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HEART CENTER

CLINICAL/THERAPEUTIC APPROACHES TO THREE SPECIFIC CARDIOMYOPAHIES: *MYOCARDITIS, AMYLOIDOSIS, AND NON-COMPACTION*

G. William Dec, MD, FACC

Massachusetts General Hospital

Harvard Medical School

American College of Cardiology

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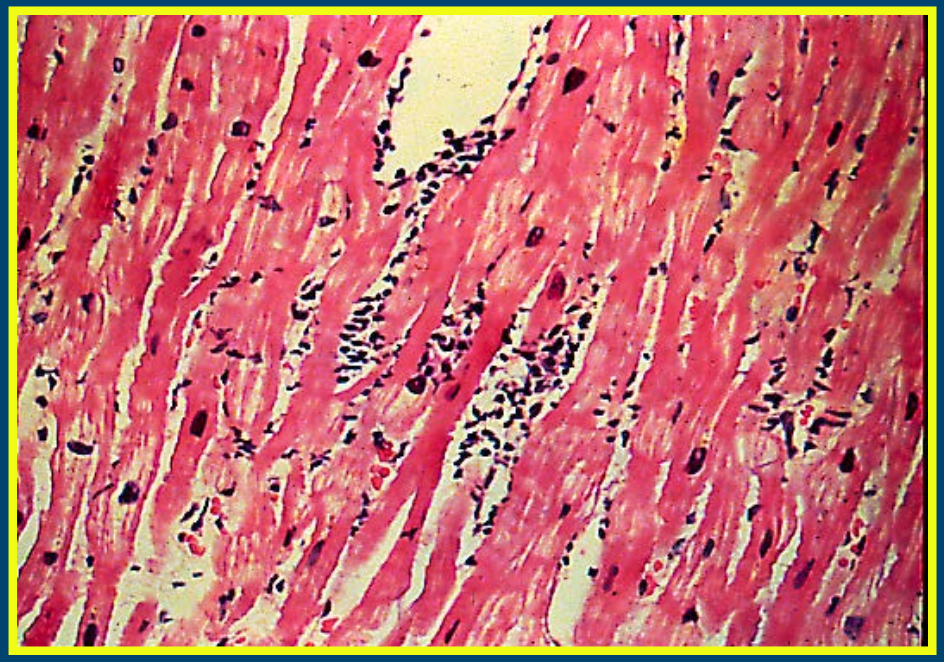
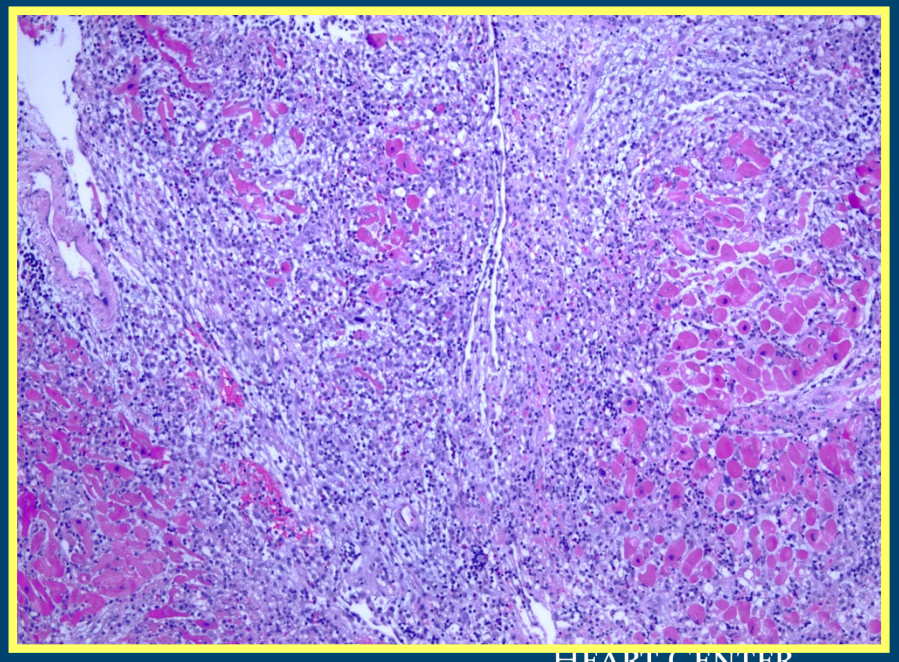
Disclosures: None

A Teaching Affiliate of Harvard Medical School

HISTOPATHOLOGY OF ACUTE MYOCARDITIS

Myocarditis is a pathologic diagnosis made by endomyocardial biopsy, at the time of cardiac explantation, LVAD placement or at autopsy. It is histologically characterized by an inflammatory cellular infiltrate (lymphocytic, eosinophilic, granulomatous) that is associated with myocyte necrosis or degeneration ("Dallas criteria").

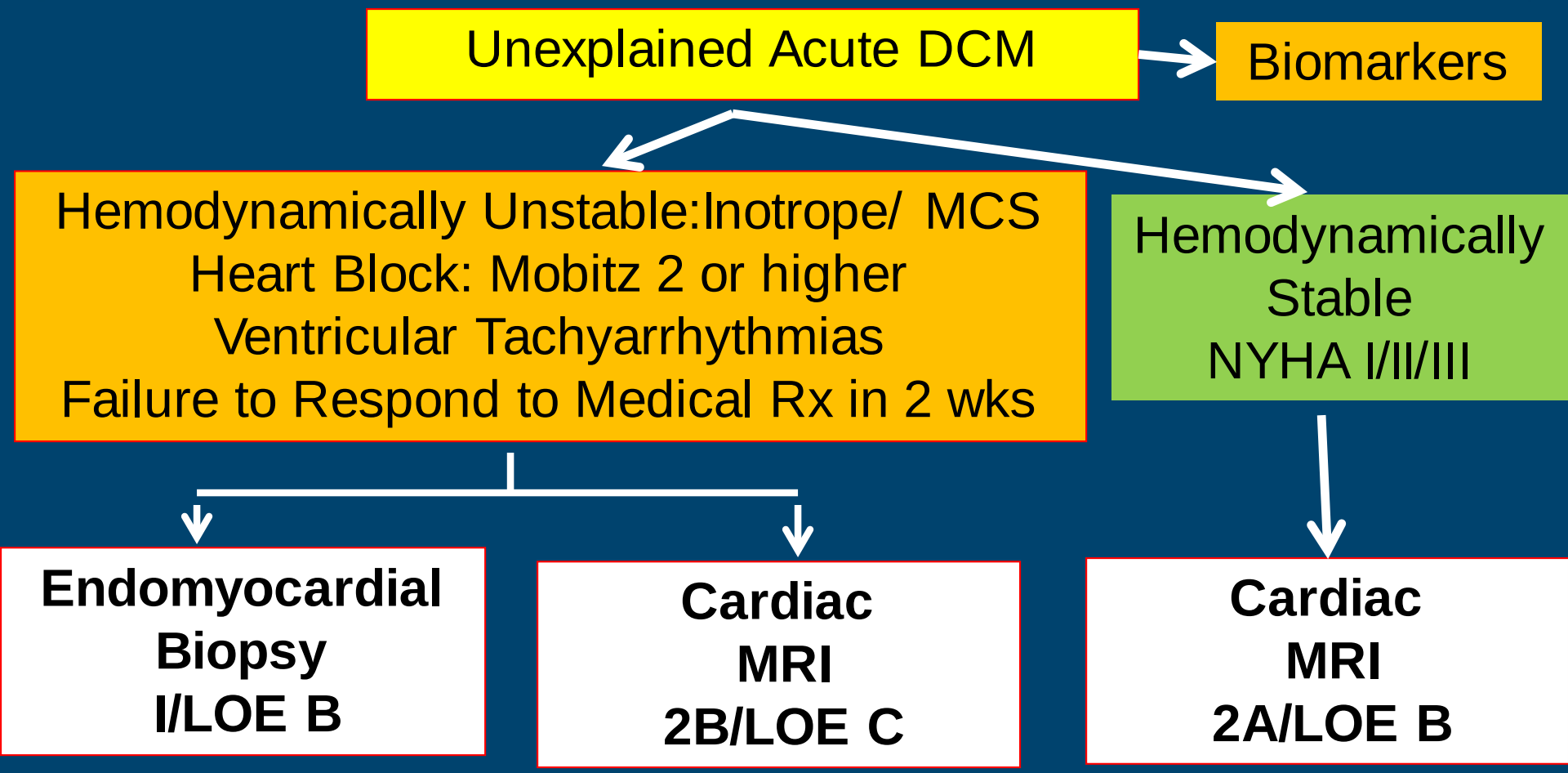




ACUTE LYMPHOCYTIC MYOCARDITIS
CLINICAL MANIFESTATIONS

- Asymptomatic ECG abnormalities
- Ventricular arrhythmias
- Myocardial infarction mimicry [parvovirus B19]
- Acute dilated cardiomyopathy
- Cardiogenic shock [fulminant]

DIAGNOSTIC APPROACH TO SUSPECTED MYOCARDITIS



Heymans S, et al. *J Am Coll Cardiol* 2016;68:2348-64.

