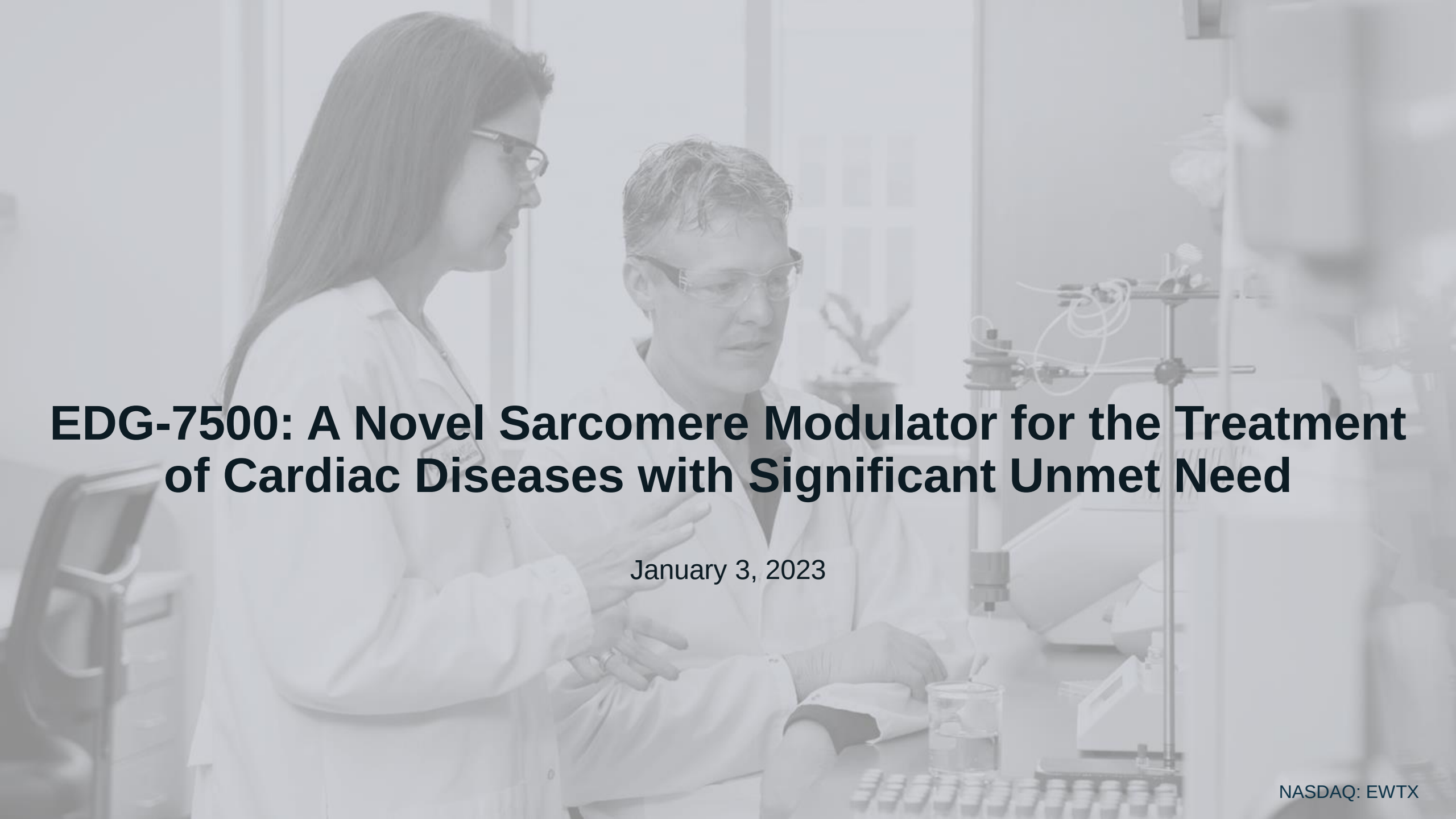

EDG-7500: A Novel Sarcomere Modulator for the Treatment of Cardiac Diseases with Significant Unmet Need

January 3, 2023

NASDAQ: EWTX

Disclaimer

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We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: negative impacts of the COVID-19 pandemic on Edgewise's operations, including clinical trials; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early clinical stage company; Edgewise's ability to develop, initiate or complete preclinical studies and clinical trials for, obtain approvals for and commercialize any of its product candidates or research programs; changes in Edgewise's plans to develop and commercialize EDG-5506 or any other product candidates or research programs; the potential for clinical trials of EDG-5506 or any other product candidates to differ from preclinical, interim, preliminary, topline or expected results; Edgewise's ability to enroll patients in its ongoing and future clinical trials; Edgewise's ability to raise funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Edgewise's reliance on third parties, including contract manufacturers and contract research organizations; Edgewise's ability to obtain and maintain intellectual property protection for its product candidates; risks associated with access to capital and credit markets; the loss of key scientific or management personnel; competition in the industry in which Edgewise operates; Edgewise's ability to develop a proprietary drug discovery platform to build a pipeline of product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in documents that Edgewise files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

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Edgewise THERAPEUTICS

Edgewise Therapeutics is a Clinical-Stage Company Focused on Advancing Innovative Treatments for Devastating Muscle Disorders

- **Experienced management team** with deep expertise in muscle physiology/rare diseases
- Leveraging our **discovery and development capabilities** to advance innovative programs
- Developing EDG-5506 to become the **foundational therapy** for muscular dystrophies
- Expanding our pipeline by developing **novel agents targeting select cardiovascular diseases**

Our vision is to improve the lives of patients and families suffering from rare muscle disorders

Edgewise is Uniquely Positioned to Identify and Develop Novel Therapies Targeting Genetically Defined Cardiovascular Diseases

The field of genetically defined cardiovascular diseases, much like oncology, is evolving as an area of significant focus

Edgewise is leveraging the knowledge of shared sarcomere biology across multiple cardiac disorders to identify unique targets for diseases of high unmet medical need

Building on our success in developing precision small molecules for neuromuscular disorders, Edgewise's EDG-7500 represents a potentially novel approach for HCM

Our Precision Medicine Platform Generated Two Portfolio Programs Across Multiple Indications Currently in Development

	Program	Indications	Preclinical	Phase 1	Phase 2	Phase 3
Skeletal	**EDG-5506** *Myosin ATPase*	BMD				
	EDG-5506 *Myosin ATPase*	DMD				
	EDG-5506 *Myosin ATPase*	LGMD, McArdle				
Cardiovascular	**EDG-7500** *Undisclosed*	HCM				
	EDG-003 *Undisclosed*	Cardiovascular				

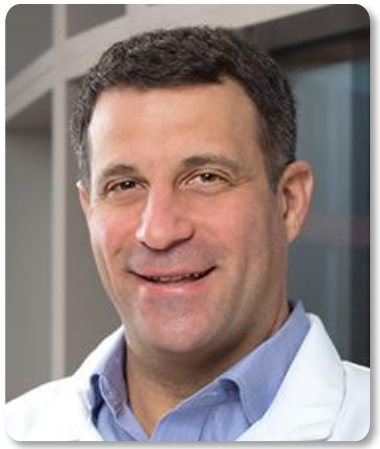


Abbreviations: BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; HCM, hypertrophic cardiomyopathy

Agenda

1. **Hypertrophic Cardiomyopathy: A Clinician's View**
   Dr. Martin Maron
2. **EDG-7500 Introduction & Scientific Overview**
   Marc Evanchik
3. **EDG-7500 Clinical Development Program**
   Dr. Marc Semigran
4. **Closing Remarks**
   Kevin Koch

Dr. Martin Maron
Director Hypertrophic Cardiomyopathy Center, Lahey Hospital



Kevin Koch
Chief Executive Officer



Dr. Marc Semigran
Chief Development Officer



Marc Evanchik
VP, Discovery



Hypertrophic Cardiomyopathy: A Clinician's View

Martin Maron, M.D.

Director Hypertrophic Cardiomyopathy Center, Lahey Hospital

Hypertrophic Cardiomyopathy: The *Unmet* Clinical Needs

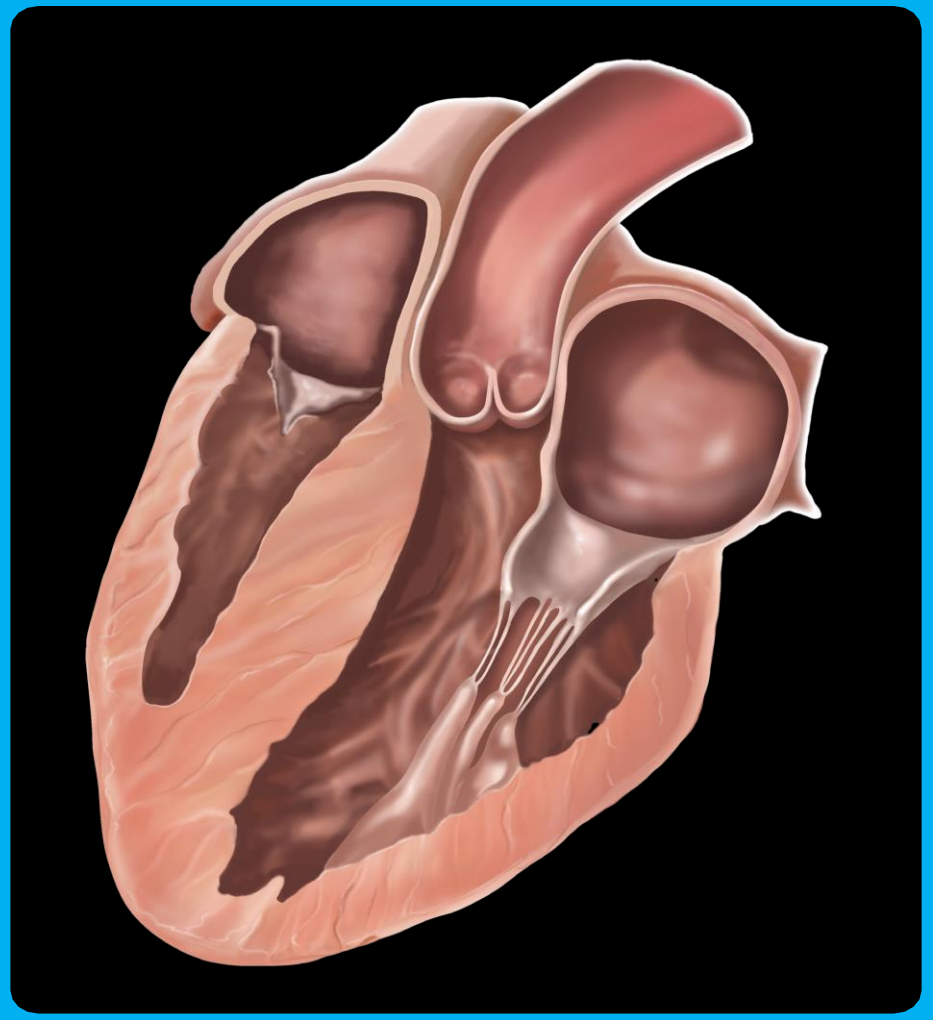
Martin Maron, MD
Director, Hypertrophic Cardiomyopathy Center
Lahey Medical Center; Burlington, MA
Assistant Professor of Medicine, Tufts School of Medicine
Chanin T. Mast Hypertrophic Cardiomyopathy Center
Morristown Medical Center, NJ

COI: Steering Committee Member, Cytokinetics; Consultant Imbria

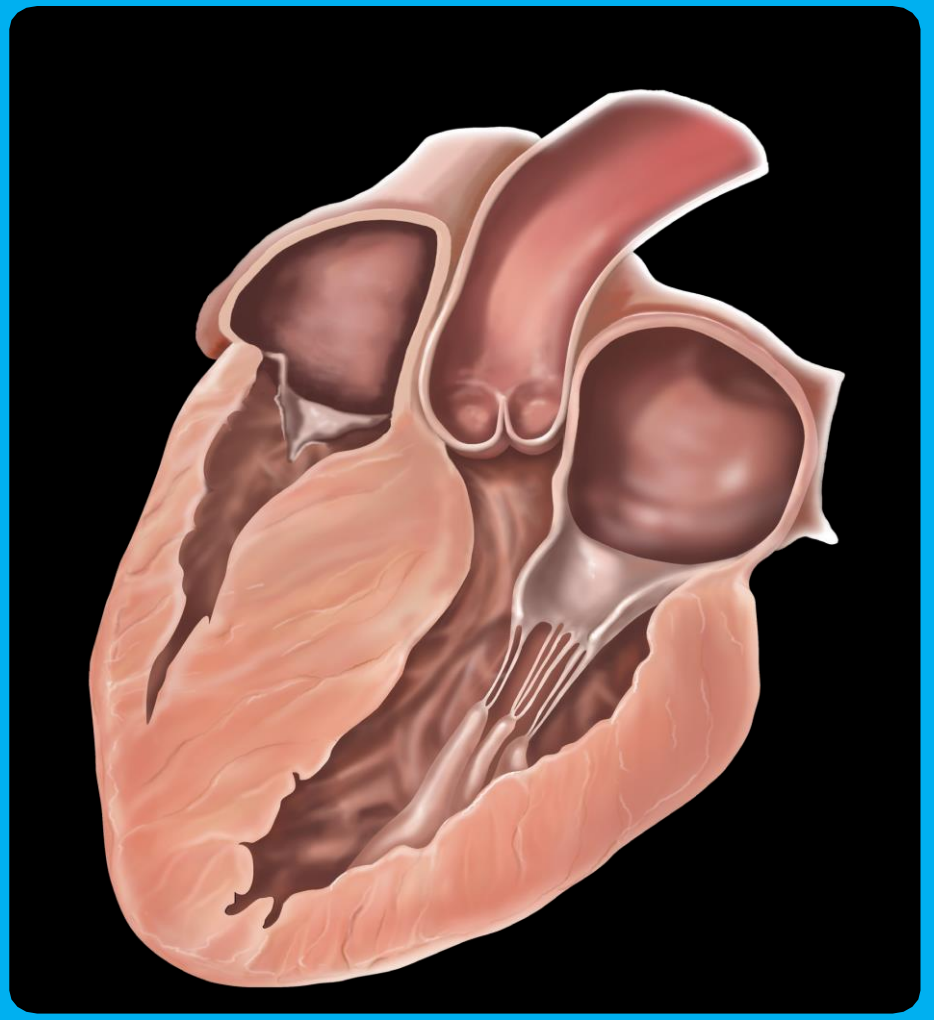
Hypertrophic Cardiomyopathy (HCM)

"Hypertrophied (increased wall thickness >15 mm) left ventricle in the absence of another cardiac or systemic disease that could produce a similar magnitude of hypertrophy"

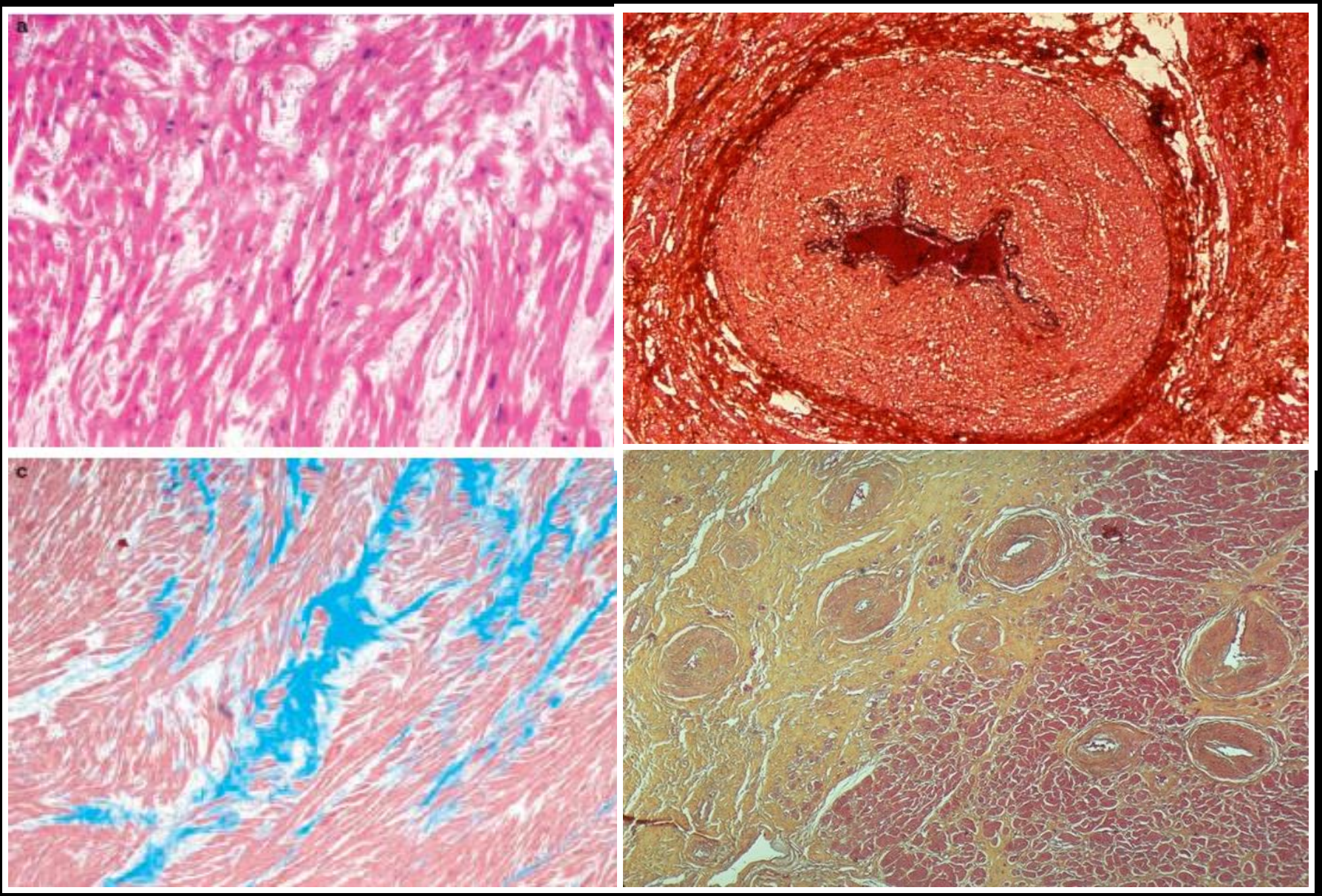
Normal Heart



Hypertrophic Cardiomyopathy



Myocardial Substrate In HCM

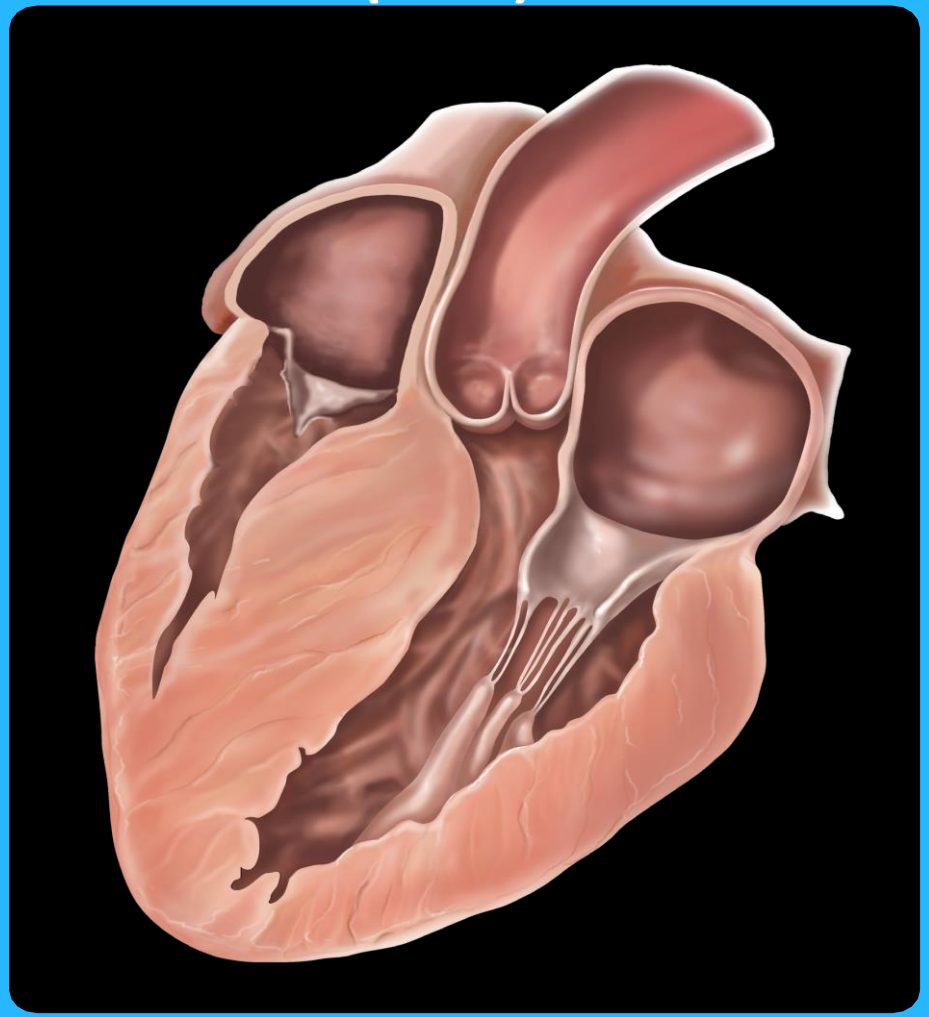


HCM: Significance

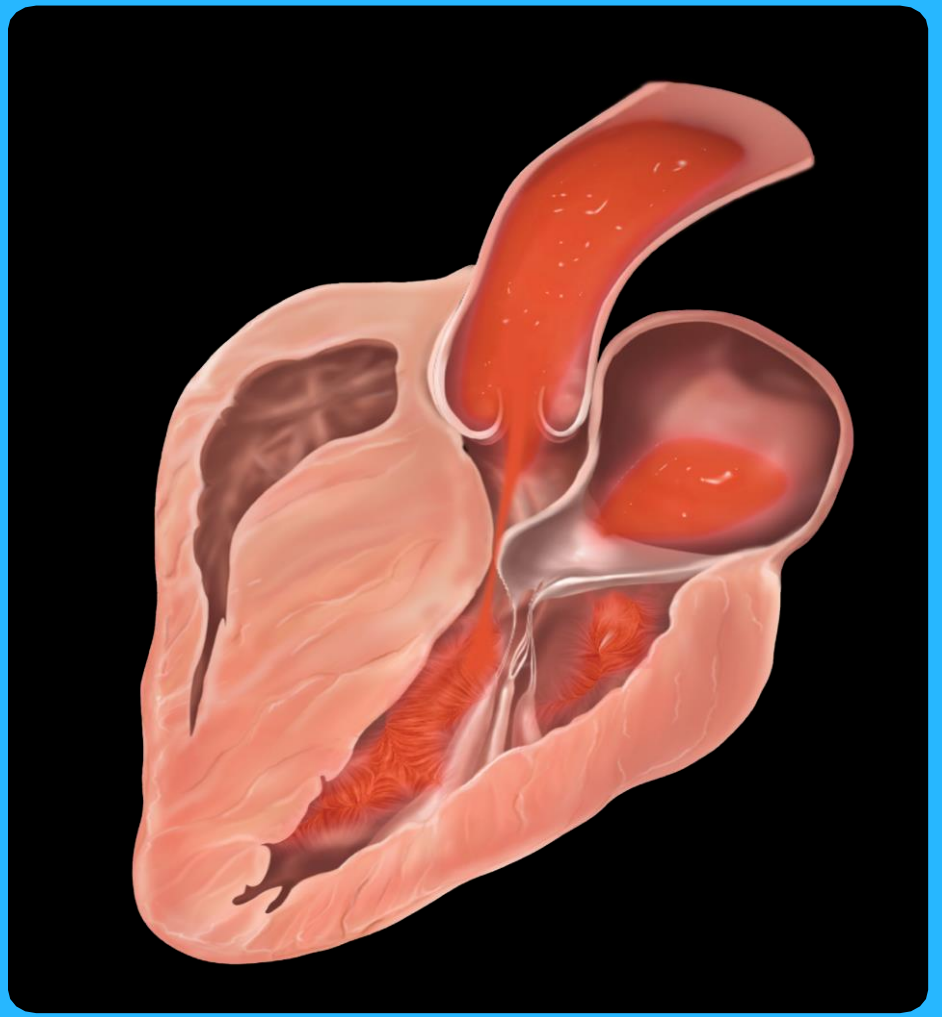
- Most common genetic cardiovascular disease
- Most common cause of SCD in the young/ athletes
- Important cause of AF and stroke
- Important cause of Heart Failure in All Ages

