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Hypertrophic Cardiomyopathy

Myosin inhibitors in context

Rob Fraser, MD
Allina Health Minneapolis Heart Institute

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Disclosures

- Bristol Myers Squibb speakers bureau

Today's Objectives

- Review history and epidemiology of HCM
- Describe the burden of obstructive HCM
- Outline current therapies for obstructive HCM
  - Traditional medical therapies
  - Traditional invasive therapies
  - Alternative invasive therapies
- Highlight the novel myosin inhibitors

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ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

From the Department of Pathology, St. George's Hospital

Received January 7, 1957

"Tumours of the heart and pericardium have evoked an extensive literature out of all proportion to their uncommon incidence and their relative unimportance as a cause of clinical heart disease." This opening sentence of Friedberg's chapter on cardiac tumours in *Diseases of the Heart* (Friedberg, 1949) fills a pathologist with diffidence in reporting eight cases that have been seen in the last six years in a series of 16,000 autopsies.

Primary tumours of the heart are undoubtedly a rarity and according to Mahaim (1945) 413 had been recorded up to 1945. There is little justification for recording rarities in young adults unless they have some relation to fitness for military service or confuse the differential diagnosis, particularly of conditions that may respond to cardiac surgery. These eight cases of asymmetrical hypertrophy or benign tumour of the heart have occurred in a large group where sudden death and indeed cardiac incapacity, particularly among men, is rare.

Primary tumours of the heart fall into three categories.

(1) Multiple tumours frequently described as congenital glycogenic tumours of the myocardium, which are often associated with other presumably congenital lesions such as tuberous sclerosis and renal tumours.

(2) Single diffuse tumours or asymmetrical hypertrophy of muscle and connective tissue, which are the subject of this article.

(3) Rare myxomata and sarcomata, occurring mainly in later life and producing a variety of symptoms and pathology.

Since the term rhabdomyoma is now firmly associated with nodular glycogenic tumours of the heart it is simpler to refer to the eight tumours under discussion as hamartomata, though they may in fact lay greater claim to being benign tumours of striped muscle than those of presumed glycogenic origin. In Mahaim's (1945) extensive review, which included 329 cases of primary tumour of the heart, only six are referred to as being diffuse tumours of the myocardium, and it would appear that the tumours discussed in this paper fall into this category.

Batchelor and Maxin (1925) in recording one case of multiple tumours of the heart in a child of three days reviewed 62 other reported cases. In 60 cases the lesions were multiple, and of the three other cases, one was recorded as having hepatomegaly, one had congenital tumour of the lung, and one had no congenital abnormality. In Eulinger's (1925) record of 37 cases, seven were single tumours and no other congenital abnormality was found. Browne and Gray (1930) record a case of a child of three months who died following a fit of crying, and there was found a diffuse tumour of the lateral wall of the left ventricle similar to the cases about to be described. Hueper (1935 and 1941) described diffuse tumours in the heart of a negro and in the heart of a guinea-pig. Saphir (1953) used the term rhabdomyoma when writing of nodular glycogenic degeneration and gives no reference to benign tumours of striped muscle. Similarly Adams, Denny-Brown, and Pearson (1953) describe nodular glycogenic tumours when referring to rhabdomyoma of the heart.

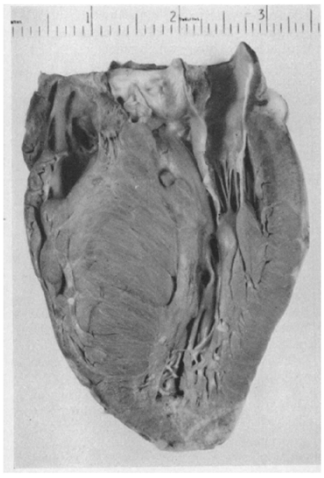

FIG. 1.—Case 1. Localized hypertrophy of the interventricular septum.

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Teare *BHJ* 1958;20(1):1-8

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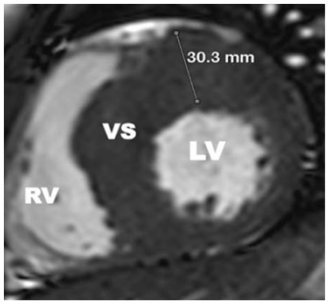
"a disease state characterized by unexplained LV hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient" ***- ACC/AHA Guidelines***



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Gersh *JACC* 2011;58(25):e212-260
Geske *JACC:Heart Failure* 2018; 6(5):364-375

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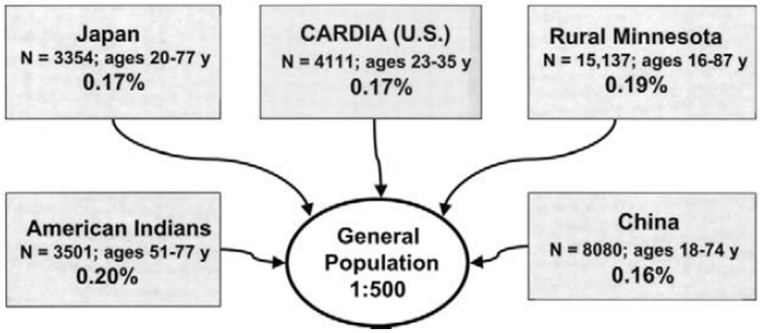

- Multiple world-wide sources have reported a similar HCM prevalence
- All studies have used echocardiographic screening
- All age groups can be affected by HCM – infancy to elderly

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Maron *AJM* 2004;116:63-66
Maron *AJM* 2004;116:14-18
Hada *AJC* 1987;59:183-184
Maron *Circulation* 2003;108:IV-664
Maron *Circulation* 1995;92:785-789
Maron *JACC* 1999;33:1590-1595

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1:500 prevalence

666,000+ with HCM in United States

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www.census.gov accessed 7/16/21
Maron *Circulation* 1995;92(4):785-789

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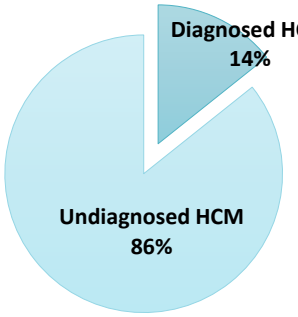
- HCM prevalence:
  - In large claims database: **1-in-3200**
  - In echocardiographic screening study: **1-in-500**



It is possible that **6-out-of-7** individuals with HCM have **not** been identified and are unaware of diagnosis

Adapted from Maron *AJC* 2016;117:1651-1654
Maron *NEJM* 2018;379:655-68

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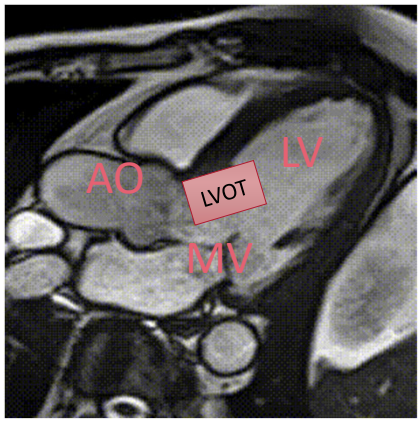
Basal septal hypertrophy with systolic anterior motion of mitral valve



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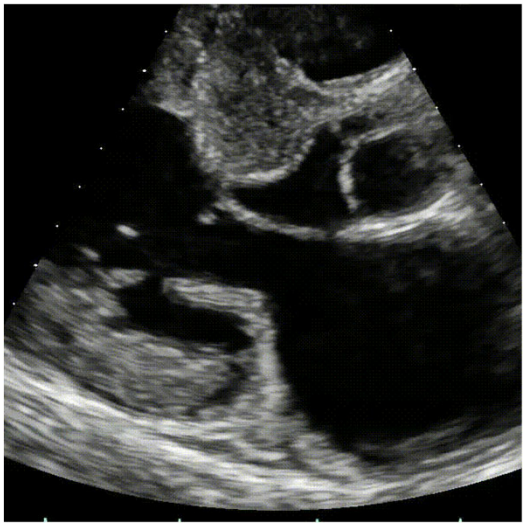

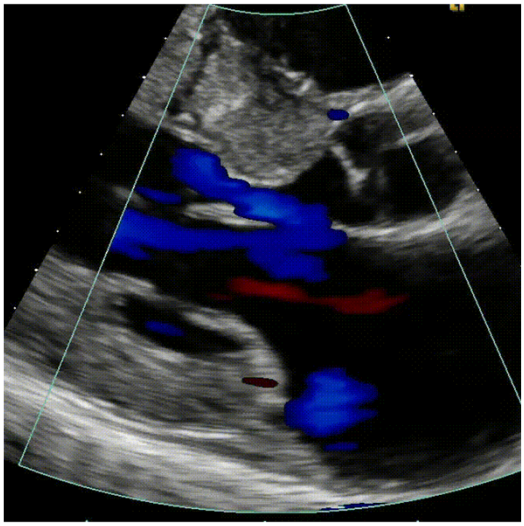

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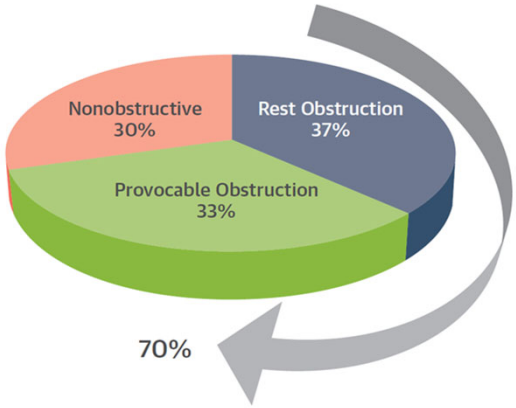
Up to 70% of HCM patients have resting or provocable LVOT obstruction

- The LVOT gradient is dependent on cardiac "loading conditions"
- The LVOT gradient can be provoked by:
  - Decreasing preload
  - Decreasing afterload
  - Increasing contractility



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Geske Clin Cardiol 2009;32(7)397-402
Rowin *JACC Imaging* 2017;10:1374–86
Maron *Circulation* 2006;114:2232-2239

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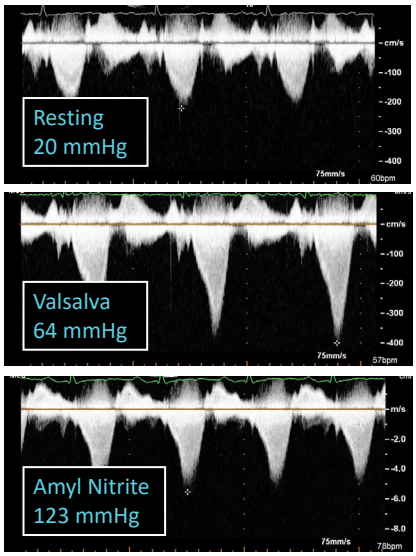

- Increase gradient with
  - Valsalva
  - Amyl Nitrate
  - Exercise (not shown)

