# Enhancing Exercise Response in Obstructive Hypertrophic Cardiomyopathy

## Insights into the Impact of Aficamten on Patients from SEQUOIA-HCM

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the SEQUOIA-HCM Investigators

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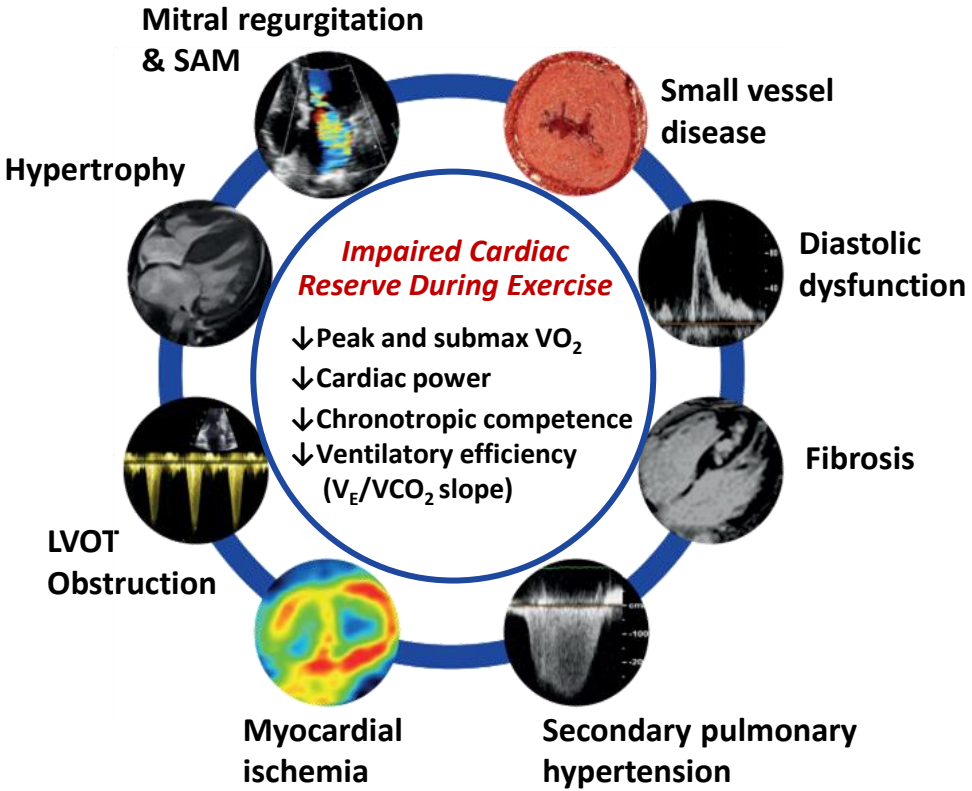
# Background: Exercise Intolerance in Obstructive HCM

**Exercise intolerance is an important clinical feature of obstructive hypertrophic cardiomyopathy (oHCM)**

## With aficamten

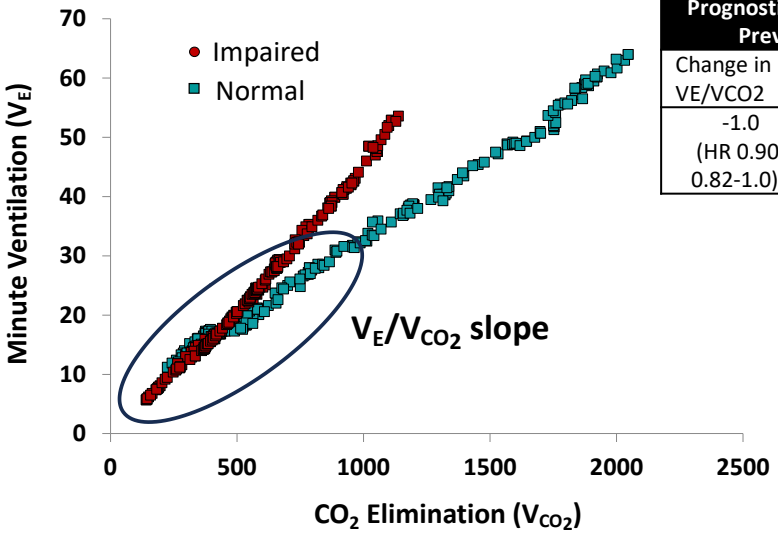
**↓Left Ventricular Outflow Tract Obstruction** → **↑ Exercise Tolerance (Peak Oxygen Uptake [$pVO_2$])**



