Amyloidosis 2020: Assessment and Treatment
An Underdiagnosed Cause of Heart Failure

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Chairman, Pacific Heart Institute, Santa Monica, CA
Co-Director, Heart Failure Focus Group, Providence Health System
## Richard F. Wright, M.D.  
**Disclosures**

<table>
<thead>
<tr>
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<th>Speaking</th>
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<td>American College of Cardiology</td>
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Definition of Heart Failure

A “syndrome”… not a disease
Definition of Heart Failure

A “syndrome”… not a disease

In which:

the heart fails to deliver an adequate volume and pressure of blood without flooding the lungs or body…
Lifetime Risk of Having Heart Failure: 20%

Framingham Heart Study

Lifetime risk for HF for given index age is cumulative through age 94 years

Contributors to Heart Failure

• Hypertension
• Myocardial infarction
• Diabetes
• Obesity
• Genetics
• Ageing/infiltration/inflammation of the heart
• Infections
• Exposure to toxic agents
• Stress (catecholamines)
Contributors to Heart Failure

- Hypertension
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- Ageing/infiltration/inflammation of the heart
- Infections
- Exposure to toxic agents
- Stress (catecholamines)
One Form of Heart Failure: “Systolic” – Reduced Ejection Fraction

- Enlarged chamber size
- Normal, high, or low mass
- Poor squeeze:
  - less vigor, less twist
  - dyssynchrony
- Poor relaxation and suction
- Abnormal valves: regurgitation
  - “Normal” pericardium

- Impaired inflow of blood
- Impaired outflow of blood
Another Form of Heart Failure:
“Diastolic” or Preserved Ejection Fraction

Small chamber size
Usually increased mass
Normal, low, or vigorous squeeze
Abnormal relaxation
Normal or abnormal valves
Normal pericardium

Impaired inflow of blood
Unimpaired or impaired outflow
Infiltrative Heart Failure
A Cause of Infiltration: Amyloidosis

- Abnormal deposition of insoluble misfolded proteins, resistant to proteolysis
A Cause of Infiltration: Amyloidosis

- Abnormal deposition of insoluble misfolded proteins, resistant to proteolysis

- Microscopy: Congo red stain (a diazo cotton fabric dye invented in 1883; used in medical pathology since 1922)
A Cause of Infiltration: Amyloidosis

- Abnormal deposition of insoluble misfolded proteins, resistant to proteolysis

- Microscopy: Congo red stain (a diazo cotton fabric dye invented in 1883; used in medical pathology since 1922) – 25-75% sensitive and 50-90% specific
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- >30 different types… five known to infiltrate the heart
A Cause of Infiltration: Amyloidosis

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• >30 different types... five known to infiltrate the heart

• 95% of cardiac amyloid due to either:
  Immunoglobulin light chains (often with myeloma): AL
  Transthyretin – mutated or “wild-type”: TTR
A Cause of Infiltration: Amyloidosis

• Abnormal deposition of insoluble misfolded proteins, resistant to proteolysis

• Microscopy: Congo red stain (a diazo cotton fabric dye invented in 1883; used in medical pathology since 1922) – 25-75% sensitive and 50-90% specific

• >30 different types… five known to infiltrate the heart

• 95% of cardiac amyloid due to either:
  Immunoglobulin light chains (often with myeloma): AL
  Transthyretin – mutated or “wild-type”: TTR

• Other proteins that can cause cardiac amyloid:
  immunoglobulin heavy chains, serum amyloid A, apolipoprotein A1
Amyloidosis

Insoluble protein aggregates in cellular and extracellular fluids

Different proteins (and different locations) lead to distinct Diseases

- transthyretin - senile systemic amyloidosis
  - familial amyloid polyneuropathy
  - familial amyloid cardiomyopathy
- β-amyloid - Alzheimer disease
- α-synuclein - Parkinson disease
- amylase - type 2 diabetes
- prion - bovine spongiform encephalopathy (BSE)
  “mad cow disease”, scrapie and Creutzfeldt-Jakob disease
Cardiac Amyloidosis: Major Types

