The Clinical Challenge of Managing a Patient with HCM

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Disclosures - Dr. Olivotto

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

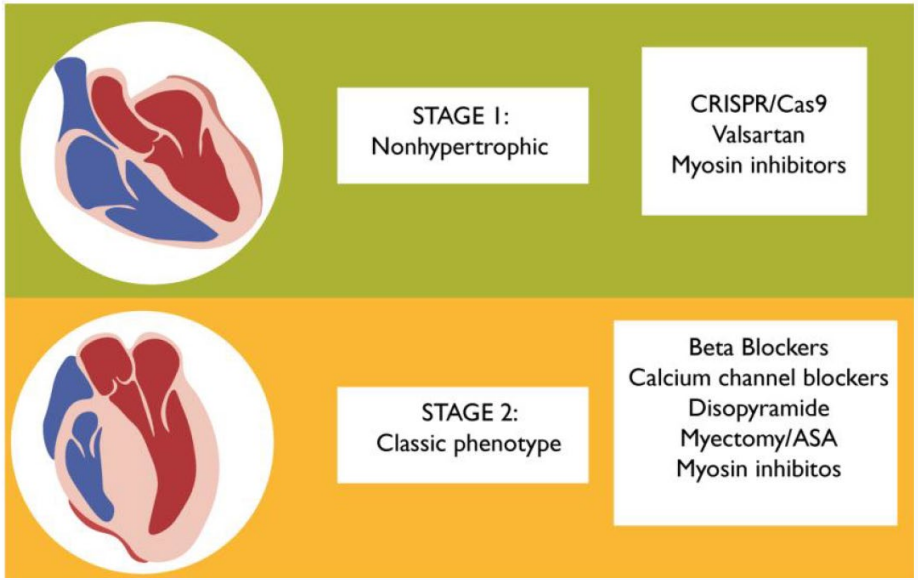
Advisory board, invited speaker: BMS-Myokardia, Cytokinetics, Sanofi Genzyme,
Chiesi, Shire Takeda, Amicus, Tenaya, Rocket Pharma, Edgewise, Lexeo.

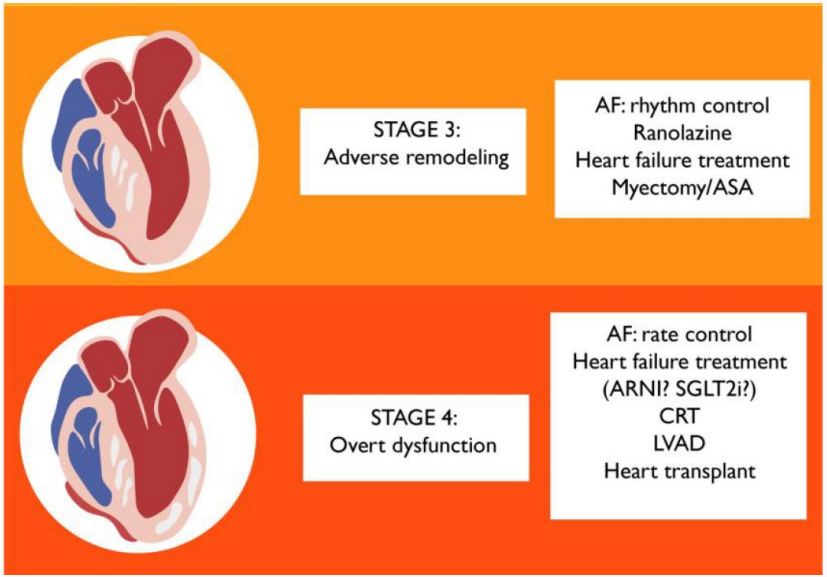
Stage-specific therapy for hypertrophic cardiomyopathy

Alessia Argirò[1]*, Mattia Zampieri[1,2], Alberto Marchi[1,2], Francesco Cappelli[1], Annamaria Del Franco[1], Carlotta Mazzoni[1], Franco Cecchi[3], and Iacopo Olivotto[1,2]

European Heart Journal Supplements (2023) **25** (Supplement C), C155-C161
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad042

ESC
European Society of Cardiology





What Will I Wear to the Ball ?

Beta-Blockers
Verapamil
Amiodarone
Disopyramide

Mavacamten
Aficamten
EDG-7500
Ninerafaxstat
Sotagliflozin
Gene Therapy

Around the Year 2020…..

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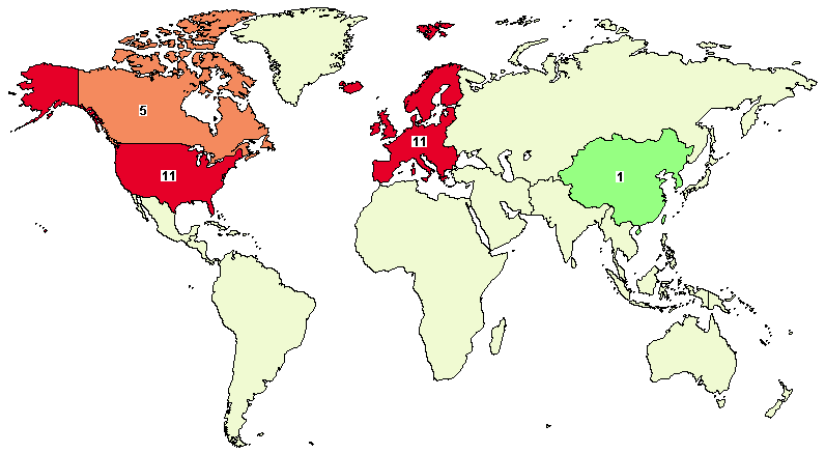
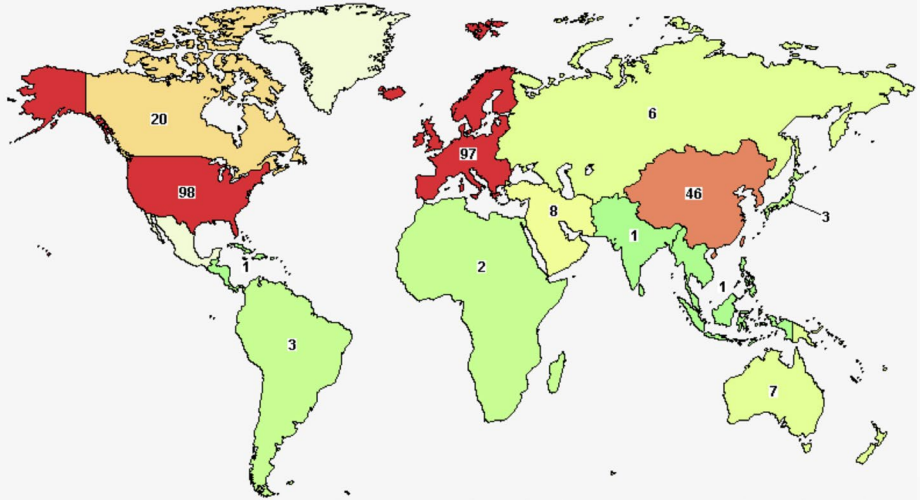
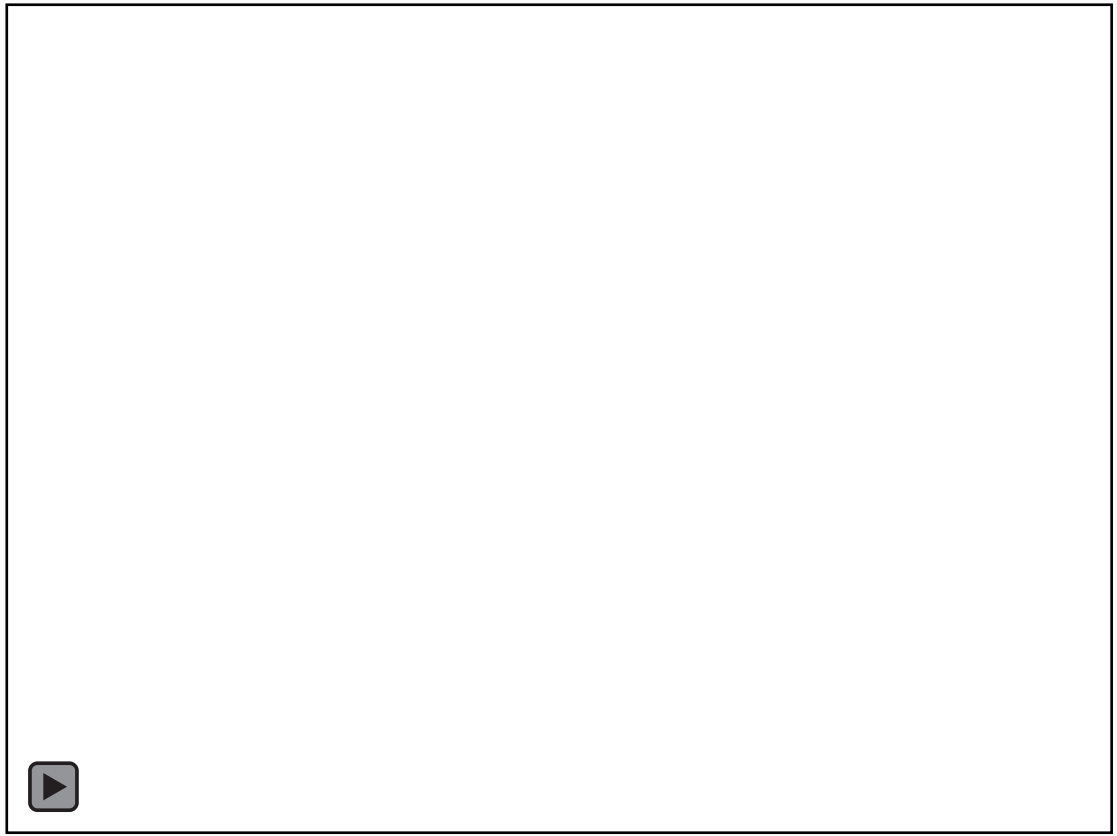
257 Studies found for: **Hypertrophic Cardiomyopathy**

