Treatment of Cardiomyopathies and Genetics

Douglas Stoller, MD PhD

State of the Heart: 2nd Annual Heart and Vascular Conference

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University of Nebraska Medical Center
Nebraska Medicine

Disclosures

I am on the speakers' bureau (nonbranded) for Bristol Myers Squibb.
I have previously served on advisory boards for Bristol Myers Squibb.

I have previously received research support from Amgen.

Objectives

1. Review guideline updates in management of hypertrophic cardiomyopathy

2. Describe the mechanism and use of myosin inhibitor therapy in hypertrophic cardiomyopathy

3. Explain the basics of genetic testing and family screening and surveillance

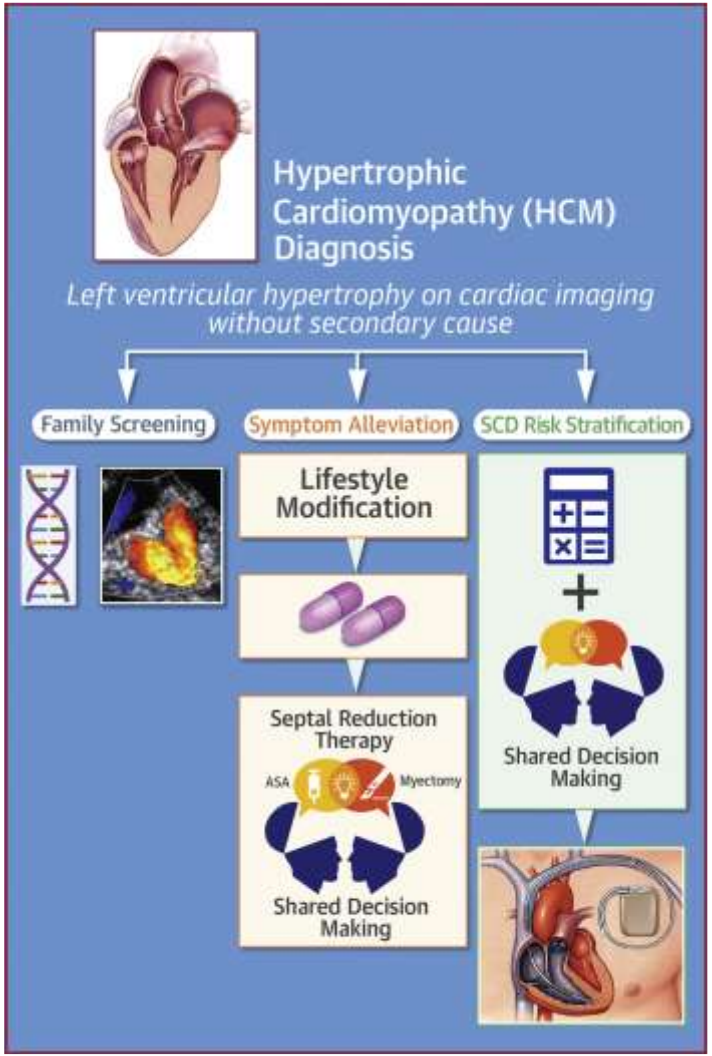
Talk Outline

Treatment of Cardiomyopathies

- Medical therapy for Hypertrophic Cardiomyopathy
- Myosin inhibitor therapy
  - Obstructive HCM
  - Non-obstructive HCM
- Horizon non-invasive therapy for HCM

Genetics of Cardiomyopathies

- Explain the basics of genetic testing and family screening/surveillance

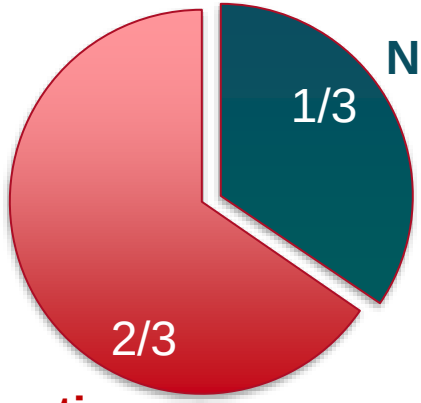


Management of Hypertrophic Cardiomyopathy

Geske et al. *JACC-HF* 2018

Obstructive vs Nonobstructive

LV outflow tract (LVOT) obstruction = pressure difference between LV and aorta due to myocardial obstruction (not a fixed obstruction)



Nonobstructive

Obstructive

LVOT gradient >30 mmHg

50:50 rest/provokable

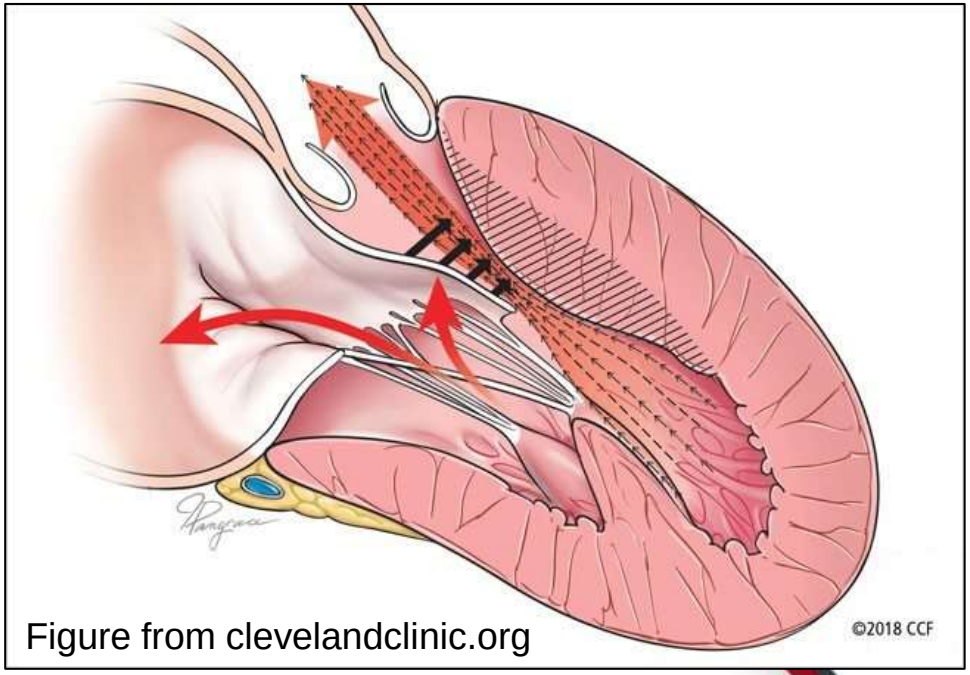


Figure from clevelandclinic.org

Symptom management overview

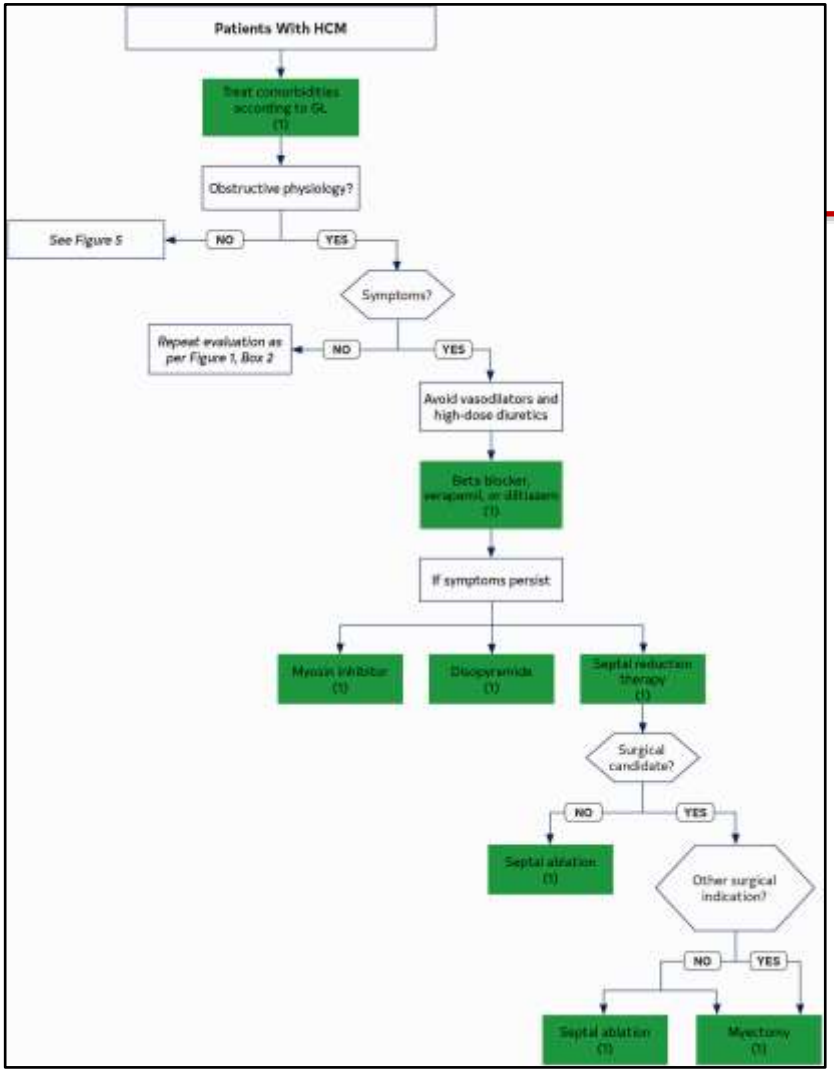
	OBSTRUCTIVE	NON-OBSTRUCTIVE

HCM 2024 Guideline update

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

COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM and symptoms* attributable to LVOTO, nonvasodilating beta blockers, titrated to effectiveness or maximally tolerated doses, are recommended.[1–3]
1	B-NR†	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta blockers are ineffective or not tolerated, substitution with nondihydropyridine calcium channel blockers (eg, verapamil,† diltiazem‡) is recommended.[4–6]
	C-LD‡	
1	B-R	3. For patients with obstructive HCM who have persistent symptoms* attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers,§ is recommended.[7–14]
1	C-LD	4. For patients with obstructive HCM and acute hypotension who do not respond to fluid administration, intravenous phenylephrine (or other vasoconstrictors without inotropic activity), alone or in combination with beta-blocking drugs, is recommended.[15]
2b	C-EO	5. For patients with obstructive HCM and persistent dyspnea with clinical evidence of volume overload and high left-sided filling pressures despite other HCM GDMT, cautious use of low-dose oral diuretics may be considered.
2b	C-EO	6. For patients with obstructive HCM, discontinuation of vasodilators (eg, 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 (eg, >100 mm Hg), as well as all children <6 weeks of age, verapamil is potentially harmful.[4,16]