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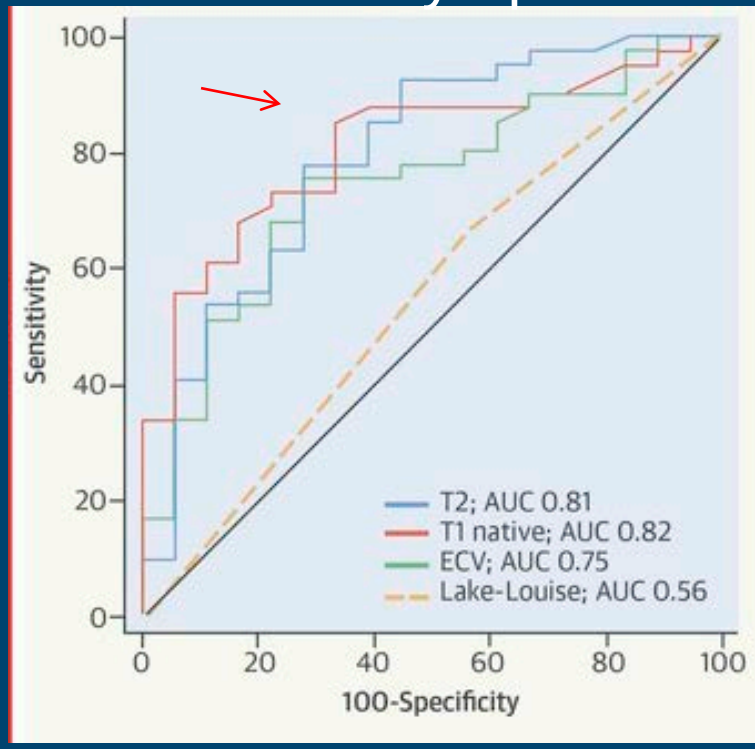
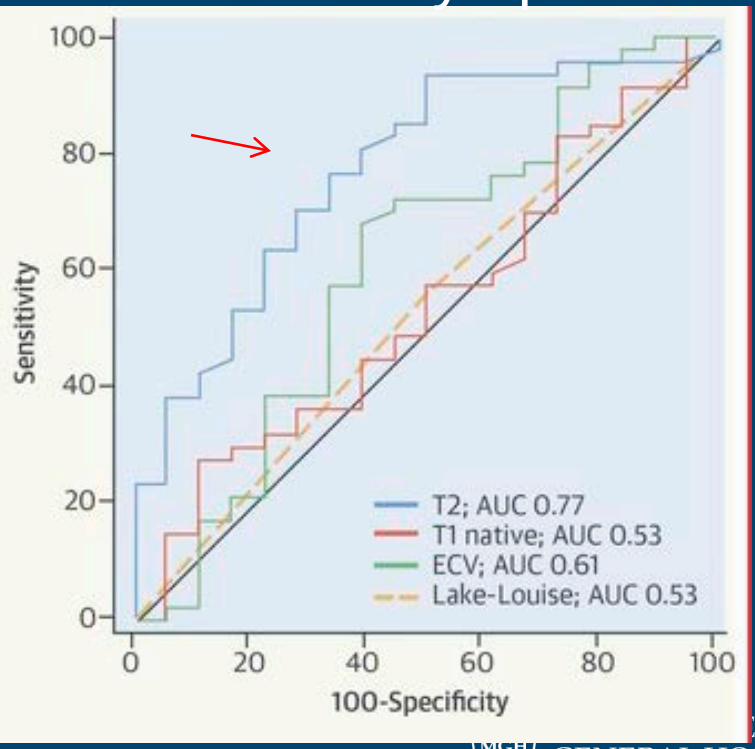
CARDIAC MR IMAGING IN SUSPECTED MYOCARDITIS
THE MYO-RACER TRIAL

129 patients underwent native T1 imaging, calculation of extracellular volume fraction (ECV), and T2 mapping

Acute Symptoms

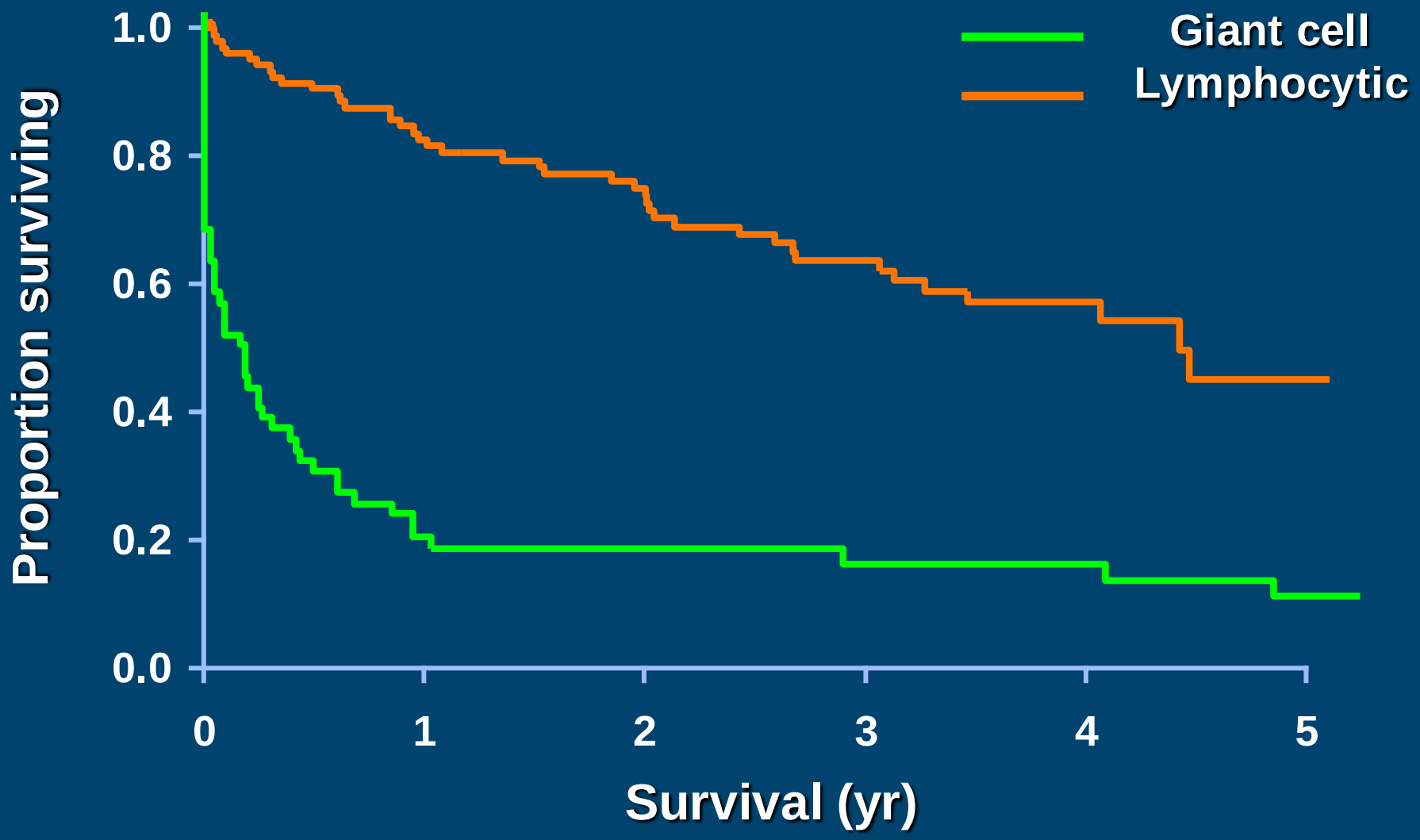


Chronic Symptoms



Lurz P, et al. *J Am Coll Cardiol* 2016;67:1800-11.

