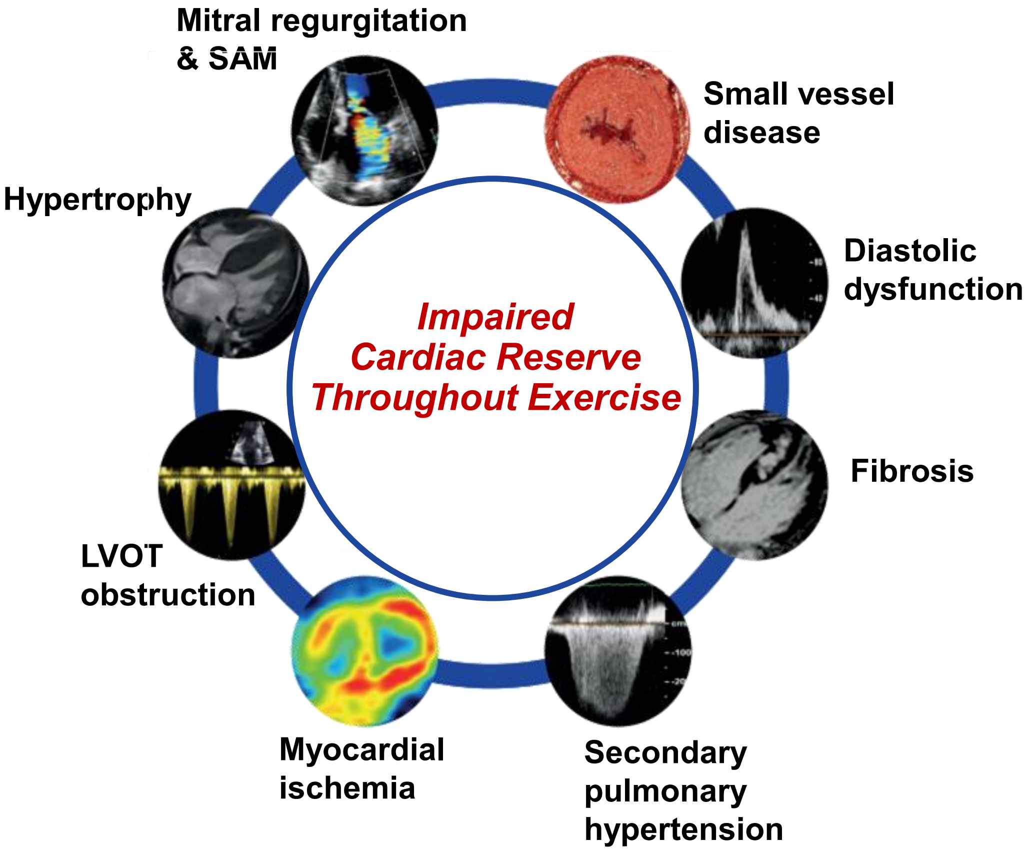
Maron MS, et al. *N Engl J Med* 2024;390(20):1849; Lee MMY, et al. *JAMA Cardiol* 2024;9:990-1100.
Figure adapted from Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.doi: epdf/10.1016/j.jchf.2023.10.004.

Background: MAPLE-HCM Demonstrated Superiority of Aficamten Compared to Metoprolol in Symptomatic oHCM



LSM Change (SE) from Baseline to Week 24

Aficamten vs. Metoprolol
Δ 2.3 (0.39) mL/kg/min
***P*<0.0001**



Secondary Endpoints[1]

- ✓ Δ LVOT gradient
- ✓ Δ NT-proBNP
- ✓ Δ NYHA Class
- ✓ Δ KCCQ
- ✓ Δ Left atrial volume index
- *NS* Δ Left ventricular mass index

