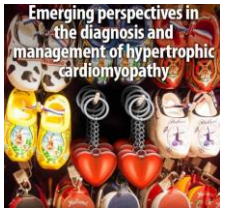
Novel approaches in managing patients with hypertrophic cardiomyopathy

Iacopo Olivotto, MD

Florence, Italy

Emerging perspectives in the diagnosis and management of hypertrophic cardiomyopathy



PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

Disclosures - Dr. Olivotto

Research Support: BMS-Myokardia, Cytokinetics, Sanofi Genzyme, Shire Takeda, Amicus, Bayer, Menarini International, Boston Scientific.

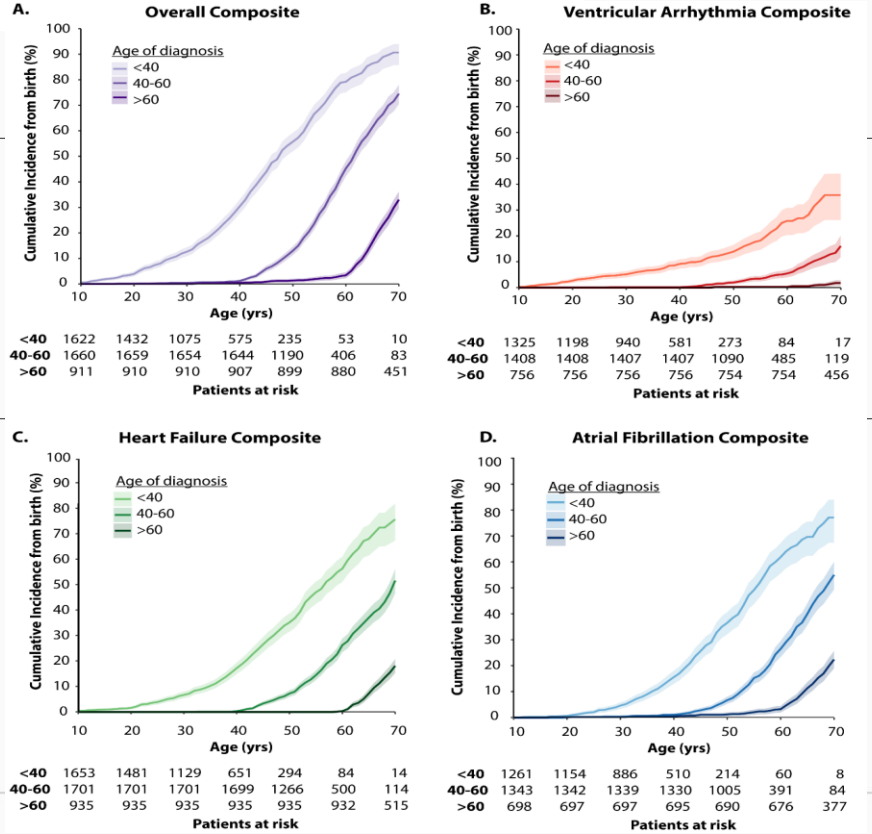
Advisory board, invited speaker: BMS-Myokardia, Cytokinetics, Sanofi, Genzyme, Shire Takeda, Amicus, Tenaya, Rocket Pharma.

ORIGINAL RESEARCH ARTICLE

Ho et al, Circulation 2018

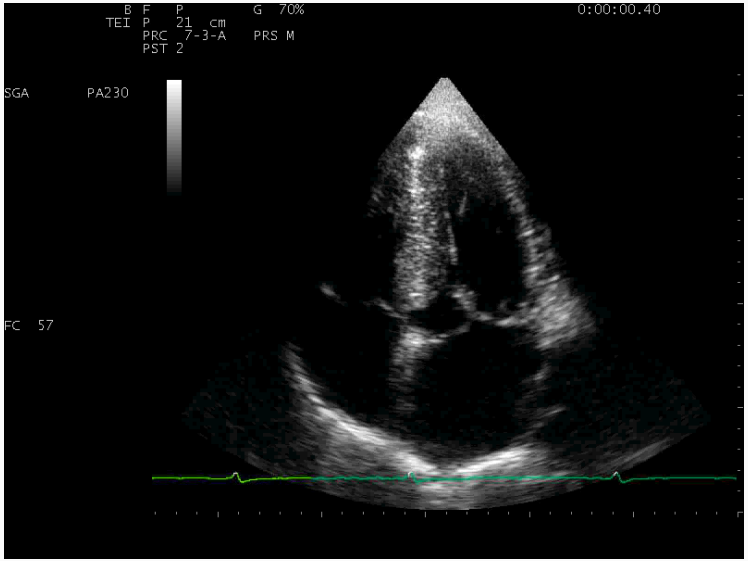
Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy

Insights From the Sarcomeric Human Cardiomyopathy Registry (SHaRe)