NATURAL HISTORY OF LYMPHOCYTIC AND GIANT CELL MYOCARDITIS

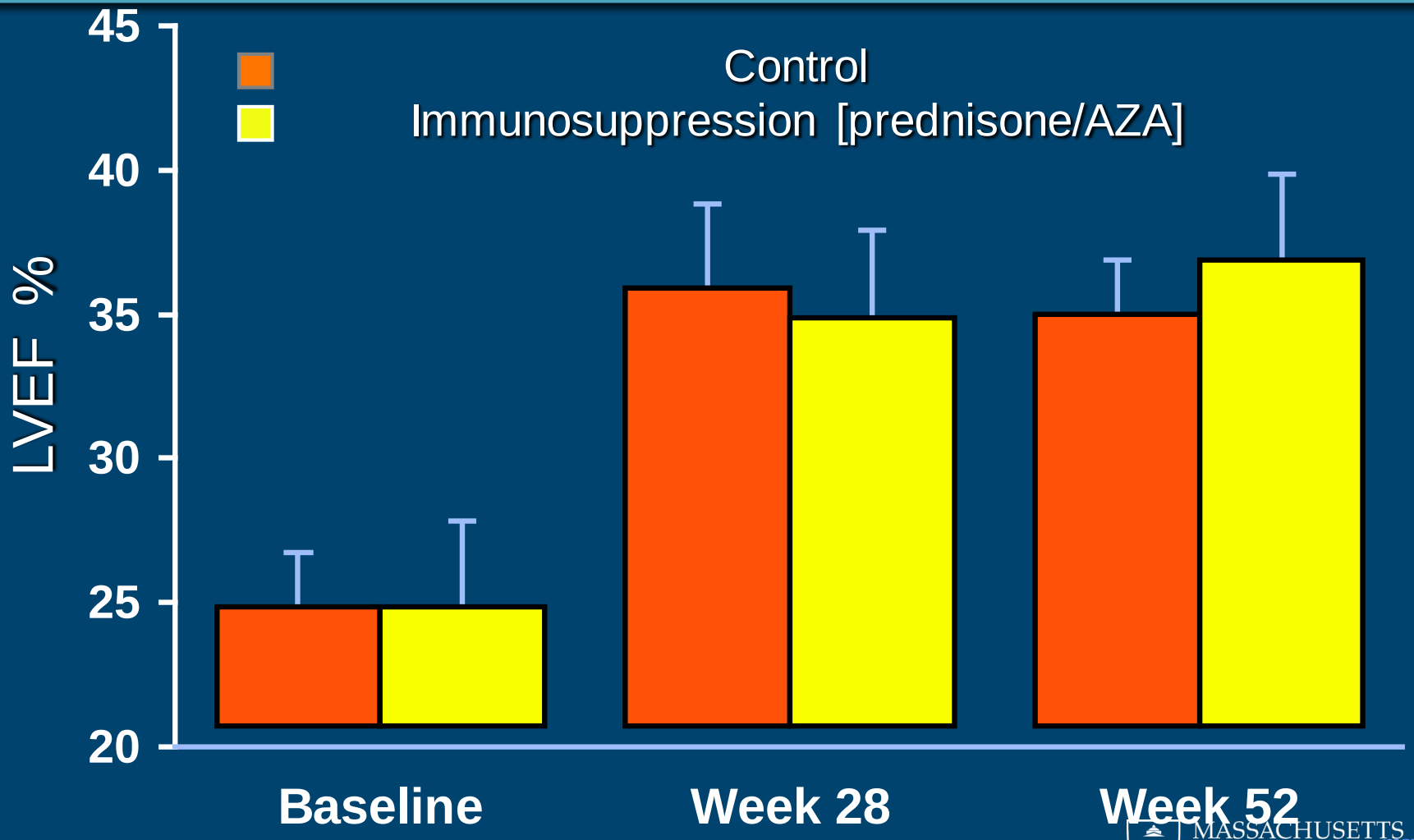


Cooper L, et al. *NEJM* 1997;336:1860-6.

LYMPHOCYTIC MYOCARDITIS
CONVENTIONAL TREATMENT

- Avoidance of strenuous exercise (3-6 months)
- ACE inhibitors, beta-blockers, spironolactone per ACC/AHA/HFSA heart failure practice guidelines to treat HF symptoms and promote favorable LV remodeling
- ICD for persistent LV dysfunction on GDMT

NIH MYOCARDITIS TREATMENT TRIAL

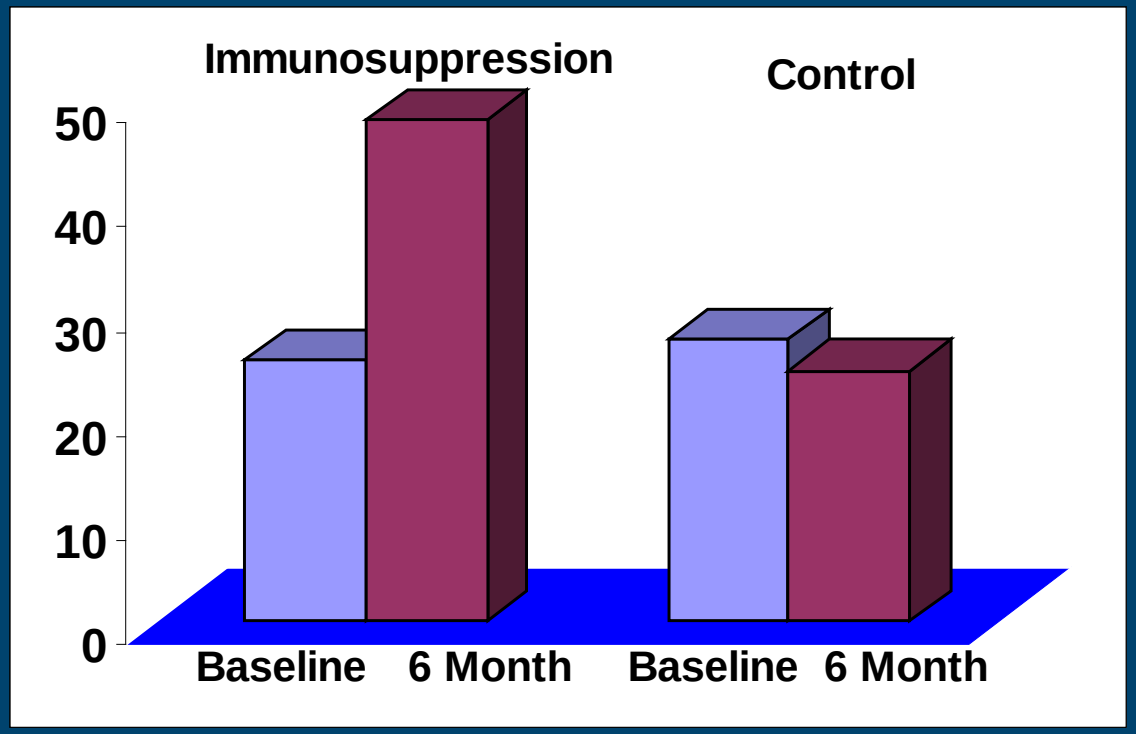


Mason JW, et al. *NEJM* 1995;333:269-75.

IMMUNOSUPPRESSIVE THERAPY IN VIRUS-NEGATIVE INFLAMMATORY CARDIOMYOPATHY

TIMIC TRIAL RESULTS

Change in LVEF by Treatment Group



- 85 pts with myocarditis, symptoms > 6 months, LVEF < 45%
- PCR negative [for adenovirus, enterovirus, HSV, influenza, CMV]
- Randomized to medical therapy +/- prednisone and azathioprine for 6 months

Frustaci A, et al *Eur Heart J* 2009;30:1995-2002.

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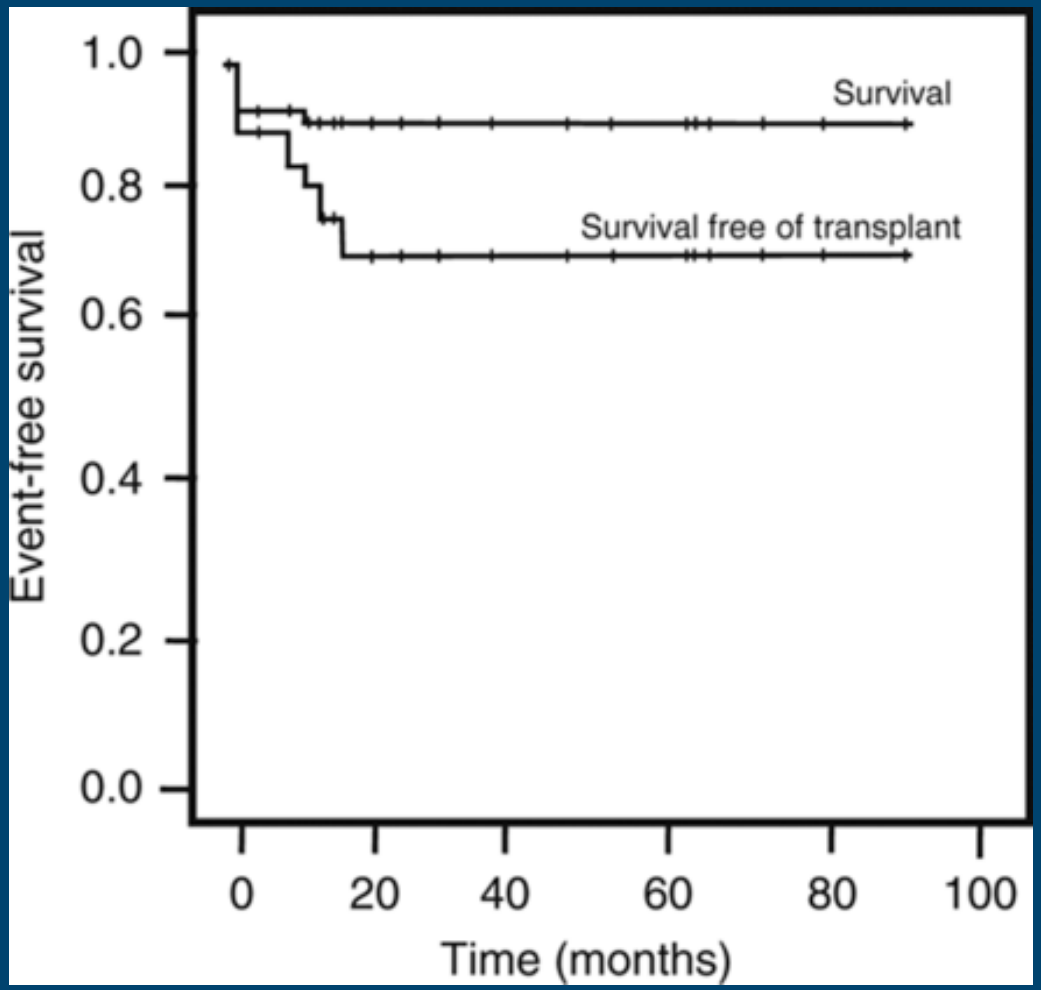
SURVIVAL IN GIANT CELL MYOCARDITIS TREATED WITH IMMUNOSUPPRESSIVE THERAPY



- 26 patients biopsy-positive for GCM
- Mean LVEF: 34% ± 8%

- Immunosuppression:
  - Pred + AZA + Cyclo (65%)
  - Prednisone+ AZA (15%)
  - Pred +Cyclo+ MMF (8%)

Kandolin R,et al. *Circulation HF* 2013;6:15-22.

