Baptist Health
HEART INSTITUTE

What's with all these "new" Cardiomyopathies?

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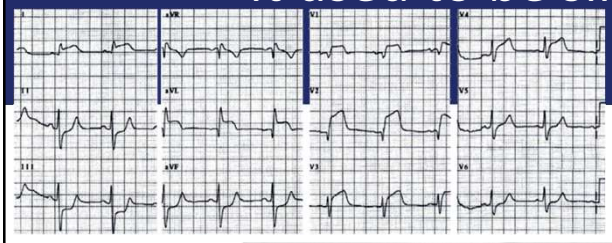
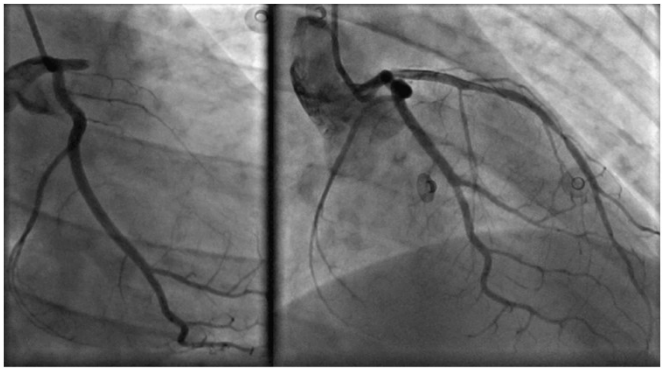
Disclosures: None

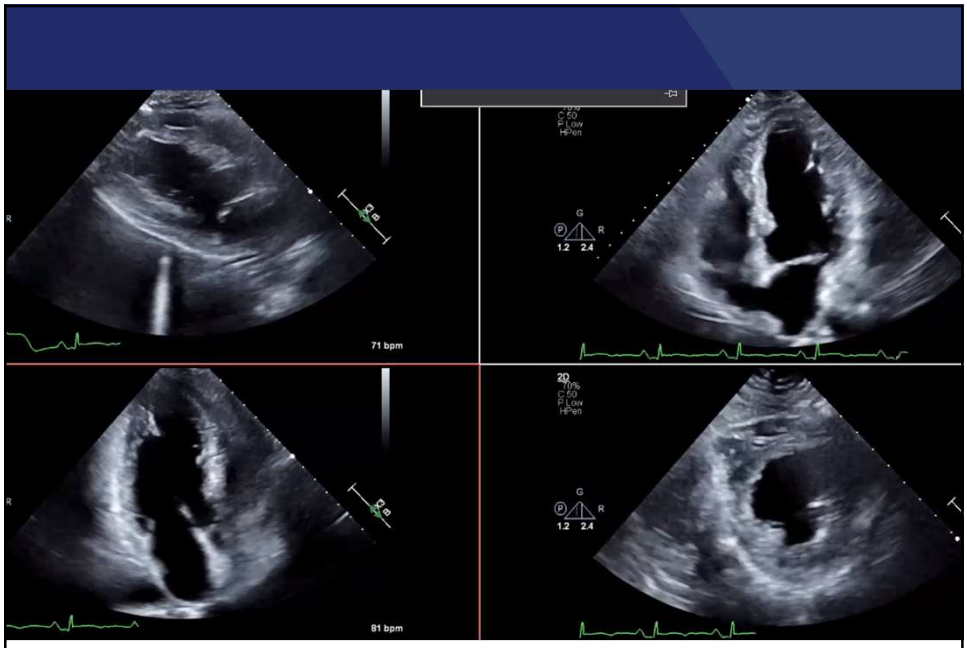
Where are we headed? (aka “Objectives”)

- Identify emerging types of cardiomyopathies.
- Discuss diagnostic pathways and imaging strategies.
- Review current treatment options and clinical implications

It used to be simple







Types of Cardiomyopathies

- Ischemic
- Nonischemic
  - Hypertrophic
  - Infiltrative
    - Amyloidosis
    - Sarcoidosis
  - Other

Ischemic Cardiomyopathy: AKA “the OG”

- Guideline Directed Medical Therapy (GDMT) depending on the Left Ventricular Ejection Fraction (LVEF): <40%, or 40-50%.
- Optimal Medical Therapy (OMT): beta blockade, ACEi/ARB/ARNi
- Antiplatelets
- Lipid reduction (statins, ezetimibe, PCSK9i, etc)

