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BACKGROUND

- Hypertension (HTN) is common in patients with obstructive hypertrophic cardiomyopathy (oHCM) and is associated with adverse outcomes.¹
- The prevalence of HTN in adults with HCM ranges from to 35–62% and is higher in patients with non-sarcomeric disease.¹
- Treatment of HTN in the setting of elevated left ventricular (LV) outflow tract gradient (LVOT-G) is clinically challenging.
- Relief of LV outflow obstruction in oHCM and adjacent diseases (aortic stenosis) is associated with increased blood pressure (BP) due to improved cardiac output.^{2,3}

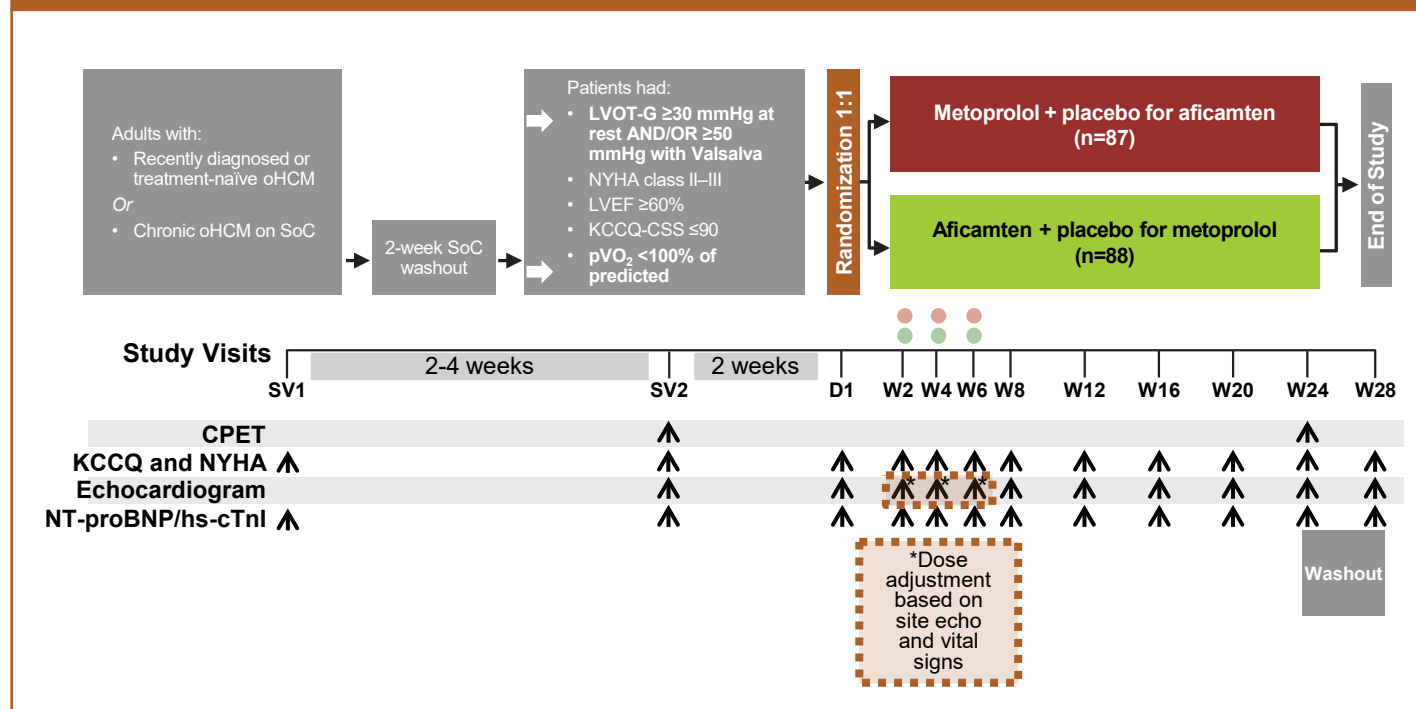
OBJECTIVE

- In this secondary analysis of MAPLE-HCM, we examined the impact of background HTN on efficacy and safety of aficamten use.
- We also examined the comparative effect of LVOT-G relief with aficamten on BP.