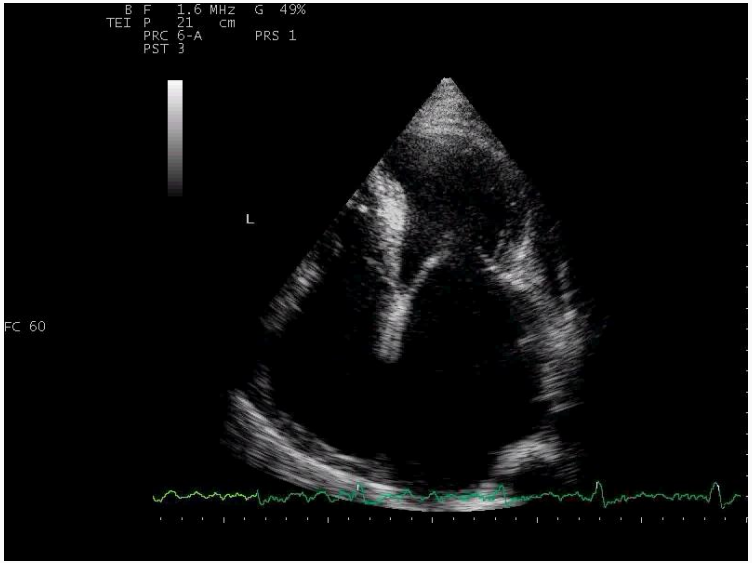


Heart Failure in HCM Occurs in 2 Contexts

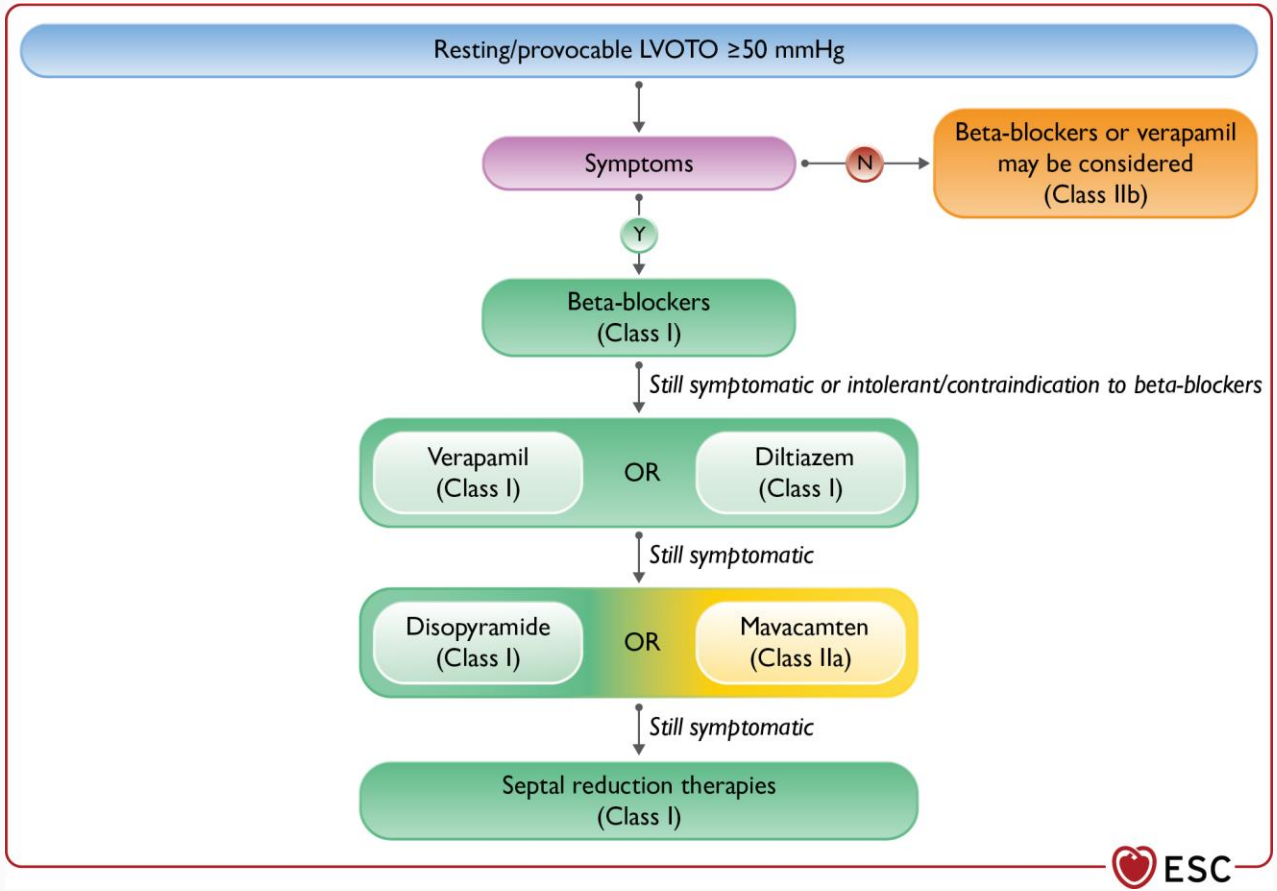
LV Outflow Obstruction



Disease Progression



Flowchart on the management of left ventricular outflow tract obstruction



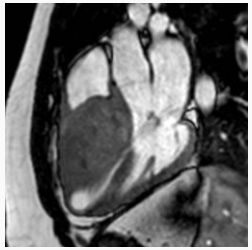
2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Recommendations for medical treatment of LV outflow tract obstruction

Recommendations	Class	Level
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provoked LVOTO.	IIa	A
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in symptomatic adult patients with resting or provoked LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/diltiazem, or disopyramide.	IIa	B

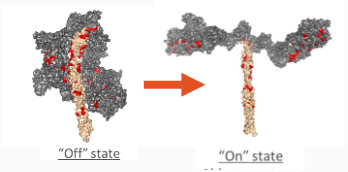
Clinical Studies

Hypercontractile LV
LVOT obstruction >>
Symptoms



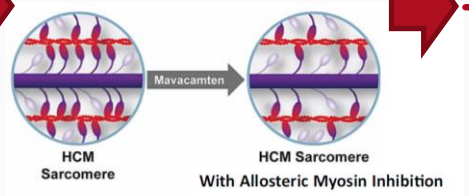
Basic Science

Gain of function MHY7 mutations



Targeted Molecular Approach

Mavacamten



Pre-clinical Data

↓ contractility
↑ compliance
↑ energetics
↓ LV hypertrophy
↓ disarray
↓ myocardial fibrosis

