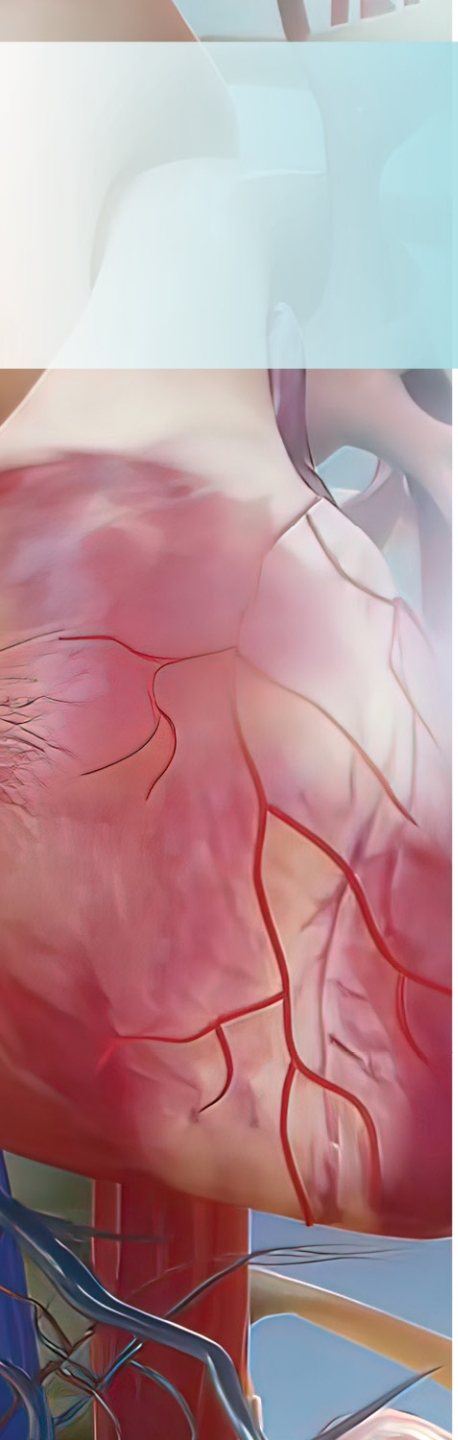
Expanding Horizons for the Management of Obstructive Hypertrophic Cardiomyopathy

Pharmacist Considerations



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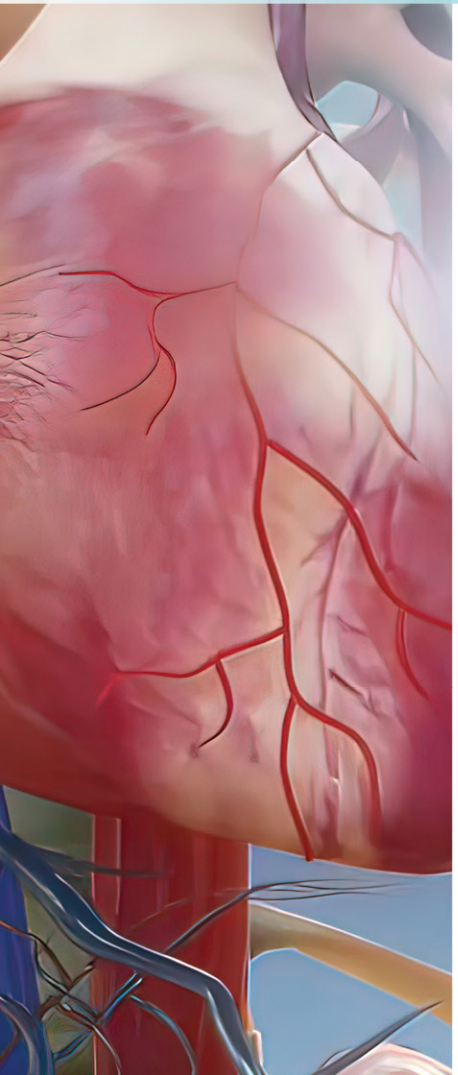

Faculty

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Associate Professor of Pharmacy
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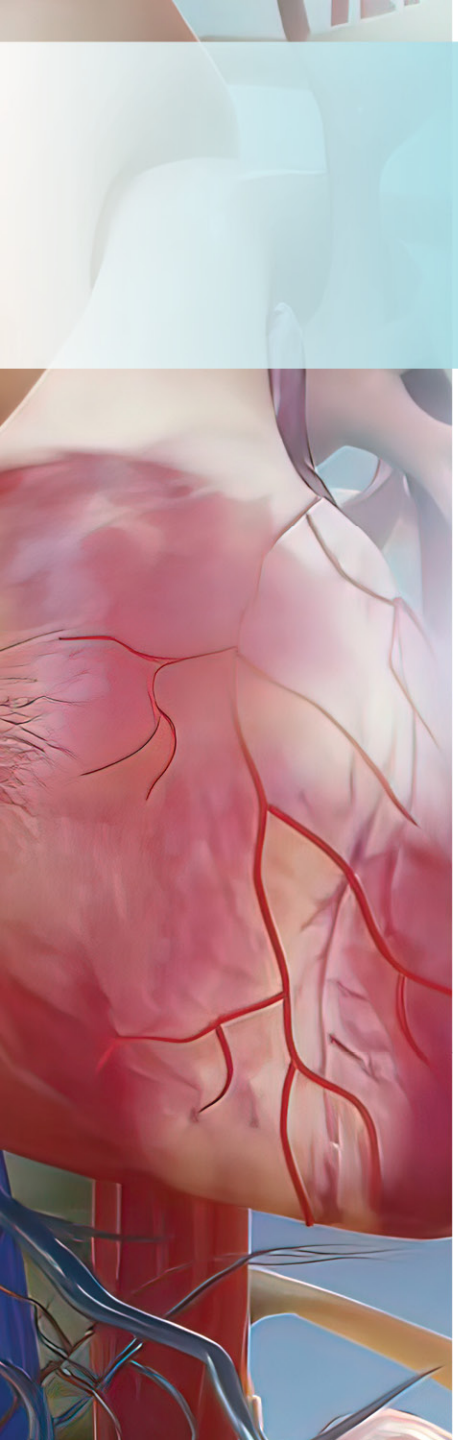
Dr. Jennings is an Associate Professor of Pharmacy at Long Island University and the clinical pharmacist for the Heart Transplant and LVAD teams at New York-Presbyterian Hospital Columbia University Irving Medical Center. He is an active researcher in his field and has published over 190 peer-reviewed abstracts and manuscripts, primarily focusing on pharmacotherapy after heart transplant or LVAD surgery. As a recognized expert in this area, he has been invited to speak at numerous national and international venues, including meetings in France, Saudi Arabia, and India. Professor Jennings is also a current member of the Advanced Heart and Transplant Leadership Council within the American College of Cardiology, and he is a contributing author on the International Society of Heart and Lung Transplant guidelines for the care of heart transplant recipients.



Disclosures

Dr. Jennings has disclosed that he has received consulting fees from Abiomed and fees for Non-CE services from Abiomed, AstraZeneca, La Jolla Pharmaceutical Company, Merck & Co., and Novartis.

The clinical reviewer, Tracy Macaulay, PharmD has disclosed that she has no actual or potential conflicts of interest related to this program.

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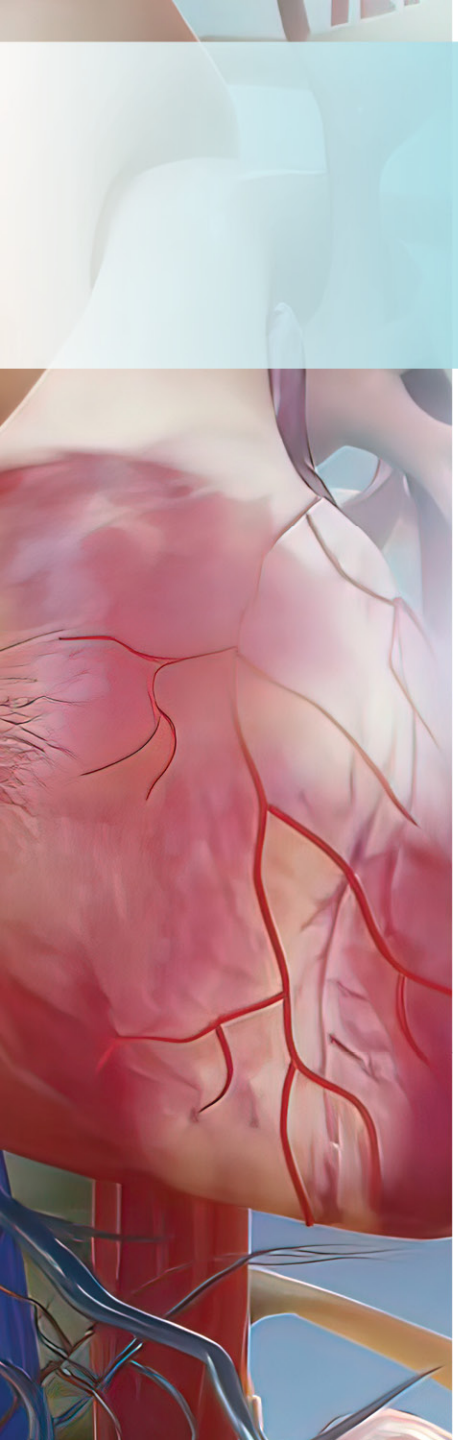

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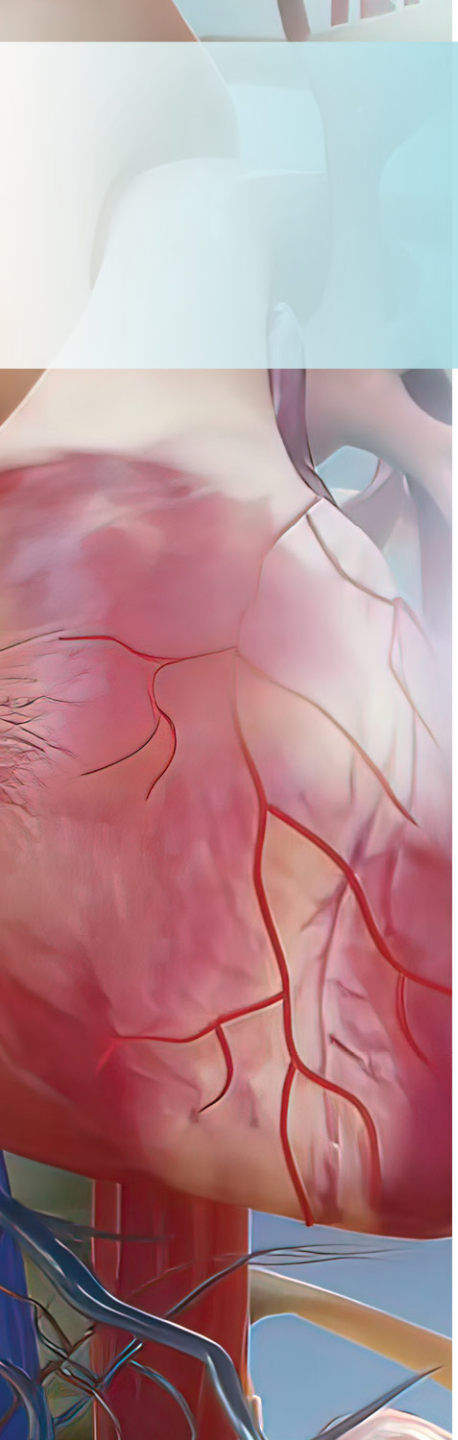
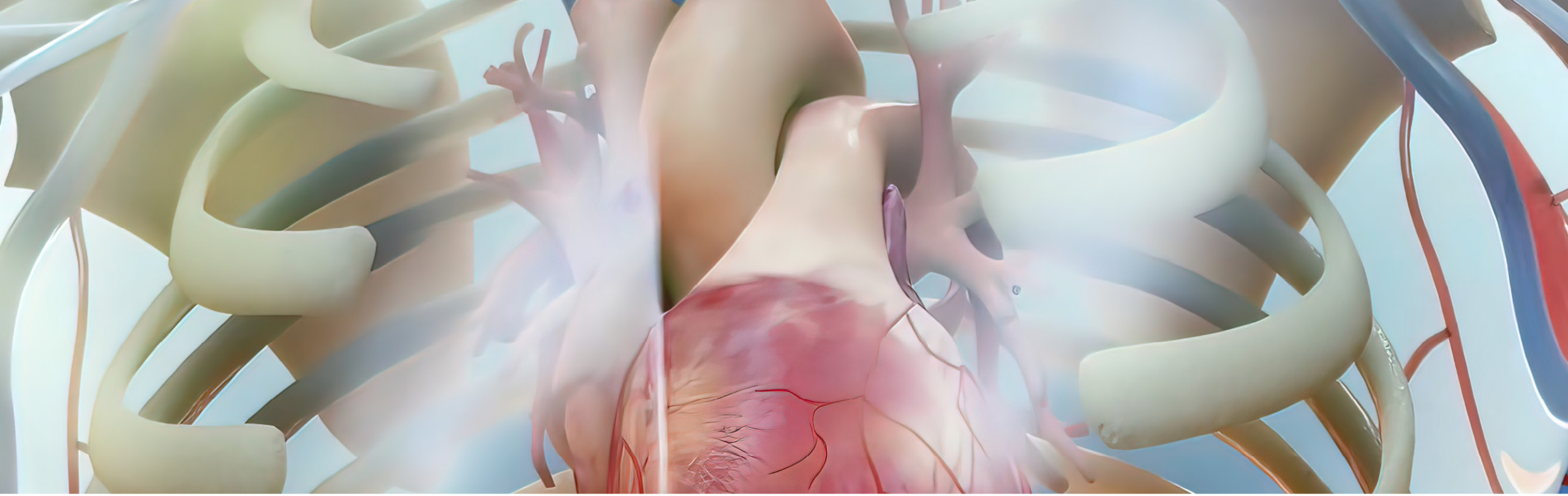
Type of Activity: Application



