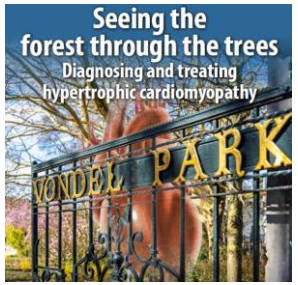
Improving quality of life in hypertrophic cardiomyopathy

Carolyn Ho, MD

Brigham and Women's Hospital – Harvard Medical School

Boston, MA, USA

Seeing the forest through the trees - Diagnosing and treating hypertrophic cardiomyopathy



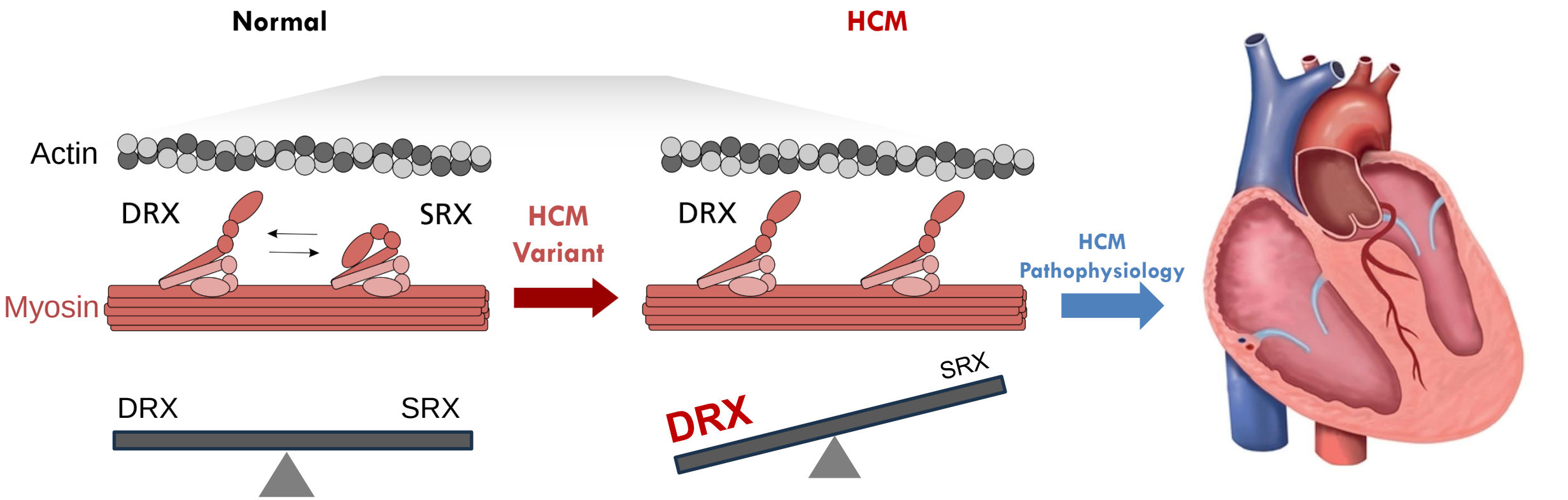
PHYSICIANS' ACADEMY FOR PACE-CME CARDIOVASCULAR EDUCATION

Disclosures

- Research Support
  - Bristol Myers Squibb
  - Pfizer
  - Cytokinetics
  - Biomarin
  - Tenaya

- Consulting/Advisory Boards/Honoraria
  - Bristol Myers Squibb
  - Cytokinetics
  - Tenaya
  - Biomarin
  - Viz.ai
  - Lexicon

HCM sarcomere variants increase force generation and impair sarcomere relaxation



- normal contractility
- optimal DRX/SRX ratio
- effective relaxation

shift toward DRX:

- ↑ 5x higher ATP consumption
- ↑ hypercontractility
- ↓ cellular relaxation

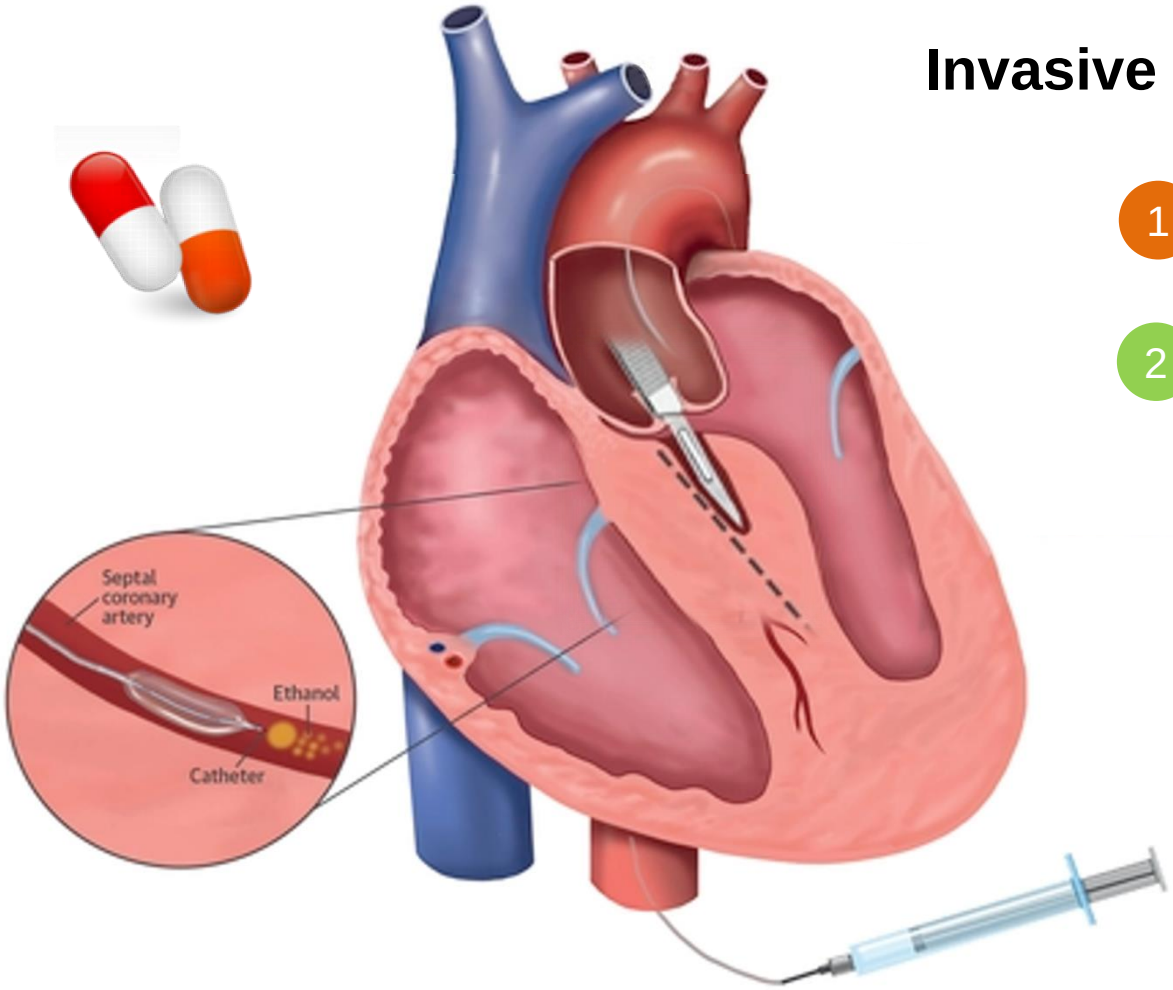
Hypercontractile LV function
Diastolic dysfunction
Fibrosis
Impaired energetics

Adapted from: Toepfer CN, et al. *Circulation*. 2020. Slide courtesy of Eric Wei, MD, PhD

Traditional therapies to reduce LVOT obstruction and improve symptoms

Medical

1. Beta blockers
2. CCB (verapamil, diltiazem)
3. Disopyramide



Invasive Septal Reduction Therapy

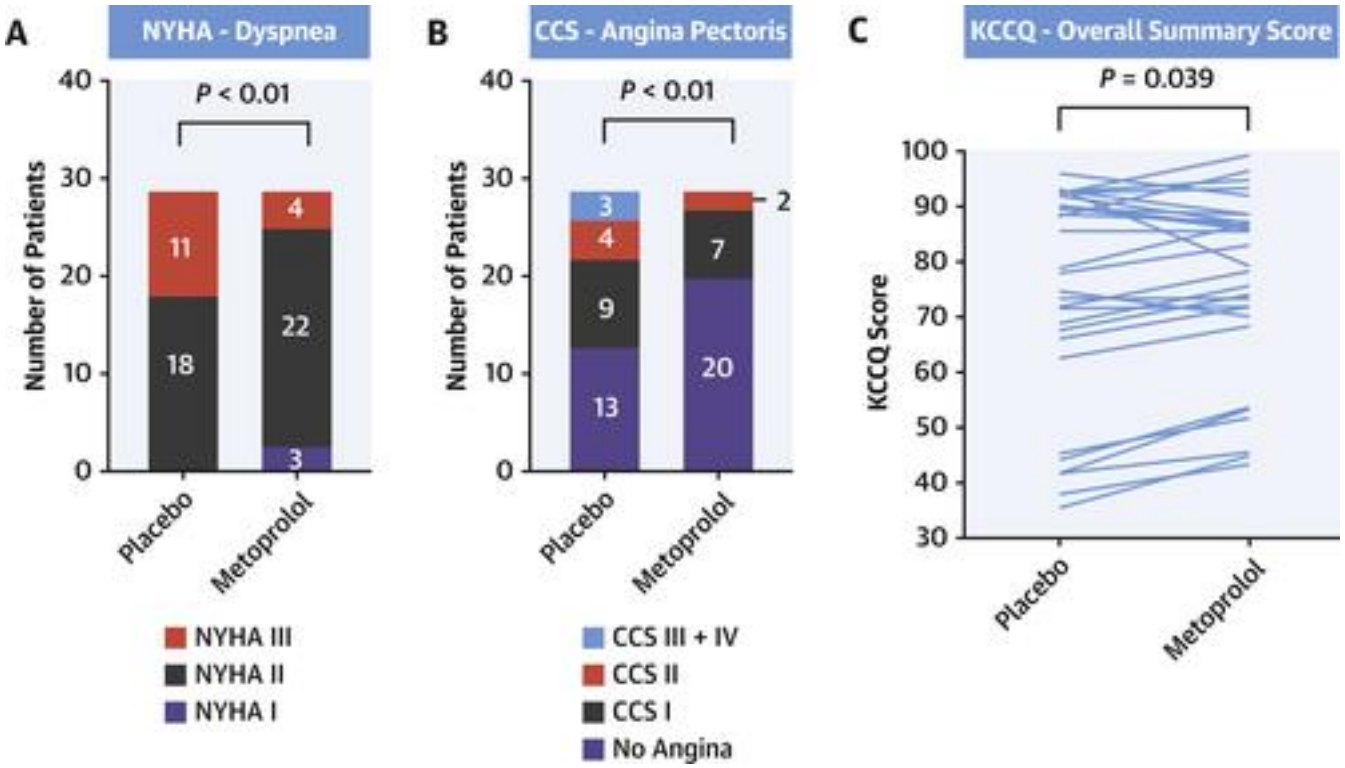
1. Alcohol septal ablation
2. Myectomy

Traditional therapies treat symptoms but do not target underlying disease biology.