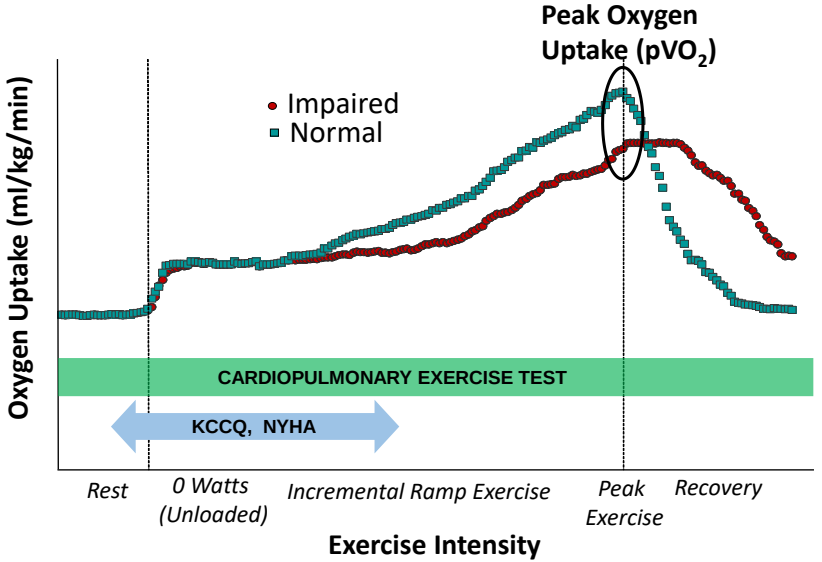

LVOT, left ventricular outflow tract; SAM, systolic anterior motion; $VO_2$, oxygen uptake. $V_E/VCO_2$ slope, slope of increase in minute ventilation (VE) relative to $CO_2$ production. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

# Background: CPET in SEQUOIA-HCM

**Cardiopulmonary exercise testing (CPET) enables objective assessment of all stages of exercise**
**– Ventilatory efficiency ($V_E/VCO_2$ slope) and peak oxygen uptake ($pVO_2$) predict clinical outcomes in oHCM**




| Prognostic Relevance from Previous Studies | |
|---|---|
| Change in VE/VCO2 | Change in Peak VO2 |
| -1.0 (HR 0.90, 0.82-1.0)* | 1.0 (HR 0.82, 0.77 -0.88)* |




**In this prespecified analysis**, we hypothesized that aficamten would improve a novel measure of integrated maximum and submaximum exercise performance, and that changes in $pVO_2$ would relate to clinically important endpoints

KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; $V_E$, minute ventilation; $VCO_2$, carbon dioxide output.
Lewis GD, et al., *Circ Heart Fail* 2022;15(5): p. e008970. *Coats C et al, Circulation HF 2015, N=198, HR for all-cause mortality after adjustment for age, sex, LA size and LVEF

# Methodology and CPET Endpoints

In SEQUOIA-HCM, **282** patients with oHCM were randomized to aficamten or placebo on top of background therapy

**142** patients were randomized to aficamten[a]

**140** patients were randomized to placebo[a]

OR

Patients exercised to maximum capacity at baseline and Week 24. Patients must have had baseline RER ≥1.05 and <90% peak predicted $pVO_2$ to be included in the study

**Primary CPET endpoint:** Integrated exercise performance
- A 2-component Z-score combining $pVO_2$ with reversed $V_E/VCO_2$ slope

**Secondary CPET endpoints:**
- $VO_2$ at AT
- $V_E/VCO_2$
- Ex Duration
- METS
- Circulatory power
- HR reserve
- Pre-VAT $V_E/VCO_2$
- Ventilatory power

