DOSE-DEPENDENT EFFECTS OF AFICAMTEN COMPARED WITH METOPROLOL IN OBSTRUCTIVE HCM: THE MAPLE-HCM STUDY

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Beta-blockers have been the first-line treatment for symptomatic oHCM for nearly 60 years despite limited evidence

1968

Chronic Beta Adrenergic Receptor Blockade in the Treatment of Idiopathic Hypertrophic Subaortic Stenosis[1]

By Lawrence S. Cohen and Eugene Braunwald

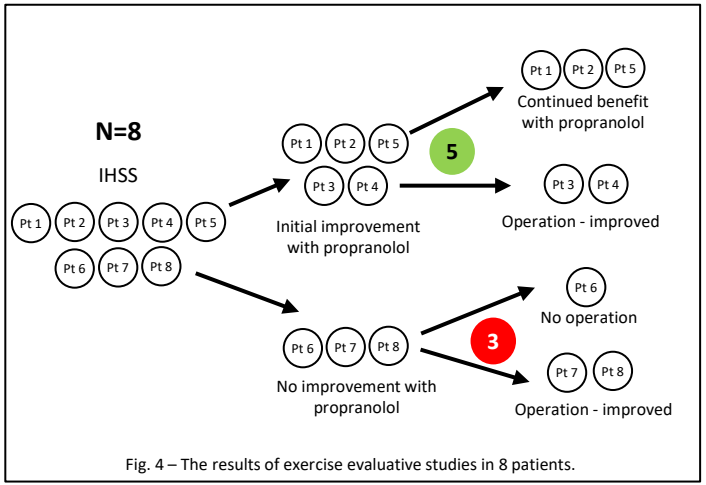


Fig. 4 – The results of exercise evaluative studies in 8 patients.

***P*=0.73**

2023 ESC Guidelines[2]

Recommendation	Class[a]	Level[b]
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked[c] LVOTO.	I	B

[a] Class of recommendation. [b] Level of evidence. [c] Provocation with Valsalva maneuver, upright exercise, or oral nitrates if unable to exercise.

2024 ACC/AHA Guidelines[3]

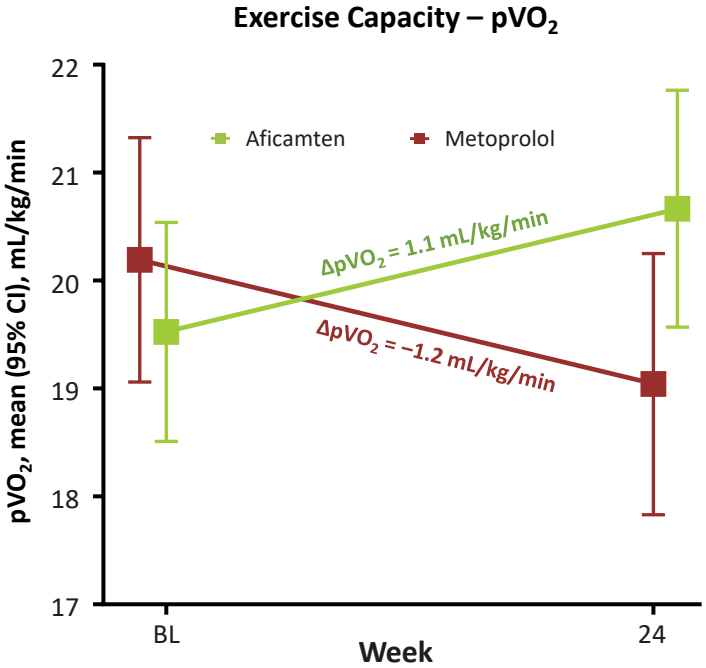
COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM and symptoms[d] attributable to LVOTO, non-vasodilating beta-blockers, titrated to effectiveness or maximally tolerated doses, are recommended.

