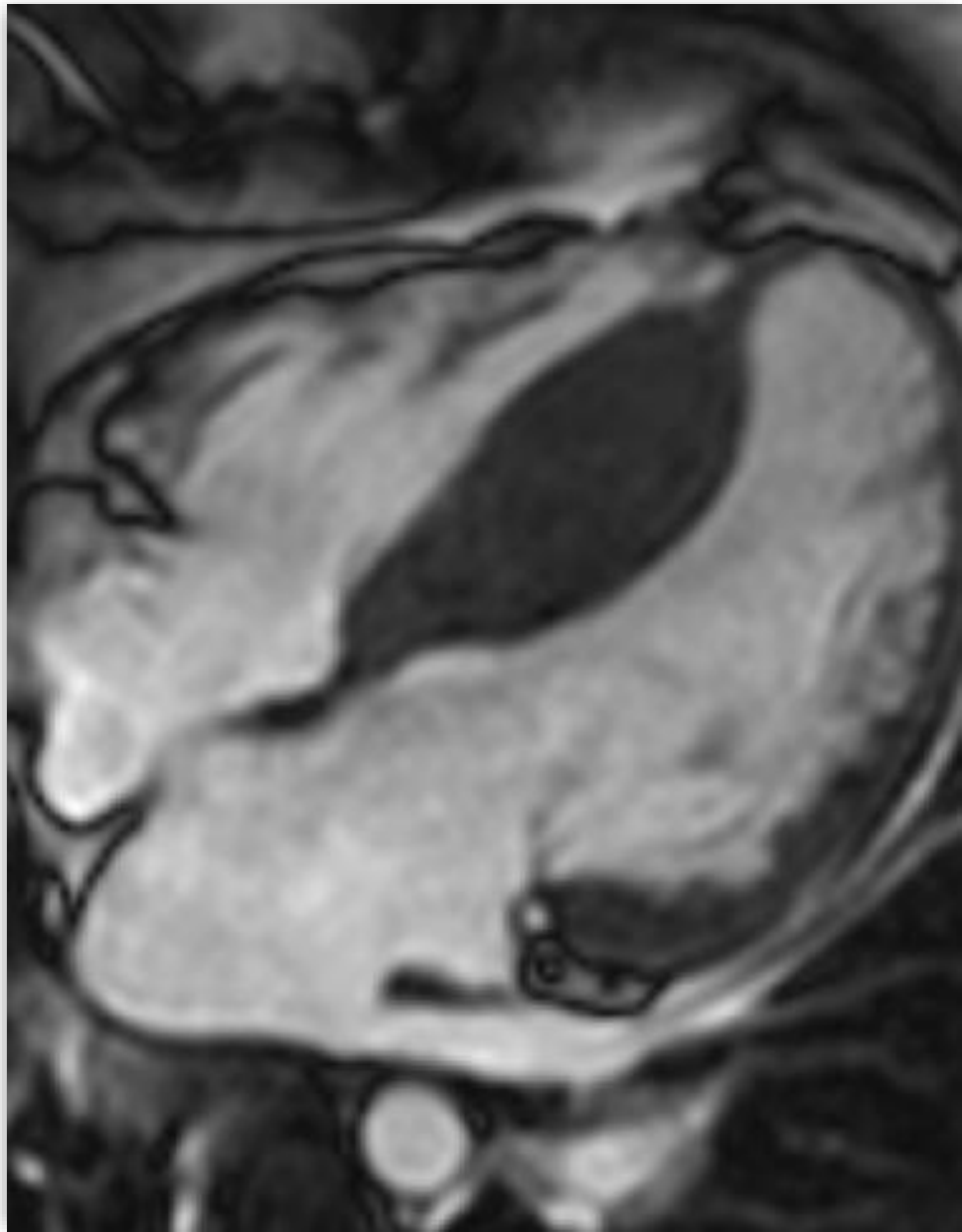
Hypertrophic CMP

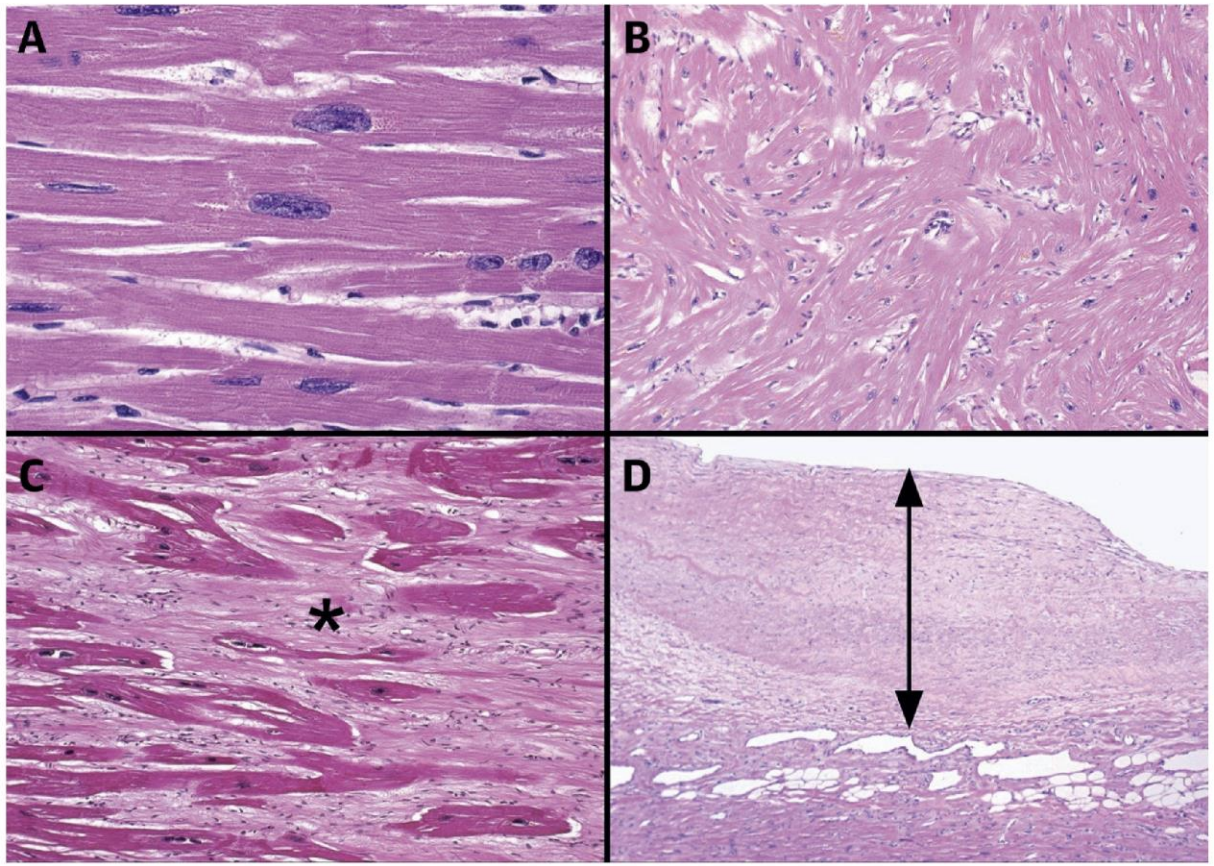
What's next

Hypertrophic cardiomyopathy

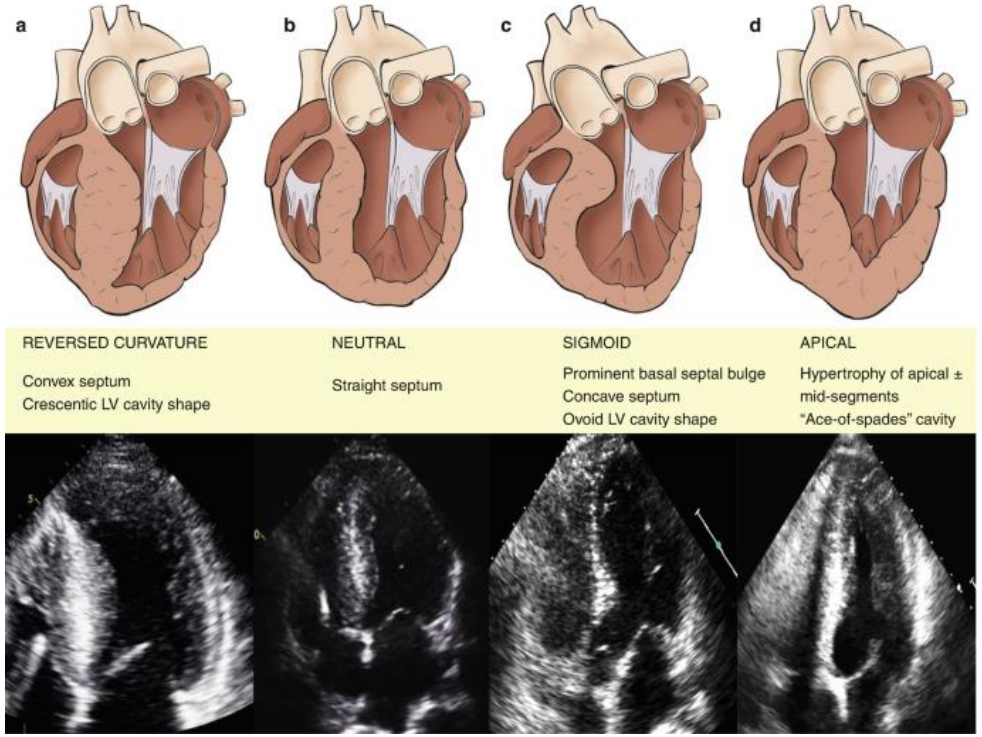
- Genetically determined heart muscle disease often (60 to 70 percent) caused by mutations in one of several sarcomere genes .
- Prevalence of HCM in the general population been estimated to be closer to 1 out of every adults (0.5 percent) or perhaps even greater
- **CLINICAL MANIFESTATIONS (symptoms/FH/Something abnormal)**
- **Echocardiography (** unexplained increased LV thickness ≥15 mm /A wall thickness of ≥13 mm + FH)
- **C MRI**

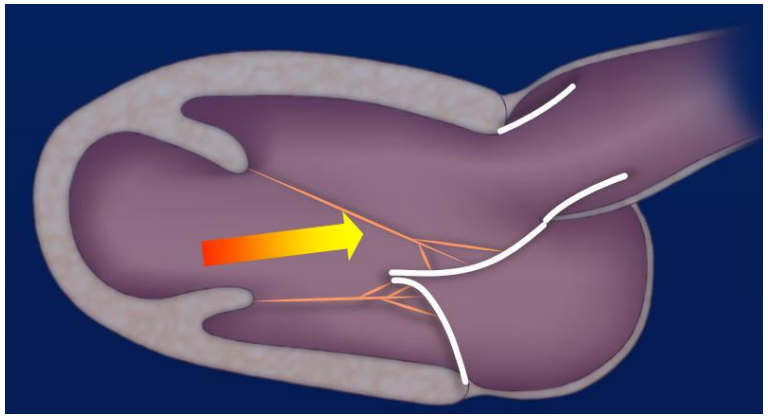


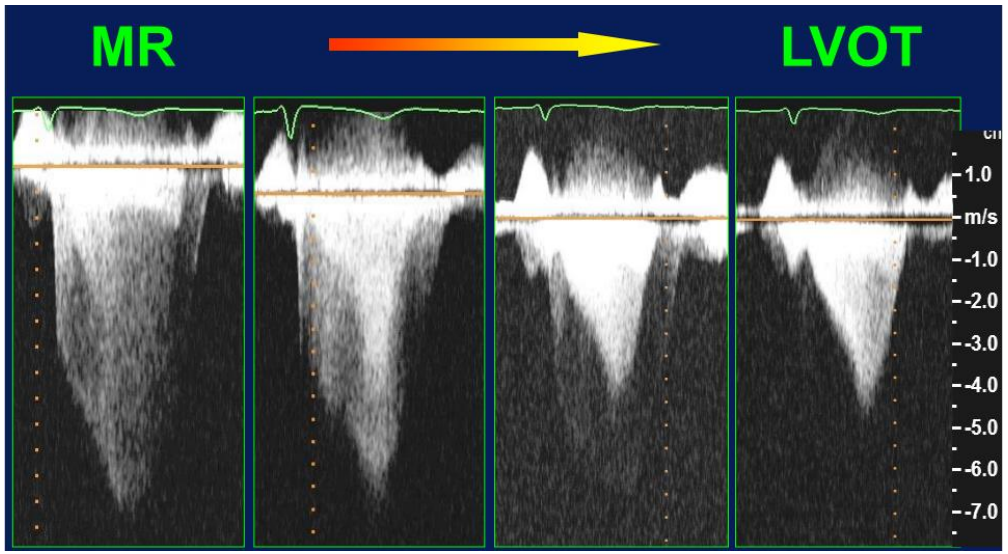
CENTRAL ILLUSTRATION: Histopathological Findings in Hypertrophic Cardiomyopathy

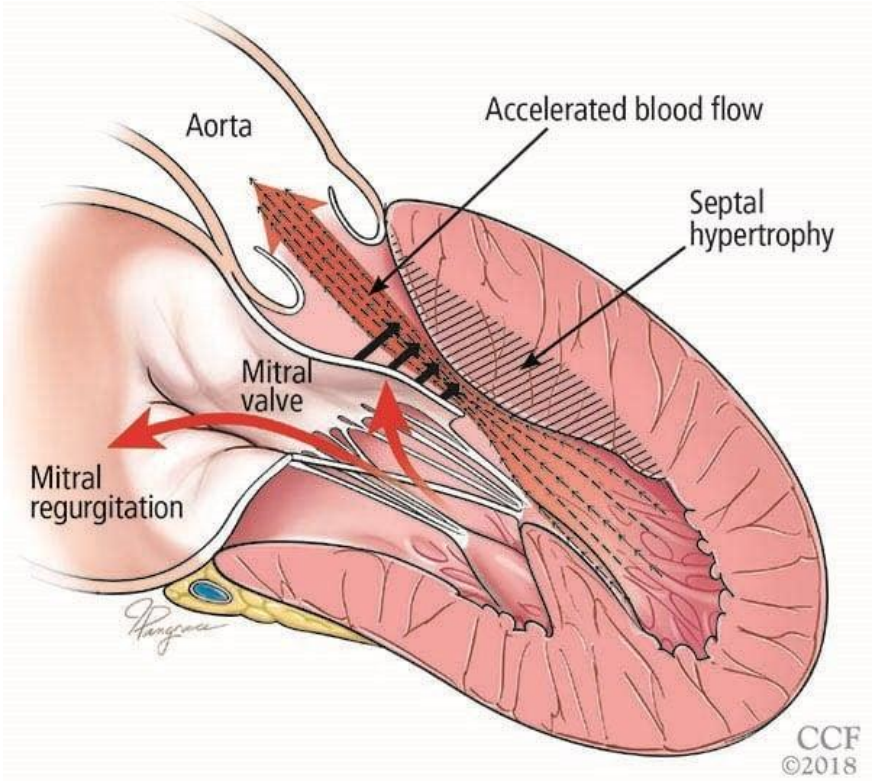


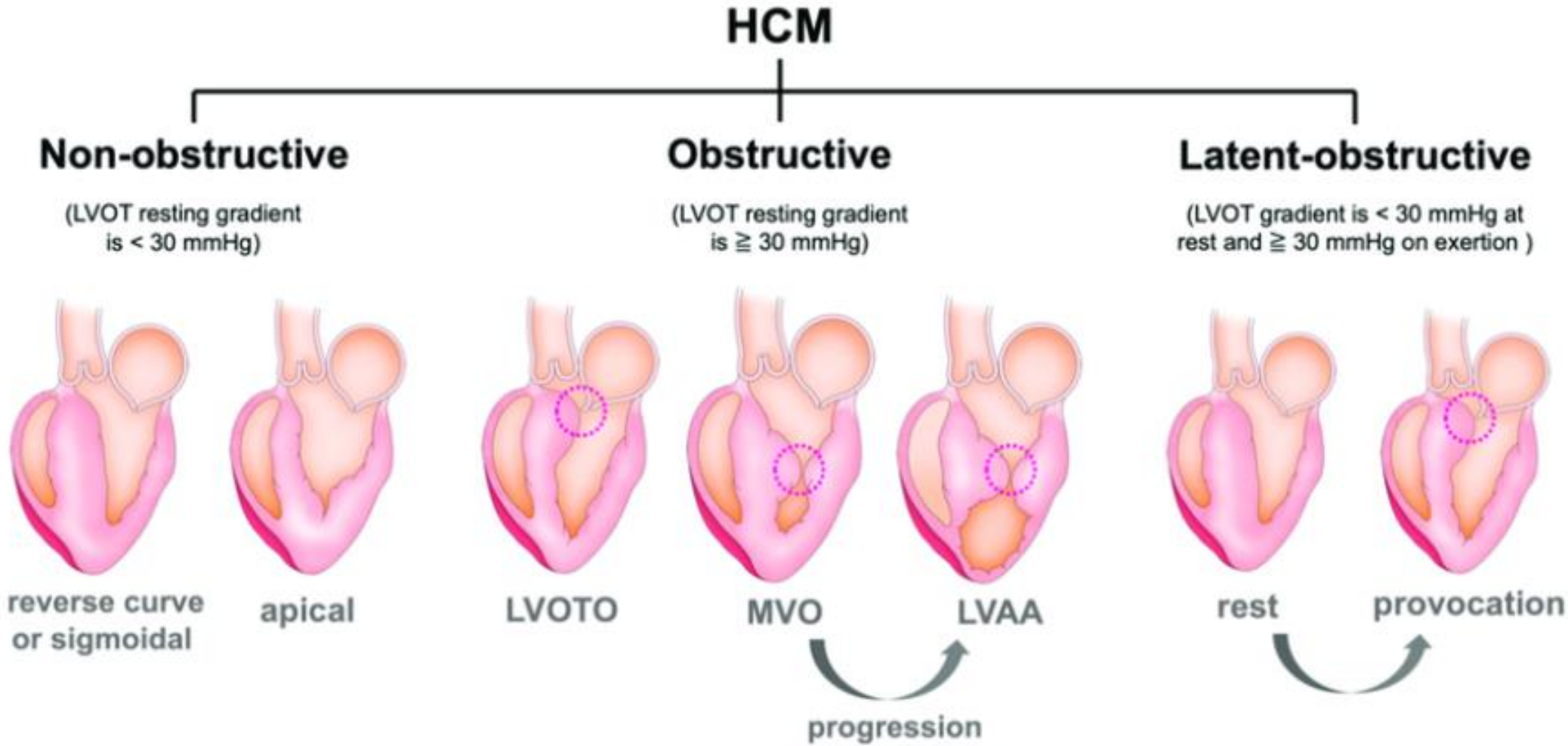
Cui, H. et al. J Am Coll Cardiol. 2021;77(17):2159-70.