2014
<20 Studies

2024
257 Studies

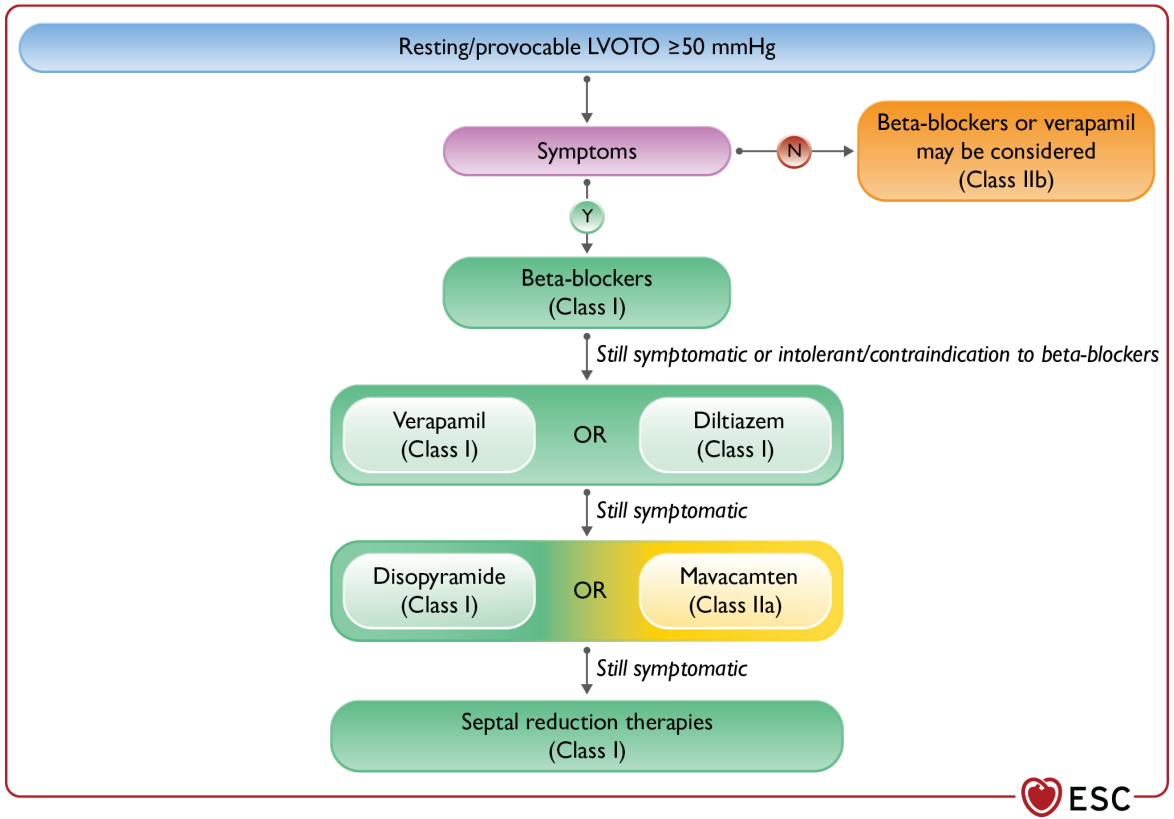






MHY7, age 10

Flowchart on the management of left ventricular outflow tract obstruction

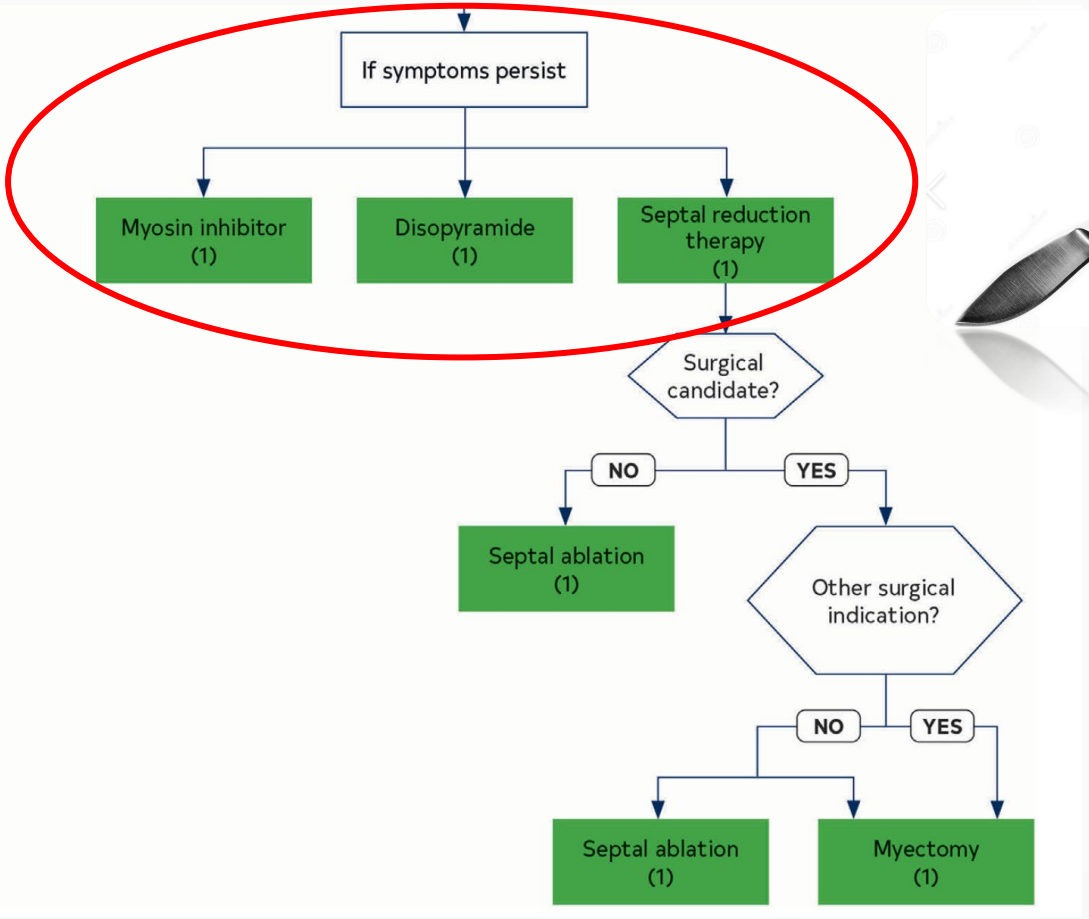


2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Recommendations for Pharmacological Management of Symptomatic Patients With Obstructive HCM
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients with obstructive HCM and symptoms* attributable to LVOTO, nonvasodilating beta blockers, titrated to effectiveness or maximally tolerated doses, are recommended.[1-3]
1	B-R	3. For patients with obstructive HCM who have persistent symptoms* attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers,§ is recommended.[7-14]
1	C-LD	4. For patients with obstructive HCM and acute hypotension who do not respond to fluid administration, intravenous phenylephrine (or other vasoconstrictors without inotropic activity), alone or in combination with beta-blocking drugs, is recommended.[15]
2b	C-EO	5. For patients with obstructive HCM and persistent dyspnea with clinical evidence of volume overload and high left-sided filling pressures despite other HCM GDMT, cautious use of low-dose oral diuretics may be considered.