[a]9 aficamten- and 10 placebo-treated patients had invalid Week 24 CPET due to technical issues or deviation from CPET MOP, or because they discontinued from the study.
AT, anaerobic threshold; HR, heart rate; METS, metabolic equivalents; MOP, manual of operations; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold.
Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

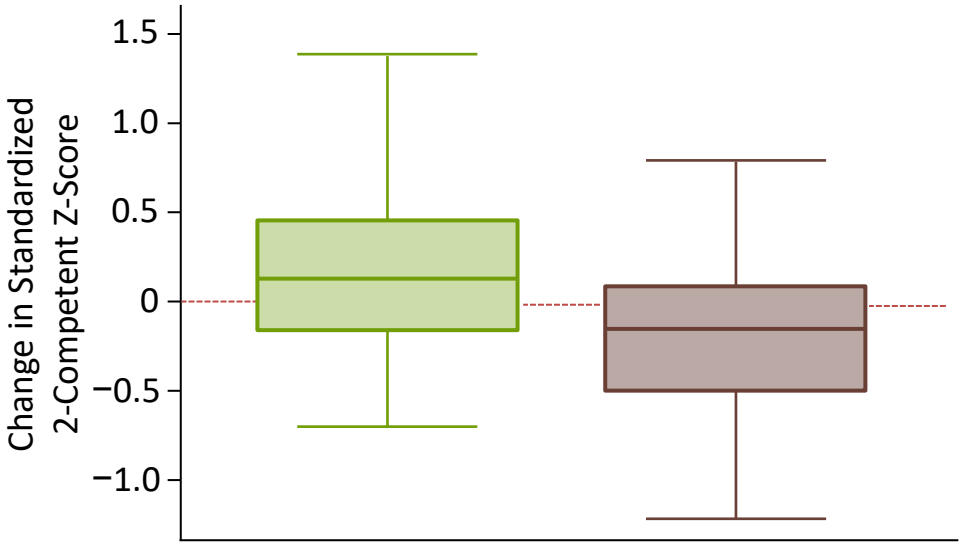
# Results: Baseline and Week 24 Values and Changes in Integrated Exercise Performance

## Integrated Exercise Performance (Z-score $pVO_2$ & $V_E/VCO_2$)

| Adjusted Difference (95% CI) | *P* value |
|---|---|
| 0.35 (0.25, 0.46) | 0.0000000006 |

| AFICAMTEN | |
|---|---|
| Mean ± SD | |
| Baseline | Week 24 |
| −0.01 ± 0.82 | 0.16 ± 0.76 |

| PLACEBO | |
|---|---|
| Mean ± SD | |
| Baseline | Week 24 |
| 0.02 ± 0.75 | −0.17 ± 0.74 |




Adjusted difference corresponds to the least squares mean treatment difference

Integrated exercise performance was defined as the 2-component Z-score of $pVO_2$ and ventilatory efficiency ($V_E/VCO_2$ slope) and will be used in ACACIA-HCM (NCT06081894). The Z-score was derived by reversing the directionality of $V_E/VCO_2$ slope values such that increases in both Z-score components indicate benefit; equal weights were used for each component.