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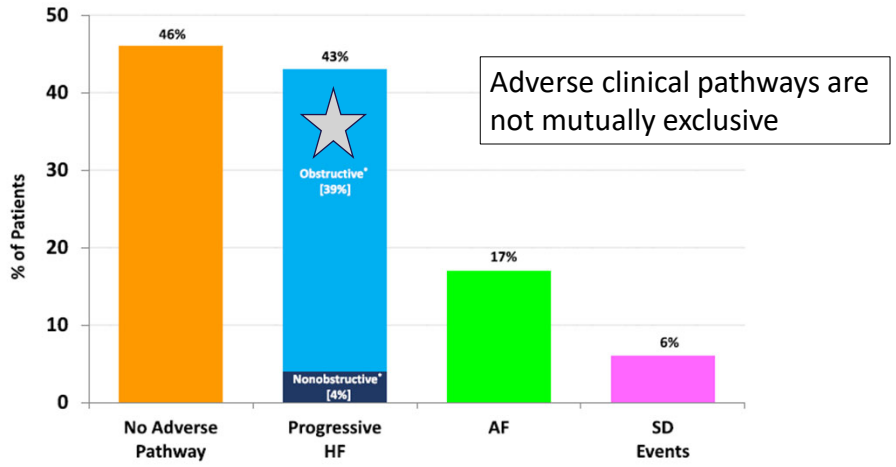
Percentage of patients who experience various HCM clinical pathways



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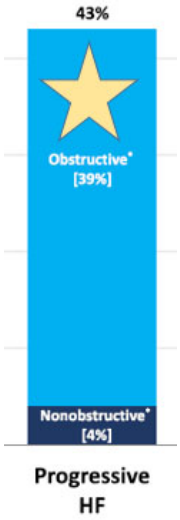
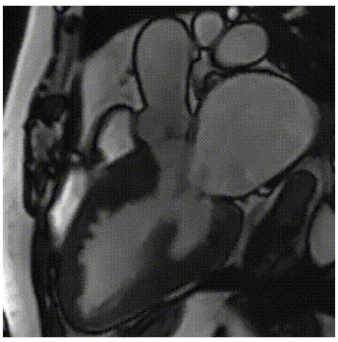
Rowin *AJC* 2017;120: 2256-64

17





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Rowin *AJC* 2017;120: 2256-64

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Obstruction is progressive and bad

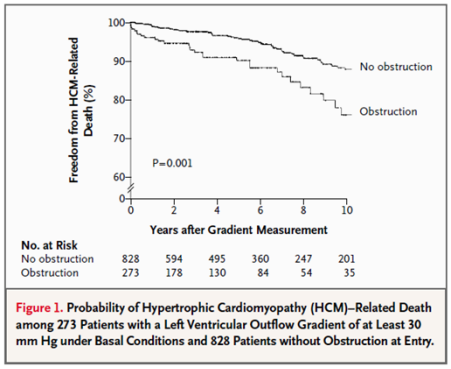

Figure 1. Probability of Hypertrophic Cardiomyopathy (HCM)–Related Death among 273 Patients with a Left Ventricular Outflow Gradient of at Least 30 mm Hg under Basal Conditions and 828 Patients without Obstruction at Entry.

Predicts HCM-related death

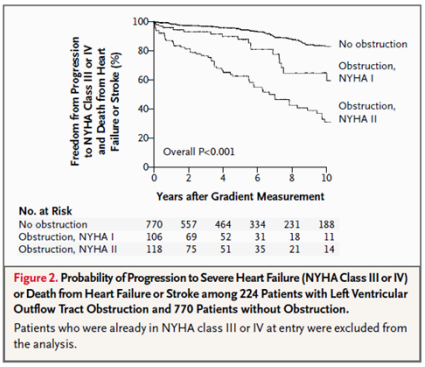

Figure 2. Probability of Progression to Severe Heart Failure (NYHA Class III or IV) or Death from Heart Failure or Stroke among 224 Patients with Left Ventricular Outflow Tract Obstruction and 770 Patients without Obstruction.
Patients who were already in NYHA class III or IV at entry were excluded from the analysis.

Predicts HF death and progression to advanced HF

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Maron NEJM 2003;348:295

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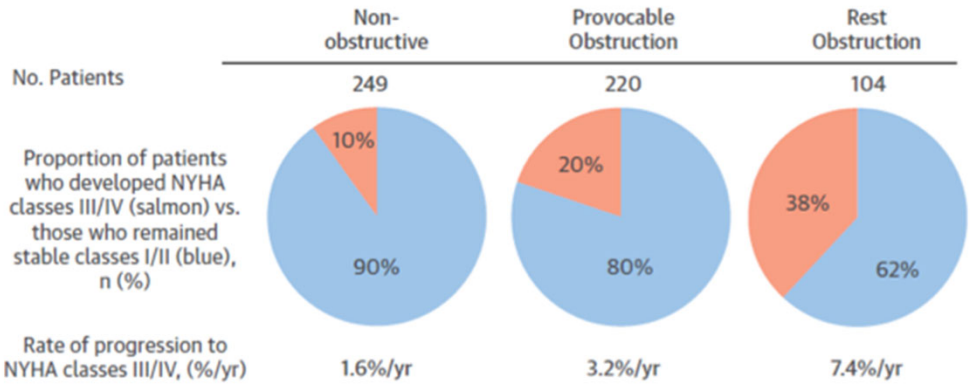
Obstruction predicts advanced HF symptoms



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Maron JACC 2016;67:1399
Rowin Circ HF 2014;7:967

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LVOT obstruction: Treatment goals

- ❖ Improve symptoms
- ❖ Improve outcomes
- ❖ Be safe and well-tolerated
- ❖ Be accessible both logistically and economically

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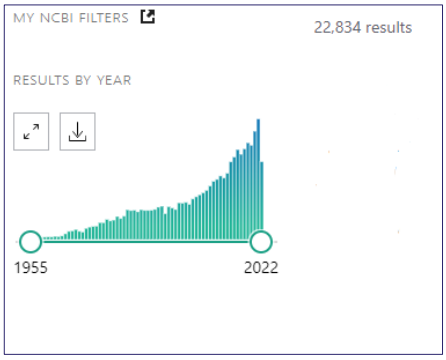

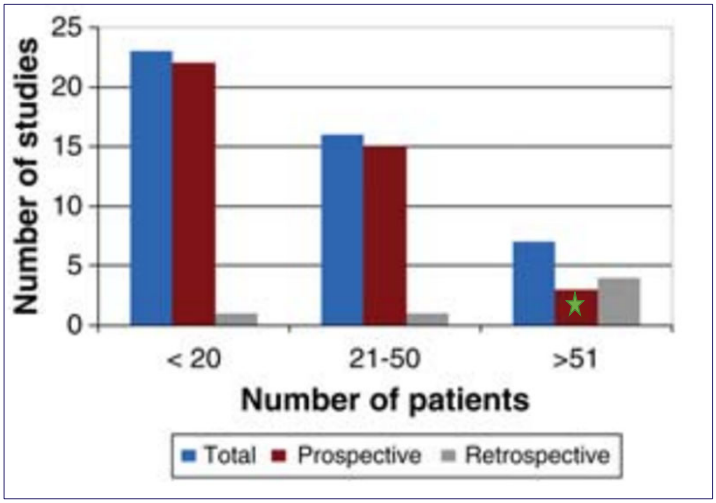

Spoladore EHJ 2012;33:1724

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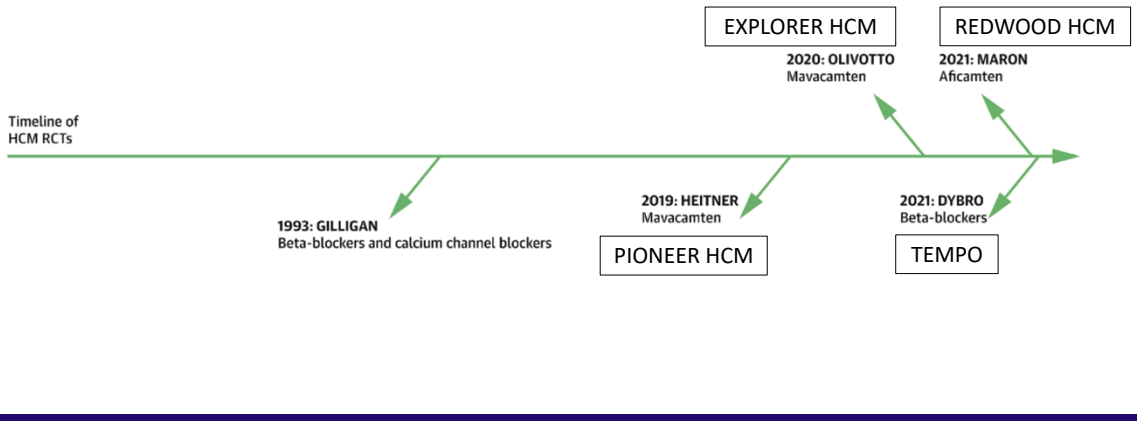

Masri *JACC* 2021;78(25):2533

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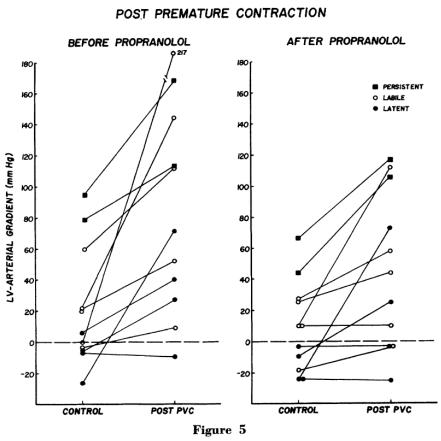

Figure 5

Amelioration of Angina Pectoris in Idiopathic Hypertrophic Subaortic Stenosis with Beta-Adrenergic Blockade

By Lawrence S. Cohen, M.D., and Eugene Braunwald, M.D.

Propranolol reduced LVOT gradient

Cohen Circ 1967;35:847

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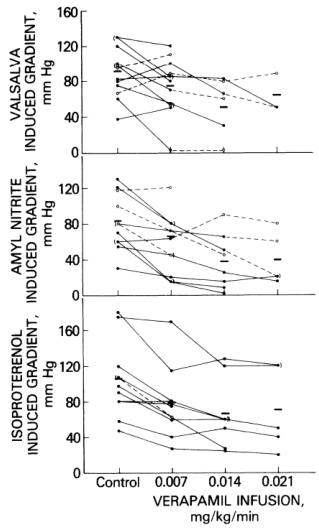

Verapamil Therapy: A New Approach to Pharmacologic Treatment of Hypertrophic Cardiomyopathy*

Douglas R. Rosing, M.D.; Kenneth M. Kent, M.D., Ph.D.; Barry J. Maron, M.D.; John Condit, B.S.; and Stephen E. Epstein, M.D.