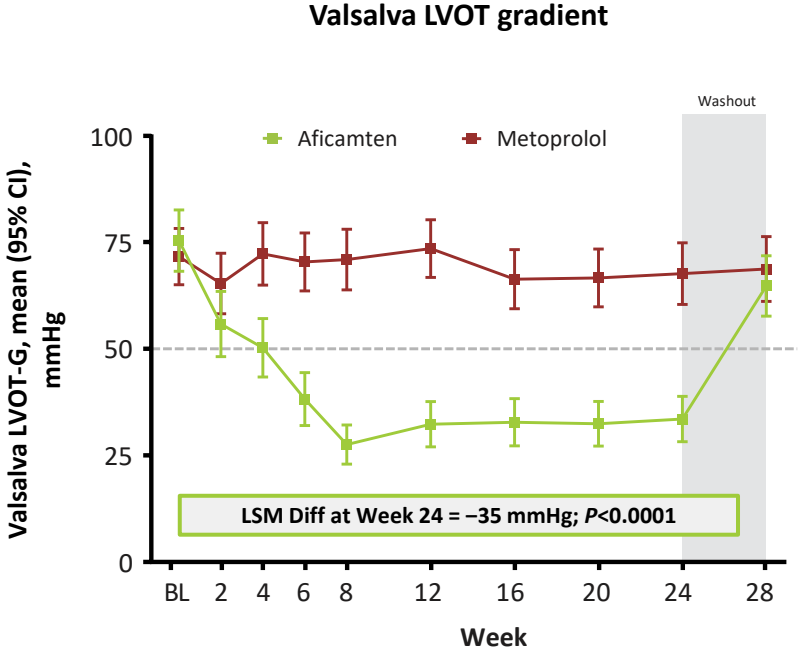
[d] Symptoms include effort-related dyspnea or chest pain and occasionally other exertional symptoms (eg, syncope, near syncope) that are attributed to LVOTO and interfere with everyday activity or quality of life.

1. Cohen LS, Braunwald E. *Prog Cardiovasc Dis* 1968;11:211-21. **2.** Arbelo E, et al. *Eur Heart J* 2023;44:3503-626. **3.** Ommen SR, et al. *Circulation* 2024;149:e1239-e1311.

COR, class of recommendation; IHHS, idiopathic hypertrophic subaortic stenosis; LOE, level of evidence; LVOTO, left ventricular outflow tract obstruction; NR, non-randomized; Pt, patient #.