Learning Objectives

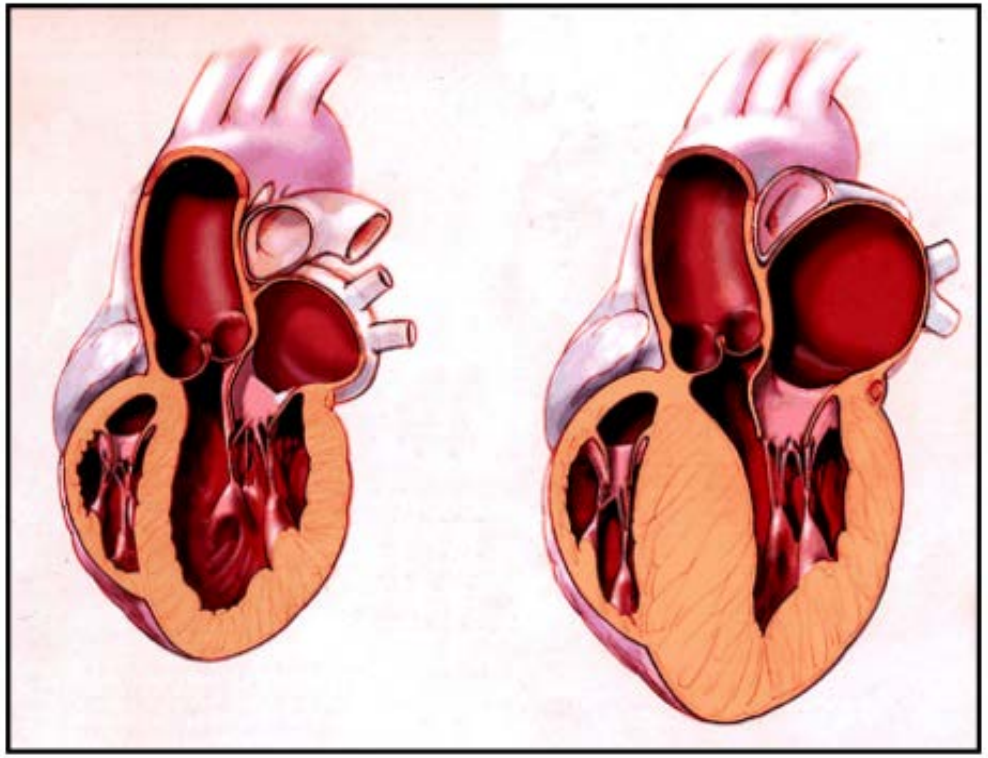
- **Explain** the pathology, pathophysiology, and epidemiology of hypertrophic cardiomyopathy (HCM) and its subtypes
- **Describe** the limitations of the current standard of care therapies for obstructive HCM (OHCM)
- **Discuss** the novel agent, mavacamten, for OHCM and its potential to improve treatment outcomes
- **Develop** effective approaches to educate patients on the safe and optimal use of the novel agent for OHCM



Overview of OHCM

Pathophysiology, Epidemiology, Etiology, and Diagnosis

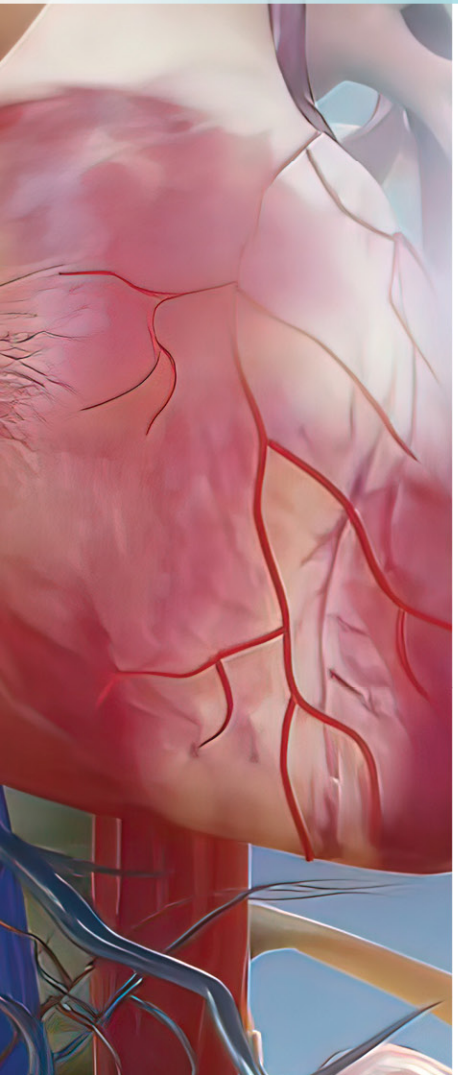
Pathophysiology and Etiology

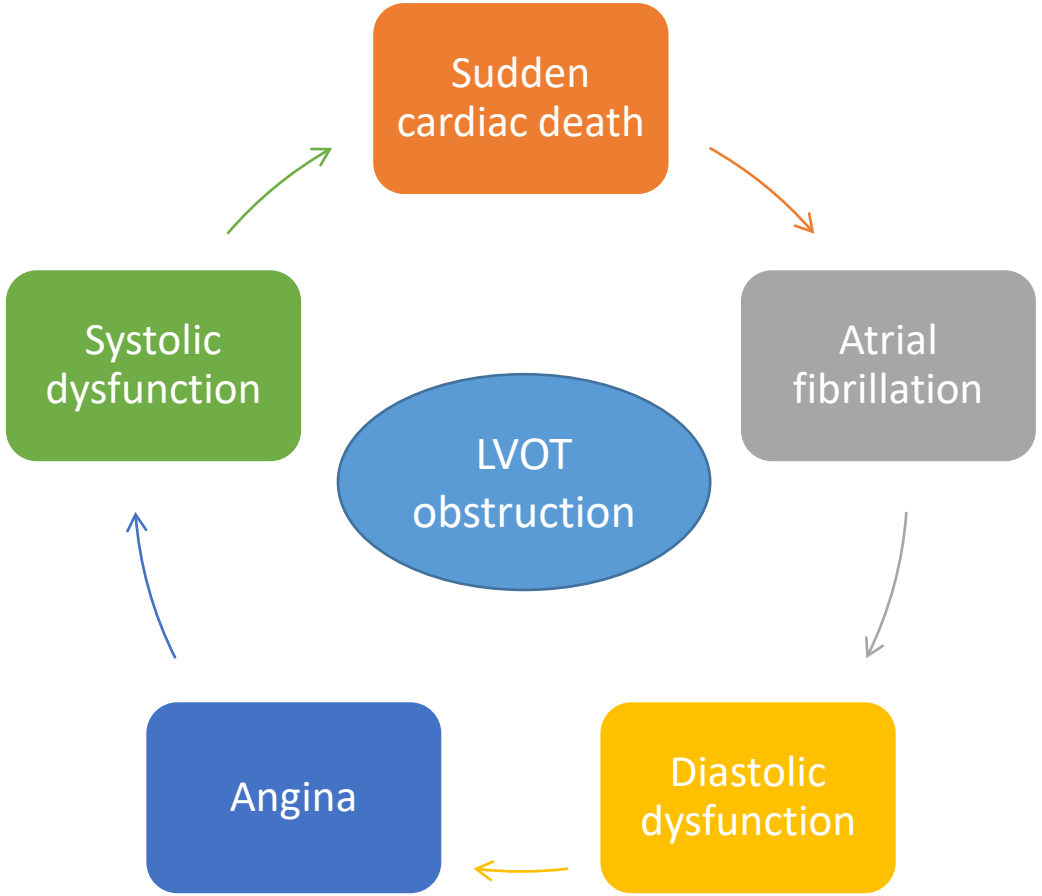


GENE	SYMBOL	LOCUS	FREQUENCY
Myosin heavy chain	MYH7	14q12	>30%
Myosin-binding protein C	MYBPC3	11p11.2	>20%
Cardiac troponin T	TNNT2	1q32	>20%
Tropomyosin	TPM1	15q22.1	>5%
Cardiac troponin I	TNNI3	19p13.2	>5%
Myosin light chain, essential	MYL3	3p21.3-p21.2	<5%
Myosin light chain, regulatory	MYL2	12q23-q24.3	<5%
Cardiac alpha-actin	ACTC	11q	<5%
Cardiac troponin C	TNNC1	3p21.3	Rare
Alpha-Myosin heavy chain	MYH6	14q	Rare
Protein kinase A, gamma-subunit of AMP activated protein kinase	PRKAG2	7q22-q31.1	unknown

Houston BA, et al. *Clin Med Insights Cardiol*. 2015;8(Suppl 1):53-65.

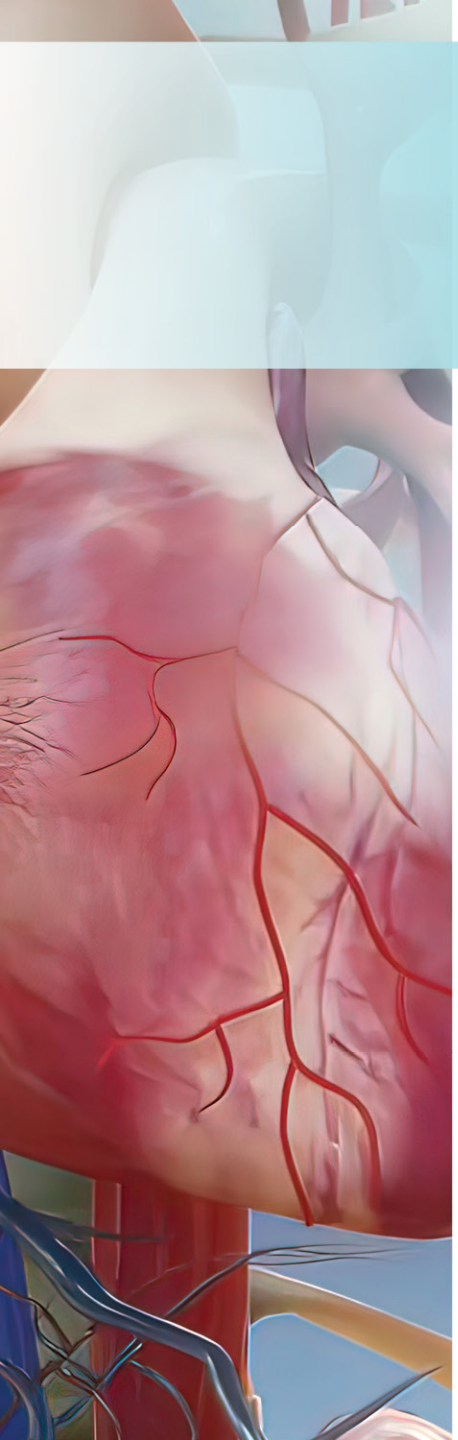
Pathophysiology





LVOT, left ventricular outflow tract

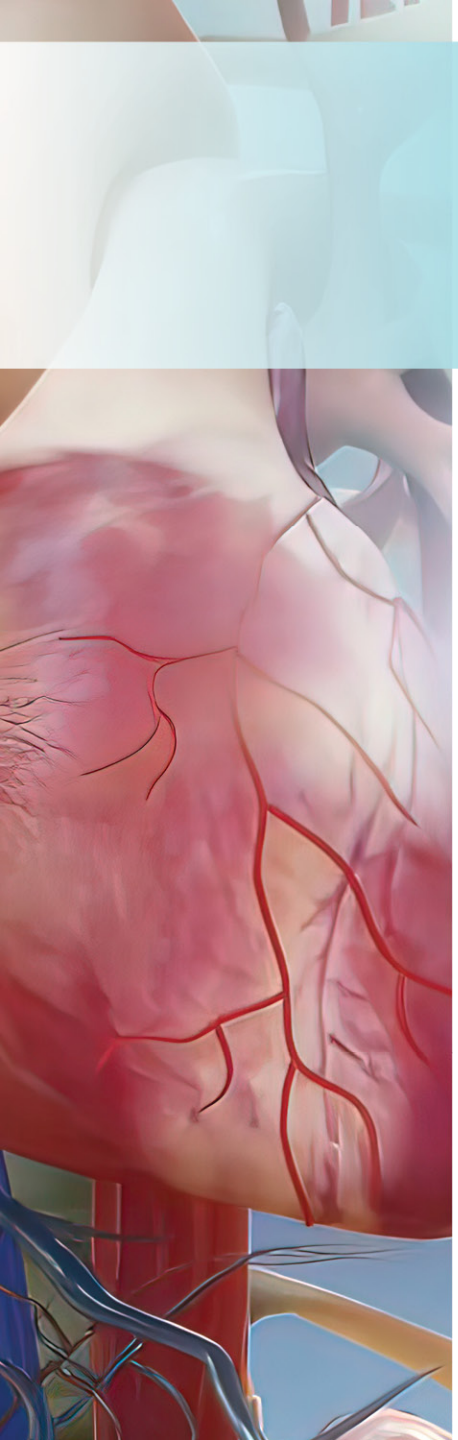
Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.