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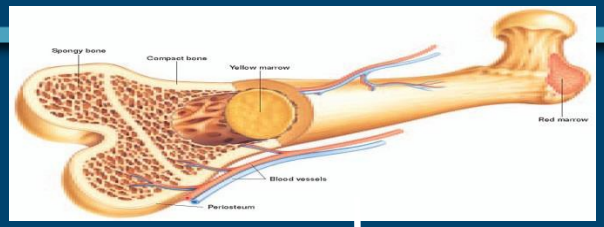
MYOCARDITIS: DIAGNOSIS AND TREATMENT 2017

- Cardiac MRI is most helpful initial diagnostic study
- RV biopsy is rarely indicated for suspected lymphocytic myocarditis but is essential when eosinophilic or giant cell myocarditis is suspected
- Steroid therapy is indicated and effective for eosinophilic myocarditis
- Immunosuppression (steroids & cytolytics) is useful for giant cell myocarditis and myocarditis associated with known autoimmune disorders (lupus, RA)*
- Immunosuppression may be considered for infection-negative lymphocytic myocarditis on an individual basis*

*Caforio A, et al. *Eur Heart J* 2013;34:2636-48.

TWO PRINCIPAL FORMS OF CARDIAC AMYLOIDOSIS

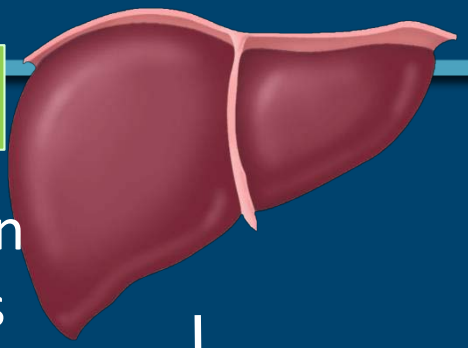


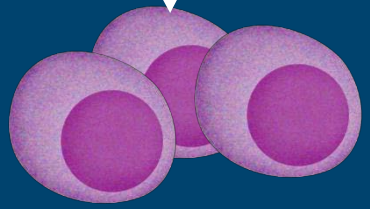
AL

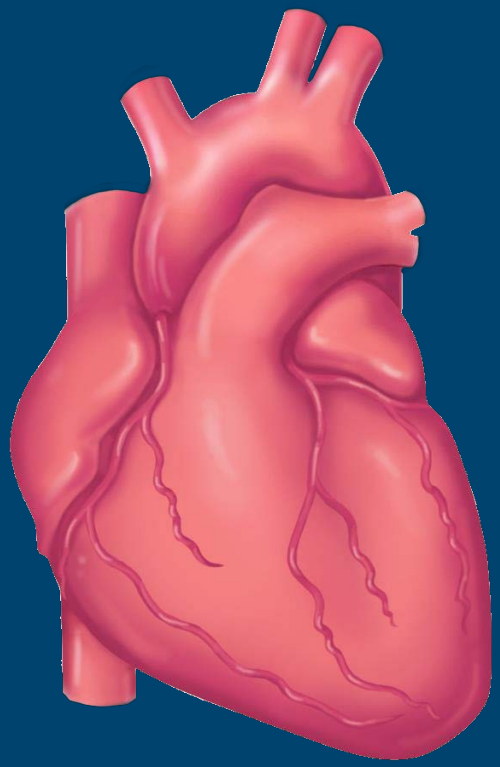
Light chain amyloidosis

ATTR

Transthyretin amyloidosis







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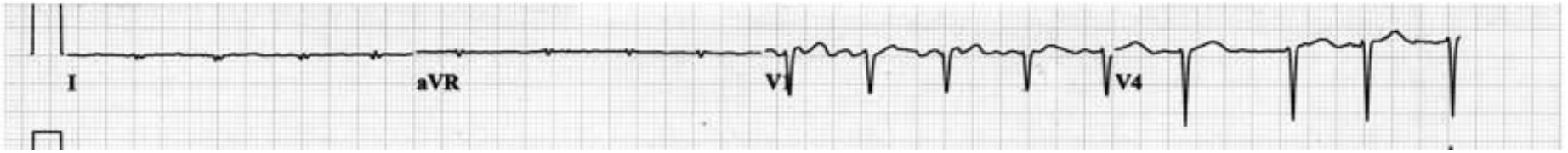
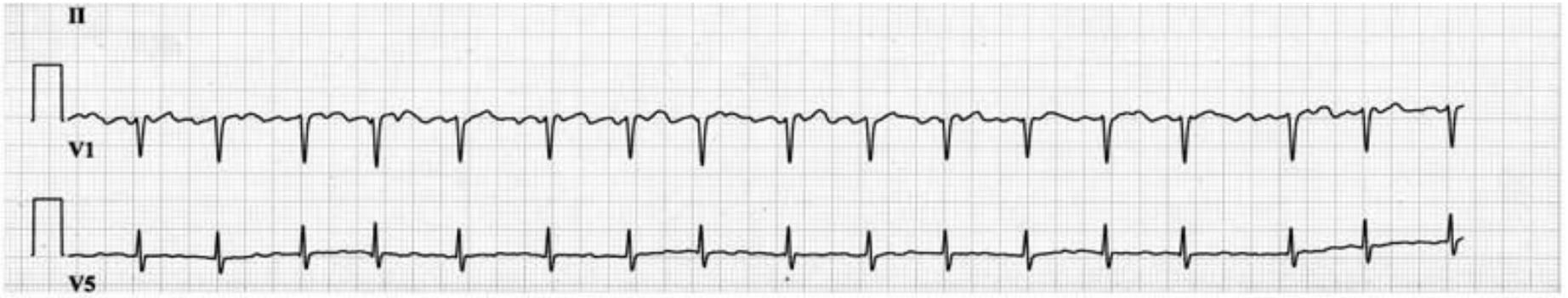
CLASSIC ECG PATTERN IN CARDIAC AMYLOIDOSIS



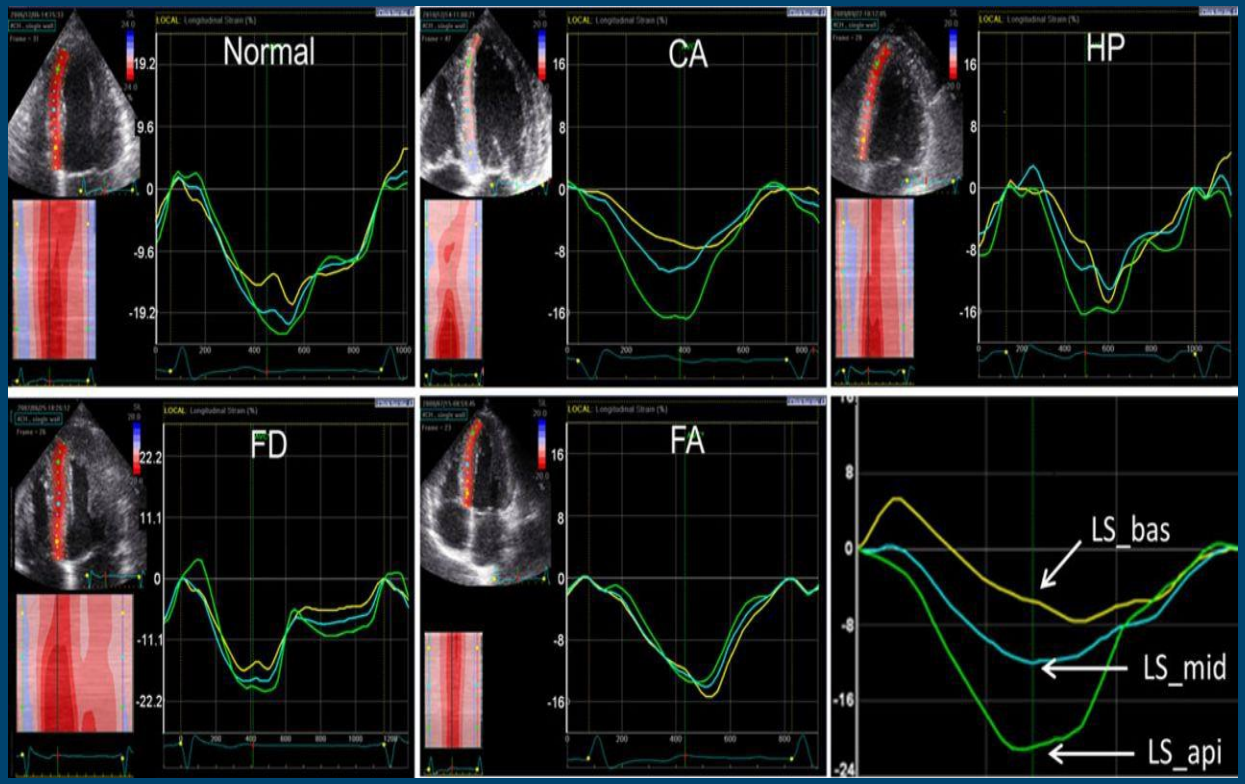
Pseudoinfarction pattern about 50% in AL

Low voltage 50% in AL

Low voltage 25% in ATTR



ECHO – STRAIN DIFFERENTIATION FROM OTHER CAUSES OF CONCENTRIC REMODELING



APICAL TO BASAL GRADIENT > 2.1

Liu et al. *Circ Cardiovasc Imaging* 2013;6:1066-72.

