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## **Abstract:**

Beta-blockers have been the initial treatment for symptomatic obstructive hypertrophic cardiomyopathy (HCM) despite limited evidence of their efficacy. Aficamten is a cardiac myosin inhibitor that reduces left ventricular outflow tract gradients, improves exercise capacity, and decreases HCM symptoms when added to standard medications. Whether aficamten as monotherapy provides greater clinical benefit than beta-blockers as monotherapy remains unknown.

We conducted an international, double-blind, double-dummy trial in which adults with symptomatic obstructive HCM were randomly assigned in a 1:1 ratio to receive aficamten (at a daily dose of 5 mg to 20 mg) plus placebo or metoprolol (at a daily dose of 50 mg to 200 mg) plus placebo. The primary end point was the change in peak oxygen uptake at week 24; secondary end points were improvement at week 24 in New York Heart Association (NYHA) functional class and changes at week 24 in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), left ventricular outflow tract gradient after the Valsalva maneuver, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, left atrial volume index, and left ventricular mass index.

A total of 88 patients were assigned to the aficamten group and 87 to the metoprolol group. The mean age of the patients was 58 years, 58.3% were men, and the mean left ventricular outflow tract gradient was 47 mm Hg at rest and 74 mm Hg after the Valsalva maneuver. At 24 weeks, the change in the peak oxygen uptake was 1.1 ml per kilogram of body weight per minute (95% confidence interval [CI], 0.5 to 1.7) in the aficamten group and -1.2 ml per kilogram per minute (95% CI, -1.7 to -0.8) in the metoprolol group (least-squares mean between-group difference, 2.3 ml per kilogram per minute; 95% CI, 1.5 to 3.1;  $P < 0.001$ ). Patients who received aficamten had significantly greater improvements in NYHA class, KCCQ-CSS, left ventricular outflow tract gradient, NT-proBNP level, and left atrial volume index than patients who received metoprolol. No significant difference in left ventricular mass index was observed. Adverse events appeared to be similar in the two treatment groups.

Among patients with symptomatic obstructive HCM, aficamten monotherapy was superior to metoprolol monotherapy in improving peak oxygen uptake and hemodynamics and decreasing symptoms. (Funded by Cytokinetics; MAPLE-HCM ClinicalTrials.gov number, [NCT05767346](https://clinicaltrials.gov/ct2/show/study/NCT05767346)).