Advances in Diagnosis and Treatment of Cardiac Amyloidosis: Key Role Novel Drug Therapy

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Disclosures

• I am under-funded
• I have research support from several pharmaceutical companies:
  – NIH/NIA - St. Jude
  – Foldrx Pharmaceuticals, Inc. - BMS
  – Novartis - ISIS Pharmaceuticals
  – Alnylam - Pfizer, Inc.
• Will discuss a novel and investigational products for cardiac amyloidosis.
Objectives

At the conclusion of this seminar, learners will be able to:

1. Identify the phenotype of cardiac amyloidosis in order to facilitate early diagnosis
2. Distinguish underlying causes of cardiac amyloidosis given differences in prevalence, genetics, prognosis and treatment
3. Enumerate three emerging strategies to address TTR cardiac amyloidosis
Case

- 62 year old white male with progressive shortness of breath for 2 years
- Had a previous ECG which revealed a “silent MI”
- Initially had atrial fibrillation which was paroxysmal but became persistent.
- Cardiac catheterization (2 years ago): 50% - first diagonal, 40% RCA, normal EF, LVEDP = 19 mm Hg
Case (continued)

- Treated with diuretics and ACE/Beta Blockers (intolerant)
- Worsening cardiac status; Echo shows EF=71%, LVH
- Right pleural effusion tapped – ~400 ml, negative cytology and thought secondary to heart failure
- Repeat echo 2 years after initial presentation shows LVEF=30%, had AV node ablation and BiV pacemaker

Referred for evaluation
<table>
<thead>
<tr>
<th>Comparison</th>
<th>HFNEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Older Adults</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Predominance</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>High</td>
</tr>
<tr>
<td>Feature</td>
<td>HFNEF</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
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<td></td>
</tr>
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<td>Blood Pressure</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>(e.g. Amyloid)</td>
</tr>
</tbody>
</table>
Pseudoinfarct Pattern & Loss of R-wave Progression
Echocardiogram
Catheterization

- Right atrium = 15 mm Hg
- Right ventricle = 44/9 mm Hg
- Pulmonary artery = 45/23/31, saturation of 52%
- Pulmonary capillary wedge pressure = 30 mm Hg
- Cardiac output = 1.99 l/min, Cardiac index = 0.97 ml/min/m²
- Left ventricle = 83/26 mm Hg
- Aortic Pressure = 85/60 mm Hg, saturation of 95%
Endomyocardial Biopsy
Endomyocardial Biopsy

Amyloid deposits are birefringent when the Congo Red stain is viewed with polarized light.
You’ve Got to Think of IT to Diagnose IT!!!

- DM Eddy “The art of the diagnosis”
- Unable to use Bayes’ theorem in routine diagnosis
- Recast the problem using comparing patterns
- Six steps:
  1. Aggregation into patterns
  2. Pivot – chief concern
  3. Generation of cause list
  4. Pruning the cause list
  5. Selection of a diagnosis
  6. Validation of diagnosis

NEJM 1982: 306:321. 1263-68
Misdiagnosis and Delayed Diagnosis of 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 or
     b. wild type (SCA)
## Types of Cardiac Amyloid

<table>
<thead>
<tr>
<th>Features</th>
<th>AL</th>
<th>ATTR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Precursor Protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutant TTR</td>
<td>Wild Type TTR</td>
</tr>
<tr>
<td>Average Age (Range)</td>
<td>55 (30-75)</td>
<td>50 (30-70)</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>Cardiac Involvement (%)</td>
<td>~30%</td>
<td>Variable</td>
</tr>
<tr>
<td>Fat Pad Biopsy</td>
<td>50-80%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Primary Referral Route</td>
<td>Hematology</td>
<td>Neurology</td>
</tr>
<tr>
<td></td>
<td>Cardiology</td>
<td>Cardiology</td>
</tr>
<tr>
<td></td>
<td>Nephrology</td>
<td></td>
</tr>
</tbody>
</table>
## Types of Cardiac Amyloid