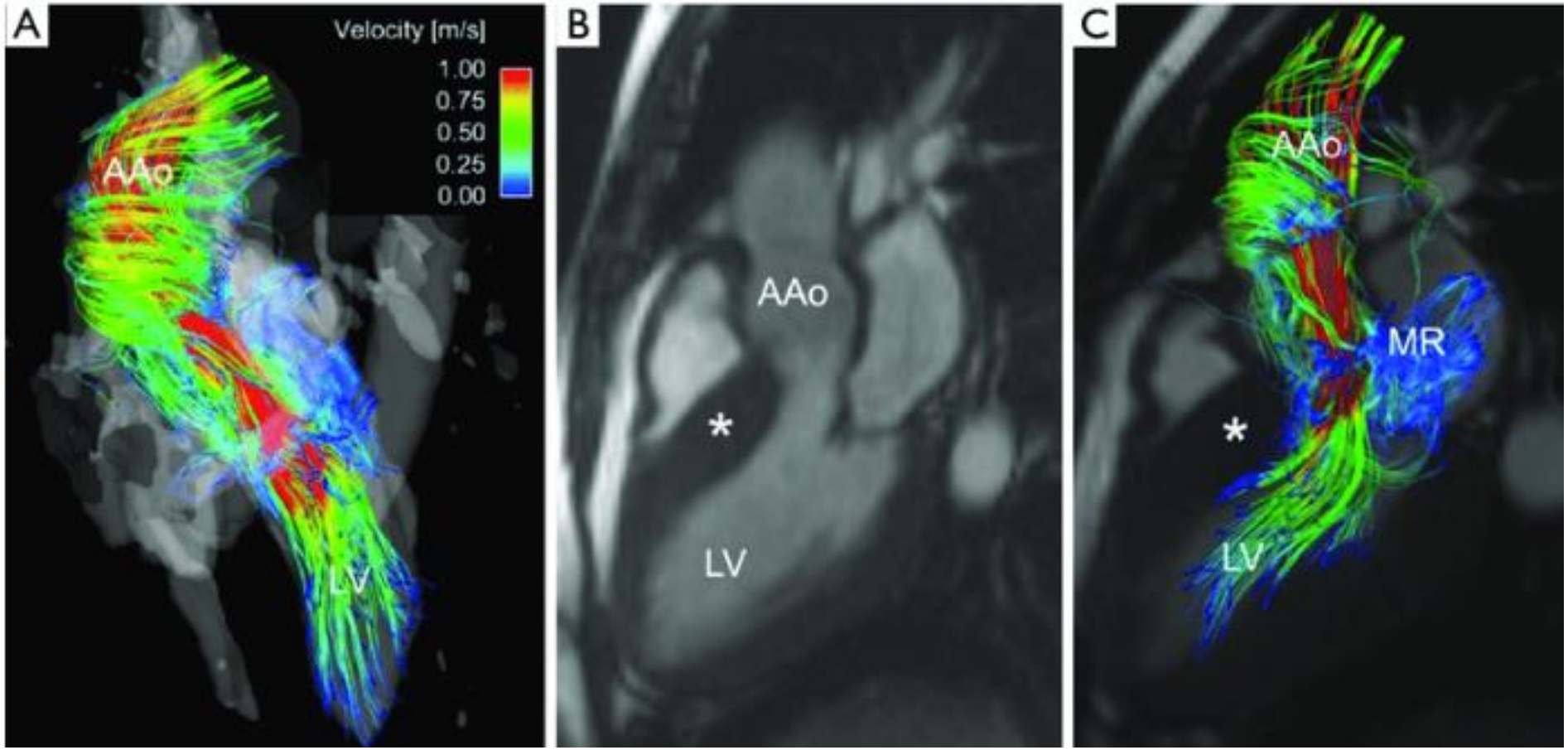

a
b
c
d
REVERSED CURVATURE
Convex septum
Crescentic LV cavity shape
NEUTRAL
Straight septum
SIGMOID
Prominent basal septal bulge
Concave septum
Ovoid LV cavity shape
APICAL
Hypertrophy of apical ± mid-segments
"Ace-of-spades" cavity

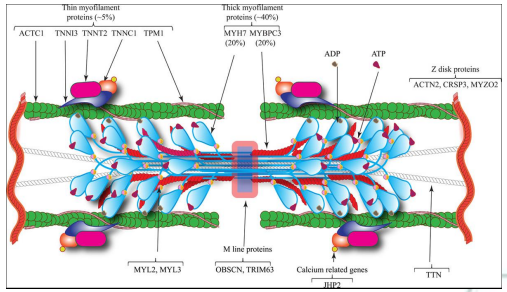



MR
LVOT
1.0
m/s
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0

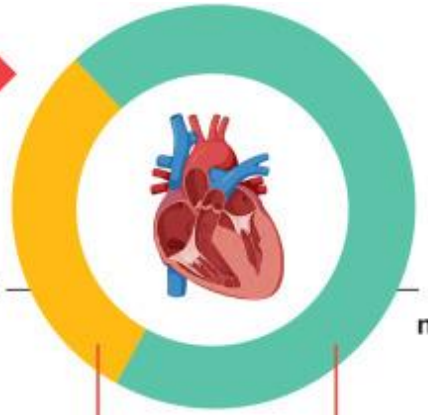

Aorta
Accelerated blood flow
Septal hypertrophy
Mitral valve
Mitral regurgitation
CCF ©2018


HCM
Non-obstructive
(LVOT resting gradient is < 30 mmHg)
Obstructive
(LVOT resting gradient is ≧ 30 mmHg)
Latent-obstructive
(LVOT gradient is < 30 mmHg at rest and ≧ 30 mmHg on exertion)
reverse curve or sigmoidal
apical
LVOTO
MVO
LVAA
progression
rest
provocation


A
Velocity [m/s]
1.00
0.75
0.50
0.25
0.00
AAo
LV
B
AAo
*
LV
C
AAo
MR
*
LV



Hypertrophic cardiomyopathy subtypes based on genetic testing (excluding mimics)



Monogenic HCM (~30%)

Polygenic/ multifactorial HCM (~70%)

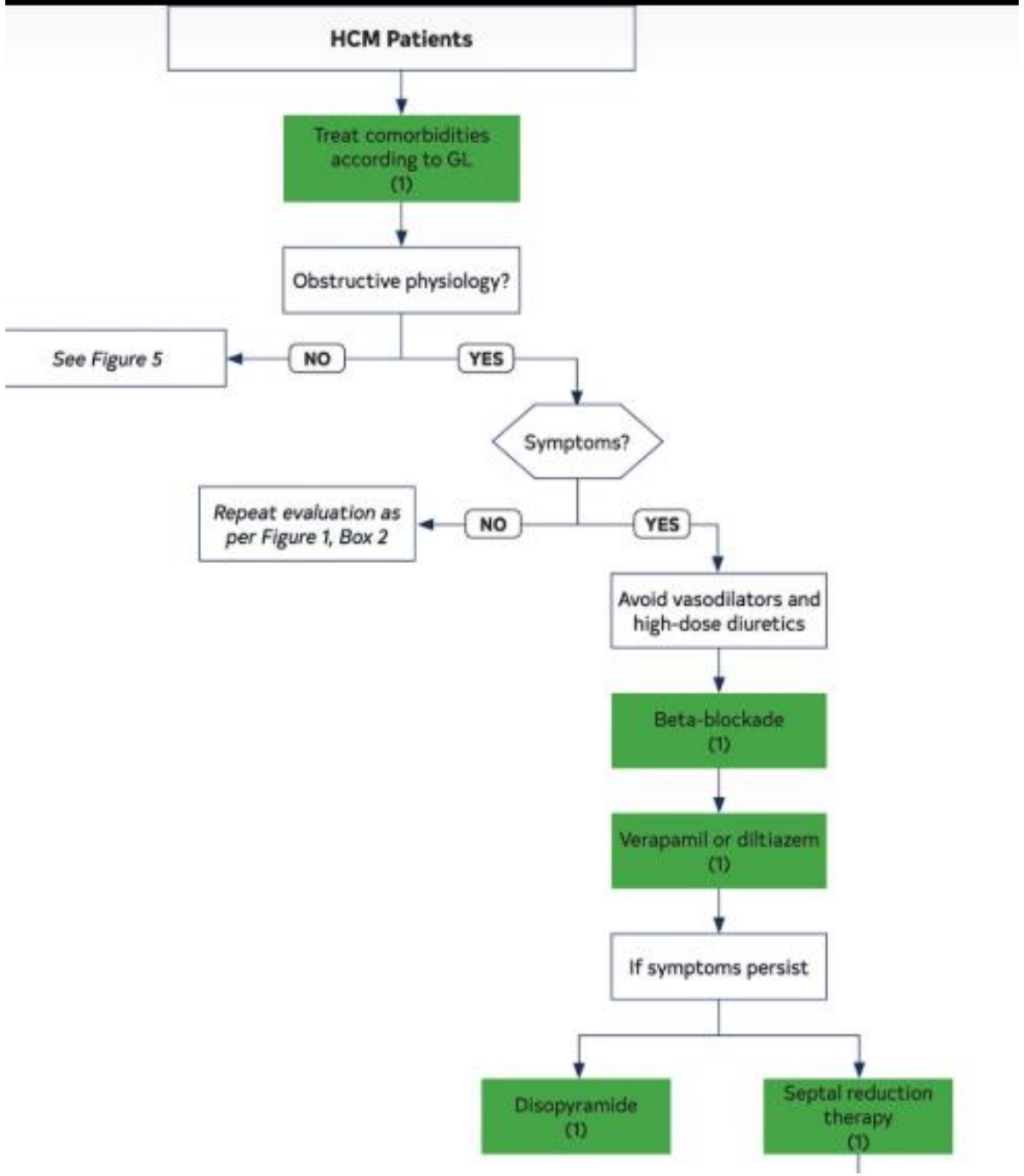
Genetic testing	Positive	Negative
Dominant cause	Pathogenic genetic variant*	Polygenic risk Comorbidities
Age at diagnosis	Younger	Older
Prevalence of LVOT obstruction	Lower	Higher
Lifetime risk of AF VT/VF/SCD Heart failure	Higher	Lower
Risk of HCM in relatives	Higher (up to 50%)	Lower**

Gene Symbol	Protein Name	Detection Rate
SARCOMERE GENES		55-70%
MYH7	β-cardiac myosin heavy chain	
MYBPC3	Cardiac myosin-binding protein c	
TNNT2	Cardiac troponin T	
TNNI3	Cardiac troponin I	
TPM1	α-Tropomyosin	
ACTC	Cardiac actin	
MYL2	Cardiac myosin regulatory light chain	
MYL3	Cardiac myosin essential light chain	
METABOLISM GENES		Unknown
PRKAG2	5-AMP-activated protein kinase, gamma-2 subunit	
LAMP2	Lysosomal associated membrane protein 2	

Guidelines for Clinical Screening with Physical Examination, Echocardiography and Electrocardiogram (ECG or EKG)*

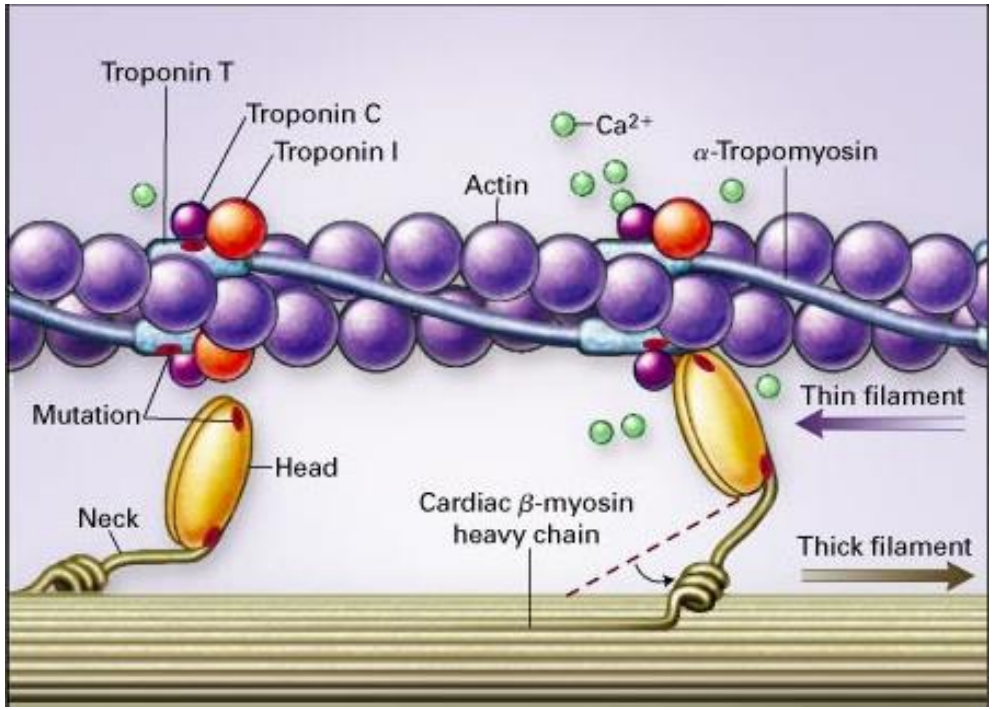
Age	Recommendation
<12 years	Optional unless: • Family history of early HCM-related death, early development of LV hypertrophy, or other adverse complications • Competitive athlete in intense training program • Onset of symptoms • Other clinical suspicion of early LV hypertrophy
12-18 years	Repeat evaluation every 12-18 months
>18-21 years	• Repeat evaluation approximately every 5 years, or in response to symptoms. • Tailor evaluation if there is a family pattern of late-onset LV hypertrophy or HCM-related complications

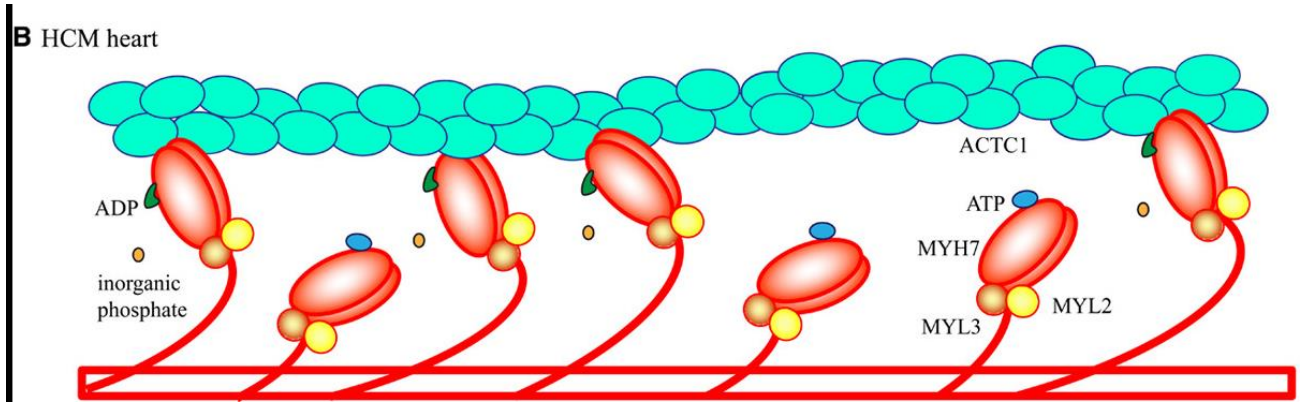
PAST!