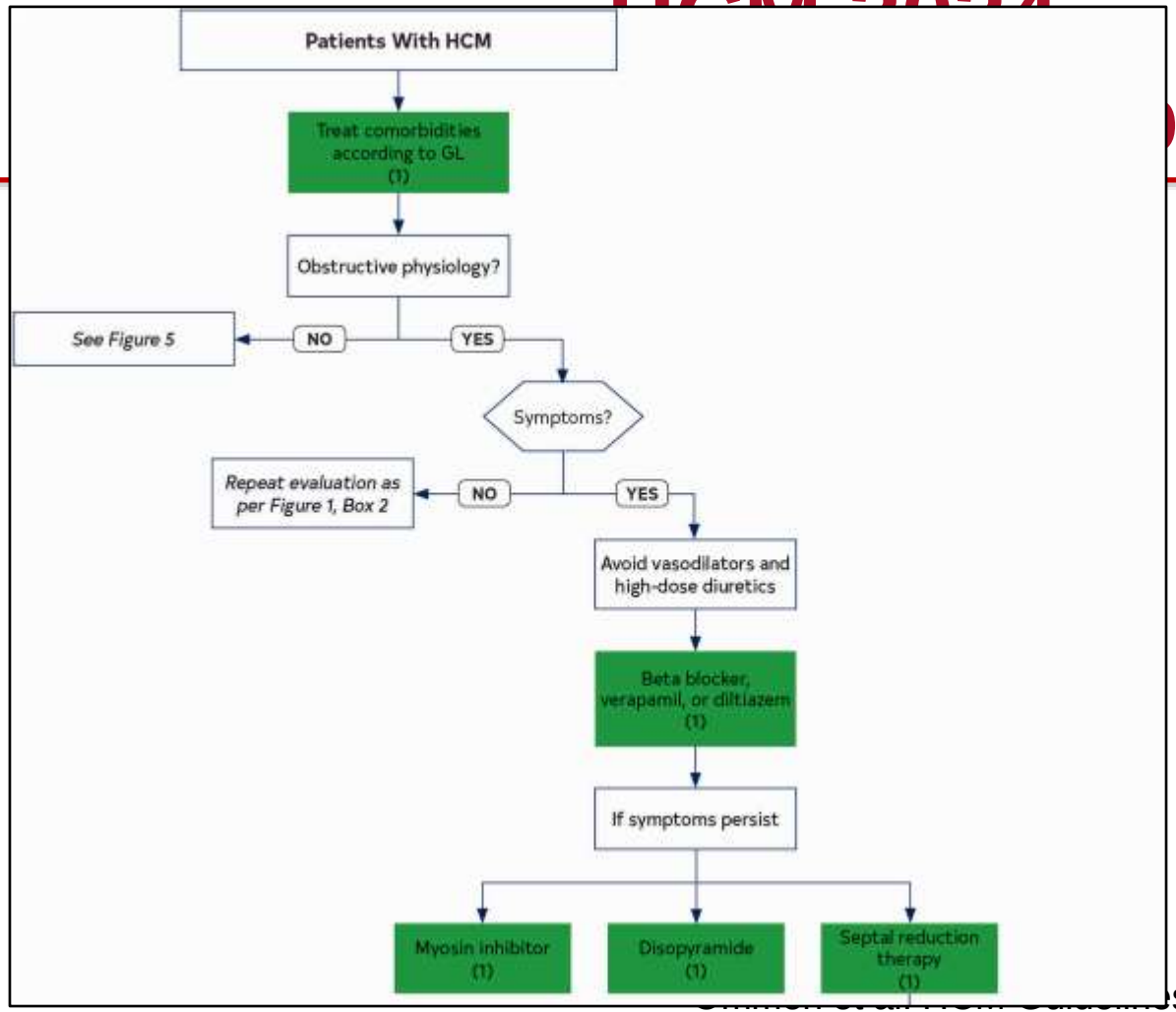
Ommen et al. HCM Guidelines 2024



HCM 2024 Guideline update

Ommen et al. HCM Guidelines 2024

HCM 2024 Update

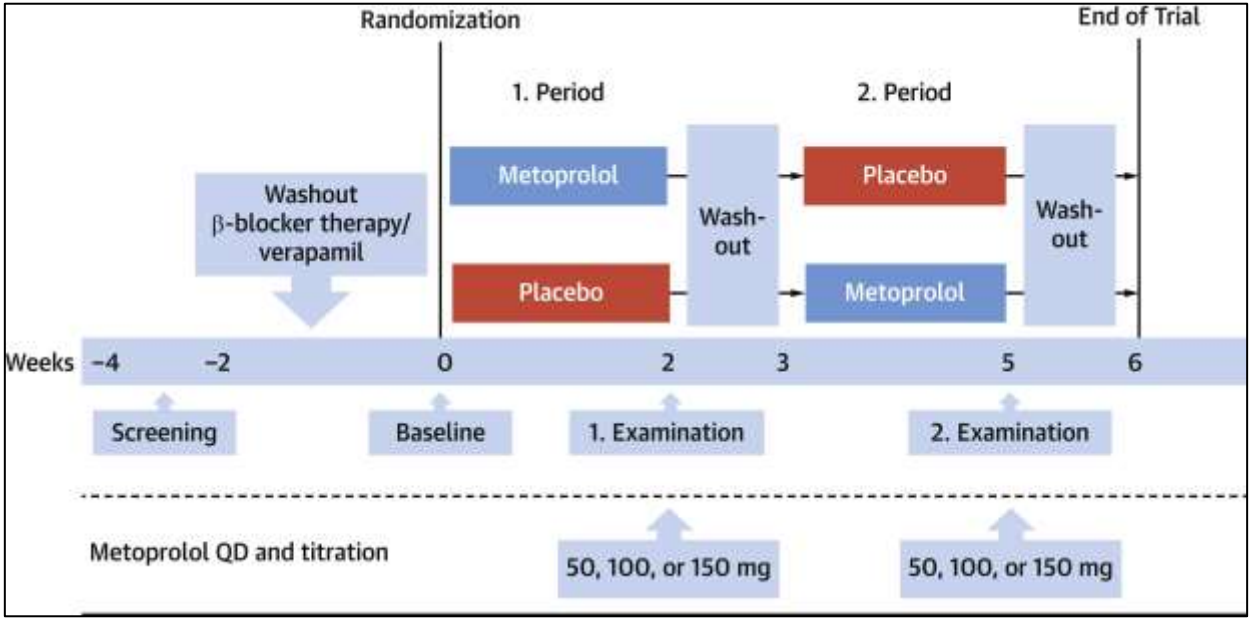


Metoprolol XL in obstructive HCM

Obstructive HCM
LVOT >30 rest or >50 stress
NYHA II+

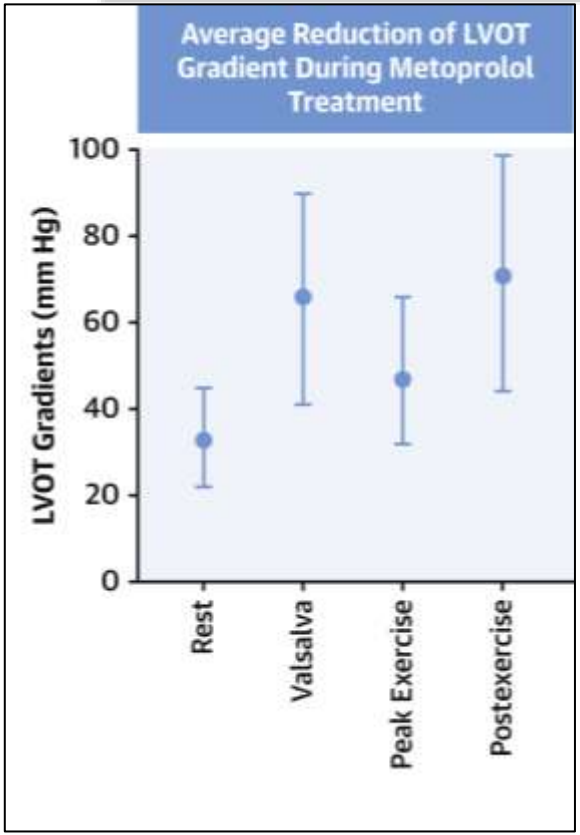
N=30

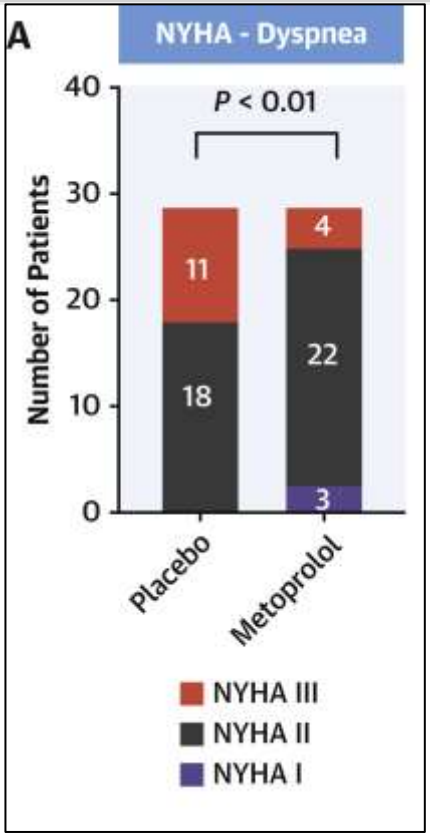
Metoprolol 50-150 mg daily
Treat x14 days



Dybro et al. *JACC* 2021

Metoprolol XL in obstructive HCM

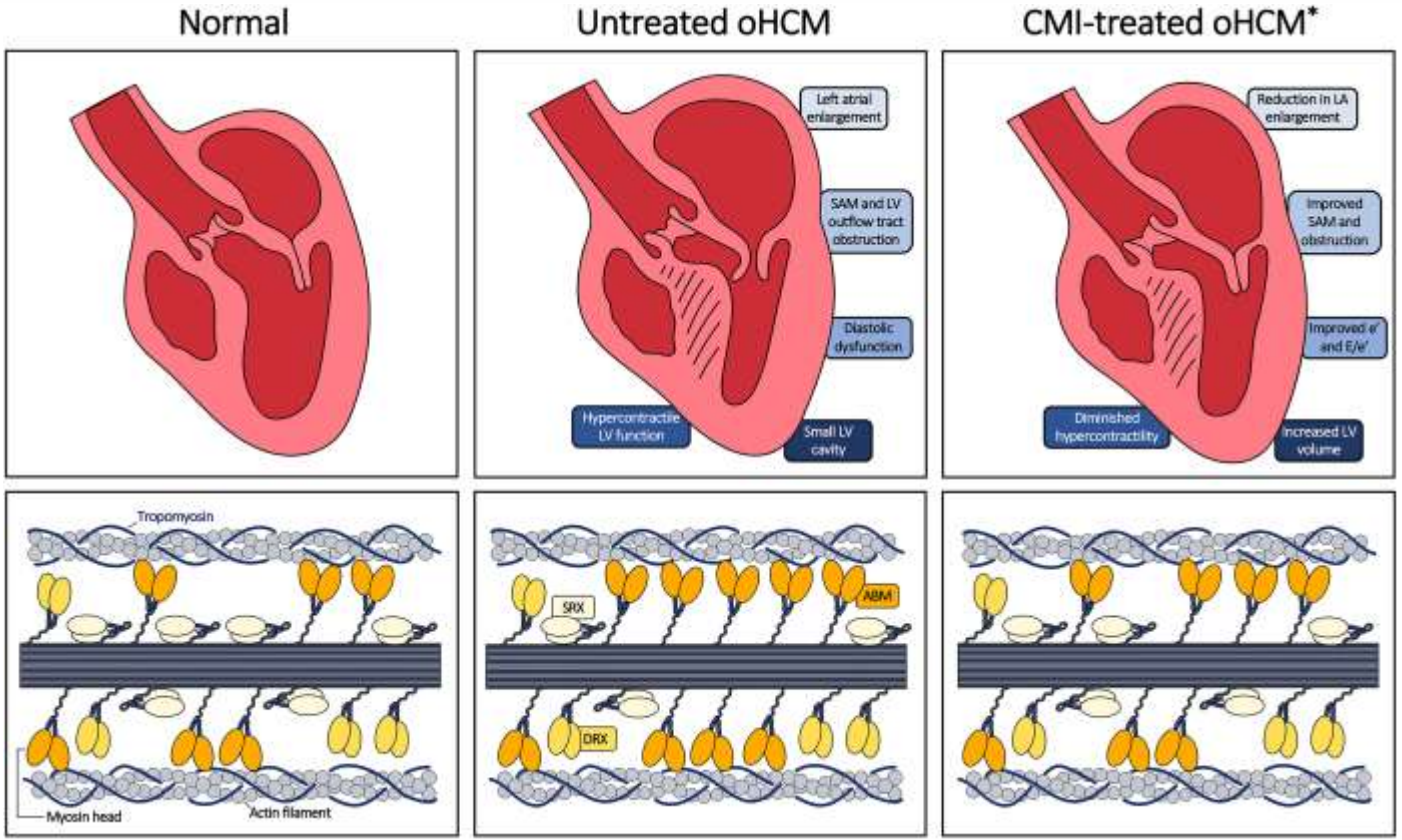




Metoprolol XL x14 days →
1. Significant LVOT grad reduction
2. Improved NYHA class

Dybro et al. *JACC* 2021

Myosin inhibitors



Ostrominski et al.
JACC-HF 2023

Mavacamten

- Reversible inhibitor of cardiac specific myosin
- FDA approved for treatment of obstructive HCM

- Published clinical trials of mavacamten
  - Obstructive HCM (EXPLORER-HCM (phase 3), Olivotto et al. *Lancet* 2020)
  - Severe obstructive HCM (VALOR-HCM (phase 3), Desai et al. *JACC* 2022)
  - Nonobstructive HCM (MAVERICK-HCM (phase 2), Ho et al. *JACC* 2020)

- Ongoing clinical trials of mavacamten