<table>
<thead>
<tr>
<th>Features</th>
<th>AL</th>
<th>ATTR Mutant</th>
<th>ATTR Wild Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-cardiac manifestations</td>
<td>Nephrotic syndrome/Renal Failure</td>
<td>Autonomic dysfunction</td>
<td>Carpal Tunnel</td>
</tr>
<tr>
<td></td>
<td>Autonomic dysfunction</td>
<td></td>
<td>?Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carpal Tunnel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Survival</td>
<td>12-36 months (4-6 with HF)</td>
<td>70</td>
<td>75</td>
</tr>
</tbody>
</table>
Reasons for Missing Diagnosis of Cardiac Amyloidosis

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

2. Misconceptions about diagnosis
   - EKG is a good screening test.
   - Fat pad analysis has high sensitivity

3. Cardiac amyloid is a great masquerader
   - There are clues for the prepared clinician

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

5. It is thought to untreatable
   - Treatment exists and are very effective if diagnosed early
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### Cardiac Amyloid: A Rare Condition?

#### Incidence/Prevalence

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence/Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° AL Amyloid</td>
<td>~2500 Cases per year, 50% have cardiac involvement</td>
</tr>
<tr>
<td>ATTRmutant</td>
<td>4% of African Americans are carriers, 25,000-120,000 US patients</td>
</tr>
<tr>
<td>ATTRwt (SCA)</td>
<td>~10-25% of adults &gt;80 years, 1 million</td>
</tr>
</tbody>
</table>
Changing Nature of Cardiac Amyloidosis
TTR Amyloid is Becoming the Most Common Form

![Bar Chart]

- **1999-2008**
  - AL: 68%
  - TTRmt: 20%
  - TTRwt: 12%

- **2008-2014**
  - AL: 45%
  - TTRmt: 34%
  - TTRwt: 21%

- **2014-2017**
  - AL: 33%
  - TTRmt: 3%
  - TTRwt: 64%
Distribution of Ejection Fraction in Subjects Hospitalized with Heart Failure

- HFrEF
- HFP EF
- HFnEF

Technetium 99m bone tracers (DPD, PYP, HDP) have ~90% sensitivity/specificity for identifying ATTR cardiac amyloid.

13% of HFnEF had ATTR Cardiac Amyloid

Eur Heart J. 2015 Jul 28
Transthyretin Cardiac Amyloid in Afro-Caribbean Patients with ADHF

- 1,392 HF patients in London
- Among 211 Afro-Caribbean patients – Amyloid was 4th most common cause of HF!!
- Survival worse in amyloid - 2.6 years median.

<table>
<thead>
<tr>
<th></th>
<th>Afro Caribbean Patients (n=211)</th>
<th>White Patients (n=974)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 (54-77)</td>
<td>74 (64-82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic CM</td>
<td>13%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>87%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>HTN cardiomyopathy</td>
<td>12.3%</td>
<td>2.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac Amyloid</td>
<td>11.4%</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ATTR V122I</td>
<td>8%</td>
<td>0.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Circ Heart Fail. 2016;9:e003352
ATTR Amyloidosis in United States: THAOS Registry

- Most common type is ATTRwt
- 76±7 years
- 97% Males
- Echo;
  - IVS = 18±3 mm
  - EF = 51±12%
- Survival: 58.5% at 3 years

JACC. 2016;68(2):161-72
## DISCOVERY

High prevalence of transthyretin (TTR) mutations in patients suspected of having cardiac amyloidosis

<table>
<thead>
<tr>
<th>Characteristic(s)</th>
<th>Likelihood of having a pathogenic TTR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 35</td>
</tr>
<tr>
<td>African American/Black</td>
<td>4%</td>
</tr>
<tr>
<td>+ IVS thickness &gt;12 mm</td>
<td>7%</td>
</tr>
<tr>
<td>+ low voltage ECG</td>
<td>8%</td>
</tr>
<tr>
<td>+ IVS thickness &gt;12 mm and low voltage ECG</td>
<td>12%</td>
</tr>
</tbody>
</table>
UNVEIL Study