Slide courtesy of Eric Wei, MD, PhD

Metoprolol versus Placebo

Improved NYHA Functional Class, CCS Class, and KCCQ Overall Summary Score



- N=29
  - Mean age 60y, 62% male
  - 62% NYHA II
- 14 days placebo or metoprolol up to 150 mg (7 days at steady state) then cross-over

No improvement in:

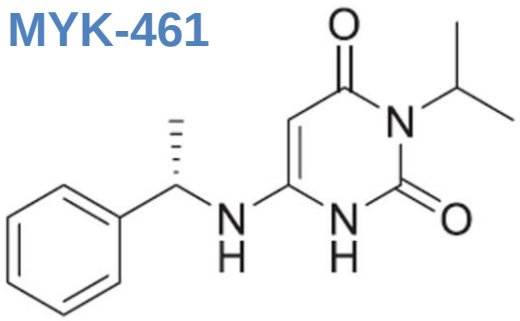
- **Exercise capacity**
- **pVO2**
- **NTproBNP**

Anne M. Dybro et al. *J Am Coll Cardiol* 2021; 78:2505-2517.

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

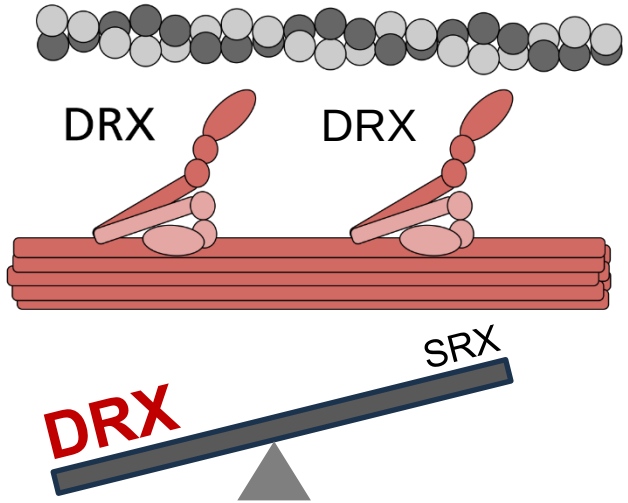
Cardiac myosin inhibitors target HCM pathophysiology

MYK-461

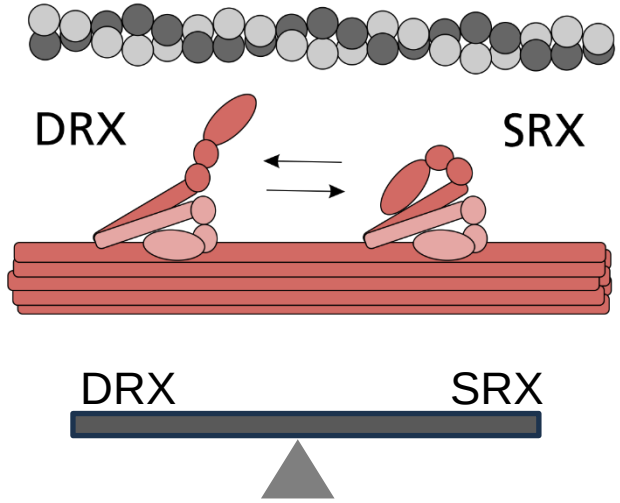


- **Mavacamten: allosteric inhibitor of myosin ATPase**
- Improves balance of myosins in the SRX/DRX conformations
- Reduces number of myosin-actin cross-bridges → decreases contractility

HCM mutation



MYK-461



↑ contractility

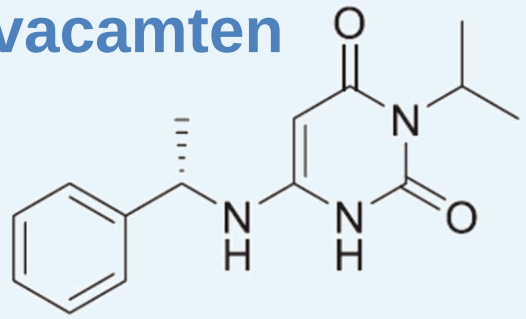
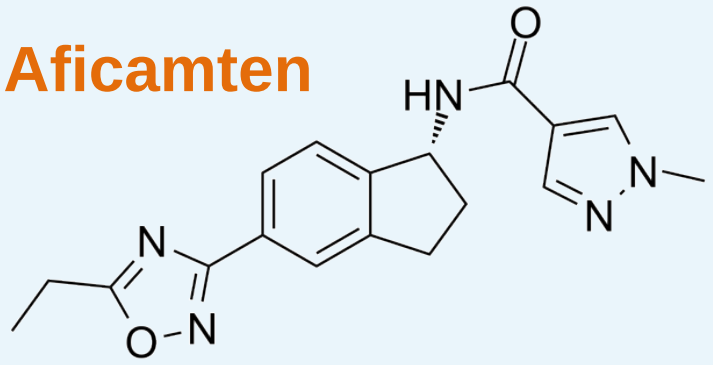
↓ relaxation and energetics

↓ hypercontractility

↑ compliance and energetics

Anderson RL, et al. *PNAS* 2018; Toepfer CN, et al. *Circulation*. 2020. Slide courtesy of Eric Wei, MD, PhD

Mavacamten vs Aficamten

	Mavacamten	Aficamten
		
Manufacturer	Bristol Myers Squibb™ MYOKARDIA	Cytokinetics
Half life	7-9 days	3-4 days
Induction of cytochrome P450 isoenzymes	CYP 3A4, CYP2C9, CYP2C19, and CYP2B6	no significant interaction