Epidemiology

- Incidence of about 1 in 500 (0.2%) of the general population
  - ≈ 600,000 patients in the United States
- Inherited in an autosomal dominant pattern
- Distribution is equal by sex
- Overall annual mortality rate ≈ 1%

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.

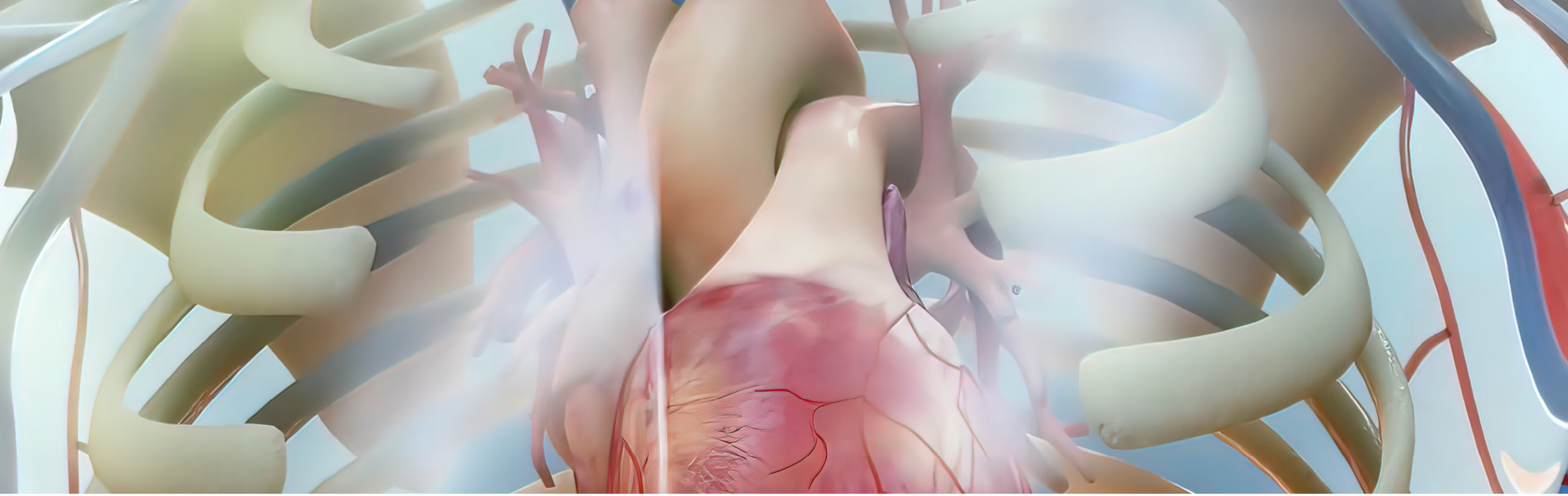


Diagnosis

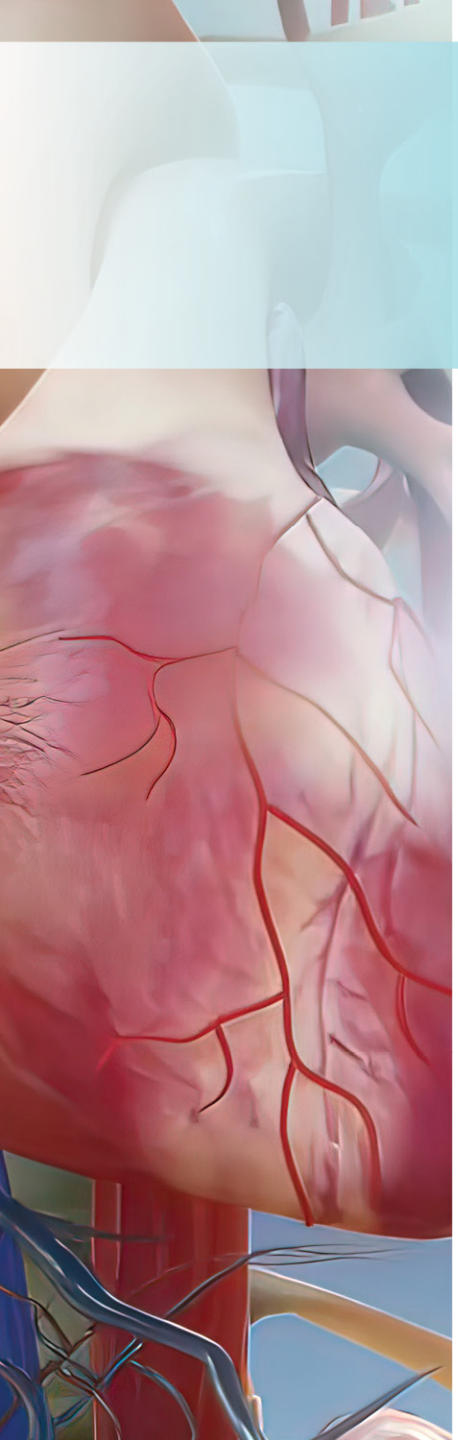
- Clinical history, physical exam findings, ECG
- Echocardiography or cardiac magnetic resonance imaging
  - Maximal end-diastolic wall thickness ≥ 15 mm anywhere in the left ventricle
- Peak LVOT gradient ≥ 30 mmHg indicates obstruction
  - Resting or provoked gradient ≥ 50 mmHg considered the threshold for septal reduction therapy (SRT) in patients with drug-refractory symptoms

ECG, electrocardiogram

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.



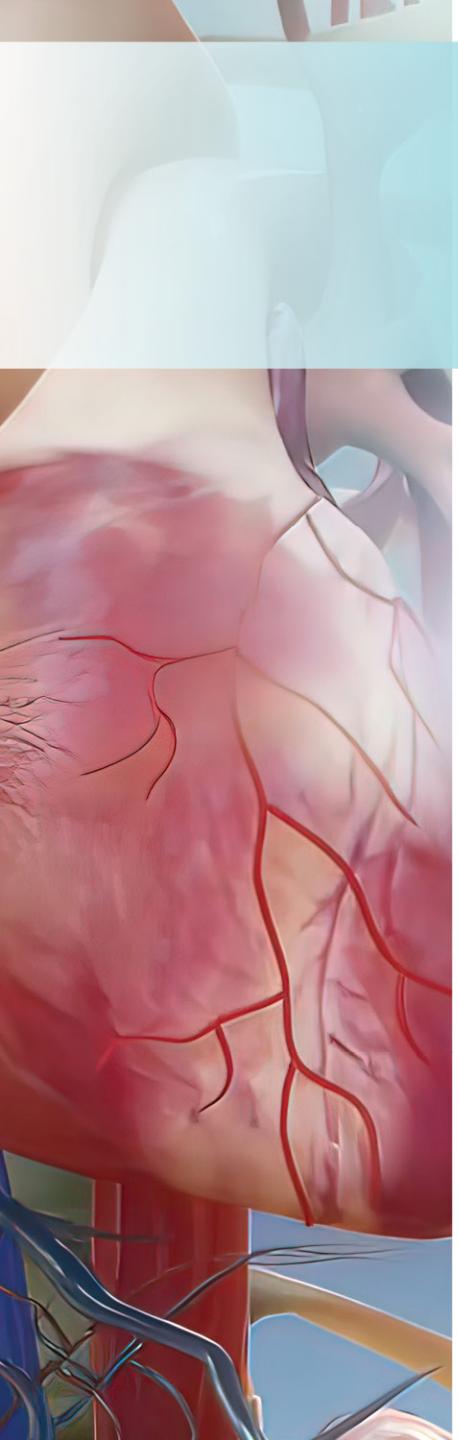
Current Treatment Approaches for OHCM



Shared Decision-Making

- Guidelines recommend shared decision-making for patients with (or at risk of) HCM
  - Patients should have the opportunity to express goals and concerns
- Care plan should include, but is not limited to
  - Genetic evaluation
  - Activity
  - Lifestyle
  - Therapy choices
- Disclose risks, benefits, and anticipated outcomes

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.

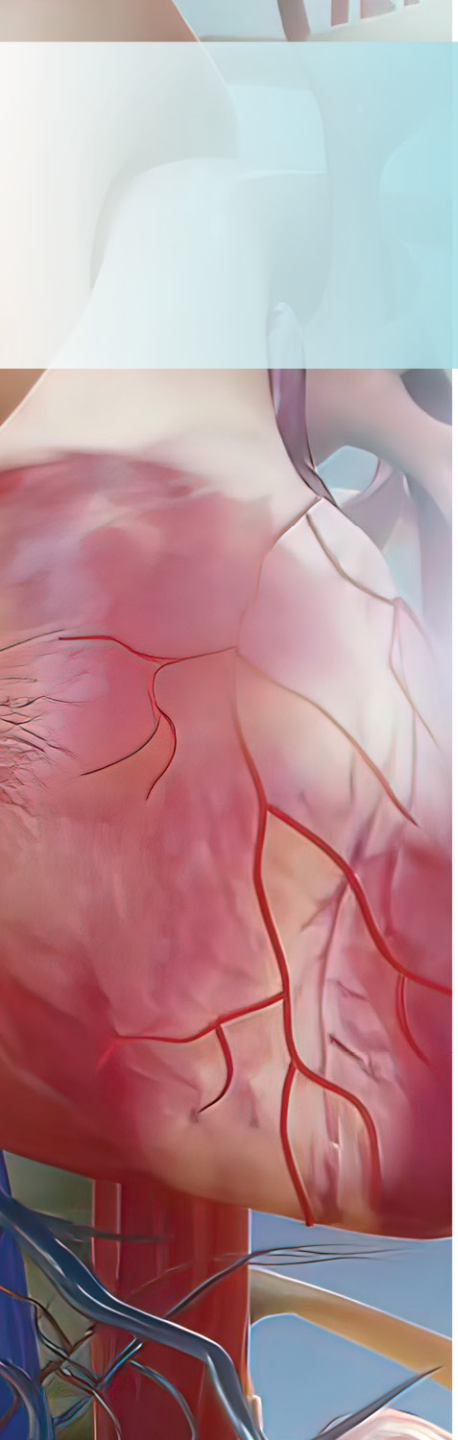


Stepwise Treatment Approach

- Lifestyle modifications
- SCD assessment +/- ICD
- Drug therapy
- Septal reduction therapy

ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.



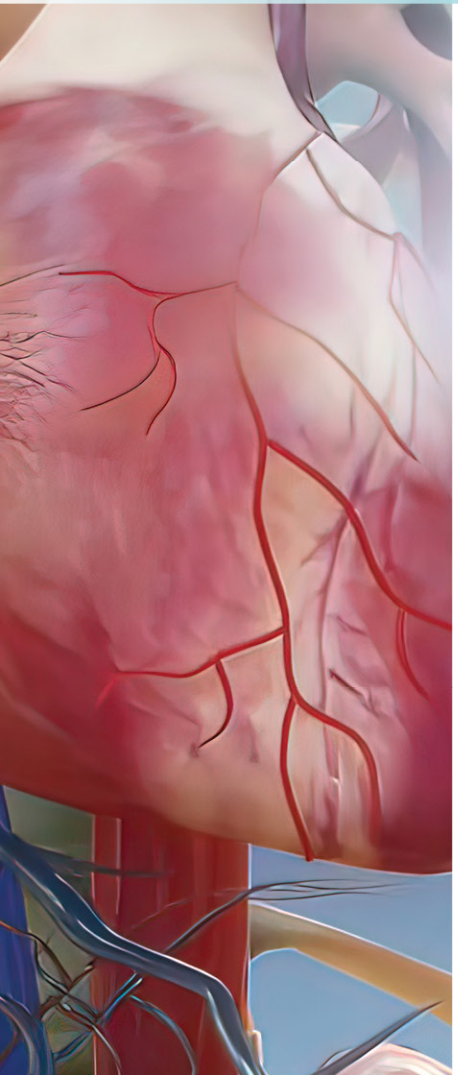
Drug Therapy Selection

- Directed by presence of obstructive physiology and symptoms:
  - Neither: not treated
  - Both: initiate guideline-directed medical treatments to alleviate symptoms (next slide)
    - Avoid high-dose diuretics and pure vasodilators
- Non-obstructive physiology: use LVEF to guide treatment

LVEF, left ventricular ejection fraction

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.

First-Line Therapies

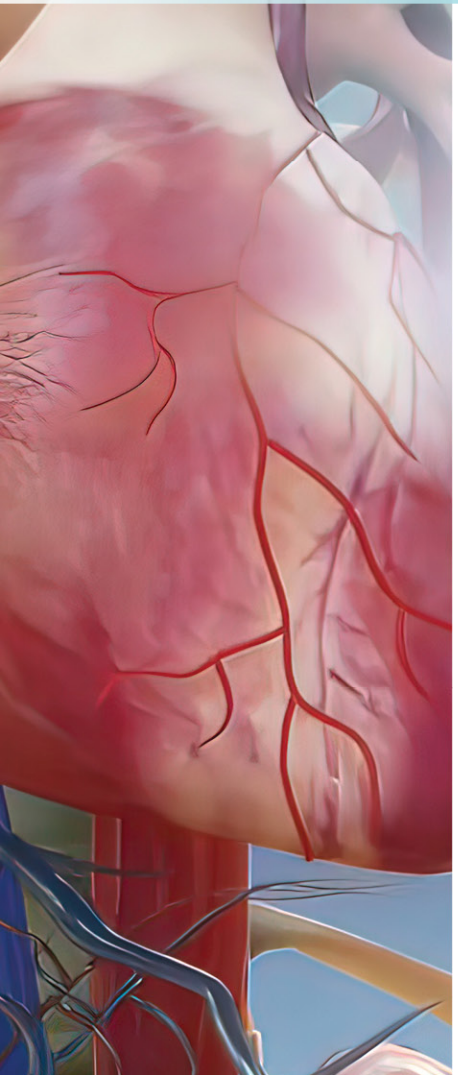


Recommendations for Pharmacologic Management of Patients With Obstructive HCM
Referenced studies that support the recommendations are summarized in Online Data Supplement 14.