Guideline Directed Medical Therapy (GDMT)

- For LVEF <40%:
  - Beta Blockers (class 1)
  - SGLT2i (class 1)
  - ACEi/ARB/ARNi (class 1)
  - Mineralocorticoid Receptor Antagonist (MRA) (class 1)
- For LVEF 40-50%
  - Diuretics (class 1)
  - SGLT2i (class 2a)
  - ACEi/ARB/ARNi, MRA, and BB (class 2b)

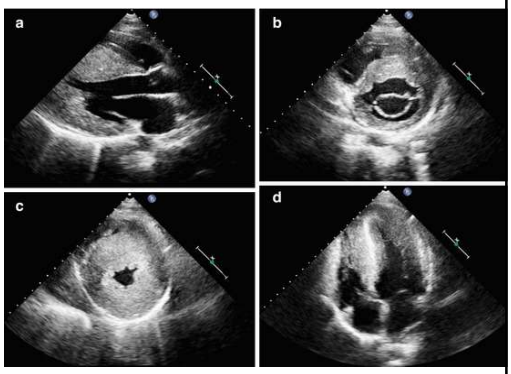
“Not Ischemic” Cardiomyopathy- the other heart failure

- If heart failure isn’t due to Coronary Artery Disease, then it fell under the umbrella “Nonischemic Cardiomyopathy”
- The diagnosis of “Nonischemic” is “Non-helpful”
  - Lack of tailored treatment
  - Likely reduced genetic/family screening

Heart Failure is no longer one disease - and now more than ever an accurate and precise diagnosis matters.

Hypertrophic Cardiomyopathy (HCM)

- Genetic disease with LV hypertrophy "independent" of LV loading conditions
- 0.2-0.5% of the population
- Both with and without LVOT obstruction



Hypertrophic Cardiomyopathy

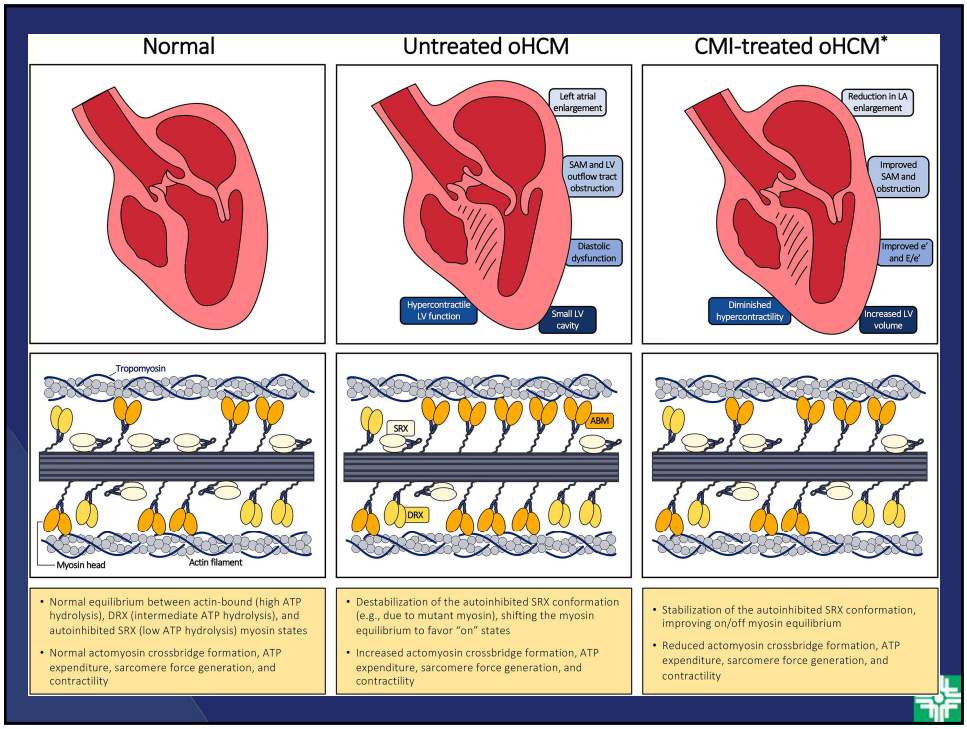
- Once the diagnosis has been made,
  - Today: control or reduce symptoms due to obstruction
  - Tomorrow: reduce the patient's risk of sudden cardiac death
  - The Future: genetic testing and evaluate relatives for extent of disease

