Standard and Novel Therapies for HCM – Thresholds and Interplay

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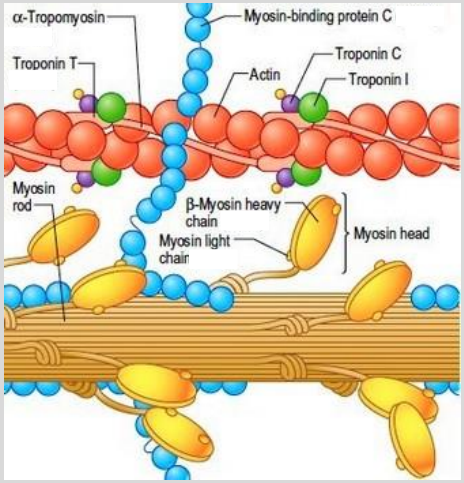
Disclosures

- Consulting Honoraria: BMS/MyoKardia, Inc.
- Steering Committee Member for the DISCOVER-HCM Registry

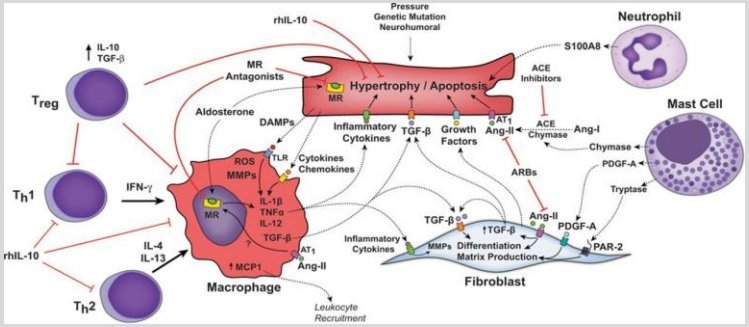
Pathogenesis of Hypertrophic Cardiomyopathy

1



Pathogenic Genetic Variant

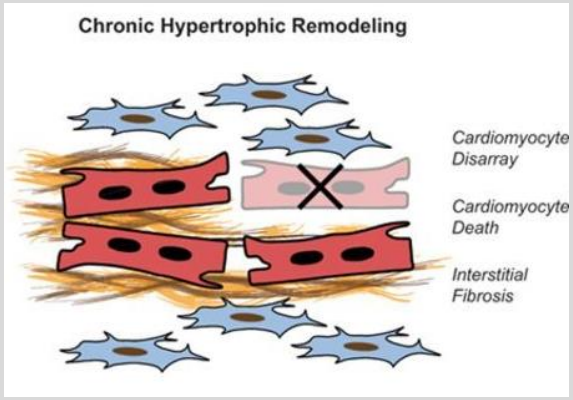
2



Adverse Remodeling

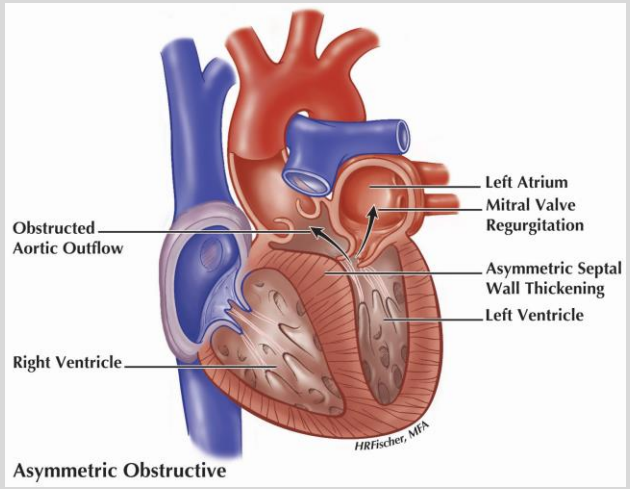
3

Cellular Changes



Pathologic Hypertrophy

4



Adapted from: Spirito et al. NEJM. 1997; 336:775-785.
Frieler & Mortensen. Circulation. 2015;131:1019-1030.

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No Disease-Modifying Therapies for HCM

Non-obstructive HCM (nHCM)

NYHA Class II-IV; LVEF ≥50% →
- β-blocker, verapamil or diltiazem
- Diuretics

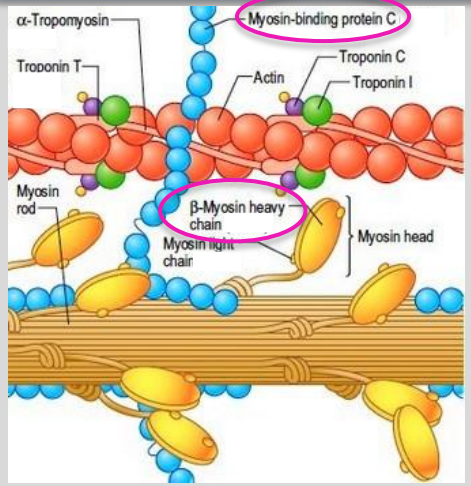
NYHA Class II-IV; LVEF < 50% →
- β-blocker
- ACE inhibitor, ARB or ARNI
- Diuretics
- MRA
- Advanced HF therapies

Obstructive HCM (oHCM)

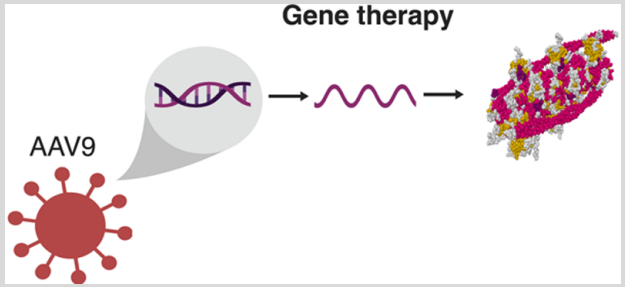
NYHA Class I →
- β-blocker, verapamil or diltiazem