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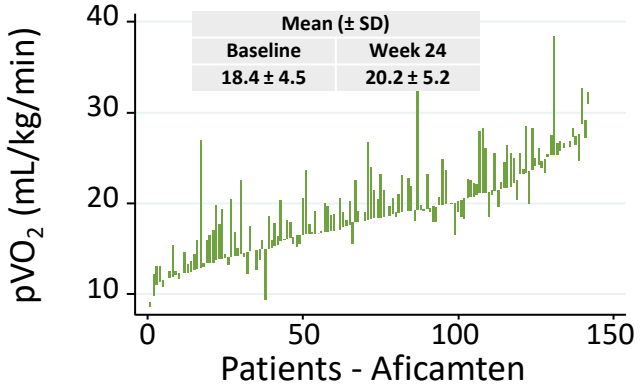
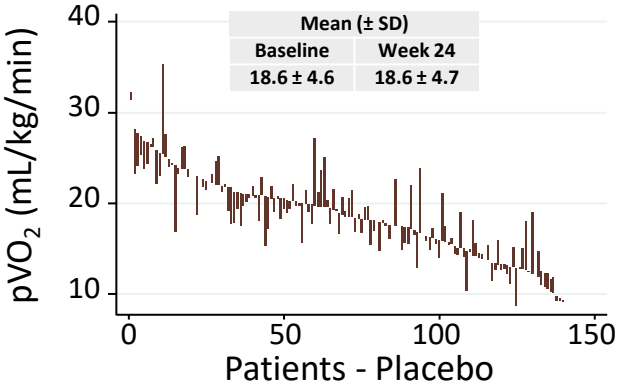
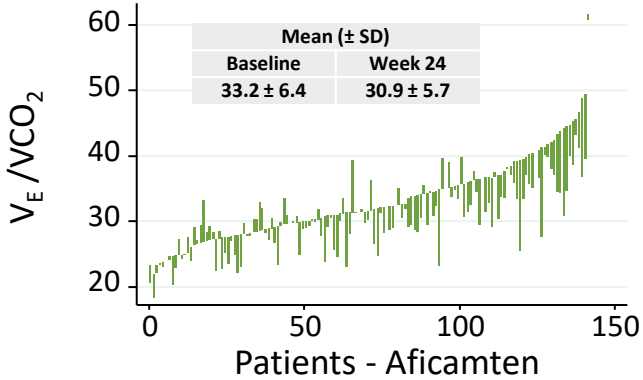
# Results: Baseline and Week 24 Values and Changes in Integrated Exercise Performance Variable Components

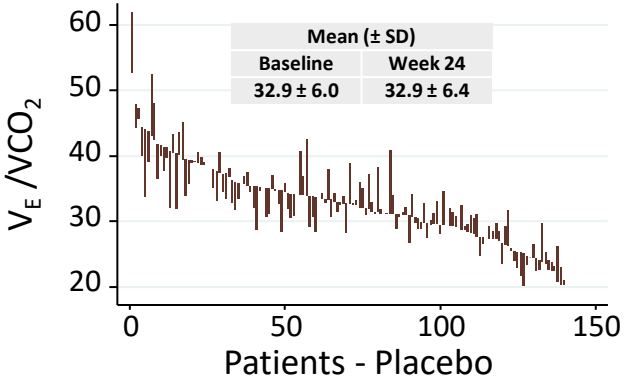



| Adjusted difference (95% CI) | *P* value |
|---|---|
| 1.7 (1.0, 2.4) | <0.001 |



