

# Cardiac Amyloid

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I Have No Disclosures



# OBJECTIVES

- Understand differences between Transthyretin (ATTR) and Light Chain (AL)
- Understand role of imaging in establishing the diagnosis
- Discuss treatment options

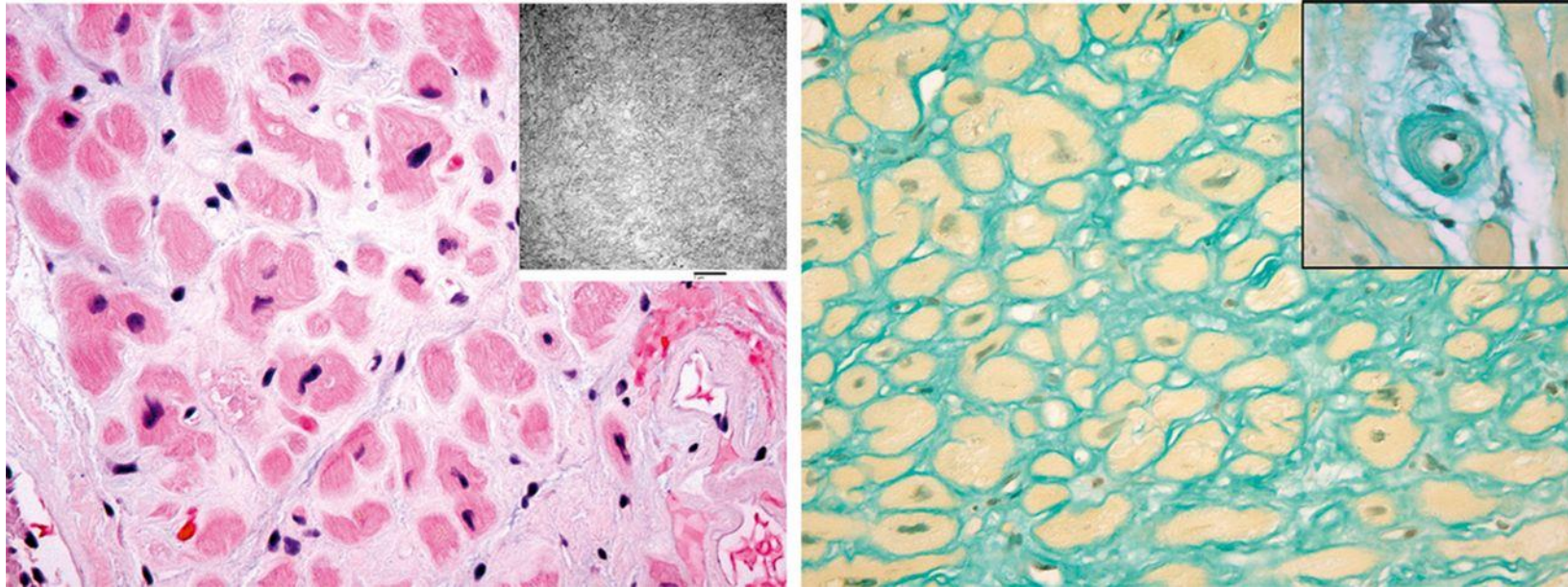


# Introduction

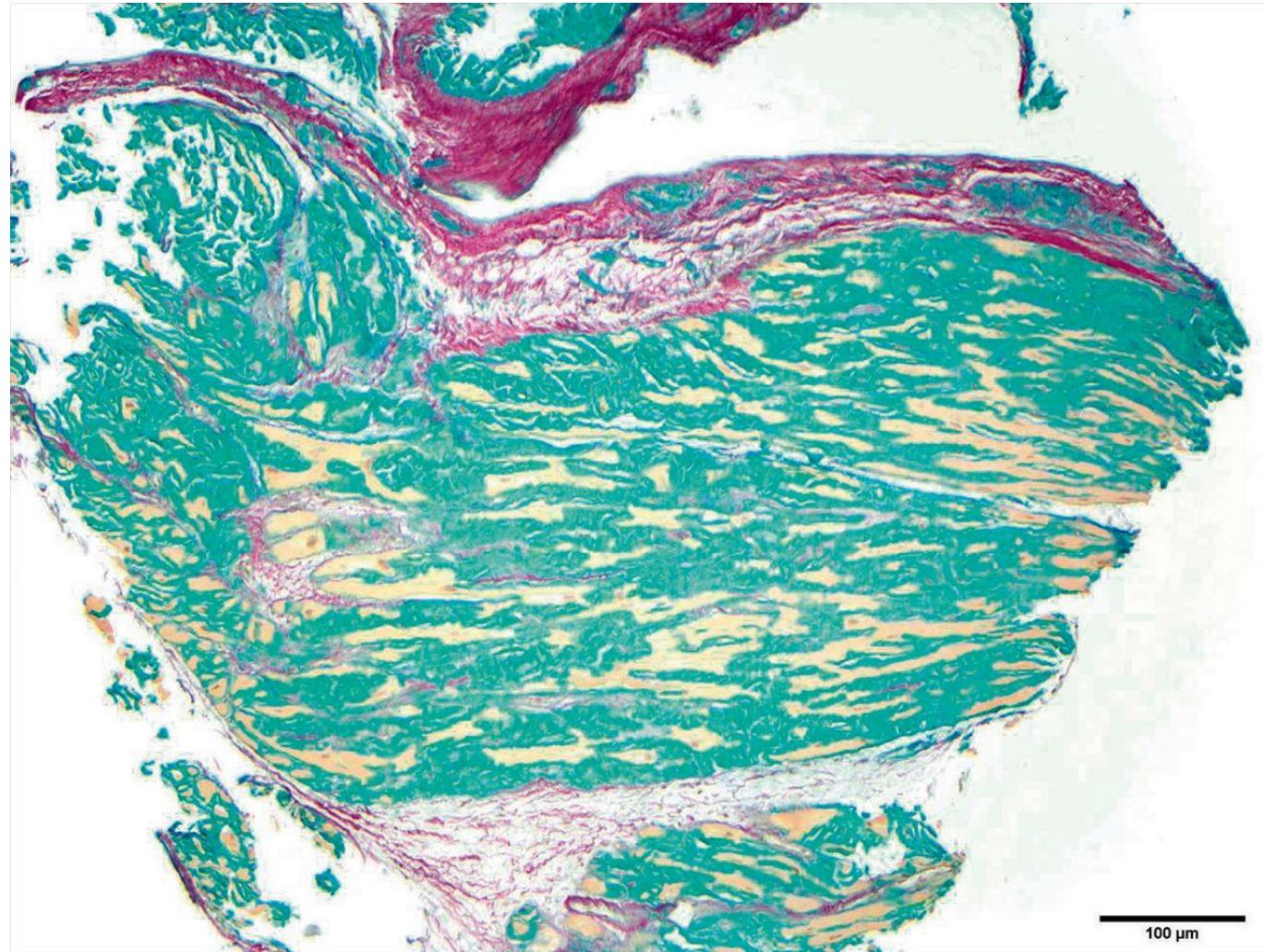
- First described by Rudolf Virchos (1853) as deposits in tissues noted with iodine and sulfuric acid stains.
- Derived from “amylum” latin for starch
- 1922 Congo red stain was discovered
- 1927 apple green birefringence noted in brains of patients with Alzheimer’s dx