  - Nonobstructive HCM (ODYSSEY-HCM (phase 3)), closed to enrollment
  - HFpEF (EMBARK-HFpEF (phase 2a)), closed to enrollment

Aficamten

- Reversible inhibitor of cardiac specific myosin

- Published clinical trials of aficamten
  - Obstructive HCM (SEQUOIA-HCM (phase 3), Olivotto et al. *NEJM* 2024)
  - Nonobstructive HCM (FOREST-HCM cohort 4 (phase 2), Masri et al. *JCF* 2024)

- Ongoing clinical trials of aficamten
  - Obstructive HCM, aficamten vs metoprolol (MAPLE-HCM (phase 3)), recruiting
  - Nonobstructive HCM (ACACIA-HCM, (phase 3)), recruiting

EXPLORER-HCM trial

Obstructive HCM

LVOT grad >50, NYHA II-III

Continued on prior medical monotherapy (BB or CCB). No disopyramide.

N=251

Treated for 30 weeks

<u>Primary Endpoint</u>:

1.5+ mL/kg/min increase in peak VO2 AND NYHA class reduction

OR

3.0+ mL/kg/min increase in peak VO2

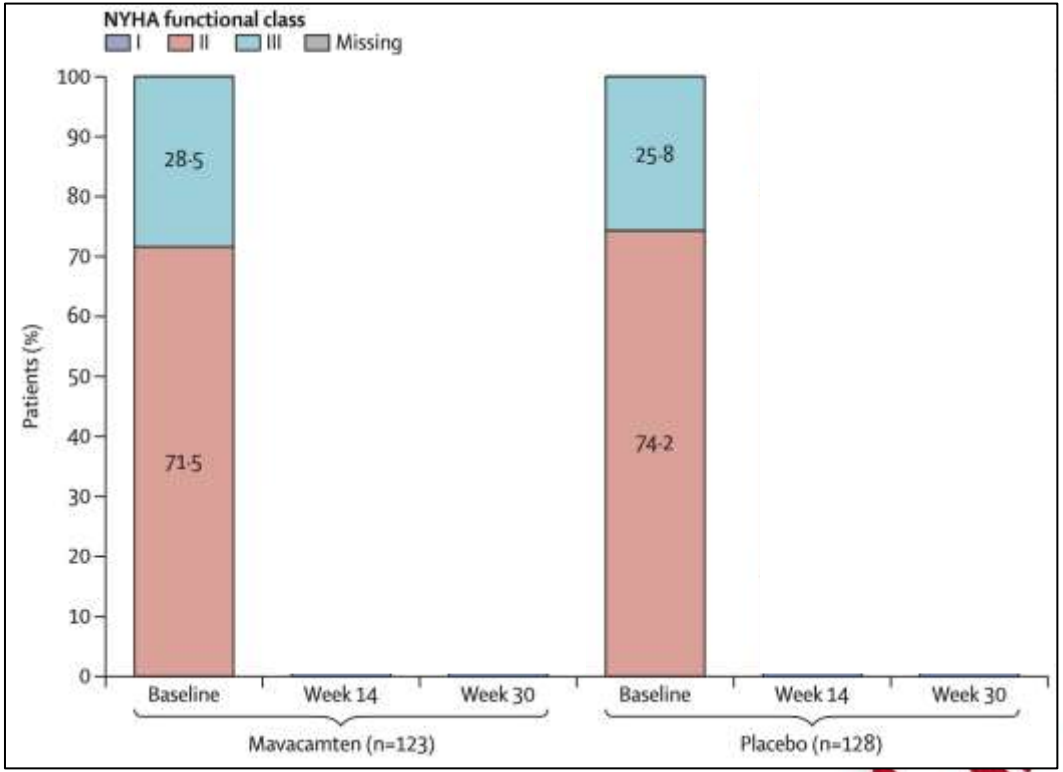
	Mavacamten (n=123)	Control (n=128)	
Primary endpoint	45/123 (37%)	22/128 (17%)	p=0.0005
Peak VO2 1.5+ml/kg/min +NYHA improvement	41/123 (33%)	18/128 (14%)	
Peak VO2 3.0 ml/kg/min	29/123 (24%)	14/128 (11%)	

