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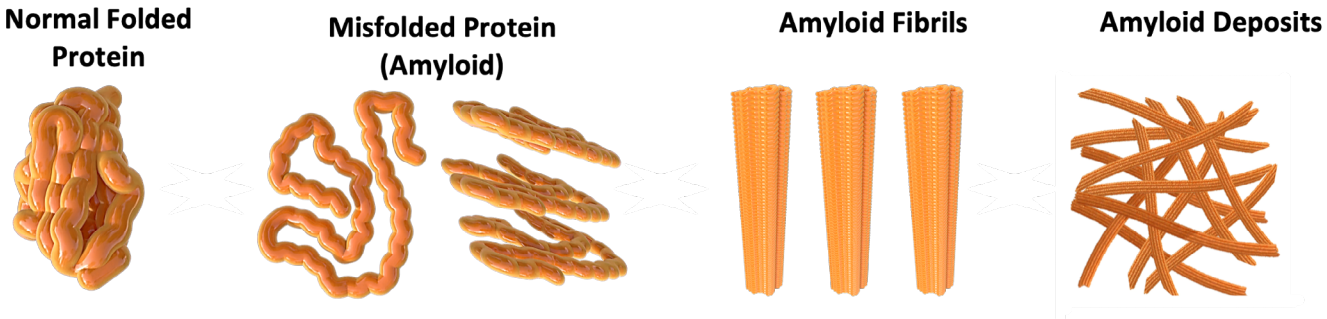
Overview of ATTR amyloidosis

Amyloidosis is a protein misfolding disorder. Misfolded polypeptides form linear structures that aggregate into rigid, non-branching, and insoluble amyloid fibrils that deposit extracellularly in tissues and organs, causing dysfunction.[1] **(Figure 1)**

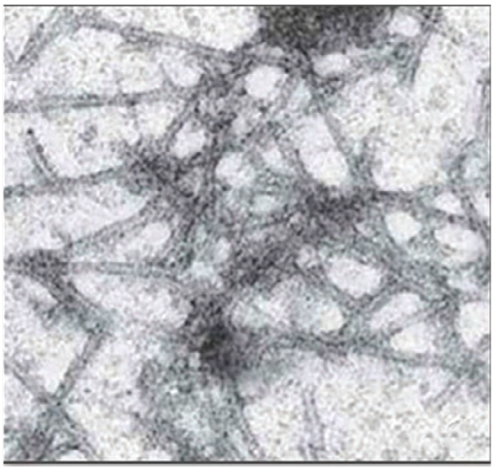
Figure 1. Amyloidosis is a protein folding disorder



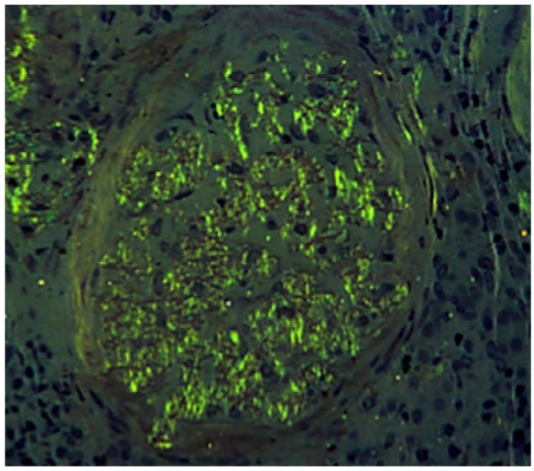
Amyloid deposits are recognizable in electron micrographs **(Figure 2A)**. When stained with Congo Red and viewed under polarized light microscopy, they have a characteristic apple green birefringence **(Figure 2B).**

Figure 2. Amyloid deposits A. Electron Microscopy B. Polarized Microscopy

A



B



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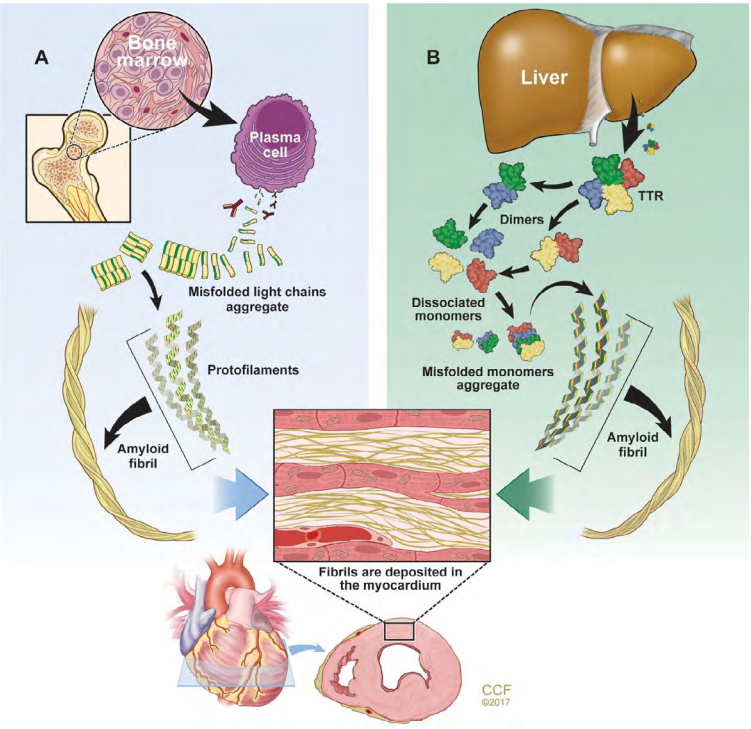
Two types of amyloid diseases account for 95% of cardiac amyloidosis—immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR).[1] **(Figure 3)**