METHODS

- MAPLE-HCM was a double-blind, double-dummy comparison of aficamten vs metoprolol monotherapy in participants with symptomatic oHCM.
- Study schema is shown in **Figure 1**.
- Key selection criteria:
 - New York Heart Association (NYHA) II–III symptoms.
 - Resting LVOT-G ≥ 30 and/or Valsalva LVOT-G ≥ 50 mmHg.
 - LV ejection fraction (LVEF) $\geq 60\%$.
 - The absence of a medical indication for either beta-blocker or non-dihydropyridine calcium channel blocker prohibiting drug discontinuation (eg, arrhythmia), beta-blocker intolerance, or systolic BP >160 mmHg at screening.

Figure 1. MAPLE-HCM study schema



CPET, Cardiopulmonary Exercise Testing; D, Day; hs-cTnI, high-sensitivity cardiac troponin I; HTN, hypertension; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; pVO₂, peak oxygen uptake; SBP, systolic blood pressure; SoC, standard of care; SV, study visit; W, Week.

RESULTS

Study Population

- Baseline characteristics were balanced between treatment groups except for history of HTN, which was significantly more prevalent in the aficamten vs metoprolol treatment group: 61% vs 38%; $P=0.002$ (**Table 1**).

Table 1. Baseline characteristics by HTN diagnosis status

| | History of HTN n=87 (50 ^a) | No history of HTN n=88 (50 ^a) | P Value |
|---|---|--|------------------|
| Randomized to aficamten, n (%) | 54 (62.1) | 34 (38.6) | 0.002 |
| Age, mean (SD), years | 63.0 ± 10.3 | 52.5 ± 13.8 | <0.001 |
| Female, n (%) | 40 (46) | 33 (37.5) | 0.26 |
| Not on background therapy with SoC, n (%) | 16 (18.4) | 26 (29.5) | 0.08 |
| Background anti-HTN therapy, n (%) | | | |
| Diuretics | 45 (51.7) | 1 (1.1) | <0.001 |
| Vasodilators | 26 (29.9) | 4 (4.5) | <0.001 |
| Systolic BP, mean (SD), mmHg | 130.2 ± 14.9 | 120.8 ± 11.6 | <0.001 |
| MAP, mean (SD), mmHg | 95.3 ± 10.8 | 91.5 ± 7.7 | 0.007 |
| Heart rate, mean (SD), bpm | 76.7 ± 12.1 | 72.0 ± 11.5 | 0.010 |
| BMI, mean (SD), kg/m ² | 28.8 ± 3.5 | 27.7 ± 3.4 | 0.034 |
| Diabetes, n (%) | 12 (13.8) | 4 (4.5) | 0.034 |
| KCCQ-CSS, mean (SD) | 64.2 ± 17.7 | 67.3 ± 15.1 | 0.22 |
| NYHA III, n (%) | 32 (36.8) | 20 (22.7) | 0.042 |
| NT-proBNP, median (IQR), pg/mL | 531 (197, 1048) | 426 (213, 844) | 0.41 |
| hs-cTnI, median (IQR), ng/L | 16 (8, 36) | 11 (6, 19) | 0.011 |
| eGFR, mean (SD), mL/min/1.73 m ² | 76.9 ± 18.4 | 85.2 ± 17.5 | 0.003 |
| pVO ₂ , mean (SD), mL/kg/min | 18.6 ± 4.9 | 21.1 ± 4.9 | 0.001 |
| LVOT-G-Resting, mean (SD), mmHg | 48.2 ± 27.4 | 46.6 ± 30.1 | 0.70 |
| LVOT-G-Valsalva, mean (SD), mmHg | 76.9 ± 30.5 | 70.1 ± 34.3 | 0.17 |
| LVEF, mean (SD), % | 68.4 ± 3.6 | 67.3 ± 4.0 | 0.06 |
| LVMI, mean (SD), mg/m ² | 128.4 ± 29.9 | 133.7 ± 32.8 | 0.27 |
| E/e' ratio, mean (SD) | 14.8 ± 7.1 | 13.0 ± 5.9 | 0.06 |

