# The Misfolding Mechanism:

## Understanding and Treating ATTR Cardiac Amyloidosis

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# Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

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# Learning Objectives

1. Recognize transthyretin cardiac amyloidosis and its underlying pathophysiology.
2. Identify different diagnostic criteria for ATTR cardiac amyloidosis.
3. Describe current and emerging therapies for ATTR cardiac amyloidosis.
4. Recall key clinical evidence supporting disease-modifying therapies.

# Key Abbreviations

AF: Atrial Fibrillation

ATTR-CM: Transthyretin Cardiomyopathy

ATTRv: Variant Transthyretin Cardiac Amyloidosis

ATTRwt: Wild-Type Transthyretin Cardiac Amyloidosis

AV: Atrioventricular

BID: Twice Daily

BP: Blood Pressure

EF: Ejection Fraction

EGFR: Estimated Glomerular Filtration Rate

EKG: Electrocardiogram

EV: Extravascular

GDMT: Guideline Directed Medical Therapy

HF: Heart Failure

HFpEF: Heart Failure with Preserved Ejection Fraction

HR: Heart Rate

Hx: History

IFE: Immunofixation Electrophoresis

IV: Intravenous

JVD: Jugular Veinous Distention

K/L: Kappa Light Chains

LE: Lower Extremity

LGE: Late Gadolinium Enhancement

LNP: Lipid Nanoparticle

LV: Left Ventricle

LVWT: Left Ventricular Wall Thickness

MRI: Magnetic Resonance Imaging

NYHA: New York Heart Association

PMH: Past Medical History

PO: By Mouth

QOL: Quality of Life

RA: Room Air

SC: Subcutaneous

SPECT: Single Photon Emission Computed Tomography

SPEP: Serum Protein Electrophoresis

$SpO_2$: Peripheral Capillary Oxygen Saturation

TTE: Transthoracic Echocardiogram

TTR: Transthyretin

UPEP: Urine Protein Electrophoresis

6MWD: 6 Minute Walking Distance

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“My heart is damaged by the disease because the amyloids are deposited in my atrium. I get tired really easily because my heart isn’t squeezing blood like it’s supposed to.”

—Milton, an ATTR cardiac amyloidosis patient

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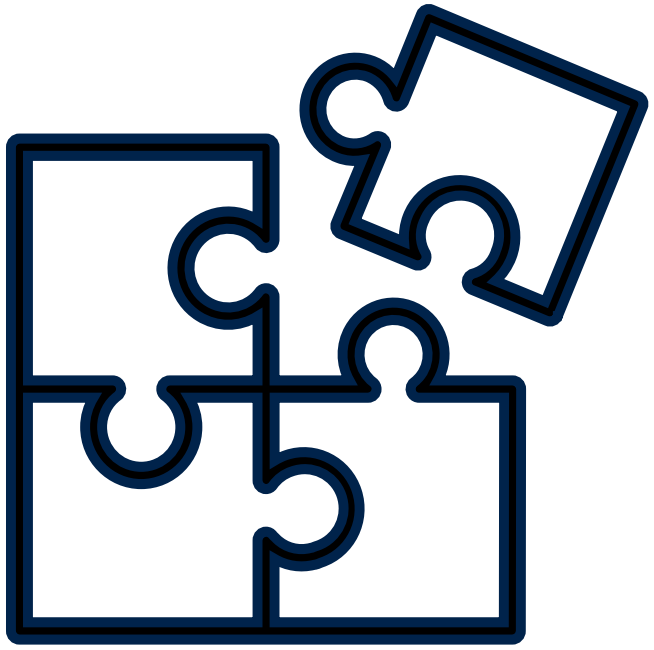
Intellia Therapeutics. Living With ATTR-CM. 2025.

# Patient Case:

*am*



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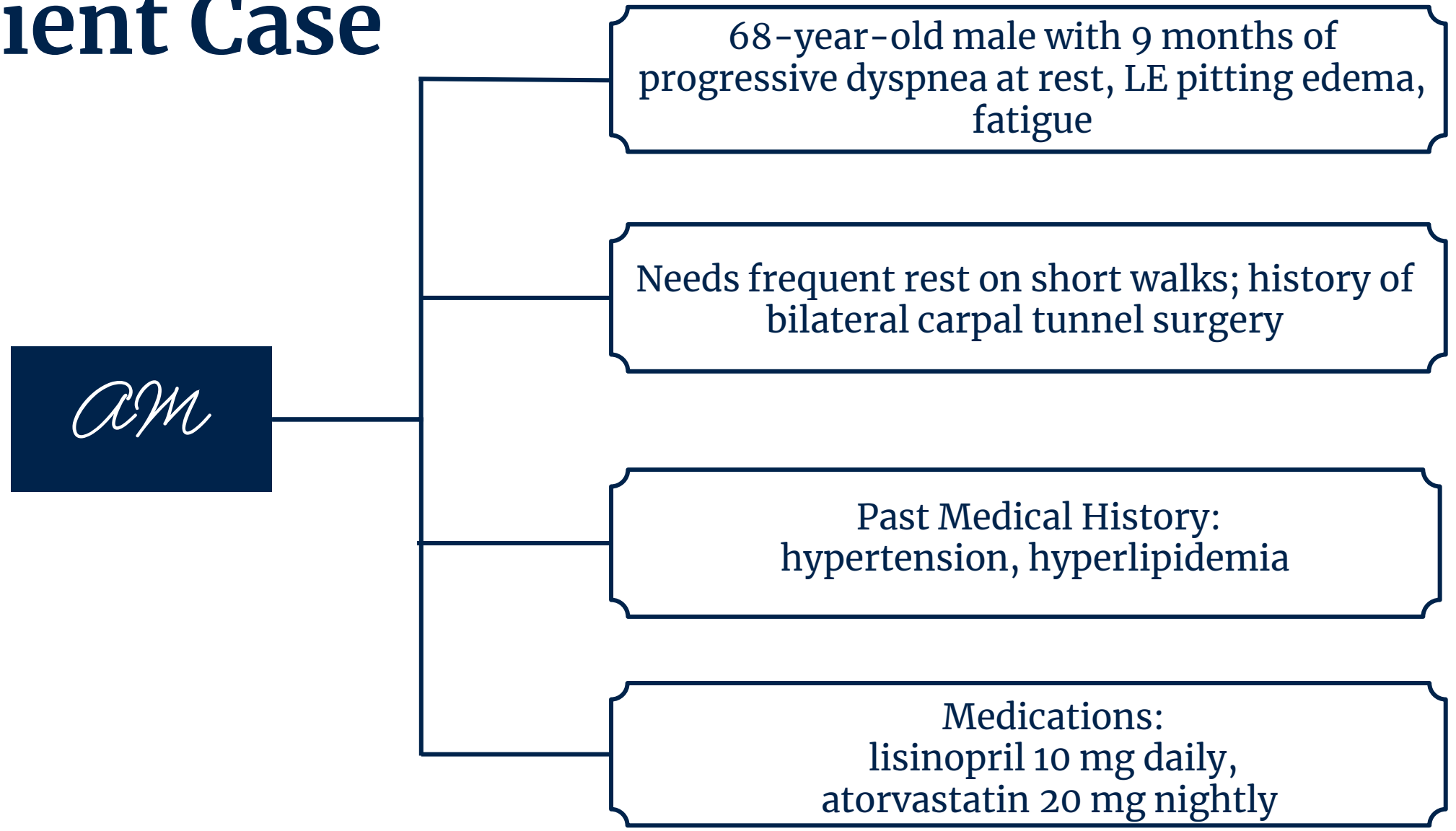
# Patient Case

