Hypertrophic Cardiomyopathy: Emerging concepts in diagnosis and management

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Consultant to Medtronic

Hypertrophic Cardiomyopathy: Some simple math

125 Countries involving 90% of world population

Prevalence
1:200-1:500

Estimated ~15-20 million
affected worldwide

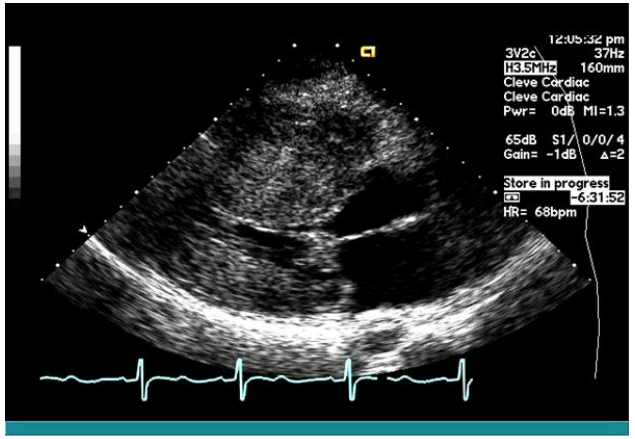
- Assuming a prevalence of HCM is at least 1:500, there are ~ 700,000 HCM patients in USA[1]
  - ≈100K patients diagnosed with HCM in USA[2,3]
  - So, ~85% (600,000) individuals are undiagnosed[2]
- Based on above math, 16 million HCM patients in the world
  - If 85% are undiagnosed, then that number is 13.6 million

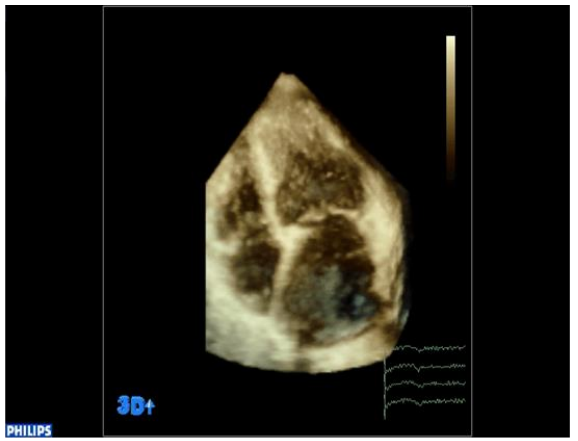
Lots of opportunities to improve diagnosis
Lots of patients to treat

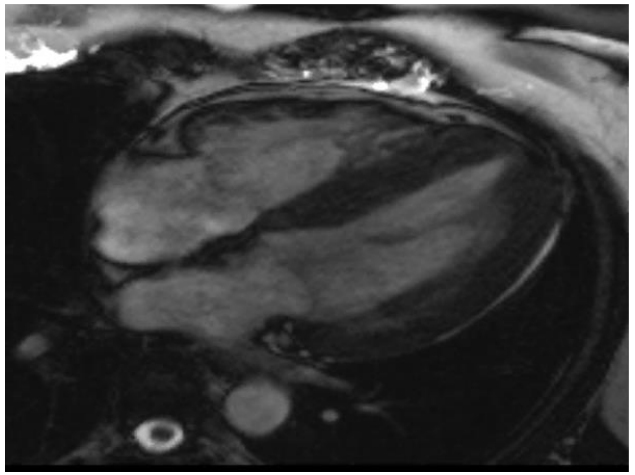
1. Semsarian C, et al. *J Am Coll Cardiol*. 2015;65:1249-1254. 2. Maron M, et al. *Am J Cardiol*. 2016;117:1651-1654. 3. Maron BJ, et al. *J Am Coll Cardiol*. 2014;64:83-99.

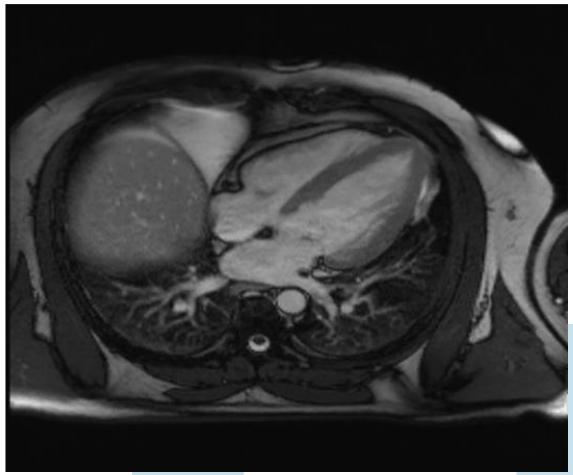
Step 1: Multimodality imaging key in diagnosing HCM

- Establish diagnosis and phenotype
  - Differential diagnosis
- Ascertain symptoms
  - Due to LVOT Obstruction (resting or provokable)
    - •Basal septal hypertrophy
    - •Mitral valve leaflets: varying sizes, presence of systolic anterior motion (SAM)
    - •Papillary muscles: location, multiplicity, laxity
  - Without LVOT obstruction
    - •Diastolic dysfunction
    - •Midcavitary/apical hypertrophy
- Risk of SCD
- Familial and genetic implications





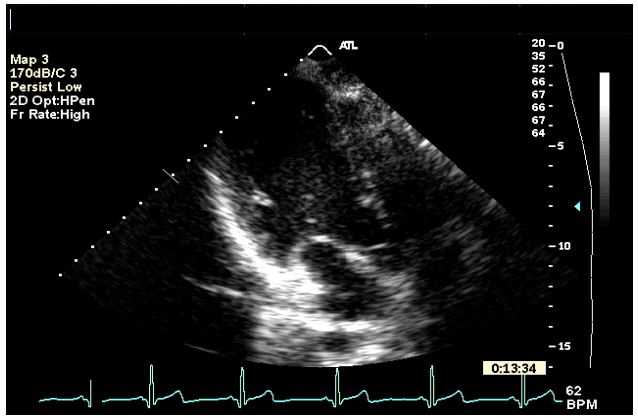


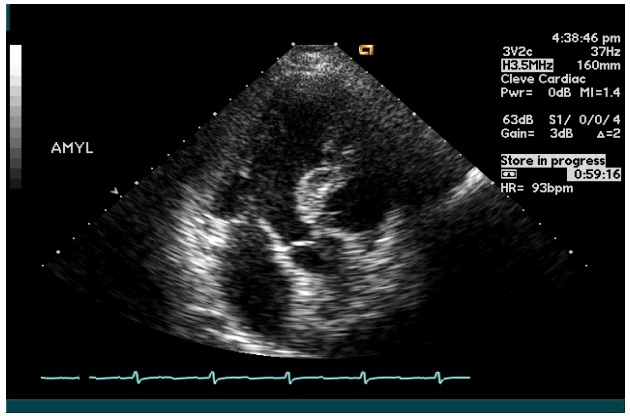


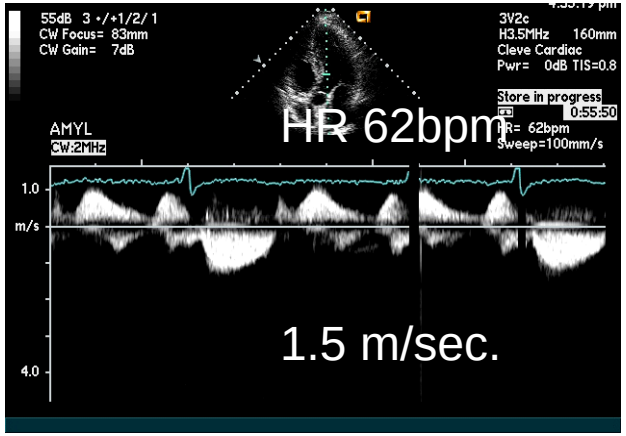
Echo is the mainstay; CMR offers complementary value

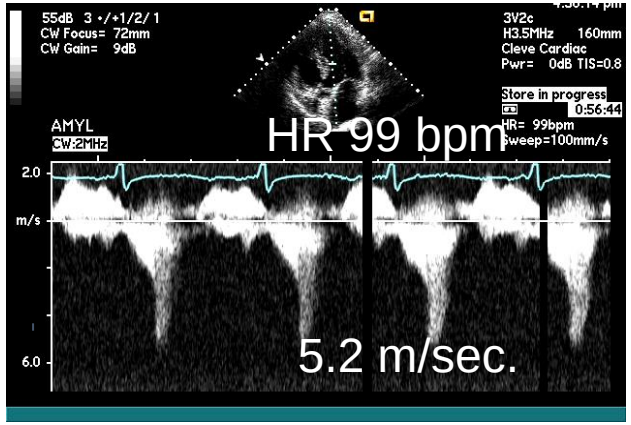
Rickers et al. Circulation 2005;112:855-61
Phelan, Desai et al. AJC 2017
Patel, Desai et al. Circ Img, 2015

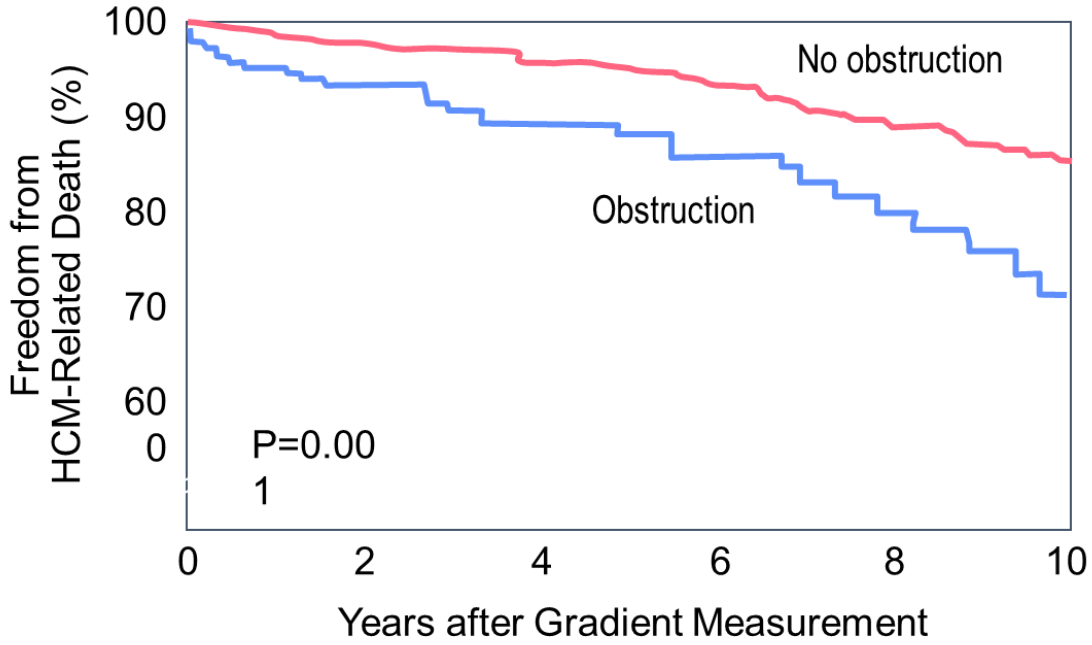
2: Elicit LVOT Obstruction: Don’t look, Won’t find, Can’t Treat











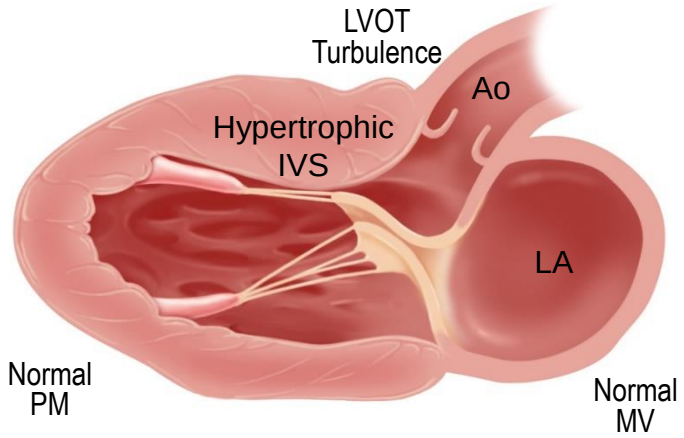
Need to Utilize All Means to Provoke LVOT Gradient: Amyl nitrite, Valsalva, Treadmill, Bike
At rest, seen in 25%, with provocation seen in ~ 70%