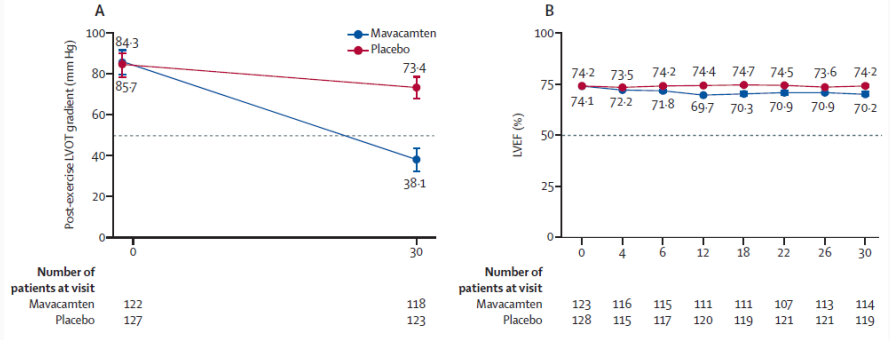
Ommen et al. Circulation 2024

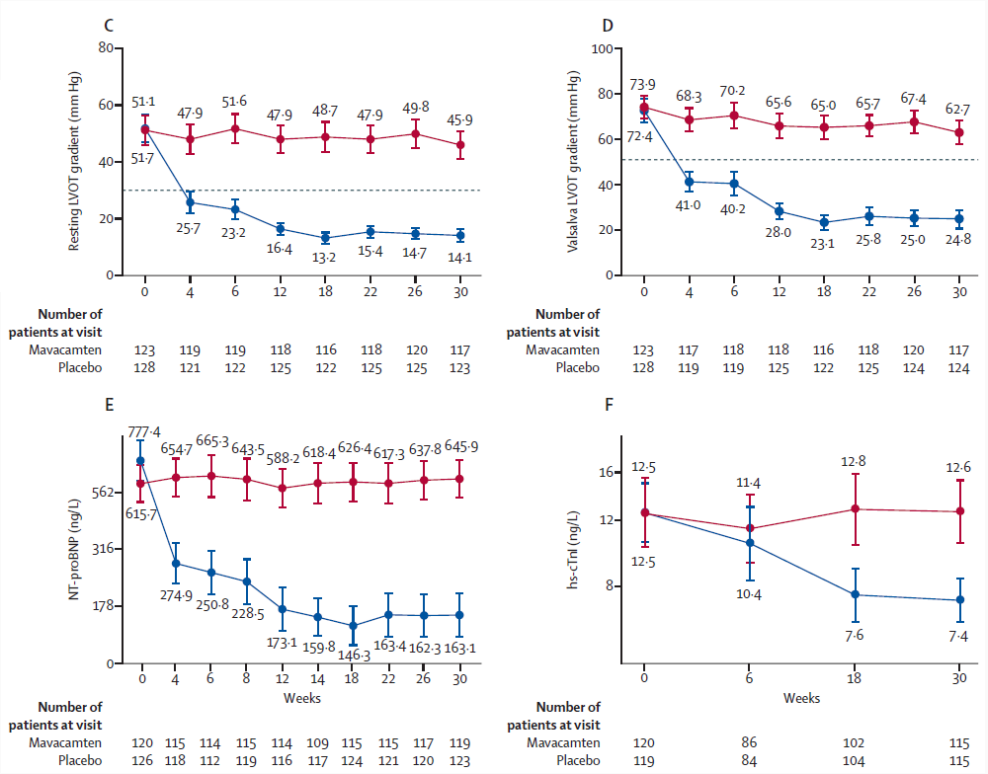


Ommen et al. Circulation 2024

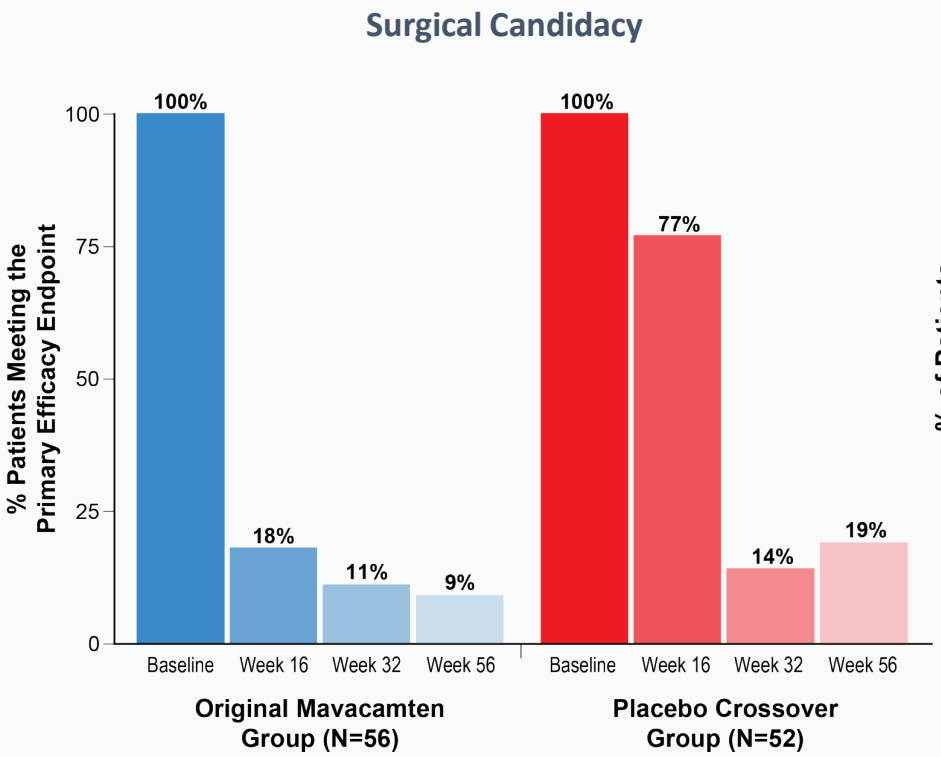
Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

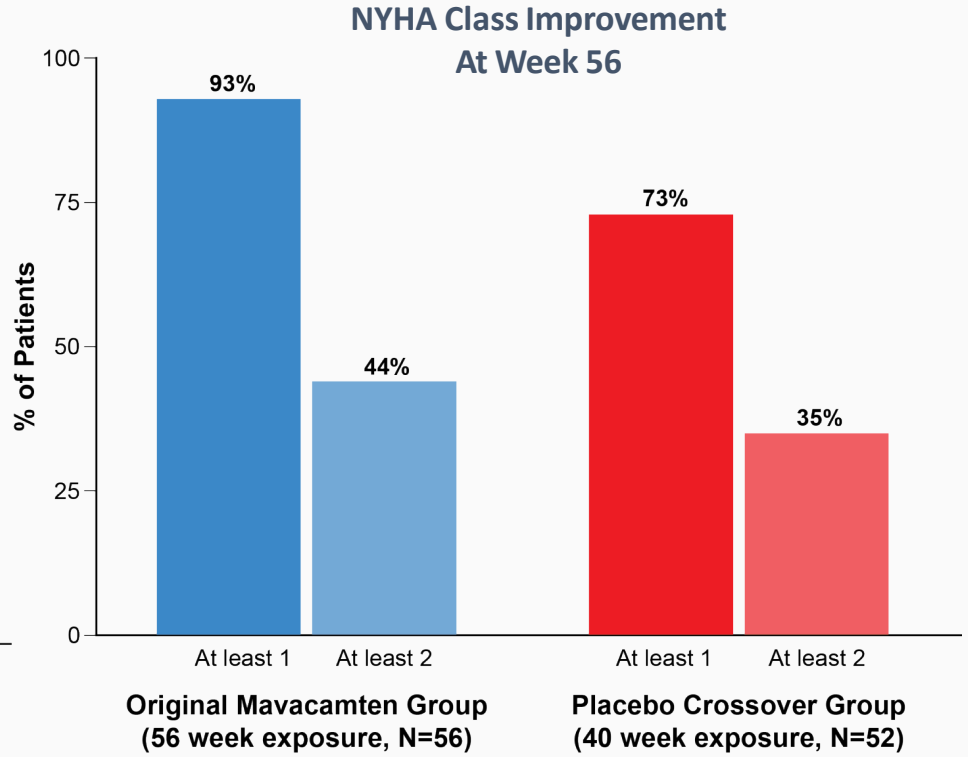
*Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, 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**



