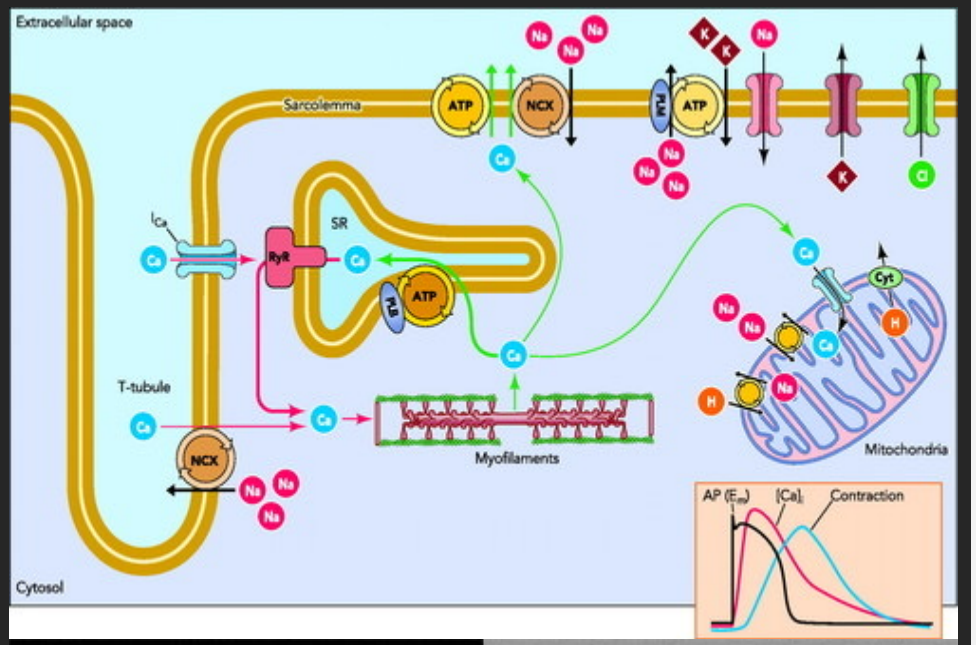
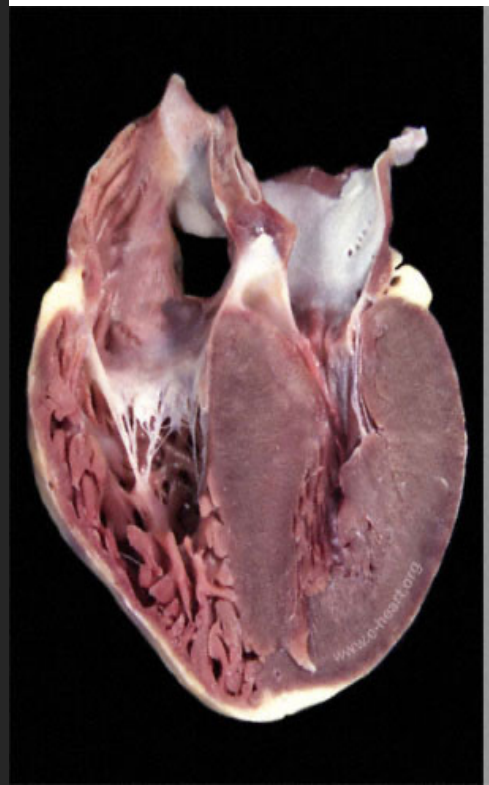
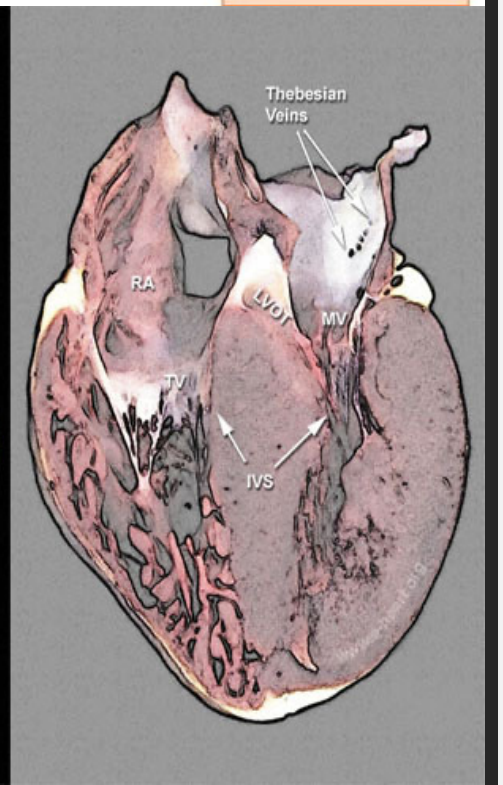






Hypertrophic Cardiomyopathy (HCM)