Light chain amyloidosis (AL) occurs when clonal plasma cells overproduce light chains that misfold and form amyloid fibers that deposit in various organs (heart, kidneys, liver, nerves, digestive tract).[1,2] It is a rare disease, with approximately 7,000 new cases annually in the US and a median age at diagnosis of 63 years.[2]

Transthyretin (ATTR) amyloidosis occurs when tetrameric transthyretin protein, which is produced in the liver, disassociates into monomers, which then form amyloid fibrils that deposit in various organs. ATTR may be an acquired mutation in wild-type (ATTRwt) or a hereditary variant (ATTRv).[1] Transthyretin gene testing must be performed to distinguish.

Figure 3. Two main types of amyloid diseases affect the heart A. Light chain (AL) B. ATTR (transthyretin)



Wild Type (ATTRwt)

- **No mutation in TTR gene**
- **Not hereditary**
- **Median age at diagnosis: 74 years**
- **Mostly white males**
- **25% of patients > 80 years have ATTRwt on autopsy**

Variant (ATTRv)

- **Mutation in TTR gene present**
- **Hereditary, autosomal dominant**
- **Age of diagnosis and organs involved depend on specific mutation**
- **3.5% of African Americans are heterozygous carriers of V122I (aka p.V1421)**

Causes late-onset cardiac amyloidosis

- **T60A is found in people of Irish descent**

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Pathology and Pathophysiology

- Diffuse amyloid deposition causing thickening of both ventricles
- Increase in LV mass without dilation
- Atrial infiltration impairing atrial contraction
- Conduction system may be affected and valves are usually thickened
- Microvascular ischemia

Clinical Presentation

Both cardiac and non-cardiac symptoms are usually present. Presence of non-cardiac symptoms, particularly the orthopedic symptoms, in conjunction with the cardiac symptoms, should raise suspicion.

Cardiac Symptoms

- **Heart Failure (HFpEF, HFmrEF, HFrEF)**
- **'Hypertrophic cardiomyopathy" (often missed diagnosis)**
- **Low-flow low-gradient aortic stenosis in elderly**
- **Atrial fibrillation/cardioembolic stroke**
- **Complete heart block/pacemaker**
- **Angina with normal coronary arteries/ cardiogenic shock**

Non-cardiac symptoms

- **Orthostatic symptoms, diarrhea, ED**
- **Peripheral neuropathy**
- **Proteinuria/nephrotic syndrome (AL*)**
- **Macroglossia or periorbital purpura (AL*)**
- **Bilateral carpal tunnel syndrome (TTR > AL)**
- **Spinal stenosis/biceps tendon rupture (ATTRwt)**

In patients with heart failure and increased wall thickness, ask about these issues, which often precede ATTR by several years:[3,4]

- Presence of bilateral carpel tunnel syndrome or surgery for the same
- Spinal stenosis
- Biceps tendon rupture
- Rotator cuff tears