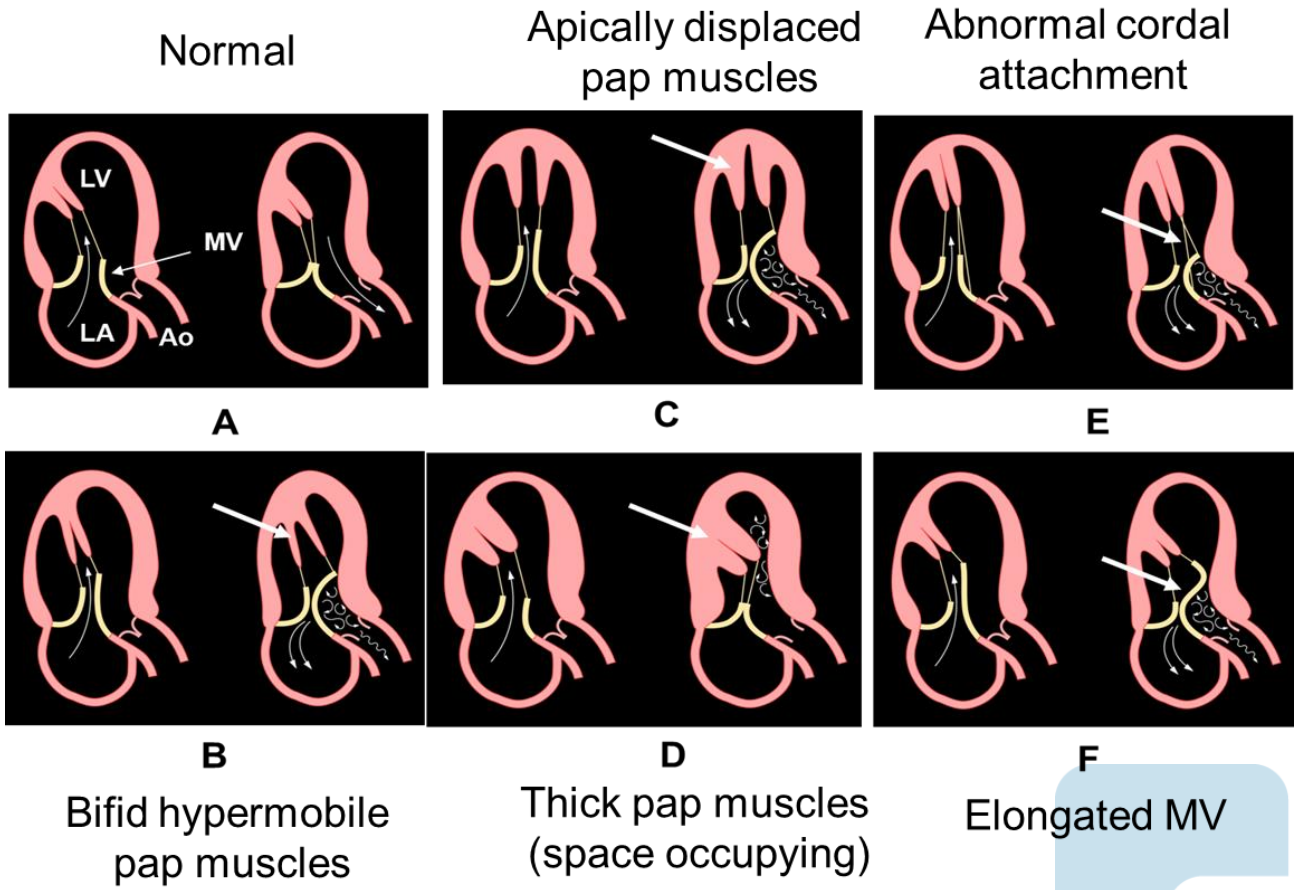
Designating someone as NONOBSTRUCTIVE HCM without the full extent of provocation is not appropriate

Maron MS et al. N Engl J Med 2003;348:295-303.

3: Recognize typical and atypical variants of obstructive HCM

OCM without the H: Abnormal mitral subvalvular morphology





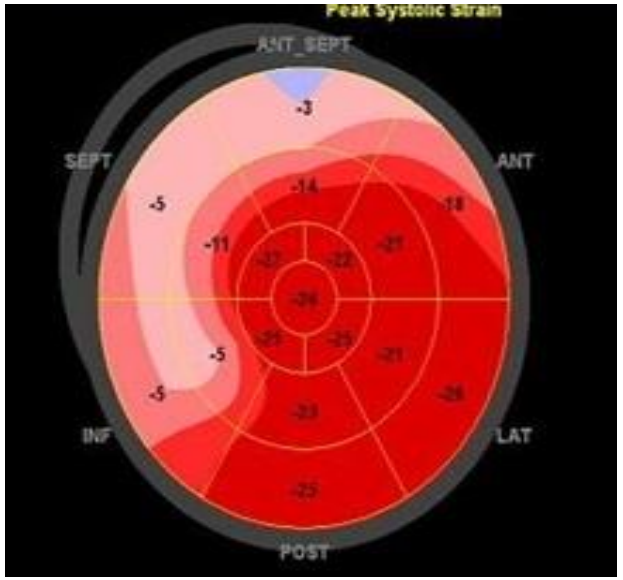
Typical oHCM

Atypical oCM without the H

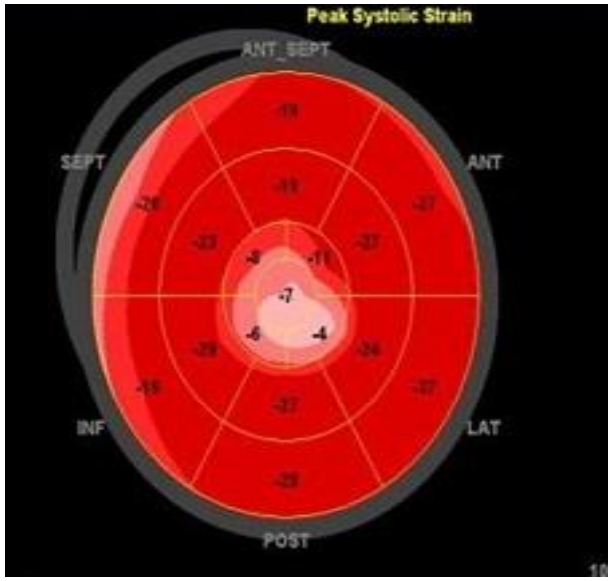
Designating someone as NOT being HCM based on lack of LVH is not appropriate

Desai, To et al. JACC Img

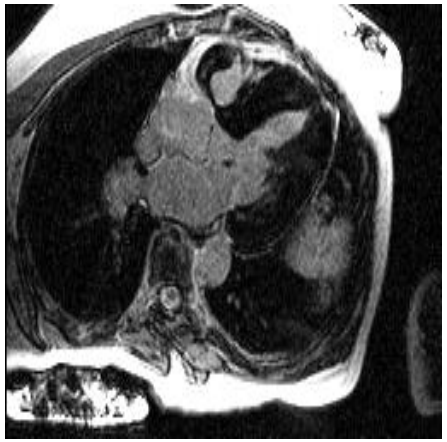
4: Differential diagnosis using multimodality imaging



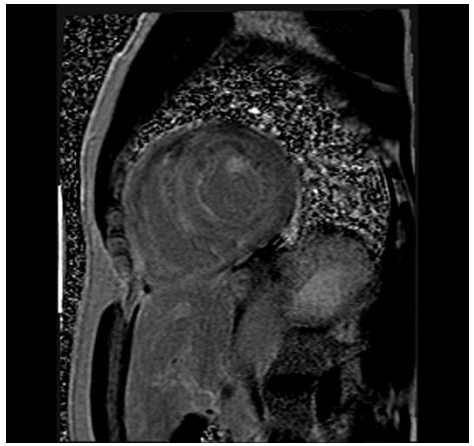
ASH variant of HCM



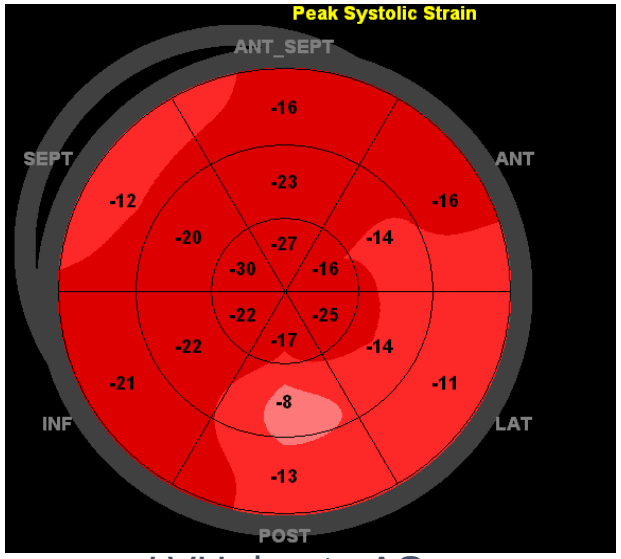
Apical HCM



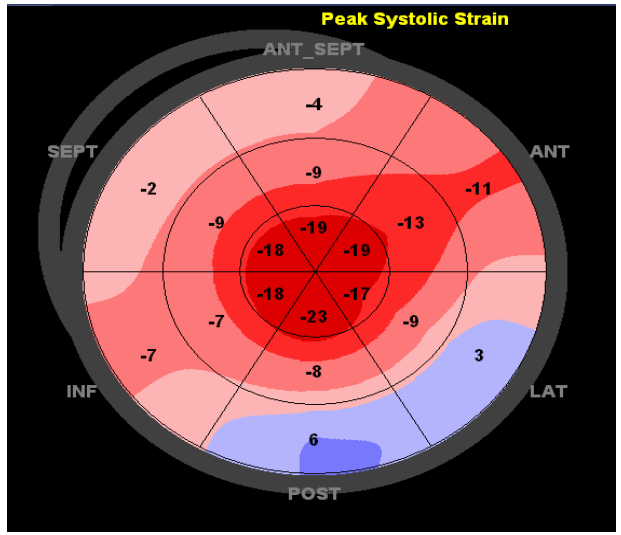
Fabry's disease



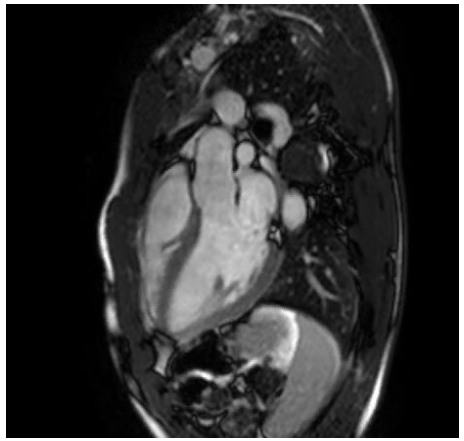
Amyloidosis



LVH due to AS



Apical sparing in amyloidosis



Athlete's heart

5: SCD risk stratification

Enhanced American Criteria	
Family history	SCD in ≥ 1 first degree relatives, ≤ 50 years of age
LVH	> 30 mm (individual discretion at 28-29 mm)
Unexplained syncope	Not vasovagal
NSVT	3 or more brief episodes of NSVT or ≥ 1 burst of ≥ 10 beats at > 130 BPM
LGE	≥ 15% of LV mass
End stage HCM	< 50% LVEF without LVOT obstruction, ? Transplant candidates
LV apical aneurysm	Often seen with apical HCM

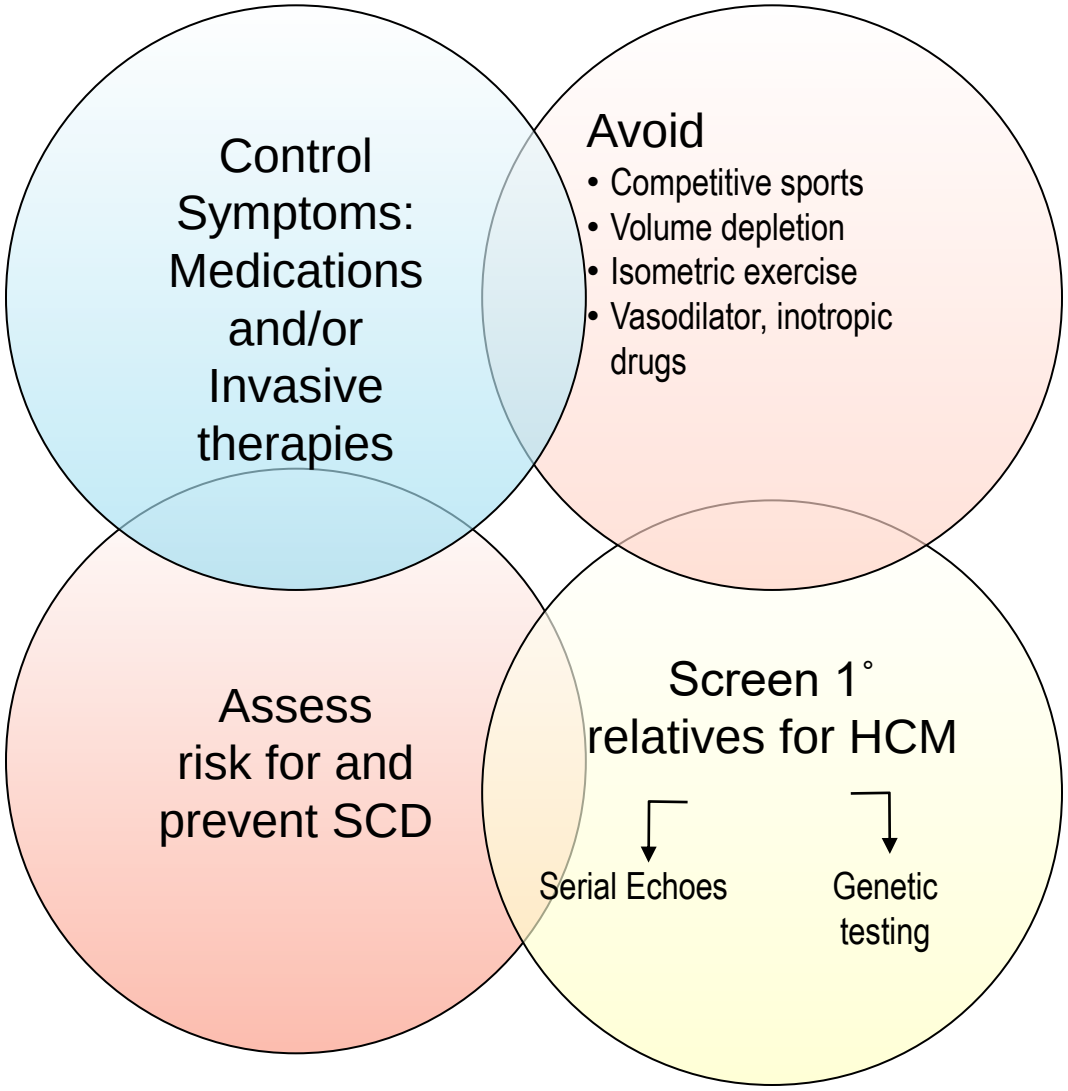
ESC Criteria	
Age	45
Maximum wall thickness	35
Left atrial size	41
LVOT gradient	100
Family history of SCD	0
NSVT	1
Syncope	0
SCD at 5y	5.666313756

