



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Cardiomyopathies

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- Clinical focus: Heart Failure, Cardiac Transplant, Mechanical Circulatory Support
 - Research focus: Heart Failure Pharmacotherapy and Disease Management, Clinical Trials



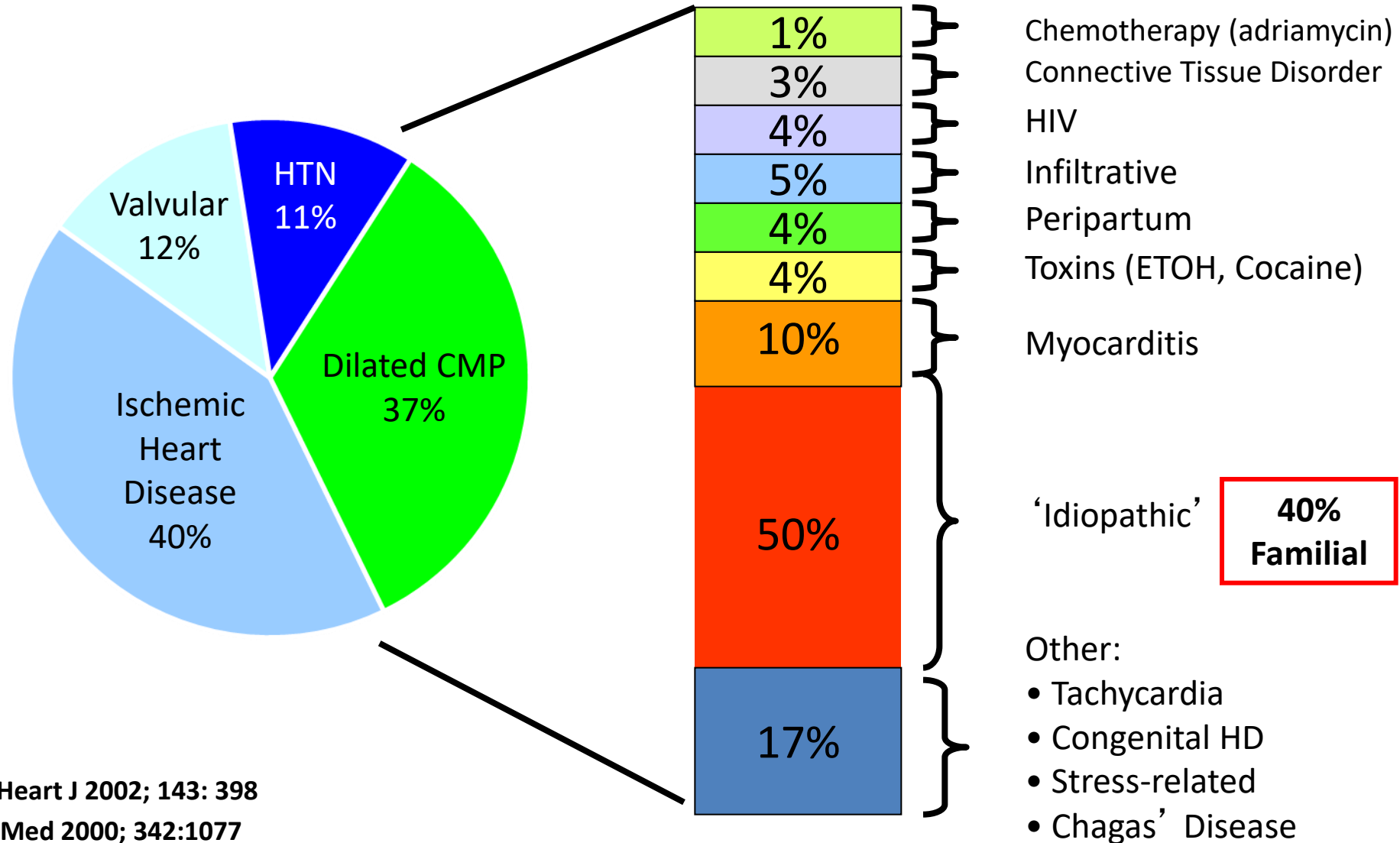
Disclosures

- **Consulting: Alnylam, Abbott, AstraZeneca, Avidity Biopharma, Axon Therapies, Bayer, Biofourmis, Boston Scientific, Endotronix, GlaxoSmithKline, Merck, Medpace, Medtronic, Novartis, Parexel, Regeneron, River2Renal, Roche, scPharmaceuticals, Veristat, Volta Medical**
- **Research Grants: Alnylam, AstraZeneca, Abbott, Bayer, and Novartis**

Objectives

- **Identify common etiologies of dilated cardiomyopathy and prognostic implications**
- **Discuss pathophysiology, diagnosis, risk stratification, and clinical management of patients with hypertrophic cardiomyopathy**
- **Discuss diagnosis and management of common infiltrative cardiomyopathies including amyloidosis and sarcoidosis**

Etiologies of LV dysfunction



Baldasseroni, Am Heart J 2002; 143: 398

Felker, New Engl J Med 2000; 342:1077

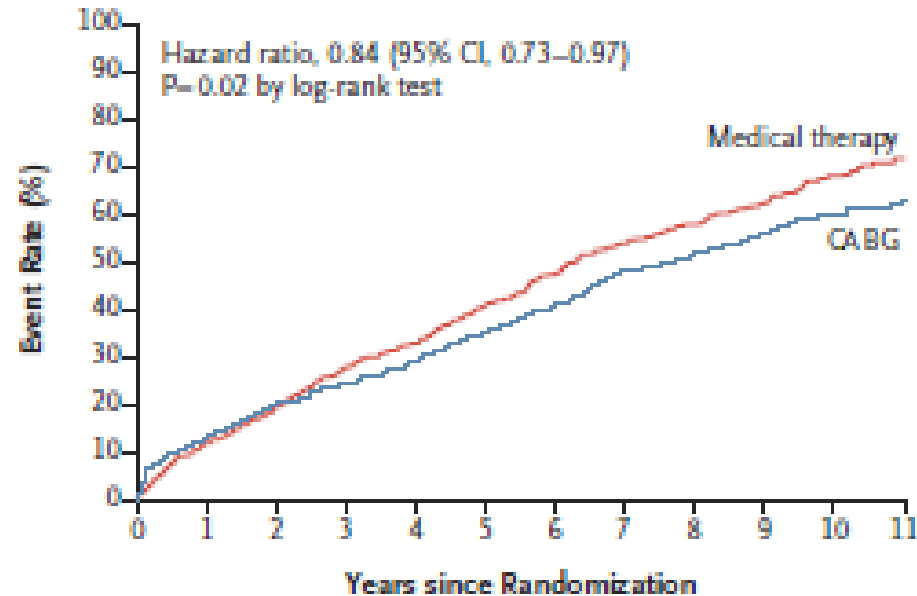
Ischemic 'Cardiomyopathy'

- **Significantly impaired LV function resulting from CAD**
- **Up to 40% of HFrEF**
- **Mechanisms**
 - **Irreversible loss of myocardium due to prior MI with ventricular remodeling**
 - **Partially reversible loss of contractility due to reduced function of ischemic, but still viable myocardium**

Coronary Revascularization in Ischemic Cardiomyopathy – STICHES (STICH 10 year F/U)

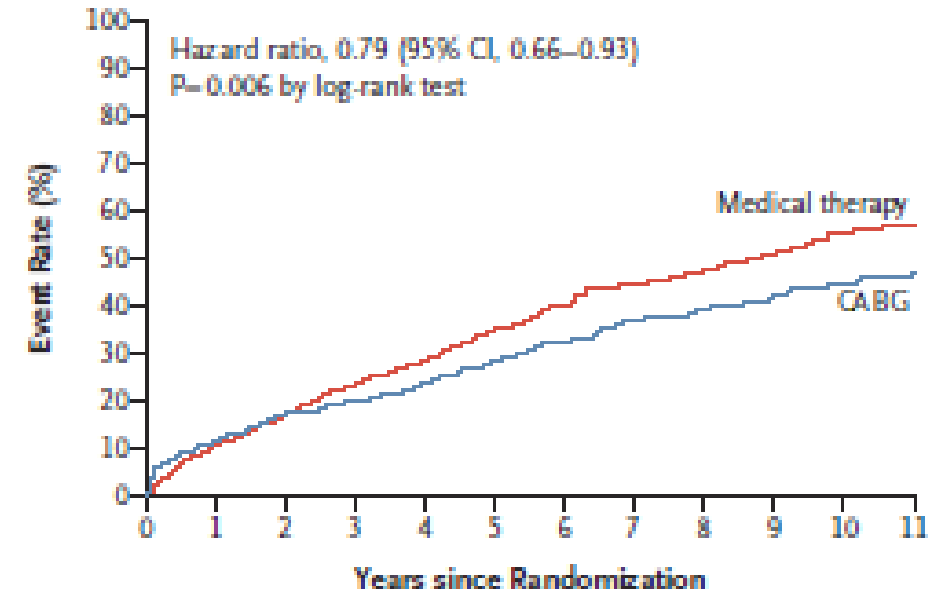
Hypothesis: In patients with HF, LVEF ≤ 0.35 and CAD amenable to surgical revascularization to CABG added to intensive MED will decrease all-cause mortality compared to MED alone.