HCM Patients
Treat comorbidities according to GL (1)
Obstructive physiology?
See Figure 5
NO
YES
Symptoms?
Repeat evaluation as per Figure 1, Box 2
NO
YES
Avoid vasodilators and high-dose diuretics
Beta-blockade (1)
Verapamil or diltiazem (1)
If symptoms persist
Disopyramide (1)
Septal reduction therapy (1)

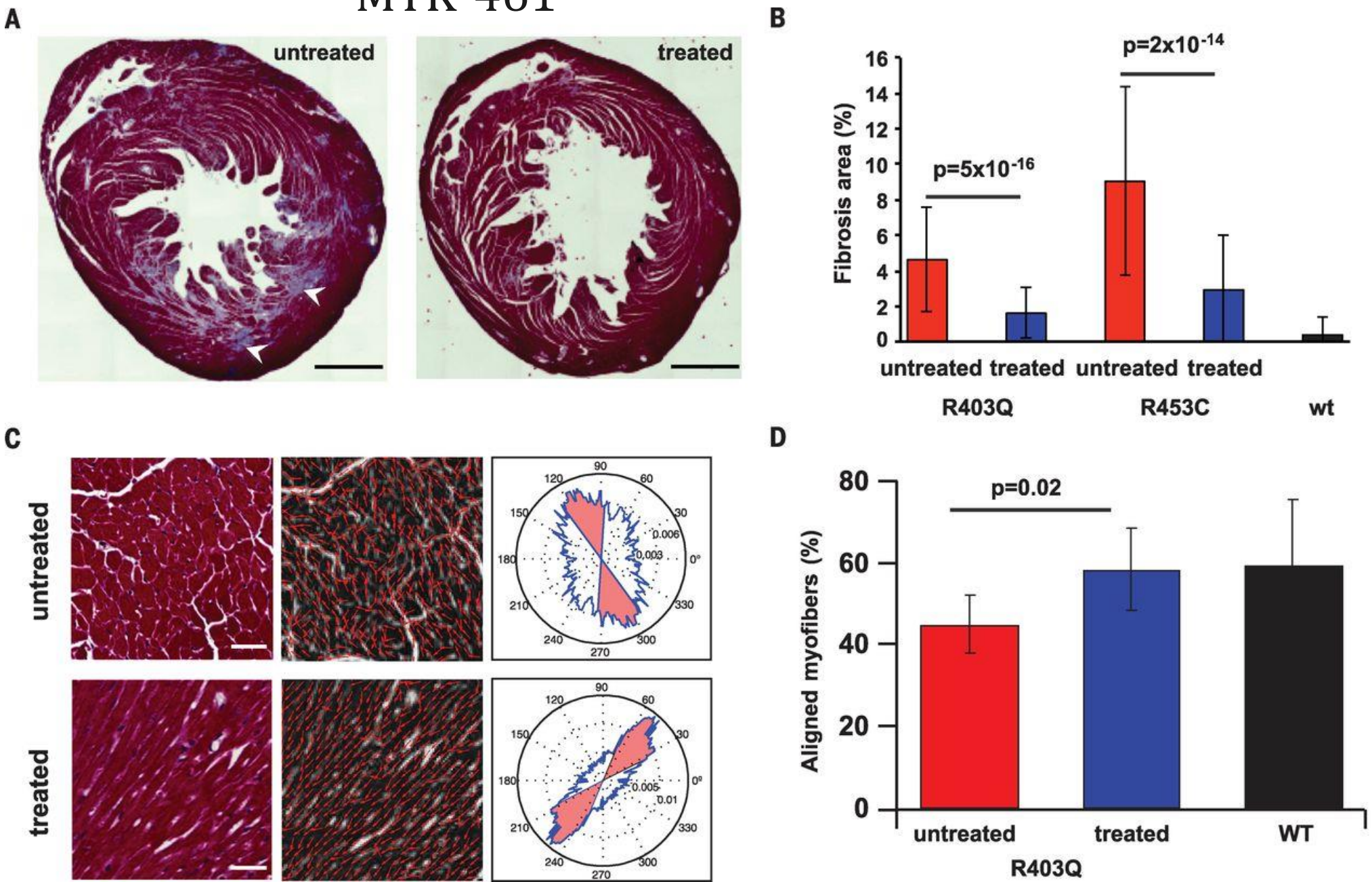
Power Stroke

What's next

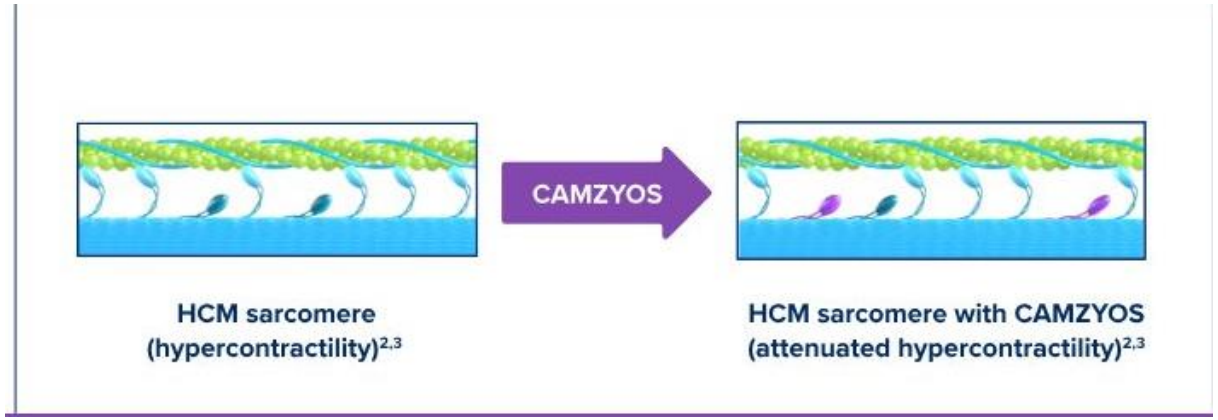




MYK-461


A
untreated
treated
B
p=2x10-14
p=5x10-16
Fibrosis area (%)
16
14
12
10
8
6
4
2
0
untreated treated untreated treated
R403Q
R453C
wt
C
untreated
treated
90
120
60
150
30
180
0°
210
330
240
300
270
0.006
0.003
0.005
0.01
D
p=0.02
Aligned myofibers (%)
80
60
40
20
0
untreated
treated
WT
R403Q

RATS to HUMANS



T0	T1	T2
Basic Science	Translation to Human	Translation to Patients
February 2016: Green, et al. *"A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice."*	June 2019: Grillo, et al. *"In vitro and in vivo pharmacokinetic characterization of Mavacamten, a first-in-class small molecule allosteric modulator of beta cardiac myosin."*	February 2020: A Phase 2 Open-label Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction (PIONEER-HCM)

EXPLORER-HCM

Randomized, double-blind, placebo-controlled, phase 3 clinical trial

251 HCM participants with both:

1) LVOT gradient ≥50 mmHg
2) NYHA class II-III

MAVACAMTEN (n=123)

Oral doses (2.5, 5, 10 or 15 mg),
to achieve a plasma concentration between 350 ng/mL and 700 ng/mL

+

HOCM background therapy (BB or CCB)

PLACEBO (n=128)

+

HOCM background therapy (BB or CCB)

Primary Endpoint:

1) 1.5 mL/kg/min or greater increase in pVO_2 and at least one NYHA class reduction

or

2) 3.0 mL/kg/min or greater pVO_2 increase without NYHA class worsening

Secondary Outcomes:

1) Post-exercise LVOT gradient
2) pVO_2
3) NYHA class
4) Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score
5) Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath Score

Question

Does mavacamten improve exercise capacity and health status in patients with obstructive HCM?

Methods

- Randomized double-blinded placebo-controlled
- n = 251, 1:1
- Mavacamten n = 123
  Placebo n = 128
- Starting dose 5 mg, titrated to goal LVOT gradient < 30
- Follow up for 30 weeks

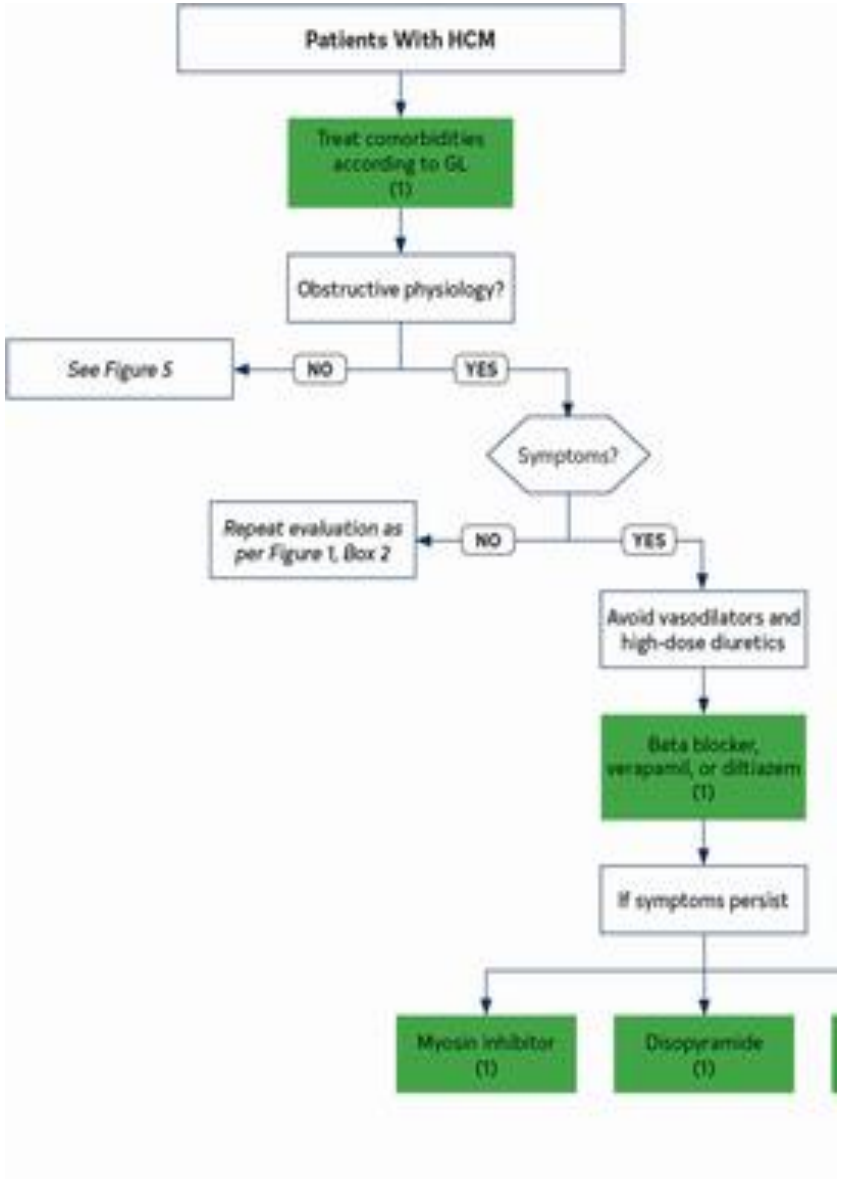
Inclusion Criteria

- Age ≥ 18
- HCM (septal thickness ≥ 15 mm or ≥ 13 with FH of HCM)
- NYHA II/III
- Dynamic LVOT gradient rest/provocation ≥ 50 mmHg
- LVEF ≥ 55%
- Able to perform CPET

Outcomes (Mavacamten vs Placebo)

Primary	Secondary				
↑ pVO2 ≥ 1.5 & ↓ NYHA ≥ 1 class OR ↑ pVO2 ≥ 3.0 & no worsening in NYHA class	Post-exercise LVOT gradient (change from baseline)	pVO2 (change from baseline)	Improvement in NYHA ≥ 1 class	KCCQ-CCS (change from baseline)	HCMSQ-SoB (change from baseline)
37% vs 17% (p < 0.0001)	-47 vs -10 (p < 0.0001)	1.4 vs -0.1 (p = 0.0006)	65% vs 31% (p < 0.0001)	13.6 vs 4.2 (p < 0.0001)	-2.8 vs -0.9 (p < 0.0001)

Conclusion:
Mavacamten improved exercise capacity and health status at 30 weeks in patients with obstructive HCM



Risk Evaluation and Mitigation Strategy (REMS) Program*

Before prescribing, healthcare providers must be certified and enrolled in the CAMZYOS REMS Program.

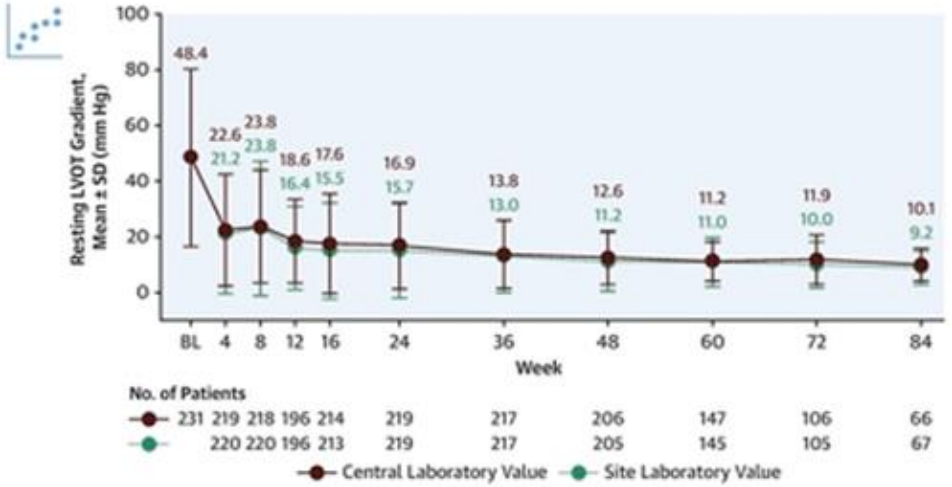
*Certified healthcare providers may designate a member of their staff who is a licensed medical professional to be a Designee. The Designee can perform REMS activities in the CAMZYOS REMS. Certified healthcare providers are responsible for all information entered and activities performed in the CAMZYOS REMS by the Designee.

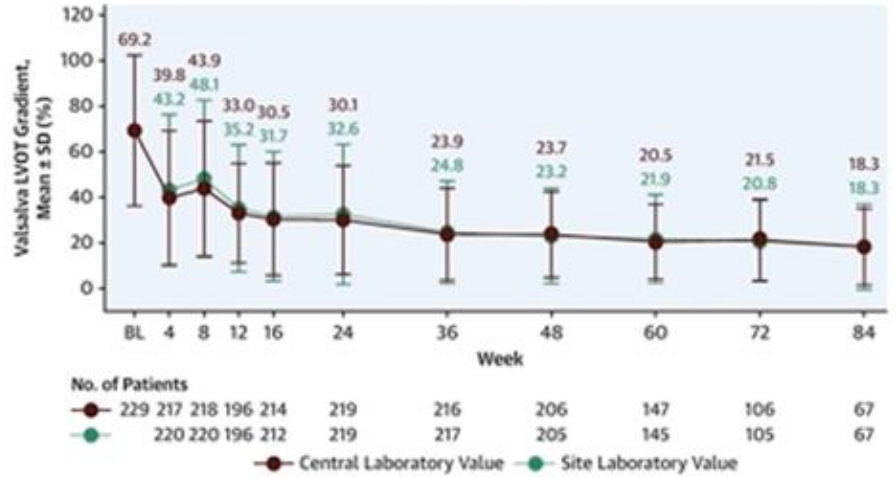
Initial and subsequent prescriptions for CAMZYOS must be written by the certified healthcare provider.