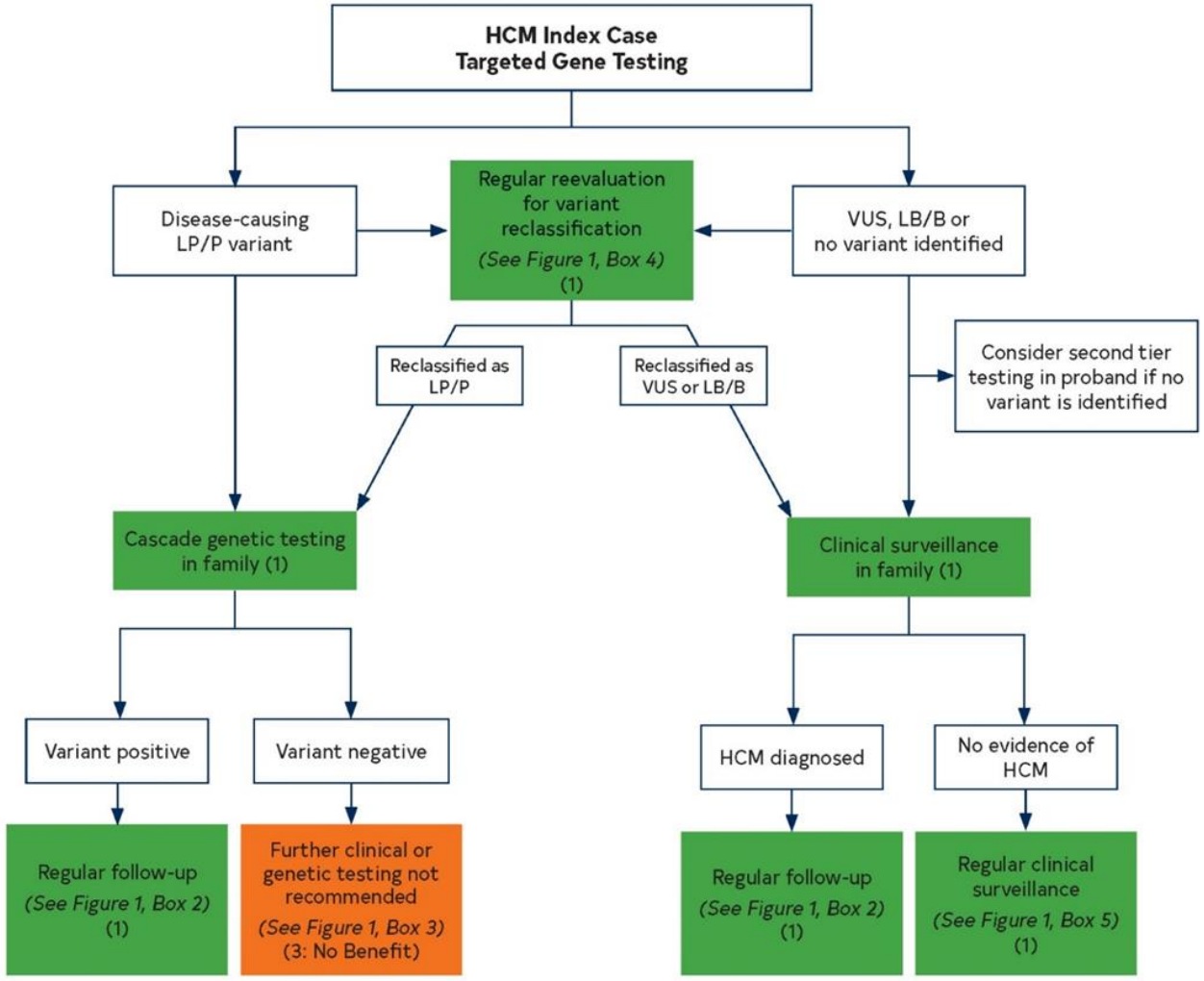
<4%: No ICD recommended
4-6%: ICD may be indicated
> 6%: ICD indicated

