Paradoxically Low Flow Aortic Stenosis in Older Adults: An Emerging Complex Phenotype.

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Columbia University Medical Center
Disclosures

• I am underfunded

• I have research support from several pharmaceutical companies and device companies but none of them are relevant to this talk:
  – NIH/NIA - St. Jude
  – Foldrx, Inc. - Daxor, Inc
  – Novartis, Inc. - Pfizer, Inc.
  – Alnylam, Inc
Objectives

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

1. Delineate the effect of aging on CV care and the unique aspect of Geriatric Cardiology.
2. Delineate the various phenotypes of aortic stenosis in older adults and enumerate the mechanisms underlying paradoxically low flow aortic stenosis.
3. Identify transthyretin cardiac amyloidosis without a biopsy
4. Access the Essentials of Cardiac Care for Older Adults (ECCOA) curriculum to advance their knowledge in this clinically relevant area.
The Aging Population

The aging of the population will have profound influences on health care in the United States and throughout the world.

It is estimated that by 2050, the number of Americans over the age of 65 will double, and the number of Americans over age 85 will increase five-fold or more.

Source: US Census
Oldest Old (>85 years) – Fastest growing segment of the population

Life Expectancy

**A. Life expectancy for women**

- Age 70: Top 25th percentile 21.3, 50th percentile 15.7, Lowest 25th percentile 9.5
- Age 75: Top 25th percentile 17, 50th percentile 11.9, Lowest 25th percentile 6.8
- Age 80: Top 25th percentile 13, 50th percentile 8.6, Lowest 25th percentile 4.6
- Age 85: Top 25th percentile 9.5, 50th percentile 5.9, Lowest 25th percentile 2.9
- Age 90: Top 25th percentile 6.8, 50th percentile 3.9, Lowest 25th percentile 1.8
- Age 95: Top 25th percentile 4.8, 50th percentile 2.7, Lowest 25th percentile 1.1

**B. Life expectancy for men**

- Age 70: Top 25th percentile 18, 50th percentile 12.4, Lowest 25th percentile 9.3
- Age 80: Top 25th percentile 10.8, 50th percentile 6.7, Lowest 25th percentile 3.3
- Age 85: Top 25th percentile 7.9, 50th percentile 4.7, Lowest 25th percentile 2.2
- Age 90: Top 25th percentile 5.8, 50th percentile 3.2, Lowest 25th percentile 1.5
- Age 95: Top 25th percentile 4.3, 50th percentile 2.3, Lowest 25th percentile 1.5
Why Geriatric Cardiology?

60% of all deaths attributable to CVD occur in the 6% of the population ≥ 75 years of age.
Aortic Valve Replacement: Increasing Need and Greater Success

JAMA. 2013;310(19):2078-2085
Age: A Non-Modifiable Risk Factor?

In the absence of sound evidence, these decisions can be strongly influenced by the stereotypic and often negative perception of older adults (1).
“Good news, honey—seventy is the new fifty.”

The above cartoon ran in June, 2000, shortly after the results of the Harris survey were announced, and it is reprinted here courtesy of The New Yorker Magazine.
## Unique Aspects of Cardiovascular Care for Older Adults

<table>
<thead>
<tr>
<th>Traditional Cardiology</th>
<th>Geriatric Cardiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment focused on the heart</td>
<td>Treatment considers the host</td>
</tr>
<tr>
<td>Few comorbidities</td>
<td>Multiple comorbidities</td>
</tr>
<tr>
<td>Treatment yields expected outcomes</td>
<td>Treatment may result in complex effects</td>
</tr>
<tr>
<td>Large simple trials apply</td>
<td>Large simple trials have limited generalizability</td>
</tr>
<tr>
<td>Evidence-based medicine</td>
<td>Patient-centered evidence-based medicine</td>
</tr>
<tr>
<td>Cardiovascular reserve usually preserved</td>
<td>Cardiovascular reserve usually compromised</td>
</tr>
<tr>
<td>Outcomes: death, MI, revascularization</td>
<td>Outcomes: morbidity, function, independence, cognition</td>
</tr>
</tbody>
</table>