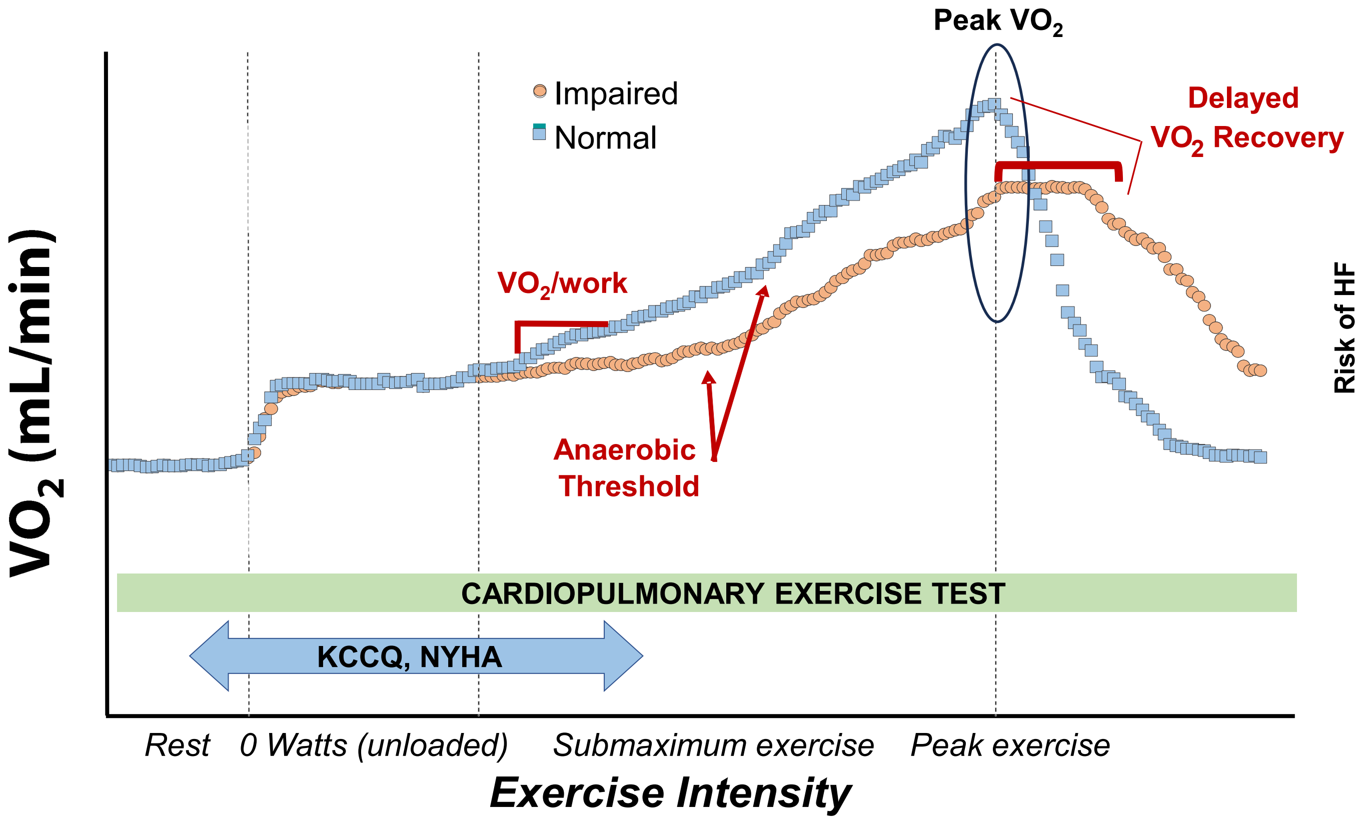
MAPLE HCM

Δ, change; BL, baseline; LSM, least squares mean; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; 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.

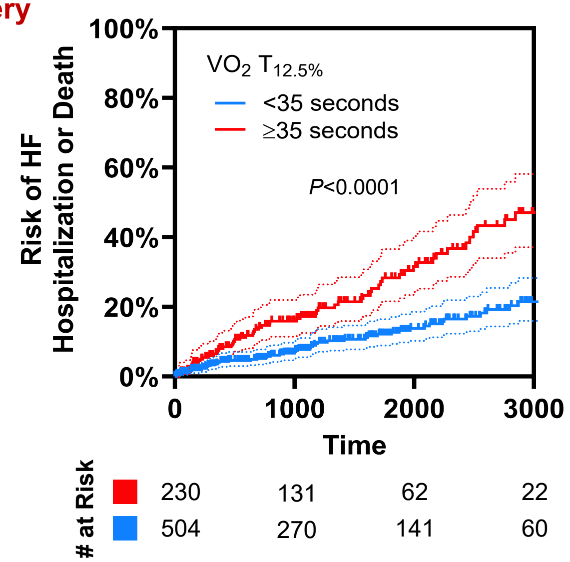
Garcia-Pavia P, et al. *N Engl J Med.* 2025;393(10):949-60. [1]All secondary endpoints (except left ventricular mass index) were statistically significant with check marks indicating P<0l01

