

Aficamten and Cardiopulmonary Exercise Test Performance

A Substudy of the SEQUOIA-HCM Randomized Clinical Trial

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IMPORTANCE Impaired exercise capacity is a cardinal manifestation of obstructive hypertrophic cardiomyopathy (HCM). The Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic Obstructive HCM (SEQUOIA-HCM) is a pivotal study characterizing the treatment effect of aficamten, a next-in-class cardiac myosin inhibitor, on a comprehensive set of exercise performance and clinical measures.

OBJECTIVE To evaluate the effect of aficamten on exercise performance using cardiopulmonary exercise testing with a novel integrated measure of maximal and submaximal exercise performance and evaluate other exercise measures and clinical correlates.

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified analysis from SEQUOIA-HCM, a double-blind, placebo-controlled, randomized clinical trial. Patients were recruited from 101 sites in 14 countries (North America, Europe, Israel, and China). Individuals with symptomatic obstructive HCM with objective exertional intolerance (peak oxygen uptake [pV_{O_2}] $\leq 90\%$ predicted) were included in the analysis. Data were analyzed from January to March 2024.

INTERVENTIONS Randomized 1:1 to aficamten (5-20 mg daily) or matching placebo for 24 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was change from baseline to week 24 in integrated exercise performance, defined as the 2-component z score of pV_{O_2} and ventilatory efficiency throughout exercise (minute ventilation [VE]/carbon dioxide output [VCO_2] slope). Response rates for achieving clinically meaningful thresholds for change in pV_{O_2} and correlations with clinical measures of treatment effect (health status, echocardiographic/cardiac biomarkers) were also assessed.

RESULTS Among 282 randomized patients (mean [SD] age, 59.1 [12.9] years; 115 female [40.8%], 167 male [59.2%]), 263 (93.3%) had core laboratory-validated exercise testing at baseline and week 24. Integrated composite exercise performance improved in the aficamten group (mean [SD] z score, 0.17 [0.51]) from baseline to week 24, whereas the placebo group deteriorated (mean [SD] z score, -0.19 [0.45]), yielding a placebo-corrected improvement of 0.35 (95% CI, 0.25-0.46; $P < .001$). Further, aficamten treatment demonstrated significant improvements in total workload, circulatory power, exercise duration, heart rate reserve, peak heart rate, ventilatory efficiency, ventilatory power, and anaerobic threshold (all $P < .001$). In the aficamten group, large improvements (≥ 3.0 mL/kg per minute) in pV_{O_2} were more common than large reductions (32% and 2%, respectively) compared with placebo (16% and 11%, respectively). Improvements in both components of the primary outcome, pV_{O_2} and VE/ VCO_2 slope throughout exercise, were significantly correlated with improvements in symptom burden and hemodynamics (all $P < .05$).

CONCLUSIONS AND RELEVANCE This prespecified analysis of the SEQUOIA-HCM randomized clinical trial found that aficamten treatment improved a broad range of exercise performance measures. These findings offer valuable insight into the therapeutic effects of aficamten.

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A cardinal clinical feature of obstructive hypertrophic cardiomyopathy (HCM) is exercise intolerance. Cardio-specific mechanisms underlying exercise intolerance are thought to arise from the following: (1) dynamic left ventricular outflow tract (LVOT) obstruction, (2) diastolic dysfunction, (3) dynamic mitral regurgitation, and (4) myocardial oxygen supply-demand mismatch resulting in ischemia.¹ The evaluation of patients with obstructive HCM during the physiologic stress of exercise with cardiopulmonary exercise testing (CPET) can ascertain the extent to which these cardio-specific limitations impair exercise performance and serve to evaluate potential functional improvements with treatment. CPET also enables an objective and reproducible assessment of all stages of exercise performance. Importantly, peak oxygen uptake (pVO_2) and other exercise physiology metrics measured by CPET have already been shown to predict clinical events in obstructive HCM.²

Cardiac myosin inhibitors (CMIs) have been developed as a therapeutic option for patients with obstructive HCM by targeting the underlying etiopathology of the disease. They act by directly reducing excessive actin-myosin crossbridges at the level of the sarcomere and mitigate cardiac hypercontractility. Mavacamten, the first-in-class CMI, has shown efficacy by improving pVO_2 and other CPET parameters.³ Aficamten, a next-in-class CMI, was designed with unique physicochemical properties. Aficamten doses can be adjusted to achieve an individualized target dose rapidly (within 6 weeks) as a result of a wide therapeutic window (modest reductions in left ventricular ejection fraction [LVEF] with each dose-level increment) and plasma half-life of 3.4 days. Additionally, minimal drug-drug interactions and rapid reversibility are safety features that allow for precision dosing and relatively infrequent low LVEF excursions less than 50% that can be managed with dose reduction without the need for treatment interruption.¹ Aficamten treatment has been demonstrated to relieve obstruction and improve symptoms, cardiac biomarkers, and measures of diastolic function in the phase 2 and open-label extension studies (REDWOOD-HCM^{4,5} and FOREST-HCM), and was recently shown to improve pVO_2 , symptoms, health status, and LVOT gradients (LVOT-G) and reduce eligibility for septal reduction therapy in the SEQUOIA-HCM trial.⁶

In this prespecified analysis of the SEQUOIA-HCM randomized clinical trial, we hypothesized that aficamten would improve a novel measure of integrated exercise performance that combines complementary measures previously independently related to obstructive HCM prognosis and incorporates both submaximal and maximal exercise capacity.⁷ We further hypothesized that changes in pVO_2 would relate to changes in symptoms and cardiac biomarkers, as well as in LVOT-G and other echocardiographic measures.

Methods

Study Oversight

All study participants provided written informed consent before enrollment. The study was conceived, designed, and conducted by an academic steering committee in conjunction with

Key Points

Question Does aficamten treatment improve exercise response beyond peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing in obstructive hypertrophic cardiomyopathy (HCM)?

