Transthyretin Cardiac Amyloidosis: Overlooked, Under-Appreciated and Treatable

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Professor of Medicine
Columbia University Irving Medical Center
26th Annual San Diego Heart Failure Symposium
6th ANNUAL STANLEY LLOYD, MD LECTURE
September 26th, 2020
Stanley Lloyd, MD

- Lived to 102 years of age
- MD from Boston University Medical Center in 1942
- Specialty certification from the American Board of Pathology in 1951
- 55+ year career,
  - Reviewed and screened > 500,000 pap smears,
  - Performed 17,000 autopsies
  - Performed and reported on several thousand frozen sections in the operating room.

“He was extremely proud to be a doctor and had an insatiable appetite to constantly learn and keep updated on research and innovations in the medical arena.”
Disclosures

• I am excited about the emergence of effective therapies for ATTR amyloidosis but disappointed at the cost of such therapies which pose a significant obstacle to adoption.

• I have research support from several pharmaceutical companies:
  – NIH/NIA/NHLBI
  – Foldrx Pharmaceuticals, Inc.
  – Akcea, Inc
  – Alnylam, Inc
  – Eidos
  – Prothena
  – Ionis Pharmaceuticals
  – Pfizer, Inc.
Misdiagnosis / Delayed Diagnosis - Cardiac Amyloidosis

- 75% saw > 3 physicians before diagnosis made
- 63% > 6 months to diagnosis
- 44% received an incorrect diagnosis first
- 31% required air travel to establish diagnosis
- Only 18% of these patients with cardiac AL had the correct diagnosis made by a cardiologist
- Cardiologists are the most common subspecialists to make a misdiagnosis – most commonly - hypertrophic cardiomyopathy

Lousada et al, European Hematology Association (EHA) 22nd Annual Congress 2017; June 22–25, 2017
Systemic Amyloidosis

- Characterized by extra-cellular deposition of a fibrillar protein
- Deposits progressively interfere with the structure / function of affected organs throughout the body
- Two dozen proteins known to form amyloid fibrils in vivo
- Two predominant types involve the heart:
  1) AL – typically associated with plasma cell dyscrasia
  2) TTR Associated – transthyretin (TTR)
      a. mutation (ATTRv or ATTRh) or
      b. wild type (ATTRwt, SCA)
## Types of cardiac amyloidosis

<table>
<thead>
<tr>
<th>Features</th>
<th>AL</th>
<th>ATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor protein</strong></td>
<td>Light chain</td>
<td>Mutant TTR</td>
</tr>
<tr>
<td><strong>Average age (range)</strong></td>
<td>55 (30-75)</td>
<td>50 (30-70)</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Cardiac involvement (%)</strong></td>
<td>~30%</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Fat pad biopsy</strong></td>
<td>50-80%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Not Genetic</td>
<td>Autosomal Dominant</td>
</tr>
</tbody>
</table>
| **Extra-cardiac manifestations**| • Nephrotic syndrome / renal failure  
• Autonomic dysfunction  
• Purpura  
• Macroglossia  
• Tendinopathy  
• Neuropathy? | • Autonomic dysfunction  
• Peripheral Neuropathy  
• Tendinopathy  
• Neuropathy? | |
| **Median survival**             | 12-36 months (4-6 with HF) | 70                     | 75                     |
ATTR Cardiac Amyloidosis: The Quintessential form of Diastolic Heart Failure

- Restrictive cardiomyopathy
  - Progressive diastolic dysfunction
  - Reduced LV capacitance – upward and leftward shifts in EDPVR
  - Declines in SV, CO and BP
## Progression of ATTR-CA

**Transthyretin Cardiac Amyloidosis Study (TRACS)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6-Month Rate of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six minute walk distance (meters)</td>
<td>-25.8</td>
</tr>
<tr>
<td>NT-pro-BNP (pg/ml)</td>
<td>1816.0</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>-3.22</td>
</tr>
</tbody>
</table>