Background: CPET in MAPLE-HCM

Cardiopulmonary exercise testing (CPET) enables objective assessment of <u>all stages</u> of exercise including patterns of O_2 uptake, ventilatory efficiency, and hemodynamic responses to exercise that predict prognosis in HCM



Delayed early VO_2 recovery correlates with ↓ exSvol, ↑ exPCWP, but not peripheral O_2 extraction[b]



Ventilatory Efficiency (VE/VCO_2 slope) -early exercise, throughout exercise

ΔHeart Rate, Δ Blood Pressure

Δ Workload, Δ Exercise Duration

Δ Composite Variables

Prognostic Relevance from Previous Studies[a]	
Change in VE/VCO_2	Change in Peak VO_2
−1.0 (HR 0.90; 0.82-1.0)[a]	1.0 (HR 0.82; 0.77-0.88)[a]

[a]Coats C, et al. *Cir Heart Fail* 2015:8(6):1022-31.N=198, HR for all-cause mortality after adjustment for age, sex, LA size, and LVEF. Figure (left panel) adapted from Lewis GD, et al. *Circ Heart Fail* 2022;15(5):p.e008970. [b]Figure (right panel) adapted from Campain, J et al. *Circulation* 2025; Epub ahead of print. CO_2, carbon dioxide; CPET, cardiopulmonary exercise test; LA, left atrial; LVEF, left ventricular ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; V_E, minute ventilation; VCO_2, carbon dioxide output; V_E/VCO_2 slope, slope of increase in minute ventilation (VE) relative to CO_2 production; VO_2, oxygen uptake.

Methods and CPET Endpoints

ASM 2025
HFSA ANNUAL SCIENTIFIC MEETING
Where Heart Failure Teams Gather
#HFSA2025

In **MAPLE-HCM**,
175 patients with oHCM,
RER ≥ 1.05 and
pVO_2 < 100% predicted

88 patients were randomized to aficamten monotherapy[a]

87 patients were randomized to metoprolol monotherapy[a]

OR

At Week 24, end of treatment, CPET

OR

CPET Endpoints:

Submaximal Exercise Measures

- Anaerobic threshold VO_2
- Aerobic efficiency (VO_2/work)
- Ventilatory efficiency pre-AT
- Ventilatory efficiency VE/VCO_2 slope

Maximal Exercise Measures

- pVO_2
- Peak workload
- Peak HR
- Exercise duration
- HR reserve
- Peak RER

Post-Exercise

- VO_2 recovery delay, >0% (sec)
- VO_2 recovery 12.5%, 25%, 50% (sec)

Composite Exercise Response

- Hemodynamic (SBP) + O_2 uptake: Circulatory power
- Ventilatory power
- O_2 uptake + ventilatory efficiency 2-component Z-score

At baseline, participants had to have peak RER ≥ 1.05 and <100% predicted pVO_2.
[a]5 aficamten- and 5 metoprolol-treated patients had invalid Week 24 CPET due to technical issues, deviation from the CPET MOP, or because of an SAE.
AT, anaerobic threshold; CPET, cardiopulmonary exercise test; HR, heart rate; MOP, manual of procedures; O_2, oxygen; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio; SAE, serious adverse event; SBP, systolic blood pressure; V_E/VCO_2 slope, slope of increase in minute ventilation (VE) relative to CO_2 production; VO_2, oxygen uptake.

MAPLE HCM

Results: Submaximal Exercise

Aficamten monotherapy significantly improved *submaximal* exercise performance compared with metoprolol monotherapy