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.[204–206]
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 (eg, verapamil, diltiazem) is recommended.[207–209]
	Diltiazem C-LD	

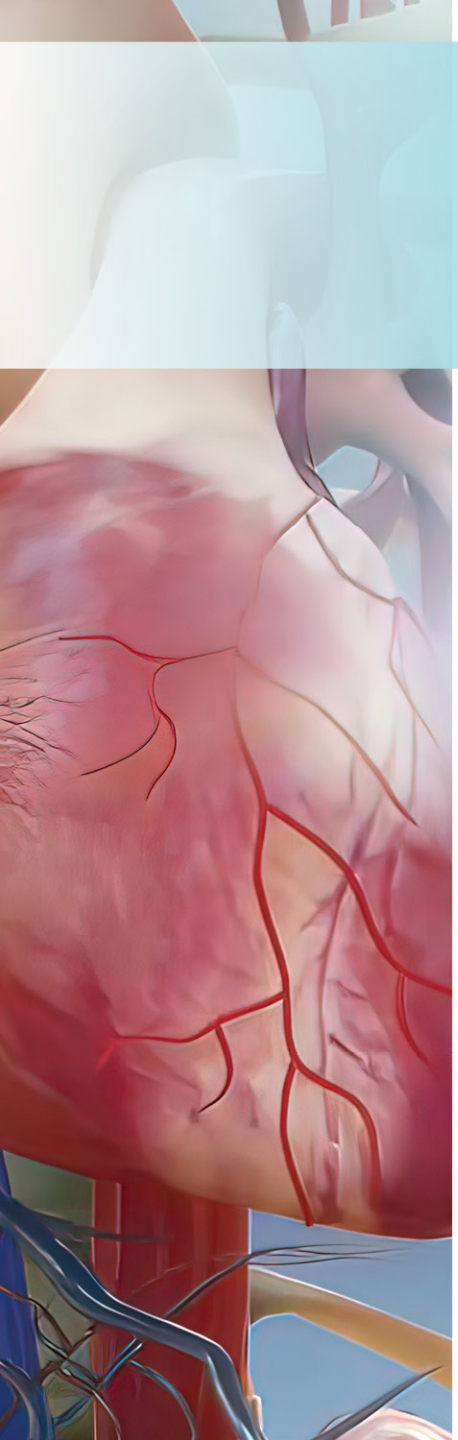
*Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.

Second-Line Therapies



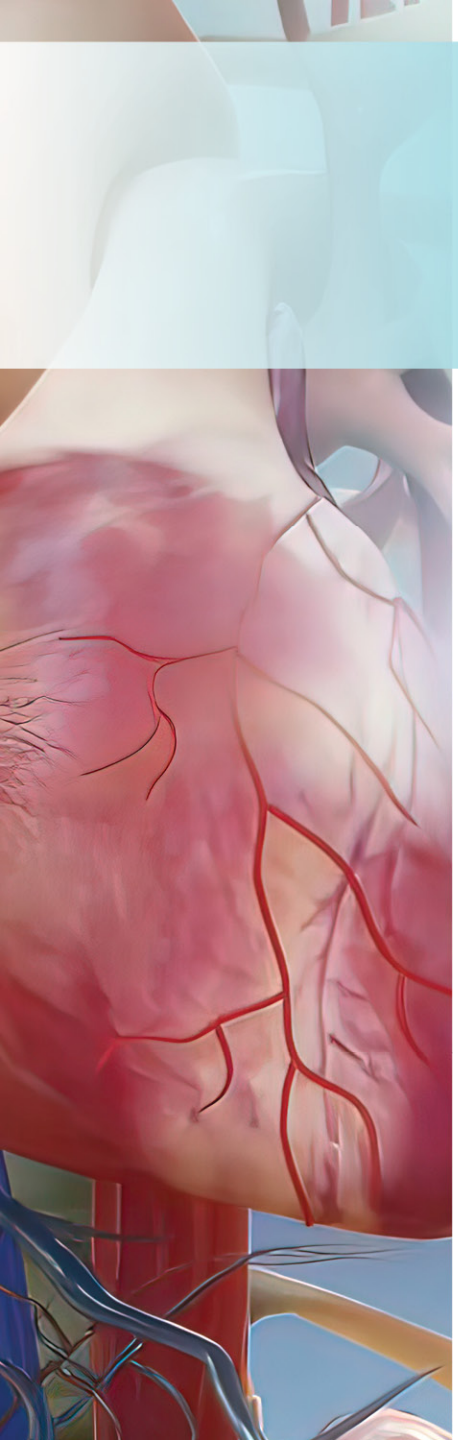
1	B-NR	3. For patients with obstructive HCM who have persistent severe symptoms* attributable to LVOTO despite beta blockers or non-dihydropyridine calcium channel blockers, either adding disopyramide in combination with 1 of the other drugs, or SRT performed at experienced centers,† is recommended.[17,50,210–213]

Ommen SR, et al. *Circulation*. 2020;142(25):e558-e631.



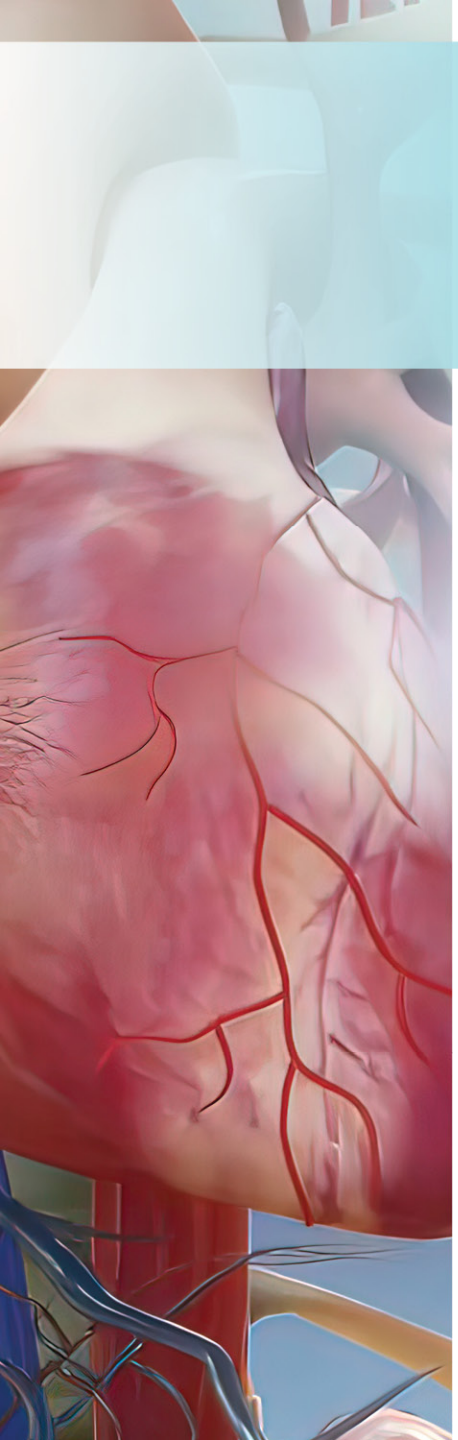
Disopyramide

- Class Ia antiarrhythmic agent: sodium channel blocker
- Improves LVOT gradient via negative inotropic properties
- Anticholinergic adverse effects
  - Can be managed with pyridostigmine
- Can increase AV nodal conduction
  - Use with beta-blocker or verapamil/diltiazem
- Use controlled-release product when possible
  - 200 to 250 mg twice daily to start
  - Increase to max 600 mg twice daily if needed



Limitations of Current Therapies

- Do not target underlying disease process
- Do not alter OHCM’s natural history
- Significant adverse effects



Septal Reduction Therapies

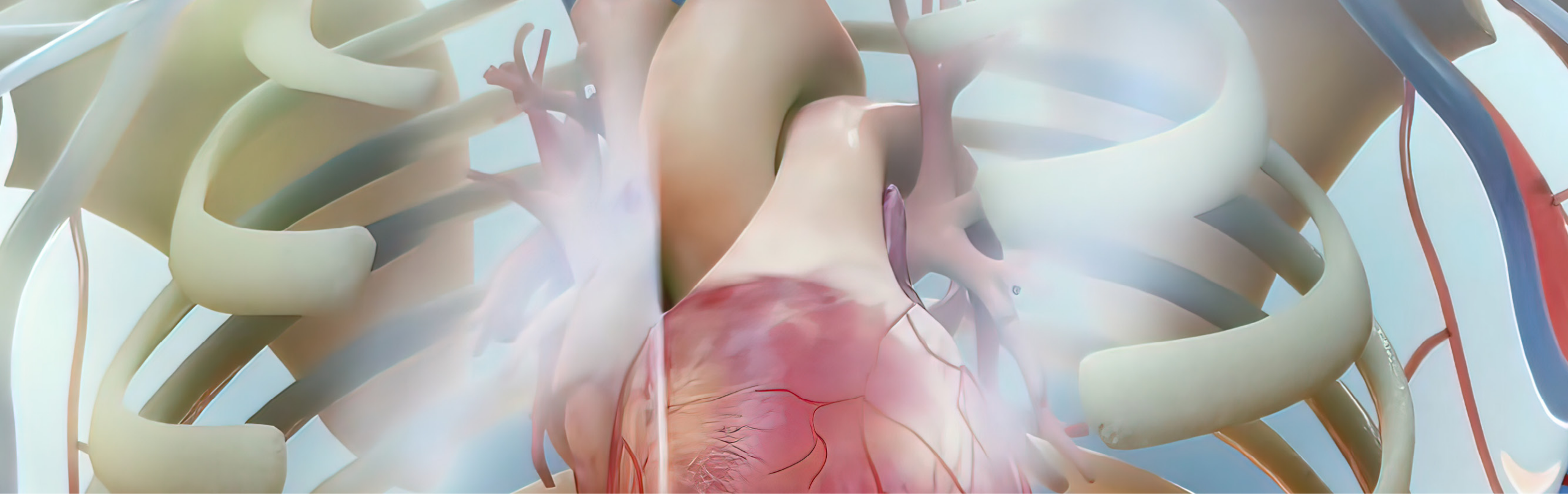
Septal Ablation:

- Older age
- Comorbidities
- Limited life expectancy
- Lower gradient
- Lesser thickness

Surgical Myectomy:

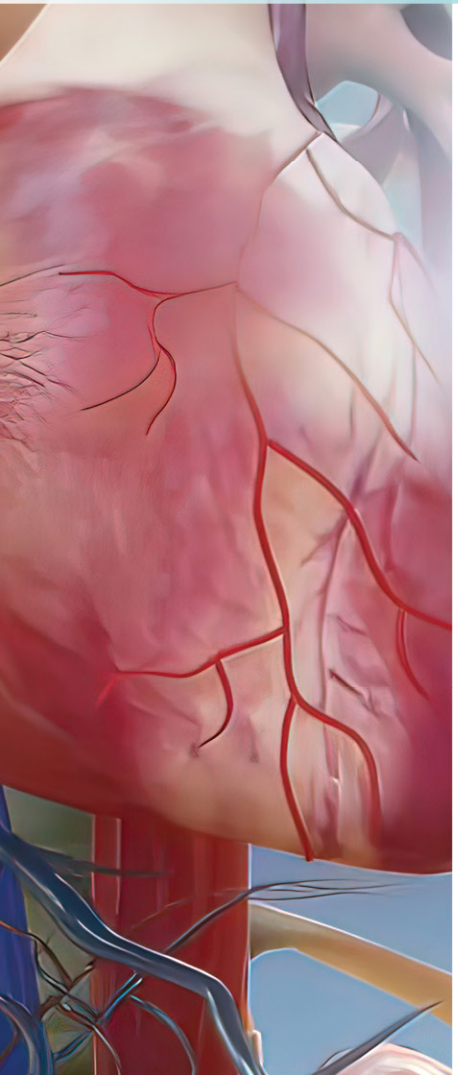
- Younger age
- Healthy
- Long life expectancy
- Higher gradient
- Other structural disease

Geske JB, et al. *JACC Heart Fail*. 2018;6(5):364-375.