In 2023, a well managed HCM patient has a risk of SCD < 1%/year
~ 0.5%/year

JAMA Cardiology 2018
EHJ 2013

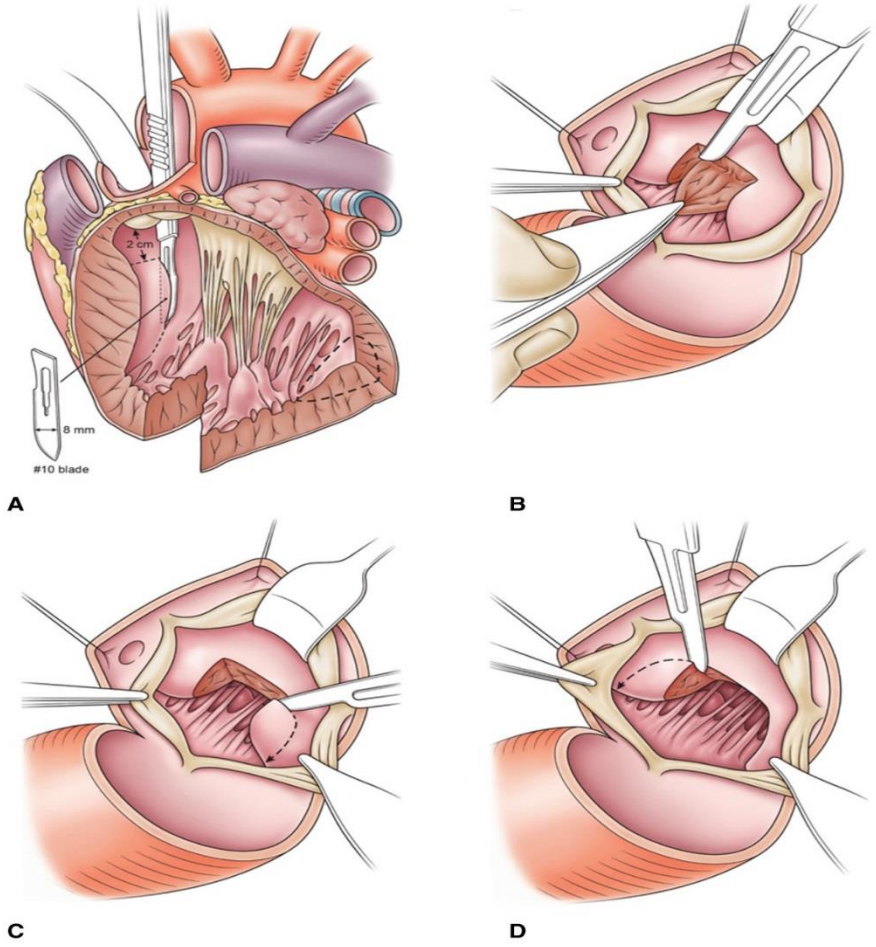
Step 6: Management in oHCM

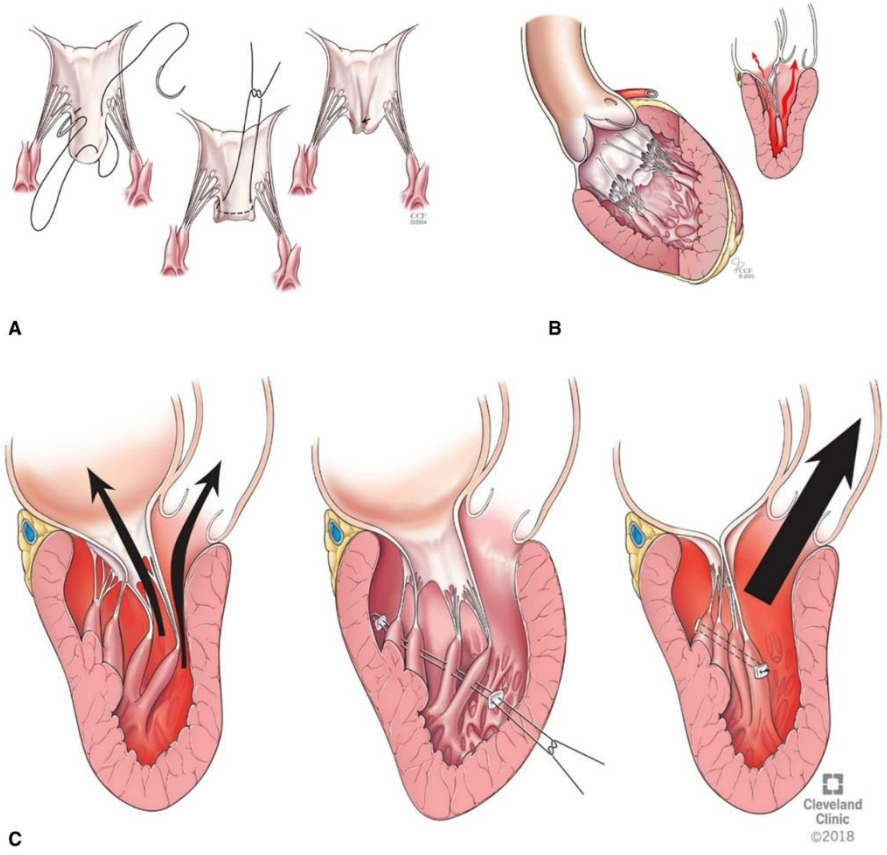


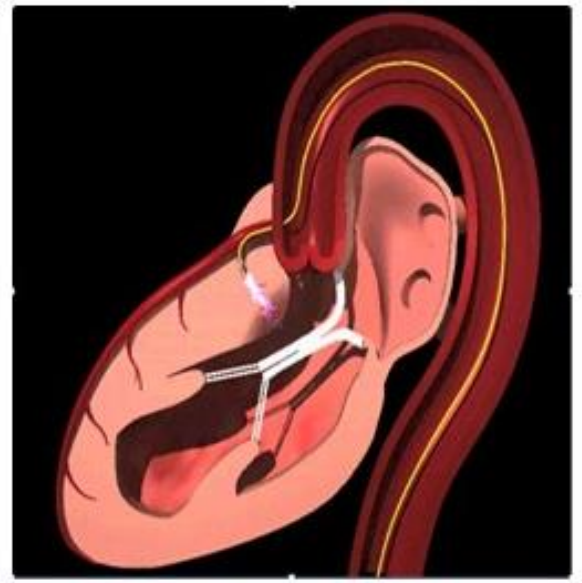


SCREEN FOR OBSTRUCTIVE SLEEP APNEA

Septal Reduction Therapy: One procedure does not fit all







Standard thick wall HOCM

OCM without the “H”
Concomitant mitral valve/papillary muscle surgeries

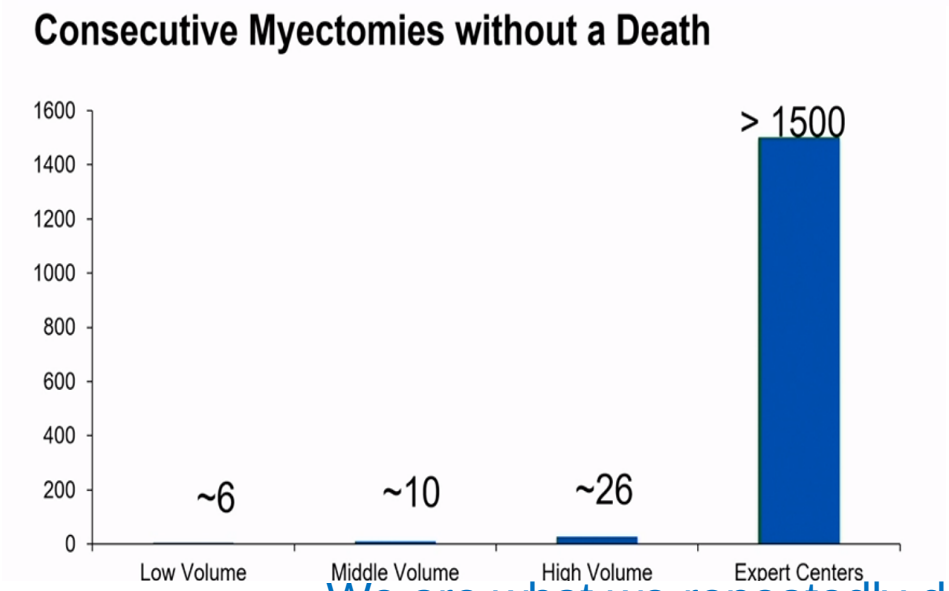
Alcohol septal ablation

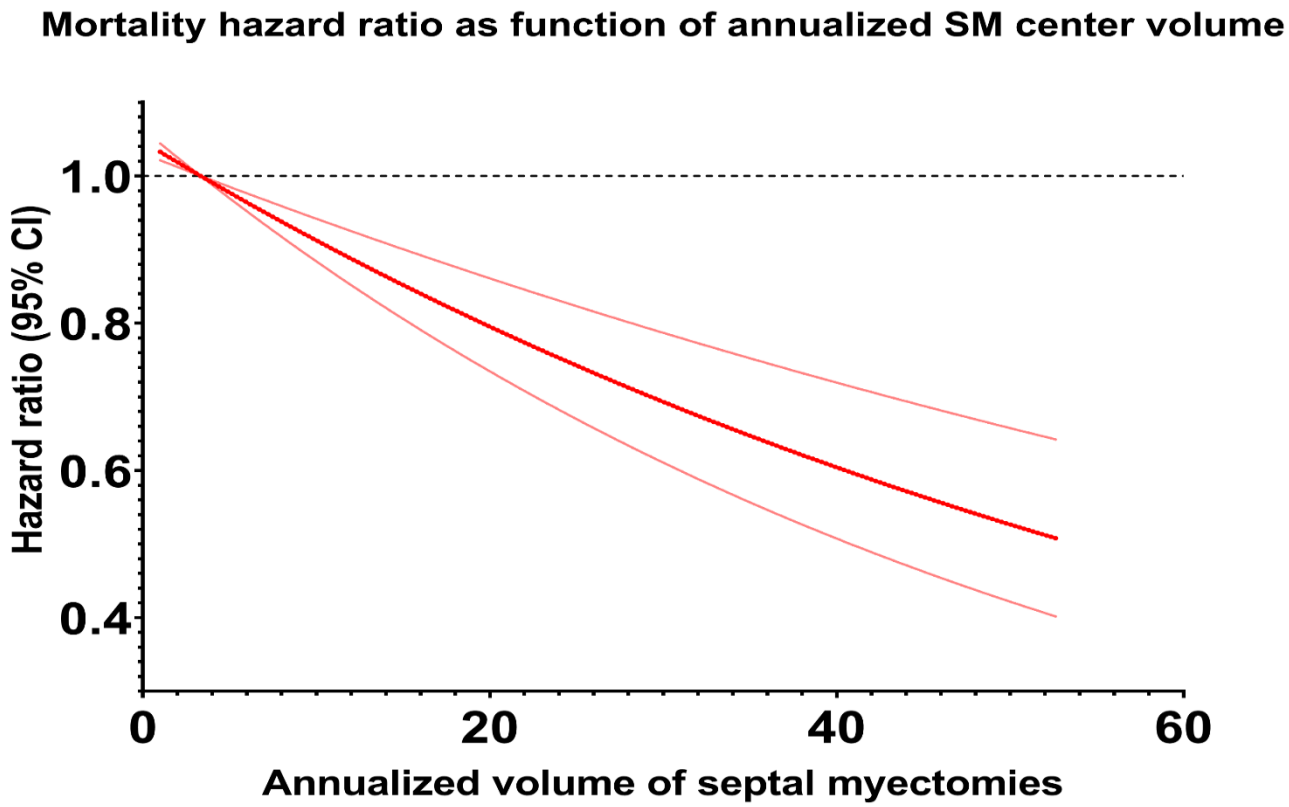
NEED AN EXPERIENCED CENTER WITH EXPERIENCED PROVIDERS

Desai et al. JTCVS 2018

Expert Centers Have Markedly Better SRT Outcomes But Access to Specialty Centers Are Limited

	Myectomy	Ablation
Gradient	<10 ✓	<25
PPM	1-2% ✓	~5%
Mortality	<1% ✓	1-2%
LOS	5 days	2-4 days ✓
Pain	++	+ ✓
Return to Activity	Weeks	Days ✓
Symptoms	Improved	Improved
Reintervention	< 2% ✓	7-10%
Late SCD	Very Low ✓	Low
Long-term Survival	Good	Good



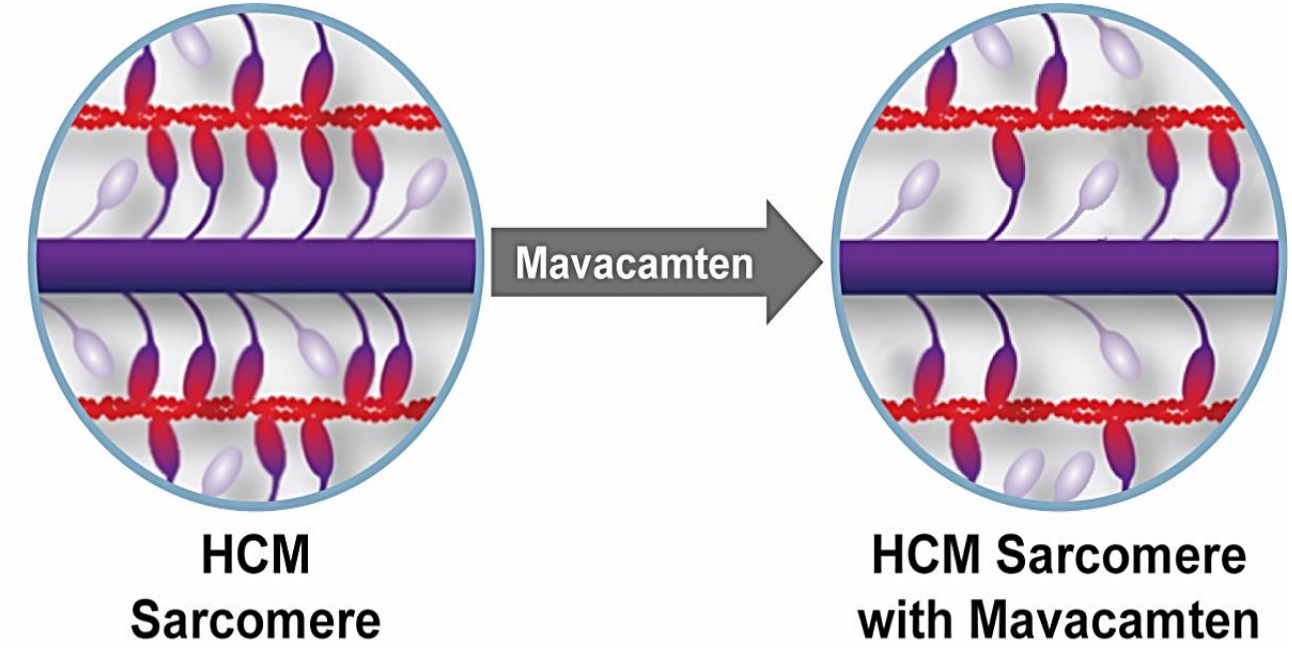


Despite higher-volume centers demonstrating better outcomes vs. lower-volume centers, 70% of SRT were performed in low volume centers

We are what we repeatedly do. Excellence, then, is not an art, but a habit. Aristotle

Kim et al. JAMA Cardiol. 2016;1(3):324-332
Mentias, Desai.. JACC 2023

Cardiac Myosin Inhibition: Mavacamten is first in class



Hyper contractility
Impaired relaxation
Altered myocardial energetics

Reduces myosin-actin cross bridges
To attenuate hypercontractility and improved compliance and energetics

- Allosteric inhibitor of myosin
  - Stabilizes myosin in a resting state
  - Reduces number of cross-bridges
  - Energy-sparing
- Does not affect myosin when bound to actin
  - Low potential to impact diastole
  - Does not alter contraction kinetics
- Does not affect calcium flux
  - Low arrhythmogenic potential

Phase III RCTs: Testing Mavacamten vs. Placebo EXPLORER-HCM vs. VALOR-HCM

EXPLORER-HCM

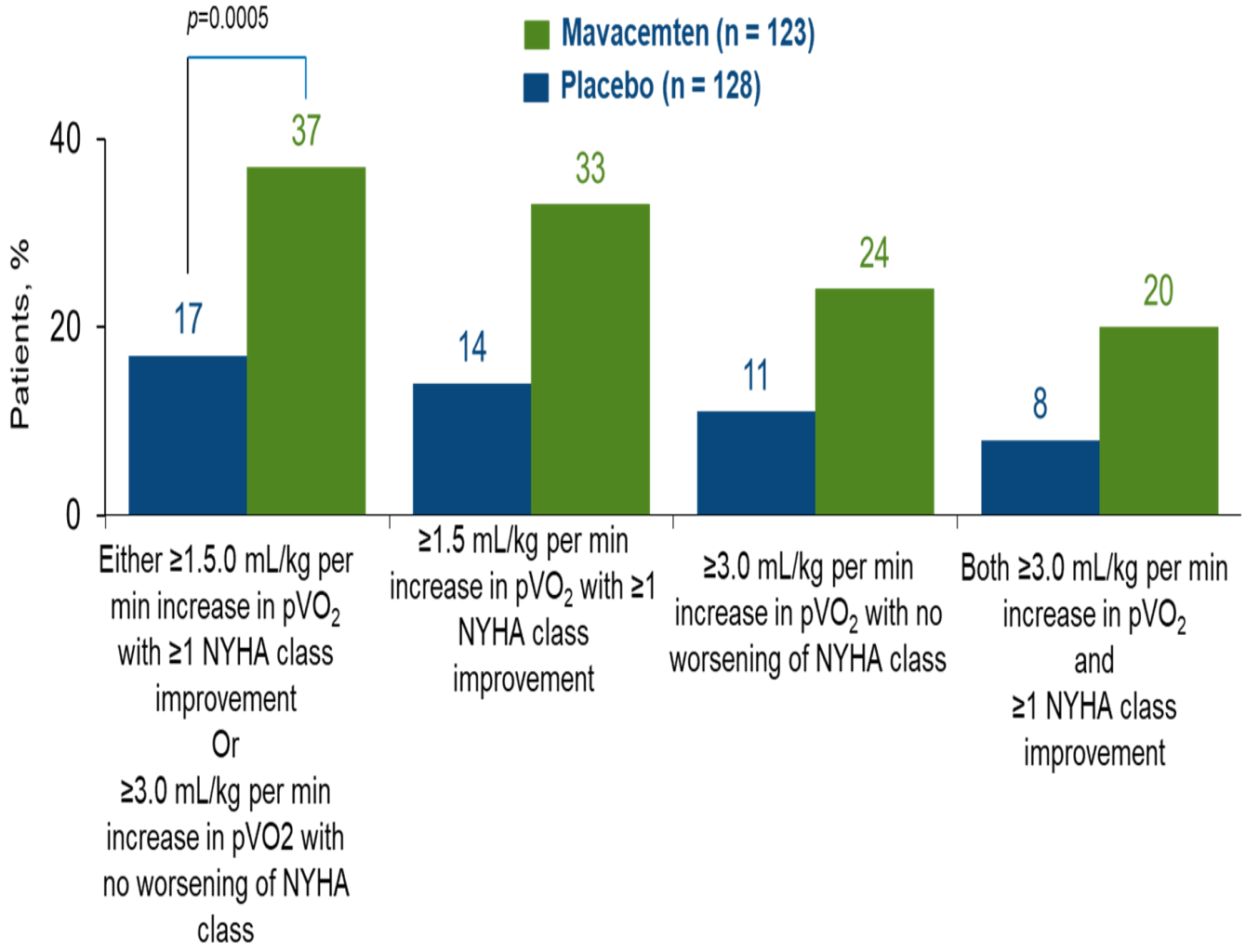
- NYHA class II-III symptoms
- Treatment with the following were not allowed:
  - Combination therapy
  - Disopyramide

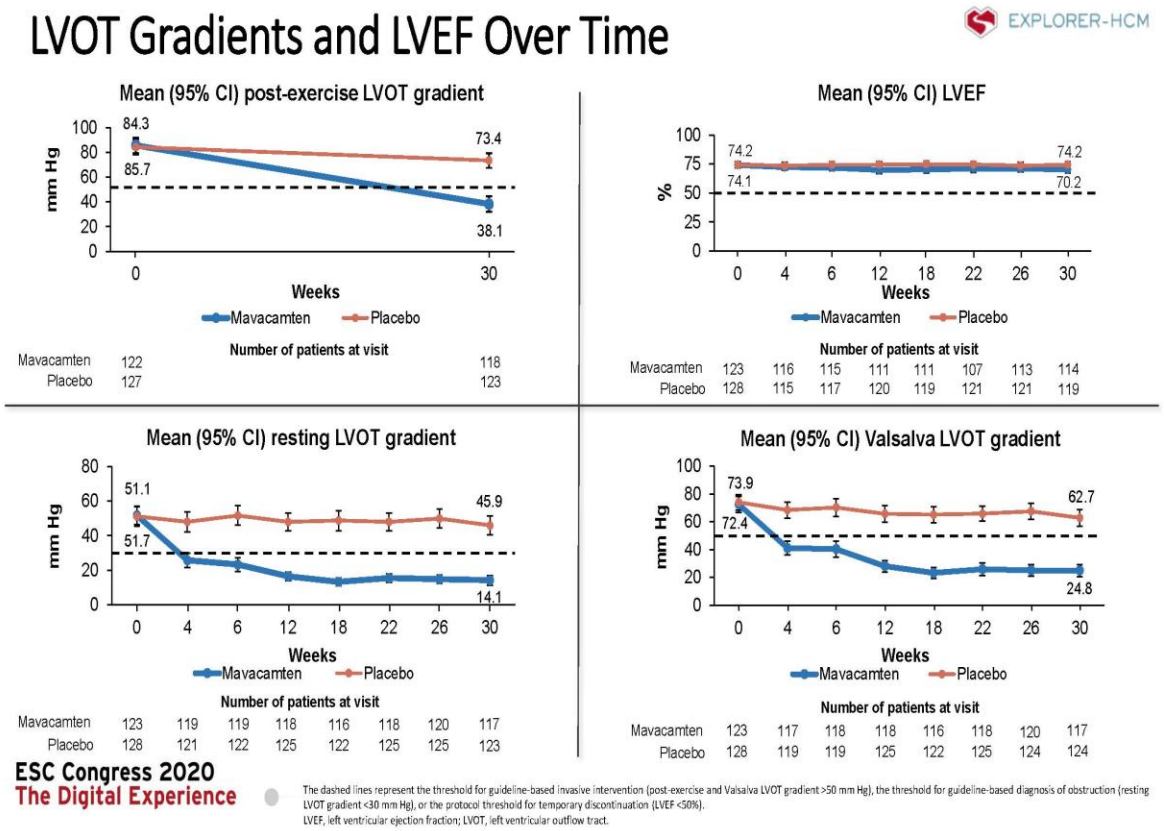
VALOR-HCM

- NYHA class III or higher
- Combination therapy was allowed
- Disopyramide was allowed
- Every patient met criteria for SRT, was referred and actively considering scheduling for SRT

Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769.
Desai M et al. JACC August 2022

