CARDIOMYOPATHY

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DEFINITION

- *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders.”*

MOGES CLASSIFICATION

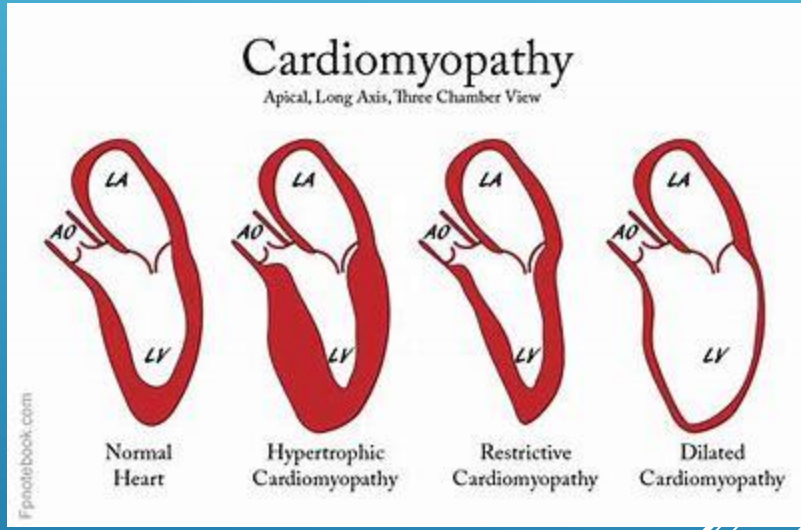
- M refers to the phenotype (eg, DCM and HCM)
- O refers to organ involvement (eg, with/without extracardiac involvement)
- G refers to genetic transmission (eg, autosomal dominant or recessive)
- E refers to etiology (genetic, idiopathic)
- S refers to disease stage.

CARDIOMYOPATHY

WHO Classification

anatomy & physiology of the LV

1. Dilated
   - Enlarged
   - Systolic dysfunction
2. Hypertrophic
   - Thickened
   - Diastolic dysfunction
3. Restrictive
   - Diastolic dysfunction
4. Arrhythmogenic RV dysplasia
   - Fibrofatty replacement
5. Unclassified
   - Fibroelastosis
   - LV noncompaction



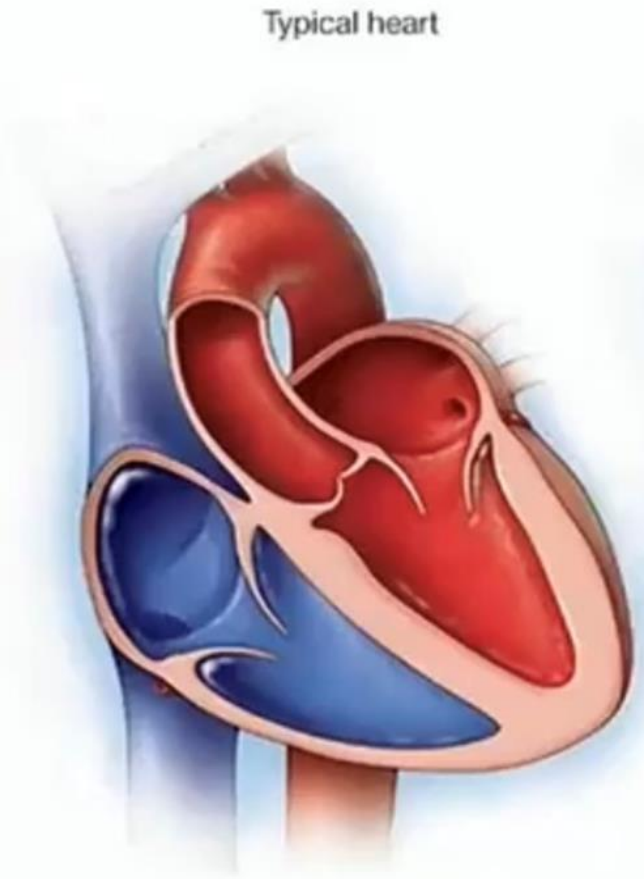
DILATED CARDIOMYOPATHY

- Dilation *and* impaired contraction of ventricles:
  - Reduced *systolic* function with or without heart failure
  - Characterized by myocyte damage
  - Multiple etiologies with similar resultant pathophysiology

- **idiopathic**
  - 3X more prevalent among males and African-Americans

Overview of genetic dilated cardiomyopathy (DCM)

- **General definition of DCM**
  - LVEF < 45% with a LVEDD > 112% of that predicted for age and body surface area
  - Not explained by abnormal loading conditions or coronary artery disease
  - Prevalence: up to 1 in 250 individuals
- **Familial DCM**
  - Proband and at least 1 family member meeting criteria for DCM
  - Proband has DCM and a first-degree family member had sudden cardiac death < 35 years of age



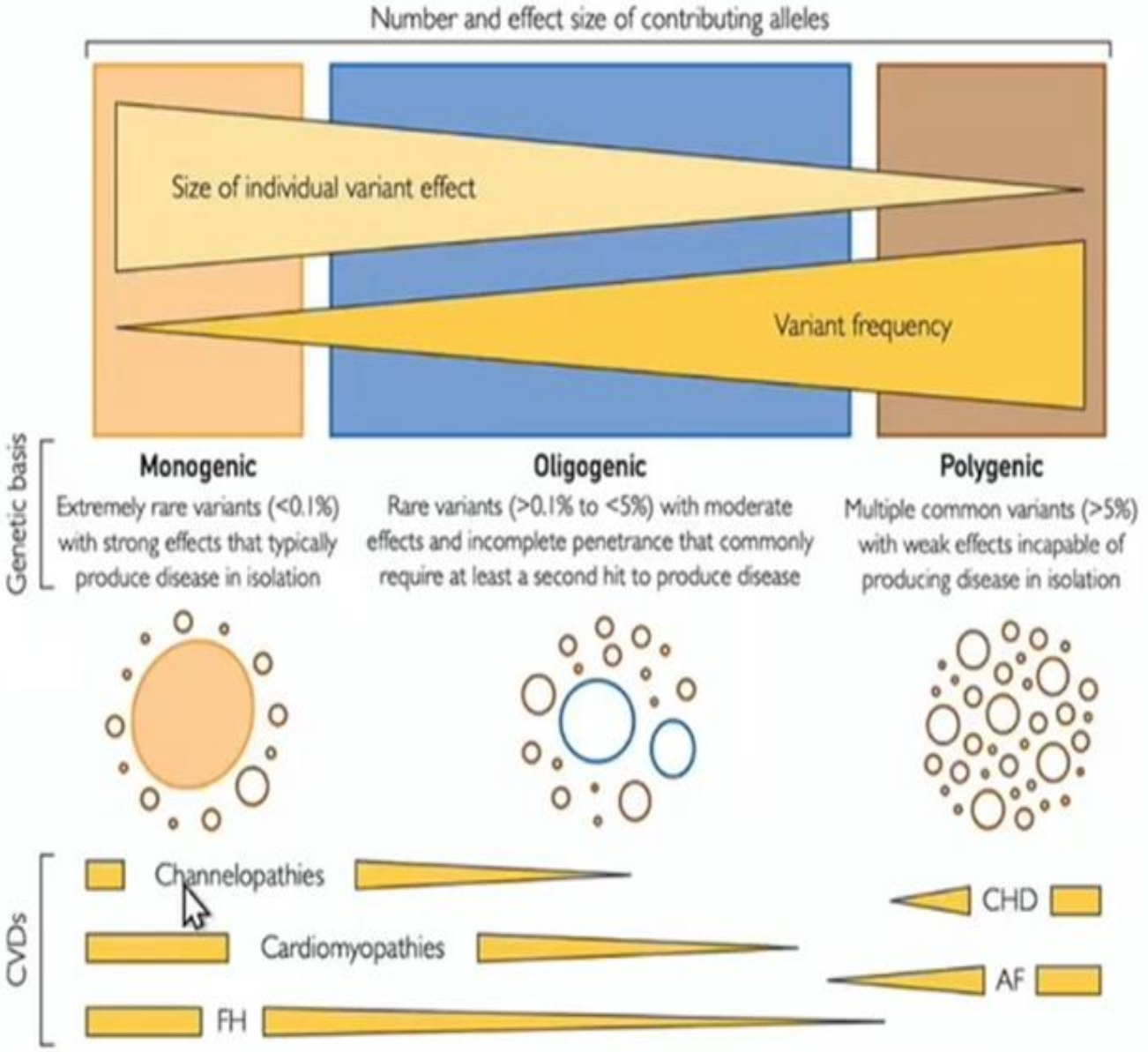
Common variants implicated in genetic DCM

Pathogenic variant with moderate-strong association with DCM	Gene	Approximate prevalence in DCM	Other phenotypes	Asso
Titin	*TTN*	12%–25%	HCM (ℳ)	In sm variar
Lamin A/C	*LMNA*	4%–8%	ℳ	High
Myosin heavy chain 7	*MYH7*	3%–4%	HCM (ℳ)	Prese
Troponin T2	*TNNT2*	2%–4%	HCM	Prese
Filamin C	*FLNC*	2%–4%*	HCM, RCM, ACM-RV, ℳ	High
RNA binding motif 20	*RBM20*	2%		High
Type V voltage-gated cardiac sodium channel	*SCN5A*	2%–3%	Brugada syndrome	High
Desmoplakin	*DSP*	2%	ACM-RV, ℳ	High
Phospholamban	*PLN*	<1%†	ACM-RV	High
Bcl-associated athanogene 3	*BAG-3*	0.1%–3%*	ℳ	Prese
Desmin	*DES*	<1%	More often RCM ℳ	High
Other sarcomeric proteins, eg		Variable representation in DCM populations	HCM, ℳ	Occa
Myosin heavy chain 6	*MYH6*			
Tropomyosin	*TPM1*			
Troponin C1	*TNNC1*			
Myosin binding protein C3	*MYBPC3*			

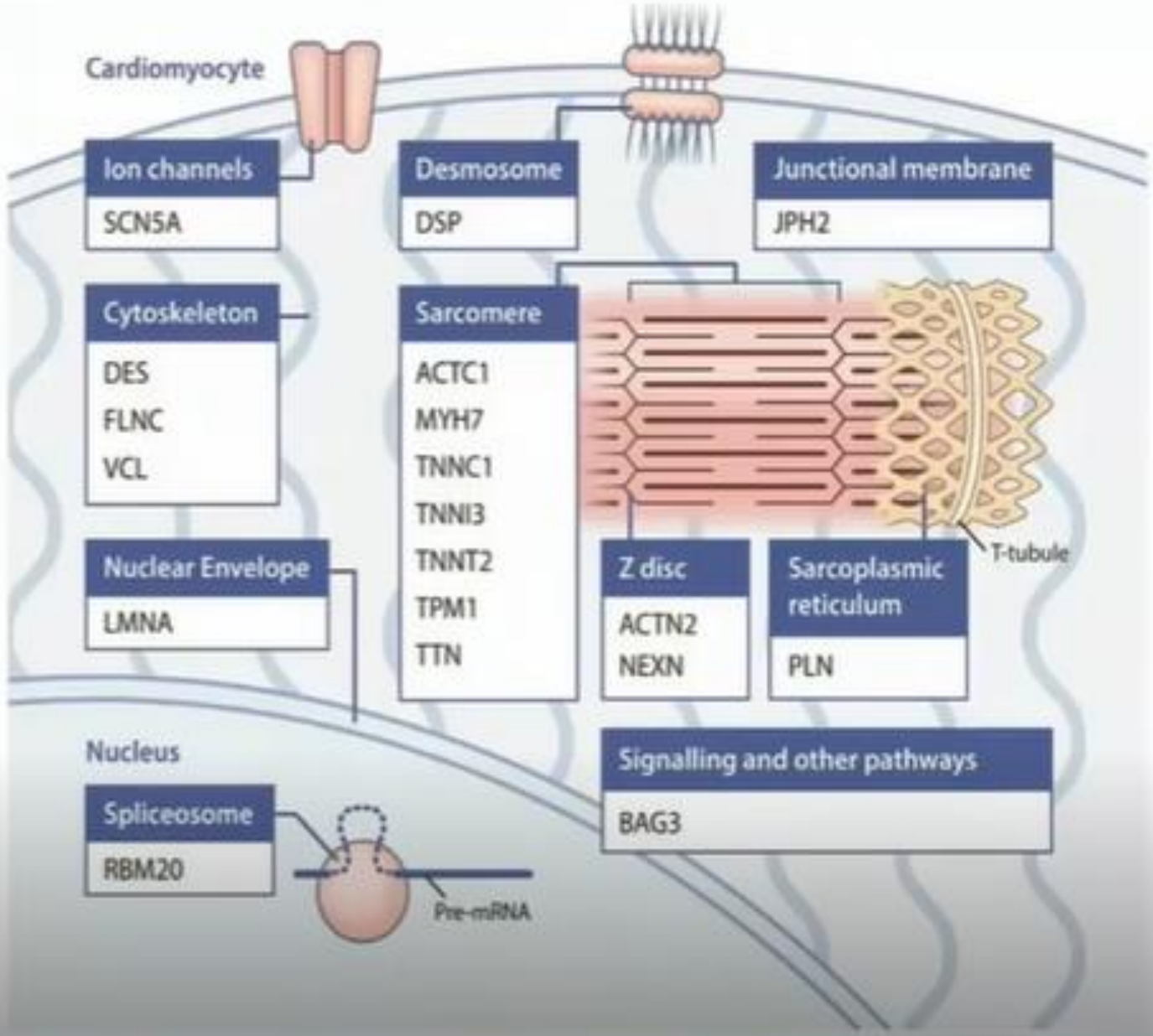
Genetic architecture of DCM

- **Genetic architecture**
  - Refers to how genetic variation (both genetic and epigenetic mechanisms) leads to phenotypic variation in a population.
  - Over 250 genes spanning over 10 gene ontologies having been implicated
  - Explanation for diverse genetic architecture may be related to a "final common pathway"
- **Inheritance pattern**
  - Predominantly autosomal dominant (especially if monogenic)
- **Penetrance**
  - Typically, it is age-related with phenotype occurring by middle age or not at all
- **Expressivity**
  - There is significant heterogeneity in phenotype