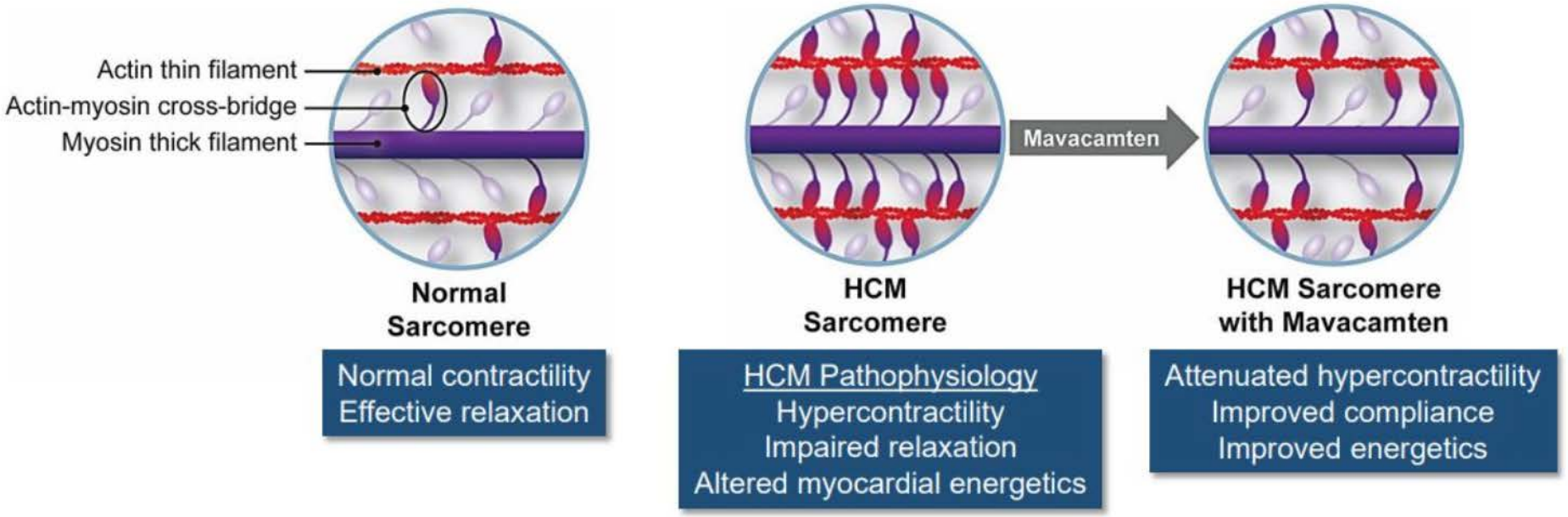


Mavacamten

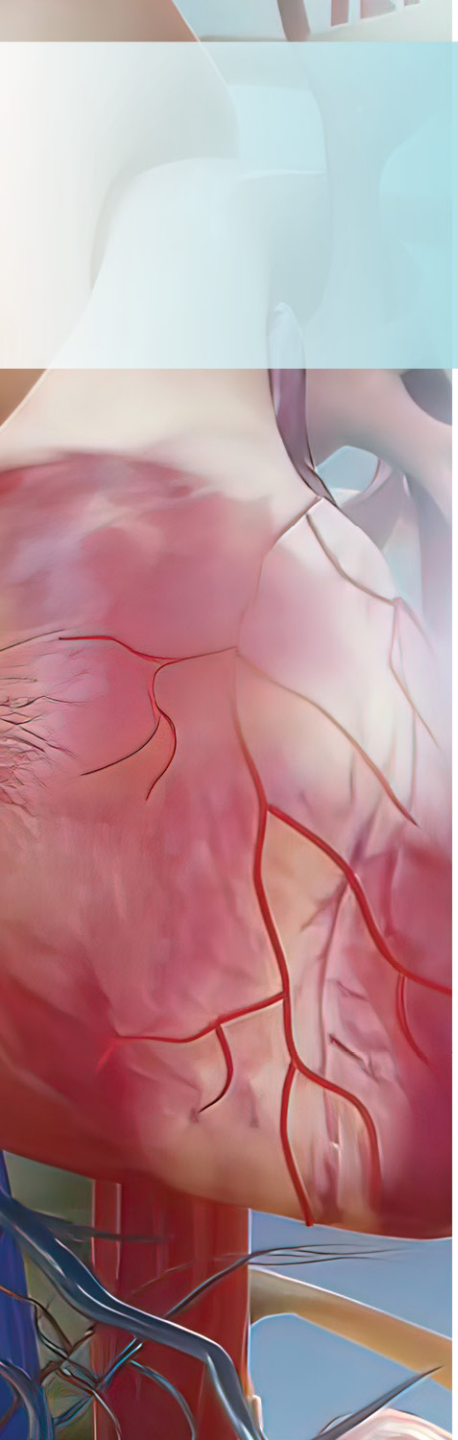
A novel therapy for OHCM



Mechanism of Action



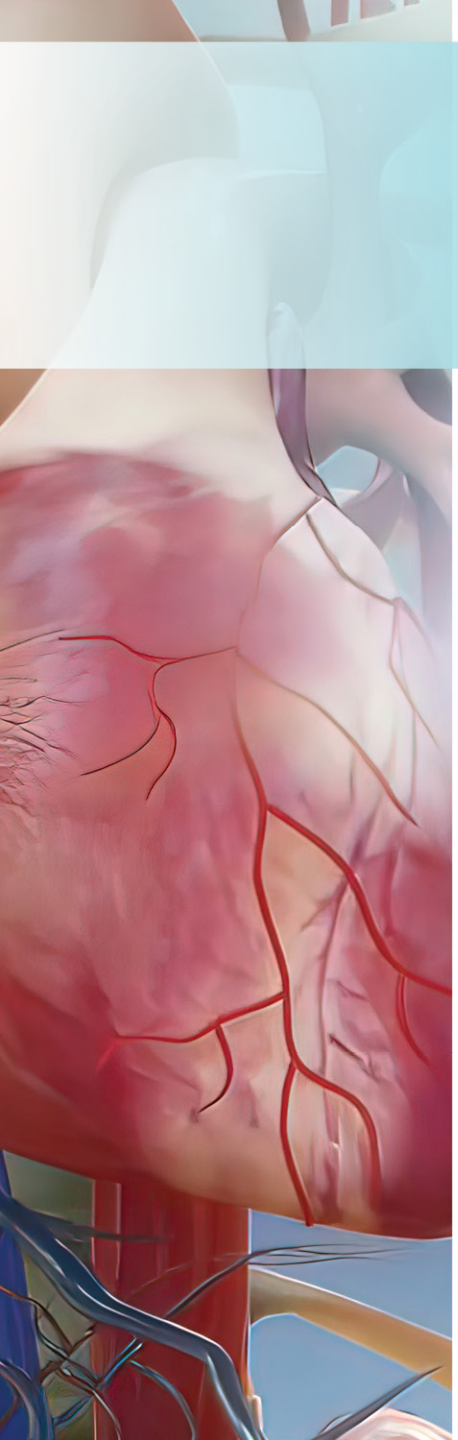
https://www.dicardiology.com/content/mavacamten-effective-treating-obstructive-hypertrophic-cardiomyopathy



Class and Indication

Drug class: first and only approved cardiac myosin inhibitor

Indication: for the treatment of adults with symptomatic New York Heart Association (NYHA) class II–III OHCM to improve functional capacity and symptoms



EXPLORER-HCM Trial

Randomized, double-blinded, placebo-controlled trial in 13 countries

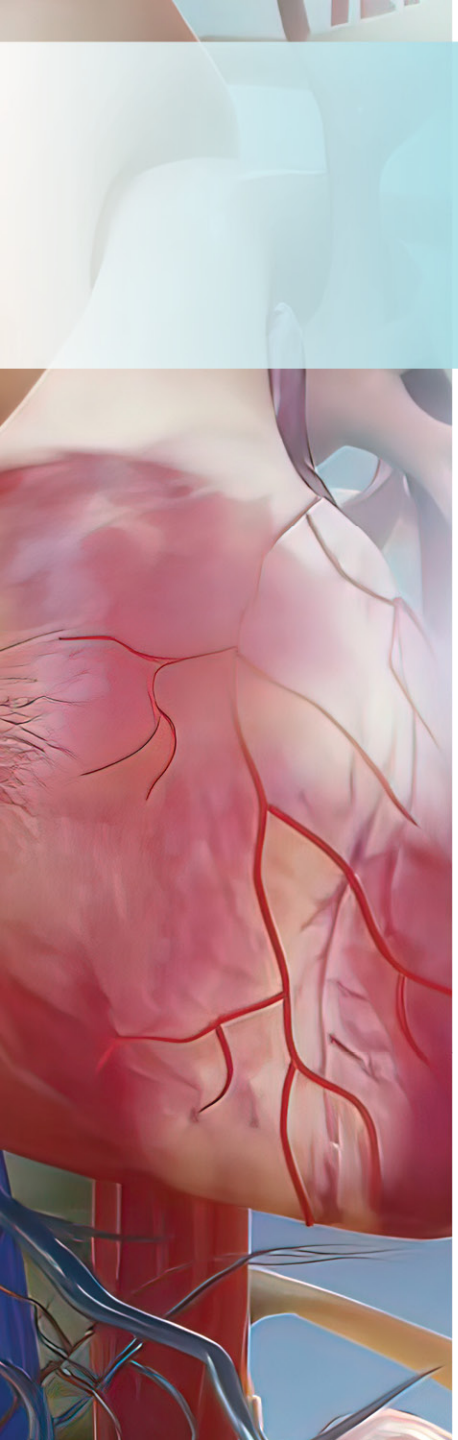
Inclusion Criteria:

- ≥ 18 years of age
- HCOM (LVOT gradient ≥ 50 mmHg)
- LVEF ≥ 55%
- NYHA class II-III symptoms

Exclusion criteria:

- Syncope
- Sustained ventricular tachycardia with exercise within 6 months

Olivotto I, et al. *Lancet*. 2020;396(10253):759-769.

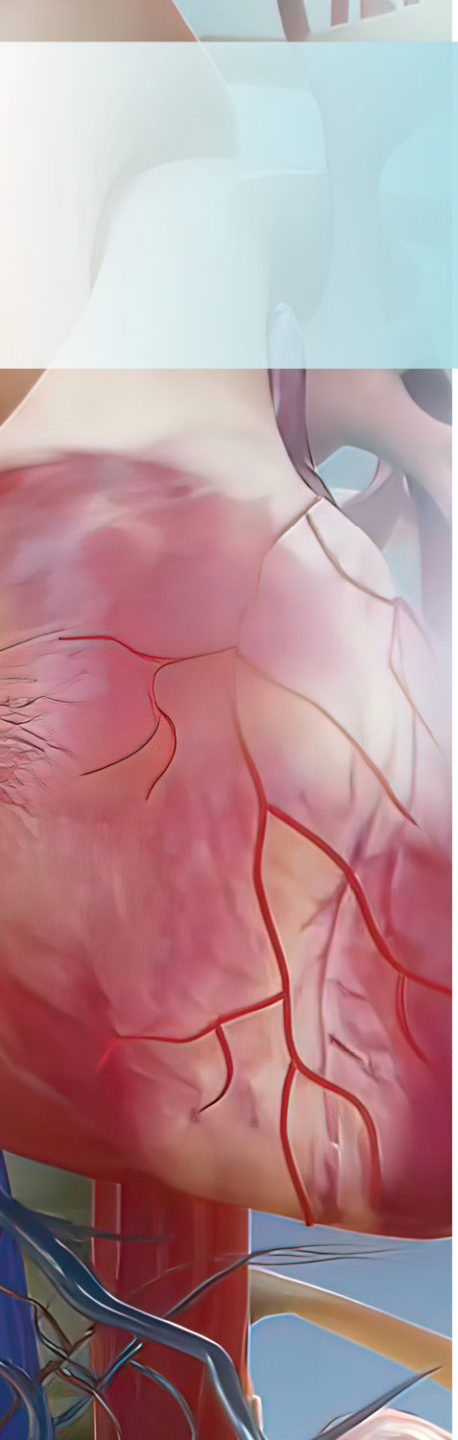


EXPLORER-HCM Trial

- Eligible patients randomized to mavacamten 5 mg daily (n = 123) or placebo (n = 128)

Total # of enrollees	251
Duration of follow-up	30 weeks
Mean patient age	59 years
% Female	46%
% White	93%
% U.S.	43%
% NYHA functional class II	72%

Olivotto I, et al. *Lancet*. 2020;396(10253):759-769.



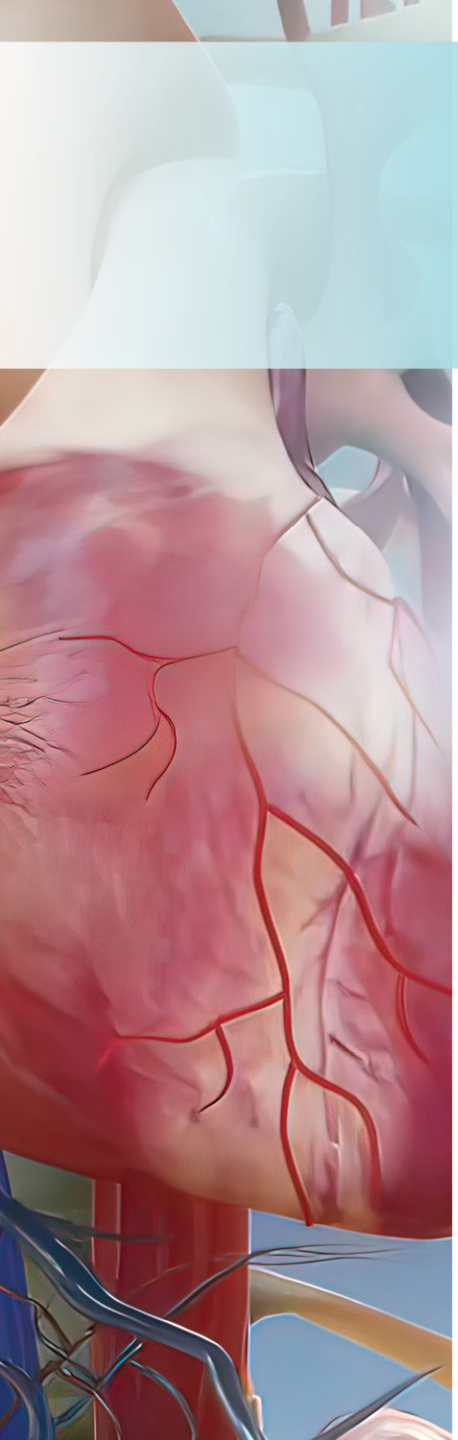
EXPLORER-HCM Trial

- Primary outcome (at 30 weeks):
  - ≥ 1.5 mL/kg/min pVO_2 increase with ≥ 1 NYHA class improvement **or**
  - ≥ 3.0 mL/kg/min pVO_2 increase with no NYHA class worsening
  - 37% of mavacamten group vs. 17% of placebo group (p = 0.0005)

Endpoint	Mavacamten	Placebo	p value
Post-exercise LVOT gradient change from baseline to week 30	-47 mmHg	-10 mmHg	< 0.0001
Peak VO_2 change from baseline to week 30	1.4 mL/kg/min	-0.1 mL/kg/min	0.0006
Change in left-ventricular mass index	-17.4 g/m^2	-1.6 g/m^2	< 0.0001
Change in left-ventricular ejection fraction	-6.6%	-0.3%	0.0025

pVO_2, peak oxygen consumption

Olivotto I, et al. *Lancet*. 2020;396(10253):759-769.