Verapamil reduces LVOT gradients

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Rosing Circ 1979;60:1201

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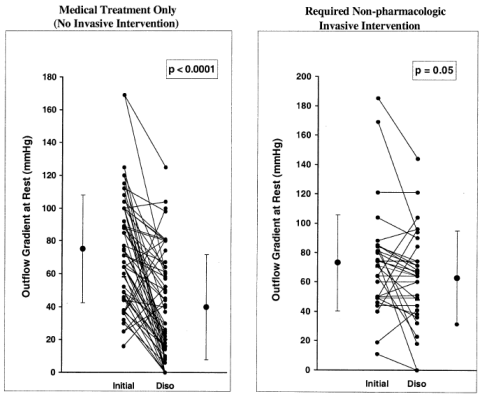
Multicenter Study of the Efficacy and Safety of Disopyramide in Obstructive Hypertrophic Cardiomyopathy

Mark V. Sherrid, MD, FACC,* Ivan Barac, MD,* William J. McKenna, MD, FACC,† Perry M. Elliott, MD, FACC,† Shaughan Dickie, DCR,† Lidia Chojnowska, MD, PhD,‡ Susan Casey, RN,§ Barry J. Maron, MD, FACC§
New York, New York; London, United Kingdom; Warsaw, Poland; and Minneapolis, Minnesota



- Disopyramide reduces LVOT gradient
- 7% stopped disopyramide for dry mouth and prostatism
- No patients stopped disopyramide for QT prolongation
- No difference in AF

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JACC 2005;45(8):1251

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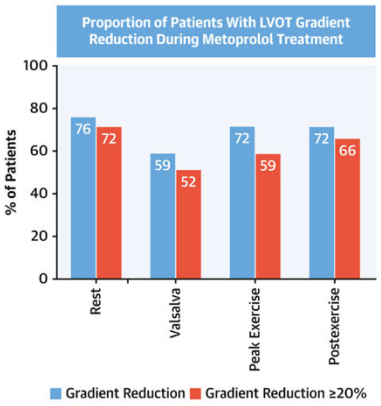
Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy

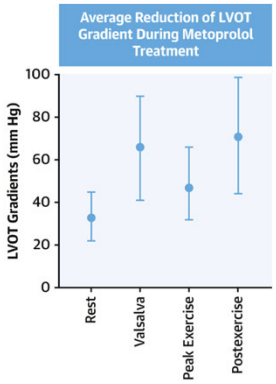
Original Investigation

Anne M. Dybro, Torsten B. Rasmussen, Roni R. Nielsen, Mads J. Andersen, Morten K. Jensen, and Steen H. Poulsen

J Am Coll Cardiol. 2021 Dec, 78 (25) 2505–2517

- BB reduced avg LVOT gradient
- BB most impactful on provocable gradient
- 25-50% of patients saw no change in gradient





Dybro JACC 2021;78:2505

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NYHA Classification of HF Severity

Class	Description
I	Patient with cardiac disease, but no limitation on ordinary physical activity
II	Comfortable at rest, ordinary activity results in symptoms (slight limitation)
III	Comfortable at rest, less than ordinary activity results in symptoms (marked limitation)
IV	Symptomatic at rest, increased discomfort with any physical activity

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KCCQ: Kansas City Cardiomyopathy Questionnaire

- Self-administered questionnaire that measures (in HF patients):
  - Symptoms
  - Physical and social limitations
  - QOL
- Scaled 0 – 100

JACC: Heart Failure

JACC Journals › JACC: Heart Failure › Archives › Vol. 10 No. 8

Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy

Clinical Research

Michael Nassif, Jennifer T. Fine, Chantal Dolan, Matthew Reaney, Prithvi Addepalli, Veleka D. Allen, Amy J. Sehnert, Kensey Gosch, and John A. Spertus

J Am Coll Cardiol HF. 2022 Aug, 10 (8) 531–539

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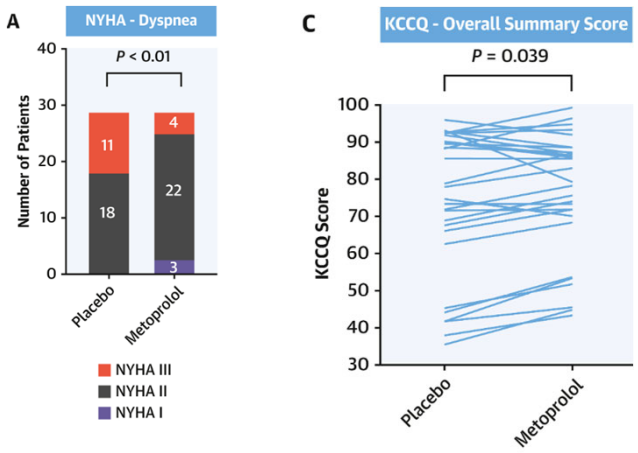
- 10% of patients on metoprolol achieved NYHA class I status
- Average KCCQ summary score was 3 points higher with metoprolol



Dybro JACC 2021;78:2505

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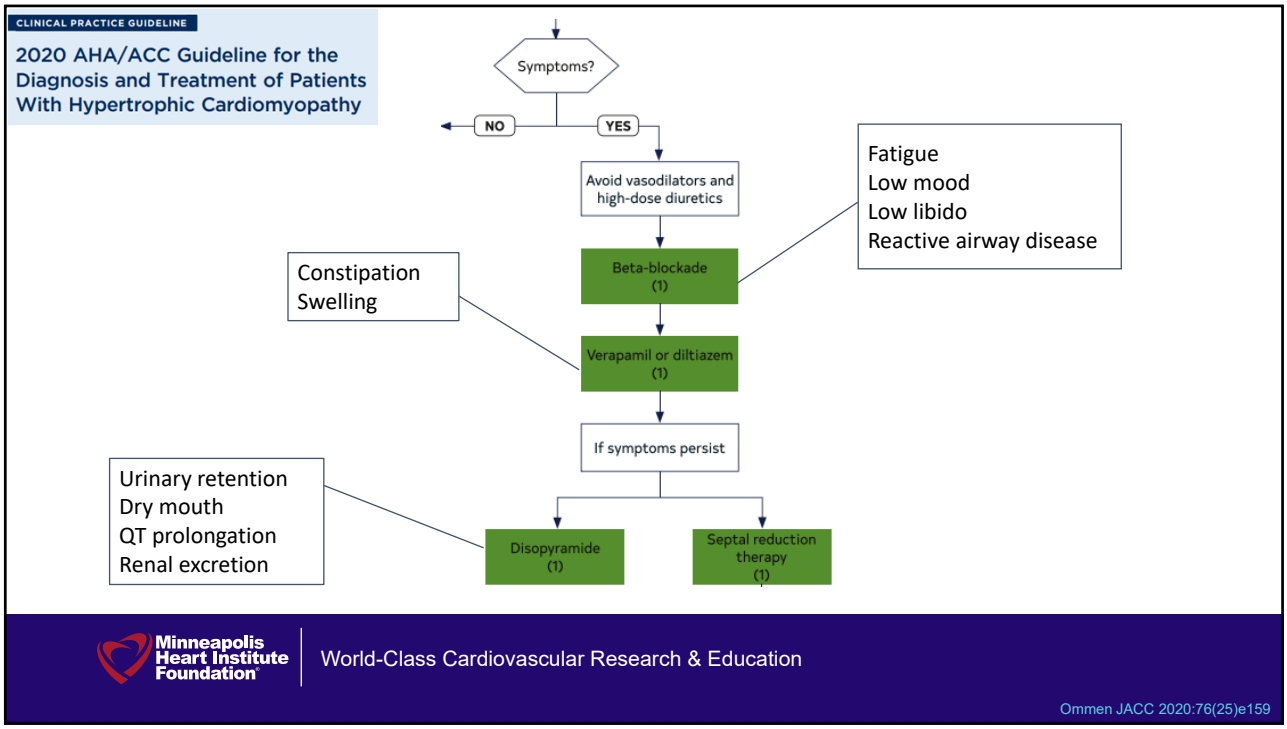

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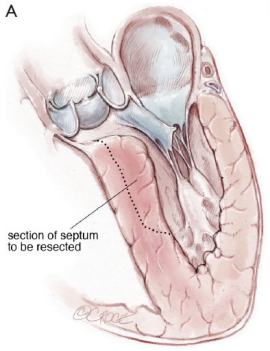
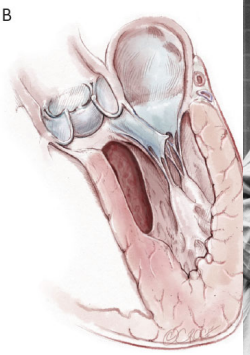
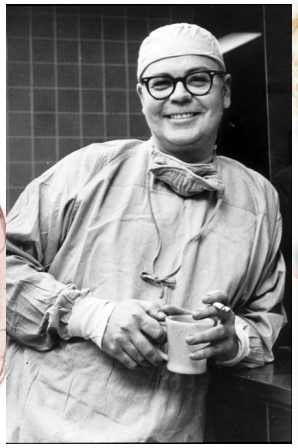
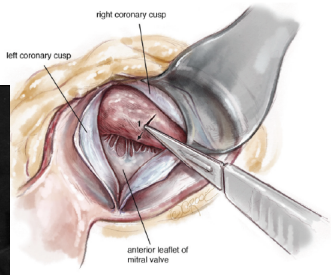
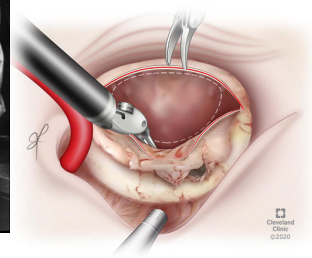
Septal Myectomy











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Kumar JCS 2020;35(11):3120
Ralph-Edwards ACS 2017;6(4):410-415

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TABLE 1 Operative Mortality Associated With Septal Myectomy* at North American Hypertrophic Cardiomyopathy Centers, 2000–2014

Institution	No. of Myectomies	Age (yrs)	Male (%)	Operative Deaths† n	Operative Deaths† %
Mayo Clinic, Rochester, Minnesota	1,411	51 ± 14	55	4‡	0.3
Cleveland Clinic, Cleveland, Ohio	1,470§	55 ± 14	55	6	0.4
Tufts Medical Center, Boston, Massachusetts‖	348	52 ± 15	56	4	1.1
Toronto General, Ontario, Canada	306	49 ± 13	62	2	0.6
Mount Sinai-St. Luke's and Roosevelt, New York, New York	160	53 ± 14	48	1	0.6
Totals	3,695	54 ± 14	55	17	0.4

*Does not include myectomy associated with valve replacement, coronary artery bypass grafting, or resection of a subaortic membrane. †Within 30 days of the myectomy. ‡Includes 2 patients with prior alcohol septal ablation; with these 2 patients considered nonpure myectomies, the Mayo mortality rate would be only 0.15%. §Includes 19% of patients with mitral valve repair. ‖Newest myectomy center with operations performed over only 11 years with first procedure in 2004, whereas data for the other centers encompass 15 years.

<1% 30-day operative mortality

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Maron JACC 2015;66(11)

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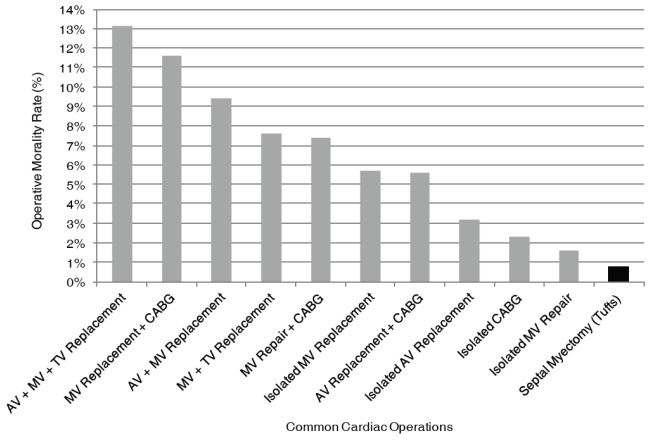
Myectomy (Tufts) mortality rate compared to other cardiac surgery (STS) mortality rates