HYPERTROPHIC CARDIOMYOPATHY

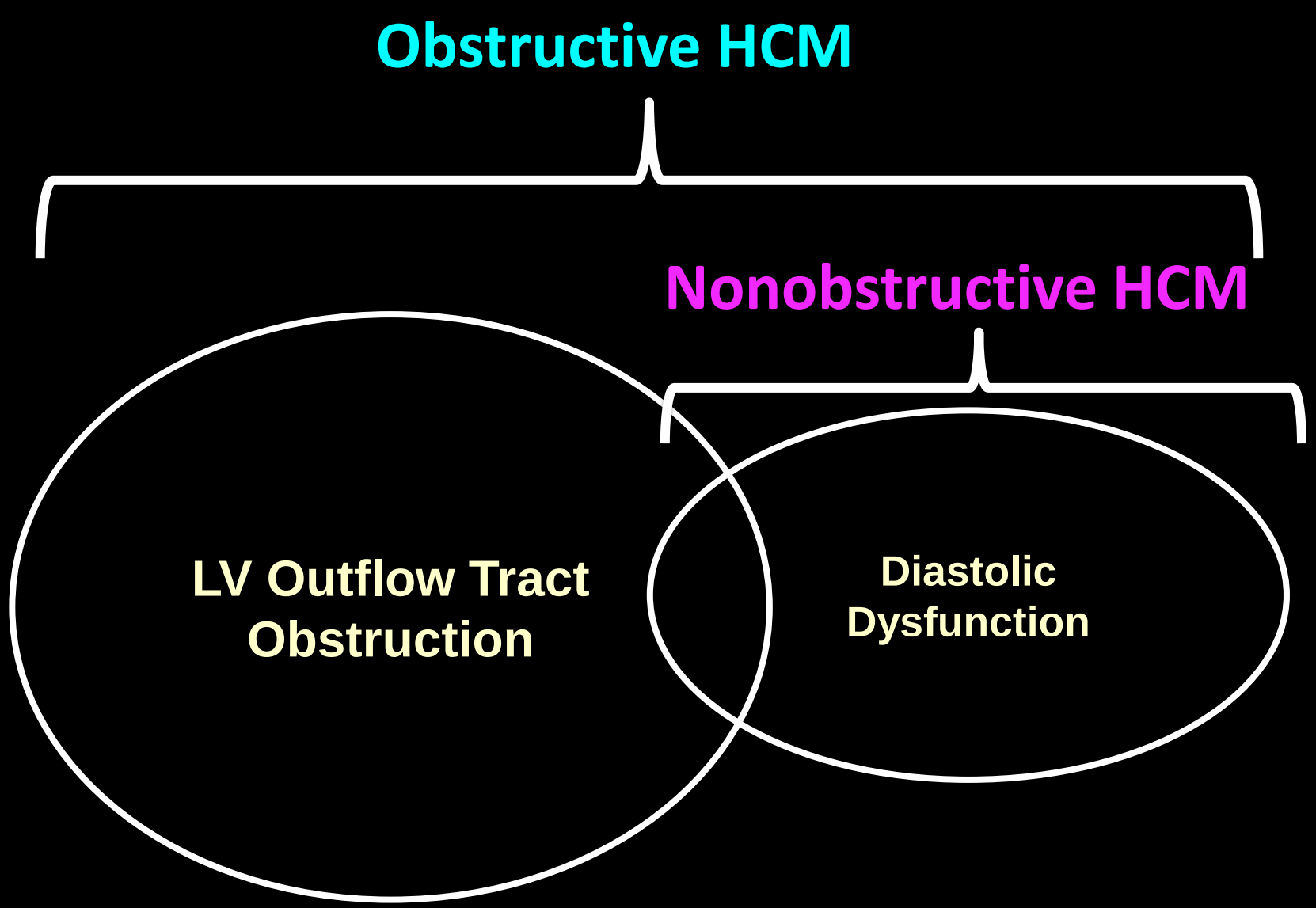
NONOBSTRUCTIVE (30%)



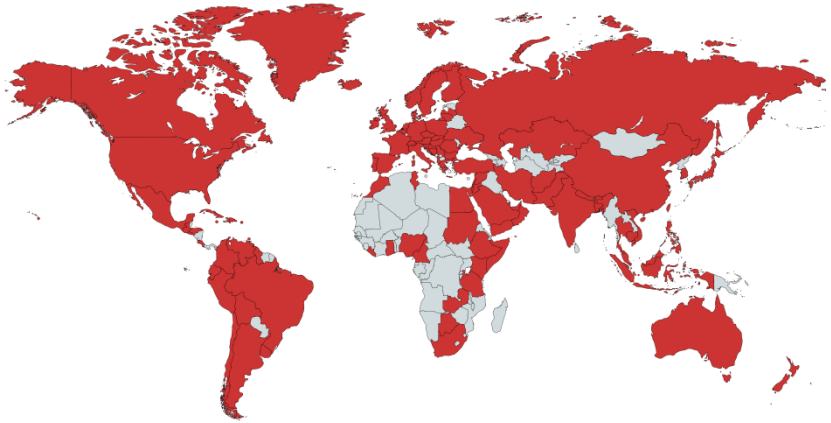
OBSTRUCTIVE (70%)



Mechanism of Heart Failure in HCM



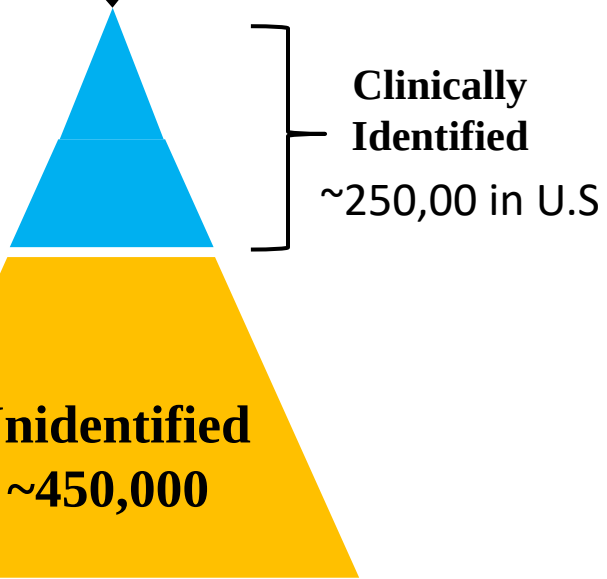
HCM: Global Burden



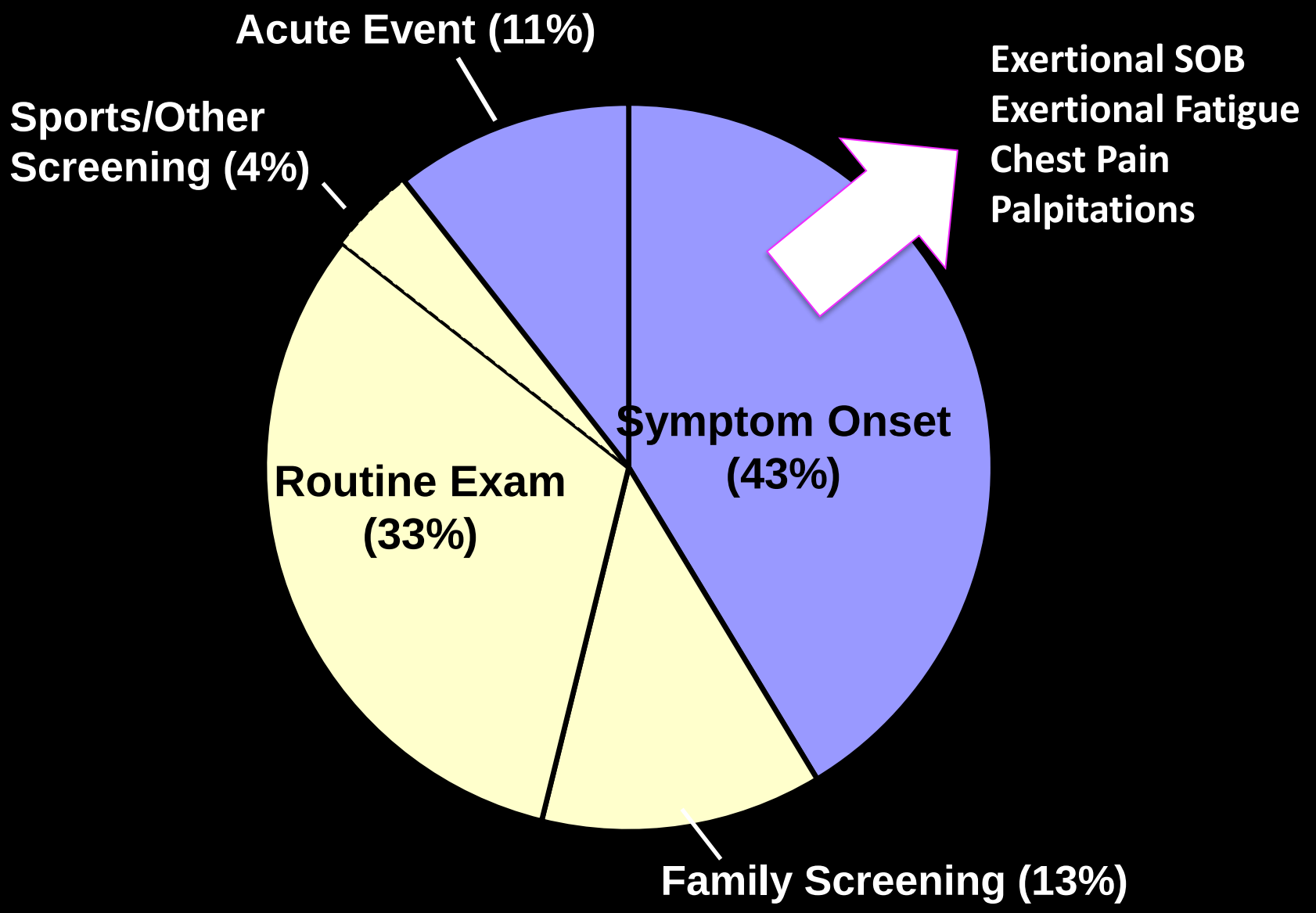
121 Countries involving 90% of world's population

Prevalence 1:200-1:500

Estimated ~15-20 million affected worldwide



Clinical Recognition of HCM



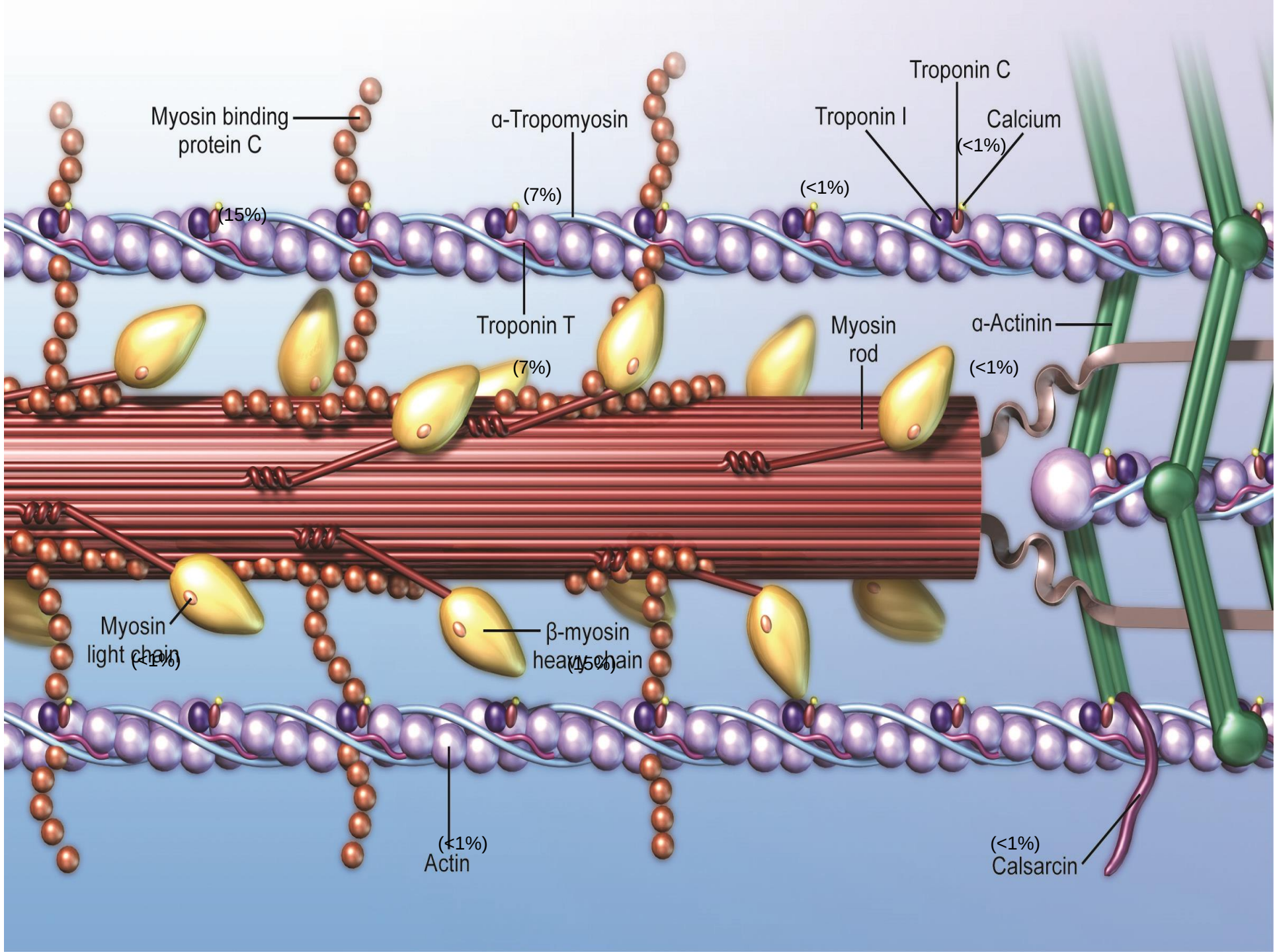
Primary Diagnosis of HCM

CLINICAL DIAGNOSIS:

Non-invasive imaging
- 2-D echocardiography
- MRI

RAISE SUSPICION of HCM:

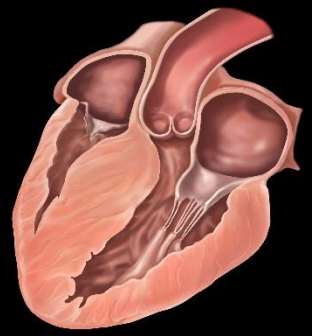
ECG (Abnormal in 90% but NS)
Physical exam: murmur
- (obstruction only)


Myosin binding protein C
(15%)
α-Tropomyosin
(7%)
Troponin C
Troponin I
Calcium
(<1%)
(<1%)
Troponin T
(7%)
Myosin rod
α-Actinin
(<1%)
Myosin light chain
(<1%)
β-myosin heavy chain
(15%)
(<1%)
Actin
(<1%)
Calsarcin

~30%
Sarcomere Positive

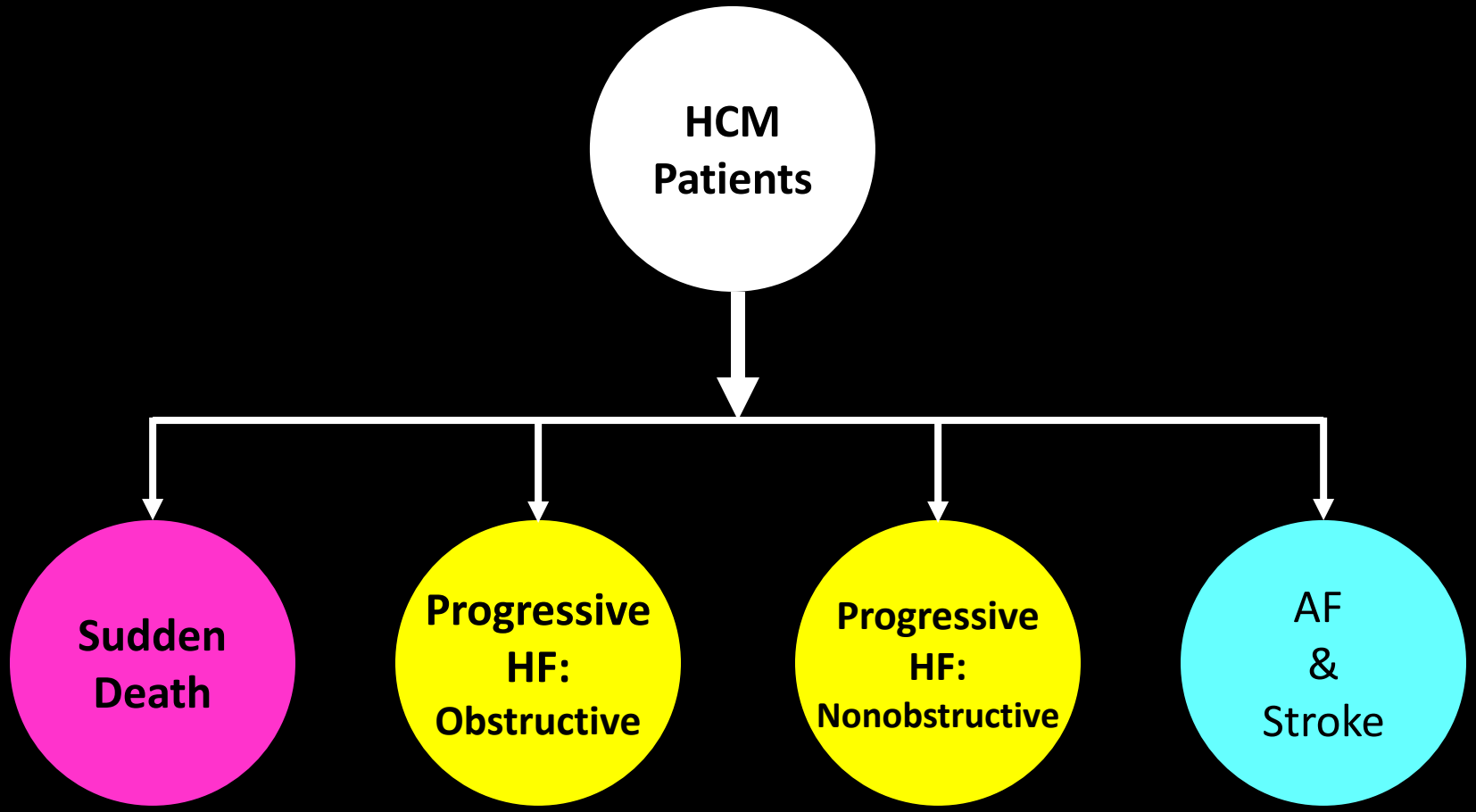
~70%
Sarcomere Negative

Multiple Variants (Polygenic)

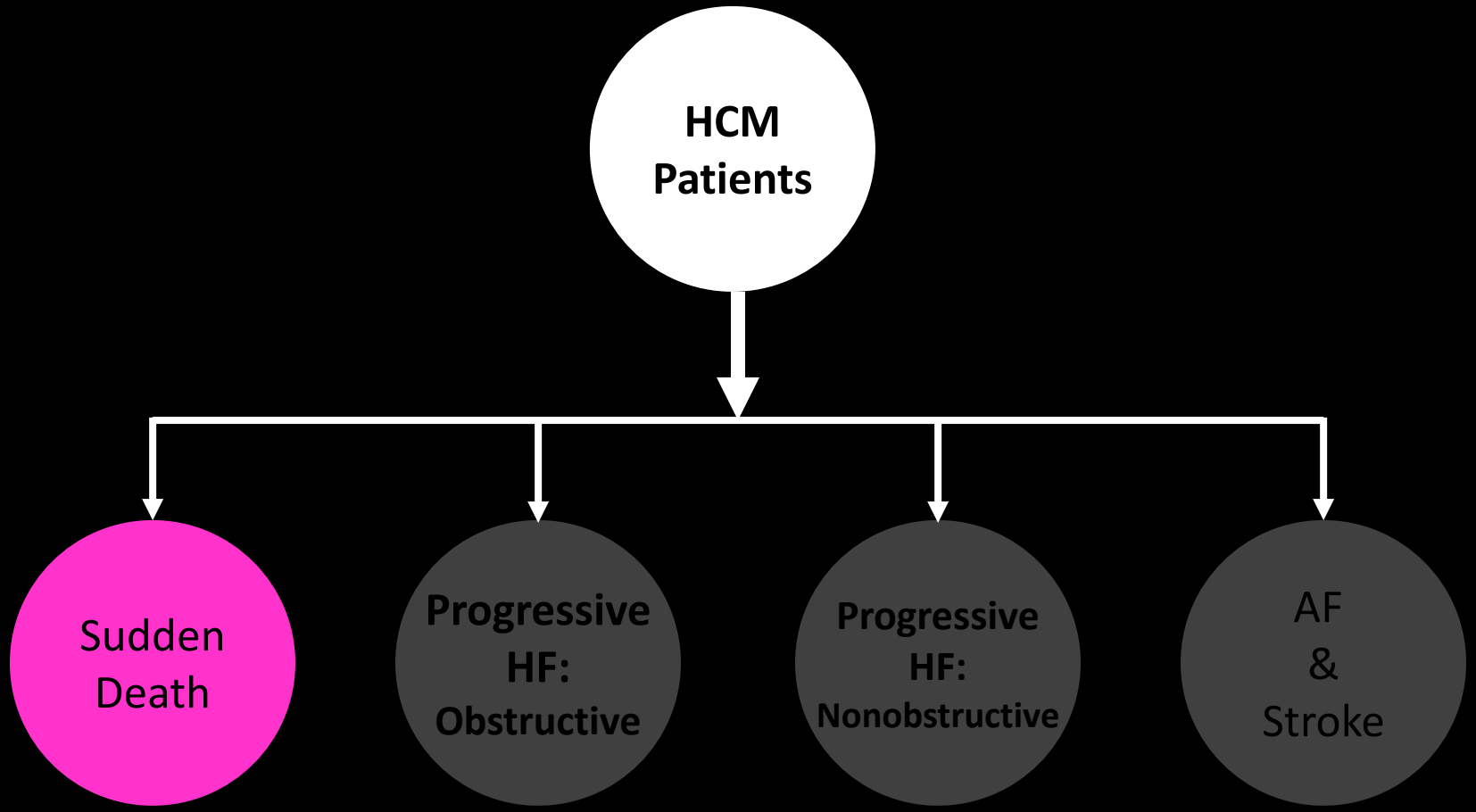


Common HCM Phenotype

Clinical Pathways of Prognosis in HCM



Clinical Pathways of Prognosis in HCM:
Sudden Death



HCM: most common causes of SCD in young people and athletes



Selection for ICD in Adult HCM Pts : 2020 AHA/ACC Guideline-Based Sudden Death Risk Markers

Major Markers (< 60 yrs of age)

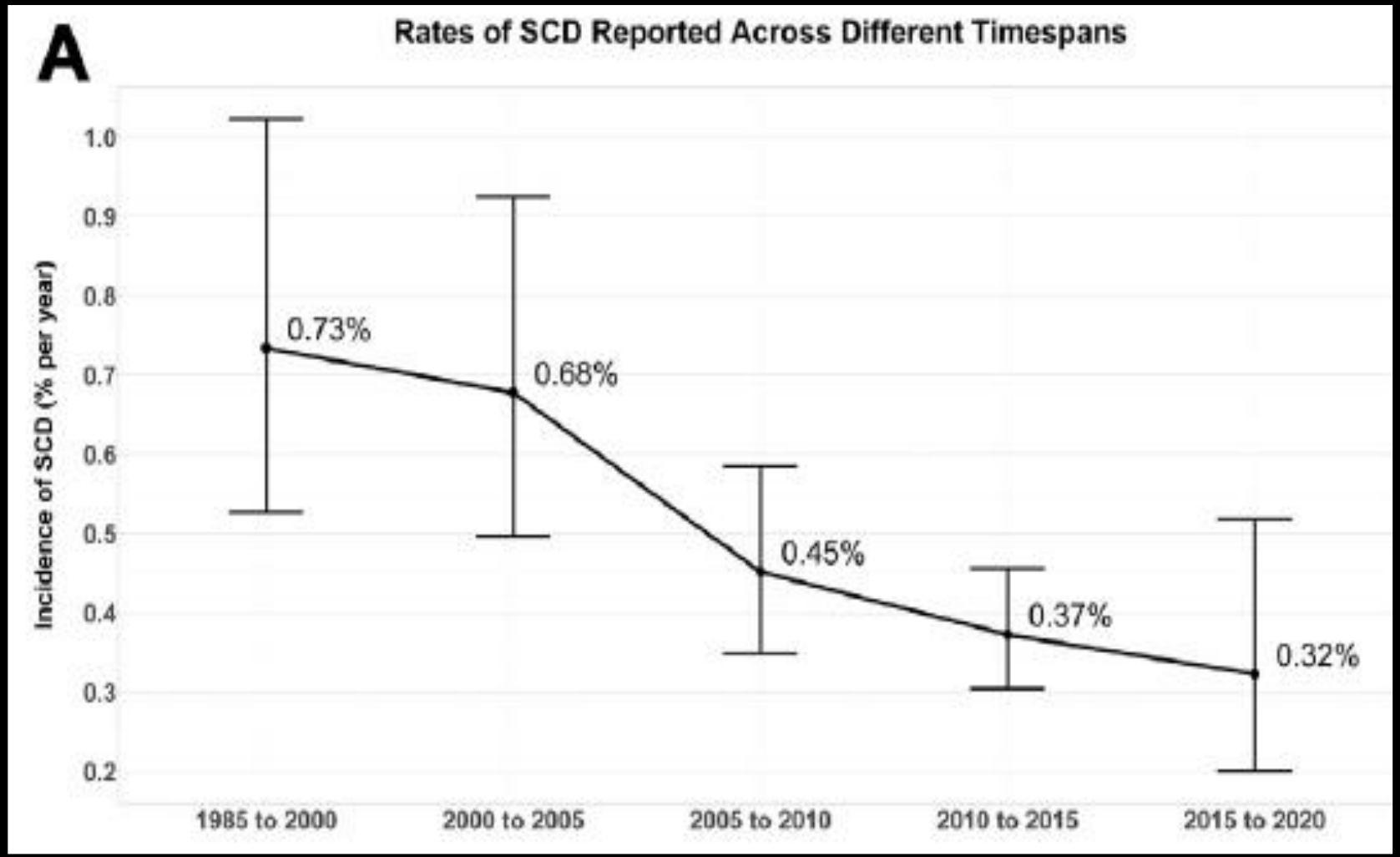
- Family History HCM-SCD
- Unexplained syncope
- Multiple-repetitive NSVT
- Massive LVH ≥ 30 mm
- *LV apical aneurysm*
- *Extensive LGE*
- *End-stage (EF < 50%)*

Increased Risk:
(≥ 1 major marker)

