Current Concepts in Hypertrophic Cardiomyopathy

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Dr. Scott Cohen
I have no disclosures

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Objectives

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

-To show that hypertrophic cardiomyopathy is a cardiovascular disease that most patients can live with having little to no symptoms and a normal lifespan

-To show treatments exist that can improve quality of life and survival for those that are symptomatic

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What is Hypertrophic Cardiomyopathy?

- Hereditary disorder of the cardiac sarcomere
- Hallmark features
  - Left ventricular hypertrophy (>15mm)
  - +/- Right ventricular hypertrophy
  - Nondilated ventricular chambers
  - Microscopic myocardial fiber disarray
  - Interstitial fibrosis

- Age dependent expression of hypertrophy
  - ½ of patients with a causal mutation by 3rd decade of life
  - ¾ of patients by 6th decade of life

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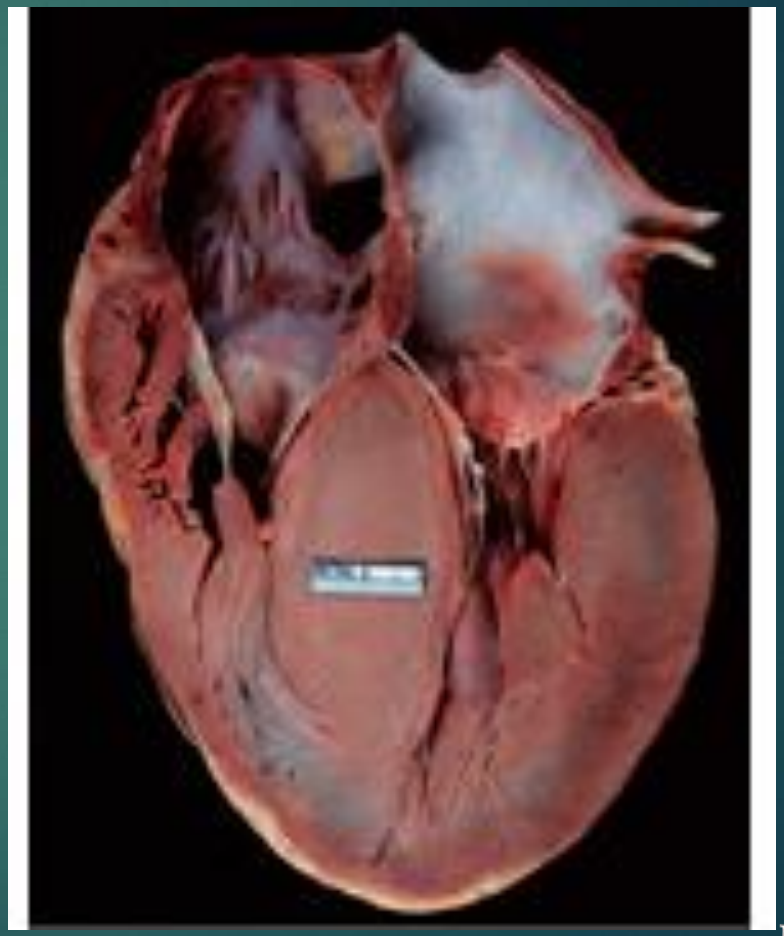
What is Hypertrophic Cardiomyopathy?

- Most common genetically transmitted CV disease
  - 0.2%
- More sensitive imaging methods, more family members evaluated and genetic testing more widely used
  - 0.6%
- Estimated frequency in population exceeds the occurrence of HCM in cardiology practices



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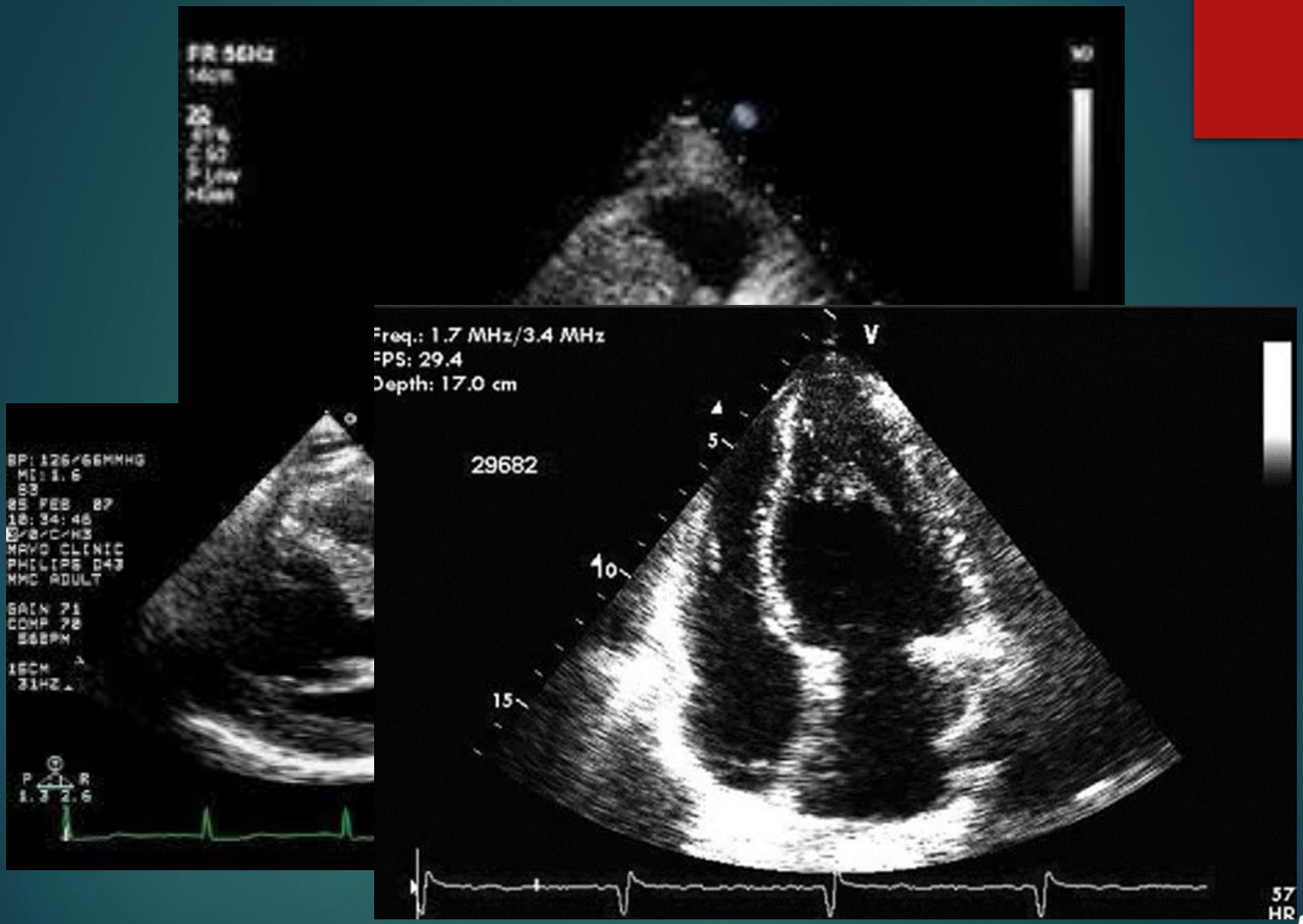

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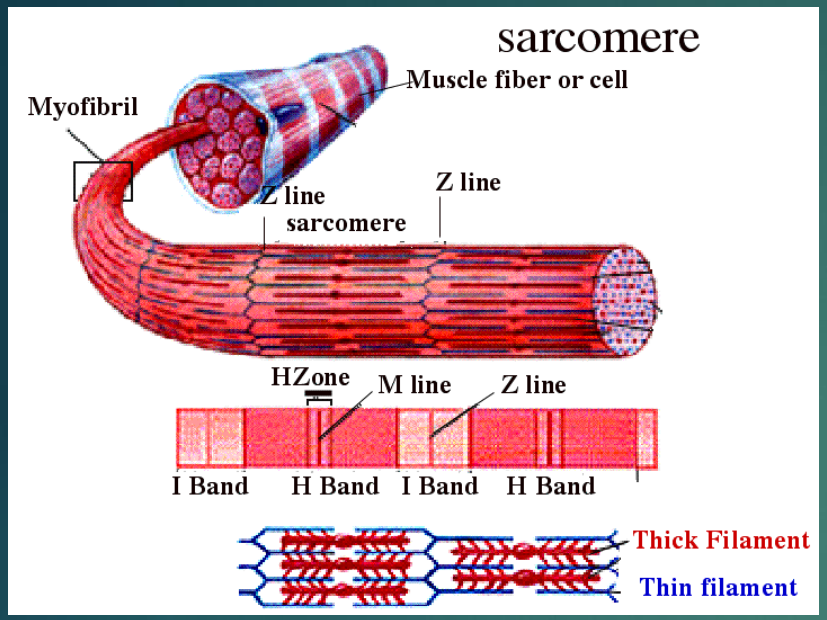
Pathogenesis of HCM



- Sarcomere is the fundamental contractile unit in striated muscle
- Proteins organized into thick and thin filaments