Phase 3 Clinical Trials

In Obstructive HCM

EXPLORER-HCM

ValorHCM

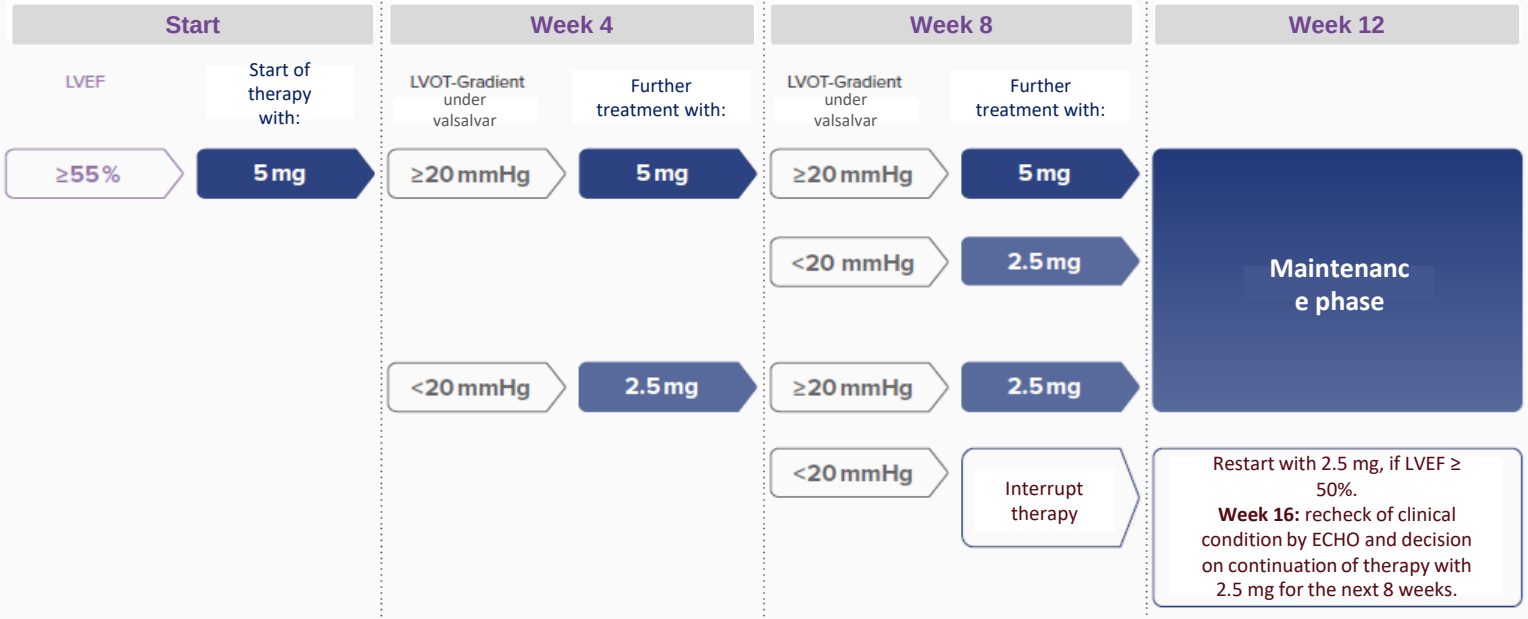
Improved Symptoms and Exercise Performance
Relief of LVOT gradient
Improved QOL
↓ LA size
↓ E/e'
↑ LV cavity size
↓ NT ProBNP and HsTnT
Reduced need for Septal Reduction Therapies

In Nonobstructive HCM → ODYSSEY HCM (Ongoing)

For Obstructive HCM: FDA Approval April 2022, **EC Approval** June 2023

Braunwald E, Saberi S, Abraham TP, Elliott PM, Olivotto I, Eur Heart J, in press

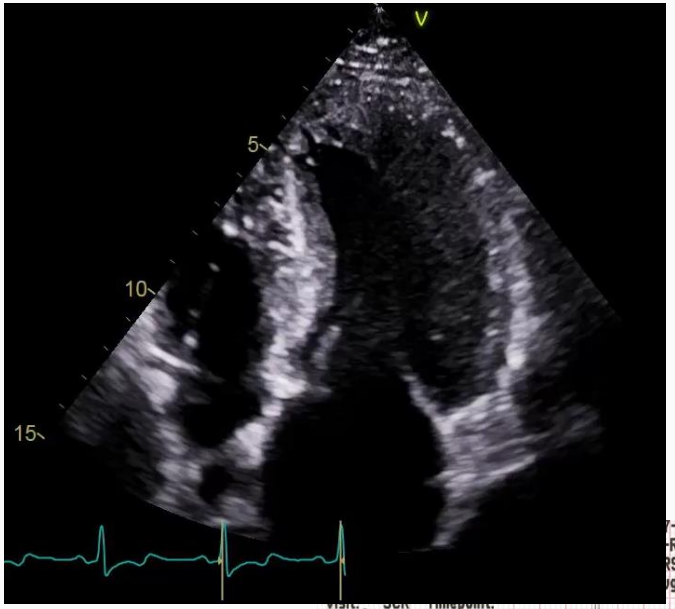
Mavacamten: QD with individual dosing for oHCM patients

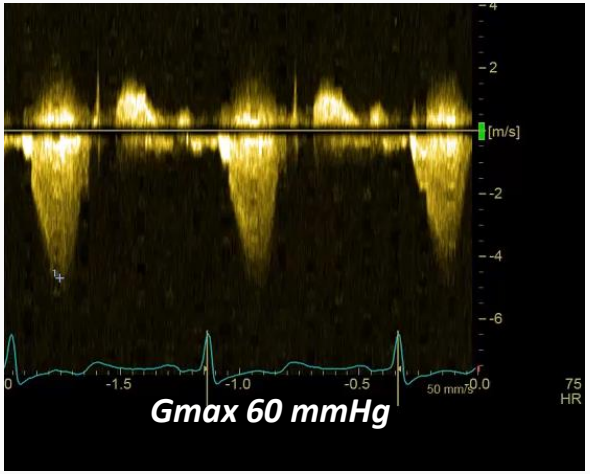


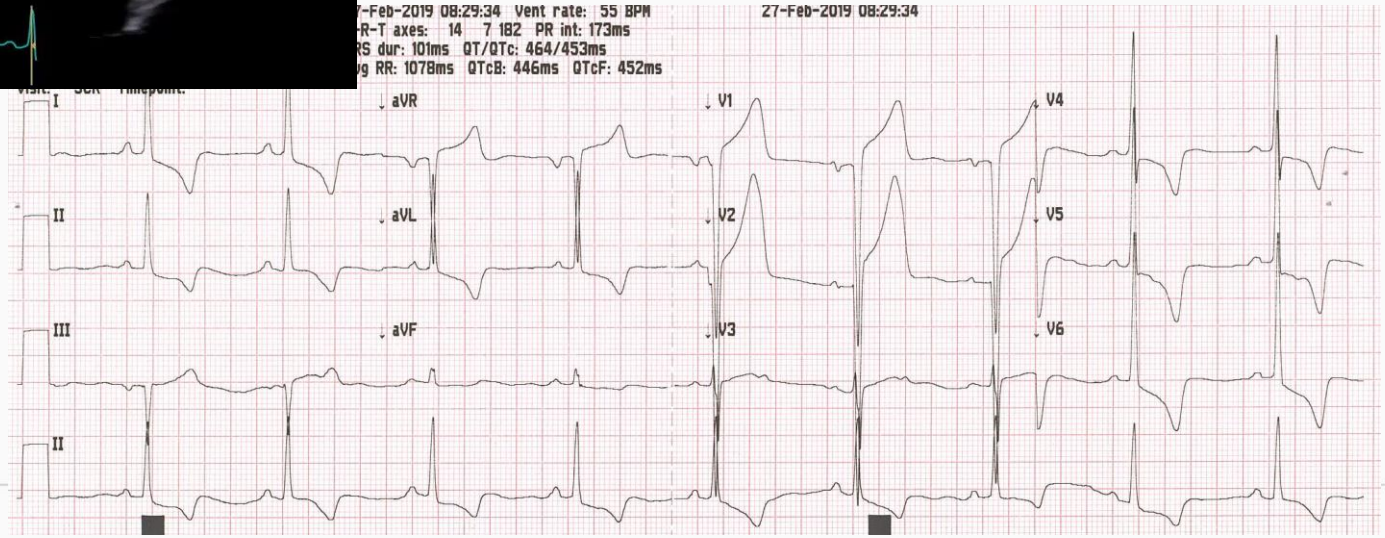
Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy

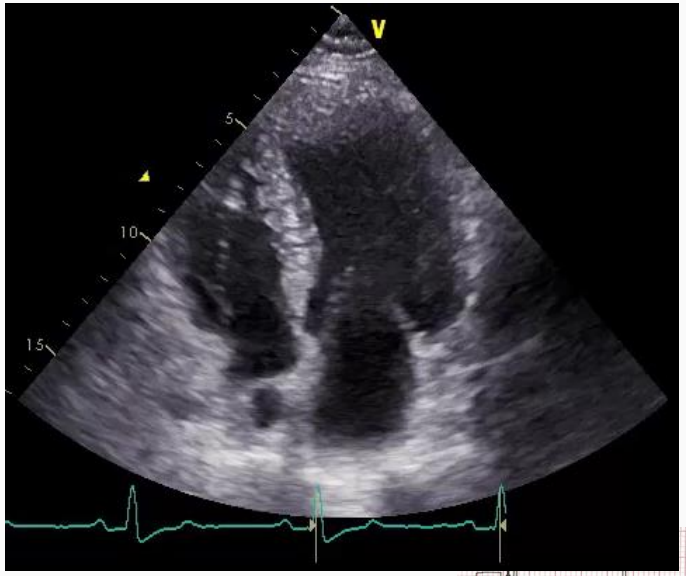
Martin S. Maron, MD,[a] Ahmad Masri, MD,[b] Lubna Choudhury, MD,[c] Iacopo Olivotto, MD,[d] Sara Saberi, MD,[e] Andrew Wang, MD,[f] Pablo Garcia-Pavia, MD, PHD,[g,h] Neal K. Lakdawala, MD,[i] Sherif F. Nagueh, MD,[j] Florian Rader, MD,[k] Albree Tower-Rader, MD,[l] Aslan T. Turer, MD,[m] Caroline Coats, MD, PHD,[n] Michael A. Fifer, MD,[l] Anjali Owens, MD,[o] Scott D. Solomon, MD,[i] Hugh Watkins, MD, PHD,[p] Roberto Barriales-Villa, MD,[q] Christopher M. Kramer, MD,[r] Timothy C. Wong, MD,[s] Sharon L. Paige, MD, PHD,[t] Stephen B. Heitner, MD,[t] Stuart Kupfer, MD,[t] Fady I. Malik, MD, PHD,[t] Lisa Meng, PHD,[t] Amy Wohltman, ME,[t] Theodore Abraham, MD,[u] on behalf of the REDWOOD-HCM Steering Committee and Investigators

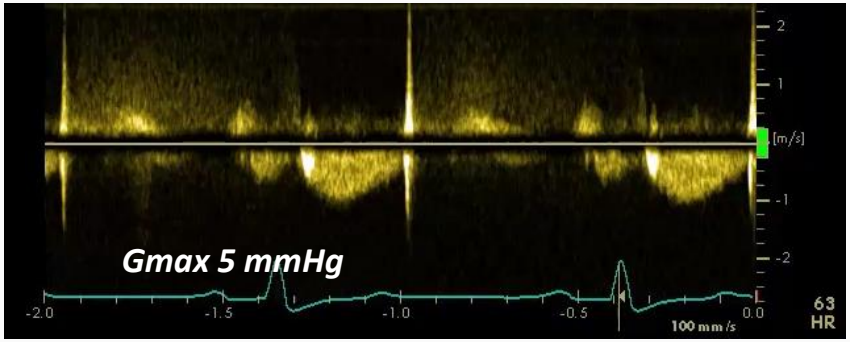
- Potential *in vivo* pharmacodynamic advantages related to distinctive binding site
- Optimized for
  - Onset of action (reach steady state within two weeks)
  - Rapid reversibility of effect
  - Minimal drug-drug interactions
  - Favorable tolerability
  - Ease of titration for personalized dosing
- Clear pharmacokinetic/pharmacodynamic (PK/PD) relationship observed
- Shallow exposure-response relationship