NYHA Class II-IV →
- Non-vasodilating β-blocker, verapamil, diltiazem
- Disopyramide
- Diuretics
- Septal reduction therapy

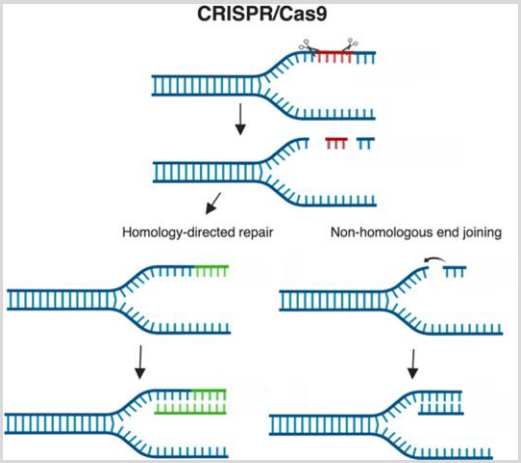
Genetic Approaches Targeting HCM Variants



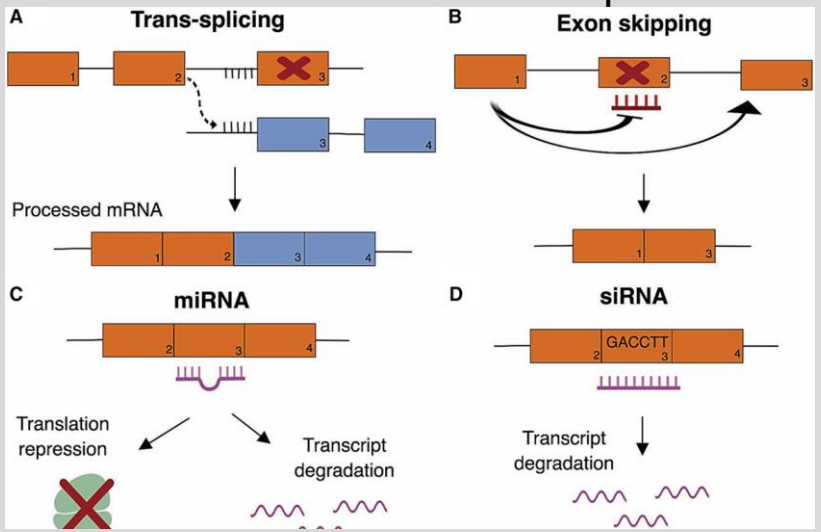
- cMyBP-C protein replacement strategies



- Correct each pathogenic variant before clinical manifestation



- Strategies to correct aberrant transcripts

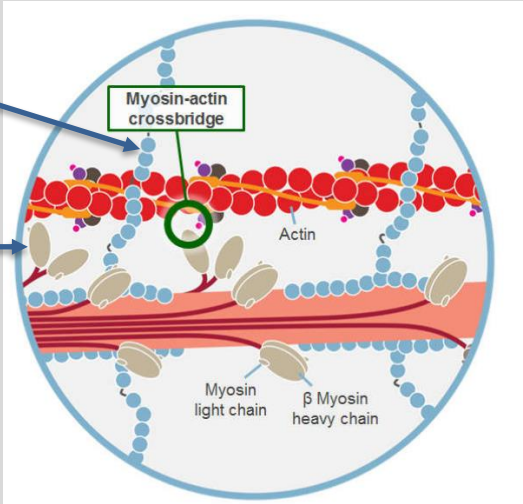


Adapted from: Spirito et al. NEJM. 1997; 336:775-785; Rapetti et al. Circ Res. 2019; 124:1536-15550.
Ma et al. Nature. 2017; 548:413-419. Mearini et al. Nat Commmun. 2014; 5:5515.

Molecular Underpinnings of Hypercontractility

Cardiac myosin-binding protein C = molecular break

Force-producing myosin head = motor



Mutations in MYH7 and MYBPC3

↓

Too many cross-bridges

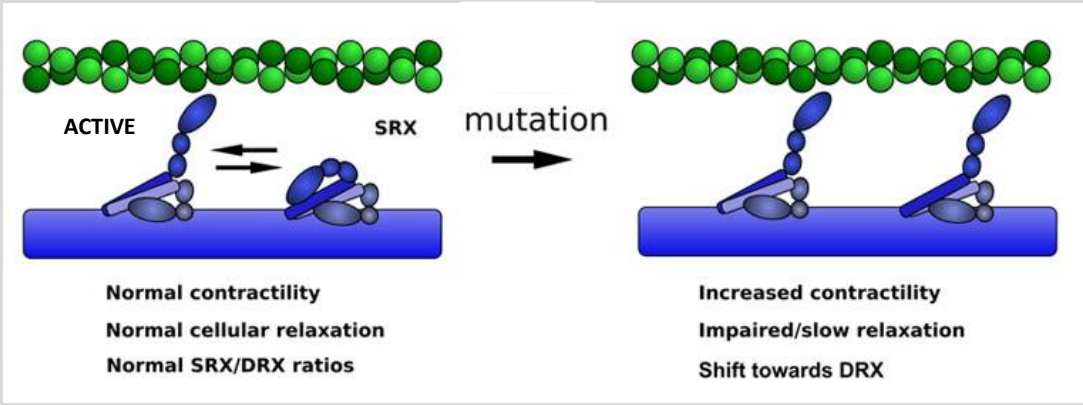
↙ ↘

Increased myocardial force generation

Abnormal relaxation

= actin monomer

= myosin S2



<u>Myosin State</u>

SRX = super relaxed state

ACTIVE = contractile state

Adapted from:

Toepfer et al. Circulation. 2020; 141:828-842.