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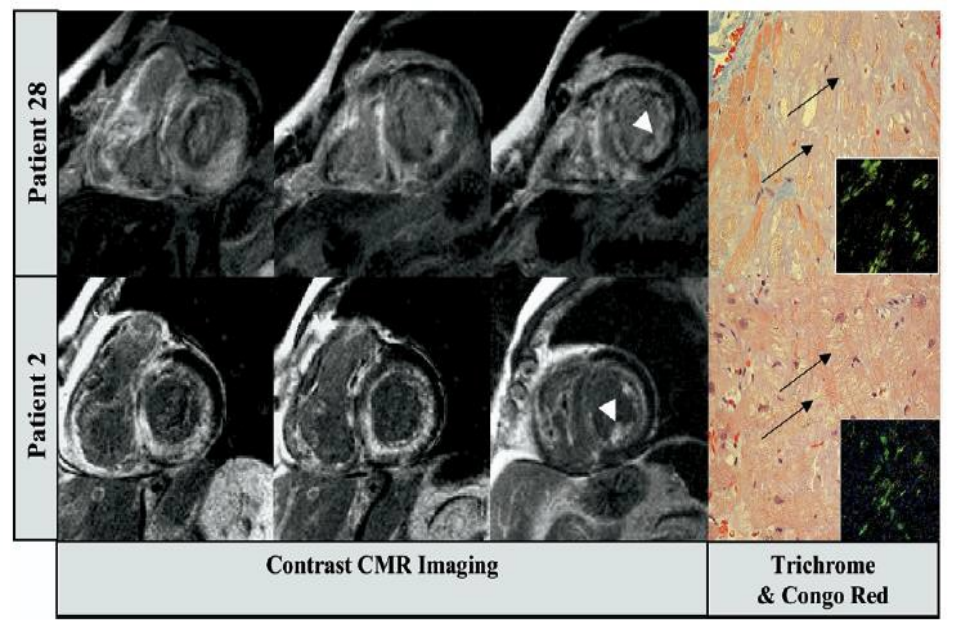
CMR WITH LGE IDENTIFIES CARDIAC AMYLOIDOSIS WITH A HIGH DEGREE OF ACCURACY

Reference	Sensitivity	Specificity	PPV	NPV
Vogelsberg et al., JACC 2008	80%	94%	92%	85%
Ruberg et al. Am J Cardiol 2009	86%	86%	95%	67%
Austin et al., JACC CVI 2009	88%	90%	88%	90%
Average	85%	90%	92%	81%



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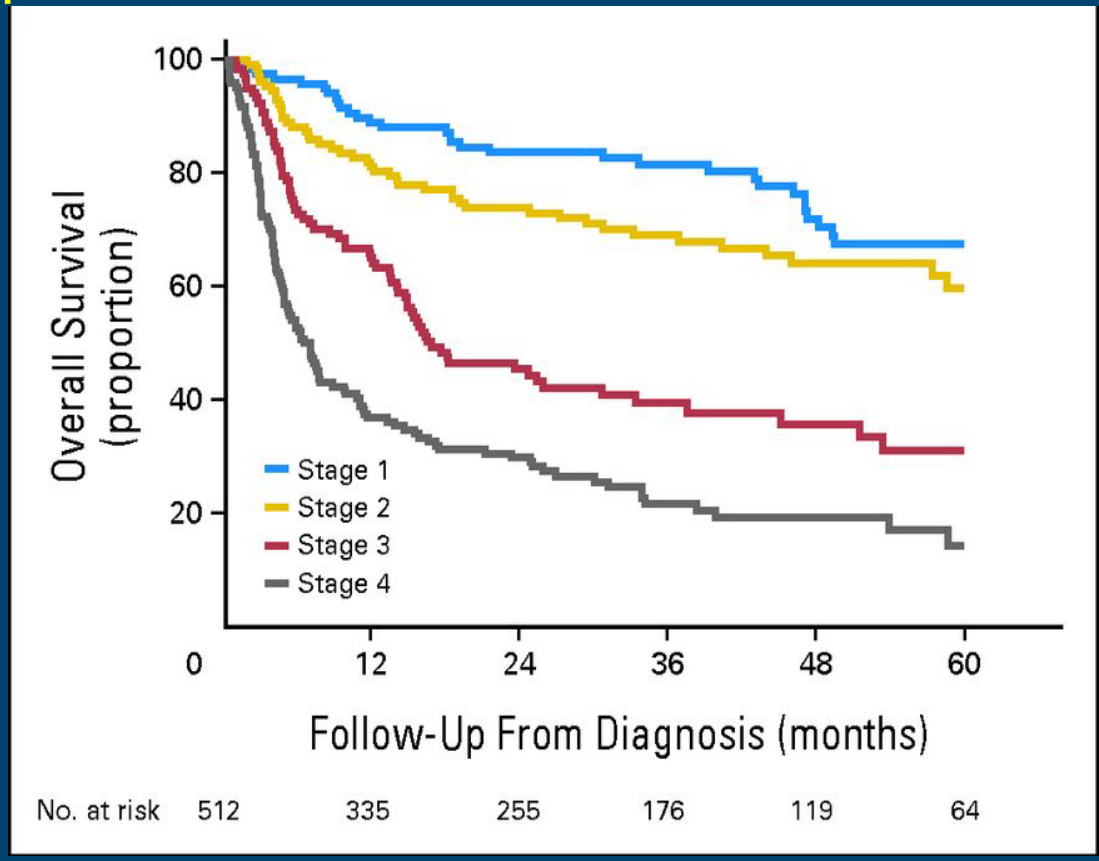
CARDIAC BIOMARKER STAGING IN AL AMYLOIDOSIS

Risk factors: 1 point each for score 0-3 → Stage 1-4

- FLC ≥ 180 mg/L
- cTnT ≥ 0.025 mcg/L
- NT-ProBNP ≥1,800 ng/L



Kumar S et al. *J. Clinical Oncology* 2012;30:989-995

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DIAGNOSTIC APPROACH TO SUSPECTED CARDIAC AMYLOIDOSIS

- Echocardiogram with strain imaging
- Cardiac MRI to more definitively identify amyloid vs. non-amyloid causes of unexplained LVH

1. AL evaluation
   -- Serum free light chain assay (kappa/lambda ratio)
   --Serum and urine immunofixation electrophoresis
   --NOT SPEP or UPEP

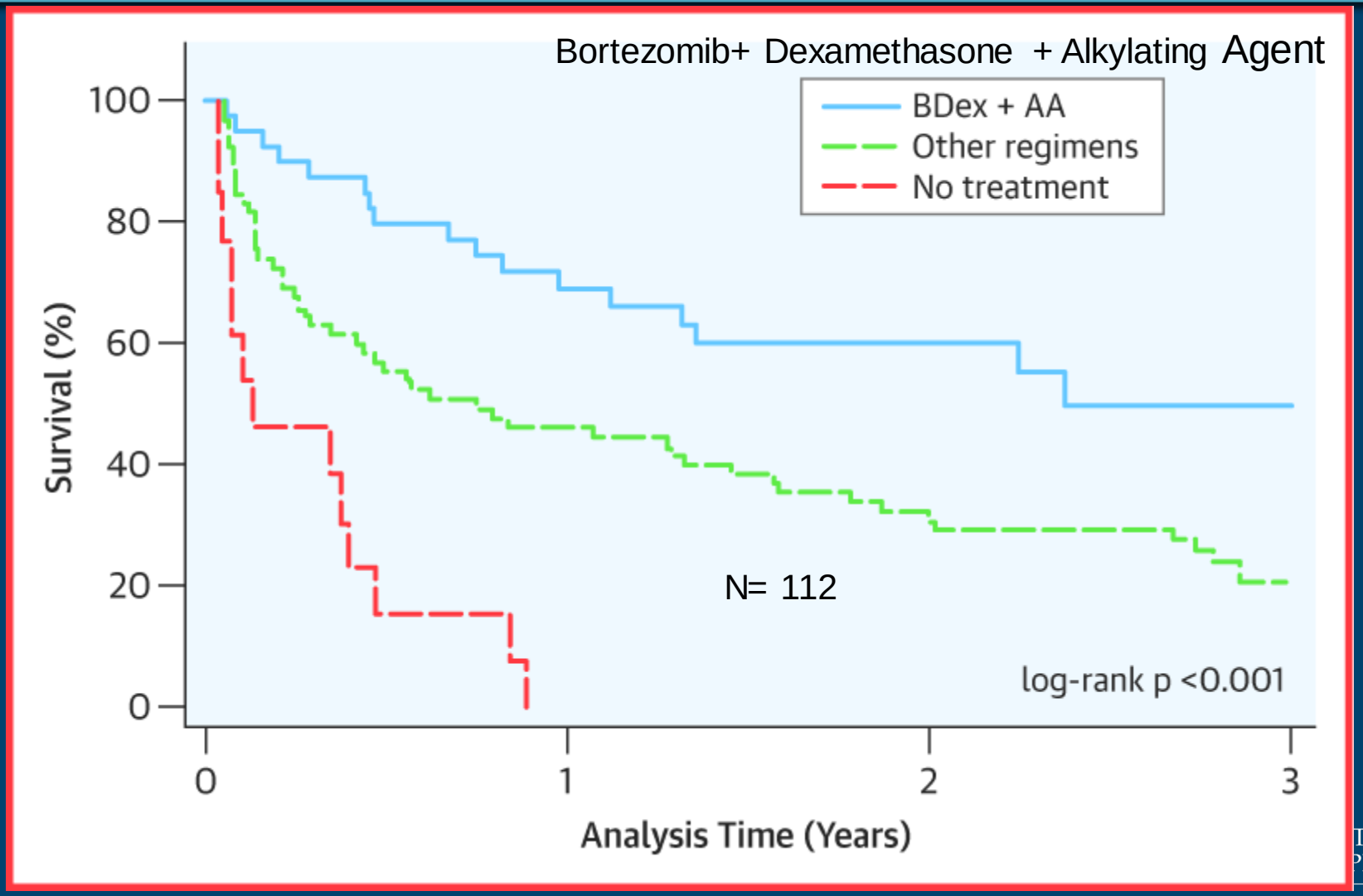
2. TTR evaluation (particularly in older patients)
   -- Pyrophosphate scan
   -- Genotyping (wild type or variant/mutant)