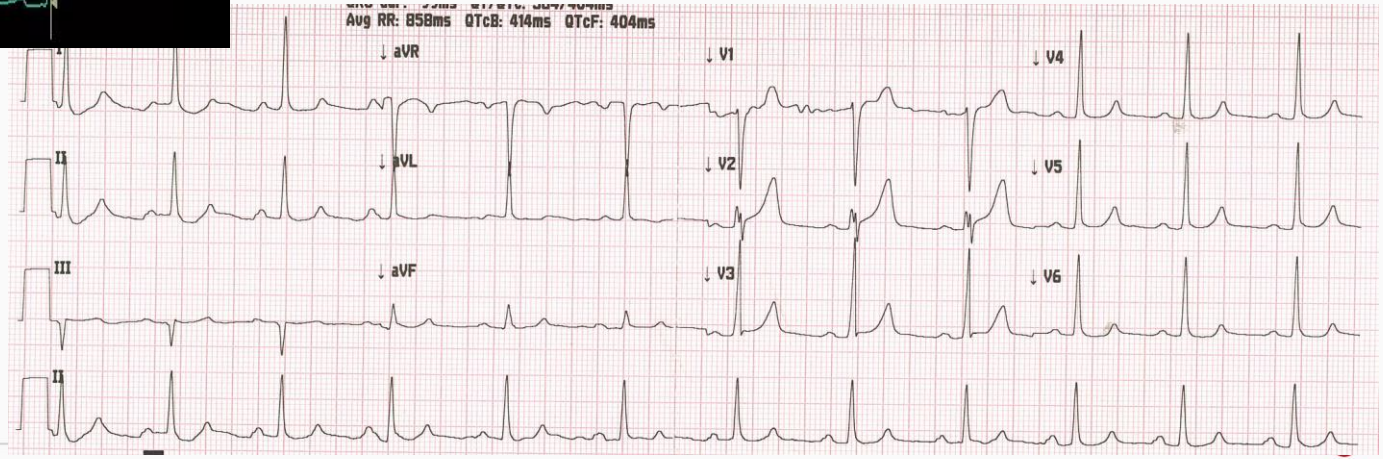

V
5
10
15


2
[m/s]
-2
-4
-6
-1.5
-1.0
-0.5
0.0
50 mm/s
75
HR
Gmax 60 mmHg

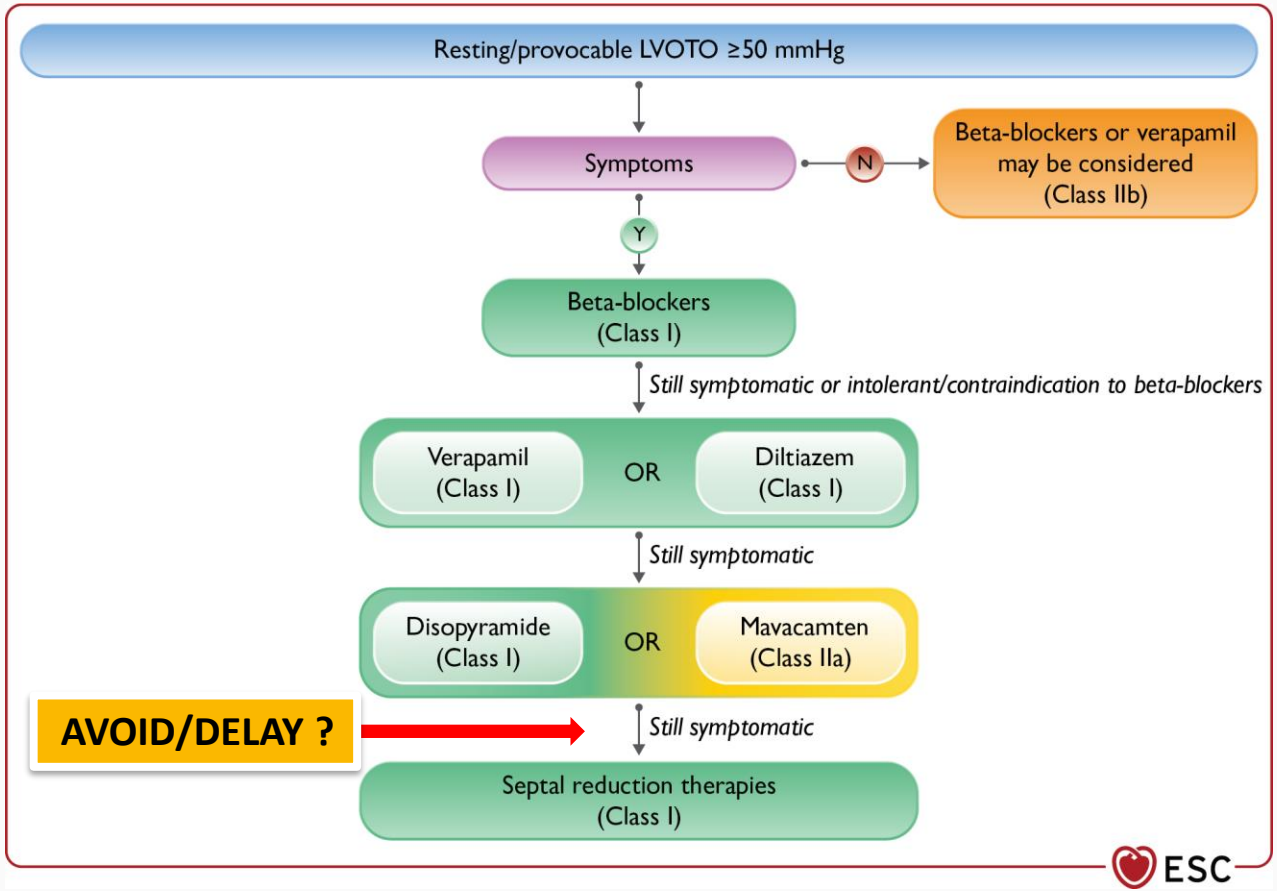

7-Feb-2019 08:29:34 Vent rate: 55 BPM
R-T axes: 14 7 182 PR int: 173ms
RS dur: 101ms QT/QTc: 464/453ms
g RR: 1078ms QTcB: 446ms QTcF: 452ms
27-Feb-2019 08:29:34
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II


V
5
10
15


Gmax 5 mmHg
2
1
[m/s]
-1
-2
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s
63
HR


Avg RR: 858ms QTcB: 414ms QTcF: 404ms
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Flowchart on the management of left ventricular outflow tract obstruction



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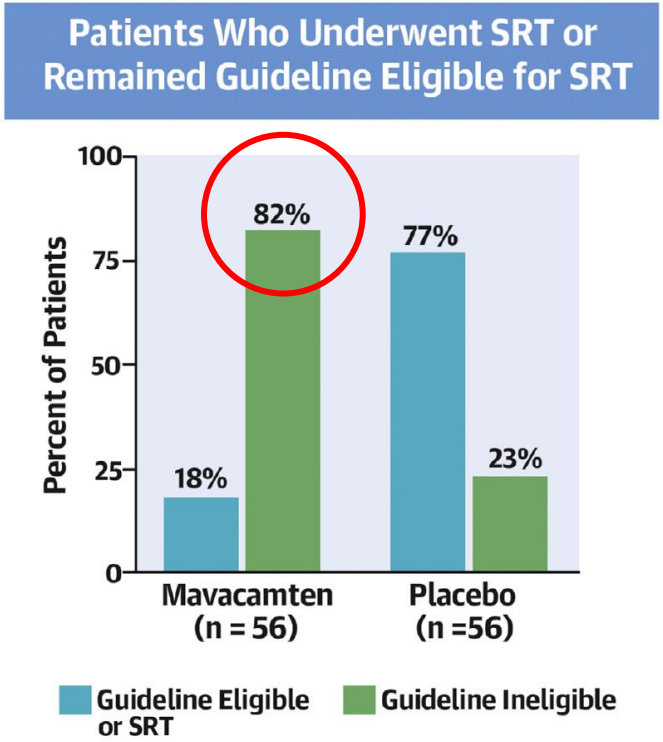
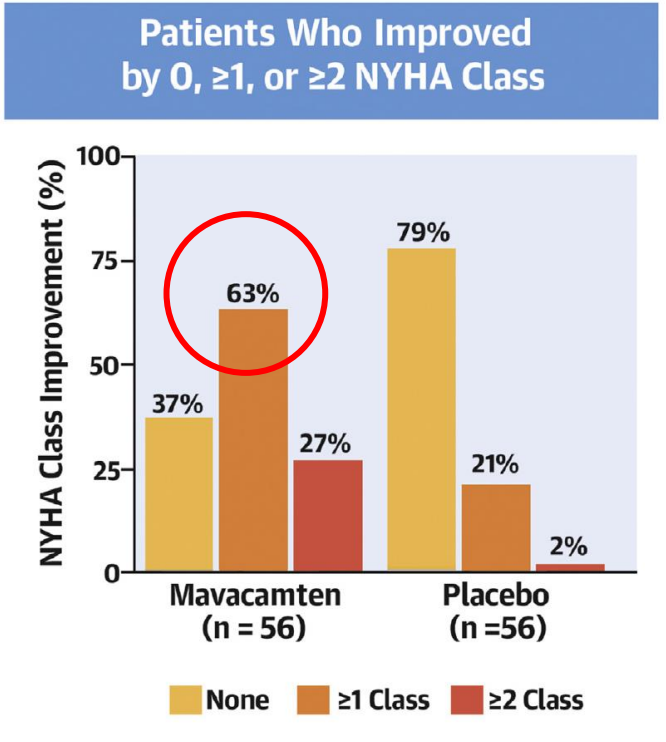


