TTR Amyloidosis

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Apparent Natural History of Cardiac Amyloidosis

Cardiac Manifestations

- Heart failure
  - Diastolic dysfunction (impaired relaxation) > Systolic dysfunction (impaired contraction)
- Electrophysiologic
  - Heart block
  - Tachyarrhythmias
  - Low voltages on EKG (*)
- Imaging/Laboratory
  - Left ventricular “hypertrophy”
  - Elevated troponin/BNP/NTproBNP
Key to Screening for Cardiac Amyloid
Understand *Amyloid Types*

- >30 proteins can form amyloid
- Only a few deposit in the heart

Only two types to know:

1. **AL** – “primary systemic” – bone marrow
2. Transthyretin* - liver
   a) Familial – mutation – less stable protein
   b) Wild type – (formerly “senile”) - unknown

Transports Thyroxine and Retinol – “TTR”
Cardiac Amyloid: Diagnosis by Imaging

- Increased ventricular thickness
  - RV thickened as well

- Combination of increased ventricular mass & low voltages
  \(\rightarrow\) quite specific for amyloid.
Typical Imaging Characteristics in Amyloidosis
Characteristics of ATTR-CM\textsuperscript{1-4}

<table>
<thead>
<tr>
<th>Wild-Type (WT)</th>
<th>Familial / Variant</th>
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<tbody>
<tr>
<td>• Estimated higher prevalence versus familial/variant</td>
<td>• Seen in \textit{men and women} age \textgreater 55</td>
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<tr>
<td>• Predominantly seen in \textit{men} age \textgreater 65</td>
<td>• \textit{3–4% of African Americans} in the US are carriers of the V122I mutation, however disease penetrance is unknown</td>
</tr>
<tr>
<td>• \textbf{Uncommon in females}; however, the onset is usually later than in males (age 80–90)</td>
<td>• \textit{Heart failure is more common} in people with a \textit{TTR} gene mutation</td>
</tr>
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<td>• Typically \textbf{Caucasian}</td>
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\begin{align*}
\text{“Neurologic”} & \quad \text{Phenotype} & \quad \text{“Cardiac”} \\
\text{G47A}, \text{A34T}, \text{A36P}, \text{T49A}, \text{P64L}, \text{G89G}, \text{V41L}, \text{H88A}, \text{S23A}, \text{T60A}, \text{T122I}, \text{L111M}, \text{I68L}, \text{V122I}, \text{C10A}, \text{P33L}, \text{V30M} & \\
\text{C10A}, \text{P33L}, \text{V30M}, \text{T60A}, \text{T122I}, \text{L111M}, \text{I68L}, \text{V122I} & \\
\text{G47A}, \text{A34T}, \text{A36P}, \text{T49A}, \text{P64L}, \text{G89G}, \text{V41L}, \text{H88A}, \text{S23A} & \\
\text{G47A}, \text{A34T}, \text{A36P}, \text{T49A}, \text{P64L}, \text{G89G}, \text{V41L}, \text{H88A}, \text{S23A}, \text{T60A}, \text{T122I}, \text{L111M}, \text{I68L}, \text{V122I}, \text{C10A}, \text{P33L}, \text{V30M} & \\
\end{align*}

Clinical presentation of ATTR-CM can have cardiovascular or neurological origins

**Cardiovascular**
- Heart Failure*
  - Fatigue
  - Dizziness
  - Shortness of breath
  - Edema
  - Chest pain
- Atrial Fibrillation

**Neurological**
- Peripheral Neuropathy
  - Tingling
  - Numbness
  - Myalgia and burning sensations
  - Weakness
  - Carpal tunnel syndrome
- Autonomic Neuropathy
  - Diarrhea
  - Weight loss
  - Orthostatic hypotension
  - Excessive sweating
  - Erectile dysfunction

Prevalence of ATTR-CM

• Exact prevalence of ATTR-CM is unknown\(^1\)
  – In Americans of European descent, transthyretin amyloidosis is estimated to affect one in 100,000 people
  – ATTR-CM is more common among people with African ancestry
    • It is estimated to affect ~3-4% of African Americans
    • ~5% of people in some areas of West Africa

• The prevalence of ATTR-CM is presently unknown; however, it is estimated that less than 1% of people with the disease are diagnosed\(^2\)