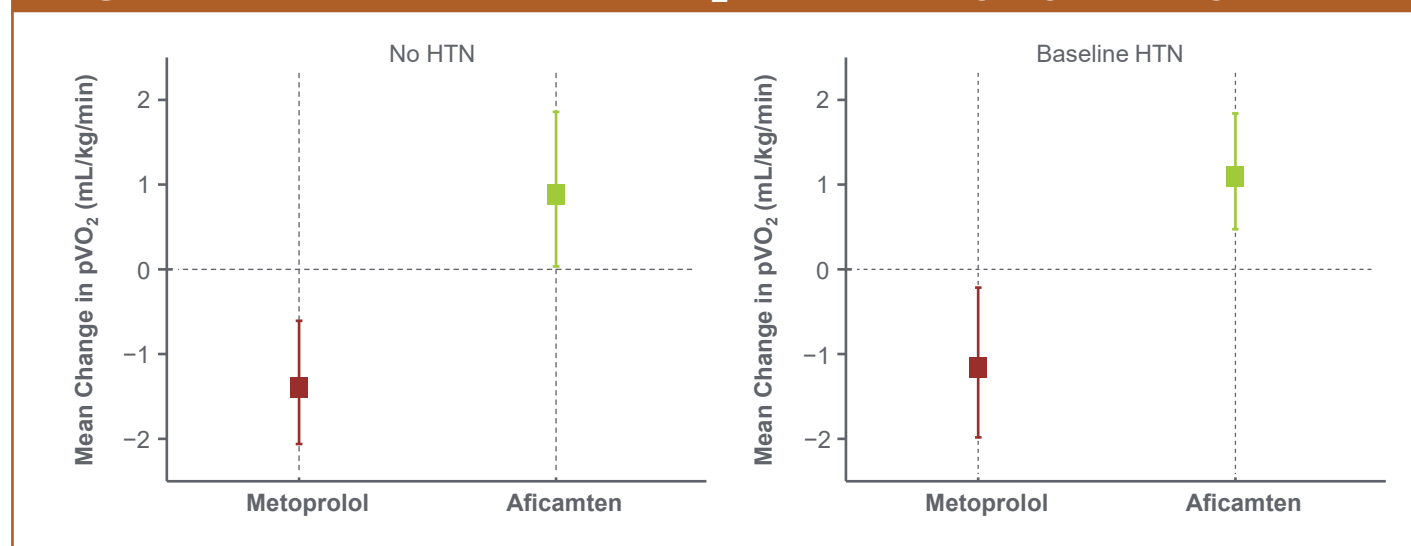
^a Percent of total randomized. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; hs-cTnI, high-sensitivity cardiac troponin I; HTN, hypertension; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT-G, left ventricular outflow tract gradient; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO₂, peak oxygen uptake; SoC, standard of care; W, Week.

Table 2. Change from baseline to Week 24 in efficacy markers stratified by history of HTN