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Light Chain</th>
<th>Transthyretin “TTR”</th>
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<tr>
<td>Protein Deposited</td>
<td>Light chain</td>
<td>ATTRm</td>
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<tr>
<td>Disease Etiology</td>
<td>Plasma cell dyscrasia with ↑ light chains</td>
<td>ATTRw</td>
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<tr>
<td>Specific Features</td>
<td>Kidney, heart and liver affected</td>
<td>Mutated TTR protein</td>
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<td>Median Survival</td>
<td>1-3 years</td>
<td>wt TTR monomers</td>
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<td>Prognostic Factors</td>
<td>Cardiac function, BNP, troponin</td>
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<tr>
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<td></td>
<td>Common in elderly aged &gt; 75 years</td>
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<td></td>
<td></td>
<td>V122I common in African Americans</td>
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<tr>
<td></td>
<td></td>
<td>Carpal tunnel; Male dominance</td>
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<tr>
<td></td>
<td></td>
<td>2 years</td>
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<tr>
<td></td>
<td></td>
<td>4-6 years</td>
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<td></td>
<td></td>
<td>Duration, HR&gt;70/min, ↓ LVEF</td>
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<td></td>
<td></td>
<td>BNP, uric acid, ↓ LVEF, ↑ Wall</td>
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<tr>
<td></td>
<td></td>
<td>Thickness</td>
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<tr>
<td></td>
<td>Liver ± heart Tx</td>
<td>?siRNA or ASO</td>
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Cardiac Amyloidosis: Major Types

### Light Chain

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10,000 in the US

### Transthyretin “TTR”

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>>100,000 in the US
Cardiac TTR Amyloidosis is Common

Transthyretin “TTR” cardiac amyloid:

- 20% of patients with HfPEF
- 10% of low-flow aortic stenosis
- 5-10% of “hypertrophic cardiomyopathy”
Cardiac TTR Amyloidosis is Common

Transthyretin “TTR” cardiac amyloid:

- 20% of patients with HfPEF (>30% if older than 75)
- 10% of low-flow aortic stenosis
- 5-10% of “hypertrophic cardiomyopathy”
- 25% of ALL autopsied adults >80 years old have some cardiac amyloid...
Cardiac TTR Amyloidosis is Common

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- 20% of patients with HfPEF (>30% if older than 75)
- 10% of low-flow aortic stenosis
- 5-10% of “hypertrophic cardiomyopathy”

- 25% of ALL autopsied adults >80 years old have some cardiac amyloid...

- Most have “wild-type” amyloidosis – especially MEN

What is Transthyretin (TTR)?

A normal protein… also called “pre-albumin”

- Made in the liver
- NOT related to albumin… just elutes off a column before albumin does (hence the name)
- Shorter half-life than albumin – used for calorie assessment
- Produced as a monomer, but circulates as a tetramer
- Role is to TRANSPORT THYroxine and RETINoic acid (vitamin A)
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- Produced as a monomer, but circulates as a tetramer
- Role is to TRANSPORT THYroxine and RETINOic acid (vitamin A)

- Can misfold… especially if mutated
Most Common Form of Amyloidosis: “TTR”

FREE TETRAMER  FOLDED PROTEIN  MISFOLDED PROTEIN  AMYLOID FIBRILS*

Functional TTR Structures  Protein Misfolding  Aggregation  TTR Structures Associated With Pathology

*Amyloid fibrils can be caused by a variety of toxic intermediates including small oligomers and amorphous aggregates.
Common Forms of Transthyretin Amyloidosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Clinical Classification</th>
<th>Population and Age of Onset</th>
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<tbody>
<tr>
<td>Senile systemic amyloidoses (SSA)</td>
<td>WT</td>
<td>Cardiomyopathy</td>
<td>10-25% of males worldwide &gt; 60 years of age</td>
</tr>
<tr>
<td>Familial amyloid cardiomyopathy (FAC)</td>
<td>V122I</td>
<td>Cardiomyopathy</td>
<td>3-4% African Americans (~1.3 Million)</td>
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<td>5% West Africans</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>High penetrance &gt; 65 years of age</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy (FAP)</td>
<td>V30M</td>
<td>Peripheral Neuropathy</td>
<td>Europe and Japan (~12,000 worldwide)</td>
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<tr>
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<td>high penetrance</td>
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<tr>
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<td></td>
<td>early and late onset 30-80 years of age</td>
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Hereditary TTR Amyloidosis: Differing Mutations and Presentations
Hereditary TTR Amyloidosis: Population Differences

Portugal
- V50M Early Onset
- C30R
- R54T
- G67A
- F84L
- L78H
- E109Q
- I127V
- S43N
- L131M
- I88L

Japan
- H3L
- S70R
- S97Y
- A56P
- T69A
- V50M Late Onset
- W61L
- H108R
- T80A
- V142I

