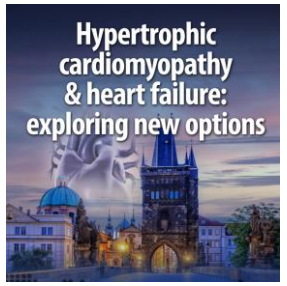
Managing patients with HCM and HF: what's new in the therapeutic landscape?

Iacopo Olivotto, MD

Florence, Italy

Hypertrophic cardiomyopathy & heart failure: exploring new options



Managing Patients With HCM and HF: What's New in the Therapeutic Landscape?

Iacopo Olivotto, MD

Meyer Children Hospital

& Careggi University Hospital

University of Florence, Italy

iacopo.olivotto@unifi.it

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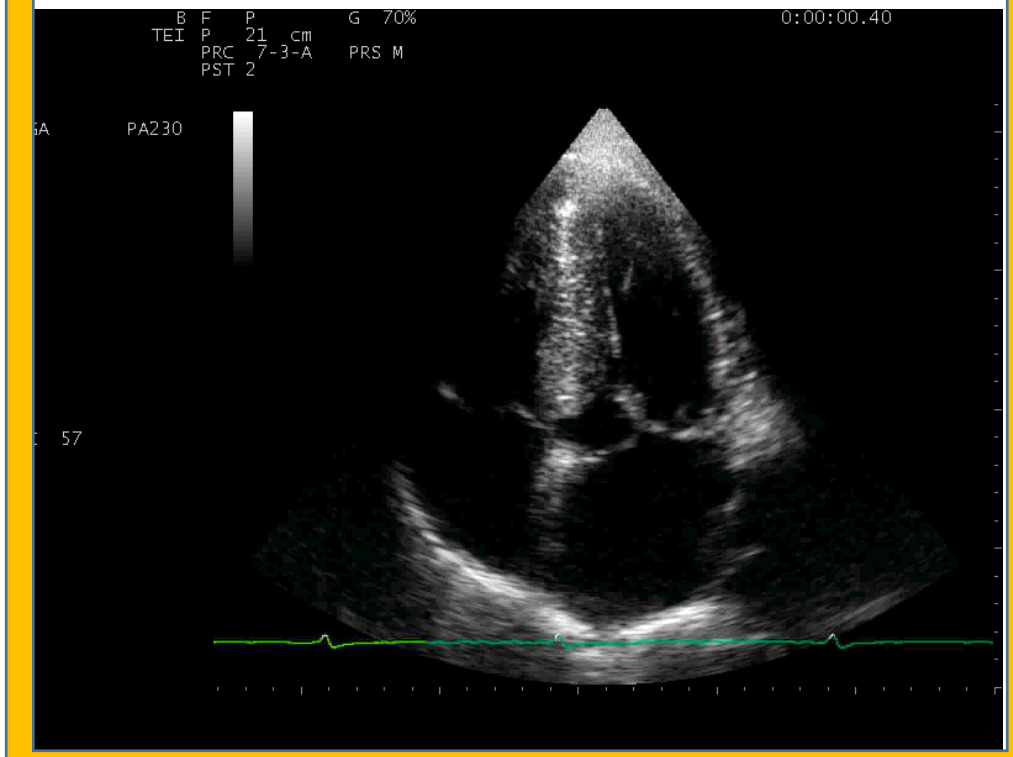
Disclosures - Dr. Olivotto

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

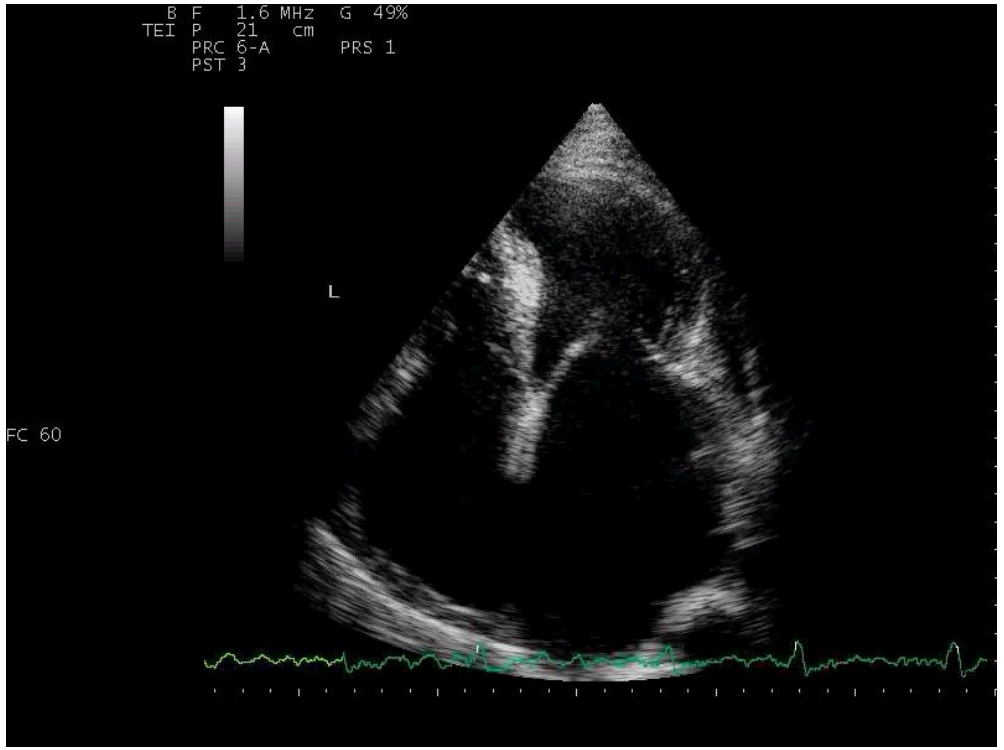
Advisory board, invited speaker: BMS-Myokardia, Cytokinetics, Sanofi, Genzyme, Shire Takeda, Amicus, Tenaya, Rocket Pharma.

Heart Failure in HCM Occurs in 2 Contexts

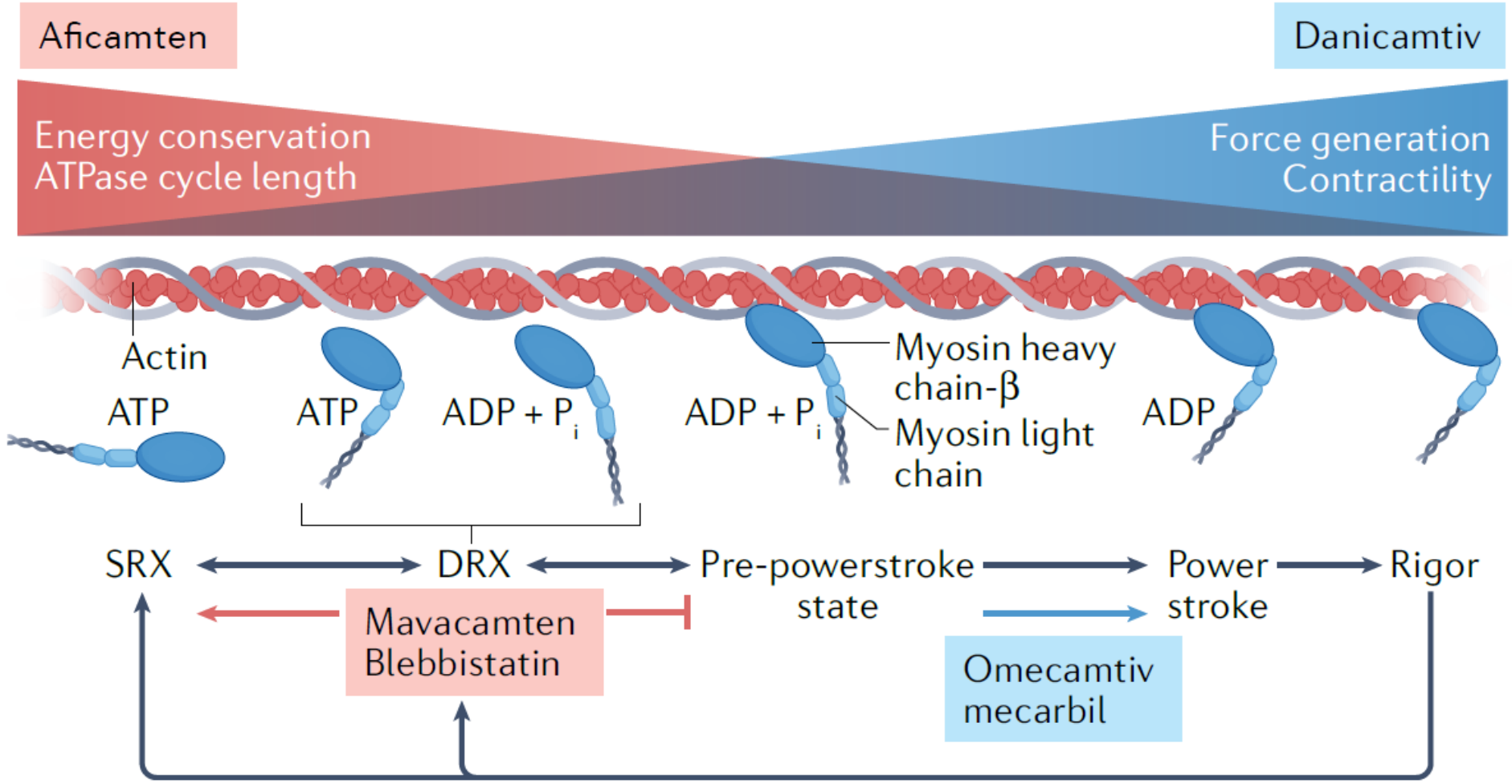
LV Outflow Obstruction



Disease Progression



The Molecular Mechanisms of Myosin Modulation by Targeted Small Molecules



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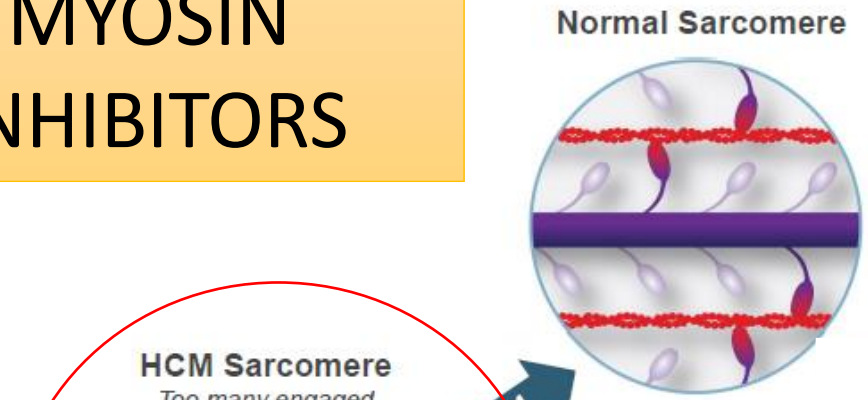
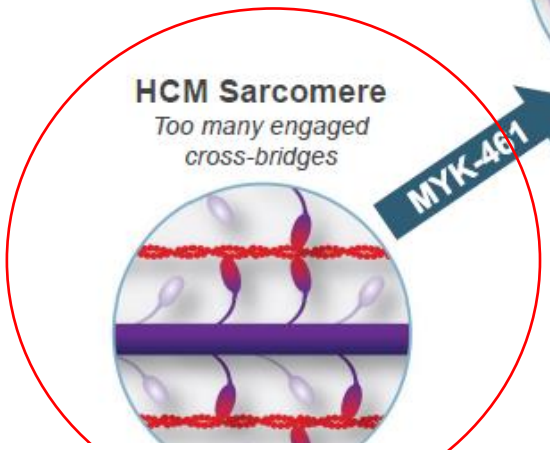
Lehman, Crocini and Leinwand, Nat Cardiol Rev 2022