# Introduction

- Extracellular space of the heart is expanded by amorphous, proteinaceous material known as amyloid
- composed of fragments of precursor protein, proteoglycans and serum amyloid P (SAP)
- Extremely resistant to degradation



Rodney H. Falk et al. JACC 2016;68:1323-1341



Morie A. Gertz et al. JACC 2015;66:2451-2466

# Introduction

- Systemic amyloidosis:
  1. AL Amyloidosis—>monoclonal plasmacytoma in the bone marrow
  2. AA Amyloidosis—>deposits of amyloid protein due to chronic inflammation (RA, Tuberculosis)
  3. Senile or wild type (ATTR subtype)
  4. Familial AF amyloid (ATTR subtype)
  5. AH amyloid—>B2-microglobulin deposits in dialysis patients



# Introduction

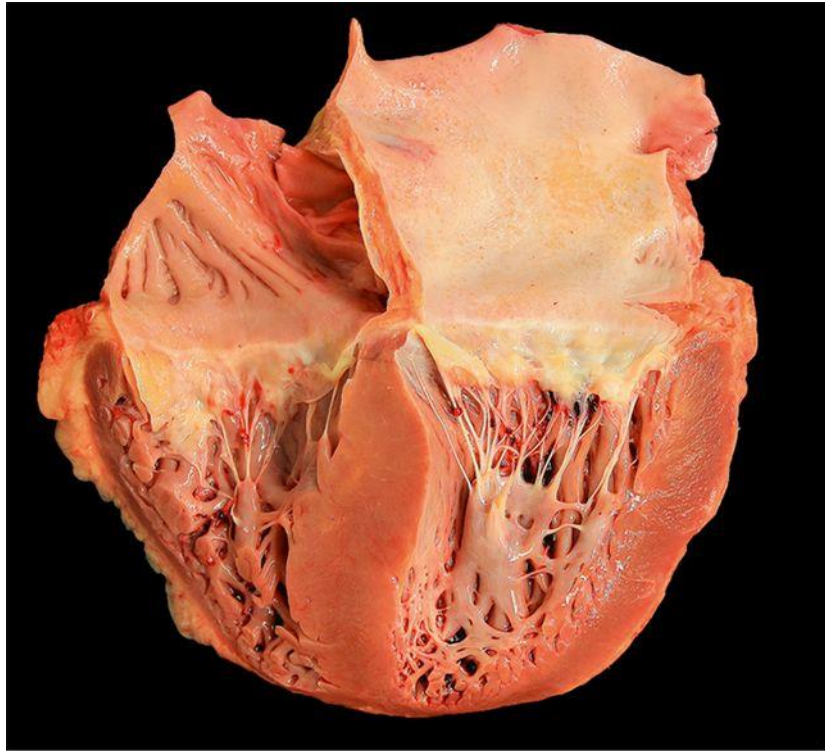
- Cardiac amyloid is systemic disease
- Most common Cardiac amyloid types:
  - Transthyretin (ATTR)
  - Light chain (AL)



**TABLE 1 Overview of the Common Forms of Amyloidosis That May Affect the Heart**

<b>Amyloid Nomenclature</b>	<b>Precursor Protein</b>	<b>Age Range, yrs</b>	<b>Sex</b>	<b>Clinical Clues</b>	<b>Laboratory Abnormalities</b>
AL	Light chains	50+	Either	Multiorgan involvement. Periorbital bruising or macroglossia are almost pathognomonic of AL in setting of typical MRI or echocardiogram. Severe hypotension with ACE inhibitors.	Elevated serum free lambda or kappa, with abnormal ratio. Monoclonal spike in serum and/or urine. Suppressed immunoglobulins. Proteinuria.
ATTRwt	Wild-type (normal) transthyretin	65+	Marked male predominance, >15:1	History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement.	No specific abnormalities. (Normal free light chain values, no proteinuria)
ATTRm	Mutant transthyretin	40+ (mutation dependent). In V122I, the common African-American variant, usual age of clinical onset is 60-65 yrs.	Either, slight male predominance.	African-American/Caribbean origin (for V122I TTR variant).	No specific abnormalities on routine testing. Genetic testing reveals mutation in TTR molecule
AA (Secondary)	Serum amyloid A (an acute phase protein)	May occur in 20s-30s upward with severe inflammatory disease.	Either	Underlying chronic inflammatory disease. Hepatomegaly, splenomegaly. Usually no cardiac involvement, but in rare cases may be severe	High ESR/CRP. Proteinuria.

ACE = angiotensin-converting enzyme; CMR = cardiac magnetic resonance; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; LBBB = left bundle branch block; TTR = transthyretin.