Olivotto et al. *Lancet* 2020

EXPLORER-HCM trial

Obstructive HCM
LVOT grad >50, NYHA II-III
N=251

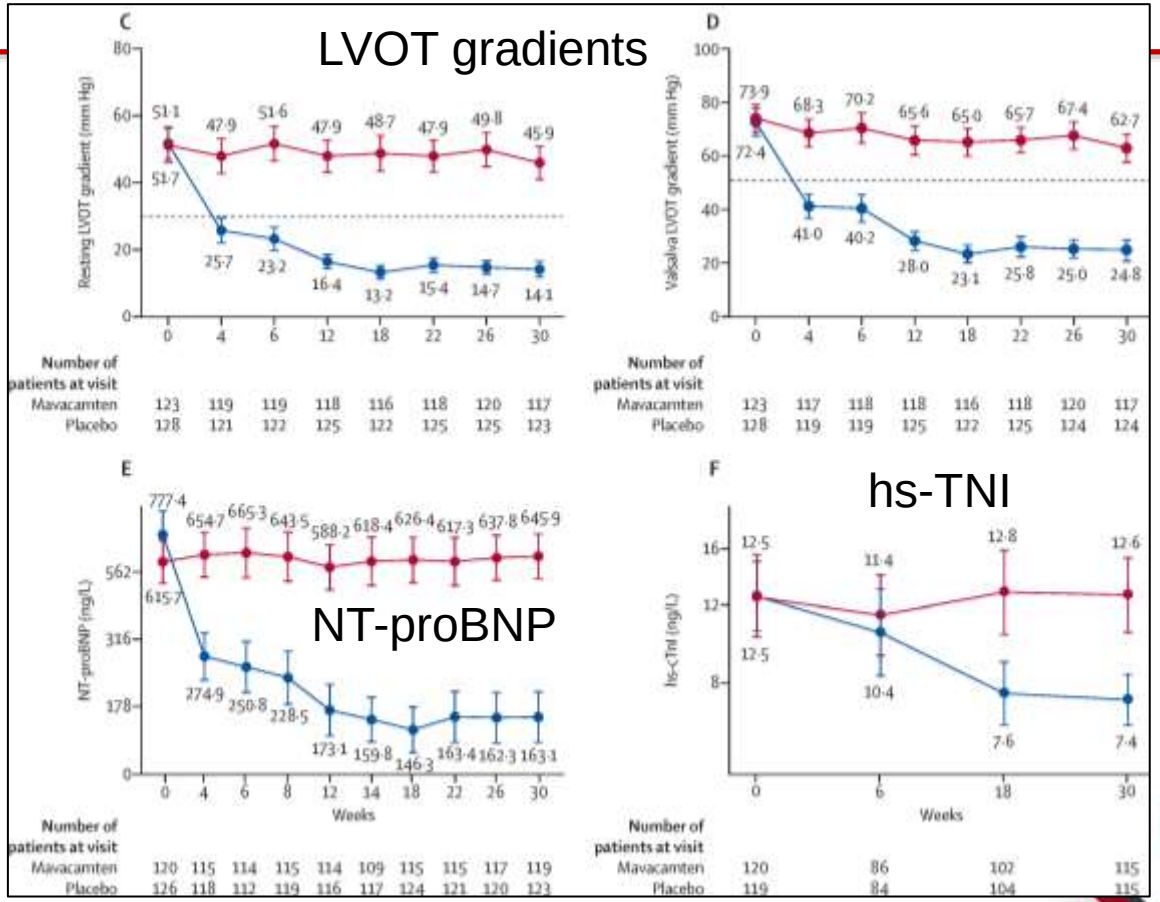
Impact on NYHA class change:



Olivotto et al. *Lancet* 2020

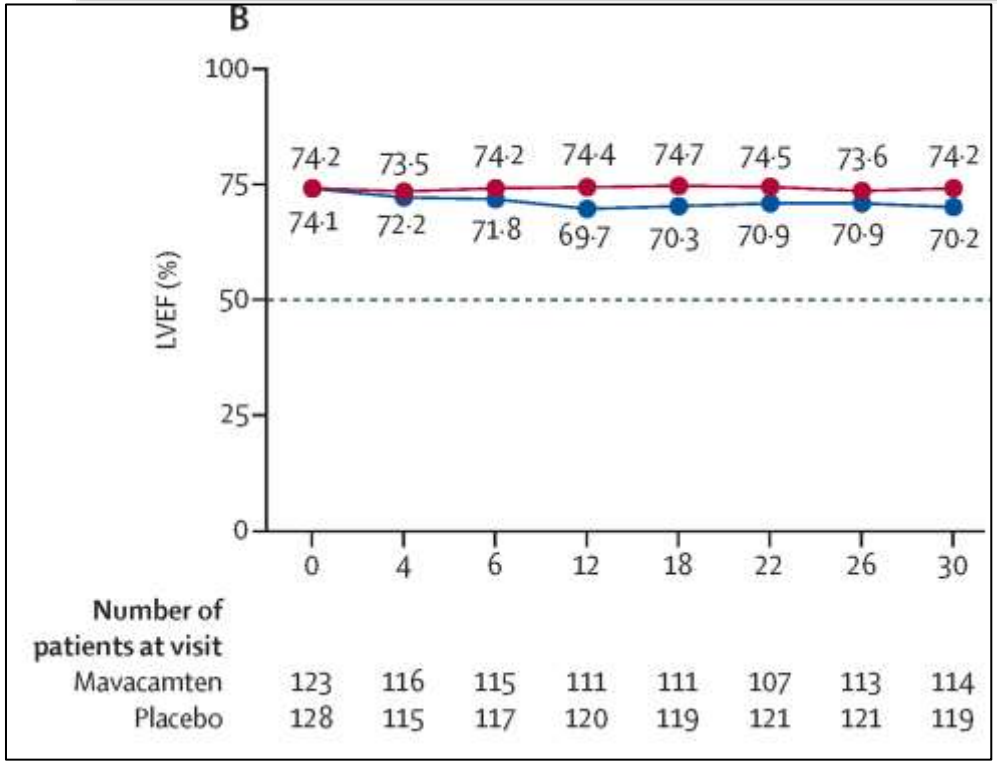
EXPLORER-HCM trial

Obstructive HCM
LVOT grad >50, NYHA II-III
N=251



Olivotto et al. *Lancet* 2020

EXPLORER-HCM trial safety events



Obstructive HCM

LVOT grad >50, NYHA II-III

N=251

For mavacamten:

> 7/123 (5.7%) had EF drop requiring adjustment

> 3/123 (2.4%) required drug stop

> All recovered EF after washout

> Side effects >5%: syncope (27%), dizziness (6%)