CPET variable	Aficamten				Metoprolol				Adjusted Δ (95% CI)[b]	*P*-value
	n	Baseline	Week 24	Absolute Δ (SD)[a]	n	Baseline	Week 24	Absolute Δ (SD)[a]		
Submaximal Exercise Response Variables										
Anaerobic threshold, mL	83	924 ± 250	961 ± 259	+37 ± 122	81	1004 ± 314	960 ± 307	−44 ± 106	+76 (41, 111)	<0.001
Aerobic efficiency (VO_2/work), mL/min/watt	83	9.2 ± 2.2	9.5 ± 2.3	+0.3 ± 2.0	80	9.6 ± 2.3	9.0 ± 2.2	−0.6 ± 1.8	+0.8 (0.2, 1.3)	0.004
Ventilatory efficiency (pre-anaerobic threshold)	82	29.5 ± 4.4	27.6 ± 3.8	−1.9 ± 4.2	81	29.2 ± 4.8	28.7 ± 4.4	−0.5 ± 3.7	−1.3 (−2.3, −0.3)	0.013
Ventilatory efficiency (VE/VCO_2 slope)	83	33.8 ± 6.4	31.1 ± 4.8	−2.8 ± 5.4	82	33.4 ± 5.8	33.6 ± 6.5	+0.2 ± 3.5	−2.8 (−4.0, −1.5)	<0.001

Data are shown as mean ± SD unless otherwise specified. [a]The absolute difference corresponds to the change from baseline to week 24. [b]The adjusted difference corresponds to the least-squares mean treatment difference.
CPET, cardiopulmonary exercise test; V_E/VCO_2 slope, slope of increase in minute ventilation (VE) relative to CO_2 production; VO_2, oxygen uptake.

MAPLE HCM

Results: Maximal Exercise

Aficamten improved *maximal* exercise performance measures compared with metoprolol

CPET variable	Aficamten				Metoprolol				Adjusted Δ (95% CI)[b]	*P*-value
	n	Baseline	Week 24	Absolute Δ (SD)[a]	n	Baseline	Week 24	Absolute Δ (SD)[a]		
Peak Exercise Response Variables										
Peak RER	*83*	*1.17 ± 0.08*	*1.18 ± 0.10*	*+0.01 ± 0.08*	*82*	*1.19 ± 0.11*	*1.19 ± 0.11*	*0.00 ± 0.10*	*+0.001 (−0.026, 0.027)*	*0.96*
Peak VO_2 per kg, mL/kg/min	83	19.6 ± 4.6	20.7 ± 5.0	+1.1 ± 2.8	82	20.3 ± 5.4	19.0 ± 5.7	−1.2 ± 2.2	+2.3 (1.5, 3.1)	<0.001
Peak workload, watt	82	119 ± 41	126 ± 43	+7 ± 16	82	119 ± 45	118 ± 45	−1 ± 17	+8 (3, 13)	0.003
Peak HR, bpm	82	149 ± 17	154 ± 17	+5 ± 11	82	151 ± 20	127 ± 21	−23 ± 16	+28 (24, 32)	<0.001
Exercise duration, min	79	11.7 ± 2.9	12.2 ± 3.1	+0.5 ± 1.2	78	11.7 ± 3.1	11.7 ± 3.2	−0.1 ± 1.3	+0.6 (0.2, 1.0)	0.002
HR reserve, bpm	82	66 ± 20	71 ± 20	+5 ± 12	80	69 ± 20	62 ± 19	−7 ± 14	+12 (8, 16)	<0.001

MAPLE HCM

Data are shown as mean ± SD unless otherwise specified. [a]The absolute difference corresponds to the change from baseline to week 24. [b]The adjusted difference corresponds to the least-squares mean treatment difference.HR, heart rate; RER, respiratory exchange ratio; VO_2, oxygen uptake.

Results: Post-Exercise Recovery Measures

Speed of VO_2 *recovery* increased with aficamten and decreased with metoprolol

CPET variable	Aficamten				Metoprolol					
	n	Baseline	Week 24	Absolute Δ (SD)[a]	n	Baseline	Week 24	Absolute Δ (SD)[a]	Adjusted Δ (95% CI)[b]	*P*-value
Submaximal Exercise Response Variables										
VO_2 Recovery Delay, >0% (sec)	82	16 ± 22	12 ± 16	-4 ± 21	78	15 ± 19	19 ± 20	4 ± 22	-7 (-12, -2)	p= 0.009
VO_2 recovery 12.5% (sec)	77	36 ± 22	31 ± 18	-6 ± 19	77	33 ± 19	39 ± 21	7 ± 19	-11 (-16, -5)	p<0.001
VO_2 recovery 25% (sec)	76	58 ± 21	53 ± 18	-5 ± 18	76	50 ± 17	57 ± 19	7 ± 16	-8 (-13, -3)	p= 0.002
VO_2 recovery 50% (sec)	75	96 ± 37	86 ± 23	-10 ± 31	72	82 ± 23	93 ± 41	11 ± 33	-14 (-24, -5)	p= 0.004