MAPLE-HCM: Aficamten vs metoprolol

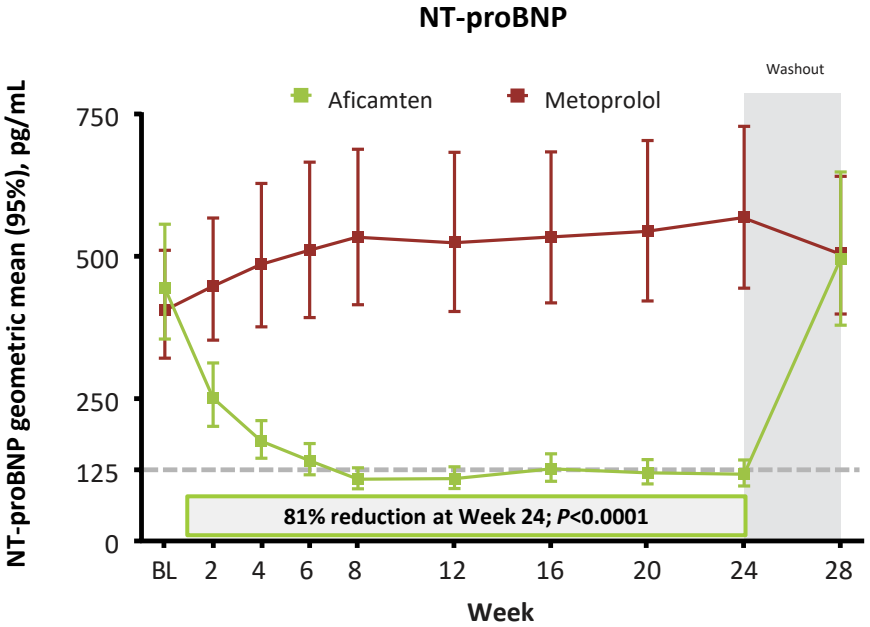


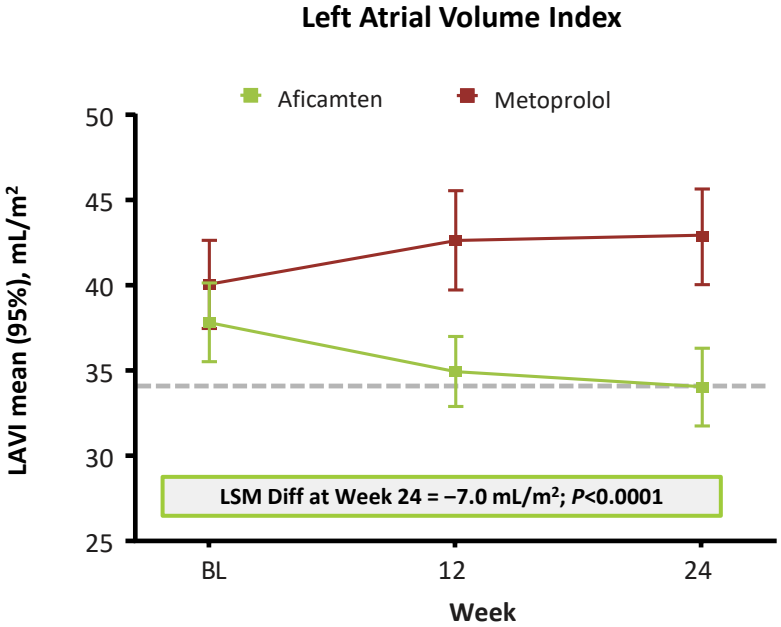


Garcia-Pavia P, et al. *N Engl J Med* 2025;393:949-60.

Δ, change; BL, baseline; Diff, difference; LSM, least squares mean; LVOT-G, left ventricular outflow tract gradient; pVO_2, peak oxygen uptake.

MAPLE-HCM: Aficamten vs metoprolol





The gray dashed lines indicate the upper limits of normal: 125 pg/mL (*left panel*) and 34 mL/m^2 (*right panel*).

Garcia-Pavia P, et al. *N Engl J Med* 2025;393:949-60.