→ **Reasonable to consider primary prevention ICD**

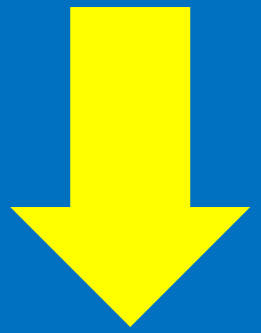
Ommen S, Mital S et al JACC 2020

Trends in HCM Sudden Cardiac Death Rates

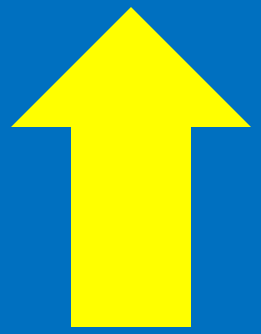


Abdelfattah O et al JACC EP 2022

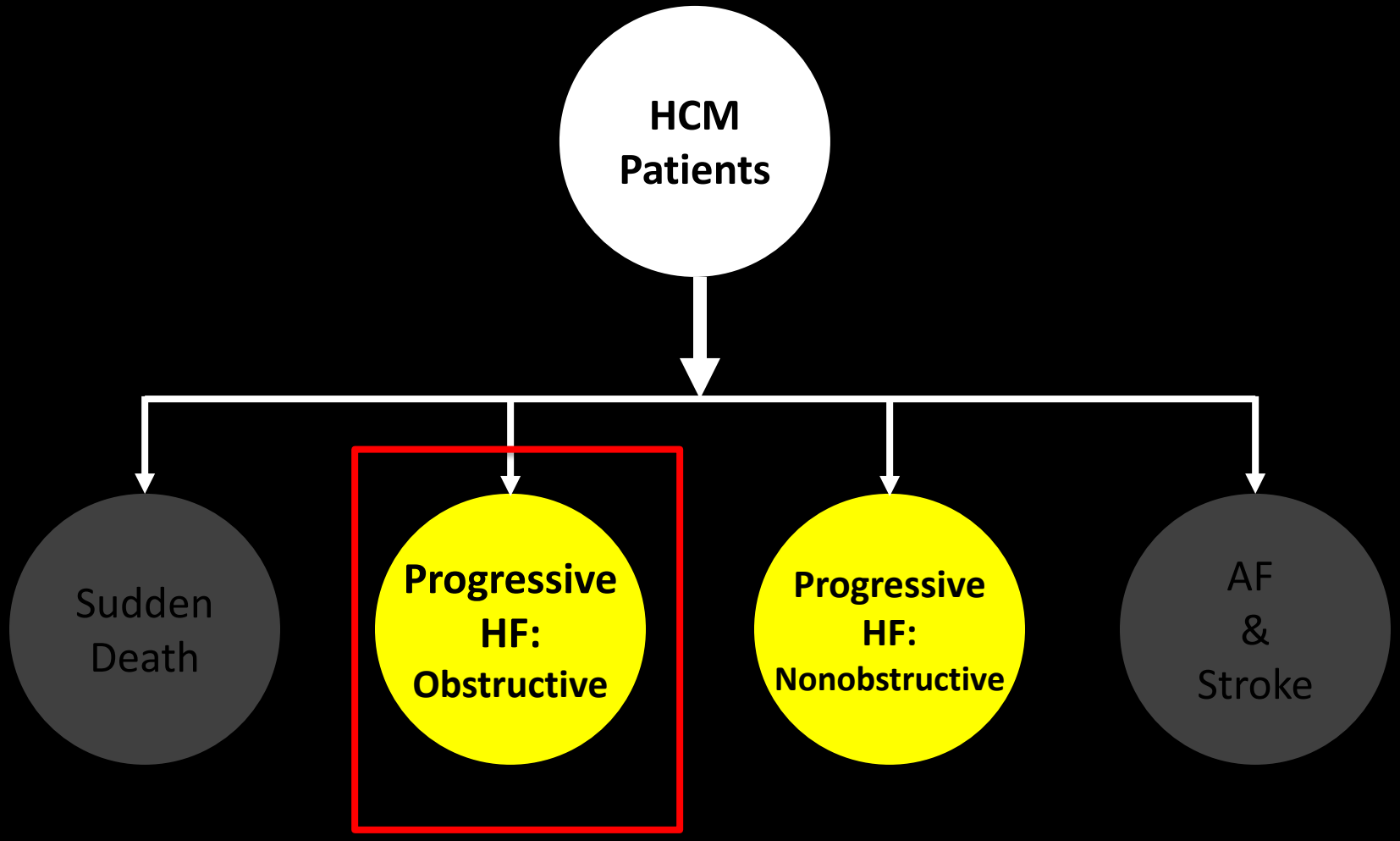
Sudden Death



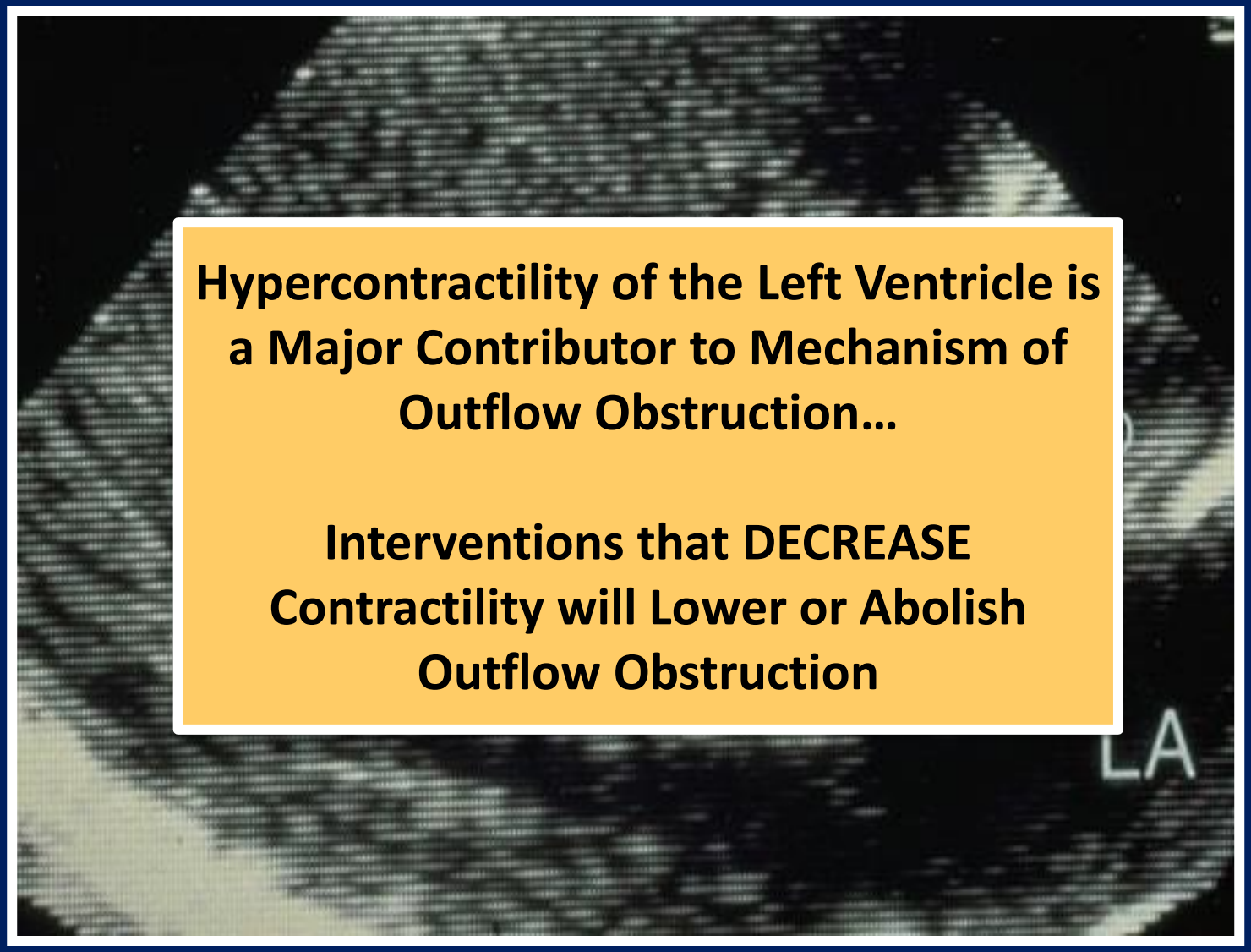
Advanced HF



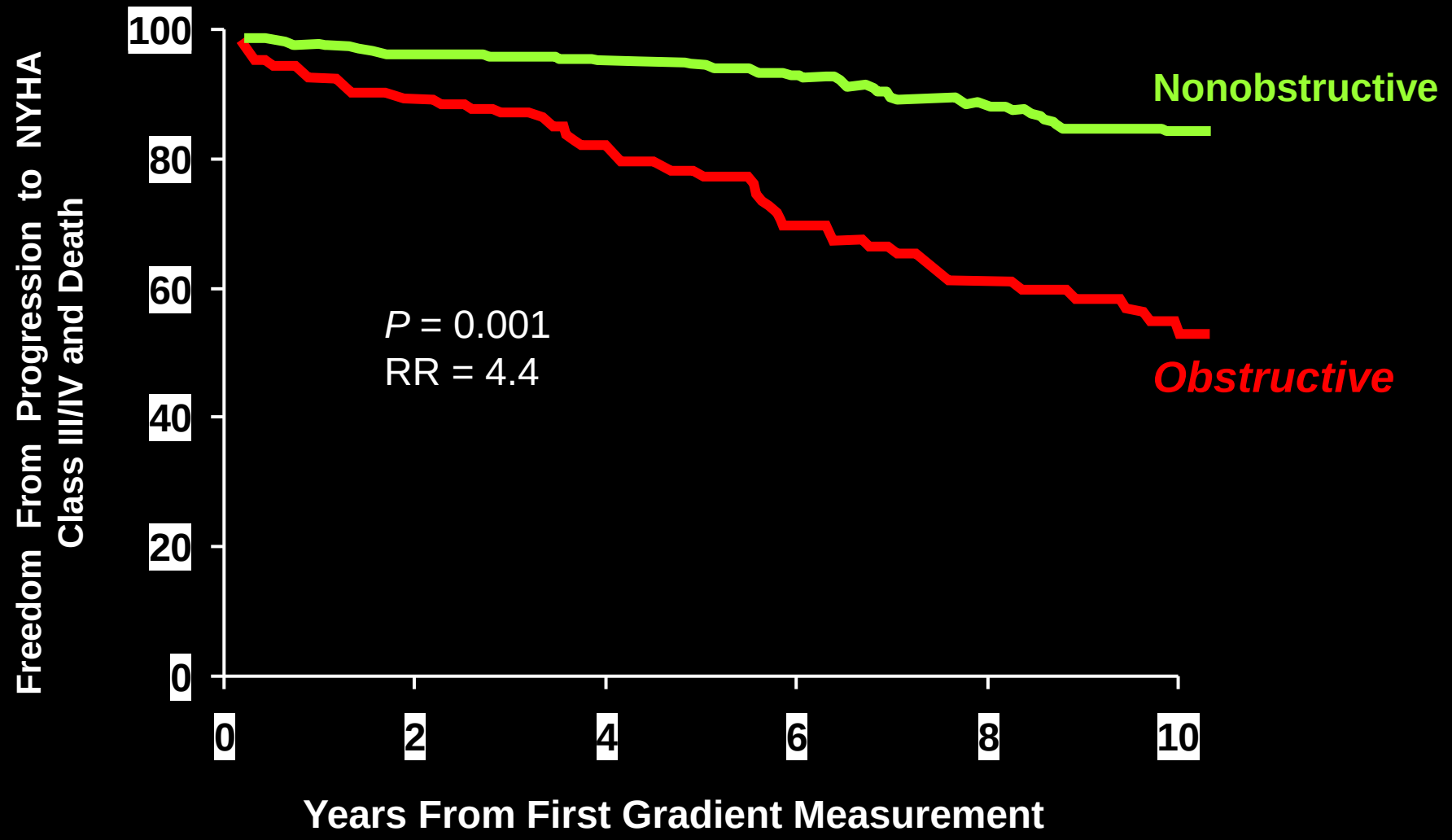
Clinical Pathways of Prognosis in HCM: Heart Failure



Obstructive HCM

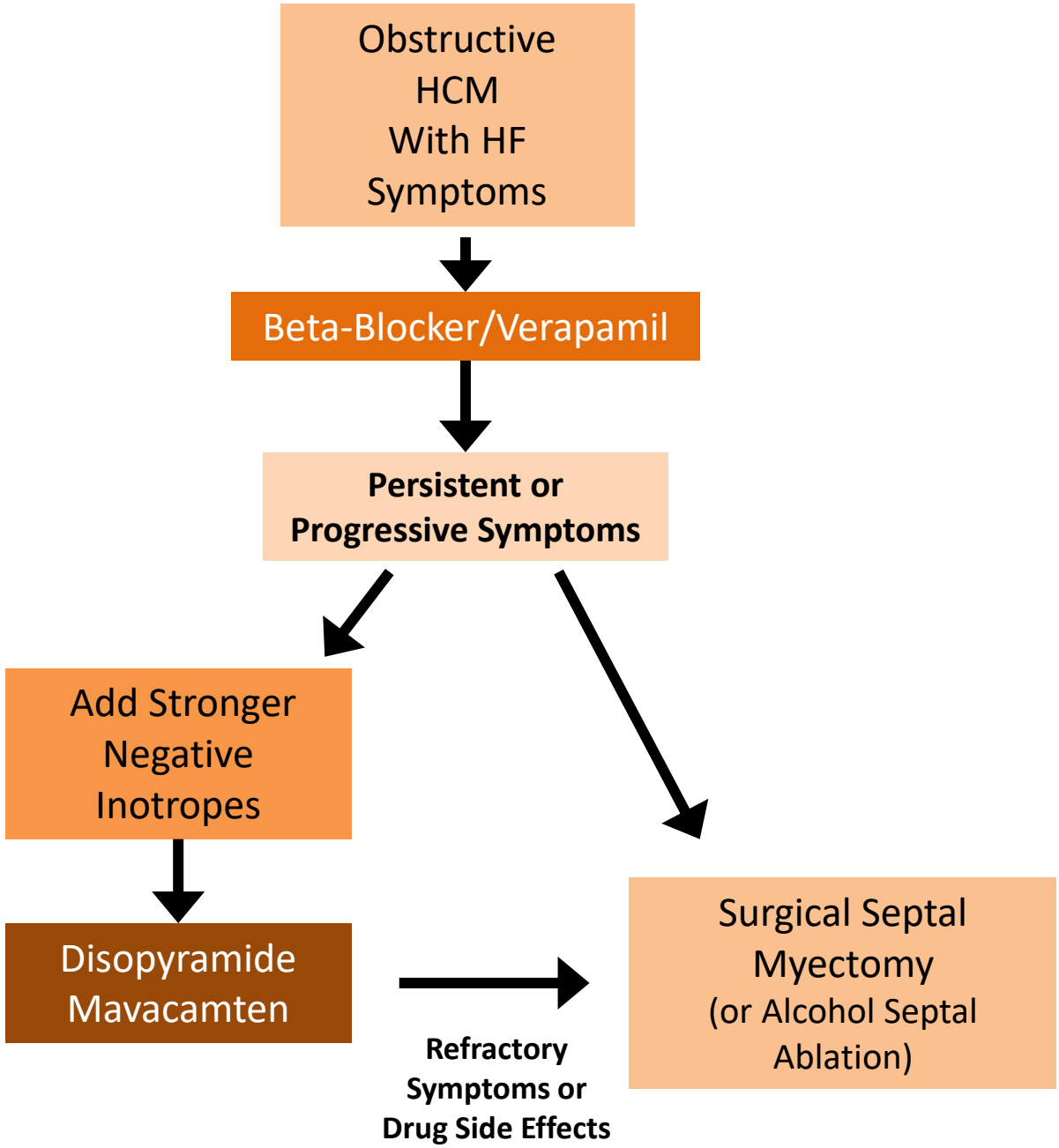


Impact of LV Outflow Obstruction (≥30 mmHg) on Progression to Advanced Heart Failure and Death



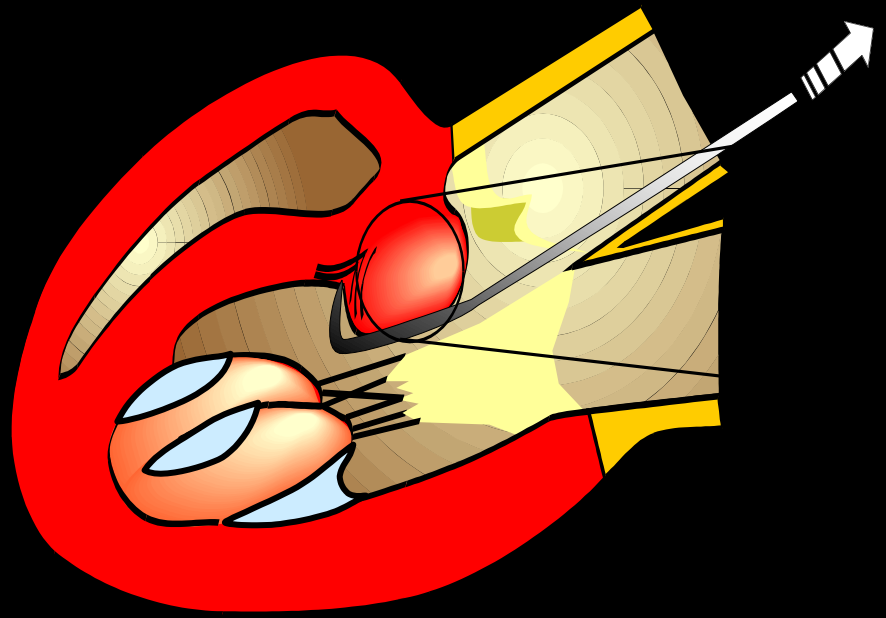
Maron MS et al. *N Engl J Med.* 2003; 348(4):295-303.

Contemporary Approach to Management of Symptomatic Obstructive HCM

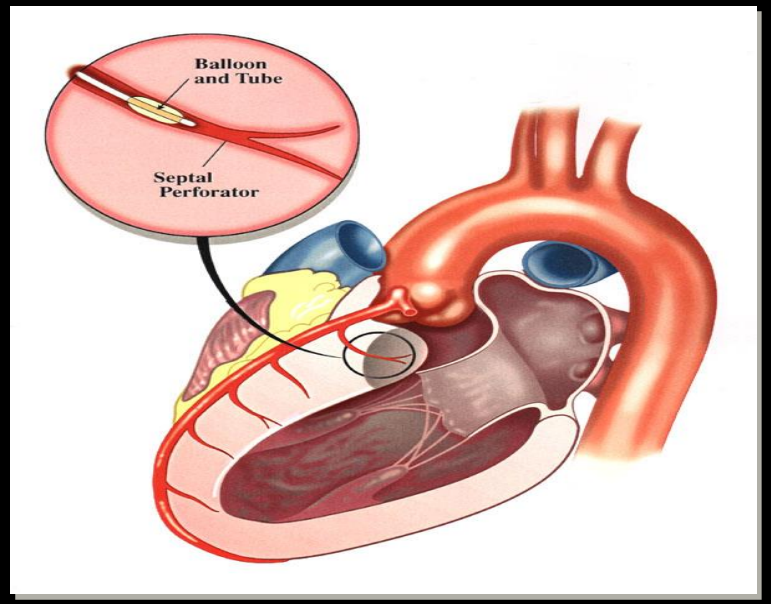


Septal Reduction Therapy (SRT)

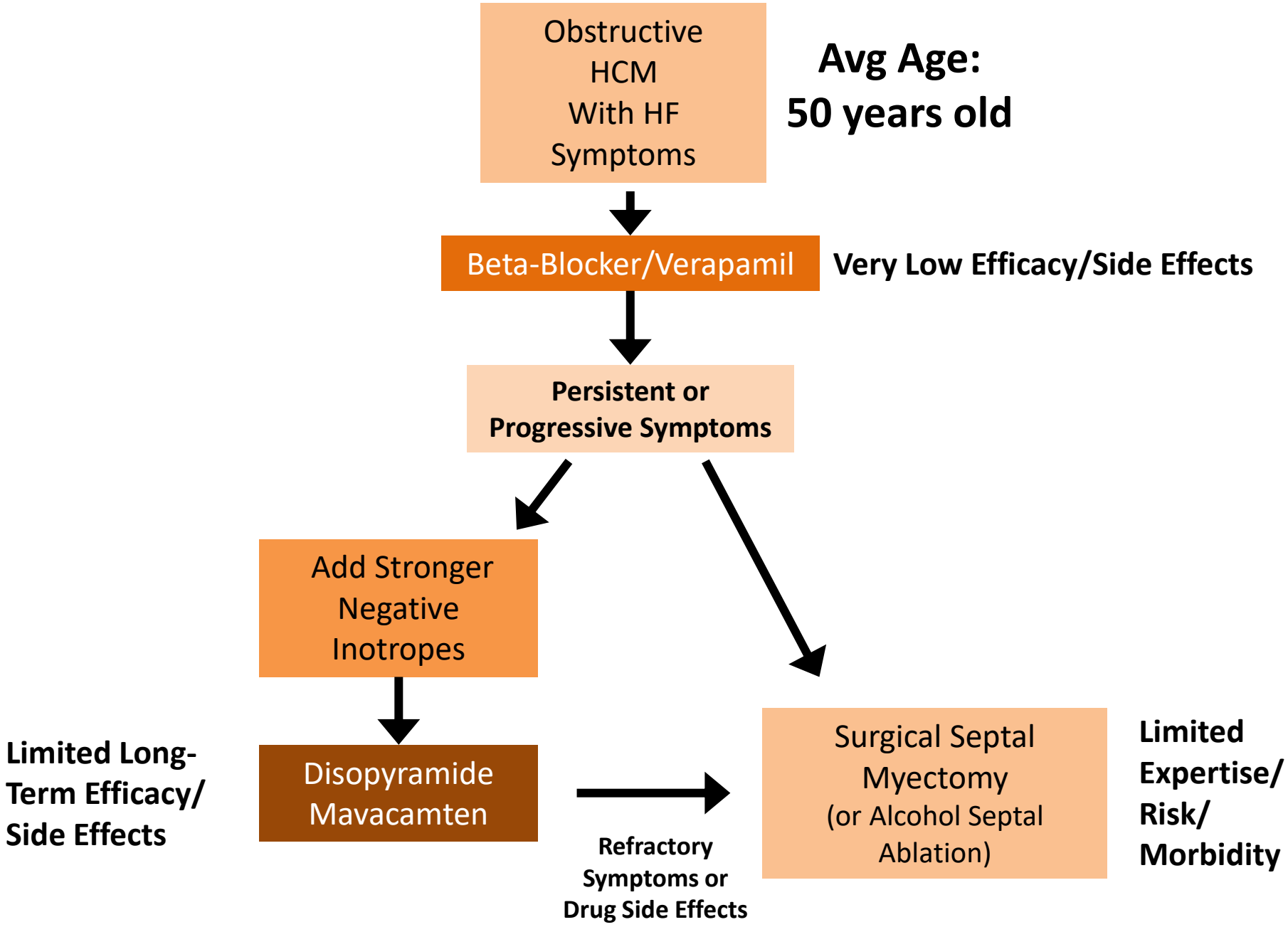
Surgical Myectomy

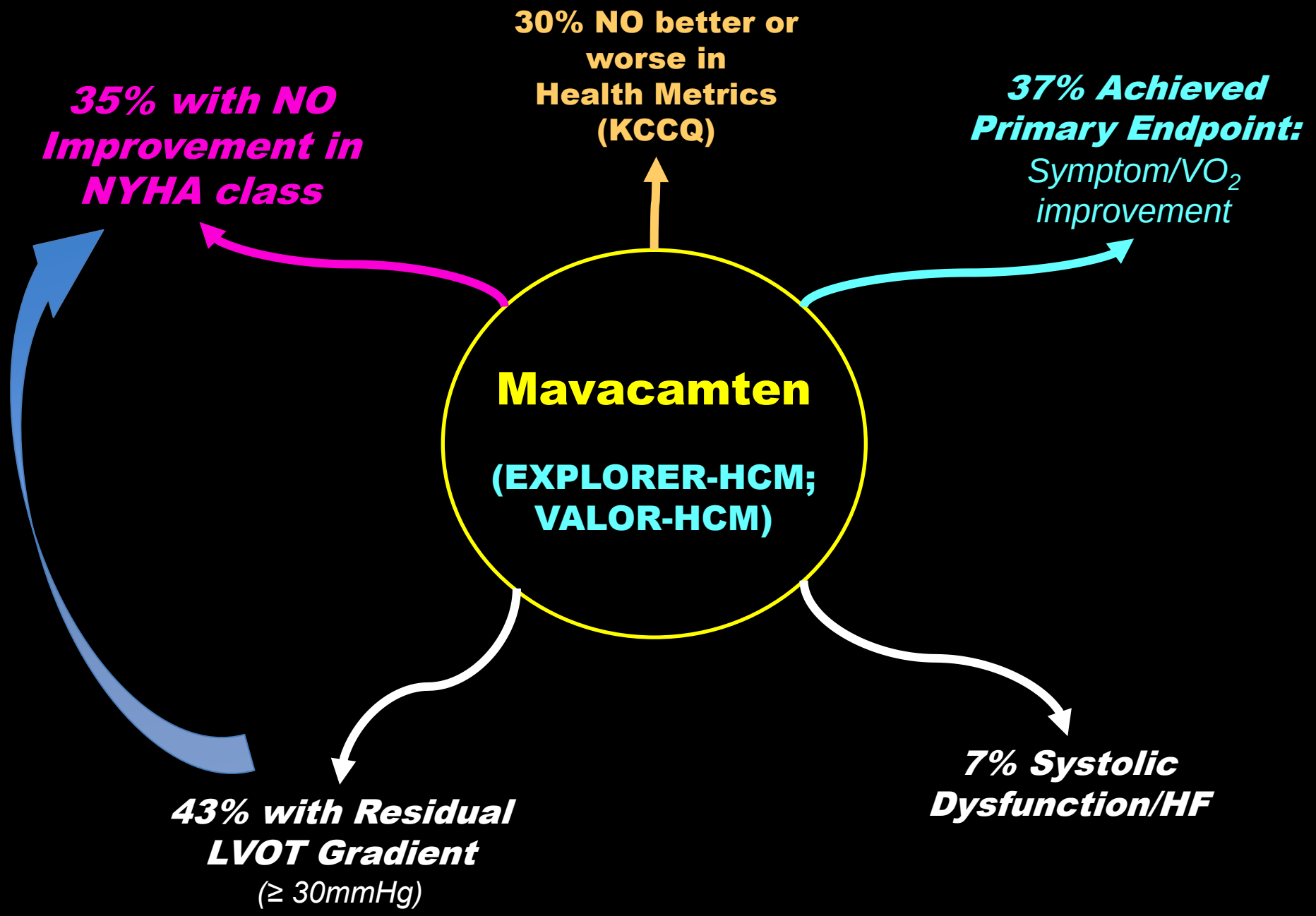


Alcohol Ablation (ASA)