Rodney H. Falk et al. JACC 2016;68:1323-1341

# Cardiac Amyloid (ATTR)

- Transthyretin (ATTR)
  - tetrameric protein rich in beta strands present in all human serum
  - functions to *transport thyroxine* and *retinol-binding protein (TTR)*
  - synthesized mostly by liver
  - important for behavior, cognition, and nerve regeneration and axonal growth
  - TTR aggregate into insoluble amyloid fibers

# Cardiac Amyloid (ATTR)

- Tranthyretin (ATTR)
  - Single point mutation increases likelihood of misfolding to beta-pleated sheets
  - More than 80 mutations described
  - V30M mutation is most common in world but in USA its second most common
  - Cluster common in Portugal, Japan and Sweden
  - T60A mutation most common in USA originated in Northwest Ireland (Appalachian amyloidosis)
  - V122I mutation originated in West Africa

# Cardiac Amyloid (AL)

- Wild type (wt) TTR can also occur.
  - sporadic
  - called senile cardiac or senile systemic
  - protein deposits occur exclusively in men >60

# General Characteristics

- Predominately men (80% of ATTR cases)
  - Mutant ATTR (72% male)
  - wt ATTR (99% male)
  - Mutant and wt ATTR better prognosis than AL amyloidosis
  - Median survival of wt ATTR is over 60 months versus 5.4 months in AL amyloidosis

# Clinical characteristics

- Amyloid infiltrating results in poor diastolic relaxation (poor filling, low end-diastolic volume, restrictive physiology)
- Right-side heart failure predominates (lower-extremity edema, hepatomegaly, ascites and elevated JVP)
- Severe atrial and ventricular infiltration results mechanical standstill and thrombus formation (even in sinus rhythm)
- EKG shows low voltage in QRS complex (useful but not reliable)
- Associated with carpal tunnel syndrome (precede cardiac manifestation 8-10yrs)



# Clinical characteristic

- Peripheral neuropathy noted in over 60%
- Suspect amyloidosis if heart failure with preserved ejection fraction or infiltrative cardiomyopathy noted on imaging
- Orthostatic hypotension, sweat abnormalities, urinary incontinence often present
- Prevalence of wt ATTR was 25% in one autopsy study of patient over 85yrs old. (clinical significance was not known)
- True prevalence is not known

# Diagnosis

- Echocardiogram
  - most common used modality when amyloid cardiomyopathy is suspected.
  - thickening of the left ventricular free wall and the septum
  - often misdiagnosed as hypertrophic cardiomyopathy or hypertensive cardiomyopathy
  - usually biventricular hypertrophy
  - left atrial enlargement

# Diagnosis

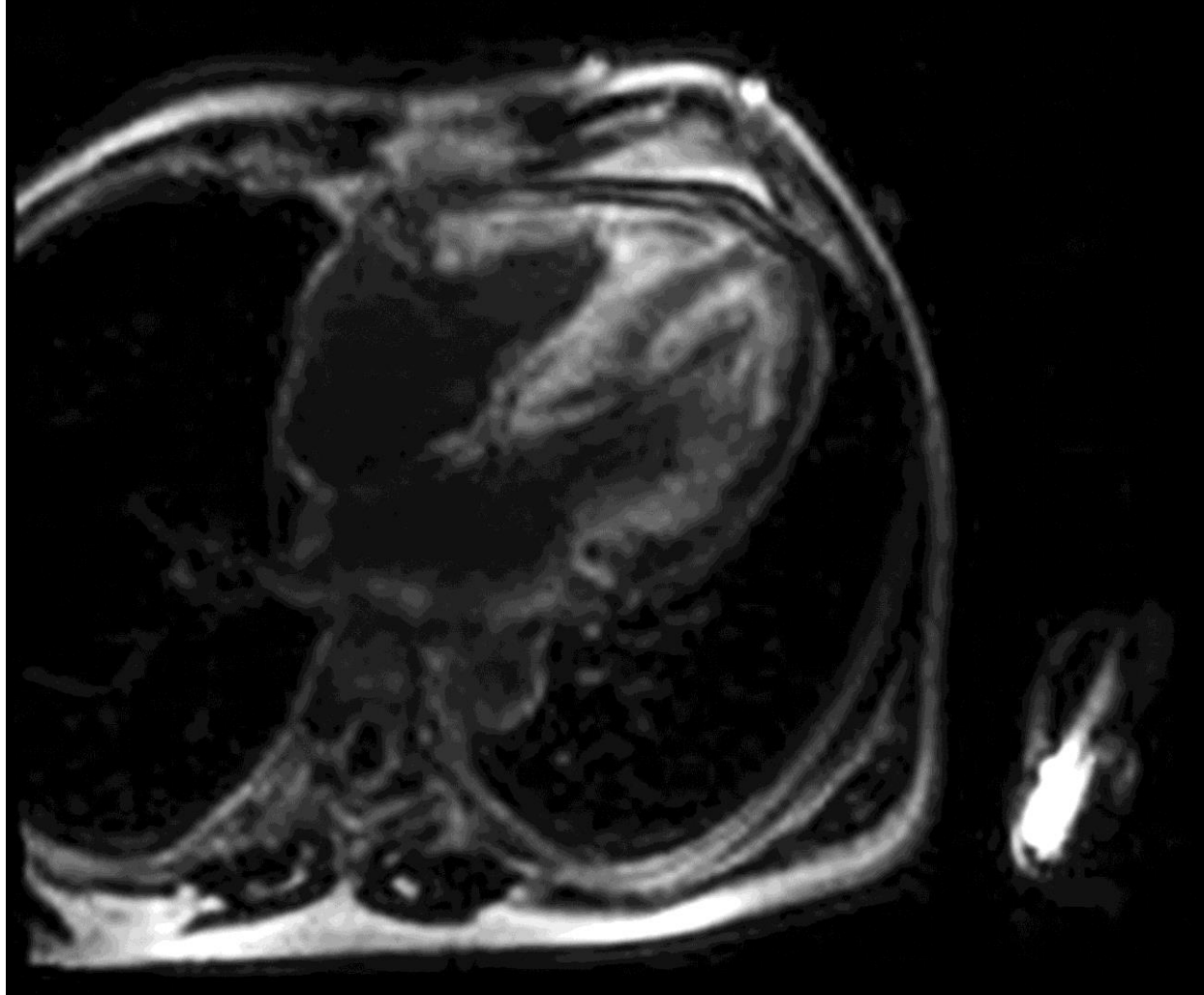
- Low tissue doppler velocities
- High E/e ratio
- Restrictive physiology
- Longitudinal strain is severely impaired for both (worse in AL amyloidosis)
- Strain and tissue doppler is picking up early amyloidosis compared to traditional echo
- Strain demonstrates “apical sparing”

# Others tests

- Right-side catheterization shows restrictive filling pattern, median PCWP 21mmHg
- ECG low-voltage (only 36%) and pseudo infarction complex with poor R-wave progression (65%)
- Cardiac MRI
- Radionuclide scan

# Cardiac MRI

- Cardiac MRI demonstrates late gadolinium enhancement over the entire subendocardial circumference
- Sensitivity 80% specificity 94% PPV 92% NPV 85%
- Useful in distinguishing between hypertrophic cardiomyopathy and hypertensive heart disease
- 90% ATTR have transmural LGE vs 37% AL