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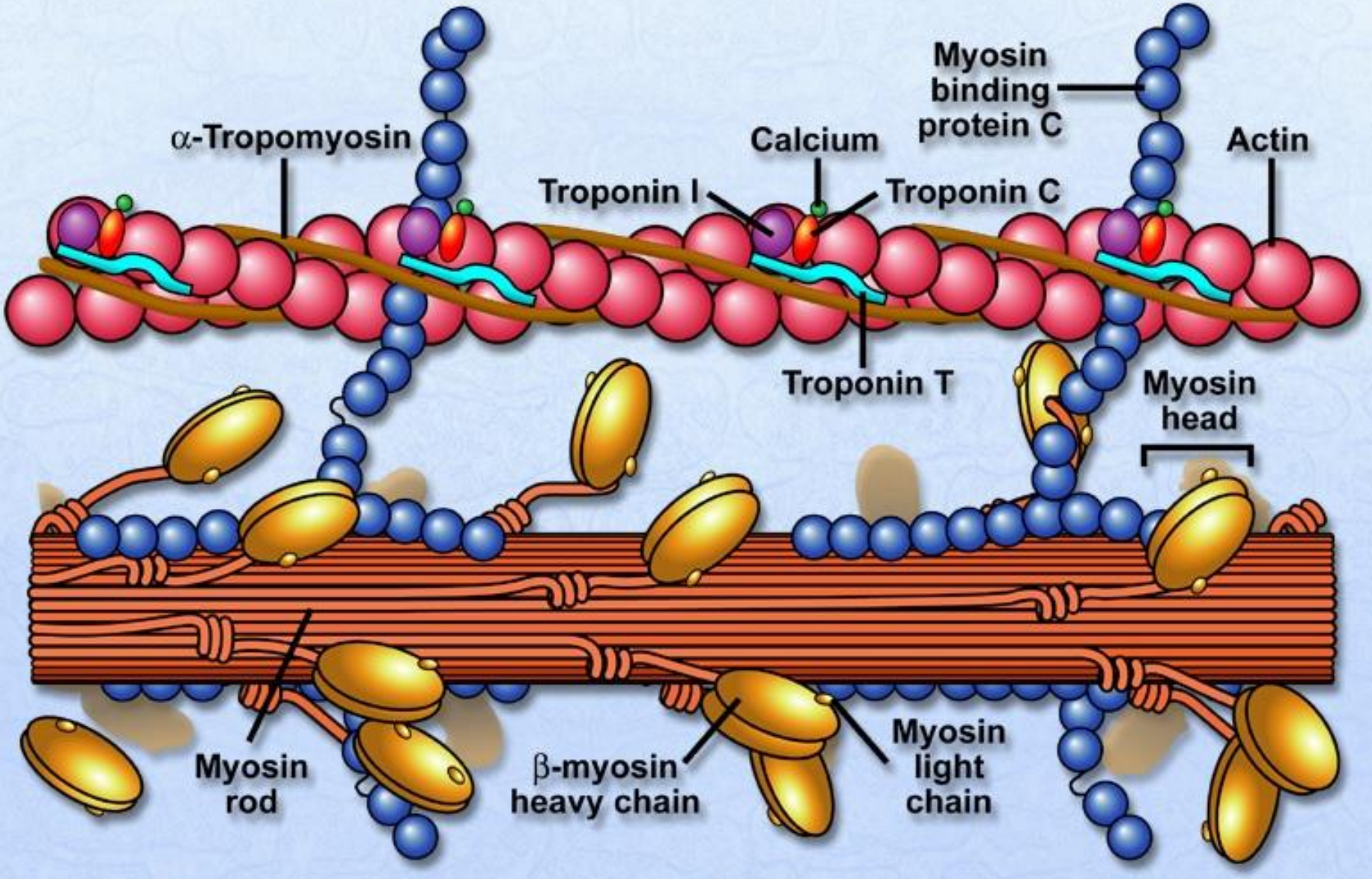
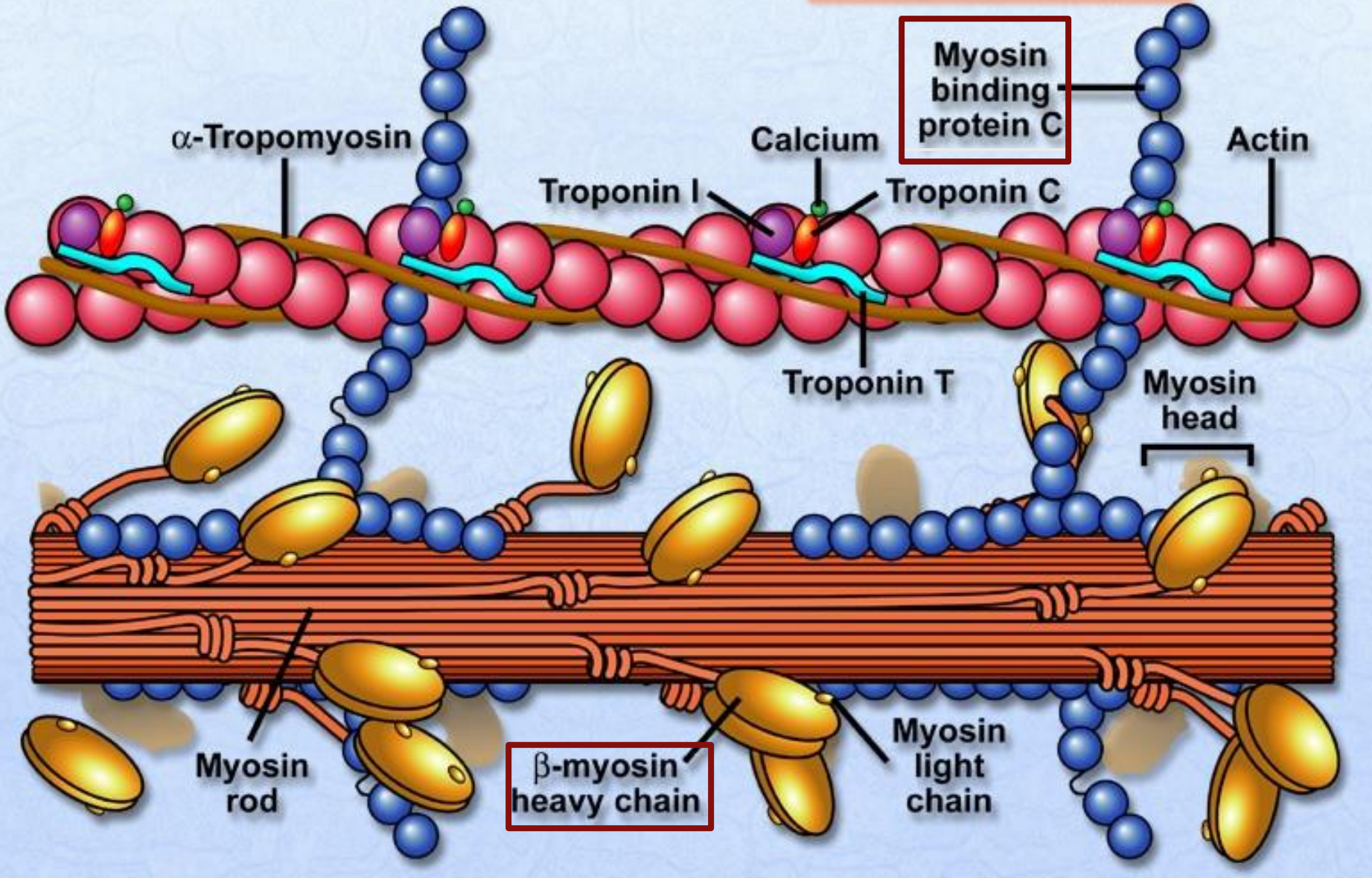
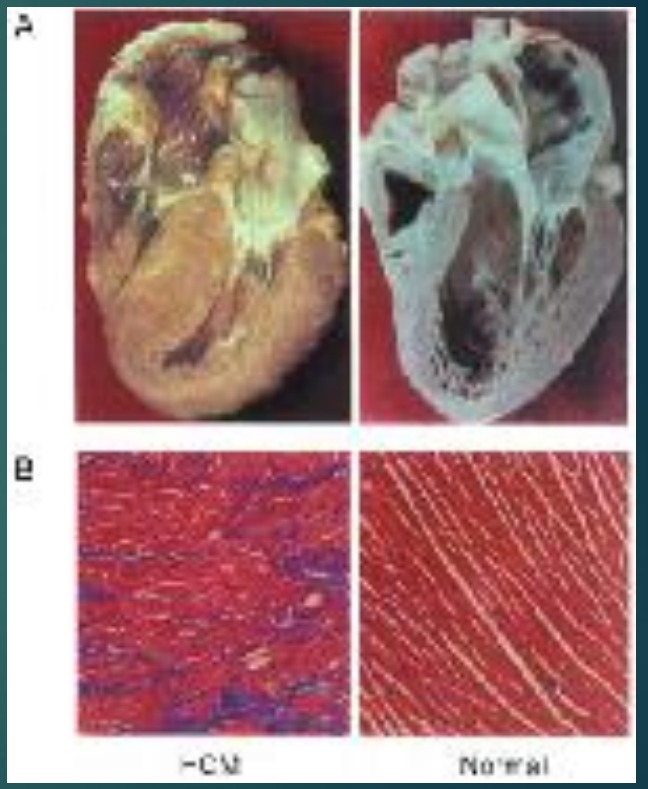