3. BNP or nT-pro-BNP and troponin I/T
4. Cardiac biopsy in equivocal cases
   – Immunohistochemistry or mass spectrometry

MANAGING THE HEART IN AL AMYLOIDOSIS

- Sudden death
  - *PEA, ventricular arrhythmias, and embolism*
  - Intracardiac thrombus as high as 35%
  - Controversial value of cardioverter-defibrillator
- Atrial arrhythmias
  - Beta-blockers & calcium channel blockers poorly tolerated
  - Digoxin has a bad reputation, but can actually be of value
  - Amiodarone is often the only medical option
  - Anticoagulation
- AV block
  - Pacing for AV block and/or chronotropic incompetence
- Heart Failure
  - Diuretics are mainstay of therapy

SURVIVAL IN AL AMYLOID CARDIOMYOPATHY BY TREATMENT



Sperry B, et al. *J Am Coll Cardiol* 2016;67:2941-7.

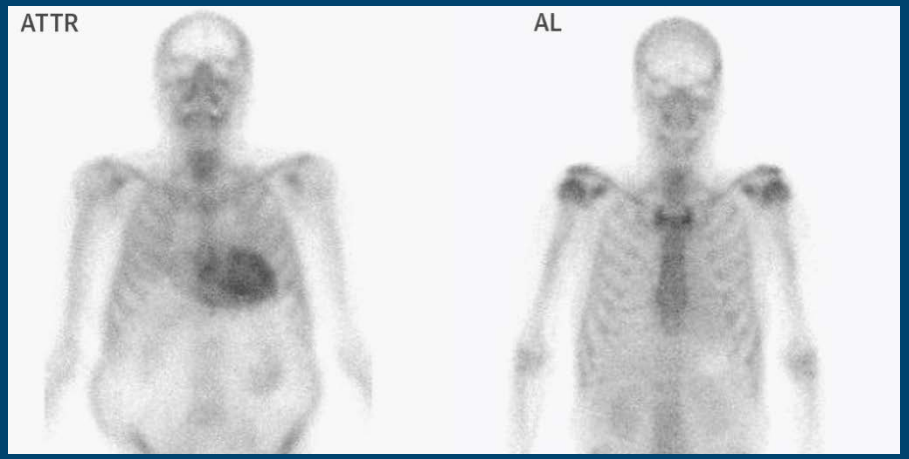
WILD TYPE TTR AMYLOID (ATTRw)

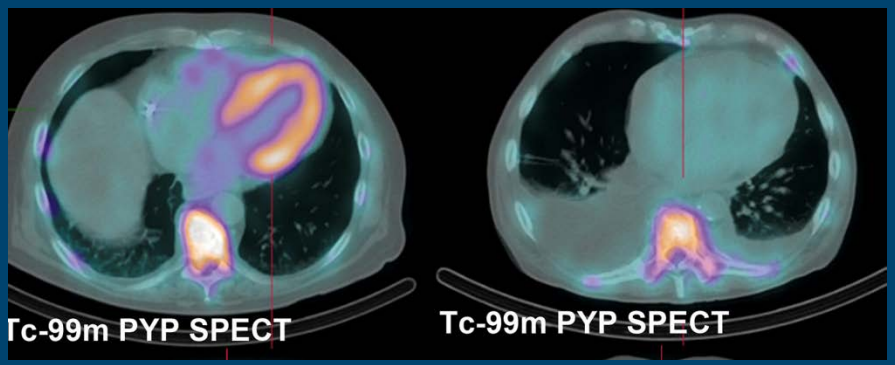
- Due to deposition of "wild-type" transthyretin
- "Senile cardiac amyloid"
- A disease of white elderly males (median age: 72)
- Bilateral carpal tunnel syndrome is common
- More "indolent", prognosis
- ~ 25% pts > 80 yrs have wild type TTR amyloid deposits in myocardium at autopsy
- ? % of clinical HF-pEF cases

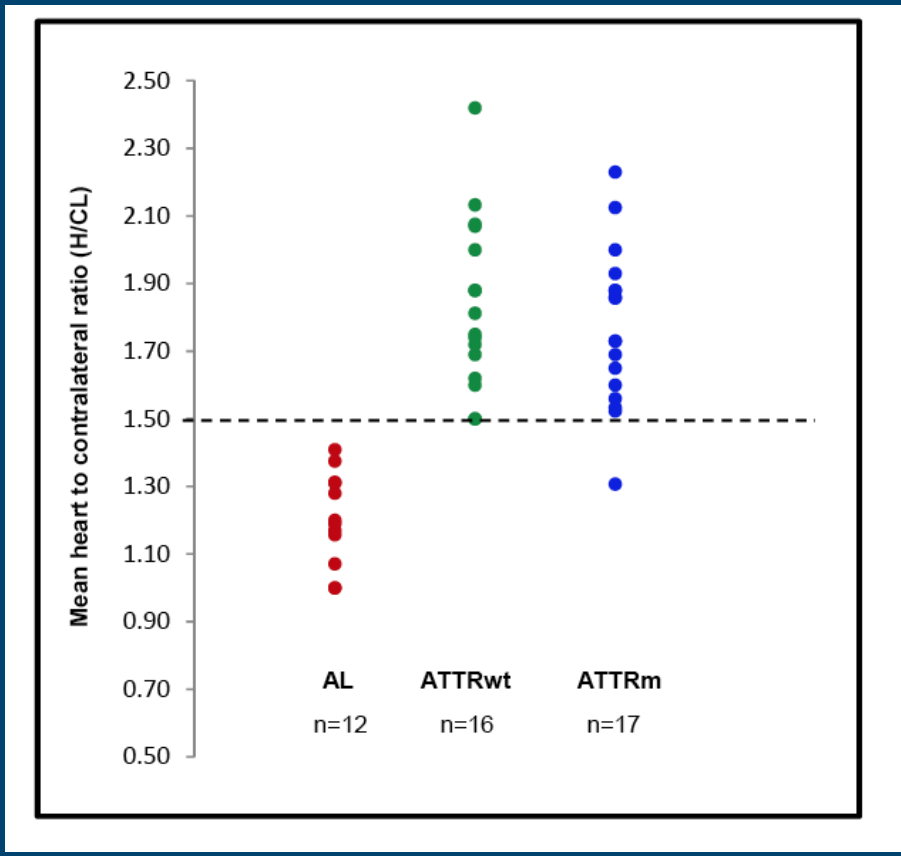
Tanskanen *Ann Med.* 2008;40(3) :232-9
Cornwell *Am J Med*. 1983;75(4): 618-23

ROLE OF TECHNITIUM PYROPHOSPHATE IN SUSPECTED CARDIAC AMYLOIDOSIS

ATTR AL







Falk R, et al. *JACC* 2016;68:1323-40.