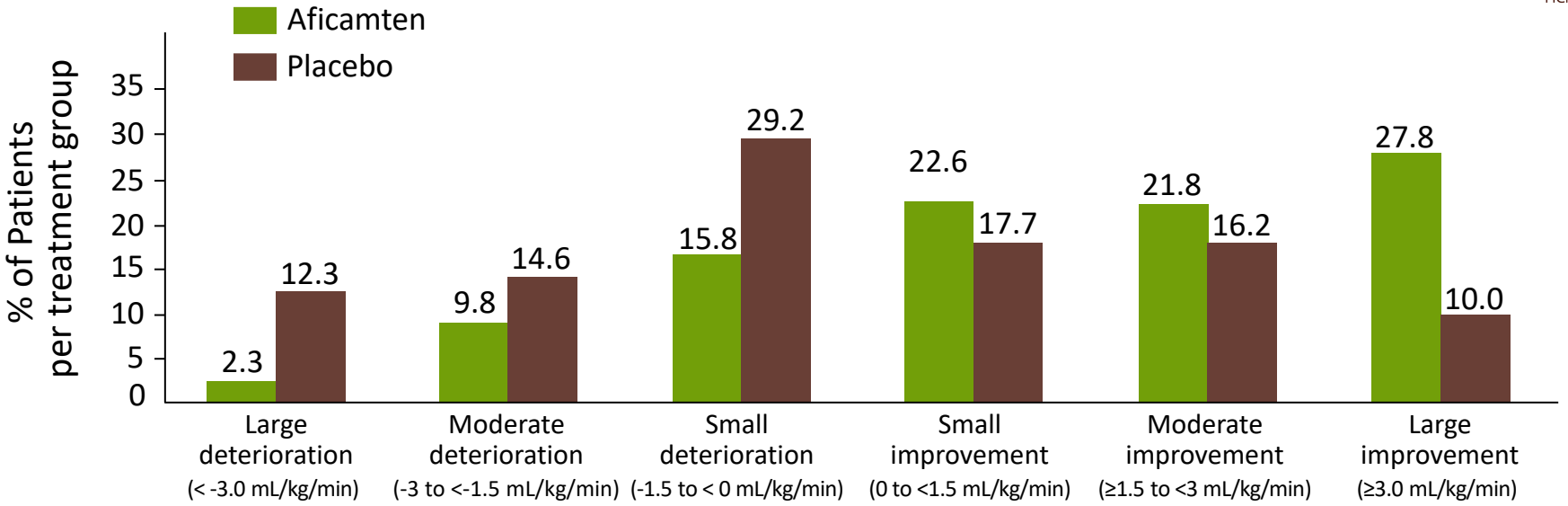




| Adjusted difference (95% CI) | *P* value |
|---|---|
| –2.3 (–3.2, –1.4) | <0.001 |




Adjusted difference corresponds to the least-squares mean treatment difference.

# Results: Categorical Changes in $pVO_2$

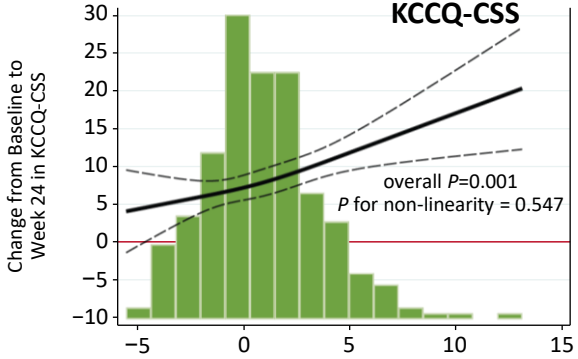


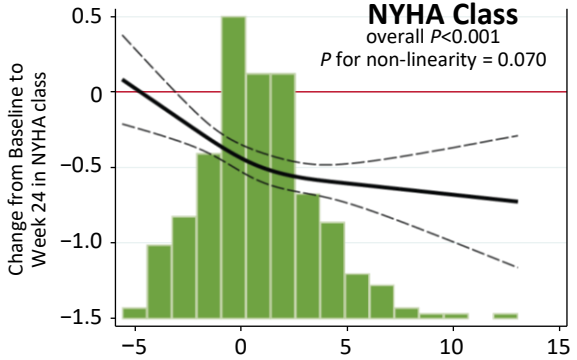

| Outcome | Odds ratio (95% CI) | NNT |
|---|---|---|
| **Any improvement (small/moderate/large)** | 3.32 (1.99, 5.54) | 3.5 |
| **Moderate/large improvement** | 2.78 (1.66, 4.66) | 4.3 |
| **Large improvement** | 3.47 (1.76, 6.83) | 5.6 |

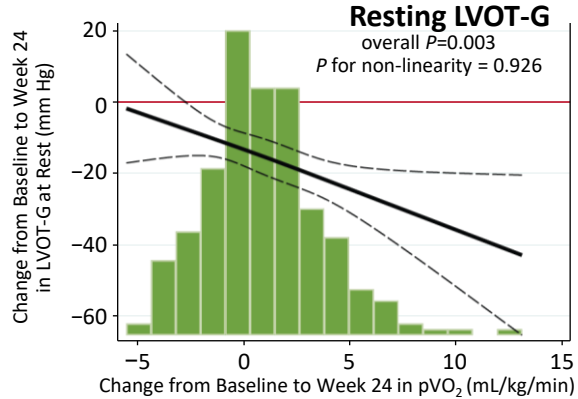
NNT, number needed to treat.