A Death from Any Cause (Primary Outcome)



No. at Risk	0	1	2	3	4	5	6	7	8	9	10	11
Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

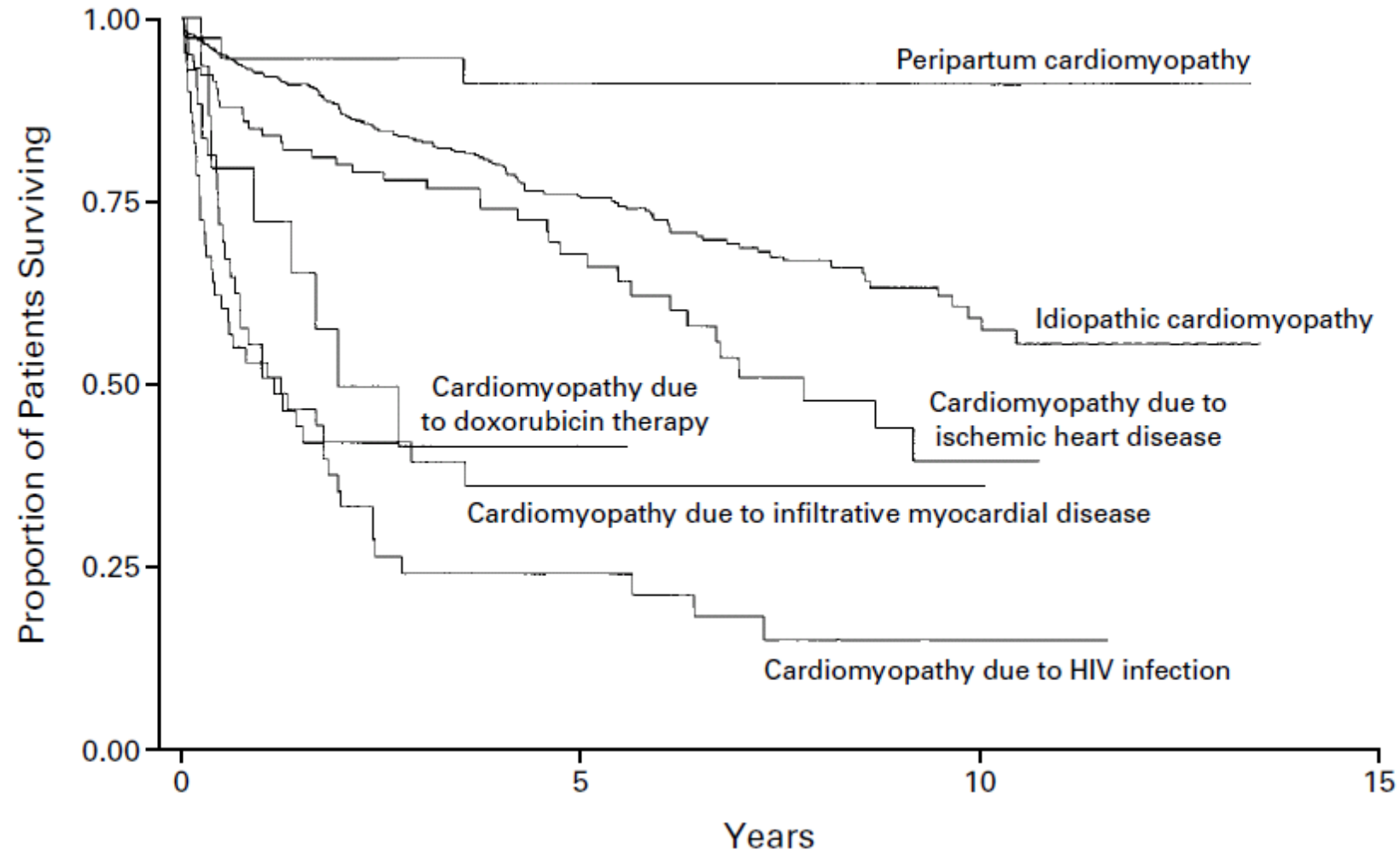
B Death from Cardiovascular Causes



No. at Risk	0	1	2	3	4	5	6	7	8	9	10	11
Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

Surgical Revascularization and Medical therapy superior to medical therapy alone for those with CAD, LVEF ≤ 0.35 , and CAD amenable to revascularization

DCM: Prognosis according to etiology



Case #1:

- A 50-year-old man with prior history of hypertension and hyperlipidemia presenting with 3 month history of progressive exertional dyspnea.
- He takes only atenolol 25 mg once daily and simvastatin 20 mg once daily. He drinks one glass of wine with dinner each night, and denies use of tobacco or illicit drugs. His family history is notable for a paternal uncle who died suddenly in his 50s.
- PE: BP 170/80 mm Hg, P 80 bpm, JVP 12 cm H₂O, clear lungs to auscultation, and mild peripheral edema. Paradoxically split S₂, soft S₃ gallop, grade 2/6 apical holosystolic murmur.
- ECG: SR with LBBB
- Echocardiogram: dilated LV with global hypokinesis, and an EF of 25%.

Question 1

Which of the following factors is LEAST likely to be responsible for his HF?

- A. Uncontrolled hypertension**
- B. Coronary artery disease**
- C. Alcohol use**
- D. Genetic factors**
- E. Myocarditis**

Secondary Cardiomyopathy

- **Drugs of Abuse**
 - Alcohol (typically > 5 standard drinks/day x yrs)
 - Cocaine
 - Amphetamines
- **Anticancer Drugs**
 - Anthracyclines (doxorubicin, epirubicin, mitoxantrone)
 - HER2 antagonists (trastuzumab, pertuzumab)
 - Tyrosine Kinase Inhibitors (sunitinib)
 - Immune Checkpoint Inhibitors
- **Other Drugs**
 - Clozapine
 - Hydroxychloroquine
- **Toxins**
 - Heavy Metals (Cobalt), Solvents

Case #2

- **25 year old male presents in transfer with EF 10%, intubated, and with balloon pump**
- **Was completely healthy until 4 days prior when he developed a flu like syndrome. In fact, ran a marathon 2 weeks ago.**
- **History is notable for growing up in Guyana, moved to Connecticut 2 years ago, may have had a tick bite. Otherwise healthy.**

Question 2

Which of the following is the most likely etiology of his cardiomyopathy?

- A. Trypanosomiasis**
- B. Toxoplasmosis**
- C. Borrelia**
- D. Coxsackievirus B**

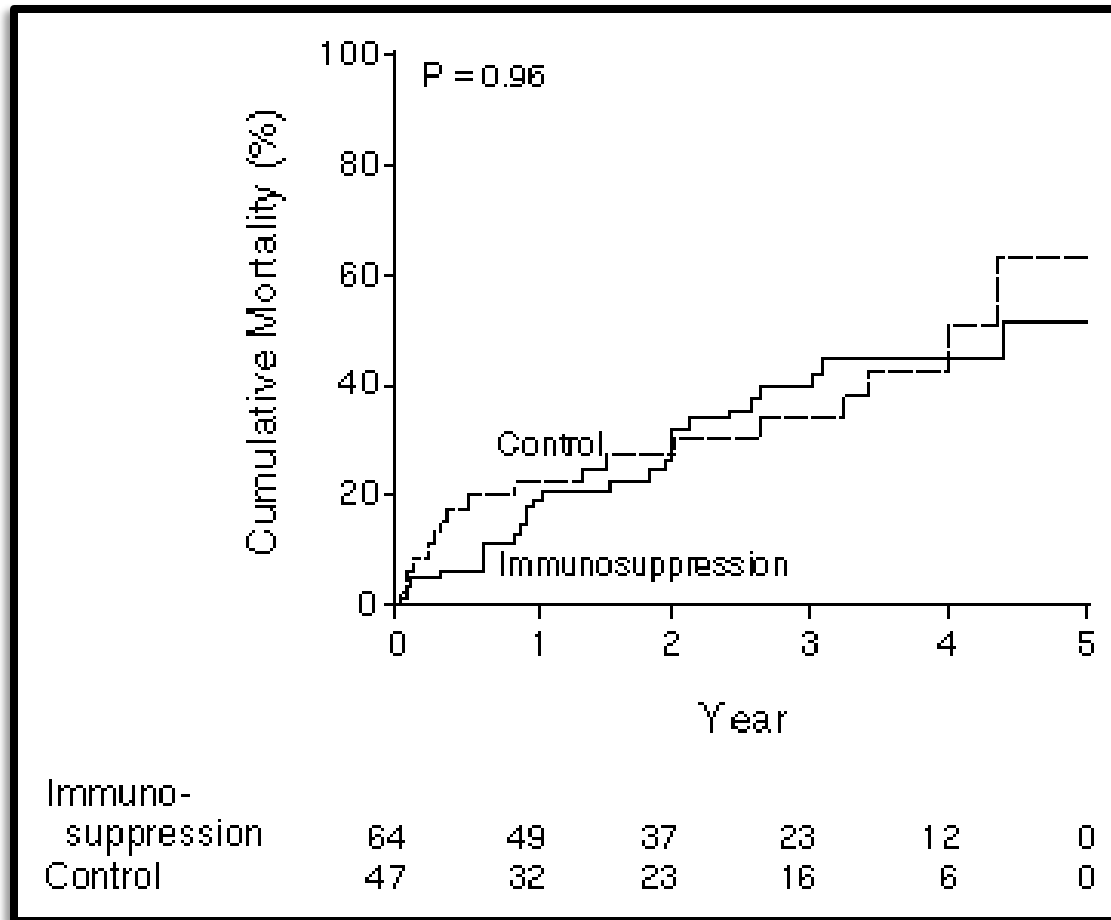
Myocarditis: Clinical Presentation

- **Acute Onset Heart Failure**
- **Viral Prodrome**
- **+/- Chest Pain**
- **+ Cardiac Biomarkers**
- **ST segment abnormalities in absence of CAD**
- **Dx: Cardiac MRI, Endomyocardial Biopsy**

Myocarditis: Etiology

- **Infectious**
 - Viral (e.g. cocksackievirus, COVID-19, parvovirus, HIV)
 - Bacterial
 - Rickettsia (*B. Burgdorferi*)
 - Fungal
 - Protozoal (*T. Cruzi*)
- **Hypersensitivity (eosinophilic)**
- **Autoimmune (e.g. Connective Tissue Disease, Giant Cell Myocarditis, Vaccine-related)**