ATTR “Wild Type” Identification and Diagnosis

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction


ATTRwt found in 13% of patients with HFpEF, ≥ 60 years, ≥ 12 mm wall thickness

* LVEF=left ventricular ejection fraction.
Diagnosis of TTR Cardiac Amyloidosis

Figure 1: Proposed Diagnostic Algorithm for Older Patients with Suspected TTR Cardiac Amyloidosis

**Heightened Clinical Suspicion for Cardiac Amyloid**
Older adult with clinical, biomarker, ECG, echocardiogram, and/or MRI imaging suggestive of cardiac amyloidosis

**Diagnostic Counseling**
Patient-centered counseling on diagnostic process which may include further blood testing, nuclear imaging, genetic testing, and potential endomyocardial biopsy

**Testing for AL Cardiac Amyloidosis**
Presence of monoclonal protein by free light chain assay and SPEP/UPEP with IFE?

- **Yes**
  - **Biopsy and Typing**

- **No**
  - **99mTc-PYP Scan**
    - **Negative**
      - Unlikely ATTR Cardiac Amyloidosis
    - **Positive**
      - ATTR cardiac amyloidosis
        - TTR genotyping
          - ATTRm
          - ATTRwt

Circulation. 2016;133:2404-2412.
DOI: 10.1161/CIRCULATIONAHA.116.021612.
<table>
<thead>
<tr>
<th>Table 1. Red Flags and Caveats in Cardiac Amyloidosis</th>
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<tr>
<td>A high index of suspicion is mandatory for the recognition of CA (ie, if you don’t think of it, you won’t diagnose it).</td>
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<tr>
<td>Cardiac amyloid should be suspected in any patient with heart failure, unexplained increased LV wall thickness, and a nondilated LV.</td>
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<td>In a patient with a suspicion for HCM, look for the infiltrative features that suggest amyloid such as pericardial effusion, AV block, interatrial septal and valvular thickening, and apical sparring.</td>
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<tr>
<td>A distinctive sign of CA is the abnormal ratio between LV thickness and QRS voltages rather than low QRS voltages alone. The absence of low QRS voltages does not rule out a CA and up to 20% of subjects with CA can have electrocardiographic evidence of LV hypertrophy.</td>
</tr>
<tr>
<td>In an elderly man with unexplained symmetrical LV hypertrophy, especially in the absence of hypertension, always consider the possibility of ATTRwtx-CA.</td>
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<tr>
<td>CA in an elderly patient with a monoclonal gammopathy is not necessarily attributable to AL; consider the possibility of ATTRwtx and MGUS.</td>
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<tr>
<td>Longitudinal LV function can be severely depressed despite a normal LVEF, and the myocardial contraction fraction is often low, suggesting reduced global myocardial shortening.</td>
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<td>Myocardial deformation is reduced in cardiac amyloidosis, but the apex is generally spared.</td>
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<tr>
<td>On cardiac MRI, both T1 signal abnormalities and marked extracellular volume expansion in patients with LV hypertrophy are strongly suggestive of CA. LGE distribution is heterogeneous, and subendocardial enhancement is not the only pattern.</td>
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<td>A history of bilateral carpal tunnel syndrome in a man with HCM-like phenotype on echocardiography is highly suggestive of ATTRwtx-CA.</td>
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AL indicates immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRwtx, wild-type amyloid transthyretin; AV, atrioventricular; CA, cardiac amyloidosis; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; and MGUS, monoclonal gammopathy of undetermined significance.
The value of specific cardiac testing for the diagnosis of Amyloidosis