MYOSIN INHIBITORS





- Improves symptoms and VO2
- Reduces gradient
- Improves quality of life
- Improves biomarker profile
- Promotes reverse LV and LA remodeling

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

*Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ho, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators**

Lancet **2020; 396: 759–69**

EXPLORER-HCM: Primary and Secondary Endpoints

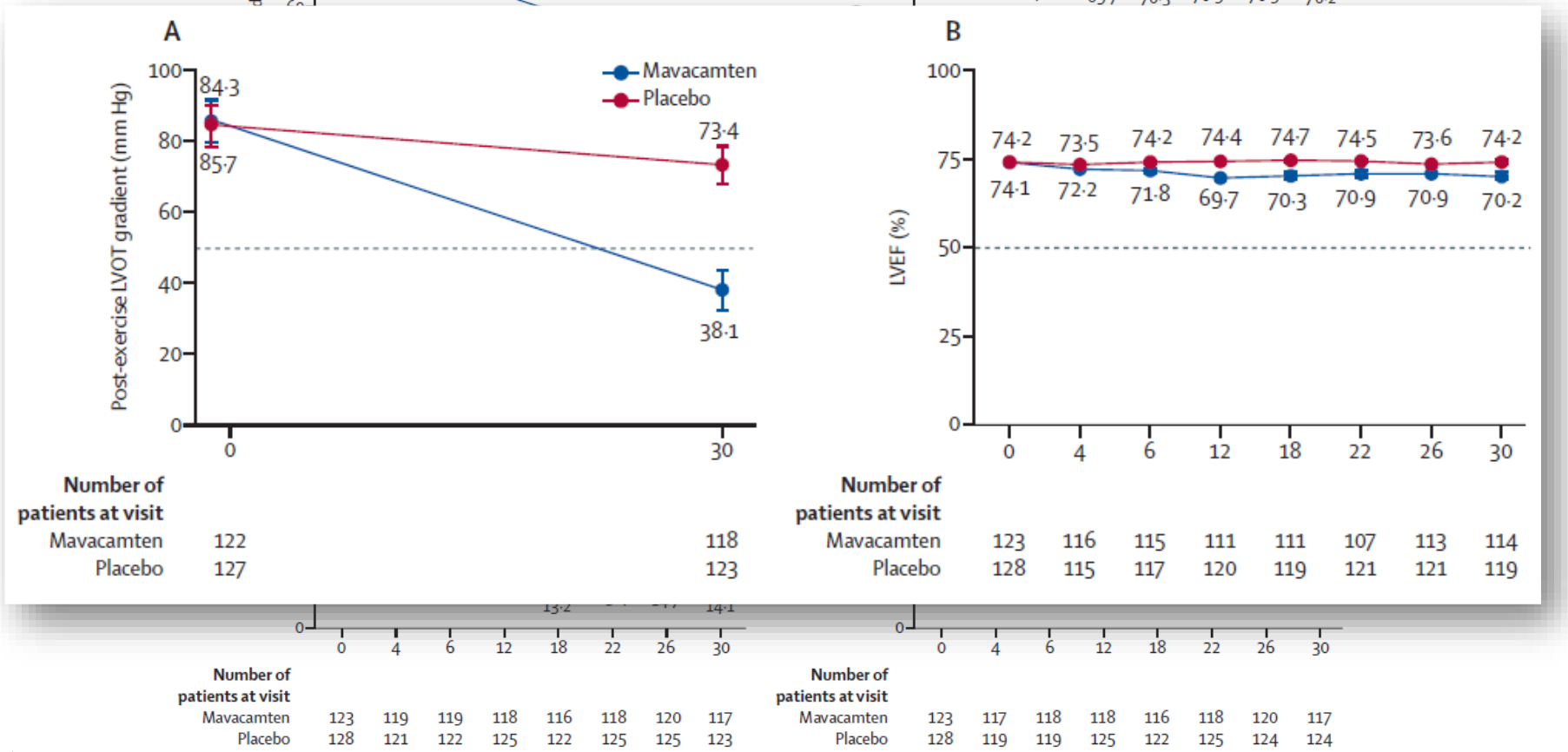
	Mavacamten (n = 123)	Placebo (n = 128)	Difference (95% CI) *P* Value
Primary endpoint			
Either ≥ 1.5 mL/kg/min increase in pVO2 with ≥ 1 NYHA class improvement or ≥ 3.0 mL/kg/min increase in pVO2 with no worsening of NYHA class	37%	17%	19.4 (8.7, 30.1) .0005
Secondary endpoints			
Postexercise LVOT gradient change from baseline to wk 30, mm Hg	–47 (40) n = 117	–10 (30) n = 122	–35.6 (–43.2, –28.1) < .0001
pVO2 change from baseline to wk 30, mL/kg/min	1.4 (3.1) n = 120	–0.1 (3.0) n = 125	1.4 (0.6, 2.1) .0006
≥ 1 NYHA class improvement from baseline to wk 30	80 (65%)	40 (31%)	34% (22%, 45%) < .0001
Change from baseline to wk 30 in KCCQ-CSS	13.6 (14.4) n = 92	4.2 (13.7) n = 88	9.1 (5.5, 12.7) < .0001
Change from baseline to wk 30 in HCMSQ-SoB score	–2.8 (2.7) n = 85	–0.9 (2.4) n = 86	–1.8 (–2.4, –1.2) < .0001

- HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score.

Olivotto I, et al. Lancet. 2020;396:759-769.

LVOT Gradients and LVEF Over Time

EXPLORER-HCM



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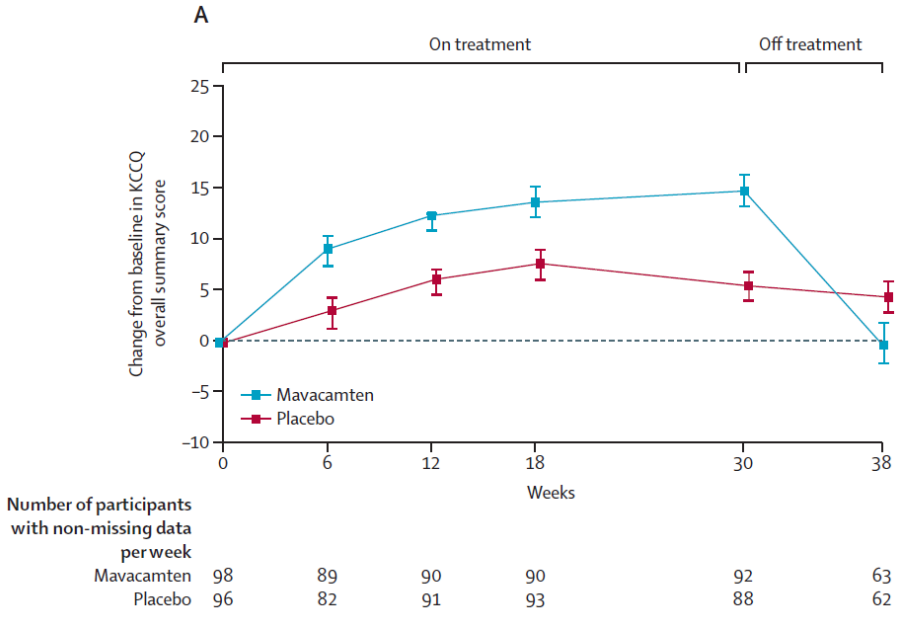
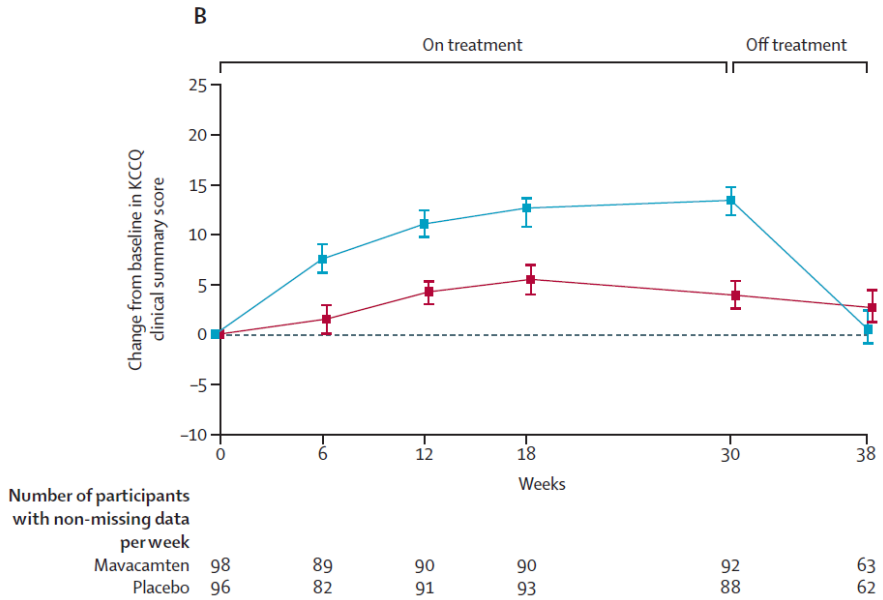
Olivotto et al, Lancet 2020

EXPLORER-HCM

Quality of Life



mean change from baseline in KCCQ-OS +9·1
(95% CI 5·5–12·8; p<0·0001)



mean change from baseline in KCCQ-CS +9·1
(95% 5.5-12.7) ; p<0·0001)