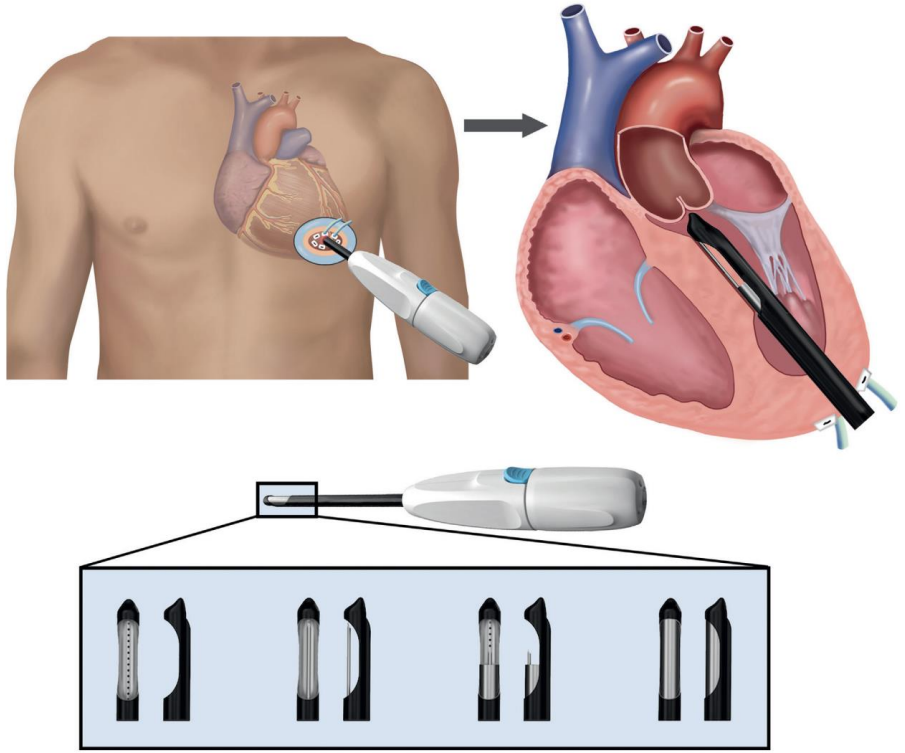


Desai M et al J Am Coll Cardiol 2022

First-in-Human Transapical Beating-Heart Septal Myectomy in Patients With Hypertrophic Obstructive Cardiomyopathy

Jing Fang, MD, PhD,[a,b,c,*] Yani Liu, MD, PhD,[d,*] Ying Zhu, MD, PhD,[d] Rui Li, l
Dao Wen Wang, MD, PhD,[e] Yunhu Song, MD, PhD,[f] Chenhe Li, MD,[a,b,c] Yue C
Lin Cheng, MD, PhD,[a,b,c] Kangchao Zheng, MD,[d] Yun Zhao, MD,[g] Shiliang Li,
Liming Xia, MD, PhD,[g] Xiaoping Chen, MD, PhD,[h] Song Wan, MD, PhD,[i] Xiang

CENTRAL ILLUSTRATION Transapical Beating-Heart Septal Myectomy and Beating-Heart Myectomy Device



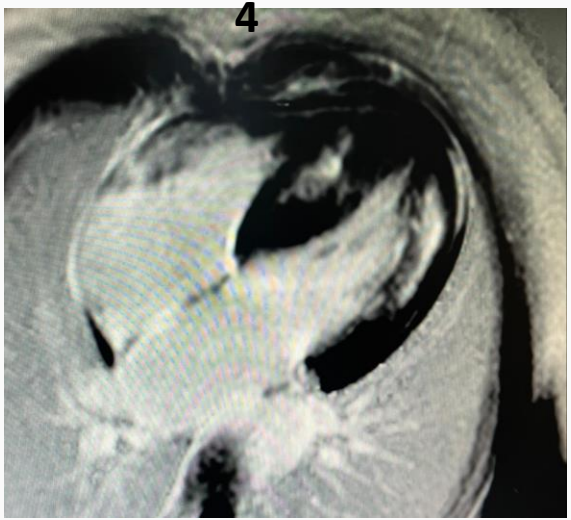
Fang J, et al. J Am Coll Cardiol. 2023;82(7):575-586.

Schematic diagram showing the principle of the beating-heart myectomy device and the surgical setup of the transapical beating-heart septal myectomy procedure.

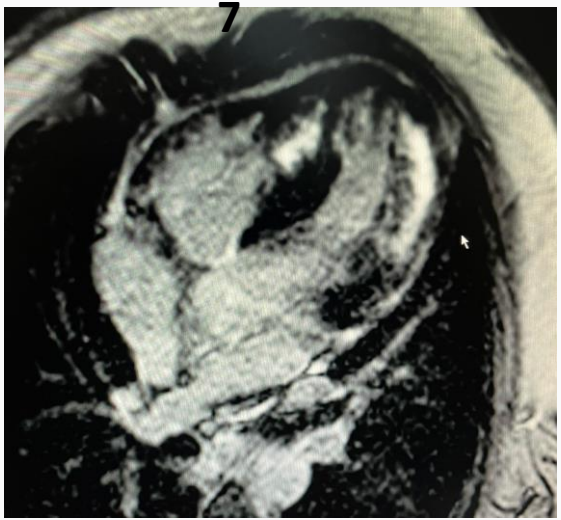
Challenges of Septal Reduction Therapies for oHCM

	Surgical Myectomy	Alcohol Septal Ablation
Operative Risk (in High Flow Centers)	Low	Low
Need for Permanent Pacing	+	++
Need for Re-do	+/-	++
Operator/Center dependent	+++	+++
Poor compliance	++	+/-
Non-eligibility	High surgical risk	Inadequate anatomy