Morie A. Gertz et al. JACC 2015;66:2451-2466

# Radionuclide imaging

- First noted 30years ago
- DPD (Tc-3,3-diphosphono-1,2-propanodicarboxylic acid) first used.
- Higher uptake in ATTR versus AL amyloidosis.
- Earlier uptake noted than CMR



# Radionuclide imaging

- Tc-pyrophosphate (more commonly available in USA) uptake showed 97% sensitivity and 100% specificity for ATTR
- Tc-hydroxymethylene diphosphate can detect ATTR
- Negative SPECT can exclude cardiac involvement

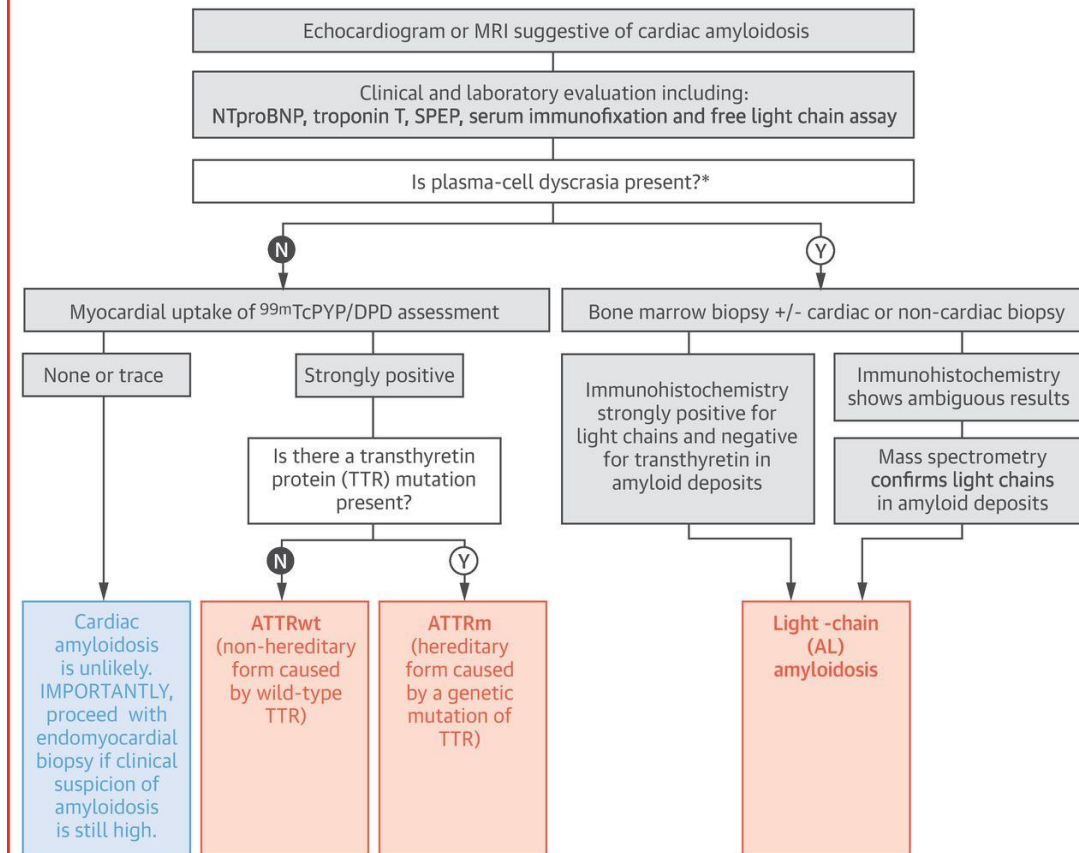




# Other testing

- Labs: elevated troponin and BNP are elevated (ATTR appears to be less toxic than AL amyloid)
- Biopsy verification is essential but not necessary (especially in elderly or debilitated pt with neuropathy)
- Noncardiac biopsies usually show amyloidosis (AL greater than ATTR) in patient with positive echo or CMR finding;
  - skin biopsy from abdominal wall (73% sensitivity)
  - bone marrow biopsy (41%)
  - rectal or sural nerve biopsy (81%)
  - minor salivary glands (61%)
- Negative biopsy of unaffected organs does not exclude diagnosis
- Confirmation of amyloid type made on immunostaining and mass spectroscopy (gold standard)

**CENTRAL ILLUSTRATION: Diagnosing and Typing Cardiac Amyloidosis in a Patient With Unexplained Heart Failure**



Falk, R.H. et al. J Am Coll Cardiol. 2016;68(12):1323-41.

Rodney H. Falk et al. JACC 2016;68:1323-1341

# ATTR Therapies

- Supportive care
  - Diuretic agents should be cautiously used
    - since there is usually low end-diastolic volumes and high filling pressures needed to distend a stiff ventricle
    - reduce stroke volume and SBP results in cerebral hypo perfusion
  - Digoxin binds to amyloid fibers and increase toxicity
  - Beta blockers, ACE and ARB are poorly tolerated

# ATTR Therapies

- Liver transplant
  - considered first-line
  - bulk TTR is produced in liver
  - mutant ATTR is removed but wt ATTR is present and cardiac deposits still occur
  - quality of life is stable for first 4years then declines
- Heart and Liver transplant do better (5year survival 80%, 10year survival 28-78% depending on mutation involved, V30M better prognosis)

# ATTR Therapies

- Pharmacologic therapy
  - Several on going trial
  - Catechin (present in green tea) inhibits amyloid fibril formation
  - Diflunisal binds to TTR and stabilizes monomers thru prevent misfolding
  - Tafamidis approved in Europe and Japan for mutant ATTR, prevents dissociation of native TTR
  - RNA inhibition technology is used to knock down disease causing TTR tissue deposits
  - Doxycycline can disrupt fibrils and in mouse models results in amyloid disaggregation

**TABLE 2 Selected Trials for TTR Amyloidosis**

Drug	Phase	TTR Type	Organs	Study Number
Doxycycline + tauroursodeoxycholic acid	II	Wild type and mutant	Cardiac, nerve	<a href="#">NCT01171859</a>
Revusiran (ALN-TTRsc), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)	III	Mutant	Cardiac	<a href="#">NCT02319005</a>
Tafamidis	III	Wild type and mutant	Cardiac	<a href="#">NCT01994889</a>
Diflunisal	II/III	Mutant	Nerve	<a href="#">NCT01432587</a>
Patisiran (ALN-TTRO2), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)	III	Mutant	Nerve	<a href="#">NCT01960348</a>
ISIS-TTR <sub>Rx</sub> Isis Pharmaceuticals (Carlsbad, California)	III	Mutant	Nerve	<a href="#">NCT01737398</a>
SOM0226, SOM Biotech SL (Barcelona, Spain)	I-II	Mutant	Nerve	<a href="#">NCT02191826</a>

TTR = transthyretin.