Genetic DCM is on the variant spectrum



Genetic variants implicated in DCM

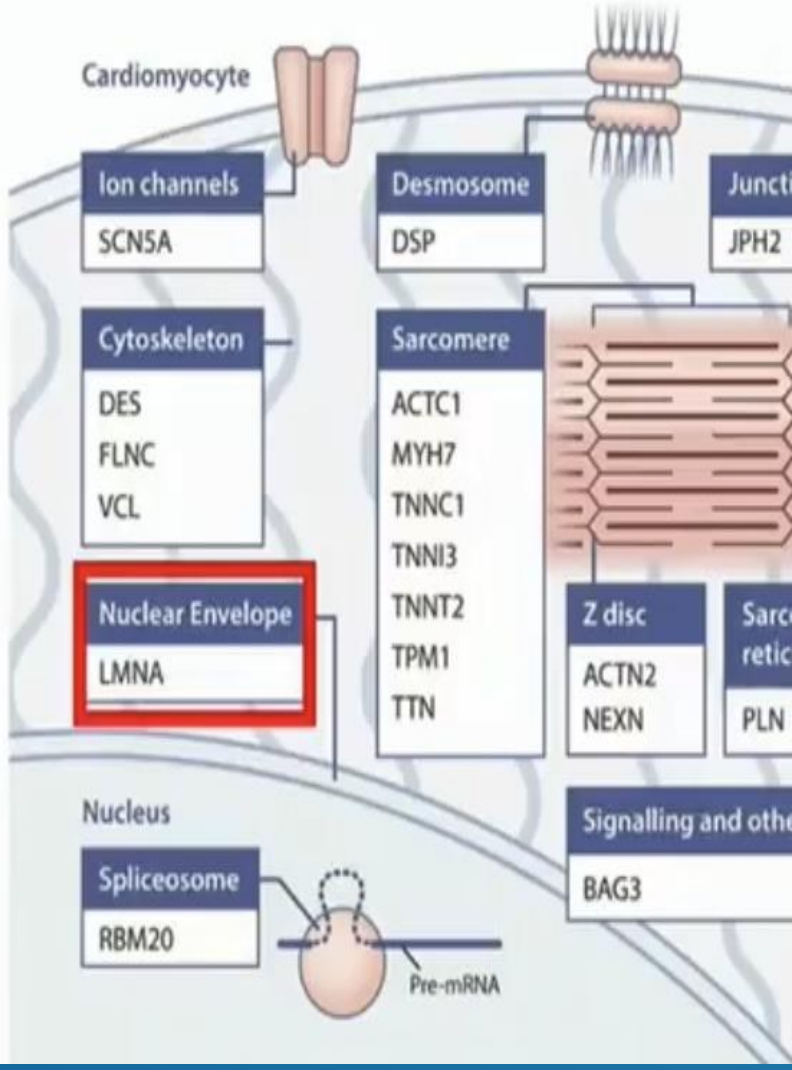


TTN-related DCM

- Titin (TTN) is the **largest sarcomeric protein** found in humans and is responsible for proper sarcomere assembly.
- TTN is commonly implicated in a **"two-hit cardiomyopathy,"** developing after an acquired insult (or another CM pathogenic variant)
- Common clinical settings in which TTN variants increase cardiomyopathy risk include postpartum, heavy alcohol use and chemotherapy.
- Has **favorable reverse remodeling response** with major LVEF improvement after initiation of GDMT (69% vs 30-40% with general DCM)

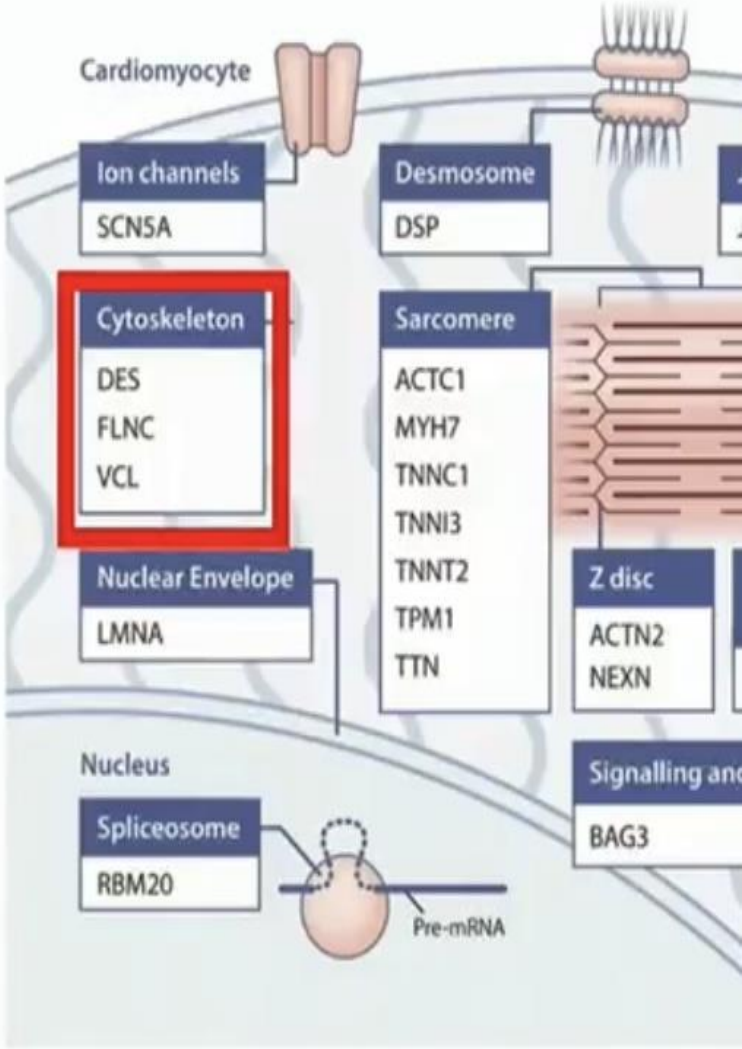
LMNA-related DCM

- Lamins (A-type) play an important role in maintaining nuclear **architectural integrity** and spatial organization of proteins of inner **nuclear membrane**.
- Considered the **most malignant** and **highly penetrant** genetic DCM
- **Arrhythmias** are frequently the **first presentation** of LMNA-variant cardiomyopathy
- Commonly associated with atrial and ventricular arrhythmias as well as conduction abnormalities (i.e. AV block). May be related to predilection to cause fibrosis in the septum.
- Carriers of pathogenic LMNA variants often have ECG abnormalities that precede DCM diagnosis by ~7 years.

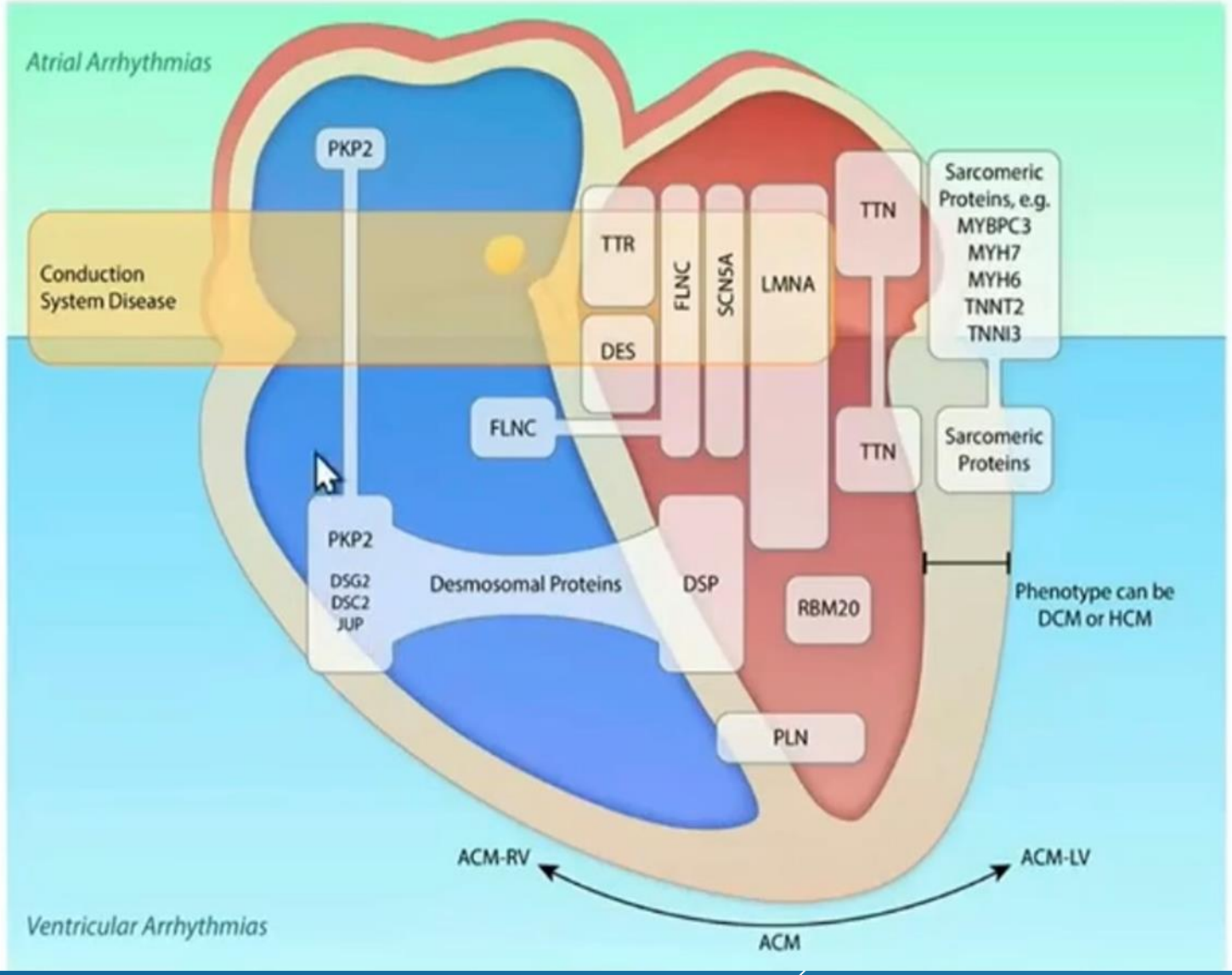


FLNC-related DCM

- Filamin C (FLNC) is a **cytoskeletal protein** that is found in both skeletal and cardiac muscle. Important in stabilization of thin filaments and force generation of the sarcomere.
- **Truncating variants** of FLNC have been associated with about **3 to 4% of DCM** cases.
- Like LMNA, FLNC-variant DCM has been associated with high rates of **ventricular arrhythmias** and **sudden cardiac death** irrespective of LVEF.
- FLNC has been a recent addition to genetic cardiomyopathy panels, so the prevalence is likely higher
- Strong association with **skeletal myofibrillar myopathies**, but cardiomyopathy often occurs without recognized skeletal myopathy



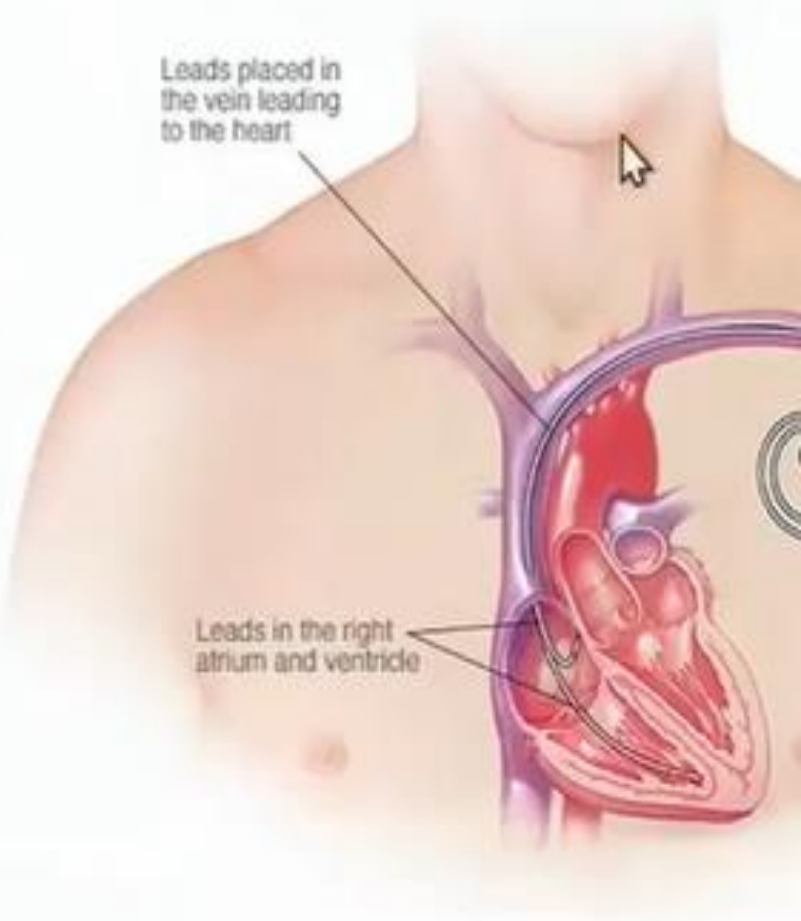
Cardiomyopathy variants associated with arrhythmias