Findings In the Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic Obstructive HCM (SEQUOIA-HCM) randomized clinical trial, 282 patients with symptomatic obstructive HCM received aficamten or placebo for 24 weeks. Aficamten treatment resulted in significant improvement in multiple exercise measures, including a novel composite of exercise performance during peak and submaximal exercise.

Meaning Aficamten treatment improves several exercise performance measures in patients with obstructive HCM, and improvements in these measures were correlated with other important clinical responses.

the study sponsor (Supplement 1). All patients provided written informed consent, and the study was carried out in accordance with the provisions of the Declaration of Helsinki and the International Council for Harmonisation Guideline for Good Clinical Practice. An independent data monitoring committee had access to unblinded data for monitoring. Study personnel remained blinded to treatment assignments, dosing, and echocardiogram results through database lock. Results were generated based on a prespecified statistical analysis plan (Supplement 2) that was finalized before database lock. The trial was approved by the regulatory agencies in the participating countries and by the institutional review board or ethics committee at each trial center. This study followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Design

The rationale for and design of the SEQUOIA-HCM trial have been previously described.¹ In brief, this was a phase 3, placebo-controlled, double-blind, multicenter, randomized clinical trial in participants with obstructive HCM. Patients with LVOT-G greater than or equal to 30 mm Hg (resting) and greater than or equal to 50 mm Hg (after Valsalva), New York Heart Association (NYHA) functional class II to III symptoms, baseline pVO_2 of 90% or less of predicted, and respiratory exchange ratio (RER) of 1.05 or greater were eligible to participate. Individuals were excluded if they had a history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months before screening or inability to exercise on a treadmill or cycle. Participants self-identified with the following races and ethnicities: Asian, Black or African American, White, and other, which included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander; multiracial; or not reported. Race and ethnicity information was included in this study to permit appropriate interpretation of the data and generalize the research.

Randomization

Participants who met screening criteria underwent baseline studies, including history, physical examination, vital signs,

echocardiography, CPET, laboratory assessments, and symptom assessments (NYHA functional class, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS], patient and clinical global impression scales), and they were then randomly assigned 1:1 to receive either aficamten or matching placebo using an interactive Web Response System (Signant Health). Central randomization was stratified by use of β -blockers (yes or no) and CPET exercise modality (treadmill or cycle).

Interventions

Patients receiving aficamten were assigned 5 mg, 10 mg, 15 mg, or 20 mg orally once daily based on site-read echocardiogram-guided titration.¹ Aficamten doses were individualized to achieve the lowest effective dose resulting in a Valsalva LVOT-G of less than 30 mm Hg while maintaining an LVEF of 50% or greater over the first 8 weeks of the study starting at 5 mg. Patients, investigators, and the study sponsor were masked to the echocardiogram results and N-terminal pro-brain natriuretic peptide (NT-proBNP) level.

CPET

The CPET core laboratory (Massachusetts General Hospital and Harvard University) certified study sites according to their having demonstrated appropriate and reproducible conduct of qualification CPETs in accordance with the CPET manual of operating procedures, version 1.3 (Supplement 1 and eAppendix in Supplement 3). To achieve within-participant consistency, where possible, CPET was performed on the same equipment, using the same protocol, and was administered by the same staff, at both baseline and week 24. All CPETs were transferred electronically to the core laboratory, where they were interpreted in a blinded fashion. Prespecified criteria for valid CPETs included the absence of equipment malfunction, major CPET protocol deviation, or transient illness/injury unrelated to HCM symptoms that precluded valid CPET completion.

CPET End Points

The primary analysis was change from baseline to week 24 in integrated exercise performance, normalized to a composite of z scores for pVO_2 and minute ventilation (VE)/carbon dioxide output (VCO_2) slope throughout exercise to capture physiologic responses to maximal and submaximal exercise. The z score was derived by reversing the directionality of the VE/ VCO_2 slope such that increases in both z score components indicate benefit, and equal weights were used for each component. For each patient, the composite z score was defined as $(z_1 + z_2) / 2$, where z_1 is the patient's pVO_2 change minus the trial-level mean pVO_2 change, divided by the trial-level SD of pVO_2 change, and z_2 was defined similarly for VE/ VCO_2 slope, then multiplied by -1 , such that positive values of both z_1 and z_2 represent changes from baseline that are better than average.

Secondary end points included assessments for changes from baseline to week 24 in CPET-derived measures during 2 phases of exercise performance: (1) peak exercise (pVO_2 , peak workload, peak metabolic equivalents, peak circulatory power

[$VO_2 \times$ systolic blood pressure], exercise duration, peak RER, heart rate reserve, peak heart rate, oxygen pulse at peak exercise, proportionate pulse pressure) and (2) during submaximal exercise (preanaerobic threshold VE/ VCO_2 slope from the onset of exercise up until and including the first ventilatory anaerobic threshold, derived from the V-slope method, VE/ VCO_2 slope throughout exercise [from rest to peak exercise], ventilatory power, ventilatory anaerobic threshold, and aerobic efficiency).

Sample Size Calculation

Sample size calculations for the SEQUOIA-HCM trial assumed a between-group difference in change from baseline in pVO_2 of 1.5 mL/kg per minute for aficamten vs placebo, a common SD of 3.5 mL/kg per minute, and 10% missing data for the primary end point. A sample size of 270 patients at a randomization ratio of 1:1 (approximately 135 randomized to aficamten and approximately 135 to placebo) was estimated to provide greater than or equal to 90% power to detect a difference of 1.5 mL/kg per minute in pVO_2 change from baseline to week 24 with a 2-sided type I error of 0.05.