Hiding in Plan Sight

Dr. Srikanth Seethala MD,MPH

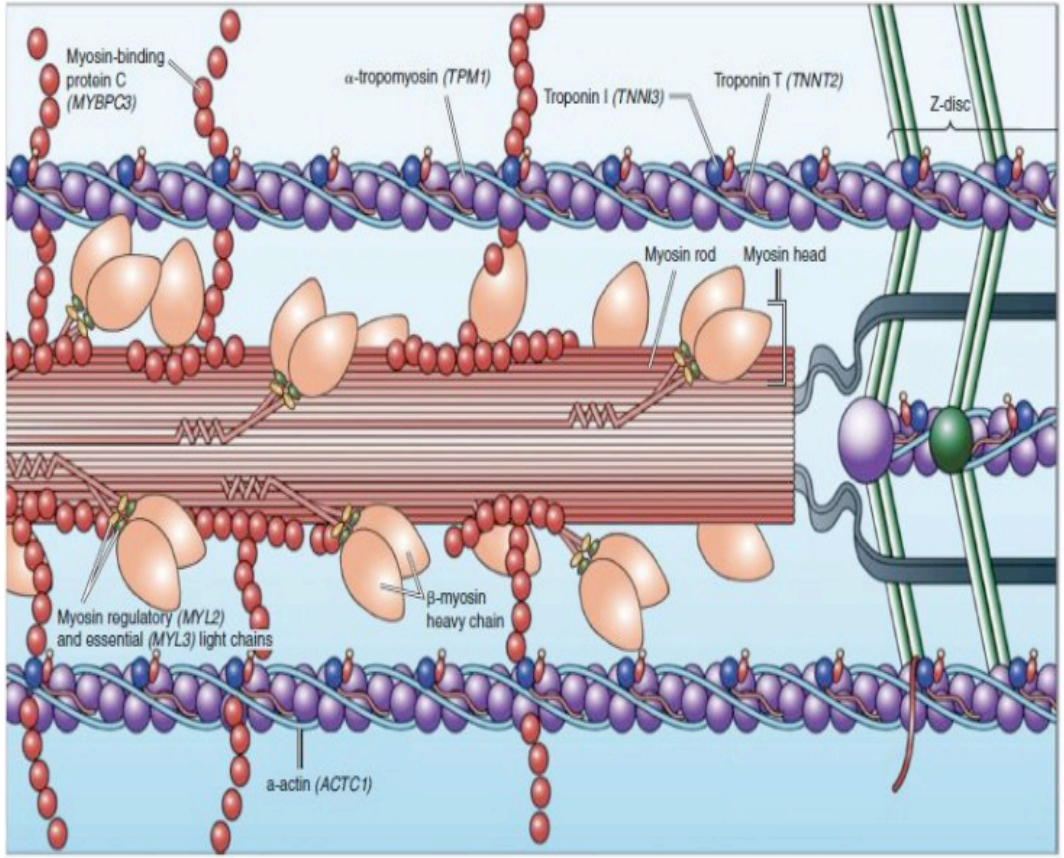
Norton Health Care

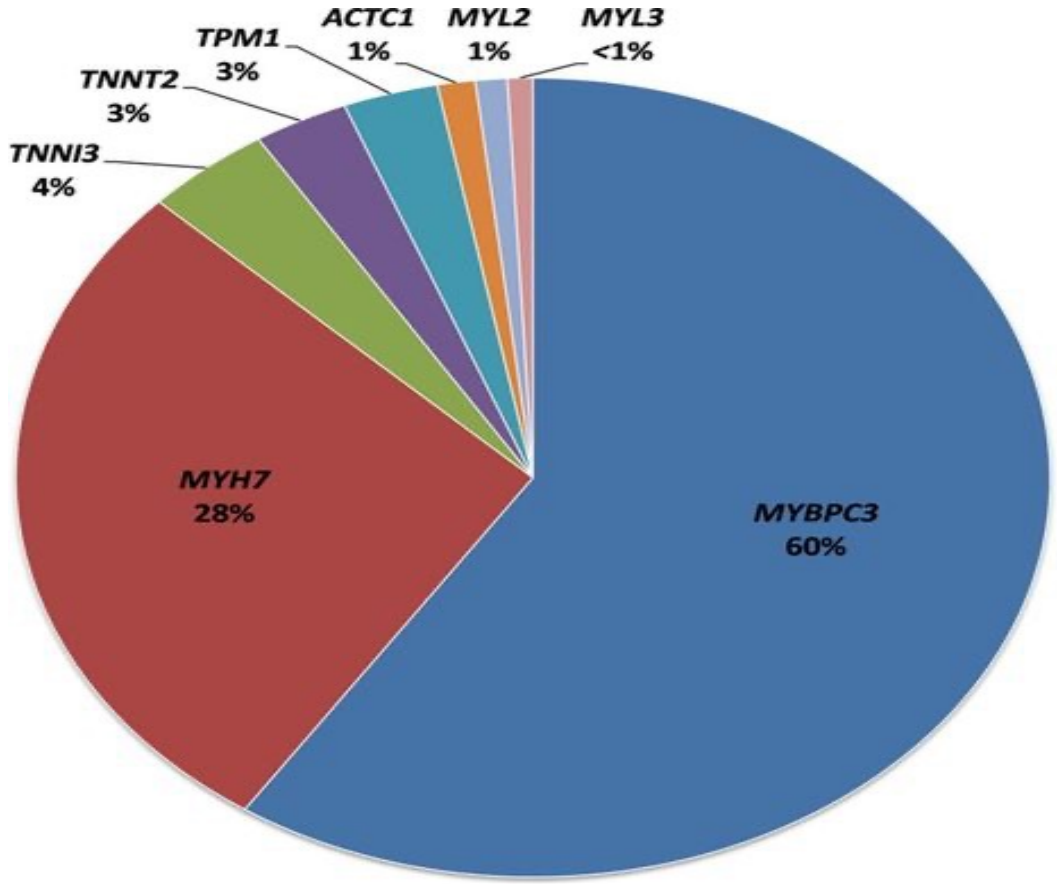
- Objectives:

A) Prevalence
B) Diagnostic criteria
C) Genes
D) Family screening
E) AICD Indication
F) Management

- Prevalence: 1 in 200-500- Asymptomatic unexplained hypertrophy
- Symptomatic: <1 in 3000
- True prevalence unknown
- Definition: maximal end-diastolic wall thickness of ≥15 mm anywhere in the left ventricle- Either by MRI or Echo
- 13-15 mm if positive genetic test or family members with HCM
- For children : a threshold of z >2.5 - asymptomatic, z >2.0 may suffice

Ommen, S. R., Mital, S., Burke, M. A., Day, S. M., Deswal, A., Elliott, P., Evanovich, L. L., Hung, J., Joglar, J. A., Kantor, P., Kimmelstiel, C., Kittleson, M., Link, M. S., Maron, M. S., Martinez, M. W., Miyake, C. Y., Schaff, H. V., Semsarian, C., & Sorajja, P. (2020). 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. *Circulation*, *142*(25). https://doi.org/10.1161/cir.0000000000000937





Prevalence and Clinical Implication of Double Mutations in Hypertrophic Cardiomyopathy

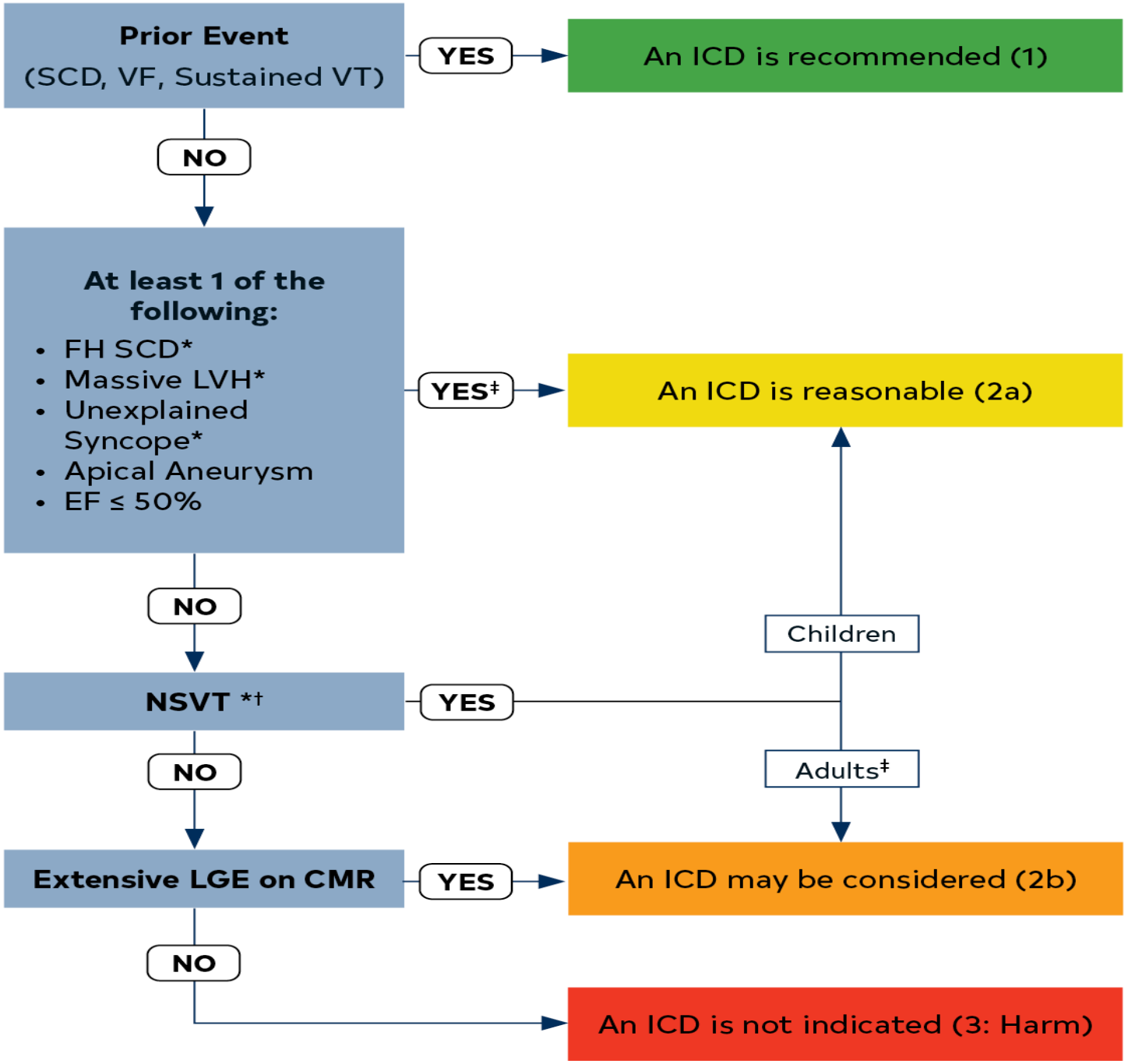
Dana Fourey, MD, Melanie Care, MSc, Katherine A. Siminovitch, MD, Adaya Weissler-Snir, MD, Waseem Hindieh, MD, Raymond H. Chan, MD, MPH, Michael H. Gollob, MD, Harry Rakowski, MD, and Arnon Adler, MD

- Genetics:
- beta myosin heavy chain 7 (*MYH7*)
- myosin-binding protein C3 *(MYBPC3*)
- TNNI3
- TNNT2

Screening Asymptomatic First-Degree Relatives of Patients with HCM

Screening Asymptomatic First-Degree Relatives of Patients With HCM		
Age of First-Degree Relative	**Initiation of Screening**	**Surveillance Interval**
Children and adolescents from genotype-positive family and/or family with early onset HCM	At the time of diagnosis in another family member	Every 1-2 y
All other children and adolescents	At any time after the diagnosis in the family, but no later than puberty	Every 2-3 y
Adults	At the time of diagnosis in another family member	Every 3-5 y

Sudden Cardiac Death Prevention/ICD indications


Prior Event
(SCD, VF, Sustained VT)
YES
An ICD is recommended (1)
NO
At least 1 of the following:
FH SCD*
Massive LVH*
Unexplained Syncope*
Apical Aneurysm
EF ≤ 50%
YES‡
An ICD is reasonable (2a)
NO
Children
NSVT *†
YES
NO
Adults‡
Extensive LGE on CMR
YES
An ICD may be considered (2b)
NO
An ICD is not indicated (3: Harm)

Management of Symptomatic Patients with Obstructive Hypertrophic Cardiomyopathy

Pharmacologic Management of Patients With Obstructive HCM

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	Verapamil B-NR	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta-blockers are ineffective or not tolerated, substitution with non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) is recommended.
	Diltiazem C-LD	

*Symptoms include effort-related dyspnea or chest pain; and occasionally other exertional symptoms (e.g., syncope, near syncope) that are attributed to LVOTO and interfere with everyday activity or quality of life.