Echocardiograms are required

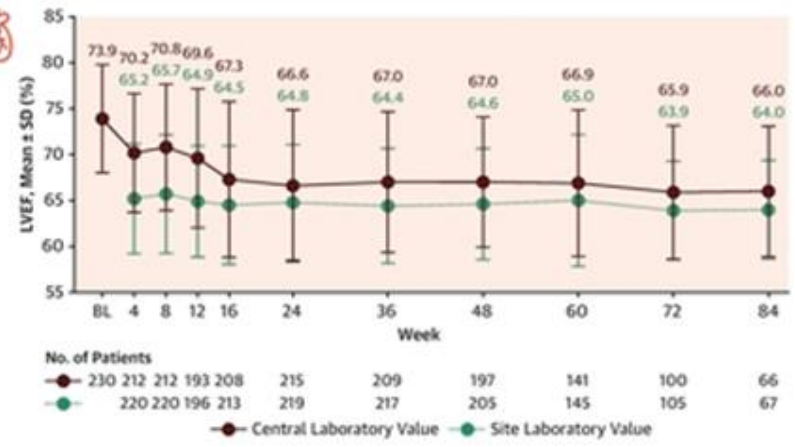
MAVA-LTE Study, EXPLORER-LTE Cohort

CENTRAL ILLUSTRATION: Longer-Term Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy With Mavacamten Shows Sustained Improvements and Is Well Tolerated





CENTRAL ILLUSTRATION: Continued



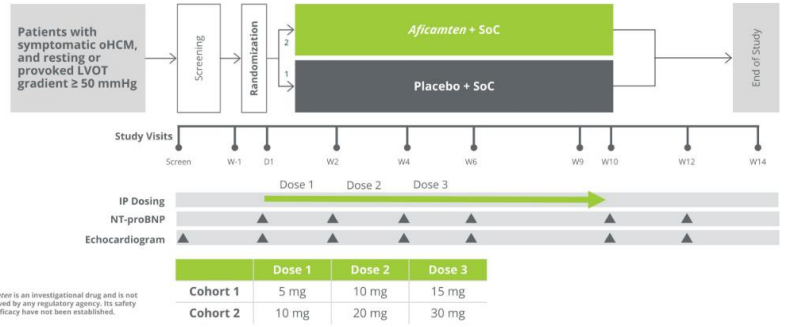
Rader F, et al. J Am Coll Cardiol HF. 2024;12(1):164-177.

Future!

REDWOOD-HCM: Cohorts 1 & 2

Patients with symptomatic oHCM on background therapy excluding *disopyramide*

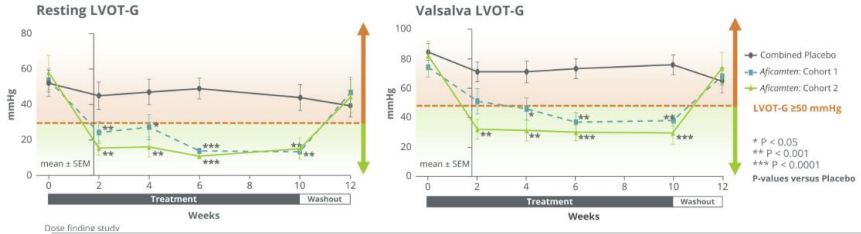
Two sequential dose-finding cohorts



Aficamten is an investigational drug and is not approved by any regulatory agency. Its safety and efficacy have not been established.

	Dose 1	Dose 2	Dose 3
Cohort 1	5 mg	10 mg	15 mg
Cohort 2	10 mg	20 mg	30 mg

Consistent, **clinically meaningful reductions in LVOT gradients** within two weeks
No treatment interruptions or discontinuations
Reversibility of drug effect demonstrated



Dose finding study

SEQUOIA-HCM: Phase 3 Trial

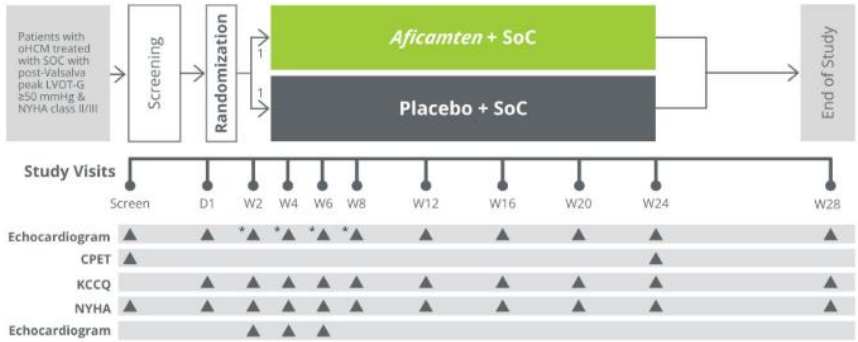
Completed enrollment; expect topline results by end of year

Primary endpoint: **Change in pVO_2 by CPET from baseline to Week 24**

Secondary objectives include measuring **change in KCCQ & improvement in NYHA class at week 12 and 24**

Enrolled 282 patients treated with standard of care with:
- **resting LVOT-G ≥30 mmHg,**
- **post-Valsalva LVOT-G ≥50 mmHg,**
- **NYHA Class II or III,**
- **exercise performance <80% predicted**

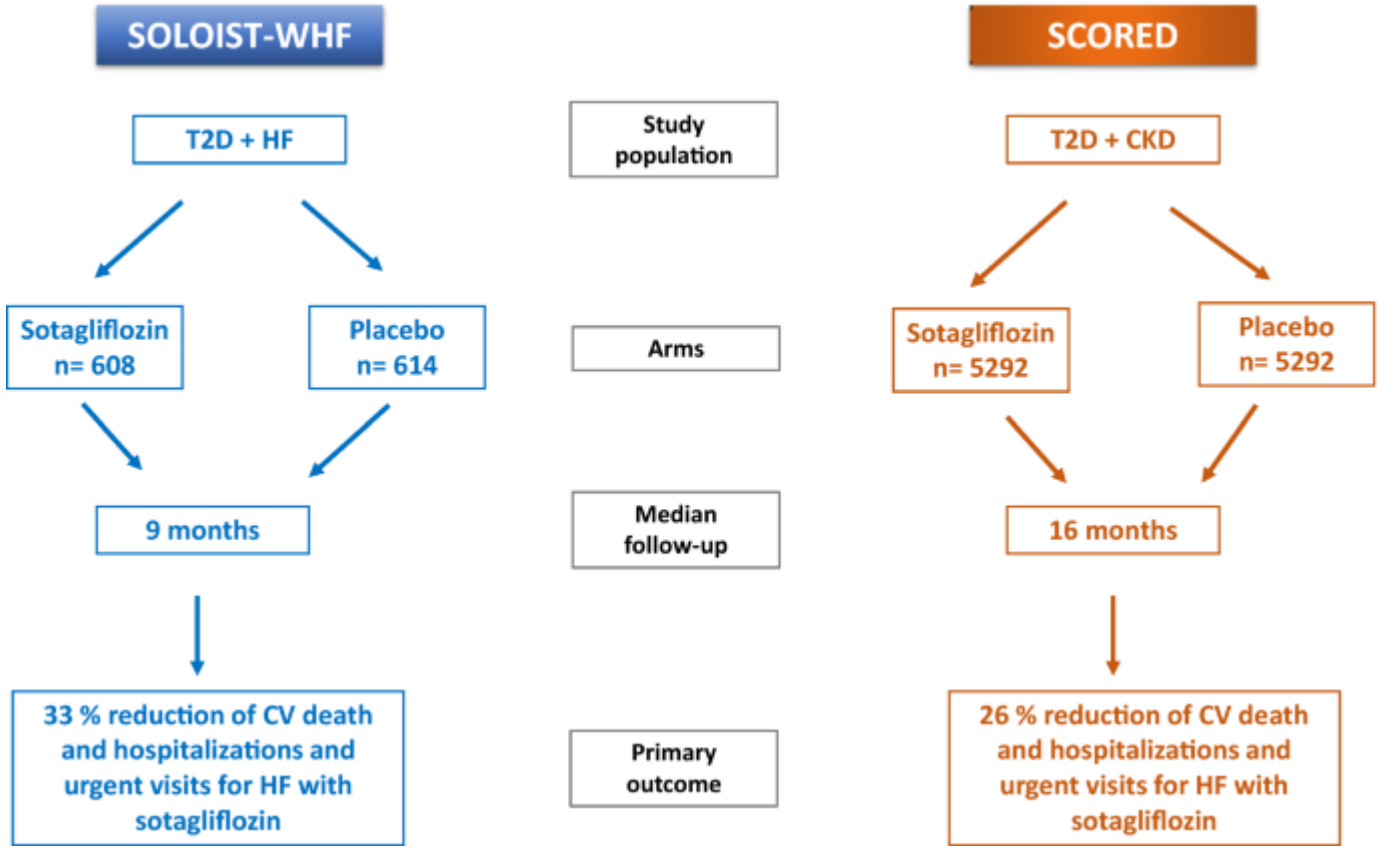
Individualized dose up-titration based on echocardiography: LVEF ≥55%, post-Valsalva LVOT-G ≥30 mmHg



Dose Options (Dose optimization completed by Week 8)

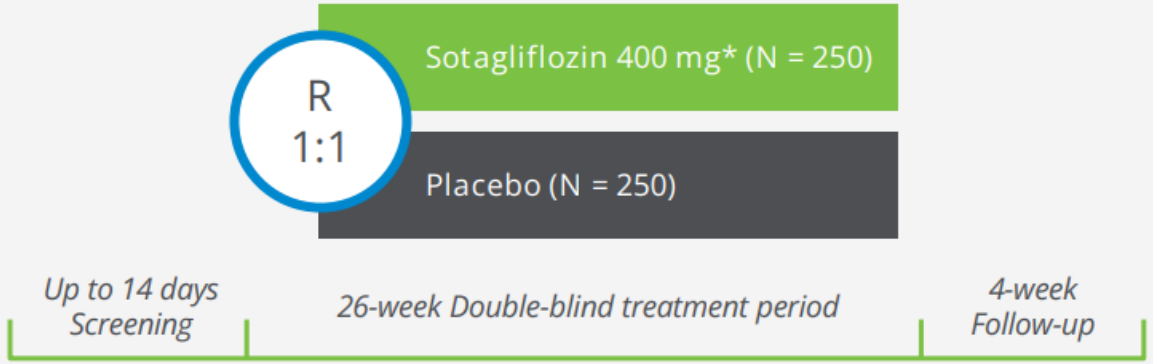
5 mg QD	10 mg QD	15 mg QD	20 mg QD

Sodium–glucose co–transporter (SGLT) 2 inhibitors



SONATA-HCM

SONATA Phase 3 study has commenced
with pragmatic design designed to enable a broad indication for HCM



- Adults with HCM (obstructive/non-obstructive)
- LVEF ≥50%
- KCCQ23 CSS <85
- NYHA Class II or III

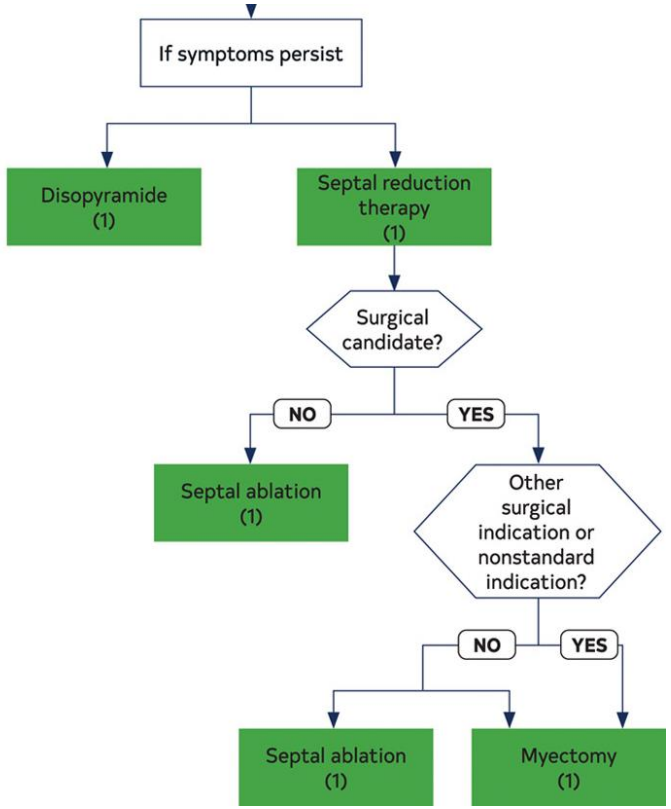
FDA Feedback Supports Potential Broad Label in HCM Based on Single Phase 3 Study

Primary endpoint: Change from baseline in KCCQ Clinical Summary Scale (CSS) score

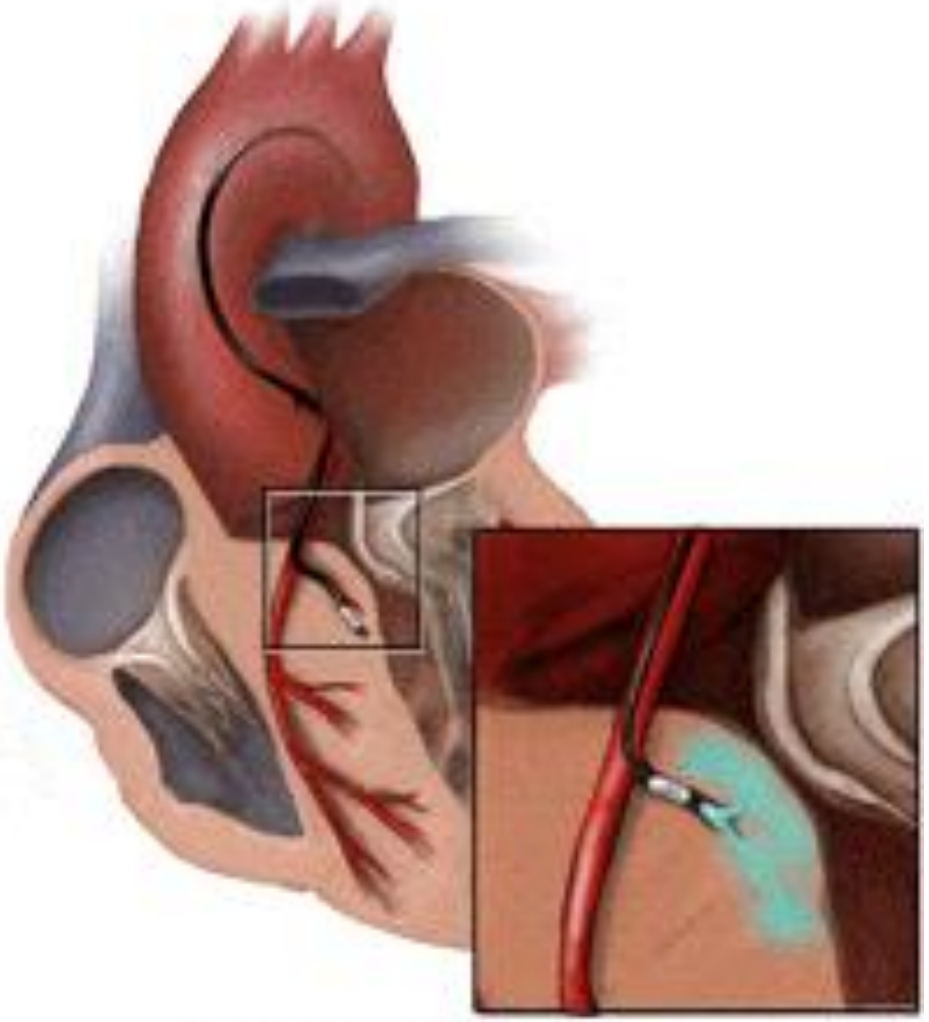
VANISH Trial

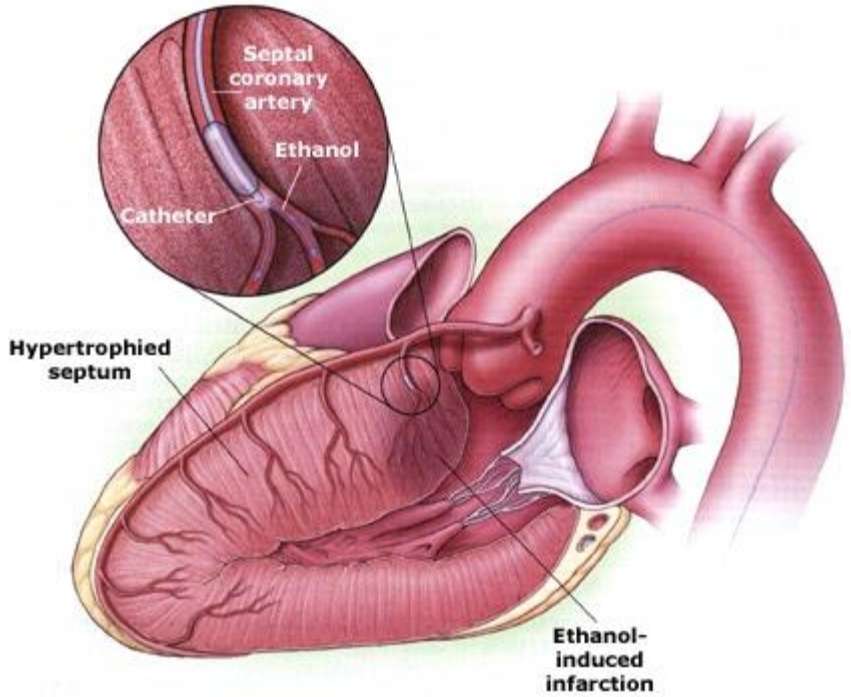
Baseline participant characteristics of the VANISH trial			
		Placebo (n=90)	Valsartan (n=88)
Mean age in years (SD)		23.5 (10.1)	23.1 (10.1)
Female		35 (39%)	34 (39%)
White		88 (98%)	85 (97%)
Sarcomeric gene	*MYH7*	36 (40%)	25 (28%)
	MYBPC3	44 (49%)	47 (53%)
	TNNT2	3 (3%)	5 (6%)
	TNNI3	2 (2%)	3 (3%)
	Other	5 (6%)	8 (9%)
Mean BMI		25.6	25.0
NYHA	Class I	84 (93%)	80 (91%)
	Class II	6 (7%)	8 (9%)
Mean maximum LV wall thickness		16.4 mm	17.9 mm
Mean LV ejection fraction		66.3%	66.1%
Median total circulating TGF-β (IQR)*		4150 pg/mL (2550-5638)	3734 pg/mL (3153-6458)
Median free circulating TGF-β (IQR)^		2.7 pg/mL (1.3-9.0)	2.9 pg/mL (1.6-8.5)