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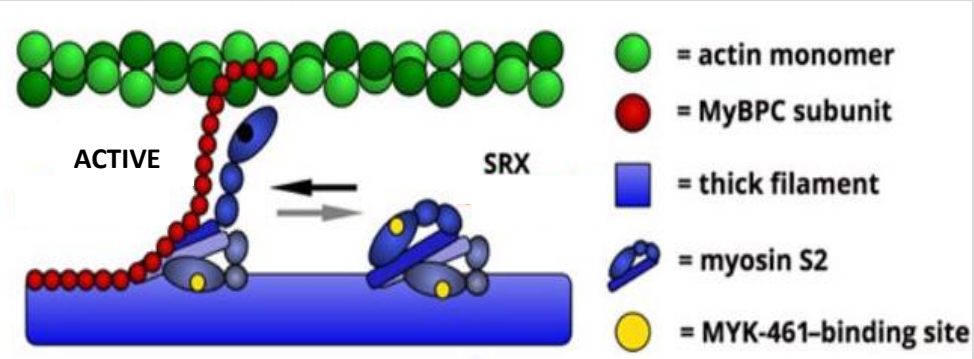
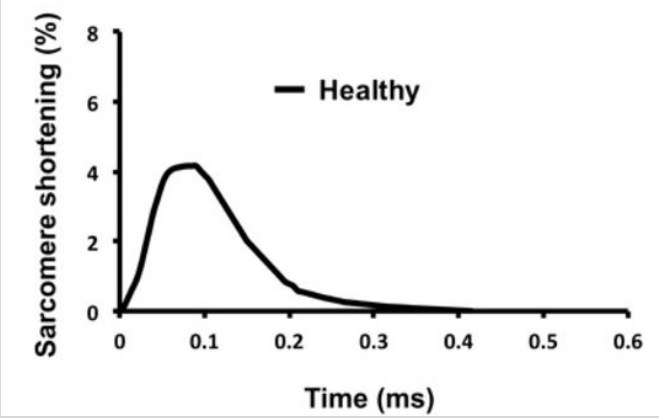
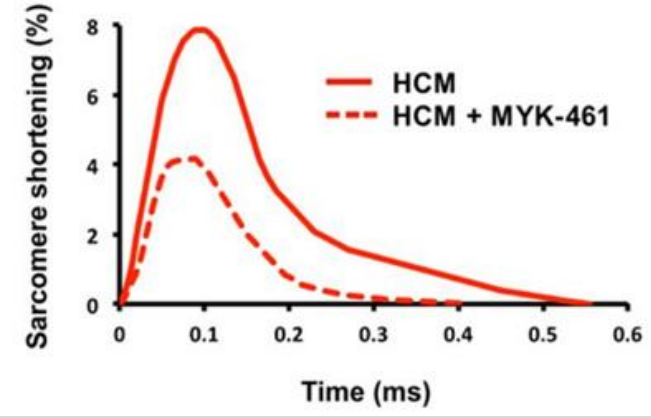
Myosin Inhibitors: Mavacamten (MYK-461)

Selective allosteric inhibitor of cardiac myoysin







Toepfer et al. Sci Transl Med. 2019; 11:eaat1199.

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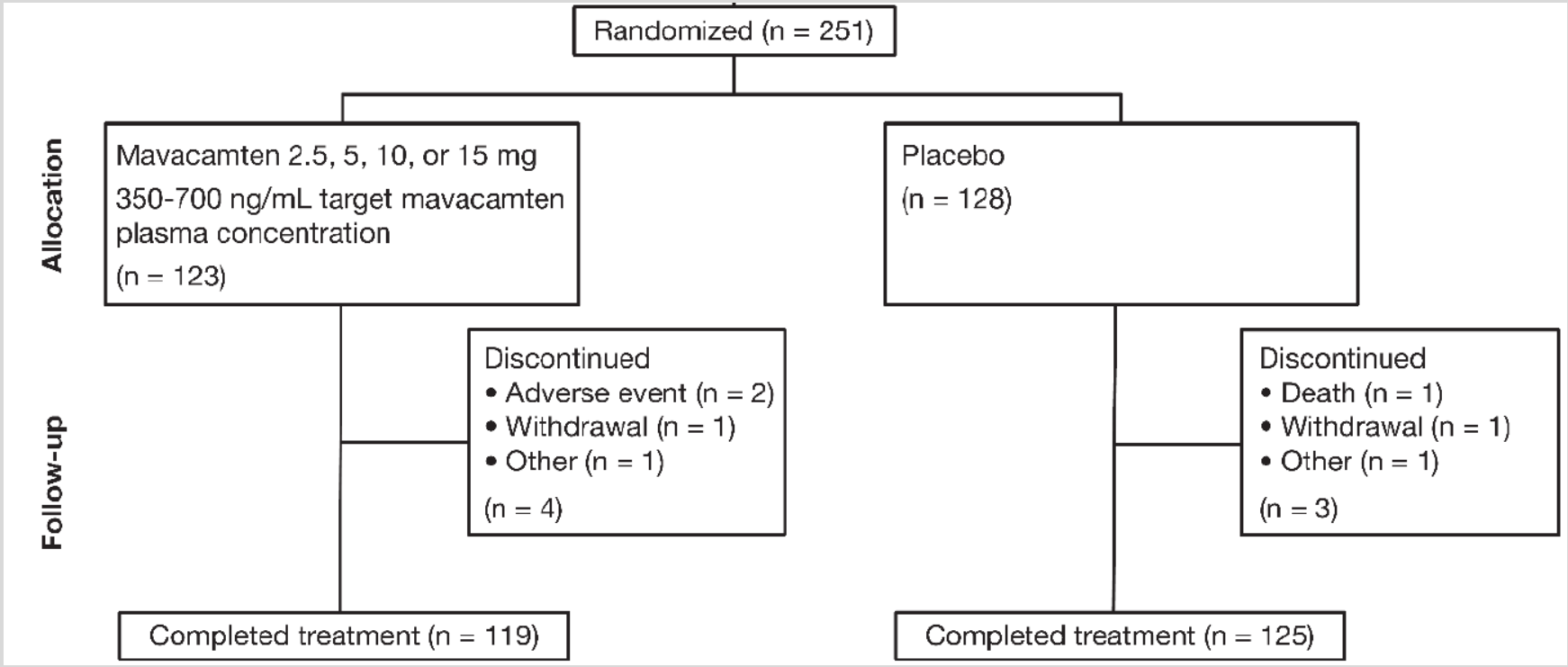
Mavacamten (MYK-461): EXPLORER-HCM