α-Tropomyosin
Myosin binding protein C
Calcium
Actin
Troponin I
Troponin C
Troponin T
Myosin head
Myosin rod
β-myosin heavy chain
Myosin light chain

80% of mutations



Pathogenesis of HCM

- Mutations in sarcomeric proteins lead to an abnormal sarcomere structure and impaired contractility
- Cellular hypertrophy
- Myocardial fiber disarray
- Profibrotic state
  - Ultimate increase in collagen deposition to collagen degradation ratio



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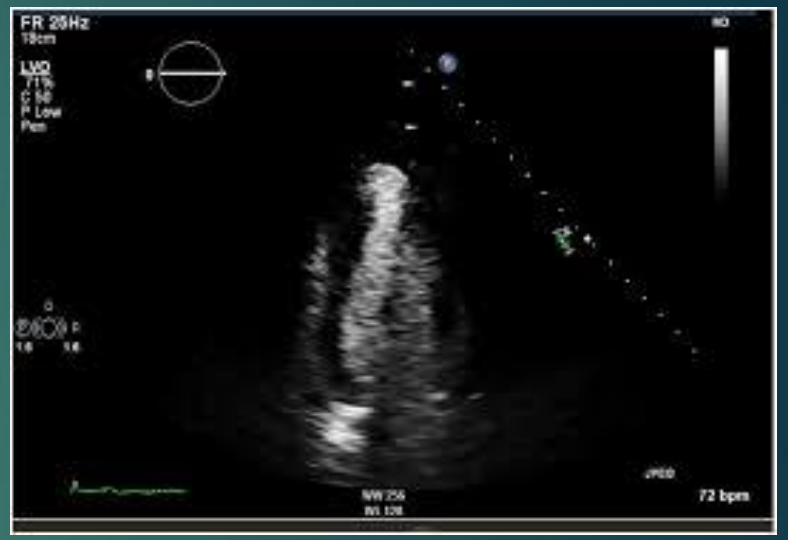
Diagnostic Evaluation

- Echocardiography: primary technique for diagnosis
  - Pattern of hypertrophy
  - Presence of LV apical aneurysm
  - Systolic and diastolic function
  - SAM of mitral valve leaflets and/or subvalvular apparatus
    - Presence/severity of LVOT obstruction
    - Degree of mitral regurgitation



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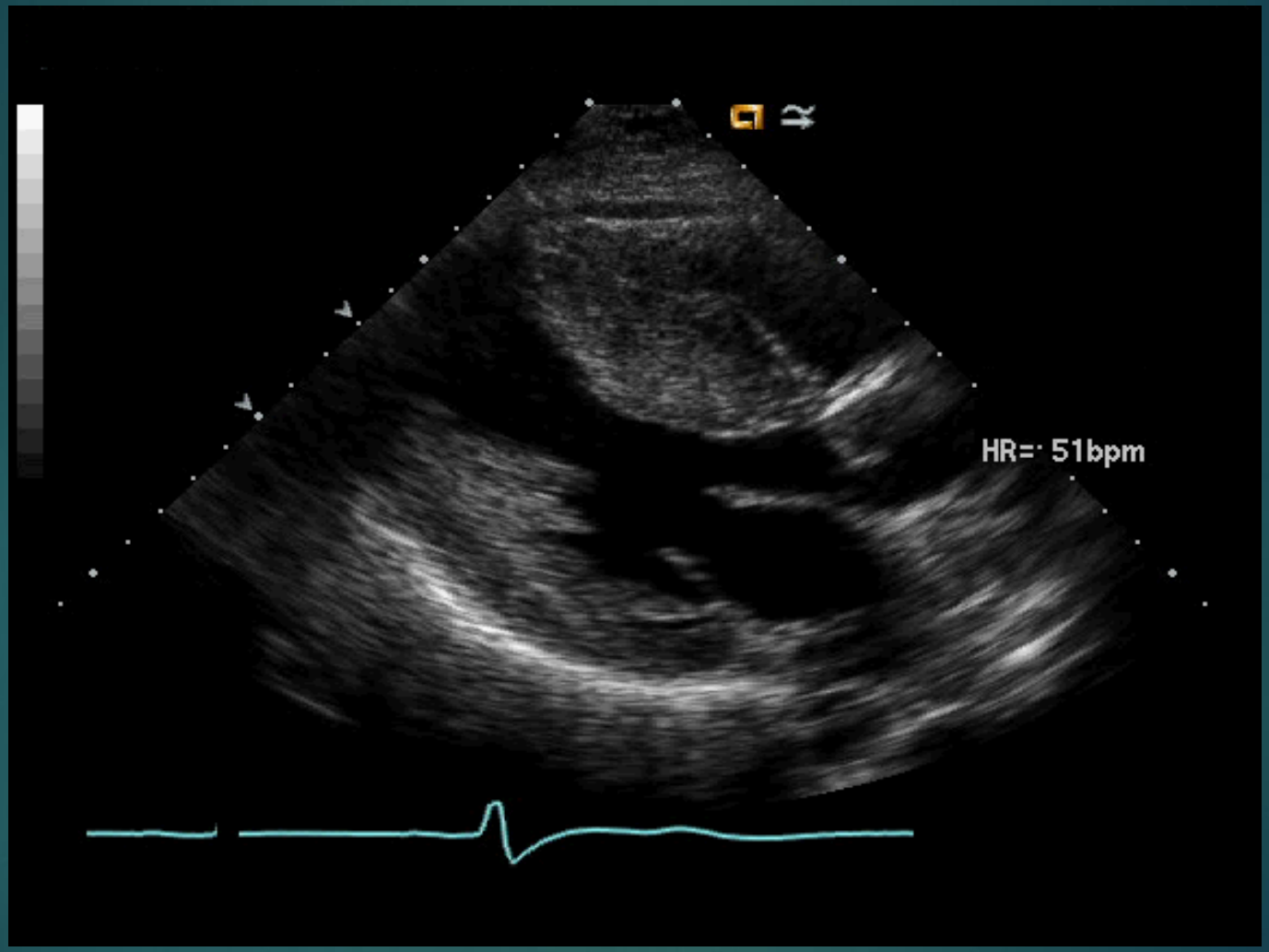
Maron et al Am J Cardiol 1987

Echo with LVOT obstruction



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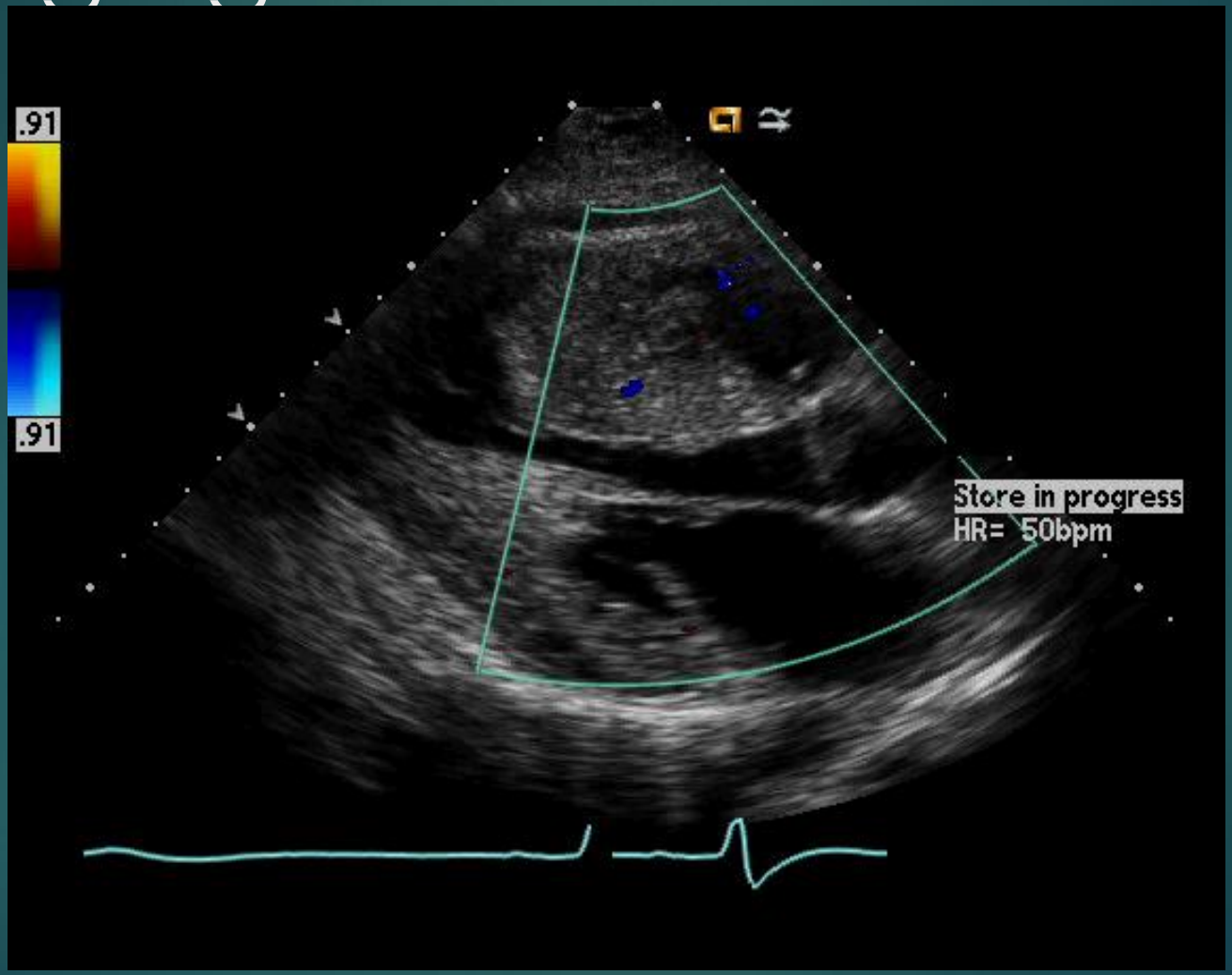
LVOT Obstruction and Mitral Regurgitation