Myocarditis: Immune Suppression not effective in general



- Myocarditis Treatment Trial
- N=111
- histologically proven myocarditis and LVEF<0.45
- 24 weeks treatment with prednisone + cyclosporine or azathioprine

**Treatment generally
supportive**

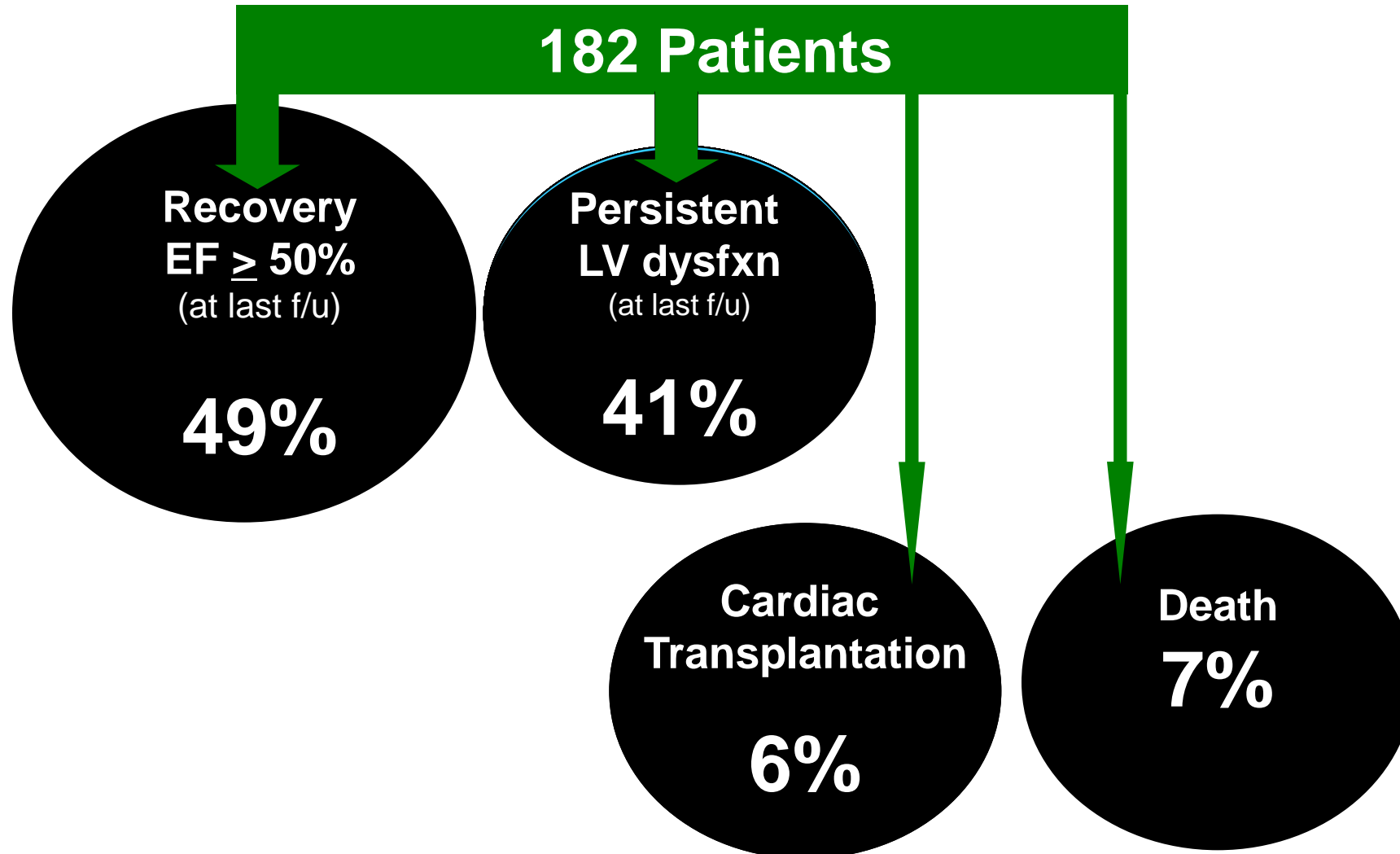
Peripartum Cardiomyopathy

- **Heart failure without other obvious etiology occurring 1 month prior to delivery or up to 5 months after**
- **Rare complication of pregnancy occurring in 1:2000 to 1:4000 live births in the US (incidence may be increasing)**
- **Inflammatory and genetic etiologies suspected, but recent data suggests a vascular hypothesis as well**

Peripartum CM: Risk factors

- **Age > 30**
- **Multiparity**
- **African American race**
- **Pregnancy with multiple fetuses**
- **Hypertension, preeclampsia**
- **Cocaine**
- **Prolonged tocolytic tx with beta agonists**

Outcome of PPCM in the US



Risk of Subsequent Pregnancy (SSP)

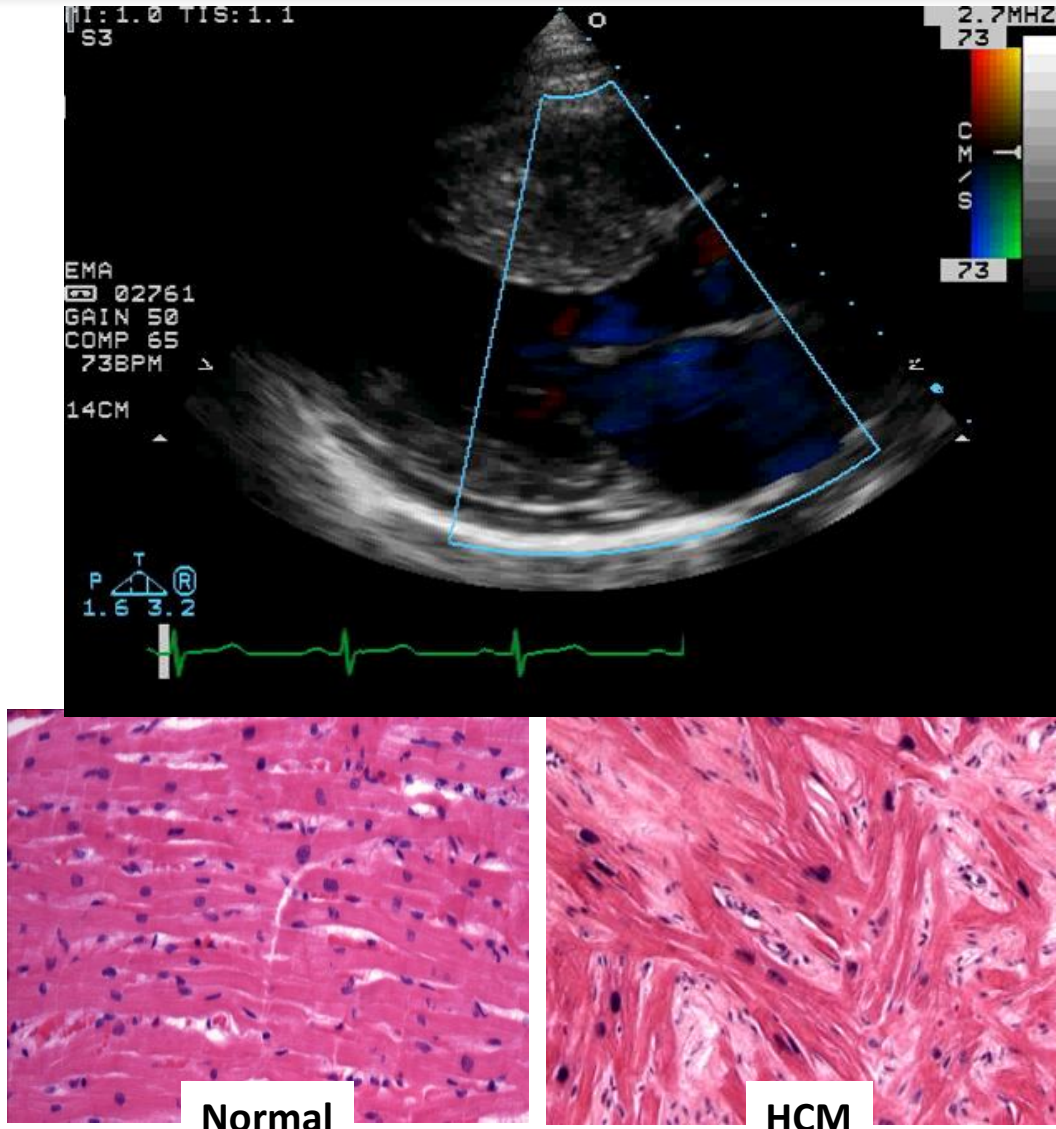
PERSISTENT LV DYSFUNCTION

- Higher Risk of Relapse with SSP
- ~50% with further deterioration in LV function
- Increased morbidity and mortality with SSP
- Premature delivery and abortion more common

RECOVERED LV FUNCTION

- Better prognosis with SSP compared to persistent LV dysfunction
- ~20% have a relapse
- Higher rate of recovery, mortality is lower
- Likely to have a normal pregnancy