Using Nuclear & Echocardiographic Vehicles to Expose Inherent Loads of Amyloid

- 151 patients with severe AS.
- $^{99m}$Tc-PYP planar imaging.
- Uptake in 16% (n=24), 22 of which were men.
- Phenotype of severe concentric LVH and low flow AS
  - Men (92%)
  - Elevated BNP 522 [302-1,023] vs 275 [124-722] pg/ml, p=0.041
  - Increased LV mass (130 vs 98 g/m$^2$, p=0.002)
  - Low SVI l(30±11 vs 36±10 ml/m$^2$, p=0.009)
  - RBBB (38% vs 16%, p=0.023).

**ATTRwt in Males Undergoing TAVR**

- 22%
## Prevalence of ATTRwt in Older Adults

Table 1

<table>
<thead>
<tr>
<th>Cut-off, years</th>
<th>All</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Prevalence</td>
<td>Males</td>
<td>Prevalence</td>
<td>Females</td>
</tr>
<tr>
<td>≥75</td>
<td>1114</td>
<td>2.78% (31)</td>
<td>722</td>
<td>3.88% (28)</td>
<td>392</td>
</tr>
<tr>
<td>≥80</td>
<td>568</td>
<td>4.58% (26)</td>
<td>379</td>
<td>6.07% (23)</td>
<td>189</td>
</tr>
<tr>
<td>≥85</td>
<td>145</td>
<td>11.03% (16)</td>
<td>108</td>
<td>13.89% (15)</td>
<td>37</td>
</tr>
<tr>
<td>≥90</td>
<td>24</td>
<td>16.67% (4)</td>
<td>20</td>
<td>20.00% (4)</td>
<td>4</td>
</tr>
</tbody>
</table>

Prevalence is expressed as % (number).
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1. It is thought to be rare.
   - It is an under-appreciated cause of HFpEF and low flow AS.

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3. Cardiac amyloid is a great masquerader
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4. Necessity of endomyocardial biopsy
   - Non-invasive techniques can diagnose TTR cardiac amyloidosis.

5. It is thought to untreatable
   - Treatment exists and are very effective if diagnosed early
Which patient has Cardiac Amyloidosis?

Both of them
ECG is Insensitive

Am J Cardiol. 2014;114(7):1089-93
Discordance Between Voltage /Wall Thickness

### Males

<table>
<thead>
<tr>
<th>AC vs other (HCM+HHD)</th>
<th>LQV</th>
<th>Symm. LVH</th>
<th>Carrol index</th>
<th>Rahman index</th>
<th>Sokolow / LVMI</th>
<th>Sokolow / LVWT</th>
<th>Sokolow / (LVWT / h^{2.7})</th>
<th>pQRS / LVMI</th>
<th>pQRS / LVWT</th>
<th>pQRS / (LVWT / h^{2.7})</th>
<th>tQRS / LVMI</th>
<th>tQRS / LVWT</th>
<th>tQRS / (LVWT / h^{2.7})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens</td>
<td>44%</td>
<td>91%</td>
<td>72%</td>
<td>8%</td>
<td>74%</td>
<td>68%</td>
<td>68%</td>
<td>76%</td>
<td>74%</td>
<td>73%</td>
<td>78%</td>
<td>77%</td>
<td>78%</td>
</tr>
<tr>
<td>Spec</td>
<td>93%</td>
<td>27%</td>
<td>83%</td>
<td>100%</td>
<td>80%</td>
<td>84%</td>
<td>83%</td>
<td>80%</td>
<td>83%</td>
<td>82%</td>
<td>72%</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>LR+</td>
<td>6.6</td>
<td>1.3</td>
<td>3.0</td>
<td>.</td>
<td>3.0</td>
<td>2.7</td>
<td>2.6</td>
<td>3.3</td>
<td>3.2</td>
<td>3.1</td>
<td>3.4</td>
<td>3.4</td>
<td>3.6</td>
</tr>
<tr>
<td>LR-</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
<td>0.9</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Females