Rastegar *ACTS* 2017;6(4):353

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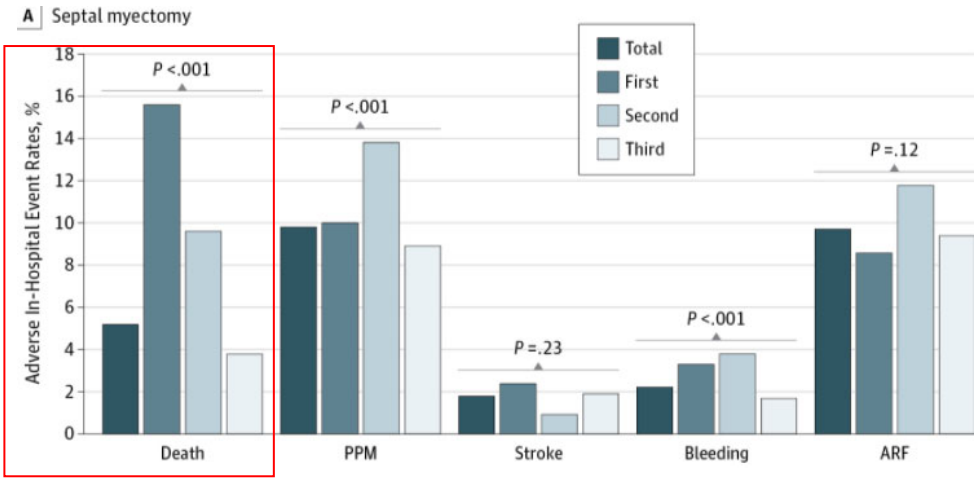
Lower volume centers have higher myectomy mortality rates



Kim JAMA Card 2016;1(3):324

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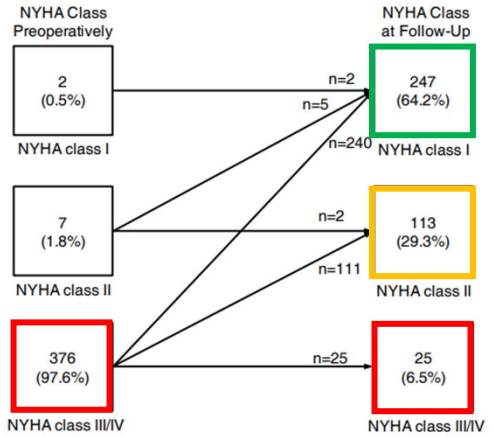

Figure 1 Comparison of NYHA functional classification for myectomy patients at preoperative and most-recent follow-up evaluation. NYHA, New York Heart Association.

What are the symptom outcomes?

- **98%** were NHYA class III/IV HF pre-operatively
- **64%** achieved NYHA class 1 status
- **29%** achieved NYHA class 2 status

Rastegar *ACTS* 2017;6(4):353

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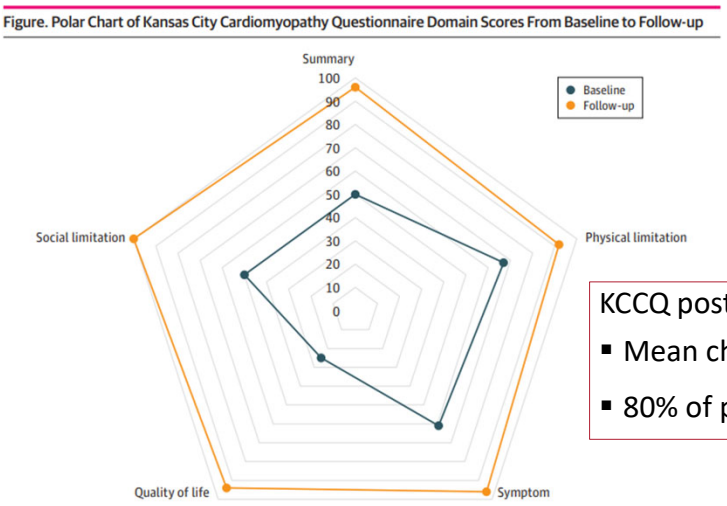
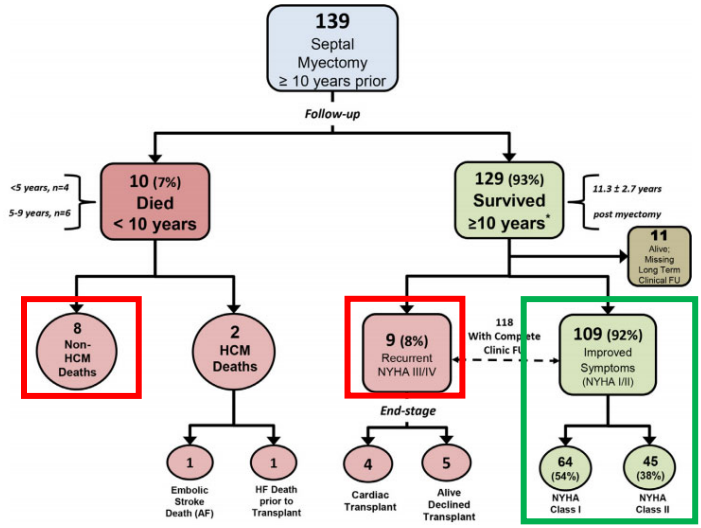


KCCQ post myectomy:

- Mean change was +38 points
- 80% of patients had 20+ point improvement

Desai JAMA Netw Open 2022;5(4)e227293

40



Long term myectomy data:

- **93%** survived 10+ years
  - Most were non-HCM deaths
- Of survivors,
  - **54%** NYHA class I
  - **38%** NYHA class II

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Maron AJC 2022;163:91

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ORIGINAL RESEARCH

Outcomes in Guideline-Based Class I Indication Versus Earlier Referral for Surgical Myectomy in Hypertrophic Obstructive Cardiomyopathy

Alaa Alashi, MD; Nicholas G. Smedira, MD; Kevin Hodges, MD; Zoran B. Popovic, MD, PhD; Maran Thamilarasan, MD; Per Wierup, MD, PhD; Harry M. Lever, MD; Milind Y. Desai, MD

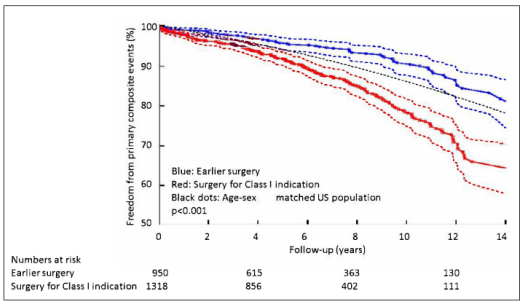

Figure 2. **Kaplan–Meier survival curves demonstrating long-term outcomes of the entire study sample (n=2268), separated on the basis of undergoing surgical relief of LVOT obstruction for Class I indication vs earlier surgery.**
LVOT indicates left ventricular outflow tract.

Early defined as:

- NYHA class II +
  - Drug intolerance or
  - Symptomatic impairment of exercise (symptoms before 85% age-predicted METs with concomitant severe LVOTO)

Early myectomy associated with improved survival

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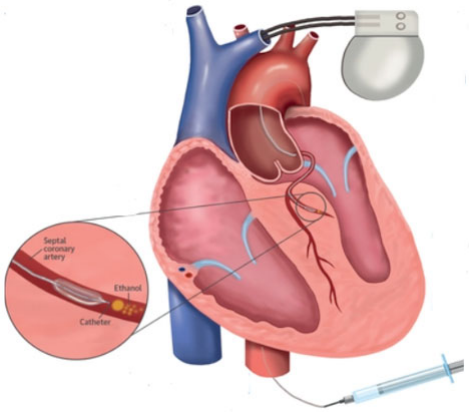
Alashi *JAHA* 2021;10:e016210

42

Alcohol Septal Ablation



Liebregts JACC 2017;70(4)

43

Table 2. Acute Procedural Results and 30-Day Clinical Events

	Ablation Patients (n=177)	Myectomy Patients (n=177)	*P*
No. septal arteries injected, mean±SD	1.1±0.4	. . .	. . .
Volume of ethanol injected, median (IQR), mL	1.8 (0.5)	. . .	. . .
Residual LVOT gradient at rest, median (IQR), mm Hg	11 (15)	5 (5)	0.001
Reduction in LVOT gradient, %	85±16	88±19	
Procedural and in-hospital complications, n (%)	51 (28.8)	10 (5.6)	<0.0001
Pacemaker dependency	36 (20.3)	4 (2.3)	
Cardiac tamponade	6 (3.3)	1 (0.6)	
Sustained ventricular tachycardia	3 (1.7)	0	
Cardiac surgery	2 (1.1)	2 (0.6)	
Resuscitated sudden cardiac arrest	2 (1.1)	1 (0.6)	
Pneumothorax	1 (0.6)	2 (1.1)	
Stroke	1 (0.6)	0	
Death	2 (1.1)	1 (0.6)	0.32
Sudden cardiac death	1 (0.6)	0	
Heart failure	1 (0.6)	1 (0.6)	

IQR indicates interquartile range; LVOT, left ventricular outflow tract; and SD, standard deviation.

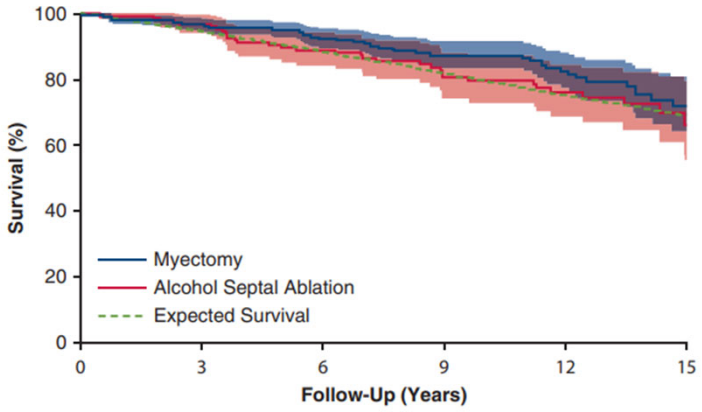
1% 30-day operative mortality

20% pacemaker dependency

Sorajja *Circ* 2012;126:2374

44

No difference in survival between ASA and myectomy



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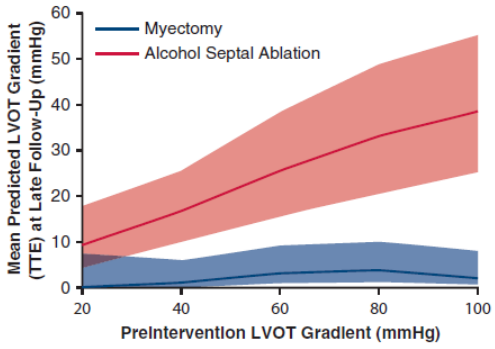
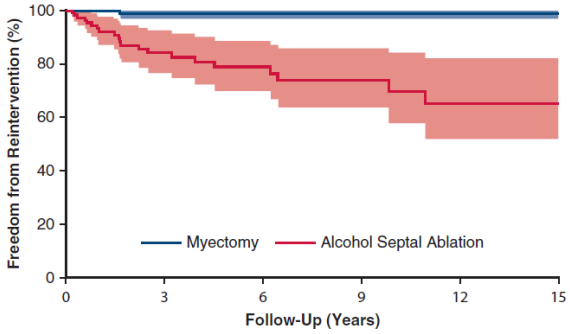
Nguyen JTCS 2019;157:306

45

Myectomy superior for
1) LVOT gradient reduction (short- and long-term)
2) Freedom from re-intervention





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Nguyen JTCS 2019;157:306

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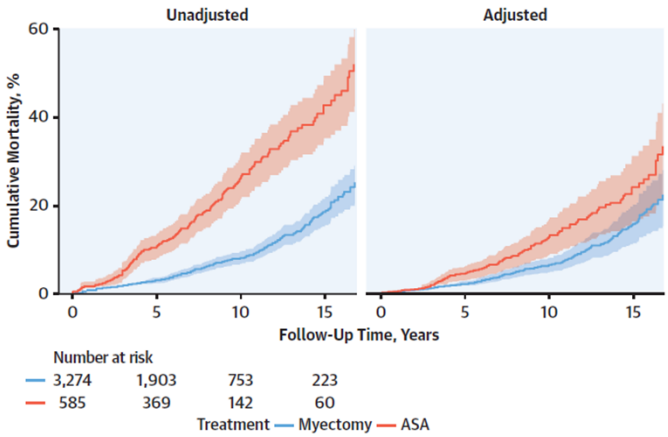
ASA was independently associated with increased long-term mortality compared to septal myectomy



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Cui JACC 2022;79(17):1647

47

Residual gradient associated with mortality

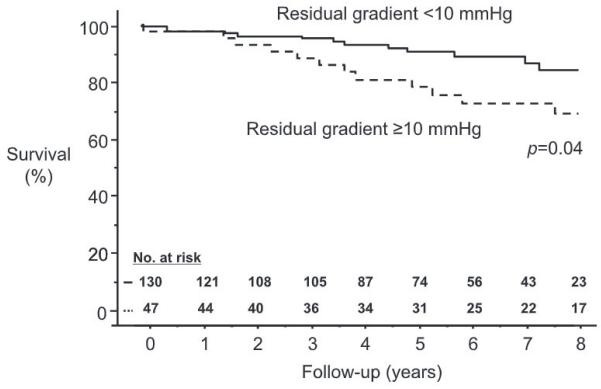

Figure 4. Residual left ventricular outflow tract (LVOT) gradient after septal ablation and survival free of all-cause mortality.