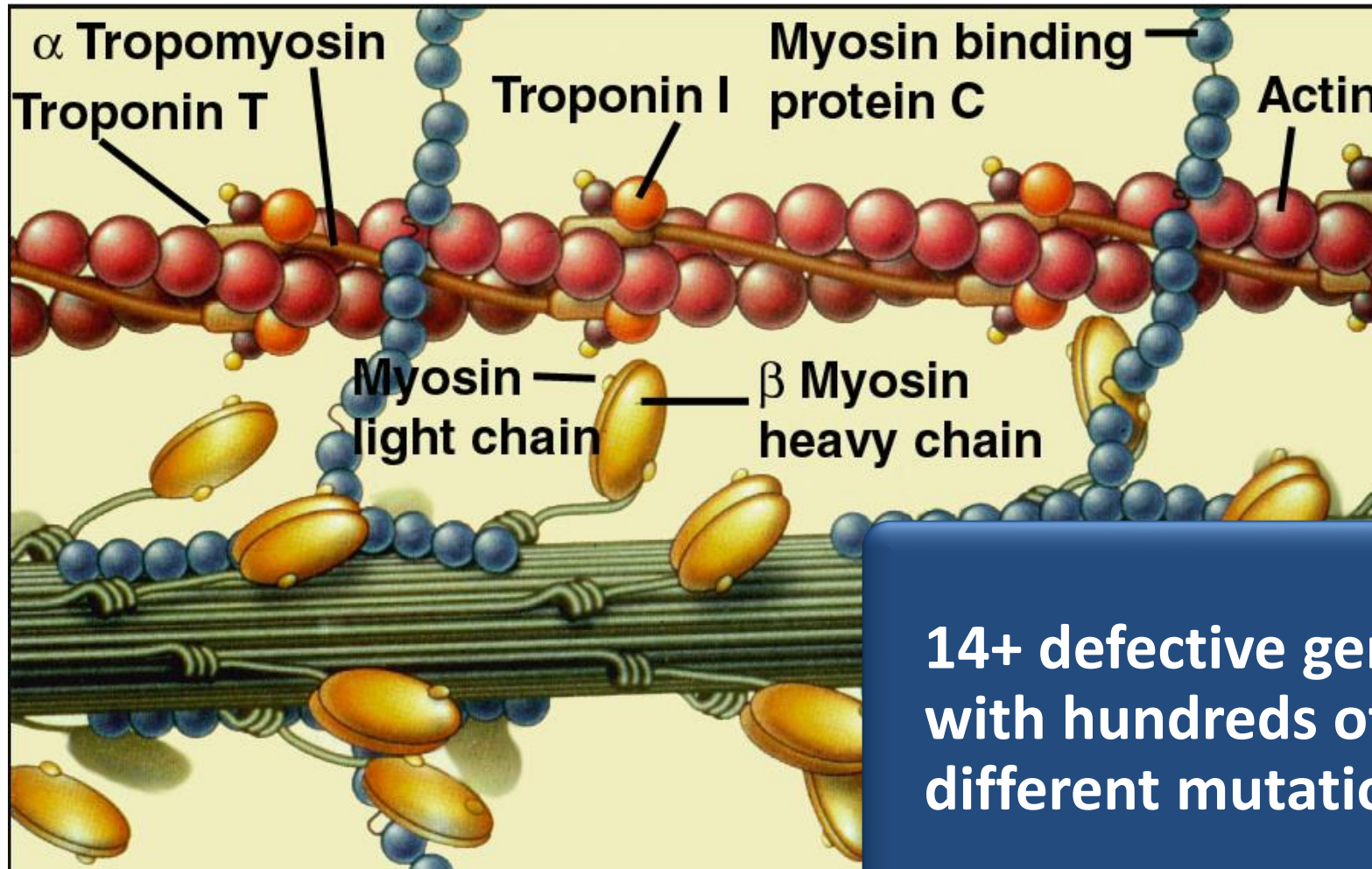
Hypertrophic Cardiomyopathy



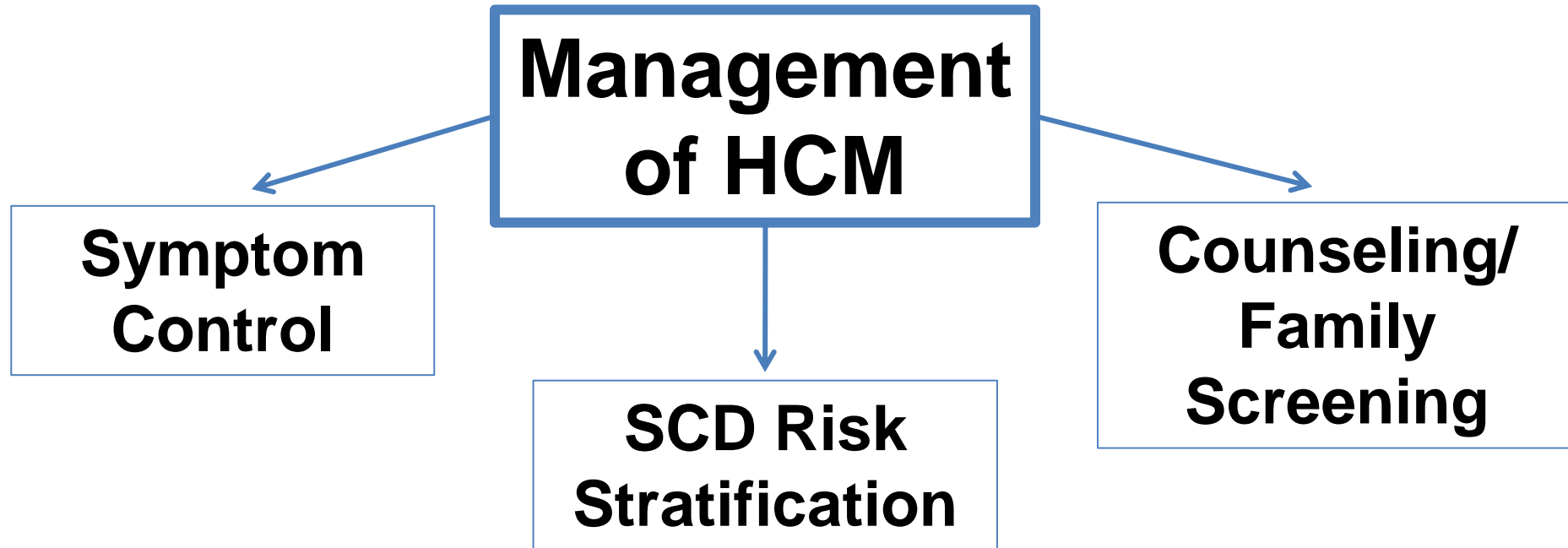
- Clinical Diagnosis:
Unexplained LVH
- Pathological Hallmarks:
Myocyte disarray and fibrosis
- Normal Longevity in most
- Serious outcomes in some
 - Sudden Death
 - Heart Failure