SAEs	11 in 10 patients: AF (2%), syncope (2%), stress cardiomyopathy (2%)	20 in 11 patients: AF (3%), syncope (1%), sudden death (1%), CHF (1%)
	7 transient LVEF < 50% (range 35-49%)	2 transient LVEF < 50% (range 35-49%)

Olivotto et al. Lancet. 2020; 396:759-69.

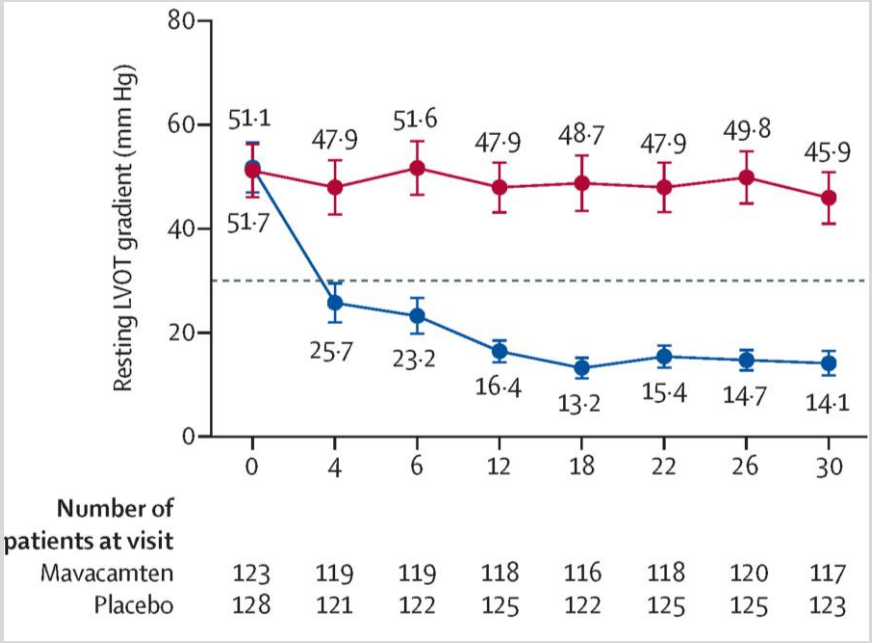
Mavacamten (MYK-461): EXPLORER-HCM

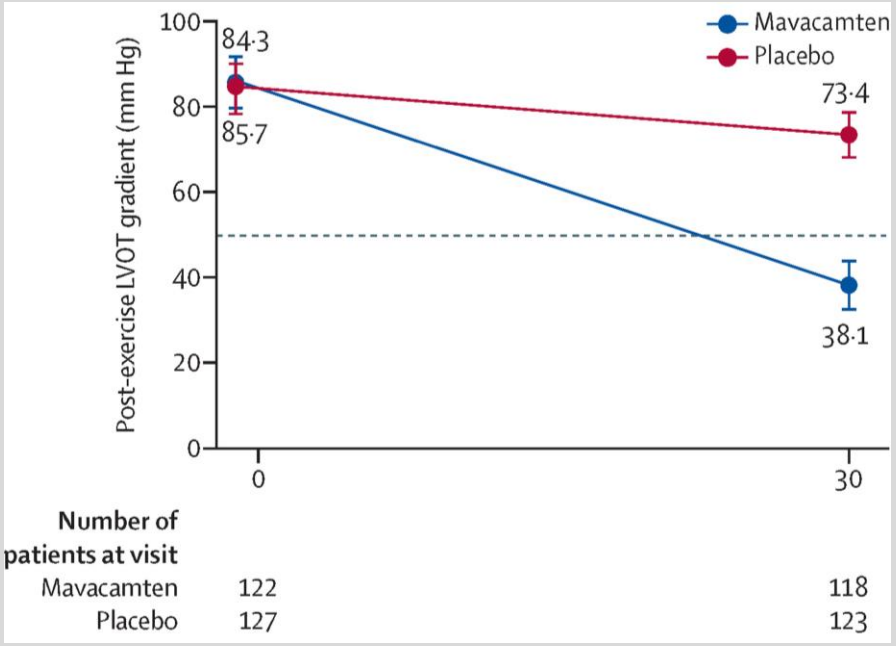
Primary Endpoint

	Mavacamten (n=123)	Placebo (n=128)	Difference (95% CI)
Either ≥1.5 mL/kg/min ↑ pVO2 + ≥1 NYHA class ↑ OR ≥3 mL/kg/min ↑ pVO2 + no ↓ NYHA class	45 (37%)	22 (17%)	19.4 (8.7 – 30.1)
≥1.5 mL/kg/min ↑ pVO2 + ≥1 NYHA class ↑	41 (33%)	18 (14%)	19.3 (9.0 – 29.6)
≥3 mL/kg/min ↑ pVO2 + no ↓ NYHA class	29 (24%)	14 (11%)	12.6 (3.4 – 21.9)
Both ≥3 mL/kg/min ↑ pVO2 + ≥1 NYHA class ↑	25 (20%)	10 (8%)	12.5 (4.0 – 21.0)

Olivotto et al. Lancet. 2020; 396:759-69.