<table>
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<tr>
<th>Diagnostic Test</th>
<th>Utility in Cardiac Amyloid TTR vs AL</th>
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<tr>
<td><strong>ECG</strong></td>
<td>AL: Reduced voltage in 46-60%, atrial fibrillation in 20%, Pseudoinfarct pattern</td>
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<tr>
<td></td>
<td>TTR: Reduced voltage in 25-40%, atrial fibrillation in 10-30%</td>
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<tr>
<td><strong>Echocardiography</strong></td>
<td>With “speckled” appearance of LV: sensitivity 87% and specificity 81%</td>
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<td>which improved to specificity when finding atrial septal thickening to 100%</td>
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<td>Decrease of longitudinal strain in mid and basal wall regions relative to the apical region has</td>
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<td></td>
<td>90-95% sensitivity and 80-85% specificity in diagnosis of CA</td>
</tr>
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<td><strong>Biomarkers (BNP, NT-proBNP, Troponin T)</strong></td>
<td>BNP as a sensitive marker to myocardial dysfunction. BNP has 93% sensitivity and 40% specificity as a predictor of echocardiography involvement.</td>
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<td></td>
<td>NT-proBNP and Troponin T are used for staging in AL amyloidosis.</td>
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<tr>
<td><strong>Cardiac Magnetic Resonance</strong></td>
<td>Late gadolinium enhancement is one of the most accurate predictors of endomyocardial biopsy-positive amyloidosis</td>
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<td>Subendocardial enhancement more common with AL</td>
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<td>RV enhancement was 100% TTR vs 72% AL</td>
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<td></td>
<td>CMR 100% sensitivity and 80% specificity in AL</td>
</tr>
<tr>
<td><strong>Radionuclide Scans (Tc99m PYP Tc99m DPD)</strong></td>
<td>Useful in TTR (both mutated and wild-type). Reported high sensitivity and specificity in differentiating TTR from AL</td>
</tr>
<tr>
<td><strong>Biopsy (abdominal fat pad vs endomyocardial)</strong></td>
<td>Abdominal fat aspirate with congo red staining 70-90% sensitive for AL but 15-45% for TTR.</td>
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<tr>
<td></td>
<td>If high suspicion, and negative fat pad biopsy will need endomyocardial biopsy with nearly 100% sensitivity (Gold Standard)</td>
</tr>
</tbody>
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**Treatment: Cardiac-Specific**

- **Diuretics/salt restriction**
  - Often have large amounts of peripheral edema/ascites, made worse by hypoalbuminemia

- **To generally be avoided:**
  - Digoxin
  - Beta-blockers
  - Calcium-blockers
  - Vasodilators (ACE-I/ARBs) unless proteinuria is a prominent feature

- Midodrine/Droxidopa
  - Can be useful in orthostatic hypotension/autonomic dysfunction that is common

- Treatment of atrial & ventricular arrhythmias
Staging for AL Amyloidosis

Using 1 point for each cutoff:

- TnT > 0.025
- NTproBNP > 1800
- Free Light chain > 18mg/dL

(cTnT ≥ 0.025 ng/mL, NT-ProBNP ≥ 1,800 pg/mL, and FLC-diff ≥ 18 mg/dL); this was used to divide patients into four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively. Fifty-two patients did not have FLC-diff values and were included in stage 0 by default.
Proposed staging for ATTR

Cutoffs:
- NTproBNP >3000 ng/L
- EGFR <45ml/min/1.73m2

If both negative = Stage I
If both present = Stage III

doi:10.1093/eurheartj/ehx589
Disease modifying therapeutic opportunities for TTR amyloidosis

Amyloidogenic TTR Cascade

- Liver
- TTR Tetramer
- TTR Monomer
- Misfolded State
- Amyloid Fibril

A: Suppression of Amyloidogenic TTR
B: TTR Stabilization
C: Fibril Degradation

- Diastolic dysfunction
- Restrictive cardiomyopathy
- Heart failure
Both WT and Hereditary Cardiac Amyloidosis

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo. (Funded by Pfizer; ATTR-ACT ClinicalTrials.gov number, NCT01994889.)
Patisiran Phase 3 APOLLO Study Results

**Study Enrollment**

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between Dec 2013 and Jan 2016

**Emerging Options for ATTR Patients and Physicians**

**Inotersen**
- Disease progression and quality of life benefit compared to placebo arm
- Benefit compared to placebo by 8 months
- One subcutaneous administration once a week
- At-home, self administration
- No chronic treatment with other medications
- No pre-treatment regimen
- Simple, routine monitoring every other week
- Thrombocytopenia and renal events observed in NEURO-TTR study
- Saline formulation

**Patisiran**
- Disease progression and quality of life benefit compared to placebo+steroid arm
- Infusion center administration
- Multi-hour infusions every 3 weeks
- HCP and infusion center visits for administration
- Chronic pre-treatment with steroids with potential associated complications
- Infusion reactions in Phase 2 open-label study and Phase 3 APOLLO study
- Lipid nanoparticle formulation
Hereditary Polyneuropathy only
The current treatment landscape for Amyloidosis

A. Light Chain Amyloidosis

- Abnormal Plasma Cells
- Light Chain Overproduction
- Misfolded Light Chain
- Removal of Light Chain Amyloid Deposits