# AL Amyloid

- AL amyloidosis effects renal, neural and/or skin
- Hematologic disorder of plasma cells closely related to multiple myeloma
- Abnormal proliferation of plasma cells overproducing lambda and kappa (less common) light chain
- Unlike multiple myeloma AL amyloid plasma cells make up less than 20% of bone marrow
- Renal involvement most common, Cardiac is second
- Cardiac AL amyloid is rarely by itself

# AL Amyloid

- Clinical aspect of AL
  - Severity of heart failure is worse
  - AL amyloid infiltration into heart is necessary before
    - Light chains cause increase in cellular reactive oxygen species and up-regulation of heme oxygenase which induces apoptosis



# AL Amyloid

- Clinical Manifestations
  - Dyspnea on exertion is most common manifestation (likely from LV diastolic dysfunction)
  - Peripheral edema (likely related to hypoalbuminemia for nephrotic syndrome)
  - Ascites also common
  - Prominent V waves noted in absence of mitral regurgitation
  - Amyloid deposits in atrium results in dysfunction and thrombus formation even in sinus rhythm
  - Exertion syncope likely form low or fixed cardiac output

# AL Amyloid

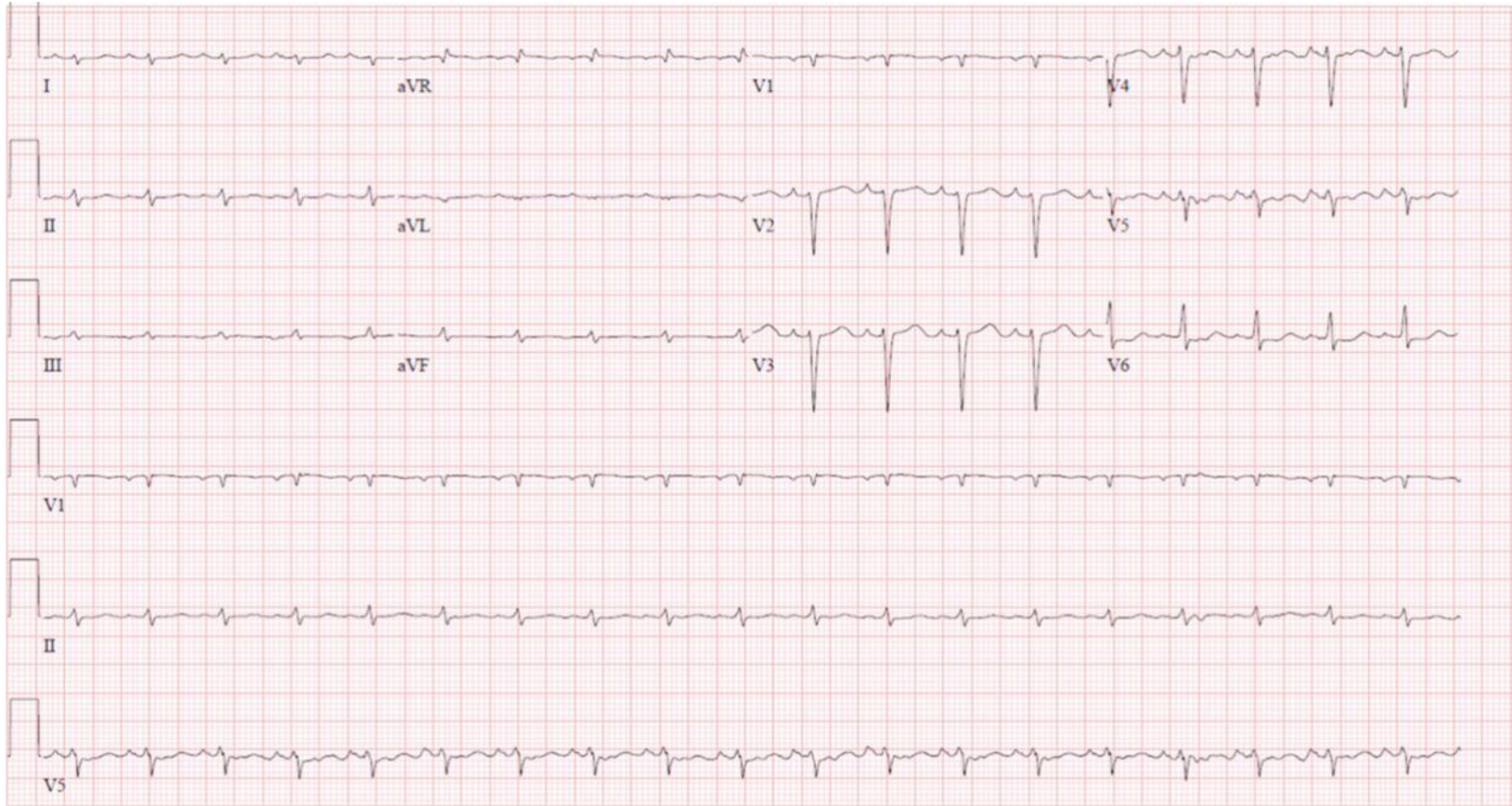
- Clinical Manifestation
  - Jaw claudication, leg claudication or angina due to small vessel amyloid deposits
  - 10% have macroglossia
  - Periorbital bruising in setting of heart failure (pathognomonic for AL)
  - Enlarged liver due to hepatic infiltration
  - Low blood pressure (decrease CO and low peripheral tone)
  - Early sensory neuropathy