Prevalence: ~1:500
~600,000 cases in US

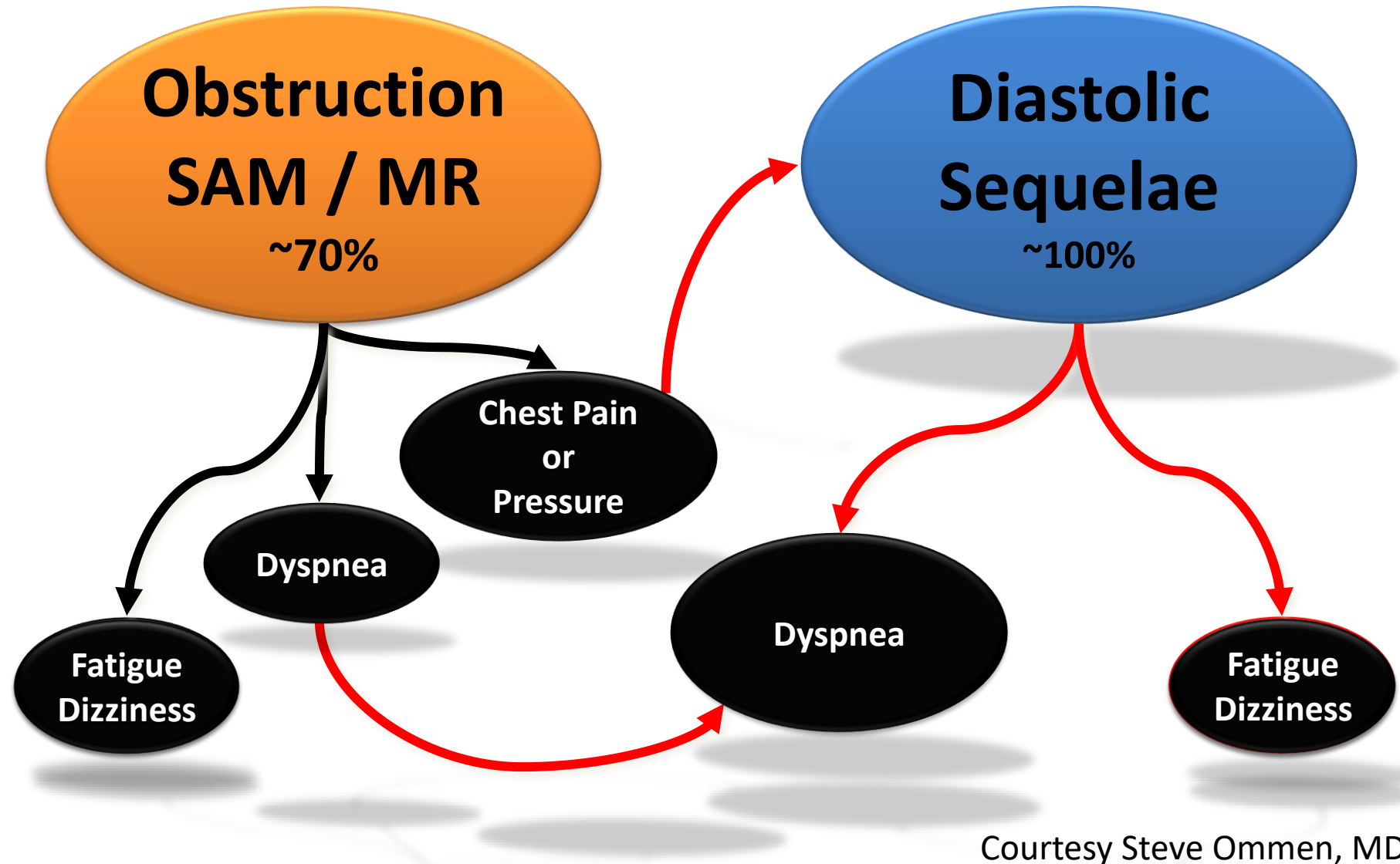
A Disease of the Sarcomere



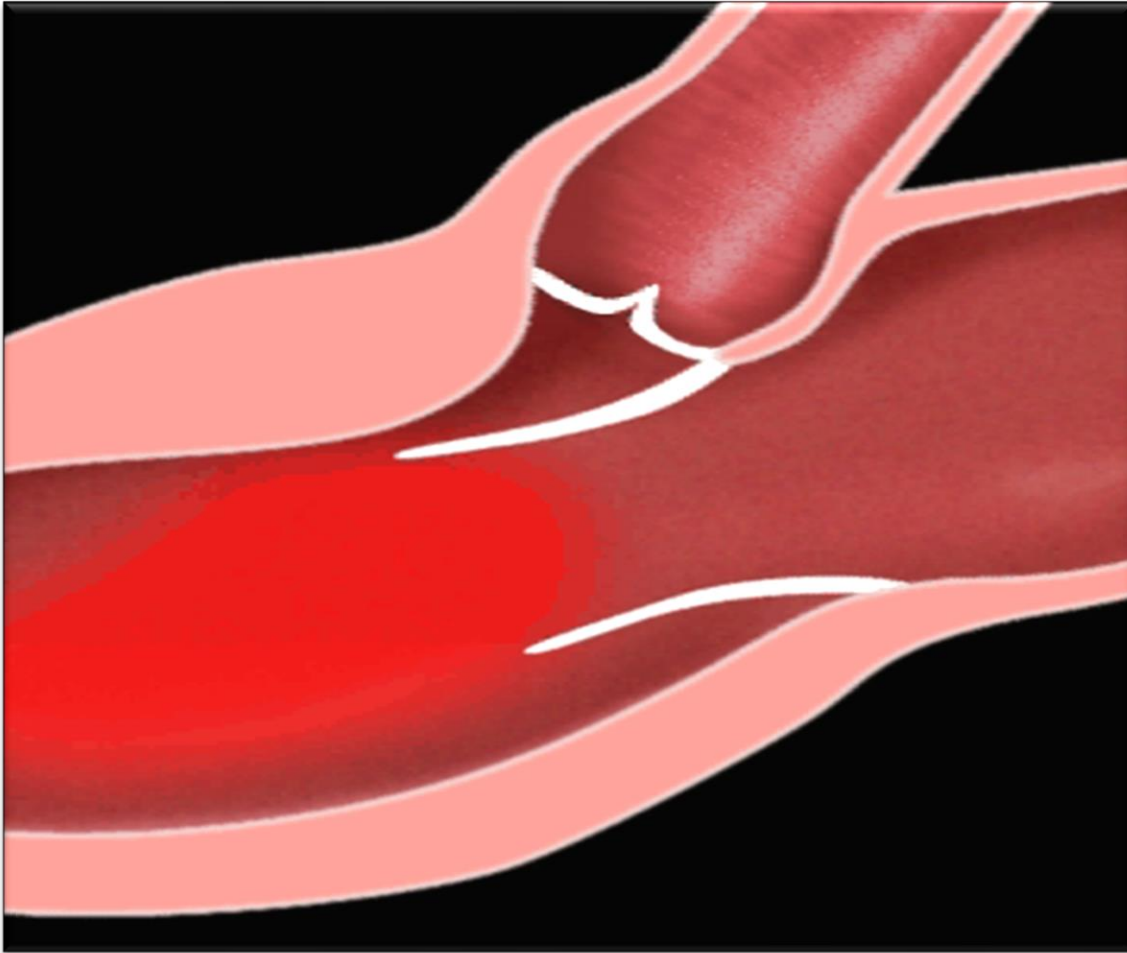
14+ defective genes
with hundreds of
different mutations



Symptoms in HCM



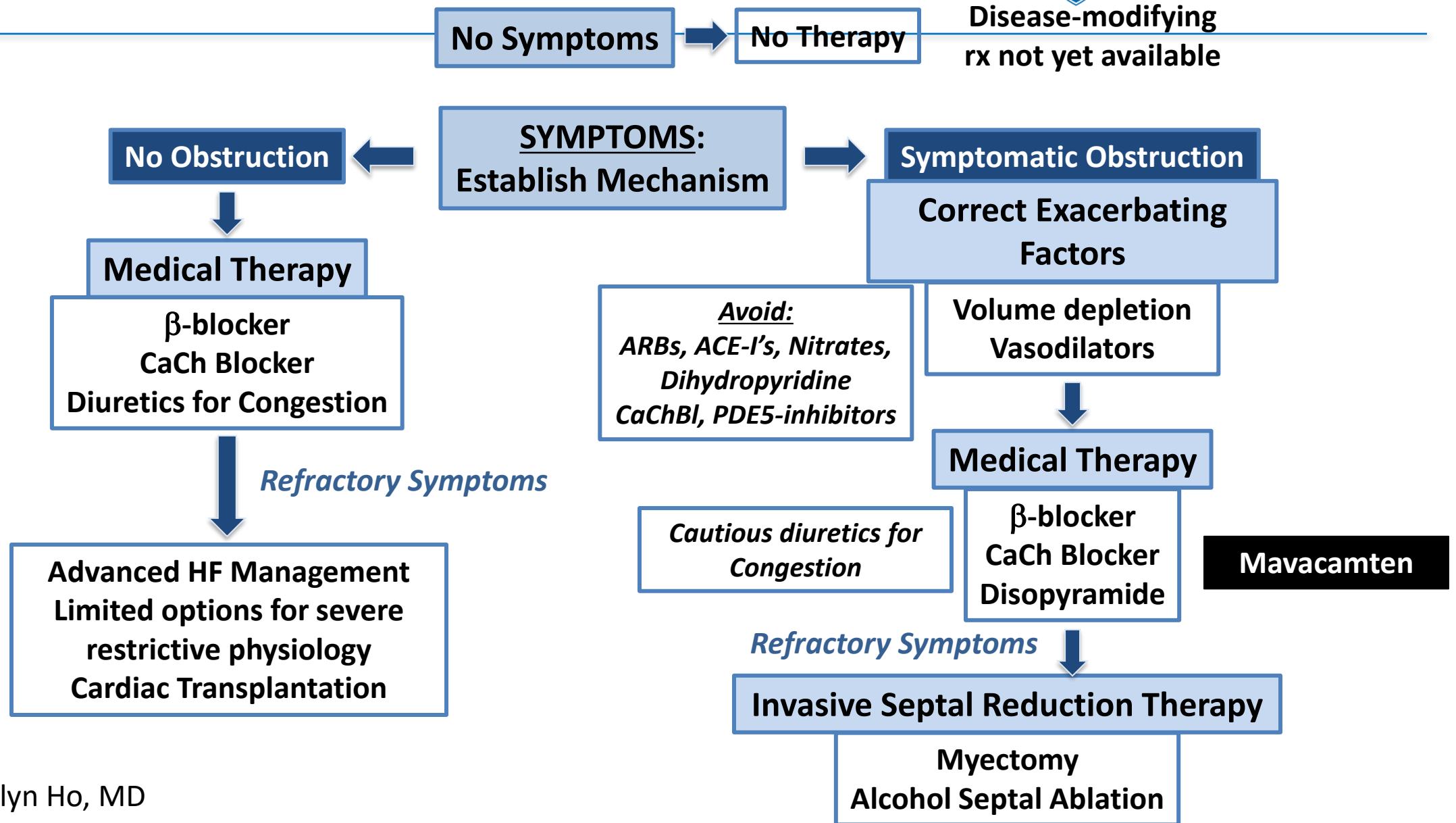
LV Outflow Obstruction



- **Obstruction Worse with**
 - **More Contractility**
 - **Decreased Afterload**
 - **Decreased Preload**

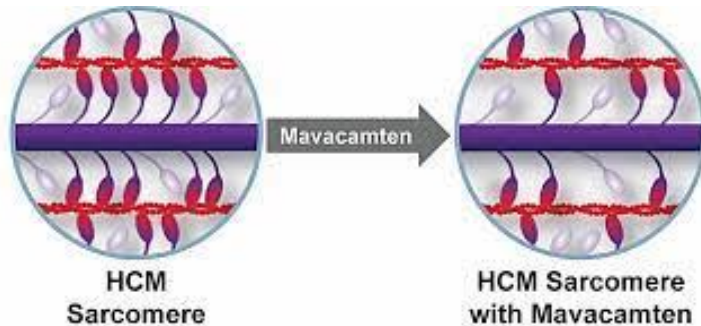
**All of these occur with
physical exertion**

HCM: Approach to Therapy



Mavacamten for Obstructive HCM

- **Mavacamten**
 - Myosin Inhibitor
 - Inhibits actin/myosin cross-bridges
 - Reduces contractility

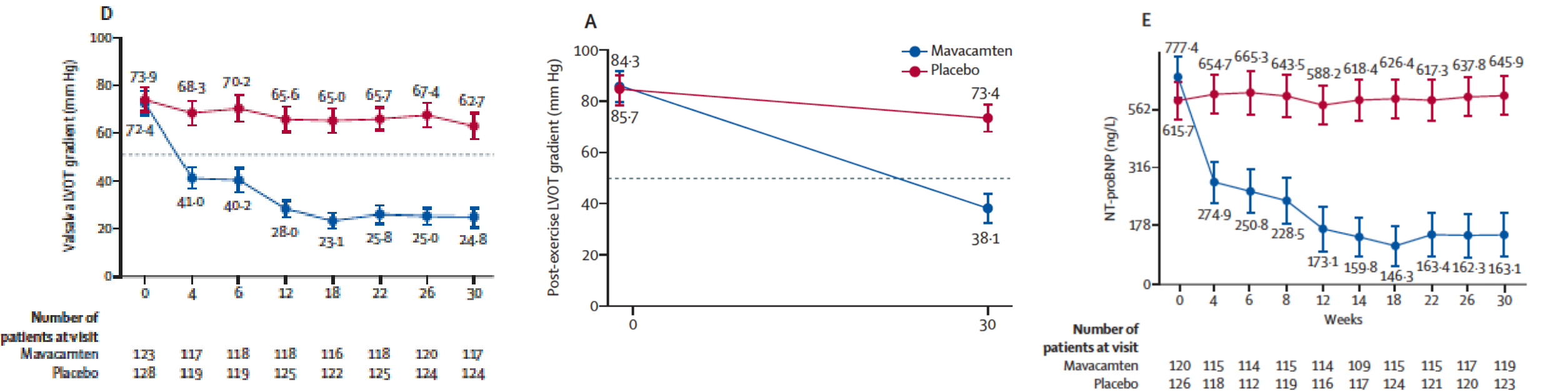


- **EXPL:ORER-HCM**
 - Randomized, Phase 3 study of Mavacamten in obstructive HCM
 - N=251
 - Duration 30 weeks