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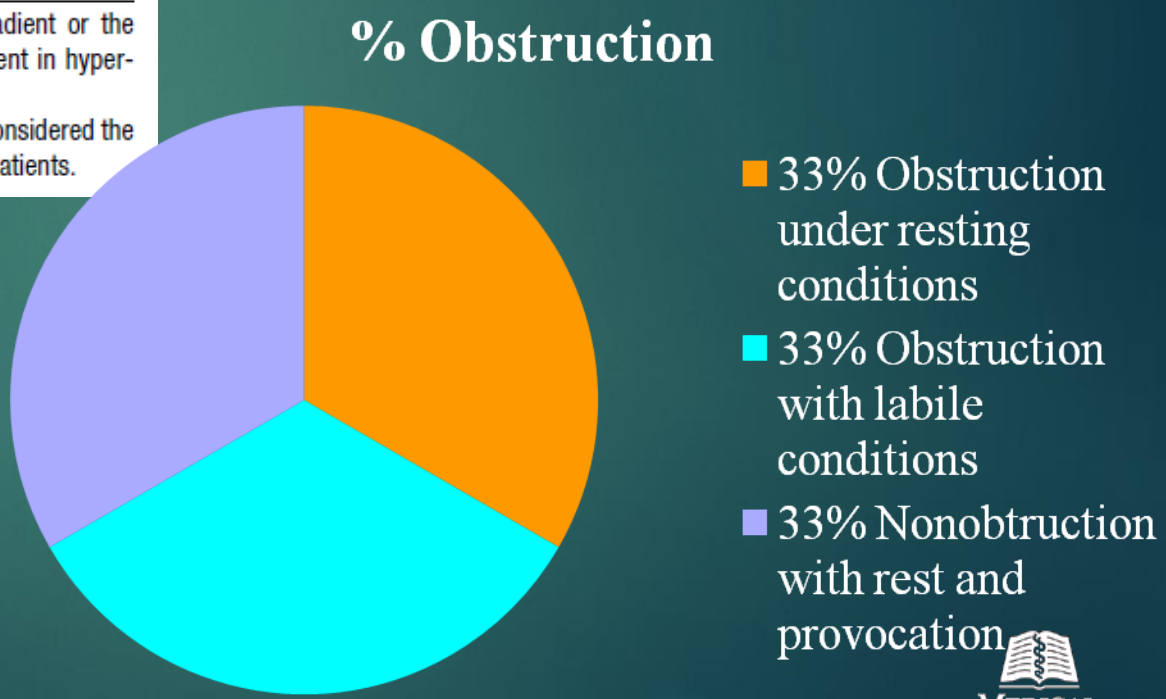
LVOT Obstruction

Table 2. Definitions of Dynamic Left Ventricular Outflow Tract Obstruction

Hemodynamic State	Conditions	Outflow Gradient*
Basal obstruction	Rest	≥30 mm Hg†
Nonobstructive	Rest	<30 mm Hg
	Physiologically provoked	<30 mm Hg
Labile obstruction	Rest	<30 mm Hg†
	Physiologically provoked	≥30 mm Hg†

*Either the peak instantaneous continuous wave Doppler gradient or the peak-to-peak cardiac catheterization gradient, which are equivalent in hypertrophic cardiomyopathy (73,74).

†Gradients ≥50 mm Hg either at rest or with provocation are considered the threshold for septal reduction therapy in severely symptomatic patients.



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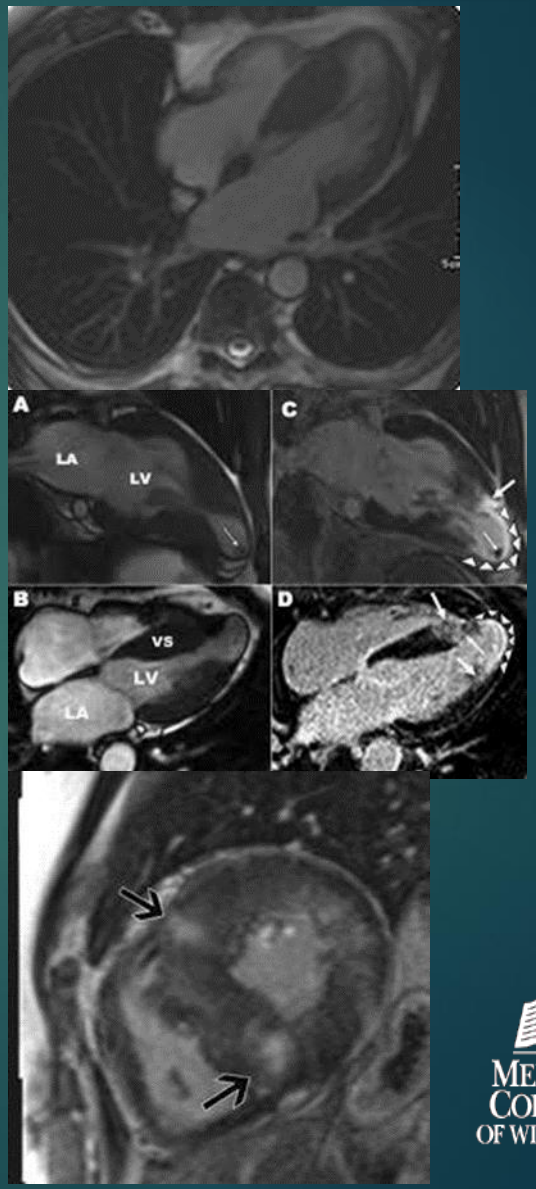
Known Diagnosis

- Echocardiography
  - Initial evaluation
  - Every 1-2 years to assess degree of hypertrophy, LVOTO, MR
  - Provocative maneuvers if LVOT gradient <50mmHg on resting echo

- Stress Echocardiogram
  - Symptomatic patients and no LVOTO >50mmHg (Class 1)
  - Asymptomatic patients without an LVOT >50 for detection of a significant LVOT dynamic gradient (Class 2a)
  - Patients whom functional capacity or symptom status is uncertain, every 2-3 years (Class 2b)

Diagnosis

- Cardiac MRI
  - If echocardiography is inconclusive
  - Suspicion of other disease process (infiltrative, storage or athletes)
  - Further risk SCD risk stratification
  - In obstructive HCM where the mechanism is inconclusive
  - Can be repeated every 3-5 years (Class 2b)



