IMPROVEMENT IN ECHO MEASURES OF DIASTOLIC FUNCTION REFLECTS IMPROVED EXERCISE PERFORMANCE IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: INSIGHTS FROM THE SEQUOIA-HCM TRIAL

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BACKGROUND/OBJECTIVE

- A key feature of obstructive hypertrophic cardiomyopathy (oHCM) is impaired exercise capacity (impacts quality of life and is a determinant of clinical outcomes).
- The mechanistic link between echo structural and functional changes, and CPET metrics of exercise capacity remains poorly defined.
- Understanding the mechanisms of exercise intolerance in oHCM remains essential to optimizing patient care.

This study assesses the relationships between changes in echo parameters and CPET metrics in patients with oHCM from the SEQUOIA-HCM trial, independent of treatment arm (aficamten or placebo).

CPET metrics included:

- pVO_2
- VE/VCO_2
- Composite peak & submaximal exercise (CPSE) Score
  - ➢ *Mean of standardized changes in peak VO_2 and inverse VE/VCO_2 slope (higher = better performance)*

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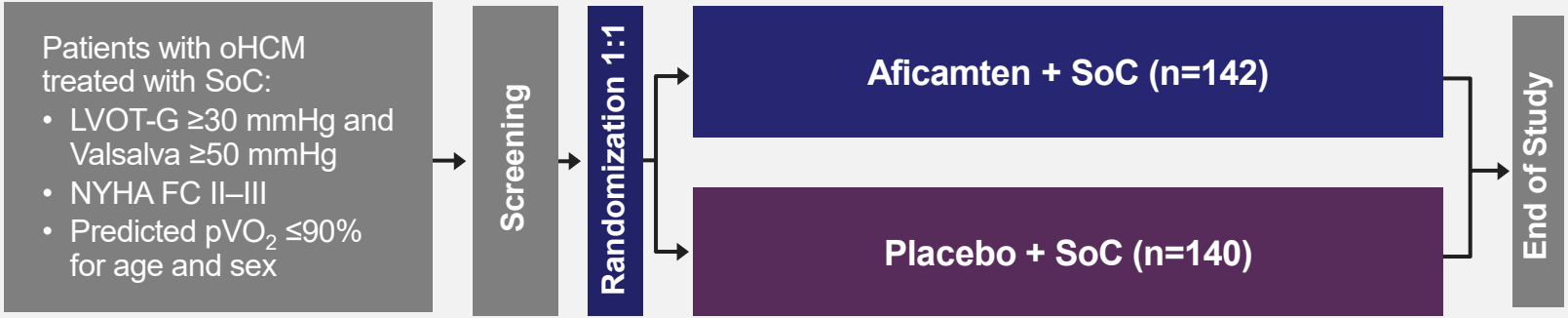
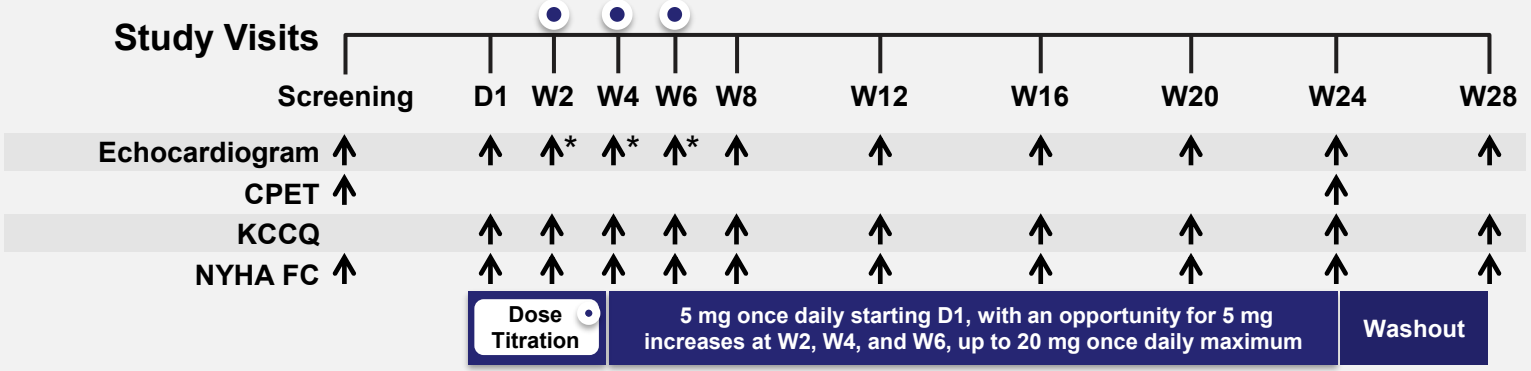
METHODS: SEQUOIA-HCM STUDY DESIGN





Echocardiographic measurements were performed by a core imaging laboratory.