Pharmacologic Management of Patients With Obstructive HCM

COR	LOE	Recommendations
1	B-NR	3. For patients with obstructive HCM who have persistent severe symptoms* attributable to LVOTO despite beta-blockers or non-dihydropyridine calcium channel blockers, either adding disopyramide in combination with 1 of the other drugs, or SRT performed at experienced centers,† is recommended.
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.

*Symptoms include effort-related dyspnea or chest pain; and occasionally other exertional symptoms (e.g., syncope, near syncope) that are attributed to LVOTO and interfere with everyday activity or quality of life.

Pharmacologic Management of Patients With Obstructive HCM

COR	LOE	Recommendations
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 guideline-directed management and therapy (GDMT), cautious use of low-dose oral diuretics may be considered.
2b	C-EO	6. For patients with obstructive HCM, discontinuation of vasodilators (e.g., angiotensin- converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers) or digoxin may be reasonable because these agents can worsen symptoms caused by dynamic outflow tract obstruction.
3: Harm	C-LD	7. For patients with obstructive HCM and severe dyspnea at rest, hypotension, very high resting gradients (e.g., >100 mm Hg), as well as all children <6 weeks of age, verapamil is potentially harmful.

Invasive Treatment of Symptomatic Patients with Obstructive HCM

COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM who remain severely symptomatic despite GDMT, SRT in eligible patients,* performed at experienced centers,† is recommended for relieving LVOTO.
1	B-NR	2. In symptomatic patients with obstructive HCM who have associated cardiac disease requiring surgical treatment (e.g., associated anomalous papillary muscle, markedly elongated anterior mitral leaflet, intrinsic mitral valve disease, multivessel CAD, valvular aortic stenosis), surgical myectomy, performed at experienced centers,† is recommended.

Invasive Treatment of Symptomatic Patients with Obstructive HCM

***General eligibility criteria for septal reduction therapy:**

a) **Clinical: Severe dyspnea or chest pain (usually NYHA functional class III or class IV), or occasionally other exertional symptoms (e.g., syncope, near syncope), when attributable to LVOTO, that interferes with everyday activity or quality of life despite optimal medical therapy.**

b) **Hemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation with approximate peak gradient of ≥50 mm Hg, associated with septal hypertrophy and SAM of mitral valve.**

c) **Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.**

†Comprehensive or primary HCM centers with demonstrated excellence in clinical outcomes for these procedures

Invasive Treatment of Symptomatic Patients with Obstructive HCM

COR	LOE	Recommendations
1	C-LD	3. In adult patients with obstructive HCM who remain severely symptomatic, despite GDMT and in whom surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation in eligible patients,* performed at experienced centers,† is recommended.

Invasive Treatment of Symptomatic Patients with Obstructive HCM

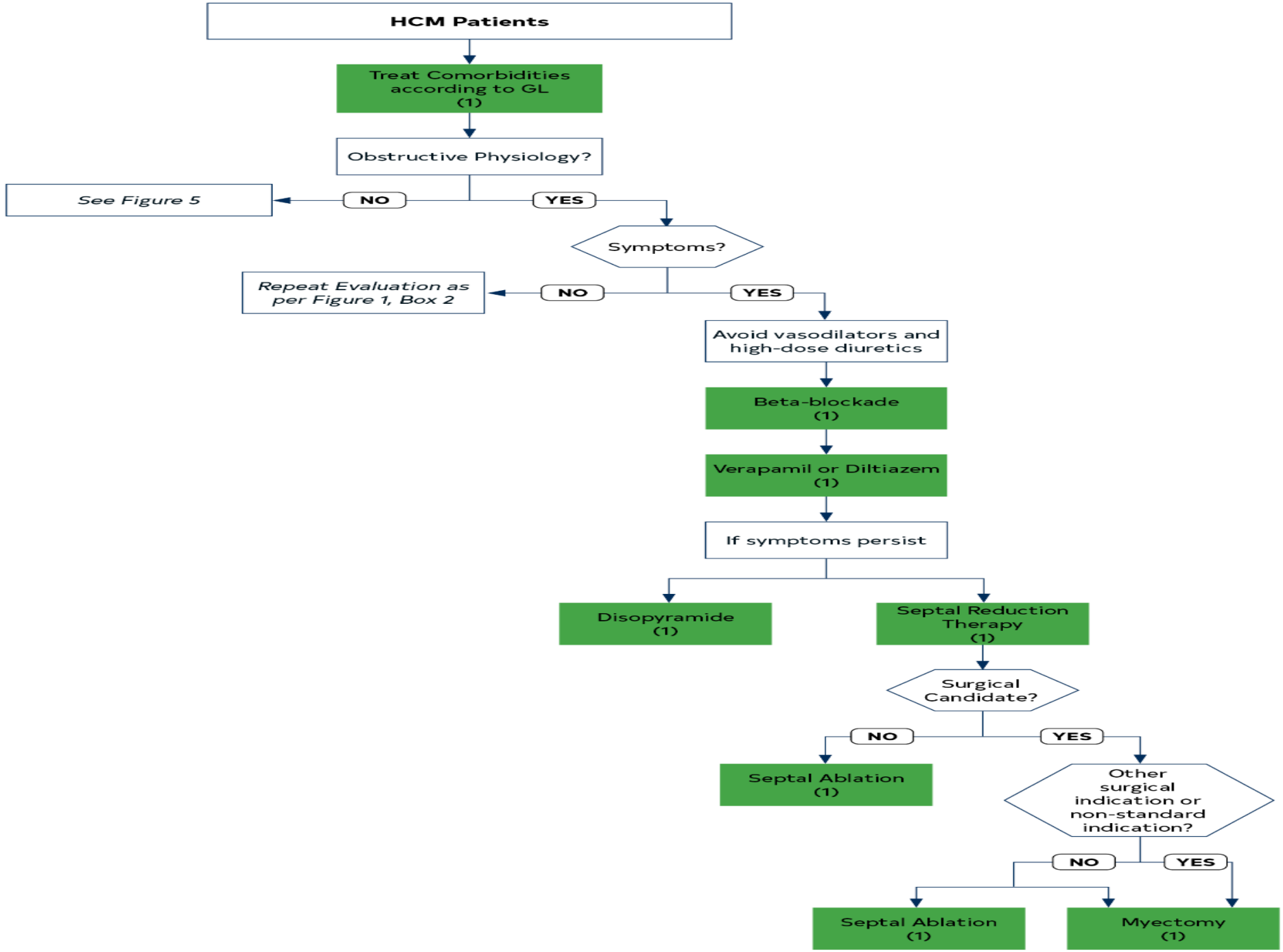
COR	LOE	Recommendations
2b	B-NR	4. In patients with obstructive HCM, earlier (NYHA class II) surgical myectomy performed at comprehensive HCM centers may be reasonable in the presence of additional clinical factors, including: a) Severe and progressive pulmonary hypertension thought to be attributable to LVOTO or associated MR. b) Left atrial enlargement with ≥1 episodes of symptomatic AF. c) Poor functional capacity attributable to LVOTO as documented on treadmill exercise testing. d) Children and young adults with very high resting LVOT gradients (>100 mm Hg).