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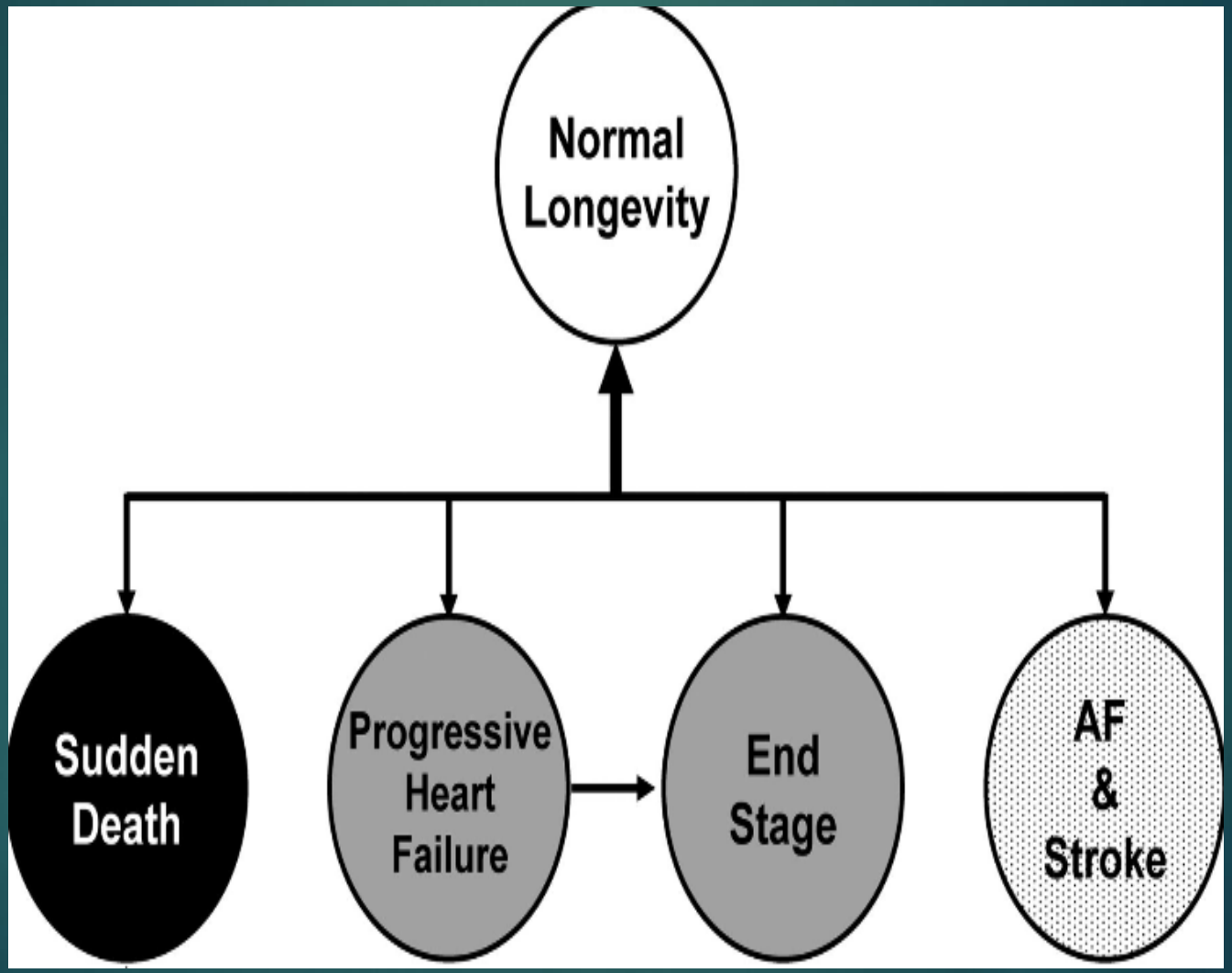
Outcomes



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Symptoms and Longevity

- 312 HCM patients in a community based center
- 77% were <75 years of age
  - Average age of diagnosis was 18 years
  - 85% of these patients had no or only mild symptoms (NYHA I-II)

- 23% were ≥75 years of age
  - Average age of HCM diagnosis was 74 years
  - 64% of these patients had no or only mild symptoms (NYHA I-II)

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Maron et al., JACC 2003

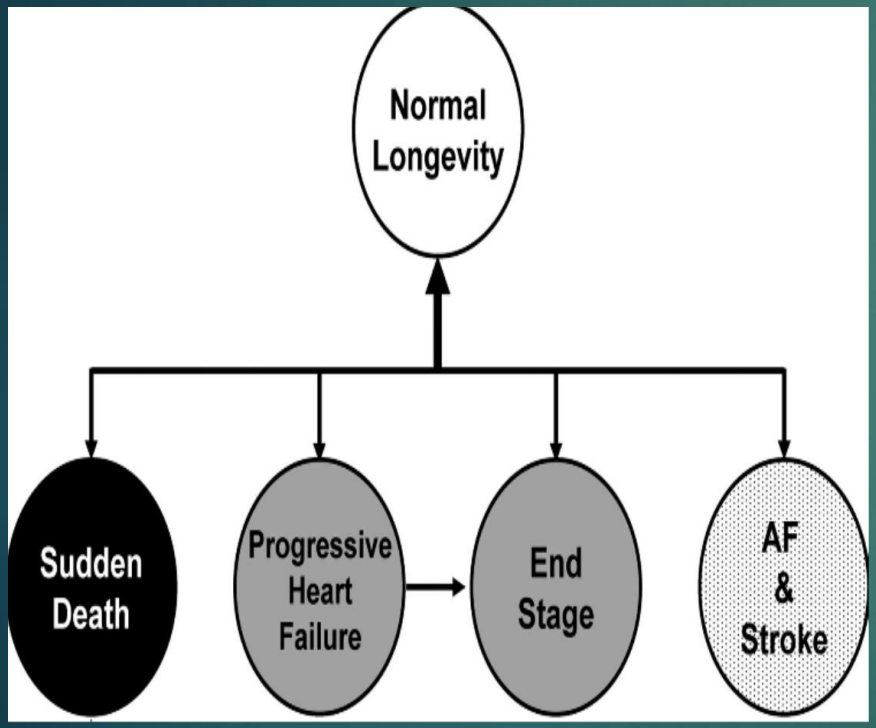
Symptoms and Longevity

- For those ≥ 50 years
  - Probability of survival 5, 10, and 15 years was not significantly different from the general population

- Conclusion:
  - HCM is frequently well tolerated
  - Compatible with normal life expectancy
  - May remain clinically dormant for long periods of time
    - Initial diagnosis may be deferred until late in life

Maron et al., JACC 2003

Outcomes



- Five mechanisms that contribute to the development of symptoms
  - Left ventricular outflow tract (LVOT) obstruction
  - Mitral regurgitation
  - Diastolic dysfunction
  - Arrhythmias
  - Myocardial ischemia

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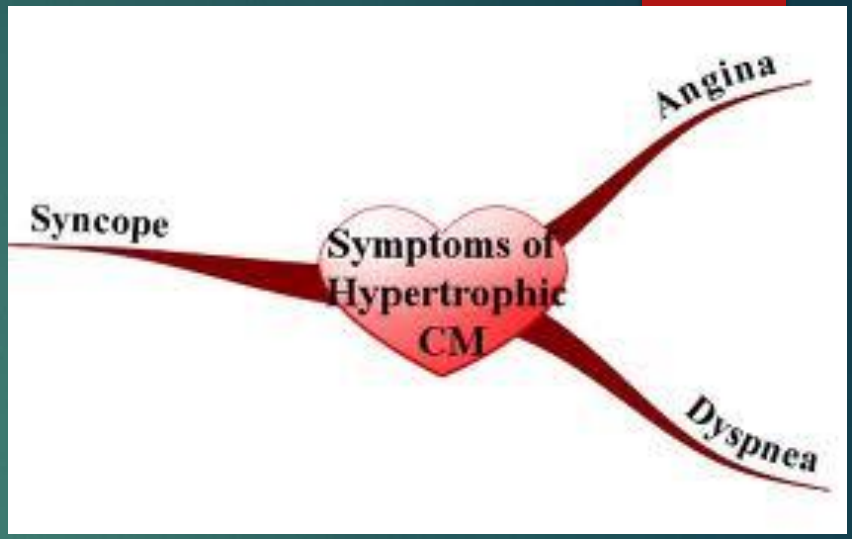
Treatment

- Symptoms
  - Medications
  - Septal reduction therapy



Treatment

- Asymptomatic Patients
  - Usefulness of beta blockers and calcium channel blockers to alter clinical outcome is not well established for the management of **asymptomatic** patients with or without obstruction
  - Avoidance of environmental situations where vasodilation may occur if there is a resting or provocable LVOT obstruction
  - Low intensity aerobic exercise program
  - Hydration

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Treatment

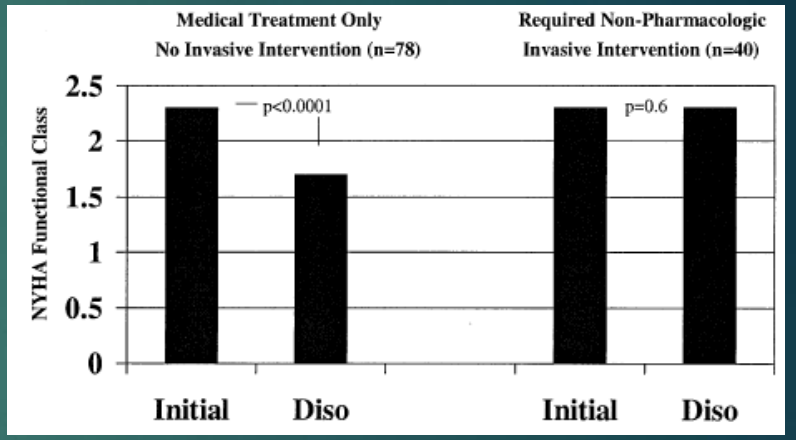
- Symptomatic Patients
- Limit or discontinue medications that can worsen symptoms related to LVOT obstruction

- Pharmacological therapy is first line to alleviate symptoms (LVOT obstruction, ischemia, MR and diastolic dysfunction)
  - Beta Blockers (first line therapy)
    - Meds should be titrated to a dose where there is symptom benefit
    - Failure of med if adequate suppression of resting HR, but continued LVOT obstruction and symptoms

  - Calcium Channel Blockers (second line therapy)
    - Caution in patients with severe outflow tract gradient of advanced heart failure

Treatment

- Symptomatic Patients (despite BB and CCB)
  - Disopyramide->Type 1A Antiarrhythmic
    - Pure negative iontropic effect (significant decrease in contractility)
    - Initiate in the hospital with telemetry (arrhythmia and prolonged QT)
    - Should be used in combination with AV nodal blocking properties
    - Anticholinergic side effects may occur and can be managed by dose reduction