Sweeden

Central West Africa

Predominant Neurologic Features

Mixed Phenotype

Predominant Cardiac Features
1034 patients with cardiac TTR cardiomyopathy in the U.K.:

- 69% of patients had wild-type TTR
- 20% had V142I mutation – worse prognosis and much less likely to have peripheral neuropathy
- 11% with other mutations - far more likely (>%95%) to have peripheral neuropathy
Amyloidosis: Often Misdiagnosed or Missed

Majority initially misdiagnosed and mistreated… typically 2-5 symptomatic years before correct diagnosis made

Average of 17 hospital services used in the 3 years prior to diagnosis

Most common specialists seen:
- Cardiology
- Hematology/oncology
- Neurology
- Gastroenterology
- Nephrology

Amyloidosis: Signs and Symptoms

Cardiovascular manifestations

Autonomic conditions

Peripheral neuropathy

Orthopedic conditions

Gastrointestinal problems

Renal dysfunction
Amyloidosis: “Red Flag” Findings

Cardiovascular manifestations

Heart failure – most commonly “diastolic”
Atrial fibrillation – especially if slow ventricular rates
Unexplained AV block or need for pacemaker
Atrial dilation – especially if bilateral and progressive
Low flow aortic valve stenosis
Increased cardiac thickness: can be any wall
Abnormal EKG – e.g. lower voltage than expected
“Apical sparing” by echo strain imaging
Technetium pyrophosphate uptake into myocardium
Chronic elevation of troponin and NT-proBNP
Transthyretin Amyloidosis: Very Common in Other Cardiac Conditions

Aortic Stenosis (Castano 2017, n=151)

- 16% No ATTR
- 84% ATTR detected

Patients tested were undergoing transcatheter aortic valve replacement

Methods: 99mTc-PYP scintigraphy

Hypertrophic Cardiomyopathy (Damy 2016, n=296)

- 5% No ATTR
- 95% hATTR mutation identified

Patients tested had idiopathic hypertrophic cardiomyopathy

Methods: TTR gene sequencing

Hereditary Transthyretin Mutation: Underdiagnosed in Certain Populations

African-Americans ≥65 years old account for ~1% of the overall US population = 3.5 million people (using US census data from 2000 and 2016)

This translates to ~100,000 Val122Ile carriers age 65+ (as also estimated by Ruberg and Berk, 2012)

Quarta et al. (2015) estimated 1.4 million carriers in the US, which will increase to 2.5 million by 2060, at an increased risk for heart failure (consistent with an estimate by Ruberg and Berk (2012): 1.5 million Val122Ile carriers)

While the clinical penetrance of this mutation is currently undefined, Val122Ile is “almost certainly underrecognized as a cause of heart failure”
Amyloidosis: EKG Almost Always Abnormal
Amyloidosis: EKG Almost Always Abnormal
... but the minority have low voltage
and 20% actually have “LVH” by voltage criteria
Amyloidosis: Most Revealing EKG Finding

Disparity of LV echo mass vs. EKG voltage
Amyloidosis: Most Revealing EKG Finding

Disparity of LV echo mass vs. EKG voltage

ESPECIALLY in a man >75 years old
99mTechnetium Pyrophosphate Scan: Most Important Test for Transthyretin Amyloid

99% sensitive, 86% specific (some AL false positives)

Usually 15-20 mCi; total body radiation exposure 3-4 mSv

Gillmore JD. Circulation 2016;133:2404-2012
Technetium Pyrophosphate Scan: Abnormal Cardiac Uptake Quantitated

Frederick L. Ruberg et al. JACC 2019;73:2872-2891

Ratio: 1.79
Common Echo Findings in Amyloidosis
Common Echo Findings in Amyloidosis

“LVH” with wall thickness >1.4 cm

Pericardial effusion

Dilated atria
Heart Failure: Echo Strain Imaging

Normal

http://dx.doi.org/10.1136/heartjnl-2012-302353
Heart Failure: Echo Strain Imaging

Anterior MI

http://dx.doi.org/10.1136/heartjnl-2012-302353
Heart Failure: Echo Strain Imaging

Inferior MI

http://dx.doi.org/10.1136/heartjnl-2012-302353
Heart Failure: Echo Strain Imaging

Takotsubo

http://dx.doi.org/10.1136/heartjnl-2012-302353
Heart Failure: Echo Strain Imaging

http://dx.doi.org/10.1136/heartjnl-2012-302353
Heart Failure: Echo Strain Imaging

Amyloidosis: “Apical Sparing”

http://dx.doi.org/10.1136/heartjnl-2012-302353
Amyloid: Echo Strain Imaging

hATTR-CM

TTR Val122Ile carrier

Frederick L. Ruberg et al. JACC 2019;73:2872-2891
Cardiac MRI Abnormal in Amyloidosis

Usually diffuse heterogeneous gadolinium enhancement, with T1 signal abnormalities and marked extracellular volume expansion.