*J Am Coll Cardiol. 2011;57(18):1801-10.*
Case: Aortic Stenosis

• 84 year old male with HTN, DM, CKD, anemia, atrial fibrillation and CAD.
• Worsening shortness of breath with systolic murmur
• Appears frail, thin, fatigued:
  – Gait speed ~0.7 m/sec,
  – No weight loss,
  – Exhausted
  – Low physical activity
  – Strong grip strength.
Paradoxically Low Flow
Aortic Stenosis

Exam: BP 140/67, HR = 90, 3/6 systolic murmur at base, soft S2, +S4
Echo: EF = 60%, AVA = 0.6 cm², gradient 32 mm Hg, peak velocity 2.8 m/sec
# Severity of AS: Echo Criteria

<table>
<thead>
<tr>
<th>Severity</th>
<th>Peak Velocity (m/s)</th>
<th>Mean gradient (mm Hg)</th>
<th>AV area (cm²)</th>
<th>AVA Index (cm²/m²)</th>
<th>LVOT:AV VTI Index (DVI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt; 3.0</td>
<td>&lt;20</td>
<td>&gt;1.5</td>
<td>&gt;0.85*</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-4.0</td>
<td>20-40</td>
<td>1.0-1.5</td>
<td>0.6-0.85*</td>
<td>0.25-0.50*</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;4.0</td>
<td>&gt;40</td>
<td>&lt;1.0</td>
<td>&lt;0.6</td>
<td>&lt; 0.25</td>
</tr>
</tbody>
</table>
Not All AS is the Same!

- NORMAL-LVEF NORMAL-FLOW HIGH-GRADIENT
- NORMAL-LVEF «PARADOXICAL» LOW-FLOW LOW-GRADIENT
- LOW-LVEF «CLASSICAL» LOW-FLOW LOW-GRADIENT

50-70% 10-25% 5-10%
## Aortic Stenosis: Changing Phenotype

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional Phenotype</th>
<th>Emerging Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>~70</td>
<td>80-100</td>
</tr>
<tr>
<td>Gender</td>
<td>Mainly male</td>
<td>Mainly female</td>
</tr>
<tr>
<td>Risk Score (STS)</td>
<td>5-6%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>Prevalent</td>
<td>Multiple Nearly Universal</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>High flow / High Gradient</td>
<td>Paradoxically Low Flow / Low Gradient</td>
</tr>
<tr>
<td>Frailty</td>
<td>Rare</td>
<td>Highly Prevalent</td>
</tr>
</tbody>
</table>
Low Flow, Low Gradient, Low EF AS

- Challenging patient population
- 5-10% of all AS cases
- CAD often present in this patient population
- Survival typically <50% at 3 years
- Operative mortality high
LVEF ≤ 40%
ΔP < 40
AVA ≤ 1.0

Dobutamine-Stress Echo

↑ SV ≥ 20 %

Contractile (Flow) Reserve

ΔP ≥ 30-40
AVA < 1.0-1.2

True-Severe AS

ΔP < 30-40 &
AVA ≥ 1.0-1.2

Pseudo-Severe AS

↑ SV < 20 %

No Contractile (Flow) Reserve

AS Severity: Indeterminate

MSCT: Ca Score ≥ 1650?

No

Pseudo-Severe AS

Yes

True-Severe AS

Pibarot, ACC 2013
Paradoxical Low Flow (PLF) Aortic Stenosis

- Severe AS
  - AVA < 0.8 cm²
  - or 0.5 cm²/m²

- EF > 50%

- Mean Gradient < 35-40 mmHg

- SVI ≤ 35 ml/m²
PLF Aortic Stenosis – Small LV

- Typically characterized by restrictive physiology similar to normal EF CHF
- Other indices of LV function such as strain, velocity or mid-wall shortening are abnormal
- Prevalence higher in women, older age, LV remodeling, myocardial fibrosis, smaller LV volumes
Doppler-Echo Features of Paradoxical Low-Flow, Low-Gradient AS

The Aortic Valve

• AVA < 1.0 cm²
• AVAi < 0.6 cm²/m²
• Severely thickened/calcified valve
• Mean gradient <40 mmHg