CPET, cardiopulmonary exercise testing; D, day; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left outflow tract gradient; NYHA FC, New York Heart Association functional class; SoC, standard of care; W, week. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

Results: Baseline Characteristics

Clinical Characteristics	N=282
Age, years	59.1 ± 12.9
Male sex	167 (59)
Race	
Asian	54 (19)
Black or African American	3 (1)
White	223 (79)
Hypertension	145 (51)
Pathogenic sarcomere variant	49 (17)
Atrial fibrillation	44 (16)
Diabetes	23 (8)
Beta-blocker	173 (61)
Calcium channel blocker	97 (34)
KCCQ-CSS	75 ± 18
NYHA Class III/IV	68 (24)
NT-proBNP, pg/mL	788 [346, 1699]

Echo Characteristics	
LVOT-G, rest, mmHg	55 ± 30
LVOT-G, Valsalva, mmHg	83 ± 32
Interventricular septal wall, cm	1.9 ± 0.3
Inferolateral wall, cm	1.3 ± 0.3
LVMi, g/m^2	132 ± 34
LVEDVi, mL/m^2	36 ± 9
LVEF, %	75 ± 6
Abs. LVGLS, %	15.4 ± 3.2
TAPSE, cm	2.1 ± 0.4
RV S' vel, cm/sec	13 ± 3
LAVi, mL/m^2	41 ± 14
Peak E-wave vel, cm/s	85 ± 29
Lateral E/e'	16 ± 8

CPET Characteristics	
CPSE Score	0.0 ± 0.8
Peak VO_2, mL/kg/min	18.5 ± 4.5
VE/VCO_2 slope	33.0 ± 6.1

Abs. LVGLS = Absolute Left Ventricular Global Longitudinal Strain; CPET = Cardiopulmonary Exercise Testing; CPSE = Composite peak & submaximal exercise; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LAVi = Left Atrial Volume Index; LVEDVi = Left Ventricular End-Diastolic Volume Index; LVEF = Left Ventricular Ejection Fraction; LVMi = Left Ventricular Mass Index; LVOTg = Left Ventricular Outflow Tract Gradient; NT-proBNP = N-terminal pro–B-type Natriuretic Peptide; NYHA = New York Heart Association; RV S′ vel = Right Ventricular Systolic (S′) Velocity; TAPSE = Tricuspid Annular Plane Systolic Excursion; VE/VCO_2 slope = Minute Ventilation to Carbon Dioxide Production Slope; VO_2 = Oxygen Uptake.

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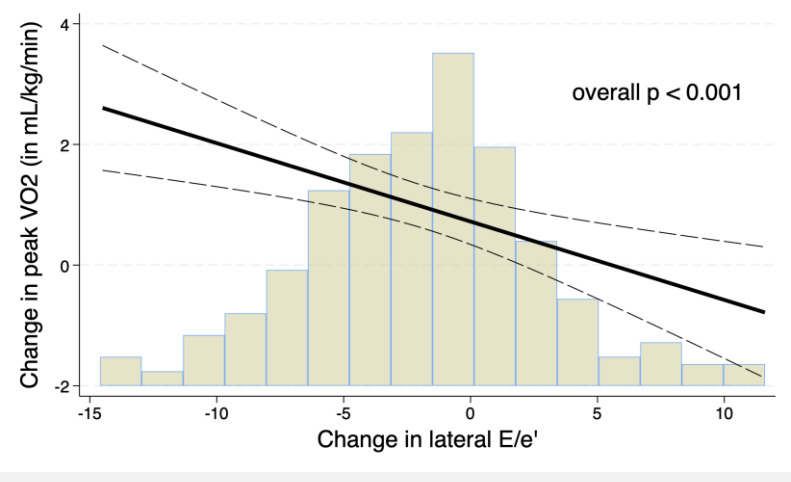
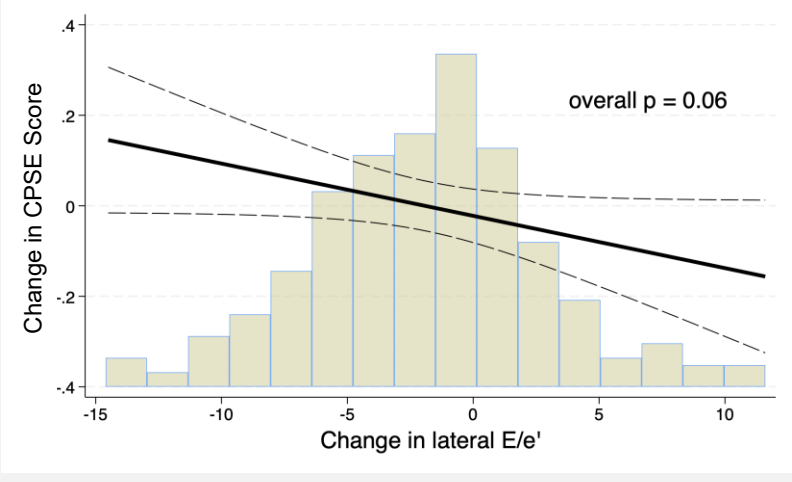
Results: Change in Lateral E/e'