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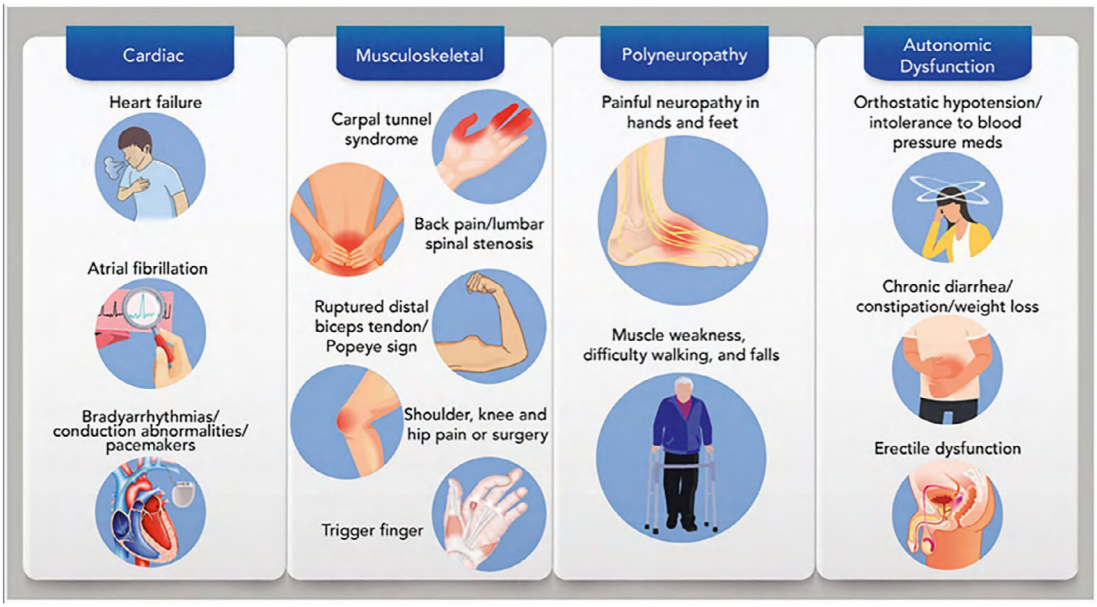
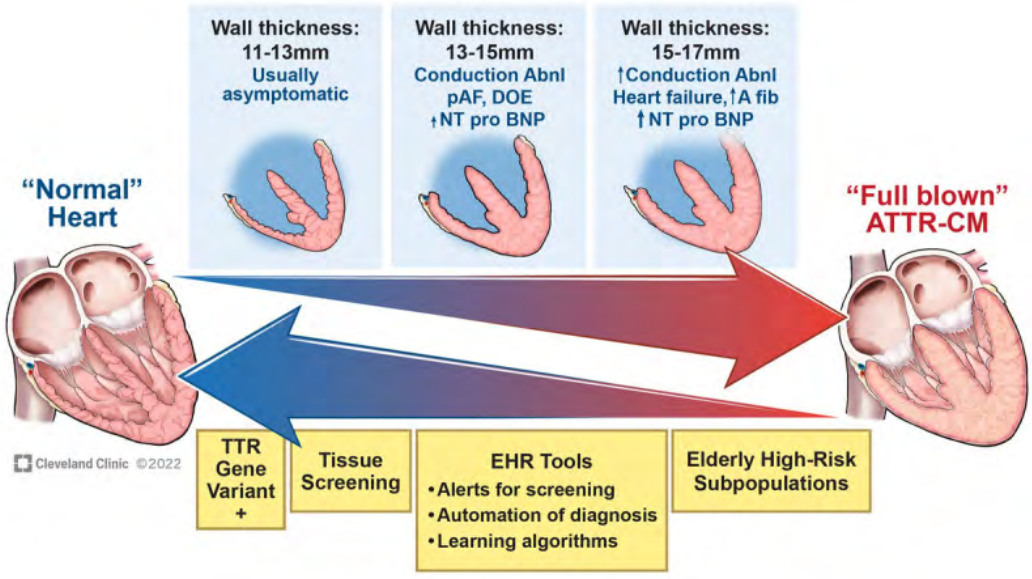
Clinical manifestations of cardiac amyloidosis[5]



Opportunities for early diagnosis of ATTR-CM



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Strategies for Identifying and Confirming ATTR

Echocardiogram and electrocardiogram

- Increased septal and posterior wall thickness (≥ 1.5 cm)[1,6]
- LVH on echocardiogram combined with low voltage on ECG is a classic finding; absence of low voltage does not exclude a diagnosis of cardiac amyloidosis [1]
- Classic low voltage only about 30% in ATTR
- Thickening of right ventricle free wall, valves[1,7]

A. Normal **B. Amyloid**

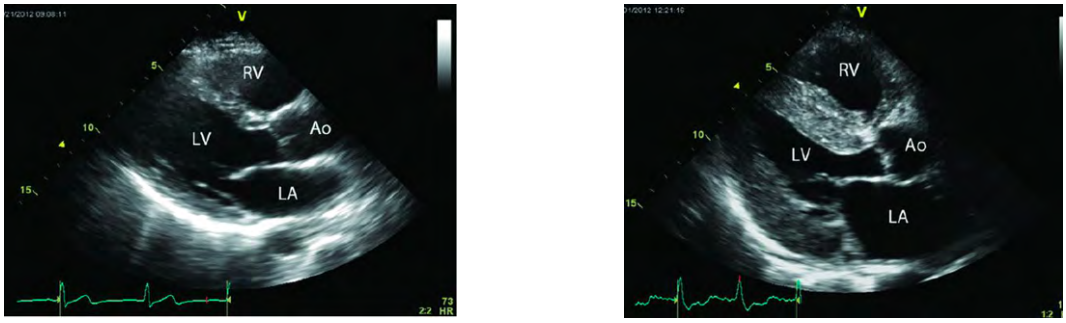

Figure 4. Echocardiogram A. Healthy patient B. Patient with cardiac amyloidosis

- View the electrocardiogram in conjunction with the echocardiogram
- Increased low voltage without hypertrophy indicative of cardiac amyloidosis
- Look for the degree of discordance between ECG voltage and LV wall thickening
- Conduction disease is very common
- About 25% of patients with wildtype ATTR cardiac amyloidosis have asymmetric septal hypertrophy[8]
- About 16% of older patients with ATTR have paradoxical low–flow low–gradient aortic stenosis[6]