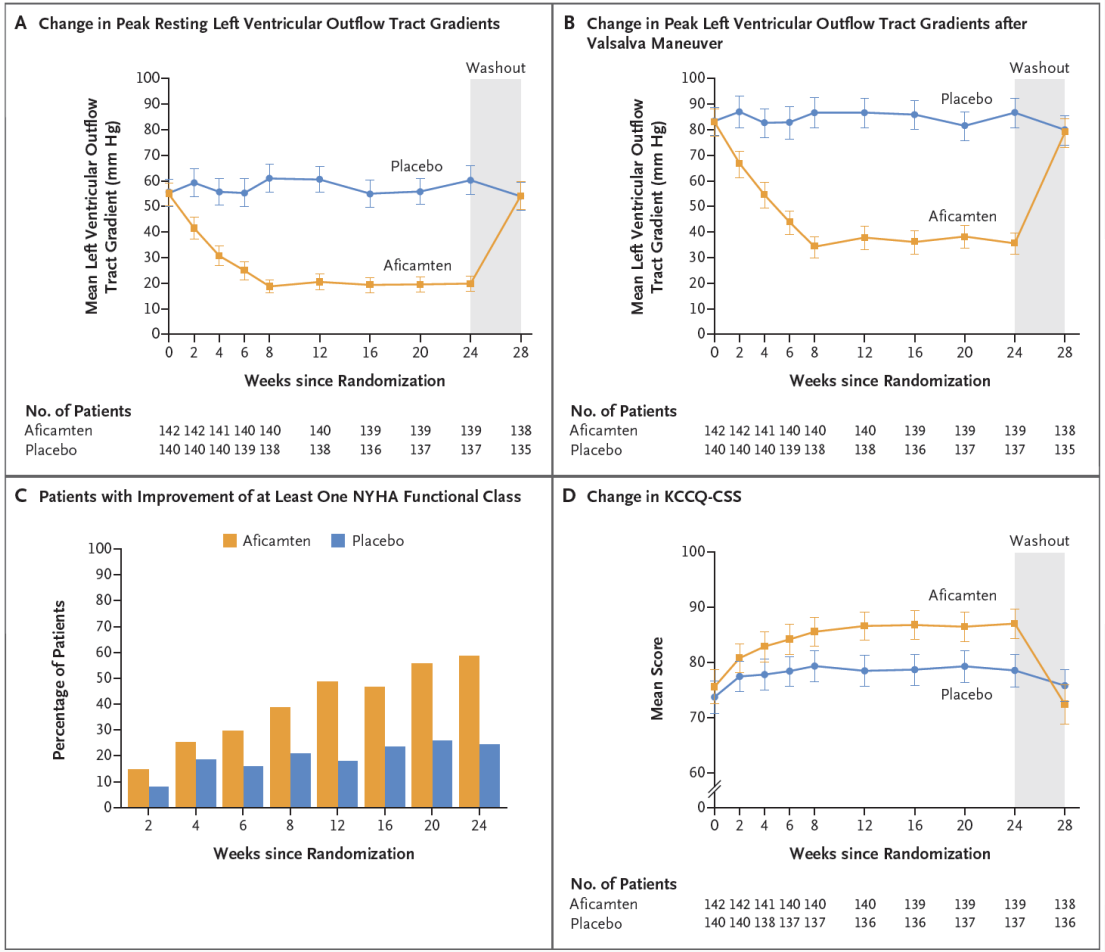


VALOR-HCM: Changes in Surgical Candidacy and NYHA Class





Desai et al. JAMA Cardiol 2023



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

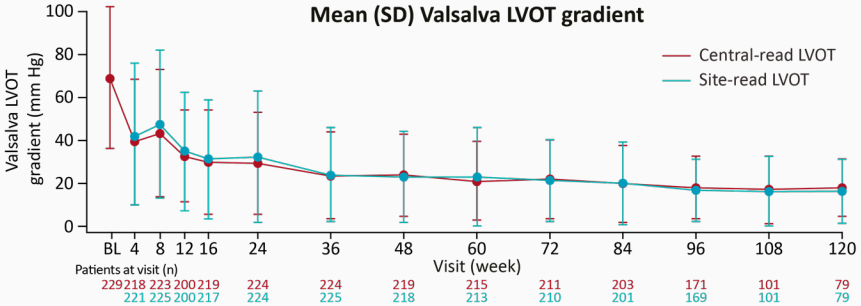
Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

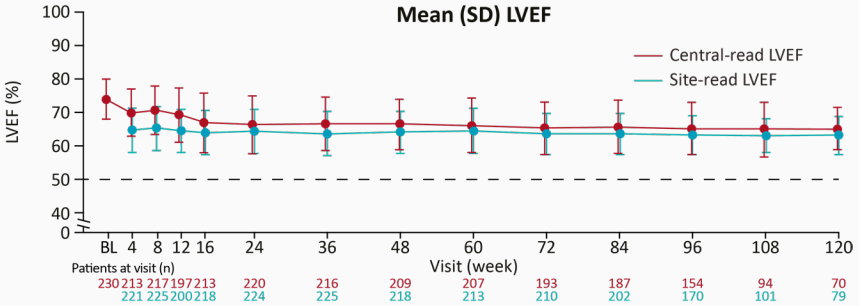
M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*

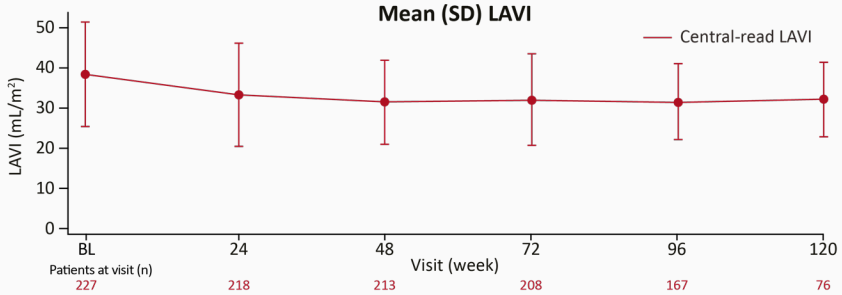
SEQUOIA HCM: Changes in Candidacy to Septal Reduction Therapy

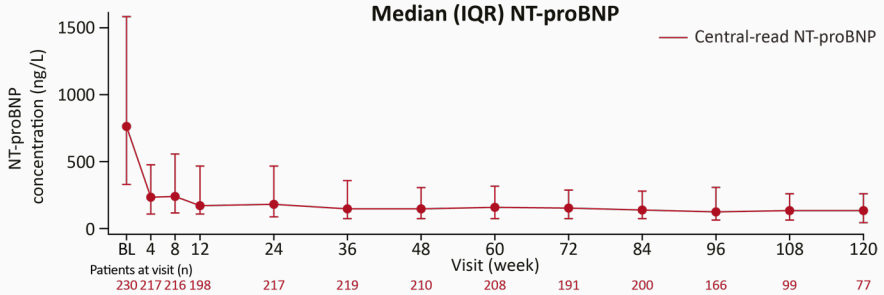
Maron et al, N Engl J Med 2024

Explorer LTE-Change in efficacy measures from baseline through week 120









- Mavacamten was associated with sustained improvements from baseline in echocardiographic parameters, including E/e' average, and NT-proBNP
- Mean LVEF remained within the normal range at all study visits

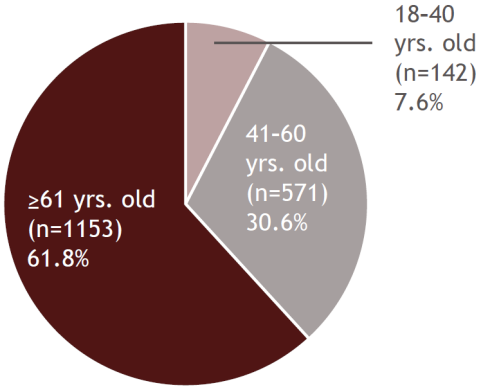
Baseline is defined as last non-missing measurement before the first dose of mavacamten in MAVA-LTE. Data presented are mean (SD) unless otherwise stated. Dotted line in LVEF figure represents the threshold for normal ejection fraction. BL, baseline; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IQR, interquartile range; LTE, long-term extension; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation

The Mavacamten REMS Program: Results From 10 Months Post-Launch

Overview of Patient Demographics and Patient Status Forms Completed[1]

REMS data collection is designed to assess that the required safe use conditions have been met, and does not provide robust clinical data on safety, efficacy, or outcomes. Provider discretion is advised.