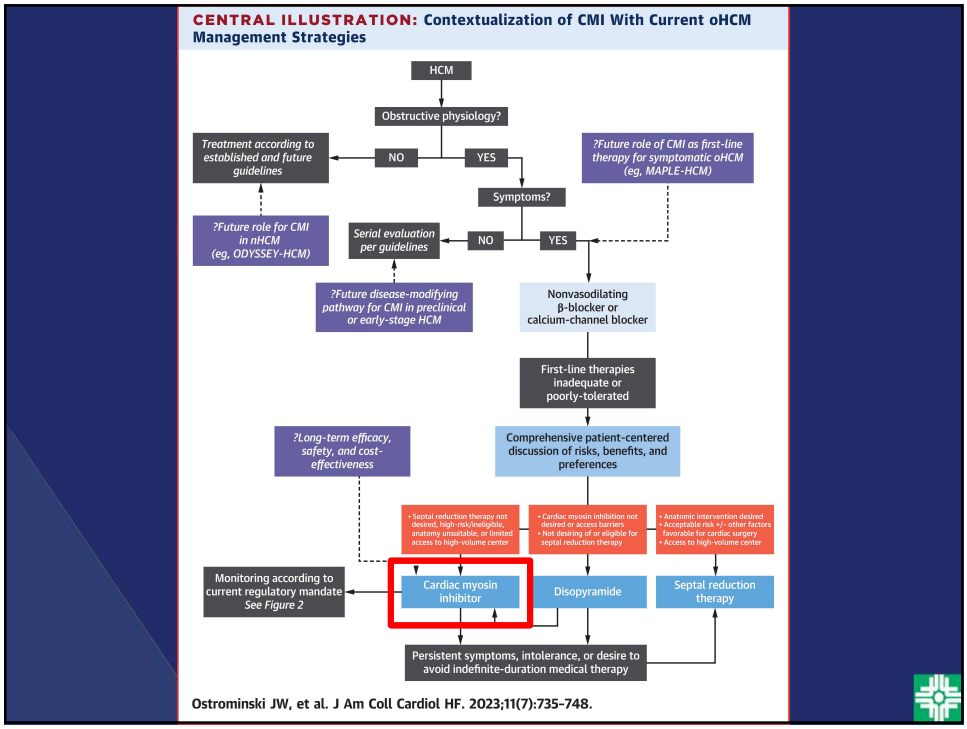
HCM: Today

- Controlling symptoms due to obstructive physiology
- Beta blockers in an attempt to reduce obstruction gradients
- Calcium channel blockers (non-dihydropyridine)
- Septal Reduction therapies when sxs refractory to meds
  - Surgical Myectomy
  - Alcohol Ablation

HCM: Today

- Novel Agents: Cardiac Myosin Inhibitors (CMI)
  - Mavacamten
  - Aficamten
- Essentially are inducing “heart failure,” an attempt to reduce hyperdynamic LV function down to normal, and reduce symptoms due to obstruction
- Very strict and rigorous surveillance protocols
- Myosin inhibitors so far are only used for symptomatic patients, have not yet shown a mortality benefit


Normal
Untreated oHCM
CMI-treated oHCM*
Left atrial enlargement
SAM and LV outflow tract obstruction
Diastolic dysfunction
Hypercontractile LV function
Small LV cavity
Reduction in LA enlargement
Improved SAM and obstruction
Improved e' and E/e'
Diminished hypercontractility
Increased LV volume
Tropomyosin
Myosin head
Actin filament
SRX
DRX
ABM
• Normal equilibrium between actin-bound (high ATP hydrolysis), DRX (intermediate ATP hydrolysis), and autoinhibited SRX (low ATP hydrolysis) myosin states
• Normal actomyosin crossbridge formation, ATP expenditure, sarcomere force generation, and contractility
• Destabilization of the autoinhibited SRX conformation (e.g., due to mutant myosin), shifting the myosin equilibrium to favor "on" states
• Increased actomyosin crossbridge formation, ATP expenditure, sarcomere force generation, and contractility
• Stabilization of the autoinhibited SRX conformation, improving on/off myosin equilibrium
• Reduced actomyosin crossbridge formation, ATP expenditure, sarcomere force generation, and contractility