| Safety and efficacy marker | History of HTN | | | No History of HTN | | | Interaction P value |
|---|----------------|-----------------|------------------|-------------------|-----------------|------------------|---------------------|
| | Aficamten n=54 | Metoprolol n=33 | Treatment Effect | Aficamten n=34 | Metoprolol n=54 | Treatment Effect | |
| pVO ₂ per kg, mean (SD), mL/kg/min | 1.2 ± 2.4 | -1.1 ± 2.3 | 2.3 (1.1, 3.4) | 0.9 ± 3.3 | -1.3 ± 2.1 | 2.3 (1.1, 3.4) | 0.97 |
| KCCQ-CSS, mean (SD) | 17.5 ± 16.2 | 7.8 ± 16.9 | 8 (1, 15) | 13.1 ± 13.6 | 9.3 ± 15.4 | 6 (-0, 12) | 0.68 |
| Peak LVOT-G at rest, mean (SD), mmHg | -30.3 ± 27.8 | -0.3 ± 28.3 | -27 (-36, -18) | -29.5 ± 30.3 | 2.0 ± 32.6 | -32 (-43, -21) | 0.49 |
| Peak LVOT-G during Valsalva, mean (SD), mmHg | -41.8 ± 33.2 | -4.5 ± 36.7 | -36 (-49, -23) | -38.8 ± 40.2 | -3.4 ± 34.1 | -35 (-47, -22) | 0.91 |
| LVMI, mean (SD), g/m ² | -7.4 ± 28.6 | 6.0 ± 21.4 | -13 (-24, -3) | -6.1 ± 16.9 | -9.6 ± 23.7 | 2 (-7, 11) | 0.029 |
| NT-proBNP, mean (95% CI), % change | -76 (-82, -70) | 58 (29, 93) | -84 (-88, -78) | -68 (-76, -56) | 34 (13, 59) | -76 (-83, -67) | 0.08 |
| hs-cTnI, mean (95% CI), % change | -49 (-59, -36) | -28 (-38, -16) | -22 (-42, 4) | -31 (-48, -10) | -9 (-24, 8) | -29 (-47, -4) | 0.68 |
| Systolic BP, mean (SD), mmHg | 3.6 ± 14.0 | -8.3 ± 18.2 | 10 (4, 17) | 6.7 ± 10.5 | -4.2 ± 11.7 | 10 (5, 15) | 0.80 |
| Diastolic BP, mean (SD), mmHg | 1.0 ± 8.3 | -5.3 ± 10.7 | 6 (2, 9) | 3.9 ± 7.3 | -3.2 ± 9.1 | 7 (4, 10) | 0.59 |

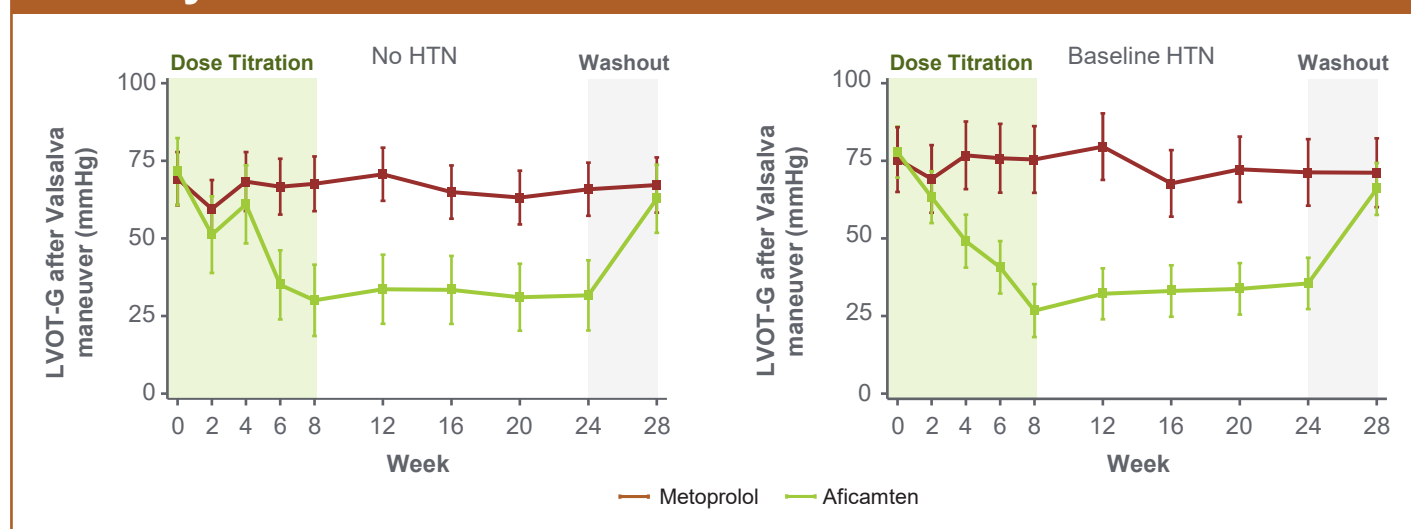
BP, blood pressure; hs-cTnI, high-sensitivity cardiac troponin I; HTN, hypertension; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO₂, peak oxygen uptake.