<table>
<thead>
<tr>
<th>AC vs other (HCM+HHD)</th>
<th>LQV</th>
<th>Symm. LVH</th>
<th>Carrol index</th>
<th>Rahman index</th>
<th>Sokolow / LVMI</th>
<th>Sokolow / LVWT</th>
<th>Sokolow / (LVWT / h^{2.7})</th>
<th>pQRS / LVMI</th>
<th>pQRS / LVWT</th>
<th>pQRS / (LVWT / h^{2.7})</th>
<th>tQRS / LVMI</th>
<th>tQRS / LVWT</th>
<th>tQRS / (LVWT / h^{2.7})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens</td>
<td>52%</td>
<td>91%</td>
<td>68%</td>
<td>5%</td>
<td>68%</td>
<td>65%</td>
<td>68%</td>
<td>72%</td>
<td>73%</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
<td>74%</td>
</tr>
<tr>
<td>Spec</td>
<td>91%</td>
<td>23%</td>
<td>81%</td>
<td>100%</td>
<td>80%</td>
<td>77%</td>
<td>81%</td>
<td>76%</td>
<td>83%</td>
<td>86%</td>
<td>69%</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>LR+</td>
<td>5.7</td>
<td>1.2</td>
<td>2.7</td>
<td>.</td>
<td>2.5</td>
<td>2.2</td>
<td>2.5</td>
<td>3.0</td>
<td>3.4</td>
<td>2.7</td>
<td>3.3</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>LR-</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.9</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Total QRS/LVWT: Males, cutoff 8.4; Females, cutoff 7.7
Total QRS / LVWT / h^{2.7}: Males, cutoff 36.4; Female, cutoff 27.3
Fat Pad Aspirate

• Sensitivity for AL amyloid of 70 % at best

• Positive in < 50 % of subjects with TTR cardiac amyloid
Reasons for Missing Diagnosis of Cardiac Amyloidosis

1. It is thought to be rare.
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5. It is thought to untreatable
   - Treatment exists and are very effective if diagnosed early
You’ve Got to Think of IT to Diagnose IT!!!

**History/Exam Clues**

- **HFPEF without hypertension**, particularly in *men* (for TTR)
- Evidence of *right-sided* heart failure (e.g. hepatomegaly, ascites, and lower extremity edema)
- **Intolerance** of ACE, Beta-blockers.
- **AL** – Periorbital purpura
- **TTR**
  - Bilateral carpal tunnel syndrome
  - Lumbar Spinal Stenosis
  - Biceps tendon rupture
Orthopedic Clues to TTR Amyloidosis

Figure 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Risk and CI</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTR-CA</td>
<td></td>
<td>5.61 (3.80-8.29)</td>
</tr>
<tr>
<td>TKA</td>
<td></td>
<td>3.23 (2.25-4.64)</td>
</tr>
<tr>
<td>THA</td>
<td></td>
<td>1.87 (0.84-4.31)</td>
</tr>
<tr>
<td>AL-CA</td>
<td></td>
<td>1.42 (0.73-2.84)</td>
</tr>
</tbody>
</table>

You’ve Got to Think of IT to Diagnose IT!!!

<table>
<thead>
<tr>
<th>History/Exam Clues</th>
<th>Imaging Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>HFPEF without hypertension</em>, particularly in <em>men</em></td>
<td><em>Low voltage to mass ratio</em></td>
</tr>
<tr>
<td>Evidence of <em>right-sided</em> heart failure (e.g. hepatomegaly, ascites, and lower extremity edema)</td>
<td><em>Diffuse delayed enhancement</em> on cardia MRI</td>
</tr>
<tr>
<td><em>Intolerance</em> of ACE, Beta-blockers.</td>
<td><em>Apical sparring</em> on strain rate imaging</td>
</tr>
<tr>
<td>Bilateral carpal tunnel syndrome</td>
<td><em>Low myocardial contraction fraction</em></td>
</tr>
<tr>
<td>Lumbar Spinal Stenosis</td>
<td><em>Myocardial Uptake on PYP Scintigraphy</em></td>
</tr>
</tbody>
</table>
Echocardiographic Clues