Explorer HCM:73% NYHA Class II

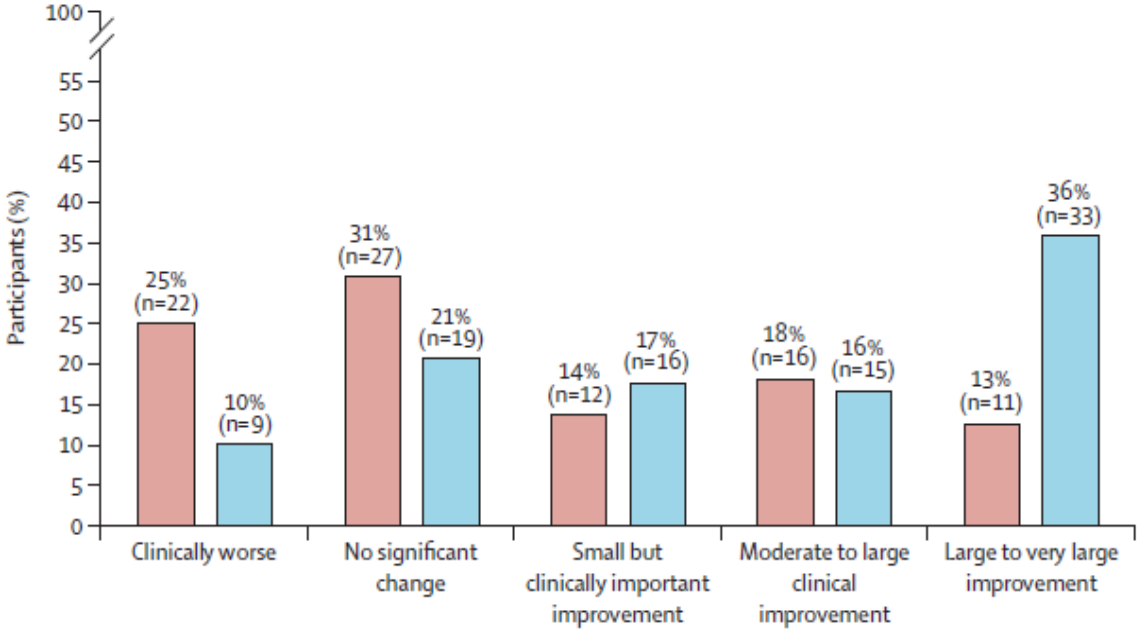




Mavacamten was significantly better than placebo for ALL primary and secondary endpoints

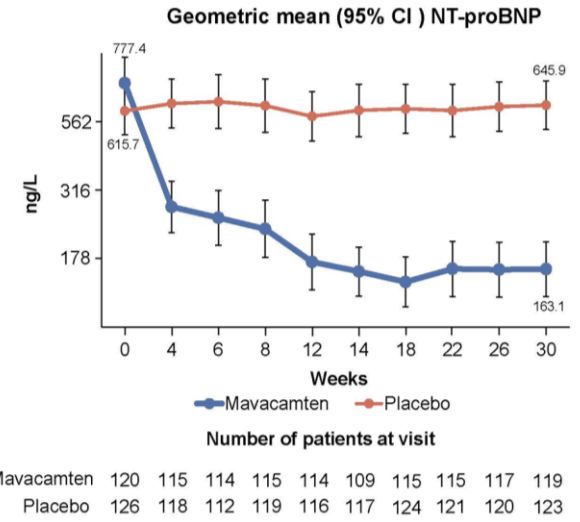
Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769

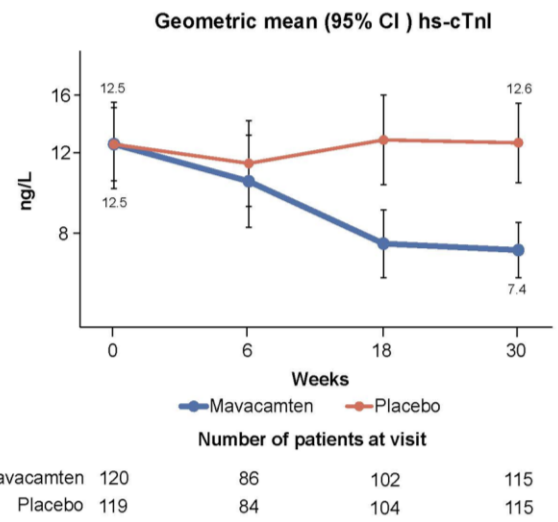
QOL, Biomarkers and Structural Improvements: EXPLORER-HCM

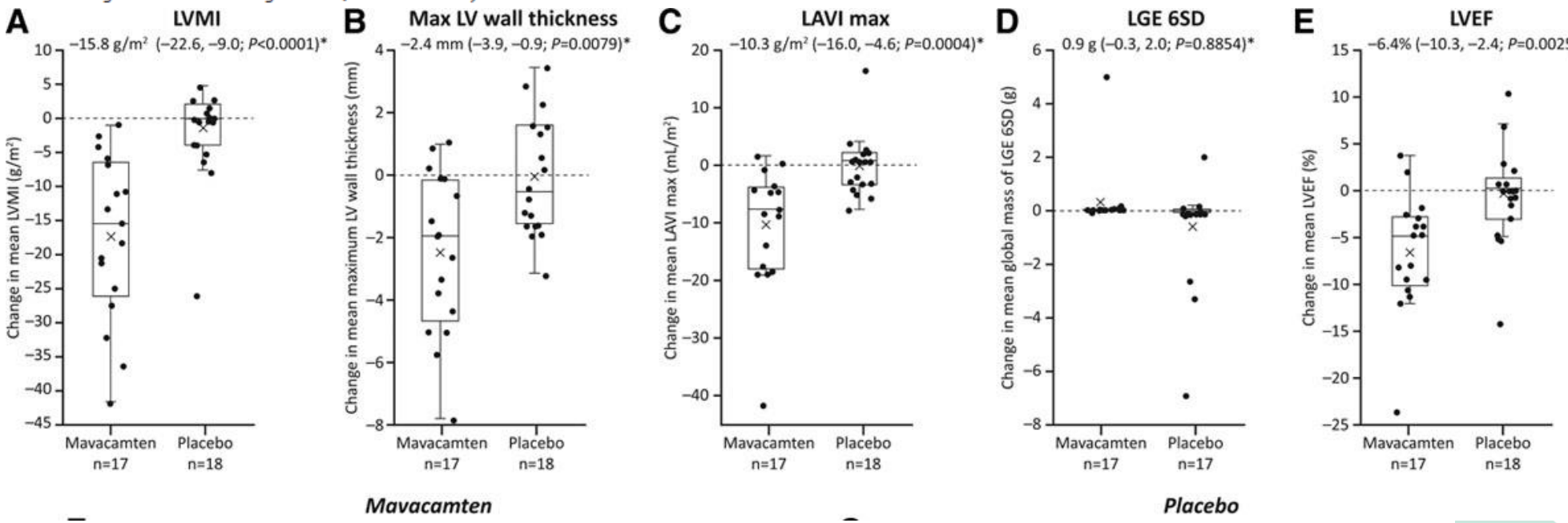


Categories of clinical change in KCCQ clinical summary score

Exploratory Endpoints: Cardiac Biomarkers





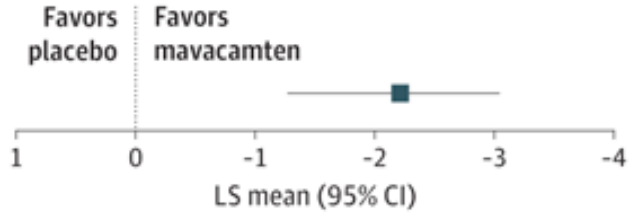


Spertus. Lancet 2021
Saberi, Circ 2021

Mavacamten in oHCM: CPET improvement in EXPLORER

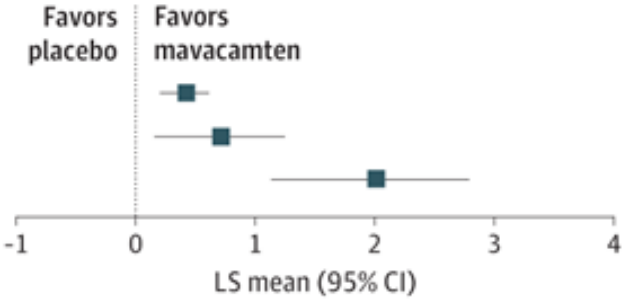
A Peak V_E/VCO_2

Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	*P* value
	Mavacamten	Placebo		
Peak V_E/VCO_2	-1.9 (3.7)	0.5 (3.8)	-2.20 (-3.05 to -1.26)	<.001



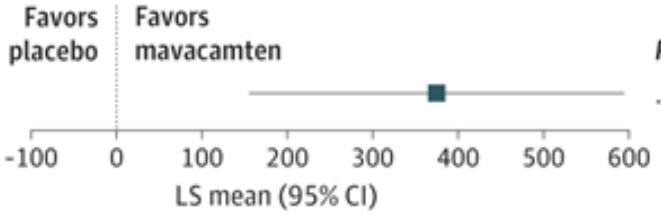
B Peak METs, exercise time, and $PETCO_2$

Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	*P* value
	Mavacamten	Placebo		
Peak METs	0.4 (0.9)	-0.02 (0.86)	0.40 (0.17 to 0.60)	<.001
Peak exercise time, min	0.8 (2.4)	0.1 (2.0)	0.70 (0.13 to 1.24)	.02
Peak $PETCO_2$, mm Hg	1.7 (3.4)	-0.4 (3.0)	2.00 (1.12 to 2.79)	<.001



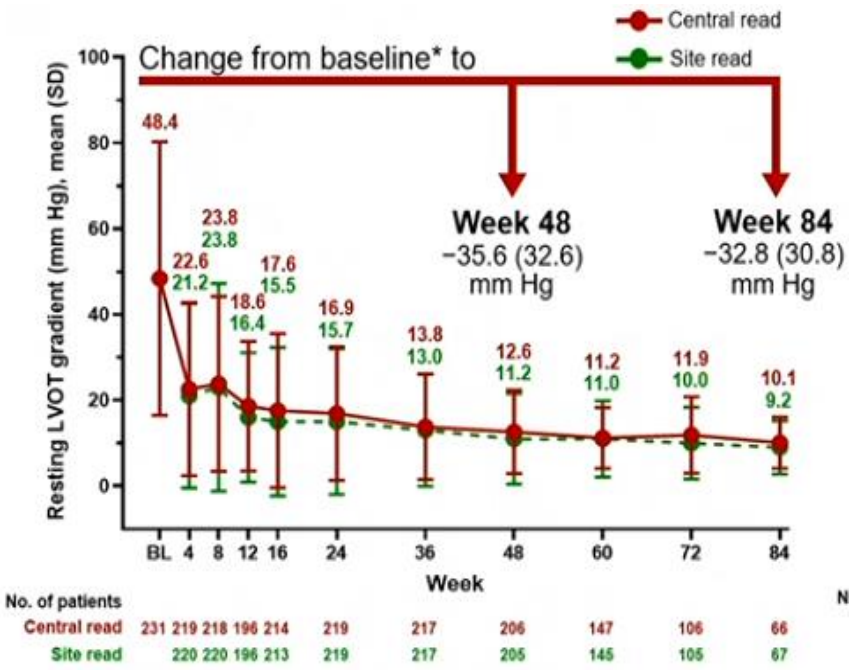
C Peak circulatory power

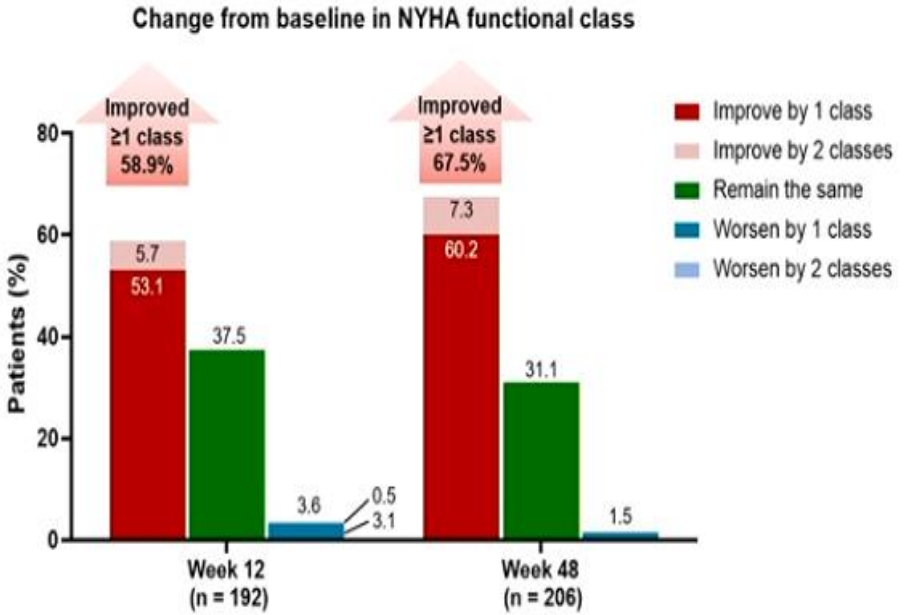
Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	*P* value
	Mavacamten	Placebo		
Peak circulatory power, mL/kg/min × mm Hg	414.1 (972.0)	-17.9 (869.1)	372.9 (153.12 to 592.61)	.001