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Sorajja *Circ* 2012;126:2374

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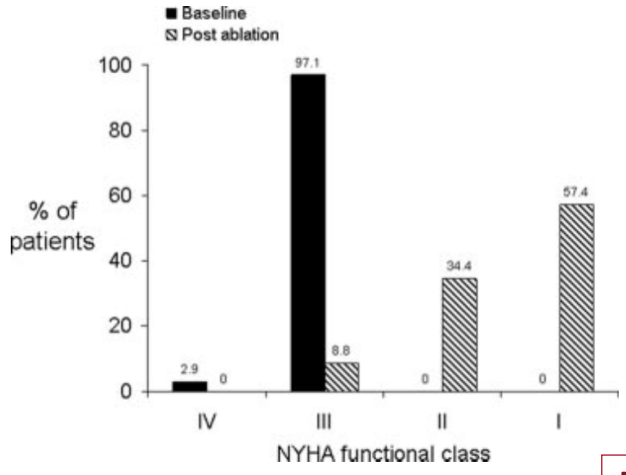

What are the symptom outcomes?

98% **100%** were NHYA class III/IV HF pre-operatively

64% **57%** achieved NYHA class 1 status

29% **34%** achieved NYHA class 2 status

Myectomy

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Sorajja *Circ* 2012;126:2374

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Myectomy	Alcohol Septal Ablation
- Operator dependent outcomes	- Operator dependent outcomes
+ Low mortality	+ Low mortality
+ Highest efficacy	+ Less invasive, shorter recovery
+ Not dependent on anatomy	- Higher rate of reintervention
	- Higher pacemaker rates
	- Anatomy dependent

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Today's Objectives

- Review history and epidemiology HCM
- Describe the burden of obstructive HCM
- Outline current therapies for obstructive HCM
  - Traditional medical therapies
  - Traditional invasive therapies: septal myectomy, alcohol septal ablation
  - Alternative invasive therapies
- Highlight the novel myosin inhibitors

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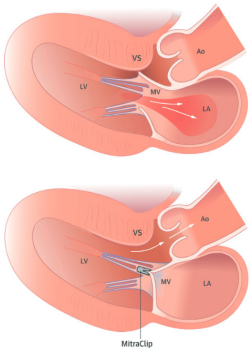
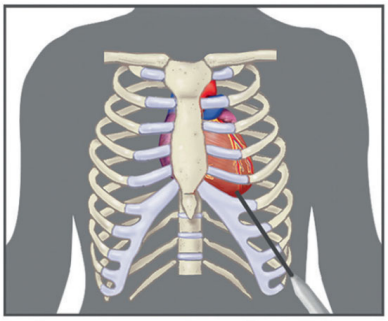
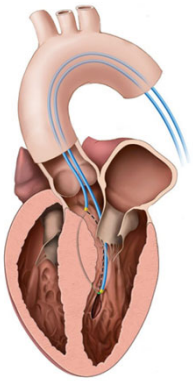
TEER



Percutaneous intramyocardial septal RFA



Transcatheter myotomy with septal scoring



Sorajja JACC 2016;67:2811
Liu JACC 2018;72:1898
Khan Circ Int 2022;15

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Today's Objectives

- Review history and epidemiology HCM
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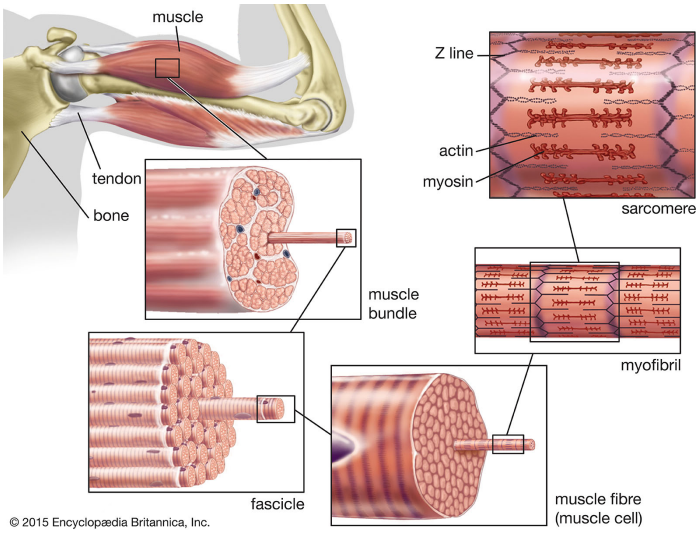
  - Traditional invasive therapies: septal myectomy, alcohol septal ablation
  - Alternative invasive therapies
- Highlight the novel myosin inhibitors


muscle
tendon
bone
muscle bundle
fascicle
Z line
actin
myosin
sarcomere
myofibril
muscle fibre (muscle cell)
© 2015 Encyclopædia Britannica, Inc.

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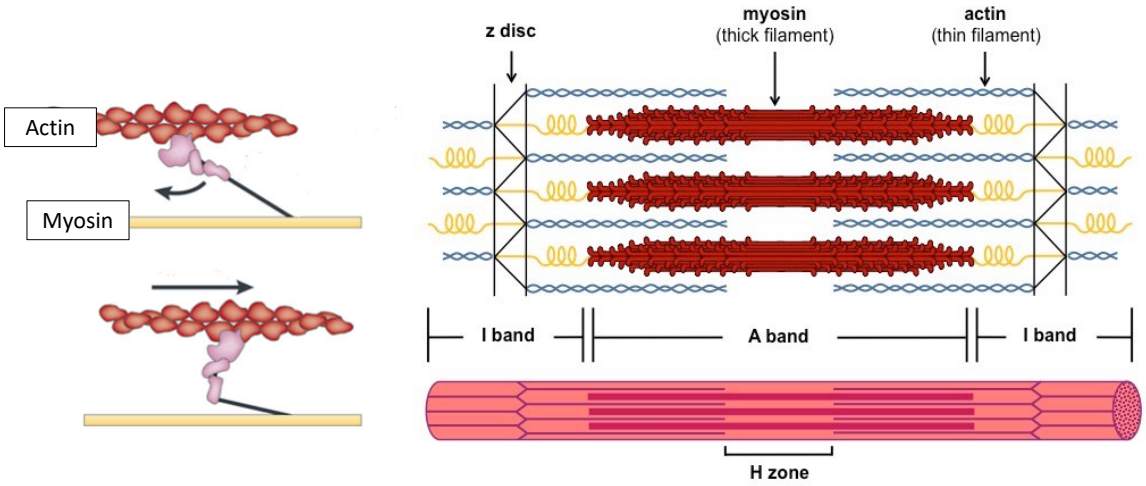
Actin
Myosin
z disc
myosin (thick filament)
actin (thin filament)
I band
A band
I band
H zone

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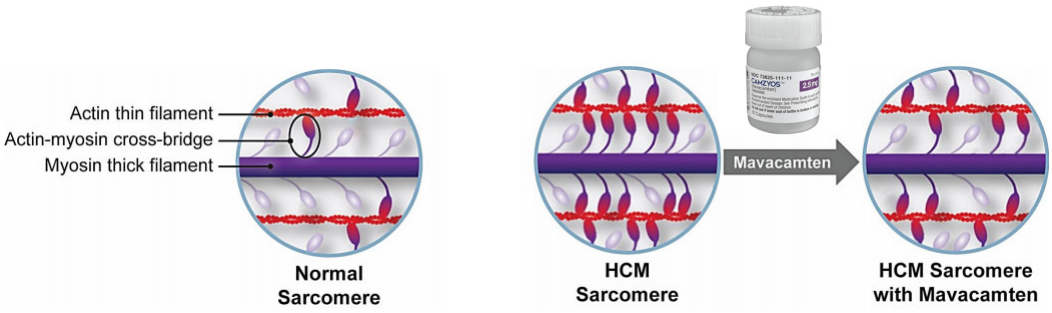
Myosin modulation



Mavacamten is a targeted inhibitor of cardiac myosin that reduces the number of myosin-actin cross-bridges and decreases contractility

Ho *Circ HF* 2020;13:6

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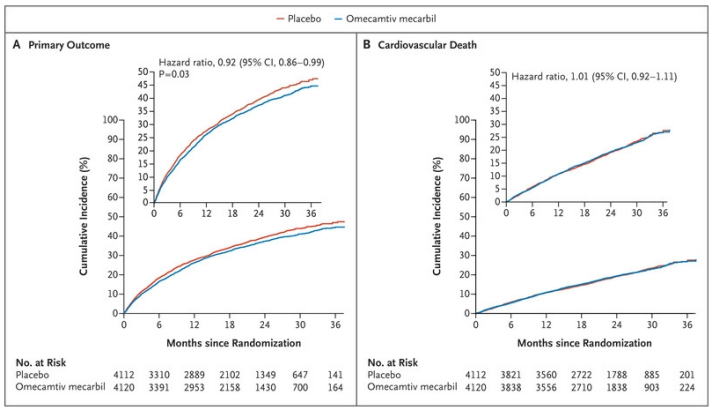
ORIGINAL ARTICLE

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

John R. Teerlink, M.D., Rafael Diaz, M.D., G. Michael Felker, M.D., M.H.S., John J.V. McMurray, M.D., Marco Metra, M.D., Scott D. Solomon, M.D., Kirkwood F. Adams, M.D., Inder Anand, M.D., D.Phil., Alexandra Arias-Mendoza, M.D., Tor Biering-Sørensen, M.D., Michael Böhm, M.D., Diana Bonderman, M.D., et al., for the GALACTIC-HF Investigators*



Teerlink NEJM 2021; 384:105

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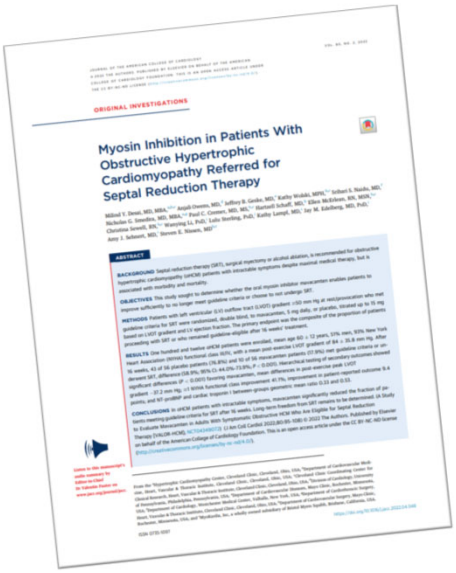
Articles