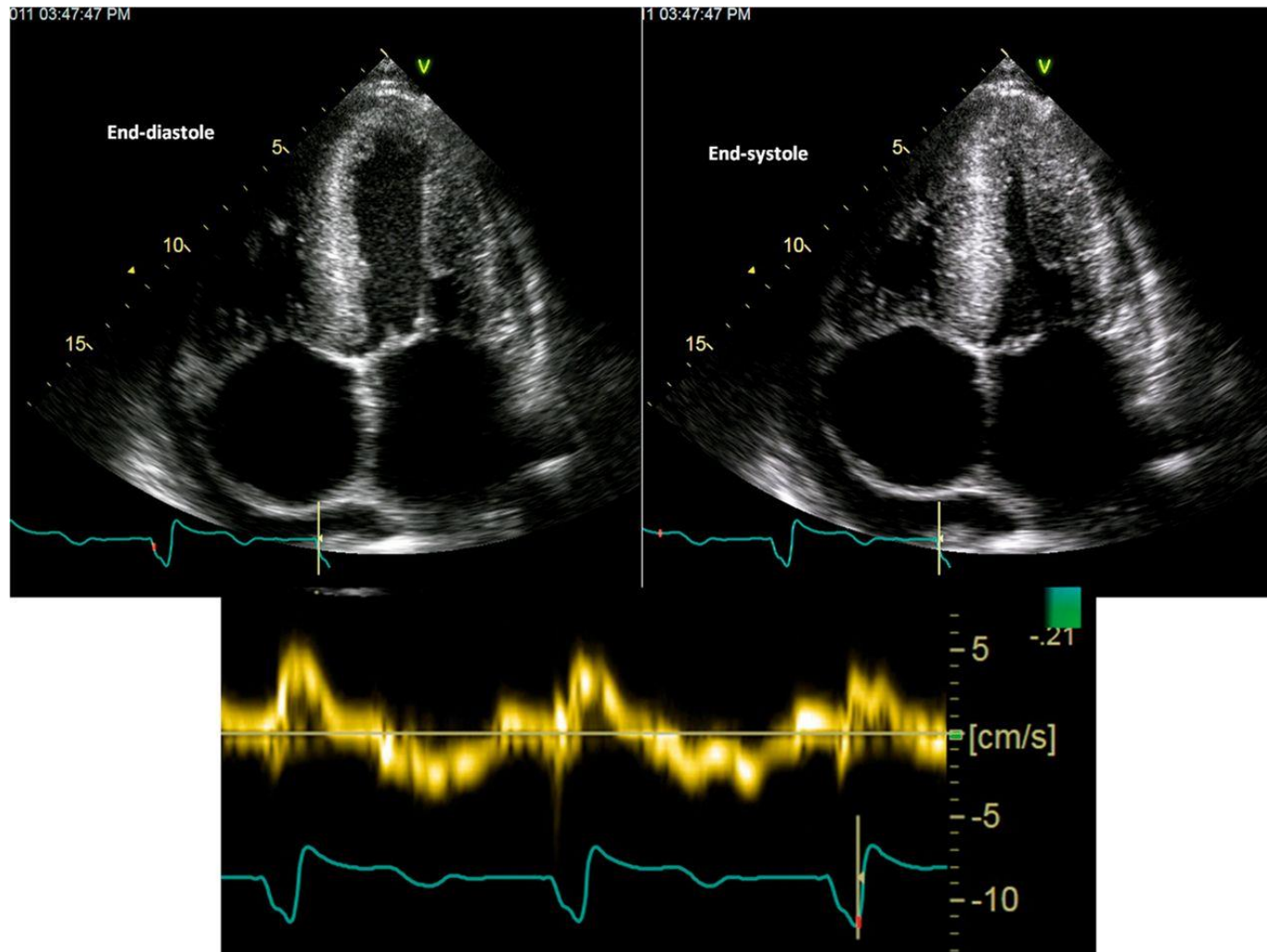
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# AL Amyloid Tests

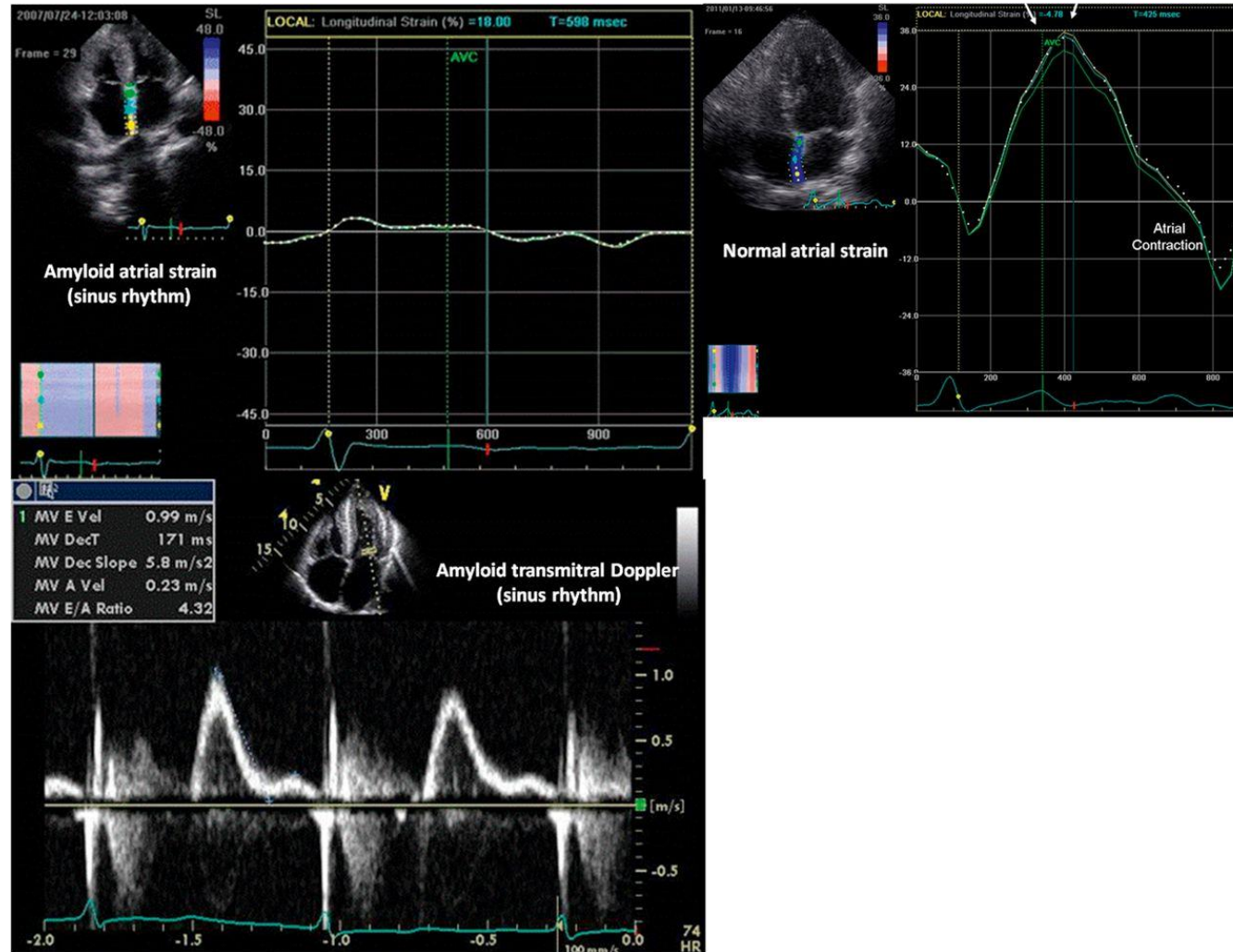
- Diagnostic tests
  - ECG shows low voltage with unusual axis (extreme right axis). QRS low voltage but P wave is often normal size
  - Echo shows LV wall thickness exceeds 15mm;
    - Hypertensive heart rarely has >15mm thickness
    - E/e exceeds 15
    - Restrictive pattern with short deceleration time
    - Pericardial effusion is common but rarely large and tamponade is rare.