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Longitudinal strain imaging

- Measures deformation of myocardium in specific LV segments and displays quantification as a polar map. A more negative value (coded red) is associated with better function.
- A specific pattern called “apical sparing” is seen in cardiac amyloidosis—the apical LV segments have normal or near-normal strain compared with the mid and basal segments **(Figure 5A)**
- The bullseye pattern on the polar map is suggestive of cardiac amyloidosis **(Figure 5B)**
- Apical sparing is typically not seen in hypertrophic cardiomyopathy and hypertensive heart

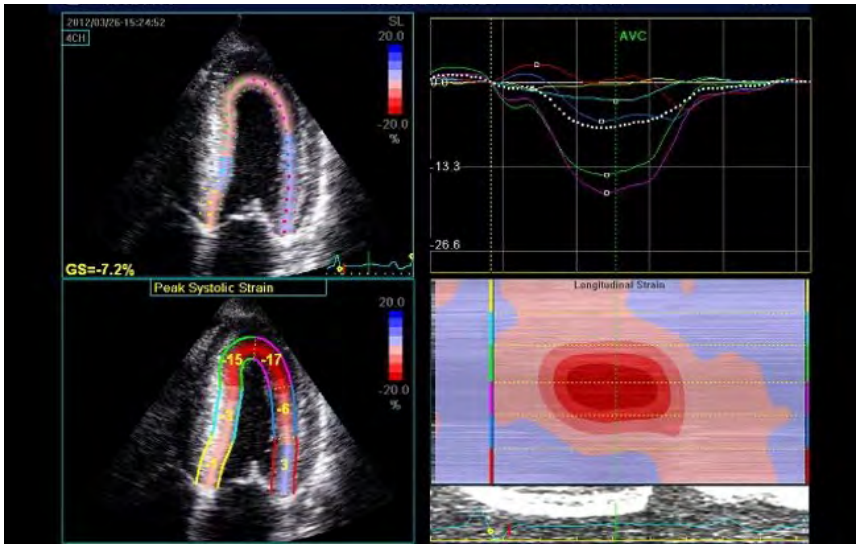

Figure 5. Longitudinal Strain Imaging A. Characteristic “apical sparing” pattern B. Polar image with bullseye pattern

Cardiac MRI

- Cardiac MRI (CMR) is an imaging technique that provides comprehensive phenotypic assessment of myocardial structure and function
- CMR can assess ventricular size, function mass, myocardial mechanics, tissue characteristics, flow quantification, myocardial perfusion, and potential underlying microvascular dysfunction
- Late gadolinium enhancement is a highly sensitive (86%) and specific (92%) tool for diagnosis of cardiac amyloidosis, with 85% negative predictive value[9]

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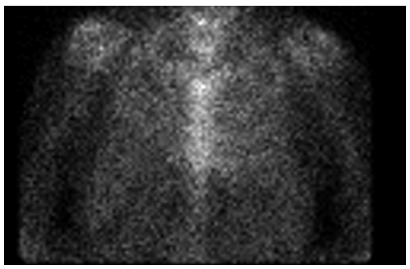
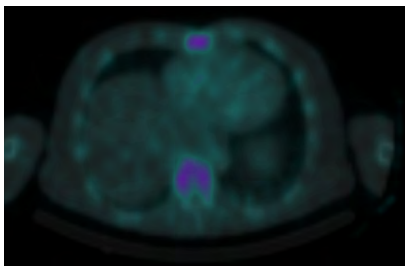
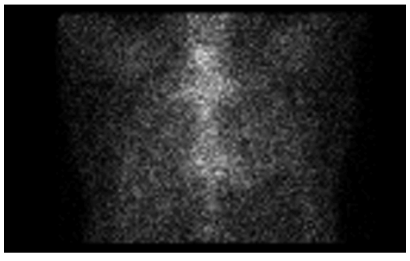
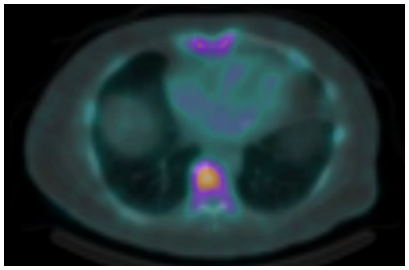
Cardiac scintigraphy