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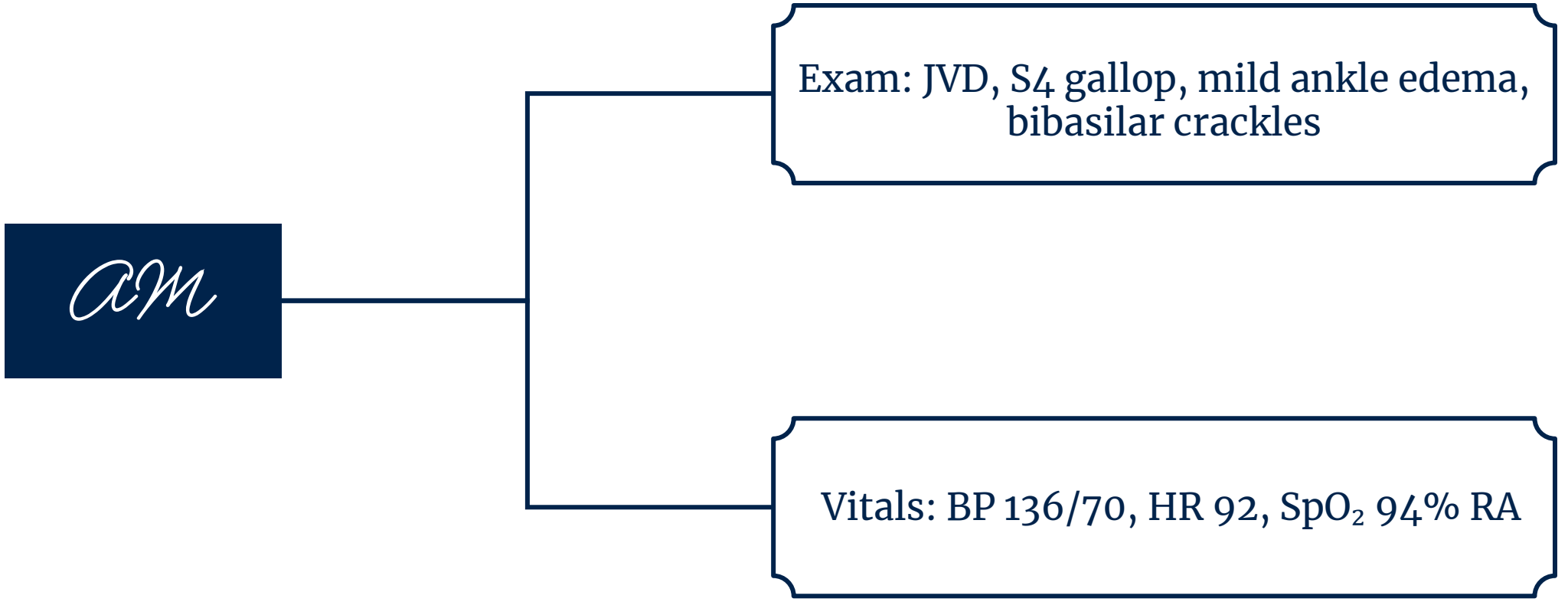
# Patient Case