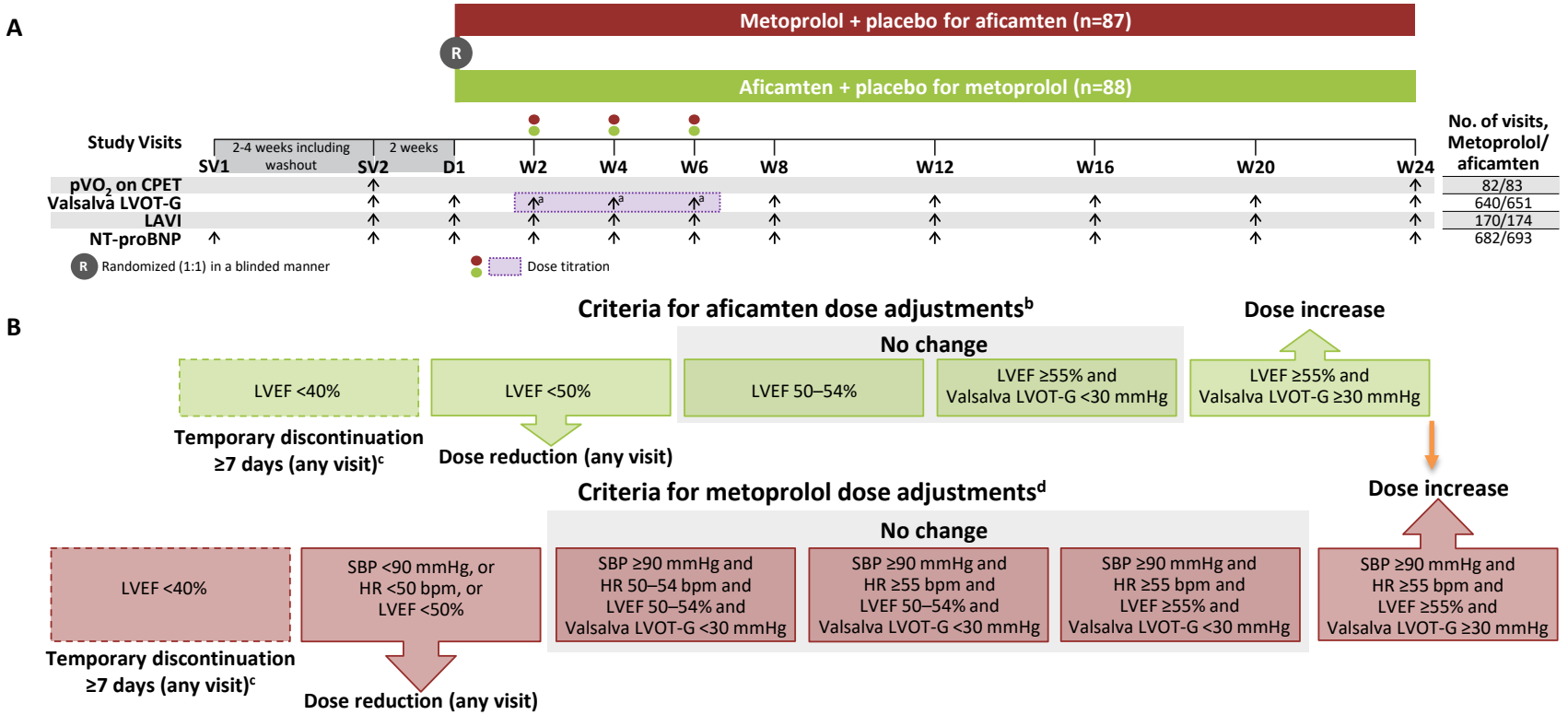
BL, baseline; Diff, difference; LAVI, left atrial volume index; LSM, least squares mean; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Objectives

- To investigate the relationship between clinically relevant outcomes in patients with symptomatic oHCM according to metoprolol and aficamten doses.
- To identify if there is a potentially optimal metoprolol dose that is well tolerated and improves clinical efficacy.

oHCM, obstructive hypertrophic cardiomyopathy.

METHODS: MAPLE-HCM study schema



[a] Titration visits for aficamten and metoprolol based upon algorithm shown in panel B. [b] Starting dose of aficamten was 5 mg QD (D1). Participants may have escalated to doses of 10, 15, and 20 mg QD per dosing algorithm. [c] If LVEF was subsequently ≥55%, study medication may have been restarted at the next lower dose per site investigator judgment after discussion with the medical monitor. [d] Starting dose of metoprolol was 50 mg QD (D1). Participants may have escalated to doses of 100, 150, and 200 mg QD per dosing algorithm.

CPET, cardiopulmonary exercise test; HR, heart rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; pVO_2, peak oxygen uptake; QD, once daily; SBP, systolic blood pressure; SV, screening visit; W, week.

Endpoints

- **Primary endpoint:** Exercise capacity (pVO_2) in 164 patients assessed based on each patient's final dose after titration at week 8.
- **Secondary endpoints:** Valsalva LVOT gradient, NT-proBNP, and LAVI assessed repeatedly from Week 2 to Week 24 across 3,010 assessments based on the steady-state dose achieved at the time of assessment.

LAVI, left atrial volume index; NT-proBNP, N-terminal pro–B-type natriuretic peptide; pVO_2, peak oxygen uptake.