Sherrid JACC 2005

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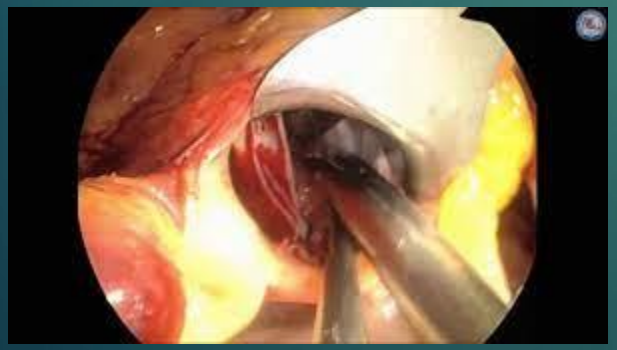
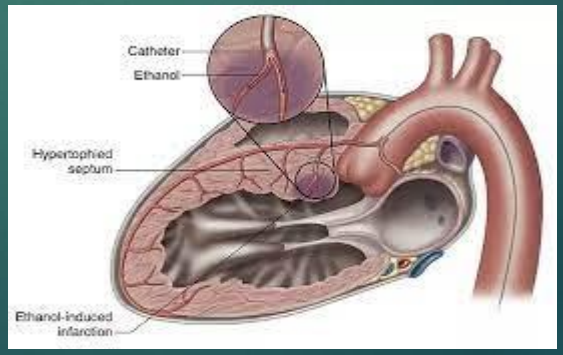
Indications for Septal Reduction Therapy

- Medical refractory heart failure and symptoms (NYHA 3-4)
- Presence of LVOT obstruction (> 50 mm Hg)
- Optimal Medical Therapy
- Septal Myectomy or Alcohol Septal Ablation





Olivotto et al JACC 2007

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Septal Myectomy

- Best for symptomatic obstructive patients with:
  - Associated cardiac disease requiring surgical treatment
  - Extreme septal thickness (>30mm and high resting gradients (>100mmHg)

- Technical success: 90-95%
- Survival free from recurrent symptoms myectomy =89% (vs. 71%)
- Procedural mortality =1%
- Low nonfatal complications <1-2%
- Mitral valve replacement increased hospital mortality >10 fold

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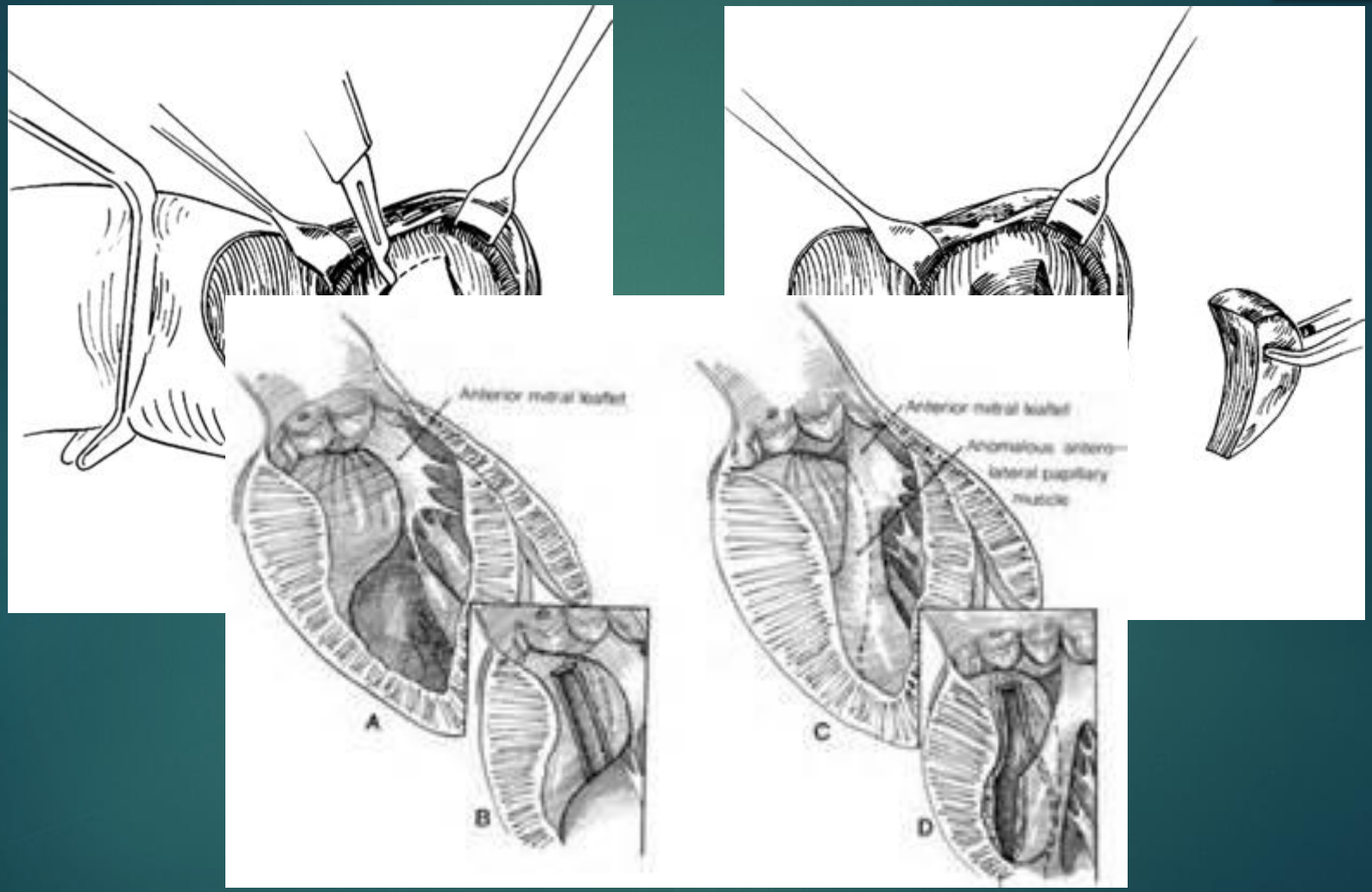
Morrow Procedure



Myectomy Outcomes

Retrospective analysis of Mayo surgical series

- Long term survival at 1, 5, 10 years was 99, 98, and 83%
- Superior to non-operated obstructed population
  - Survival of 61% at 10 years
- No significant difference compared to matched USA population
- ↓ long-term risk for ventricular arrhythmias and sudden cardiac death

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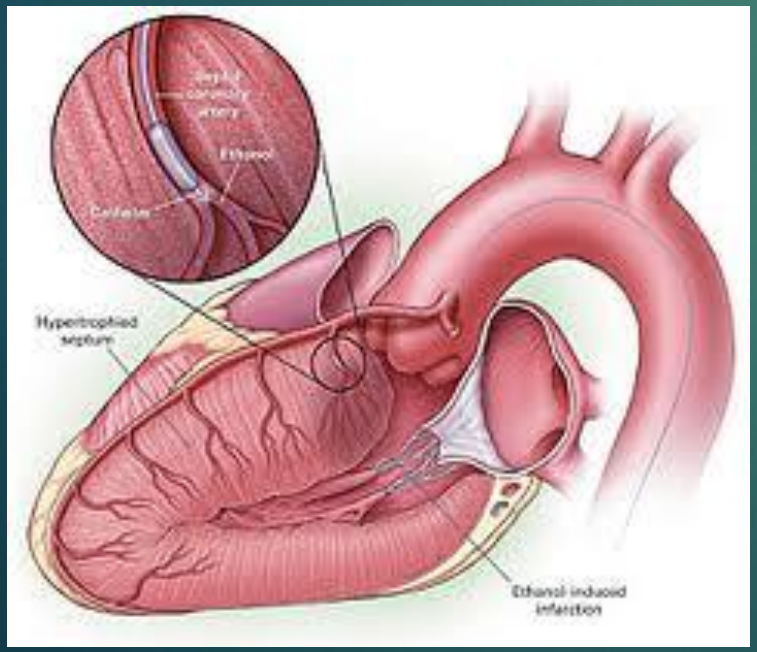
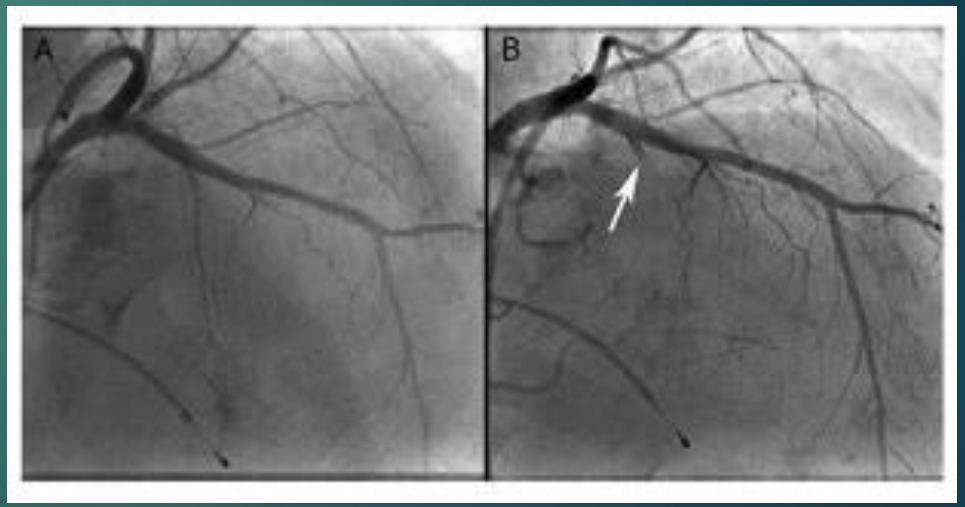
Ommen et al J Am Coll Cardiol 2004