Change in VO_2 recovery $T_{12.5\%}$ differed by >30% between groups, reflecting large effect size of aficamten on this cardio-specific measurement

Change in VO_2 recovery ($T_{12.5\%}$) was associated with significant changes in all functional status/quality of life, and NT-proBNP changes, and had the strongest correlation with changes in LVOT gradient (r=0.37, *P*<0.001)

MAPLE HCM

Data are shown as mean ± SD unless otherwise specified. [a]The absolute difference corresponds to the change from baseline to week 24. [b]The adjusted difference corresponds to the least-squares mean treatment difference. CPET, cardiopulmonary exercise test; V_E/VCO_2 slope, slope of increase in minute ventilation (VE) relative to CO_2 production; VO_2, oxygen uptake.

Result: Integrative Measures

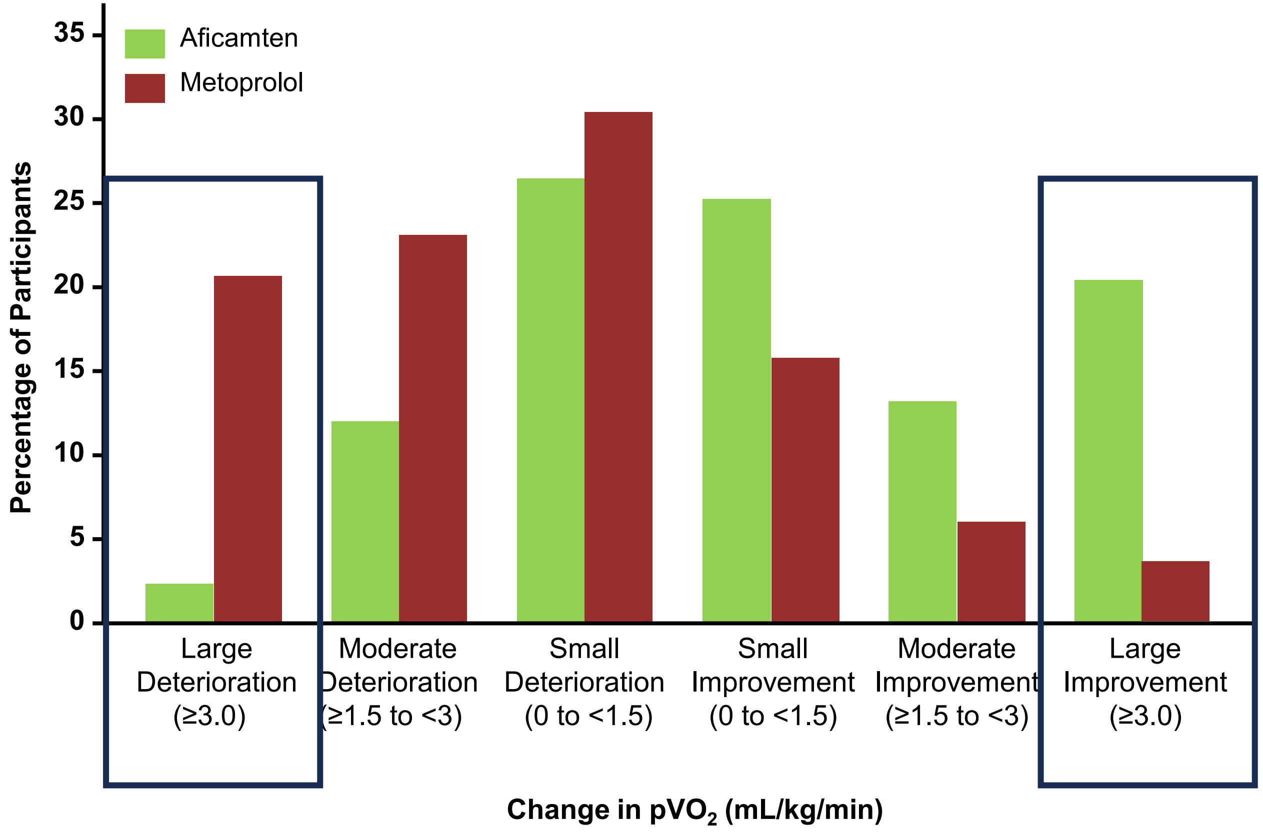
CPET variable	Aficamten				Metoprolol				Adjusted Δ (95% CI)[b]	*P*-value
	n	Baseline	Week 24	Absolute Δ (SD)[a]	n	Baseline	Week 24	Absolute Δ (SD)[a]		
Composite Exercise Response Variables										
Hemodynamic (SBP) + O_2 uptake: circulatory power, mmHg*mL/min/kg	83	3413 ± 1116	3782 ± 1273	+369 ± 993	81	3439 ± 1131	2993 ± 1013	−446 ± 738	+819 (569, 1070)	<0.001
Hemodynamic + ventilatory efficiency, ventilatory power, mmHg	82	5.3 ± 1.6	6.0 ± 1.4	+0.7 ± 1.3	81	5.2 ± 1.4	4.9 ± 1.3	−0.4 ± 1.1	+1.1 (0.8, 1.4)	<0.001
O_2 uptake + ventilatory efficiency, standardized 2-component Z-score[c]	**83**	**−0.05 ± 0.80**	**0.18 ± 0.67**	**+0.23 ± 0.57**	**82**	**0.06 ± 0.75**	**−0.18 ± 0.81**	**−0.24 ± 0.38**	**+0.45 (0.31, 0.59)**	**<0.001**