The Left Ventricle

• EDD <47 mm, EDV <55 mL/m²
• RWT ratio > 0.50
• Impaired LV filling
• LVEF > 50%
• Global longitudinal strain < 15%
• SVi < 35 mL/m²

JACC 58;413-415, 2011
Factors that Decrease Flow in PLF

Prolongations in LV Ejection and Relaxation with Aging

Effect of Afterload Reduction in AS

Normal EF

- **Echo**
  - EF = 60%
  - Moderate to Severe MR
  - Moderate to Severe AS
    - Velocity 3.3 m/s, Mean Gradient – 30 mmHg
    - AVA = 0.9 cm², AVAi = 0.5 cm²/m²

- **Cath**
  - Mean gradient – 25 mmHg
  - Peak gradient – 30 mmHg
  - AVA = 0.6 cm²
Effect of Afterload Reduction in AS

*Normal EF*

- In cath lab, nipride titrated up to final dose 125 mcg/min
- Echo
  - Peak velocity – 4.2 m/s
  - Mean gradient – 36 mmHg
  - AVA – 0.7 cm²
  - AVAi – 0.4 cm²/m²
- Cath
  - Mean gradient – 35 mmHg
  - Peak gradient – 45 mmHg
Paradoxical Low-Flow, Low-Gradient Severe Aortic Stenosis Despite Preserved Ejection Fraction Is Associated With Higher Afterload and Reduced Survival

Zeineb Hachicha, MD; Jean G. Dumesnil, MD; Peter Bogaty, MD; Philippe Pibarot, DVM, PhD

Followed 331 patients with NF AS and 181 patients PLF AS

Hypertension in Paradoxically Low Flow Aortic Stenosis

Circulation. 2013;128:1349-1353

<table>
<thead>
<tr>
<th></th>
<th>Before NTP</th>
<th>After NTP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>74±14</td>
<td>76±14</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>39±12</td>
<td>25±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance, Wood units</td>
<td>4.41±2.93</td>
<td>2.68±1.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure, mm Hg</td>
<td>19±5</td>
<td>11±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular mean diastolic pressure, mm Hg</td>
<td>13±5</td>
<td>8±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic systolic pressure, mm Hg</td>
<td>176±26</td>
<td>108±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic diastolic pressure, mm Hg</td>
<td>75±13</td>
<td>54±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic mean pressure, mm Hg</td>
<td>115±17</td>
<td>77±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic pulse pressure, mm Hg</td>
<td>101±26</td>
<td>54±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>33±8</td>
<td>36±7</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.44±0.40</td>
<td>2.70±0.51</td>
<td>0.09</td>
</tr>
<tr>
<td>Effective arterial elastance, mm Hg·mL⁻¹·m⁻²</td>
<td>4.86±1.30</td>
<td>2.75±0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total arterial compliance, mL·m⁻²·mm Hg</td>
<td>0.37±0.12</td>
<td>0.71±0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic arterial resistance index, dynes·s·m⁻²·cm⁵</td>
<td>3441±840</td>
<td>2155±827</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean aortic valve gradient, mm Hg</td>
<td>27±5</td>
<td>29±6</td>
<td>0.02</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.86±0.11</td>
<td>1.02±0.16</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Impact of Low Flow on Event Rates

- 150 consecutive asymptomatic patients characterized by flow and gradient and followed
- Low flow had the highest event rate defined as CV death or need for AVR

JACC 2012; 59: 325-43
Low Flow in the PARTNER Trial
Flow is More Important than EF or Gradient

**ITT - Cohorts A & B**

### Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>LF LEF</th>
<th>LF NEF</th>
<th>LF LEF LG</th>
<th>LF LEF NG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>530</td>
<td>368</td>
<td>147</td>
<td>78</td>
</tr>
<tr>
<td>NF</td>
<td>441</td>
<td>342</td>
<td>115</td>
<td>62</td>
</tr>
</tbody>
</table>

**2-Yr Death (%)**

- **Flow** (LF): 47.2%
- **Normal Flow** (NF): 33.9%
- **Low Flow with EF** (LF LEF): 48.9%
- **Low Flow with Gradient** (LF LEF LG): 50.9%
- **Normal Flow with EF** (LF NEF): 46.1%
- **Normal Flow with Gradient** (LF LEF NG): 48.0%