- Increased bi-ventricular wall thickness
- Thickened interatrial septum
- Valvular thickening
- Bi-atrial enlargement

Diastolic dysfunction
Restrictive phenotype
Pericardial effusion
Preserved ejection fraction (early)
Systolic heart failure (late)
Preserved Apical Strain
“Cherry on Top”
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Endomyocardial Biopsy
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
  – Absence of a detectable monoclonal protein despite serum and urine IFE, and serum free light chains

TTR Amyloid Cascade

- Biopsy
- Nuclear Scintigraphy
- cMRI
- Cardiac Biomarkers
- Echo
- Symptoms
- ECG

- Systolic Dysfunction
- Low voltage
- Dyspnea, Fatigue
- Diastolic dysfunction
- Elevated Natriuretic peptides
- Late Gadolinium Enhancement
- Myocardial retention of technetium
- Amyloid deposits in myocardium

Time from onset of TTR amyloid deposits / Disease progression
How should we facilitate the diagnosis of cardiac amyloidosis?

- With an endomyocardial biopsy?
  - Limited to specialized center
  - 143 Cardiac Transplant Centers

- With a PYP Scan?
  - Available in most cardiology practices
  - 9,664 Cardiology Practices
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>
Scintigraphy is associated with improved survival!!
Algorithm for Non-Invasive Diagnosis of 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
- No

**Biopsy**
- Congo Red Positive
  - Tissue Typing
    - Immunohistochemistry & Mass Spectrometry (AL vs. TTR vs. Other)
  - Unlikely AL cardiac amyloidosis
- Congo Red Negative
  - 99mTc-PYP Scan
    - Negative
      - Unlikely ATTR Cardiac Amyloidosis
    - Positive
      - ATTR Cardiac Amyloidosis

*If suspicion remains high for infiltrative cardiomyopathy in spite of a negative 99mTc-PYP scan, biopsy may be considered to evaluate for other types of infiltrative cardiomyopathy (e.g. AA).*

Reasons for Missing Diagnosis of Cardiac Amyloidosis

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

2. Misconceptions about diagnosis
   - EKG is a good screening test.
   - Fat pad analysis has high sensitivity

3. Cardiac amyloid is a great masquerader
   - There are clues for the prepared clinician

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

5. It is thought to untreatable
   - Treatment exists and are very effective if diagnosed early
General Treatment for Amyloid Cardiomyopathy

- Diuretics and Salt Restriction – Mainstay of therapy
  - Aldosterone Antagonists and Bioavailable Loop Diuretics
- Calcium channel blockers and ?digoxin - contraindicated
- ACE, ARBs and Beta Blockers – often intolerant and potentially associated with worse outcomes
- Hypotension – compression stockings and midodrine.
- AICD / pacer – more of a role for pacing
Less is More!!!
ACE/ARB and Beta Blockers in Cardiac Amyloid

F. aus dem Siepen, ISA 2016
## Serum Free Light Chain Assay

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLC κ/λ ratio</td>
<td>91%</td>
</tr>
<tr>
<td>Serum IFE</td>
<td>69%</td>
</tr>
<tr>
<td>Urine IFE</td>
<td>83%</td>
</tr>
<tr>
<td>FLC κ/λ ratio and urine IFE</td>
<td>91%</td>
</tr>
<tr>
<td>FLC κ/λ ratio and serum IFE</td>
<td>99%</td>
</tr>
<tr>
<td>Serum IFE and urine IFE</td>
<td>95%</td>
</tr>
<tr>
<td>All three tests</td>
<td>99%</td>
</tr>
</tbody>
</table>
### AL Cardiac Amyloid: Biomarker Staging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT</td>
<td>0.025 ng/mL</td>
</tr>
<tr>
<td>NT-ProBNP</td>
<td>1,800 pg/mL</td>
</tr>
<tr>
<td>FLC-diff</td>
<td>18 mg/dL</td>
</tr>
</tbody>
</table>