Primary prevention ICD guidelines differ for genetic DCM

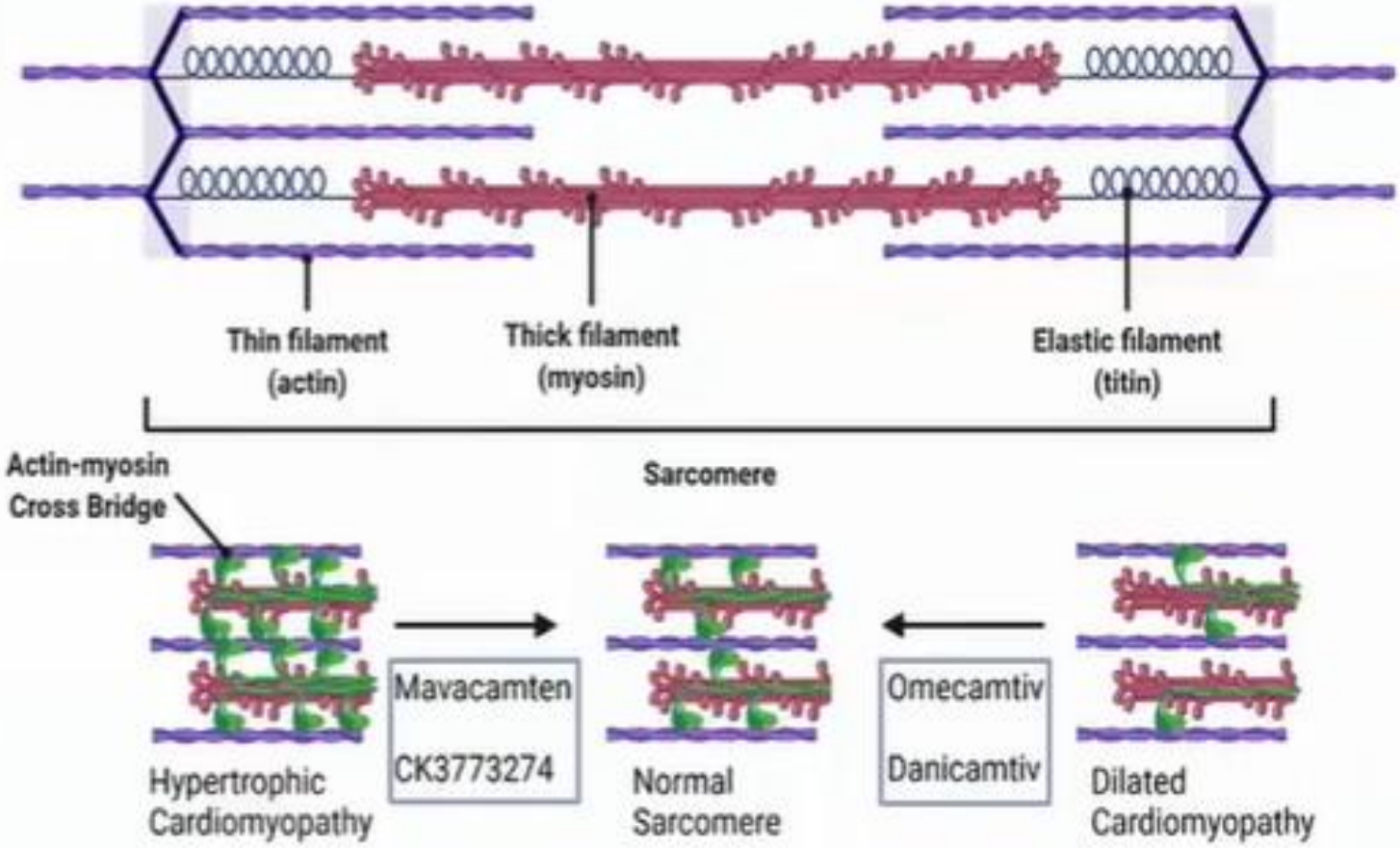
- **2019 Heart Rhythm Society Guidelines**
  - Primary prevention ICDs are recommended in DCM patients with LVEF < 45% with LMNA, FLNC, PLN genetic variants

- **2022 European Society of Cardiology Guidelines**
  - Primary prevention ICDs are recommended in DCM patients with a LVEF < 50% and more than 2 of the following risk factors (syncope, late gadolinium enhancement on cardiac MRI, inducible sustained monomorphic ventricular tachycardia at programmed electrical stimulation and pathogenic variants in LMNA, PLN, FLNC, and RBM20)



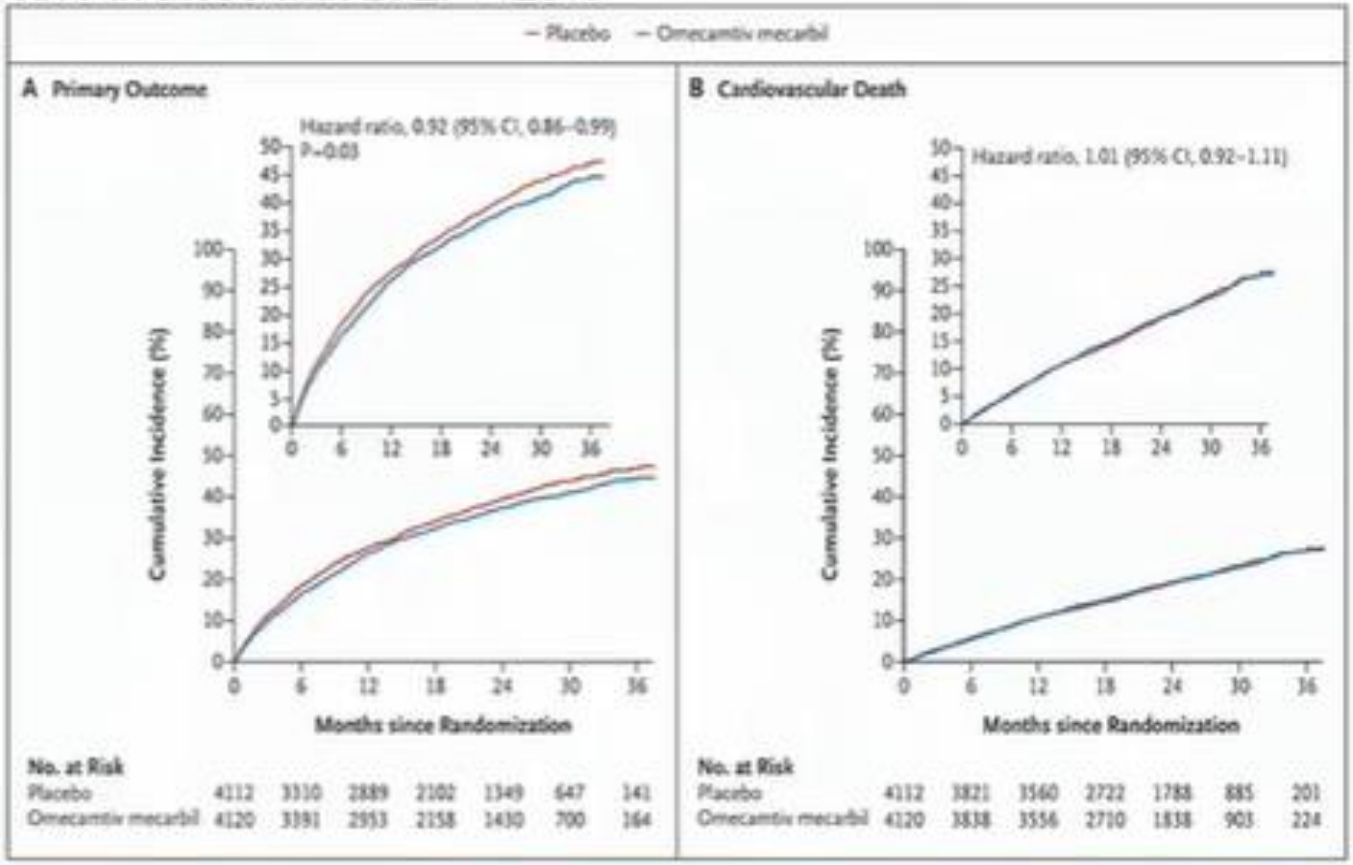
Cardiac myosin modulators

- Mechanism: accelerates actin-activated rate of phosphate release and structurally primes the myosin mole interaction with actin



Omecamtiv mecarbil in GALACTIC-HF (2021)

- **GALACTIC-HF**
  - Phase 3 RCT of 8,256 patients with chronic HFrEF (LVEF ≤ 35%), omecamtiv vs placebo
  - Omecamtiv cohort demonstrated an absolute risk reduction of 2.1% in composite outcome (death), most effective in those with LVEF ≤ 28%



CONCLUSION

- Cardiac genetic evaluation of DCM begins with awareness of genetic etiology
- Genetic testing is generally necessary in all NICMP
- Genetic architecture of DCM is very complex
- May present with arrhythmia first
- Genotype is important for prognosis and ICD indications

HYPERTROPHIC CARDIOMYOPATHY

Left ventricular hypertrophy not due to pressure overload
Hypertrpohy is variable in both severity and location:

- -asymmetric septal hypertrophy
- -symmetric (non-obstructive)
- -apical hypertrophy

Vigorous systolic function, but impaired diastolic function

- impaired relaxation of ventricles
- elevated diastolic pressures

prevalence as high as 1/500 in general population

- mortality 1% /y

ETIOLOGY

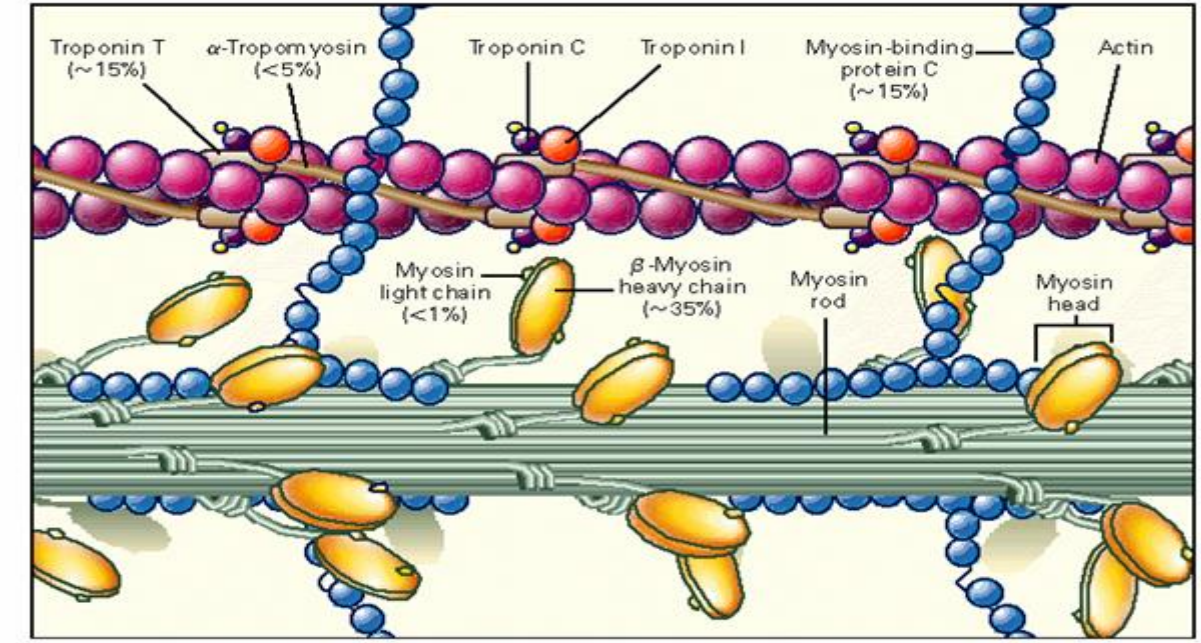
Familial in ~ 55% of cases with autosomal dominant transmission
Mutations in one of 4 genes encoding proteins of cardiac sarcomere
account for majority of familial cases