CENTRAL ILLUSTRATION: Contextualization of CMI With Current oHCM Management Strategies
HCM
Obstructive physiology?
NO
YES
Treatment according to established and future guidelines
?Future role of CMI as first-line therapy for symptomatic oHCM (eg, MAPLE-HCM)
Symptoms?
?Future role for CMI in nHCM (eg, ODYSSEY-HCM)
Serial evaluation per guidelines
NO
YES
?Future disease-modifying pathway for CMI in preclinical or early-stage HCM
Nonvasodilating β-blocker or calcium-channel blocker
First-line therapies inadequate or poorly-tolerated
?Long-term efficacy, safety, and cost-effectiveness
Comprehensive patient-centered discussion of risks, benefits, and preferences
• Septal reduction therapy not desired, high-risk/ineligible, anatomy unsuitable, or limited access to high-volume center
• Cardiac myosin inhibition not desired or access barriers
• Not desiring of or eligible for septal reduction therapy
• Anatomic intervention desired
• Acceptable risk +/- other factors favorable for cardiac surgery
• Access to high-volume center
Monitoring according to current regulatory mandate See Figure 2
Cardiac myosin inhibitor
Disopyramide
Septal reduction therapy
Persistent symptoms, intolerance, or desire to avoid indefinite-duration medical therapy
Ostrominski JW, et al. J Am Coll Cardiol HF. 2023;11(7):735-748.

HCM: Tomorrow

It's all about Sudden Cardiac Death risk reduction

Recommendations for ICD Placement in High-Risk Patients With HCM
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

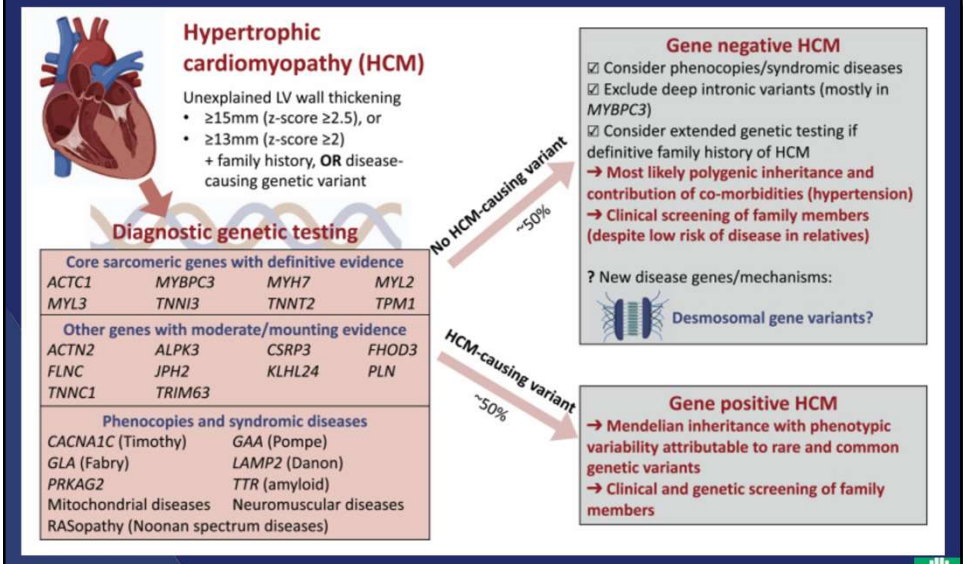
COR	LOE	Recommendations
1	C-EO	1. In patients with HCM, application of individual clinical judgment is recommended when assessing the prognostic strength of conventional risk marker(s) within the clinical profile of the individual patient, as well as a thorough and balanced discussion of the evidence, benefits, and estimated risks to engage the fully informed patient's active participation in ICD decision-making.[1–5]
1	B-NR	2. For patients with HCM and previous documented cardiac arrest or sustained VT, ICD placement is recommended (Figure 3, Table 8).[2–6]

2a	B-NR	3. For adult patients with HCM with ≥1 major risk factors for SCD, it is reasonable to offer an ICD. These major risk factors include (Figure 3, Table 8)[2,3,7–21]: a. Sudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 years of age; b. Massive LVH ≥30 mm in any LV segment; c. ≥1 recent episodes of syncope suspected by clinical history to be arrhythmic (ie, unlikely to be of neurocardiogenic [vasovagal] etiology, or related to LVOTO); d. LV apical aneurysm with transmural scar or LGE; e. LV systolic dysfunction (EF <50%).
2a	B-NR	4. For children with HCM who have ≥1 conventional risk factors, including unexplained syncope, massive LVH, NSVT, or family history of early HCM-related SCD, ICD placement is reasonable after considering the relatively high complication rates of long-term ICD placement in younger patients (Figure 3, Table 8).[22–30]
2a	B-NR	5. For patients with HCM with ≥1 major SCD risk factors, discussion of the estimated 5-year sudden death risk and mortality rates can be useful during the shared decision-making process for ICD placement (Figure 3, Table 8).[3,19,29,30]