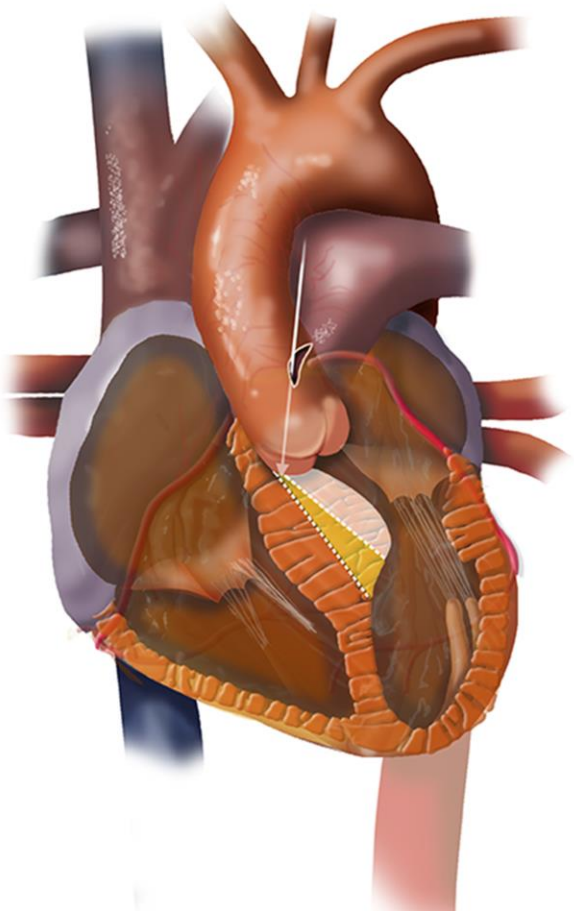
More than Pills!

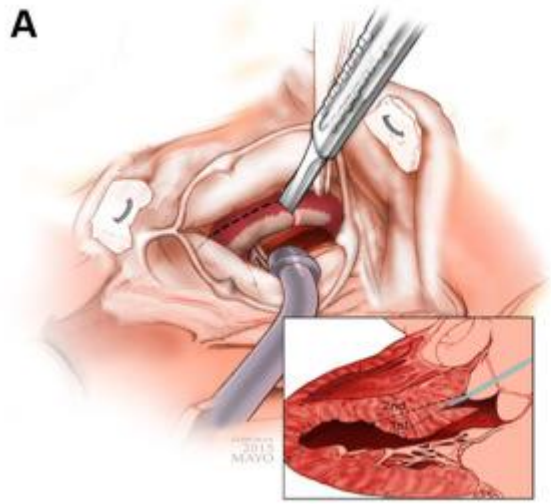


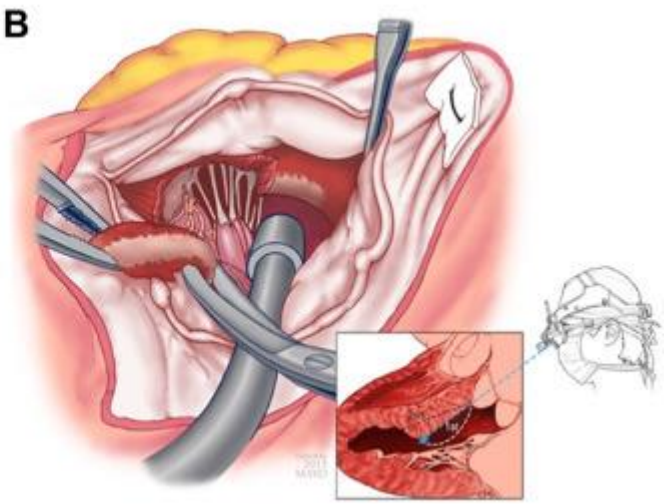
Past

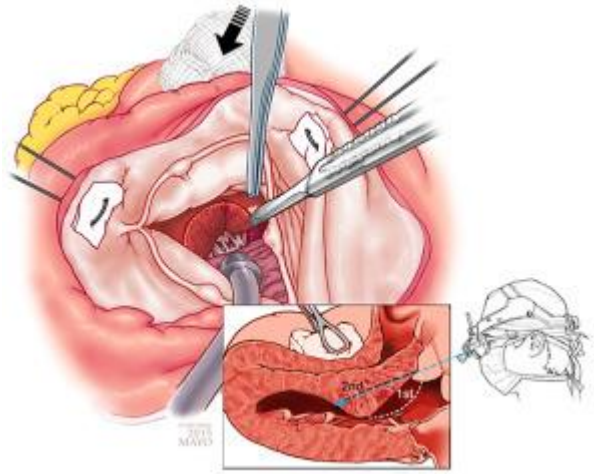

Alcohol Septal Ablation

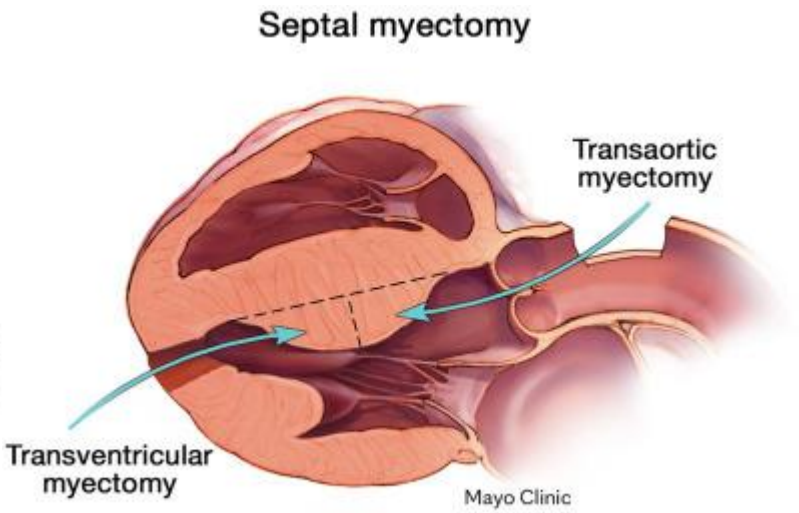

Septal coronary artery
Ethanol
Catheter
Hypertrophied septum
Ethanol-induced infarction

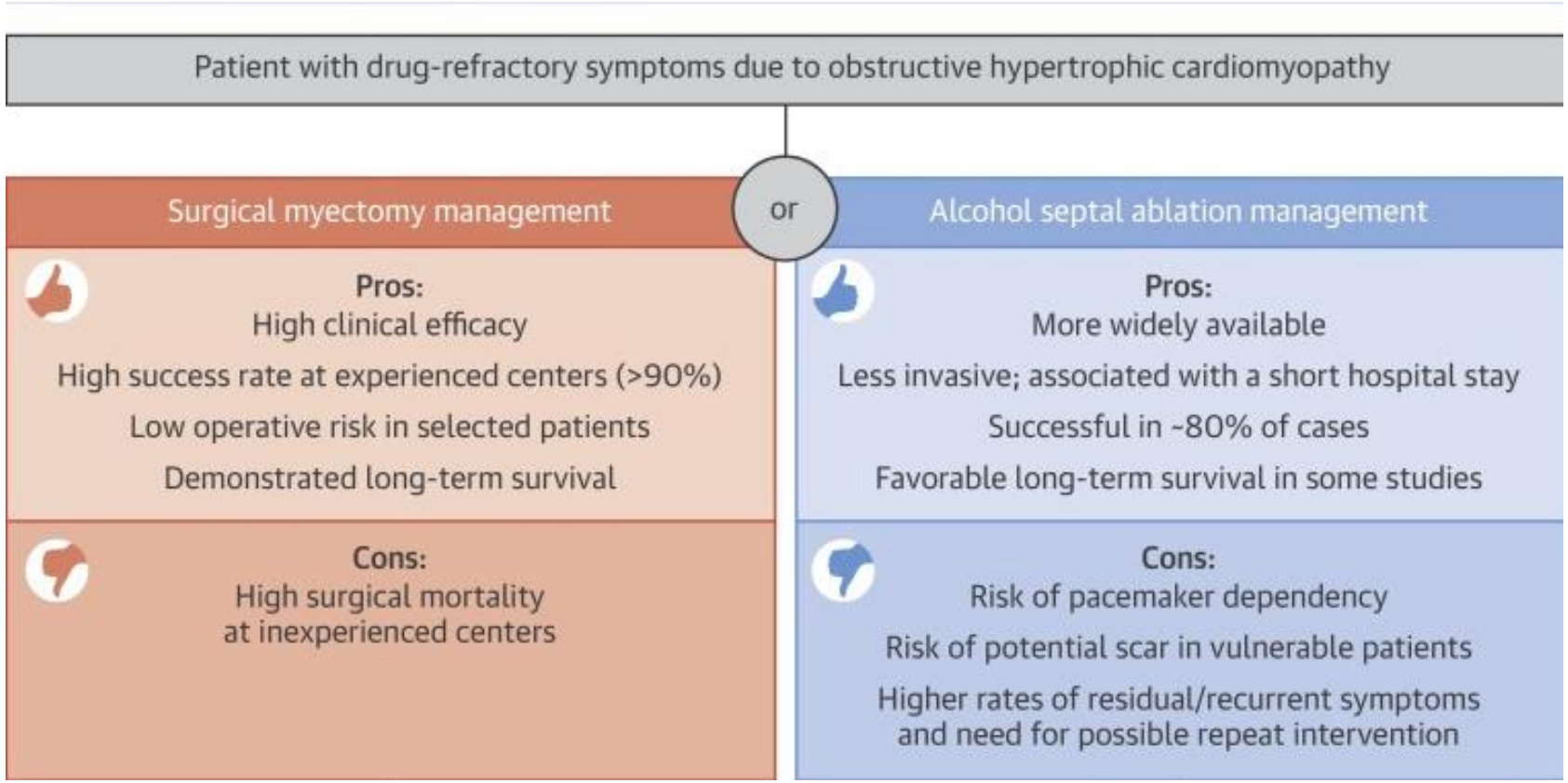



A


B

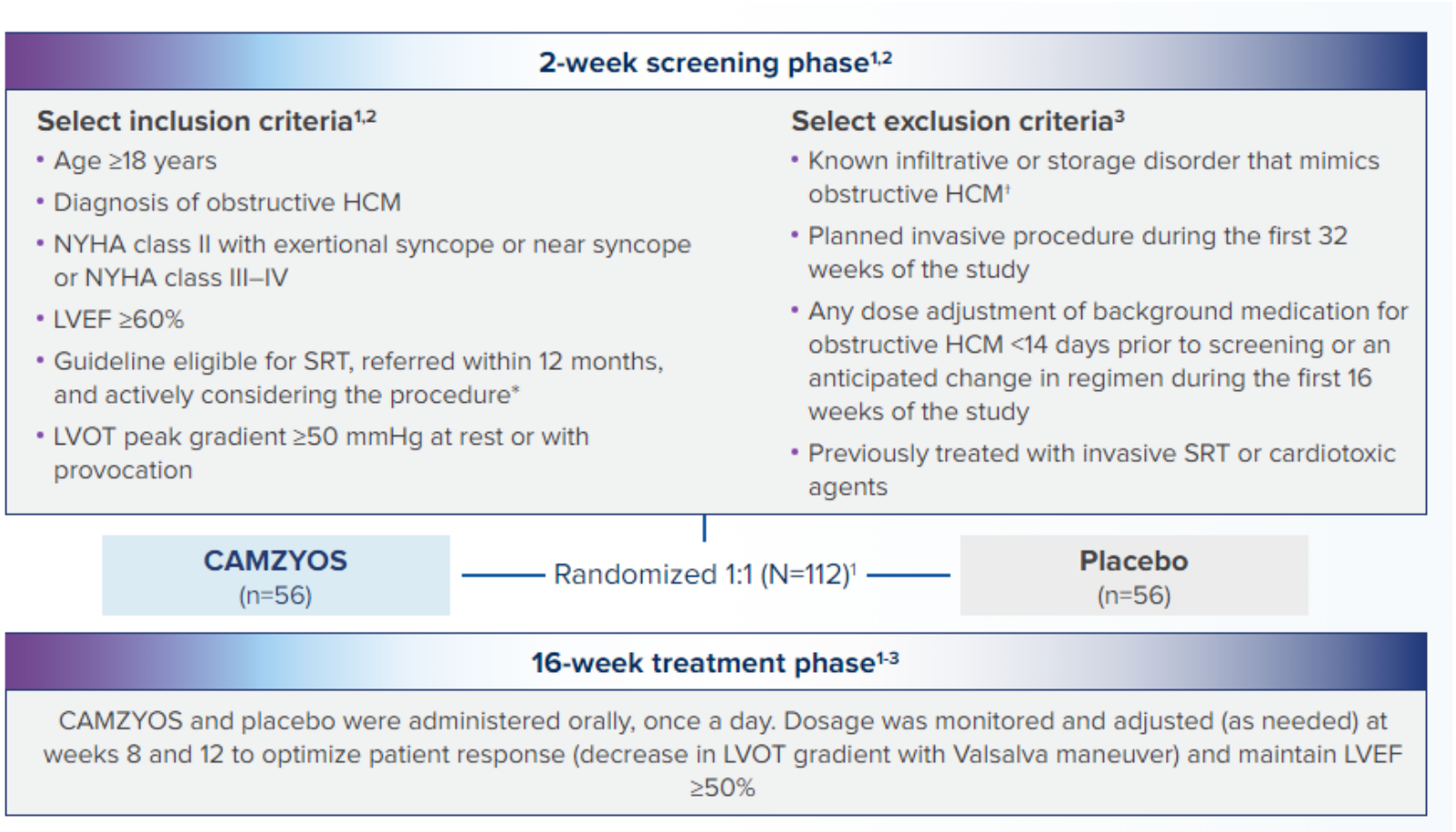



Septal myectomy
Transaortic myectomy
Transventricular myectomy
Mayo Clinic


Patient with drug-refractory symptoms due to obstructive hypertrophic cardiomyopathy
Surgical myectomy management
or
Alcohol septal ablation management
Pros:
High clinical efficacy
High success rate at experienced centers (>90%)
Low operative risk in selected patients
Demonstrated long-term survival
Cons:
High surgical mortality
at inexperienced centers
Pros:
More widely available
Less invasive; associated with a short hospital stay
Successful in ~80% of cases
Favorable long-term survival in some studies
Cons:
Risk of pacemaker dependency
Risk of potential scar in vulnerable patients
Higher rates of residual/recurrent symptoms
and need for possible repeat intervention