*Am Heart J. 2012 Aug;164(2):222-228*
## Outcomes in ATTR-CA

Transthyretin Cardiac Amyloidosis Study (TRACS)

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease from diagnosis</td>
<td>1.05</td>
<td>1.01 – 1.09</td>
</tr>
<tr>
<td>Heart rate &gt;70 BPM</td>
<td>7.17</td>
<td>1.52 – 33.9</td>
</tr>
<tr>
<td>Stroke volume (per ml)</td>
<td>0.90</td>
<td>0.83 – 0.98</td>
</tr>
<tr>
<td>LV ejection fraction &lt;50%</td>
<td>4.12</td>
<td>1.24 – 13.6</td>
</tr>
<tr>
<td>ATTRv vs. AATTRwt</td>
<td>3.73</td>
<td>1.11 – 12.6</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (per ml)</td>
<td>0.83</td>
<td>0.73 – 0.95</td>
</tr>
<tr>
<td>Duration of disease from diagnosis</td>
<td>1.11</td>
<td>1.03 – 1.19</td>
</tr>
</tbody>
</table>

Am Heart J. 2012 Aug;164(2):222-228
Progression of ATTR-CA Pressure Volume Analysis

Early Diagnosis is Essential

• Disease is progressive and prognosis is poor for late stage disease.
• Emerging treatments that prevent progression but do not reverse disease.
• Diagnosis was complicated and included:
  – Cardiac biopsy (invasive)
  – Genetic testing (not widely available, ? acceptance)
Reasons for Missing Diagnosis of Cardiac Amyloidosis

• Necessity of endomyocardial biopsy
  – Non-invasive techniques can diagnose TTR cardiac amyloidosis.

• It is thought to be rare.
  – It is an under-appreciated cause of HFpEF and low flow AS.

• It is thought to be untreatable
  – Treatment exists and are very effective if diagnosed early
Reasons for Missing Diagnosis of Cardiac Amyloidosis

• Necessity of endomyocardial biopsy
  – Non-invasive techniques can diagnose TTR cardiac amyloidosis.

• It is thought to be rare.
  – It is an under-appreciated cause of HFpEF and low flow AS.

• It is thought to untreated.
  – Treatment exists and are very effective if diagnosed early.
How can we facilitate a diagnosis of cardiac amyloidosis?

With an endomyocardial biopsy?

- Available in most cardiology practices
- 9,664 Cardiology Practices

OR

With a PYP Scan?

- Limited to specialized centers
- 143 Cardiac Transplant Centers

Differences in Cardiac Retention with Tc-99 in Controls, AL and ATTR Amyloid

Bone Scintigraphy for TTR Cardiac Amyloidosis

• Consensus that ATTR cardiac amyloidosis can be reliably diagnosed in the absence of histology provided that all of the following criteria are met:
  – Heart failure with an echocardiogram or CMR that is consistent with or suggestive of amyloidosis
  – Grade 2 or 3 cardiac uptake on a bone scan, using either DPD, PYP or HMDP confirmed by SPECT imaging
  – Absence of a detectable monoclonal protein despite serum and urine IFE, and serum free light chains

PYP enables earlier diagnosis!

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PYP (n=126)</th>
<th>EMB (n=149)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class (median)</td>
<td>2</td>
<td>3</td>
<td>0.0051</td>
</tr>
<tr>
<td>Total QRS voltage (mv)</td>
<td>76±52</td>
<td>57±33</td>
<td>0.0291</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>119±17</td>
<td>113±13</td>
<td>0.0069</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>354±290</td>
<td>691±552</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>48±14</td>
<td>42±16</td>
<td>0.0008</td>
</tr>
<tr>
<td>IVS thickness (mm)</td>
<td>1.5±0.4</td>
<td>1.7±0.6</td>
<td>0.0097</td>
</tr>
<tr>
<td>LV mass (grams)</td>
<td>278±100</td>
<td>333±199</td>
<td>0.0058</td>
</tr>
</tbody>
</table>