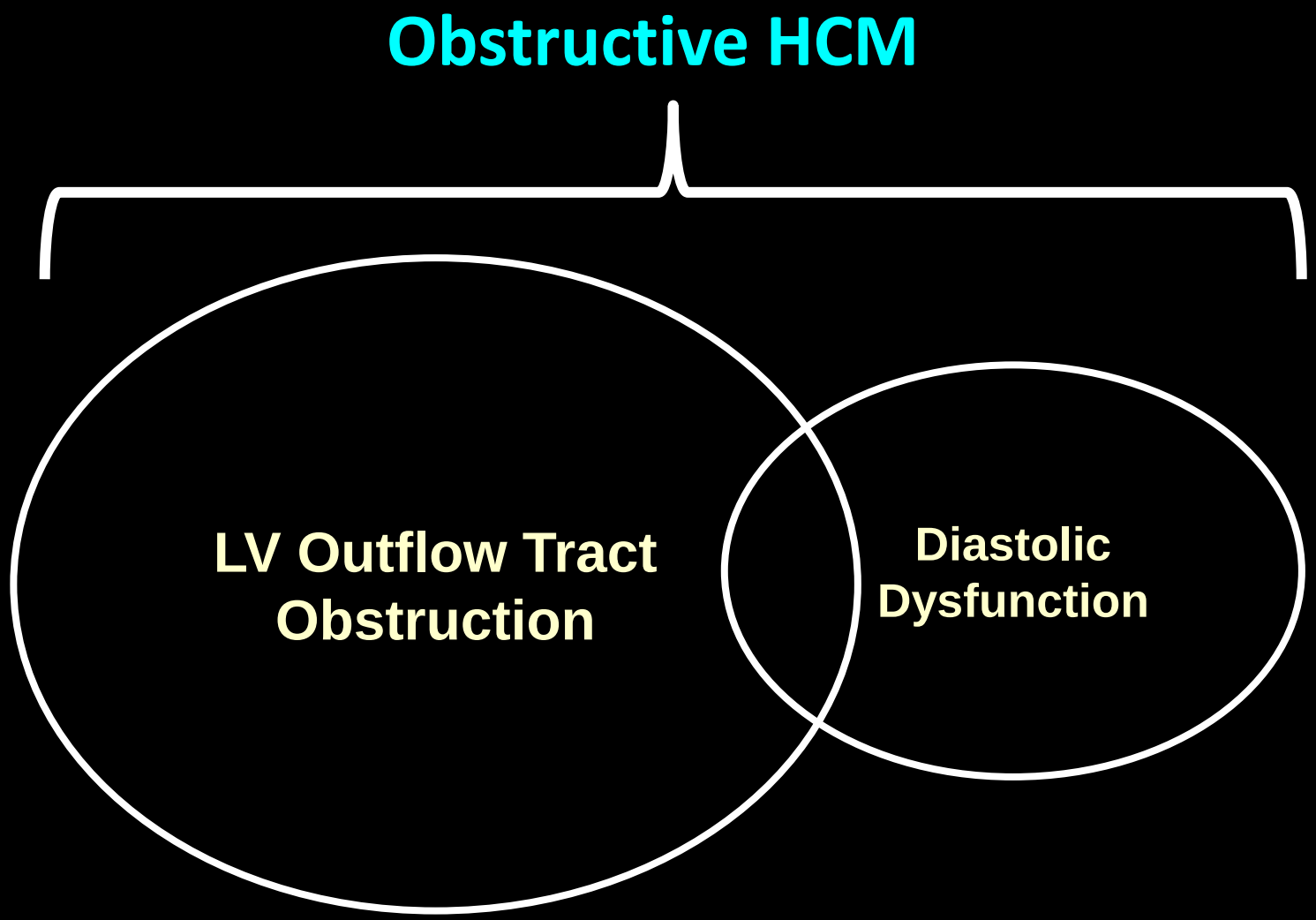


Current Unmet Treatment Needs in Obstructive HCM

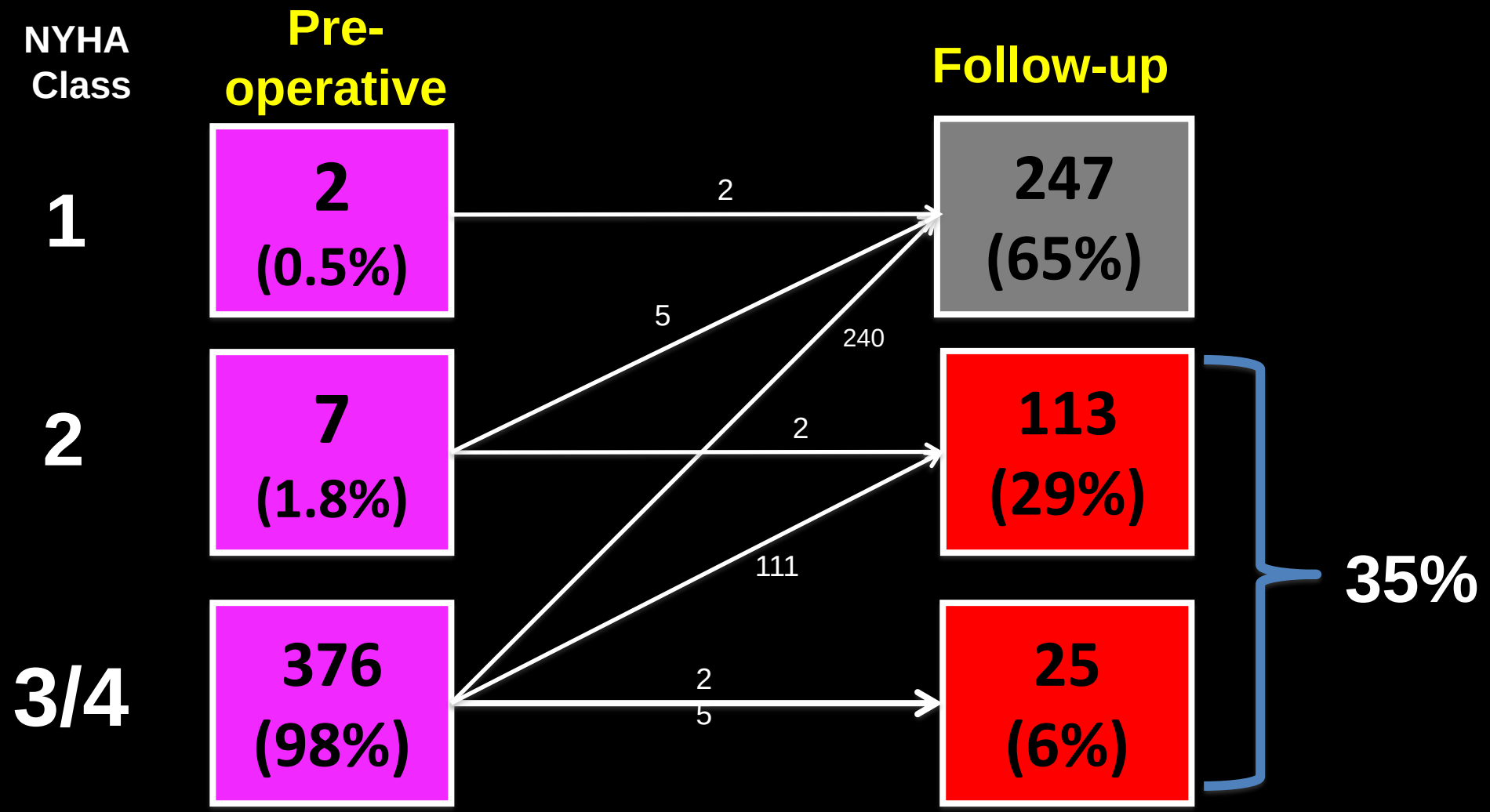



30% NO better or worse in Health Metrics (KCCQ)
35% with NO Improvement in NYHA class
37% Achieved Primary Endpoint: Symptom/VO2 improvement
Mavacamten
(EXPLORER-HCM; VALOR-HCM)
43% with Residual LVOT Gradient (≥ 30mmHg)
7% Systolic Dysfunction/HF

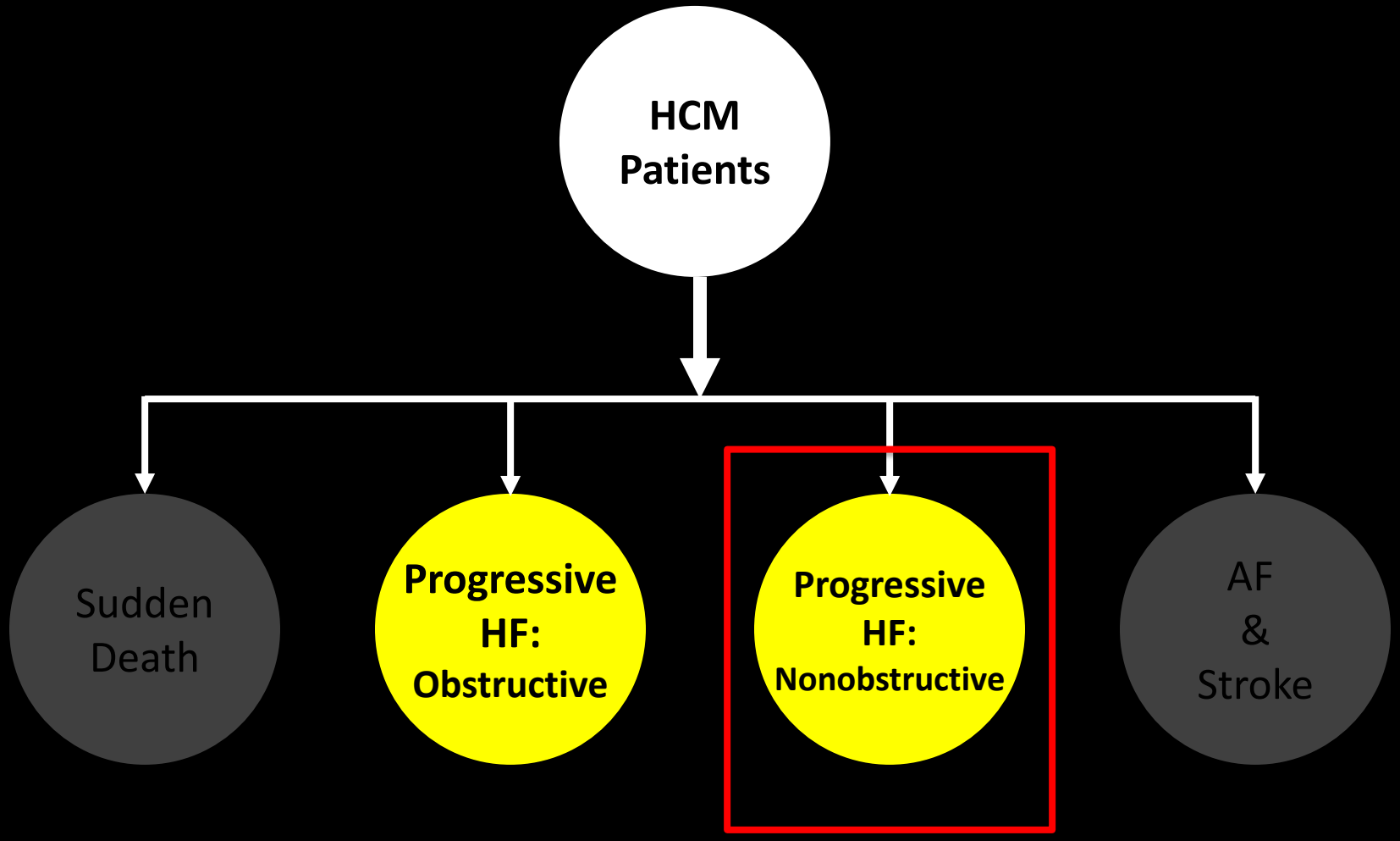
Mechanism of Heart Failure in HCM



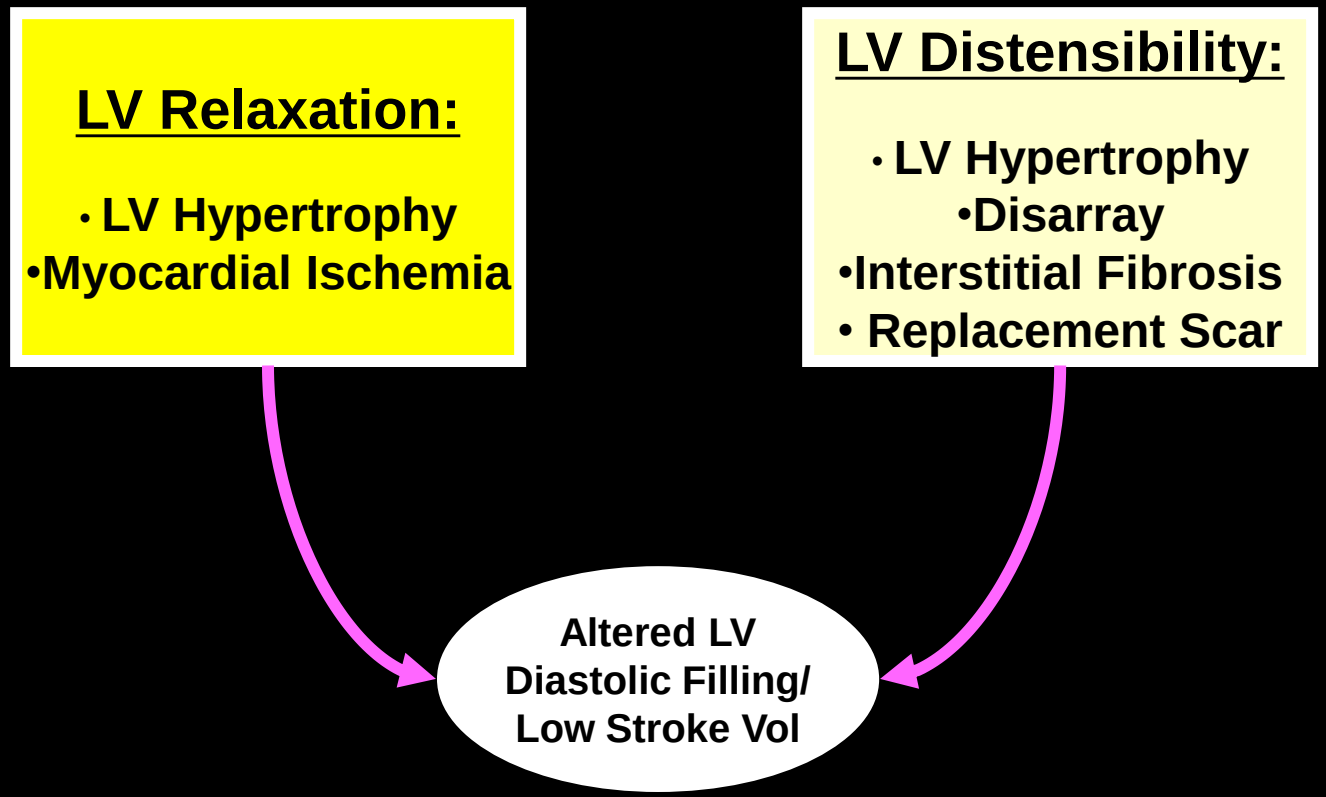
Change in NYHA Functional Class Following Surgical Myectomy



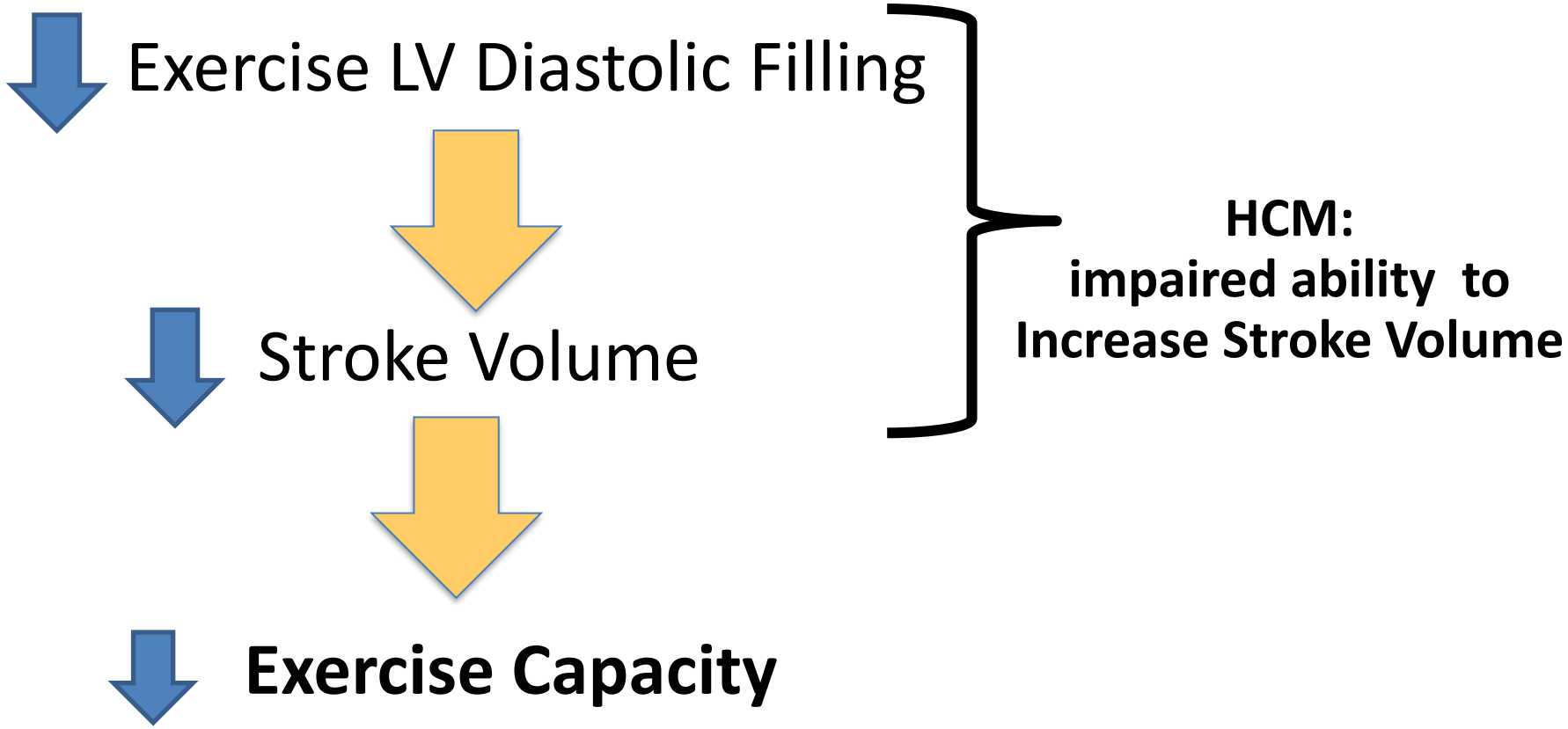
Clinical Pathways of Prognosis in HCM



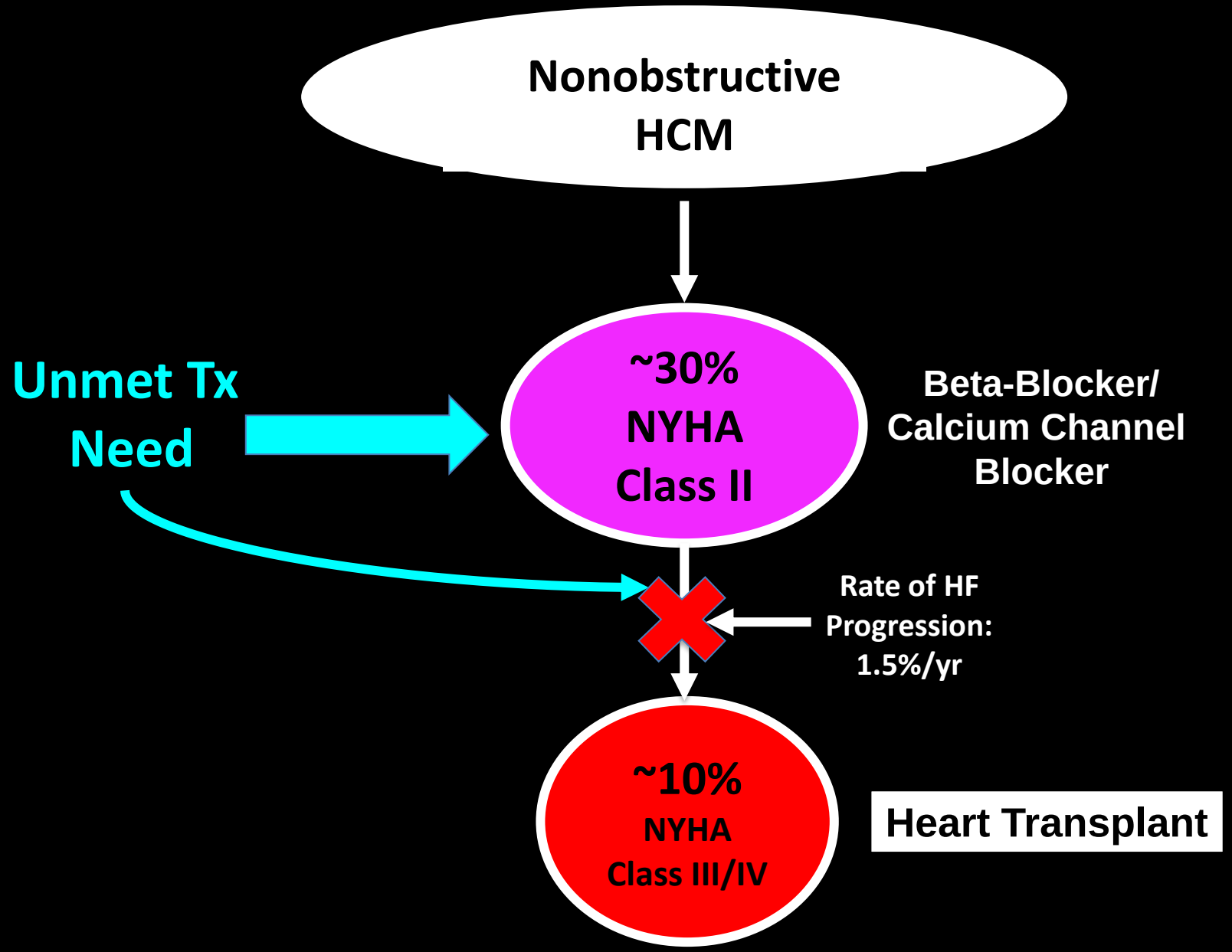
Diastolic Dysfunction in HCM



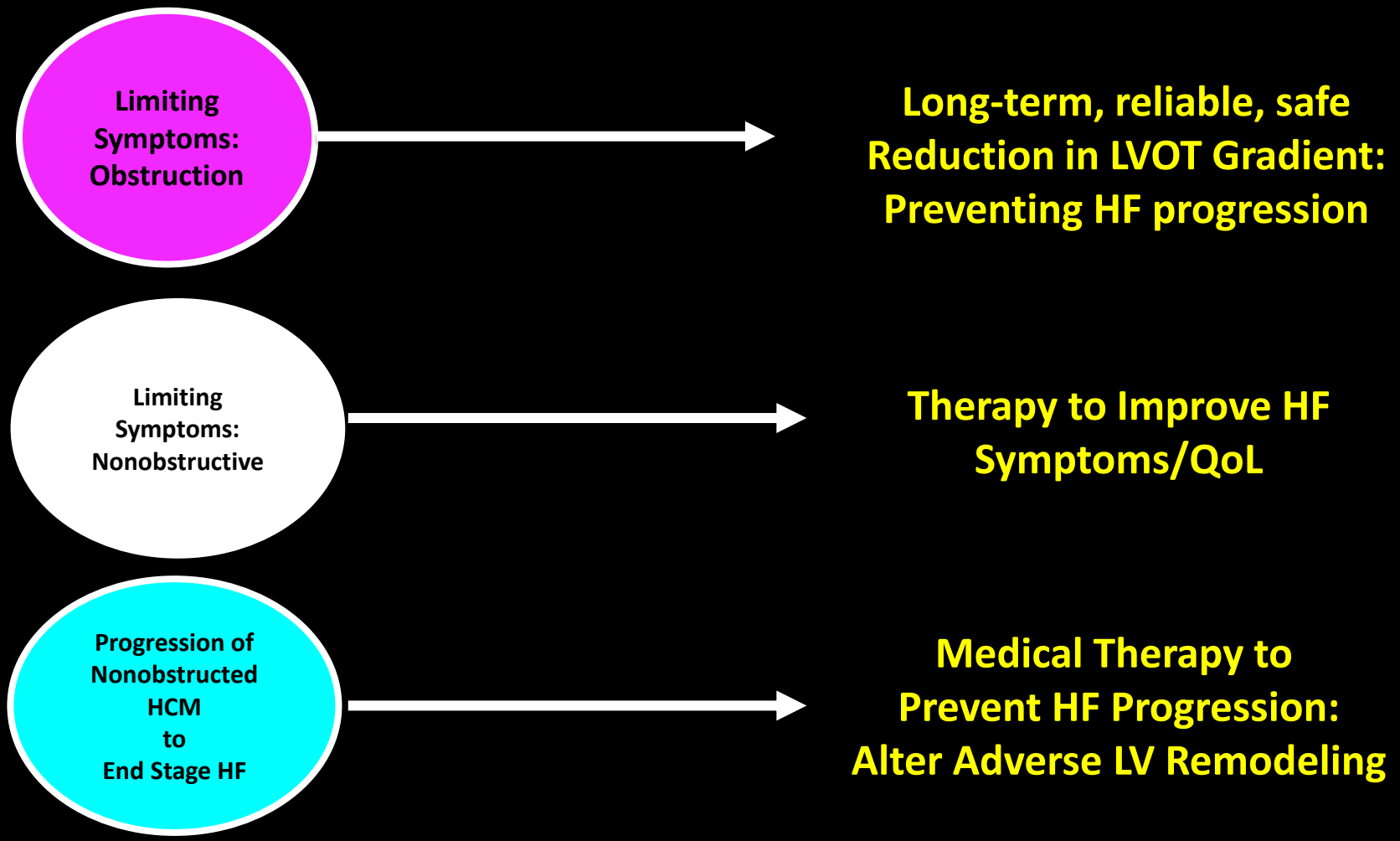
Exercise Capacity in HCM Dependent on Diastolic Filling Characteristics