Alcohol Septal Ablation

- Generally reserved for symptomatic, obstructive patients
  - Surgery is contraindicated/high risk
  - Advanced age
- Requires appropriate coronary anatomy





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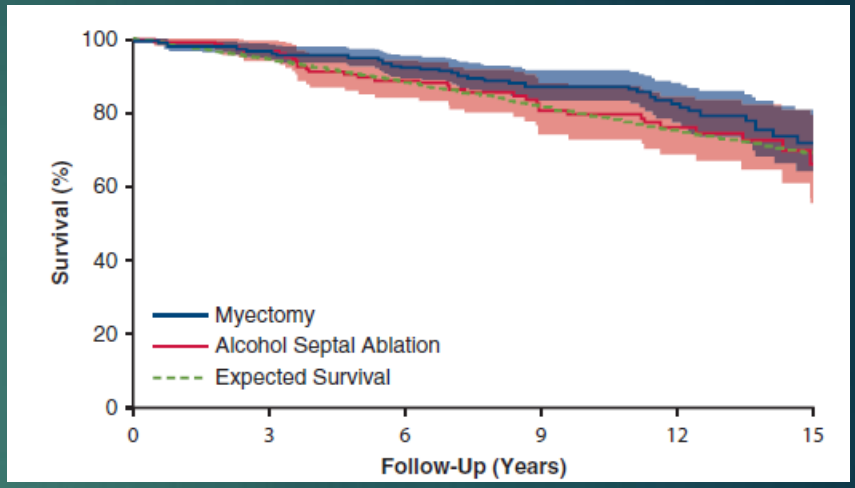
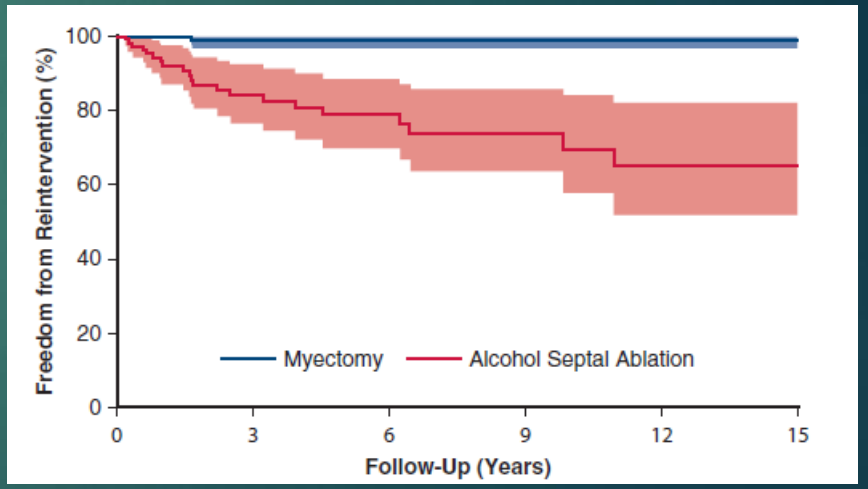
Alcohol Septal Ablation

- Benefits
  - No sternotomy/less pain
  - Procedural mortality <1%
  - Intermediate term survival is similar to myectomy
- However……..
  - Increased risk of repeat intervention
    - 7-20%
  - Increased risk of need for pacemaker





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Nguyen et al., J Thor Cardio Surg 2019

Mavacamten

- Modulator of cardiac myosin (myosin inhibitor)
- Explorer HCM
  - Phase 3, randomized, double blinded, placebo controlled study
  - 251 HCM obstructive patients
  - Improved exercise capacity, LVOT obstruction, NYHA class and health status
- Hope to be FDA approved in 1/2022

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Olivotto et al., Lancet 2020

Sudden Cardiac Death Assessment

- 7 Established Risk Factors for SCD in HCM patients
  - Family history of SCD from HCM (first degree relative <50 years of age)
  - Massive LVH (>30mm, linear relationship)
  - Unexplained syncope within 6 months of evaluation (unlikely vasovagal or related LVOT obstruction)
  - LV systolic dysfunction (<50%)
  - LV apical aneurysm
  - Extensive LGE on CMR (>15% of total LV mass)
  - NSVT on ambulatory monitor (more frequent, longer and faster runs have higher risk)
- Low risk of SCD in patients >60 years

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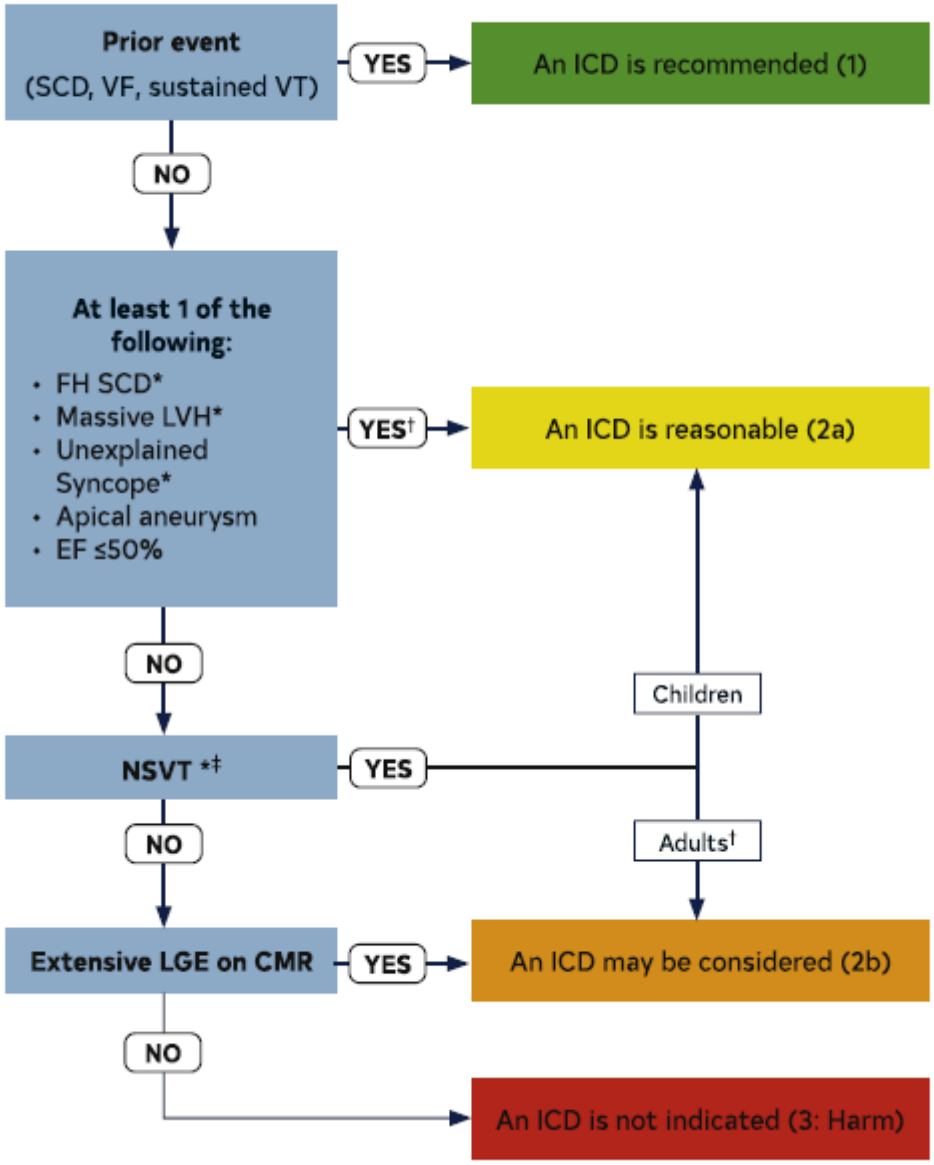
FIGURE 3 ICD Patient Selection



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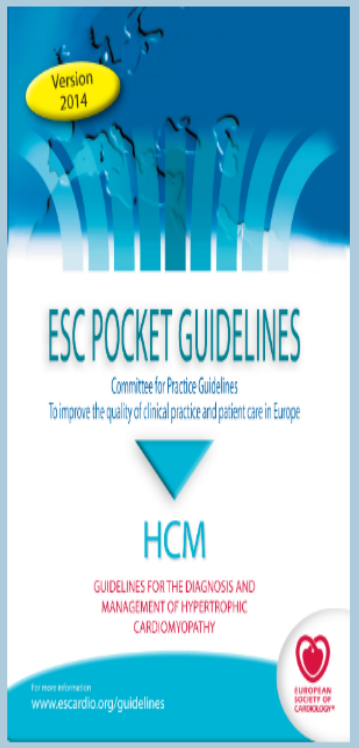
HCM Risk-SCD Calculator