Slide courtesy of Eric Wei, MD, PhD

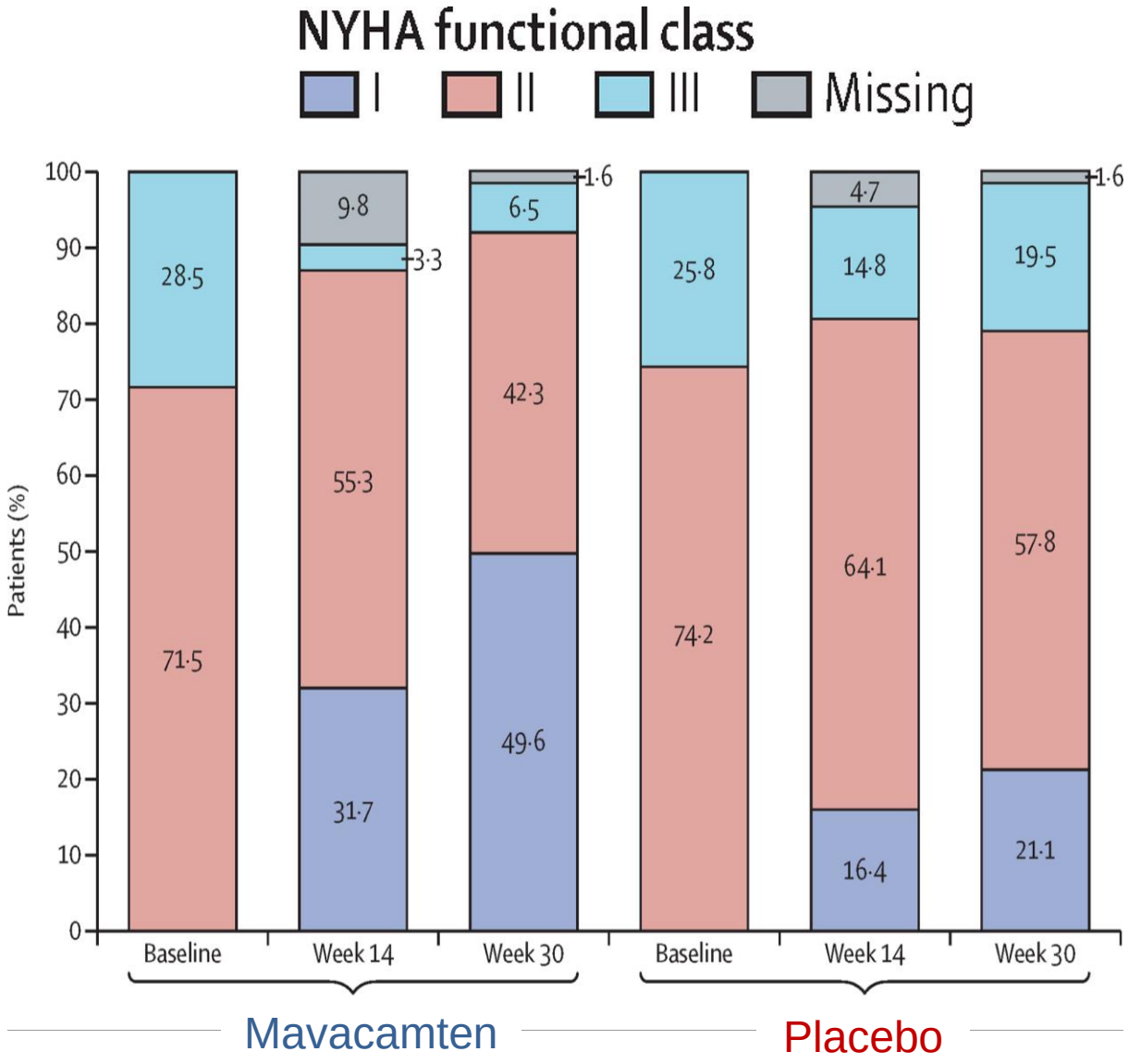
CMI Trial Outcomes: feel and function

EXPLORER-HCM: PRIMARY ENDPOINT

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Difference (95% CI) P value
EITHER ≥1.5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement **OR** ≥3.0 ml/kg/min increase in pVO_2 with no worsening of NYHA class	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1) 0.0005
BOTH ≥3.0 ml/kg/min increase in pVO_2 **AND** ≥1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.0, 21.0) 0.0005*