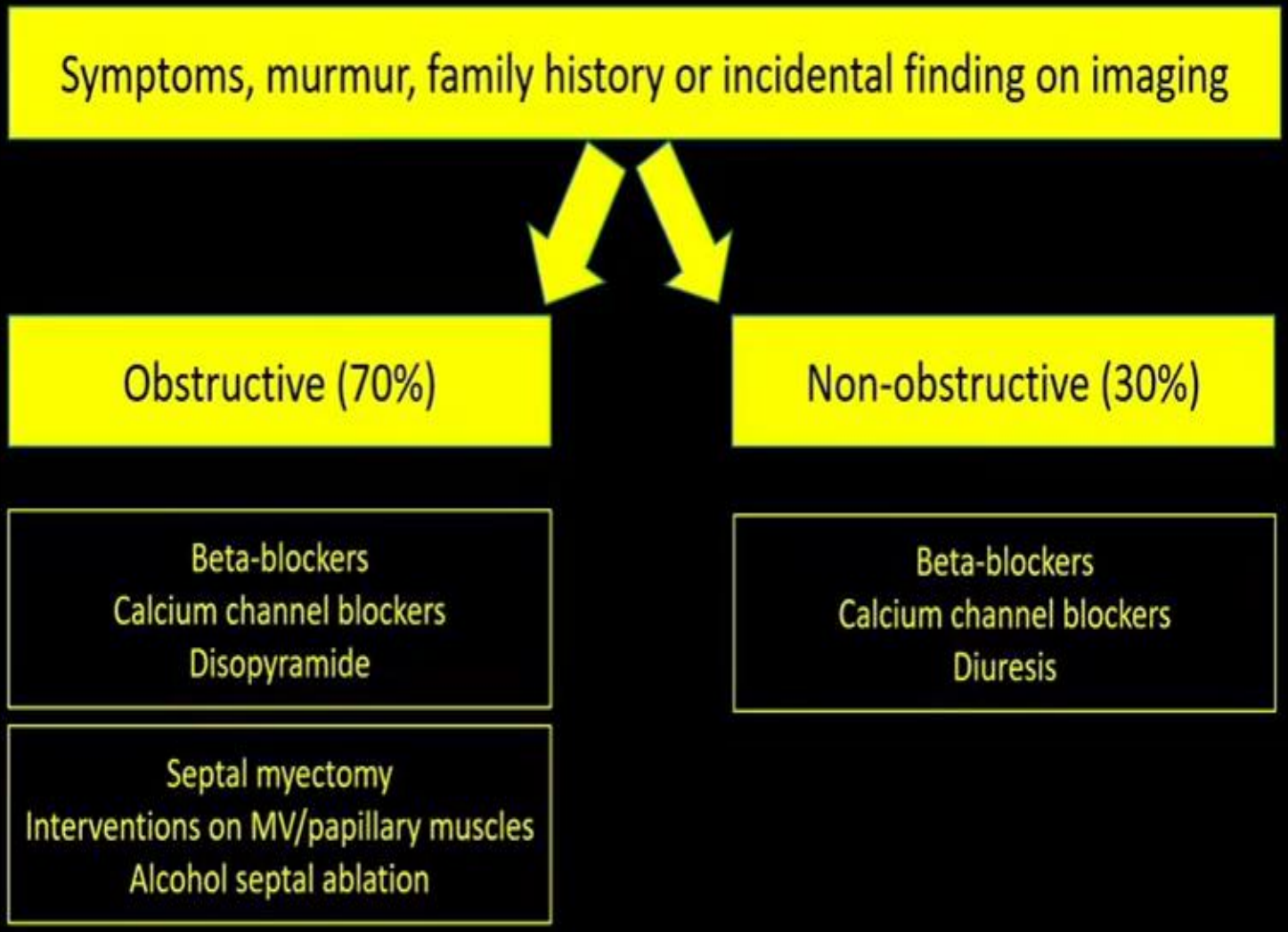
β-MHC (Beta Myocin Heavy Chain)