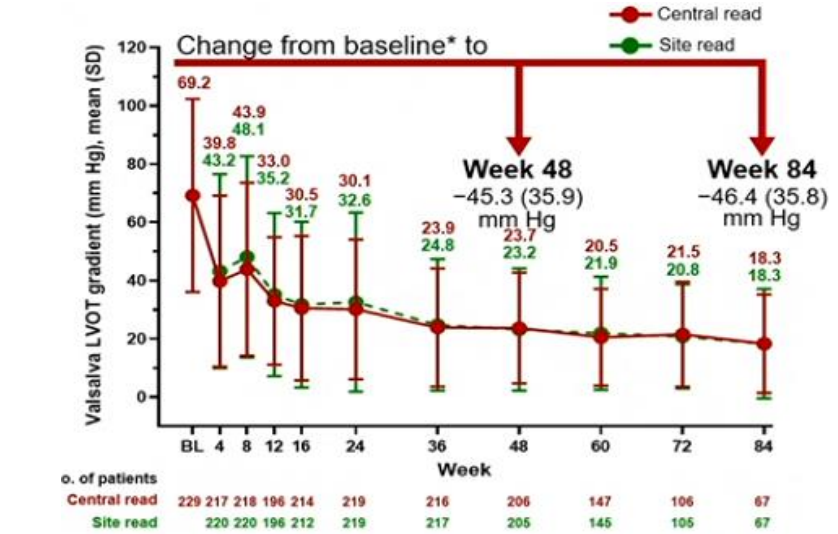


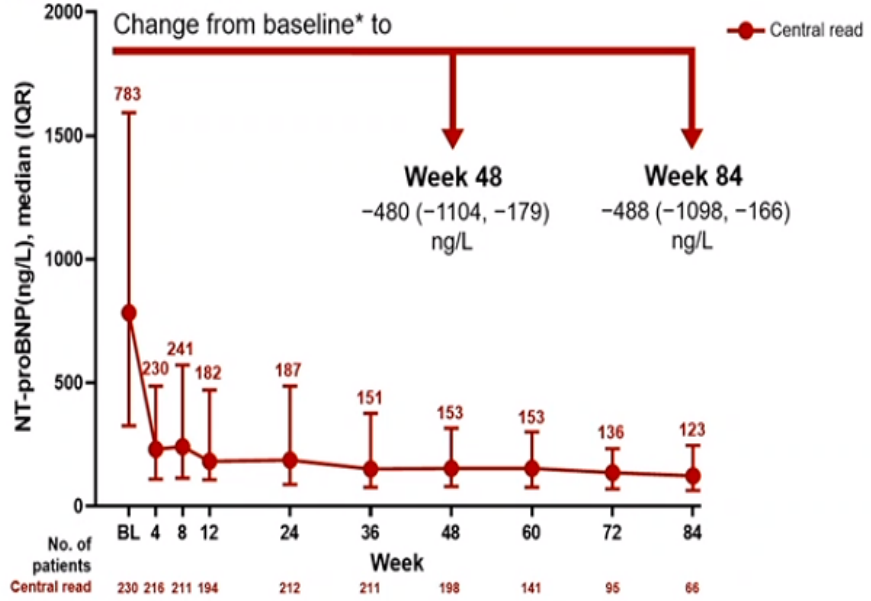
Wheeler et al. JAMA Cardiology Jan 2023

Mavacamten LTE study





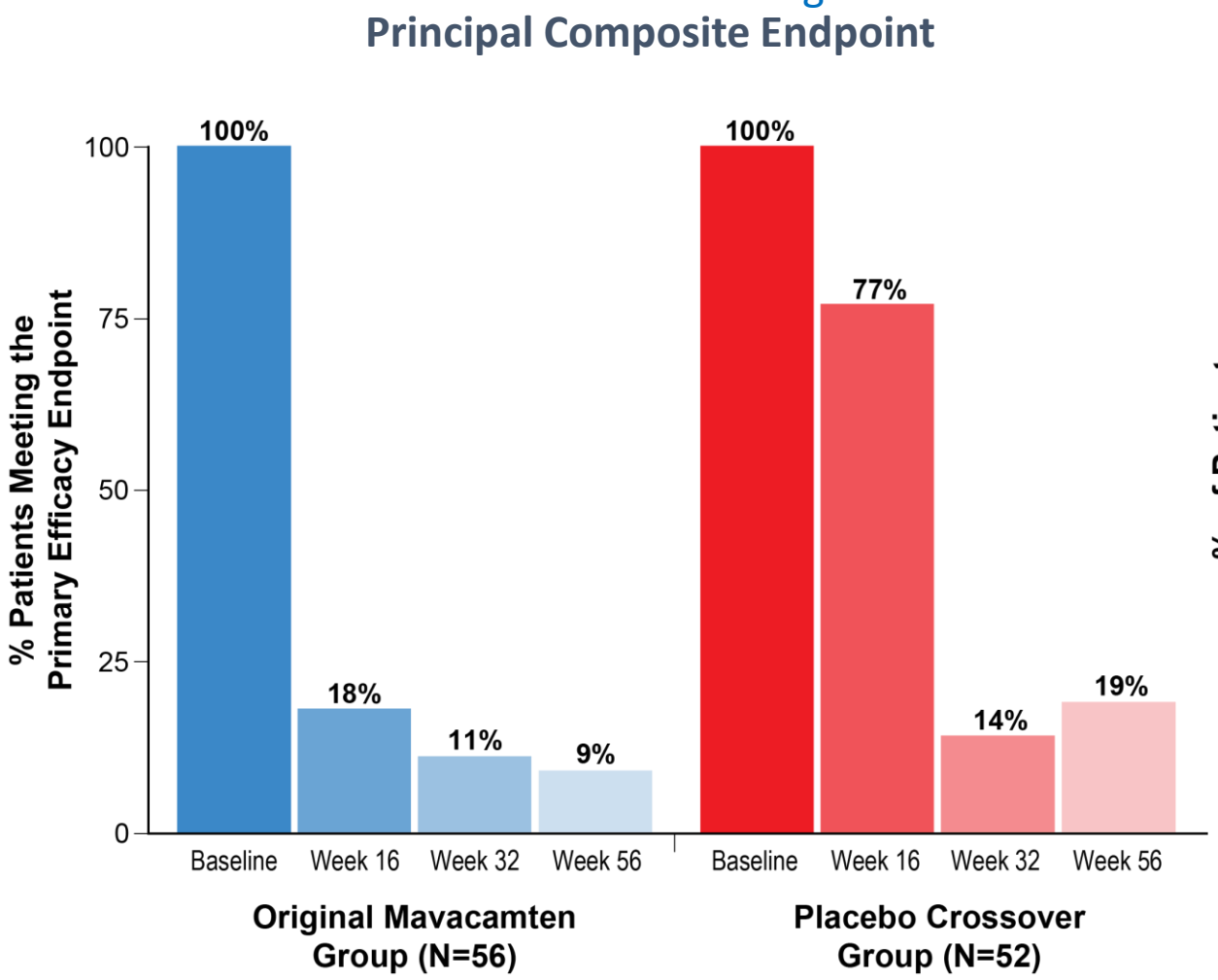


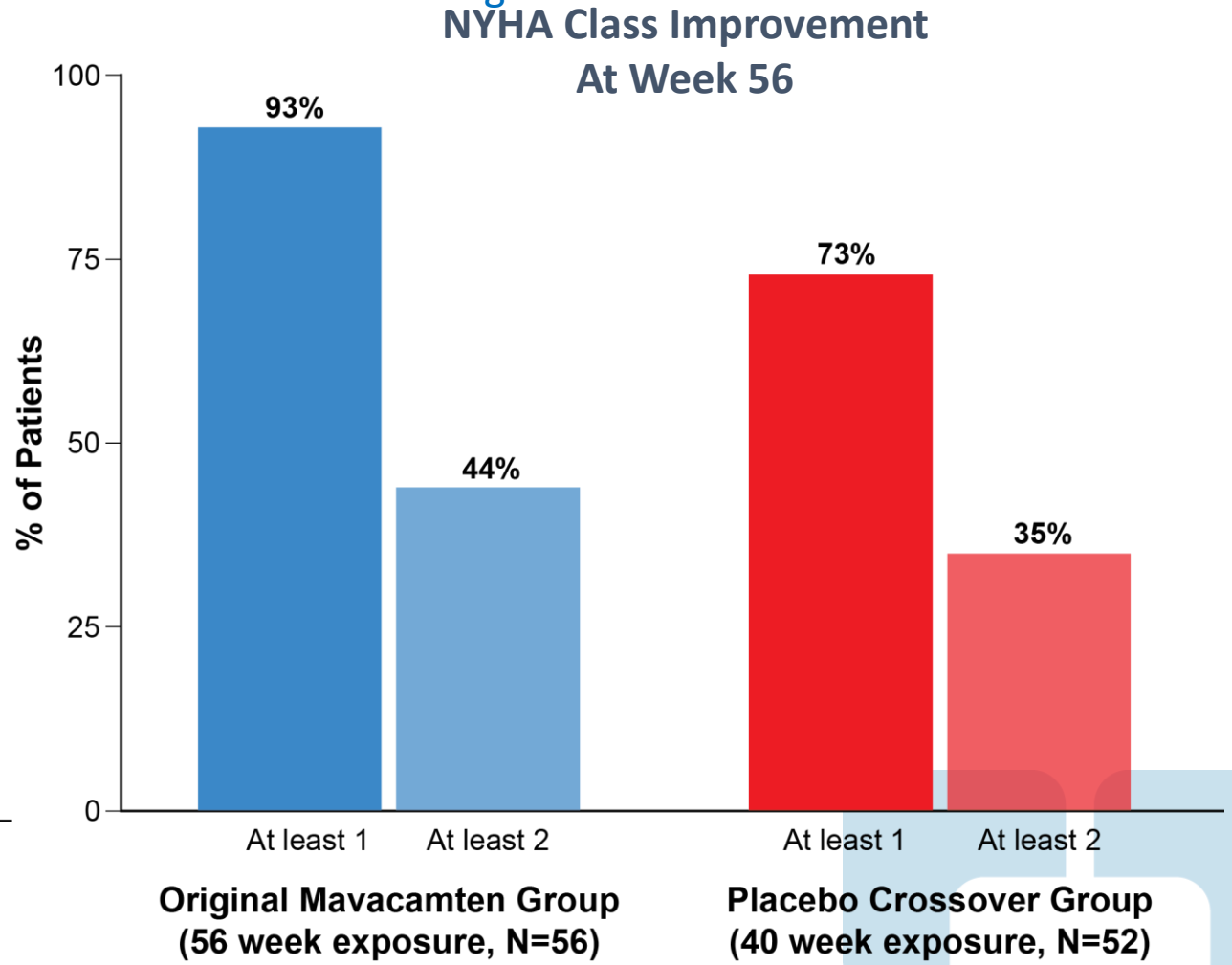


Rader F et al, ACC 22, April 2-4, 2022, Washington, DC; 406-16.

Valor-HCM: 92% NYHA Class III

Would addition of mavacamten to maximally-tolerated medical therapy allow severely symptomatic oHCM patients to not meet guideline criteria for SRT or chose not to undergo SRT ?





36 (32%) on combination medical therapy; 22 (20%) were on disopyramide (mono or combination therapy)

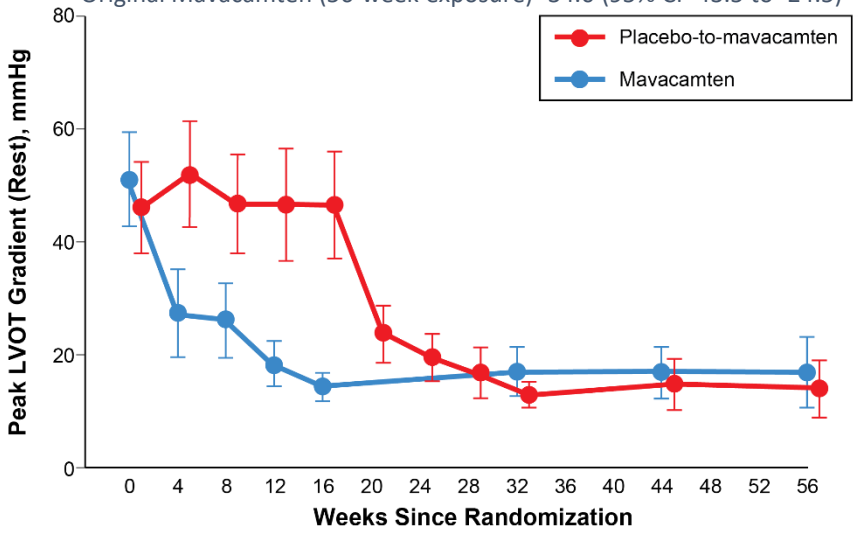
9 out of 10 patients chose to continue in LTE after week 56

Desai JAMA Cardio Aug 2023
Desai et al. JACC 2022
Desai et al. Circulation 2022

Sustained Improvement in Efficacy Endpoints

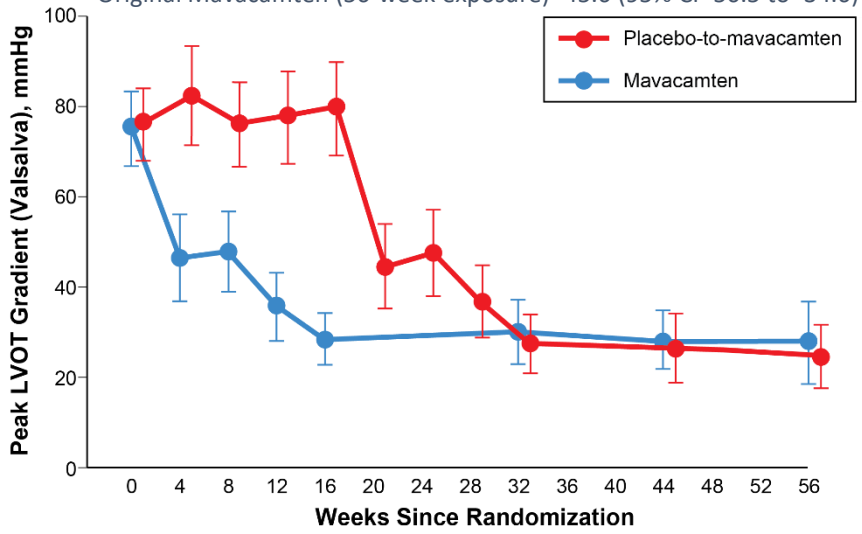
Resting LVOT Gradient

Original Placebo (40-week exposure) -33.2 (95% CI -41.9 to -24.5)
Original Mavacamten (56-week exposure) -34.0 (95% CI -43.5 to -24.5)