Statistical Analysis

The full statistical analysis plan for CPET analyses is provided in Supplement 2. Unless otherwise specified, efficacy analyses were performed on the full analysis set, which includes all randomized patients who received 1 or more doses of study drug and had 1 or more postbaseline efficacy assessments. The primary analysis was performed using an analysis of covariance model that included terms of treatment, randomization stratification factors (β -blocker use status and CPET modality), baseline value of the outcome, and baseline body weight as covariates. Missing data were imputed 100 times according to the missing at random (MAR) paradigm. Least squares mean (LSM) treatment difference and SE were combined using Rubin rules to produce an LSM estimate of the treatment difference, its 95% CI, and P value for the test of null hypothesis of no treatment effect. Secondary exercise testing efficacy end points were analyzed using the same methodology as used for the primary end points.

Additional analyses included the following: (1) a sensitivity analysis using an alternate z score with the VE/ VCO_2 slope preanaerobic threshold (rather than throughout exercise), (2) a responder analysis for the proportional achievement of clinically meaningful thresholds for shifts in pVO_2 (small [0 to <1.5 mL/kg per minute], moderate [≥ 1.5 to <3 mL/kg per minute], or large [≥ 3.0 mL/kg per minute]) by treatment group and correlations between change in pVO_2 and other measures of treatment effect (symptoms, hemodynamics, biomarkers), and (3) an evaluation of how change in the z score and its components relates to change in other SEQUOIA-HCM CPET, symptom-based, echocardiographic, and biomarker end points by correlation and multivariate regression analysis.

Baseline data are presented as number (%), mean (SD), and median (IQR). Two-sided P values $< .05$ were considered statistically significant. Missing CPET end points at week 24, regardless of type of intercurrent events, were imputed using multiple imputation methodology under the MAR assumption.

tion for the primary analysis of the primary estimate because the proportion of patients with week 24 CPET missing was expected to be very low.

Statistical analyses were performed from January to March 2024 by the Brigham and Women's Hospital Clinical Trials Outcomes Center.

Results

Patient Population

Between February 1, 2022, and May 15, 2023, 282 eligible patients were randomized to aficamten or placebo at 101 sites in 14 countries. Baseline characteristics have been previously published and are shown in [Table 1](#).^{1,6} The mean (SD) age of participants was 59.1 (12.9) years, 115 (40.8%) were female, and 167 (59.2%) were male. Patients self-identified with the following races and ethnicities: 54 Asian (19.1%), 3 Black or African American (1.1%), 223 White (79.1%), and 2 other (0.7%). Background HCM therapy included 173 participants (61.3%) receiving β -blockers, 81 (28.7%) receiving nondihydropyridine calcium channel blockers, 36 (12.8%) receiving disopyramide, and 41 (14.5%) not taking any HCM medication. Exercise capacity was reduced as evidenced by the baseline mean (SD) pV_{O_2} of 18.5 (4.5) mL/kg per minute, representing a mean (SD) of 56.9% (11.8%) of age- and sex-predicted pV_{O_2} ,⁸ and a reduced VE/VCO₂ slope throughout exercise mean (SD) of 33.0 (6.1). Other key baseline CPET parameters included workload (mean [SD], 122.5 [40.1] W) and metabolic equivalents (mean [SD], 5.3 [1.3] mL/kg per minute), both of which were impaired.

Patient Disposition

At least 1 dose of study medication was received by all randomized patients (eFigure in [Supplement 3](#)). At week 24, the number (%) of patients taking each aficamten dose was 5 (3.6), 21 (15.3), 48 (35), and 63 (46) for 5 mg, 10 mg, 15 mg, and 20 mg, respectively. Of those randomized, 263 patients (93.3%) completed both baseline and week 24 CPETs that were deemed physiologically interpretable and valid by the core laboratory. Of the 19 patients (7%; 9 aficamten and 10 placebo) who did not have a core laboratory-interpretable week 24 CPET available for analysis, 6 (2.1%; 3 aficamten and 3 placebo) terminated early from the study before week 24 CPET, and 13 (4.6%; 6 aficamten and 7 placebo) were determined by the core laboratory to have an invalid week 24 CPET (3 did not follow the CPET manual of operations, and 10 were technical failures).

Primary and Secondary End Points

The change from baseline to week 24 in the integrated composite for exercise performance demonstrated improvement in the aficamten group (mean [SD] z score, 0.17 [0.51]) compared with a deterioration in the placebo group (mean [SD] z score, -0.19 [0.45]), yielding a significant placebo-corrected increase (mean [SD] z score, 0.35; 95% CI, 0.25-0.46; $P < .001$) ([Figure 1](#) and [Table 2](#)). Aficamten improved peak exercise performance as measured by the total workload (LSM

difference, 12 W; 95% CI, 6-18 W; $P < .001$), circulatory power (LSM difference, 586 mm Hg \times mL/kg/min; 95% CI, 379-793 mm Hg \times mL/kg/min; $P < .001$), exercise duration (LSM difference, 1.0 minute; 95% CI, 0.5-1.4 minutes; $P < .001$), heart rate reserve (LSM difference, 6 beats per minute; 95% CI, 3-9 beats per minute; $P < .001$), and peak heart rate (LSM difference, 9 beats per minute; 95% CI, 6-12 beats per minute; $P < .001$) ([Table 2](#)). Aficamten also improved submaximal exercise performance as measured by ventilatory efficiency (both preanaerobic threshold: LSM difference, -1.5; 95% CI, -2.5 to -0.6; $P = .002$ and throughout exercise: LSM difference, -2.3; 95% CI, -3.2 to -1.4; $P < .001$), increased ventilatory power (LSM difference, 0.9 mm Hg; 95% CI, 0.6-1.1 mm Hg; $P < .001$), and increased ventilatory anaerobic threshold (LSM difference, 59 mL per minute; 95% CI, 33-85 mL per minute; $P < .001$) ([Table 2](#)). As anticipated, aficamten treatment was not associated with improvements in oxygen pulse at peak exercise, proportionate pulse pressure at peak or rest, or aerobic efficiency, and there were no between-group differences in peak RER.