Invasive Treatment of Symptomatic Patients with Obstructive HCM

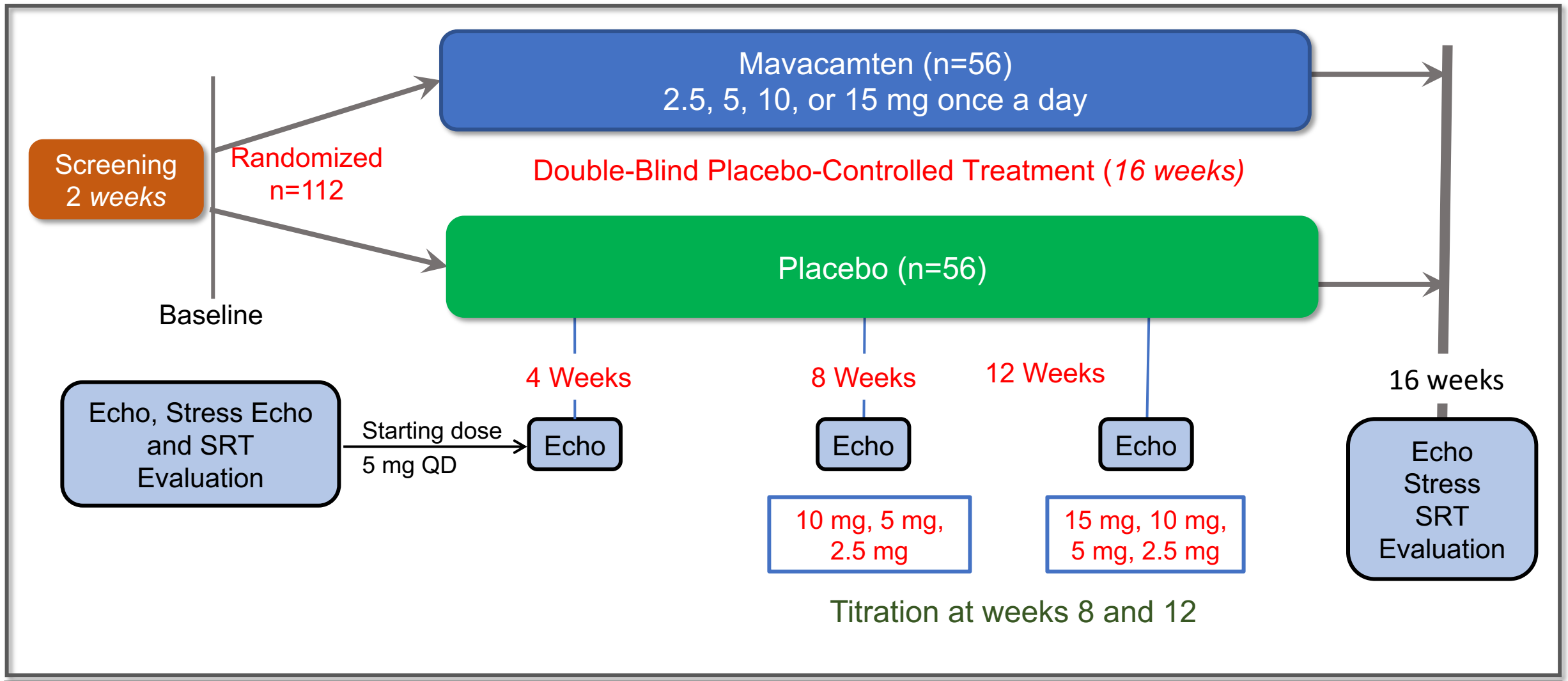
COR	LOE	Recommendations
2b	B-NR	5. For severely symptomatic patients with obstructive HCM, SRT in eligible patients,* performed at experienced centers† may be considered as an alternative to escalation of medical therapy after shared decision-making including risks and benefits of all treatment options.

Invasive Treatment of Symptomatic Patients with Obstructive HCM

COR	LOE	Recommendations
3: Harm	C-LD	6. For patients with HCM who are asymptomatic and have normal exercise capacity, SRT is not recommended.
3: Harm	B-NR	7. For symptomatic patients with obstructive HCM in whom SRT is an option, mitral valve replacement should not be performed for the sole purpose of relief of LVOTO.


HCM Patients
Treat Comorbidities according to GL (1)
Obstructive Physiology?
See Figure 5
NO
YES
Symptoms?
Repeat Evaluation as per Figure 1, Box 2
NO
YES
Avoid vasodilators and high-dose diuretics
Beta-blockade (1)
Verapamil or Diltiazem (1)
If symptoms persist
Disopyramide (1)
Septal Reduction Therapy (1)
Surgical Candidate?
NO
YES
Septal Ablation (1)
Other surgical indication or non-standard indication?
NO
YES
Septal Ablation (1)
Myectomy (1)

VALOR-HCM Study Design (19 US HCM Centers)



Mavacamten titrated using core-lab measured ECHO LVEF and LVOT gradient at rest and Valsalva provocation

Desai M et al. Am Heart J 2021 Sep;239:80-89

Key inclusion criteria

- Age ≥18 years
- Documented HCM with maximum septal wall thickness ≥15 mm or ≥13 mm with family history of HCM (determined by a core echo laboratory)
- Severe symptoms despite maximally-tolerated medical therapy
  - NYHA functional Class III/IV or Class II with exertional syncope or near syncope
  - Maximal medical HCM therapy could include disopyramide and/or combination beta blockers and calcium channel blockers
- Dynamic LVOT gradient at rest or with provocation (Valsalva maneuver or exercise) ≥50 mmHg
- Documented LV ejection fraction ≥60%
- Must have been referred within the past 12 months for SRT and actively considering scheduling the procedure
  - Patients could elect to proceed to SRT at any time following randomization

Desai M et al. 2021 Sep;239:80-89

Primary and Secondary Endpoints

- Primary endpoint: Composite of patient decision to proceed with SRT or continue to meet 2011 ACC/AHA guideline eligibility for SRT after 16 weeks.

- Five secondary endpoints tested in a hierarchical fashion, comparing Week 16 to baseline:

    1) Change in post-exercise LVOT gradient

    2) Number of patients with a ≥1 class of NYHA improvement

    3) Change in KCCQ clinical summary score

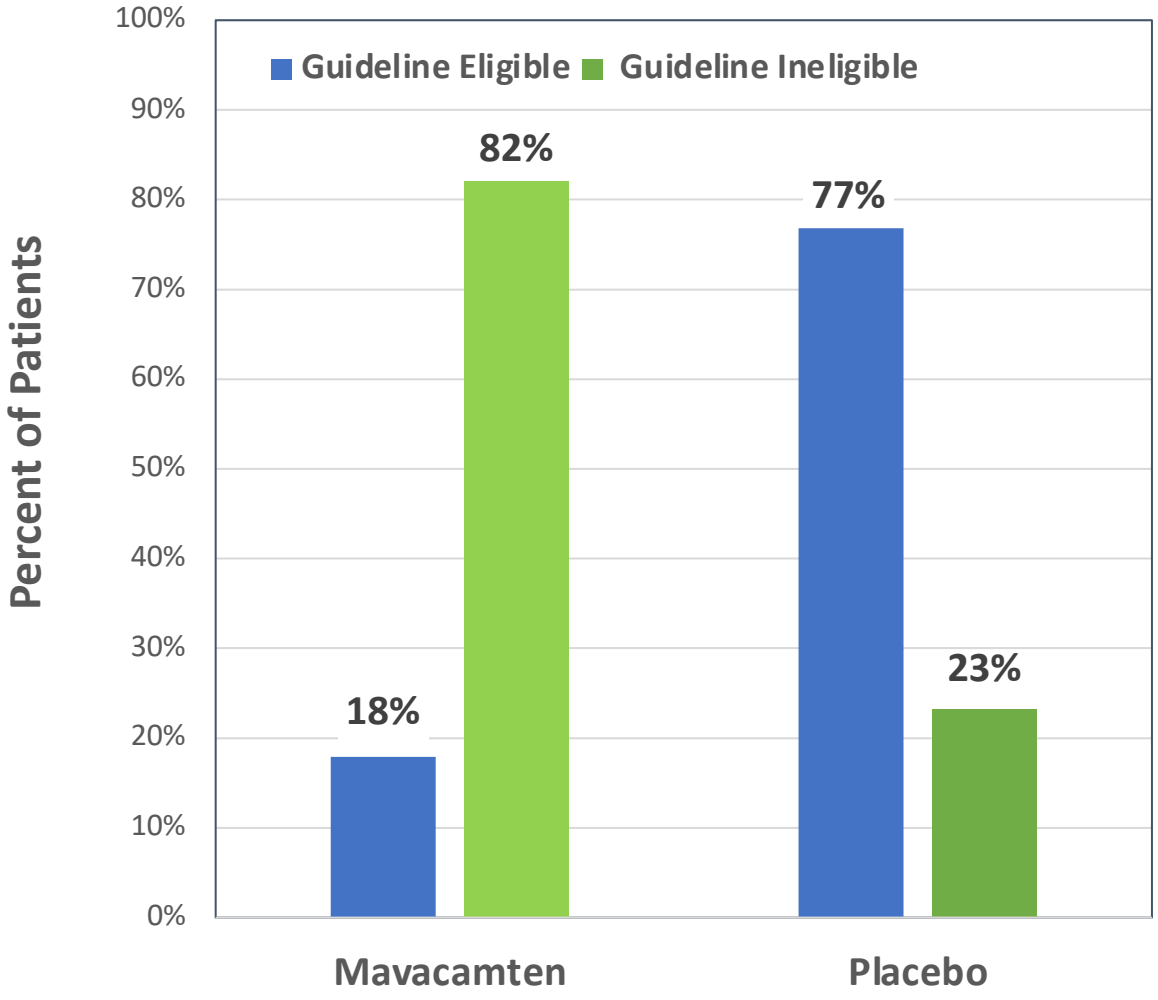
    4) Change in NT-proBNP

    5) Change in Troponin I

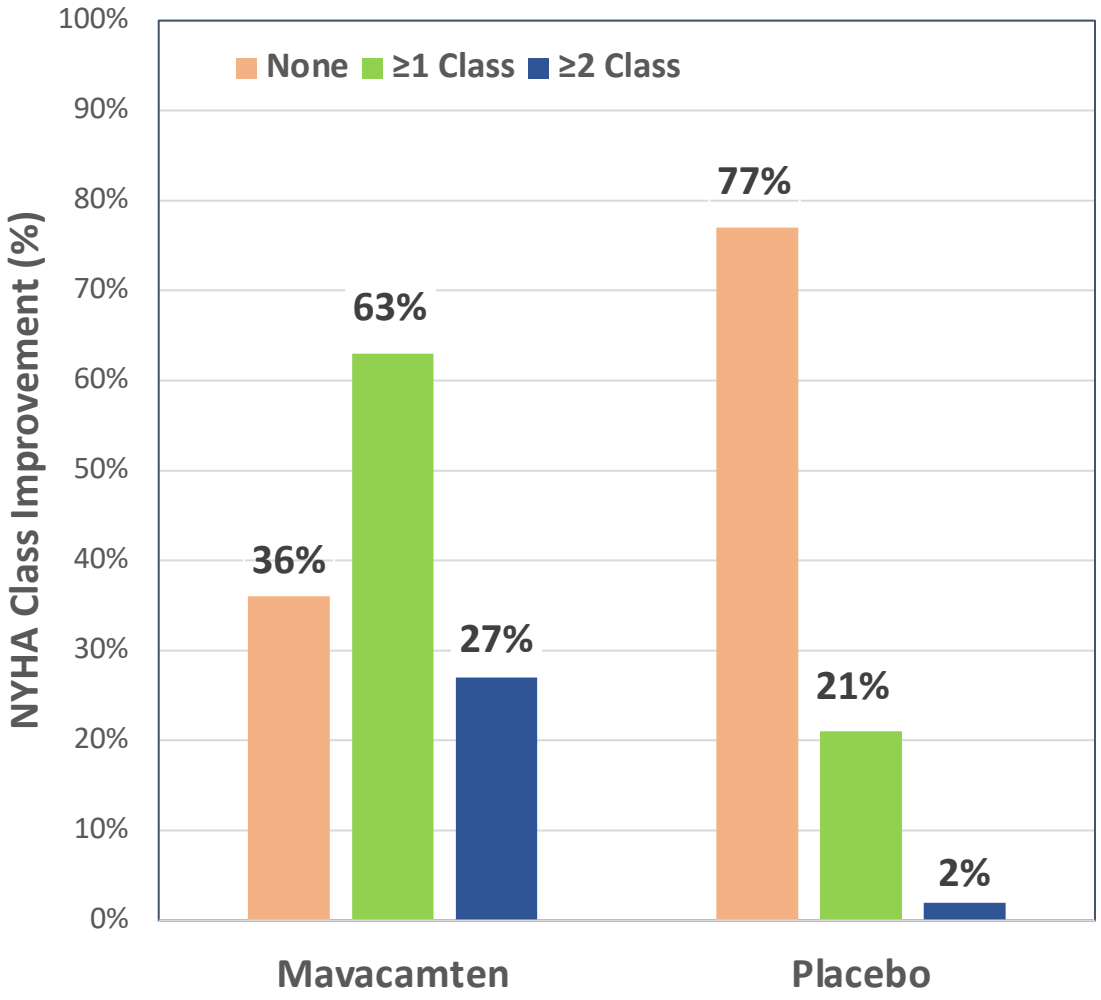
Gersh et al. HCM Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60