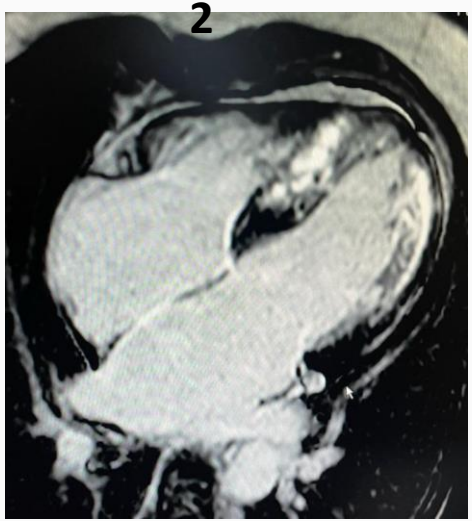
2014



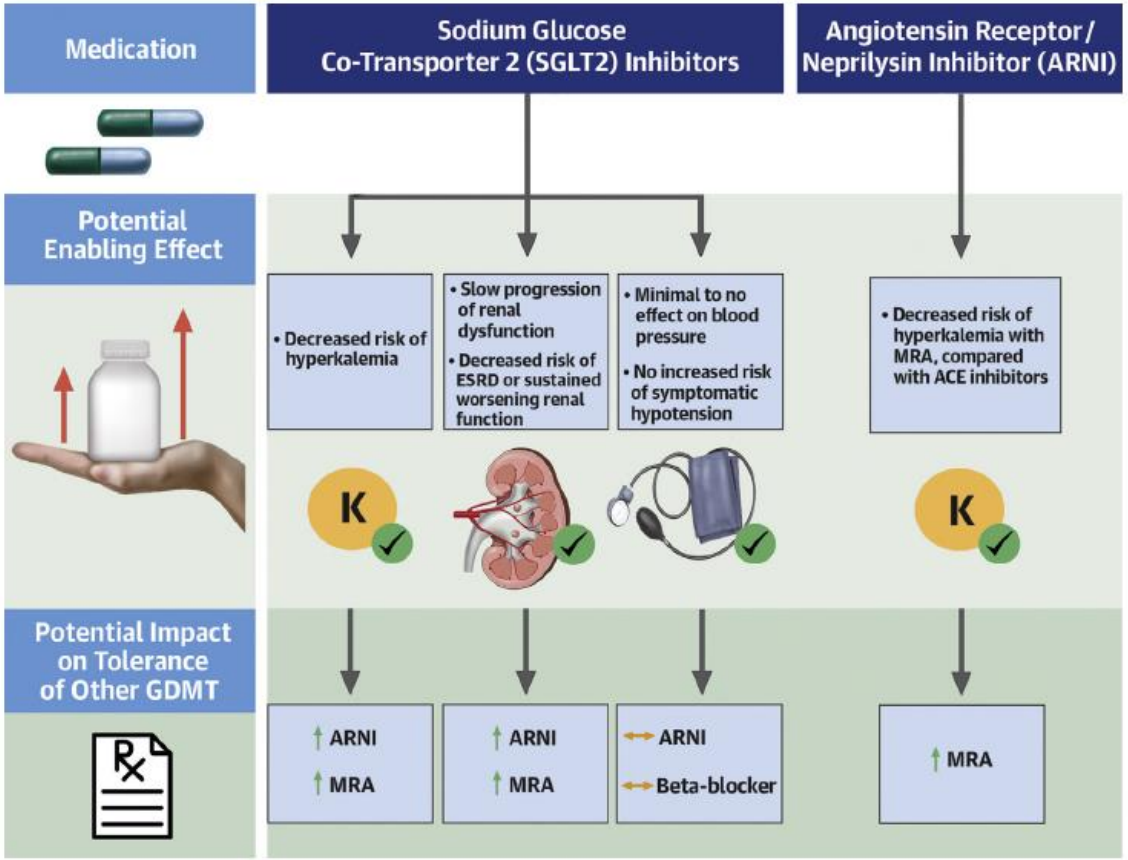
2017



2022



THE FANTASTIC 4: Synergy and Troubleshooting



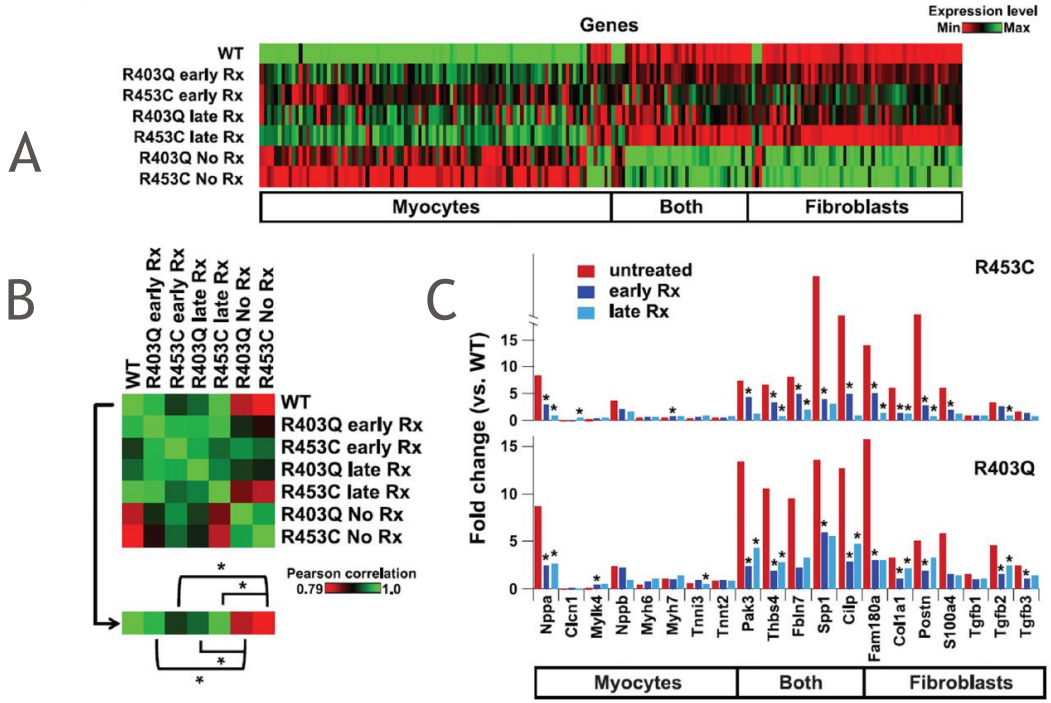
J Am Coll Cardiol. 2021 Mar, 77 (11) 1408–1411