Mavacamten (MYK-461): EXPLORER-HCM





Olivotto et al. Lancet. 2020; 396:759-69.

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REDWOOD-HCM

Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM

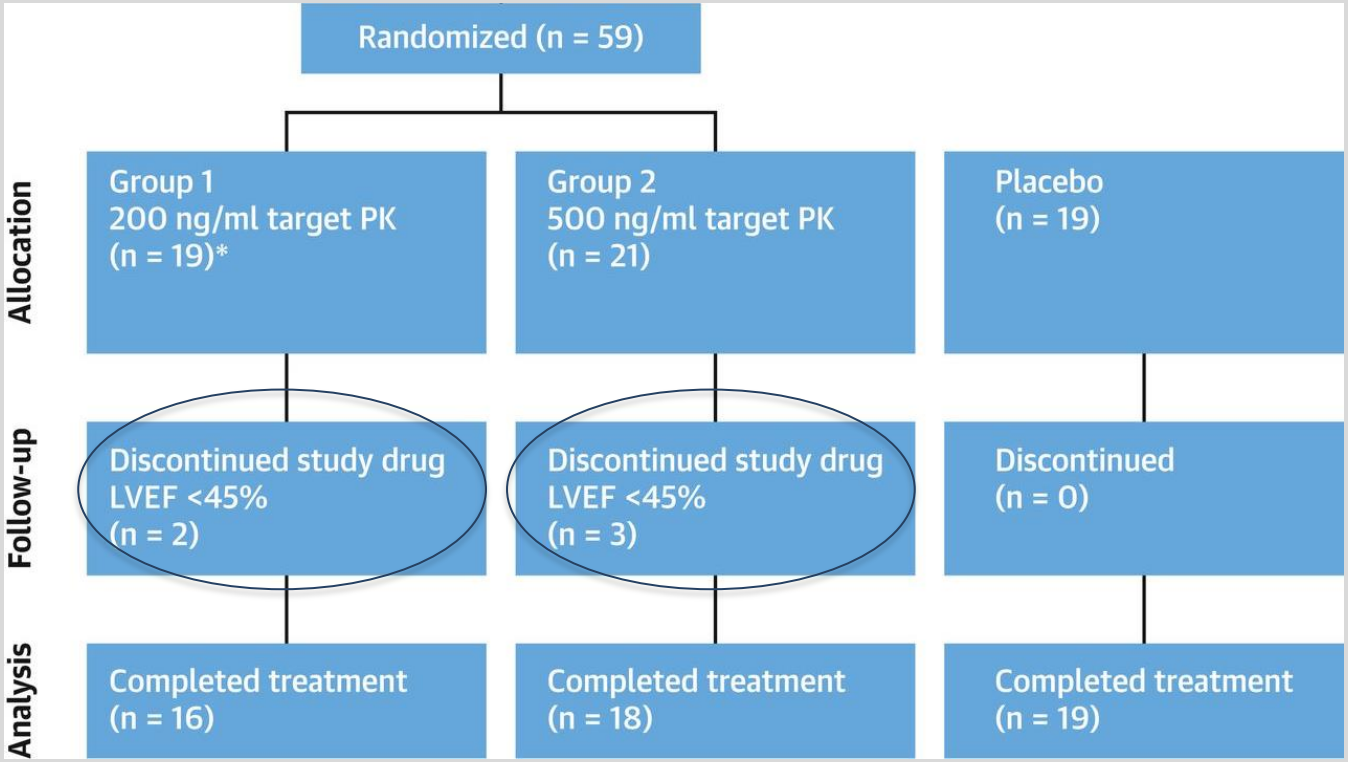
NCT04219826

Phase II
Population: Adult oHCM, LVEF ≥60%, NYHA II-III
Target Enrollment: 60

Primary Endpoint:
Safety and Tolerability
AEs, SAEs, incidence of LVEF<50%

Secondary Endpoints:
Define concentration- and dose-relationship of CK-274 with resting and Valsalva LVOT gradients over 10 weeks of treatment

Mavacamten (MYK-461): MAVERICK-HCM



Efficacy of mavacamten in management of symptomatic nonobstructive HCM?