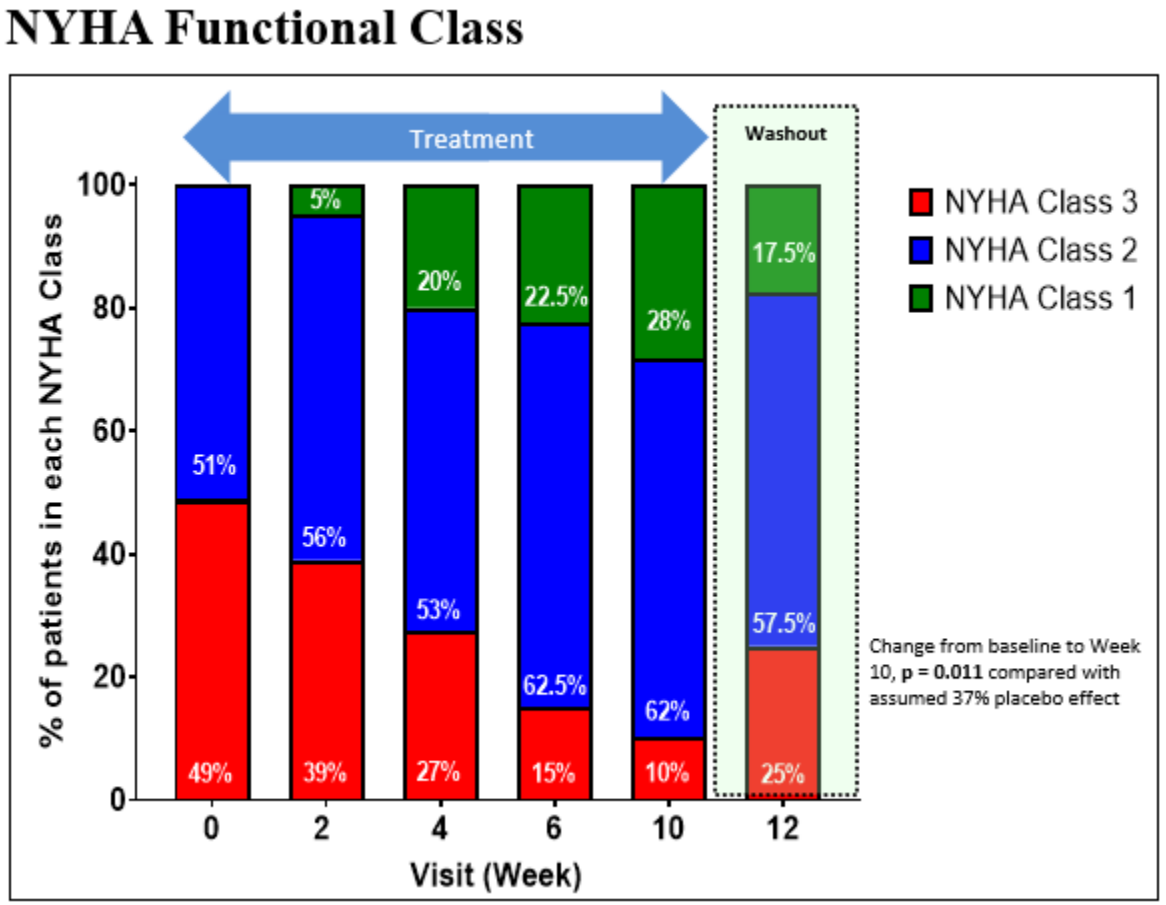
Olivotto, et al. *Lancet*. 2020

EXPLORER-HCM



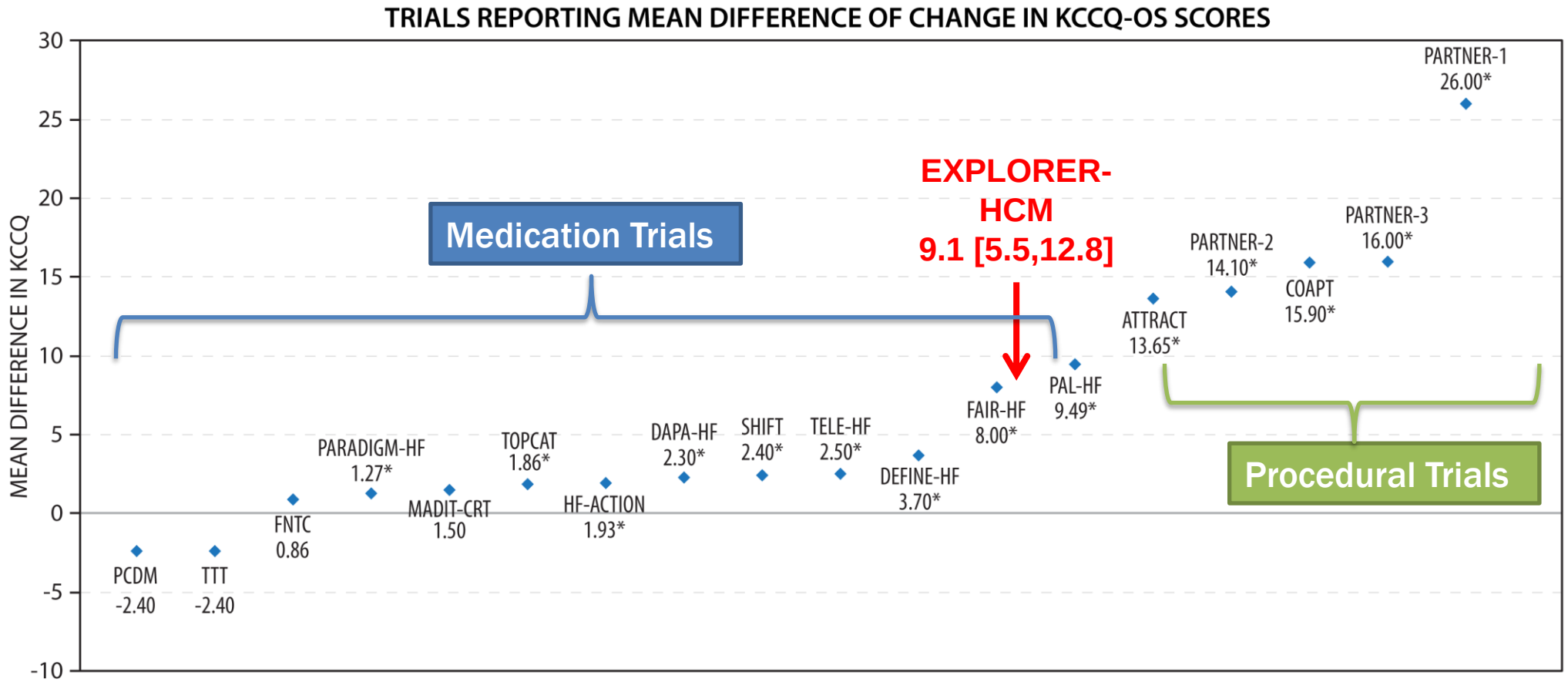
Olivotto, et al. *Lancet*. 2020

REDWOOD-HCM



Masri A, ESC HF 2023

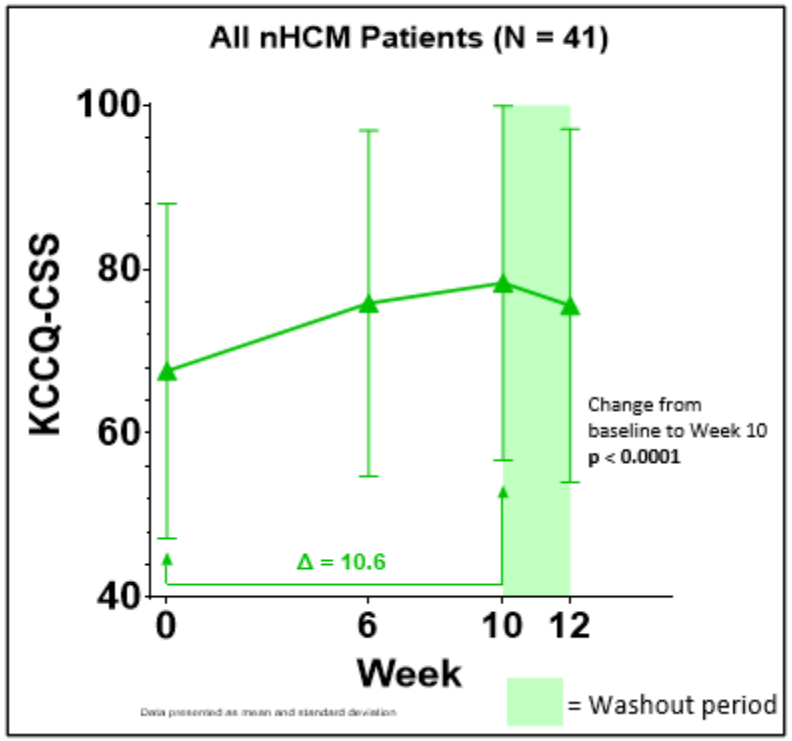
EXPLORER-HCM: MEAN KCCQ-OS IMPROVEMENT GREATER THAN MOST MEDICATION TRIALS

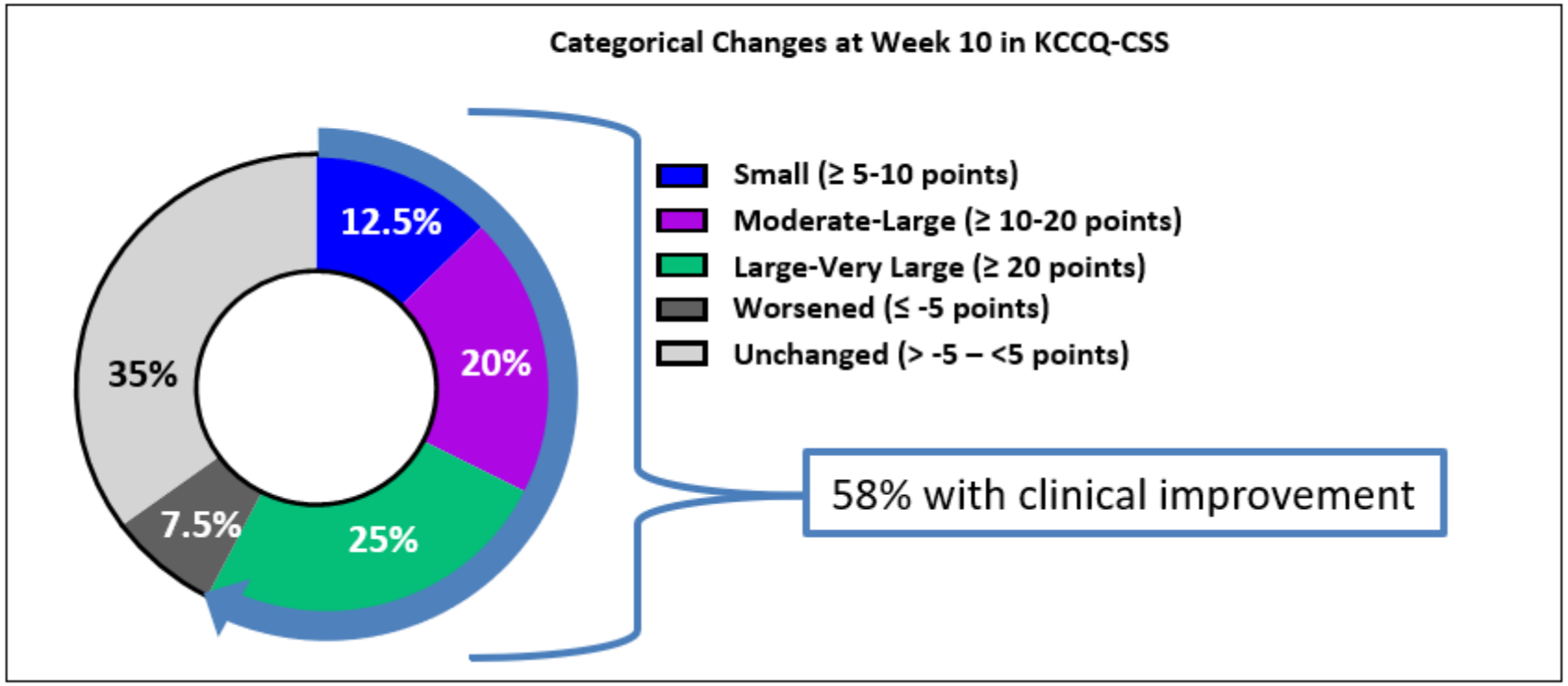


Spertus, et al. *Lancet.* 2021

REDWOOD-HCM: Cohort 4

Kansas City Cardiomyopathy Questionnaire





Mean improvement 10.6 points

Masri A, ESC HF 2023

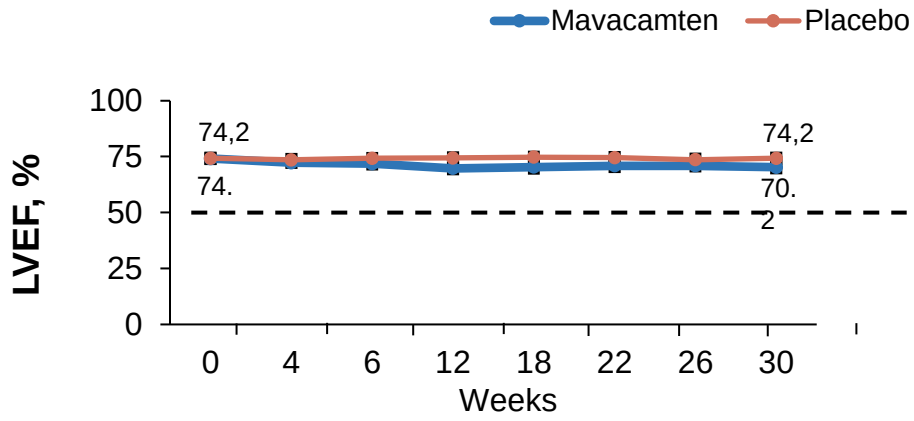
VALOR-HCM

Mavacamten provided adequate clinical improvement for patients to defer invasive SRT

Desai, et al. *J Am Coll Cardiol* 2022

EXPLORER-HCM

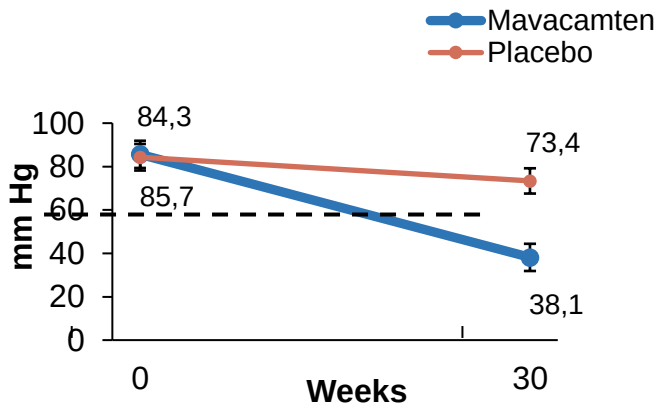
Modest Change in LVEF



Number of patients at visit

Mavacamten	123	116	115	111	111	107	113	114
Placebo	128	115	117	120	119	121	121	119

Large Decrease in LVOT Gradient



Number of patients at visit

Mavacamten	122	118
Placebo	127	123

Some patients (~7%) had more dramatic (reversible) decrease in LVEF (<50%)

US FDA REMS Program

Olivotto, et al. *Lancet.* 2020

WHERE DO MYOSIN INHIBITORS CURRENTLY FIT INTO PRACTICE?