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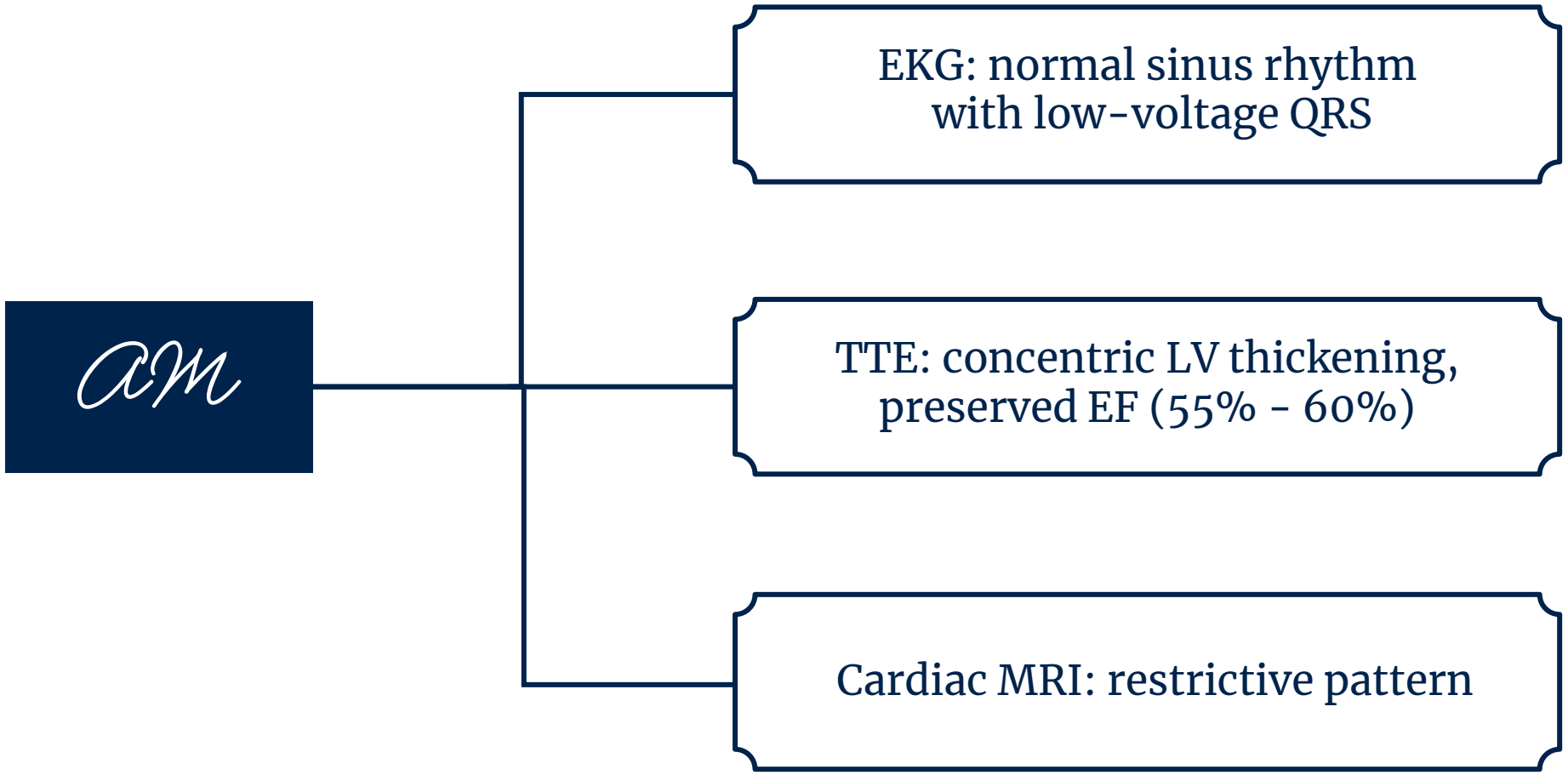
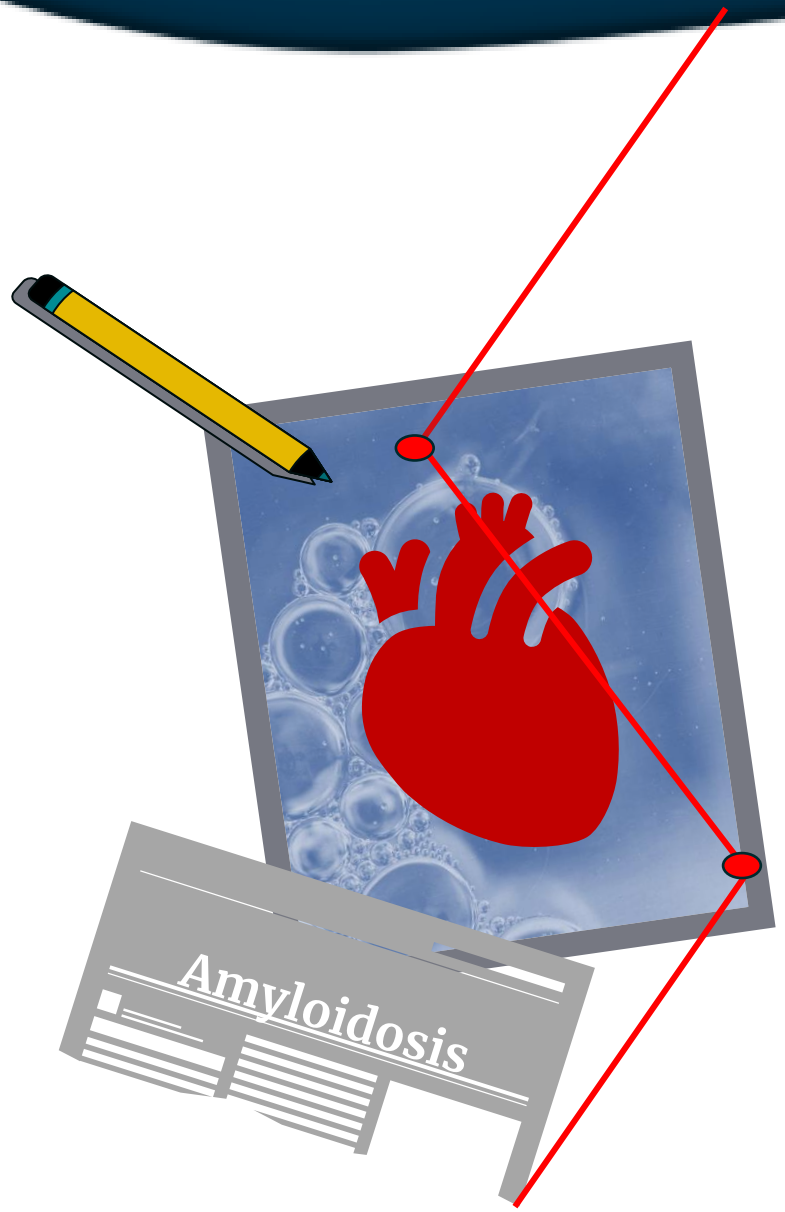
# Patient Case