Unpublished data
PYP Scintigraphy is associated with improved survival,
P<0.0001

Unpublished data
Key Causes of Misdiagnosis of ATTR Cardiac Amyloidosis with PYP Scanning

- Positive PYP ≠ ATTR; Diagnosis = AL
  - Always screen for AL

- Positive PYP = blood pool uptake, no amyloid
  - Always perform SPECT

- ✓ Heart Failure with typical echo and/or CMR
- ✓ Negative sFLC, serum/urine IFE
- ✓ Positive PYP with SPECT
- Accurate Diagnosis = ATTR-CM
- Perform TTR DNA sequence

Positive PYP, Clinical suspicion persists
Cardiac biopsy: Diagnosis = ATTRv
- Perform biopsy if strong clinical suspicion

Poturecha T, Elias P, et. al. JACC Cardiovascular Imaging, In press
Among Grade 2 scans (n=25) 16 or 64% were false positives.

Poturecha T, Elias P, et. al. JACC Cardiovascular Imaging, In press
Reasons for Missing Diagnosis of Cardiac Amyloidosis

- Necessity of endomyocardial biopsy
  - Non-invasive techniques can diagnose TTR cardiac amyloidosis.
- It is thought to be rare.
  - It is an under-appreciated cause of HFpEF and low flow AS.
- It is thought to be untreatable
  - Treatment exists and are very effective if diagnosed early
ATTR-CA is Everywhere!!
Common in HFpEF, Afro-Caribbeans, TAVR and Older Adults

- 13% of hospitalized HFpEF with wall thickness >12 mm
- 16% of TAVR patients (22% of men)
- 3.4% of AA are carriers of Val122Ile and ~1% of Caribbean Hispanics/Latino
- 40% of Blacks with HF, wall thickness > 12 mm and low voltage have Val122Ile
- 11.4% of Afro-Caribbeans with ADHF – 4th most common cause of HF
- 3.8% of men and 0.88% of women > 75 years of age

Reasons for Missing Diagnosis of Cardiac Amyloidosis

• Necessity of endomyocardial biopsy
  – Non-invasive techniques can diagnose TTR cardiac amyloidosis.
• It is thought to be rare.
  – It is an under-appreciated cause of HFpEF and low flow AS.
• It is thought to be untreatable
  – Treatment exists and are very effective if diagnosed early
Pathogenesis of ATTR Amyloidosis

- Free tetramer → Folded monomer → Misfolded monomer → Aggregates

- TTR structures associated with pathology

- Functional TTR structures

- Sensorimotor Polyneuropathy (Deposition in Peripheral Nerves)
- Amyloid Fibrils
- Deposition in Cardiac Tissues
- Restrictive Cardiomyopathy

- TTR Amyloid Polyneuropathy (ATTR-PN)
  - Onset: 30-40s

- TTR Amyloid Cardiomyopathy (ATTR-CM)
  - Onset: 60-70s
TTR Therapeutic Opportunities: The Era of Therapeutic Nihilism is Over

J Am Coll Cardiol. 2019;73(22):2872-2891
A Gift From Mother Nature

- V30M FAP highly penetrant in Portugal
- Family with V30M mutation that does not develop FAP
- These individuals also have a mutation, T119M, on their second allele
- Hence the T119M TTR mutation appears to protect against V30M amyloidogenesis in trans through mixed tetramer formation