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


ORIGINAL INVESTIGATIONS

Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy

Minneapolis Heart Institute Foundation | World-Class Cardiovascular Research & Education

Olivotto Lancet 2020;396(10253):759
Desai JACC 2022;80(2):95

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EXPLORER	Mavacamten n= 123	Placebo n= 128
Transient LVEF < 50%	7 (12%)	2 (3%)
Temporary RX hold for EF < 50%	3 (5%)	2 (3%)
At end of trial EF < 50%	4 (7%)	0

3-12% risk of systolic dysfunction

VALOR	Mavacamten (n = 56)	Placebo (n = 55)
Safety endpoints		
LV ejection fraction <50%	2 (3.6)	0 (0.0)
Permanent discontinuation for LV ejection fraction <30%	0 (0.0)	0 (0.0)
Death, myocardial infarction or stroke	0 (0.0)	0 (0.0)

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Olivotto Lancet 2020;396(10253):759
Desai JACC 2022;80(2):95

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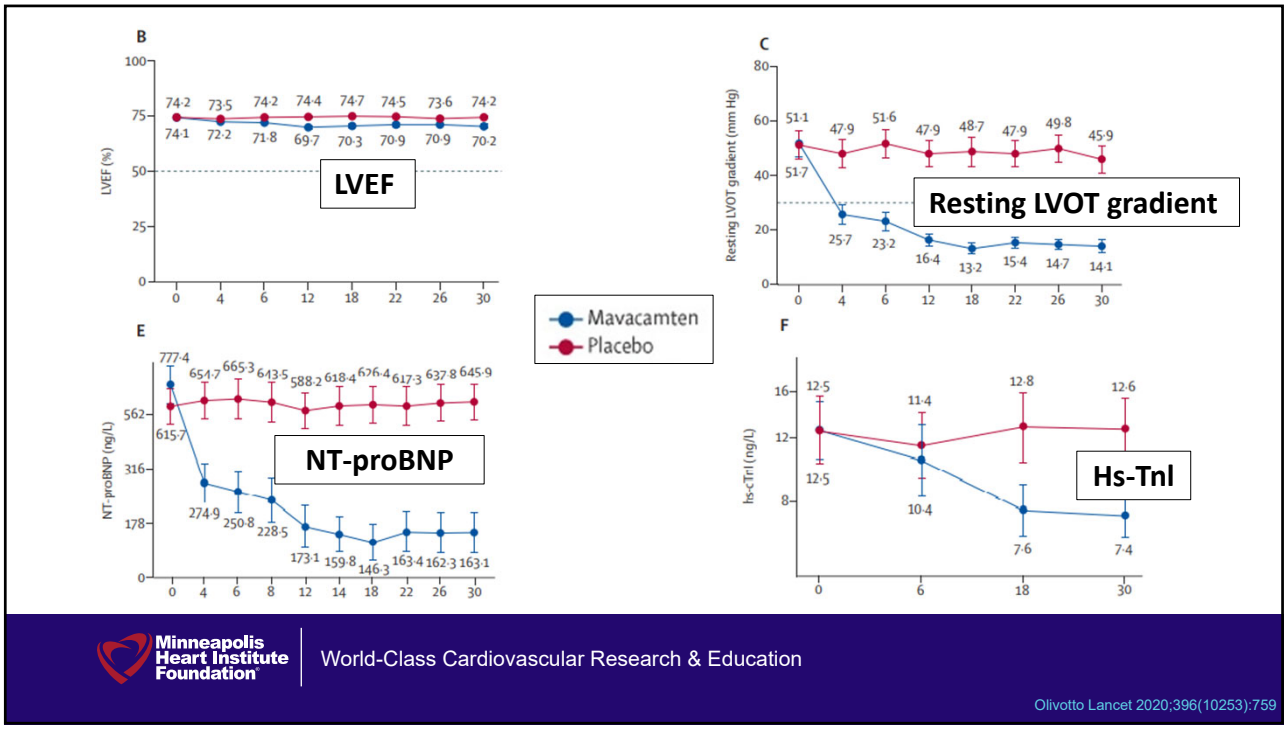
B
LVEF (%)
LVEF
C
Resting LVOT gradient (mm Hg)
Resting LVOT gradient
Mavacamten
Placebo
E
NT-proBNP (ng/L)
NT-proBNP
F
hs-cTnI (ng/L)
Hs-TnI
Minneapolis Heart Institute Foundation
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Olivotto Lancet 2020;396(10253):759

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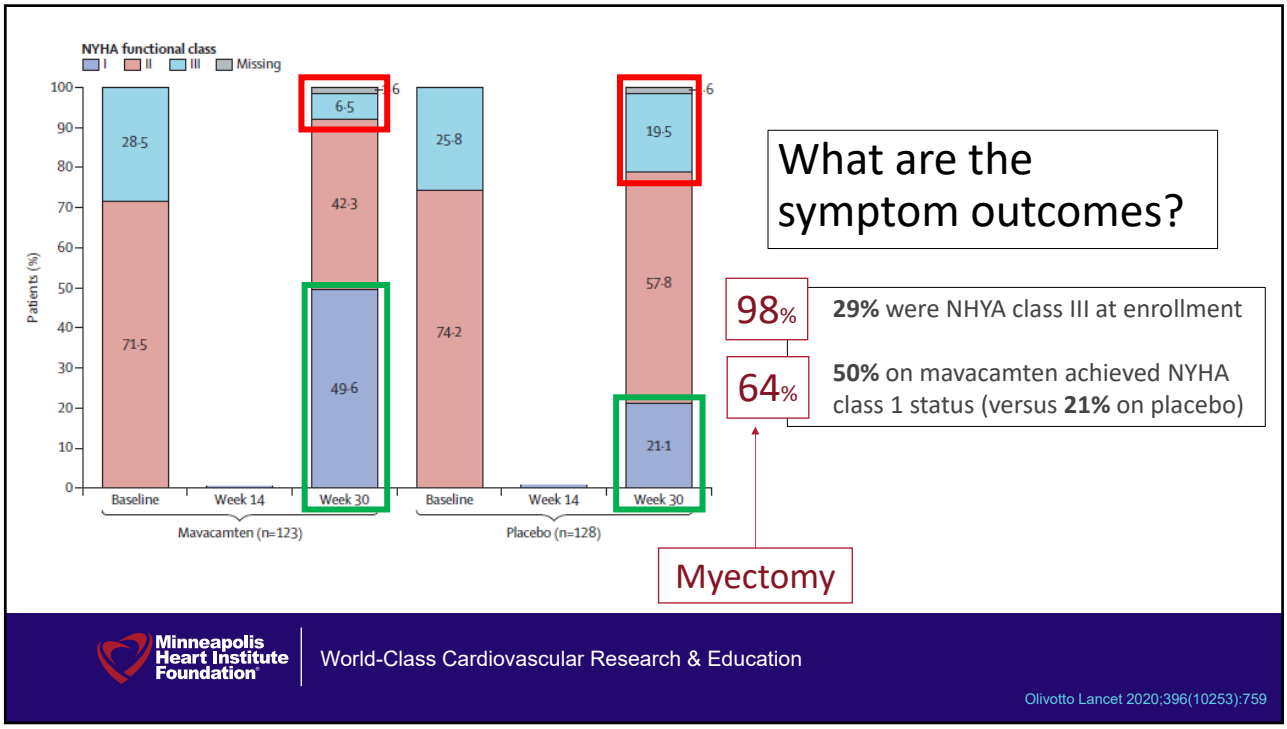
NYHA functional class
I
II
III
Missing
Patients (%)
Baseline
Week 14
Week 30
Mavacamten (n=123)
Placebo (n=128)
What are the symptom outcomes?
98%
29% were NHYA class III at enrollment
64%
50% on mavacamten achieved NYHA class 1 status (versus 21% on placebo)
Myectomy
Minneapolis Heart Institute Foundation
World-Class Cardiovascular Research & Education
Olivotto Lancet 2020;396(10253):759

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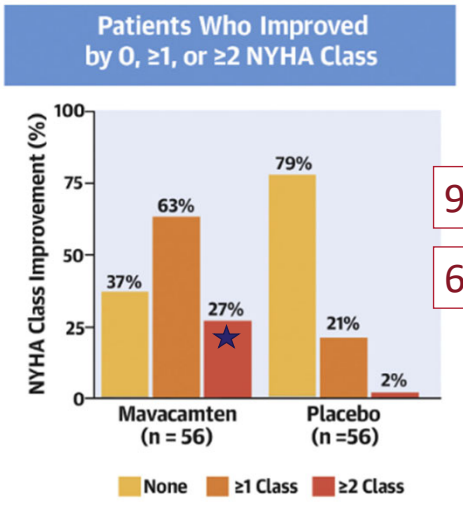

98% 93% NYHA Class III at enrollment

64% ~27% on mavacamten achieved NHYA class I status (versus ~2% on placebo)

Myectomy

Desai JACC 2022;80(2):95

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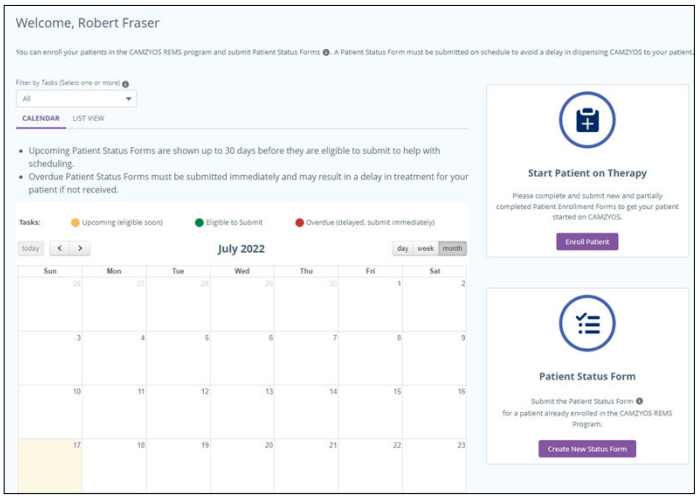
CAMZYOS™ REMS
Program Overview



1. Prescriber
2. Patient
3. Dispensing pharmacy

Camzyosrems.com

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Echocardiogram Requirements for CAMZYOS

Before treatment starts	At 4 weeks after treatment is started	At 8 weeks after treatment is started	At 12 weeks after treatment is started	Every 12 weeks thereafter

Echocardiograms may also be needed:

- 4 weeks after a change in the dose of CAMZYOS
- After a break in treatment (as directed by your healthcare provider)
- 4 weeks and 12 weeks after starting certain medicines that are known to affect CAMZYOS

Your healthcare provider will let you know if these echocardiograms are required.