**HR**

- **Flow**: 1.52 [95% CI: 1.24, 1.87]
- **Normal Flow**: 0.97 [95% CI: 0.65, 1.44]
- **Low Flow with EF**: 1.07 [95% CI: 0.83, 1.37]
- **Normal Flow with Gradient**: 0.97 [95% CI: 0.65, 1.44]

**Log-Rank p**

- **Flow**: <.001
- **Normal Flow**: 0.886
- **Low Flow with EF**: 0.616
- **Normal Flow with Gradient**: 0.886
AVR Improves Survival in All Groups

Eur Heart J (2010) 31, 281-89
Mortality Reductions with Valve Replacement in Paradoxically Low Flow Aortic Stenosis

<table>
<thead>
<tr>
<th>Citation</th>
<th>N</th>
<th>Age</th>
<th>Prevalence</th>
<th>Mode</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohty D, 2013</td>
<td>768</td>
<td>77±6</td>
<td>13%</td>
<td>Surgery</td>
<td>0.23 (0.09-0.59)</td>
</tr>
<tr>
<td>O'Sullivan, 2013</td>
<td>385</td>
<td>82±5</td>
<td>22%</td>
<td>TAVR</td>
<td>0.78 (0.29–2.13)</td>
</tr>
<tr>
<td>Herrmann HC, 2013</td>
<td>971</td>
<td>84±8</td>
<td>31%</td>
<td>TAVR</td>
<td>0.48 (0.28–0.80)</td>
</tr>
<tr>
<td>Tarantini G, 2011</td>
<td>102</td>
<td>78</td>
<td>N/A</td>
<td>Surgery</td>
<td>0.24 (0.12 -0.47)</td>
</tr>
</tbody>
</table>
PARTNER Trial: AVR Beneficial in PLF

log rank p= <.001

2-Year Death (%)

Days

0 60 120 180 240 300 360 420 480 540 600 660 720

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>A – TAVR</th>
<th>A – Surgery</th>
<th>B – TAVR</th>
<th>B – Standard Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>103</td>
<td>93</td>
<td>103</td>
<td>93</td>
</tr>
<tr>
<td>120</td>
<td>93</td>
<td>83</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>240</td>
<td>80</td>
<td>80</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>360</td>
<td>70</td>
<td>71</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>480</td>
<td>69</td>
<td>69</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>600</td>
<td>63</td>
<td>66</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>720</td>
<td>59</td>
<td>65</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

LF NEF – A - TAVR
LF NEF – A - Surgery
LF NEF – B - TAVR
LF NEF – B - Standard Rx
PARTNER Trials: TAVR has early benefit in Low Flow AS

All LF Patients by Treatment Received

log rank p = <.001

2-Year Death (%)

LF – A – TAVR
LF – A – Surgery
LF – B – TAVR
LF – B – Standard Rx

0% 10% 20% 30% 40% 50% 60% 70% 80%

0 60 120 180 240 300 360 420 480 540 600 660 720

39.3% 38.1% 45.9% 76.2%

25% to 16% (40% RR, p=0.04)

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LF – A – TAVR</td>
<td>170</td>
<td>152</td>
<td>143</td>
<td>127</td>
<td>123</td>
<td>116</td>
<td>109</td>
<td>102</td>
<td>86</td>
</tr>
<tr>
<td>LF – A – Surgery</td>
<td>180</td>
<td>138</td>
<td>127</td>
<td>123</td>
<td>119</td>
<td>115</td>
<td>111</td>
<td>105</td>
<td>90</td>
</tr>
<tr>
<td>LF – B – TAVR</td>
<td>85</td>
<td>74</td>
<td>65</td>
<td>58</td>
<td>55</td>
<td>50</td>
<td>47</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>LF – B – Std Rx</td>
<td>95</td>
<td>78</td>
<td>60</td>
<td>47</td>
<td>39</td>
<td>35</td>
<td>26</td>
<td>25</td>
<td>18</td>
</tr>
</tbody>
</table>
Shared Decision Making (SDM)

• **What it is not!**
  – I made a decision
  – Then I shared it with the patient