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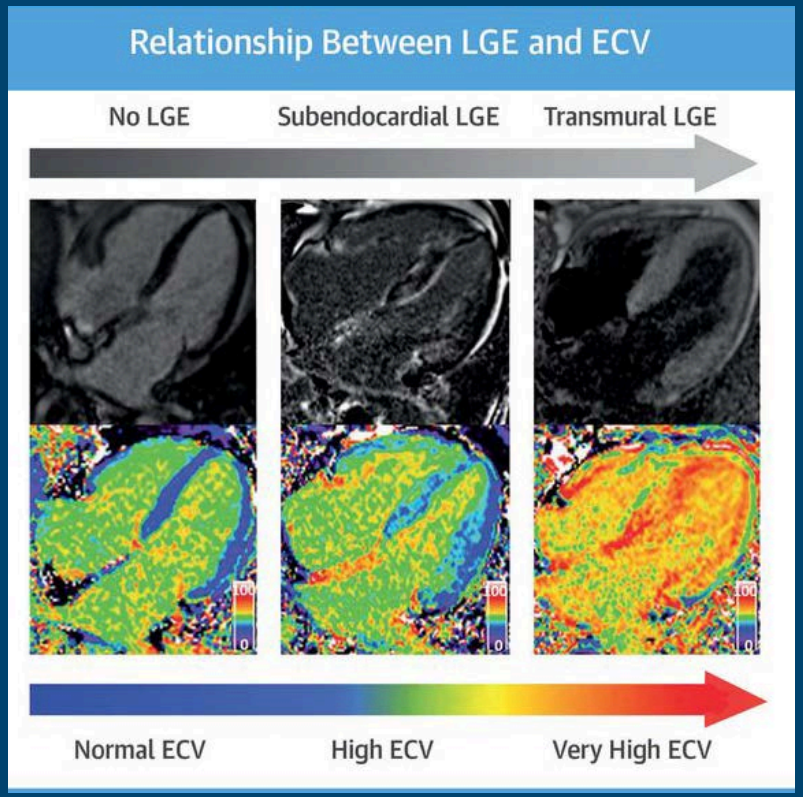
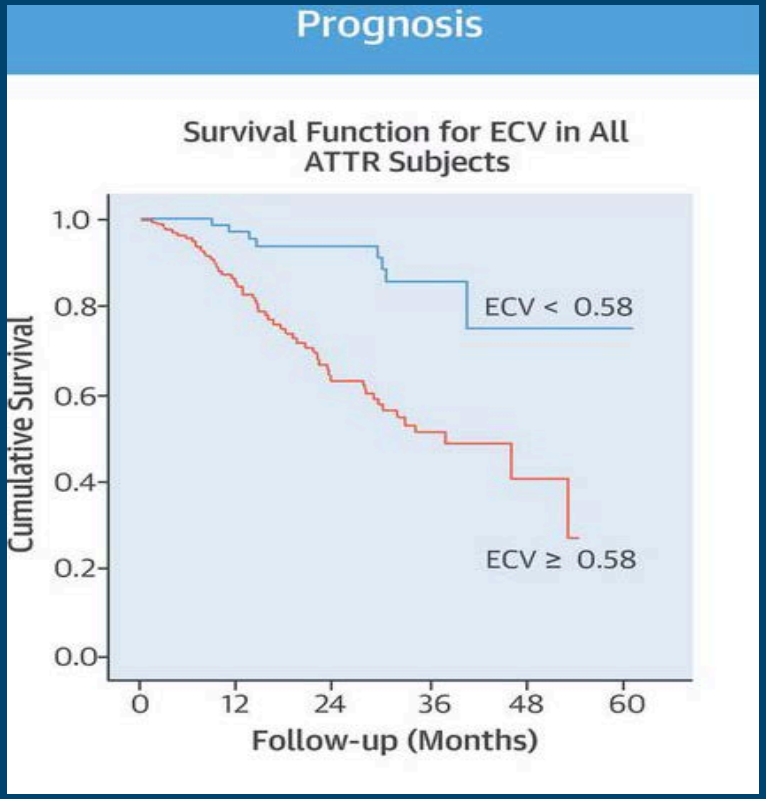
EXTRACELLULAR VOLUME BY MRI AND OUTCOME IN ATTR





Martinez-Naharro A, et al. *J Am Coll Cardiol* 2017;70:466-77.

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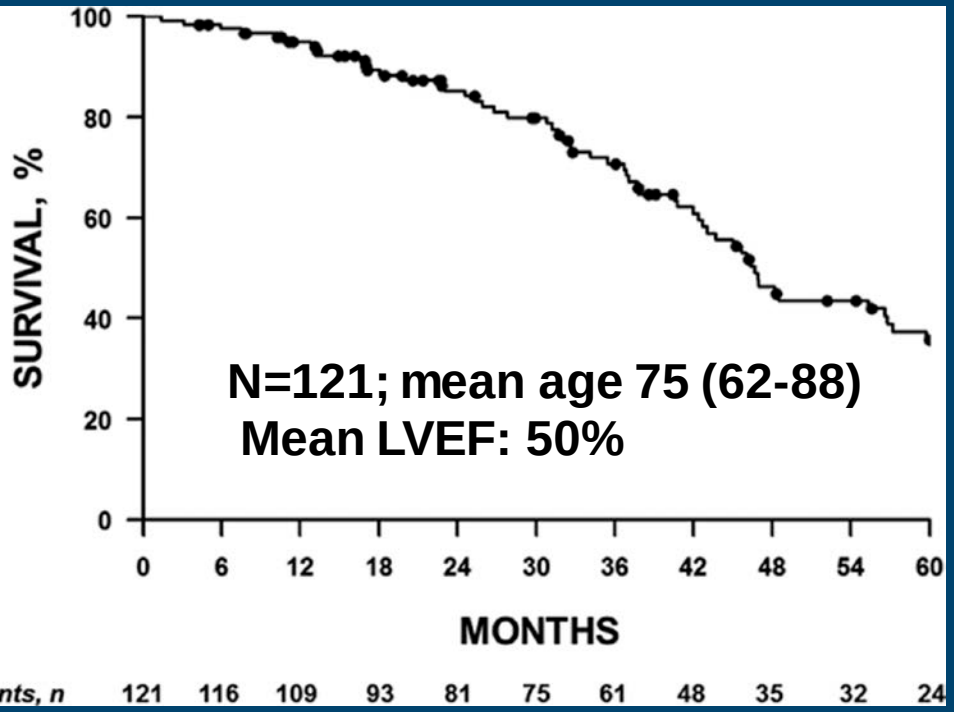
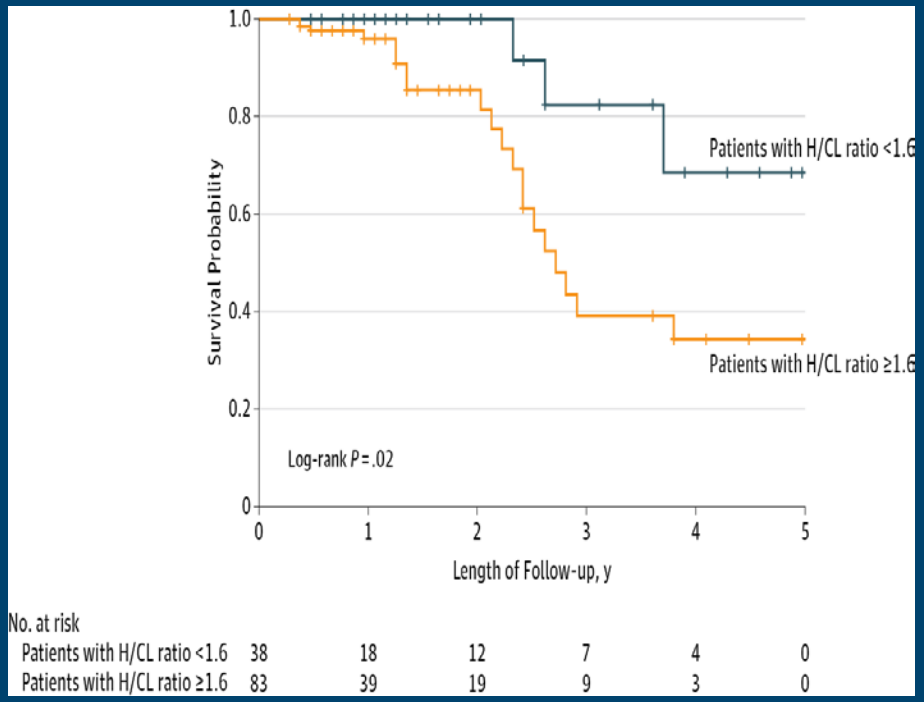
SURVIVAL FOR WILD TYPE ATTR AMYLOIDOSIS

Natural history



Survival by PPY Uptake



Connor LH, et al. *Circulation* 2016;133:282-90

Castano A. et al JAMA Cardiol 2016;1:880-9.

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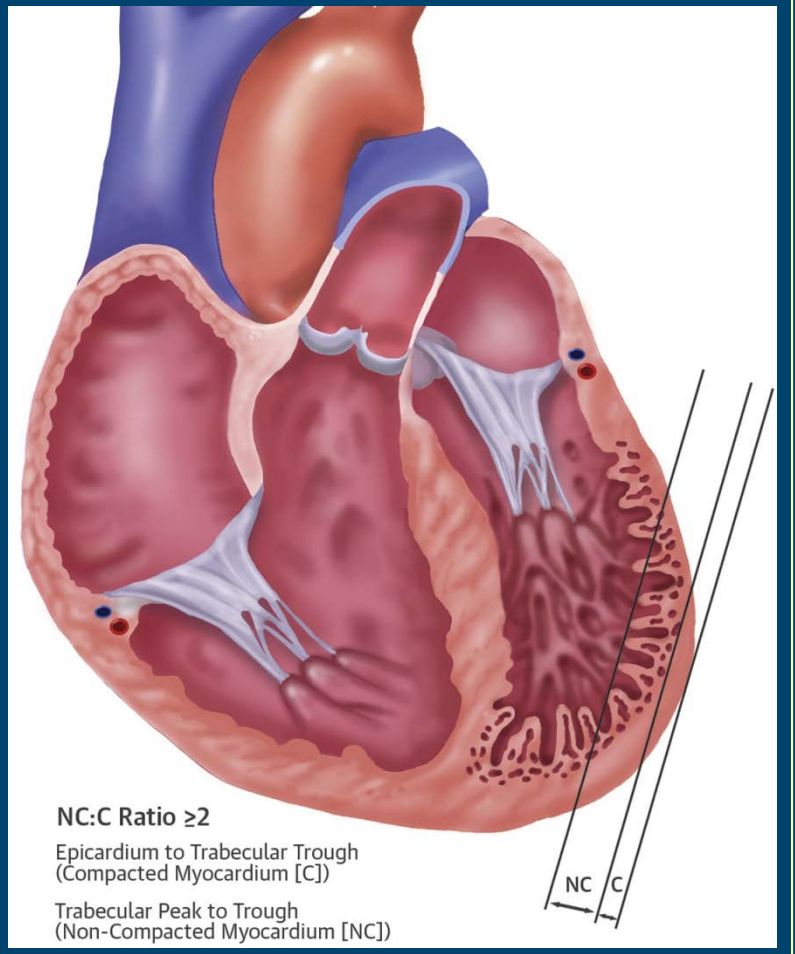
ATTR THERAPY: STABILIZERS, SILENCERS, AND SERUM AMYLOID PROTEIN DEPLETION

Emerging therapies focus on 3 general mechanisms:

- Stabilization of the TTR complex [Tafamidis and tolcapone]
- Silencing expression of the TTR gene [RNAi and antisense therapies]
- Removal of amyloid plaques from diseased tissue by targeting serum amyloid protein (SAP) [Humanized monoclonal antibodies: NEOD001]
- Heart (AL) and/or heart-liver transplantation (WTTR) may be appropriate in carefully selected patients

LEFT VENTRICULAR NONCOMPACTION



- LVNC results from intrauterine arrest of compaction of the loose network of primordial fetal myocardium
- NC/C ratio > 2.0-2.3
- Hypertrabeculation + LV dysfunction = cardiomyopathy
- Familial: 18%-50%
- Increased trabeculation is a common finding during pregnancy, black individuals, CKD, and athletes and often regresses

Hussein A, et al. *J Am Coll Cardiol* 2015;66:578-85.