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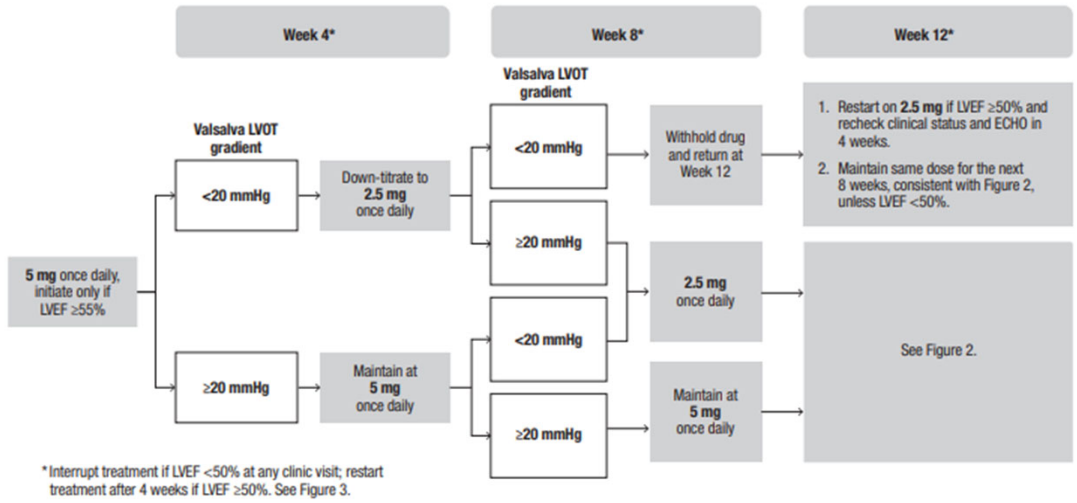
Figure 1: Initiation Phase



*Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See Figure 3.

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	Metoprolol	Mavacamten*	ASA	Myectomy
% NYHA 1	3%	27%	57%	67%
Change in KCCQ	3	16	25	38
Change in resting LVOT gradient	-33 mmHg	-33 mmHg	-49 mmHg	-64 mmHg (Zero)

* Using VALOR data, most comparable to invasive septal reduction cohorts
50% achieved NYHA class I status in EXPLORER but 72% were NYHA Class II at baseline (versus 93% in VALOR)

Therapies are not compared head-to-head

Desai *JACC* 2022;80(2):95
Olivotto *Lancet* 2020;396:759
Spertus *Lancet* 2021;397(10293):2467
Akita *Open Heart* 2018;5:e000786
Sorajja *Circ* 2012;126:2374
Dybro *JACC* 2021;78:2505
Desai *JAMA Open* 2022;5(4):e227293
Nguyen *JTCS* 2019;157:306

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	Metoprolol	Mavacamten	Septal Ablation	Myectomy
Safety	Excellent	Short term	Good	Excellent
Access	Easy	Evolving	Fair	Poor
Hemodynamic Effect	Fair	Fair	Good	Best
Symptom Effect	Little	Good	Very good	Excellent

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- DISCOVER Registry - Obstructive HCM patients
- MAVA-LTE Registry - Long term mavacamten data
- SEQUOIA RCT - Phase III Aficamten in obstructive HCM
- AMARONE Trial - Septal ablation versus myectomy

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Take Home

- HCM is not uncommon and can be a progressive disease
- LVOT obstruction is the primary cause of HCM HF symptoms and predicts poor outcomes
- There are multiple treatment strategies for symptomatic LVOT obstruction and the best option is patient-dependent and best chosen via shared-decision
- Mavacamten is a novel myosin inhibitor that is an effective treatment for obstructive HCM but requires FDA-mandated monitoring via REMS program

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	Mavacamten group (n=123)	Placebo group (n=128)
Age, years	58·5 (12·2)	58·5 (11·8)
Sex		
Women	57 (46%)	45 (35%)
Men	66 (54%)	83 (65%)
Race		
White	115 (93%)	114 (89%)
Black or African American	1 (1%)	5 (4%)
Native American or Alaskan Native	0	1 (1%)
Asian	4 (3%)	2 (2%)
Unknown	3 (2%)	6 (5%)
Region		
USA	53 (43%)	55 (43%)
Spain	17 (14%)	16 (13%)
Poland	16 (13%)	16 (13%)
Other*	37 (30%)	41 (32%)
Hypertrophic cardiomyopathy genetic testing performed	90 (73%)	100 (78%)
Pathogenic or likely pathogenic hypertrophic cardiomyopathy gene variant	28/90 (31%)	22/100 (22%)
Medical history		
Family history of hypertrophic cardiomyopathy	33 (27%)	36 (28%)
Atrial fibrillation	12 (10%)	23 (18%)
Septal reduction therapy	11 (9%)	8 (6%)
Hypertension	57 (46%)	53 (41%)
Hyperlipidaemia	27 (22%)	39 (30%)
Coronary artery disease	12 (10%)	6 (5%)
Obesity	15 (12%)	14 (11%)
Type 2 diabetes	6 (5%)	7 (6%)
Asthma	17 (14%)	11 (9%)
Chronic obstructive pulmonary disease	2 (2%)	3 (2%)
Background hypertrophic cardiomyopathy therapy		
β blocker	94 (76%)	95 (74%)
Calcium channel blocker	25 (20%)	17 (13%)
Implantable cardioverter-defibrillator	27 (22%)	29 (23%)
Body-mass index, kg/m²	29·7 (4·9)	29·2 (5·6)
Heart rate, beats per min	63 (10·1)	62 (10·6)
Systolic blood pressure, mm Hg	128 (16·2)	128 (14·6)

(Table 1 continues on next page)

	Mavacamten group (n=123)	Placebo group (n=128)
(Continued from previous page)		
Diastolic blood pressure, mm Hg	75 (10·8)	76 (9·9)
NYHA functional class II	88 (72%)	95 (74%)
NYHA functional class III	35 (28%)	33 (26%)
pVO_2, mL/kg per min	18·9 (4·9)	19·9 (4·9)
NT-proBNP, geometric mean, ng/L (CV%)†	777 (136)	616 (108)
High-sensitivity cardiac troponin I, geometric mean, ng/L (CV%)‡	12·5 (208)	12·5 (373)
Echocardiographic parameters		
LVEF, %	74 (6)	74 (6)
Maximum left ventricular wall thickness, mm	20 (4)	20 (3)
LVOT gradient, rest, mm Hg	52 (29)	51 (32)
LVOT gradient, Valsalva, mm Hg	72 (32)	74 (32)
LVOT gradient, post-exercise, mm Hg§	86 (34)	84 (36)
Left atrial volume index, mL/m²¶	40 (12)	41 (14)
Left atrial diameter, mm‖	42 (5)	42 (6)

Data are mean (SD), n (%), or n/N (%), unless otherwise indicated. LVEF=left ventricular ejection fraction. LVOT=left ventricular outflow tract. NYHA=New York Heart Association. NT-proBNP=N-terminal pro B-type natriuretic peptide. pVO_2=peak oxygen consumption. *Other comprised Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, and the UK (ordered by number of patients). †Data missing for three patients in the mavacamten group and two patients in the placebo group. The variation number (CV%) is the coefficient of variation, which is defined as the ratio of the SD to the mean. ‡Data missing for three patients in the mavacamten group and nine patients in the placebo group. §Data missing for one patient in the mavacamten group and one patient in the placebo group. ¶Data missing for one patient in the mavacamten group. ‖Data missing for five patients in each group.

Table 1: **Baseline characteristics**

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	Mavacamten group (n=123)	Placebo group (n=128)	Difference* (95% CI), p value
Primary endpoint†			
Either ≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	45 (37%)	22 (17%)	19·4 (8·7 to 30·1; p=0·0005)
≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement	41 (33%)	18 (14%)	19·3 (9·0 to 29·6)
≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	29 (24%)	14 (11%)	12·6 (3·4 to 21·9)
Both ≥3·0 mL/kg per min increase in pVO_2 and ≥1 NYHA class improvement	25 (20%)	10 (8%)	12·5 (4·0 to 21·0)
Secondary endpoints‡			
Post-exercise LVOT gradient change from baseline to week 30, mm Hg	−47 (40), n=117	−10 (30), n=122	−35·6 (−43·2 to −28·1; p<0·0001)
pVO_2 change from baseline to week 30, mL/kg per min	1·4 (3·1), n=120	−0·1 (3·0), n=125	1·4 (0·6 to 2·1; p=0·0006)
≥1 NYHA class improvement from baseline to week 30§	80 (65%)	40 (31%)	34% (22 to 45; p<0·0001)
Change from baseline to week 30 in KCCQ-CSS§	13·6 (14·4), n=92	4·2 (13·7), n=88	9·1 (5·5 to 12·7; p<0·0001)
Change from baseline to week 30 in HCMSQ-SoB§	−2·8 (2·7), n=85	−0·9 (2·4), n=86	−1·8 (−2·4 to −1·2; p<0·0001)

Data are n (%) or mean (SD). HCMSQ-SoB=Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore. KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score. LVOT=left ventricular outflow tract. pVO_2=peak oxygen consumption. NYHA=New York Heart Association. *Model estimated least-square mean differences were reported for continuous variables. †Patients with a non-evaluable primary endpoint and NYHA secondary endpoint were considered as non-responders. The response rates were calculated with the N value as the denominator. ‡N was the number analysable for secondary endpoints based on availability of both baseline and week 30 values. §Due to the smaller numbers evaluable for patient-reported outcome endpoints, additional post-hoc analyses compared the reasons for missing data.

Table 2: **Primary and secondary endpoints**

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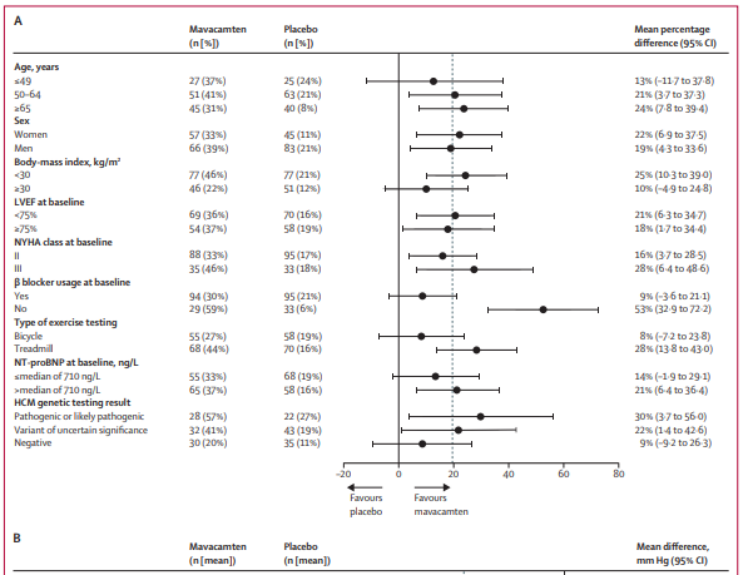
	Mavacamten group	Placebo group	Difference (95% CI)
Complete response*	32/117 (27%)	1/126 (1%)	26·6 (18·3–34·8)
Post-exercise LVOT peak gradient <50 mm Hg†	75/101 (74%)	22/106 (21%)	53·5 (42·0–65·0)
Post-exercise LVOT peak gradient <30 mm Hg‡	64/113 (57%)	8/114 (7%)	49·6 (39·3–59·9)

Data are n/N (%), unless otherwise indicated. LVOT=left ventricular outflow tract. *Defined as New York Heart Association class I and all LVOT peak gradients less than 30 mm Hg (post exercise, resting, and Valsalva). †Threshold for guideline-based invasive intervention. Only patients with baseline post-exercise LVOT peak gradient of at least 50 mm Hg were assessed. ‡Threshold for guideline-based diagnosis of obstruction. Only patients with baseline post-exercise LVOT peak gradient of at least 30 mm Hg were assessed.