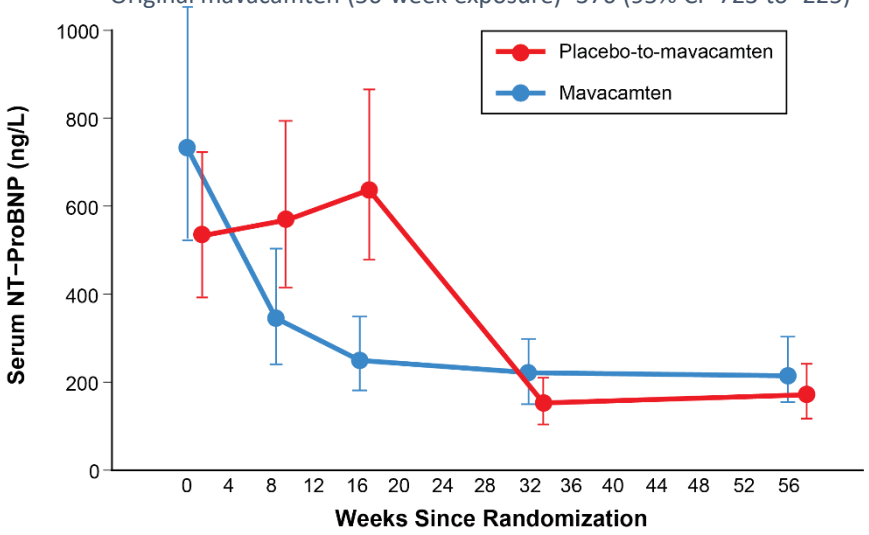
Valsalva LVOT Gradient

Original Placebo (40-week exposure) -54.6 (95% CI -66.0 to -43.3)
Original Mavacamten (56-week exposure) -45.6 (95% CI -56.5 to -34.6)



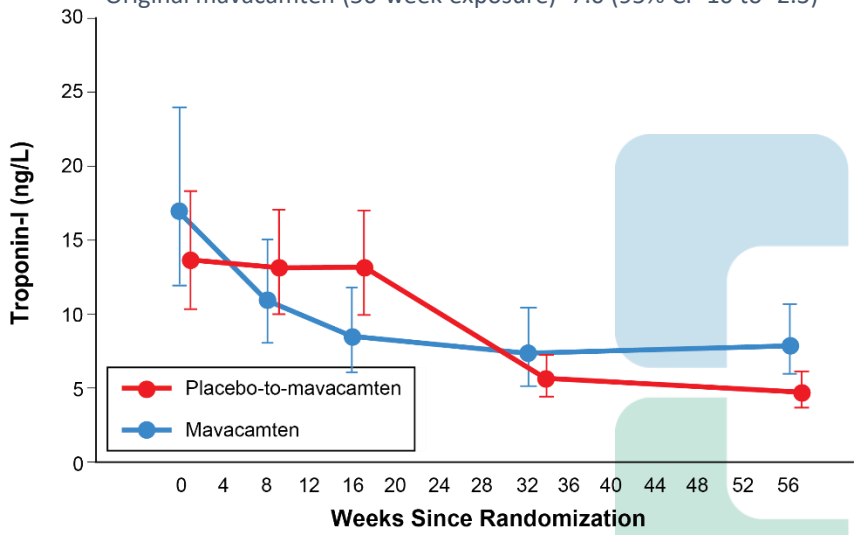
NT-ProBNP

Original placebo (40-week exposure) -423 (95% CI -624 to -252)
Original mavacamten (56-week exposure) -376 (95% CI -723 to -225)



Troponin I

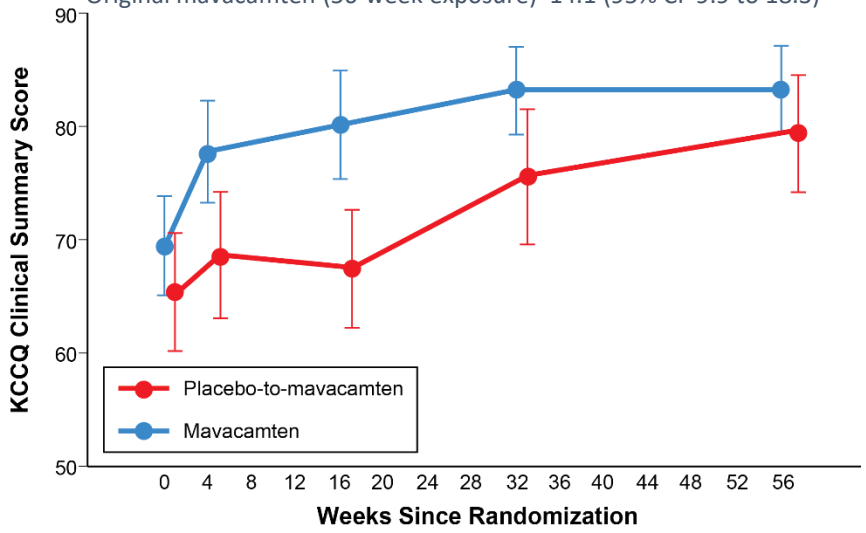
Original placebo (40-week exposure) -6.2 (95% CI -11.5 to -3.3)
Original mavacamten (56-week exposure) -7.0 (95% CI -10 to -2.3)



Sustained Improvement in QOL and Favorable Cardiac Remodeling

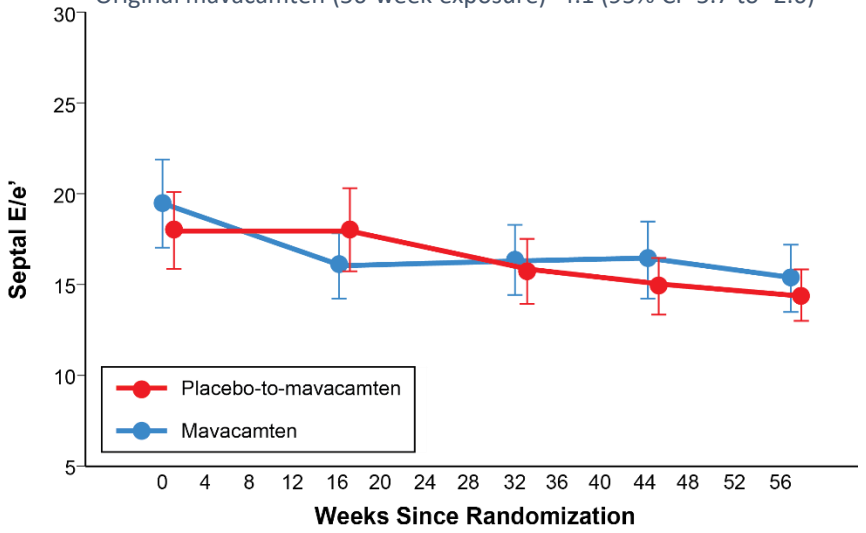
KCCQ Score

Original placebo (40-week exposure) 11.7 (95% CI 6.9 to 16.4)
Original mavacamten (56-week exposure) 14.1 (95% CI 9.9 to 18.3)



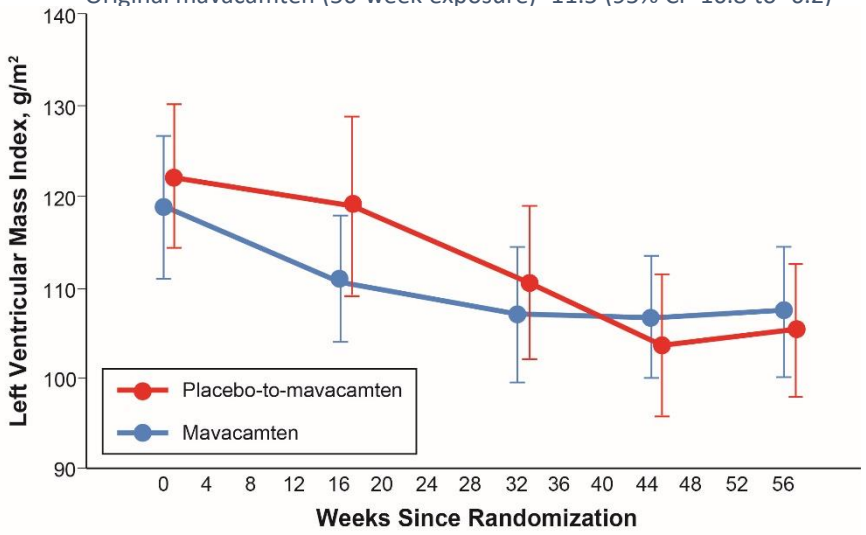
Septal E/e'

Original placebo (40-week exposure) -3.6 (95% CI -5.8 to -1.5)
Original mavacamten (56-week exposure) -4.1 (95% CI -5.7 to -2.6)



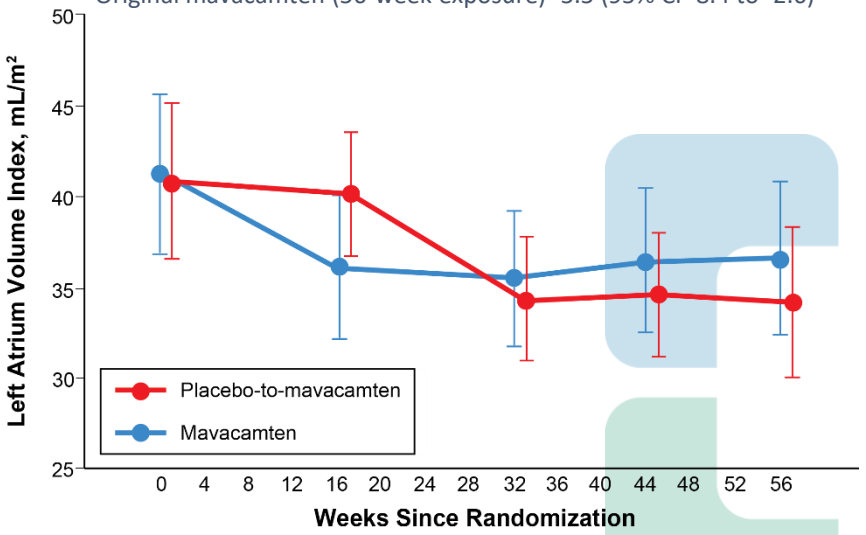
LV-Mass Index

Original placebo (40-week exposure) -14.5 (95% CI -20.8 to -8.3)
Original mavacamten (56-week exposure) -11.5 (95% CI -16.8 to -6.2)



LA Volume Index

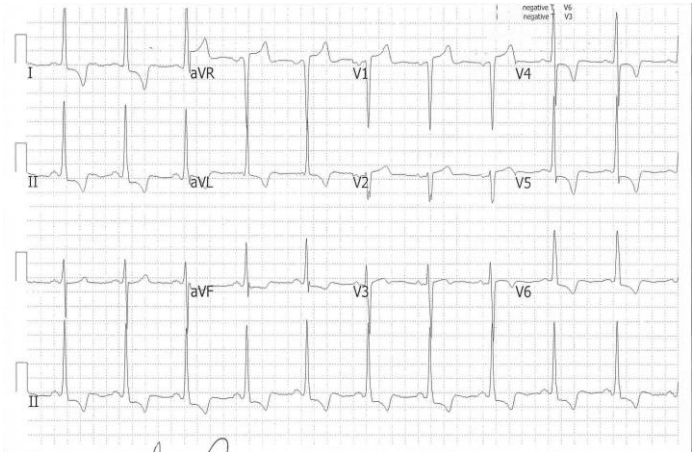
Original placebo (40-week exposure) -5.3 (95% CI -7.6 to -2.9)
Original mavacamten (56-week exposure) -5.5 (95% CI -8.4 to -2.6)

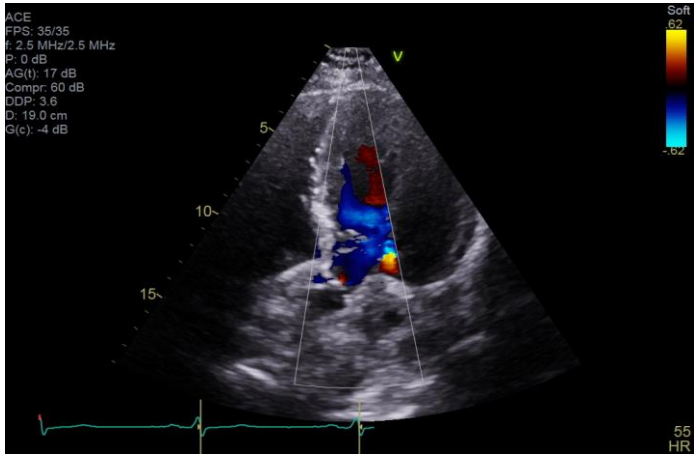


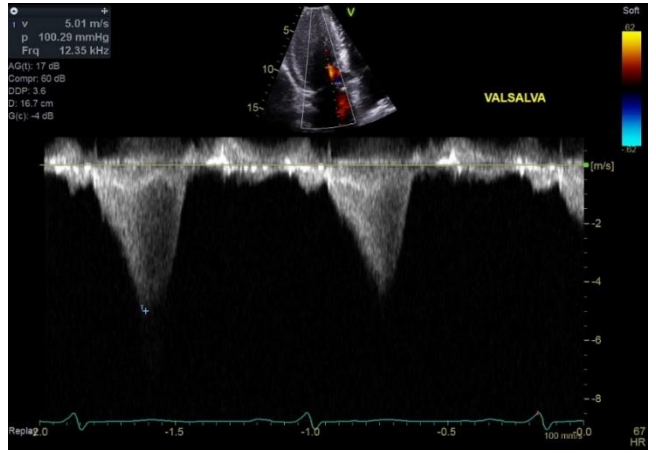
A Mavacamten Story

- 71 year old male with oHCM
  - Prior failed alcohol septal ablation, NYHA Class III, unable to do ADLs
  - On maximally tolerated betablockers, now having positional dizziness, sarted on mavacamten