To Be Determined

SAEs

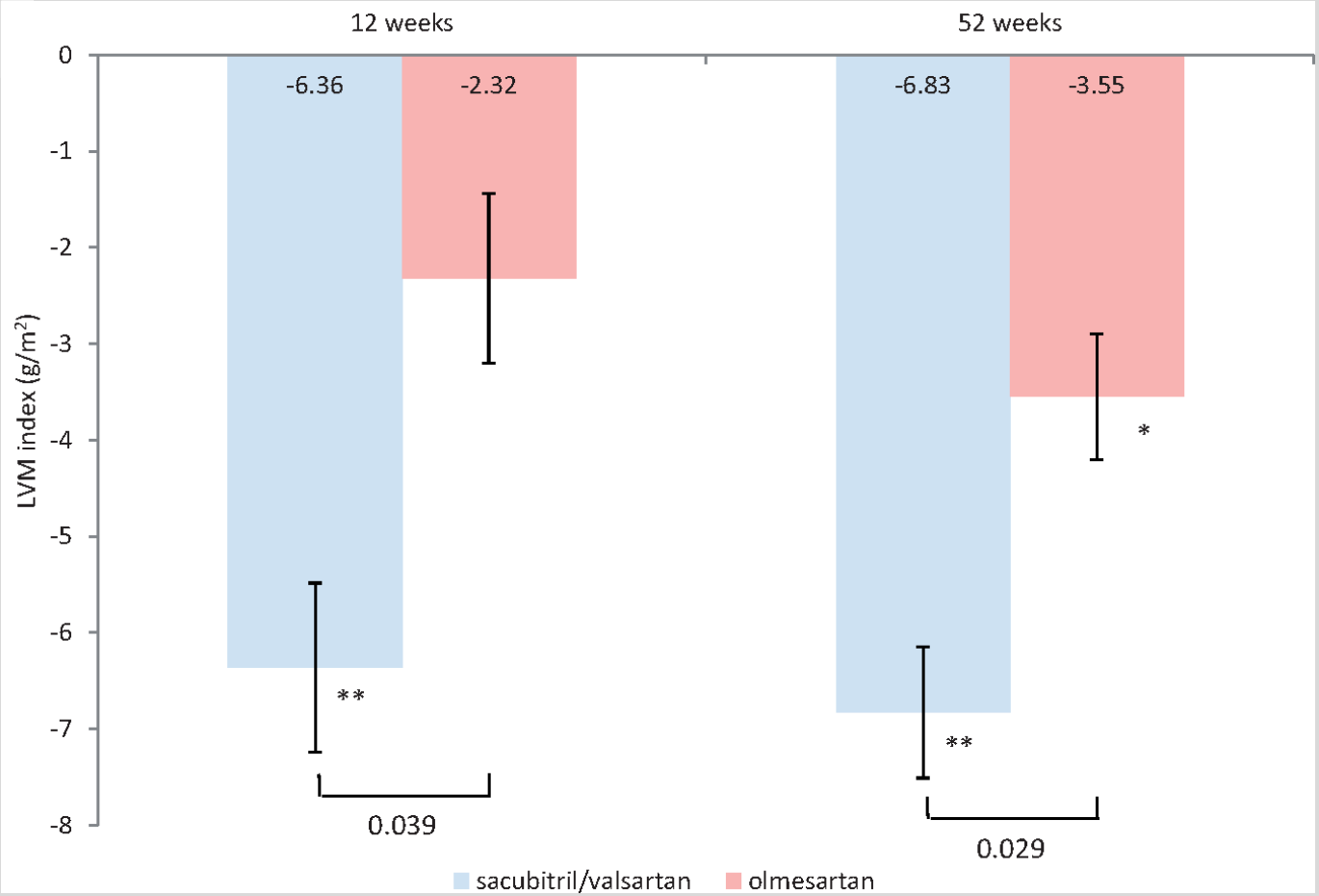
4 (10%) w/ 6 SAEs: **AF**, ↓ LVEF, arthritis, mental status changes, renal failure

4 (21%) w/ 4 SAEs: **AF**, angina, CAD

5 (12.5%, 2 Grp 1, 3 Grp 2) ↓ LVEF < 45% (range: 38-45%)

Ho et al. JACC. 2020; 75:2649-60.

Fibrosis & Adverse Remodeling: Sacubitril/Valsartan



Reduction in LV mass remains significant with adjustment for SBP

Schmieder et al. Eur Heart J. 2017; 38:3308-17.

ENTRESTO-HCM

Study of efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy.

NCT04164732

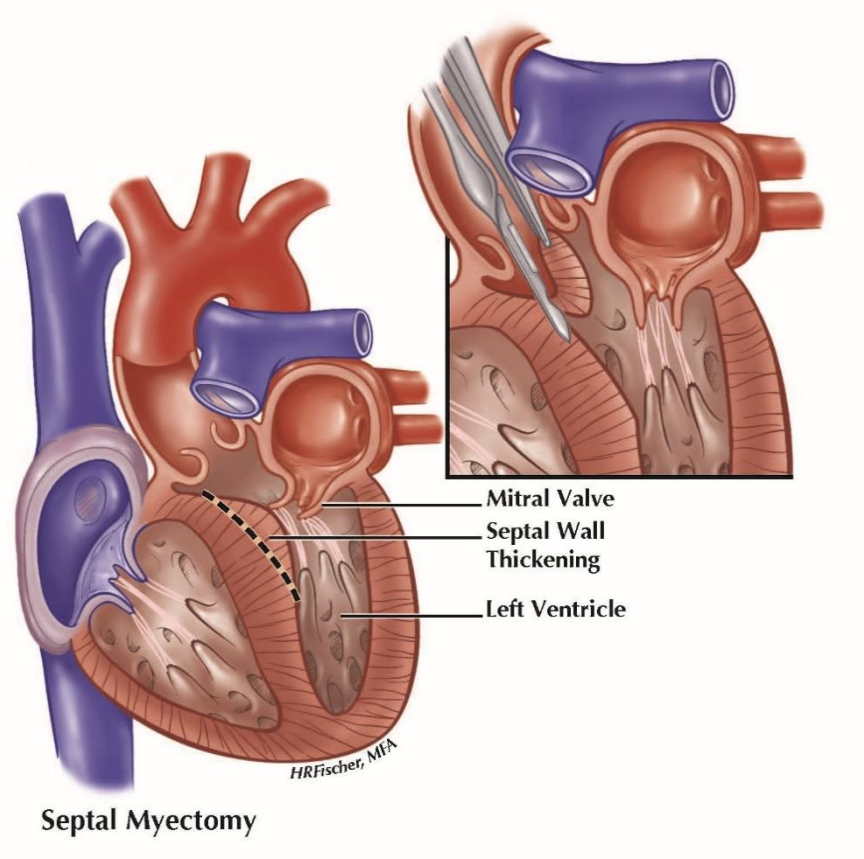
Phase II
Population: Adult nHCM, LFEV ≥50%, NYHA II-III, pVO2 ≤80% of predicted
Target Enrollment: 44