- Also known as pyrophosphate (PYP) scan; a non-biopsy method to diagnose ATTR cardiac amyloidosis
- Nuclear imaging is a simple, easy to interpret test that is highly sensitive and specific for ATTR
- Diagnosis of ATTR is planar grade 2/3 + positive SPECT/CT + negative evaluation for AL (serum and urine immunofixation)
- Planar imaging compares uptake in the heart to that in the ribs and uses the Perugini score/planar grade to assess the results
  - Grade 0: No cardiac uptake
  - Grade 1: Cardiac uptake less than rib
  - Grade 2: Cardiac uptake equal to rib
  - Grade 3: Cardiac uptake greater than rib
- SPECT/CT overlays low–dose CT imaging with the nuclear imaging, which shows focal and diffuse uptake of tracer

	Planar Imaging	SPECT/CT	
Grade 0			**No uptake**
Grade 1			**Persistant blood pool**

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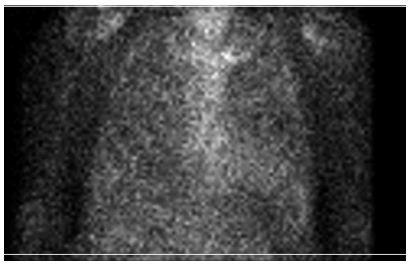
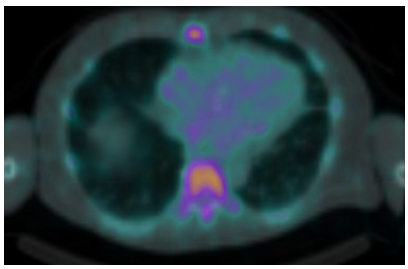
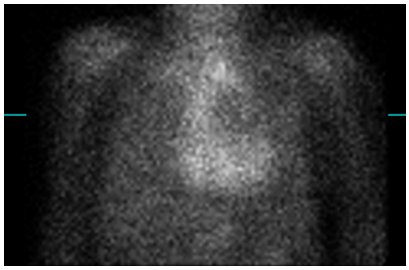
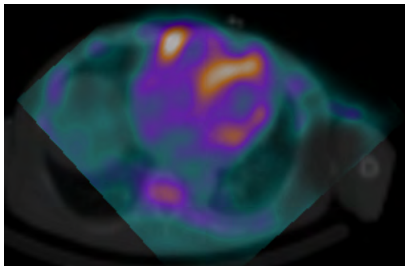
Cardiac scintigraphy (cont.)

	Planar Imaging	SPECT/CT	
Grade 2			Diffuse uptake
Grade 3			Diffuse uptake

- Prevalence of ATTR in patients with aortic stenosis (AS) is estimated to be approximately 4-24%[10]
- Both ATTR and AS are associated with thick walls, poor diastolic function, and abnormal LV strain—which makes identifying ATTR in patients with AS challenging. PYP imaging can simplify diagnosis
- In the table on the next page, echocardiogram and PYP images for two patients—one with and the other without ATTR—are provided for comparison

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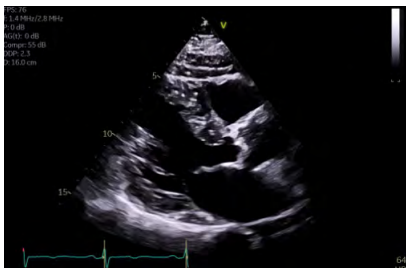
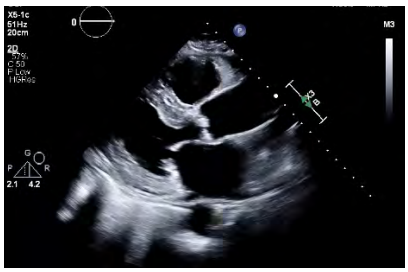
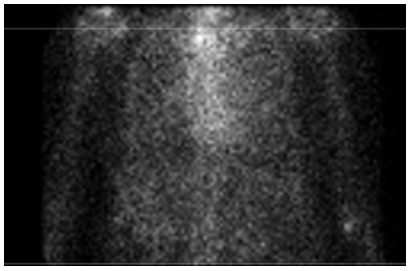
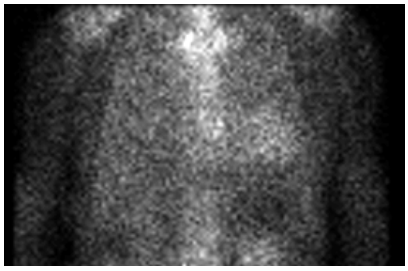
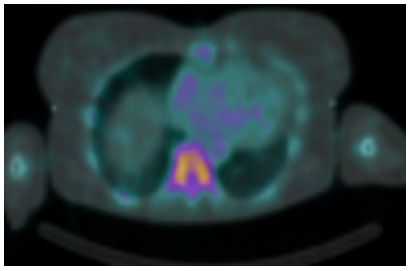
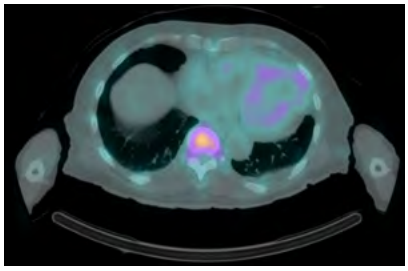
	PATIENT A	PATIENT B
Echocardiogram		
Scintigraphy		
Planar grade 0		
Planar grade 2		
Persistent blood pool		
Diffusely positive		