Frederick L. Ruberg et al. JACC 2019;73:2872-2891
Amyloidosis: Other “Red Flag” Findings

**Neurologic condition**
- Peripheral neuropathy

**Autonomic conditions**
- Orthostatic hypotension
- Urinary incontinence
- Erectile dysfunction
- Abnormal sweating

**Gastrointestinal problems**
- Chronic diarrhea
- Fecal incontinence
- Diarrhea/constipation
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- Peripheral neuropathy

**Autonomic conditions**
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Amyloidosis: Other “Red Flag” Findings

Orthopedic conditions
- Carpal tunnel syndrome
- Spinal stenosis
- Biceps tendon rupture

Family history of amyloid

Rapid or unexpected progression

Failure to respond to normal “treatment”
Amyloidosis: Other “Red Flag” Findings

Orthopedic conditions:
- Carpal tunnel syndrome
- Spinal stenosis
- Biceps tendon rupture

Family history of amyloid

Rapid or unexpected progression

Failure to respond to normal “treatment”

- 12-fold lifetime risk of amyloidosis
- Present in 50% ATTR cardiomyopathy pts.
- Precedes amyloid diagnosis by >5 years

Nakagawa M. Amyloid 2016;23:58-63
Amyloidosis in Carpal Tunnel

A  Cumulative Incidence of Amyloidosis

B  Cumulative Incidence of Heart Failure  C  Cumulative Incidence of Death

Emil L. Fosbøl et al. JACC 2019;74:15-23
Survival in Cardiac TTR Amyloidosis

Stage 1
Stage 2
Stage 3

Survival probability

Follow up (months)

Number at risk

Stage I 89
Stage II 79
Stage III 33

Stage I 51 21 9
Stage II 37 12 5
Stage III 11 2 2

Legend:
- Blue: Stage I
- Red: Stage II
- Green: Stage III
Cardiac Amyloidosis: Poor Outcome While Awaiting Transplant

8416 with dilated cardiomyopathy, 306 with amyloid cardiomyopathy, and 183 with idiopathic restrictive cardiomyopathy

Mortality while on transplant list

Amyloid

Cardiac Amyloidosis: Poor Outcome While Awaiting Transplant

Mortality while on transplant list

- 59% deaths: cardiac
- 4% deaths: cardiac
- 40% deaths: cardiac

Amyloid

0 12 months 24 months 36 months
0 5 10 15 20 25 30 35 40 45

Amyloid CMP
Non-amyloid restrictive CMP
Dilated CMP

Potential Treatments for TTR Amyloidosis
Potential Treatments for TTR Amyloidosis

- Liver transplantation
- Genetic silencers
  - siRNA (ALN-TTR)
  - AOs (ISIS-TTR<sub>Rx</sub>)

Synthesis suppression

Amyloid fibrils

TTR tetramer

Dissociation

Dimers

Monomers
Potential Treatments for TTR Amyloidosis

- Tafamidis
- Diflunisal
- AG10

TTR stabilization

Dissociation

TTR tetramer

Amyloid fibrils

Dimers

Monomers
Potential Treatments for TTR Amyloidosis

- Doxycycline
- Doxycycline-TUDCA
- EGCG (green tea)
- PRX004
- Anti-SAP + CPHPC
Potential Treatments for TTR Amyloidosis

- Liver transplantation
- Genetic silencers
  - siRNA (ALN-TTR)
  - AOs (ISIS-TTR<sub>RX</sub>)

Synthesis suppression

TTR stabilization
- Tafamidis
- Diflunisal
- AG10

Elimination of deposits
- Doxycycline
- Doxycycline-TUDCA
- EGCG (green tea)
- PRX004
- Anti-SAP + CPHPC

Amyloid fibrils
- TTR tetramer
- Dissociation
- Dimers
- Monomers
Treatment for TTR Amyloidosis: Inotersen Injections to Reduce TTR mRNA
An antisense oligonucleotide

Median Percent Change from Baseline in Serum TTR Over Time

Median serum TTR reductions were 75% to 79% below baseline from week 13 to week 65.
Treatment for TTR Amyloidosis: Inotersen Injections and Quality of Life