---

**J Clin Oncol, 2012; 30:989-995**

**Delayed Diagnosis**
A major factor in poor prognosis!
Treatment for AL Amyloid
Don’t Do this Alone – Get a Hematologist

• Plasma cell therapy
  – Oral melphalan and dexamethasone
  – Thalidomide and dexamethasone
  – Bortezomib, Carfilzomib and Ixazomib
  – Lenalidomide and Pomalidomide
  – Daratumumab
  – Intermediate- or high-dose melphalan and stem cell transplant
Pathogenesis of ATTR Amyloidosis

TTR Amyloid Polyneuropathy (ATTR-PN)

Onset: 30-40s

TTR Amyloid Cardiomyopathy (ATTR-CM)

Onset: 60-70s

Sensorimotor Polyneuropathy

Deposition in Peripheral Nerves

Amyloid Fibrils

Deposition in Cardiac Tissues

Restrictive Cardiomyopathy
TTR Disease Modifying Opportunities

**A. Suppression of TTR Synthesis**
- Liver transplantation
- Gene silencing (siRNA):
  - IONIS TTR-Rx
  - ALN-TTRsc

**B. TTR Stabilization**
- Tafamidis (selective)
- Diflunisal (non-selective)
- EGCG (Green Tea)
- AG-10

**C. Fibril Degradation & Reabsorption**
- Doxycycline + TUDCA
- CPHPC + SAP Antibodies
- NEOD001
- PRX004
- 11-1F4

---

Liver

TTR Tetramer

Monomer

Monomer Misfolding

Amyloid Fibrils

Liver transplantation

Gene silencing (siRNA):
- IONIS TTR-Rx
- ALN-TTRsc

siRNA and Oligonucleotides

DNA

mRNA

Transthyretin

Unstable

Stable

Intact fibrils

Degrade fibrils

Doxycycline
Therapeutic Gene Silencing
RNAi and Oligonucleotides

• Goal to treat disease with therapeutic gene silencing
  - Potentially any gene in genome
  - Unique opportunities for development of innovative medicines

siRNA or Oligos silences mRNA
--blocks protein production
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)

siRNA and ASO acts to knock down hepatic mutant and wild-type TTR production
## TTR Silencing with siRNA or ASO

<table>
<thead>
<tr>
<th>New England Journal of Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patisiran</strong>, an RNAi therapeutic, for hereditary transthyretin amyloidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New England Journal of Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inotersen</strong> treatment for patients with hereditary transthyretin amyloidosis</td>
</tr>
</tbody>
</table>


Patisiran Phase 3 APOLLO Study Results: Neurologic Exam

– mNIS+7: Change from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Worse</th>
<th>Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean (SEM) change in mNIS+7 from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80.93 (8.0, 165.0)</td>
<td></td>
</tr>
<tr>
<td>9 Months</td>
<td>-2.04 (1.50)</td>
<td>-6.03 (1.74)</td>
</tr>
<tr>
<td>18 Months</td>
<td>27.96 (2.60)</td>
<td>13.95 (2.10)</td>
</tr>
</tbody>
</table>

Difference at 18 months (Pati – PBO): -33.99
P value: $9.26 \times 10^{-24}$

Patisiran Phase 3 APOLLO Study Results
Quality of Life

—Norfolk QOL-DN: Change from Baseline

Inotersen Phase 3 NEURO-TTR

— mNIS+7 Primary Endpoint

Statistically significant difference was observed at both 8 months and 15 months.