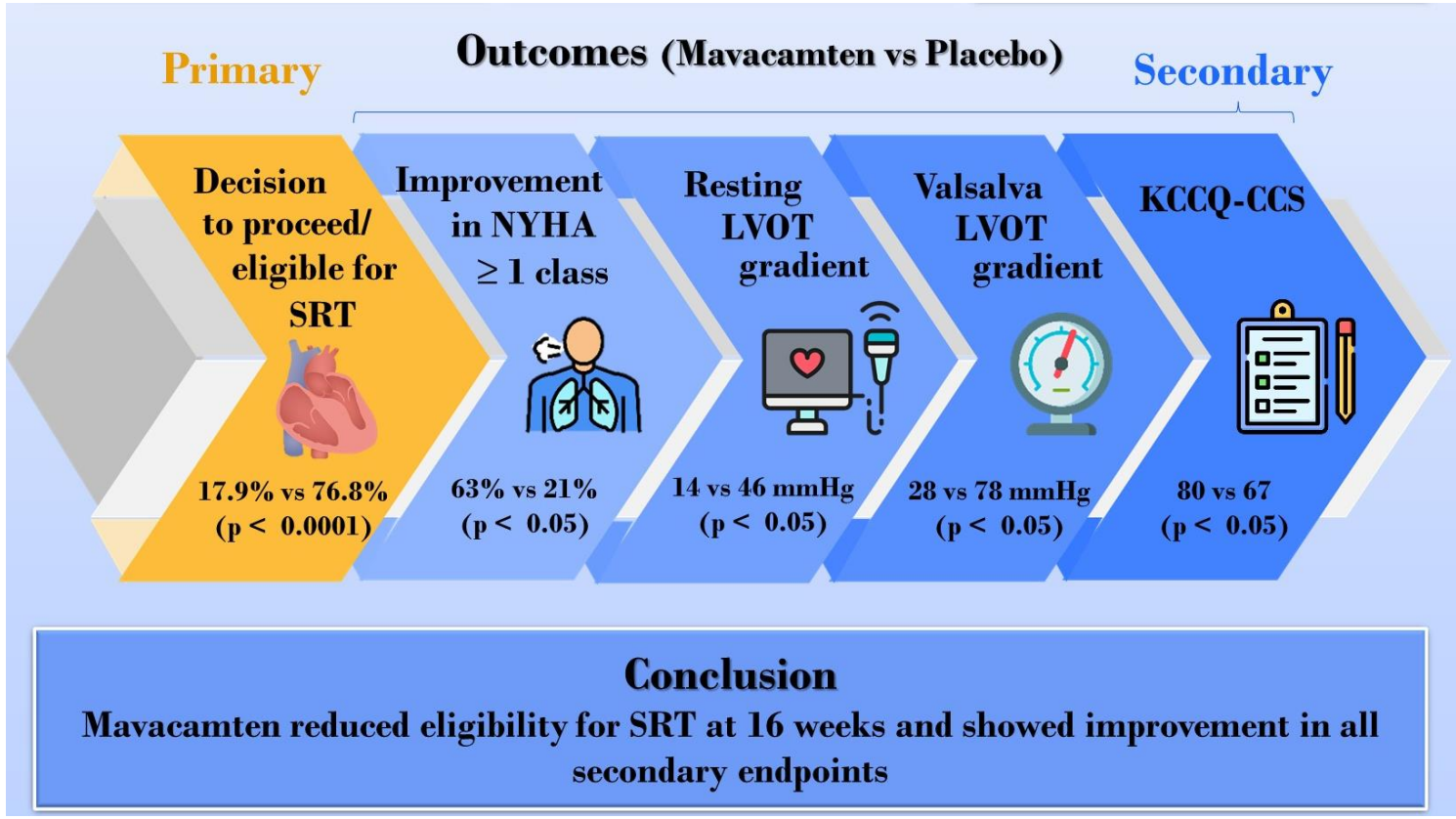
What's Next / VALOR-HCM

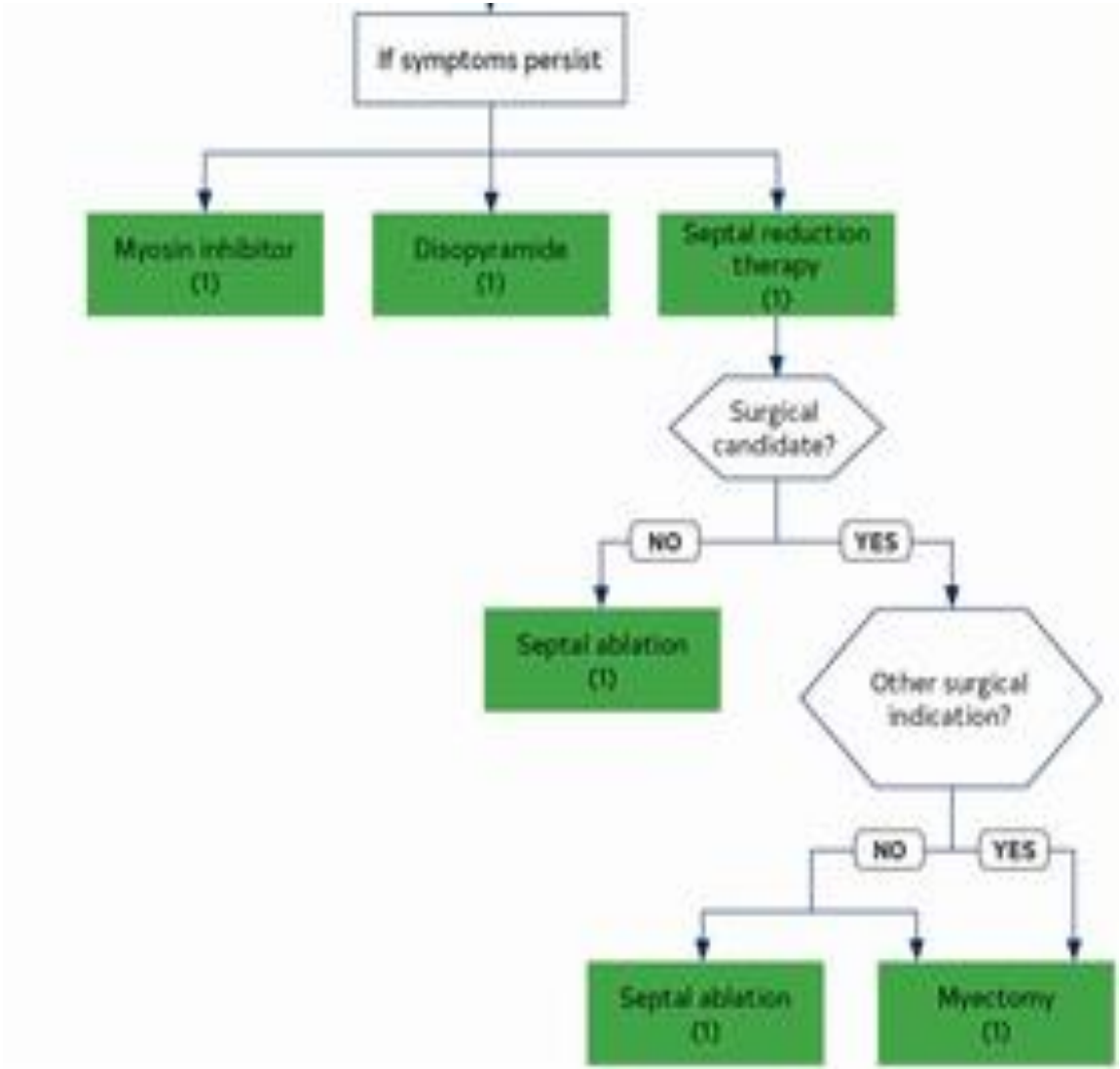
To assess if Mavacamten is safe and efficacious in reducing the need for SRT when added to maximally tolerated medical therapy among patients with obstructive hypertrophic cardiomyopathy



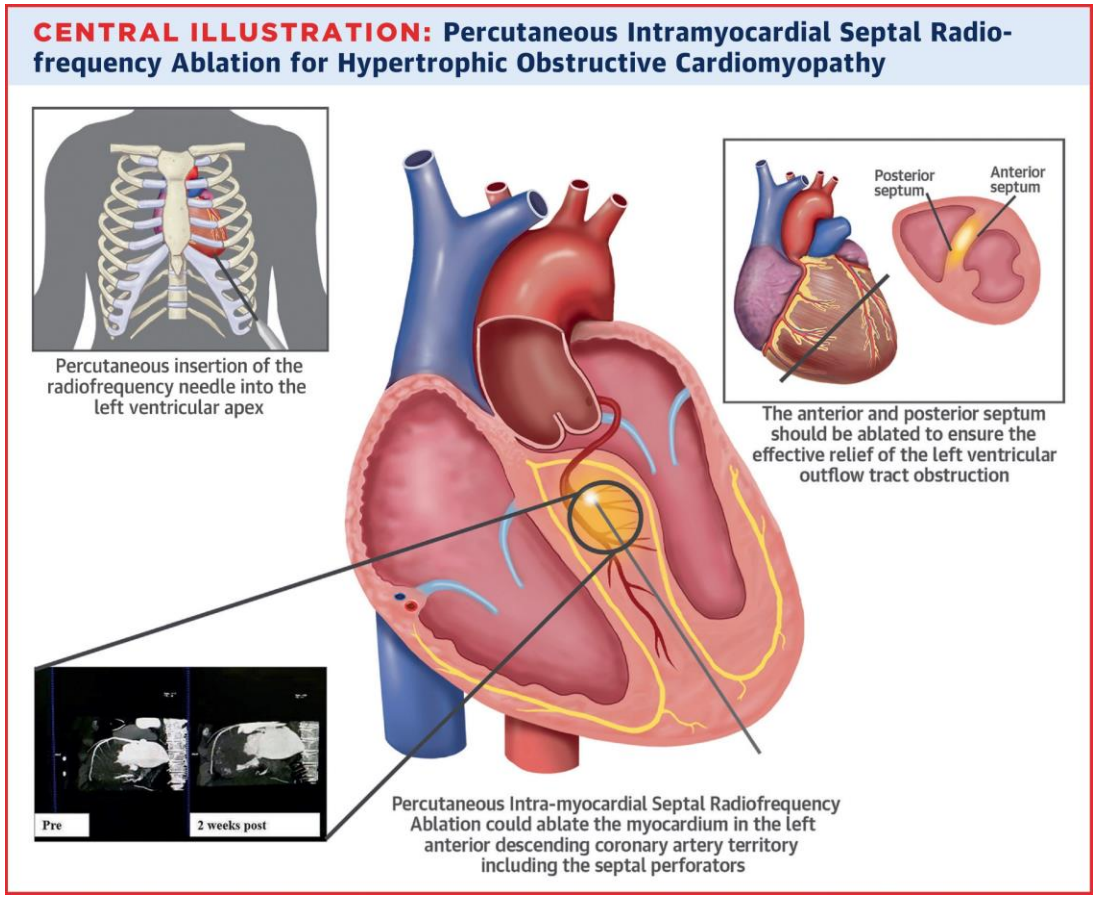
VALOR-HCM

- Primary Outcome: Composite – decision to proceed with SRT or considered guideline eligible for SRT.
- Secondary Outcomes: Change in postexercise LVOT gradient, NYHA Class, KCCQ-23 CSS, NT-proBNP, and cardiac troponin.
- 46% were on beta blockers, 15% were taking calcium channel blockers, and 32% were on combination therapy.
- 20% of patients were taking disopyramide.
- Baseline mean LV ejection fraction (LVEF) was 76%.
- Peak resting LVOT gradient was 49 mmHg and mean post-exercise LVOT gradient was 84 mmHg.

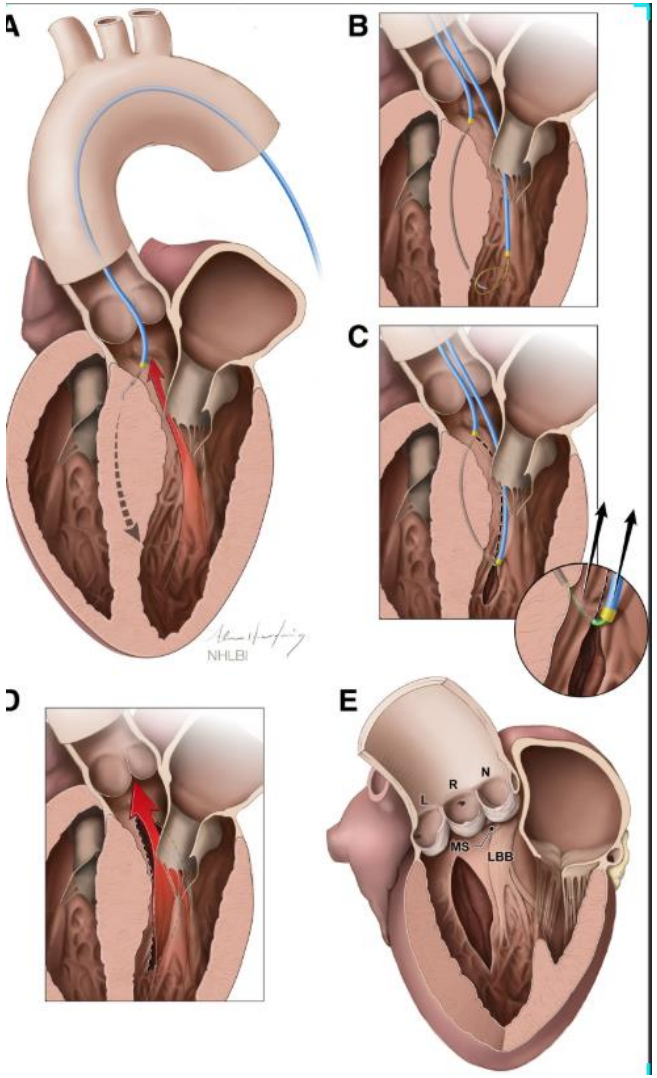

Primary
Outcomes (Mavacamten vs Placebo)
Secondary
Decision to proceed/ eligible for SRT
17.9% vs 76.8% (p < 0.0001)
Improvement in NYHA ≥ 1 class
63% vs 21% (p < 0.05)
Resting LVOT gradient
14 vs 46 mmHg (p < 0.05)
Valsalva LVOT gradient
28 vs 78 mmHg (p < 0.05)
KCCQ-CCS
80 vs 67 (p < 0.05)
Conclusion
Mavacamten reduced eligibility for SRT at 16 weeks and showed improvement in all secondary endpoints