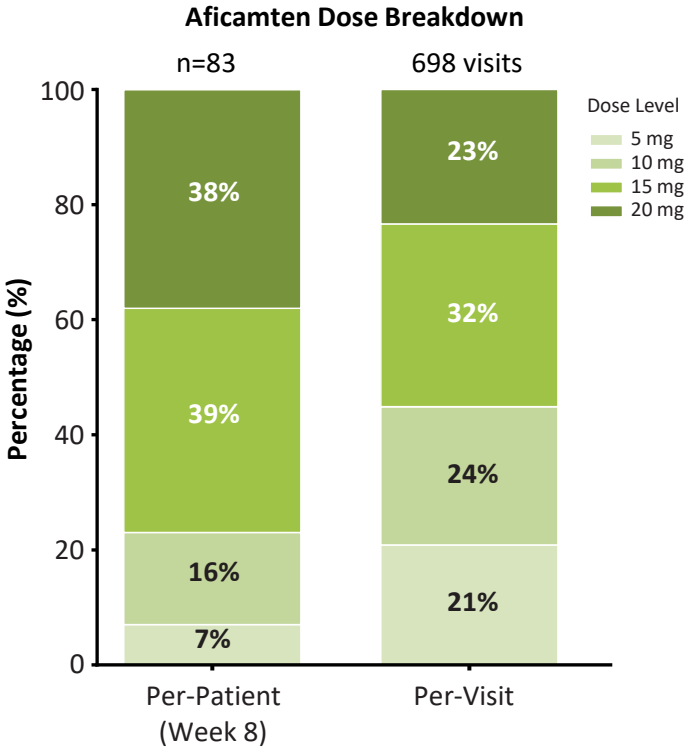
Baseline characteristics of patients on low vs high doses of aficamten and metoprolol

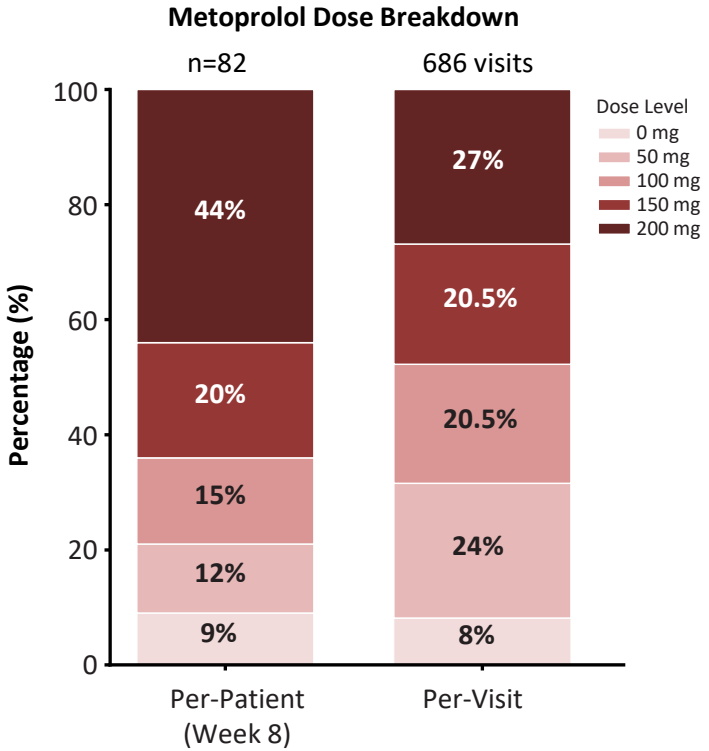
Characteristic	Low dose (n=51)[a]	High dose (n=122)[b]	*P* value
Age, years	57 ± 13.3	58 ± 13.3	0.77
Female, n (%)	20 (39.2)	51 (41.8)	0.75
History of HTN, n (%)	19 (37.3)	67 (54.9)	0.03
Known HCM-causing gene mutation, n (%)	7 (13.7)	20 (16.4)	0.66
Positive family history of HCM, n (%)	13 (25.5)	20 (16.4)	0.16
Paroxysmal AF, n (%)	1 (2.0)	0 (0.0)	0.12
Systolic BP, mmHg	124 ± 14	126 ± 14	0.32
Diastolic BP, mmHg	76 ± 12	78 ± 8	0.20
Resting HR, bpm	78.0 ± 14.1	83.0 ± 12.0	0.018
NYHA class III, n (%)	9 (17.6)	42 (34.4)	0.027