Science 2001, 293, 2459-2461
TTR Stabilization: Treatment for TTR Amyloidosis

Ligand Stabilized Folded TTR

Amyloidogenic Variant

Amyloid Protein
ATTR-ACT Study Design

# Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pooled Tafamidis (N=264)</th>
<th>Placebo (N=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.5 (7.2)</td>
<td>74.1 (6.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>241 (91.3)</td>
<td>157 (88.7)</td>
</tr>
<tr>
<td>ATTRwt, n (%)</td>
<td>201 (76.1)</td>
<td>134 (75.7)</td>
</tr>
<tr>
<td>LV ejection fraction, mean (SD)</td>
<td>48.4 (10.3)</td>
<td>48.6 (9.5)</td>
</tr>
<tr>
<td>Interventricular wall thickness, mean (SD)</td>
<td>16.7 (3.8)</td>
<td>16.2 (3.5)</td>
</tr>
<tr>
<td>LV stroke volume mean (SD)</td>
<td>45.8 (16.1)</td>
<td>45.1 (16.9)</td>
</tr>
<tr>
<td>Global longitudinal strain, mean (SD)</td>
<td>-9.3 (3.5)</td>
<td>-9.4 (3.6)</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class I</td>
<td>24 (9.1)</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>162 (61.4)</td>
<td>101 (57.1)</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>78 (29.5)</td>
<td>63 (35.6)</td>
</tr>
<tr>
<td>NT-proBNP, median (Q1, Q3)</td>
<td>2995.9 (1751.5, 4861.5)</td>
<td>3161.0 (1864.4, 4825.0)</td>
</tr>
<tr>
<td>Troponin I, median (Q1, Q3)</td>
<td>0.14 (0.09, 0.20)</td>
<td>0.14 (0.08, 0.19)</td>
</tr>
</tbody>
</table>
Primary Analysis using Finkelstein-Schoenfeld (F-S) Method

<table>
<thead>
<tr>
<th></th>
<th>Pooled Tafamidis (n=264)</th>
<th>Placebo (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-value from F-S method</strong></td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td>Patients alive(^a) at Month 30, n (%)</td>
<td>186 (70.5)</td>
<td>101 (57.1)</td>
</tr>
<tr>
<td>Average cardiovascular-related hospitalizations during 30 mo (per pt per yr) among those alive at Month 30</td>
<td>0.297</td>
<td>0.455</td>
</tr>
<tr>
<td>Win-Ratio(^b) (95% CI)</td>
<td>1.695 (1.255, 2.289)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Heart transplant and implantation of a cardiac mechanical assist device were treated as death for this analysis

\(^b\)Number of pairs of tafamidis-treated patient wins divided by number of pairs of placebo patient wins
Tafamidis Reduces All-cause Mortality and Hospitalizations.

33% reduction (P=0.018) in overall mortality – need to treat 7–8 patients to prevent one death over 2 ½ years.

There was a 32% reduction in the rate of hospitalization with tafamidis compared with placebo – need to treat 4 patients to prevent 1 hospitalization per year.

Pre-specified Subgroup Results: All-cause Mortality, and CV-related Hospitalization

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>P Value from Finkelstein-Schoenfeld Method</th>
<th>Survival Analysis Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>Cardiovascular Hospitalization Relative Risk Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall — pooled tafamidis vs. placebo</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TTR genotype</td>
<td></td>
<td>0.79</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>ATTRm</td>
<td>0.30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NYHA baseline</td>
<td></td>
<td>0.22</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Class I or II</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Class III</td>
<td>0.78</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg vs. placebo</td>
<td>0.003</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20 mg vs. placebo</td>
<td>0.005</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

The Earlier the Better!!!
Therapeutic Hypothesis for siRNA and ASO in TTR Cardiac Amyloid

- Production of mutant and wild type TTR
- Reduction of unstable circulating TTR tetramers
- Prevention of organ deposition of TTR monomers and amyloid fibrils (and potential clearance)
- Stabilization of cardiomyopathy/neuropathy (and potential recovery)
Patisiran Effects on NTproBNP

