Effect of Aficamten Compared with Metoprolol in Women vs. Men: Analysis of MAPLE-HCM

Xiaowen Wang, MD, MPH

Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

On behalf of: Maria Pabon, MD, Brian Claggett, PhD, Pablo Garcia-Pavia, MD, PhD, Michael A. Fifer, MD, Ozlem Bilen, MD, Edileide Correra de Barros, MD, Amy Mann, BA, Martin S. Maron, MD, Andrew Wang, MD, Donna R. Zwas, MD, MPH, Regina Sohn, MD, PhD, Stephen B. Heitner, MD, Scott D. Solomon, MD, Sheila Hegde, MD, MPH, MAPLE-HCM Investigators.

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

@wendywangmd xwang15@mgb.org

Background and Aim

- Aficamten is a next-in-class cardiac myosin inhibitor that reduces contractility by reversibly binding to cardiac myosin and reducing excessive myosin-actin cross-bridges.
- In **MAPLE-HCM**, patients with symptomatic oHCM were randomized to aficamten plus placebo or metoprolol plus placebo.
  - **Primary end point:** change in peak oxygen uptake (pVO_2) by cardiopulmonary exercise test at 24 weeks.
- Aficamten was superior to metoprolol in improving pVO_2 and decreasing symptoms.

Aim: To evaluate sex differences in baseline characteristics and the efficacy of aficamten compared with metoprolol in MAPLE-HCM.

Baseline Characteristics

	Women (N=73)	Men (N=102)	P-value
Age	62.3 ± 11.8	54.4 ± 13.2	<0.001
NYHA Class III	33 (45.2%)	19 (18.6%)	<0.001
Baseline KCCQ-CSS	61.9 ± 16.7	68.6 ± 15.8	0.008
NT-ProBNP, pg/mL	558 [315, 1402]	386 [148, 733]	0.001
pVO_2 at CPET, mL/kg/min	16.9 ± 4.1	22.0 ± 4.6	<0.001
Total Workload on CPET, Watt	90.5 ± 32.3	137.8 ± 37.6	<0.001
% of Predicted Oxygen Uptake	59.8 ± 14.7	61.2 ± 12.8	0.51
Echocardiographic characteristics			
Peak LVOT Gradient, rest, mmHg	52 ± 30	44 ± 28	0.06
Peak LVOT Gradient, Valsalva, mmHg	79 ± 33	69 ± 32	0.038
Interventricular septum, mm	19.1 ± 2.7	19.8 ± 2.8	0.08
LVEF, %	69 ± 4	67 ± 4	0.004
Septal e' Velocity, cm/s	4.6 ± 1.3	5.3 ± 1.5	0.002
Septal E/e'	21.2 ± 9.4	15.9 ± 6.0	<0.001
LA volume index, ml/m^2	38.2 ± 9.3	39.5 ± 12.9	0.47

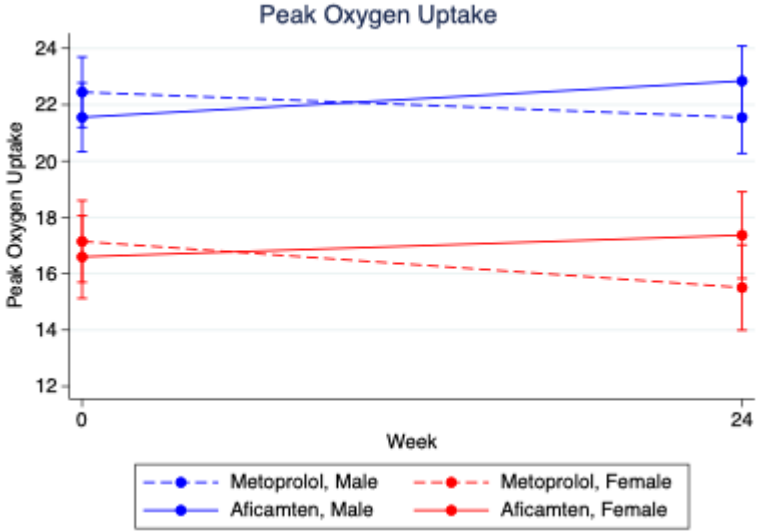
In Women♀

- ↑ NYHA Class
- ↑ NT-proBNP
- ↓ KCCQ-CSS
- ↓ pVO_2

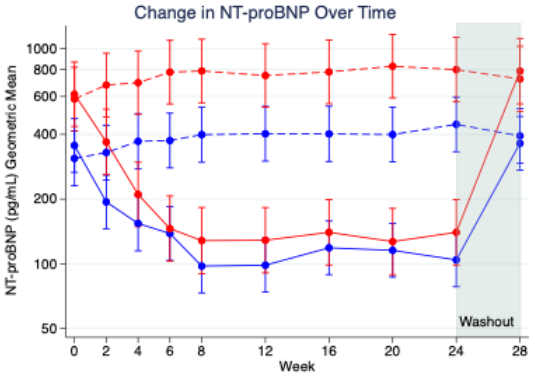
- ↑ LVOT gradients
- ↑ LVEF
- ↑ E/e' ratios
- ↓ e' velocities

KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen uptake. GLS = global longitudinal strain; LA: left atrium; LV: left ventricular; LVEF: LV ejection fraction; LVOT: LV outflow tract.