Spertus et al. Lancet, May 15 2021

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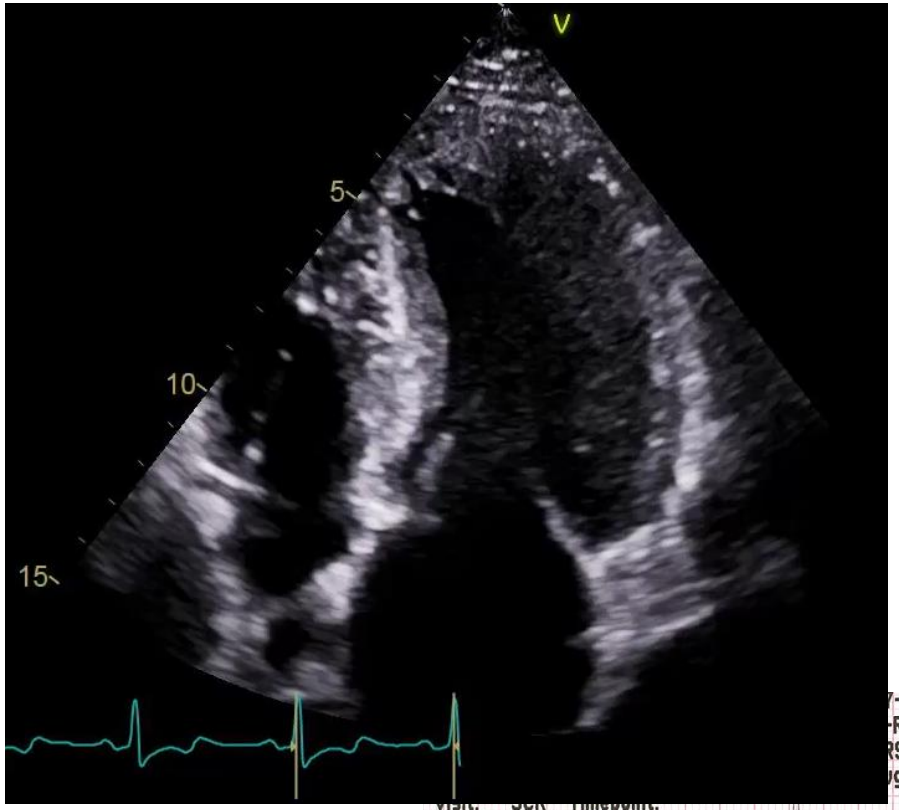
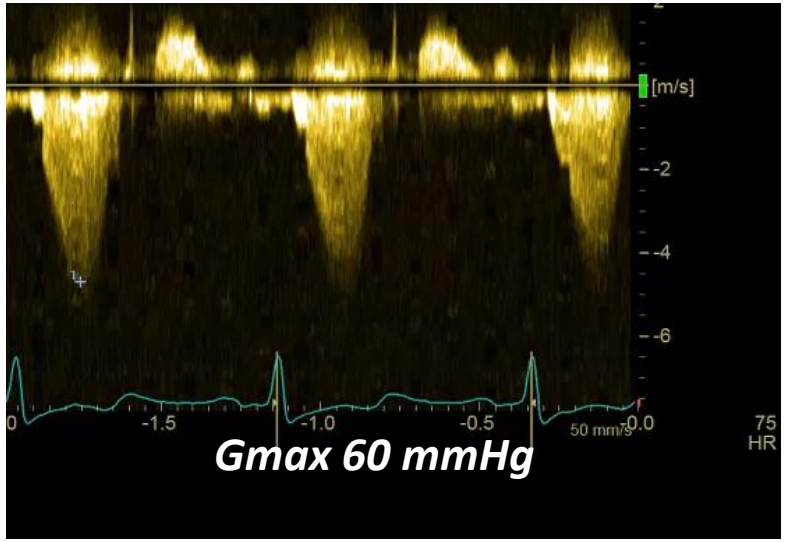
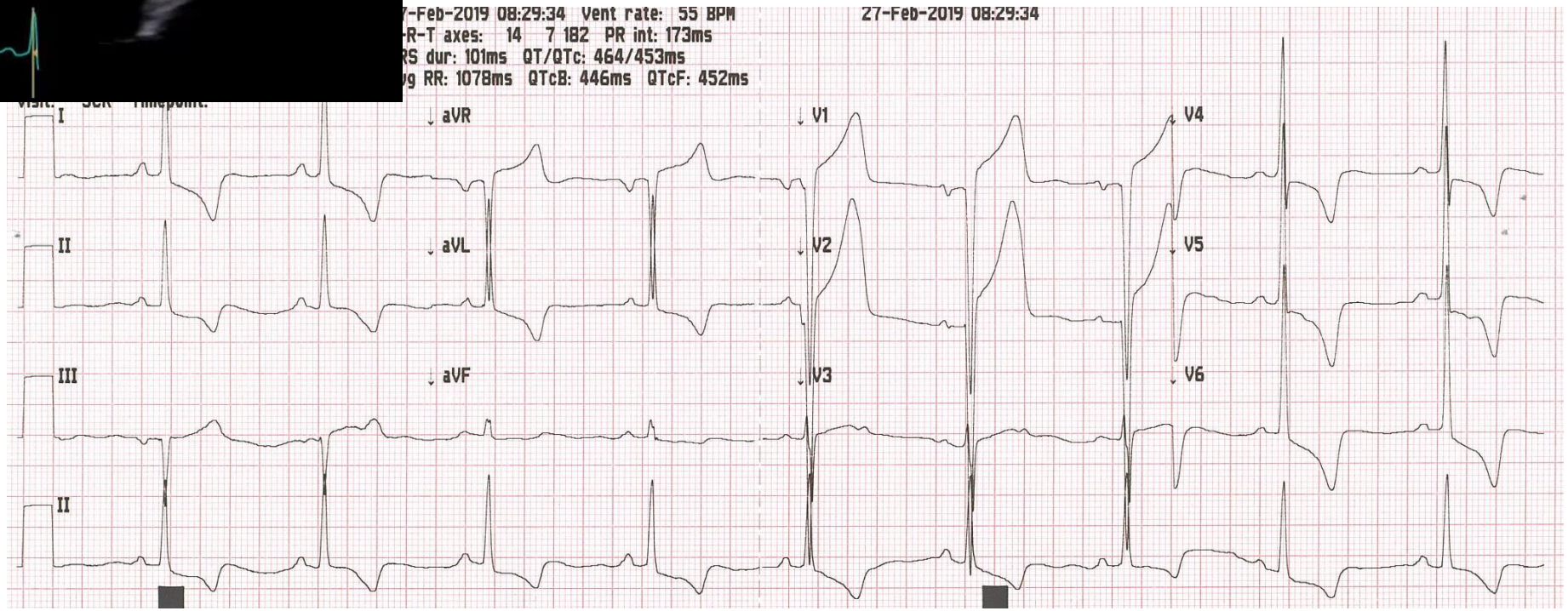
EXPLORER-HCM







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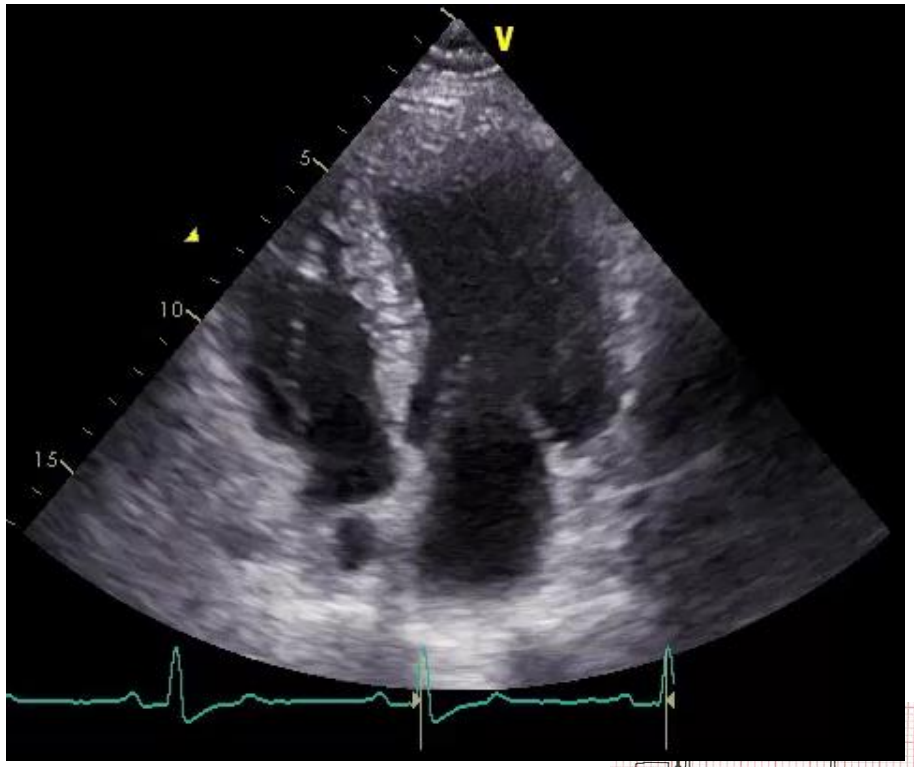
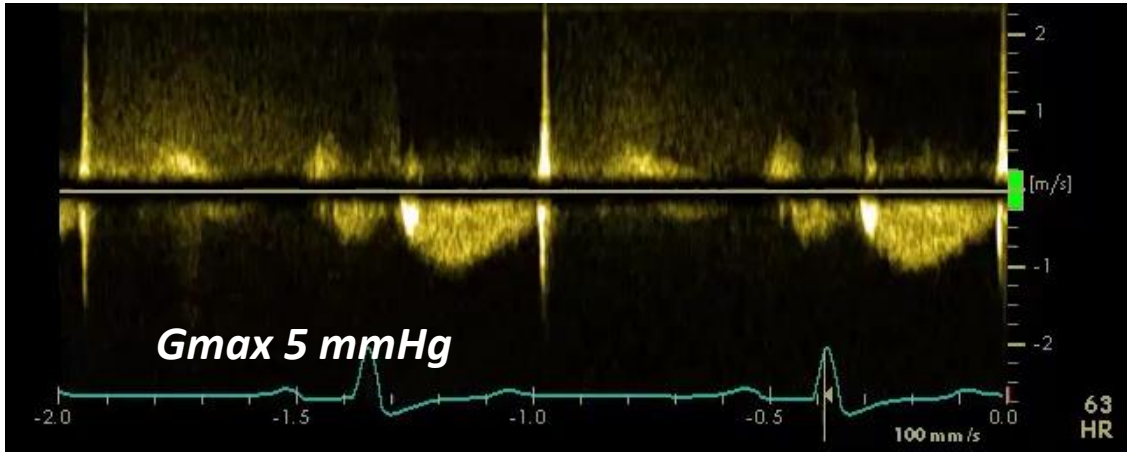
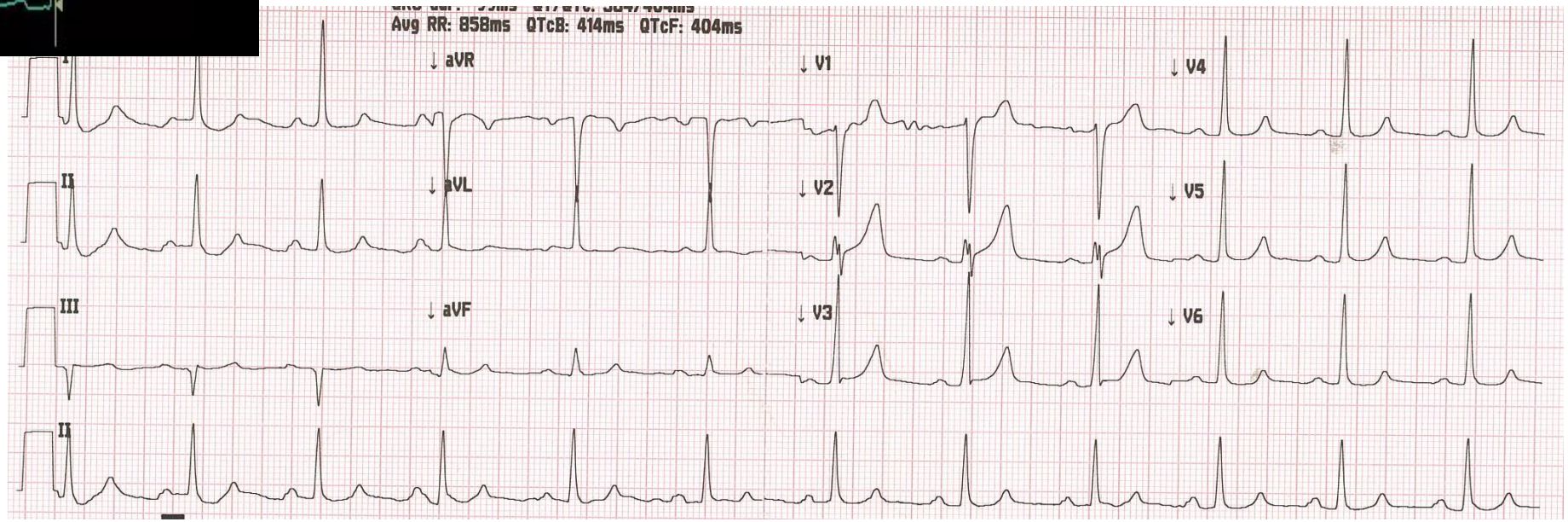