Mavacamten may improve diastole by countering multiple mechanisms

- Excess availability of ON state(s) myosin heads, with elevations in residual cross-bridges hindering compliance and filling.
- Biochemical events prolonging cross-bridge detachment
- Alterations in Ca2+ handling resulting in elevated diastolic levels
- Structural remodeling (e.g., fibrosis)

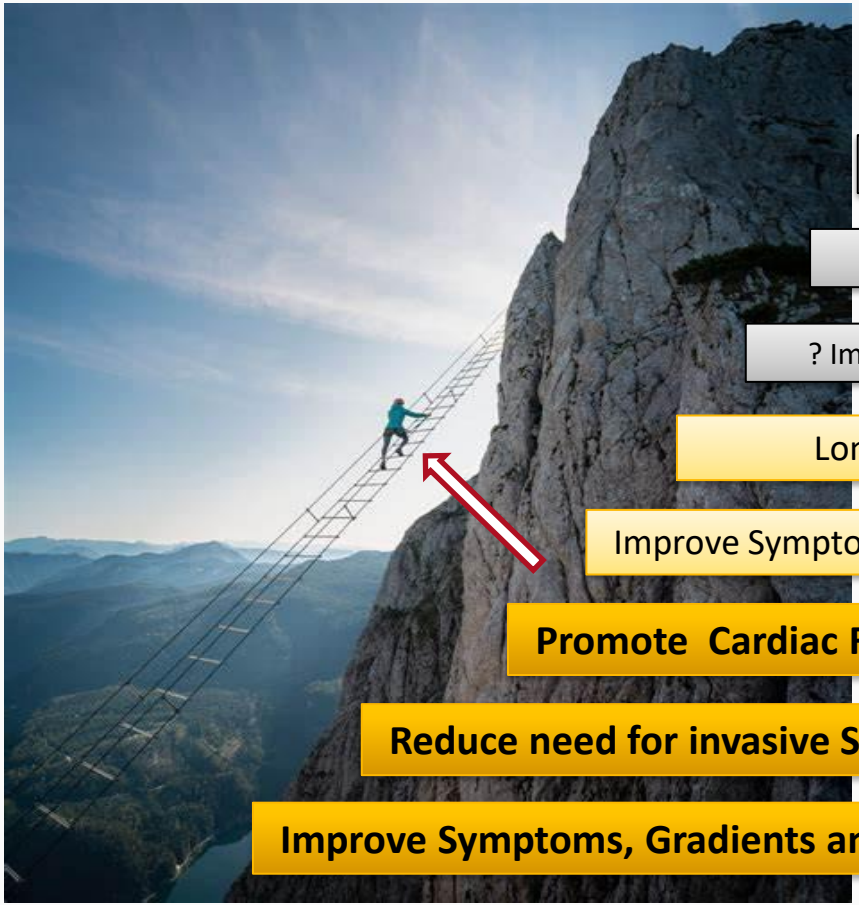
Modified from Nag *et al.*, *Sci. Adv.* **9**, eabo7622 (2023) 28 July 2023

Mavacamten suppresses hypertrophic and pro-fibrotic pathways in genetic HCM mouse models



Green et al, Science 2016

CARDIAC MYOSIN INHIBITORS: A LOOK AT THE FUTURE



Non Sarcomeric HCM ? HFpEF?

? Prevent disease in gene+ individuals

? Reduce arrhythmic risk

? Improve HF-related outcomes

Long-term Safety

Improve Symptoms and QOL in nHCM

Promote Cardiac Remodeling in oHCM

Reduce need for invasive SRTs

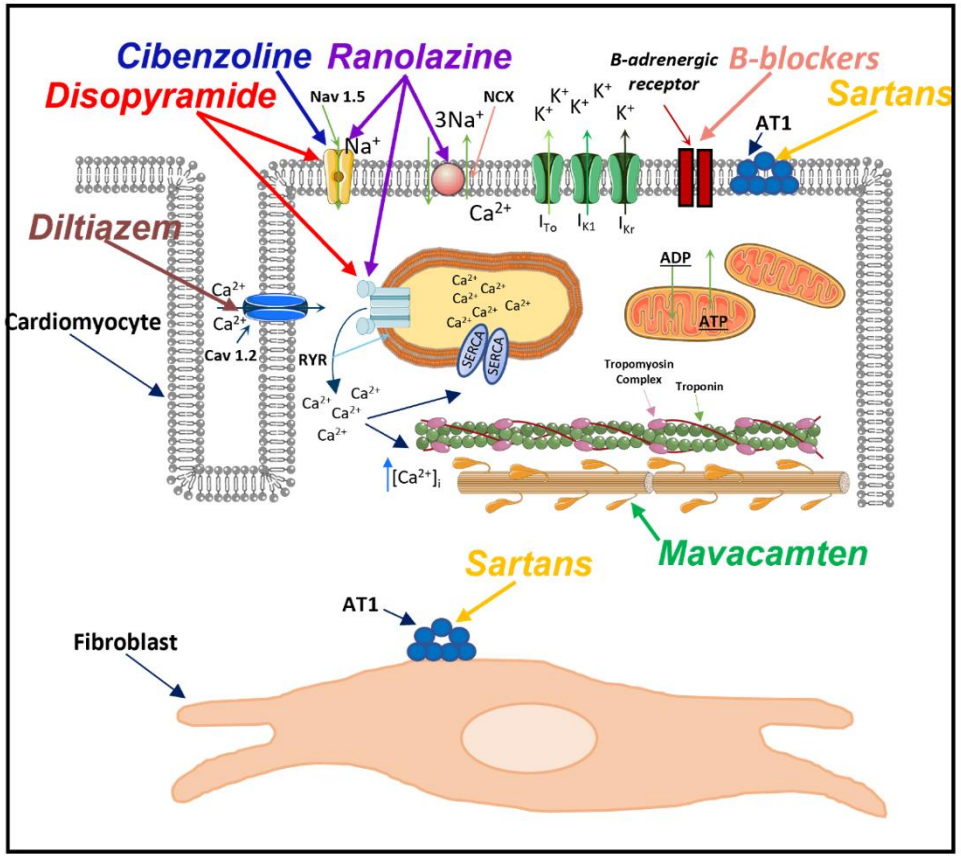
Improve Symptoms, Gradients and QOL in oHCM

2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Back up slides

IDEAL ENDPOINT

- Objective
- Reproducible
- Easy to measure
- Captures overall disease burden
- Has prognostic implications
- Relevant to the Regulatory Bodies
- RELEVANT TO PATIENTS



Coppini et al, Drugs 2022