Figure 2. Improvement in pVO₂ did not vary by history of HTN



HTN, hypertension; pVO₂, peak oxygen uptake.

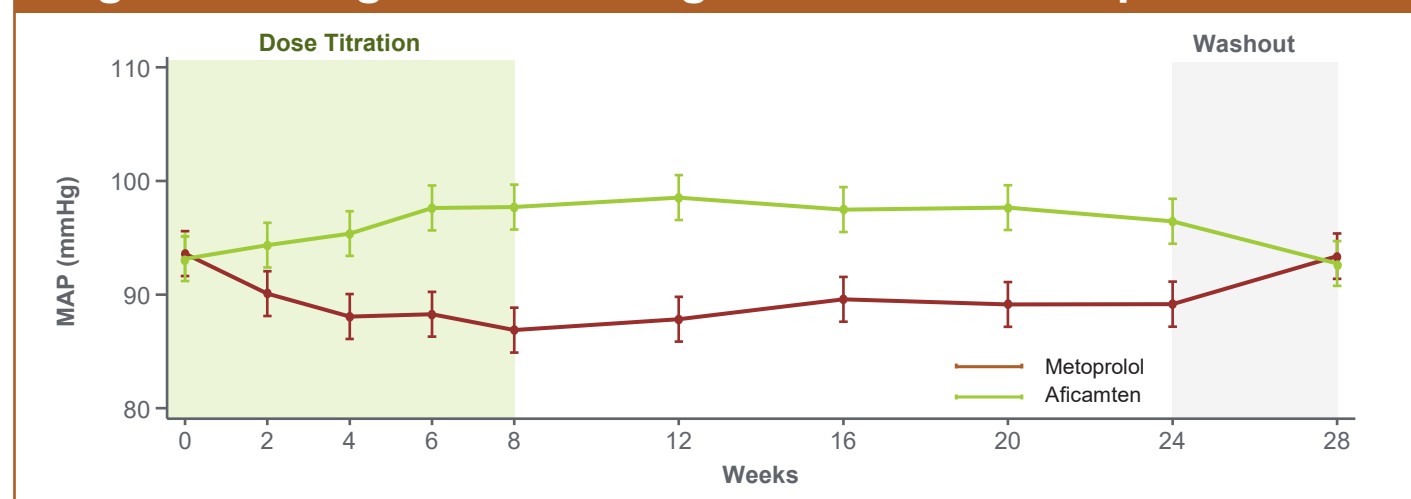
Figure 3. Improvement in Valsalva LVOT-G did not vary by history of HTN



HTN, hypertension; LVOT-G, left ventricular outflow tract gradient.

- Improvement in peak oxygen uptake (pVO₂) did not vary by history of HTN.
- Improvement in Valsalva LVOT-G did not vary by history of HTN.