V
5
10
15


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

Effects of Mavacamten on Measures of Cardiopulmonary Exercise Testing Beyond Peak Oxygen Consumption

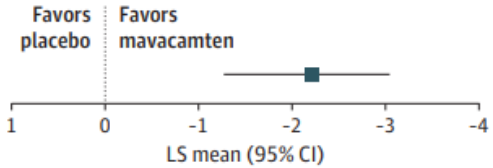
A Secondary Analysis of the EXPLORER-HCM Randomized Trial

Matthew T. Wheeler, MD, PhD; Iacopo Olivotto, MD; Perry M. Elliott, MD; Sara Saberi, MD; Anjali T. Owens, MD; Mathew S. Maurer, MD; Ahmad Masri, MD; Amy J. Sehnert, MD; Jay M. Edelberg, MD, PhD; Yu-Mao Chen, MSc; Victoria Florea, MD; Rajeev Malhotra, MD; Andrew Wang, MD; Artur Oręziak, MD; Jonathan Myers, PhD

Figure 2. Treatment Difference of the Change From Baseline to Week 30 Between Mavacamten and Placebo in Peak-Exercise Cardiopulmonary Exercise Testing (CPET) Parameters

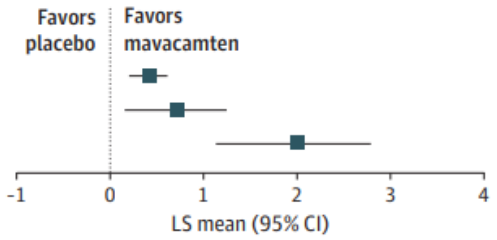
A Peak V_E/VCO_2

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



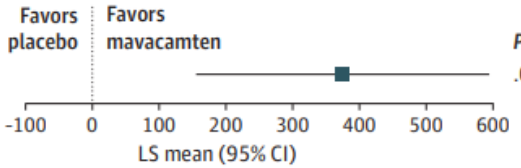
B Peak METs, exercise time, and $PETCO_2$

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



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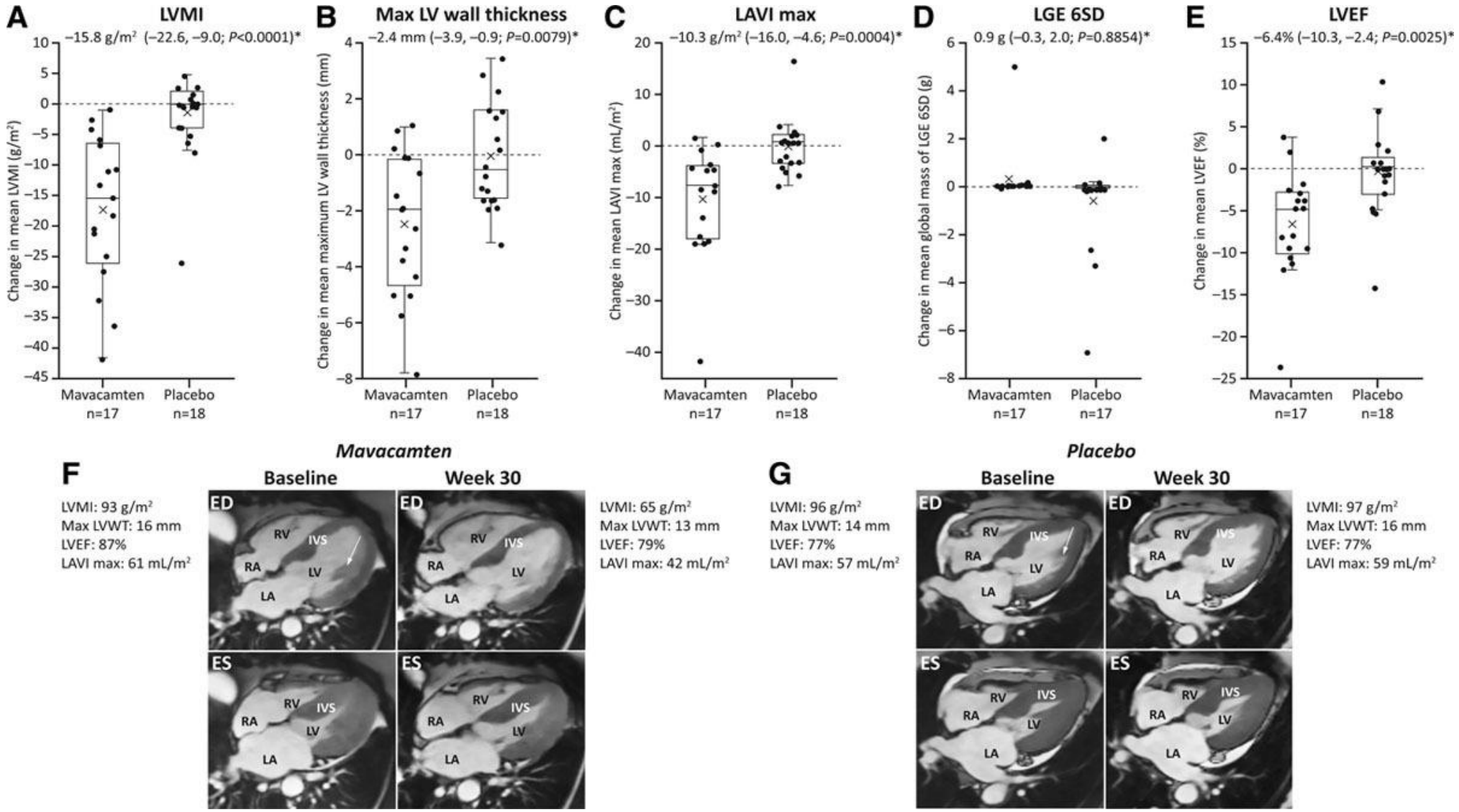
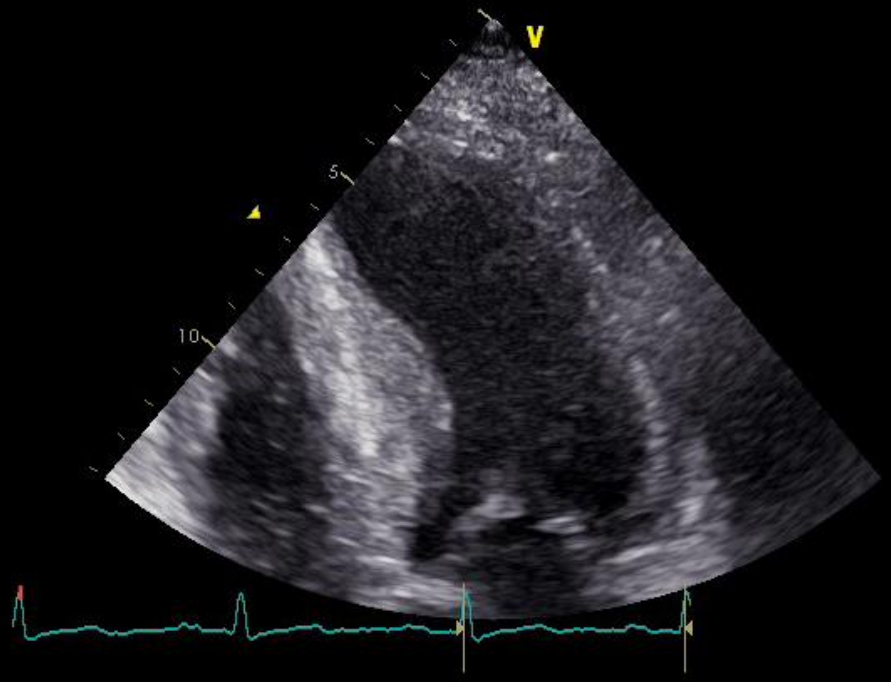
JAMA Cardiol. 2023;8(3):240-247. doi:10.1001/jamacardio.2022.5099



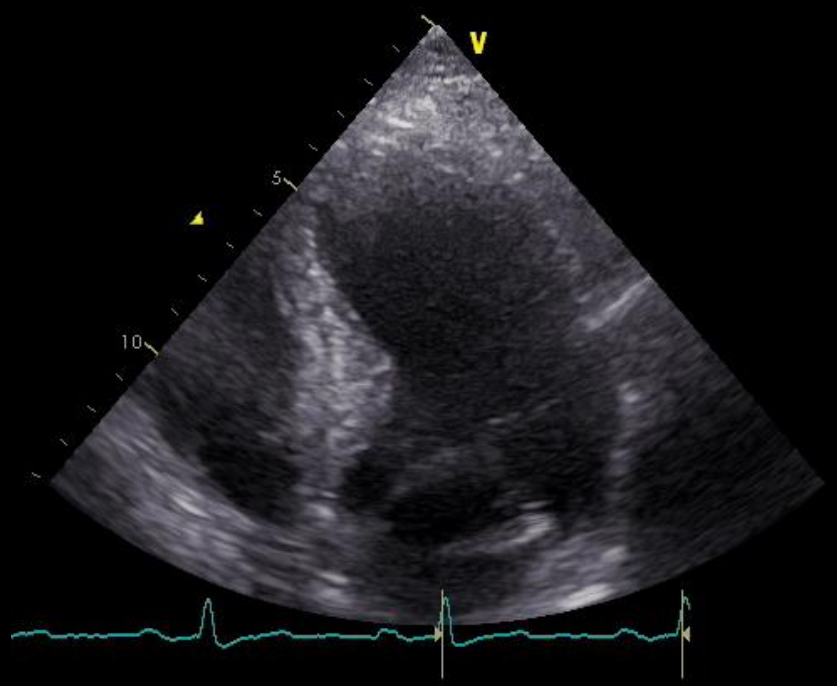
Sara Saberi. Circulation. Mavacamten Favorably Impacts Cardiac Structure in Obstructive Hypertrophic Cardiomyopathy, Volume: 143, Issue: 6, Pages: 606-608, DOI: (10.1161/CIRCULATIONAHA.120.052359)