Primary Endpoint and NYHA Class Improvement

Patients who Underwent SRT or Remained Guideline Eligible for SRT

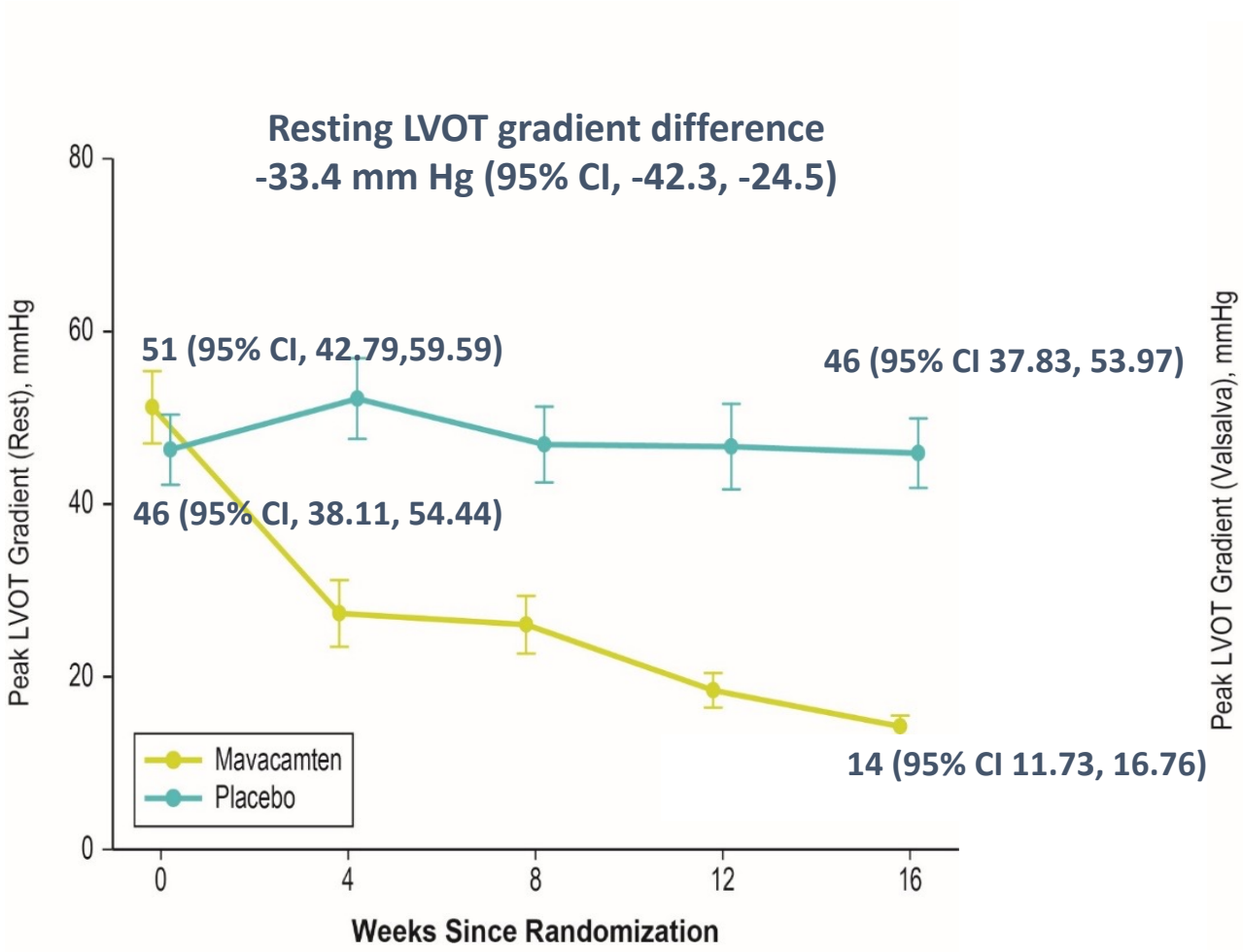


Patients Who Improved by 0, ≥1, or ≥2 NYHA Class

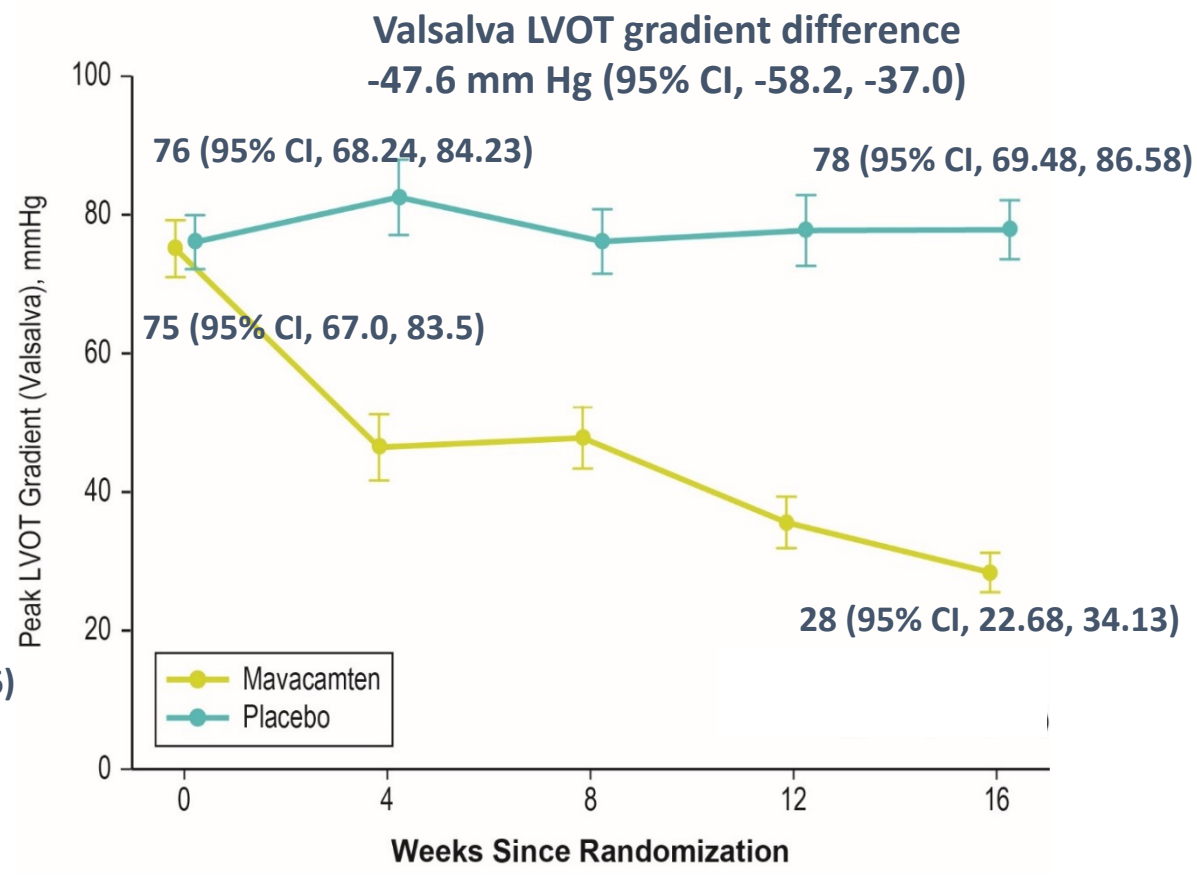


Secondary Efficacy Endpoints: Change in LVOT Gradient at Rest and Valsalva

Resting LVOT gradient (mm Hg)



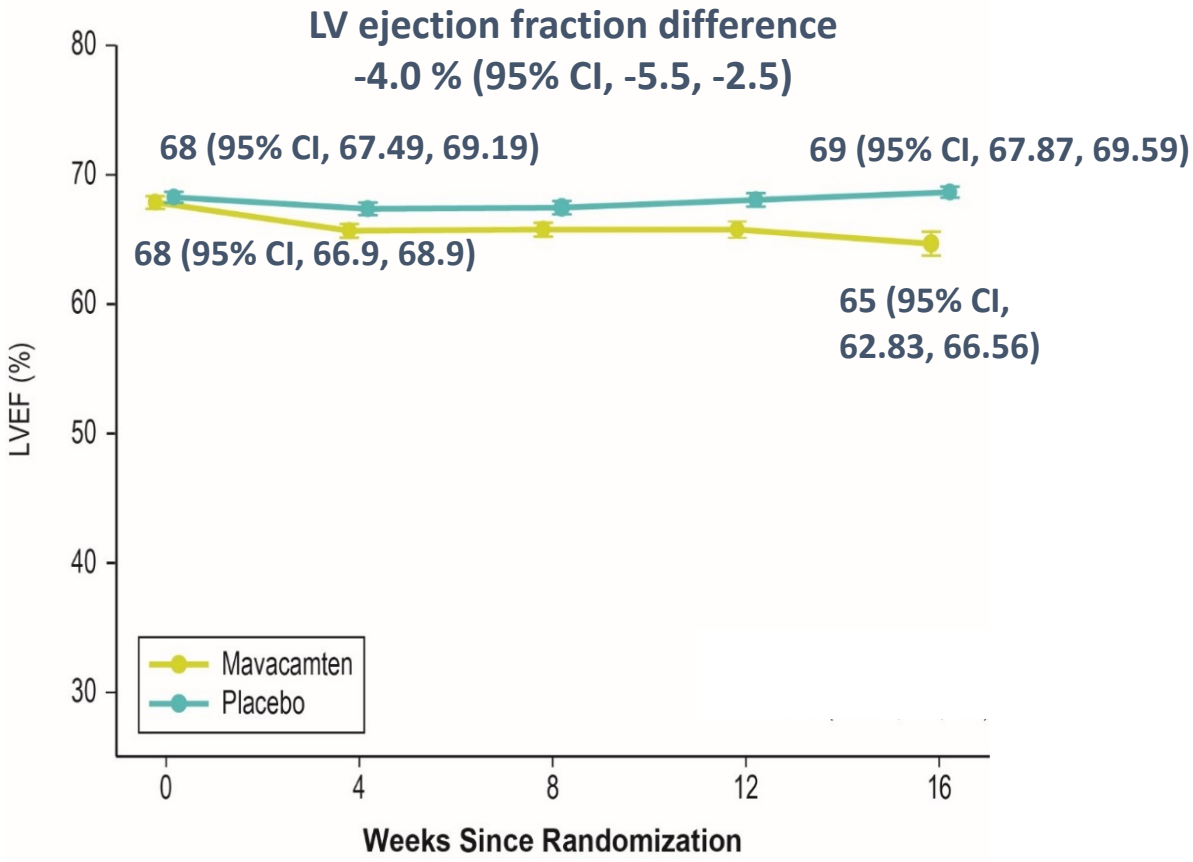
Valsalva LVOT gradient (mm Hg)



All p < 0.001

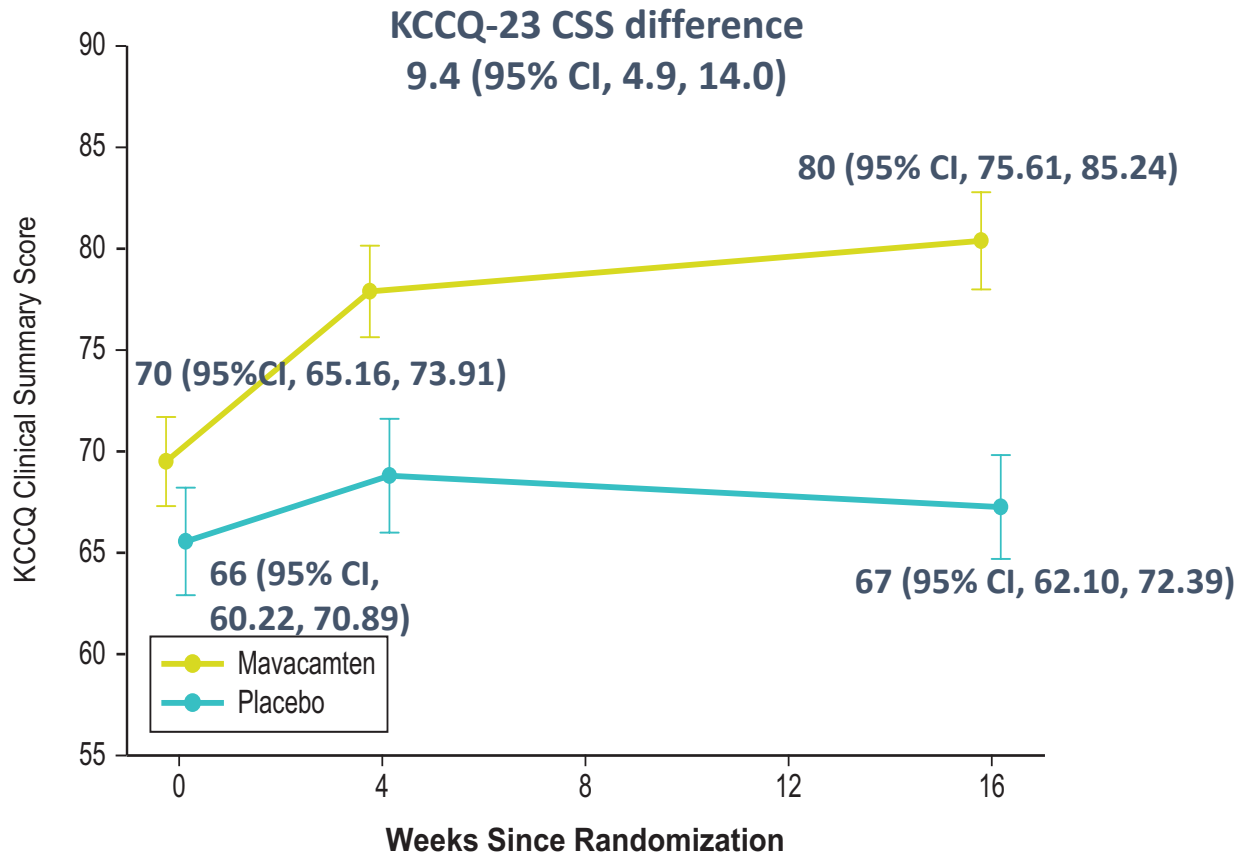
Safety and Secondary Efficacy Endpoints: LV Ejection Fraction and KCCQ Change Over Time