• **What it is!**
  – SDM is a collaborative process that allows patients and their providers to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values and preferences.
Comprehensive Geriatric Assessment: A critical part of TAVR Assessment

- Comprehensive Geriatric Assessment revealed:
  - Frail: 3/5 criteria (slow gait speed = 0.7 m/sec, normal > 1 m/sec; Exhausted, Low physical activity but no weight loss and strong grip strength = 30 kg/).
  - Short physical performance batter: SPPB
  - Cognitively intact: normal mini-Cog and MOCA
  - Strong social support
Co-Morbidity, Frailty and Disability

- **Co-morbidity**
  - Concurrent presence of two or more medically diagnosed diseases in the same individual

- **Frailty**
  - A physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves causing homeostenosis.

- **Disability**
  - Difficulty or dependency in carrying out activities essential to independent living (e.g. Loss of ADLs and IADLs).

**Diagram:**
- 60% of the population had comorbidity.
- 8% had disability and frailty.
- 7% had frailty.
- 26.6% had disability.
- 46.2% had comorbidity.
- 21.5% had disability without frailty.
- 5.7% had frailty without disability.
### Operationalizing Frailty

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tool(s)</th>
<th>Common Cutoffs for Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowness</td>
<td>5-m gait speed test</td>
<td>Extremely slow: &lt;0.50 m/s (&gt;10 s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very slow: &lt;0.65 m/s (&gt;7.7 s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slow: &lt;0.80 m/s (&gt;6.25 s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Borderline slow: &lt;1.00 m/s (&gt;5 s)</td>
</tr>
<tr>
<td>Weakness</td>
<td>Handgrip strength test</td>
<td>Men: &lt;30 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: &lt;20 kg</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>Minnesota Leisure Time Activity Questionnaire</td>
<td>Men: &lt;383 kcal/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women: &lt;270 kcal/week</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>CES-D questionnaire</td>
<td>Either question positive</td>
</tr>
<tr>
<td>Shrinking</td>
<td>Weight loss</td>
<td>Unintentional weight change not due to dieting or exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 lbs in past year</td>
</tr>
</tbody>
</table>
Due to the aging and increasingly complex nature of our patients, frailty has become a high-priority theme in cardiovascular medicine. Despite the recognition of frailty as a pivotal element in the evaluation of older adults with cardiovascular disease (CVD), there has yet to be a road map to facilitate its adoption in routine clinical practice. Thus, we sought to synthesize the existing body of evidence and offer a perspective on how to integrate frailty into clinical practice. Frailty is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors. Upward of 20 frailty assessment tools have been developed, with most tools revolving around the core phenotypic domains of frailty—slow walking speed, weakness, inactivity, exhaustion, and shrinking—as measured by physical performance tests and questionnaires. The prevalence of frailty ranges from 20% to 60%, depending on the cardiovascular pathology, as well as the tool and cutoff chosen to define frailty. Epidemiological studies have consistently demonstrated that frailty carries a relative risk of $>2$ for mortality and morbidity across a spectrum of stable CVD, acute coronary syndromes, heart failure, and surgical and transcatheter interventions. Frailty contributes valuable prognostic insights incremental to existing risk models and assists clinicians in defining optimal care pathways for their patients. Interventions designed to improve outcomes in frail elders with CVD such as multidisciplinary cardiac rehabilitation are being actively tested. Ultimately, frailty should not be viewed as a reason to withhold care but rather as a means of delivering it in a more patient-centered fashion. (J Am Coll Cardiol 2013;[:::---] © 2013 by the American College of Cardiology Foundation)
Case (Continued)

• After long discussions, in part, driven by desire to be at grandsons bar mitzvah, he pursued TAVR.