Age	35	**Years**	*Age at evaluation*
Maximum LV wall thickness	20	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	45	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	75	**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	◉ No ○ Yes		*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ◉ Yes		*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	◉ No ○ Yes		*History of unexplained syncope at or prior to evaluation.*



Risk of SCD at 5 years (%):	7.84
ESC recommendation:	ICD should be considered

Reset

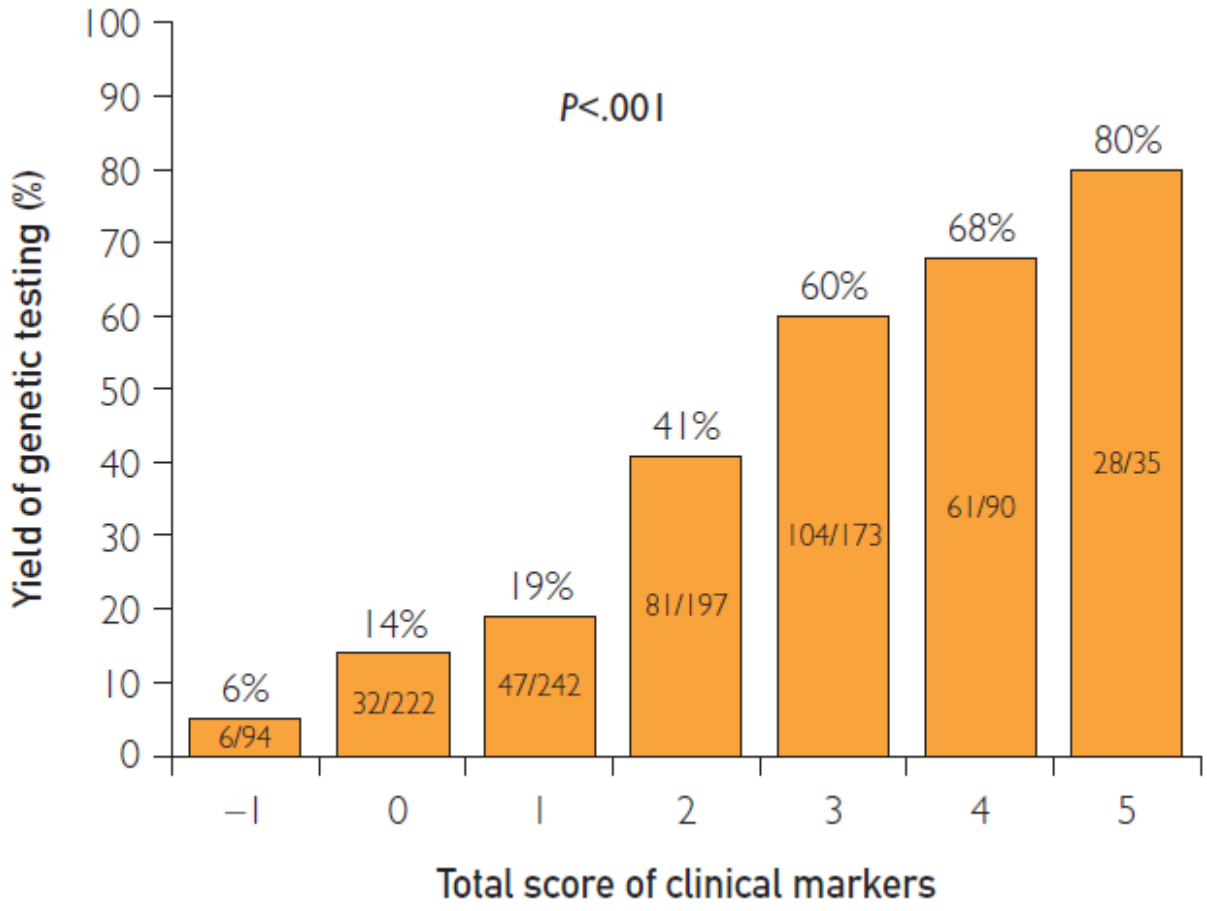
2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy (Eur Heart J 2014 – doi:10.1093/eurheartj/ehu284)

Family Screening: Genetic Testing

Clinical markers for positive genetic test results

Marker	Points
☐ Age at Dx <45 y	1
☐ MLVWT ≥20 mm	1
☐ Family Hx of HCM	1
☐ Family Hx SCD	1
☐ Reverse-curve HCM	1
☐ Hx of hypertension	−1

Scoring range: −1 to 5 points



done if strong Fhx of SCD to screen for arrhythmias

Bos et al., Mayo Clinic Proc 2014
Canepa et al., Heart 2015

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Family Screening

- Clinical screening vs genetic testing
- Clinical Screening: Echocardiogram, ECG and clinic visit
  - Kids and adolescents with (+)genotype families or early disease
    - Start at time HCM is diagnosed in family member
    - Every 1-2 years
  - All other children and adolescents
    - Start at time HCM is diagnosed in family member, but no later than puberty
    - Every 2-3 years
  - Adults
    - At time HCM is diagnosed in another family member
    - Every 3-5 years (until mid 50's)

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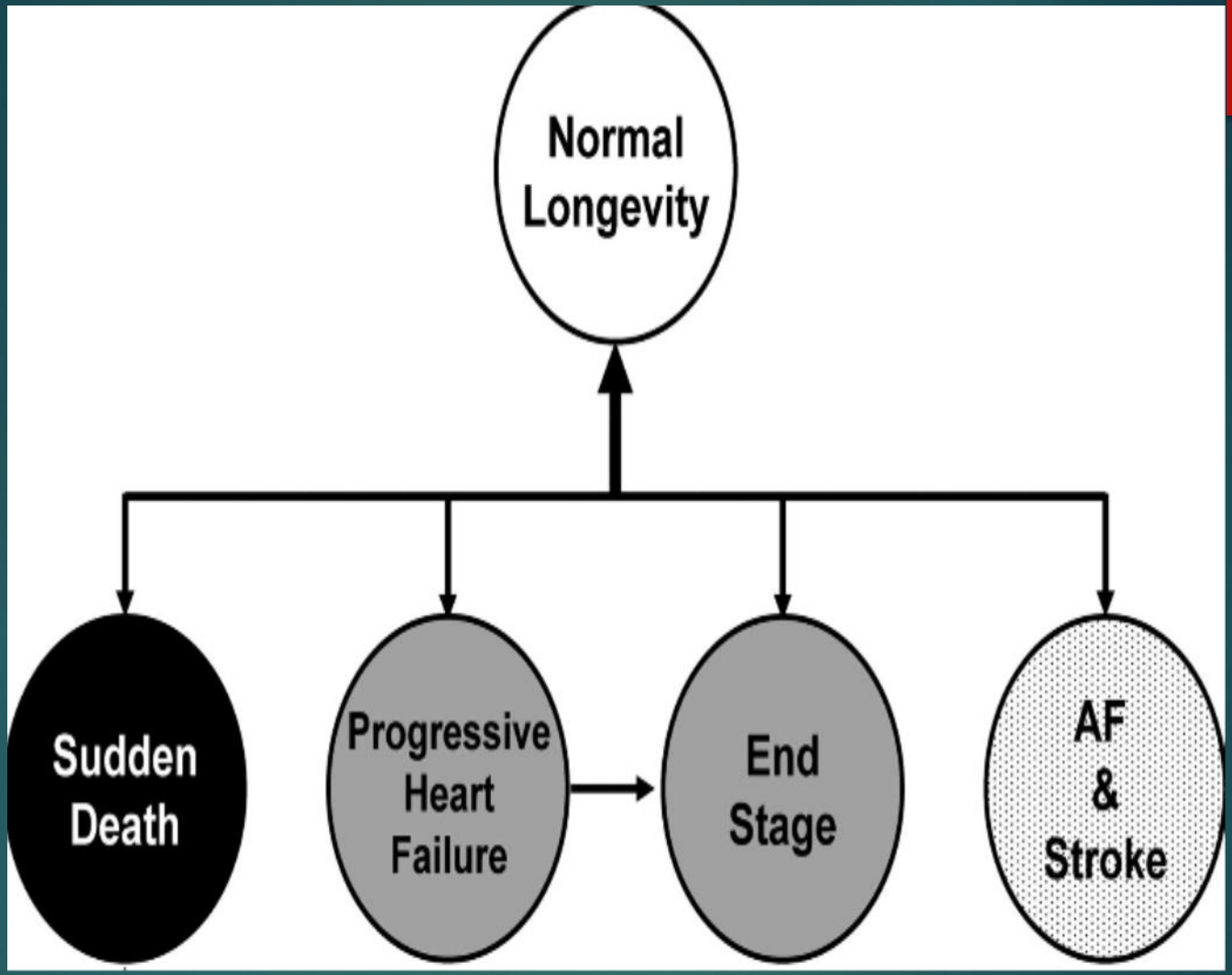

ICD

Pharmacological Therapy
SRT and Txp

Antiarrhythmics
Anticoagulants

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Thank You

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