- The Cleveland Clinic started screening all TAVR patients aged ≥ 70 years and found that NT-pro BNP is a sensitive marker for detecting ATTR-CA

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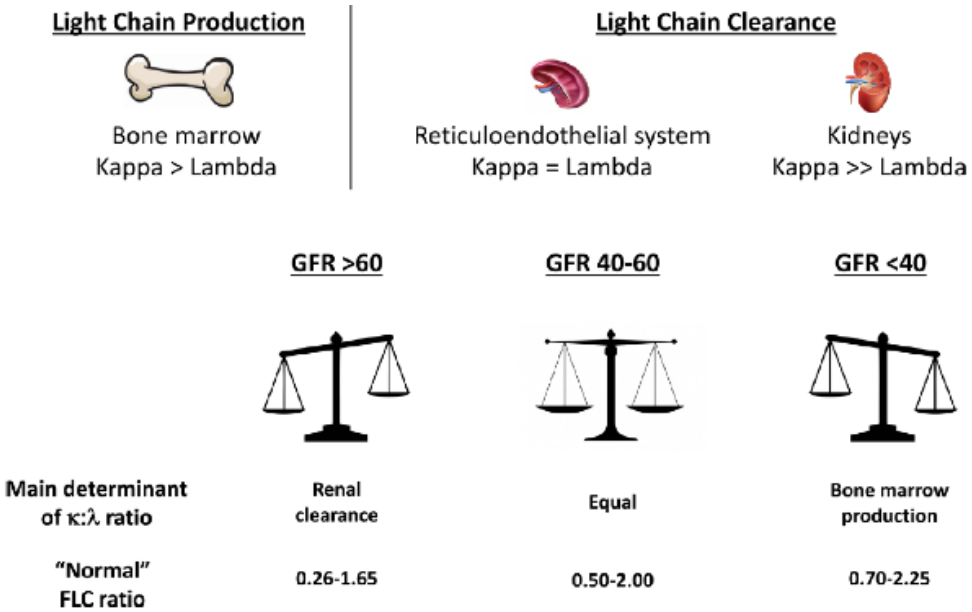
Ruling out AL

- Use the following assays
  - Serum free light chain assay (kappa/lambda)
  - Serum immunofixation
  - Urine immunofixation
- Don't use SPEP and UPEP
- PYP scan positive but kappa and lambda values normal = exclude AL; no heart biopsy required
- PYP scan positive, kappa and lambda values high, K/L ratio low = requires a tissue diagnosis—heart biopsy, salivary gland biopsy
- PYP scan positive, no monoclonal protein, kappa and lambda high, ratio normal = probably AL, confirm with biopsy
- Decreased renal clearance leads to increases in the sFLC ration (K > L) in the absence of monoclonal gammopathy **(Figure 6)**[11]

Figure 6. Differences in the production and clearance of free κ and λ light chains



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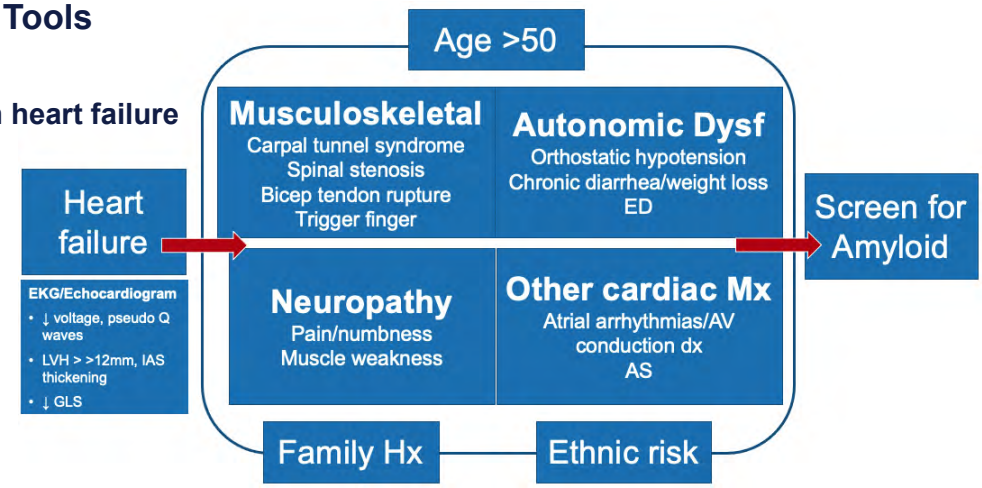
Processes, Tools, and Strategies for Clinical Practice