# Do AM's Findings Point to Something More?

HFpEF + low-voltage QRS

ECHO: concentric LV thickening; preserved EF

Musculoskeletal symptoms

# Pathophysiology

# Epidemiology

Underdiagnosed; prevalence rising with improved imaging and awareness

Estimated 10–15% of HFpEF in older adults may have cardiac amyloidosis

ATTRwt: most common cause of cardiac amyloidosis
- Predominantly men >65 years
- Cardiac involvement is near-universal
- Median survival ~3–5 years from diagnosis

ATTRv: earlier onset; mutation-dependent phenotype
- Cardiac involvement in ~50–70%

AL amyloidosis: least common but most aggressive
- Median survival <6 months if untreated

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Kittleson et al. J Am Coll Cardiol. 2023.

# What is Amyloidosis?

Misfolded proteins aggregate into rigid, non-degradable fibrils

These fibrils deposit extracellularly

Accumulation disrupts normal organ architecture and function

**Bottom line:**
Amyloidosis is a disorder of protein misfolding that leads to the formation and deposition of insoluble β-pleated amyloid fibrils in tissues

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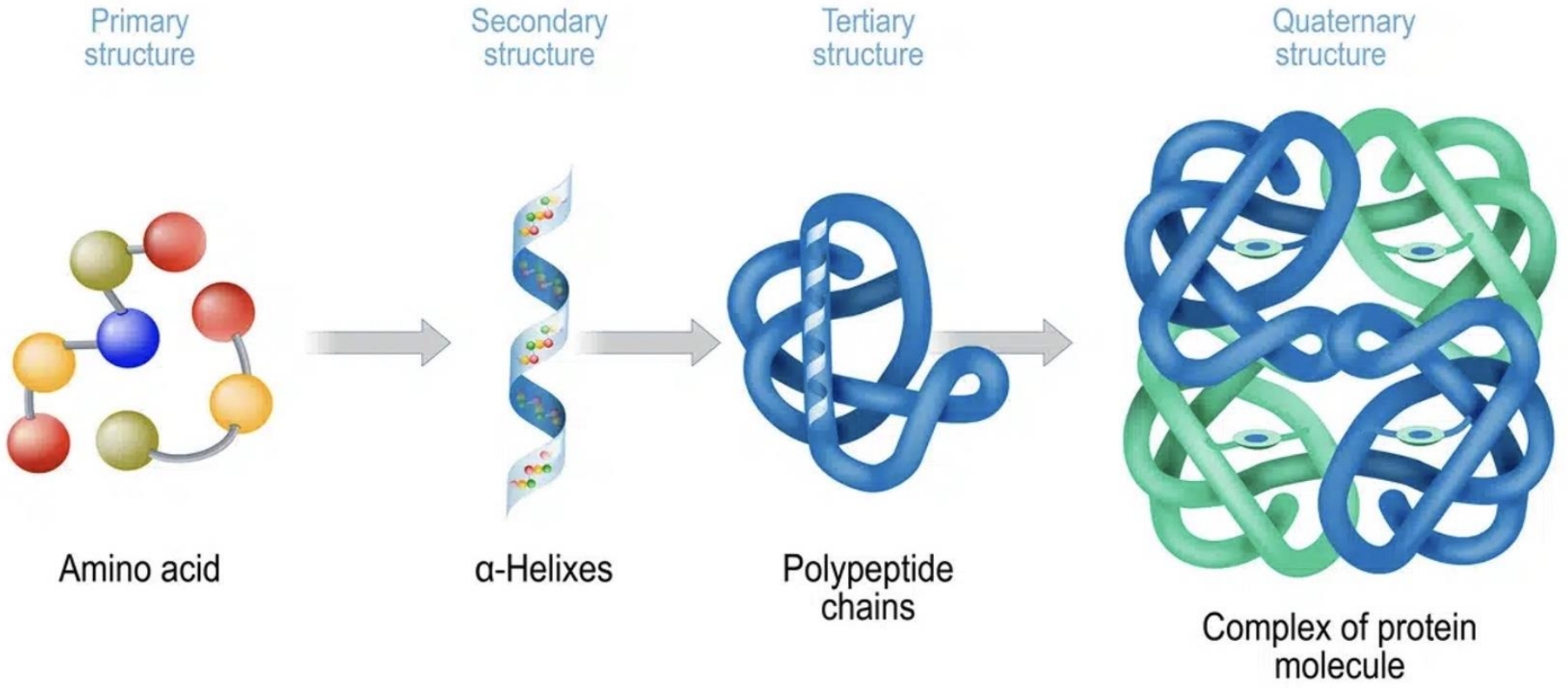
Cleveland Clinic. Cardiac Amyloidosis: Causes & Treatment. 2022.