Cardiac Effects of siRNA

Cardiac Effects of ASO

**Left Ventricle Mass**
- **Inotersen (n=35)**
- **Placebo (n=16)**

**Interventricular Septum Thickness (IVS)**
- **Inotersen (n=35)**
- **Placebo (n=16)**

**Posterior Wall Thickness**
- **Inotersen (n=35)**
- **Placebo (n=16)**

**Global Longitudinal Strain**
- **Inotersen (n=35)**
- **Placebo (n=16)**

**p-values**
- **Left Ventricle Mass**: p=0.0288
- **Interventricular Septum Thickness (IVS)**: p=0.0150
- **Posterior Wall Thickness**: p=0.0425
- **Global Longitudinal Strain**: p=0.5753
# Phase 3 Trials for ATTR-CM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism/Delivery</th>
<th>Trial Name</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG10 (Eidos)</td>
<td>Stabilizer Oral</td>
<td>ATTRIBUTE-CM</td>
<td>Placebo controlled, RCT; 2:1 allocation</td>
</tr>
<tr>
<td>Patisiran (Alnylam)</td>
<td>Silencer Intravenous</td>
<td>APOLLO-B</td>
<td>Placebo controlled, RCT; 1:1 allocation</td>
</tr>
<tr>
<td>ION-682884 (Ionis/Akcea)</td>
<td>Silencer: SQ</td>
<td>IONIS LICA-CM</td>
<td>Placebo controlled, RCT; 1:1 allocation</td>
</tr>
<tr>
<td>Vutrisiran (Alnylam)</td>
<td>Silencer: SQ</td>
<td>HELIOS-B</td>
<td>Placebo controlled, RCT; 1:1 allocation</td>
</tr>
</tbody>
</table>
ATTR Cardiac Amyloidosis

Transition from a rare, underdiagnosed and untreatable condition to increasingly and easily recognized and treatable

- 13% in hospitalized HFrEF
- 16% in patients undergoing TAVR
- 5% in patients with presumed TAVR
- 1-2% in older adults > 75 years of age
Summary

1. If you don’t think of it, you won’t diagnose it!!!
   • The key to identifying patients with cardiac amyloidosis and facilitating an early diagnosis is to consider this diagnosis in your differential

2. ATTR cardiac amyloidosis can be diagnosed without a biopsy using nuclear imaging with SPECT in combination with an assessment for monoclonal proteins.
   • With the aging of the population ATTRwt will become the most commonly form of cardiac amyloidosis.

3. Effective treatments for TTR cardiac amyloidosis exist and can dramatically improve outcomes especially if administered early in the course of the disease.
Consensus Statements and Guidelines on Cardiac Amyloidosis

Circulation. 2016;133(24):2404-12; Circ Heart Fail. 2015;8:519-526;
Circ Heart Fail. 2019;12:e006075
Pseudoinfarct Pattern & Loss of R-wave Progression
Consensus Statements and Guidelines on Cardiac Amyloidosis

Cardiac Amyloidosis: Evolving Diagnosis and Management
A Scientific Statement From the American Heart Association

ABSTRACT: Transthyretin amyloid cardiomyopathy (ATTR-CM) results in a restrictive cardiomyopathy caused by extracellular deposition of transthyretin, normally involved in the transportation of the hormone thyroxine and retinol-binding protein, in the myocardium. Enthusiasm

Circulation. 2016;133(24):2404-12; Circ Heart Fail. 2015;8:519-526; Circ Heart Fail. 2019;12:e006075
Heart Failure with Preserved Ejection Fraction*

Hypertension

Yes

True DHF

Wall thickness ~ QRS Voltage

Increased

- Hypertrophic Cardiomyopathy

Discordance

- Infiltrative diseases
- Restrictive CM

No

?
## HFNEF vs. DHF

<table>
<thead>
<tr>
<th></th>
<th>HFNEF</th>
<th>DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Older Adults</td>
<td>Middle Aged</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Predominance</strong></td>
<td>Predominance</td>
<td>Predominance</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>(e.g. Amyloid)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>