cardiac troponin T

myosin binding protein C

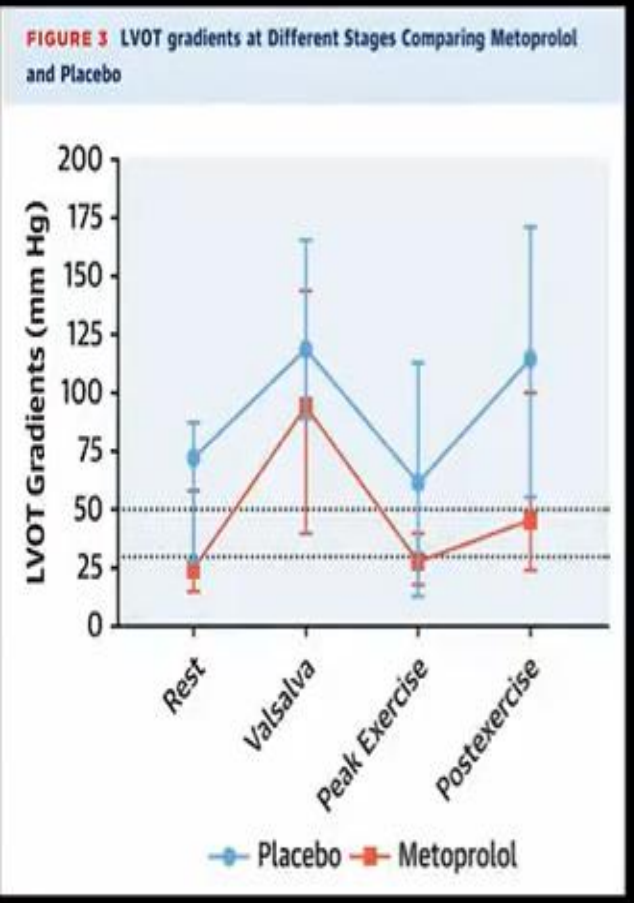
α-tropomyosin

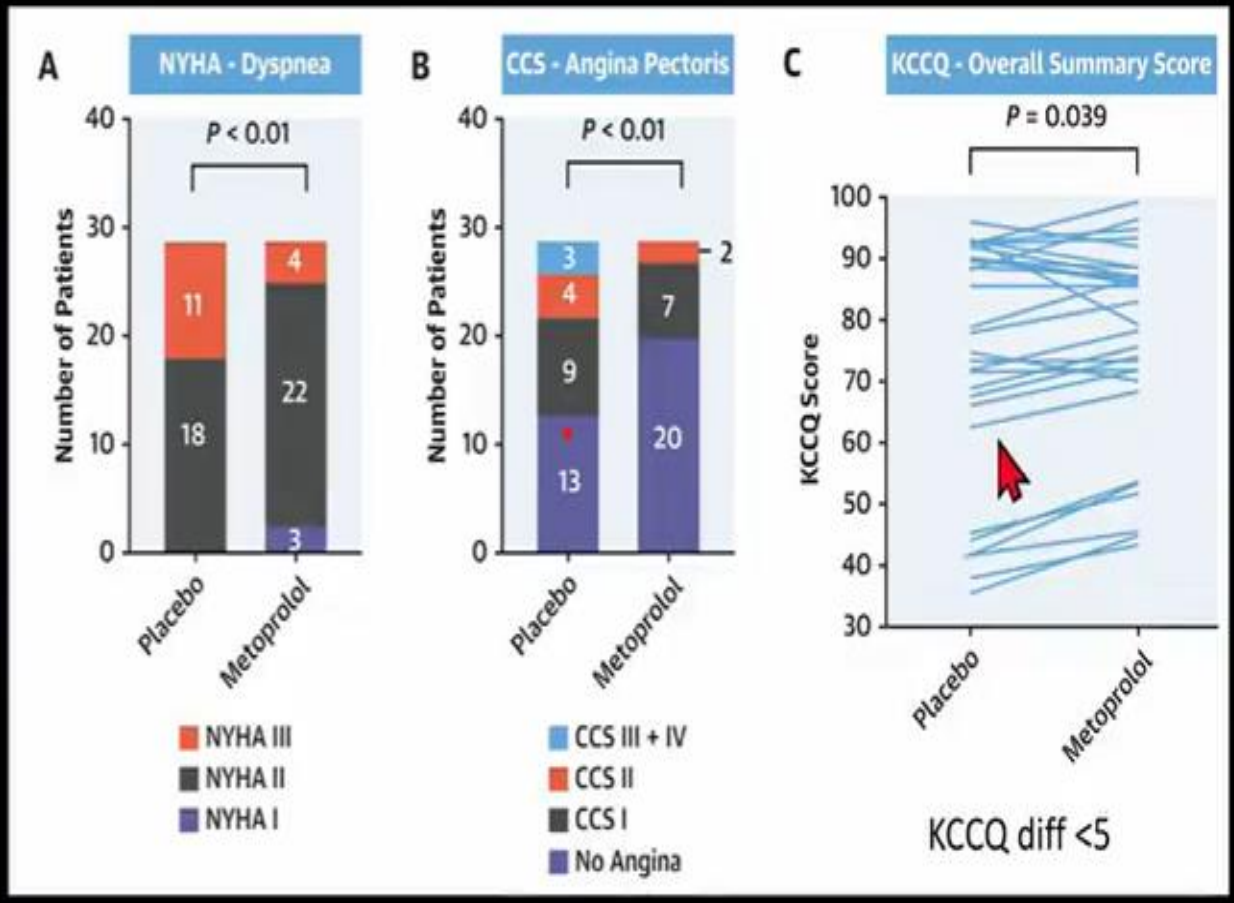




Ommen et al. JACC 2020

63 Years Later – First Randomized Trial of Upfront BB



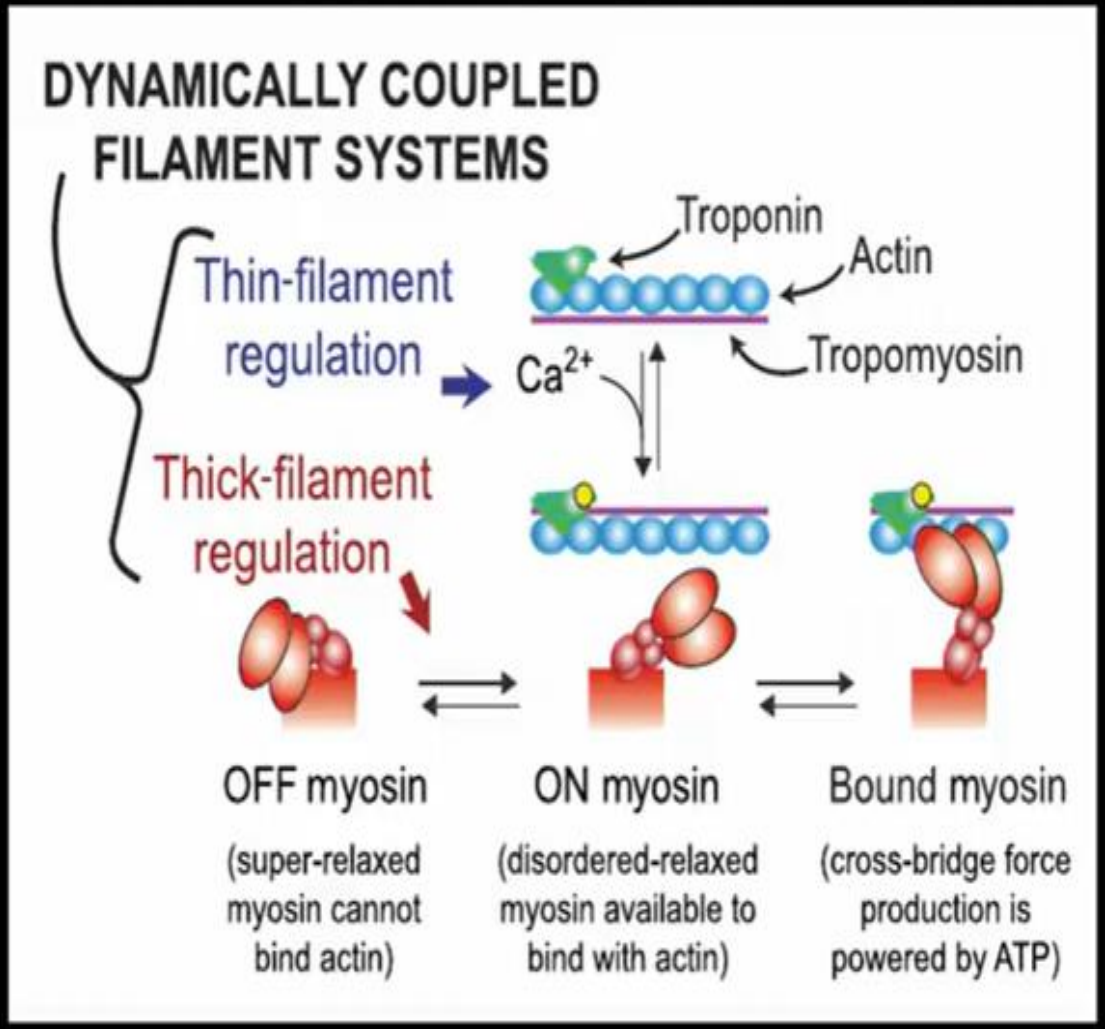


No difference in pVO2

No difference in NTproBNP

Dybro et al. JACC 2021

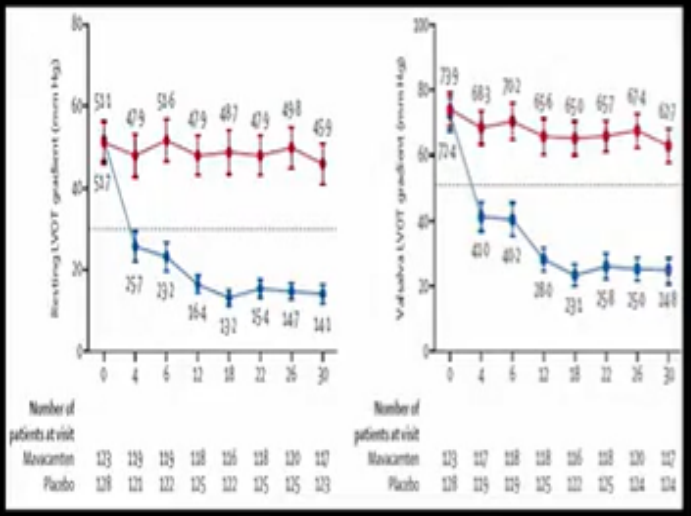
Myosin Super-relaxed State

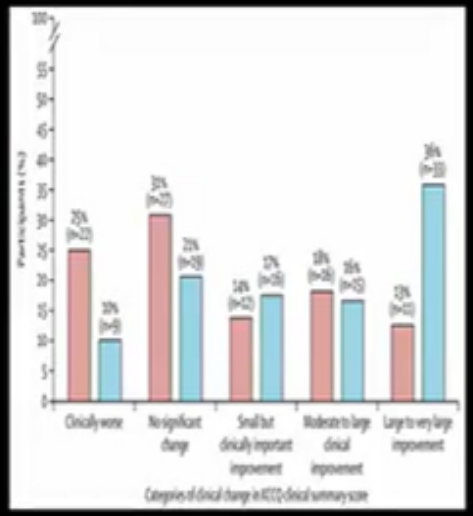


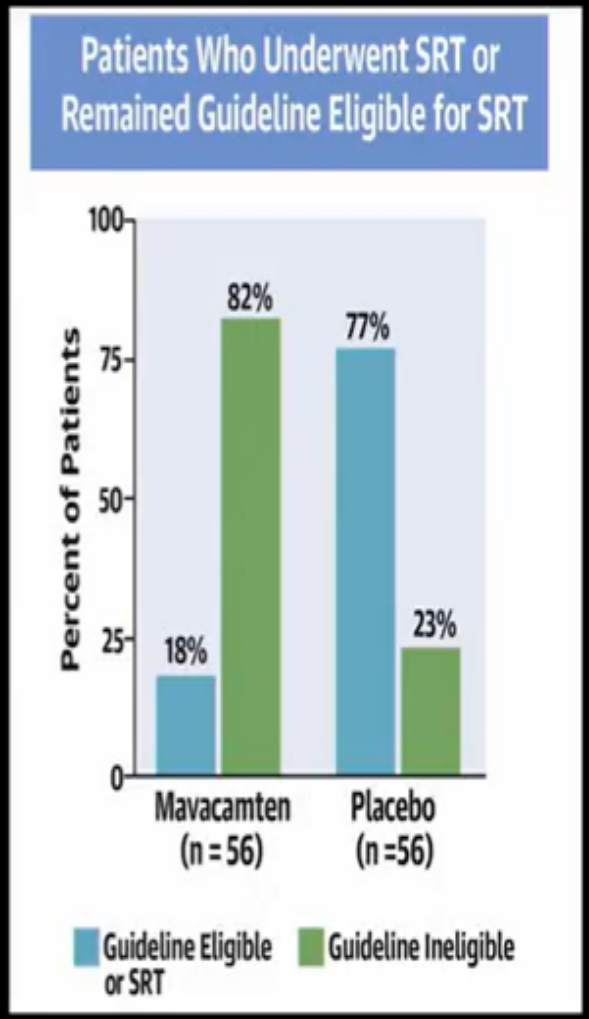
- Awinda PO, et al. Br J Pharmacol. 2020;177:5609-5621.

Mavacamten

Outcome	Mavacamten (n = 123)	Placebo (n = 128)
Either 1) pVO2 increase ≥ 1.5 ml/kg/min + ≥ 1 NYHA class 2) pVO2 increase ≥ 3 ml/kg/min + no worsening of NYHA class	37%	17%







Olivotto, et al. Lancet. 2020;396(10253):759-769.
Spertus J, et al. Lancet. 2020;397: 2467-2475
Desai et al. J Am Coll Cardiol. 2022;80:95-108.

Mavacamten's Safety

- Risk of LVEF < 50% and/or heart failure
  - EXPLORER-HCM 5%
  - VALOR-HCM 12%
  - MAVA-LTE 5.2%
  - Up to 27% in the non-obstructive patients over 156 weeks
- Atrial fibrillation
  - 8.6% in MAVA-LTE over 62 weeks, half are new onset disease
- Logistics and monitoring

Olivotto et al. Lancet. 2020;396(10253):759-769.
Desai et al. J Am Coll Cardiol. 2022;80:95-108.
Rader et al. JACC HF 2024

Mavacamten

- Effective medication
  - Negative inotropy
  - Relief of LVOTO
  - Lusitropy

Step in the right direction

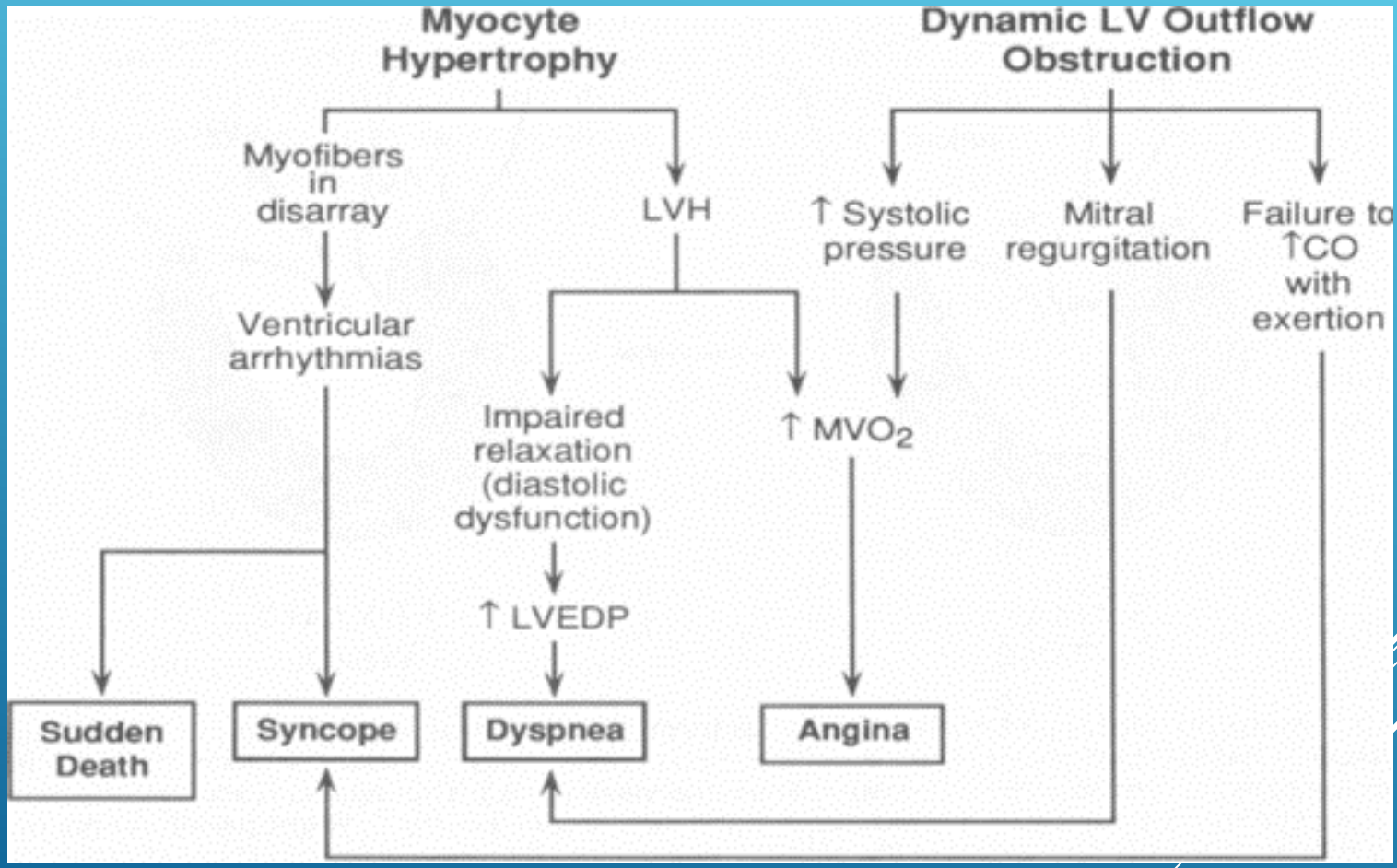
- Complicated label
- PK/PD relationship
- Echo monitoring
- Drug-drug interactions
  - Major issue for pharmacists and for workflow
- Systolic dysfunction
  - Complicates care
- REMS program
- Fetal teratogenicity
- Expensive
  - Medication cost (> $89,000 / year)
  - Monitoring cost

Aficamten

- Binds to a different site than mavacamten
- Shorter half life (3.4 days)
- Consistent PK/PD relationship
- Monitoring will likely be different
- No significant drug-drug interactions
- Appears promising in non-obstructive HCM

- Maron, Masri et al. JACC 2023, Owens, Masri et al. JCF 2023 , Coats,..., Masri et al. JACC HF 2023

PATHOPHYSIOLOGY



PHYSICAL EXAM

Bisferiens pulse ("spike and dome")
S4 gallop
Crescendo/Descrescendo systolic ejection murmur

HOCM vs. Valvular AS

Intensity of murmur	HOCM	AS
Valsalva (↓preload, ↓ afterload)	↑	↓
Squatting (↑ preload, ↑ afterload)	↓	↑
Standing (↓preload, ↓ afterload)	↑	↓

Holosystolic apical blowing murmur of mitral regurgitation

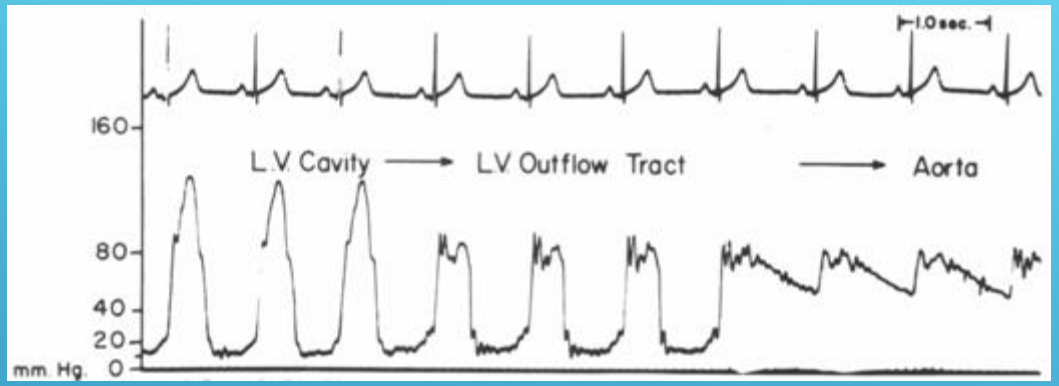
DIAGNOSTIC STUDIES

- EKG
  - NSR
  - LVH
  - septal Q waves
- 2D-Echocardiography
  - LVH; septum >1.4x free wall
  - LVOT gradient by Doppler
  - Systolic anterior motion of the mitral valve
- Cardiac Catheterization
  - LVOT gradient and pullback
  - provocative maneuvers
  - Brockenbrough phen