Figure 4. Longitudinal change in mean arterial pressure

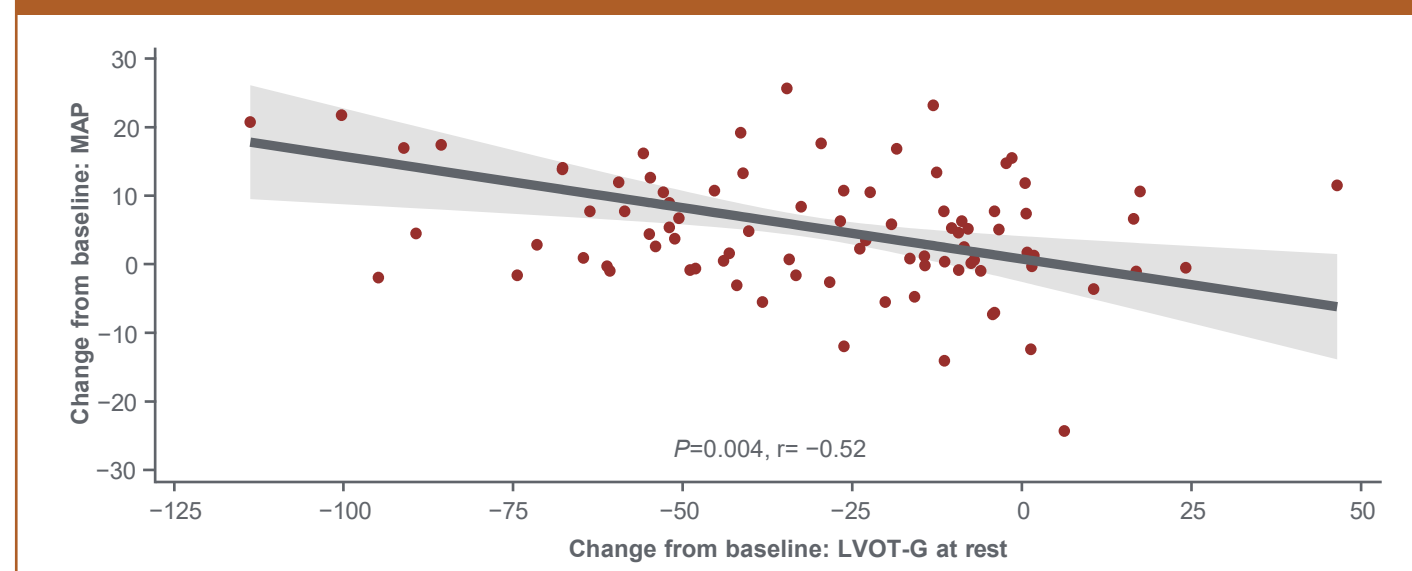


MAP, mean arterial pressure.

Safety

- Non-significant differences in adverse events (AEs) for HTN in aficamten- vs metoprolol-treated participants (n=9 vs 3; $P=0.08$).
- Non-significant differences in AEs for uncontrolled HTN (34% with aficamten vs 25% with metoprolol; $P=0.38$).
- Non-significant differences in AEs for hypotension (1 with aficamten vs 3 with metoprolol; $P=0.31$).
- New anti-HTN medications were more commonly prescribed to participants randomized to aficamten (14.8% vs 4.6%; $P=0.039$) during the trial.

Figure 5. Significant correlation between relief of LVOT-G and increase in BP



BP, blood pressure; LVOT-G, left ventricular outflow tract gradient; MAP, mean arterial pressure.

- At Week 12, in aficamten-treated patients, for each 10 mmHg reduction in LVOT-G at rest, there was a 1.5 mmHg increase in mean arterial pressure ($P=0.004$).

CONCLUSIONS

- Benefits of aficamten on the primary and secondary measures of efficacy were not affected by HTN history and uniformly favored aficamten vs metoprolol.
- Directly associated with relief of LVOT obstruction, aficamten treatment increased BP comparable to other treatments that resolve LVOT gradient.
- Aficamten is suitable as first-line therapy for patients with oHCM and HTN and may enable prescription of anti-HTN treatment classes otherwise contraindicated in the setting of obstruction.

References

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Disclosures

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