### Patients within cardiac subpopulation had substantial cardiac involvement

<table>
<thead>
<tr>
<th>Exploratory endpoint</th>
<th>Placebo (N=36)</th>
<th>Patisiran (N=90)</th>
<th>Treatment Difference (Pati - PBO)</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>Baseline, median</td>
<td>845.7</td>
<td>756.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, median</td>
<td>320.4</td>
<td>-49.9</td>
<td>-370.2</td>
</tr>
<tr>
<td>Troponin-I, mg/L</td>
<td>Baseline, mean</td>
<td>0.11</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>0.00</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV wall thickness, cm</td>
<td>Baseline, mean</td>
<td>1.64</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>-0.007</td>
<td>-0.100</td>
<td>-0.093</td>
</tr>
<tr>
<td>LV Mass, g</td>
<td>Baseline, mean</td>
<td>264.52</td>
<td>275.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>0.63</td>
<td>-15.12</td>
<td>-15.75</td>
</tr>
<tr>
<td>Longitudinal Strain, %</td>
<td>Baseline, mean</td>
<td>-15.66</td>
<td>-15.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos, LS mean</td>
<td>1.46</td>
<td>0.08</td>
<td>-1.37</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>Baseline, mean</td>
<td>62.2</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos; LS mean</td>
<td>0.57</td>
<td>1.00</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Functional Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-MWT gait speed, m/sec</td>
<td>Baseline, mean</td>
<td>0.73</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CFB to 18 mos; LS mean</td>
<td>-0.35</td>
<td>0.01</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*The expanded cardiac subpopulation includes patients with evidence of progressive cardiac involvement if both without non-cardiac death.*

**siRNA for TTR-FAP**
Cardiac Effects of siRNA

Circulation, 2018, September 14.
Cardiac Effects of ASO

**Left Ventricle Mass**

<table>
<thead>
<tr>
<th>Change from Baseline (LSM±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotersen (n=35)</td>
</tr>
<tr>
<td>Placebo (n=16)</td>
</tr>
</tbody>
</table>

**Interventricular Septum Thickness (IVS)**

<table>
<thead>
<tr>
<th>Change from Baseline (LSM±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotersen (n=35)</td>
</tr>
<tr>
<td>Placebo (n=16)</td>
</tr>
</tbody>
</table>

**Posterior Wall Thickness**

<table>
<thead>
<tr>
<th>Change from Baseline (LSM±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotersen (n=35)</td>
</tr>
<tr>
<td>Placebo (n=16)</td>
</tr>
</tbody>
</table>

**Global Longitudinal Strain**

<table>
<thead>
<tr>
<th>Change from Baseline (LSM±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotersen (n=35)</td>
</tr>
<tr>
<td>Placebo (n=16)</td>
</tr>
</tbody>
</table>
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

TTR Amyloidogenic Variant

Ligand Stabilized Folded TTR

Amyloidogenic Variant
ATTR-ACT Study Design

Inclusion/Exclusion Criteria

**Key Inclusion Criteria**
- Presence of amyloid deposits in biopsy tissue (cardiac or non-cardiac) and TTR precursor protein identification by mass spectrometry, immunohistochemistry or scintigraphy
- Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm
- A medical history of heart failure (HF) with at least 1 prior hospitalization for HF signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic for improvement
- NT-proBNP concentration ≥600 pg/mL
- 6-Minute Walk Test distance >100 meters

**Key Exclusion Criteria**
- New York Heart Association (NYHA) class IV
- Glomerular filtration rate (eGFR) of <25 mL/min/1.73 m2
- Concurrent treatment with non-steroidal anti-inflammatory drugs
- Modified body mass Index (mBMI) <600 kg/m2·g/L

---

Efficacy Outcomes

• The primary efficacy analysis was a hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations comparing pooled tafamidis data with placebo using the Finkelstein–Schoenfeld (F-S) method\(^1\)
  – The F-S method compares each patient with every other patient within each strata in a pairwise manner
  – The pair-wise comparison proceeds in hierarchical fashion using frequency of CV-related hospitalizations when patients cannot be differentiated based on the all-cause mortality endpoint
  – Thereby the F-S method preserves the higher importance of the all-cause mortality endpoint and allows later CV-related hospitalizations to remain informative.