vs Change in peak VO_2



vs Change in CPSE Score



CPSE Score:*
Represents the mean of standardized changes in peak VO_2 and inverse VE/VCO_2 slope (higher values = better performance)

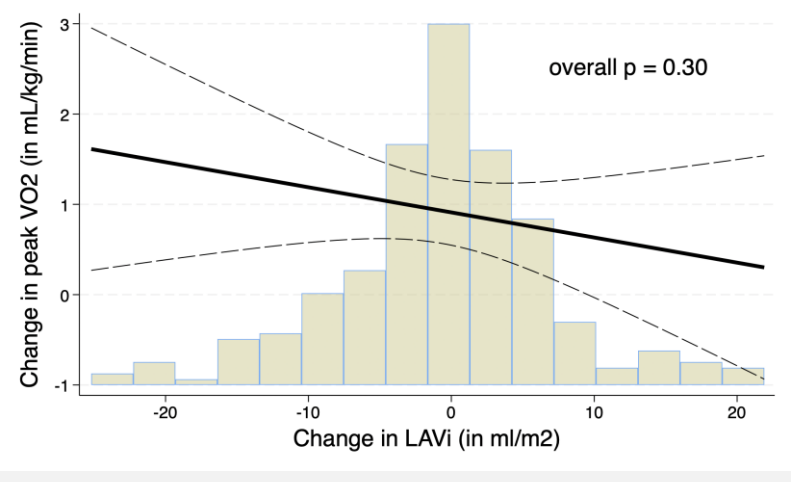
Panels demonstrate multivariable linear regression adjusted for baseline lateral E/e' and CPET values, and treatment arm.

VE/VCO_2 slope = Minute Ventilation to Carbon Dioxide Production Slope; VO_2 = Oxygen Uptake.

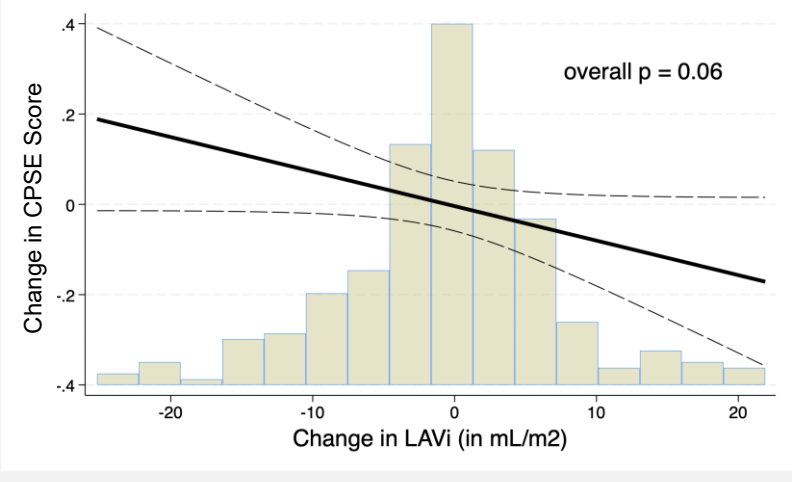
*Lee MMY, et al. Aficamten and Cardiopulmonary Exercise Test Performance: A Substudy of the SEQUOIA-HCM Randomized Clinical Trial. *JAMA Cardiol.* 2024;9:990-1000