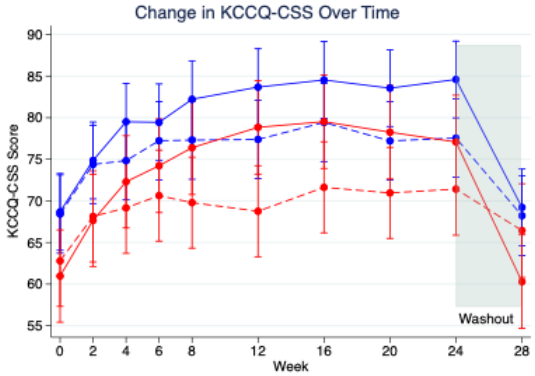
Effect of Aficamten vs Metoprolol on Clinical Outcomes



Women: +2.2 (+1.1 to +3.2);
Men: +2.2 (+1.1 to +3.3);
P-interaction: 0.96



Women: -87% (-77% to -88%);
Men: -79% (-71% to -84%);
P-interaction: 0.22



Women: +6.1 (-1.8 to +14.1);
Men: +6.6 (+1.4 to +11.8);
P-interaction: 0.90

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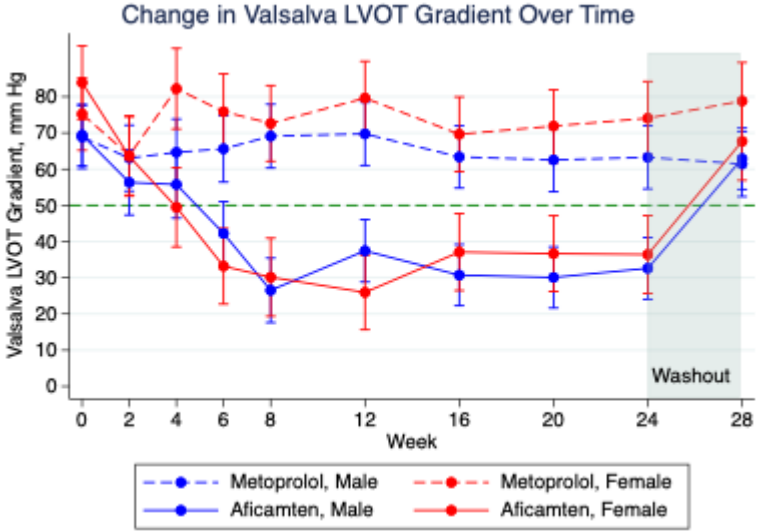
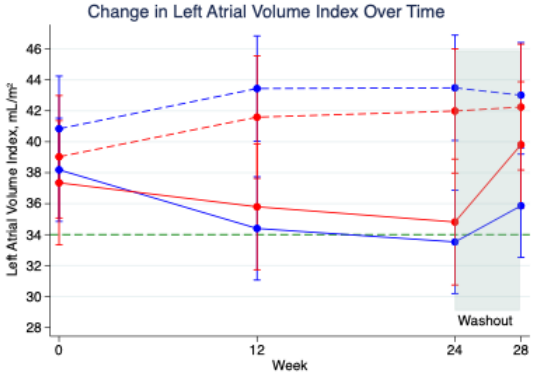
Effect of aficamten (solid) compared to metoprolol (dashed) on pVO_2, KCCQ-CSS and NT-proBNP levels over time in women (red) and men (blue).
Treatment effects and P-interactions included baseline values, exercise mode, and diagnosis group as covariates
P-interactions represent treatment-by-sex interaction at week 24.

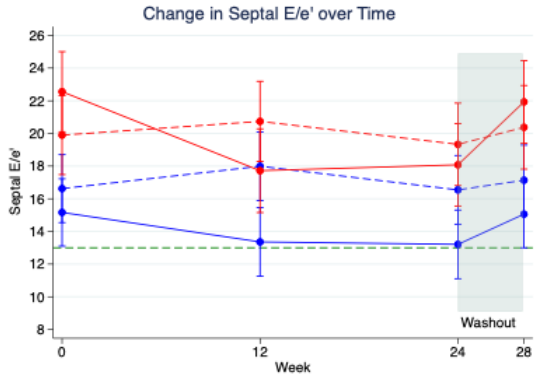
Effect of Aficamten vs Metoprolol on Key Echo Measures



Women: -43 (-57 to -28);
Men: -30 (-41 to -19);
P-interaction: 0.14



Women: -6.3 (-9.8 to -2.8);
Men: -7.5 (-10.3 to -4.7);
P-interaction: 0.42



Women: -3.8 (-6.4 to -1.3);
Men: -2.6 (-4.2 to -0.9);
P-interaction: 0.34

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Effect of aficamten (solid) compared to metoprolol (dashed) on Valsalva LVOT-G, LAVi and Septal E/e' levels over time in women (red) and men (blue).
Treatment effects and P-interactions included baseline values, exercise mode, and diagnosis group as covariates
P-interactions represent treatment-by-sex interaction at week 24.

Conclusions

- Women in MAPLE-HCM were older and had greater disease burden, with more symptom burden, worse patient-reported health status, higher NT-proBNP levels, higher LVOT gradients, and more severe diastolic dysfunction.

- Despite worse disease severity at baseline, aficamten monotherapy related improvements in exercise capacity, health status, LVOT gradients, and measures of diastolic function were similar between women and men.

- Metoprolol monotherapy did not improve LVOT gradients, exercise capacity or other endpoints in men or women.