EXPLORER-HCM Trial

Kansas City Cardiomyopathy Questionnaire (KCCQ):

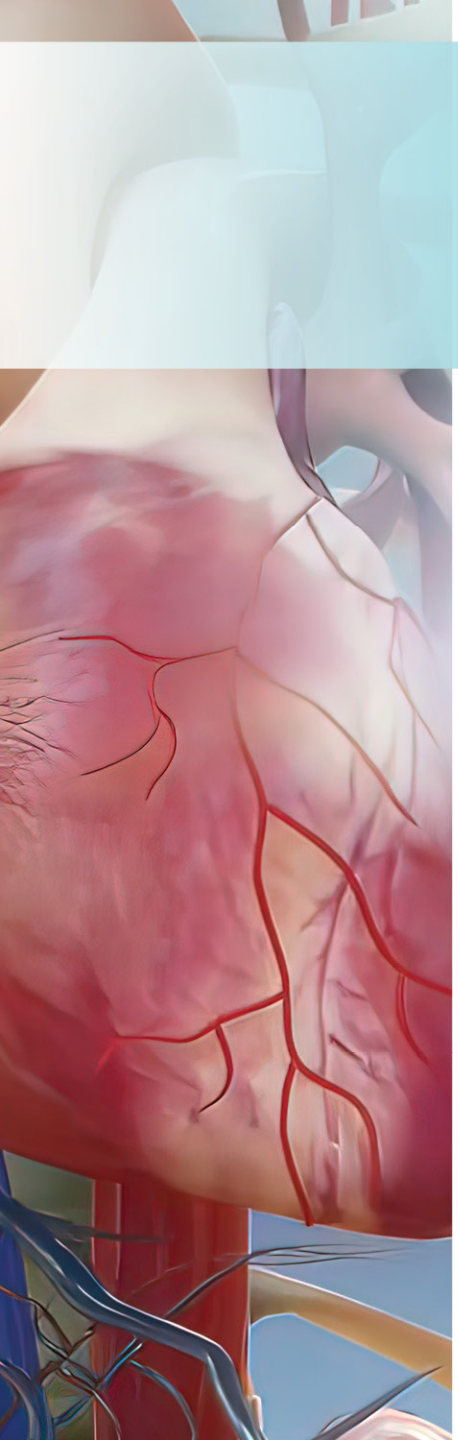
At 30 weeks, change in KCCQ-overall summary score: 14.9 for mavacamten vs. 5.4 for placebo (difference +9.1, $p < 0.0001$)

Long-term extension study (n = 231, median 62 weeks):

Treatment-emergent adverse effects	4.3%
Resting LVOT gradient change from baseline to 84 weeks	-32.8 mmHg
LVEF change from baseline to 84 weeks	-9%
NT-proBNP change from baseline to 84 weeks	-488 ng/L

NT-proBNP, N-terminal pro–B-type natriuretic peptide

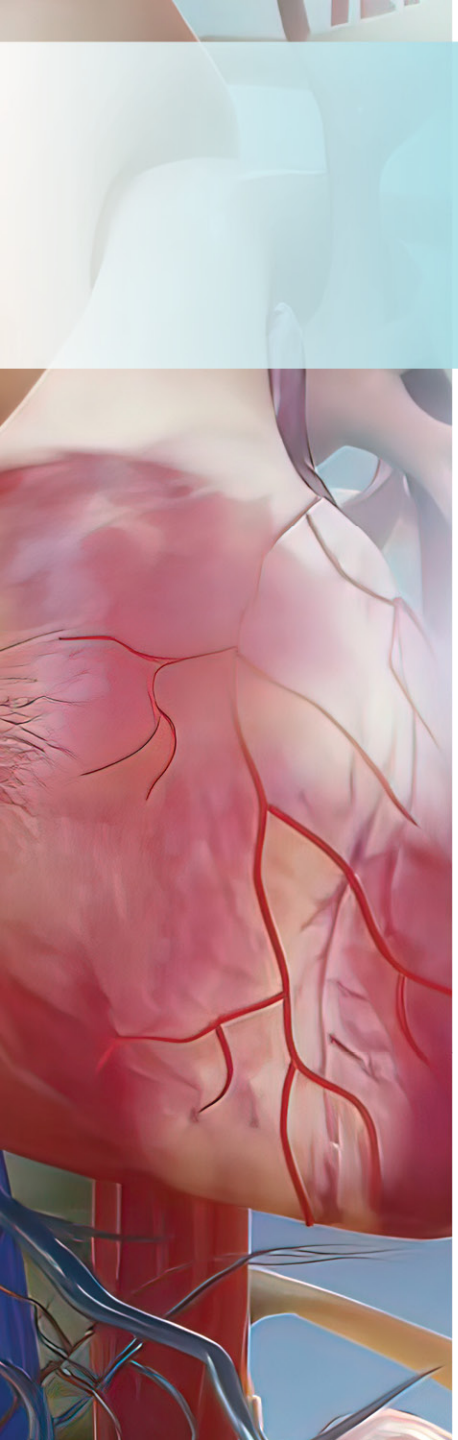
Olivotto I, et al. *Lancet*. 2020;396(10253):759-769. https://www.acc.org/latest-in-cardiology/clinical-trials/2020/08/28/16/14/explorer-hcm



EXPLORER-HCM Adverse Events

	Mavacamten (n = 123)	Placebo (n = 128)
Total # serious adverse events	11	20
Atrial fibrillation	2 (2%)	4 (3%)
Syncope	2 (2%)	1 (1%)
Sudden death	0	1 (1%)
Cardiac failure	0	1 (1%)

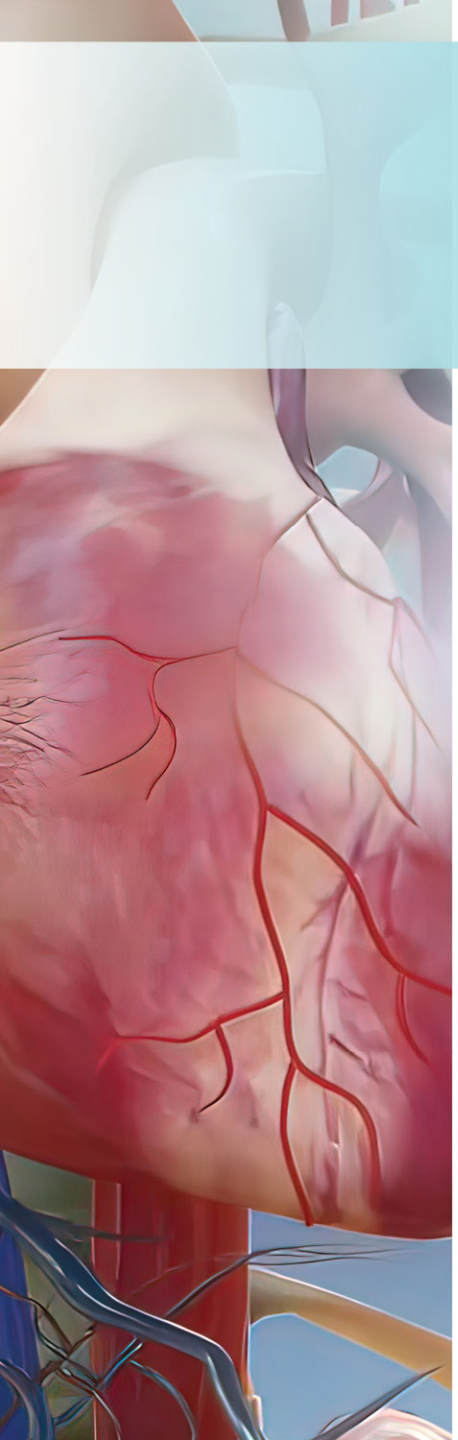
Olivotto I, et al. *Lancet*. 2020;396(10253):759-769.



Mavacamten Boxed Warning

- Mavacamten reduces LVEF and can cause heart failure (HF) due to systolic dysfunction
- Echocardiogram assessments of LVEF are required prior to and during treatment
- Initiation in patients with LVEF < 55% not recommended
- Interrupt treatment if
  - LVEF is < 50% at any visit **OR**
  - the patient experiences HF symptoms or worsening clinical status

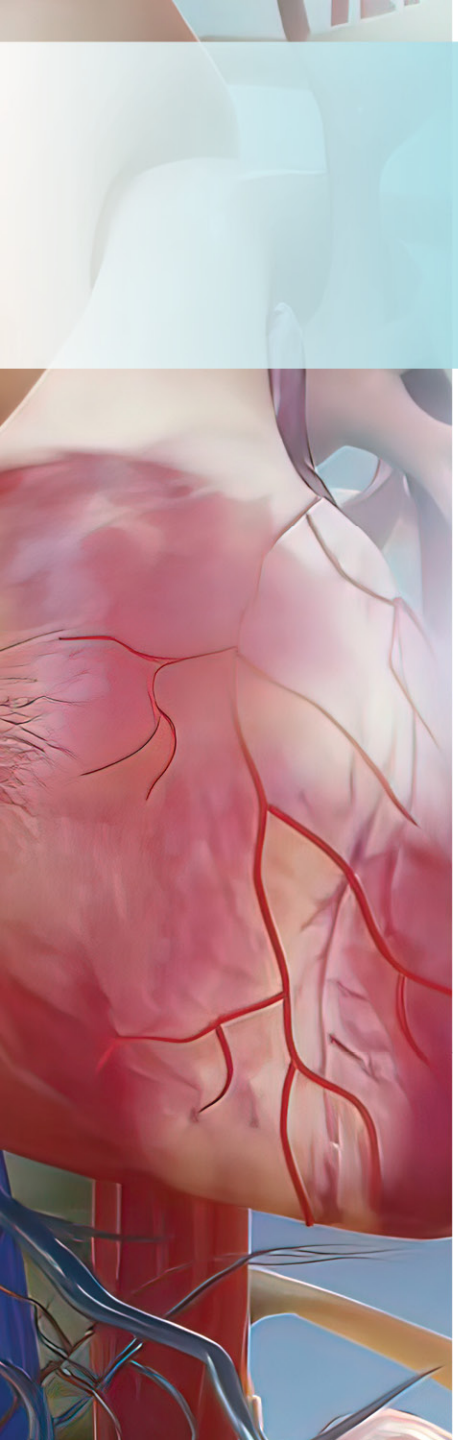
Camzyos [prescribing information]. Bristol Myers Squibb; 2022.



Interactions Increase HF Risk

- Undergoes cytochrome P450 (CYP) metabolism
- Use with certain CYP inhibitors or discontinuation of certain CYP inducers may increase HF risk
- Mavacamten use is contraindicated with
  - Moderate-to-strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
  - Moderate-to-strong CYP2C19 inducers or moderate-to-strong CYP3A4 inducers
  - Disopyramide, ranolazine, verapamil + beta blocker, or diltiazem + beta blocker

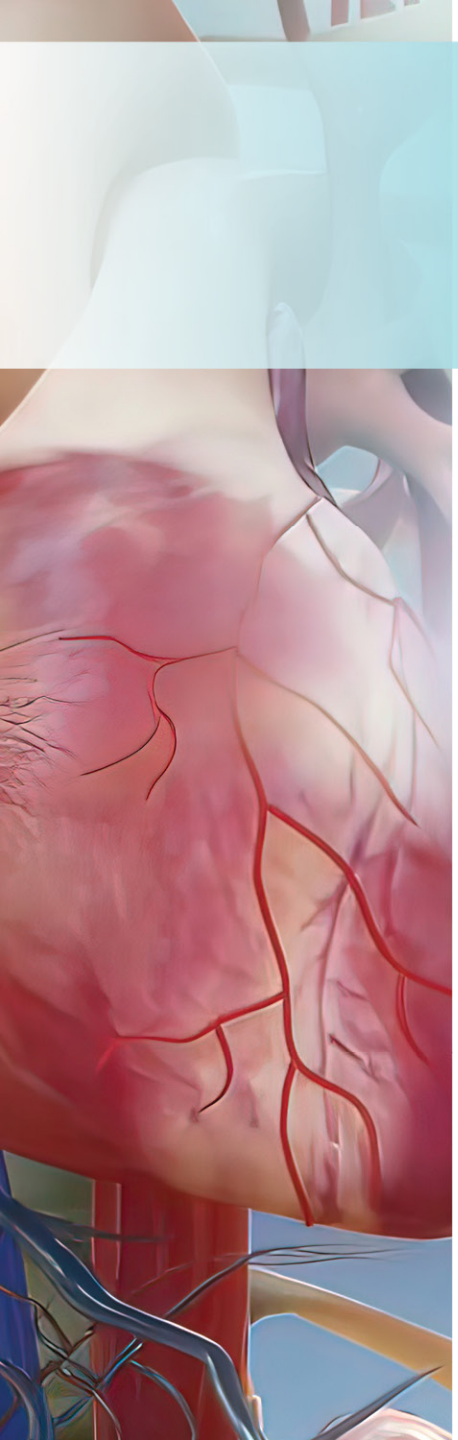
Camzyos [prescribing information]. Bristol Myers Squibb; 2022.