In a sensitivity analysis using an alternate z score using the VE/VCO₂ slope preanaerobic threshold (rather than throughout exercise), the change from baseline to week 24 in this alternate z score also showed improvement in the aficamten group (mean [SD] z score, 0.15 [0.63]) compared with a deterioration in the placebo group (mean [SD] z score, -0.18 [0.57]), resulting in a significant placebo-corrected increase (mean [SD] z score, 0.32; 95% CI, 0.18-0.45; $P < .001$).

Responder Analysis

Large pV_{O_2} improvements (≥ 3.0 mL/kg per minute) were more frequent with aficamten treatment compared with placebo (32% vs 16%, respectively), and large pV_{O_2} deteriorations (≤ -3.0 mL/kg per minute) were less frequent with aficamten treatment vs placebo (2% vs 11%, respectively) ([Figure 2](#)). The odds ratios (ORs) for achieving any improvement (OR, 3.09; 95% CI, 1.88-5.09), moderate to large improvements greater than or equal to 1.5 mL/kg per minute (OR, 2.44; 95% CI, 1.50-3.96), and large improvements greater than or equal to 3.0 mL/kg per minute (OR, 2.44; 95% CI, 1.38-4.29) all favor aficamten treatment and correspond with a number needed to treat of 3.8, 4.7, and 6.3 patients, respectively (eTable 1 in [Supplement 3](#)).

Clinical Correlations

Cubic spline graphs and univariate correlation analyses revealed significant associations between improvements in pV_{O_2} and improvements in KCCQ-CSS score, NYHA functional class, septal E/e' (peak E-wave velocity divided by peak e' velocity, an estimate of left ventricular end-diastolic pressure), resting and Valsalva LVOT-G, NT-proBNP level, and high-sensitivity cardiac troponin I (hs-cTnI) level ([Figure 3](#) and eTable 2 in [Supplement 3](#)). Sequential regression multivariate analyses revealed that changes in NT-proBNP level accounted for the greatest amount of variance in change in pV_{O_2} , whereas changes in E/e' and KCCQ-CSS score also significantly added to the observed variance (eTable 3 in [Supplement 3](#)). In a univariate analysis, improvements in VE/VCO₂ slope throughout exercise were associated with changes in many of the same clinical

Table 1. Baseline Characteristics^a

Characteristic	Aficamten (n = 142)	Placebo (n = 140)
Age, y	59.2 (12.6)	59.0 (13.3)
Sex, No. (%)		
Female	56 (39.4)	59 (42.1)
Male	86 (60.6)	81 (57.9)
Race, No. (%)		
Asian	29 (20.4)	25 (17.9)
Black or African American	3 (2.1)	0
White	108 (76.1)	115 (82.1)
Other ^b	2 (1.4)	0
Geographic region, No. (%)		
North America	49 (34.5)	45 (32.1)
China	24 (16.9)	22 (15.7)
Europe and Israel	69 (48.6)	73 (52.1)
Medical history, No. (%)		
Hypertension	75 (52.8)	70 (50.0)
Family history or known gene variant	47 (33.1)	44 (31.4)
Family history of HCM	41 (28.9)	34 (24.3)
Pathogenic sarcomere variant	24 (16.9)	25 (17.9)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Coronary artery disease	19 (13.4)	16 (11.4)
Diabetes	14 (9.9)	9 (6.4)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
Background HCM therapy, No. (%)		
β-Blocker	86 (60.6)	87 (62.1)
Calcium channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
Symptoms		
KCCQ-CSS	76 (18)	74 (18)
NYHA functional class, No. (%)		
II	108 (76.1)	106 (75.7)
III	34 (23.9)	33 (23.6)
IV	0	1 (0.7)
Cardiac biomarkers		
Median NT-proBNP (IQR), pg/mL	818 (377-1630)	692 (335-1795)
Median hs-cTnI (IQR), ng/L	12.9 (7.6-33.6)	11.5 (7.7-25.0)
Echocardiographic parameters		
Valsalva LVOT-G, mm Hg	83 (32)	83 (33)
Resting LVOT-G, mm Hg	55 (27)	55 (32)
LVEF, %	75 (5.5)	75 (6.3)
LAVI, mL/m ²	40.1 (12.7)	40.9 (15.1)
Maximal wall thickness, cm	2.1 (0.3)	2.1 (0.3)
Cardiopulmonary exercise test parameters		
Integrated 2-component exercise performance metric	-0.01 (0.82)	0.02 (0.75)
pVO ₂ , mL/kg/min	18.4 (4.5)	18.6 (4.6)
Workload, W	120 (40)	126 (43)
Metabolic equivalents, METS	5.3 (1.3)	5.3 (1.3)
Ventilatory efficiency throughout exercise (VE/VCO ₂ slope)	33.2 (6.4)	32.9 (6.0)

Abbreviations: HCM, hypertrophic cardiomyopathy; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; pVO₂, peak oxygen uptake; VCO₂, carbon dioxide output; VE, minute ventilation.

SI conversion factors: To convert hs-cTnI to micrograms per liter, divide by 1000 and multiply by 1; NT-proBNP to nanograms per liter, multiply by 1.