Characteristic	Low dose (n=51)[a]	High dose (n=122)[b]	*P* value
NT-proBNP, pg/mL	351 [155-702]	510 [230-983]	0.08
hs-troponin I, ng/L	10 [6-26]	13 [8-30]	0.29
CPET modality: bicycle, n (%)	19 (37.3)	50 (41.0)	0.65
% Predicted pVO_2	65.8 ± 14.0	58.6 ± 12.9	0.001
pVO_2, mL/kg/min	21.8 ± 5.2	19.2 ± 4.8	0.002
Peak respiratory exchange ratio	1.18 ± 0.11	1.18 ± 0.09	0.69
LV maximal wall thickness, mm	19.97 ± 2.86	21.19 ± 3.07	0.016
LVEF, %	68 ± 5	68 ± 4	0.96
Resting LVOT-G, mmHg	41 ± 27	50 ± 29	0.08
Valsalva LVOT-G, mmHg	62 ± 31	78 ± 32	0.002
LAVI (mL/m^2)	40 ± 14.0	38 ± 10.5	0.27

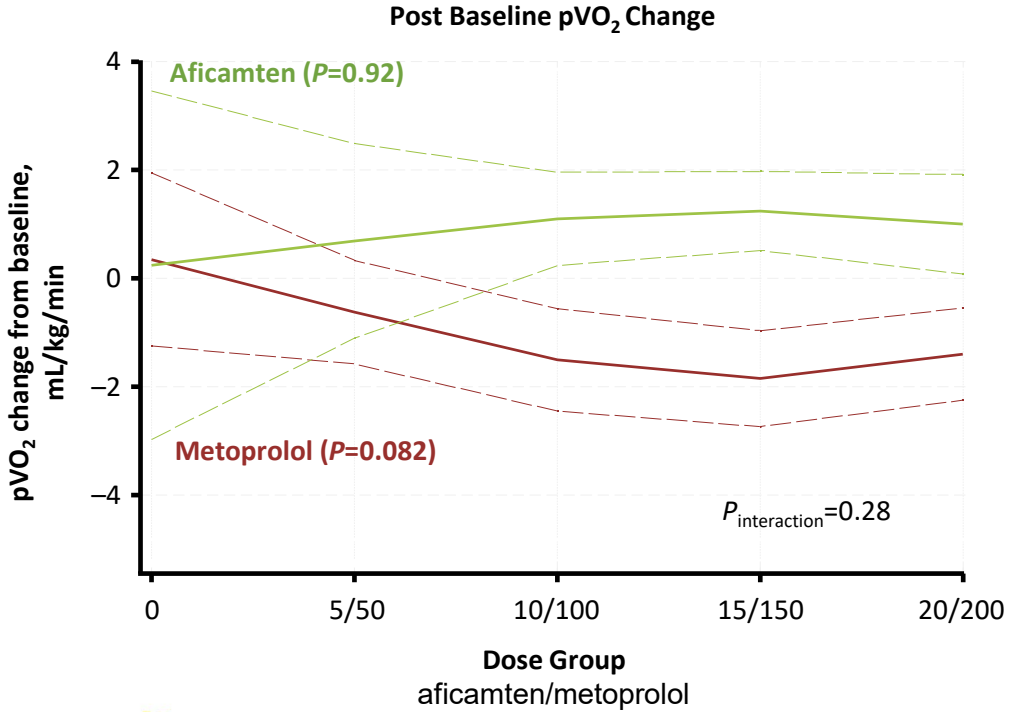
[a] Low dose: aficamten 5–10 mg and metoprolol 0–100 mg QD. [b] High dose: aficamten 15–20 mg and metoprolol 150–200 mg QD.
AF, atrial fibrillation; BP, blood pressure; CPET, cardiac pulmonary exercise test; HCM, hypertrophic cardiomyopathy; HR, heart rate; hs, high-sensitivity; LAVI, left atrial volume index; LV, left ventricular; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake. QD, once daily.