Treatment Gaps in *Nonobstructive* HCM



Summary: Unmet Treatment Needs in HCM

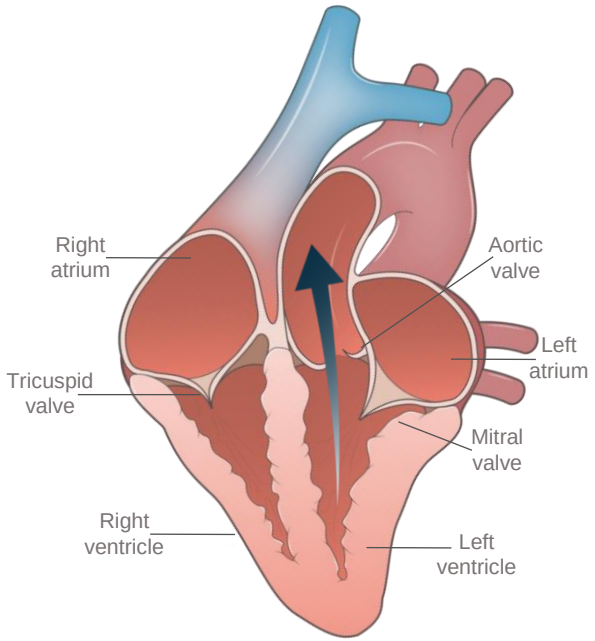


EDG-7500: A Novel Sarcomere Modulator for HCM and Diastolic Disease

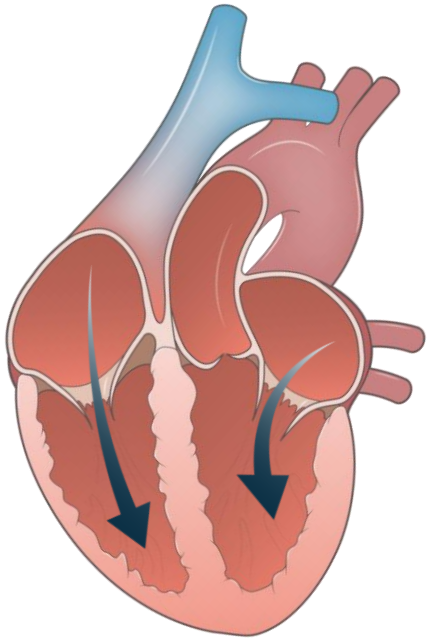
Marc Evanchik
Edgewise VP of Discovery

The Cardiac Cycle: Pressure Volume Loops Inform Cardiac Function and Performance

Ventricular Systole
(Pumping)

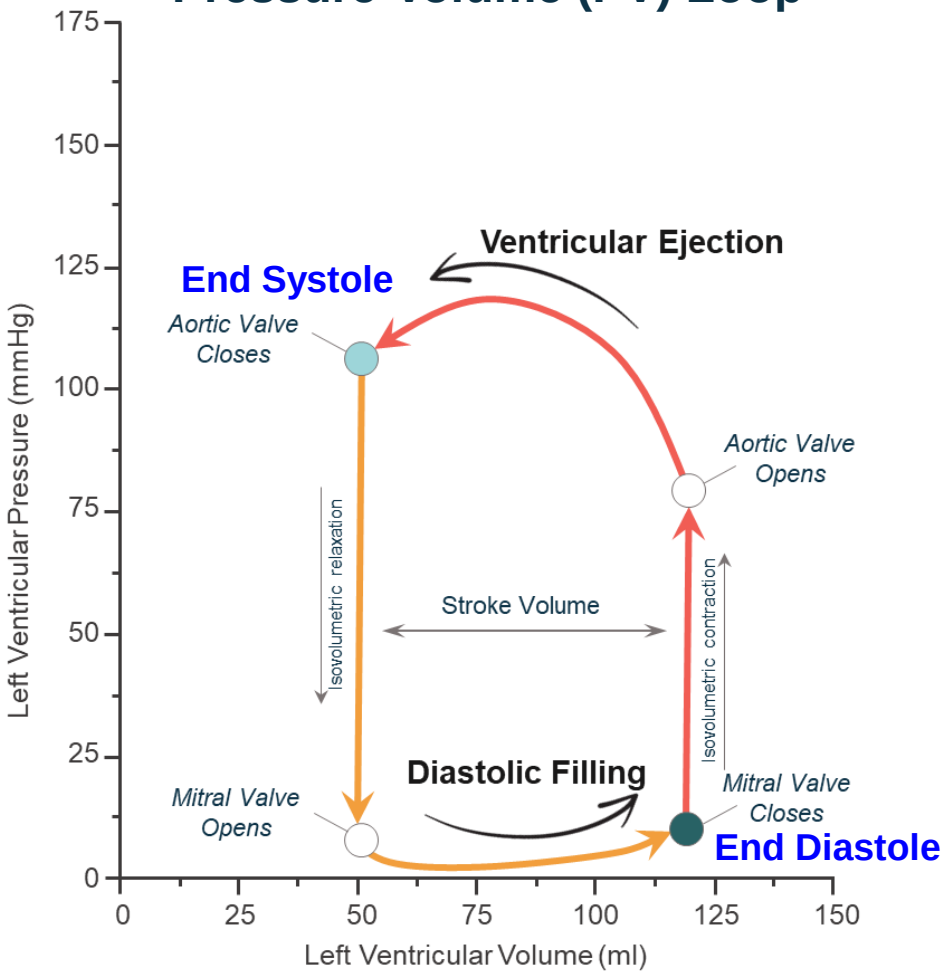


Diastole
(Filling)



Healthy Heart

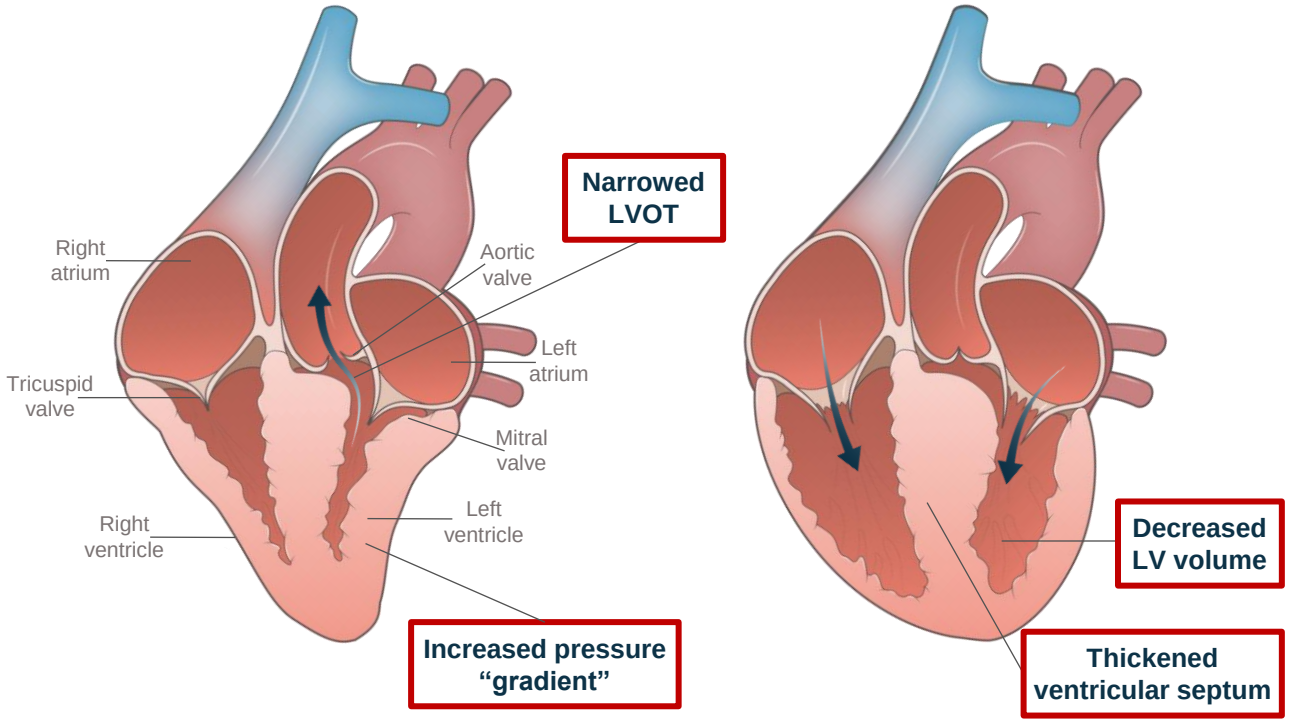
Healthy Heart
Pressure-Volume (PV) Loop



In oHCM, Hearts Operate With Reduced Forward Blood Flow and Experience Higher Pressures

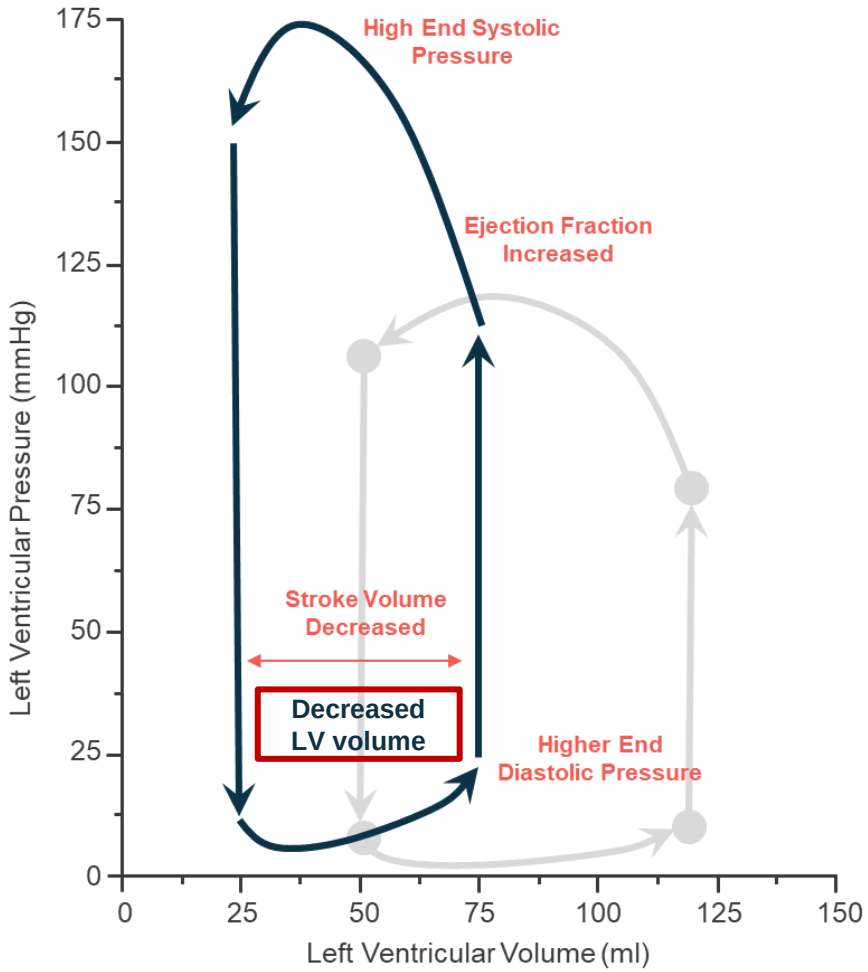
Ventricular Systole
(Pumping)

Diastole
(Filling)



Hypertrophied Heart

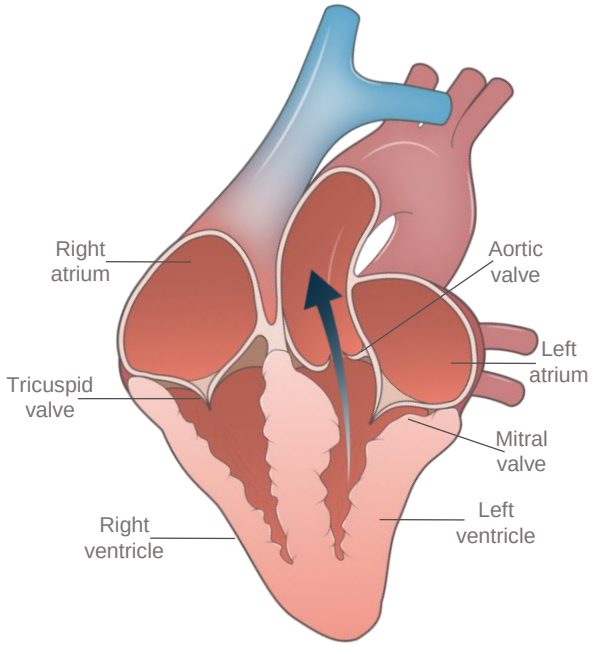
oHCM Heart PV Loop



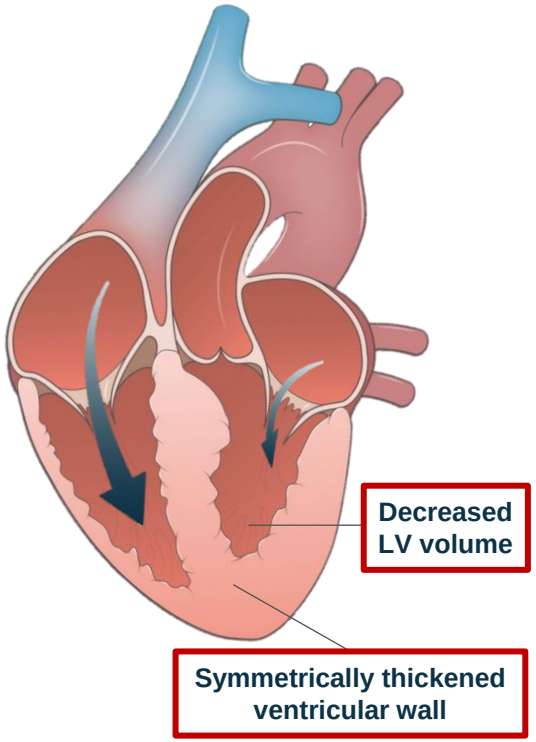
Abbreviations: HCM, hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LV volume, left ventricular volume; EF, ejection fraction; PV, pressure-volume

In nHCM, No LVOT Obstruction, But Stroke Volume is Limited by Higher End Diastolic Pressure

Ventricular Systole
(Pumping)

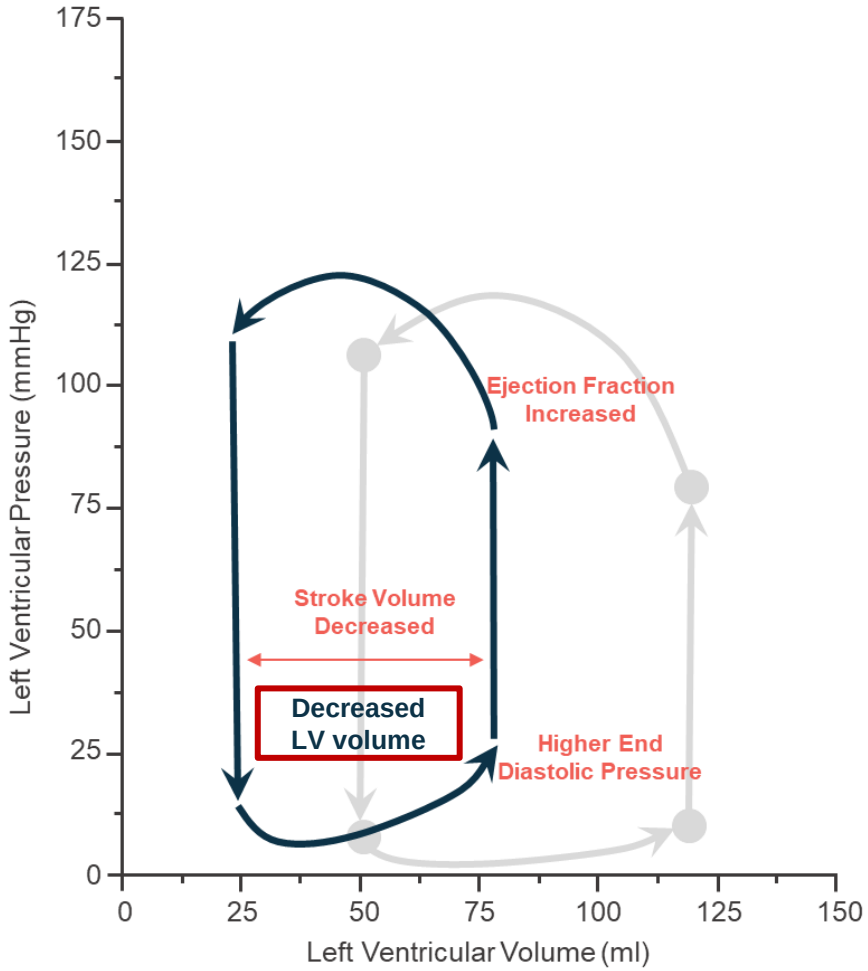


Diastole
(Filling)



Hypertrophied Heart

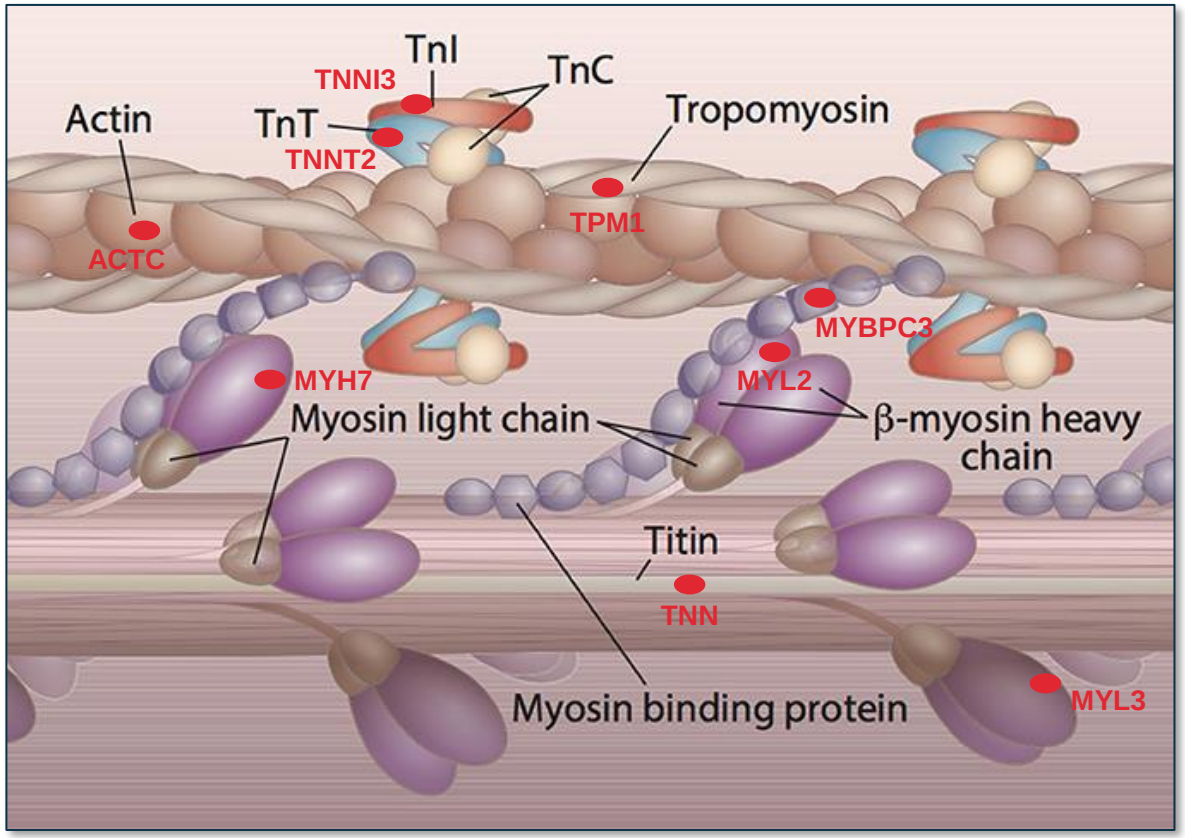
nHCM Heart PV Loop



Abbreviations: HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LV volume, left ventricular volume; EF, ejection fraction; PV, pressure-volume

The Sarcomere is the Molecular Unit in Cardiac Muscle Responsible for Heart Contraction and Relaxation

Sarcomeric gene mutations cause HCM, and mutations in cardiac myosin binding protein C and β-myosin heavy chain account for 80% of all genetic HCM cases



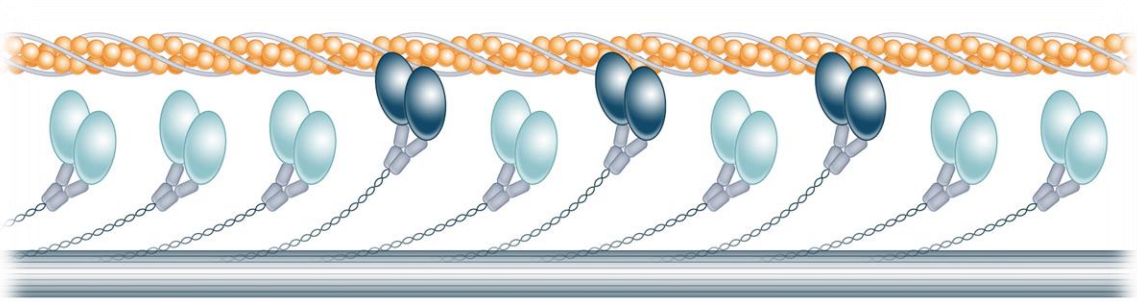
Protein	Gene Symbol	# of mutations to cause HCM
Cardiac β-MyHC	***MYH7***	**194**
Cardiac MyBP-C	***MYBPC3***	**197**
Cardiac TnT	*TNNT2*	31
Cardiac TnI	*TNNI3*	27
α-Tropomyosin	*TPM1*	11
Regulatory Light Chain	*MYL2*	10
Cardiac α-actin	*ACTC*	7
Essential Light Chain	*MYL3*	5
Titin	*TNN*	3

References: www.hypertrophiccardiomyopathy.com; https://sadayappanlab.org/hypertrophic_cardio.html; Kraker J, *et. al., Frontiers in Physiology*, 2016; Seidman CE & Seidman JG, *Circulation Research*, 2011

HCM Hearts are Hyperdynamic, and Relaxation is Impaired

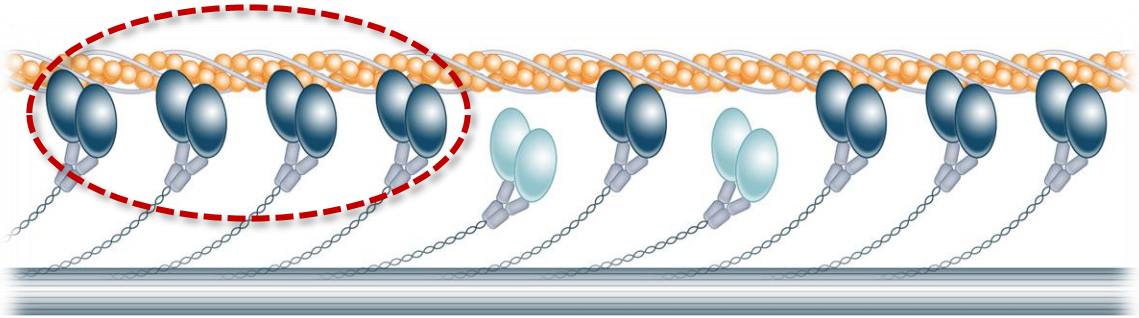
HCM is a Disease of the Sarcomere

Healthy sarcomere



Normal contraction

In HCM too many ‘motors’ engaged during systole and diastole



Excessive contraction and impaired relaxation

Abbreviations: HCM, hypertrophic cardiomyopathy

Why Develop a Novel Approach for HCM?