SYMPTOMATIC OBSTRUCTIVE HCM

Exploratory: Test the impact of improving obstruction

- Does gradient reduction improve symptoms in patients with multiple comorbidities?

"Destination Therapy"

Long term medical therapy

Bridge to decision for invasive septal reduction therapy

FUTURE:

- Long-term safety/efficacy
- 1st line therapy
- Non-obstructive HCM
- Pediatric HCM
- Disease modification

JUST
relax

CMIs in *non-obstructive* HCM: Phase 3 Trials

ODYSSEY - Mavacamten
ACACIA – Aficamten

AFICAMTEN CLINICAL TRIALS

REDWOOD HCM	SEQUOIA HCM	FOREST HCM	MAPLE HCM
Phase II dose-finding trial of aficamten in oHCM	**Phase III trial of aficamtem in oHCM**	**Aficamten long term extension**	**Aficamten vs metoprolol**
Jan 2020 – June 2023	Feb 2022 – Sep 2023	May 2021 – March 2026	June 2023 – Oct 2025

Aficamten Phase III Study: SEQUOIA-HCM

Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of *Aficamten* (CK-3773274) in Adults With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

SEQUOIA HCM: Phase 3 Trial Design Highlights

Patient Population:

- Enroll 270 patients, randomized on a 1:1 basis to receive *aficamten* or placebo in addition to standard-of-care treatment
- **Regions: United States, United Kingdom, European Union, Israel, and China**
- **Symptomatic oHCM Patients**
  - **LVOT-G: Resting ≥30mmHg and post-Valsalva ≥50mmHg**
  - **NYHA Class II or III**
- **Standard of Care medications**
  - **Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or calcium channel blocker.**

LVOT-G, Left Ventricular Outflow Tract Gradient; NYHA, New York Heart Association; oHCM, Obstructive Hypertrophic Cardiomyopathy

SEQUOIA-HCM: CY 6031 Study Will Evaluate the Effects of Treatment With Aficamten (CK-3773274) Over a 24-week Period on Cardiopulmonary Exercise Capacity and Health Status in Patients With Symptomatic oHCM (SEQUOIA-HCM). ClinicalTrials.gov Identifier: NCT05186818. Updated March 13, 2023. Accessed April 3, 2023. https://www.clinicaltrials.gov/ct2/show/NCT05186818

SEQUOIA-HCM: Primary Objective/Endpoint

Primary Objective	Primary Endpoint
To evaluate the effect of *aficamten* on exercise capacity in patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)	• Change in peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing (CPET) from Baseline to Week 24