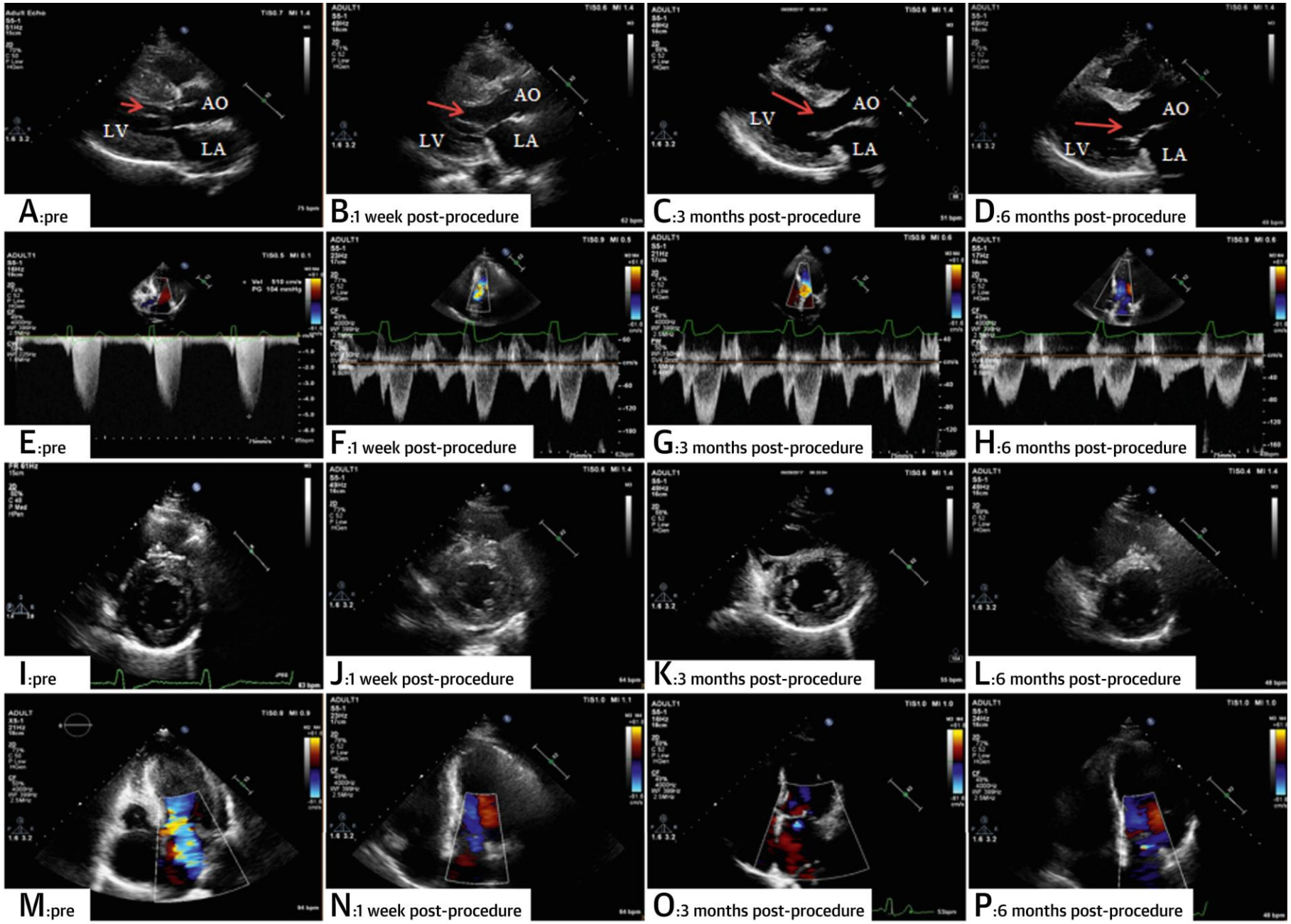

If symptoms persist
Myosin inhibitor (1)
Disopyramide (1)
Septal reduction therapy (1)
Surgical candidate?
NO
YES
Septal ablation (1)
Other surgical indication?
NO
YES
Septal ablation (1)
Myectomy (1)

What's Next

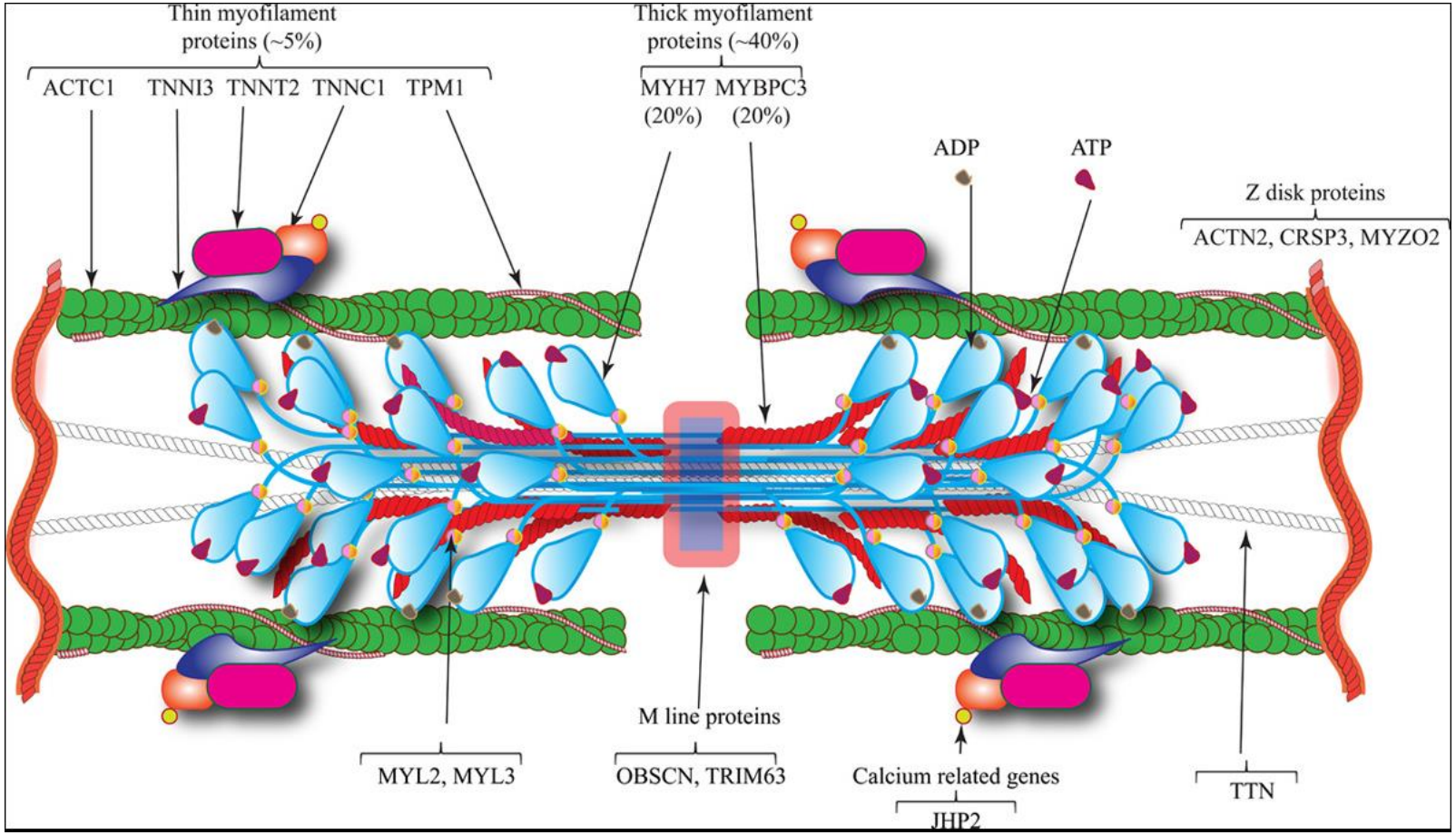


SESAME




AO
LV
LA
A:pre
B:1 week post-procedure
C:3 months post-procedure
D:6 months post-procedure
E:pre
F:1 week post-procedure
G:3 months post-procedure
H:6 months post-procedure
I:pre
J:1 week post-procedure
K:3 months post-procedure
L:6 months post-procedure
M:pre
N:1 week post-procedure
O:3 months post-procedure
P:6 months post-procedure

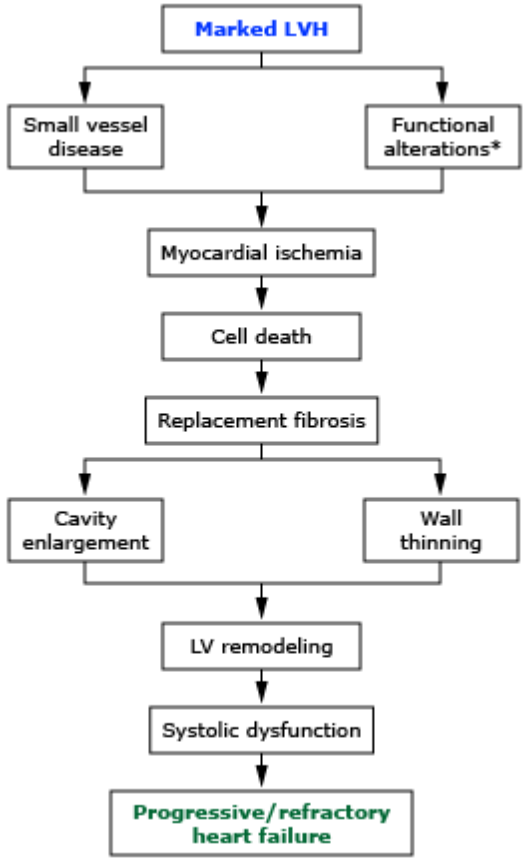
What's Next- Beyond Pills! Gene therapy

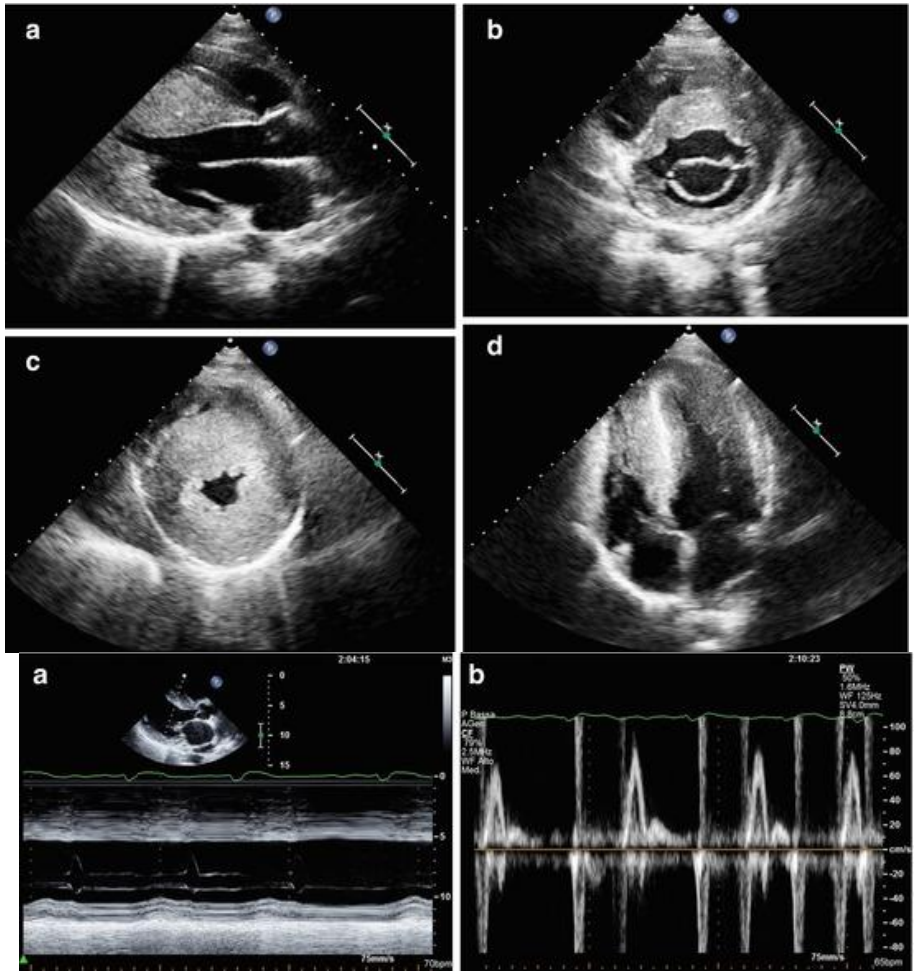


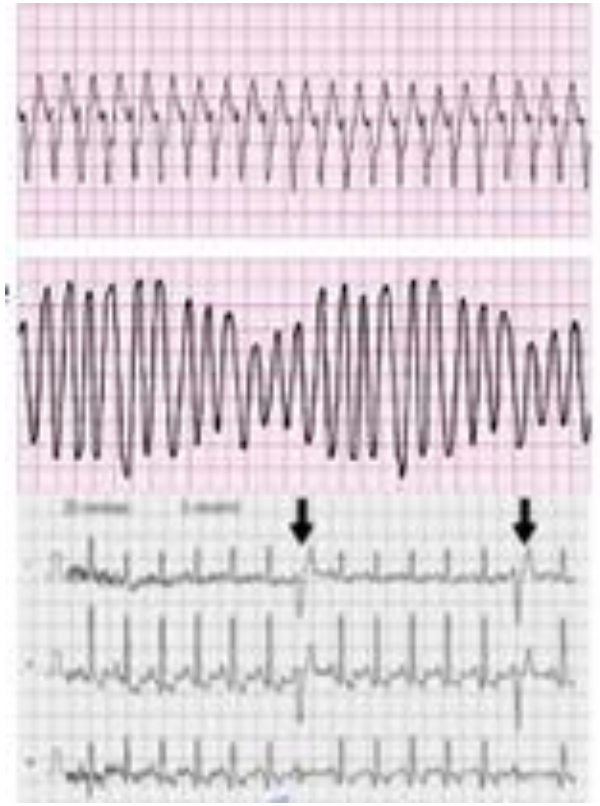
Several strategies are being investigated in the realm of gene therapy for HCM

- **Gene replacement**: This involves introducing functional copies of the affected gene or a related gene to compensate for the defective or mutated gene's role in causing HCM. Myosin binding protein C 3 (MYBPC3) mutation.
- **Gene editing:** Techniques such as CRISPR–Cas9 have shown promise in correcting specific genetic mutations associated with HCM, by precise targeting and modification of the problematic genes within cardiac cells.
- **Gene silencing:** RNA interference (RNAi) is a method used to silence or reduce the expression of specific genes
- **Signaling pathway modulation:** This approach involves modifying signaling pathways or biological processes that play a crucial role in the pathogenesis of the disease.

End-stage phase of hypertrophic cardiomyopathy







Warning Signs!

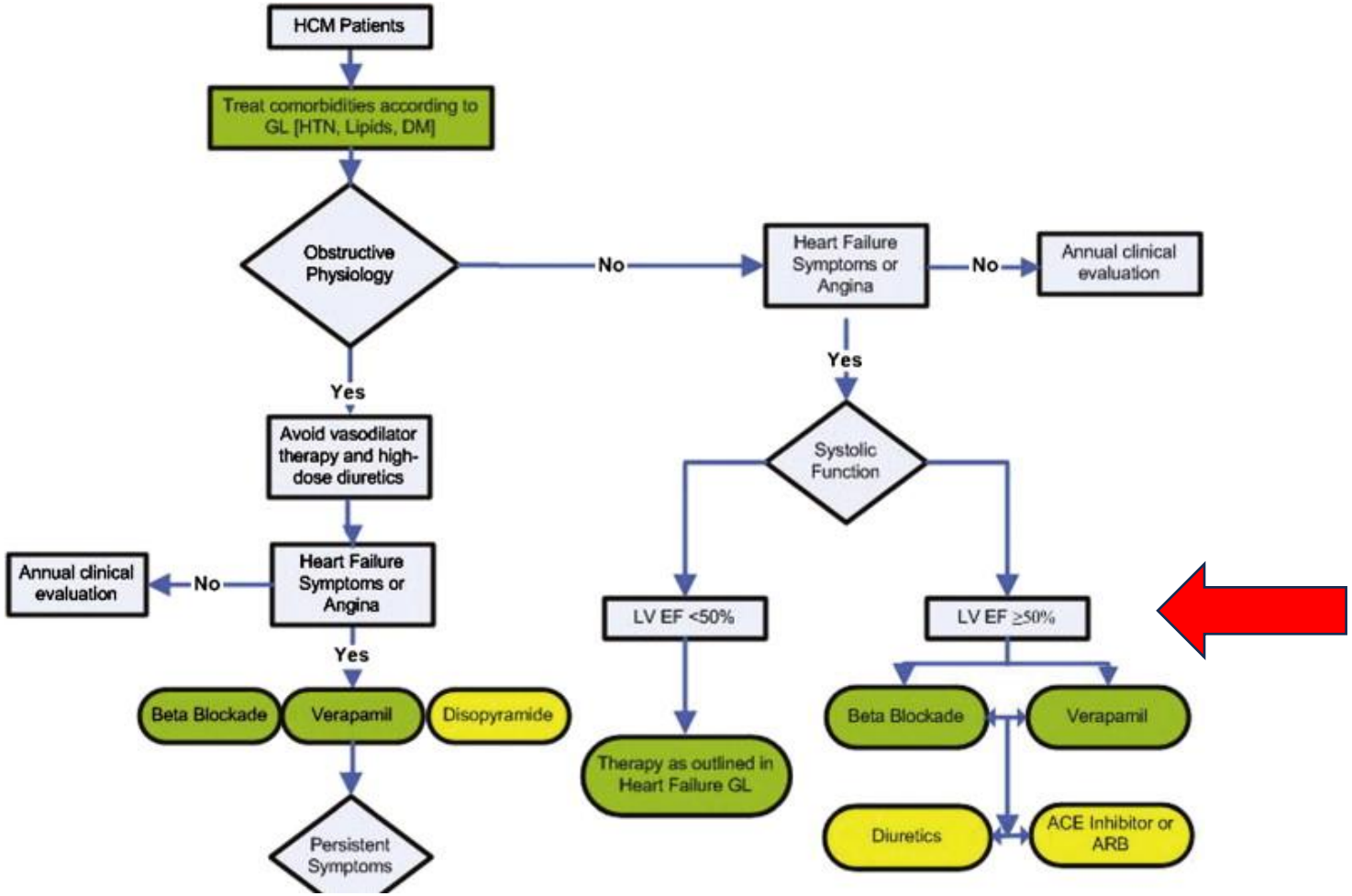
- EF falls below 50%
- Increasing diuretic requirements
- Intolerance of their Negative inotropic agents.
- Frequent Arrythmias.
- Frequent ER visits.