Olivotto et al. *Lancet* 2020

SEQUOIA-HCM trial

Obstructive HCM

EF 60, LVOT grad >30 rest, >50 valsalva
NYHA II-III

Continued on background medical therapy

N=282

Treated for 24 weeks

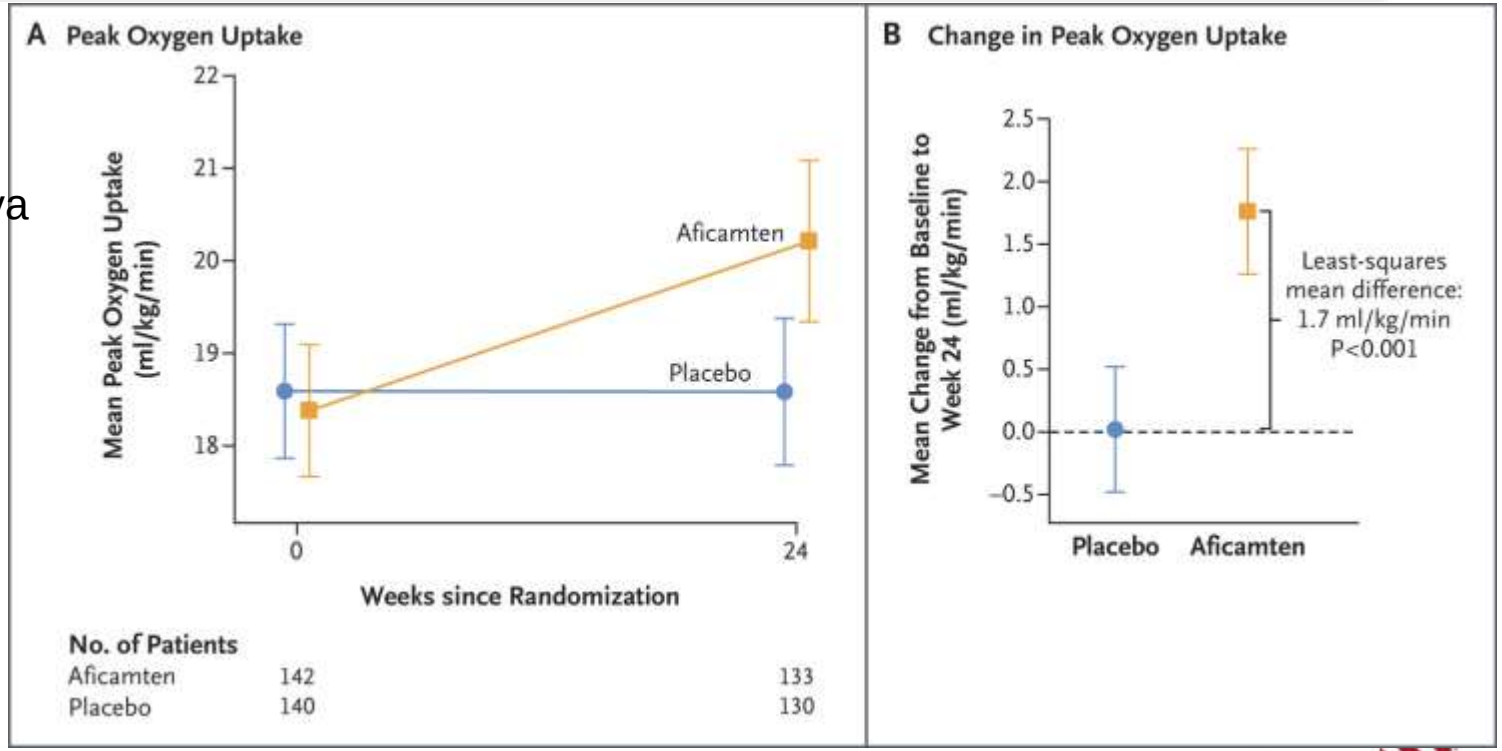
Primary Endpoint:
Change in peak VO2

	Aficamten (n=142)	Control (n=140)	
Change in peak VO2	1.7 ml/kg/min	0.0 ml/kg/min	P<0.001

Maron et al. *NEJM* 2024

SEQUOIA-HCM trial

Obstructive HCM
EF 60
LVOTg >30 rest
LVOTg >50 Valsalva
NYHA II-III



Maron et al. *NEJM* 2024

Mavacamten and Aficamten have similar clinical impact

	Mavacamten	Aficamten
Change in VO2 (ml/kg/min)	1.4	1.7
LVOT gradient (mmHg)	-47	-48
Change in KCCQ score	13.6	11
Reduction of 1 NYHA class (%)	65	59
EF <50% (incidence)	5.7%	3.6%
	FDA approved	Quicker titration
		Fewer drug-drug interactions

Olivotto et al. *Lancet* 2020, Maron et al. *NEJM* 2024

VALOR-HCM trial

Obstructive HCM
Severe sx (NYHA III/IV or II+syncope
Maximal med therapy
LVOT grad >50, LVEF >60
REFERRED for septal reduction therapy
N=112

Primary Endpoint:
Decision to proceed with SRT or guideline eligible at week 16

	Mavacamten (n=56)	Control (n=56)	
Primary endpoint	10/56 (18%)	43/56 (77%)	P<0.001
Proceeded with SRT	2/56 (4%)	2/56 (4%)	
Guideline eligible for SRT	8/56 (14%)	39/56 (70%)	

Desai et al. *JACC* 2022

Myosin Inhibitors – Do’s and Don’ts

CONTRAINDICATED: LVEF <55%

Prescribing providers must complete REMS certification and documentation. Provide echo monitoring minimum of q3 months.

Be mindful of drug-drug interactions

HCM and NONobstructive HCM

Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

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 nondihydropyridine calcium channel blockers are recommended.[1–5]
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 nondihydropyridine 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.[6]
2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA functional 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.[7]
2b	C-EO	5. In asymptomatic patients with nonobstructive HCM, the benefit of beta blockers or calcium channel blockers is not well established.
2b	B-R	6. For younger (eg, ≤45 years of age) patients with nonobstructive HCM due to a pathogenic or likely pathogenic cardiac sarcomere genetic variant, and a mild phenotype,* valsartan may be beneficial to slow adverse cardiac remodeling.[8]

Ommen et al. HCM Guidelines 2024

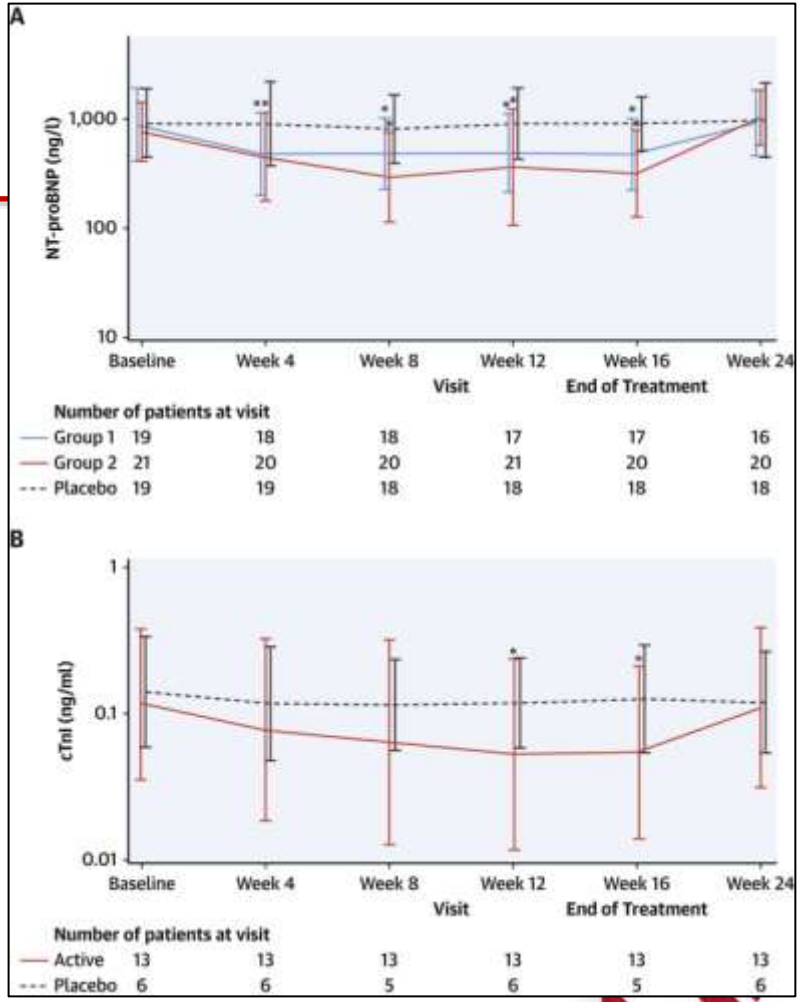
MAVERICK-HCM trial

Mavacamten in Nonobstructive HCM

N=59

EF >55% and NTproBNP >300

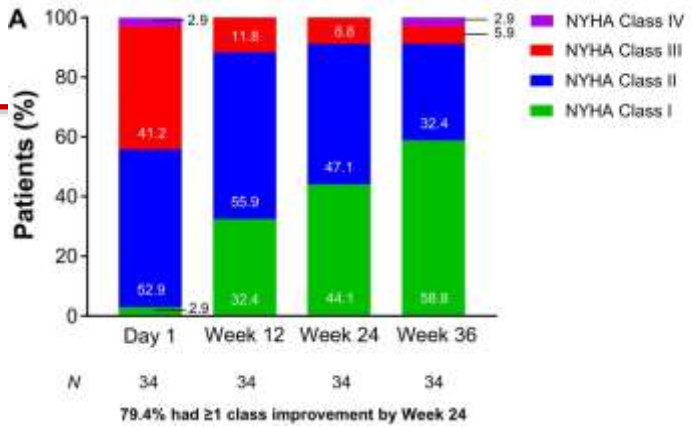
Treated patients exhibited a reversible drop in cardiac troponin and NT-proBNP