Primary Endpoint:
Peak VO2 after 50 weeks

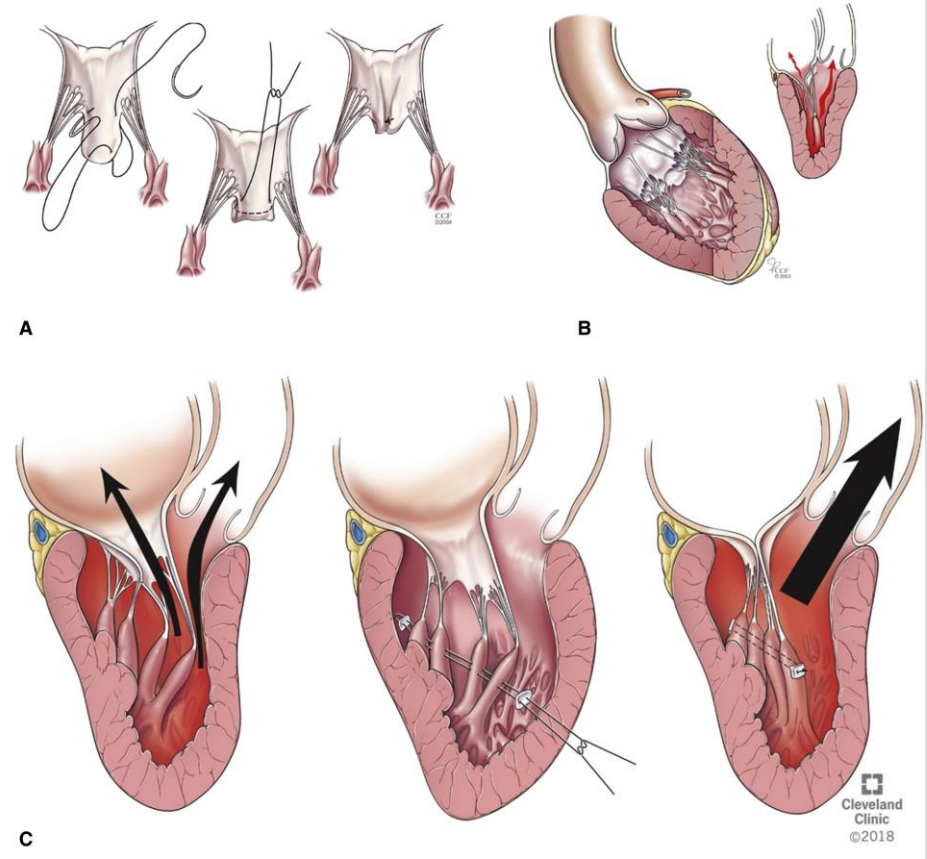
Secondary Endpoints:
Safety and tolerability

Surgical Strategies For Management of oHCM

Septal Myectomy



Mitral Valve Interventions



Hodges et al. J Thorac Cardiovasc Surg. 2019; 157:2289-99.

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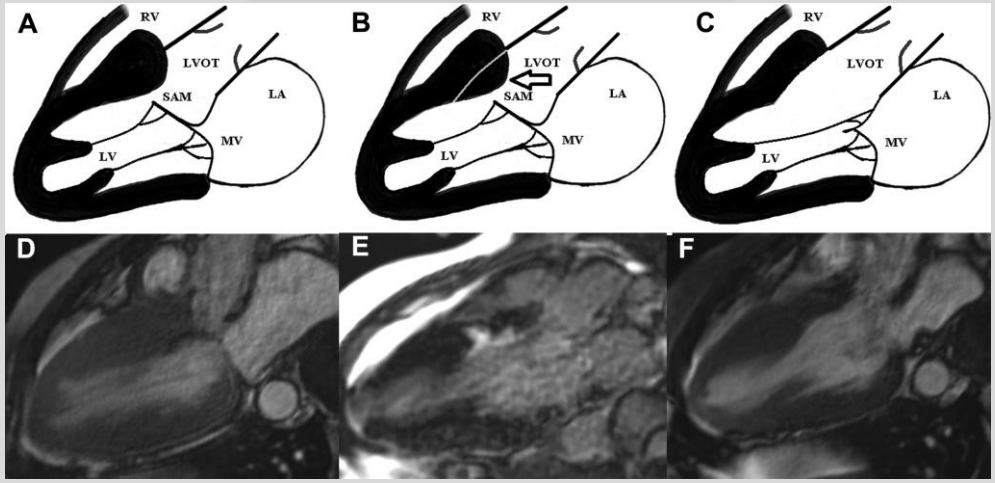
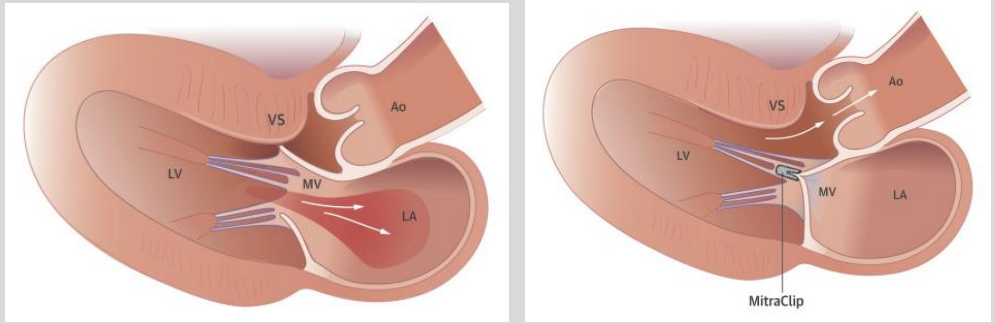
Percutaneous Strategies For Management of oHCM