2b	B-NR	6. In select adult patients with HCM and without major SCD risk factors after clinical assessment, or in whom the decision to proceed with ICD placement remains otherwise uncertain, ICD may be considered in patients with extensive LGE by contrast-enhanced CMR imaging or NSVT present on ambulatory monitoring (Figure 3, Table 8).[2,3,16,19,31–33]
2b	B-NR	7. In pediatric patients with HCM, it can be useful to consider additional factors such as extensive LGE on contrast-enhanced CMR imaging and systolic dysfunction in risk stratification for ICD shared decision-making (Figure 3, Table 8).[34,35]

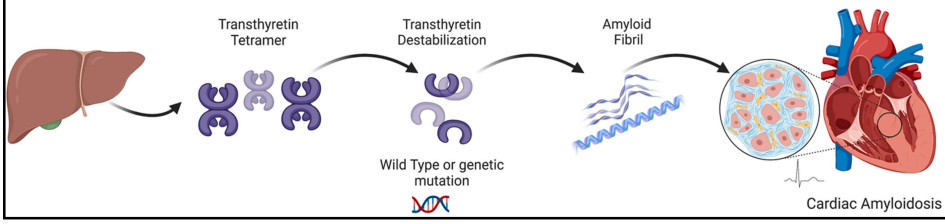
3: Harm	**B-NR**	8. In patients with HCM without risk factors, ICD placement should not be performed.[2]
3: Harm	**B-NR**	9. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed.[36]

HCM: Future



Transthyretin Amyloidosis (ATTR)

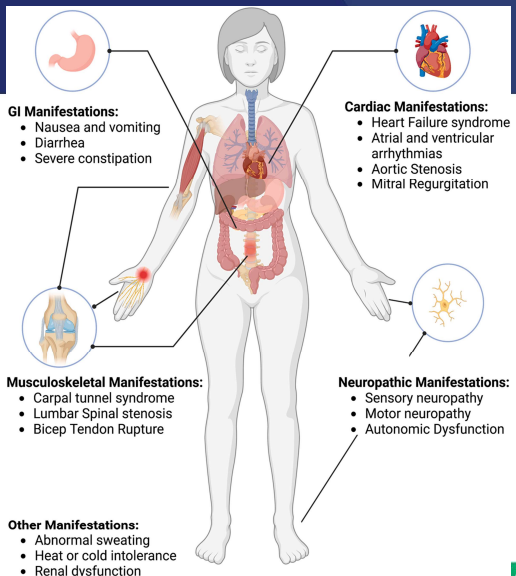
- Due to misfolded Transthyretin (TTR) deposition in the myocardium, leading to a progressive restrictive heart failure.
- 2 different versions:
  - Wild type (age related)
  - Hereditary (mutant TTR)



Transthyretin Amyloidosis (ATTR)

Clinical Pearls

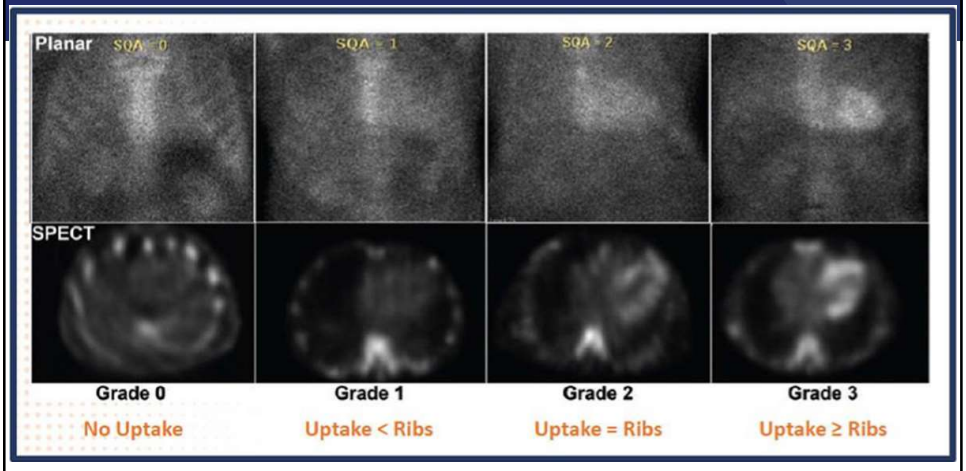
- HFpEF + LVH
- Bilateral Carpal Tunnel
- Biceps Tendon Rupture
- Aortic Stenosis + Heart Failure