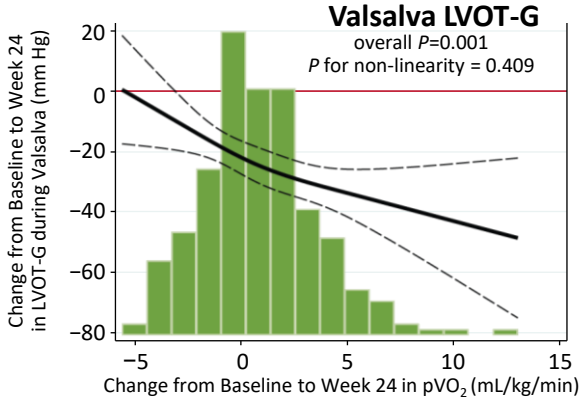
# Results: Relationships between Changes in $pVO_2$ and Changes in other Important Clinical Measures

**Cubic Spline Analyses Relating Changes in $pVO_2$ to Changes in other Clinical Measures**



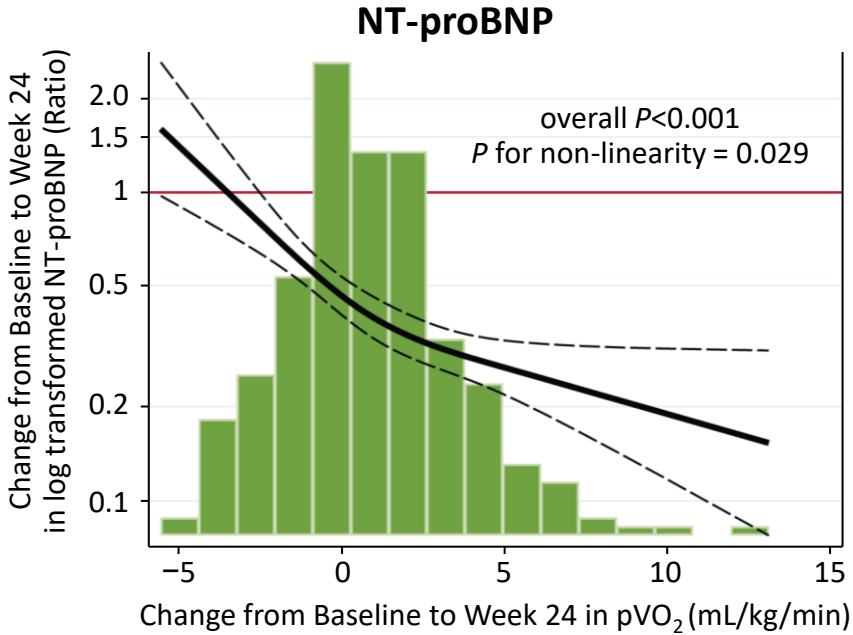



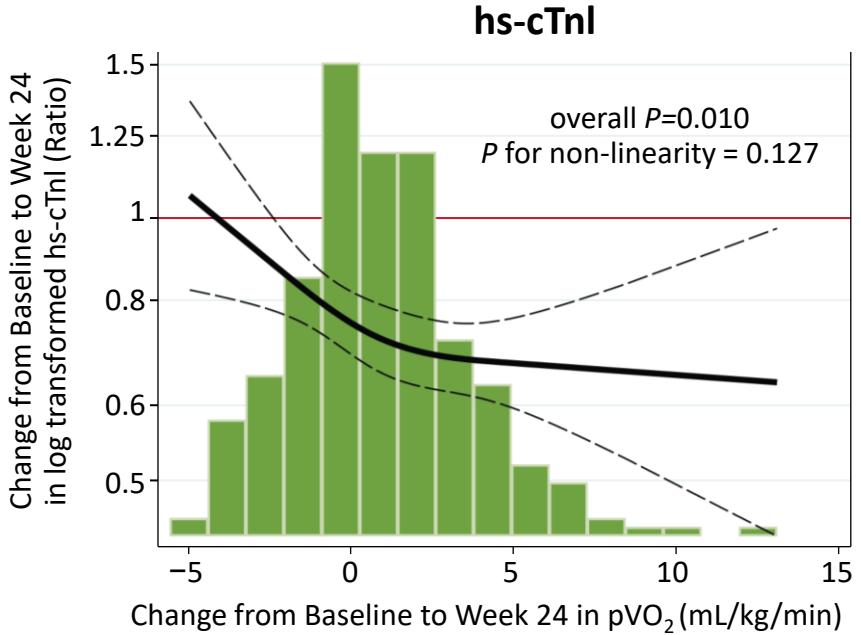




Solid and dotted lines show the association with 95% CIs. Histograms show the distribution of change in $pVO_2$. Red lines indicate no change from baseline.
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