1. **Direct inhibition of the myosin motor (CMIs) reduces cross-bridges during the entire cardiac cycle**
   - Inhibitors limit cardiac function during both systole and diastole with a steep dose response requiring careful echo-guided dose titration
   - Inhibition of cardiac function limits treatment of HCM populations with low LVEF

2. **Regulation of the number of diastolic actin-myosin cross-bridges without direct inhibition of the motor maintains cardiac function**
   - Selective control of diastolic cross-bridges is possible by indirectly regulating myosin via targeting other sarcomere proteins

Abbreviations: CMI, cardiac myosin inhibitor; LVEF, left ventricular ejection fraction;

Edgewise's Approach – Develop an Indirect Myosin Modulator

- EDG-7500 regulates myosin by targeting the complex sarcomere protein-protein interactions that control contraction and relaxation processes
- Reduce the excessive residual actin-myosin cross-bridges during diastole, facilitating relaxation and ventricular filling
- Speed the rate of relaxation and slow contraction without inhibiting myosin to avoid undesired excessive drop in systolic function

EDG-7500 Normalizes Cross-Bridge Formation and Facilitates Ventricular Filling

EDG-7500 has Demonstrated Improvement in a Variety of HCM Clinical Manifestations in Translatable Models of Both oHCM and nHCM

	Key Result	Preclinical Model
Novel target	✓ Preserves myosin head motor function ✓ Slows contraction, increases compliance	*In vitro:* Myofibril systems *In vivo*: Pressure Volume loops
Validated models of oHCM and nHCM	✓ Potent gradient reduction ✓ Well tolerated at supratherapeutic exposures	*In vivo*: *MYBPC3* A31P feline **oHCM** model†
	✓ Normalizes hyperdynamic contraction ✓ Improves ventricular filling	*In vivo*: *MYH7* R403Q porcine **nHCM** model‡

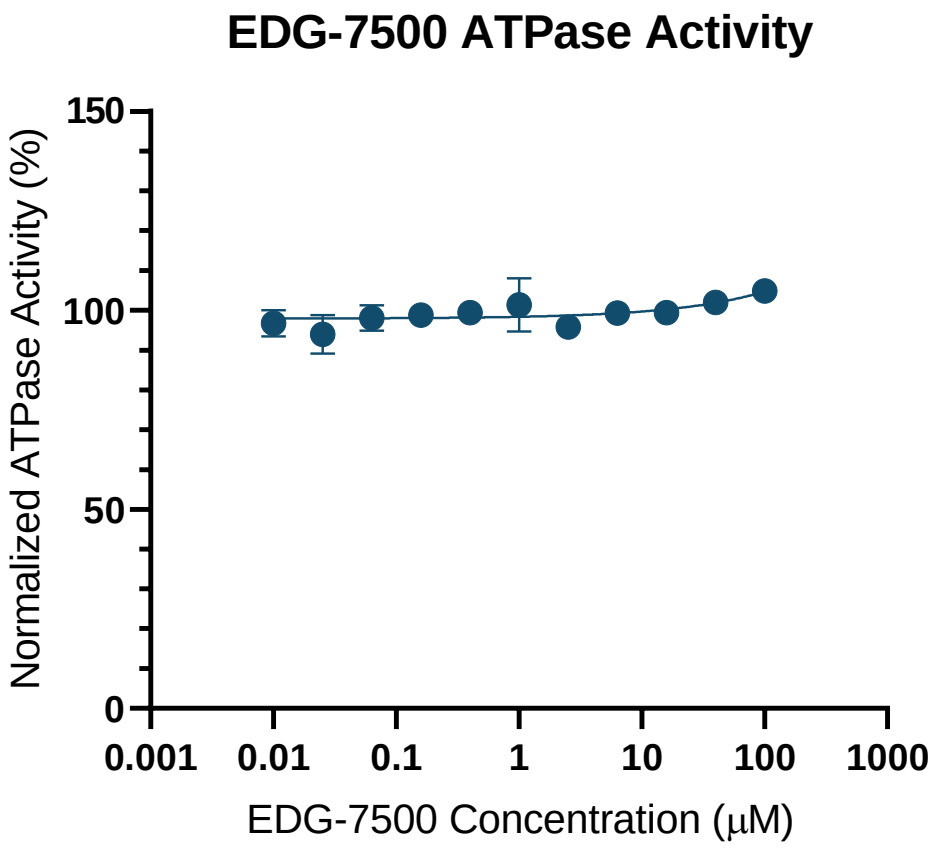
Limits reduction in systolic contractility, even at highest exposures

Edgewise THERAPEUTICS

Abbreviations: oHCM/nHCM, obstructive/non-obstructive hypertrophic cardiomyopathy; *MYBPC3* A31P, cardiac myosin binding protein C3 alanine to proline substitution at residue 31; *MYH7* R403Q, β-myosin heavy chain 7 arginine to glutamine substitution at residue 403

Reference: †Meurs K, *et. al., H Mol Gen.,* 2005; ‡del Rio C, *et. al., Circulation* 2018; 136. Abstract 20770.

EDG-7500 was Designed to Work Independently of Myosin Motor Activity

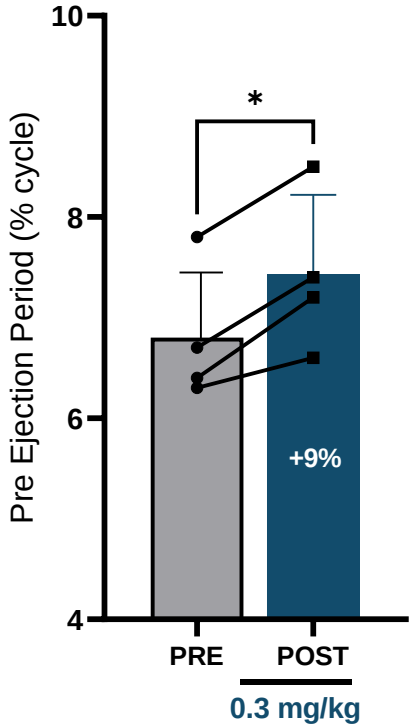


EDG-7500 was designed specifically to preserve full motor activity in isolated myosin ('S1') systems demonstrating a **novel mechanism of action**

Abbreviations: S1, isolated myosin sub-fragment 1

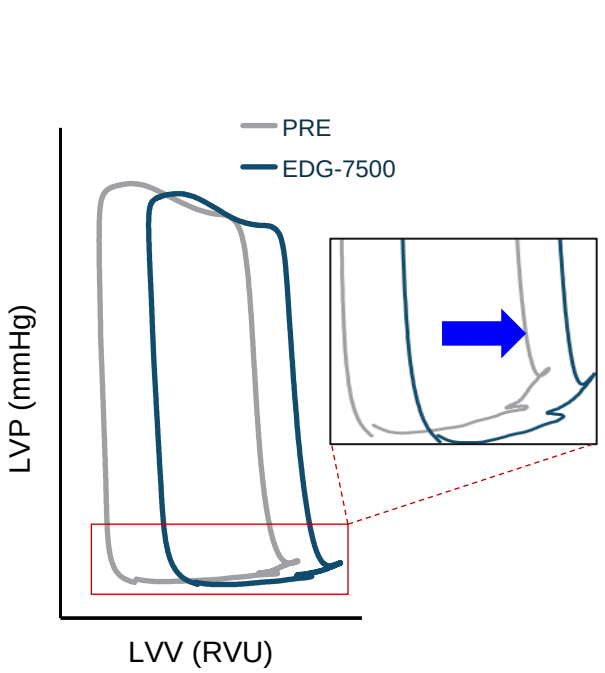
EDG-7500 Slows Contraction and Improves Compliance/ Dispensability in Healthy Canines

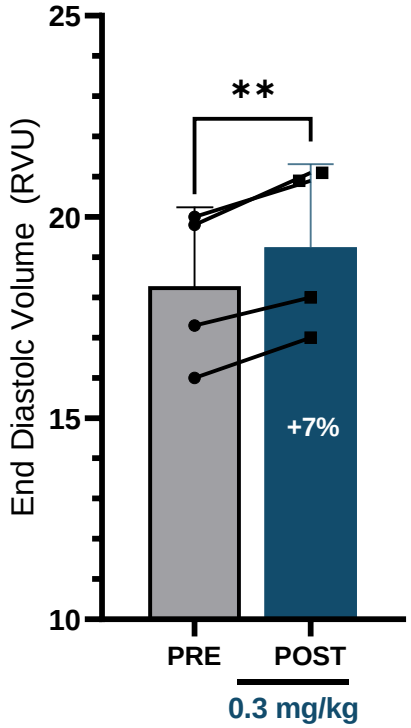
EDG-7500 Slows Contraction



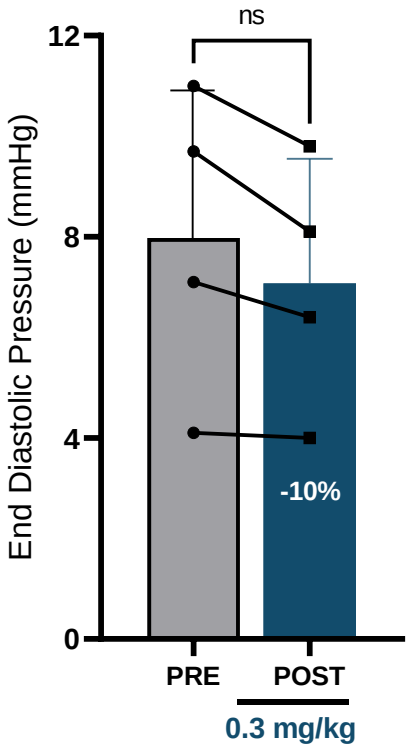
EDG-7500 Increases Compliance

End diastolic volume increased; end diastolic pressure maintained





End Diastolic Volume

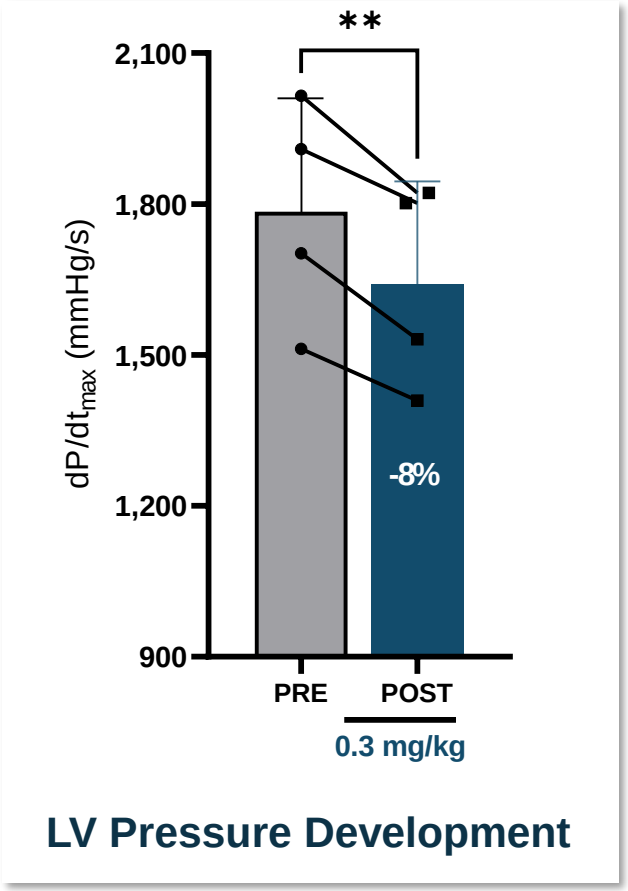


End Diastolic Pressure

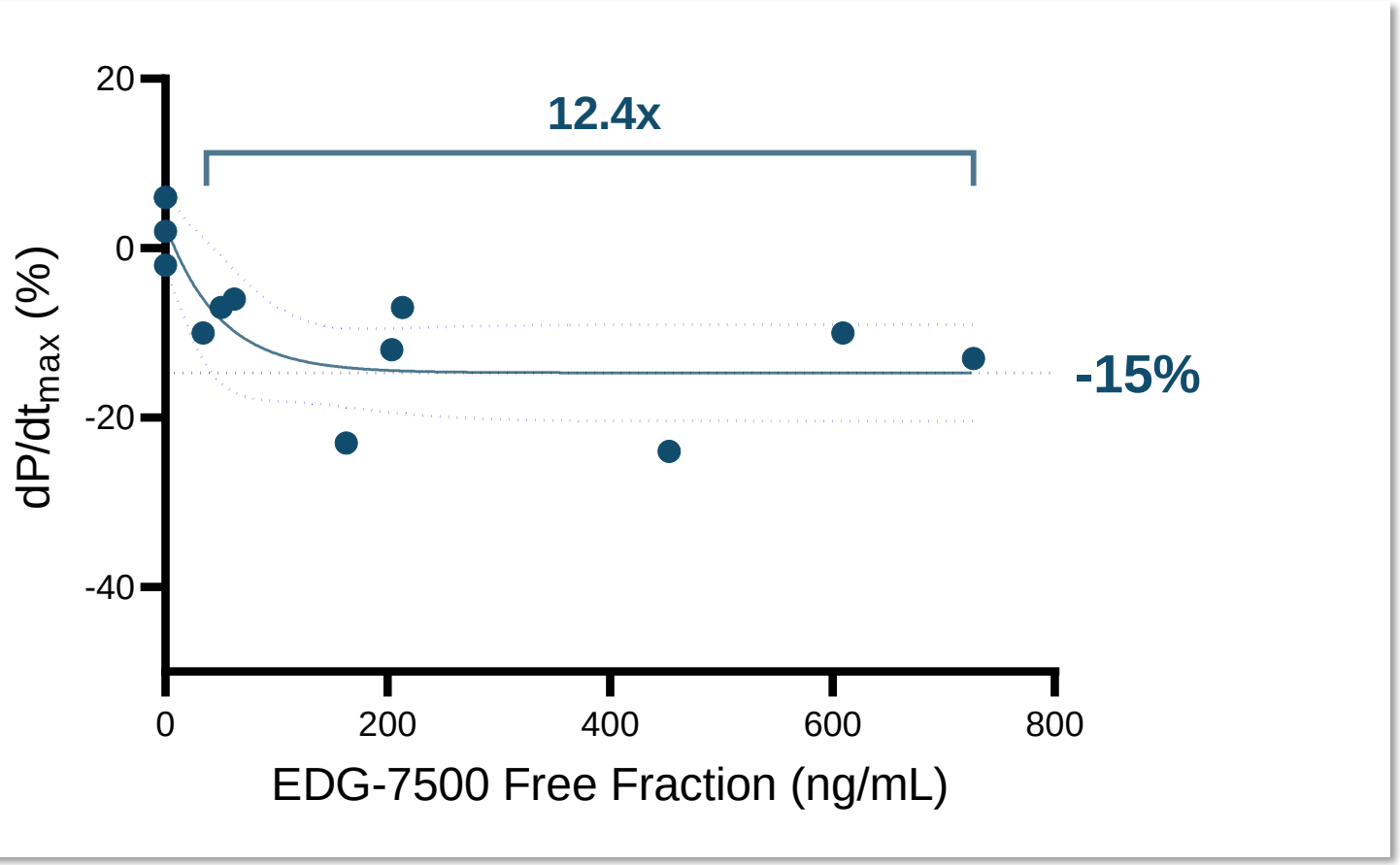
Footnotes: * *p< 0.05*; ** *p < 0.01;* SD shown

Abbreviations: LVV left ventricular volume; RVU relative volume units; ; PRE, predose; POST, postdose; LVP, left ventricular pressure

Moreover, the Reduction in Systolic Contraction is Self-Limiting in Healthy Canines Treated with EDG-7500

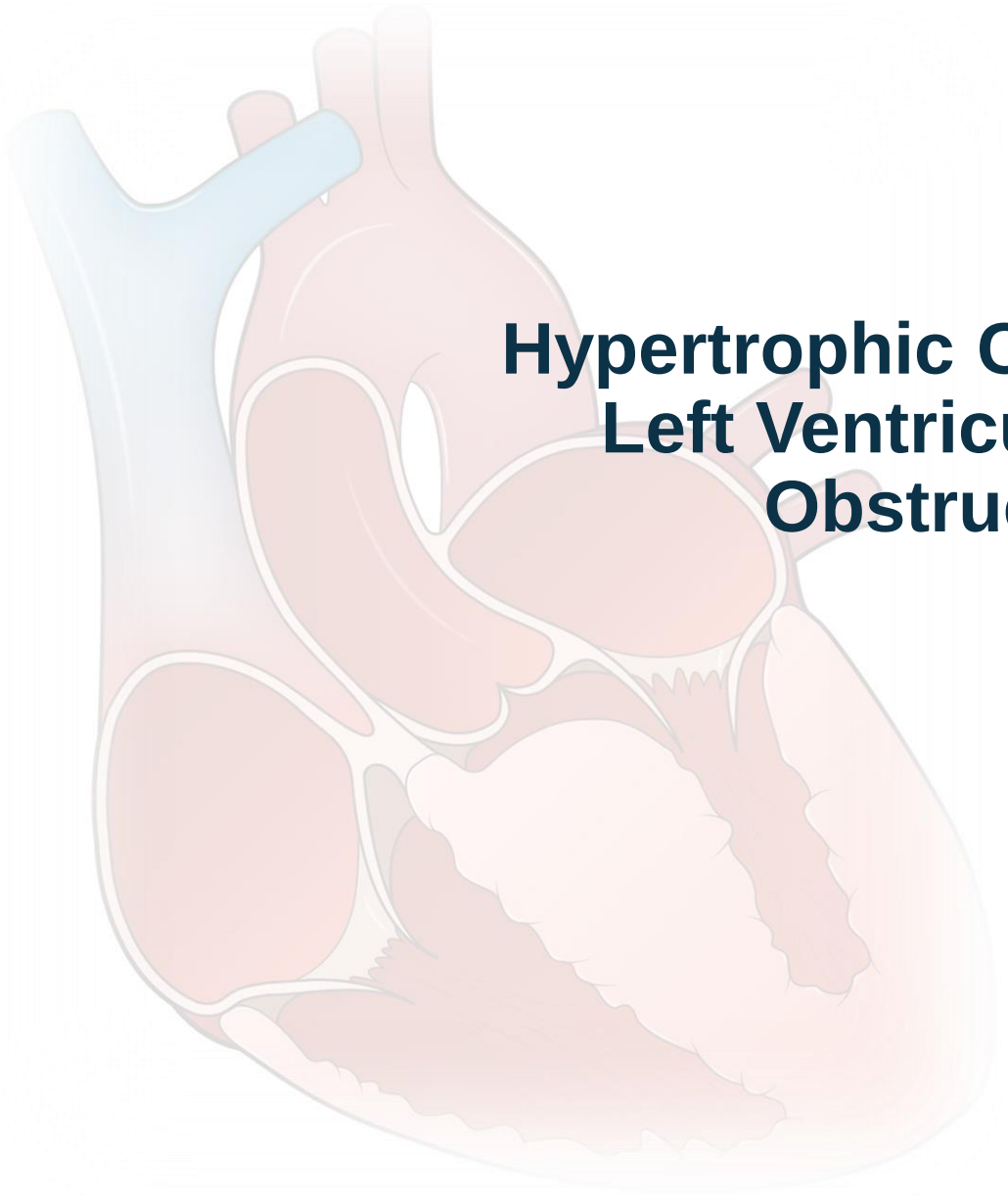


LV Pressure Development



SD shown; Footnotes: * *p< 0.05*; ** *p < 0.01*

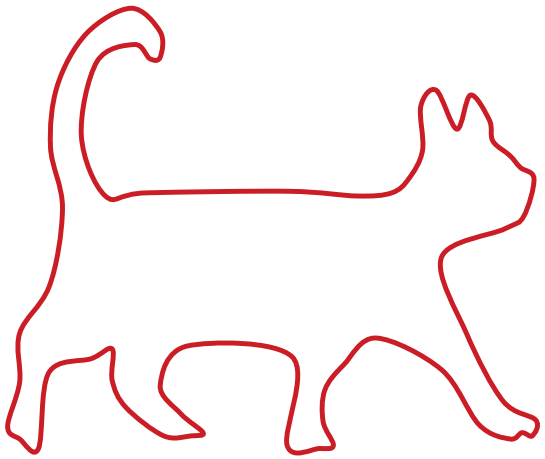
Abbreviations: dP/dt_{max}, the maximum rate of rise in ventricular pressure; LV, left ventricle

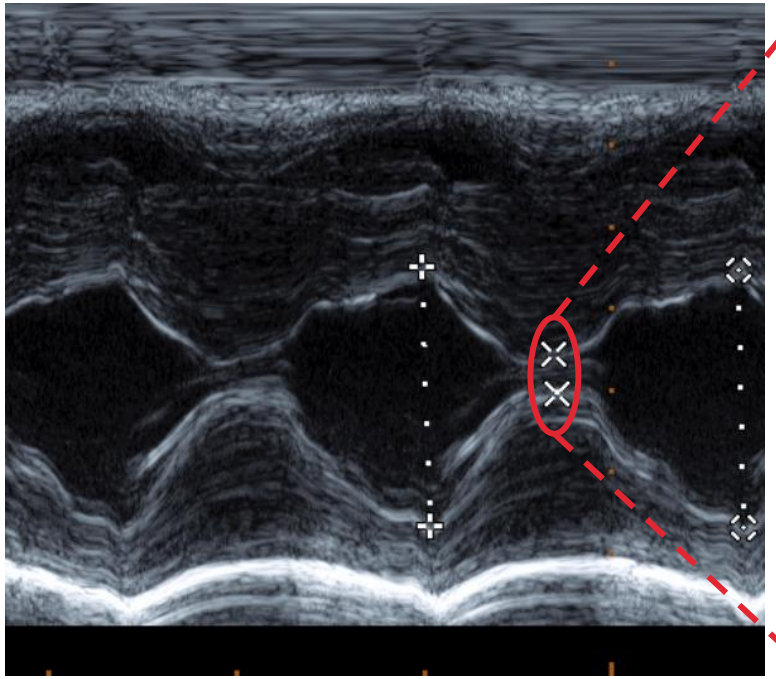


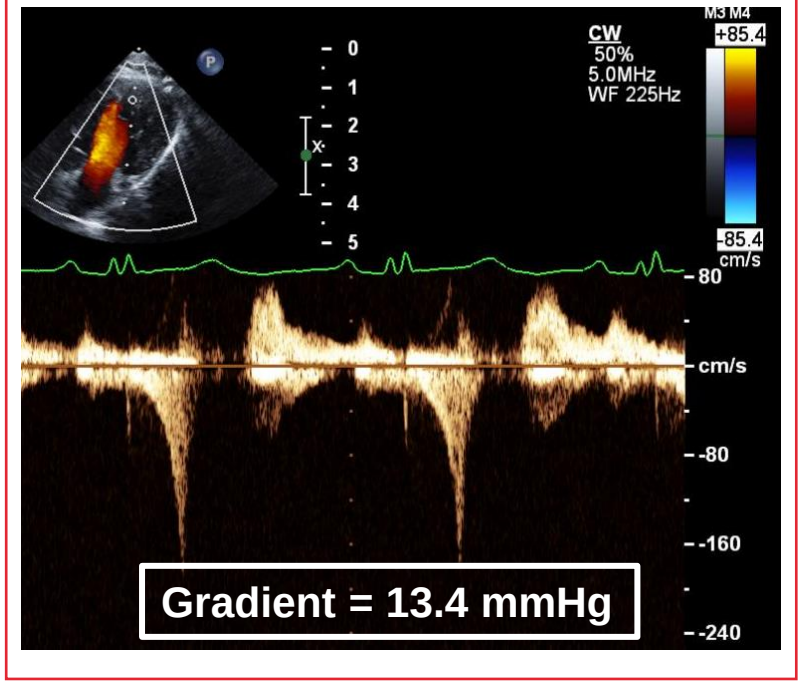
Hypertrophic Cardiomyopathy with Left Ventricular Outflow Tract Obstruction (oHCM)

MYBPC3 A31P Feline Model Exhibits HCM Phenotype with Left Ventricular Outflow Tract (LVOT) Obstruction

MYBPC3 A31P Feline Model of oHCM







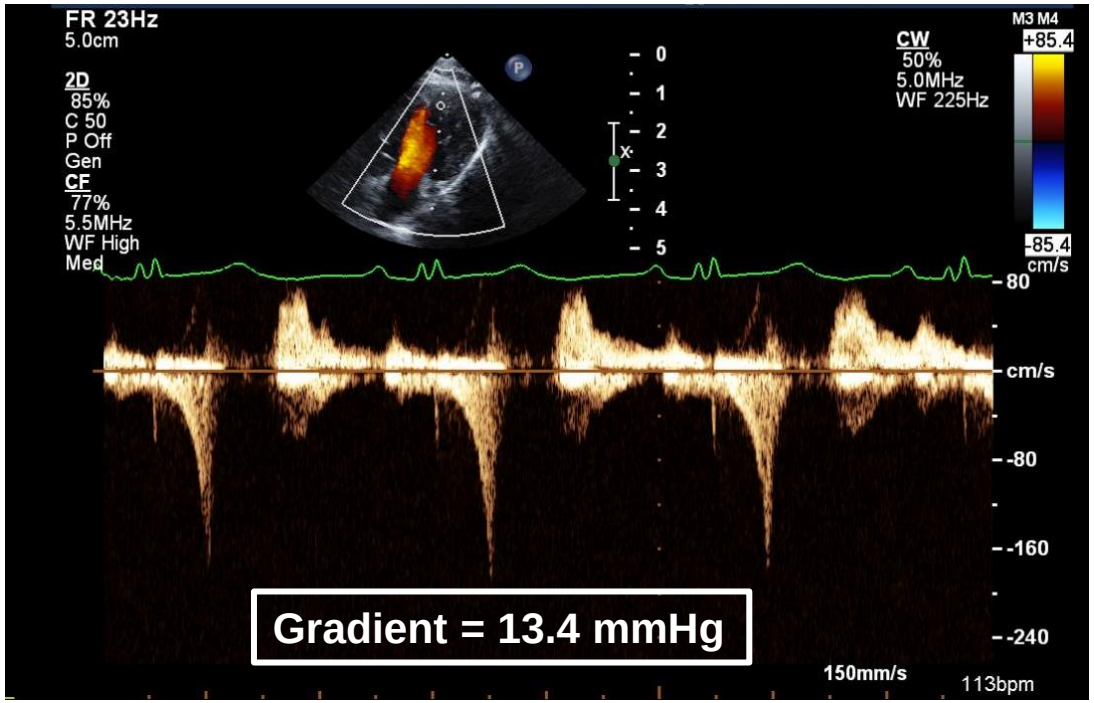
- Purpose bred felines with naturally occurring homozygous *MYBPC3* A31P mutation
- *MYBPC3* A31P felines exhibit left ventricular hypertrophy and obstruction consistent with oHCM