Baseline



LV EF = 73 %

3rd year on mavacamten



LV EF = 58%

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

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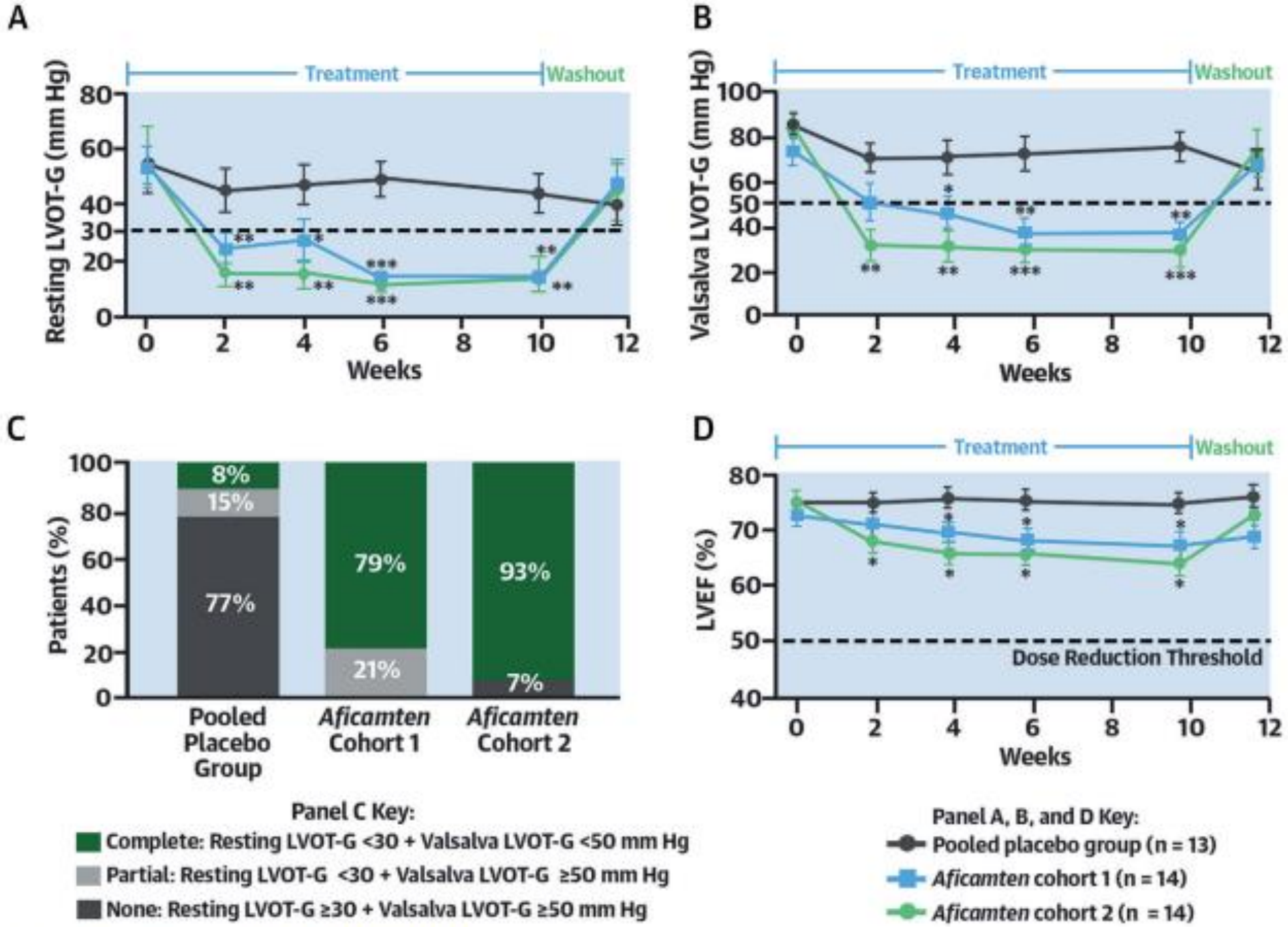
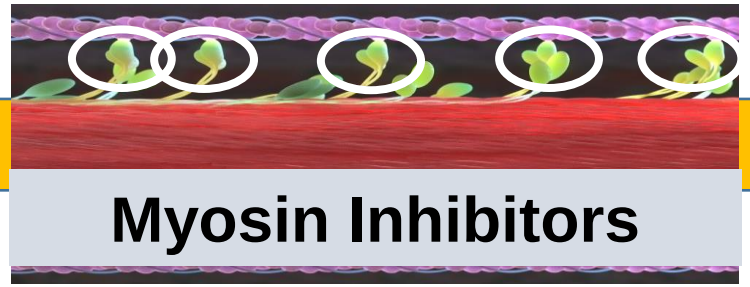


Maron MS, et al. J Am Coll Cardiol. 2023;81(1):34–45.

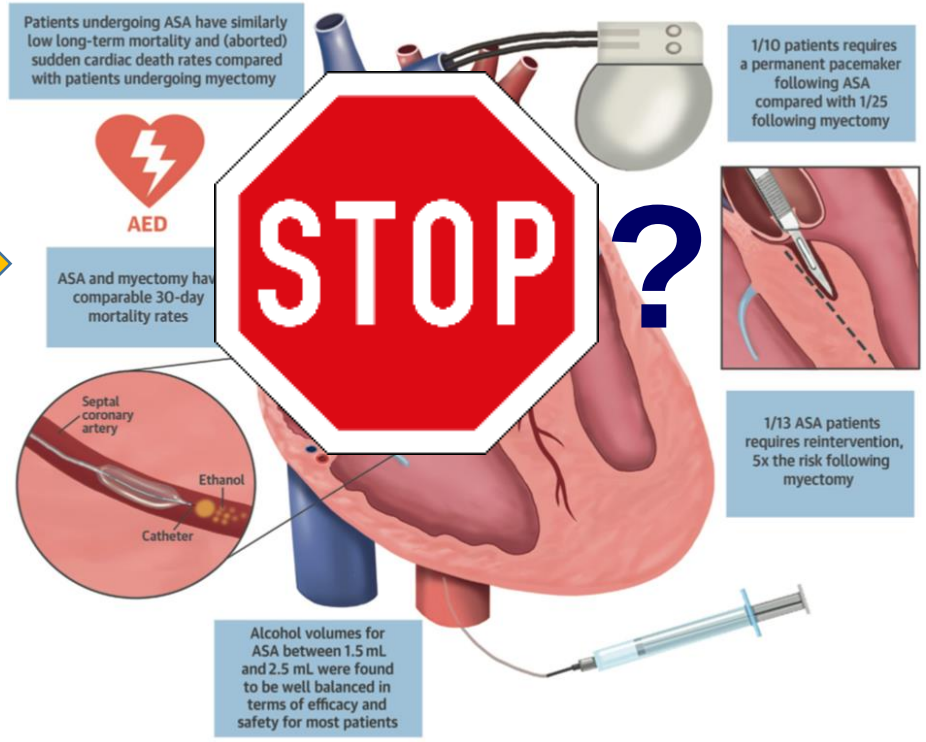
Treatment Options for Symptomatic LVOT Obstruction: WHAT WILL CHANGE?

Standard Pharmacological Options

(BB, CA, Disopyramide)



Invasive Options



Liebregts, M. et al. J Am Coll Cardiol. 2017;70(4):481-8.

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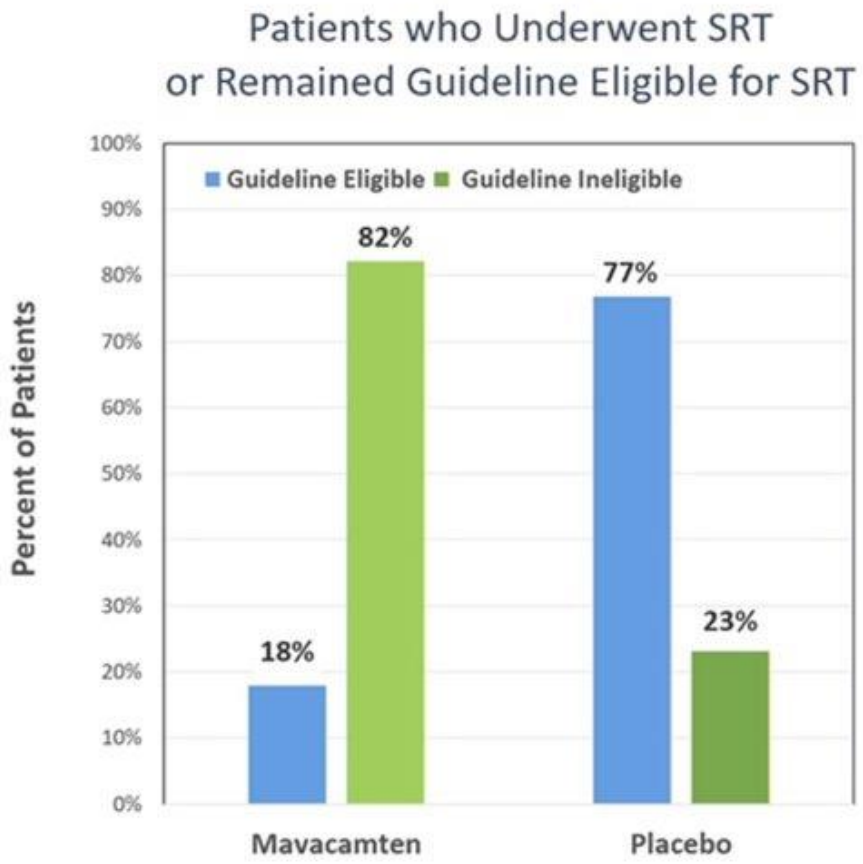
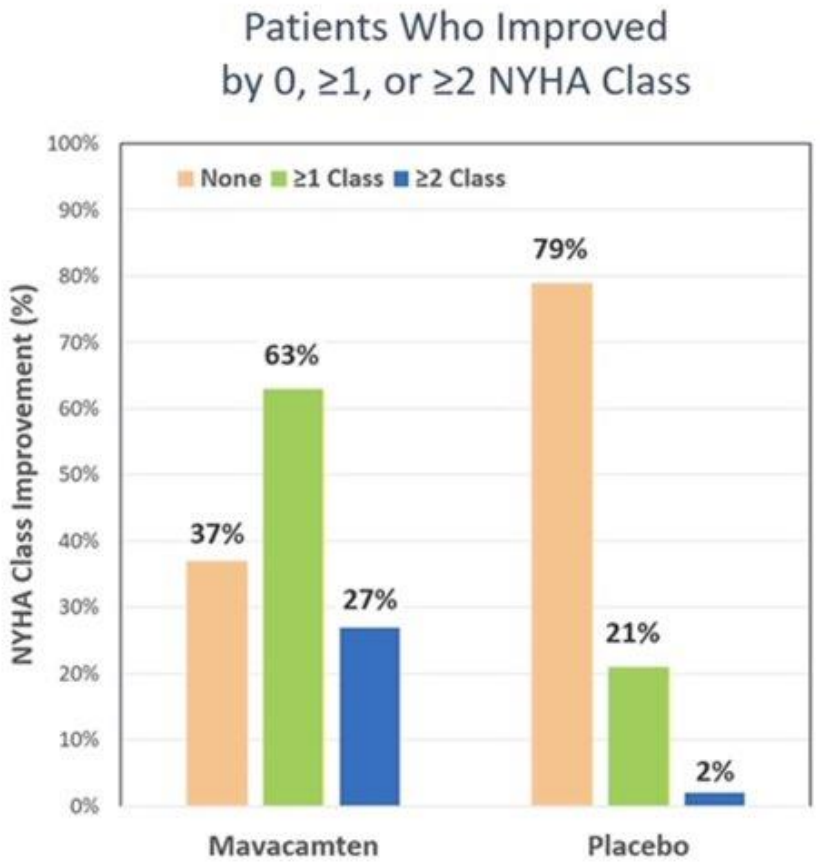
ValorHCM