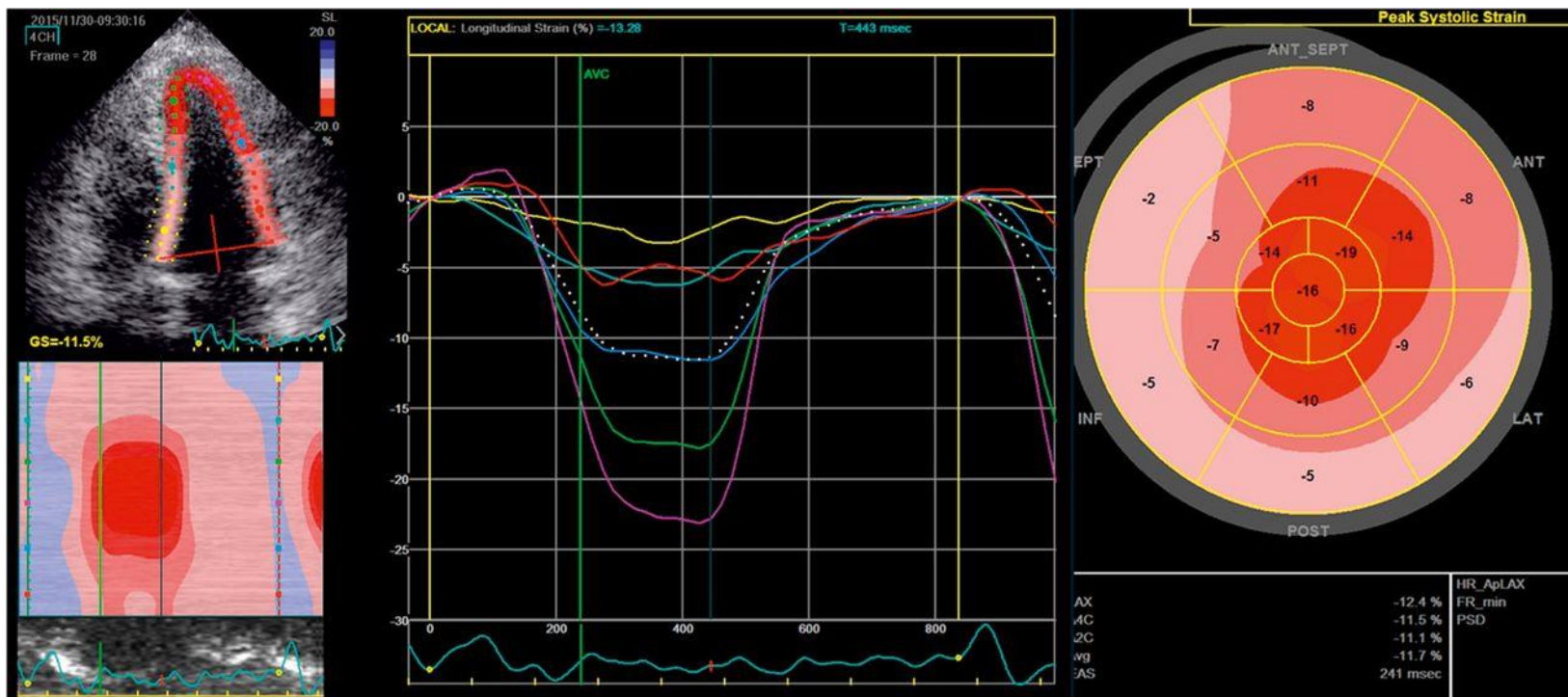
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# AL Amyloid Tests

- Cardiac MRI features:
  - difficulty in nulling the myocardium following gadolinium injection
  - noncoronary usually subendocardial pattern of delayed gadolinium enhancement