Other Helpful tools – CPET/RHC/Serial MRI/Hepatic –Renal profiles

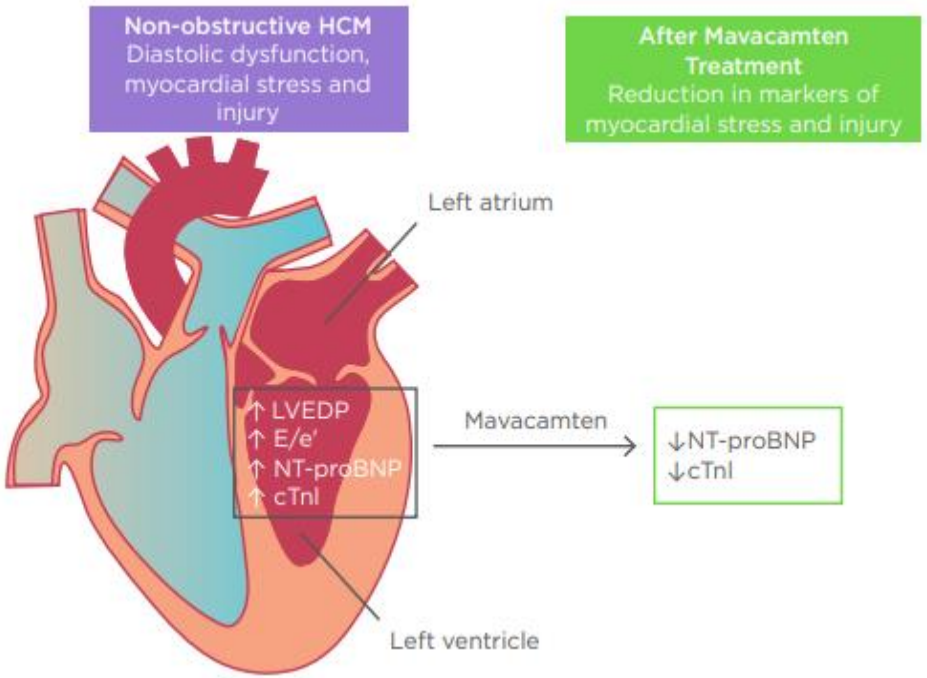
Cardiac transplant /Bridge to transplant.

- ISLT Listing Criteria. Different from DCMP.
- Dilated Morphology
- Restrictive Anatomical Limitations.

nHCM


HCM Patients
Treat comorbidities according to GL [HTN, Lipids, DM]
Obstructive Physiology
No
Heart Failure Symptoms or Angina
No
Annual clinical evaluation
Yes
Yes
Avoid vasodilator therapy and high-dose diuretics
Systolic Function
Annual clinical evaluation
No
Heart Failure Symptoms or Angina
LV EF <50%
LV EF ≥50%
Yes
Beta Blockade
Verapamil
Disopyramide
Therapy as outlined in Heart Failure GL
Beta Blockade
Verapamil
Persistent Symptoms
Diuretics
ACE Inhibitor or ARB

The MAVERICK-HCM Study



REDWOOD-HCM Trial, Cohort 4

Efficacy and Safety of *Aficamten* in Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy: Results from the REDWOOD-HCM trial, Cohort 4

TRIAL DESIGN

- **41 patients** with symptomatic (NYHA class II–III) non-obstructive HCM (LVOT-G <30 mm Hg; LVEF ≥60%; NT-proBNP >300 pg/mL)
- **Individualized dosing of aficamten** (5–15 mg once daily) based on site-read LVEF ≥55%
- **10 weeks of treatment + 2-week washout**

KEY RESULTS

- Clinically relevant improvements in **NYHA class, KCCQ-CSS and biomarkers** at Week 10 (panels A-C)
- Modest **reduction in LVEF** (panel D)
- Most parameters returned to baseline during the 2-week washout, demonstrating **reversibility of pharmacodynamic effects**

The efficacy and safety of *aficamten* were demonstrated during 10 weeks of treatment

Non-Obstructive HCM

Large Phase 3's & Promising Preclinical Asset

Myosin Inhibitors

2x Phase 3 Trials in nHCM (approved in oHCM)

Mavacamten

- Phase 3 (ODYSSEY-HCM)
- Started in Dec 2022
- N=420
- Primary Endpoint: KCCQ-CSS at week 48, change from baseline in pVO_2
- Projected data readout 2025

Aficamten

- Phase 3 (ACACIA-HCM)
- Started in Sep 2023
- N=420
- Primary Endpoint: KCCQ-CSS from baseline to week 36

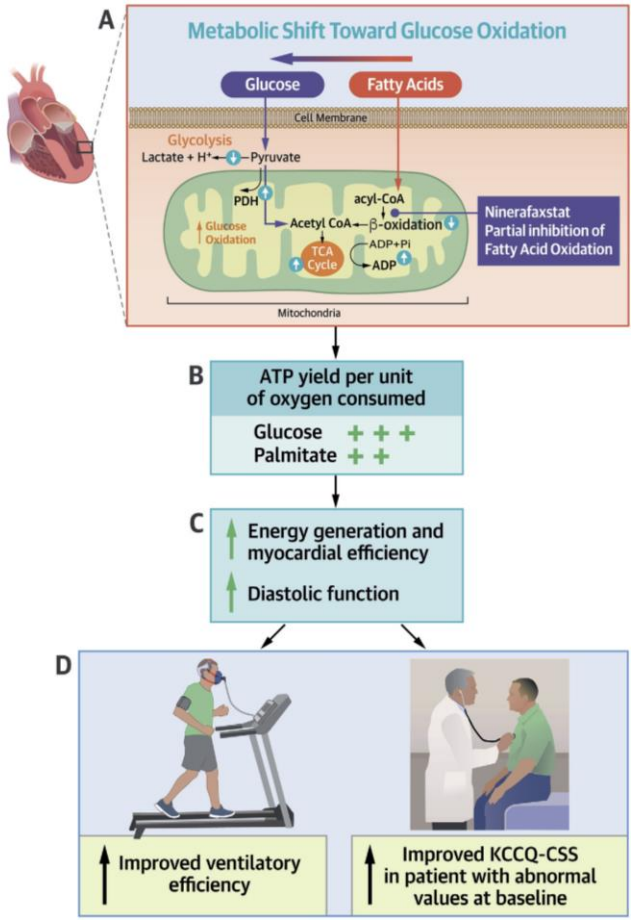
New Comers!

- Ion channel Blockers (Ranolazine /Eleclazine)

  Restyle HCM , Liberty HCM.

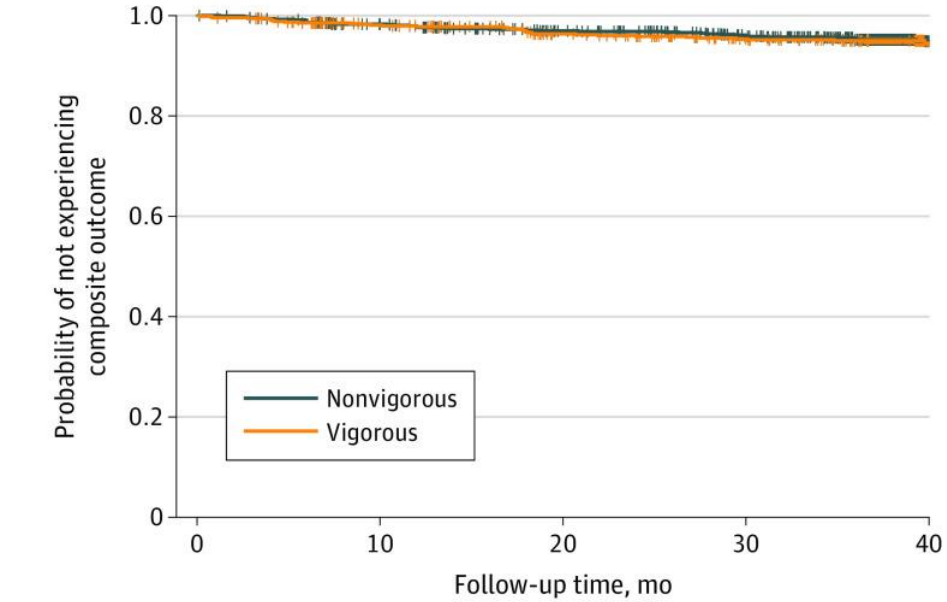
. Cardiac Mitotrope , Ninerafaxtat (IMPROVE-HCM)

. (SGLT) 2 inhibitors – SONATA-HCM



Exercise in Genetic heart disease

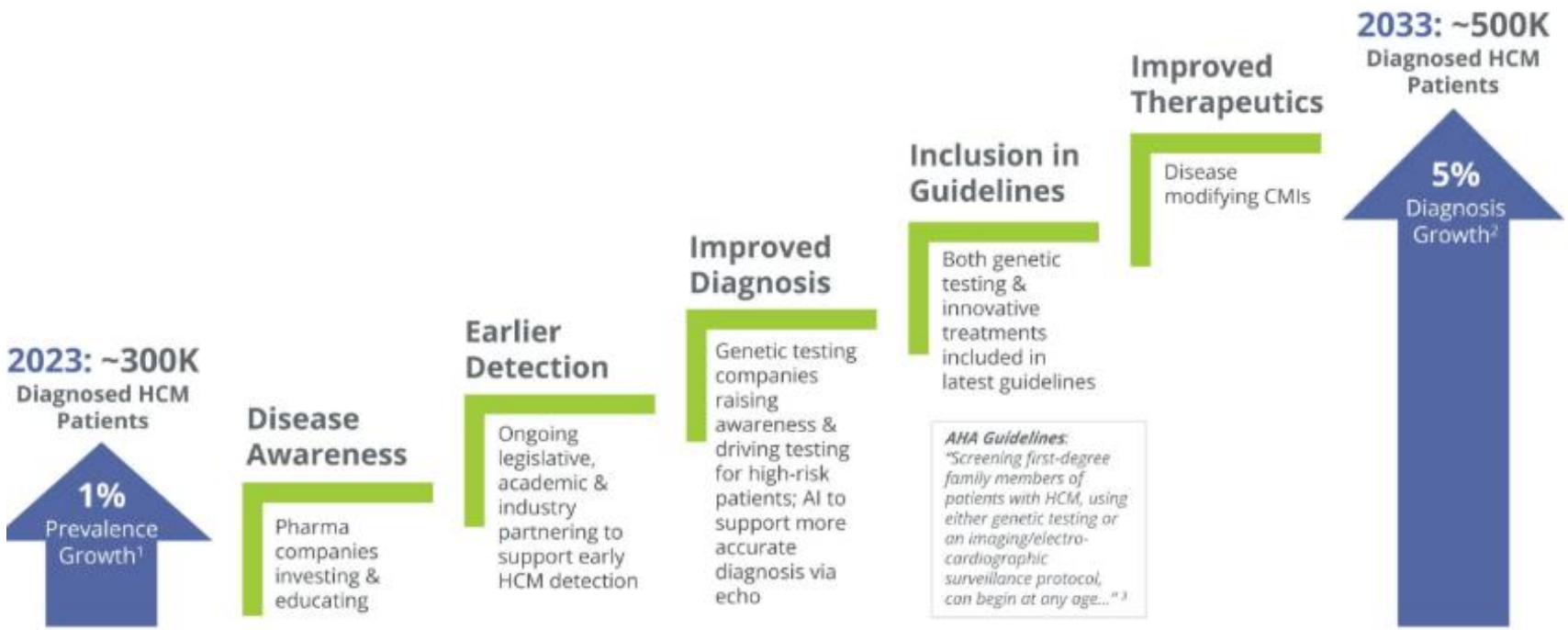
- LIVE-HCM
- Return-to-Play with Genetic Heart Disease



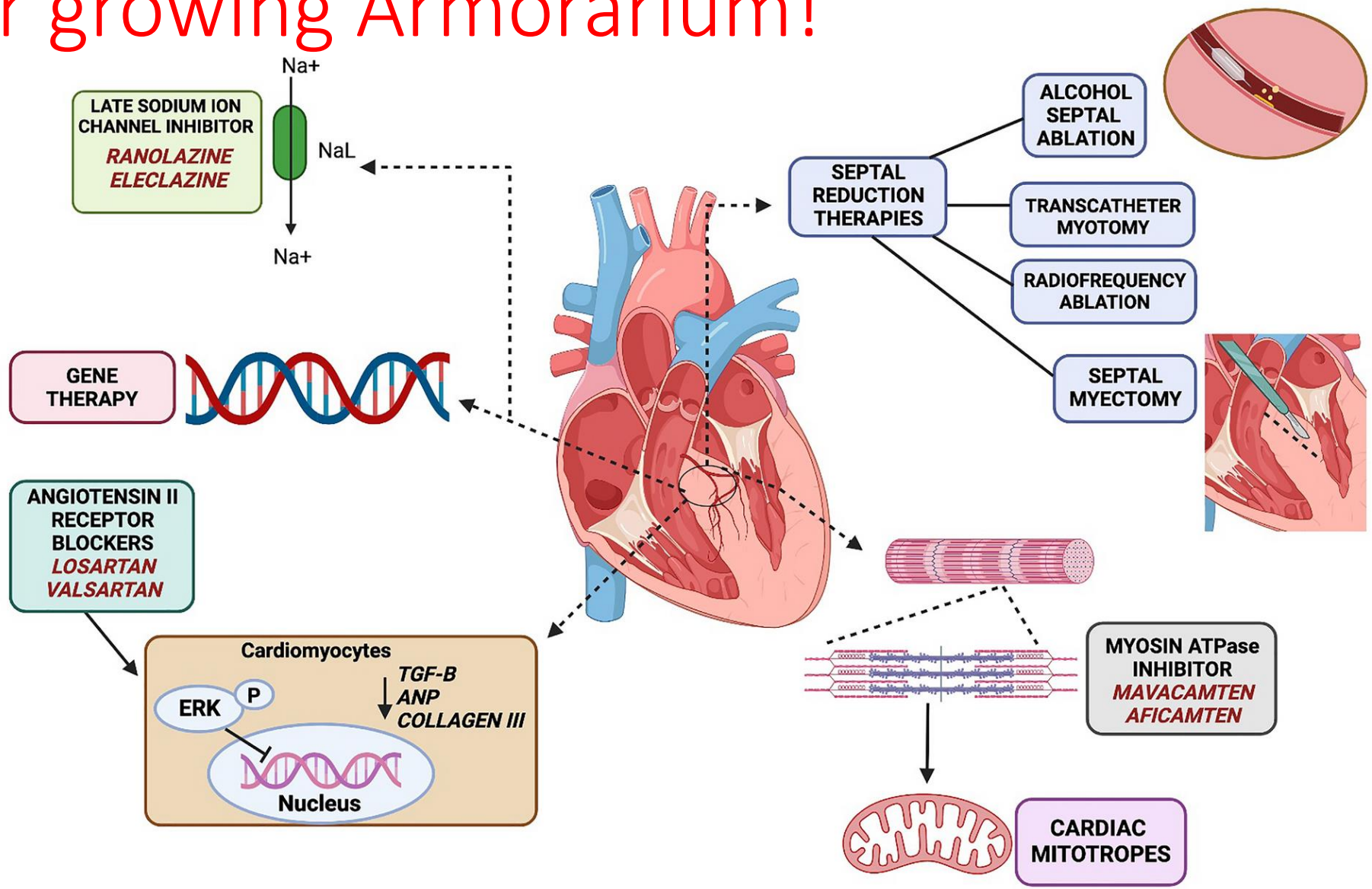
No. at risk			
Nonvigorous	961	852	262
Vigorous	699	608	193

- Vigorous exercise may be safe in individuals with hypertrophic cardiomyopathy (HCM) who are evaluated and appropriately risk stratified by an expert.
- Return to play among athletes with genetic heart disease (HCM, long QT syndrome, dilated cardiomyopathy) is possible in a subset of athletes who have been evaluated by an expert and for whom a risk assessment and emergency action plan have been established with all stakeholders

Diagnosis of HCM Anticipated to Grow 5x the Rate of the General Population



Our growing Armorarium!




END OF PRESENTATION
ANY QUESTIONS?