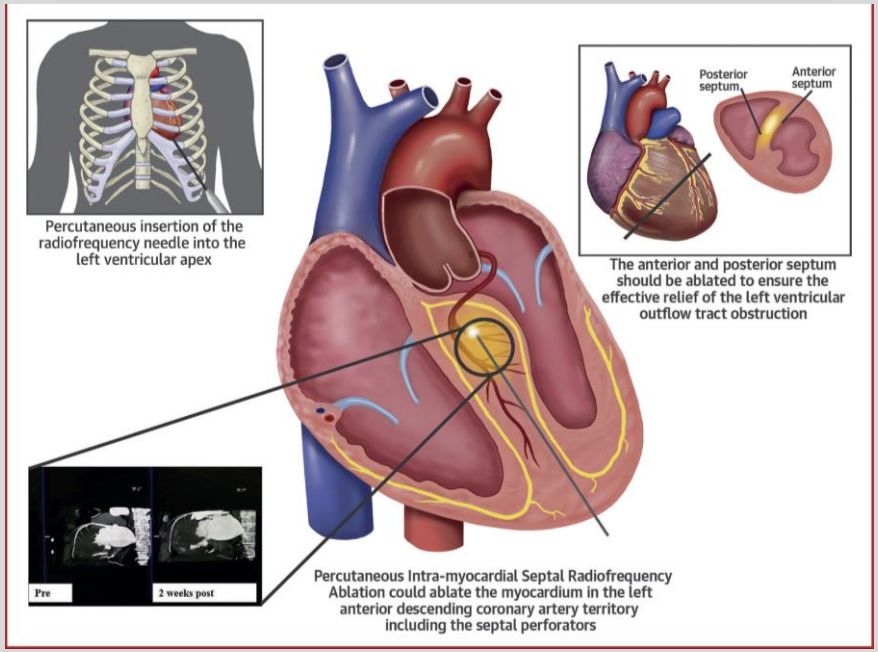
Alcohol Septal Ablation



Percutaneous Mitral Valve Plication



Percutaneous Intramyocardial Septal Radiofrequency Ablation



Cooper et al. Can J Cardiol. 2017; 33:1254-1265.
Liu et al. JACC. 2018; 72:1898-909.
Sorajja et al. JACC 2016; 67:2811-8.

VALOR-HCM

A Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Who are Eligible for Septal Reduction Therapy

NCT04349072

Phase III
Population: Adult oHCM, referred/considered for SRT within previous 12mo, appropriate SRT anatomy

Primary Endpoint: Evaluate ability of mavacamten to reduce need for SRT

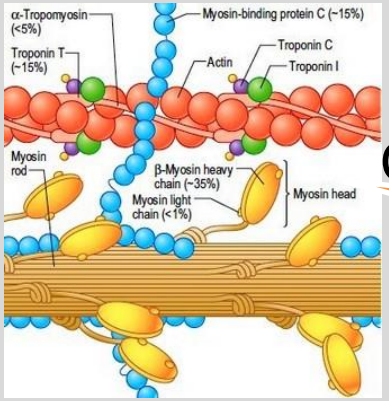
Composite of
1) Decision to proceed with SRT prior to or at Week 16
2) SRT guideline eligible at Week 16, but declined by subject

Secondary Endpoint: Evaluate persistence of effects of mavacamten in reducing # SRT procedures

Composite of outcomes at Week 32 compared with Week 16 in mavacamten group of decision to proceed with SRT.

Conclusions

1



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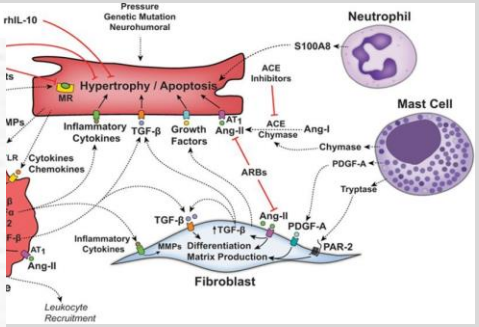

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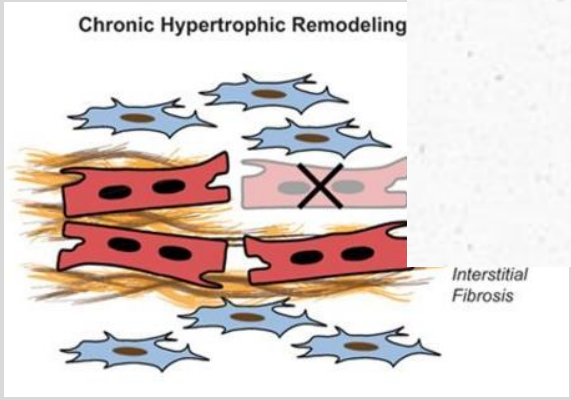
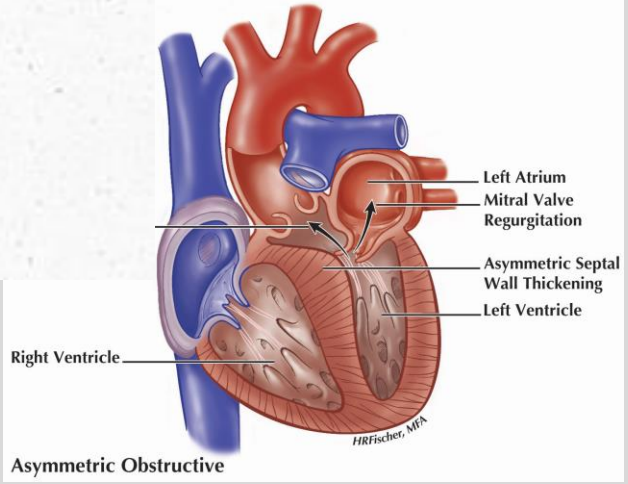


Pathologic Hypertrophy



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