HCM-ASH using contrast

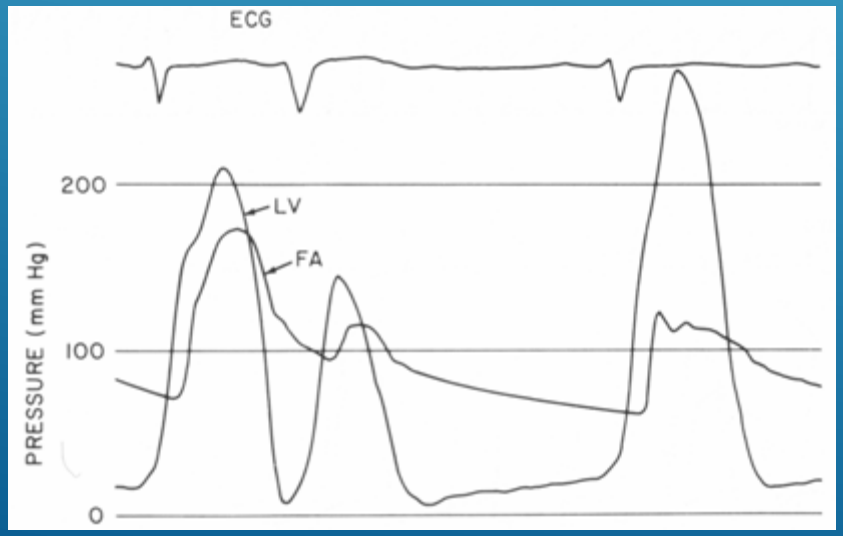
CARDIAC CATHETERIZATION

LV pullback



Brockenbrough-Braunwald Sign

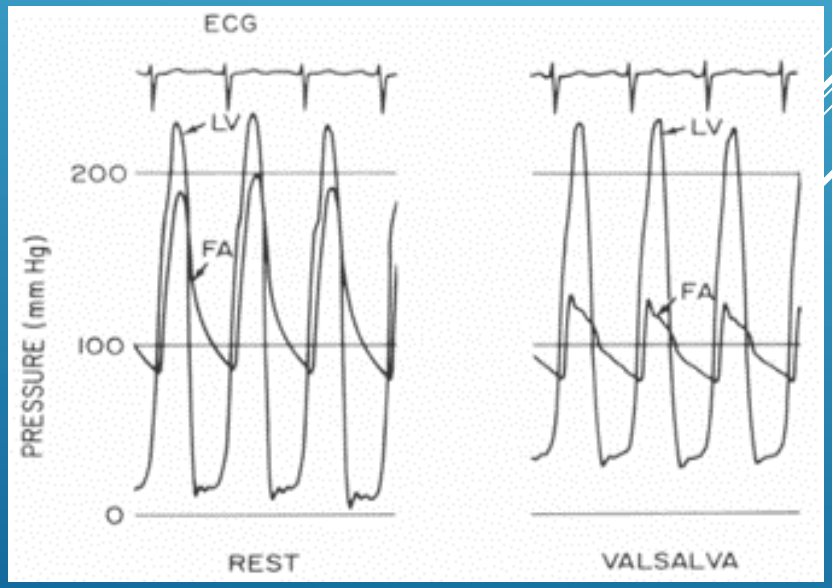
failure of aortic pulse pressure to rise post PVC



Provocative maneuvers:

Valsalva

amyl nitrate inhalation



TREATMENT

For symptomatic benefit

β-blockers

↓ mvO2

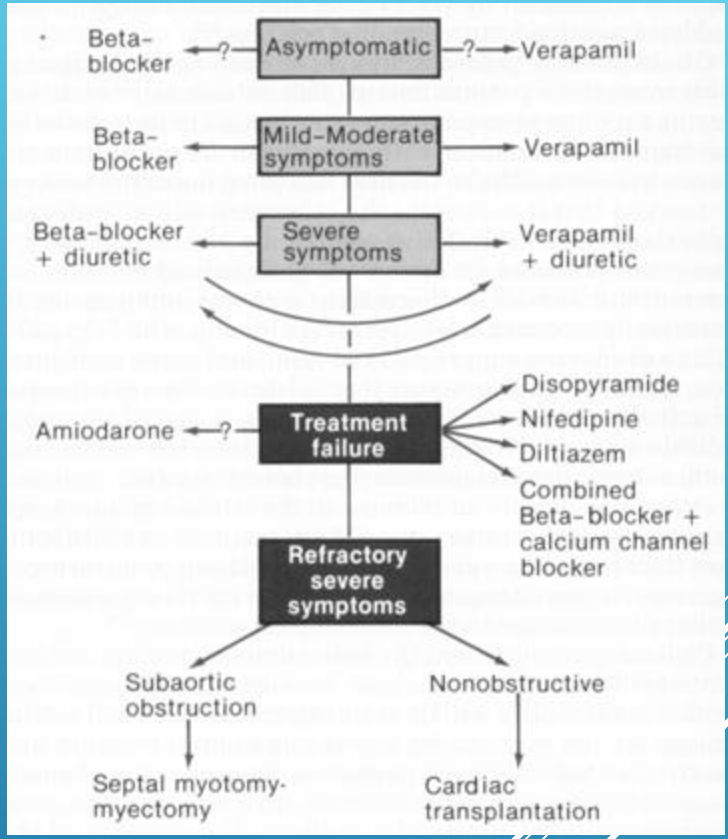
↓ gradient (exercise)

↓ arrythmias

Calcium Channel blockers

AICD for sudden death

Antibiotic prophylaxis for endocarditis



HCM: SURGICAL TREATMENT

For severe symptoms with high outflow gradient

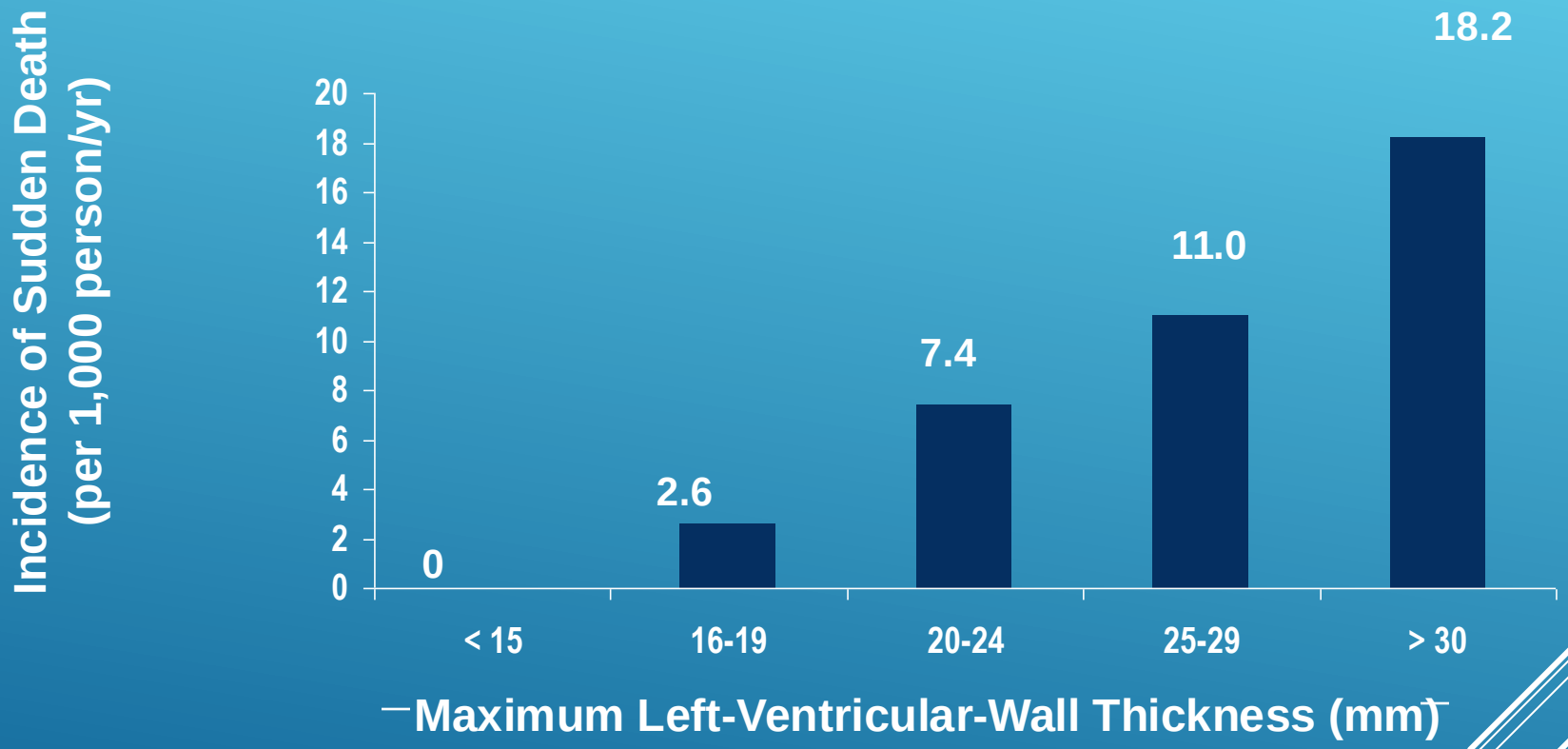
Myomyectomy

- removal of small portion of upper IV septum
- +/- mitral valve replacement
- 5 year symptomatic benefit in ~ 70% of patients

ETOH septal ablation

AICD to prevent sudden death

WALL THICKNESS AND SUDDEN DEATH IN HCM



Spirito P. *N Engl J Med*. 2000;342:1778-1785.

AICD INDICATIONS

- Survivors of SCD
- Non-Sustained VT
- Family hx of SCD in young family members
- Septal thickness ≥30 mm
- Uexplained syncope

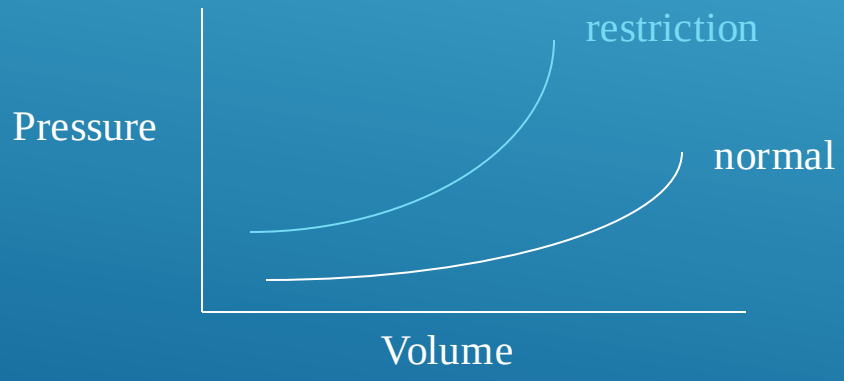
RESTRICTIVE CARDIOMYOPATHY

Characterized by:

• impaired ventricular filling due to an abnormally stiff (rigid) ventricle

•normal systolic function

•intraventricular pressure rises precipitously with small increases in volume



Causes : infiltration of myocardium by abnormal substance
fibrosis or scarring of endocardium

AMYLOIDOSIS

Amyloidosis is caused by protein misfolding in which extracellular aggregates of the misfolded proteins form fibrils

Immunoglobulin light chain Amyloid and Transthyretin ATTR Amyloid

Restriction caused by replacement of normal myocardial contractile elements by infiltrative interstitial deposits

Amyloidosis-2 types

- AL-monoclonal immunoglulin light chains produced in bone marrow plasma disorders
  - 2200 new cases/yr
  - Affects all organs except brain (60% with cardiac involvement)-considered more aggressive
- ATTR-transthyretin-a transport protein mainly produced by the liver
  - incidence increasing as recognition and diagnostic capabilities improve
  - Wild type (wt)-genetically normal protein-previously known as senile or age-related
  - Hereditary (h)-due to genetic mutations that cause TTR protein to misfold->130 TTR known variants

Amyloidosis-2 types

Thus you have:

- AL-CA
- ATTRwt-CA
- ATTRh-CA

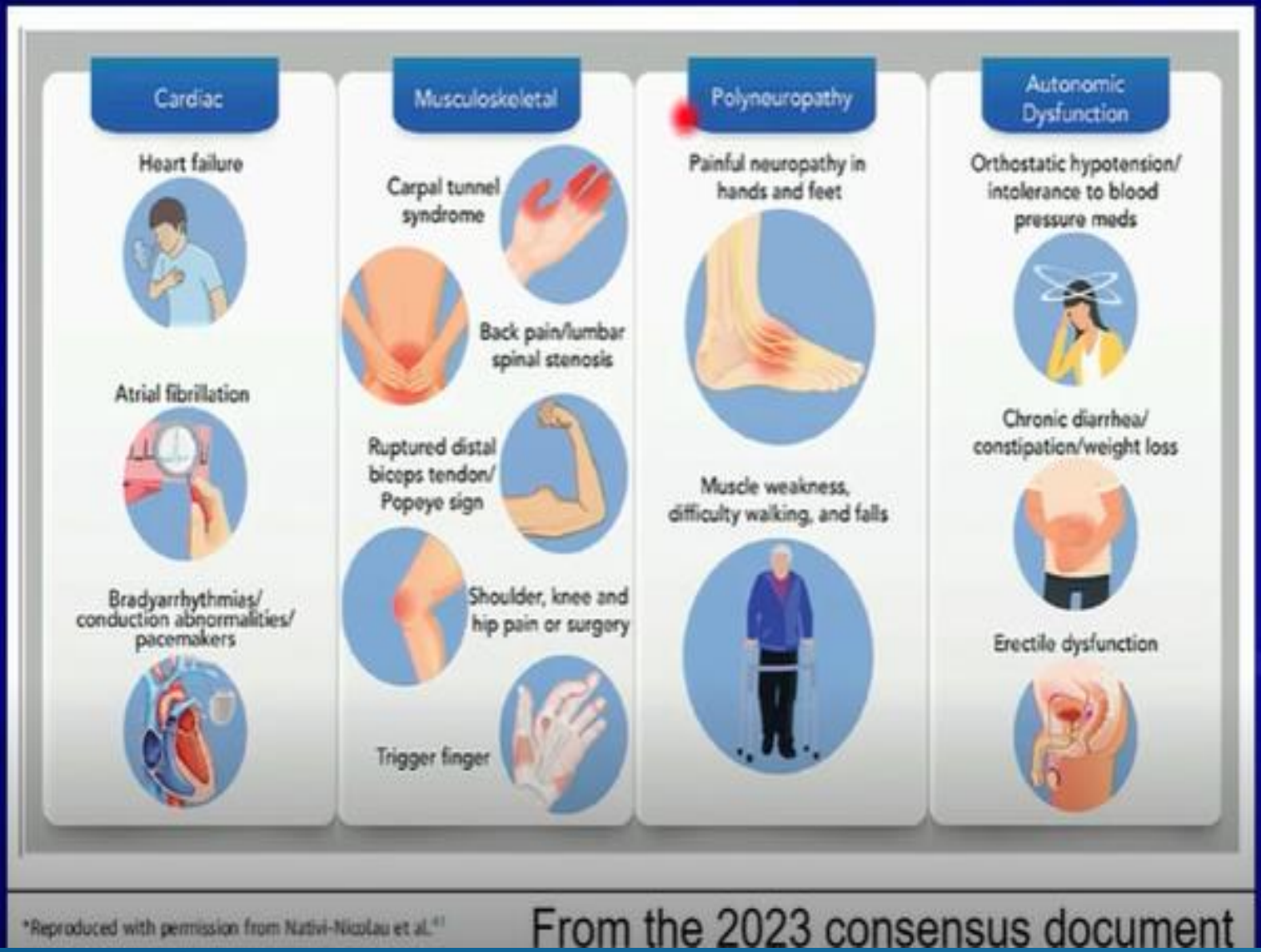
Each type with different implications for long-term outcome