Patient demographics (N=1866)



Of the 1866 active patients in the US in this study, 733 (39.3%) were male and 1131 (60.6%) were female

Patient Status Forms completed

1866 unique patients received CAMZYOS (mavacamten)

1524 unique patients with Patient Status Forms submitted*

141 (9.3%) patients
HCP did not authorize to continue

- 43 (2.8%) patients†: Decrease in LVEF to <50%
- 17 (1.1%) patients†: Heart failure event requiring hospitalization
- 86 (5.6%) patients: Other reason (not reported)

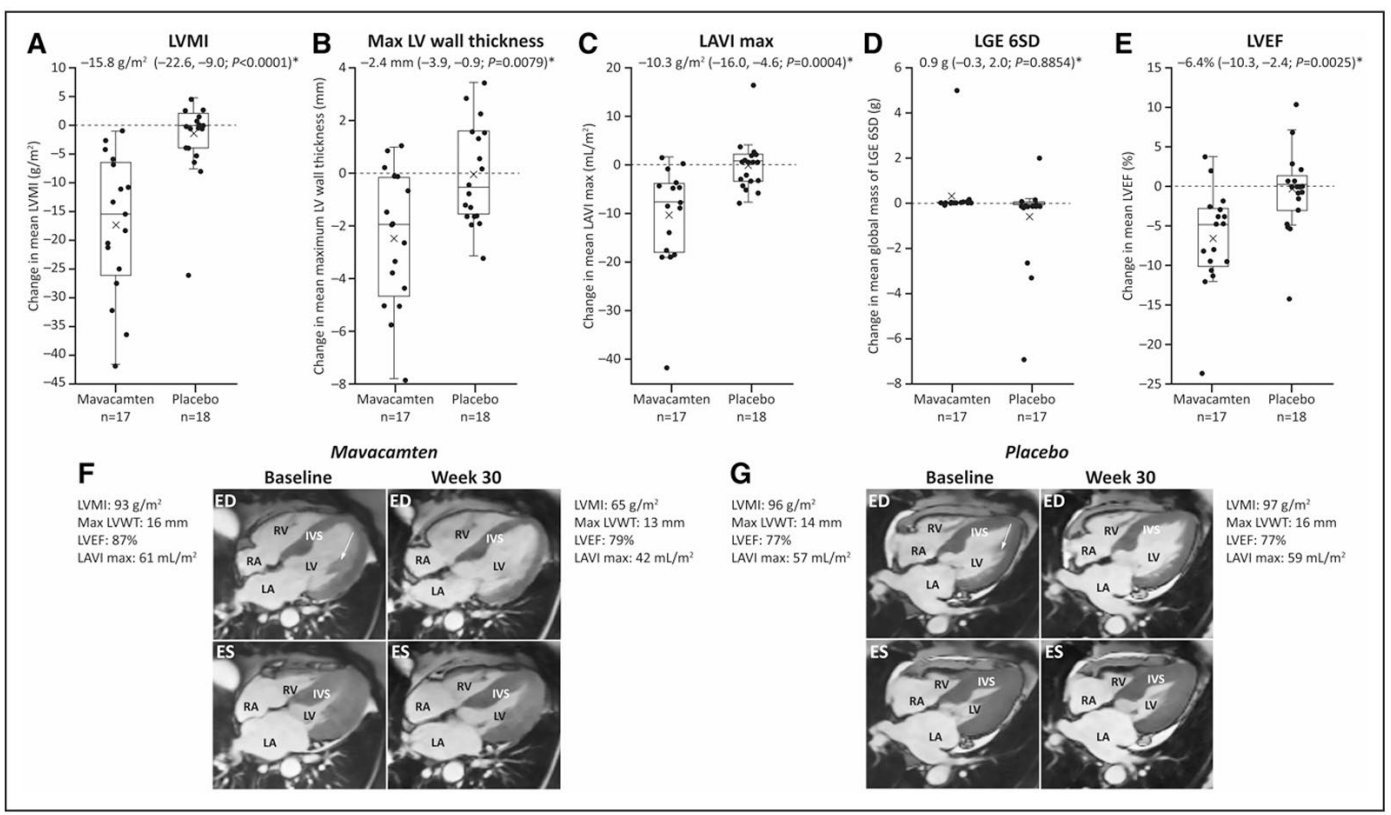
During the reporting period, 5527 PSFs were expected; of these, 5094 (92.2%) were received and 433 (7.8%) were outstanding

*Completed by a certified HCP or designee. †5 patients experienced both LVEF <50% and clinical heart failure.
HCP=healthcare provider; LVEF=left ventricular ejection fraction; PSF=patient status forms; REMS=Risk Evaluation and Mitigation Strategy; yrs=years.

1. Martinez MW, et al. Presented at ACC 2024. Poster 1075-07.

Mavacamten Favorably Impacts Cardiac Structure in Obstructive HCM

EXPLORER-HCM Cardiac Magnetic Resonance Substudy Analysis



Saberi et al Circulation 2021

Cardiac Myosin Inhibitors may improve diastole by countering multiple mechanisms

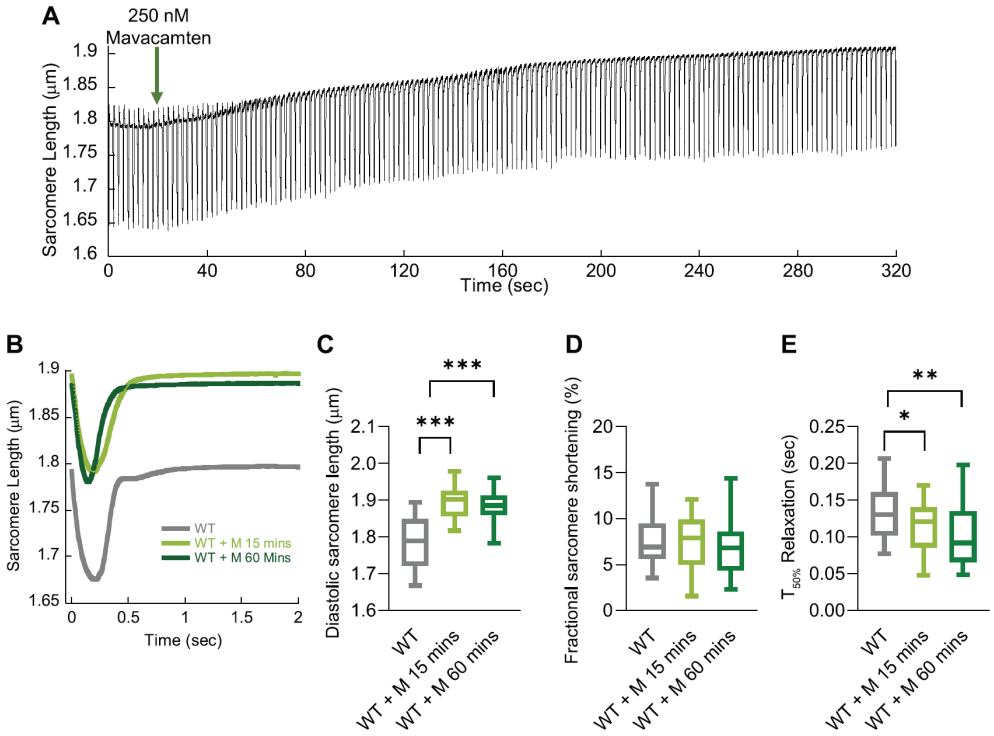
- Excess availability of ON state(s) myosin heads, with elevations in residual cross-bridges hindering compliance and filling.
- Biochemical events prolonging cross-bridge detachment
- Alterations in Ca2+ handling resulting in elevated diastolic levels
- Structural remodeling (e.g., fibrosis)