1. Reduction in Light Chain Production
   - Carfilzomib
   - Daratumumab
   - Elotuzumab
   - Isatuximab
2. Heavy chain
3. Inhibition of Amyloid Fibril Formation
   - Ixazomib
   - Pomalidomide
   - Venetoclax
4. Deposition in Organs
   - Heart
   - Kidney
   - Liver
   - Gastrointestinal Tract
   - Soft Tissue
   - Peripheral/Autonomic Nervous System

B. Transthyretin Amyloidosis

- Transthyretin Synthesis Inhibition
  - Inotersen
  - Patisiran
- Misfolded Monomers
- Transthyretin Tetramer Stabilization
  - AG10
  - Diflunisal
  - Tolcapone
- Removal of Misfolded Transthyretin
  - PRX004
- Removal of Transthyretin Amyloid Deposits
  - GSK2398852
  - PRX004
Drugs used for the treatment of Amyloidosis

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug names</th>
<th>Current use</th>
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</table>
| Stabilizers that inhibit dissociation of TTR into monomers | 1. Tafamidis  
2. Diflusinal  
3. AG10 (selective to TTR-V112I) | 1. Currently in a phase 3 clinical trial [30]  
2. Randomized controlled trial data available [8]  
3. Currently in a Phase 1 clinical trial [32] |
| Binding leads to degradation and reduced transcription of TTR | 1. Patisiran (with siRNA)  
2. Ionis (of ASO) | 1. Phase 3 clinical trial in patients with FAP [33]  
2. Phase 2/3 randomized controlled trial in patients with FAP [35] |
| Disruption of TTR amyloid deposition | 1. Doxycycline  
2. TUDCA  
3. Combination of Doxy/TUDCA | 1. Currently in a Phase 2 clinical trial alone [69]  
2. Not studied alone  
3. Currently in a Phase 2 clinical trial [37] |
| Clearance of TTR with antibody | 1. PRX004 | 1. Not yet recruiting for phase 1 clinical trial in patients with hTTR amyloidosis [63] |
| Normalization of AL amyloid light chain concentration | 1. High dose Melphalan (alkalating agent)  
2. Bortezomib (proteasome inhibitor)  
3. CyBorD (alkylator with PI) | 1-3. First line therapy [38-41] |
| Normalizing AL amyloid light chain concentrations with immunomodulatory drugs | 1. Thalidomide following low-dose Melphalan  
2. Lenalidomide  
3. Pomalidomide | 1. Phase 2 clinical trial in patients with cardiac amyloidosis [67]  
2. Phase 2 clinical trial in patients with AL amyloidosis [68]  
3. Currently in a Phase 2 clinical trial [49] |
| Normalizing AL amyloid light chain concentrations with proteasome inhibitors | 1. Bortezomib (reversible)  
2. Carfilzomib (irreversible)  
3. Ixazomib (reversible) | 1. Phase 3 clinical trial in patients with AL amyloidosis [40]  
2. Phase 1 clinical trial data for patients with AL amyloidosis [48]  
3. Currently in a Phase 3 clinical trial [47] |
| Normalization of AL amyloid light chain concentrations with monoclonal antibody | 1. Daratumumab | 1. Currently in a Phase 3 clinical trial [47] |
| Clearance of AL amyloid light chain concentrations with directed monoclonal antibodies | 1. mAb anti-SAP  
2. mAb NEOD001  
3. mAb 11-1F4 | 1. Currently in a phase 2 clinical trial [54]  
2. Phase 1/2 clinical trial in patients with AL amyloidosis [52]  
3. Currently in a Phase 1 clinical trial [55] |
Amyloidosis: Diagnosis

“The only way to diagnose amyloidosis is to consider the diagnosis.”
Cardiac Amyloidosis

Current strategies

- Clinical awareness and early diagnosis are critical.
- Cardiac amyloidosis results from distinctive disease processes with differing treatment strategies and prognoses.
- Initial presentation is insidious, LVH on imaging is commonly the first phenotypic abnormality.
- The optimal treatment varies greatly from the usual treatment of HF.
- Transplantation may provide a mostly definitive therapy in selected patients with AL and ATTR cardiac amyloidosis.
- New therapies are needed and are in development.
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Multidisciplinary Team

- Cardiology
- Neurology
- Nephrology
- Gastroenterology
- Hepatology
- BMT
- Hematology
- Pulmonology
- Radiology
- Pathology