Change from Baseline in SF-36

Mean (±SE) change from NEURO-TTR baseline in SF-36 PCS

Placebo-inotersen

- Placebo-inotersen  n= 50
- Inotersen continuous  n= 80

Potential Treatments for TTR Amyloidosis: “Stabilizing Agents”
Potential Treatments for TTR Amyloidosis: Stabilizing Agents
Potential Treatments for TTR Amyloidosis: Stabilizing Drug Tafamadis

The current *Proceedings of the National Academy of Sciences* study provides new molecular and structural data showing how tafamadis works. (Image courtesy of the Wilson and Kelly labs, The Scripps Research Institute.)
Cardiac TTR Amyloid: Stabilization of Tetramer Assessed by TTR Levels
Survival in Cardiac TTR Amyloid: Tafamadis

B Analysis of All-Cause Mortality

Hazard ratio, 0.70 (95% CI, 0.51–0.96)

No. at Risk (cumulative no. of events)
Pooled tafamidis 264 (0) 259 (5) 252 (12) 244 (20) 235 (29) 222 (42) 216 (48) 209 (55) 200 (64) 193 (71) 99 (78) 0 (78)
Placebo 177 (0) 173 (4) 171 (6) 163 (14) 161 (16) 150 (27) 141 (36) 131 (46) 118 (59) 113 (64) 51 (75) 0 (76)
Symptoms in Cardiac TTR Amyloid: Tafamadis

A  Change from Baseline in 6-Minute Walk Test

- Change in LS Mean Change from Baseline (m)
- Month

<table>
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<tr>
<th>Month</th>
<th>Tafamadis</th>
<th>Placebo</th>
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<td>0</td>
<td>264</td>
<td>177</td>
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<td>6</td>
<td>233</td>
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<td>24</td>
<td>163</td>
<td>85</td>
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<tr>
<td>30</td>
<td>155</td>
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Evaluation of Suspected Cardiac Amyloid

**Heightened Index of Suspicion**

- Increased wall thickness without obvious cause
- HFrEF with concomitant right heart failure (+JVP, hepatomegaly, edema)
- Discordance of wall thickness and electrocardiographic voltage
- History of carpal tunnel syndrome, lumbar spinal stenosis, or spontaneous biceps tendon rupture
- Low flow, low gradient aortic stenosis
- Diffuse late gadolinium enhancement or increased extracellular volume of cardiac MRI
- Apical longitudinal strain preservation
- Natriuretic peptides elevated out of proportion to clinical syndrome
- Persistently positive troponin in the absence of acute coronary syndrome
Assess for presence of monoclonal protein by:

- Serum kappa/lambda free light chain ratio (NOT SPEP) AND
- Immunofixation electrophoresis of serum and urine

Obtain biomarkers for staging including NTproBNP, Troponin I/T and eGFR.
ALL suspected cardiac amyloid patients, even with documented monoclonal gammopathy, MUST also have exclusion of transthyretin amyloid, as 25% of TTR patients have co-existent MGUS.
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- Immunofixation electrophoresis of serum and urine

Obtain biomarkers for staging including NTproBNP, Troponin I/T and eGFR.

Monoclonal Protein Present

Referral to hematology, and
- Biopsy of clinically involved organ or fat pad (if fat pad negative, biopsy of clinically involved organ should be pursued)
  - Congo red staining, and
  - Identification of precursor protein with mass spectroscopy or IHC

Monoclonal Protein Absent

Bone Scintigraphy Available?

Yes
- Non-invasive Evaluation with PYP, DPD or HMDP

No
- Endomyocardial Biopsy with
  - Congo red staining, and
  - Identification of precursor protein with mass spectroscopy or IHC

Frederick L. Ruberg et al. JACC 2019;73:2872-2891
Evaluation of Suspected Cardiac Amyloid

Non-invasive Evaluation with PYP, DPD or HMDP

+ → ATTR Cardiac Amyloidosis
- → Cardiac Amyloidosis Unlikely

ATTR Cardiac Amyloidosis

TTR Gene Sequencing

+ → hATTR
- → wtATTR
Evaluation of Suspected Cardiac Amyloid

If uncertain, obtain tissue for congo red and/or electron microscopy:

Myocardium
Fat pad
Bone marrow
Rectal
Carpal tunnel
Salivary gland
Evaluation of Suspected Cardiac Amyloid

IMMEDIATELY INITIATE TREATMENT IF POSITIVE...
Evaluation of Suspected Cardiac Amyloid

Thank you!