ATTRwt Amyloidosis

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This is the little bugger that causes the problem

- A protein made of 4 identical subunits
- Has two names
  1. Prealbumin
  2. Transthyretin
The latter because it transports (trans), thyroid hormone (thy) and retinol (retin), which is Vitamin A.
Transthyretin (aka Prealbumin)

A protein with a lot of beta pleated sheets
How does one get TTR amyloidosis?
Other names for Wild Type TTR Amyloidosis (note I am not responsible for them!)

- Senile Cardiac Amyloidosis (SCA)
  - Because patients are older not cognitively impaired

- Senile Systemic Amyloidosis (SSA)
  - Because while it affects mainly the heart other organs can have amyloid depositions

- Age Related Cardiac Amyloidosis
Age Dependent Penetrance: A fancy term for, when does it show up?

- Using THAOS – Transthyretin Amyloid Outcomes Survey (www.THAOS.net)

111 persons meeting inclusion criteria were identified.

- 4 genotypes were represented:
  - Wild-type (59%),
  - Val122Ile (23%),
  - Thr60Ala (9%),
  - Leu111Met (9%).
Production of Proteins
Protein Folding: A Shout Out to Mother Nature

- Proteins - most abundant molecules in biology other than water.
- Must be converted into tightly folded compact structures in order to function.
- Single simple protein has $10^{16}$ possible starting configurations.
- Folding is usually extremely efficient - a remarkable testament to the power of mother nature (biology).
Protein Misfolding
Tissue Tropism

• Why does transthyretin like the heart?
• Or the ligaments?
• What factors affect the clinical manifestations and progression of the condition?
How does ATTRwt affect the heart?

Normal

Amyloidosis
## ATTRm and ATTRwt

<table>
<thead>
<tr>
<th></th>
<th>ATTRm</th>
<th>ATTRwt</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Variable (depends on mutation)</td>
<td>&gt;65</td>
</tr>
<tr>
<td><strong>Gender (%M/%F)</strong></td>
<td>50%/50%</td>
<td>95%/5%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Depend on mutation</td>
<td>Predominately Caucasians</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(To date)</td>
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<tr>
<td><strong>Affected Organs</strong></td>
<td>Nerves, Heart, Eyes</td>
<td>Heart</td>
</tr>
</tbody>
</table>
Why Ejection Fraction (EF) Sucks in Cardiac Amyloidosis

**Normal**

- EDV: 100 ml
- ESV: 30 ml
- Contraction: 70 ml
- **EF** = \( \frac{70}{100} \) = 70%

**Amyloidosis**

- EDV: 50 ml
- ESV: 15 ml
- Contraction: 35 ml
- **EF** = \( \frac{35}{50} \) = 70%

20 mm or 2 cm Thick all around
Endomyocardial Biopsy
The previous way to diagnose TTR cardiac amyloidosis
PYP Scan for Diagnosing TTR cardiac amyloidosis

General Treatment for Amyloid Cardiomyopathy

• Diuretics and Salt Restriction – Mainstay of therapy
  • Aldosterone Antagonists and Bioavailable Loop Diuretics

• Atrial Fibrillation – Nearly Universal Over Time
  • Prevalence - At least 1/3 in large series and 53% in the ATTR-ACT study
  • Incidence - ~90% develop AF over time
  • Anticoagulation in atrial fibrillation irrespective of CHADs-Vasc Score

• Calcium channel blockers – some contraindicated

• Hypotension – compression stockings and midodrine.

• AICD / pacer - More of a role for pacing
ATTRwt Cardiomyopathy Clinically Available Options

- **Tafamidis**
  - Approved
  - Cost could limit access

- **Difenisal**
  - Off label use

- **NSAID** – use cautiously
  - No recent decompensation
  - Good renal function
  - Daily diuretic dose < 80 mg Lasix, no metalozone
  - ? Use with anticoagulation

Ruberg, F, JACC. 2019;73(22):2872-2891
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism /Delivery</th>
<th>Trial Name</th>
<th>Trial Design</th>
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</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>
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<tr>
<td>ION-682884 (Ionis/Akcea)</td>
<td>Silencer SQ</td>
<td>IONIS LICA-CM</td>
<td>Placebo controlled, RCT; 1:1 allocation</td>
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<tr>
<td>Vutrisiran (Alnylam)</td>
<td>Silencer SQ</td>
<td>HELIOS-B</td>
<td>Placebo controlled, RCT; 1:1 allocation</td>
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