Transthyretin Amyloidosis (ATTR)

- Initial workup:
  - Transthoracic Echo: likely concentric LVH with diastolic dysfunction
  - EKG: low voltage or pseudoinfarct pattern
  - Labwork: serum free light chains, serum and urine protein electrophoresis (SPEP, UPEP) must be obtained to rule out Primary Amyloidosis
  - PYP Scan (bone scintigraphy): showing cardiac deposition of TTR

PYP scan



Primary (Light Chain) Amyloidosis

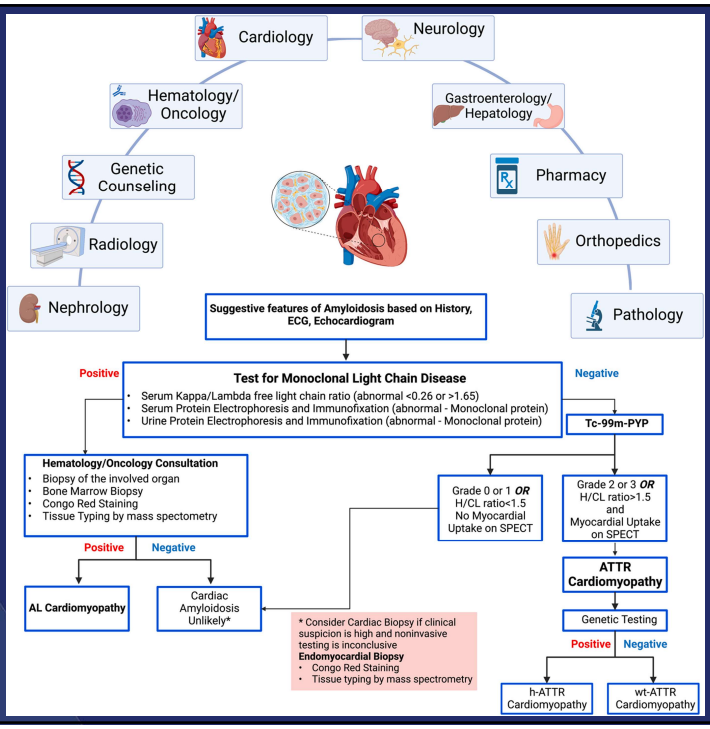
- Similar in clinical presentation of ATTR, but rather is due to malignant amyloid light chain deposition.
- To diagnose ATTR, you MUST exclude light chain amyloidosis as it is associated with a significantly worse prognosis and requires chemotherapy-based treatment.
- Prompt Oncology referral

Transthyretin Amyloidosis (ATTR) Treatment

- GDMT (ACEi/ARB/ARNi, SGLT2i, and MRA)
  - with the caveat that beta blockers are not always well tolerated given the infiltrative nature.

Transthyretin Amyloidosis (ATTR) Specific Treatment

- Disease modifying therapies
  - Tafamidis:
    - Binds TTR tetramer
    - reduced mortality and HF hospitalizations
  - Acoramidis:
    - TTR stabilizer
    - Reduced mortality and HF hospitalizations
  - Vutrisiran:
    - A hepatic TTR mRNA silencer, to reduce the production of pathogenic TTR