MAPLE HCM

Data are shown as mean ± SD unless otherwise specified..[a]The absolute difference corresponds to the change from baseline to week 24 [b]The adjusted difference corresponds to the least-squares mean treatment. difference.[c]The Z-score was derived by reversing the directionality of VE/VCO_2
CPET, cardiopulmonary exercise test; O_2, oxygen; SBP, systolic blood pressure

Results: Responder Analysis

'Any improvement' was more common with aficamten (NNT 3.0)
'Any deterioration' was more common with metoprolol (NNH 3.0)



Outcome	Metoprolol	Aficamten	OR (95% CI)	Risk difference (95% CI)	NNT/ NNH
Reference = aficamten group					**NNT**
Any improvement (small/moderate/large)	21 (25.6%)	49 (59.0%)	4.2 (2.2, 8.1)	+33% (+19%, +48%)	**3.0**
Moderate/large improvement (≥1.5 mL/kg)	8 (9.8%)	28 (33.7%)	4.7 (2.0, 10.9)	+24% (+12%, +36%)	**4.2**
Large improvement (≥3 mL/kg)	3 (3.7%)	17 (20.5%)	6.8 (2.0, 22.5)	+16% (+7%, +26%)	**5.9**
Large advantage of treatment choice (large improvement vs. large deterioration)	−14 (−17%)	15 (18.1%)	8.3 (3.1, 22.5)	+35% (+21%, +49%)	**2.8**
Reference = metoprolol group					**NNH**
Any deterioration (small/moderate/large)	61 (74.4%)	34 (41.0%)	4.2 (2.2, 8.1)	+33% (+19%, +48%)	**3.0**
Moderate/large deterioration	36 (43.9%)	12 (14.5%)	4.6 (2.2, 9.7)	+29% (+16%, +43%)	**3.4**
Large deterioration	17 (20.7%)	2 (2.4%)	10.6 (2.6, ∞)	+18% (+9%, +28%)	**5.5**

NNT indicates number needed to treat with aficamten as the reference group; NNH indicates number needed to harm with metoprolol as the reference group; OR, odds ratio; pVO_2, peak oxygen uptake

Conclusions

- This prespecified analysis from MAPLE-HCM provides novel comparative data for monotherapy with either aficamten or metoprolol in oHCM.
- Treatment with aficamten was superior to metoprolol in improving all 16 measures of exercise (submaximal, peak, and recovery, number needed to treat for any improvement of pVO_2 =3).
- Metoprolol treatment was detrimental to patients as measured by multiple metrics of response to exercise (number needed to harm for any deterioration pVO_2 =3).
- These findings support the use of aficamten over metoprolol as monotherapy in patients with symptomatic oHCM.

Disclosures & Acknowledgments

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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

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