SEQUOIA-HCM: Secondary Objective/Endpoint

To evaluate the effect of *aficamten* on:	Secondary Endpoint
Health status	• Change in Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) from Baseline to Week 12 and Week 24
New York Heart Association (NYHA) Functional Classification	• Proportion of patients with ≥ 1 NYHA Class improvement from Baseline to Week 12 and Week 24
Post-Valsalva left ventricular outflow tract gradients (LVOT-G)	• Change in post-Valsalva LVOT-G from Baseline to Week 12 and Week 24 • Proportion of patients with post-Valsalva LVOT-G <30 mmHg
Exercise capacity	• Change in Total Workload during cardiopulmonary exercise test (CPET) from Baseline to Week 24
Duration of eligibility for septal reduction therapy	• Duration of eligibility for septal reduction therapy (SRT) during the 24-week treatment period in patients who were eligible for SRT at baseline

SEQUOIA HCM: Safety Endpoints

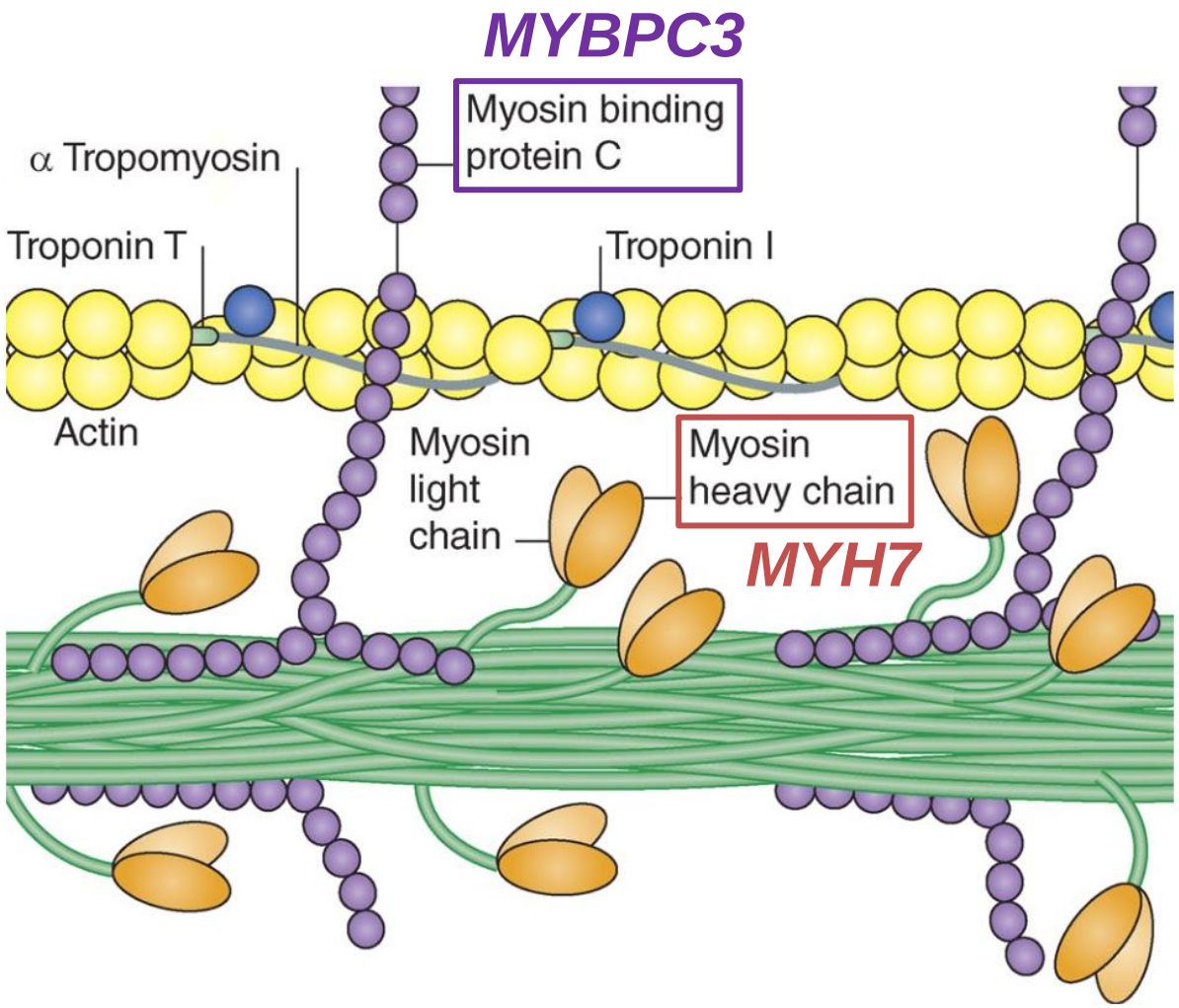
- **Incidence of reported major adverse cardiac events (cardiovascular [CV] death, cardiac arrest, non-fatal stroke, non-fatal myocardial infarction, CV hospitalization)**
- **Incidence of new onset persistent atrial fibrillation**
- **Incidence of appropriate implantable cardiac defibrillator (ICD) discharges and aborted sudden cardiac death**
- **Incidence of left ventricular ejection fraction (LVEF) <50%**
- **Incidence of treatment emergent adverse events**

HCM Genetics

- **Genetic testing is (+) in:**
  - **30%** of all-comers with HCM
  - **>60%** of HCM with (+)FH

- Variants in **Sarcomere Genes** are most definitively and frequently associated with HCM

- ***MYH7*** and ***MYBPC3*** collectively account for >80% of all clinical cases of HCM in which the underlying mutation has been defined.



Teekakirikul, P. *et al.* (2012) 'Hypertrophic cardiomyopathy: translating cellular cross talk into therapeutics', *JCB*, 199(3), pp. 417–421.