Cardiac Sarcoidosis

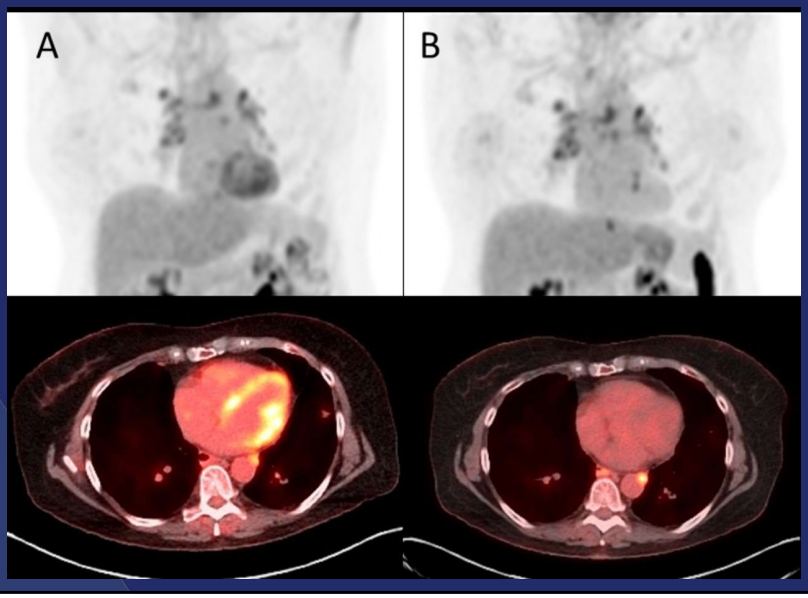
- Inflammatory granulomatous disease involving the myocardium
  - Leads to LV dysfunction, arrhythmias, and conduction disease
- Clinical Pearls
  - Unexplained AV block or conduction disease
  - Ventricular Arrhythmias
  - Known extracardiac sarcoid

Cardiac Sarcoidosis

Diagnosis:

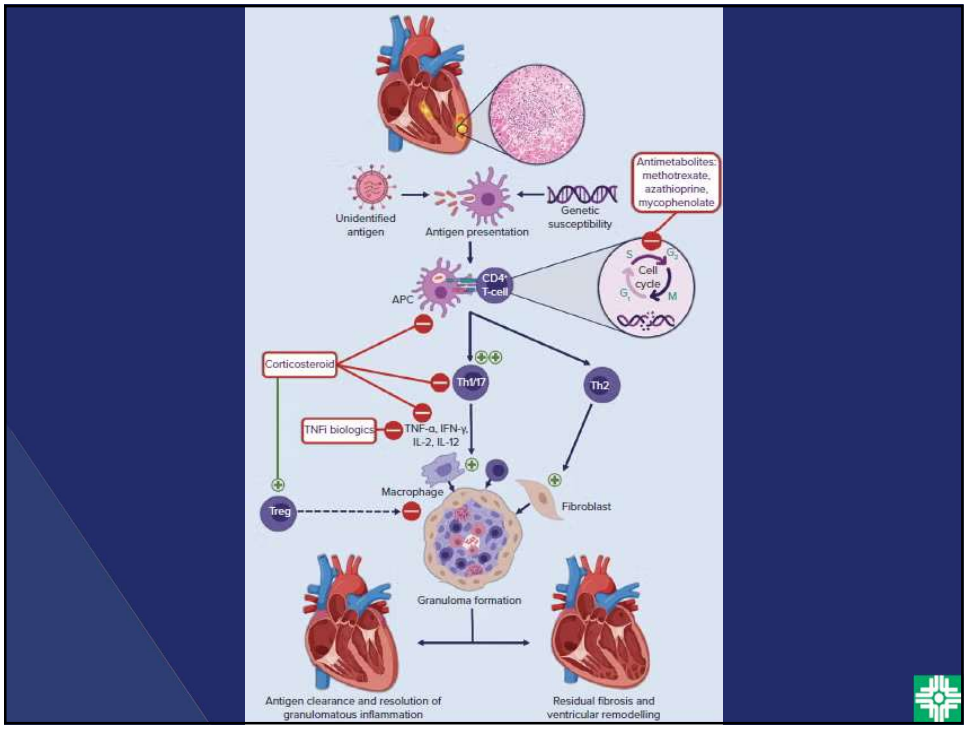
- Cardiac MRI (CMR) can identify areas of scar/fibrosis, along with T2 to evaluate for edema
  - "patchy" pattern of scar (or "late gadolinium enhancement")
- Endomyocardial biopsy has low sensitivity
- FDG-PET best to identify extent of active inflammation, can be used to monitor response to therapies with serial exams.