	MAVA	Placebo	P-value
Primary outcome ≥1.5 ml/kg/min increase in VO2 and NYHA improvement or ≥3.0 ml/kg/min increase in VO2	37%	17%	0.0005
Complete response (NYHA 1, no gradient)	27%	1%	
NYHA increase ≥1	65%	31%	<0.0001
Change in KCCQ	+14.9	+5.4	<0.0001
Change in LVEF	-3.9%	-0.01%	<0.0001

Olivotto Lancet 2020;396:759,
 Spertus Lancet 2021;397:2467

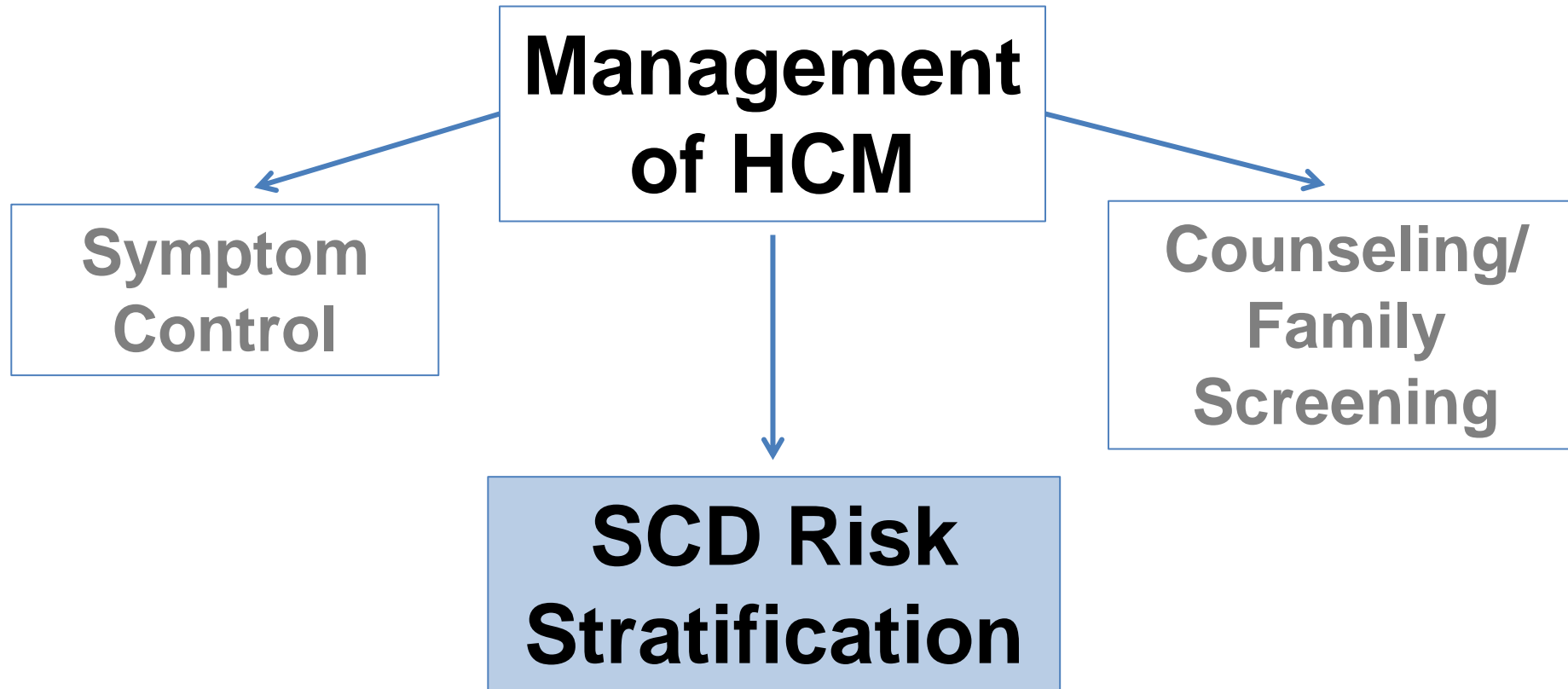
EXPLORER-HCM: Mavacamten treatment associated with marked reduction on LVOTO and NT-BNP



Heightened risk of LVEF<50%

Similar data with aficamten from SEQUOIA-HCM

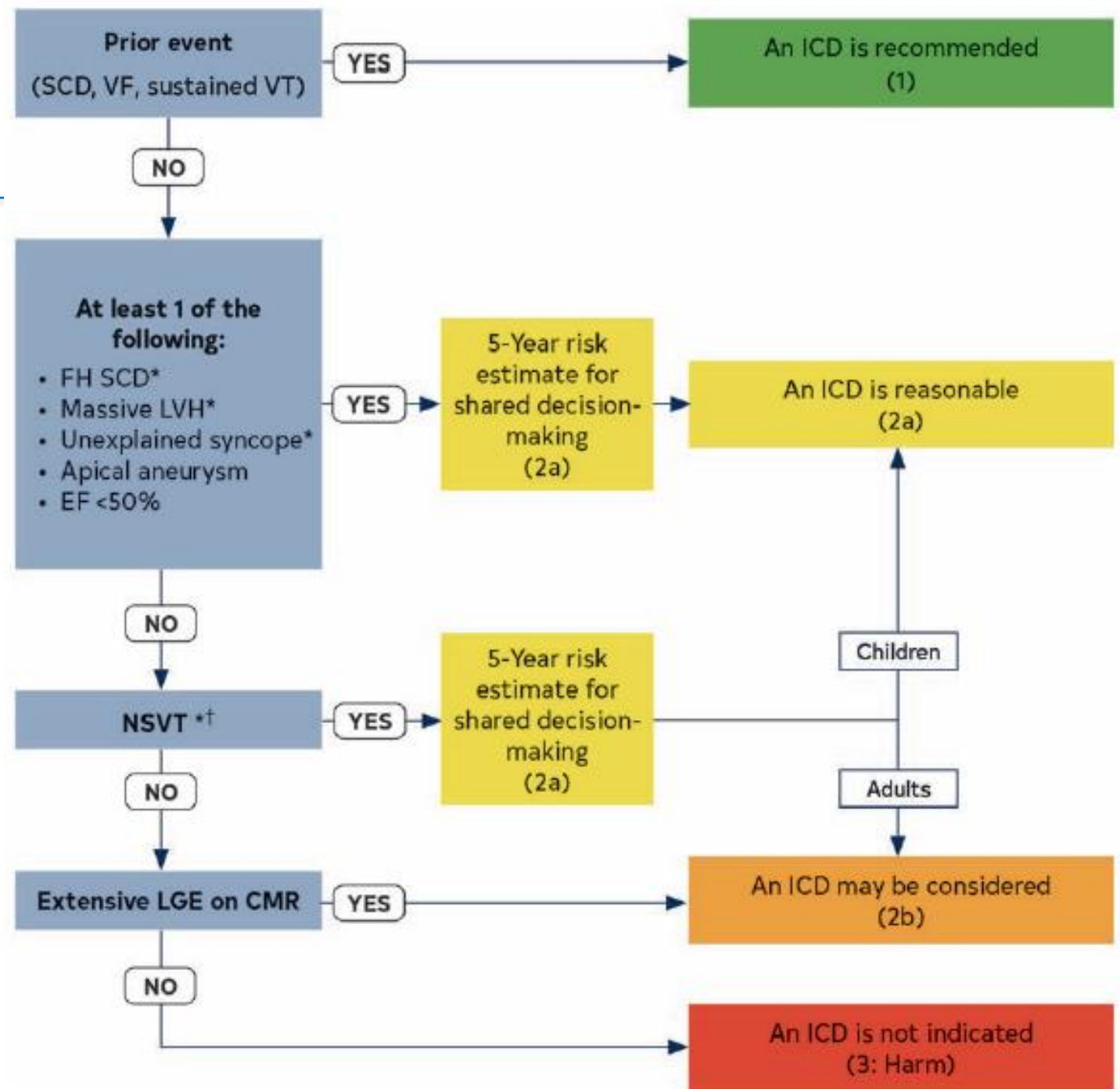
Mavacamten FDA approved with REMS in 2022