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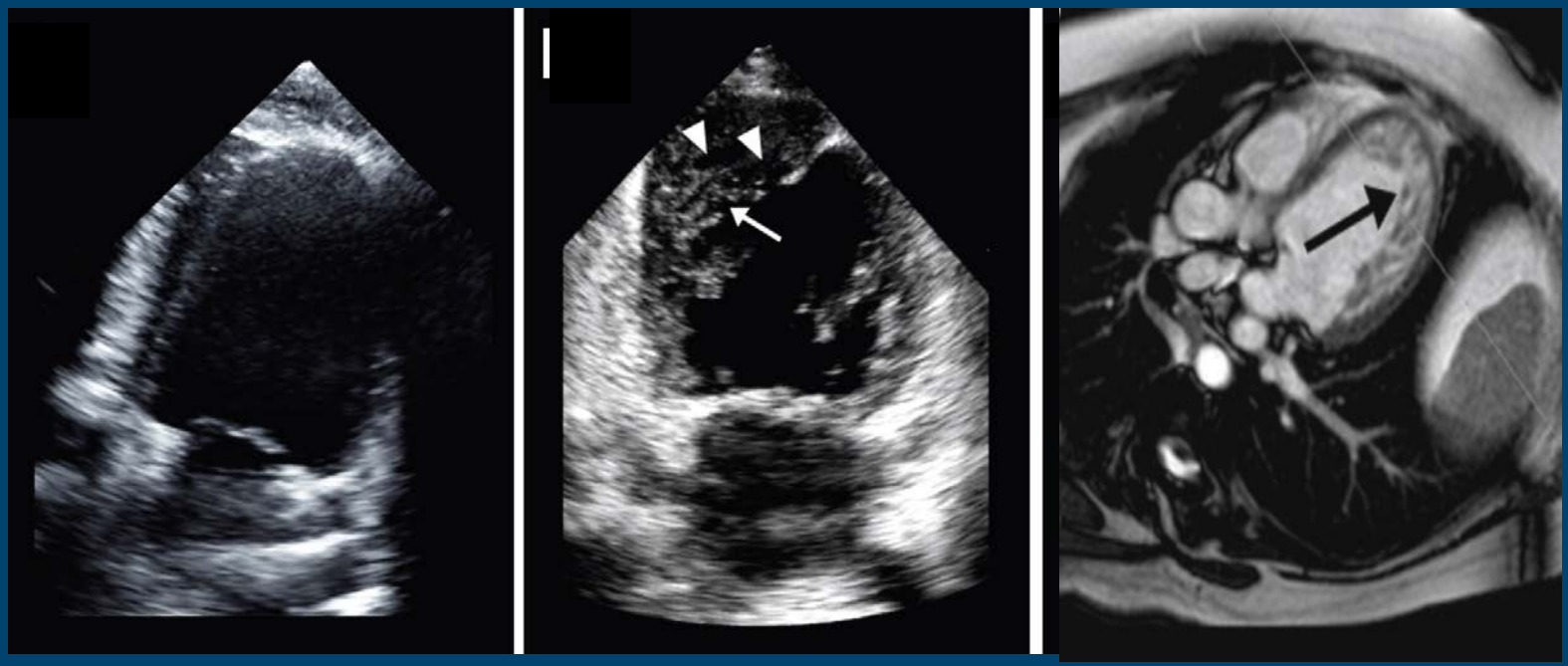
LEFT VENTRICULAR NONCOMPACTION

Normal LVNC LVNC



Hussein A, et al. *J Am Coll Cardiol* 2015;66:578-85.

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LEFT VENTRICULAR NONCOMPACTION
CLINICAL PRESENTATIONS

- Dyspnea: 60%
- Chest pain: 15%
- Palpitations: 18%
- Syncope: 9%
- Stroke: 3%

- Asymptomatic: 15%-18%

- NYHA class III/IV heart failure: 31%

Bhatia NL, et al. *J Cardiac Fail* 2011;17:771-8

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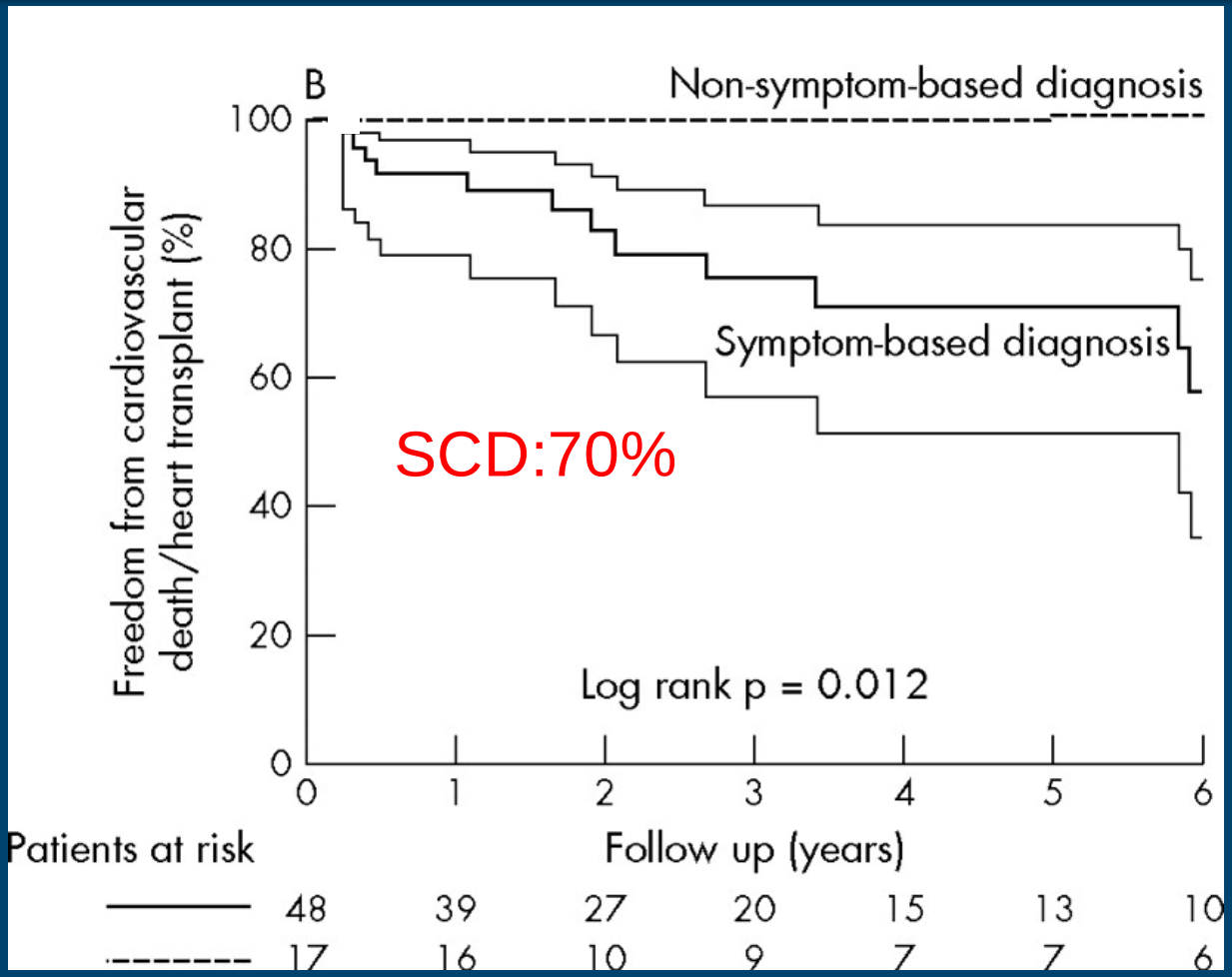
NATURAL HISTORY OF LEFT VENTRICULAR NONCOMPACTION



Lofiego C, et al. *Heart* 2007;93:65-71

Peters F, et al. *J Card Failure* 2014;20:709-15.

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LEFT VENTRICULAR NONCOMPACTION
MAJOR COMPLICATIONS

- Heart Failure
  - Conventional pharmacological agents: beta-blockers, ARB or ACE-I, aldosterone antagonist
- Thromboembolic Complications
  - Anticoagulation for documented thrombus, atrial fibrillation or prior TIA/CVA
  - ? Dense trabeculations
- Atrial Arrhythmias
  - Atrial fibrillation in 10-20%
- Ventricular Arrhythmias/Sudden Death
  - ICD for LVEF < 35%