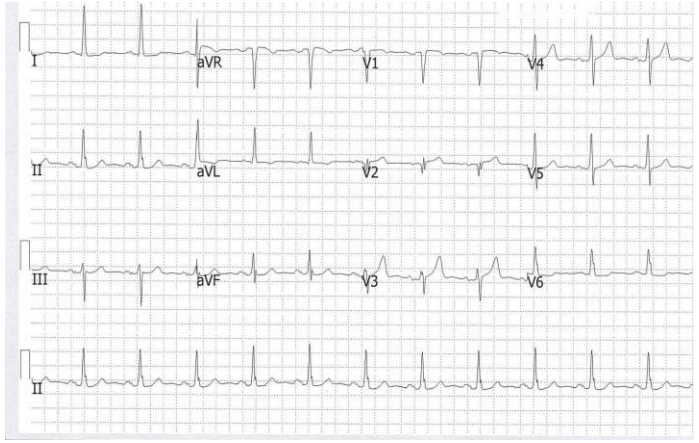
Pre-mava

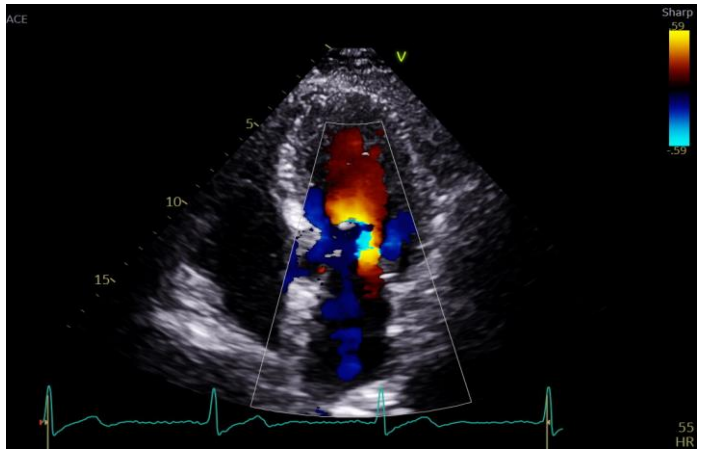


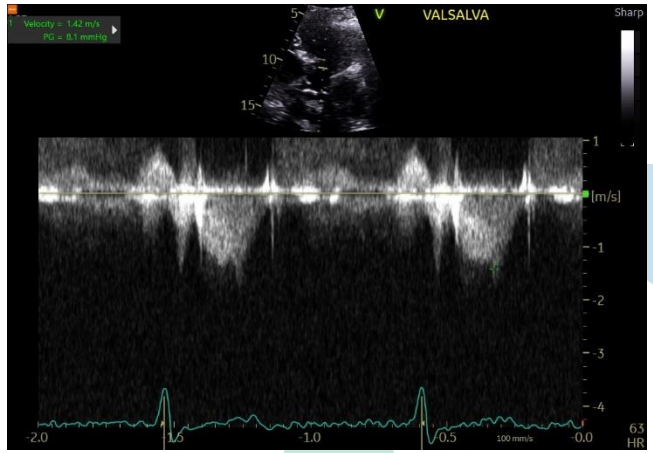




Post-mava
at 32 weeks



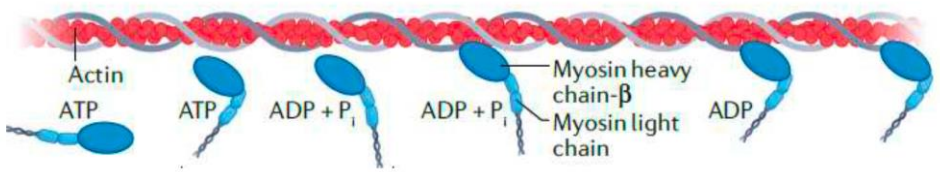




NORMALIZATION OF EKG AFTER RELIEF OF LVOT GRADIENT. PATIENT IN NYHA 1

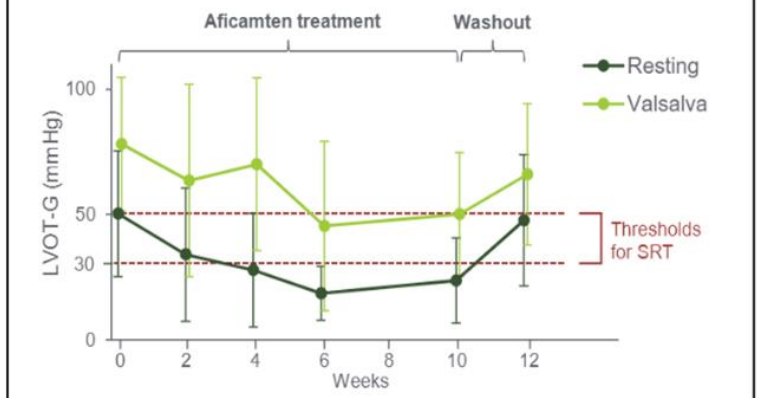
Aficamten: Next in class

REDWOOD-HCM Phase II trial in oHCM



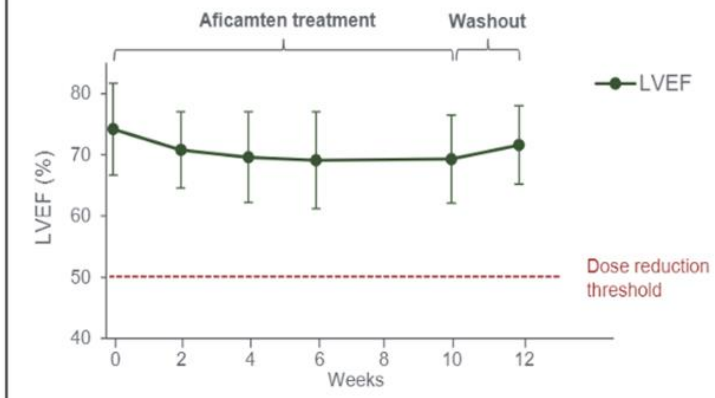
- Next-in-class agent
- Targets myosin heavy chain-beta
- Reduces myosin-actin cross bridges
- Stabilization of weak actin-binding myosin conformation
- Attenuates hypercontractility

Fig 1: Cohort 3 LVOT Gradients



Values are mean ± SD. Core-lab read echocardiograms. SRT, septal reduction therapy

Fig 2: Cohort 3 LVEF



Values are mean ± SD. Core-lab read echocardiograms.

Fig 3: Hemodynamic Response

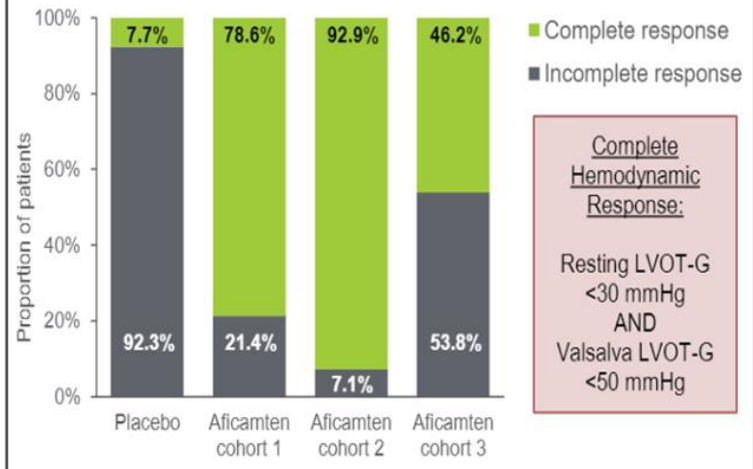
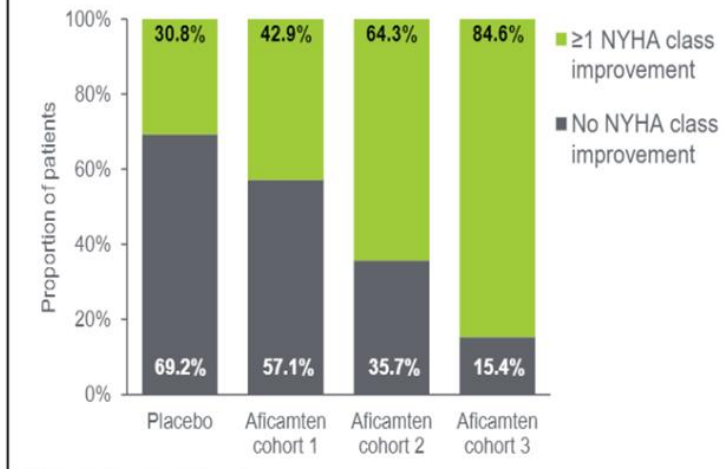


Fig 4: NYHA Response



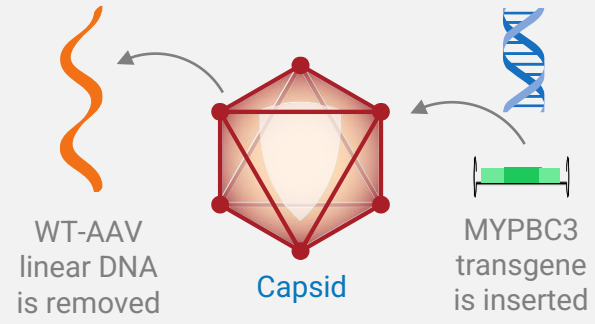
NYHA, New York Heart Association

Maron M et al. JACC Jan 2023

Gene-therapy: Adeno-associated Virus mediated

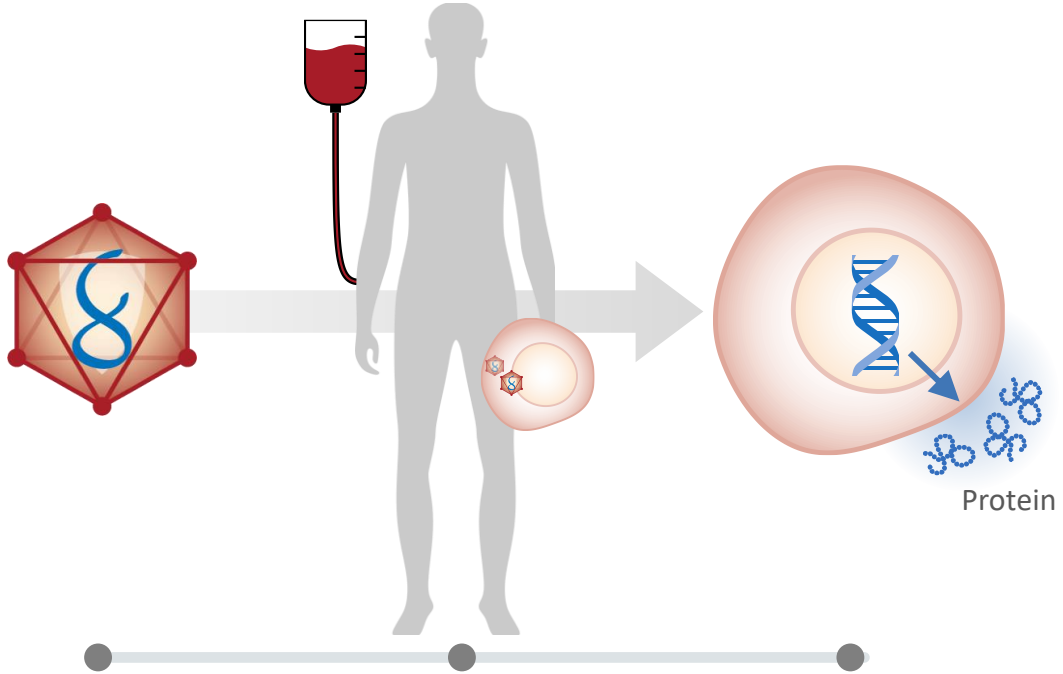
AAV is Non-pathogenic and the Leading Vector for Delivering Genetic Medicines

Constructing Recombinant AAV



AAV Vector

Viral DNA is removed and replaced with working copy of MYPBC3 (transgene). A cardiac promoter directs MyBP-C protein expression in cardiomyocytes.



With TN-201 gene therapy, the potential for restoration of wild-type, or normal levels of MyBP-C protein can be achieved after a single intravenous infusion

We will be recruiting for this trial. We have an ongoing Phase 0 study

Kantor B, et al. *Adv Genet.* 2014;87:125; Wang D, Gao G. *Discov Med.* 2014;18:67–77.

These new therapies are going to bring new logistic scenarios, assuming long-term safety and efficacy

A: Need for EF monitoring: How often ?

B: Who dispenses these meds: COE vs. Primary Cardiologist vs. other

C: Cost of long-term medical Rx vs. one time cost of surgery

D: Would you have a suboptimal SRT at a less-experienced center/unsuitable anatomy vs. a trial of mavacamten ?

D: What about non-obstructive HCM?

Phase III RCT of Mavacamten vs. Placebo in nonobstructive HCM

We have started to randomize and screen

Conclusions

Future is bright in HCM

Precision medicine will add an additional option in the fight towards a normal life in HCM

Remember, it is NOT about my pill is better than your procedure

Not “this vs. that”, but rather “this ± that”

It is about what you can do to provide the best QOL in that given patient

Patients first!!!!