• Participated in research study post TAVR (ACC Merck Award to Dr. Adam Castano) to define prevalence of TTR cardiac amyloid (e.g. senile cardiac amyloid) in TAVR.
  – Hypotheses:
    • *The odds of ATTR among severe AS patients with PLF are higher compared to the odds of ATTR in non-PLF severe AS controls*
    • *Factors associated with the diagnosis of ATTR among patients with PLF may include older age, elevated cardiac biomarkers (troponin I and brain natriuretic peptide – BNP), thicker left ventricular posterior wall (LVPW), low tissue Doppler velocities, and higher LVEF.*
Increased PYP Uptake: Indicative of TTR Cardiac Amyloid
ATTRwt Cardiac Amyloid: Common in TAVR

- 118 patients with severe AS.
- $^{99m}$Tc-PYP planar imaging.
- Uptake in 14.4% (n=17), 15 of which were men.
- Phenotype of severe concentric LVH and low flow AS
  - Men (88%)
  - Elevated BNP (498 vs. 275 pg/mL, p=0.04)
  - Higher LV mass index (127 vs. 96 g/m², p=0.005),
  - Low SVI (27 vs. 37 ml/m², p=0.023)
  - RBBB (50% vs 14%, p = 0.007).

20% ATTRwt in Males Undergoing TAVR

Poster 90: Monday April 4, 2016
• Emerging 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
5 Things we know about Senile (ATTRwt) Cardiac Amyloidosis

1. Senile cardiac amyloid (ATTRwt) is the most common form of cardiac amyloidosis.
2. ATTRwt cardiac amyloid is an under-appreciated cause of HFpEF.
3. An EKG is not a good screening test for ATTRwt.
4. SCA is a great masquerader but there are clues.
5. Non-invasive bone scintigraphy is highly specific for ATTR cardiac amyloid.
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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</td>
</tr>
<tr>
<td></td>
<td>50% have cardiac involvement</td>
</tr>
<tr>
<td>ATTRmutant</td>
<td>4% of African Americans are carriers</td>
</tr>
<tr>
<td></td>
<td>25,000-120,000 US patients</td>
</tr>
<tr>
<td>ATTRwt (SCA)</td>
<td>~10-25% of adults &gt;80 years</td>
</tr>
<tr>
<td></td>
<td>~1 million</td>
</tr>
</tbody>
</table>
TTR (Prealbumin)

- Tetramer of subunits of 127 amino acids each
- TTR is a plasma transport protein for thyroxine (T4) and for retinol.

Sensorimotor Polyneuropathy
Deposition in Peripheral Nerves
Amyloid Fibrils

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

TTR Amyloid Cardiomyopathy (ATTR-CM)
Deposition in Cardiac Tissues
Onset: 60-70s

Restrictive Cardiomyopathy
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
5 Things we know about Senile (ATTRwt) Cardiac Amyloidosis

1. Senile cardiac amyloid (ATTRwt) is the most common form of CA.

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3. An EKG is not a good screening test for ATTRwt.

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5. Non-invasive bone scintigraphy is highly specific for ATTR cardiac amyloid.
TTR Cardiac Amyloidosis: A underappreciated cause of HFpEF

Transthyretin Cardiac Amyloid in Afro-Caribbean Patients with ADHF

- 1,142 ADHF patients
- 170 (14.9%) Afro-Caribbean patients
  - 17 (10%) were confirmed to have cardiac ATTR V122I.
- Survival worse in amyloid compared to non-amyloid cardiomyopathy
  - 34 vs 59 months, p<0.01.

<table>
<thead>
<tr>
<th></th>
<th>Black Patients (n=170)</th>
<th>All Other Patients (n=972)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 (53-77)</td>
<td>73 (63-81)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>64.7%</td>
<td>67.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>87.1%</td>
<td>58.2%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ATTR V122I</td>
<td>10%</td>
<td>0.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HTN disease</td>
<td>18.8%</td>
<td>7%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

JACC 2012; 59 (13): E993
ATTRwt Cardiac Amyloid: Common in HFnEF

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

17% of HFnEF have ATTR Cardiac Amyloid.

Eur Heart J. 2015 Jul 28
5 Things we know about Senile (ATTRwt) Cardiac Amyloidosis

1. Senile cardiac amyloid (ATTRwt) is the most common form of CA.
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Which patient has Cardiac Amyloid?