Treatment varies by type

Recognition of CA

- Some clues to diagnosis of amyloidosis:
  - HFpEF
    - ATTR-CM found in 13% of pts diagnosed with HFpEF
  - Left ventricular hypertrophy especially if out of proportion to degree of HTN or aortic stenosis
    - ATTR-CM found in 16% of pts undergoing AVR for AS
  - Orthopedic problems including spinal stenosis, carpal tunnel syndrome, rupture of biceps tendon
  - Nephrotic syndrome
  - Hepatomegaly

Clinical Manifestations of Amyloidosis



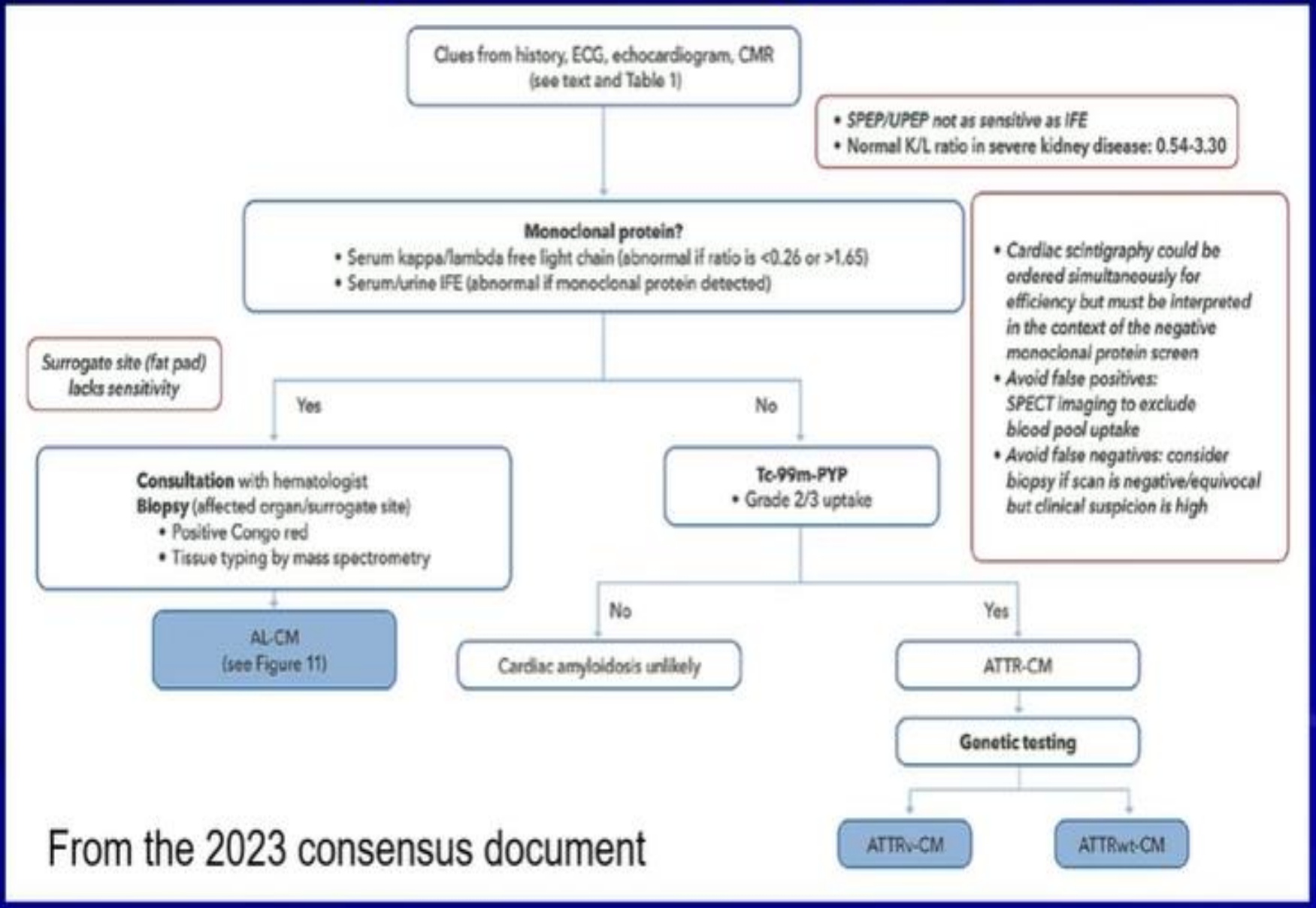
*Reproduced with permission from Nativi-Nicolau et al.[41]

From the 2023 consensus document

Diagnostic Testing

- ECG-low voltage seen in 30%
- Echocardiography
  - ”LVH”, RVH, granular speckled pattern, diastolic dysfunction, low flow/low gradient AS, abnormal strain pattern with apical sparing
- Cardiac MRI
  - Diffuse subendocardial and/or transmural LGE
- Serum and urine protein electrophoresis and serum free light chains
- Nuclear scintigraphy (PYP scan)-if SPEP, UPEP negative
  - 100% specific for ATTR CM
- Biopsy-to make diagnosis of AL CS
- Biomarkers-BNP, troponin-both likely elevated

Diagnostic Testing for CA



From the 2023 consensus document

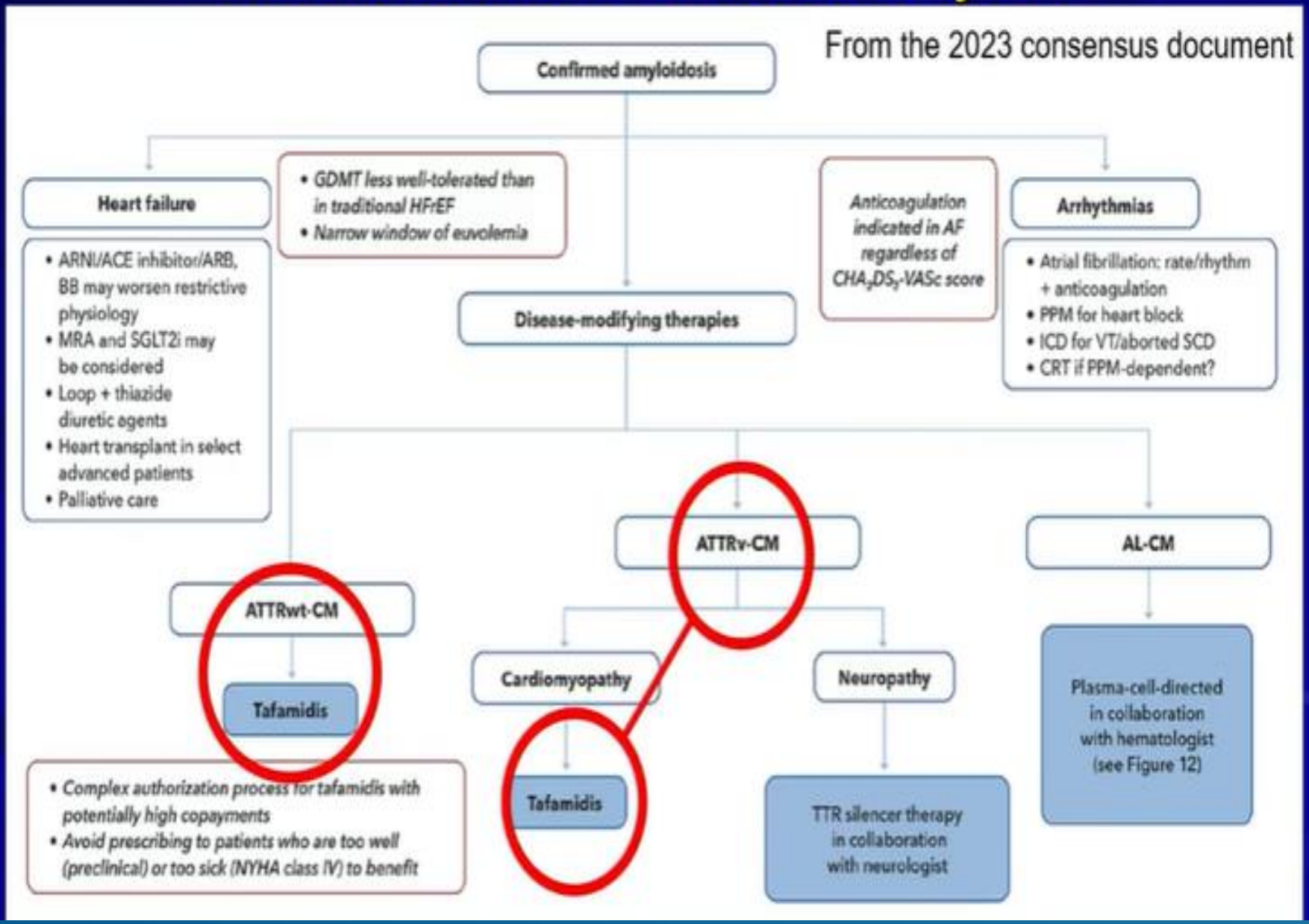
Atrial Arrhythmias in CA

- AF incidence in up to 56% in AL-CA and 70% in ATTR-CA
- Rate control typically not well tolerated
  - Due to loss of atrial contribution in setting of diastolic dysfunction
  - Beta blockers not well tolerated because pts with CA are heart rate dependent due to low fixed stroke volume
  - Diltiazem and digoxin bind avidly to amyloid fibrils and can have exaggerated effect and are usually avoided
- Amiodarone is first line rhythm control AAD choice
  - Flecainide and propafenone contraindicated in presence of scar
  - Many pts with CA have CKD and therefore dofetilide and sotalol may not be acceptable

Atrial Arrhythmias in CA

- High risk of thromboembolism even in chronically anticoagulated pts
  - **All pts with CA and AF need to be on chronic oral anticoagulation regardless of CHA_2DS_2-VASc score**
  - **No studies on NOAC vs warfarin**
  - **TEE should be done before CV even if fully and chronically anticoagulated**
  - Role of LAAO unclear

Treatment of Cardiac Amyloid



Summary

- CA can cause difficult to treat heart failure and arrhythmias leading to high mortality rates in advanced disease
- Learn to recognize clues and initiate appropriate testing as early diagnosis and treatment key to improving outcome

SARCOIDOSIS

- Sarcoidosis is an inflammatory condition in which non-caseating granulomas involve multiple organs
- Restriction
- Conduction System Disease
- Ventricular Arrhythmias (Sudden Cardiac Death)

Current therapy involves glucocorticoids, supplemented by other immunosuppressive agents if necessary.