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

Mavacamten rescues increased myofilament calcium sensitivity and dysregulation of Ca^{2+} flux caused by thin filament hypertrophic cardiomyopathy mutations

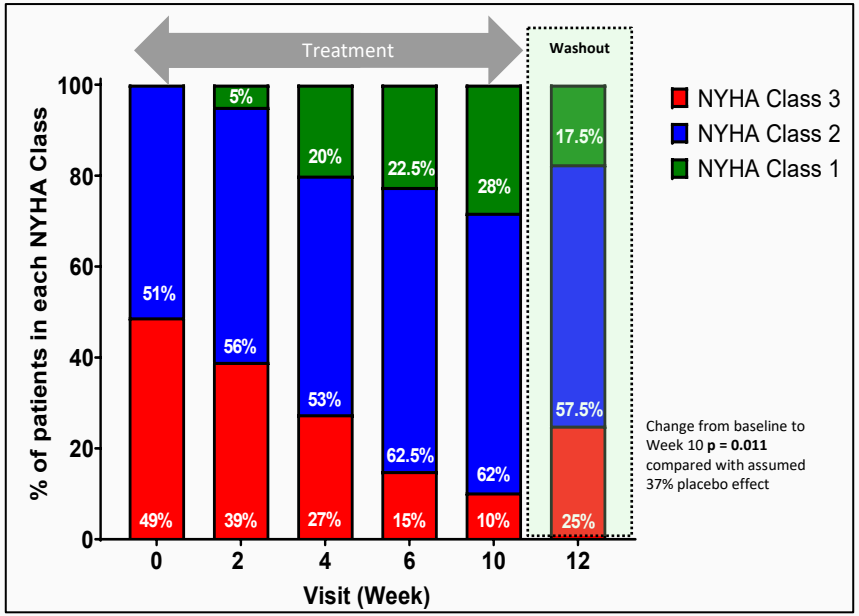
Alexander J. Sparrow,[1,2] Hugh Watkins,[1,2] Matthew J. Daniels,[1,2,3]* Charles Redwood,[1,2]* and Paul Robinson[1,2]*

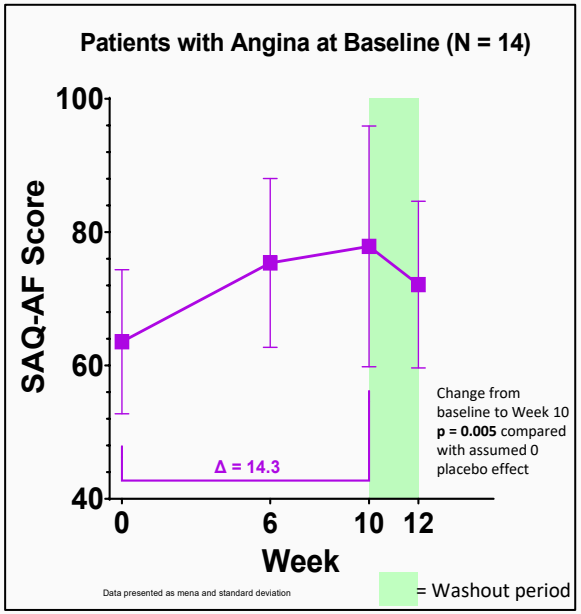
[1]*Division of Cardiovascular Medicine, Ra*
[2]*British Heart Foundation Centre of Resea*
Cardiovascular Sciences, University of Ma



Am J Physiol Heart Circ Physiol 318: H715–H722, 2020

Patient Functional Class and Angina Symptoms

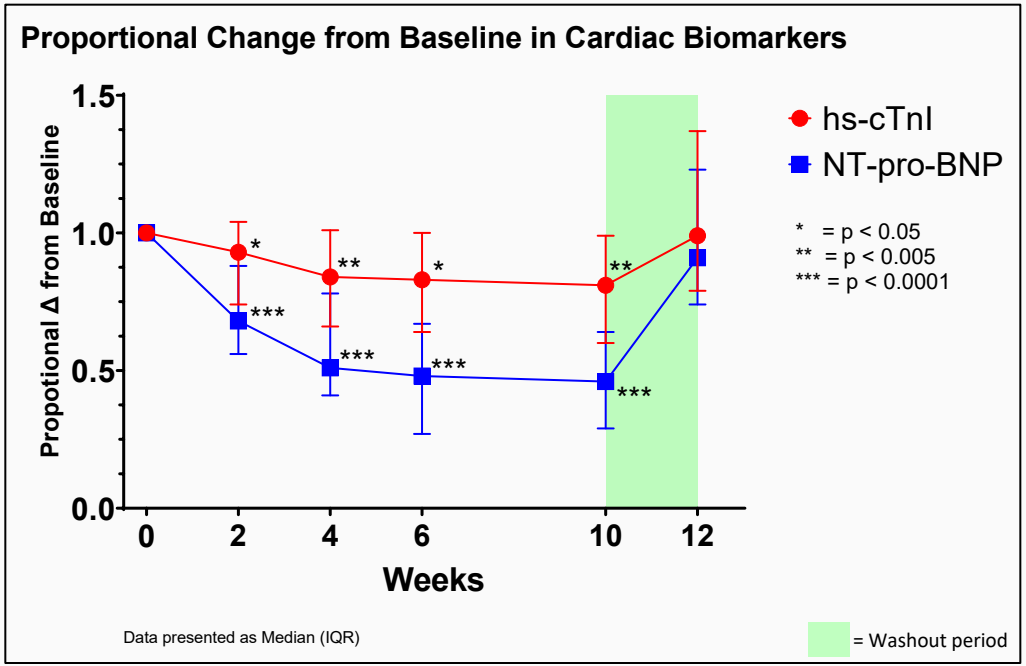




- 56% of all patients demonstrated functional improvement of ≥ 1 NYHA class and 25% patients were completely asymptomatic
- Mean reduction in angina frequency score of 14.3 points - translates to a reduction in the frequency of angina from daily or weekly, to weekly or monthly.

Masri et al J Card Fail 2024

Cardiac Biomarkers



- **Patients were found to have →**
  - Mean relative reduction in **high-sensitivity cardiac Troponin** of 21% by Week 10 by -24.8 ng/L (73.53)
  - Mean relative reduction **NT-proBNP** of 55% by Week 10 by -869.7 pg/mL (969.65)

Masri et al J Card Fail 2024

Design of ODYSSEY-HCM: A Phase 3 Randomized Placebo-controlled Study to Assess the Efficacy and Safety of Mavacamten in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM)

Milind Desai[1] MD MBA, Anjali Owens[2] MD, Kathy Wolski[1] MPH, Pablo Garcia-Pavia[3] MD PhD, Theodore Abraham[4] MD, Christina Sewell[1] RN, Ronald Aronson[5] MD, Thomas Rano[5] PhD, Victoria Florea[5] MD, Steven Nissen MD[1], Iacopo Olivotto MD[6]

[1]Cardiovascuar Medicine, Cleveland Clinic, Cleveland, OH, USA; [2]Center for Inherited Cardiac Disease, University of Pennsylvania, Philadelphia, PA, USA,[3]Department of Cardiology of Hospital Universitario Puerta de Hierro, Madrid, Spain., [4]UCSF HCM Center of Excellence, University of California at San Francisco San Francisco, CA, USA [5]Bristol Myers Squibb, Inc., Lawrence Township, NJ, USA, [6]Cardiovascular Medicine, University of Florence, Florence, Italy

Purpose

The purpose of ODYSSEY-HCM is to assess the efficacy and safety of mavacamten in patients with **symptomatic nHCM**, a population for whom no disease-specific drug therapy is approved.

Methods

Study Design: Phase 3, randomized, double-blind, placebo-controlled, multi-center, international clinical trial.