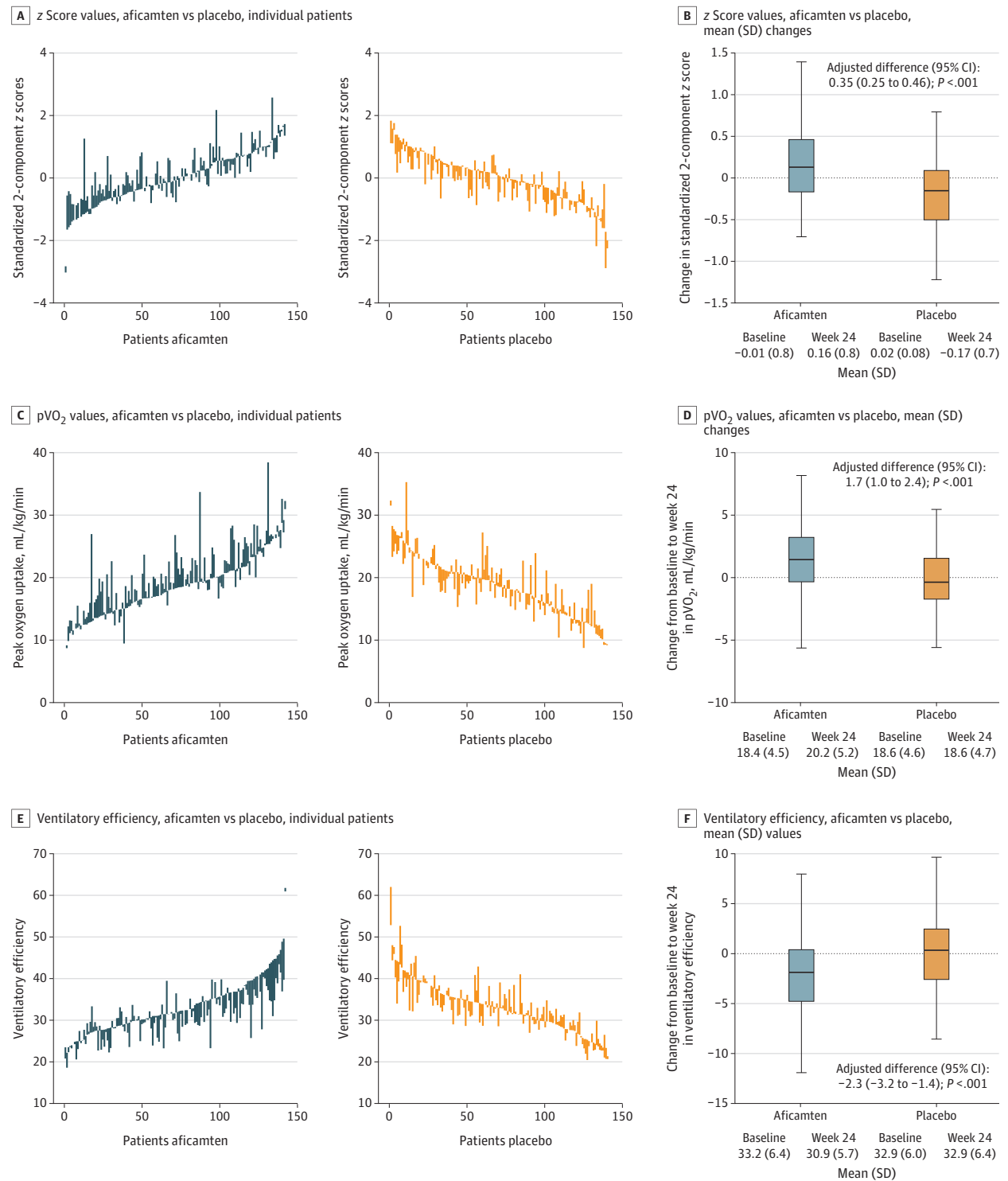
^a Percentages may not total 100 because of rounding. Value in parenthesis represents the SD unless otherwise specified.

^b Race was denoted by the patient as part of baseline characteristics. Other ethnic groups included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander; multiracial; and not reported.

cal measures as change in pVO₂. However, change in VE/VCO₂ slope demonstrated higher correlation with changes in LVOT-G (rest and Valsalva) and left atrial volume index (LAVI) and lower correlation with changes in E/e' and hs-cTnI level.

In the multivariate analysis, changes in NT-proBNP level, LAVI, and mitral regurgitation significantly explained variance in VE/VCO₂ slope (eTable 3 in Supplement 3). In addition to distinct correlates for pVO₂ and VE/VCO₂ slope, only a modest

Figure 1. Baseline and Week 24 Values and Changes in Integrated Exercise Performance and Its Component Variables



Baseline and week 24 values, connected by vertical lines, are shown for individual patients receiving aficamten (left) and placebo (right) for z score values (A), peak oxygen uptake (pVO₂) values (C), and ventilatory efficiency values (E). Integrated exercise performance and its component variables (standardized 2-component z score of pVO₂ and VE as measured by minute ventilation [VE]/carbon dioxide output [VCO₂] slope throughout all of exercise). The z score was derived by

reversing the directionality of VE/VCO₂ slope values such that increases in both z score components indicate benefit; equal weights were used for each component. Changes in values (median and IQR) from baseline to week 24 are shown in panels B, D, and F. Box edges indicate the IQRs; the horizontal lines in between the edges indicate the median values. Whiskers extend to the upper and lower adjacent values, and dots represent outside values.

Table 2. Cardiopulmonary Exercise Testing (CPET) Parameters by Treatment Assignment