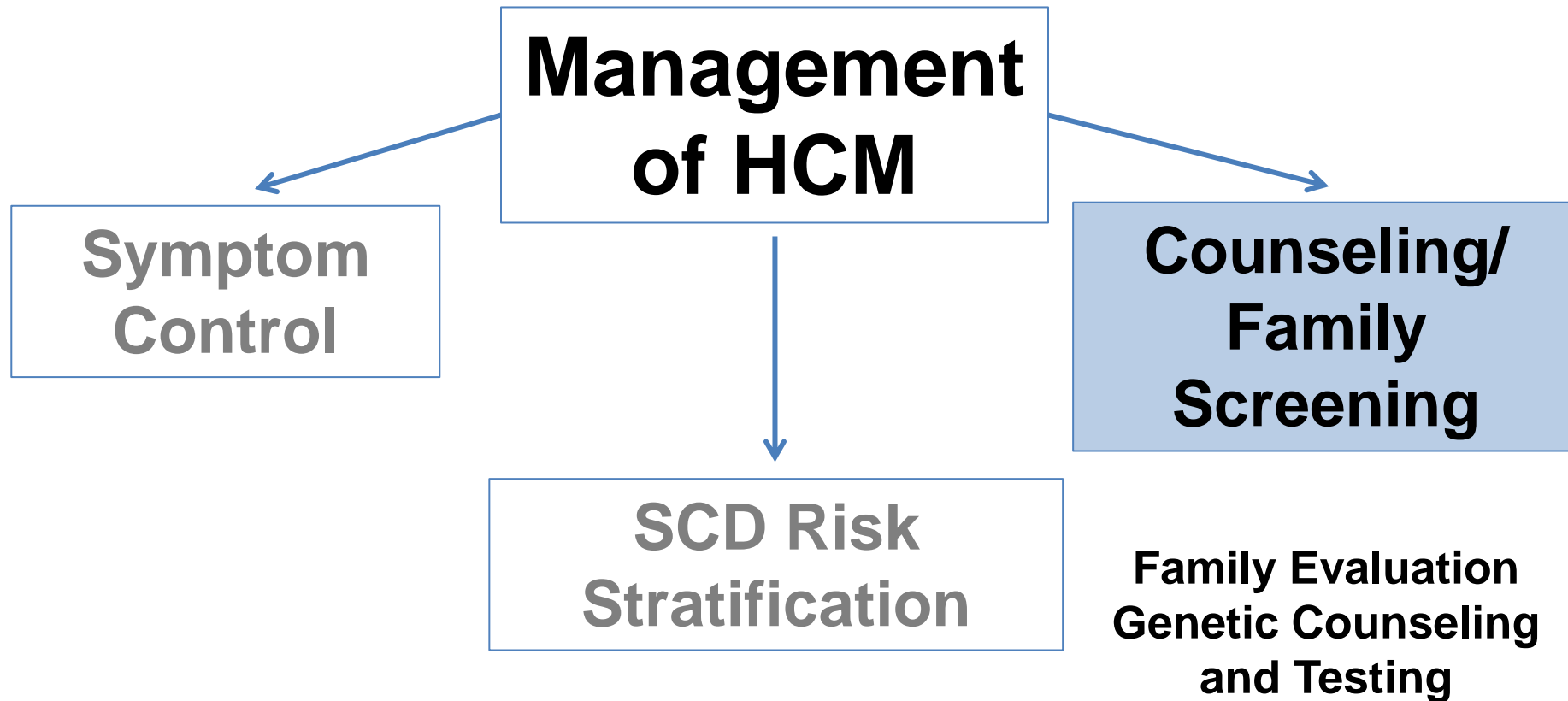


SCD Risk Predictors

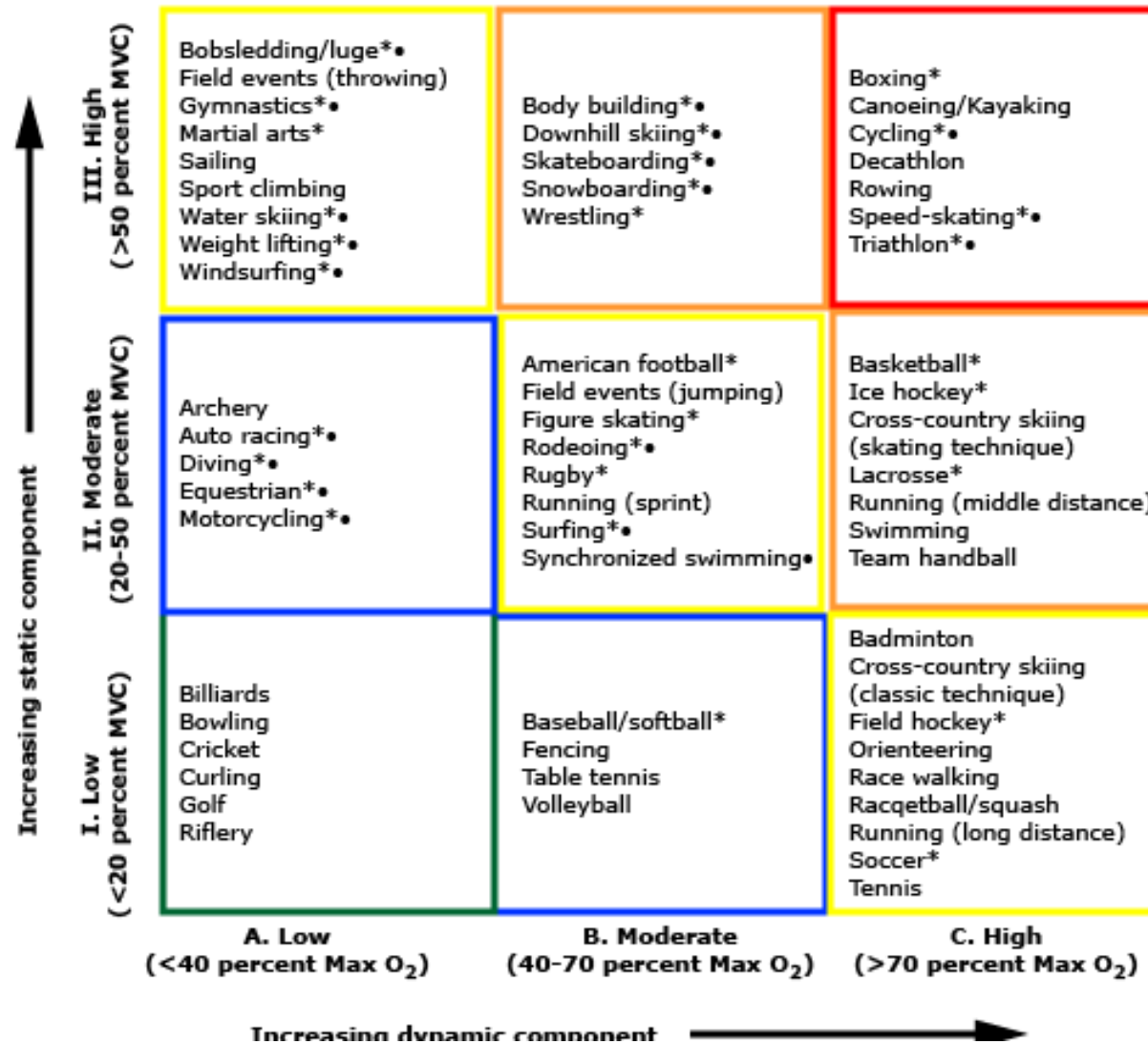
- Unexplained **Syncope**
- **Family history** of ≥ 1 SCD event
 - Consider family size, proportion of affected individuals, reliability of information
- **Severe LVH** ($>30\text{mm}$; should probably consider as continuous variable)
- **Abnormal BP response** to exercise ($<25\text{ mmHg}$ rise or $>15\text{ mmHg}$ fall) in patients $<40\text{-}50\text{ yrs}$
- **NSVT** on Holter, especially in children

Risk Stratification for ICD in HCM





Exercise Guidelines in HCM



- **Moderate recreational activity**
 - Conversational pace
 - Avoid sprint/burst
 - Avoid heavy isometric weight lifting

Differential Diagnoses

Thick Walls

Physiologic Left Ventricular Hypertrophy

Hypertrophic Cardiomyopathy

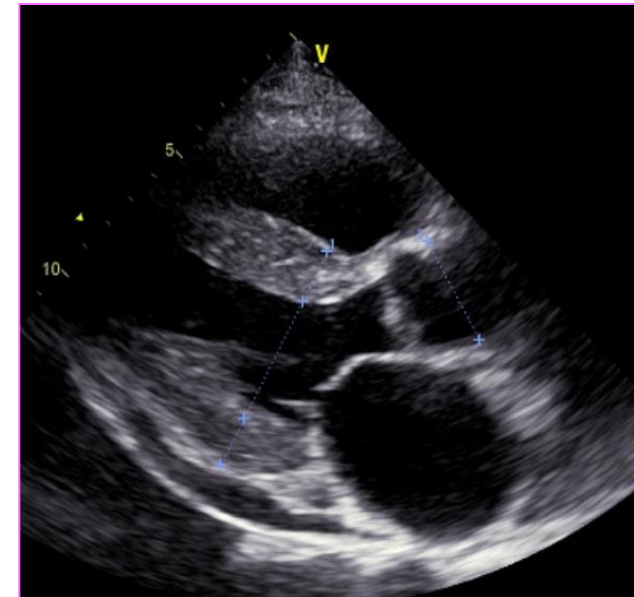
Renal failure

Infiltrative Disease (Amyloidosis, Hemochromatosis)

Storage disease (Gaucher, PRKAG2, LAMP2)

Anderson-Fabry disease

Freidreich's ataxia



Amyloidosis

- **Group of disorders characterized by extra-cellular deposition of fibrillar protein**
- **Deposits composed of amyloid fibrils → progressive end-organ dysfunction**
- **> 20 proteins form amyloid fibrils *in vivo***
- **2 predominant types involve the heart:**
 - ✓ **Transthyretin (TTR)-associated: hereditary and wild-type**
 - ✓ **AL: typically associated with plasma cell dyscrasia**

Cardiac Amyloid: A Rare Condition?