LV Ejection Fraction (%)



p = ns

KCCQ-23 Clinical Summary Score



p < 0.001

Selected Adverse Events in Safety Population

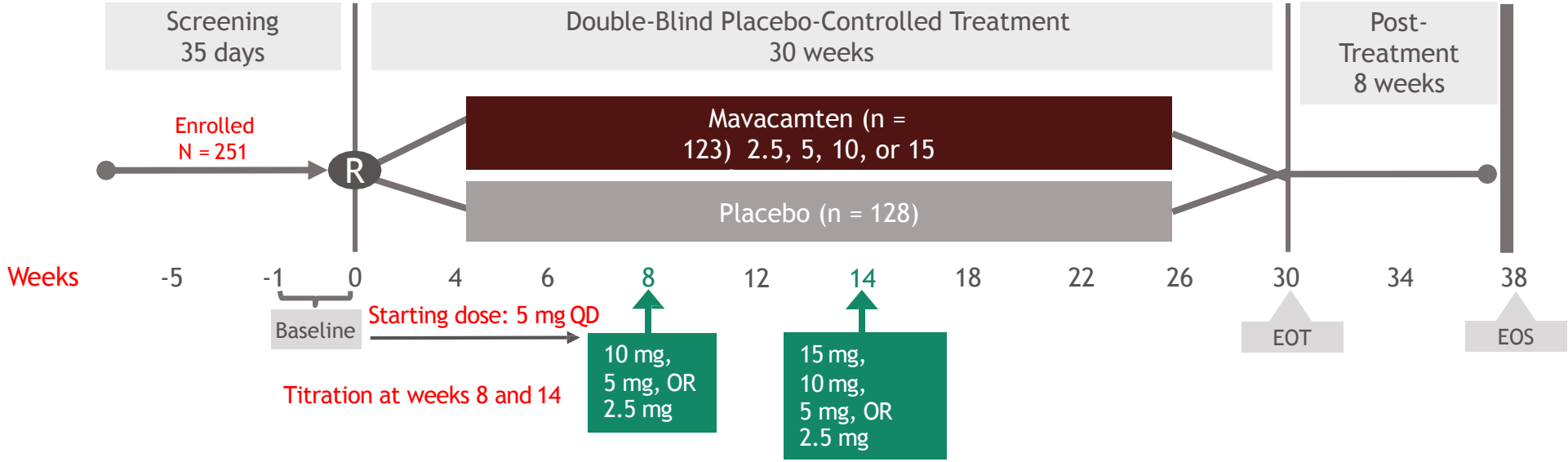
	Mavacamten (n=56)	Placebo (n=55)
Ejection Fraction <50%	2 (3.6%)	0 (0%)
Atrial Fibrillation	4 (7.1%)	0 (0%)
Nonsustained VT	0 (0%)	5 (9.1%)
Chest Pain	2 (3.6%)	3 (5.5%)
Fatigue	5 (8.9%)	2 (3.6%)
Nausea	4 (7.1%)	1 (1.8%)
Headache	2 (3.6%)	5 (9.1%)
Rash	4 (7.1%)	0 (0%)

No permanent treatment discontinuations due to LVEF ≤30%

No subjects experienced SAEs of CHF, Syncope, or Sudden Cardiac Death

EXPLORER-HCM: study design

Patients with symptomatic NYHA class II and III obstructive HCM, LVEF ≥55% and Valsalva LVOT peak gradient ≥50 mmHg at rest or with provocation, were randomized 1:1 to receive once-daily oral CAMZYOS™ (mavacamten) (n = 123) or placebo (n = 128) for 30 weeks.



Temporary treatment discontinuation criteria: LVEF <50%, plasma drug concentration >1000 ng/mL, excessive QTcF prolongation

Olivotto, I., Oreziak, A., Barriales-Villa, R., et al Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (explorer-HCM): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, *396*(10253), 759-769. https://doi.org/10.1016/s0140-6736(20)31792-x

EXPLORER-HCM: endpoints

Primary composite functional endpoint

Change from baseline to Week 30	pVO_2 improvement		NYHA classification
Composite 1	≥1.5 mL/kg/min	*and*	Improvement by ≥1 class
OR			
Composite 2	≥3.0 mL/kg/min	*and*	No worsening
Primary endpoint can be achieved through either composite 1 or composite 2			

Secondary efficacy endpoints (from baseline to week 30)

- Change in post-exercise LVOT peak gradient
- Change in pVO_2
- Proportion of patients with ≥1 NYHA class improvement
- Change in KCCQ-23 CSS
- Change in HCMSQ-SoB domain score

EXPLORER-HCM: primary endpoint

A greater proportion of patients met the primary endpoint at Week 30 in the CAMZYOS™ (mavacamten) group compared to the placebo group (37% vs 17%, respectively; *P* = 0.0005).

Parameters	CAMZYOS n = 123	Placebo n = 128	Treatment difference (95% CI) *P value*
Total responders	45 (37%)	22 (17%)	19% (9, 30) *P* = 0.0005
ΔpVO_2 ≥1.5 mL/kg/min and decreased NYHA	41 (33%)	18 (14%)	19% (9, 30)
ΔpVO_2 ≥3 mL/kg/min and NYHA not increased	29 (23%)	14 (11%)	13% (3, 22)

9.

EXPLORER-HCM secondary endpoints

Patients receiving Mavacamten had greater improvement compared to placebo group across all secondary endpoints from baseline to Week 30.

Parameter	CAMZYOS n = 123	Placebo n = 128	Treatment difference (95% CI) *P* value
Postexercise LVOT gradient (mmHg), mean (SD)	−47 (40)	−10 (30)	−35 (−43, −28) *P* <0.0001
pVO_2 (mL/kg/min), mean (SD)	1.4 (3.1)	−0.1 (3.0)	1.4 (0.6, 2.1) *P* <0.0006
Number (%) with NYHA class improved ≥1	80 (65%)	40 (31%)	34% (22%, 45%) *P* <0.0001
KCCQ-23 CSS (SD)	n = 99 14 (14)	n = 97 4 (14)	9 (5, 13) *P* <0.0001
HCMSQ-SoB (SD)	n = 108 −3 (3)	n = 109 −1 (2)	−2 (−2, −1) *P* <0.0001

Please see additional Important Safety Information for CAMZYOS, including **Boxed WARNING**, throughout this presentation, and US Full Prescribing Information for CAMZYOS provided.

CSS, clinical summary score; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness-of-Breath; KCCQ-23, 23-item Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; NYHA, New York Heart Association, pVO_2, mixed venous oxygen tension *or* peak oxygen consumption.

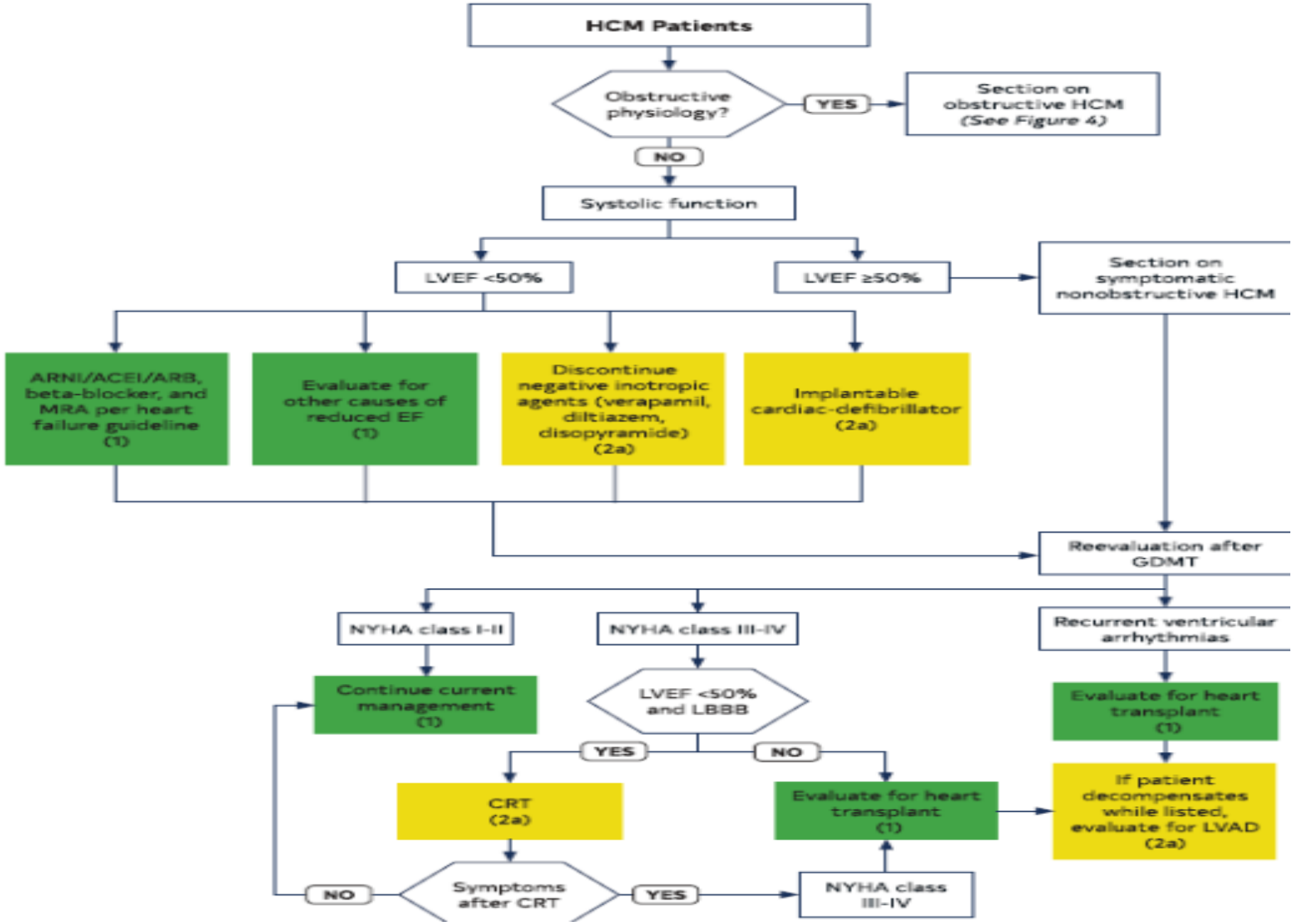
1. CAMZYOS. Prescribing information. Princeton, NJ: Bristol Myers Squibb Company; 2022. 2. Olivotto I et al. *Lancet*. 2020;396:759–769.