# Normal Protein Folding

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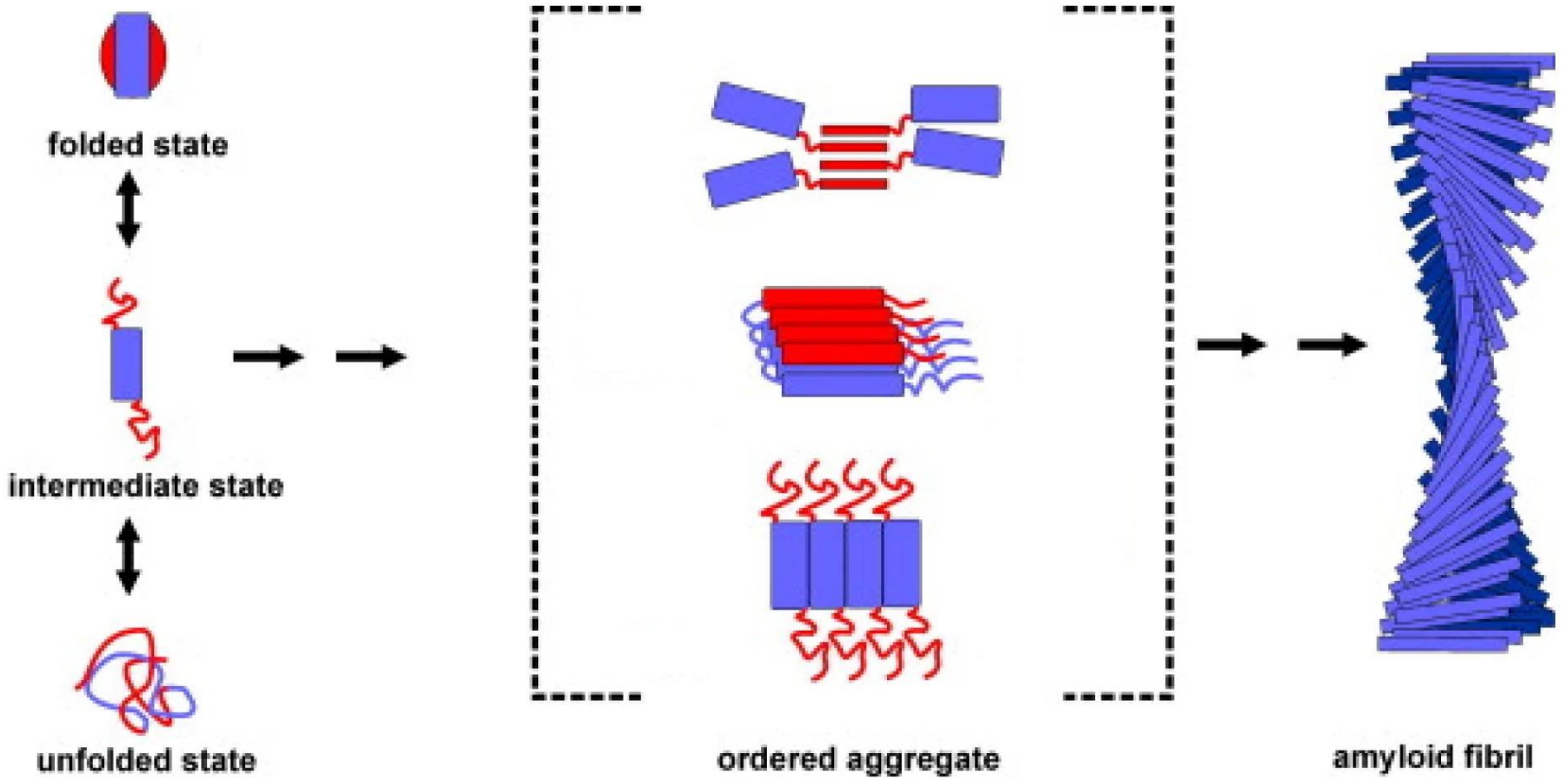
SARomics Biostructures. Protein Structure Overview. 2025.