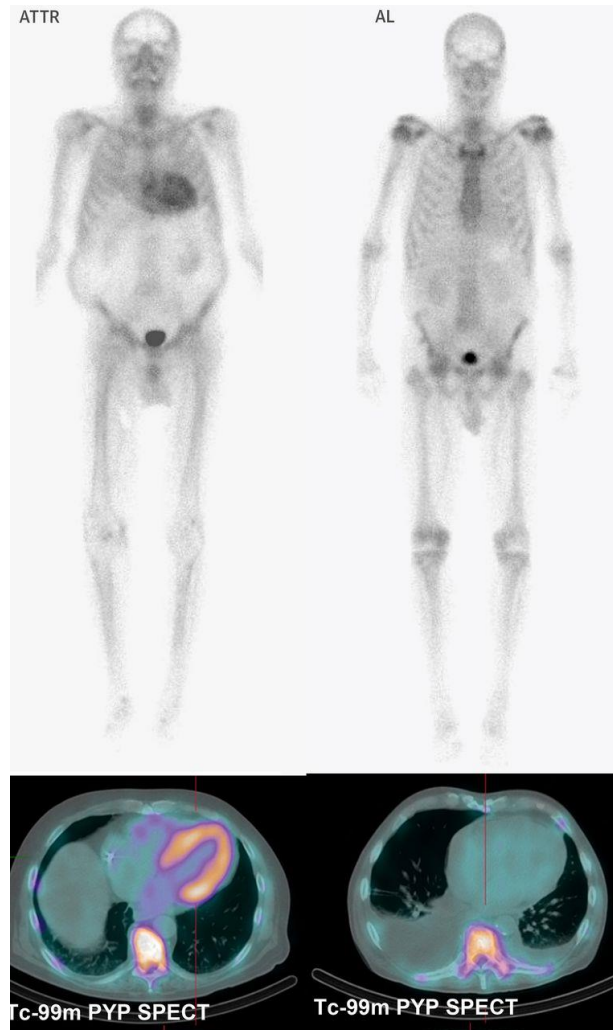


# AL Amyloid Tests

- SPECT
  - 1980s Tc-PYP was noted as marker for cardiac amyloid but fell out of favor due to low sensitivity
  - However, recently it was noted that Tc-PYP and DPD are avidly taken up by hearts infiltrated by TTR amyloid but none or minimal uptake in AL amyloid

# AL Amyloid

- SPECT
  - If Tc-PYP or DPD is positive and there is absence of plasma cell dyscrasia, it has been deemed acceptable as specific enough for TTR amyloidosis without cardiac biopsy
  - Positive Tc-PYP is helpful if to identify TTR amyloidosis with unrelated MUGS (~20% of TTR pts)



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# AL Amyloid

- Labs:
  - Usually unrevealing but often have
    - hypoalbuminemia,
    - hypercholesterolemia,
    - low troponin elevation
  - Free light chain kappa/lambda ratio is >90% in untreated AL
  - All patient with suspected AL should have bone marrow biopsy to determine percentage of plasma cells involved to rule out both multiple myeloma

# AL Amyloid

- Therapy for AL:
  - optimize heart failure
  - chemotherapy aimed at getting rid of amyloidogenic plasma cell dysuria



# AL Amyloid

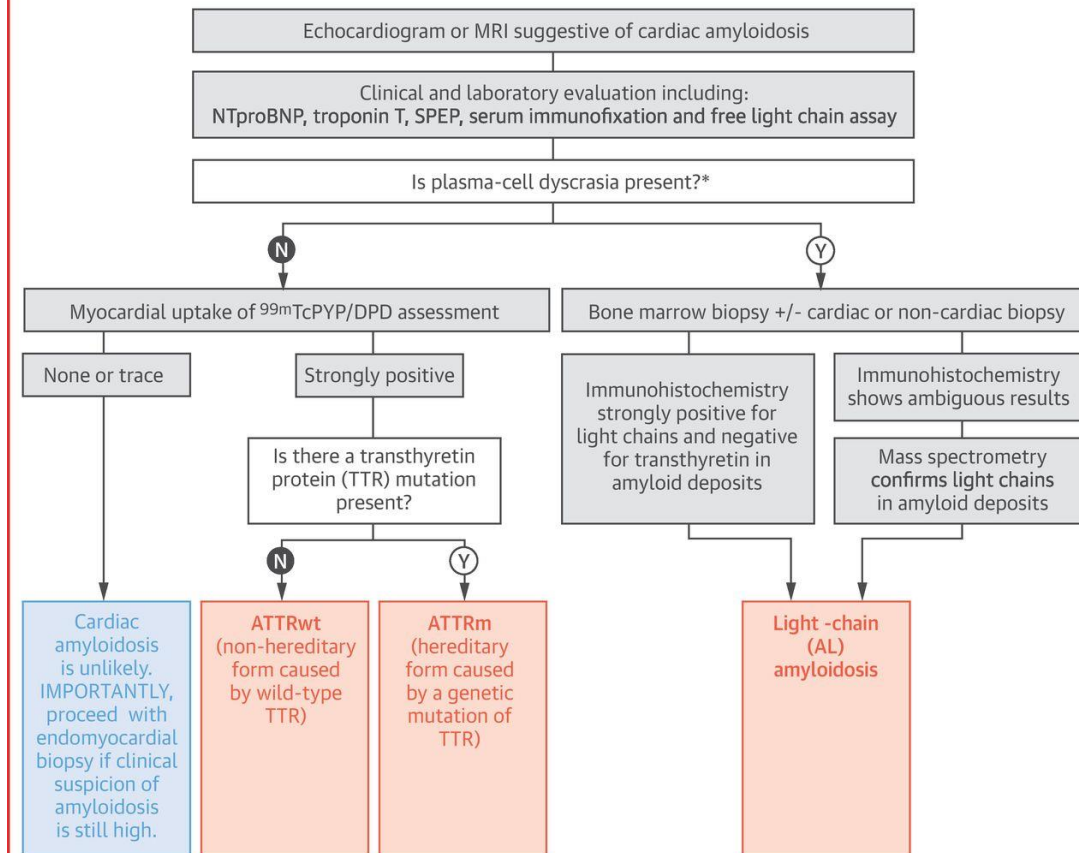
- Therapy:
  - atrial tachycardia and arrhythmia common
    - treat with amiodarone and sometimes dofetilide;
    - anticoagulation should be given (even if pt in sinus rhythm)
    - no proven benefit of pacing or prophylactic ICD

# AL Amyloid

- Therapy
  - high dose melphalan and stem cell transplant was tried but high treatment related mortality
  - bortezomib with dexamethasone and low-dose cyclophosphamide has some success
  - cardiac transplant has been tried with concomitant chemotherapy
    - high mortality rate



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# Conclusion

- Amyloidosis is a condition where the extracellular space of the heart is expanded by amorphous, proteinaceous material which is extremely difficult to degrade.
- The source of these proteins are the liver (ATTR) or plasma cells (AL).
- Amyloidosis leads to restrictive cardiac physiology

# Conclusion

- Speckled echocardiogram and strain analysis have advanced the ability to detect early changes from amyloidosis
- Cardiac MRI and SPECT Tc-PYP images can help differentiate between ATTR and AL amyloidosis.

# References

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Pai RG, Varadarajan P. Deeper into cardiac amyloid. J AM Coll Cardiol: Cardiovascular imaging, 2017; Vol 10, No 4:408-10

Maurer M, Castano, A. Prognosticating in Cardiac Amyloidosis. J AM Coll Cardiol: Cardiovascular imaging, 2018; in press

ASNC Practice points: 99mTechnetium-Pyrophosphate imaging for transthyretin cardiac amyloidosis.



**Every life deserves world class care.**