Sarcoidosis

- Etiology not entirely clear
  - General hypothesis is that environmental factors trigger immune response in (likely) genetically susceptible individuals
  - Body produces non-necrotizing granulomas leading to inflammation, injury and fibrosis in a variety of organs (lung, skin, eye)
- Cardiac sarcoid (CS)
  - Can occur in isolation (20-25% of cases) or together with extracardiac involvement

Clues and Diagnosis

- Consider CS
  - Unexplained high grade AV block
  - PVCs or VT with multiple (septal) morphologies
- Diagnostic tests:
  - Cardiac MRI
    - Late gadolinium enhancement (LGE) –basal septum and/or multiple areas
  - FDG-PET
    - Sites of inflammation avidly take up glucose
    - When combined with whole body scanning, can find extracardiac sarcoid
    - Repeat scans can assess treatment effect

Diagnosis

- Biopsy
  - Extracardiac
    - If other sites of inflammation/suspected sarcoid noted on PET or other imaging
  - Cardiac-RV
    - Targeted biopsy based on imaging
      - Areas of LGE or inflammation
      - 3-D mapping of low voltage areas to target

Treatment of CS

- Immunosuppression
  - To suppress active inflammation seen on PET
  - Prednisone first line
  - Methotrexate, azathioprine
  - Effect on ventricular arrhythmias is unpredictable
- Device therapy for the consequences of CS
  - heart block, ventricular arrhythmias, risk of SCD

Treatment of Arrhythmias in CS

- Antiarrhythmic medications
  - Class III AAD
  - Class I contraindicated in presence of scarring
- Ablation
  - Can be useful in VT storm
  - VT can be reentrant (scar) or triggered (inflammation)
  - Timing related to immunosuppression not clearly worked out

Factors Associated with Poor Prognosis in CS

More ominous

- Decreased LV and/or RV EF
- Extensive scarring
- Presentation with sustained VT, aborted SCD, heart failure
- Isolated CS
- Definite (EMB proven) CS

Less Ominous

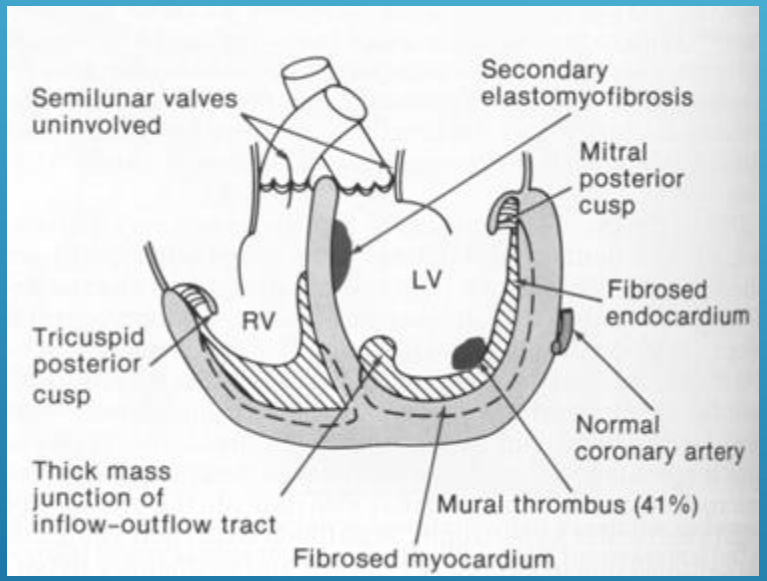
- Preserved LV function
- Presentation with lone AV block
- Probable (extracardiac biopsy proven) CS

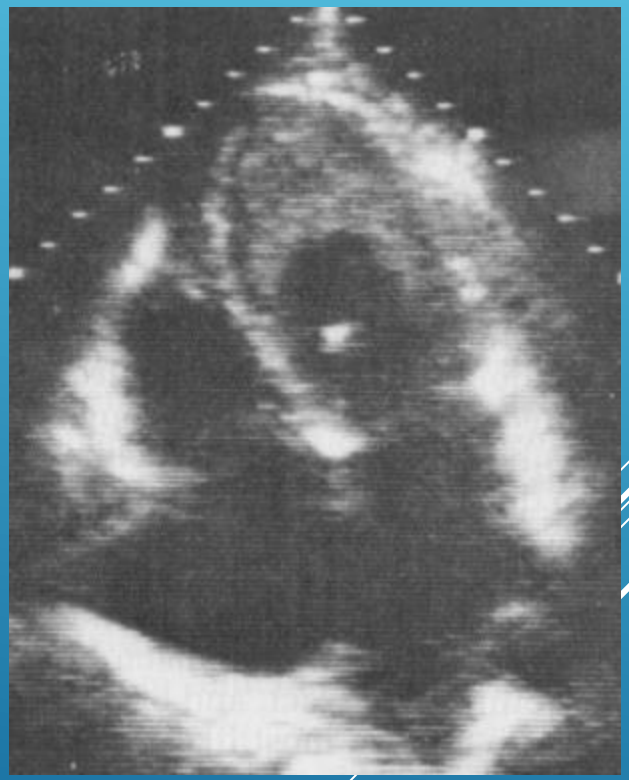
Summary

- Cardiac sarcoid and cardiac amyloid are increasing in incidence
  - Likely due to greater recognition
- Treatments aim to modify disease and prevent the consequences of disease
- Multidisciplinary care is very important in both conditions

ENDOMYOCARDIAL FIBROSIS

Endemic in parts of Africa, 15-25% of cardiac deaths in equatorial Africa
hypereosinophilic syndrome (Loffler's endocarditis)





Thickening of basal inferior wall
endocardial deposition of thrombus
apical obliteration
mitral regurgitation
80-90% die within 1-2 years

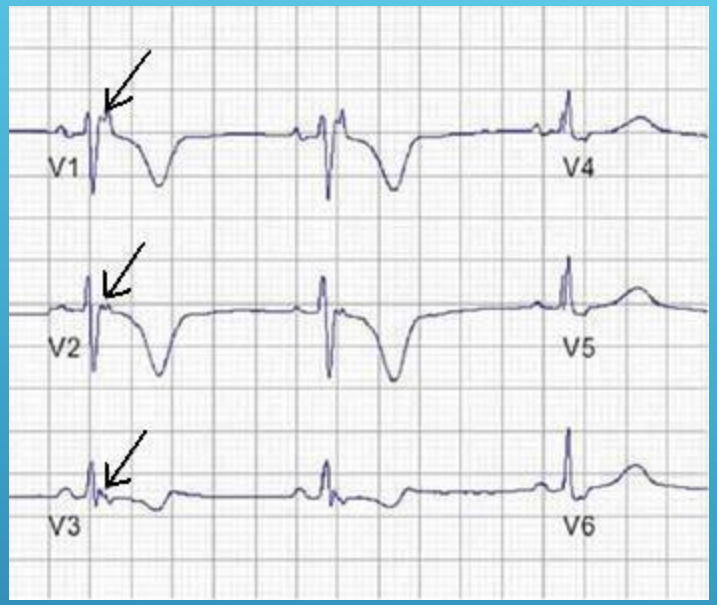
ARRHYTHMOGENIC RV DYSPLASIA(ARVD)

- Myocardium of RV free wall replaced:
  - Fibrofatty tissue
  - Regional wall motion/function is reduced
- Ventricular arrhythmias
  - SCD in young

ARVD

- Abnormalities in intercellular adhesion molecules, desmosomes, cause cell death and fibrofatty replacement.
- These abnormalities are caused by mutations in genes, such as *PKP2* and *DSP*, encoding plakophilin 2 and desmoplaking, respectively. Inheritance in most cases is by Mendelian dominant transmission.
- The epsilon wave of delayed repolarization following the QRS complex is helpful in diagnosis.
- Contrast-enhanced cardiac magnetic resonance (CMR)

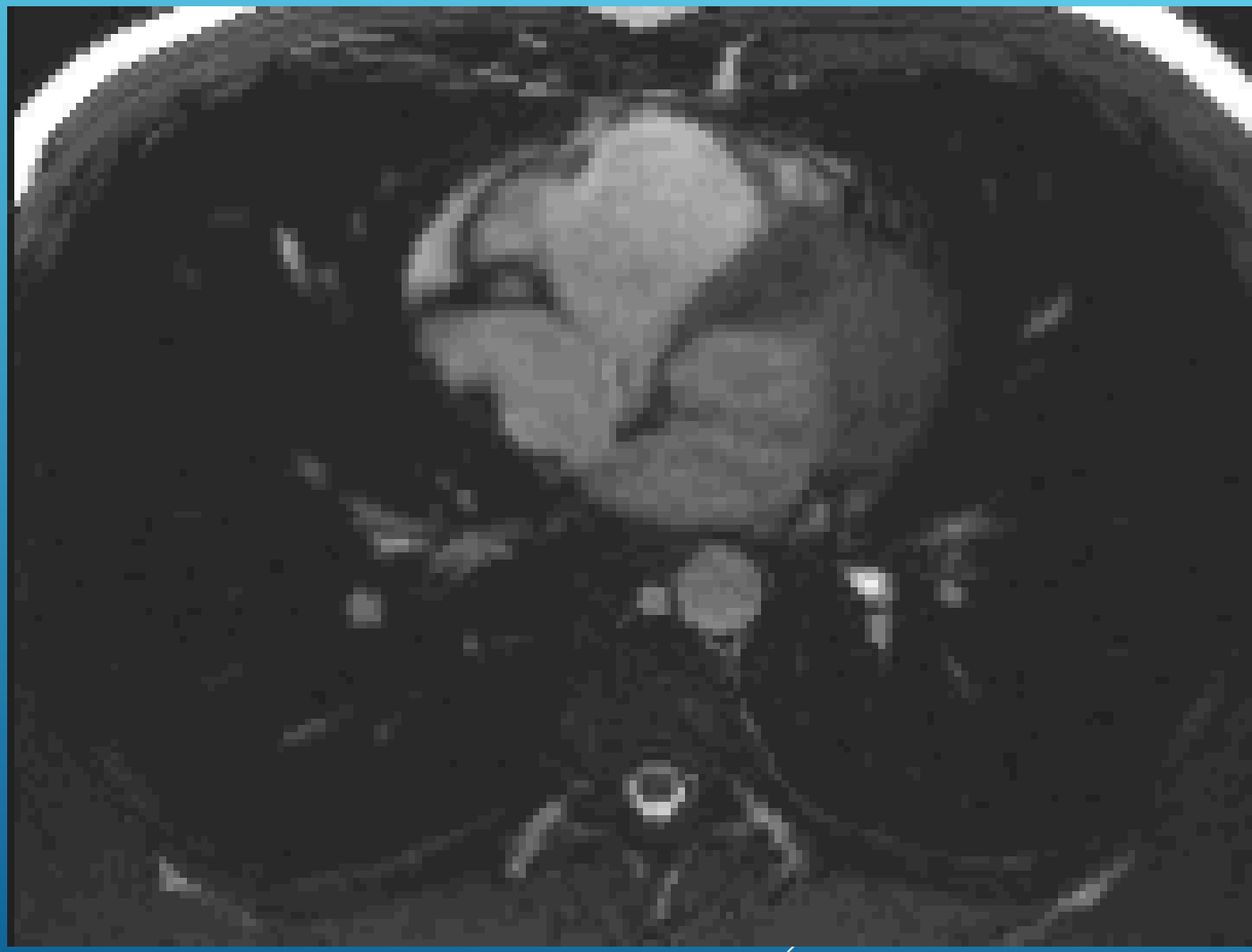
ARVD ECG-EPSILON WAVE



ARVD TREATMENT

- Treatment consists of the cessation of heavy physical exertion and competitive athletics.
- recurrent ventricular tachycardia, epicardial catheter ablation may be effective. Implantation of a cardioverter/defibrillator is indicated in patients who have experienced ventricular fibrillation or refractory ventricular tachycardia.
- Patients with intractable HF may require cardiac transplantation.
- Genetic screening should be performed in family members

MRI: RV DYSPLASIA



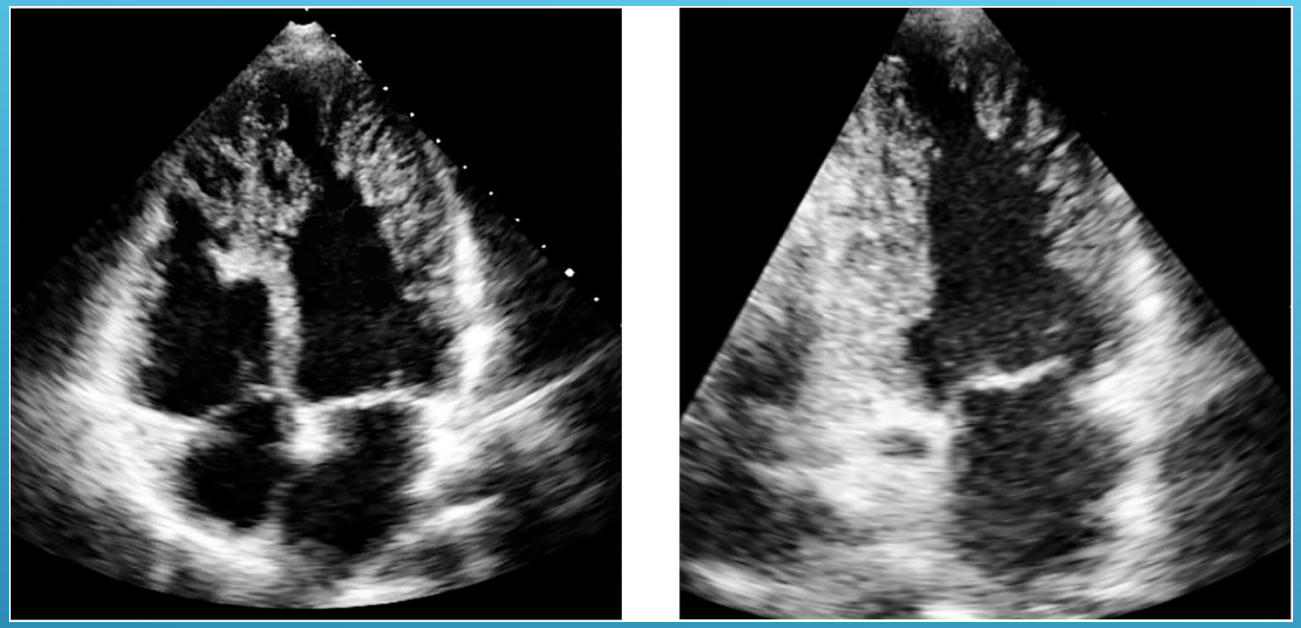
LV NONCOMPACTION

Diagnostic Criteria

- Prominent trabeculations, deep recesses in LV apex

Prognosis and Treatment

- Increased risk of CHF, VT/SCD, thrombosis
- Hereditary risk
  - Screening of offspring



LV NONCOMPACTION

THANK YOU