Both of them
ECG is Relatively Insensitive

Overall (n=210)
AL (n=110)
ATTRmt (n=45)
ATTRwt (n=45)

Atrial Fibrillation
Pseudoinfarct
PPWRP
Low Limb Lead Voltage
Low Precordial Lead Voltage
Sokolow Criteria Abnormal Voltage to Masss Ratio

Am J Cardiol. 2014;114(7):1089-93
5 Things we know about Senile (ATTRwt) Cardiac Amyloidosis

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5. Non-invasive bone scintigraphy is highly specific for ATTR cardiac amyloid.
### History/ Exam Clues

- **HFPEF without hypertension**, particularly in men
- Evidence of **right-sided** heart failure (e.g. hepatomegaly, ascites, and lower extremity edema)
- **Intolerance** of ACE, Beta-blockers.
- Bilateral carpal tunnel syndrome

### Imaging Clues

- **Thick septum** and granular sparkling on 2D TTE
- **Low voltage to mass ratio**
- **Low** tissue Doppler velocities, strain, or strain rate
- **Apical sparring** on strain rate imaging
- **Delayed** gadolinium enhancement on CMRI
Preserved Apical Strain
Echocardiographic Clue
Delayed Enhancement in Amyloid
5 Things we know about TTR Cardiac Amyloidosis

1. TTR amyloid is the most common form of CA.
2. TTR cardiac amyloid is an under-appreciated cause of HFpEF
3. An EKG is not a good screening test for TTR amyloidosis
4. Clues to TTR Cardiac Amyloidosis are available
5. Non-invasive bone scintigraphy is highly specific for TTR amyloid
Noninvasive Diagnosis of TTR Cardiac Amyloidosis Using 99mTc-DPD Scintigraphy

J Am Coll Cardiol 2005;46:1076–84
Differences in Cardiac Retention with Tc-99 in Controls, AL and ATTR Amyloid

TTR (Prealbumin)

- Transthyretin - TTR
  - Tetramer of subunits of 127 amino acids each;
  - TTR is a plasma transport protein for thyroxine - T4 - and for retinol.

### Transthyretin Amyloidoses

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Predominant Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val30Met</td>
<td>PN, AN</td>
</tr>
<tr>
<td>Val122Ile</td>
<td>Heart</td>
</tr>
<tr>
<td>Thr60Ala</td>
<td>Heart, Carpal Tunnel Syndrome</td>
</tr>
</tbody>
</table>
Transthyretin (TTR) amyloidoses

- Amyloidogenic mutations destabilize TTR homotetramer to form monomeric amyloidogenic intermediates that self-assemble into amyloid fibrils.
Pathogenesis of ATTR Amyloidosis
Geriatric Cardiology:
A delicate balance
Geriatric Cardiology: Opportunities for Engagement

Membership
- >2,700 clinicians, researchers, and healthcare associates:
  - 63% being physicians,
  - 11% CV Team members (RNs, NPs, PAs, PharmDs)
  - 26% FITs (> 700)

Working Groups
- Research
- Education
- Advocacy
- Palliative Care
- International
- Communications
- FIT/ECP
Essential of Cardiac Care for Older Adults (ECCOA)

• Online curriculum – FREE!!!
  – Available at acc.org/ECCOA
• CME/CE activity and MOC
  – 17 credits
  – Available to all practitioners.
• Developed in response to national mandates to improve the understanding and care of older adults.
• Current grant funded by Retirement Research Foundation.

Modules
• Cardiovascular Physiology in the Older Adult
• Pharmacology for Older Adults
• Care of Older Adults
• Decision Making for Older Adults
• Heart Failure in Older Adults
• Chronic Coronary Disease in Older Adults
• Acute Coronary Syndromes in Older Adults
• Electrophysiology and Heart Rhythm Disorders in Older Adults
• Syncope in Older Adults
• Perioperative Care in Older Adults
• Palliative Care in Older Adults
• Prevention in Older Adults
• Vascular Disease in Older Adults
• Valvular Disease in Older Adults
Summary

- Embracing the inherent complexity in caring for older adults with cardiovascular disease is essential to deliver the highest quality care and treat the “whole patient”.

- While “age” is not modifiable the health care system is and has been altered over the last few decades to better address the needs of a rapidly expanding older adult population.

- Device based therapies and sophisticated procedures for CV disorders are emerging and selection of appropriate candidates will be key.

- Non-pharmacologic interventions hold great promise for reducing morbidity or mortality in older adults with HF.