Primary Endpoint and NYHA Class Improvement





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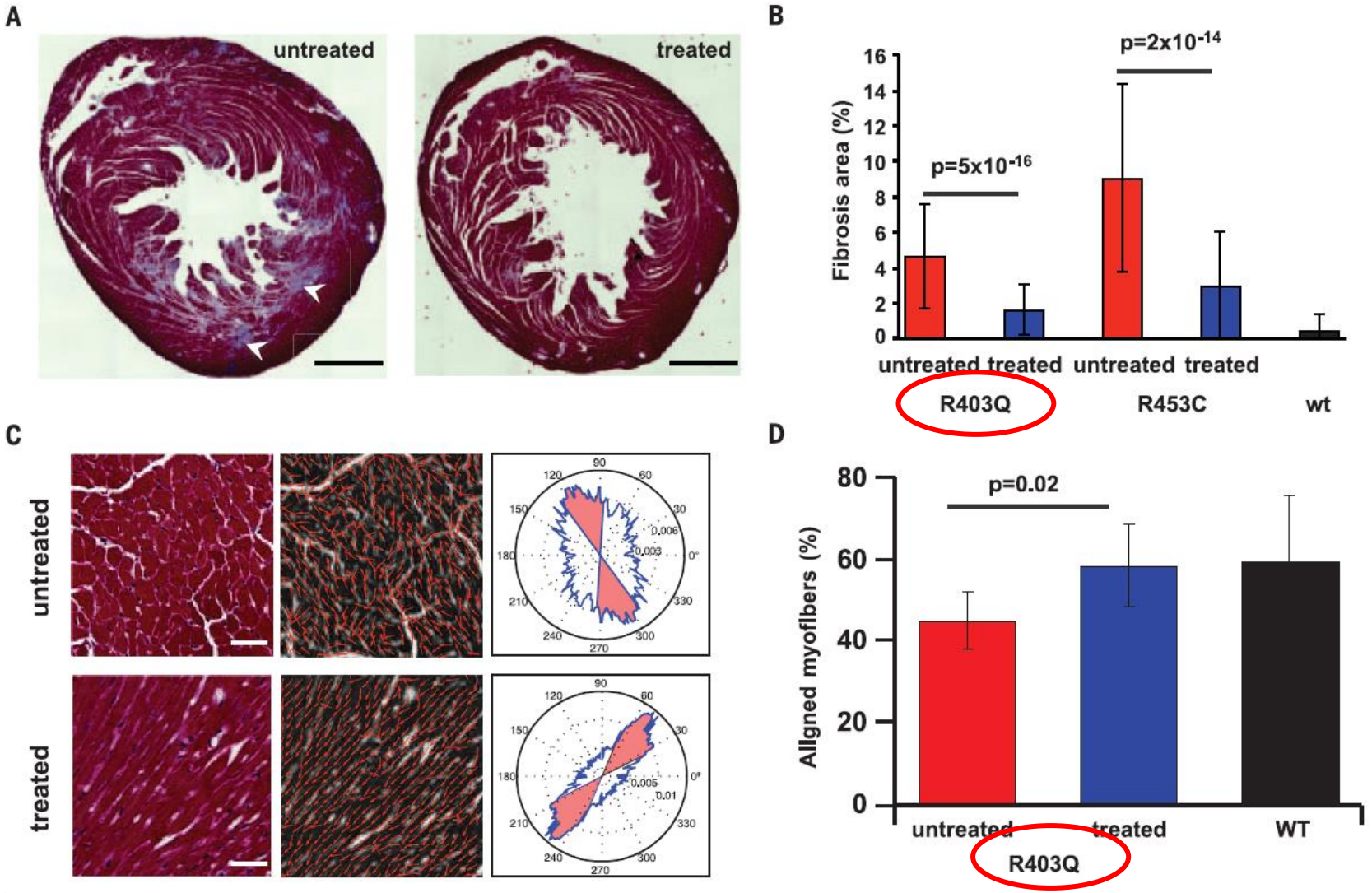
Desai M et al J Am Coll Cardiol 2022

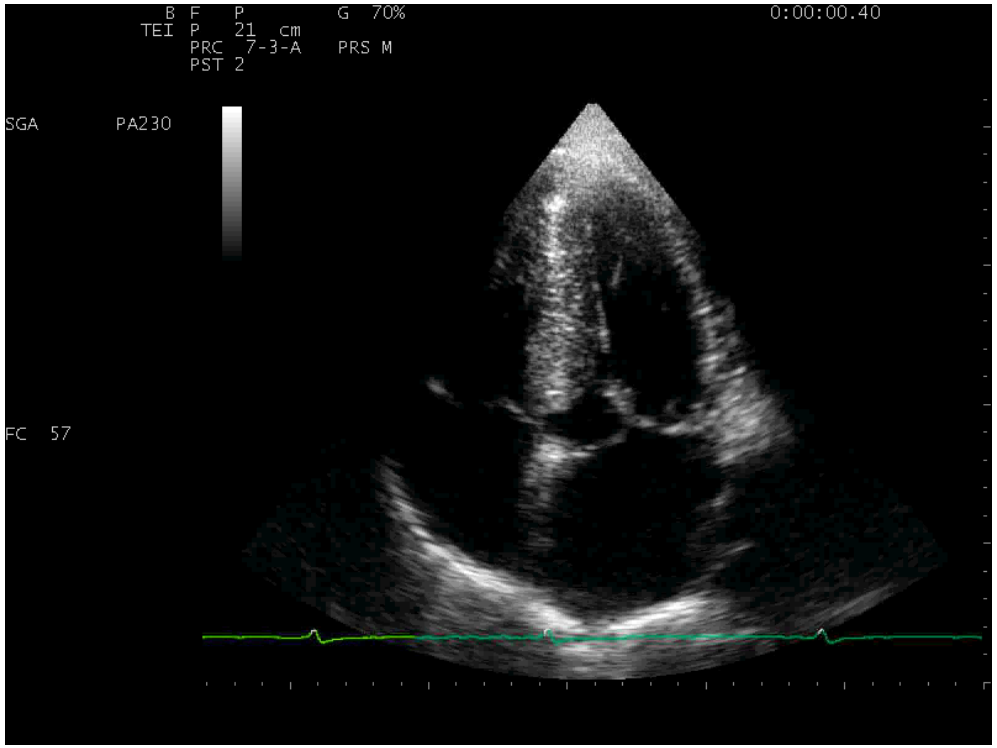
POTENTIAL FOR DISEASE MODIFICATION ?