CPET variable	Aficamten, mean (SD) (n = 133)			Placebo, mean (SD) (n = 130)			Adjusted difference (95% CI) ^b	P value
	Baseline	Week 24	Absolute difference (SD) ^a	Baseline	Week 24	Absolute difference (SD) ^a		
Integrated 2-component z score metric ^c	-0.01 (0.82)	0.16 (0.76)	0.17 (0.51)	0.02 (0.75)	-0.17 (0.74)	-0.19 (0.45)	0.35 (0.25 to 0.46)	<.001
pVO ₂ , mL/kg/min	18.4 (4.5)	20.2 (5.2)	1.8 (3.1)	18.6 (4.6)	18.6 (4.7)	0 (2.7)	1.7 (1.0 to 2.4)	<.001
Peak workload, W	120 (40)	134 (50)	14 (27)	126 (43)	127 (44)	1 (21)	12 (6 to 18)	<.001
Peak METS, metabolic equivalents	5.3 (1.3)	5.8 (1.5)	0.51 (0.89)	5.3 (1.3)	5.3 (1.3)	0 (0.78)	0.49 (0.29 to 0.69)	<.001
Peak circulatory power, mm Hg × mL/kg/min	3013 (924)	3550 (1140)	537 (995)	3160 (1136)	3074 (1152)	-86 (731)	586 (379 to 793)	<.001
Exercise duration, min	11.2 (3.0)	12.4 (3.9)	1.2 (2.1)	11.5 (3.0)	11.7 (3.2)	0.1 (1.5)	1.0 (0.5 to 1.4)	<.001
Peak RER	1.19 (0.10)	1.20 (0.11)	0.01 (0.10)	1.18 (0.09)	1.19 (0.10)	0.01 (0.10)	0.00 (-0.02 to 0.02)	.84
Heart rate reserve, beats/min	59 (18)	66 (22)	7 (15)	57 (19)	59 (20)	1 (10)	6 (3 to 9)	<.001
Peak heart rate, beats/min	128 (20)	135 (23)	8 (14)	128 (23)	127 (23)	-1 (12)	9 (6 to 12)	<.001
Oxygen pulse at peak exercise, mL/beat	0.14 (0.03)	0.15 (0.03)	0 (0.02)	0.15 (0.03)	0.15 (0.03)	0 (0.02)	0.003 (-0.002 to 0.008)	.21
Proportionate pulse pressure, peak exercise	0.49 (0.11)	0.51 (0.12)	0.02 (0.14)	0.50 (0.10)	0.50 (0.11)	0 (0.10)	0.01 (-0.01 to 0.04)	.29
Proportionate pulse pressure, rest	0.39 (0.10)	0.37 (0.09)	-0.02 (0.10)	0.39 (0.10)	0.38 (0.10)	-0.01 (0.11)	-0.01 (-0.03 to 0.01)	.33
Ventilatory efficiency pre-VAT, VE/VCO ₂ slope	29.2 (5.4)	27.4 (4.4)	-1.9 (4.7)	29.1 (4.7)	28.8 (5.6)	-0.3 (4.2)	-1.5 (-2.5 to -0.6)	.002
Ventilatory efficiency throughout exercise, VE/VCO ₂ slope	33.2 (6.4)	30.9 (5.7)	-2.2 (4.0)	32.9 (6.0)	32.9 (6.4)	0.1 (3.7)	-2.3 (-3.2 to -1.4)	<.001
Ventilatory power, mm Hg	5.1 (1.5)	5.9 (1.6)	0.8 (1.3)	5.2 (1.6)	5.1 (1.5)	-0.1 (1.0)	0.9 (0.6 to 1.1)	<.001
Ventilatory anaerobic threshold, mL/min	898 (266)	958 (276)	60 (107)	931 (261)	927 (257)	-3 (108)	59 (33 to 85)	<.001
Aerobic efficiency, mL/min/W	8.3 (2.5)	8.6 (2.5)	0.3 (1.8)	8.2 (2.3)	8.2 (2.4)	0.1 (1.7)	0.2 (-0.2 to 0.6)	.22

Abbreviations: LSM, least squares mean; METS, metabolic equivalents; pVO₂, peak oxygen uptake; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; VCO₂, carbon dioxide output; VE, minute ventilation.

^a The absolute difference corresponds to the change from baseline to week 24.

^b The adjusted difference corresponds to the LSM treatment difference.

^c Integrated exercise performance was defined as the 2-component z score of pVO₂ and ventilatory efficiency throughout exercise (VE/VCO₂ slope). The z score was derived by reversing the directionality of VE/VCO₂ slope values such that increases in both z score components indicate benefit; equal weights were used for each component.

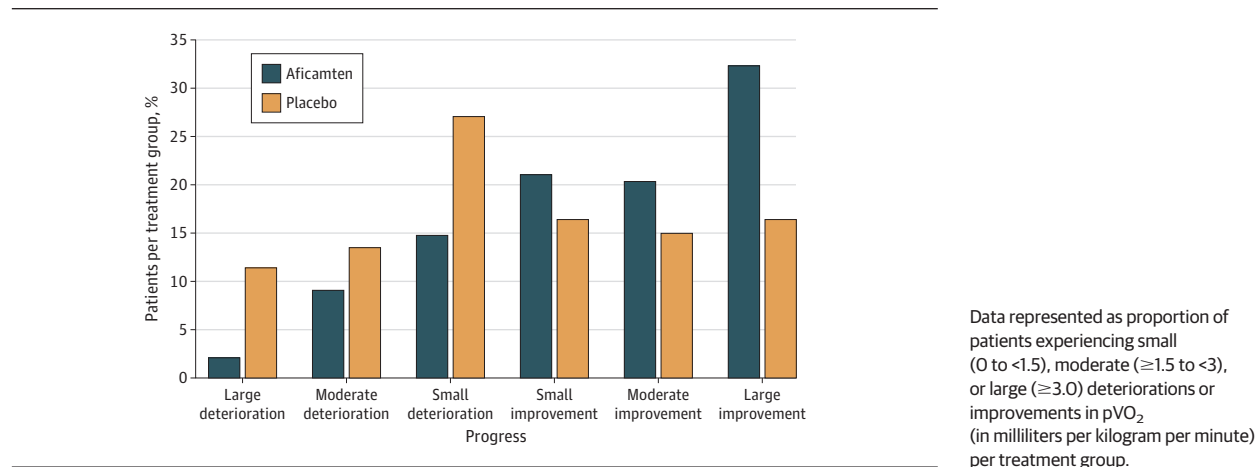
relationship between the change in pVO₂ and the change in VE/VCO₂ slope (correlation coefficient = -0.23) was observed, highlighting the orthogonal nature of the 2 variables selected for our 2-component z score.