Pressure gradient is calculated by the modified Bernoulli equation: Gradient proportional to $4V^2$

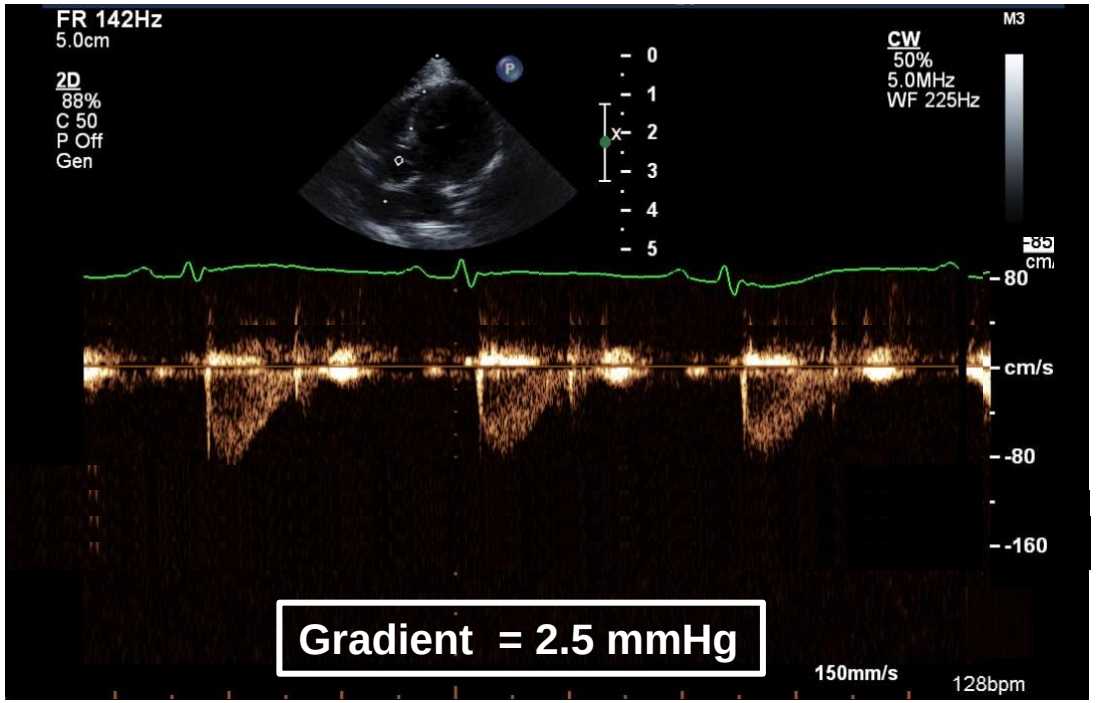
Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; *MYBPC3* A31P, cardiac myosin binding protein C3 alanine to proline substitution at residue 31

MYBPC3 A31P Feline Model LVOT Gradient Alleviated with EDG-7500

MYBPC3 A31P felines exhibit left ventricular hypertrophy and outflow tract obstruction consistent with oHCM



EDG-7500 treated *MYBPC* A31P feline shows LVOT gradient relief

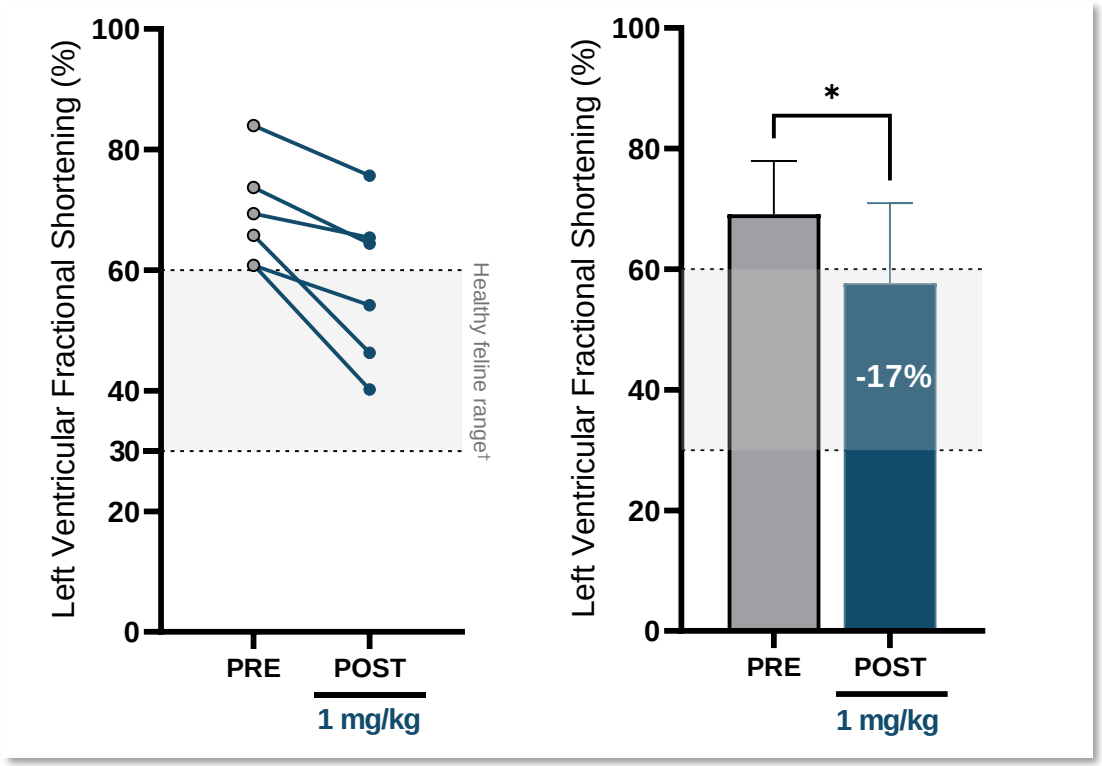


Pressure gradient is calculated by the modified Bernoulli equation: Gradient proportional to $4V^2$

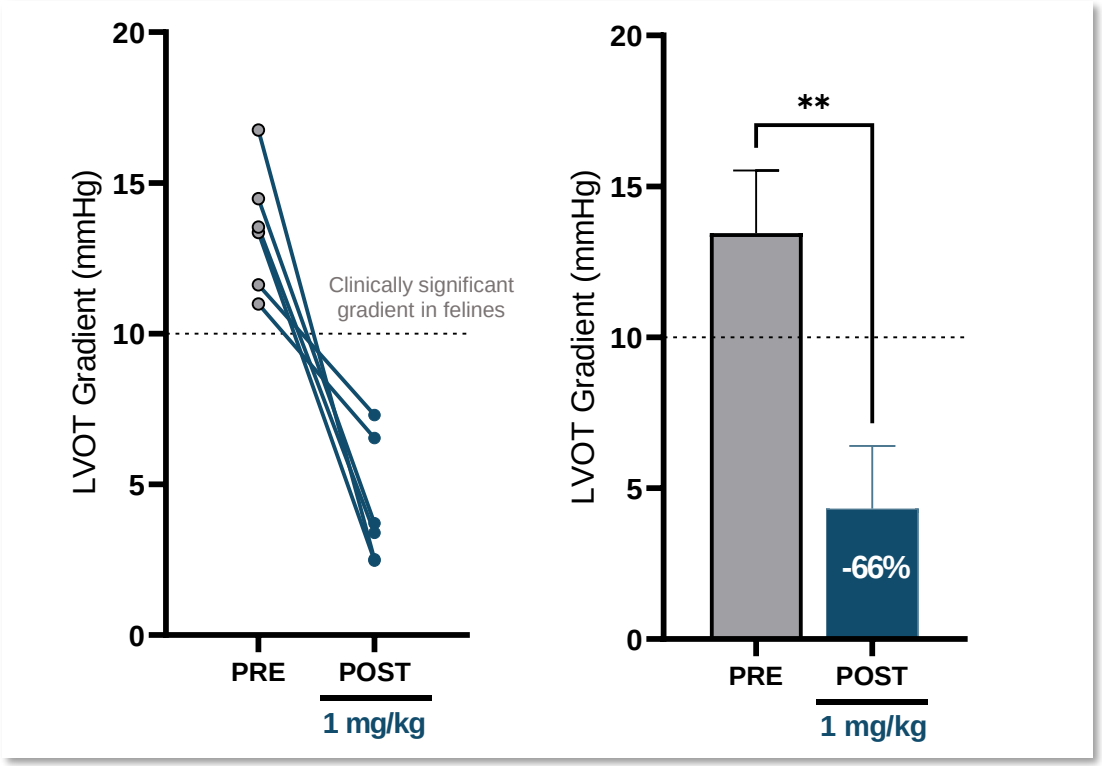
Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; *MYBPC3* A31P, cardiac myosin binding protein C alanine to proline substitution at residue 31

EDG-7500 Improves Contractility and Alleviates LVOT Gradient in an Established Feline Model of oHCM

Hypercontractility Improved to within Normal Range



LVOT Gradient Removed

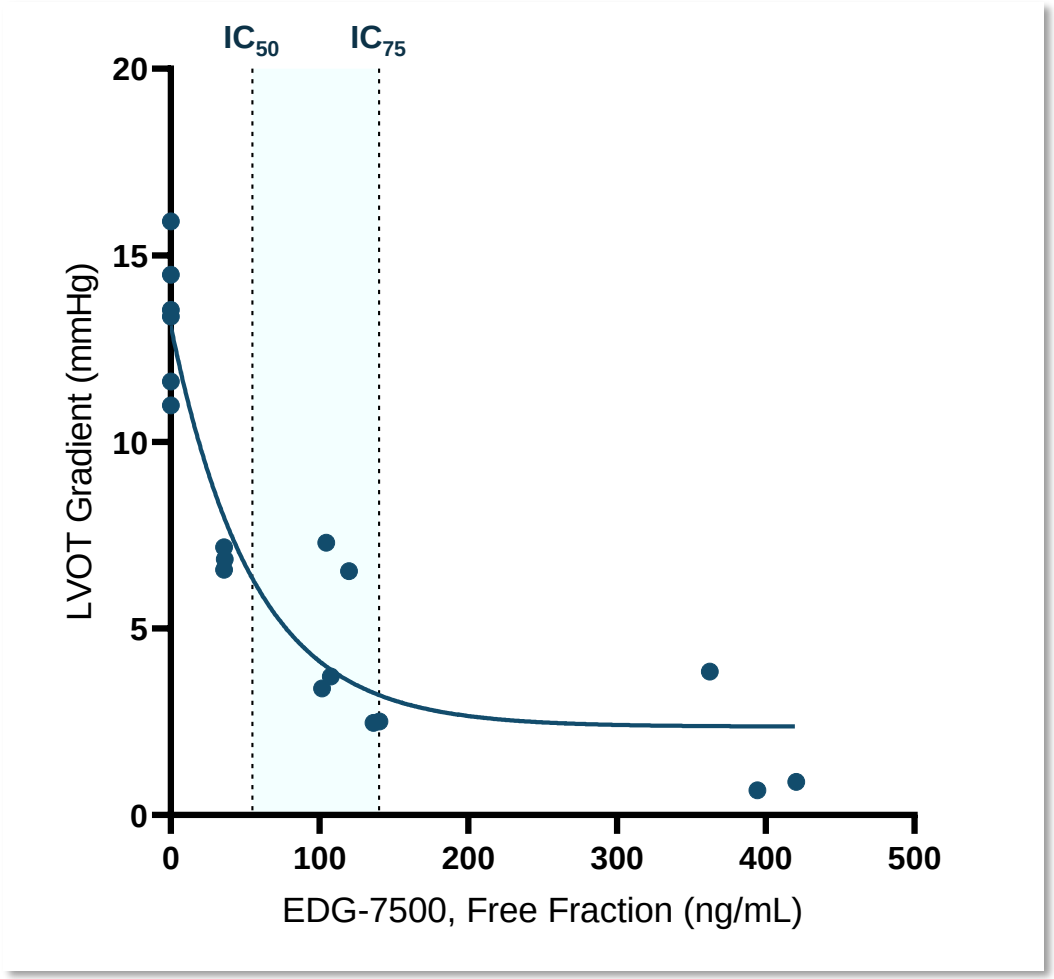


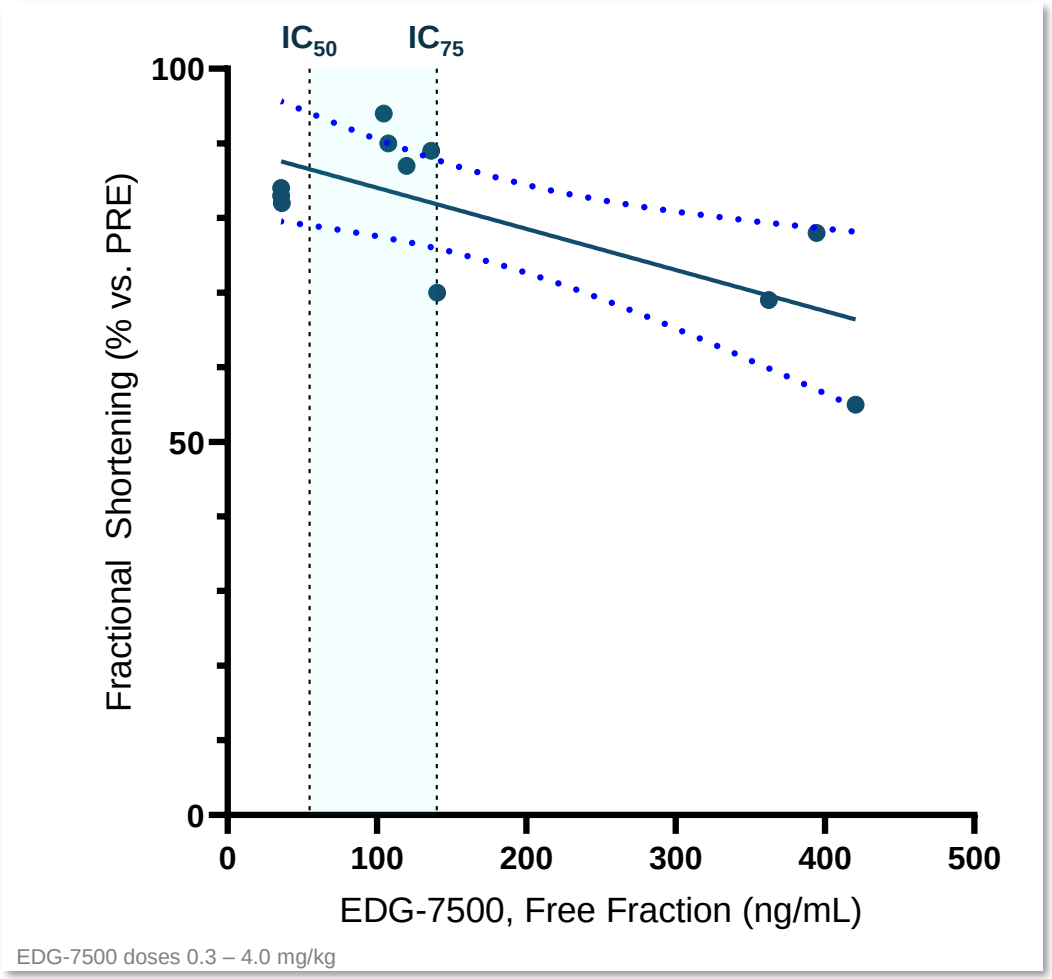
† Fox PR *et al., Circulation*, 1995

Footnotes: * $p < 0.05$, ** $p < 0.01$

EDG-7500 Markedly Reduces LVOT Gradient at Plasma Concentrations Associated with Modest Changes in Contractility

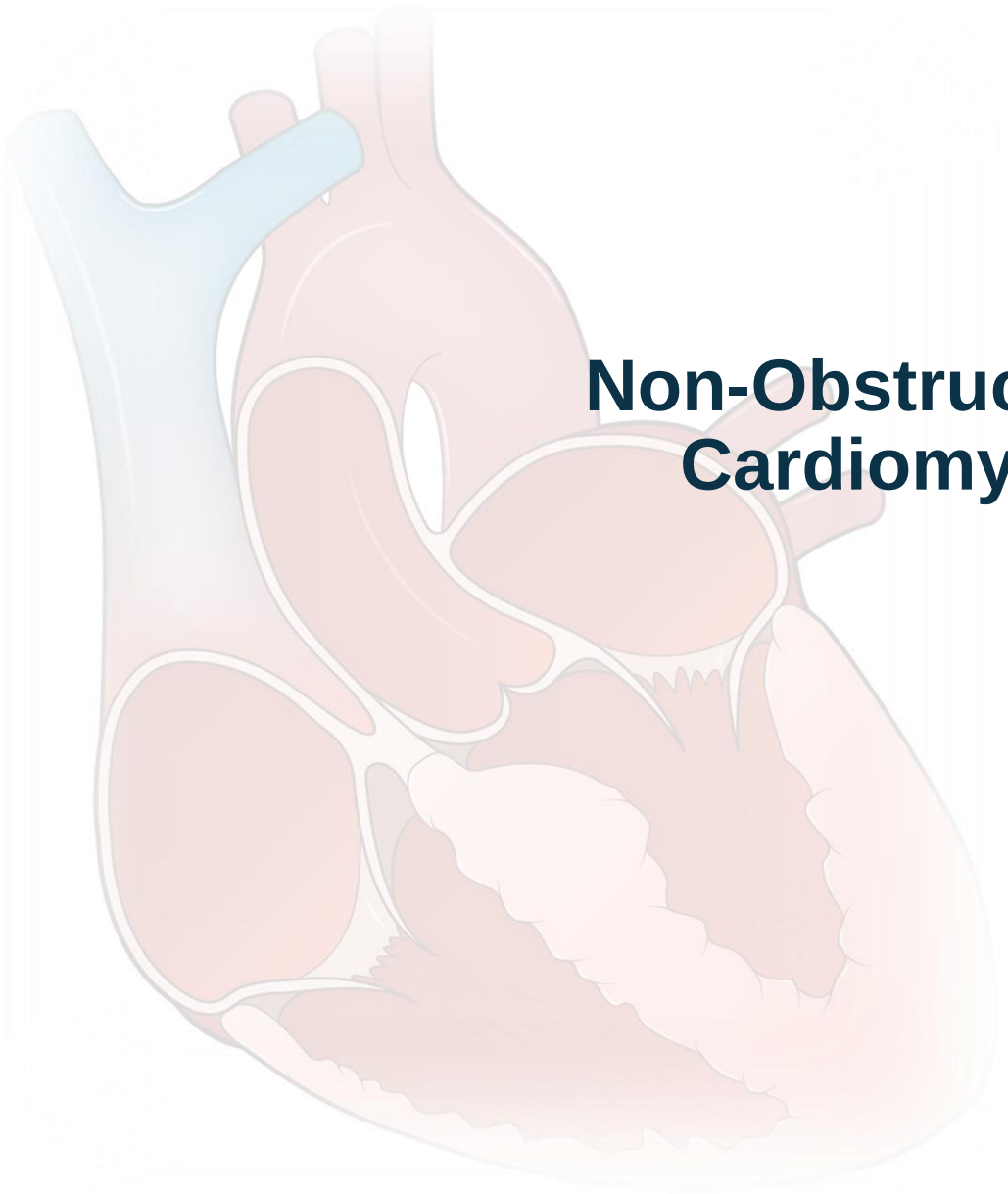
MYBPC3 A31C Feline Model of oHCM





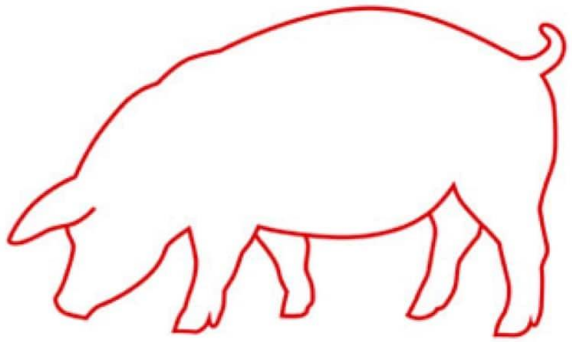
EDG-7500 doses 0.3 – 4.0 mg/kg

Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; FS, left ventricular fractional shortening; *MYBPC3* A31P, cardiac myosin binding protein C3 alanine to proline substitution at residue 31



Non-Obstructive Hypertrophic Cardiomyopathy (nHCM)

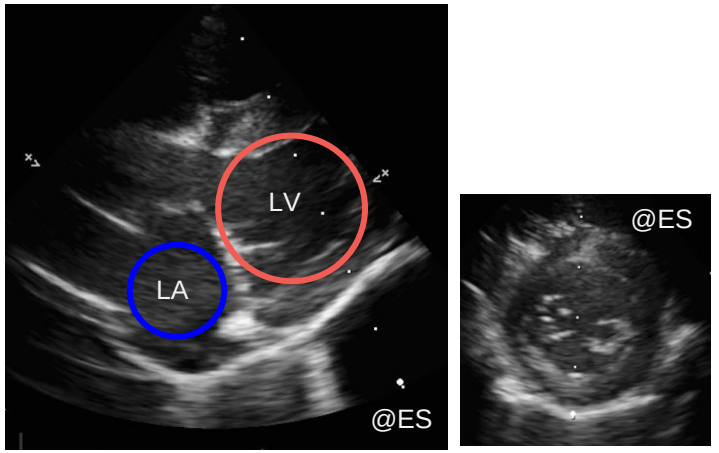
Myosin Heavy Chain R403Q Porcine Model of nHCM Presents with Characteristic Non-Obstructive HCM Phenotype Observed in Humans



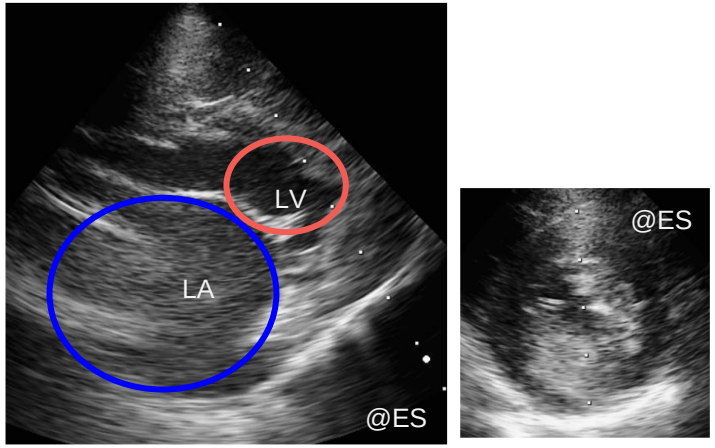
- Genetically engineered porcine model with the *MYH7* R403Q HCM mutation
- *MYH7* R403Q porcine exhibit structural and functional abnormalities consistent with nHCM

Left ventricular (LV) hypertrophy, small cavity, and increased filling pressure leads to increased left atrial (LA) size

Wild Type



Non-Obstructive HCM

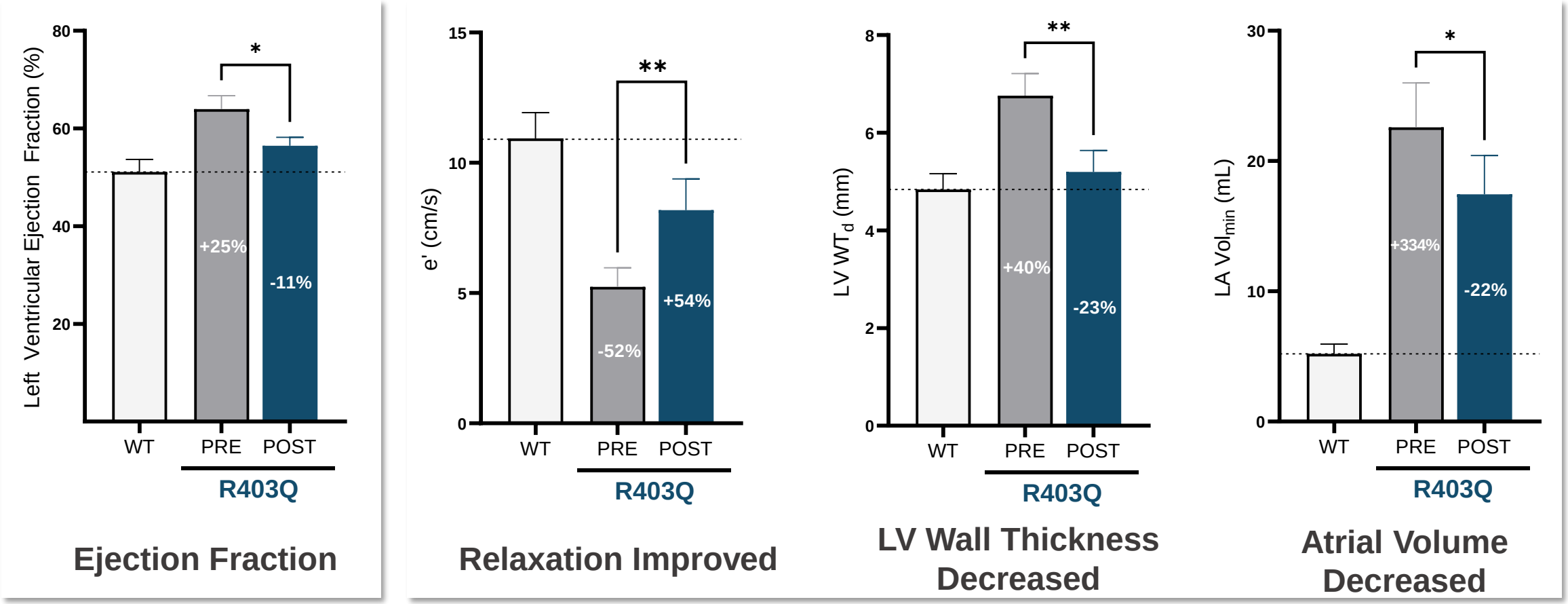


Abbreviations: WT, wild type; HCM, hypertrophic cardiomyopathy; nHCM, non-obstructive hypertrophic cardiomyopathy, *MYH7* R403Q, β-myosin heavy chain 7 arginine to glutamine substitution at residue 403; @ES, at end systole; LA, left atrium; LV, left ventricle