# Misfolding/Amyloid Formation



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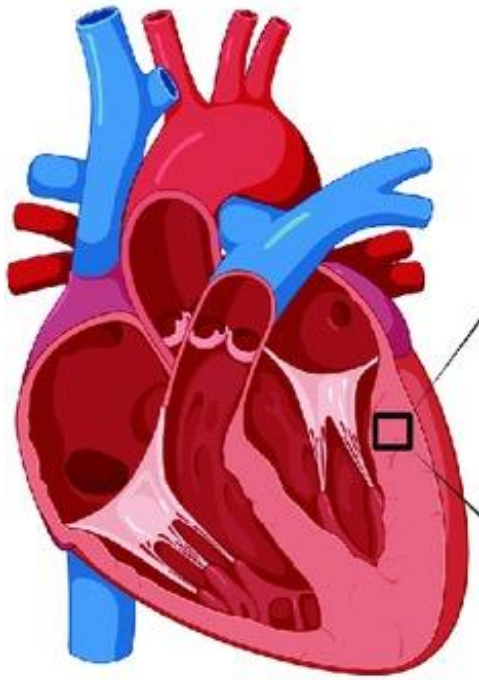
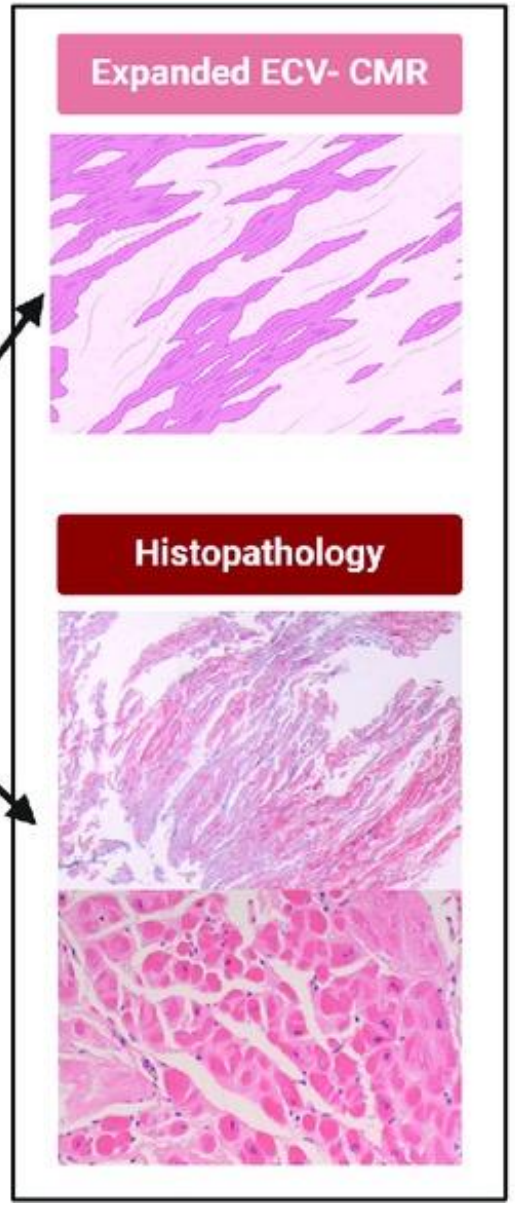
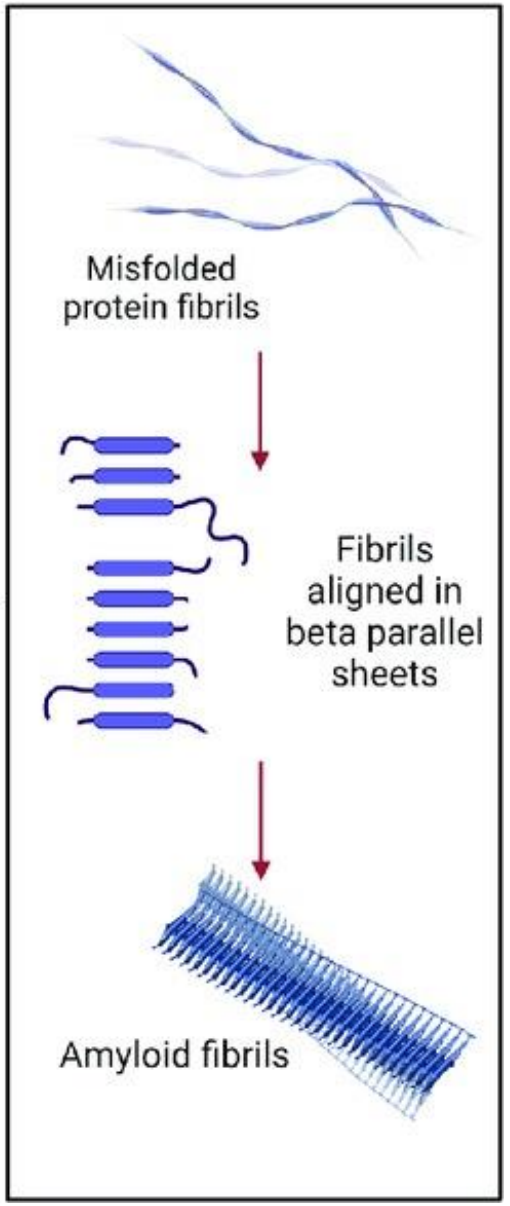
Iannuzzi et al. Int J Mol Sci. 2013.



Gross cardiac changes:

- Increased chamber wall thickness
- Valvular thickening
- Pericardial effusion

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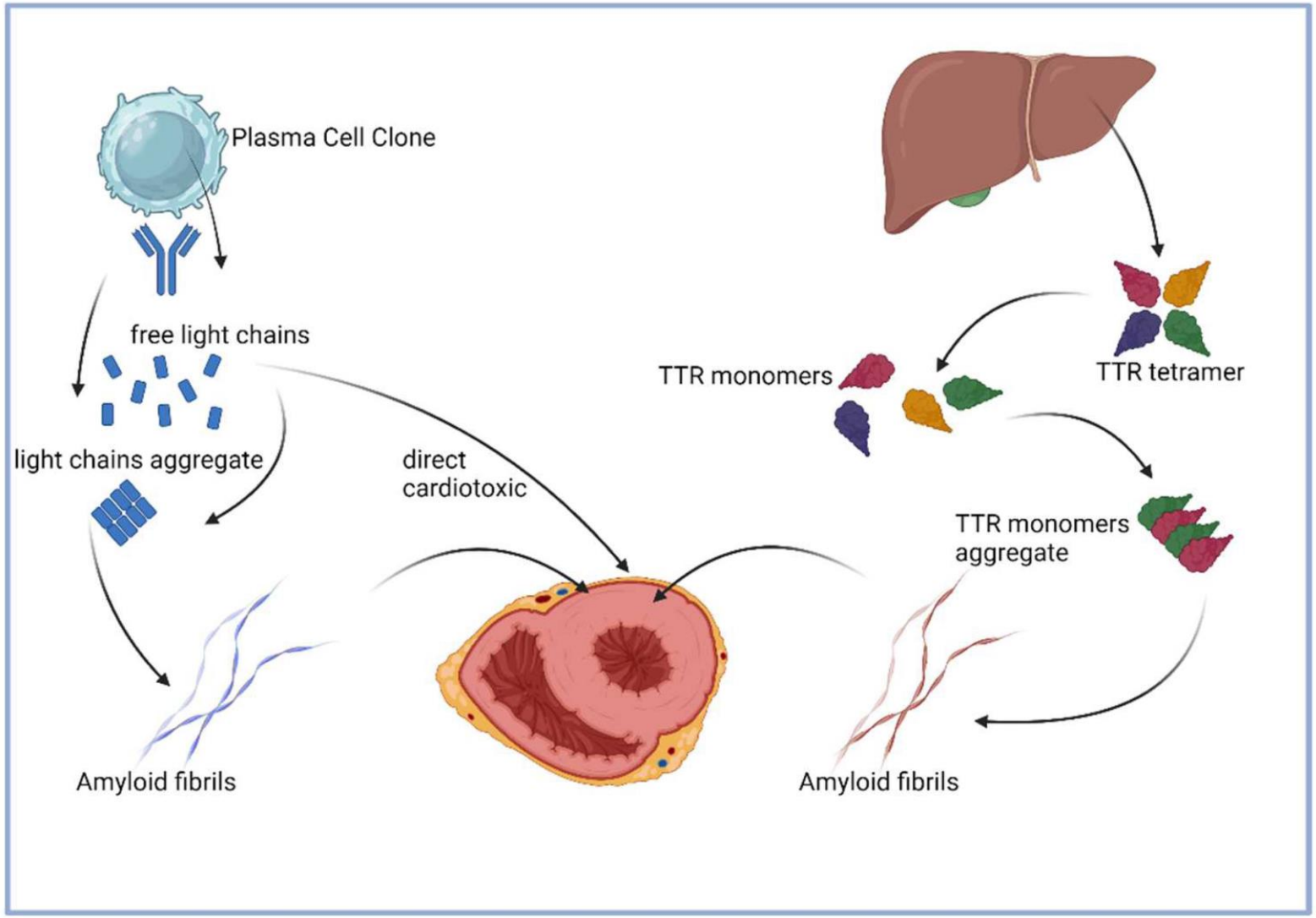
Gorrie et al. npj Cardiovasc Health. 2025.