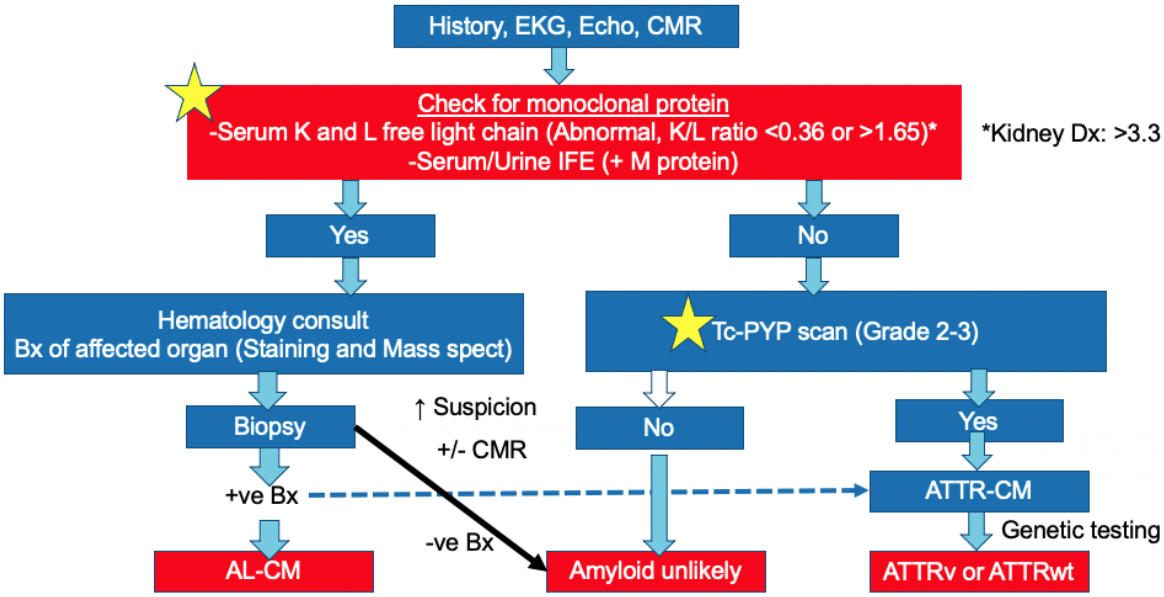
Clinical Decision-making Tools

Evaluating a patient with heart failure



Diagnostic algorithm if amyloidosis is suspected

Adapted from the 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis[5]



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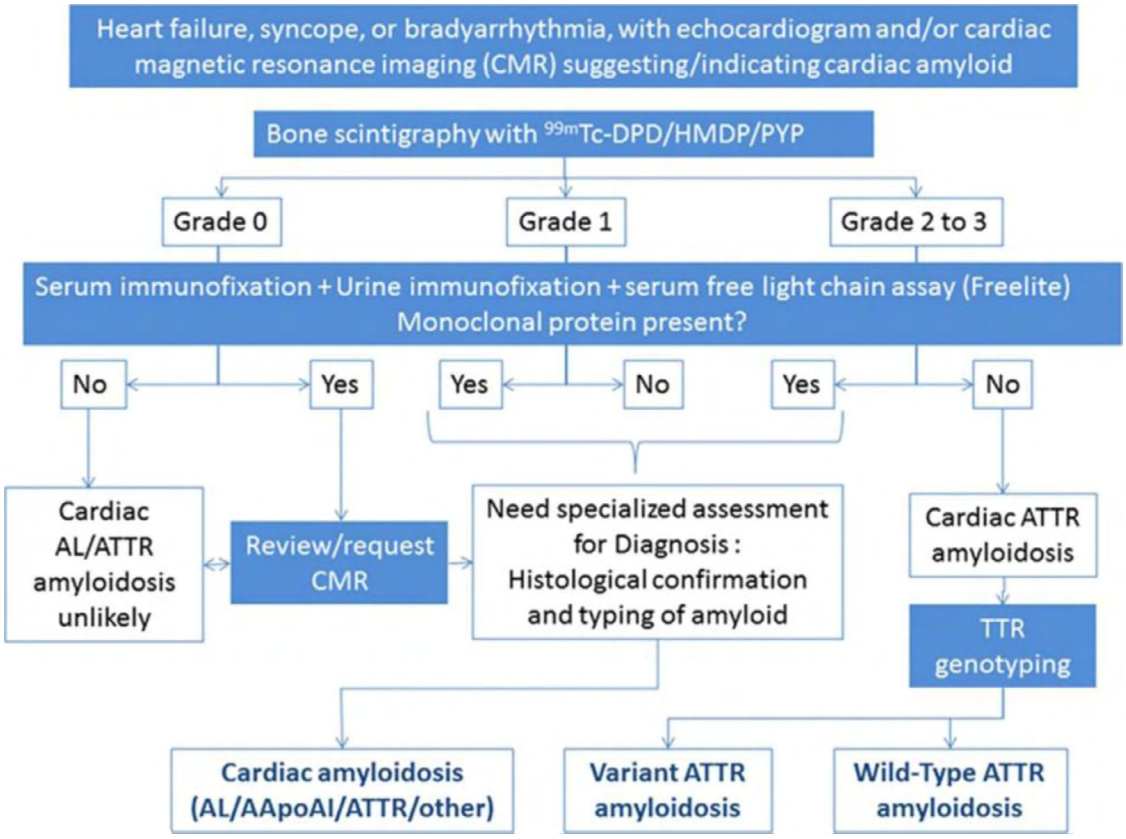
Processes, Tools, and Strategies for Clinical Practice