Incidence/Prevalence

Type	Incidence/Prevalence
1° AL Amyloid (plasma cell dyscrasia)	~2500 Cases per year 50% have cardiac involvement
ATTRmutant (Familial)	4% of African Americans are carriers 25,000-120,000 US patients
ATTRwt (Senile)	~10-25% of adults >80 years ~1 million ~13% of Hospitalized HFpEF

When to Suspect Amyloidosis

History/ Exam Clues

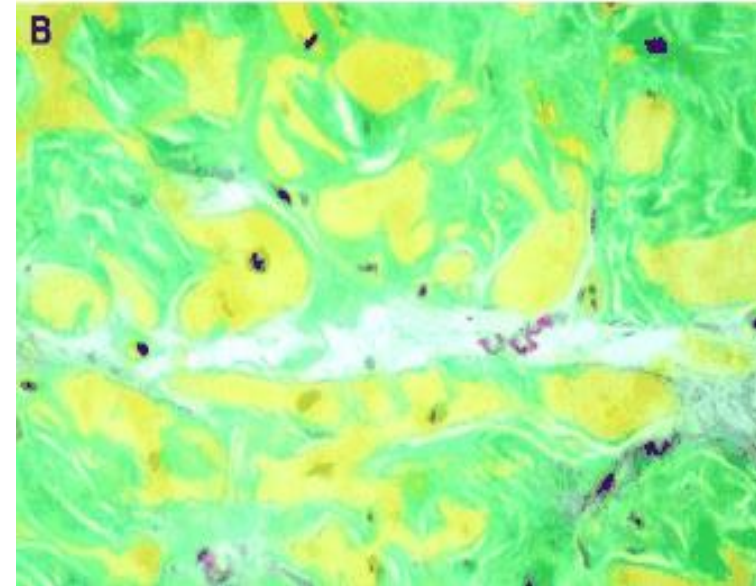
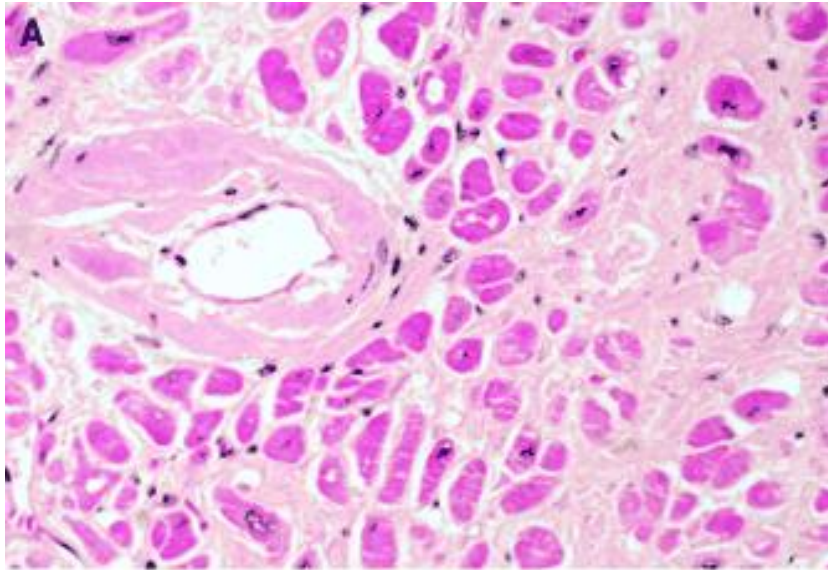
- *HFPEF without hypertension*
- *Unexplained right-sided heart failure*
- *Autonomic neuropathy*
- *Bilateral carpal tunnel syndrome*
- *Macroglossia*
- *Periorbital bruising*

Imaging Clues

- *Thick septum and granular sparkling on TTE*
- *Low voltage to mass ratio on ECG*
- *Low tissue Doppler velocities, strain, or strain rate*
- *Apical sparing on strain rate imaging*
- *Diffuse LGE and suboptimal myocardial nulling on MRI*

Cardiac Amyloidosis: Diagnosis

- Serum immunofixation for light chains (not SPEP/UPEP)
- Endomyocardial biopsy



Noninvasive Dx of TTR Amyloidosis

Bone scintigraphy (^{99m}Tc -PYP)



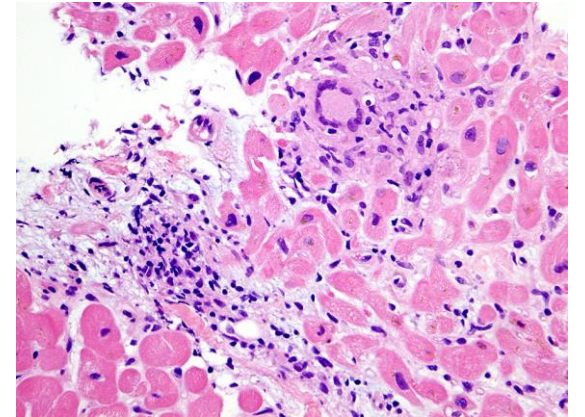
- TTR amyloid fibrils are Ca^{2+} avid
- Bone scintigraphy (e.g., Tc-PYP) differentiates TTR from AL cardiac amyloid
- Heart/contralateral lung ratio:
 - > 1.5 diagnostic*, < 1.0 ruled out
 - $> 1.6 \rightarrow$ poor prognosis
- Must first rule out AL amyloidosis with serum/urine immunofixation, free light chains

Treatment of Cardiac Amyloidosis

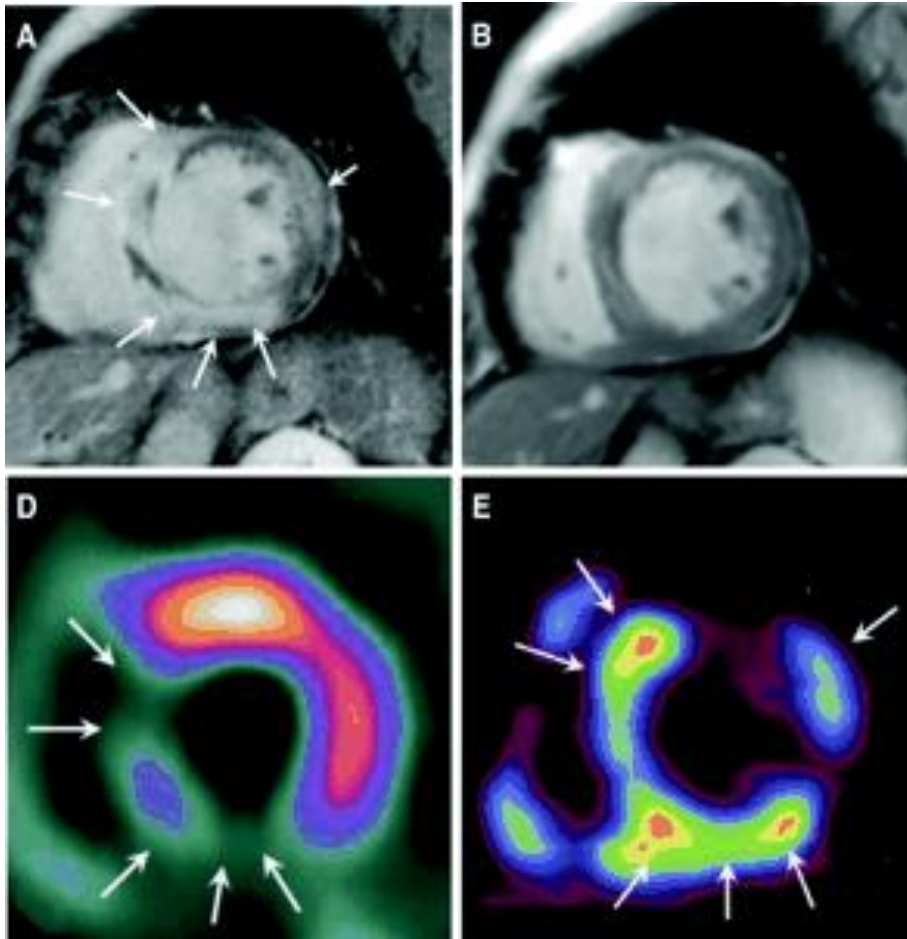
- **Treat Congestion**
- **Avoid Digoxin**
- **Low threshold for anticoagulation to prevent stroke (particularly if AF)**
- **AL Amyloidosis**
 - Manage underlying plasma cell dyscrasia to reduce light chain production
 - Selected patients may be eligible for sequential heart and stem cell transplantation
- **TTR Amyloidosis**
 - ATTR-wt: TTR stabilizers – Tafamadis, Acoramidis
 - ATTR-mutant: TTR Stabilizers, RNAi/antisense oligonucleotides: e.g. vutrisiran

Sarcoidosis

- **Inflammatory disease of unclear etiology**
 - Pathologic Hallmark: Non-caseating granulomas
- **Typical onset prior to age 60**
 - ↑ prevalence in Scandinavians, African-Americans
- **Many Systemic Manifestations**
 - Interstitial lung disease, Lymphadenopathy (hilar), Iritis, Erythema nodosum
- **Cardiac involvement in up to 25%**
 - High Grade AV block, Ventricular arrhythmias, Syncope +/- LV dysfunction/Heart Failure
 - Isolated Cardiac Disease Possible
 - Endomyocardial biopsy is gold standard, but sampling error limits sensitivity



Cardiac Imaging for Sarcoid



Cardiac MRI

LGE + T2 hyperenhancement
+/- LV dysfunction

¹⁸F-FDG PET

Increased FDG uptake in myocardium
and other affected tissues

diagnosis, prognostication, and
monitoring response to therapy

Management of Cardiac Sarcoidosis

- **Consider Immune Suppression**
 - Prednisone 30-40 mg/day tapered gradually
 - MTX 15-20 mg/wk + leucovorin/folic acid for steroid-sparing
 - Other agents: azathioprine, leflunomide, infliximab, cyclosporine
 - Most effective in symptomatic patients with high grade AV block, ventricular arrhythmias, or HF/LV dysfunction
- **Consider ICD if...**
 - Cardiac Arrest or Sustained VT
 - EF<35% despite immune suppression
 - Indication for permanent pacing
 - Unexplained Syncope
 - Inducible VT/VF on EP testing



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