# AL vs ATTR Pathophysiology




**Bottom line:**
*Cardiac amyloidosis is classified by the protein forming amyloid fibrils: AL or ATTR*

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aus dem Siepen & Hansen. J Clin Med. 2024.

# Amyloid Involvement

In the heart, amyloid infiltration of the myocardium produces a restrictive phenotype

Transthyretin amyloid also deposits in extra-cardiac tissues, leading to:

- Carpal tunnel
- Lumbar spinal stenosis
- Biceps tendon rupture
- Rotator cuff disease

These extra-cardiac signs may appear years before cardiac involvement

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Renzoni et al. Circ Res. 2022.

# Non-cardiac clues:

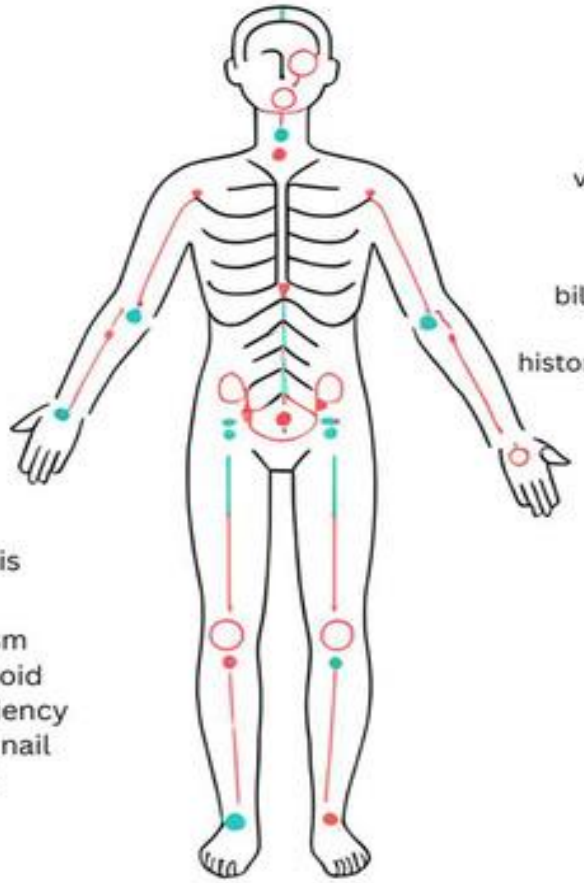
## AL

macroglossia
submandibular gland enlargement
periorbital ecchymosis

pleural effusions
nephrotic syndrome

gi bleeding
hyperbillirubinemia, hepatomegaly, cholestasis

functional hyposplenism
easy bruising from amyloid deposits or factor X deficiency
cutaneous ecchymoses, nail dystrophy, alopecia



## ATTR

vitreos opaacitis, gluacoma

lumbar spinal stenosis
biceps tendon rupture
bilateral carpal tunnel syndrome
arthropathy
history of multiple joint replacements

## ATTR and AL

small-fiber neuropathy
autonomic dysfunction (orthostatic hypotension, gastroparesis, neurogenic bladder, erectile dysfunction, early satiety, dry eyes and mouth)

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Alashqar et al. J Clin Med. 2025.

# Question 1: In transthyretin cardiac amyloidosis, disease begins when TTR…

A. Is overproduced by the bone marrow

B. Forms immune complexes

C. Is degraded too quickly by the liver

D. Become unstable and dissociates into monomers

# Diagnosis


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# Step 1: PMH

**Clues from history, ECG, and imaging**

**Cardiac Manifestations:**
Fatigue
HF symptoms
Aortic stenosis
Family hx of HF
Conduction system disease/pacemaker
Atrial fibrillation

**Extracardiac Manifestations:**
Bilateral carpal tunnel syndrome
Lumbar/cervical spinal stenosis
Spontaneous biceps tendon rupture
Hip or knee replacement
Sensory peripheral neuropathy
Family hx of neuropathy
Autonomic dysfunction

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Kittleson et al. J Am Coll Cardiol. 2025.