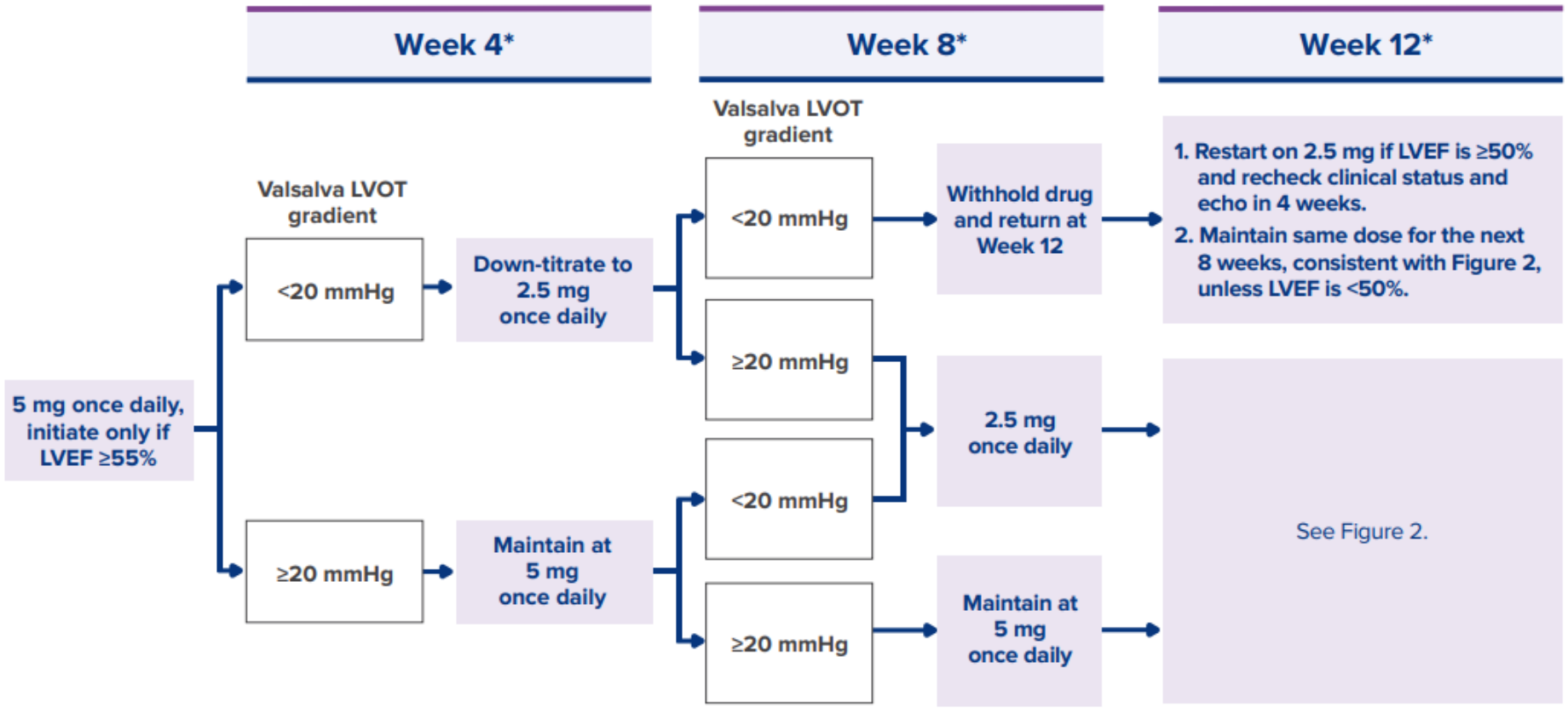
REMS Reduces Risk

- Mavacamten is only available through a risk evaluation and mitigation strategy (REMS) program because of the risk of HF due to systolic dysfunction
- Notable REMS requirements include the following:
  - Prescribers must be certified by enrolling in the REMS program
  - Patients must enroll in the REMS program and comply with ongoing monitoring requirements
  - Pharmacies must be certified by enrolling in the REMS Program and must only dispense to patients authorized to receive mavacamten
  - Wholesalers and distributors must only distribute to certified pharmacies
  - Further information: www.CAMZYOSREMS.com **or** 1-833-628-7367

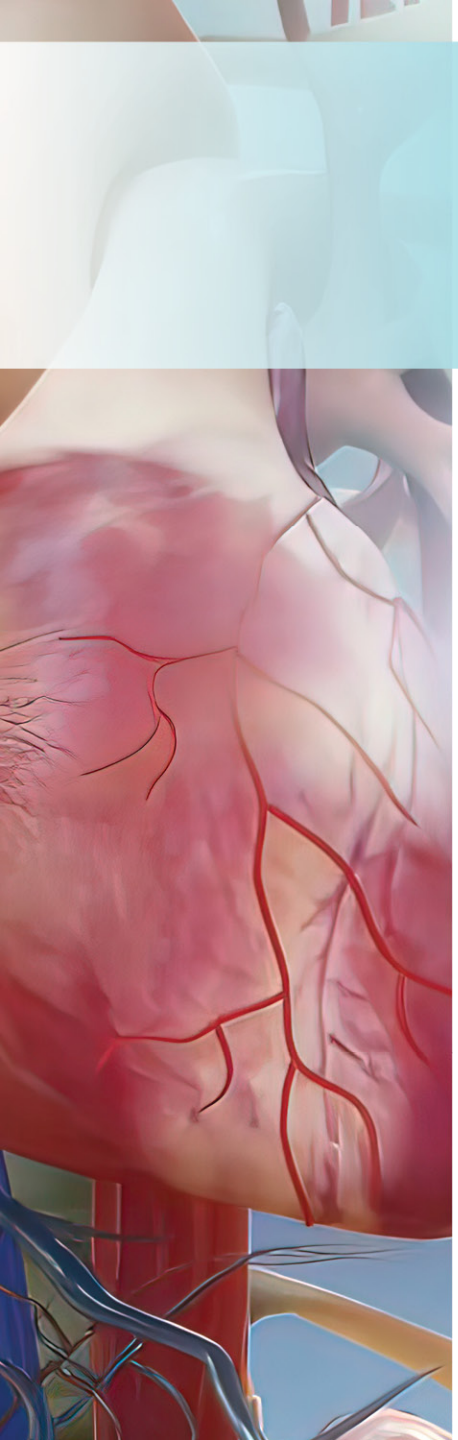
Camzyos [prescribing information]. Bristol Myers Squibb; 2022.



Mavacamten Initial Dosing



Camzyos dosing guide. Accessed September 28, 2022. https://www.camzyoshcp.com/dosing-guide

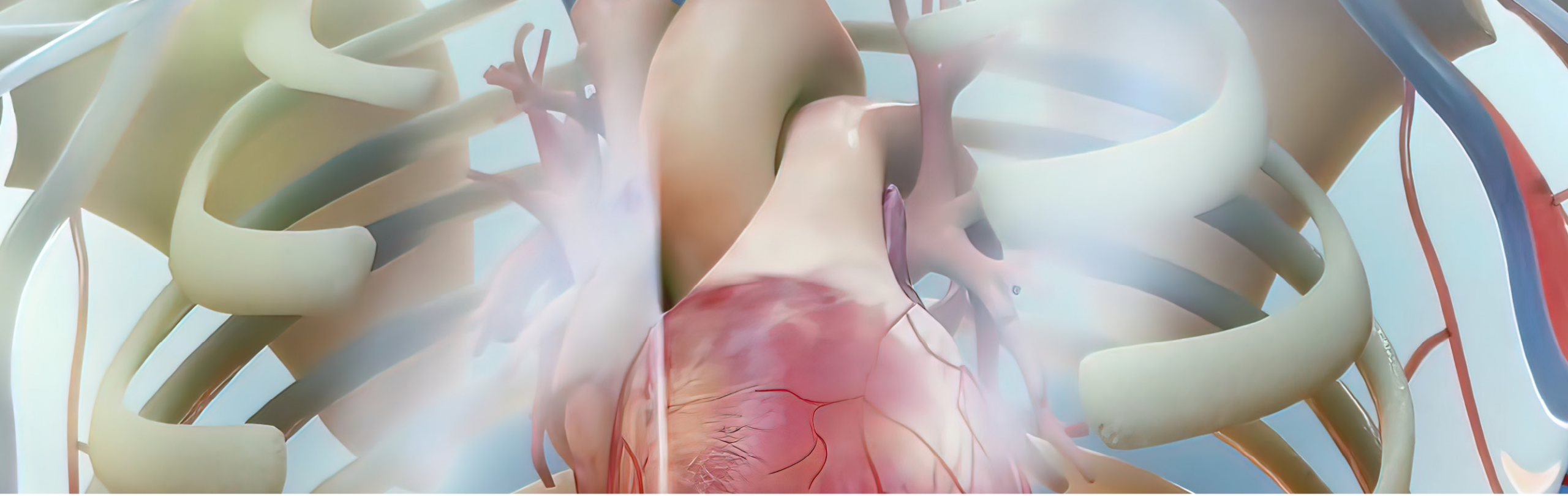


Mavacamten Maintenance Dosing

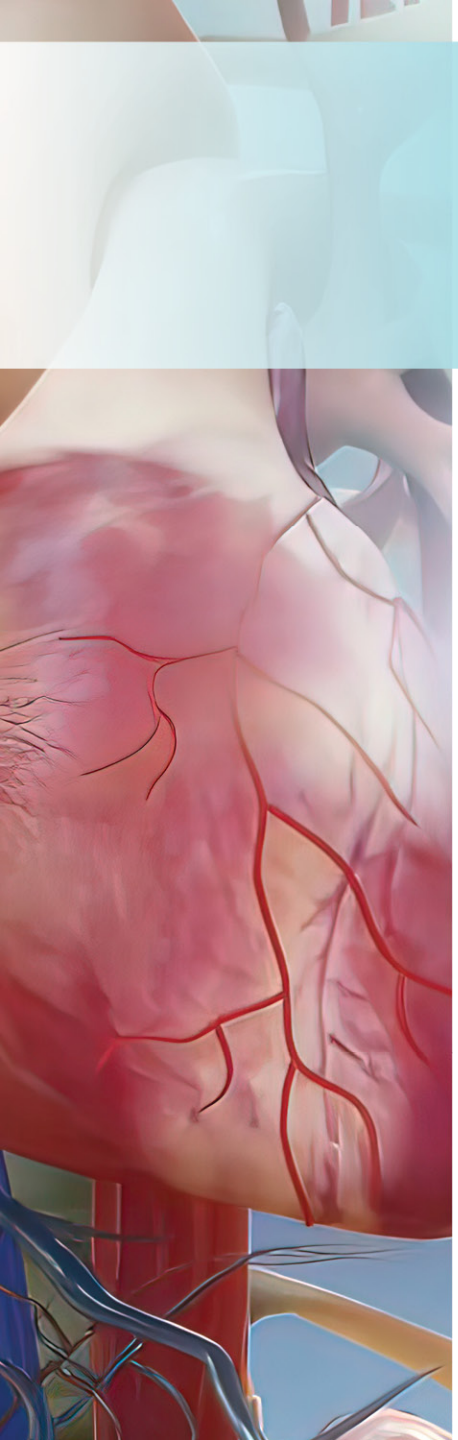
Week 12 + every 12 weeks

Current dose		
	LVEF <50%	**Interrupt treatment.** See Figure 3.
	LVEF 50%–55%, regardless of Valsalva LVOT gradient or LVEF >55% and Valsalva LVOT gradient <30 mmHg	**Maintain on the same dose and follow up 12 weeks later.**
	LVEF ≥55% and Valsalva LVOT gradient ≥30 mmHg	1. **Up-titration to next higher daily (mg) dose level:** 2.5 ➔ 5; 5 ➔ 10; 10 ➔ 15. 2. Recheck clinical status and echo in 4 weeks, and maintain the same dose for the next 8 weeks unless LVEF is <50%. 3. Further up-titration is allowed after 12 weeks of treatment on the same dose level.