• Key secondary endpoints were change from baseline to Month 30 in 6MWT and KCCQ-OS score

• Tafamidis treatment groups were pooled for comparison with placebo

## Baseline Demographic 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>ATTRm, n (%)</td>
<td>63 (23.9)</td>
<td>43 (24.3)</td>
</tr>
<tr>
<td>ATTRwt, n (%)</td>
<td>201 (76.1)</td>
<td>134 (75.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>211 (79.9)</td>
<td>146 (82.5)</td>
</tr>
<tr>
<td>Black</td>
<td>37 (14.0)</td>
<td>26 (14.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (4.9)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>mBMI, mean (SD)</td>
<td>1058.8 (173.8)</td>
<td>1066.4 (194.4)</td>
</tr>
</tbody>
</table>
## 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>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 posterior wall thickness, mean (SD)</td>
<td>17.0 (3.9)</td>
<td>16.7 (4.1)</td>
</tr>
<tr>
<td>LA anterior-posterior diameter size, mean (SD)</td>
<td>43.8 (7.0)</td>
<td>43.7 (6.1)</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><strong>Patients alive(^a) at Month 30, n (%)</strong></td>
<td>186 (70.5)</td>
<td>101 (57.1)</td>
</tr>
<tr>
<td><strong>Average cardiovascular-related hospitalizations during 30 mo (per pt per yr) among those alive at Month 30</strong></td>
<td>0.297</td>
<td>0.455</td>
</tr>
<tr>
<td><strong>Win-Ratio(^b) (95% CI)</strong></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 2½ 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.

The Earlier the Better!!!

## Frequency of CV-related Hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>Pooled Tafamidis n=264</th>
<th>Placebo n=177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (%) number of patients with CV-related hospitalizations</td>
<td>138 (52.3)</td>
<td>107 (60.5)</td>
</tr>
<tr>
<td>CV-related hospitalizations per yr</td>
<td>0.4750</td>
<td>0.7025</td>
</tr>
<tr>
<td>Pooled tafamidis vs placebo treatment difference (relative risk ratio)</td>
<td>0.6761</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

There was a 32% reduction in the risk of hospitalization with tafamidis compared with placebo

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

Timing of Therapy is Key
Key Secondary Endpoints: 6-minute Walk Test and KCCQ-OS

Summary of ATTR-ACT Results

• Tafamidis significantly reduced all-cause mortality and cardiovascular-related hospitalizations compared with placebo
• Tafamidis significantly reduced the decline in functional capacity (as measured by 6-minute walk test) and quality of life (as measured by KCCQ-OS)
• Additional analyses further support the efficacy of tafamidis in both wild-type and variant patients and highlight the importance of early diagnosis and treatment
• Tafamidis was well tolerated with a favorable safety profile comparable with placebo
• These findings provide strong evidence that tafamidis is an effective therapy for patients with ATTR-CM
AG10: Another TTR Stabilizer

Serum TTR concentration
Δ from baseline to day 28 (%)

-60% -30% 0% 30% 60% 90% 120% 150%

Placebo
Mean = -7%
Median = -3%

400 mg AG10
Mean = 36%
Median = 28%

800 mg AG10
Mean = 50%
Median = 43%

p < 0.0001

p < 0.0001

ATTRwt-CM
ATTRm-CM
Below normal TTR at Day 28

J Am Coll Cardiol. 2019 Mar 12. pii: S0735-1097
ATTR Cardiac Amyloidosis
Transition from a rare, underdiagnosed and untreatable condition to increasingly and easily recognized and treatable
Objectives

1. Identify the phenotype of cardiac amyloidosis in order to facilitate early diagnosis
   - The diagnosis of cardiac amyloidosis continues to be made in patients with late-stage disease
   - More needs to be done to improve awareness of its clinical manifestations and the potential of therapeutic intervention to improve prognosis

2. Distinguish underlying causes of cardiac amyloidosis given differences in prevalence, prognosis and treatment
   - Light chain cardiac amyloidosis, in particular, if recognized early and treated with targeted plasma cell therapy, can be managed very effectively.
   - With the aging of population, ATTRwt will become the most commonly form of cardiac amyloidosis.
Objectives

3. Enumerate three emerging strategies to address TTR cardiac amyloidosis
   – Therapies based on a biologic understanding have been shown to be effective in late phase clinical trials.
   – Non-biopsy diagnosis of TTR cardiac amyloidosis can be made with bone scintigraphy assuming there is no evidence of a monoclonal protein.