# Results: Relationships between Changes in $pVO_2$ and Changes in Cardiac Biomarkers




In Multivariate Regression, change in logNT-proBNP explained the greatest variance in change in $pVO_2$

Solid and dotted lines show the association correlate with 95% CIs. Histograms show the distribution of change in $pVO_2$.
hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

# Results: CPET Parameters by Treatment Assignment

| CPET variable | Aficamten (n=133) | | | Placebo (n=130) | | | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Week 24 | Absolute diff ± SD[a] | Baseline | Week 24 | Absolute diff ± SD[a] | Adjusted diff (95% CI)[b] | |
| **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, 0.46) | <0.001 |
| **MAXIMUM EXERCISE PARAMETERS** | | | | | | | | |
| **$pVO_2$, mL/kg/min** | 18.4 ± 4.5 | 20.2 ± 5.2 | 1.8 ± 3.1 | 18.6 ± 4.6 | 18.6 ± 4.7 | 0.0 ± 2.7 | 1.7 (1.0, 2.4) | <0.001 |
| **Peak workload, watts** | 120 ± 40 | 134 ± 50 | 14 ± 27 | 126 ± 43 | 127 ± 44 | 1 ± 21 | 12 (6, 18) | <0.001 |
| **Peak METS, mL/kg/min** | 5.3 ± 1.3 | 5.8 ± 1.5 | 0.51 ± 0.89 | 5.3 ± 1.3 | 5.3 ± 1.3 | 0.00 ± 0.78 | 0.49 (0.29, 0.69) | <0.001 |
| **Peak circulatory power, mmHg·mL/min/kg** | 3013 ± 924 | 3550 ± 1140 | 537 ± 995 | 3160 ± 1136 | 3074 ± 1152 | −86 ± 731 | 586 (379, 793) | <0.001 |
| **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, 1.4) | <0.001 |
| **HR reserve, beats/min** | 59 ± 18 | 66 ± 22 | 7 ± 15 | 57 ± 19 | 59 ± 20 | 1 ± 10 | 6 (3, 9) | <0.001 |
| **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, 0.02) | =0.84 |
| **SUBMAXIMUM EXERCISE PARAMETERS** | | | | | | | | |
| **Ventil efficiency pre-VAT, $V_E/VCO_2$ 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, −0.6) | =0.002 |
| **All of exercise, $V_E/VCO_2$ 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, −1.4) | <0.001 |
| **Ventil power, mmHg** | 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, 1.1) | <0.001 |
| **$VO_2$ at anaerobic threshold, mL/min** | 898 ± 266 | 958 ± 276 | 60 ± 107 | 931 ± 261 | 927 ± 257 | −3 ± 108 | 59 (33, 85) | <0.001 |
| **$VO_2$/work slope, mL/min/watt** | 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, 0.6) | =0.22 |

Data are shown as mean ± SD unless otherwise specified. Green indicates significant *P* value. Adjusted diff, least-squares mean treatment difference.
[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 $pVO_2$ and ventilatory efficiency ($V_E/VCO_2$ slope). The Z-score was derived by reversing the directionality of $V_E/VCO_2$ slope values such that increases in both Z-score components indicate benefit; equal weights were used for each component. Diff, difference; LSM, least square mean; Ventil, ventilatory.

# Conclusions

- Our comprehensive prespecified analysis of CPET metrics in SEQUOIA-HCM demonstrates significant improvement in:
  - A novel integrated exercise performance metric combining maximal and submaximal exercise parameters ($pVO_2$ and $V_E/VCO_2$)
  - Multiple other measures of exercise performance
- Enhanced exercise responses correlated with significant improvements in cardiac structure and function extending beyond reduction in LVOT-Gradient
- These findings offer valuable mechanistic and clinical insights into the beneficial therapeutic effects of aficamten in patients with oHCM

# Acknowledgments

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