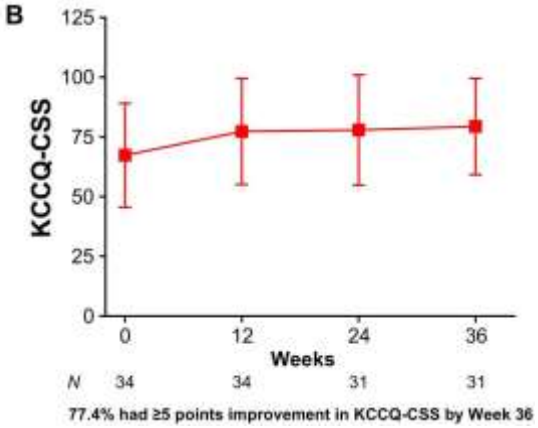


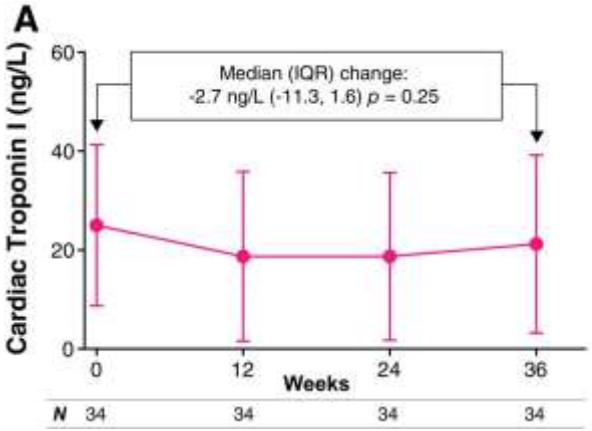
Ho et al. *JACC* 2020

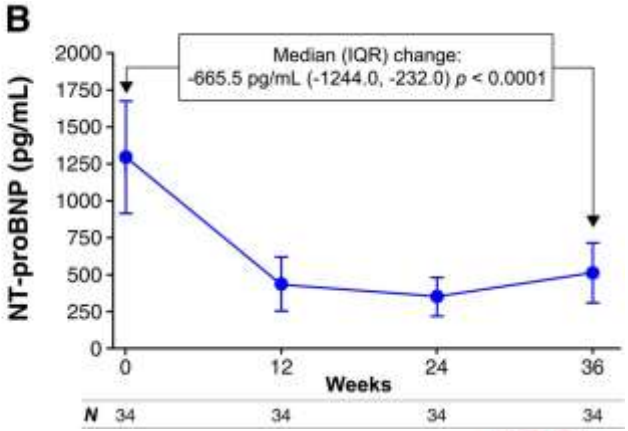
FOREST-HCM

Aficamten
Nonobstructive HCM
N=34
EF >55%







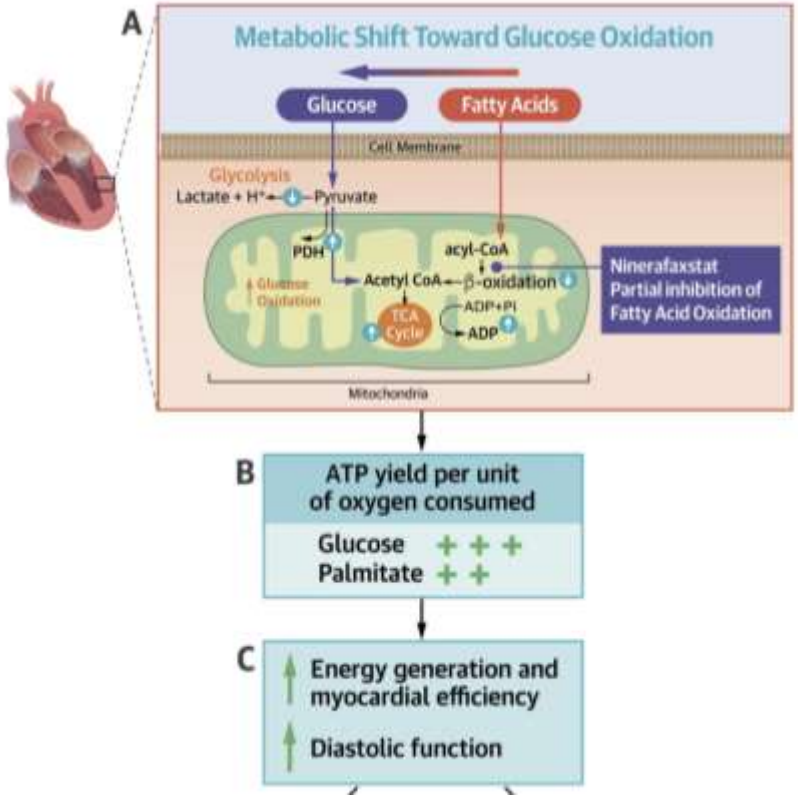


Masri et al. *JCF* 2024

Phase 3 trials: myosin inhibitor in nonobstructive HCM

ODYSSEY-HCM	ACACIA-HCM
Mavacamten	Aficamten
EF >60, LVOT <50 Valsalva, NYHA II-III, (+) biomarkers	
48 weeks	36 weeks
Change in KCCQ Change in peak VO2	Change in KCCQ
Ongoing, closed to enrollment	Recruiting

Ninerafaxstat for Nonobstructive HCM



Ninerafaxstat

--Inhibits FA oxidation

--Shifts metabolism FA > glucose oxidation (less O2 per ATP unit)

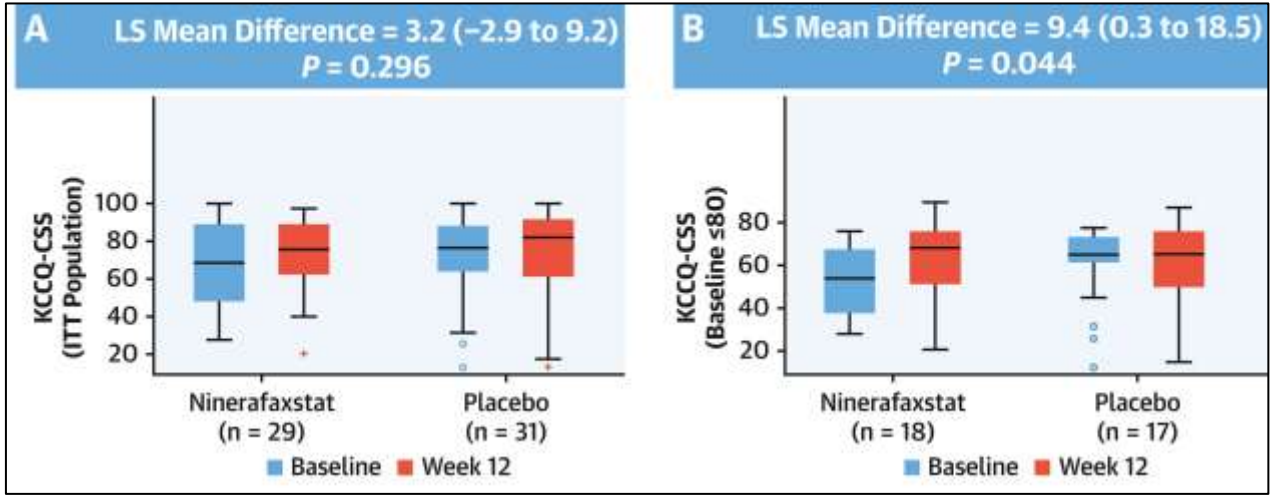
--Enhances cardiac efficiency by increasing recoupling of glucose oxidation and greater energy generation.

Maron et al. *JACC-HF* 2024

Ninerafaxstat for Nonobstructive HCM

Nonobstructive HCM
N=67
EF >50%, LVOT grad <30
Ninerafaxstat vs placebo
12 weeks
Primary endpoint was safety

Secondary endpoints assessed exercise capacity, biomarkers



No impact on BNP, hs-troponin

Maron et al. *JACC-HF* 2024

GENETIC TESTING

Genetic testing options

Gene Panel tests 

- Sequencing of genes (5-100 genes for cardiac) known to cause the disease
- Coverage and depth enriched for genes of interest (often 100x depth)

Exome sequencing 

- Sequencing focused on the exome (coding regions, splicing sites)
- Lower sequencing coverage and depth

Whole genome sequencing 

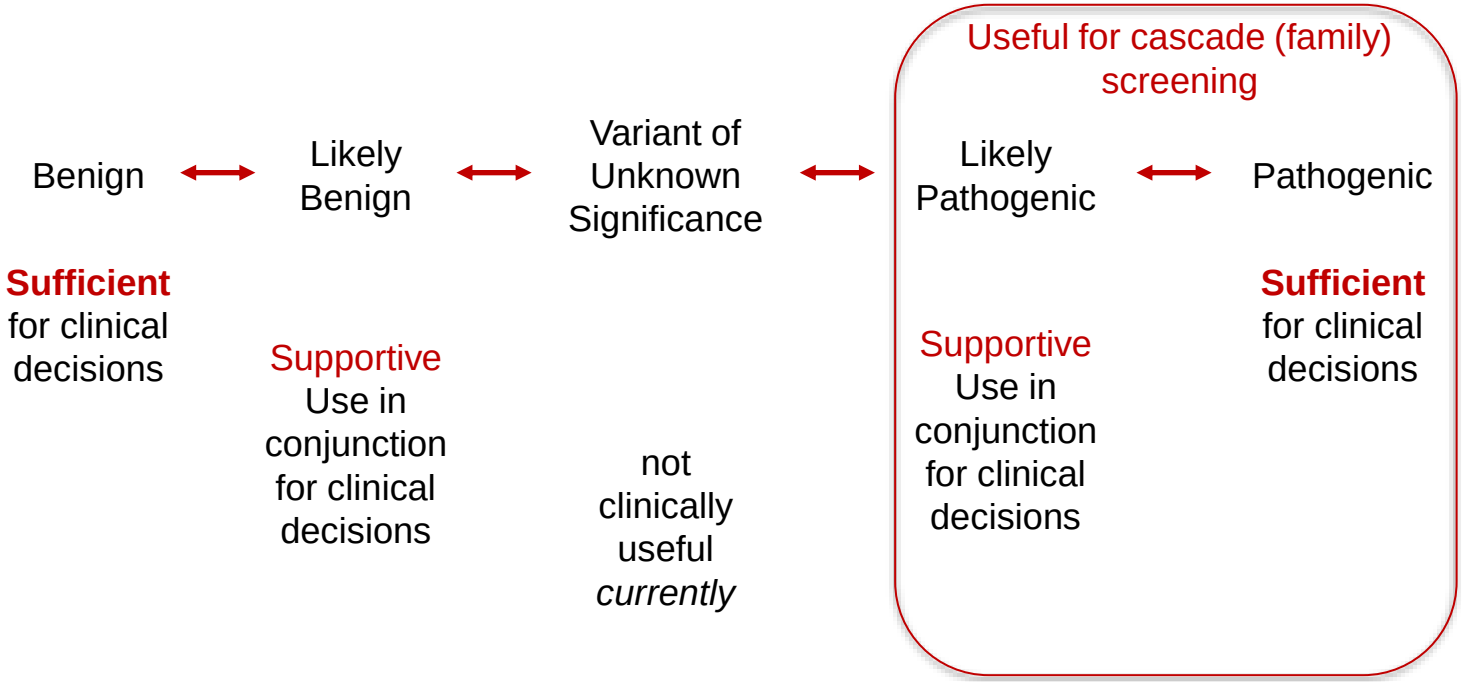
- Sequencing of the entire genome
- Most expensive and time consuming
- Lowest sequence coverage and depth