Sample Size: 420 participants

Study Periods: Screening up to 5 weeks followed by Part A, placebo-controlled double-blind treatment; Part B, placebo-cross-over treatment, and Part C, long-term treatment and follow-up. After the last dose of study drug in Part C, participants are followed for 120 days.

Dual Primary Endpoints: Change from baseline to Week 48 in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and peak oxygen consumption (pV02).

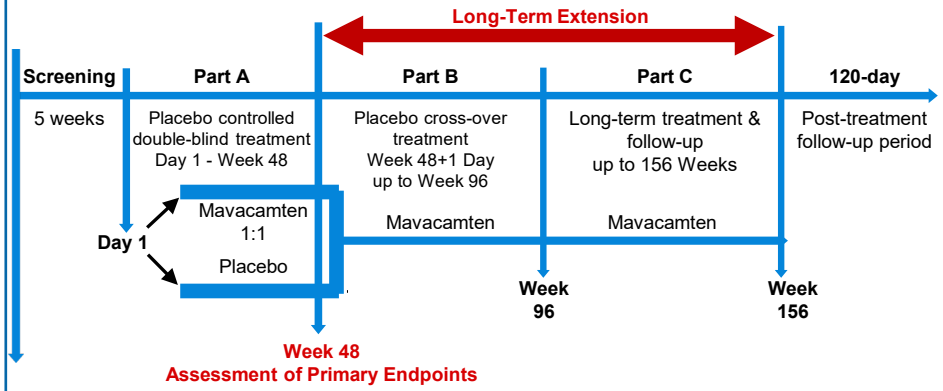
Key Secondary Endpoints: Change from baseline to Week 48 in the slope of the ratio of minute ventilation to carbon dioxide production (VE/VCO2), N-terminal pro brain natriuretic peptide (NT-proBNP), cardiac troponin-T (cTn-T), and the proportion of participants with improvement by least 1 category of New York Heart Association Functional Class (NYHA).

Methods continued

Safety Endpoints: Any cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, hospitalization for arrhythmias or appropriate defibrillator therapy.

Key Inclusion Criteria: Adults with symptomatic nHCM ≥18 years of age, NYHA Class II-III, KCCQ-CSS ≤ 85, left ventricular ejection fraction (LVEF) ≥ 60%, able to achieve pVO2 on cardiopulmonary exercise test (CPET), and elevated NT-proBNP and cTn-T.

Study Conduct: During Parts A and B, the dose of study drug will be titrated according to values of LVEF obtained at visit intervals determined by PK/PD modelling that provided the best balance between efficacy and safety. Echocardiograms and CPETs will be analyzed by core laboratories. Investigators and participants will be blinded to the results of these tests and to study drug and dose.



Results

Enrollment in ODYSSEY-HCM has been completed

Conclusion

Completion of enrollment of participants with symptomatic nHCM supports the use of the ODYSSEY-HCM study design to assess efficacy and safety of new therapies that require close monitoring in this population.

CTC-005

A Phase 3, Multicenter, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of *Aficamten* Compared with Placebo in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

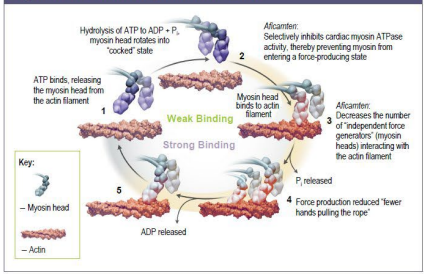
Ahmad Masri[1], Theodore P. Abraham[2], Michael Arad[3], Melissa Burroughs[4], Caroline J. Coats[5], Edileide de Barros Correia[6], Juan Pablo Costabel[7], Perry Elliott[8], Jorge E. Silva Enciso[9], Gregory D. Lewis[10], Matthew W. Martinez[11], Mathew S. Maurer[12], Michelle Michels[13], Sumeet S. Mitter[14], Jesus E. Pino Moreno[15], Iacopo Olivotto[16], Anjali T. Owens[17], Steen H. Poulsen[18], Florian Rader[19], P. Christian Schulze[20], Mark V. Sherrid[21], Scott D. Solomon[22], John A. Spertus[23], Punag H. Divanji[24], Stephen B. Heitner[24], Daniel L. Jacoby[24], Stuart Kupfer[24], Fady I. Malik[24], Lisa Meng[24], Amy Wohltman[24], Carolyn Y. Ho[25]

[1]Oregon Health and Science University School of Medicine, Portland, OR, USA; [2]University of California, San Francisco Medical Center, San Francisco, CA, USA; [3]The Chaim Sheba Medical Center - The Olga and Lev Levitev Heart Center (The Heart Institute), Ramat-Gan, Israel; [4]Wellstar Health System, Atlanta, GA, USA; [5]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [6]Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; [7]Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina; [8]Barts Heart Centre and University College London Hospitals NHS Trust, London, UK; [9]University of California-San Diego, San Diego, CA, USA; [10]Massachusetts General Hospital, Boston, MA, USA; [11]Morristown Medical Center, Morristown, NJ, USA; [12]Columbia University, New York, NY, USA; [13]Erasmus University Medical Center, Rotterdam, Netherlands; [14]Inova Schar Heart and Vascular, Falls Church, VA, USA; [15]The Queen's Medical Center, Honolulu, HI, USA; [16]Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Florence, Italy; [17]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [18]Aarhus University, Aarhus, Denmark; [19]Sanidi Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [20]University of Jena; Friedrich-Schiller-University, Jena, Germany; [21]New York University Langone Health, New York, NY, USA; [22]Brigham and Women's Hospital, Boston, MA, USA; [23]University of Missouri-Kansas City, Kansas City, MO, USA; [24]Cytokinetics, Incorporated, South San Francisco, CA, USA; [25]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

BACKGROUND

- The fundamental pathophysiologic abnormality underlying hypertrophic cardiomyopathy (HCM) is myocardial hypercontractility with associated cardiac hypertrophy, impaired relaxation, and altered myocardial energetics.
- Patients with non-obstructive HCM (nHCM) have limited therapeutic options.
- *Aficamten* is a next-in-class small-molecule allosteric cardiac myosin inhibitor that decreases cardiac hypercontractility by selectively and reversibly inhibiting cardiac myosin (**Figure 1**).[1]

Figure 1. *Aficamten* mechanism of action



Note: *Aficamten* is an investigational agent that is not approved by any regulatory agency, including the US FDA. Its safety and efficacy have not been established.
ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate.

- In the Phase 2 REDWOOD-HCM trial (Cohort 4), 10 weeks of treatment with *aficamten* was well tolerated in 41 participants with symptomatic nHCM, and with a reassuring safety profile.[2]
  - Echocardiogram-based dose titration led to a 10.6-point improvement in mean KCCQ-CSS, with 55% of participants experiencing ≥1 NYHA functional class (FC) improvement.
  - Overall, LVEF decreased by 5.4% by Week 10, which reversed during a 2-week washout period, with no treatment-related serious adverse events.
  - From baseline to Week 10, there was a 22% reduction in hs-cTnI and a 56% reduction in NT-proBNP.

ACACIA-HCM Study

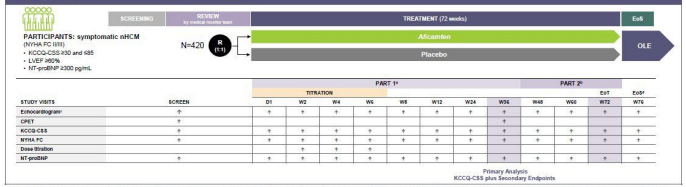
- The data from the Phase 2 study confirmed support for further evaluation of *aficamten* in participants with symptomatic nHCM in the Phase 3 trial, ACACIA-HCM (**A**ssessment **C**omparing *Aficamten* to Placebo on **C**ardiac Endpoints **I**n **A**dults with Non-Obstructive **HCM**).
- The trial will evaluate the effect of ≥36 weeks (up to 72 weeks) of treatment with *aficamten* on health status, cardiac biomarkers, cardiac remodeling, and clinical outcomes in participants with symptomatic nHCM.

STUDY DESIGN

Study Schema

- Phase 3, randomized, placebo-controlled, double-blind trial of *aficamten* in participants with symptomatic nHCM (**Figure 2**).
- Streamlined trial protocol to emphasize rapid titration to maximum tolerated dose and few visits post titration.
- A cardiac MRI and a PK substudy will enroll up to 100 and 30 participants, respectively.
- At the end of study participation, participants will roll over into an open-label extension (OLE) study.