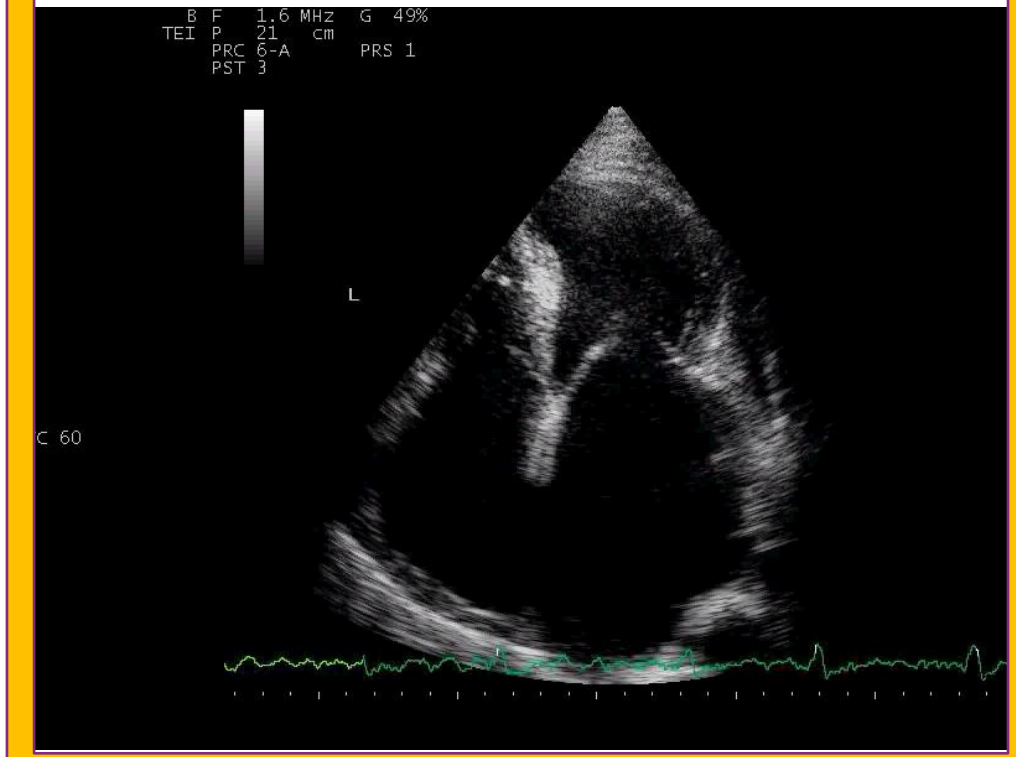
Green et al, Science, 2016

Heart Failure in HCM Occurs in 2 Contexts

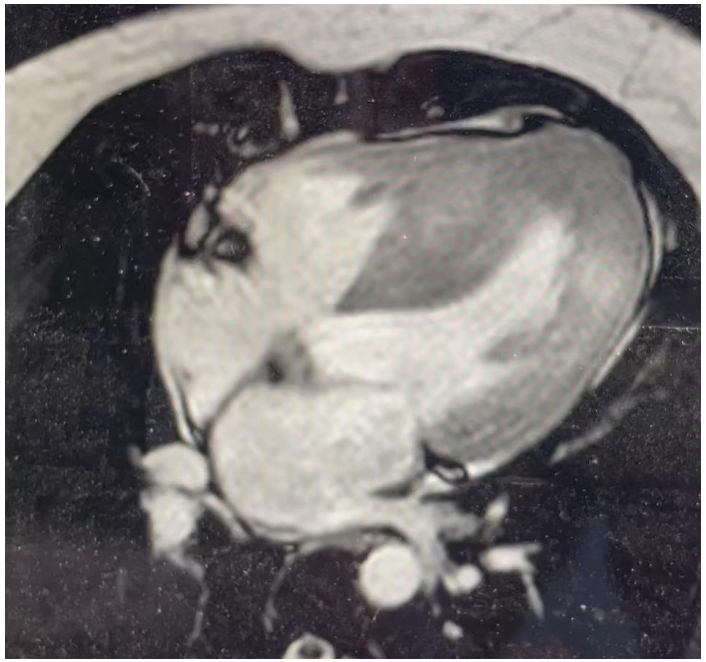
LV Outflow Obstruction



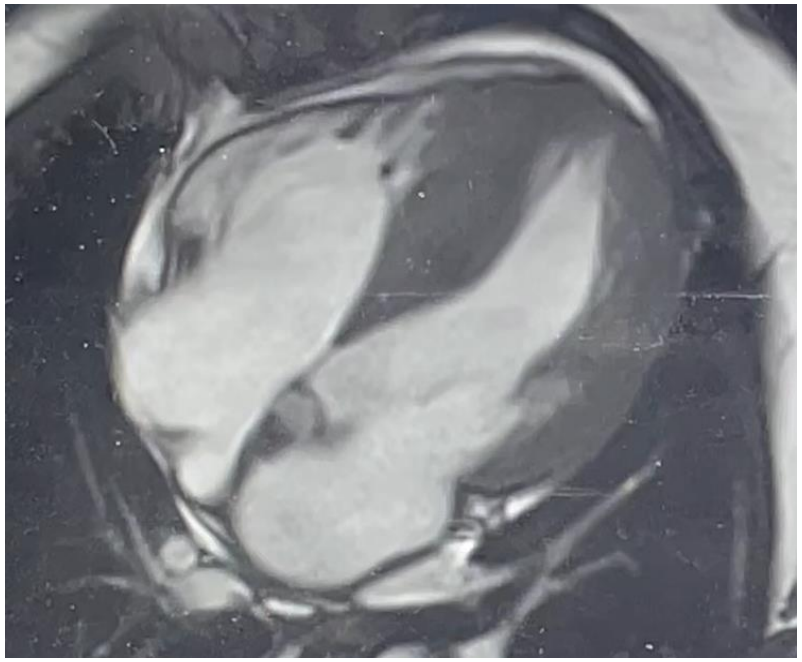
Disease Progression



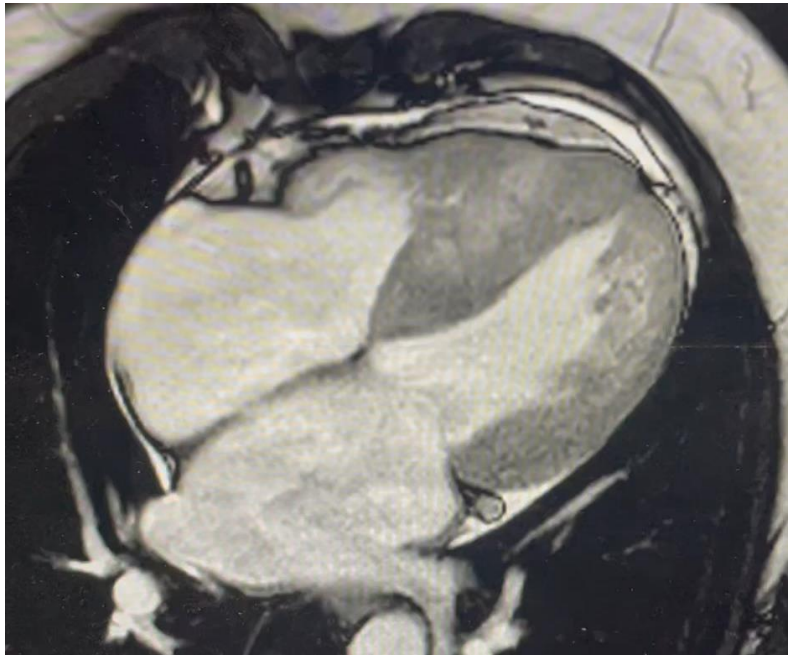
2014



2017



2022



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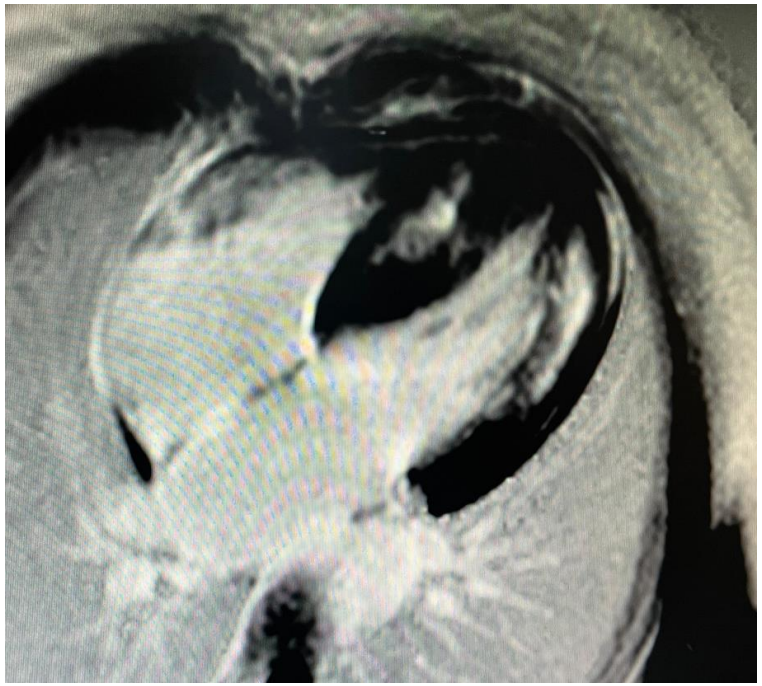
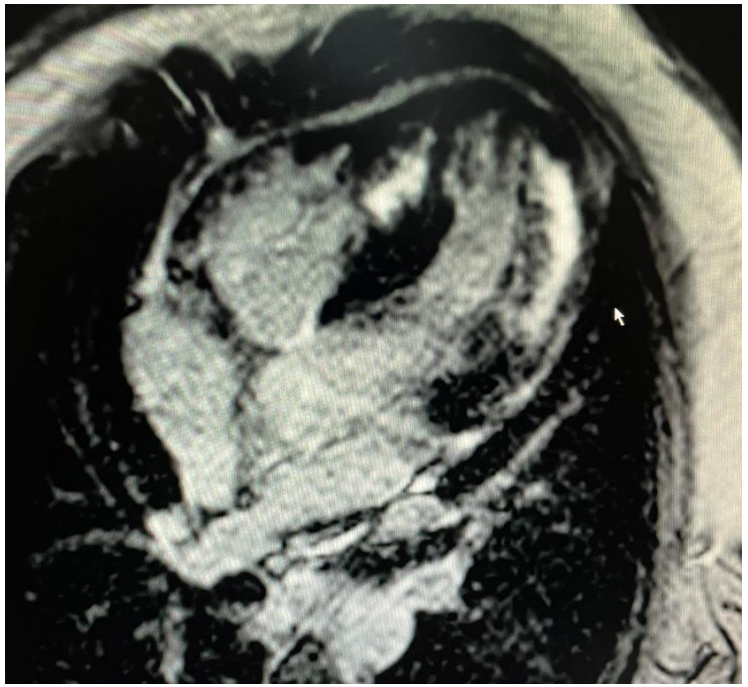
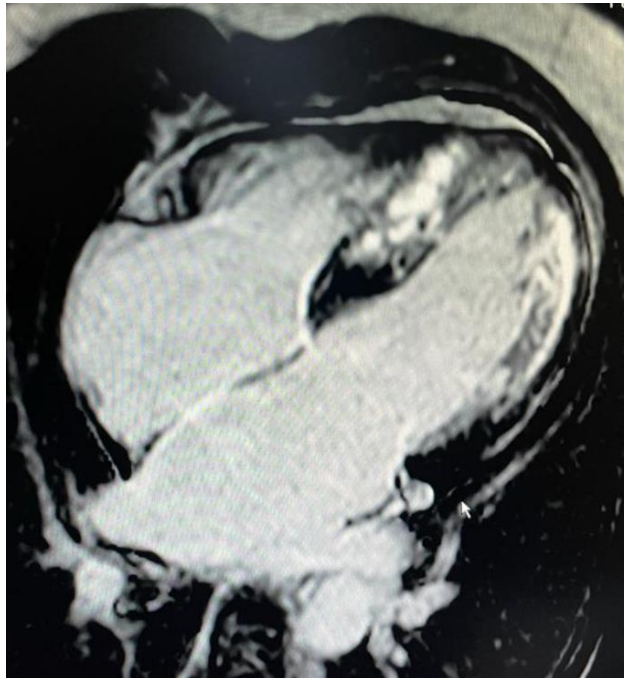
2014



2017



2022



NOT YET RECRUITING

ClinicalTrials.gov Identifier: NCT05582395

A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy (ODYSSEY_HCM)

Information provided by Bristol-Myers Squibb (Responsible Party)

Last Updated: October 25, 2022

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Evaluation of *Aficamten* in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy: REDWOOD-HCM Cohort 4

An open label, dose finding study evaluating the safety and efficacy of aficamten, the next-in-class cardiac myosin inhibitor, in patients with non-obstructive HCM

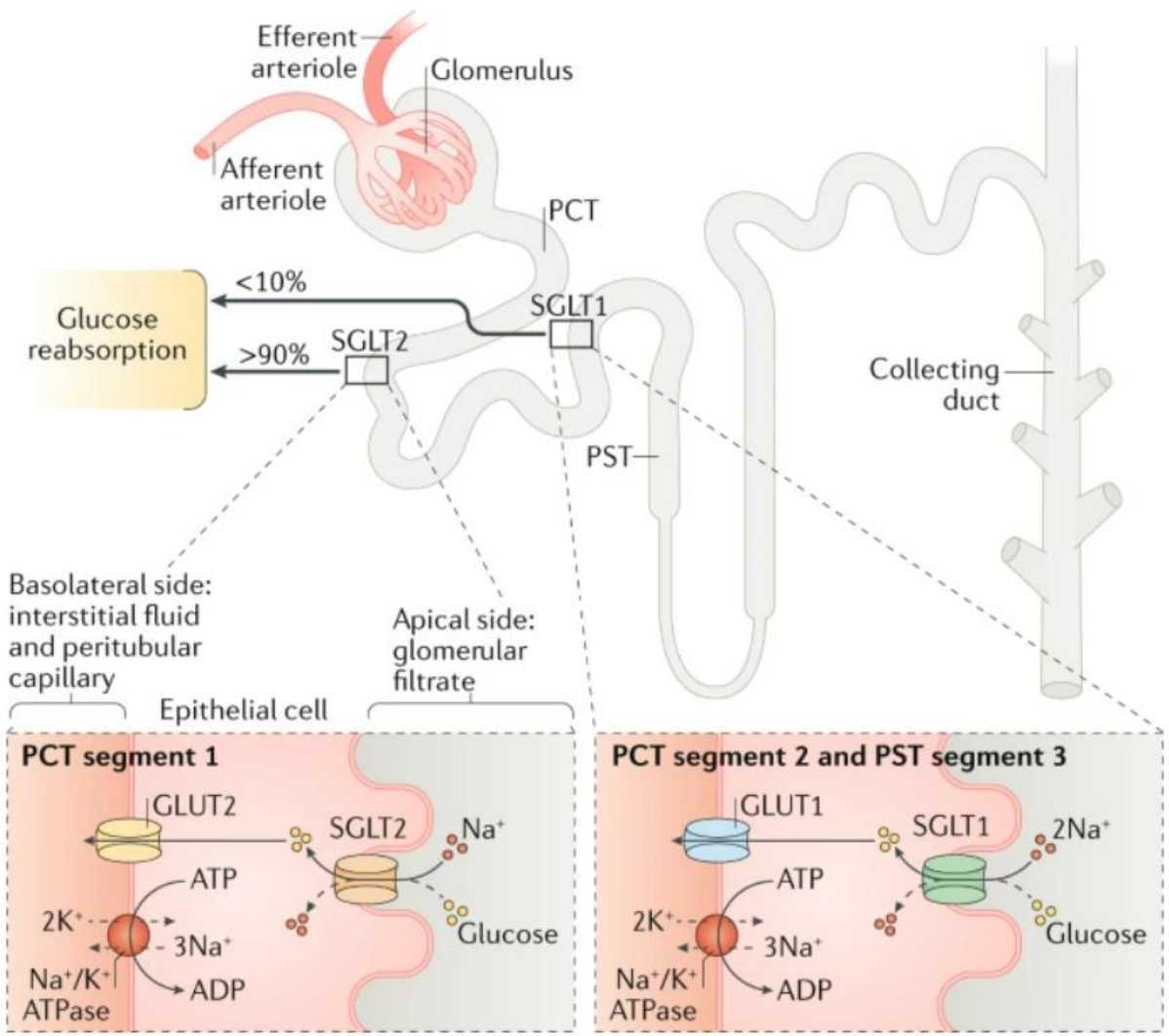
Ahmad Masri, MD, MSc; Oregon Health & Science University, Portland Oregon, USA