Camzyos dosing guide. Accessed September 28, 2022. https://www.camzyoshcp.com/dosing-guide

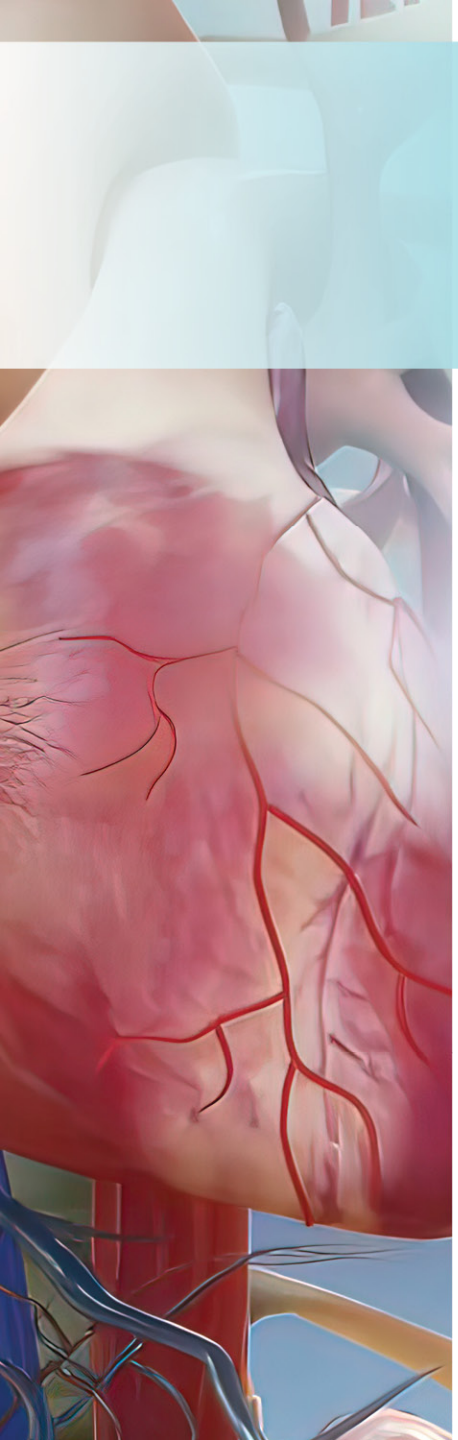


Considerations for Pharmacists



Patient-Centered Therapy Selection

- Drug therapy only indicated for symptomatic patients with obstructive physiology
- Patients with atrial fibrillation require stroke prevention and rhythm control therapies
- Patients with LVEF < 50% should receive standard HF guideline-directed medical therapies
- Patients with high gradient LVOT obstruction and refractory symptoms should receive SRT

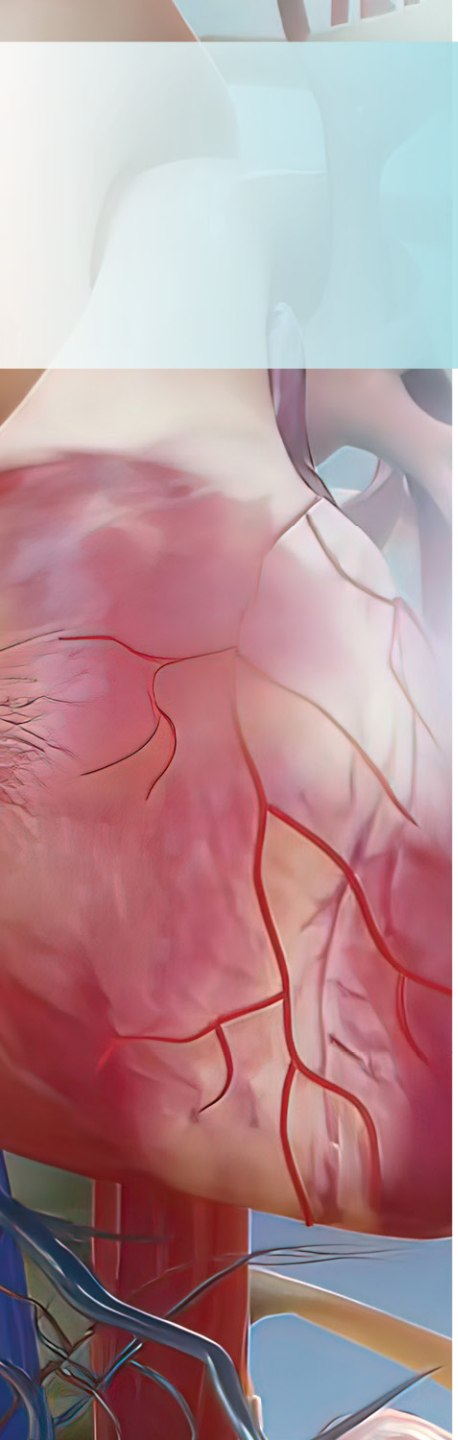


REMS Program

To become certified in the mavacamten REMS program, pharmacies must

1. Designate a representative to complete the program
2. Complete the training program online
   - Complete the pharmacy enrollment form online
   - Train all relevant staff
3. Before dispensing each dose:
   - Counsel the patient on drug interactions and complete the checklist
   - Confirm the patient and provider are enrolled
4. Dispense no more than a 35-day supply
5. Report any adverse events to the manufacturer

Camzyos REMS. Accessed September 28, 2022. https://www.camzyoshcp.com



Adverse Event Monitoring

Interrupt treatment if LVEF <50% at any visit

LVEF <50%

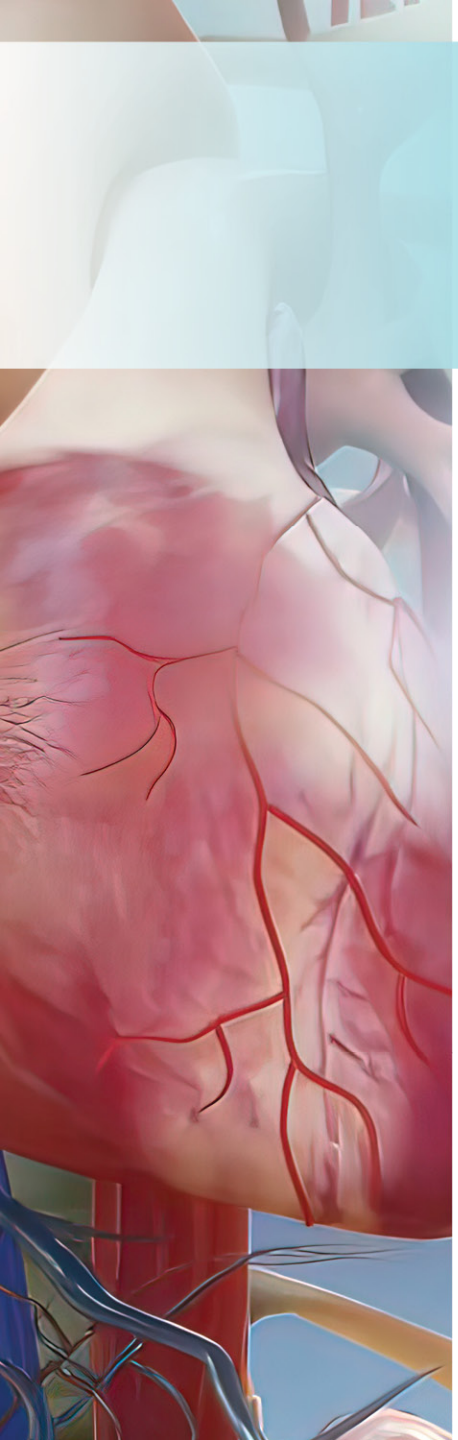
1. **Interrupt treatment.**
2. Recheck echo parameters every 4 weeks until LVEF is ≥50%.

Permanently discontinue treatment if LVEF is <50% twice on 2.5 mg daily.

LVEF ≥50%

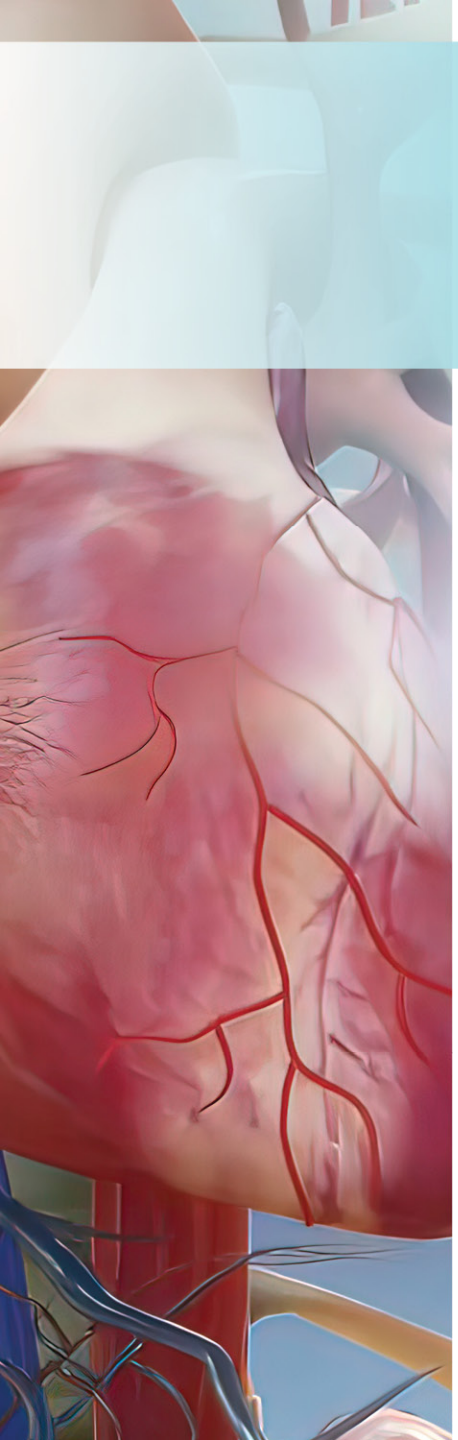
1. **Restart treatment at the next lower daily (mg) dose level:**
   5 → 2.5; 10 → 5; 15 → 10.
   - If interrupted at 2.5 mg, restart at 2.5 mg
2. Recheck clinical status and echo in 4 weeks, and maintain the same dose for the next 8 weeks unless LVEF is <50%.
3. Follow Figure 2.

Camzyos dosing guide. Accessed September 28, 2022. https://www.camzyoshcp.com/dosing-guide



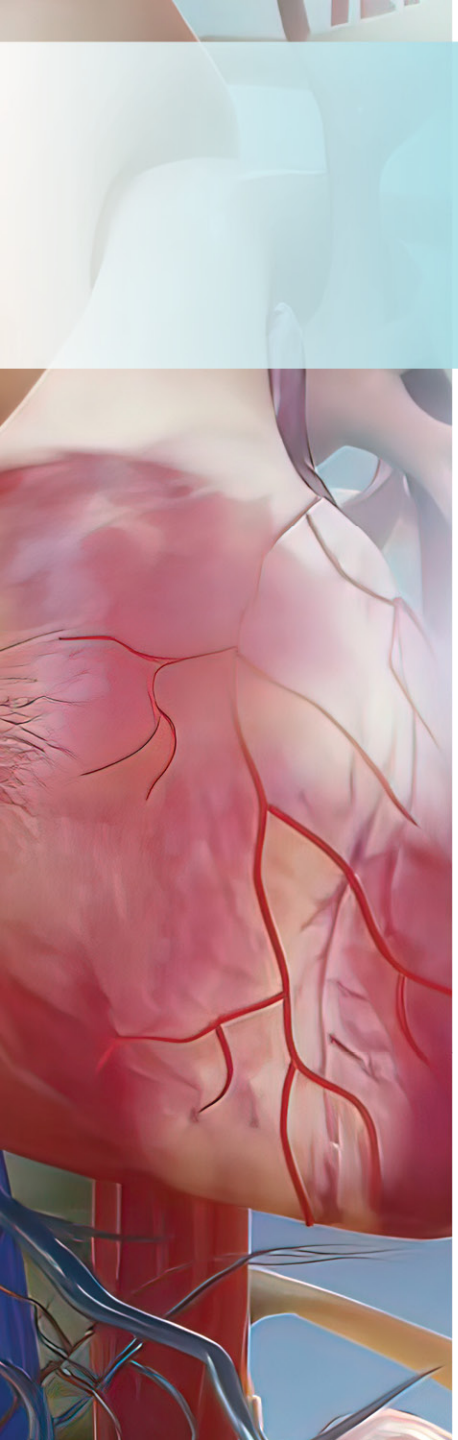
Mavacamten Drug Interactions

Drug(s)	Management
Moderate-to-strong CYP2C19 inhibitors and inducers	• Contraindicated
Strong CYP3A4 inhibitors and inducers	• Contraindicated
Weak CYP219 or moderate CYP3A4 inhibitors	• Taper mavacamten one level and assess LVEF in 4 weeks • Avoid in patients on mavacamten 2.5 mg daily
Substrates of CYP3A4, CYP2C19, and CYP2C9	• Monitor for decreased mavacamten effectiveness • Monitor for decreased substrate effectiveness
Drugs that reduce cardiac contractility	• Monitor LVEF closely • Avoid with disopyramide + verapamil/diltiazem • Avoid with beta-blocker + verapamil/diltiazem/disopyramide



Formulary Considerations

- Approximate cost of $300 per day
- Relatively low use based on disease prevalence
- No pharmacoeconomic data available
- Not included in most recent guidelines from 2020



Place in Therapy

Beta-blockers

- First-line therapy
- SCD reduction

CCB +/- disopyramide

- Reasonable second-line therapy
- Inexpensive

Mavacamten

- Appropriate third-line option
- Prior to SRT

Questions and Answers

Thank You!