Rapid Normalization of HCM Cardiac Structure and Function in the *MYH7* R403Q Porcine with a Single Dose of EDG-7500

Hypercontraction Retuned to WT Levels

EDG-7500 Drives Improvement in LV Filling and Reduction in LA Size Consistent with Reduced Filling Pressure



Footnotes: % change PRE is relative to WT and % change POST is relative to PRE; * *p< 0.05*; ** *p < 0.01*

Abbreviations: *MYH7* R403Q, β-myosin heavy chain 7 arginine to glutamine substitution at residue 403; LVEF, left ventricular ejection fraction; e', early filling; $LVWT_d$, left ventricular wall thickness at end diastole; LAVol, left atrial volume; LA, left atrium; WT, wild type; PRE, predose; POST, postdose 1 mg/kg

EDG-7500: First-in-Class Sarcomere Modulator Intended to Address the Molecular Underpinning of HCM

- EDG-7500 is an **oral, selective cardiac sarcomere modulator**
- EDG-7500 **normalizes excess systolic and diastolic cross-bridges, the underlying pathology of both obstructive and non-obstructive HCM**, without inactivating the myosin motor
- EDG-7500 preclinical data supports activity in both **oHCM and nHCM** with minimal changes in LVEF
- EDG-7500's novel MOA supports investigating fixed dose regimens

Abbreviations: HCM, hypertrophic cardiomyopathy; oHCM, obstructive HCM; nHCM, non-obstructive HCM; LVEF, left ventricular ejection fraction; MOA, mechanism of action

HCM Clinical Development Program

Marc Semigran, M.D.
Edgewise Chief Development Officer

HCM Represents a Patient Population with Significant Unmet Need and Ample Opportunity for a Novel Therapy Such as EDG-7500

Perceived Limitations of Approved and In Development Cardiac Myosin Inhibitors:

1. **Complex pharmacology and variable metabolism** based largely on genetics, resulting in potentially excessive reduction in cardiac function
2. Largely only address **excessive contractility**, which may limit their efficacy

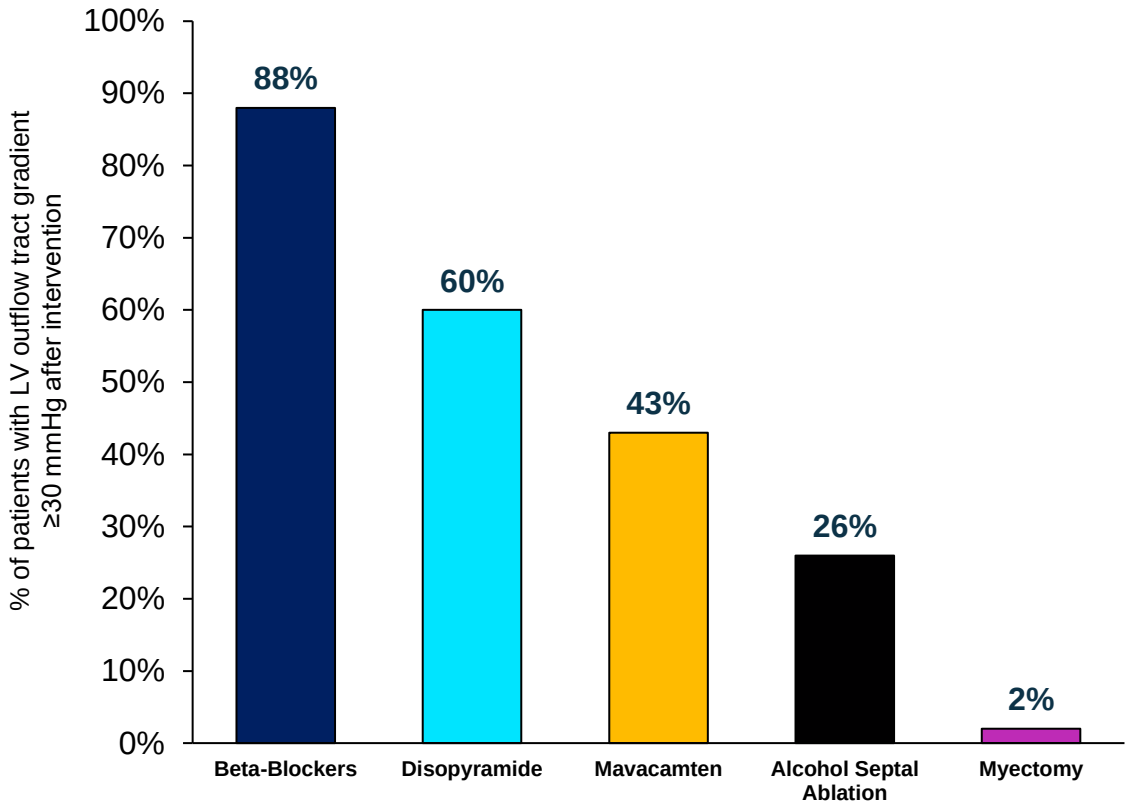
Thus, CMIs are generally:

- ❑ **Difficult to initially dose** and reach an efficacious maintenance dose
- ❑ **Complicated by the need to avoid DDIs** with common OTC and prescription drugs
- ❑ Potentially **deleterious during intercurrent diseases** that lower cardiac contractility
- ❑ Accompanied by need for **frequent, indefinite patient follow-up with specialized cardiac imaging** at expert HCM centers to which access remains limited
- ❑ **Insufficient to treat all oHCM and nHCM** patients
- ❑ Of unproven benefit to patients with **non-obstructive disease with impaired relaxation**

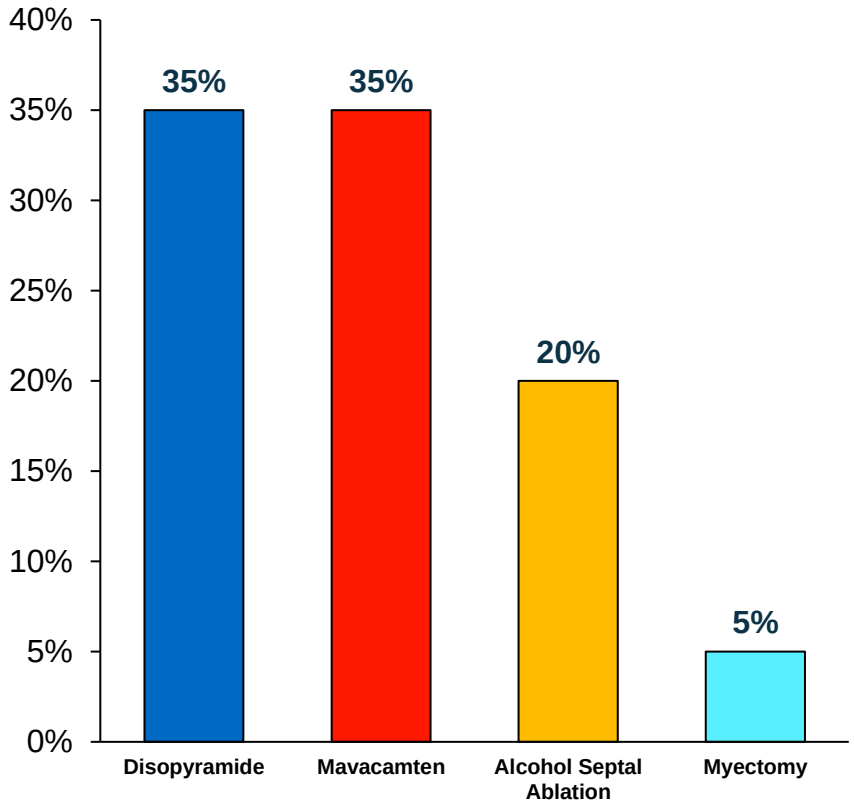
Abbreviations: HCM, hypertrophic cardiomyopathy; DDI, drug-drug interaction; OTC, over-the-counter;

The Limited Efficacy of Current Therapeutic Approaches is One of the Unmet Needs in the Management of oHCM Patients

Residual LV Outflow Tract Gradients After Treatment



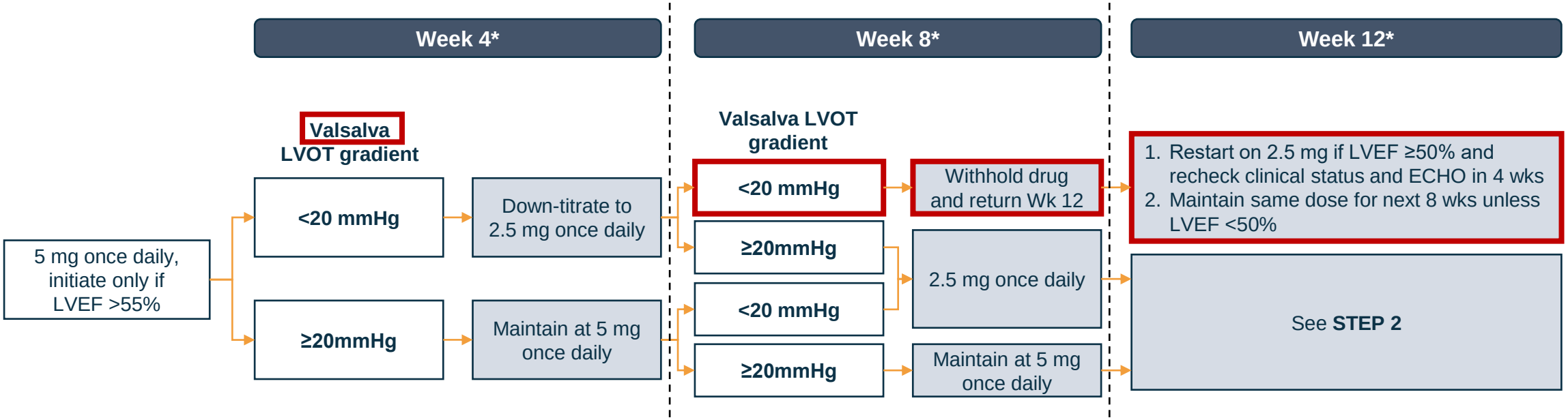
% of Patients with No Improvement in NYHA Functional Class Following Treatment



Reference: Martin S. Maron and Steve R. Ommen, *Circulation,* 2021. Exploring New and Old Therapies for Obstructive Hypertrophic Cardiomyopathy, Volume: 143

Algorithm for Reaching a Safe and Efficacious Dose of Camzyos® Requires Multiple Clinic Visits; Lack of Adherence Can Result in HF (1/3)

STEP 1: Initiation Phase

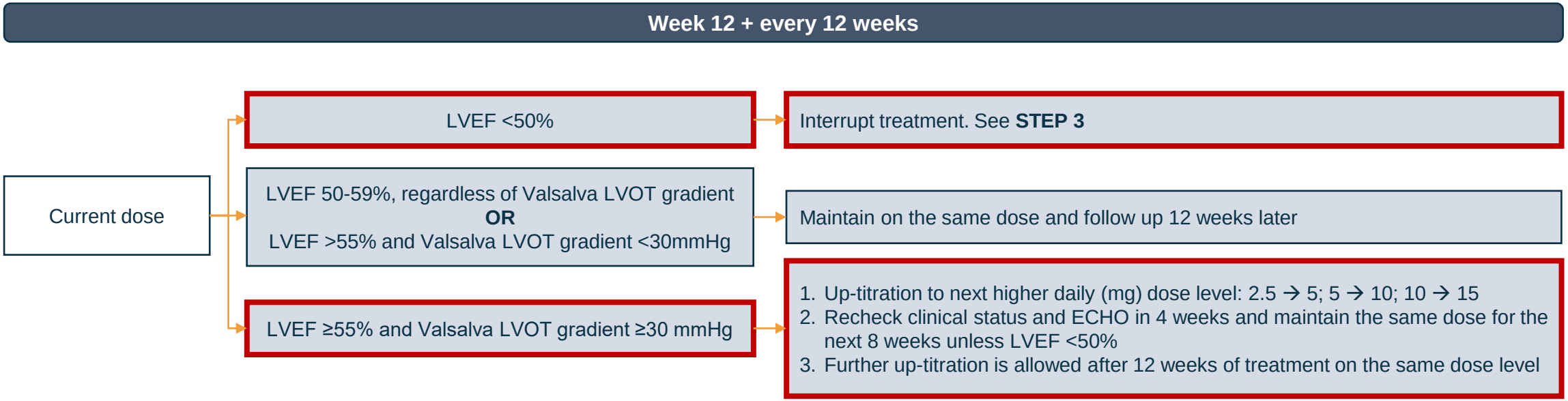


* Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See **STEP 3**

Reference: Camzyos Prescribing Information www.packageinserts.bms.com/pi/pi_camzyos.pdf

Algorithm for Reaching a Safe and Efficacious Dose of Camzyos® Requires Multiple Clinic Visits; Lack of Adherence Can Result in HF (2/3)

STEP 2: Continued Dose Adjustments to Achieve Maintenance Dose



Reference: Camzyos Prescribing Information www.packageinserts.bms.com/pi/pi_camzyos.pdf

Algorithm for Reaching a Safe and Efficacious Dose of Camzyos® Requires Multiple Clinic Visits; Lack of Adherence Can Result in HF (3/3)

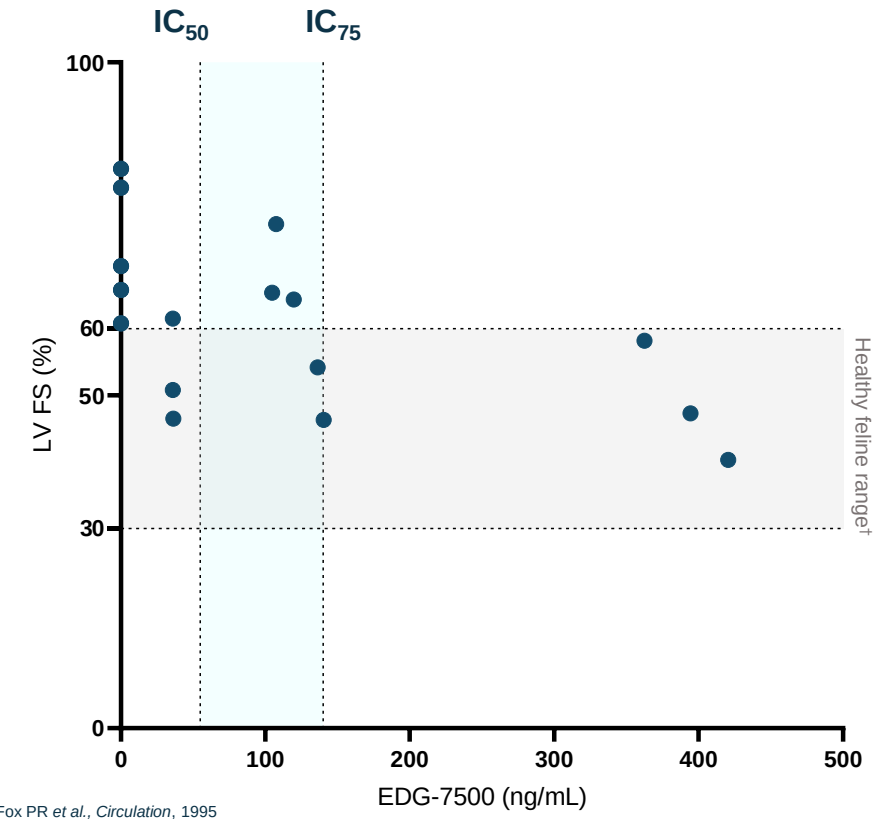
STEP 3: Treatment interruption at any clinic visit if LVEF <50%



There is a pressing need for **new agents** that address both major underlying pathophysiologies in HCM patients and could be **used across the entire spectrum of patients**

Reference: Camzyos Prescribing Information www.packageinserts.bms.com/pi/pi_camzyos.pdf

EDG-7500 has a Modest Effect on Cardiac Contractility at Plasma Levels that Eliminate LVOT Obstruction



† Fox PR *et al.*, *Circulation*, 1995

Treatment with EDG-7500 is associated with a modest effect on contractility with free drug levels of **~55 to 140 ng/mL** achieving IC_{50} to IC_{75} **gradient removal in the feline model of oHCM**

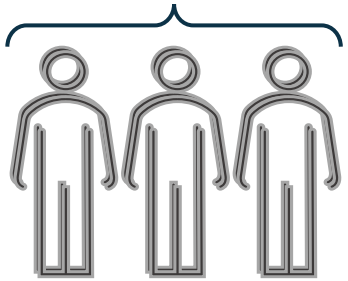
A Fixed Dose Regimen of EDG-7500 Requiring Less Intense Follow-up Than Current Therapies May Be Possible

Abbreviations: LVFS, left ventricular fractional shortening; oHCM, obstructive hypertrophic cardiomyopathy; IC, half-maximal inhibitory concentration

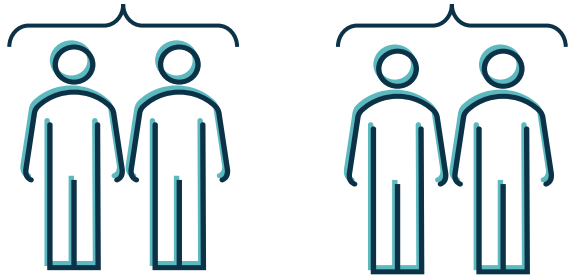
Phase 1 Study of EDG-7500 in Healthy Volunteers and HCM Patients to Start in 2023

GOAL: To evaluate safety and tolerability of EDG-7500 and establish POM and POC in HCM patients

Healthy Volunteers



HCM Patients



oHCM nHCM

SAD/MAD Study design
Treatment Duration: 21 days

Key Outcome Measures

Safety and tolerability

PK and Cardiovascular PD

- Echocardiogram
- Resting LVOT gradient
- Post-Valsalva LVOT gradient
- Objective assessment of Functional Capacity (in patients)

Biomarkers

- NT-proBNP
- hsTnI

Study on track to start in 2H2023

Abbreviations: HCM, hypertrophic cardiomyopathy; oHCM, obstructive HCM; nHCM, non-obstructive HCM; POM, proof of mechanism; POC, proof of concept; SAD, single ascending dose; MAD, multiple ascending dose; PK/PD, pharmacokinetics/pharmacodynamics; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; hsTnI, high-sensitivity troponin I

Summary

- EDG-7500's unique MOA targets both **abnormal systolic and diastolic function in HCM patients**, suggesting the ability to drive a broad efficacy response at a **low risk of decreasing LVEF below normal**

- EDG-7500's **excellent selectivity, bioavailability, and favorable half-life** should potentially make it easy to use by clinicians and patients

- We anticipate an **efficient pathway** for the **rapid clinical development** of EDG-7500 in a wide range of HCM patients

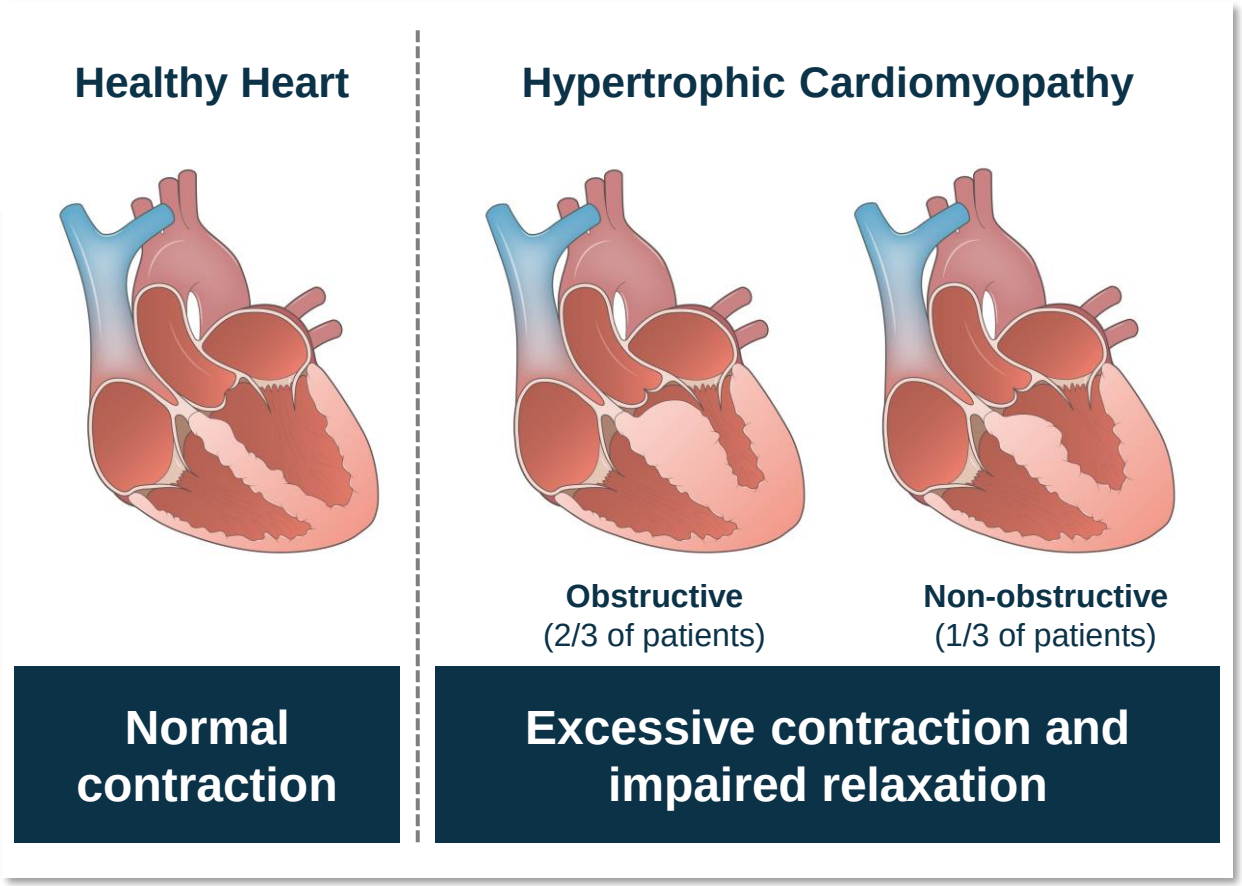
Abbreviations: HCM, hypertrophic cardiomyopathy; MOA, mechanism of action; LVEF, left ventricular ejection fraction

Future Direction and Closing Remarks

Kevin Koch
Edgewise Chief Executive Officer

HCM Represents a Patient Population with Significant Unmet Need and Ample Opportunity for a Novel Therapy Such as EDG-7500

- HCM patients **rely on polypharmacy and SRT**, an invasive surgical option
- Optimal care and patient outcomes require highly specialized **HCM centers of excellence to which access remains limited**
- There is a **need for noninvasive approaches** that address the underlying pathophysiology of HCM and could be **used across the entire spectrum of patients**



Abbreviations: HCM, hypertrophic cardiomyopathy; SRT, septal reduction therapy

EDG-7500 has Attractive First-in-Class Drug Attributes

- **Oral, once daily therapy**
- **Rapid onset of action**
- **Easily reversible**

EDG-7500 Preclinical Drug Attributes

Target	Non-myosin motor, sarcomeric protein
LVFS	Limited reduction
Human $t_{1/2}$ (projected)	1-2 days
CYP450 induction EC_{50}	>30 µM
CYP450 inhibition IC_{50}	>30 µM
Broad off target profiling	>30 µM
P450 Substrate	CYP3A4; most common enzyme
Predicted Clinical Dosing	Oral, once daily
Anticipated time to steady state	<1 week

Abbreviations: LVFS, left ventricular fractional shortening; $t_{1/2}$, half-life; EC_{50}, half maximal effective concentration; IC_{50},half maximal inhibitory concentration; CYP, cytochrome P

Highly Innovative and Differentiated Cardiac Clinical Candidate for HCM Progressing into IND-Enabling Studies with IND Projected 3Q/23

Our goal is to **reverse the causal pathophysiology of HCM** without the limitations observed with cardiac myosin inhibitors

- **Non-Myosin Motor Targeted Sarcomere Modulator Preferentially Active in Diastole**
- **Avoid the Need for Complex Echo Guided Dose Titration**
- **Eliminate LVOT Gradient with Minimize Drop in LVEF**
- **Potential to Positively Impact NYHA Class and Increase pVO_2 in oHCM and nHCM**

Abbreviations: oHCM, obstructive hypertrophic cardiomyopathy; nHCM, non-obstructive hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; pVO_2, peak oxygen consumption

Strong Execution in 2022 Allowed Edgewise to Achieve Multiple Key Milestones

- **CANYON Becker Phase 2/3 Study Start** ✓
- **LYNX Duchenne Phase 2 Dose-Ranging Study Start** ✓
- **ARCH BMD OL Study Data 6 Month Readout** ✓
- **Phase 2 Exercise Challenge Start in LGMD2i and McArdle** ✓
- **Selection of a Novel Cardiac Candidate** ✓

Abbreviations: OL, open label; LGMD2i, limb-girdle muscular dystrophy 2i

Well-Capitalized to Execute Important Value-Driving Milestones Across EDG-5506, EDG-7500 and Other Pipeline Programs

$365M[(1)]

Cash, Cash Equivalents and Marketable Securities

No Debt

63.2M[(1)]

Common Shares Outstanding

NASDAQ: EWTX

(1) As of September 30, 2022

Thank You and Questions

NASDAQ: EWTX