Discussion

We report a comprehensive prespecified assessment of CPET, in the context of the largest (to our knowledge) placebo-controlled randomized clinical trial in patients with obstructive HCM to date. Given that pVO₂ is a metric of maximal exercise capacity that is not necessarily relevant to daily physical activity, we developed a novel metric that integrates both maximal and submaximal exercise perfor-

mance by CPET (z score of change in pVO₂ and VE/VCO₂ throughout exercise). We then evaluated whether aficamten treatment would improve this more global metric of exercise performance in this prespecified analysis from the SEQUOIA-HCM trial. This integrated exercise measure was significantly improved with aficamten vs placebo in patients with obstructive HCM, indicating that exercise benefits accrue in a combined fashion during both maximal and submaximal activity reflective of all stages of exertion in everyday life. Further, there is only a modest relationship between changes in pVO₂ and VE/VCO₂ throughout exercise (correlation coefficient <0.25) but a stronger correlation of both variables with changes in NT-proBNP level. Thus, the measures of pVO₂ and VE/VCO₂ throughout exercise embedded in the 2-component z score are complementary.

Figure 2. Responder Analyses of Categorical Change in Peak Oxygen Uptake (pVO₂) With Aficamten vs Placebo at 24 Weeks



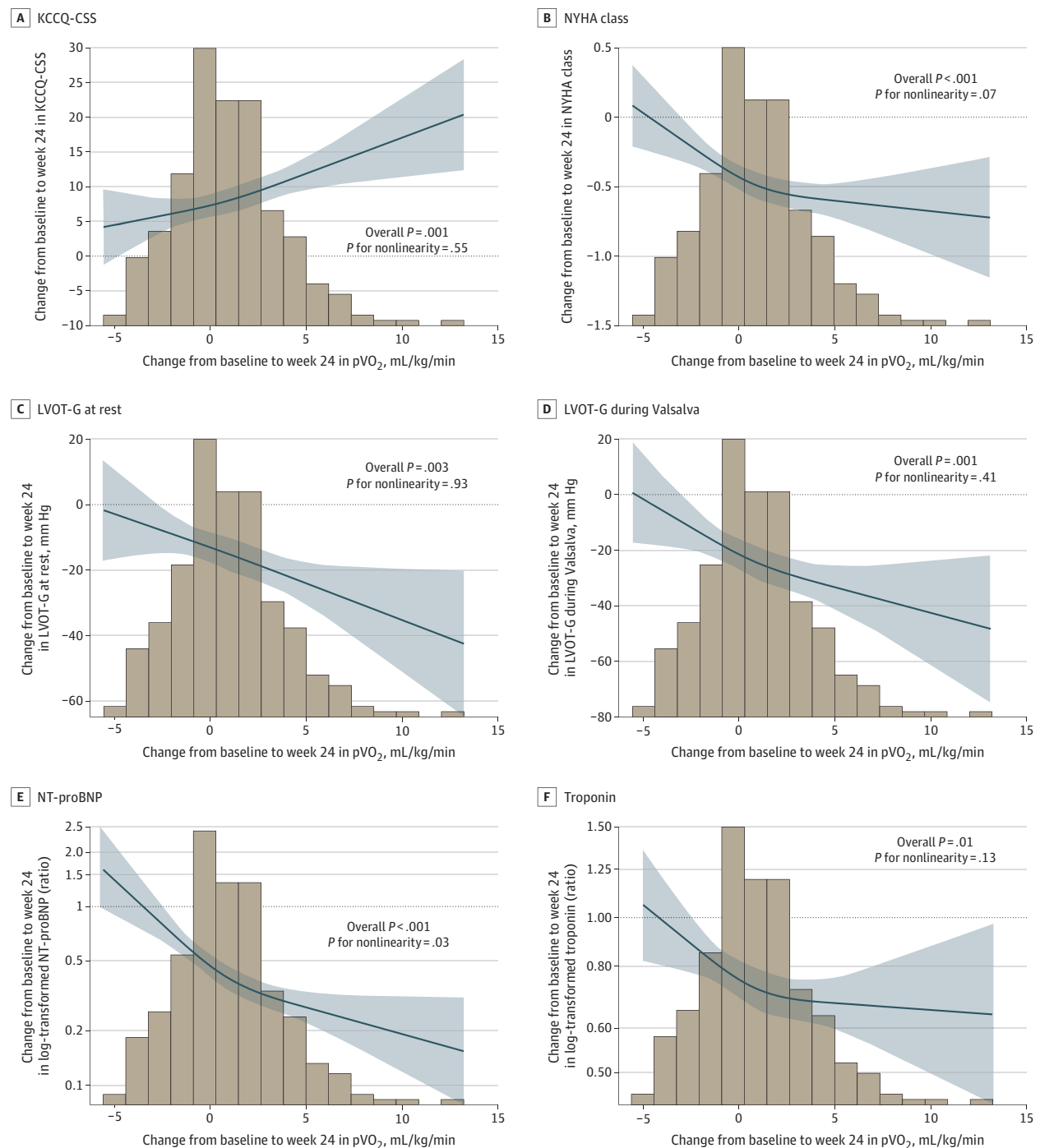
The impact of therapies on morbidity and mortality is difficult to assess in patients with HCM given the low event rate. Thus, defining clinically important outcome measures that serve as effective end points for clinical trials and also meaningfully reflect the treatment's impact on patient symptoms and function is critical. One approach is to categorize improvements into clinically meaningful increments and evaluate the number needed to treat to achieve those outcomes. In our categorical threshold analyses, patients taking aficamten were twice as likely to achieve a large pVO₂ increase (≥3.0 mL/kg per minute) and greater than 5 times less likely to experience worsening than those receiving placebo (Figure 2 and eTable 1 in Supplement 3), with fewer than 4 patients requiring treatment with aficamten to achieve exercise capacity improvement vs placebo. These findings are particularly noteworthy given that improvements in pVO₂ of the magnitude and consistency seen in the SEQUOIA-HCM trial are rarely achieved with existing medical therapies for individuals with either HCM or heart failure.^{1,9}