Aficamten vs metoprolol dose distribution





No significant relationship between metoprolol dose and change in pVO_2

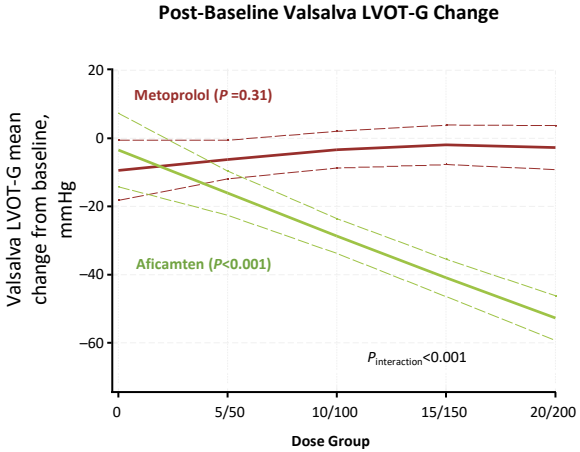


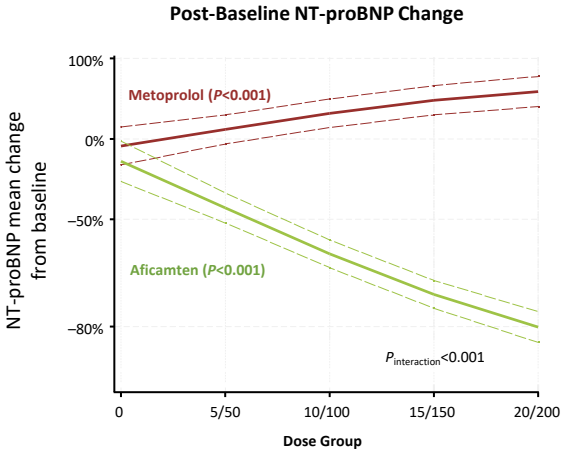
Aficamten slope:
β= 0.04 (95% CI −0.68, 0.75); *P*=0.9

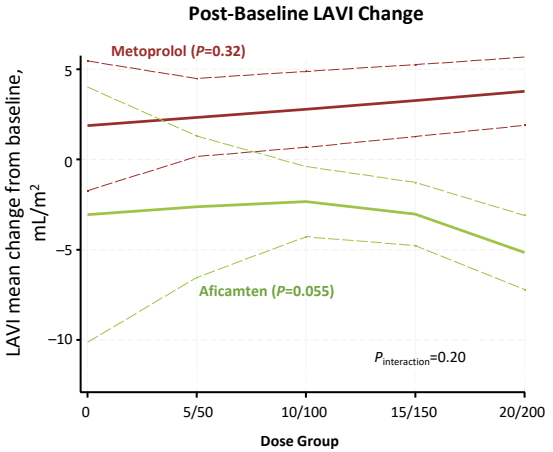
Metoprolol slope:
β= −0.35 (95% CI −0.75, 0.05); *P*=0.08

pVO_2, peak oxygen uptake.

Metoprolol did not improve secondary endpoints at any dose







Aficamten was associated with a dose-dependent improvement in **Valsalva LVOT gradient** (slope: β= −12.3 [95% CI −14.2, −10.4]), while **metoprolol** was not (slope: β= 0.9 [95% CI −0.9, 2.7]).

NT-proBNP improved with **aficamten** (slope: β= −29% [95% CI −31%, −27%]) and worsened with **metoprolol** (slope: β= +12% [95% CI +8%, +15%]).

Aficamten was associated with a dose-dependent trend in improving **LAVI** (slope: β= −1.1% [95% CI −2.2, 0.0]) vs there was no dose-dependent relationship between **metoprolol** and LAVI (slope: β= 0.6 [95% CI −0.6, 1.7])

LAVI, left atrial volume index; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; pVO_2, peak oxygen uptake.

Conclusions

- Aficamten improved all clinically relevant measures of efficacy (pVO_2, NT-proBNP, LVOT-G, and LAVI); metoprolol did not.
- There was no specific dose-level whereby metoprolol was effective, but higher doses of metoprolol did show significant increases in NT-proBNP.
- These data support the application of an echocardiographic-based treat-to-effect strategy for aficamten but fail to support metoprolol treatment at any dose level in patients with symptomatic oHCM.

LAVI, left atrial volume index; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; pVO_2, peak oxygen uptake.