Table 3: **Key exploratory efficacy endpoints**



	Mavacamten group (n=123)	Placebo group (n=128)
Patients with ≥1 treatment-emergent adverse event	108 (88%)	101 (79%)
Total number of serious adverse events	11	20
Patients with ≥1 serious adverse event	10 (8%)	11 (9%)
Atrial fibrillation	2 (2%)	4 (3%)
Syncope	2 (2%)	1 (1%)
Stress cardiomyopathy	2 (2%)	0
Sudden death	0	1 (1%)
Transient ischaemic attack	0	1 (1%)
Cardiac failure congestive	0	1 (1%)
Diverticulitis	1 (1%)	0
Viral gastroenteritis	0	1 (1%)
Urinary tract infection	0	2 (2%)
Infection	1 (1%)	0
Rheumatoid arthritis	0	1 (1%)
Contusion	1 (1%)	0
Forearm fracture	1 (1%)	0
Dehydration	0	1 (1%)
Vocal cord polyp	0	1 (1%)
Cholesteatoma	0	1 (1%)
Prostate cancer	0	1 (1%)

Data are n (%).

Table 4: Summary of treatment-emergent adverse events and serious adverse events

TABLE 1 Characteristics of Patients Enrolled in the Trial (N = 112)

	Mavacamten (n = 56)	Placebo (n = 56)
Age, y	59.8 ± 14.2	60.9 ± 10.5
Sex		
Male	29 (51.8)	28 (50.0)
Female	27 (48.2)	28 (50.0)
Race[a]		
White	48 (85.7)	52 (92.9)
Black	3 (5.4)	0 (0.0)
Asian	2 (3.6)	0 (0.0)
Unspecified or other	3 (5.4)	4 (7.1)
Vital signs		
Body mass index,[b] kg/m^2	29.3 ± 4.8	31.9 ± 6.2
Systolic blood pressure, mm Hg	130.4 ± 16.5	131.2 ± 16.6
Diastolic blood pressure, mm Hg	74.0 ± 10.5	74.2 ± 8.9
Duration of obstructive hypertrophic cardiomyopathy disease, y	7.5 ± 9.4	6.7 ± 7.4
Medical history		
Family history of hypertrophic cardiomyopathy	17 (30.4)	15 (26.8)
Atrial fibrillation	11 (19.6)	8 (14.3)
Hypertension	36 (64.3)	34 (60.7)
Syncope or presyncope	29 (51.8)	30 (53.6)
Internal cardioverter defibrillator	9 (16.1)	10 (17.9)
New York Heart Association functional class		
Class II with exertional syncope	4 (7.1)	4 (7.1)
Class III or higher	52 (92.9)	52 (92.9)
Type of septal reduction therapy recommended		
Alcohol septal ablation	8 (14.3)	7 (12.5)
Myectomy	48 (85.7)	49 (87.5)
Background hypertrophic cardiomyopathy therapy		
Beta-blocker monotherapy	26 (46.4)	25 (44.6)
Nondihydropyridine calcium-channel blocker monotherapy	7 (12.5)	10 (17.9)
Disopyramide monotherapy	0 (0.0)	2 (3.6)
Beta-blocker and calcium-channel blocker	6 (10.7)	10 (17.9)
Beta-blocker and disopyramide	11 (19.6)	3 (5.4)
Calcium-channel blocker and disopyramide	1 (1.8)	2 (3.6)
Beta-blocker, calcium-channel blocker, and disopyramide	2 (3.6)	1 (1.8)
None, medication intolerance	3 (5.4)	3 (5.4)
Echocardiographic parameters		
LVOT gradient, mm Hg		
Resting	51.2 ± 31.4	46.3 ± 30.5
Valsalva	75.3 ± 30.8	76.2 ± 29.9
Post-exercise	82.5 ± 34.7	85.2 ± 37.0
LV ejection fraction, %	67.9 ± 3.7	68.3 ± 3.2
Left atrial volume index, mL/m^2	41.3 ± 16.5	40.9 ± 15.2
KCCQ-23 CSS,[c] points	69.5 ± 16.3	65.6 ± 19.9
Laboratory measurements		
NT-proBNP, ng/L	724 (291-1913)	743 (275-1,196)
Cardiac troponin I, ng/L	17.3 (7.0-31.6)	12.9 (6.1-26.0)
Cardiac troponin T, µg/L	0.014 (0.01-0.02)	0.011 (0.008-0.02)

TABLE 2 Primary and Secondary Efficacy Endpoints at Week 16

	Mavacamten (n = 56)	Placebo (n = 56)	Treatment Difference (95% CI)[a]	*P* Value
Primary efficacy composite endpoint[b]	10 (17.9)	43 (76.8)	58.9 (44.0 to 73.9)	<0.001
Patient decision to proceed with SRT	2 (3.6)	2 (3.6)		
SRT-eligible based on guideline criteria[c]	8 (14.3)	39 (69.6)		
SRT status not evaluable, imputed as meeting criteria[d]	0 (0.0)	2 (3.6)		
Secondary efficacy endpoints listed in hierarchical testing order				
Change from baseline in post-exercise LVOT gradient, mm Hg	−39.1 ± 36.5	−1.8 ± 28.8	−37.2 (−48.1 to −26.2)	<0.001
At least 1 class of NYHA improvement	35 (62.5)	12 (21.4)	41.1 (24.5 to 57.7)	<0.001
Change from baseline in KCCQ-23 CSS, points	10.4 (16.1)	1.9 (12.0)	9.4 (4.9 to 14.0)	<0.001
Change from baseline in NT-proBNP, ng/L	−399 (−1,146 to −138)	40 (−155 to 203)	0.33 (0.26 to 0.42)[e]	<0.001
Change from baseline in cardiac troponin I, ng/L	−9.2 (−18.1 to −1.8)	0.07 (−2.0 to 3.3)	0.53 (0.41 to 0.70)[e]	<0.001
Exploratory endpoints				
Change from baseline in hemodynamic parameters				
LVOT gradient at rest	−36.0 ± 28.8	−1.5 ± 26.5	−33.4 (42.3 to −24.5)	
LVOT gradient induced by Valsalva	−45.2 ± 28.5	0.4 ± 29.7	−47.6 (−58.2 to −37.0)	
LV ejection fraction	−3.4 ± 6.2	0.3 ± 4.2	−4.0 (−5.5 to −2.5)	
LV filling pressures, E/e'	−3.5 ± 5.6	0.7 ± 3.8	−3.3 (−4.9 to −1.8)	
LV stroke volume index	−1.4 ± 6.6	0.14 ± 5.7	−1.9 (−4.3 to 0.5)	
Left atrial volume index	−5.2 ± 7.8	−0.5 ± 8.1	−4.4 (−7.1 to −1.7)	
LV end-systolic volume index	1.4 ± 3.7	0.1 ± 3.3	1.1 (−0.3 to 2.6)	
LV end-diastolic volume index	0.01 ± 8.3	0.19 ± 8.3	−0.7 (−4.0 to 2.6)	
LV mass index	−7.9 ± 17.7	−1.9 ± 16.6	−6.5 (−13.2 to 0.11)	

Values are n (%), mean ± SD, or median (IQR). [a]Treatment difference and 95% CI were generated in analysis of covariance model including baseline variable as a covariate and baseline stratification factors for type of SRT recommended (alcohol septal ablation or myectomy) and NYHA functional class (class II or class III/IV). [b]Cochran-Mantel-Haenszel (CMH) method stratified by baseline NYHA criteria (II vs higher) and type of SRT recommended (myectomy vs alcohol septal ablation). Difference in proportions estimated as placebo rate minus mavacamten rate, where a positive value indicates a beneficial treatment effect. [c]The guideline criteria are based of the 2011 ACCF/AHA HCM clinical and hemodynamic criteria. Patients with maximum LVOT ≥50 mm Hg gradient (from rest, Valsalva, or post-exercise) and no improvement in NYHA functional class at week 16 are considered eligible for SRT. [d]If assumed that both patients in the placebo group did not meet the primary endpoint, the result shows treatment difference of similar magnitude to the primary analysis with same level of significance. Treatment difference 55.36 (95% CI: 40.02-70.69); $P < 0.0001$. [e]Geometric mean ratios <1.0 represent an x-fold decrease for mavacamten compared with placebo.

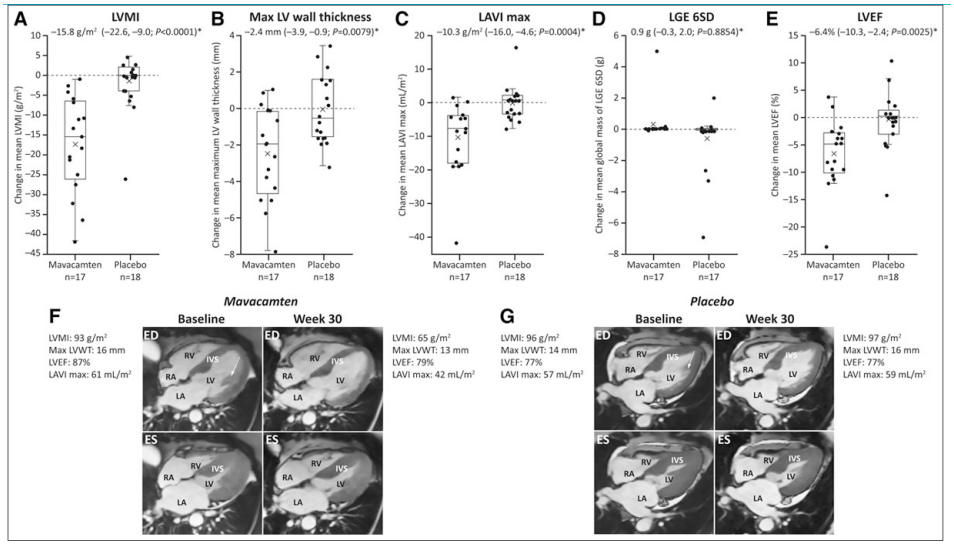
SRT = septal reduction therapy; other abbreviations as in Table 1.

TABLE 3 Safety Endpoints and Adverse Events

	Mavacamten (n = 56)	Placebo (n = 55)
Safety endpoints		
LV ejection fraction <50%	2 (3.6)	0 (0.0)
Permanent discontinuation for LV ejection fraction <30%	0 (0.0)	0 (0.0)
Death, myocardial infarction or stroke	0 (0.0)	0 (0.0)
On-treatment adverse events		
Total number of on-treatment adverse events	123	93
Total number of subjects with at least one on-treatment adverse event	41 (73.2)	34 (61.8)
Serious on-treatment adverse events		
Number of serious on-treatment adverse events[a]	4	1
Number of subjects with serious adverse events	3 (5.4)	1 (1.8)
Atrial fibrillation	2 (3.6)	0 (0.0)
Coronavirus disease-2019	1 (1.8)	0 (0.0)
Alcohol poisoning	0 (0.0)	1 (1.8)
Nonserious on-treatment adverse events		
Number of nonserious on-treatment adverse events	119	92
Cardiovascular, number of subjects		
Chest pain	2 (3.6)	3 (5.5)
Palpitations	2 (3.6)	2 (3.6)
Presyncope	1 (1.8)	0 (0.0)
Syncope	1 (1.8)	0 (0.0)
Atrial fibrillation	2 (3.6)	0 (0.0)
Nonsustained ventricular tachycardia	0 (0.0)	5 (9.1)
Bradycardia	2 (3.6)	0 (0.0)
Atrioventricular block second degree	1 (1.8)	0 (0.0)
Other adverse events of interest		
Fatigue	5 (8.9)	2 (3.6)
Headache	2 (3.6)	5 (9.1)
Dyspnea	4 (7.1)	3 (5.5)
Dizziness	4 (7.1)	3 (5.5)
Nausea	4 (7.1)	1 (1.8)
Rash	4 (7.1)	0 (0.0)
Coronavirus disease-2019	1 (1.8)	2 (3.6)

Values are n (%) or n. [a]Serious adverse events in 4 patients also involved hospitalization.

LV = left ventricular.



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