POORLY DETECTED BY NGS

Gene duplications

Insertion/Deletions

Interpreting results of genetic testing



Richards et al. *Genetics in Medicine* 2015

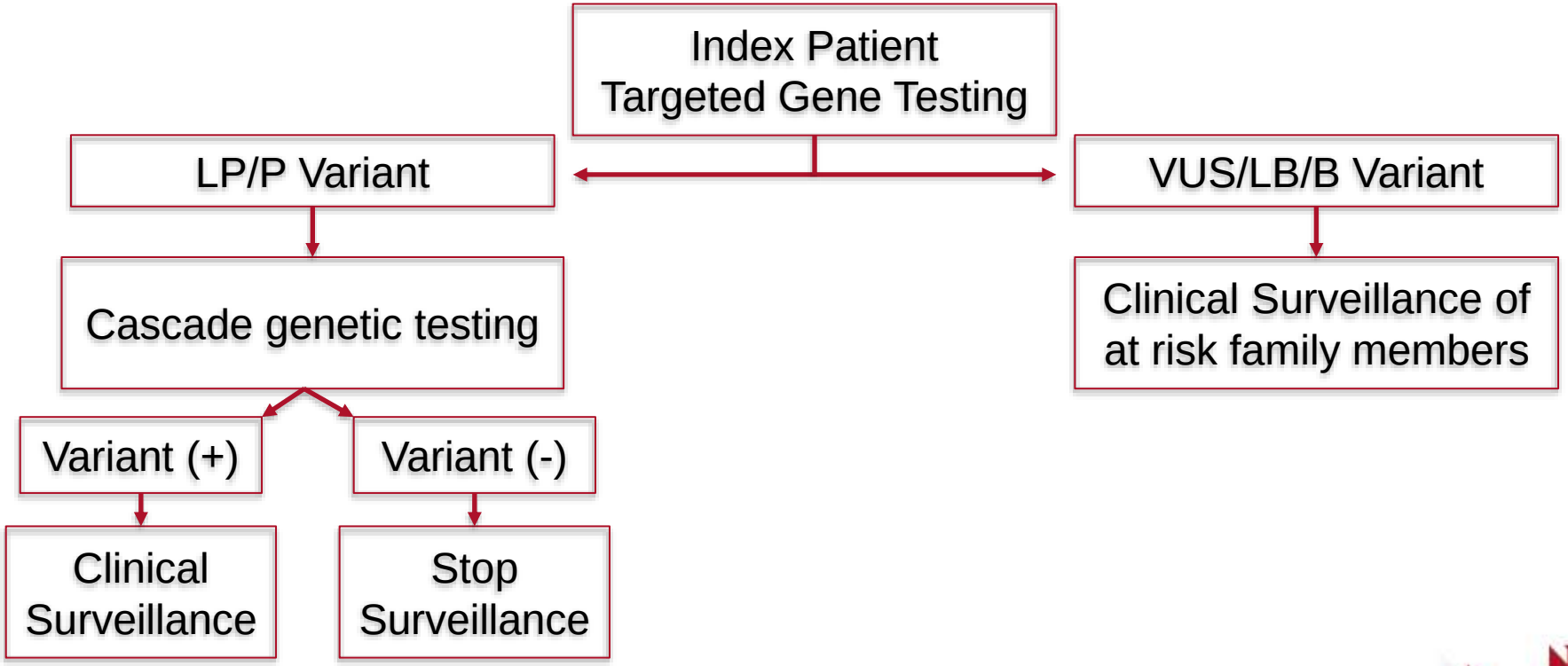
Table 1. Detection Rates and Clinical Utility of Diagnostic Genetic Testing for Selected Inherited Cardiovascular Diseases

Condition	Major Genes or Gene Families Analyzed[a]	Detection Rate, %[b]	Utility of Genetic Testing		
			Diagnostic Criterion	Effect on Proband Management	Predictive Genetic Testing
Hypertrophic cardiomyopathy	Sarcomere genes	30 to >60	NA	+[c]	Yes
Dilated cardiomyopathy	Sarcomere and cytoskeleton genes (including *TTN*)	30-40	NA	NA	Yes
	LMNA	<5 to 10	Yes	++[d]	Yes
Arrhythmogenic cardiomyopathy	Desmosomal genes	~ 60	Yes	+	Yes
Long QT syndrome	Transmembrane ion channel genes	50-75	Yes	++	Yes
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*, *CASQ2*, *TRDN*, and *CALM1*	50-55	Yes	++	Yes
Brugada syndrome	*SCN5A*	20-25	NA	+	Yes
Marfan syndrome	*FBN1*	>90	Yes	++	Yes
Loeys-Dietz syndrome	*TGFBR1/2*, *SMAD3*, and *TGFB2/3*	70-90	Yes	++	Yes
Familial thoracic aortic aneurysms and dissections	*ACTA2*, *MYH11*, and *MYLK*	20-25	NA	++	Yes
Vascular Ehlers Danlos syndrome	*COL3A1*	~ 95	Yes	++	Yes
Familial hypercholesterolemia	*LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*	60-80	Yes	++	Yes

Clinical Utility of Cardiac Genetic Testing

Cirino et al. *JAMA Card* 2020

How to: cascade genetic testing



Take-Home points

- Myosin inhibitors significantly reduce symptom burden in obstructive HCM. Ongoing clinical monitoring is required while on therapy.
- Clinical trials investigating myosin inhibitor therapy in nonobstructive HCM are ongoing.
- Expect clinical trials assessing benefit of myosin inhibitors in HFpEF.
- Time will tell if improved cardiac metabolism is a viable therapeutic target.
- Genetic testing is a valuable tool for family screening.

University of Nebraska Medical Center

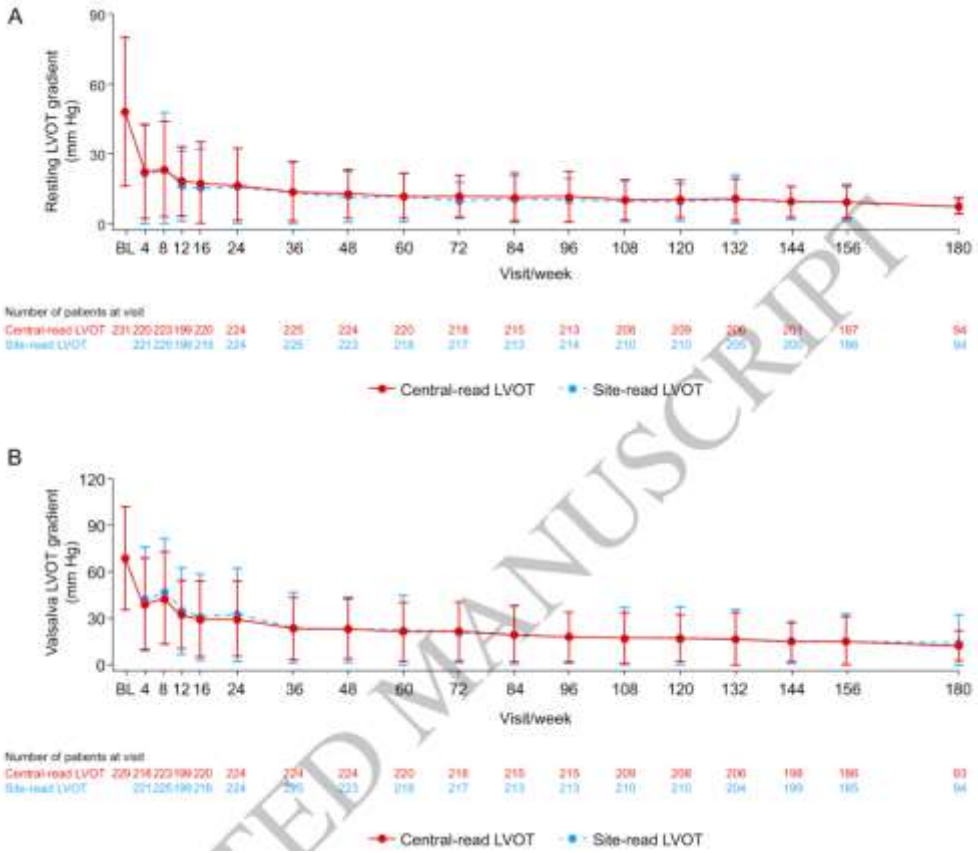
Nebraska Medicine

Mavacamten drug-drug interactions

- Metabolized by **CYP2C19 (74%)**, CYP3A4 (18%) and CYP2C9.