Correlations between observed changes in pVO₂ and VE/VCO₂ throughout exercise in the SEQUOIA-HCM trial and changes in measures of cardiac structure and function begin to provide mechanistic insights into predominant contributions to exercise limitation in obstructive HCM and their modifiability with aficamten. The observed correlation between changes in LVOT-G with and without Valsalva was expected, although notably higher correlation coefficients were observed between changes in pVO₂ and changes in NT-proBNP level as well as E/e' values. In fact, NT-proBNP level accounted for the highest relative variance explained in change in pVO₂ and change in VE/VCO₂ throughout exercise in multivariate modeling, suggesting that the drivers of NT-proBNP-level reduction extend beyond simply reducing LVOT-G. Further, these findings support current efforts to understand whether CMI, which has been observed to substantially lower NT-proBNP level in phase 2 studies in nonobstructive HCM, may presage its role in improving functional capacity in nonobstructive HCM also.¹⁰ This approach is currently under investigation in the ongoing Phase 3 Trial to Evaluate the

Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic Nonobstructive HCM (ACACIA-HCM), which will leverage the integrated exercise performance end point first described in this study.

CPET metrics that are cardiocentric (VE/VCO₂ slope, circulatory power, heart rate reserve, peak heart rate), as well as those that are highly integrated with whole-body physiology (ie, pVO₂) (Table 2 and eTable 2 in Supplement 3), improved in the setting of aficamten treatment. We did not observe significant improvement in peak oxygen pulse, the product of stroke volume and peripheral oxygen extraction, likely because peripheral oxygen extraction is far more dynamic than stroke volume in accounting for peak oxygen pulse, and aficamten was not expected to influence peripheral oxygen extraction, which falls in a reciprocal manner in response to increases in cardiac output at peak exercise. Proportional pulse pressure also did not change with aficamten, which may reflect the multitude of inputs to blood pressure and challenges with measurement of diastolic blood pressure at peak exercise (which proportionate pulse pressure largely depends on).

By expanding the range of CPET parameters evaluated, we gain a more holistic understanding of the physiologic responses to exercise in patients with obstructive HCM. Within this context, pVO₂ is primarily influenced by cardiac output, whereby failure to increase cardiac output relative to increased peripheral oxygen extraction has been observed in the setting of obstructive HCM during exercise.¹¹⁻¹³ In contrast, for other conditions (eg, heart failure with preserved EF), the determinants of pVO₂ frequently extend beyond cardiac output to include factors such as peripheral abnormalities (ie, impaired peripheral oxygen extraction by muscles), making improvement in exercise capacity harder to achieve with cardiospecific pharmacologic interventions.^{14,15} Finally, the observation that aficamten improved both heart rate reserve and peak heart rate independent of β-blockade is particularly interesting. It suggests a mechanism that may account for the absence of interaction with β-blocker use for the primary end point of change in pVO₂ in the SEQUOIA-HCM trial, and it

Figure 3. Cubic Spline Graphs: Correlation Between Change in Peak Oxygen Uptake (pV_{O_2}) and Clinical Metrics

The panels display the change in pV_{O_2} from baseline to 24 weeks for the following: Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) (A), New York Heart Association (NYHA) functional class (B), resting left ventricular outflow tract gradient (LVOT-G) (C), Valsalva LVOT-G (D), N-terminal pro-brain natriuretic peptide (NT-proBNP) (E), and high-sensitivity

cardiac troponin I (hs-cTnI) (F). Graphs display linear regression with cubic terms. Analyses adjusted for baseline values of both parameters. Solid lines show the association correlate, and shaded areas show the 95% CIs. Histograms show the distribution of change in pV_{O_2} .

stands in contrast to the β -blocker interaction observed with mavacamten in the Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM).¹⁶

We further showed that CPET is a reproducible tool for use in clinical trials, performed at over 100 sites in 14 countries. These data also strengthen justification for CPET as a clinical tool to explain exertional intolerance in patients with obstructive

tive HCM, assess response to treatment, and provide data for potential prognostic extrapolation from other observational studies.^{7,17} CPET enables simultaneous assessment of multiple pathophysiologic abnormalities characteristic of HCM, including early anaerobic threshold, ventilatory inefficiency, chronotropic incompetence, and reduced blood pressure augmentation. Collectively, improvement in these findings supports the effect that aficamten has on both submaximal and maximal exercise performance, spanning the array of experiences and activities that are important to patients with symptomatic obstructive HCM.

Limitations

This study has limitations. First, patients with prior septal reduction therapy and those with nonobstructive HCM were excluded from the study, as were those unable to exercise, thereby limiting the generalizability of our study population to all patients with HCM. Second, CPET assessments were conducted at only 2 time points (baseline and week 24), and the study

duration of 24 weeks may not inform what happens to exercise response patterns relative to placebo over shorter or longer exposure periods. Third, 13 patients (4.6%) were not included in this analysis due to CPET technical issues or deviations from the CPET manual of operations.

Conclusions

Our comprehensive prespecified analysis of CPET metrics in the SEQUOIA-HCM randomized clinical trial, including a novel integrated exercise performance metric, showed improved exercise response patterns in patients with obstructive HCM who were treated with aficamten. Improvements in exercise performance correlated with improvements in cardiac structure and function extending beyond reduction in LVOT-G and also with change in symptom burden. These findings offer valuable mechanistic and clinical insights into the beneficial therapeutic effects of aficamten in patients with obstructive HCM.

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Author Contributions: Drs Lewis and Claggett had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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