20 May 2023

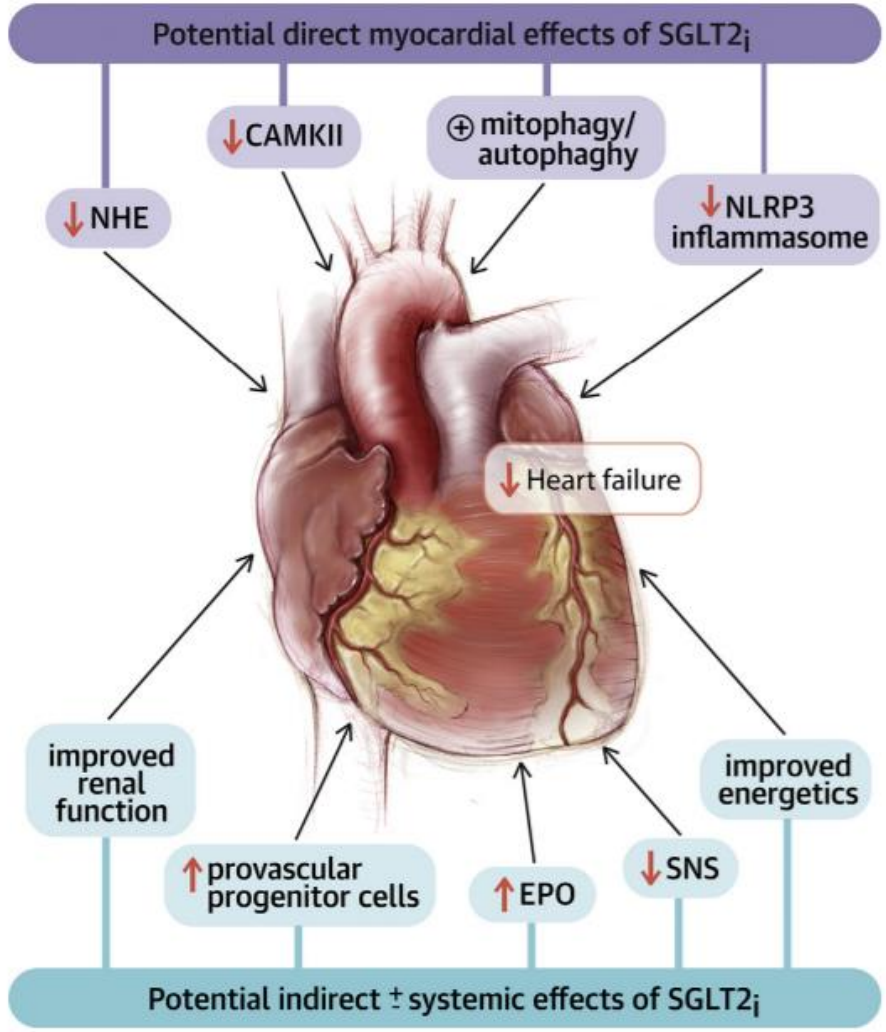
Heart Failure & World Congress on Acute Heart Failure 2023

REDWOOD-HCM (NCT04219826) was sponsored by Cytokinetics Inc.

SGLT2 inhibitors: effects



[Nature Reviews Cardiology](#) **volume 17**, pages761–772 (2020)



Lopaschuk, G.D. et al. J Am Coll Cardiol Basic Trans Science. 2020;5(6):632-44.

CAMKII = calmodulin-dependent protein kinase II; EPO = erythropoietin; NHE = sodium/hydrogen exchanger; NLRP3 = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3; SGLT2i = sodium glucose co-transporter 1(2) inhibitor; SNS = sympathetic nervous system.

Empagliflozin in Hypertrophic Cardiomyopathy (EMPA-REPAIR)

ClinicalTrials.gov Identifier: NCT05182658

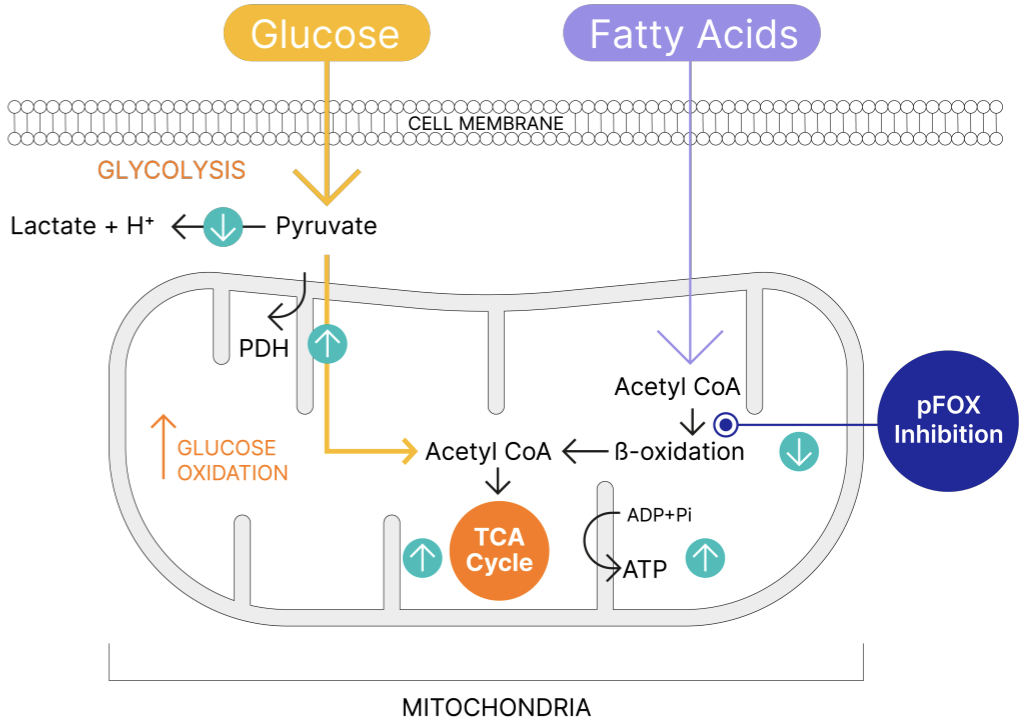
Recruitment Status : Not yet recruiting
First Posted : January 10, 2022
Last Update Posted : April 12, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Ninerafaxstat is a novel mitotrope designed to optimize the efficiency of ATP generation and enhance cardiac function

- Uncoupling of glycolysis and glucose oxidation has an important role in the development of cardiac inefficiency and functional impairment in cardiac disease
- Ninerafaxstat acts through partial inhibition of mitochondrial fatty acid oxidation (pFOX)
  - This reciprocally stimulates mitochondrial glucose oxidation
  - Net effect of shifting cardiac substrate metabolism towards glucose is increased efficiency of ATP generation
  - This results in improved cardiac mechanical efficiency



Modified from Lopaschuk et al., Physiol. Rev 2010 &
Verma et al J Am Coll Cardiol Basic Trans Science 2018; 3:575-587

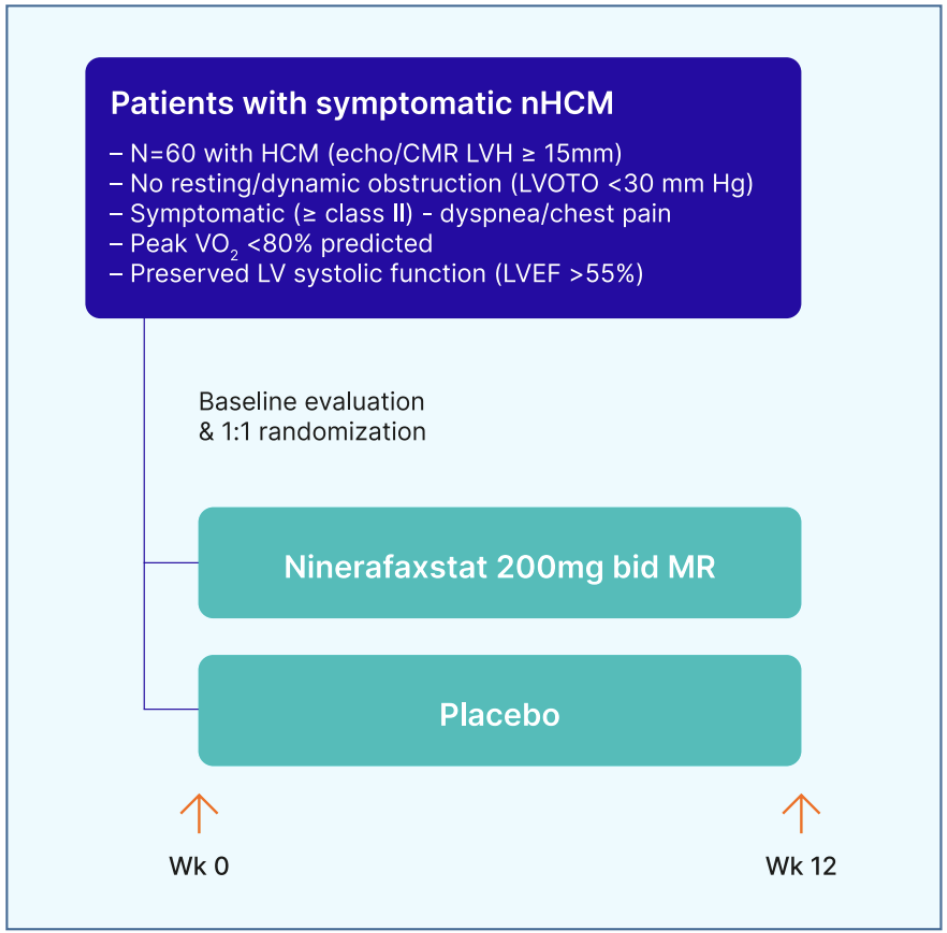
Phase II Study in Nonobstructive HCM
IMPROVE-HCM

- 60 nonobstructive HCM patients Class II or II with

  pVO2 max <80% predicted with EF>55% randomized Ninerafaxstat vs. Placebo for 12 wks

- Key efficacy endpoints
  - Peak VO_2
  - PCr/ATP ratio

- Other efficacy endpoints
  - LV function, including LV GLS, LV diastolic function and LA strain by echo and CMR
  - Arrhythmia burden
  - Biomarkers incl., cardiac troponin, NT-proBNP
  - Symptoms & health status incl., NYHA functional class and KCCQ



Conclusions

Heart failure has a bi-modal distribution in HCM

Myosin inhibitors are likely to change the panorama of HF associated with obstructive HCM, by reducing or postponing the need for invasive treatment options, and triggering favourable cardiac remodeling.

Major challenges remain and further data are needed, to validate this molecular approach the whole disease spectrum including nonobstructive HCM.

Treatment of HF associated with advanced LV dysfunction and myocardial fibrosis. Use of mitotropes and SGLTi is currently under investigation in this setting.