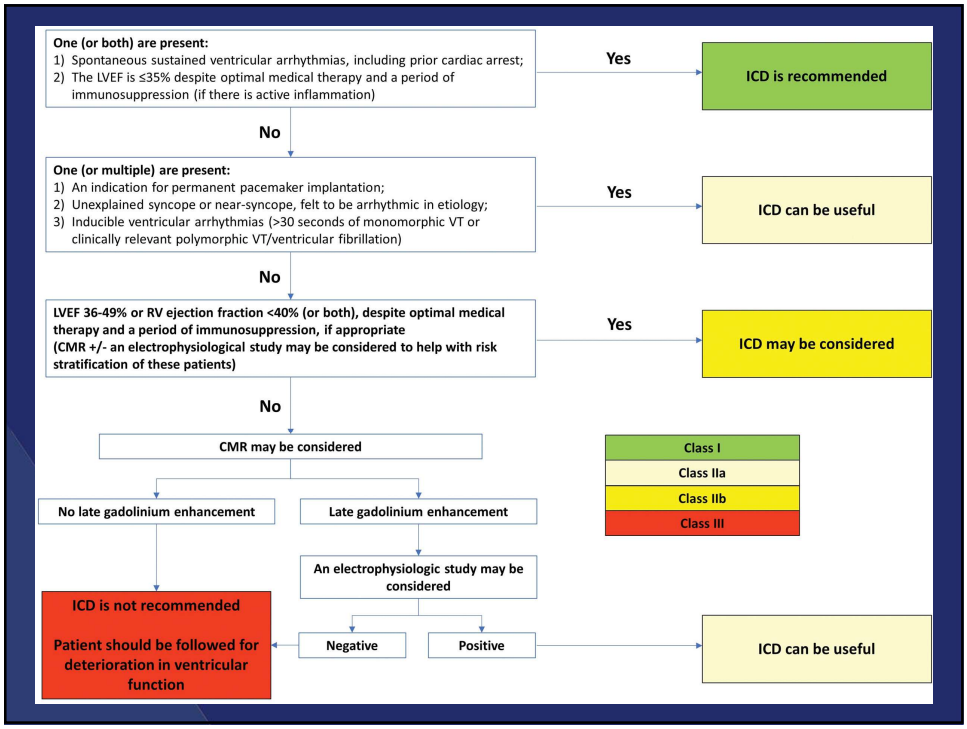
Cardiac Sarcoidosis



Cardiac Sarcoidosis Treatment

- Immunosuppression
  - Corticosteroids
  - Methotrexate, Mycophenolate, Azathioprine, or Leflunomide
  - For worsening inflammation despite 6-12 months of maximally tolerated above: add biologic agent (inflixamab or adalimumab)
- Standard GDMT (BB, ACEi/ARB/ARNi, SGLT2i, and MRA)
- Consideration for ICD, due to significant arrhythmic risk
- Consider early referral to Advanced Heart Failure specialist


Unidentified antigen
Antigen presentation
Genetic susceptibility
Antimetabolites: methotrexate, azathioprine, mycophenolate
Cell cycle
APC
CD4+ T-cell
Corticosteroid
Th1/17
Th2
TNFi biologics
TNF-α, IFN-γ, IL-2, IL-12
Macrophage
Treg
Fibroblast
Granuloma formation
Antigen clearance and resolution of granulomatous inflammation
Residual fibrosis and ventricular remodelling


One (or both) are present:
1) Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest;
2) The LVEF is ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)
Yes
ICD is recommended
No
One (or multiple) are present:
1) An indication for permanent pacemaker implantation;
2) Unexplained syncope or near-syncope, felt to be arrhythmic in etiology;
3) Inducible ventricular arrhythmias (>30 seconds of monomorphic VT or clinically relevant polymorphic VT/ventricular fibrillation)
Yes
ICD can be useful
No
LVEF 36-49% or RV ejection fraction <40% (or both), despite optimal medical therapy and a period of immunosuppression, if appropriate
(CMR +/- an electrophysiological study may be considered to help with risk stratification of these patients)
Yes
ICD may be considered
No
CMR may be considered
Class I
Class IIa
Class IIb
Class III
No late gadolinium enhancement
Late gadolinium enhancement
An electrophysiologic study may be considered
ICD is not recommended
Patient should be followed for deterioration in ventricular function
Negative
Positive
ICD can be useful

Dilated Cardiomyopathy

The current “Umbrella” diagnosis

Causes:

- Genetic
- Inflammatory (i.e. myocarditis)
- Peripartum
- Takotsubo
- Chemotherapy/toxic

Honorable Mentions

- Hemochromatosis
- Mitochondrial Cardiomyopathy
- Glycogen Storage Disease (Fabry’s Disease)
- LV Noncompaction

Thank You