Figure 2. ACACIA-HCM: Study schema



[a]Part 1: All participants followed until Week 36. [b]Part 2: Participants completing Week 36 continue until either Week 72 (followed by EoS at Week 76) or until the last randomized participant in Part 1 completes Week 36. [c]Site-read focused echocardiogram for titration visit (sole criterion). *Aficamten* dose range 5–20 mg. [d]4-week follow-up after last dose.
D, day; EoS, end of study; EoT, end of treatment; R, randomization; W, Week.

Study Drug

- *Aficamten* or placebo will be administered orally once per day (QD).
- All participants will start on 5 mg *aficamten* QD, with the potential to escalate through 10, 15, and 20 mg QD. Dose adjustments will be driven by blinded, site-read echocardiograms at 2-week intervals (Weeks 2, 4, and 6) (**Tables 1** and **2**).

Table 1. Titration period dose titration

	Dose 1 (Starting Dose) (Day 1)	Dose 2[a] (Week 2)	Dose 3[a] (Week 4)	Dose 4[a] (Week 6)
LVEF ≥60% on echocardiogram	5 mg	Next higher dose, 10 mg max	Next higher dose, 15 mg max	Next higher dose, 20 mg max

[a]After a dose is downtitrated, no further uptitration is permitted. If LVEF <50% on 5 mg, participants will receive placebo.

Table 2. Echocardiogram criteria for scheduled dose titration

LVEF	*Aficamten*
≥60%	Increase dose (Weeks 2, 4, and 6 only)
≥50% to <60%	Remain on the same dose
<50%	Reduce dose (any visit)
<40%	Temporary discontinuation (any visit)

Procedures

- Primary and secondary endpoints will be assessed at Week 36 (**Figure 2**).
- After Week 36 (Part 1), participants can continue in the same arm until Week 72 (Part 2) until the last randomized patient has completed follow-up at Week 36; after that, participants can roll over into a long-term OLE study.
- When participants exit the study, they will have an end-of-treatment visit followed by a 4-week washout period, after which they will have a repeat echocardiogram, clinical examination, and blood work (end of study).

Statistical Power

- The study will randomize ~420 participants in a 1:1 ratio, providing >90% power to detect a difference in the mean KCCQ-CSS of 5 (SD 15) between the 2 treatment arms, with a 2-sided type I error of 0.05 and an assumed 10% rate of missing data.

ENDPOINTS

Primary Endpoint

- Change from baseline to Week 36 in KCCQ-CSS

Secondary Endpoints

- Change from baseline to Week 36 in:
  - Composite of 2 Z-scores of CPET parameters: pVO_2 and VE/VCO_2 slope
  - Proportion of participants with ≥1 class improvement in NYHA FC
  - NT-proBNP
  - Left atrial volume index
- Time to first event for the composite of cardiovascular death, heart transplantation or LVAD, aborted sudden cardiac death, non-fatal stroke, heart failure hospitalization, or cardiac arrhythmia (atrial fibrillation or ventricular tachyarrhythmia) requiring treatment or hospitalization

Safety Endpoints

- Incidence of adverse events
- Incidence of LVEF <50% and worsening HF and/or 30% increase in NT-proBNP
- Incidence of LVEF <40%

Key Criteria

Key Inclusion Criteria

- 18–85 years of age
- LVOT-G <30 mmHg at rest and <50 mmHg with provocation
- BMI <40 kg/m²
- Symptomatic (NYHA FC II/III) nHCM
- KCCQ-CSS score ≥30 and ≤85
- LVEF ≥60%
- CPET: Respiratory exchange ratio ≥1.00; pVO_2 ≤90% of age and sex predicted maximum
- NT-proBNP:
  - ≥300 pg/mL or ≥900 pg/mL if in AFF
  - Black participants: ≥225 pg/mL or ≥675 pg/mL if in AFF
- Hemoglobin ≥10 g/dL
- Beta-blocker use stabilized ≥2 weeks

Key Exclusion Criteria

- Significant valvular heart disease
- Infiltrative, genetic, or storage disorder causing cardiac hypertrophy that mimics nHCM
- Current ≥70% coronary artery stenosis
- History of:
  - LV systolic dysfunction (LVEF <45%)
  - Syncope, symptomatic ventricular arrhythmia, or sustained ventricular tachyarrhythmia with exercise within 3 months
  - Resistant hypertension
- Inability to exercise on a treadmill or bicycle
- Oxygen saturation reading <90%
- Prior treatment with *aficamten* or, within the last 3 months, treatment with mavacamten
- Septal reduction therapy within 6 months of screening

Trial Status and Locations

- The trial is currently enrolling participants.
- ~150 international sites are planned worldwide in 20+ countries.

SUMMARY

- ACACIA-HCM is a pivotal Phase 3 trial evaluating *aficamten* for nHCM.
- The trial is ongoing, with participation worldwide.

References

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Abbreviations

AFF, atrial fibrillation/flutter; BMI, body mass index; CPET, cardiopulmonary exercise testing; FC, functional class; HCM, hypertrophic cardiomyopathy; HF, heart failure; hs-cTnI, high-sensitivity cardiac troponin-I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LV, left ventricular; LVAD, left ventricular assist device; LVOT, left ventricular outflow tract; LVOT-G, LVOT gradient; nHCM, non-obstructive HCM; OLE, open-label extension; pVO_2, peak oxygen uptake; PK, pharmacokinetics; QD, once daily; VE/VCO_2, minute ventilation/carbon dioxide production.

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Stage-specific therapy for hypertrophic cardiomyopathy

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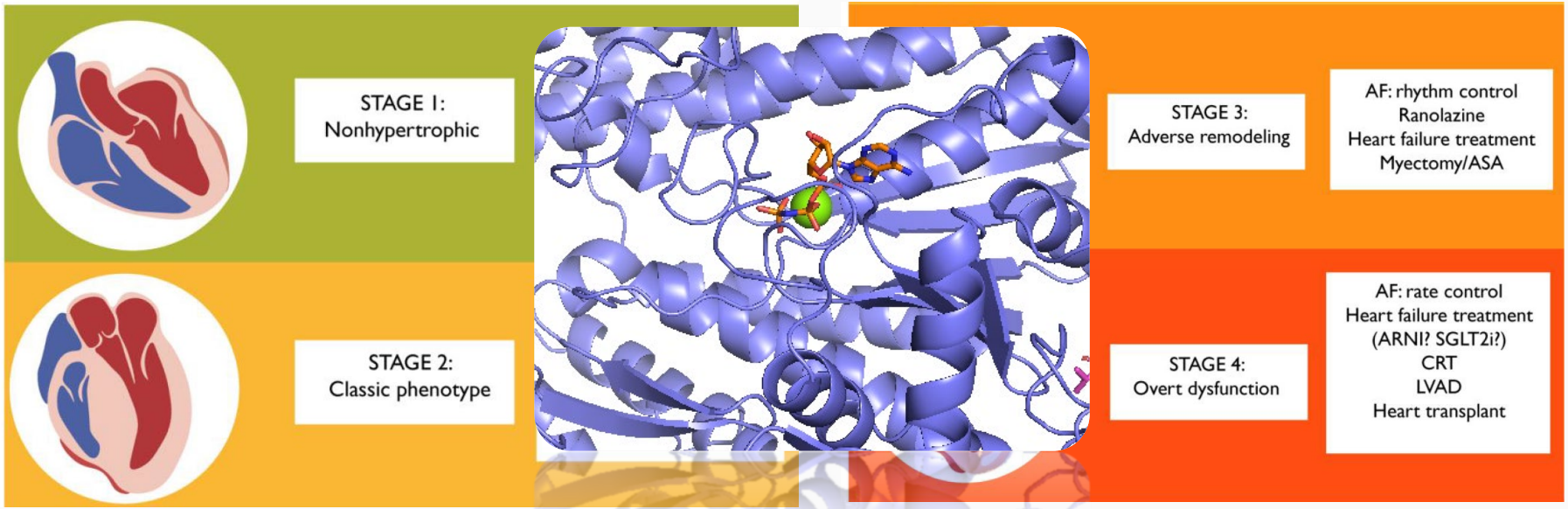

«A treatment becomes *standard* when one must consider when NOT to give it, rather than when to give it»

Claudio Rapezzi