	Inhibitor (↑exposure)	Inducer (↓exposure)
2C19	Contraindicated for moderate or strong Down-adjust dose for weak	
	Mod/Strong: PPIs Weak: omeprazole	Mod/Strong: rifampin Weak:
3A4	Contraindicated for strong Down-adjust dose for moderate	
	Strong: ketoconazole, HIV meds Mod: verapamil, diltiazem, grapefruit juice	Strong: rifampin, phenytoin Mod: St Johns wort

Longterm followup for mavacamten



Extension of EXPLORER-HCM trial
Open label
N=231
Median followup 3.2 yrs
Mavacamten 5 mg > titration

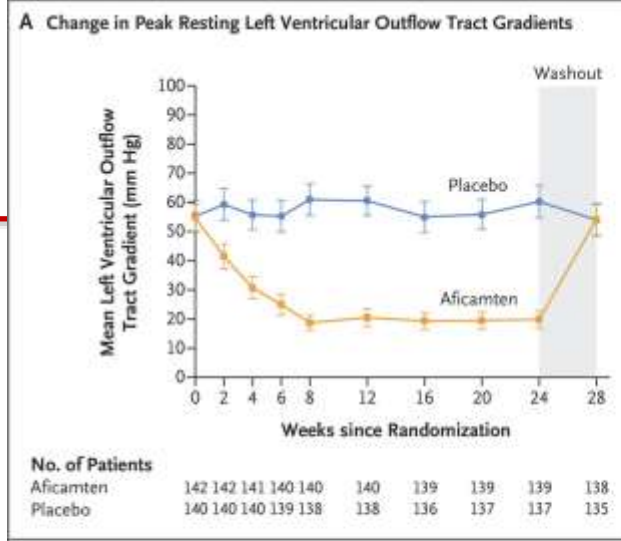
Sustained clinical improvement

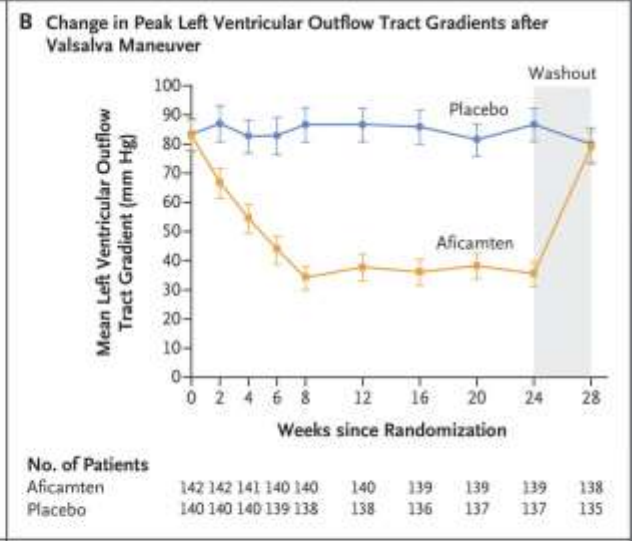
20/231 (8.7%) had incident EF<50% at some point

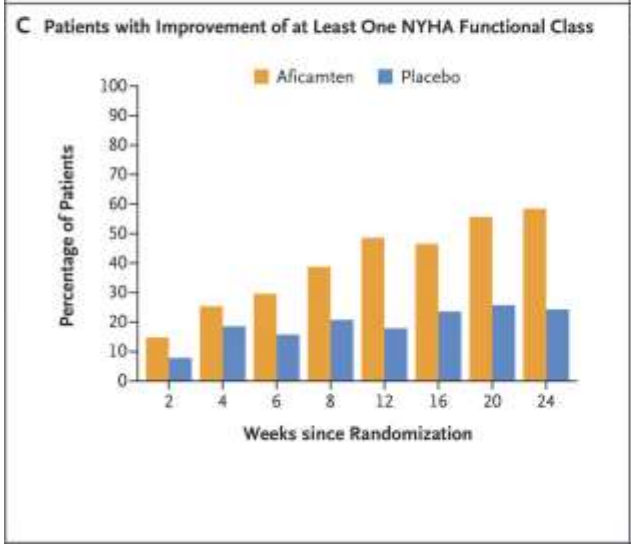
Garcia-Pavia et al. *EHJ* 2024

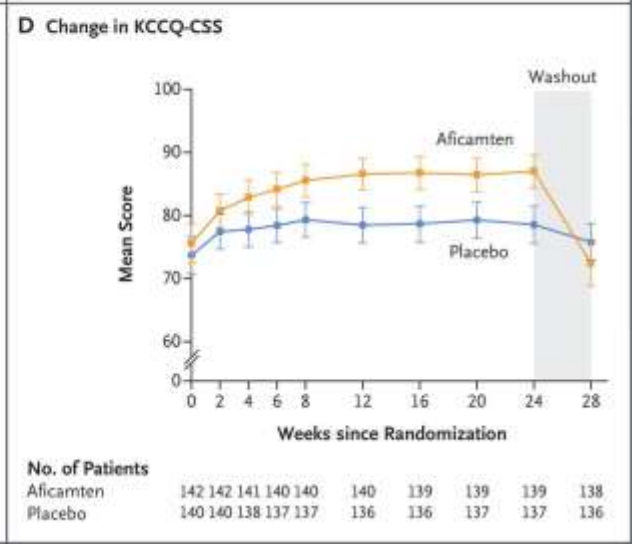
SEQUOIA-HCM

Obstructive HCM
EF 60
LVOTg >30 rest
LVOTg >50 Valsalva
NYHA II-III



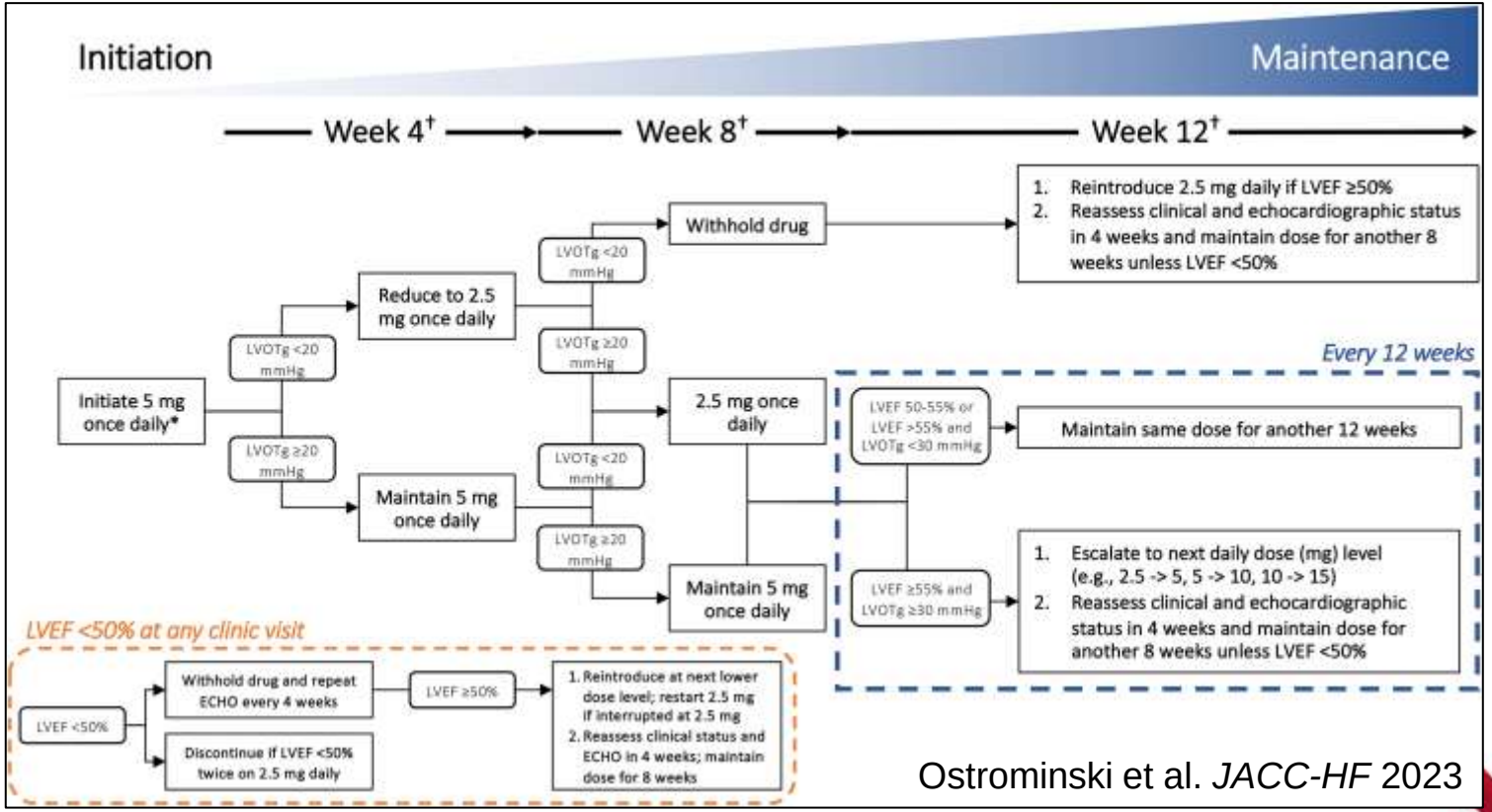






Maron et al. *NEJM* 2024

Mavacamten monitoring



Ostrominski et al. *JACC-HF* 2023