Results: Change in LA Volume index

vs Change in peak VO_2



vs Change in CPSE Score

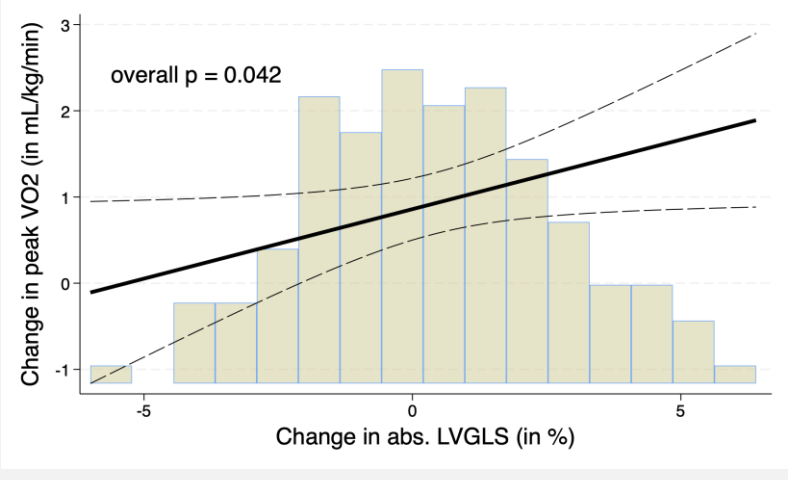


Panels demonstrate multivariable linear regression adjusted for baseline lateral E/e' and CPET values, and treatment arm.

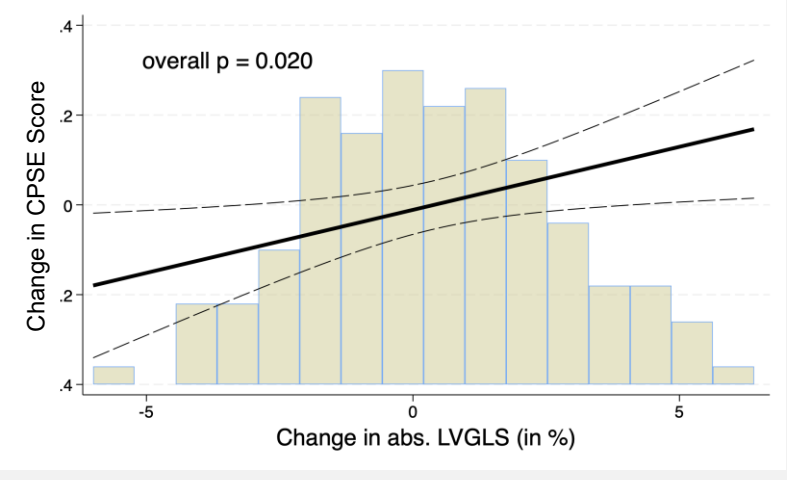
LAVi = Left Atrial Volume Index; VO_2 = Oxygen Uptake.

Results: Change in Absolute LV GLS

vs Change in peak VO_2



vs Change in CPSE Score



GLS presented as absolute values; lower values indicate impaired function

Panels demonstrate multivariable linear regression adjusted for baseline lateral E/e' and CPET values, and treatment arm.

Abs. LVGLS = Absolute Left Ventricular Global Longitudinal Strain; VO_2 = Oxygen Uptake.

RESULTS

- No significant association was found between changes in CPET metrics and changes in other echo parameters, after adjusting for treatment (LVOT-G at rest and Valsalva, IVS wall thickness, IL wall thickness, LVMi, LVEDVi, LVEF, TAPSE, RV S' vel, peak E-wave vel).

LIMITATIONS

- Echo assessments were performed at rest and may not fully capture exercise hemodynamics.

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CONCLUSIONS

In this secondary analysis of SEQUOIA-HCM, including 282 patients with echo and CPET follow-up:

- Improvement in myocardial mechanics (GLS) and E/e' were both associated with enhanced exercise capacity after 24 weeks, independent of treatment.
- Changes in measures of diastolic function correlated with changes in exercise performance, supporting echo parameters as useful surrogate markers for exercise tolerance.
- These findings underscore diastolic dysfunction as a central pathophysiologic feature of oHCM.

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THANK YOU

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