Norton Healthcare HF clinic Protocol

We are assessing treatment

- BNP
- Troponins
- We are trying adopt KCCQ questionnaire every other visit
- 6 Minute walk test
- Chest pain and SOB symptoms
- LVOT gradient and LVEF (which are part of REMS program)
- Education, exercise program, genetic testing, support groups
- We will see them in within 24-48 hrs if patient is having any symptoms.
- All new consults will be addressed in 3 business days

HCM with-out obstruction


HCM Patients
Obstructive physiology?
YES
Section on obstructive HCM (See Figure 4)
NO
Systolic function
LVEF <50%
LVEF ≥50%
Section on symptomatic nonobstructive HCM
ARNI/ACEI/ARB, beta-blocker, and MRA per heart failure guideline (1)
Evaluate for other causes of reduced EF (1)
Discontinue negative inotropic agents (verapamil, diltiazem, disopyramide) (2a)
Implantable cardiac-defibrillator (2a)
Reevaluation after GDMT
NYHA class I-II
NYHA class III-IV
Recurrent ventricular arrhythmias
Continue current management (1)
LVEF <50% and LBBB
Evaluate for heart transplant (1)
YES
NO
CRT (2a)
Evaluate for heart transplant (1)
If patient decompensates while listed, evaluate for LVAD (2a)
NO
Symptoms after CRT
YES
NYHA class III-IV

HCM with out obstruction

COR	LOE	Recommendations
1	C-LD	1. In patients with nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea, beta-blockers or non-dihydropyridine calcium channel blockers are recommended.[1–10]
2a	C-EO	2. In patients with nonobstructive HCM with preserved EF, it is reasonable to add oral diuretics when exertional dyspnea persists despite the use of beta-blockers or non-dihydropyridine calcium channel blockers.
2b	C-LD	3. In patients with nonobstructive HCM with preserved EF, the usefulness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of symptoms (angina and dyspnea) is not well established.[11]
2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA class III or class IV) despite maximal medical therapy, and with preserved EF and small LV cavity size (LV end-diastolic volume <50 mL/m^2 and LV stroke volume <30 mL/m^2), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms.[12]
2b	C-EO	5. In asymptomatic patients with nonobstructive HCM, the benefit of beta-blockers or calcium channel blockers is not well established.

AF and HCM

Recommendations for Management of Atrial Fibrillation
Referenced studies that support the recommendations are summarized in Online Data Supplement 16.

COR	LOE	Recommendations
1	B-NR	1. In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants (DOAC) as first-line option and vitamin K antagonists as second-line option, independent of CHA_2DS_2-VASc score.[1–5]
1	C-LD	2. In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 hours' duration for a given episode, anticoagulation is recommended with DOAC as first-line option and vitamin K antagonists as second-line option, independent of CHA_2DS_2-VASc score.[1,6–8]
1	C-LD	3. In patients with AF in whom rate control strategy is planned, either beta-blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions.[9,10]
2a	C-LD	4. In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' but <24 hours' duration for a given episode, anticoagulation with DOAC as first-line option and vitamin K antagonists as second-line option can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk.[1,6–8,11]
2a	B-NR	5. In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions.[10,12–24]
2a	B-NR	6. In patients with HCM and symptomatic AF, as part of a AF rhythm control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference.[12,25,26]

Management of Patients with Hypertrophic Cardiomyopathy and Atrial Fibrillation (AF)

Antiarrhythmic Drug	Efficacy for AF	Side Effects	Toxicities	Use in HCM
Disopyramide	Modest	Anticholinergic	Prolonged QTC	Early AF
Flecainide, propafenone	?		Proarrhythmic	Not generally recommended in absence of an ICD
Sotalol	Modest	Bradycardia and fatigue	Prolonged QTc Prolonged QTc Proarrhythmia	reasonable
Dofetilide	Modest	headache	QTC prololngation	reasonable
Dronedarone	low	HF		? Don't used it-my take
Amio	Modest to high	Bradycardia	Liver, lung, thyroid, skin,neurologic	Reasonable
PVI/box isolation	If patient is going to have surgical mymectomy -2a			Risk if relapse is high and patient may end up with more meds

VT in HCM

Recommendations for the Management of Patients With HCM and Ventricular Arrhythmias

Referenced studies that support the recommendations are summarized in Online Data Supplement 17.

COR	LOE	Recommendations
1	B-NR	1. In patients with HCM and recurrent poorly tolerated life-threatening ventricular tachyarrhythmias refractory to maximal antiarrhythmic drug therapy and ablation, heart transplantation assessment is indicated in accordance with current listing criteria.[1,2]
1	Amiodarone, B-NR	2. In adults with HCM and symptomatic ventricular arrhythmias or recurrent ICD shocks despite beta-blocker use, antiarrhythmic drug therapy listed is recommended, with the choice of agent guided by age, underlying comorbidities, severity of disease, patient preferences, and balance between efficacy and safety.[3–6]
	Dofetilide, C-LD1 Mexiletine, C-LD2 Sotalol, C-LD3	

HCM and advanced HF therapies

Recommendations for Patients With HCM and Advanced HF
Referenced studies that support the recommendations are summarized in Online Data Supplement 18.

COR	LOE	Recommendations
1	C-LD	1. In patients with HCM who develop systolic dysfunction with an LVEF <50%, guideline-directed therapy for HF with reduced EF is recommended.[1-3]
1	C-LD	2. In patients with HCM and systolic dysfunction, diagnostic testing to assess for concomitant causes of systolic dysfunction (such as CAD) is recommended.[4-6]
1	B-NR	3. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite guideline-directed therapy), CPET should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support.[7,8]
1	B-NR	4. In patients with nonobstructive HCM and advanced HF (NYHA class III to class IV despite guideline-directed therapy) or with life-threatening ventricular arrhythmias refractory to maximal guideline-directed therapy, assessment for heart transplantation in accordance with current listing criteria is recommended.[9-12]

HCM and activity

Recommendations for Sports and Activity

Referenced studies that support the recommendations are summarized in Online Data Supplement 19.

COR	LOE	Recommendations
1	B-NR	1. For most patients with HCM, mild- to moderate-intensity recreational* exercise is beneficial to improve cardiorespiratory fitness, physical functioning, and quality of life, and for their overall health in keeping with physical activity guidelines for the general population.[1–3]
1	C-EO	2. For athletes with HCM, a comprehensive evaluation and shared discussion of potential risks of sports participation by an expert provider is recommended.[4]
2a	C-EO	3. For most patients with HCM, participation in low-intensity competitive sports is reasonable.[5,6]
2a	C-LD	4. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable.[5–11]
2b	C-LD	5. For patients with HCM, participation in high-intensity recreational activities or moderate- to high-intensity competitive sports activities may be considered after a comprehensive evaluation and shared discussion, repeated annually with an expert provider who conveys that the risk of sudden death and ICD shocks may be increased, and with the understanding that eligibility decisions for competitive sports participation often involve third parties (eg, team physicians, consultants, and other institutional leadership) acting on behalf of the schools or teams.[4,7–11]
3: Harm	B-NR	6. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed.[5,7,12]

Thank you