Diagnostic algorithm from expert consensus recommendations for multimodal imaging in cardiac amyloidosis[12]



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EHR order sets

These are order sets in the Cleveland Clinic EHR that physicians can use if they suspect amyloidosis. Similar order sets can be set up in any EHR to aid in diagnosis of cardiac amyloidosis. Troponin or other tests can be added as needed.

OUTPATIENT

CARDIAC AMYLOID ORDER PANEL
- Free Kappa/Lmabda Light Chains, Blood
  Expected: 8/13/2023, Lab, Routine, BLOOD, Resulting Agency - CLEVELAND CLINIC LAB
- Immunofixation Screen, Serum
  Expected: 8/13/2023, Lab, Routine, BLOOD, Resulting Agency - CLEVELAND CLINIC LAB
- Urine Monoclonal Protein Analysis
  Expected: 8/13/2023, Lab, Routine, URINE, Resulting Agency - CLEVELAND CLINIC LAB
- PROTEIN CREATININE RATIO
  Expected: 8/13/2023, Lab, Routine, URINE, Resulting Agency - CLEVELAND CLINIC LAB
- NM SPECT/CT CARDIAC AMYLOID
  Routine
- CONSULT TO MEDICAL GENETICS - GENERAL
  Routine
- MRI CARDIAC MORPH FUNC WO/W IVCON
  Routine
- MRI CARDIAC VELOCITY FLOW MAP
  Routine

iv contrast (will be provided with radiology test)
MRI Cardiac w/Qflow Inject, intravenously, once for 1 dose. No IV access, insert saline lock prior to the beginning of sedation, infusion, injection of imaging exam. Discontinue saline lock post exam. If Pt has a central line or IVAD, may access for administration according to line specific nursing protocol. Once exam is complete flush line and de-access according to line specific nursing protocol in the MR contrast administration guidelines link
In Office, Disp-1 Each, R-0

INPATIENT

Work Up for AL Amyloidosis
- Work Up For AL Amyloidosis
- KAPPA/LAMB.FREE.SER
  Add to specimen collected 22h ago?
  Routine, ONCE, today at 2200, For 1 occurrence, Clinician Collect, BLOOD, New collection
- IMMUNOFIXATION SCREEN, SERUM
  Routine, ONCE, today at 2200, For 1 occurrence, Clinician Collect, BLOOD
- MONOCLONAL PROT UR W/INTERP
  Routine, ONCE, today at 2200, For 1 occurrence, Clinician Collect, URINE
- PROTEIN CREATININE RATIO
  Add to specimen collected 4d ago?
  Routine, ONCE, today at 2200, For 1 occurrence, Clinician Collect, URINE, New collection

Work Up for Transthyretin (TTR) Amyloidosis
- NM SPECT/CT CARDIAC AMYLOID
  Routine, ONCE, today at 2200, For 1 occurrence
- Cardiac Amyloid Other Testing
  - MRI CARDIAC WO/W IV CONTRAST AND W/QFLOW (HL.MC.MO)
  - MRI CARDIAC VELOCITY FLOW MAP
  - MRI CHEST POST PROCESSING
  - NT PRO BNP
  - High Sensitivity Troponin T

Resources

Cleveland Clinic. Amyloidosis Center.

Amyloid Clinic at Cleveland Clinic—Joint Hematology and Heart Failure Clinic every Monday afternoon at MC J3-4.

Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2-Diagnostic criteria and appropriate utilization [published correction appears in J Nucl Cardiol. 2021 Aug;28(4):1763-1767]. *J Nucl Cardiol*. 2020;27(2):659-673.

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Resources (continued)

Dorbala S, Ando Y, Bokhari S, et al. Addendum to ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2-Evidence Base and Standardized Methods of Imaging. *J Card Fail*. 2022;28(7):e1-e4.

Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail*. 2021;23(4):512-526.

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2. Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance: a review. *Immunol Rev*. 2003;194:112-139.

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