# Step 1: PMH

**Clues from history, ECG, and imaging**

EKG signs: low voltage to LV mass ratio, arrhythmias

Echocardiogram signs: concentric thickening

Cardiac MRI signs: diffuse LGE, elevated ECV

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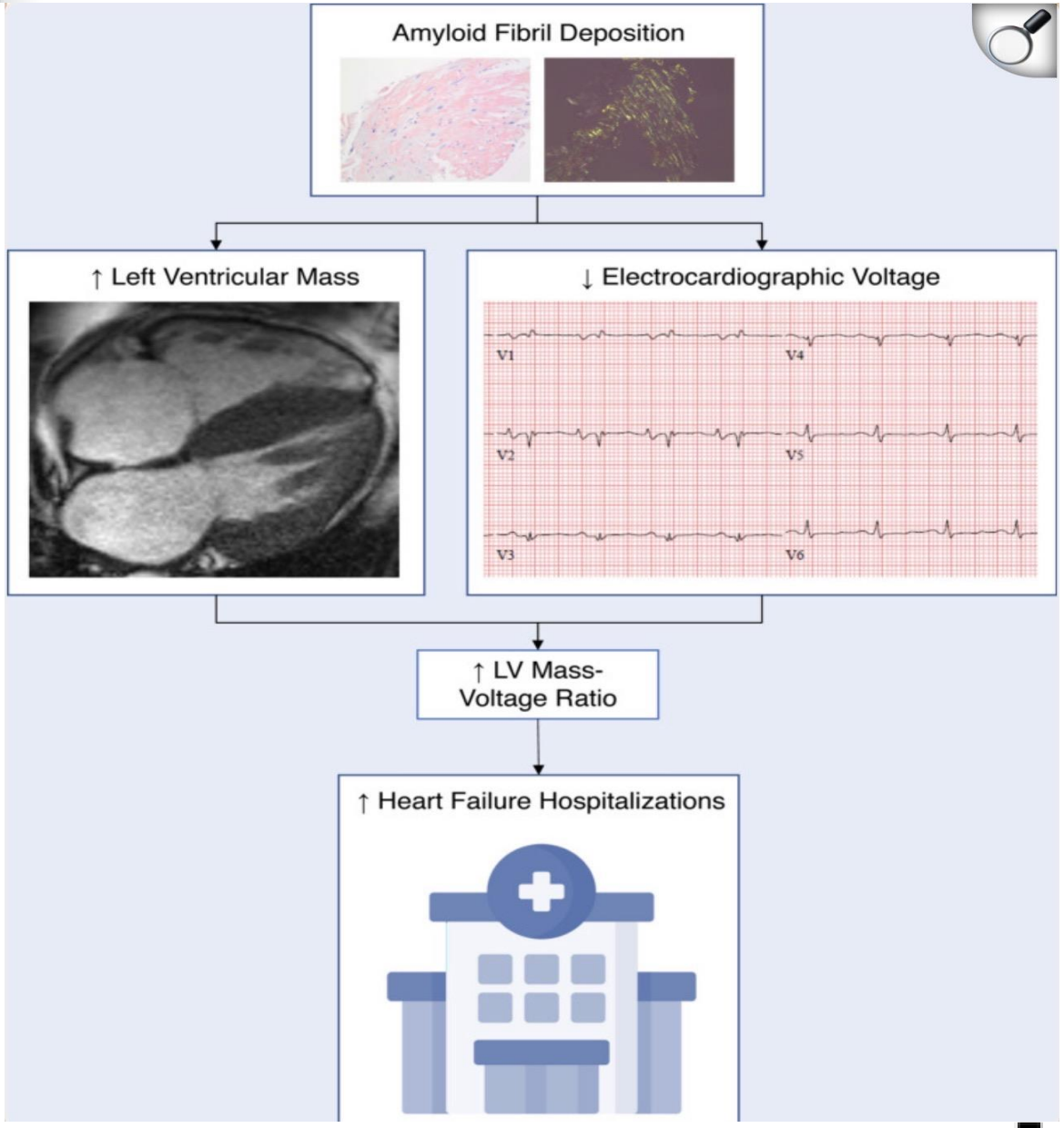
Kittleson et al. J Am Coll Cardiol. 2025.




Slivnick et al. Int J Cardiovasc Imaging. 2021.

# Step 2: Rule out AL

## Monoclonal Protein?

Abnormal serum/kappa/lambda free light chain (depends on eGFR)

Monoclonal protein on serum/urine IFE

Serum & urine immunofixation + serum free kappa/lambda light chains

SPEP/UPEP not as sensitive as IFE

Reference kappa/lambda ratio is higher in chronic kidney disease

| eGFR | Acceptable Free Light Chain Ratio Range |
|---|---|
| 45 – 59 mL/min/1.73 $m^2$ | 0.46 - 2.62 |
| 30 – 44 mL/min/1.73 $m^2$ | 0.48 - 3.38 |
| 15 – 29 mL/min/1.73 $m^2$ | 0.54 - 3.30 |
| <15 mL/min/1.73 $m^2$ | 0.54 - 3.30 |

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Kittleson et al. J Am Coll Cardiol. 2025.

# Step 2: Rule out AL

**If monoclonal protein is positive** → AL workup (hematology, tissue biopsy as indicated)

Consultation with hematologist

Biopsy (affected organ/surrogate site)

- Positive Congo Red
- Tissue typing by mass spectrometry

**If monoclonal protein is negative** → proceed to cardiac amyloid imaging

| Amyloid Type | Fat Pad Sensitivity | Bone Marrow Sensitivity |
|---|---|---|
| AL | 73%-84% | 60% |
| ATTRv | 45%-67% | 41%-47% |
| ATTRwt | 14%-16% | 30%-38% |

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Kittleson et al. J Am Coll Cardiol. 2025.

# Step 3: Confirming ATTR Amyloidosis

**Radionuclide scintigraphy (with SPECT)**
- Grade 2/3 uptake

**Positive** → ATTR-CM

**Negative** → Cardiac amyloidosis is unlikely

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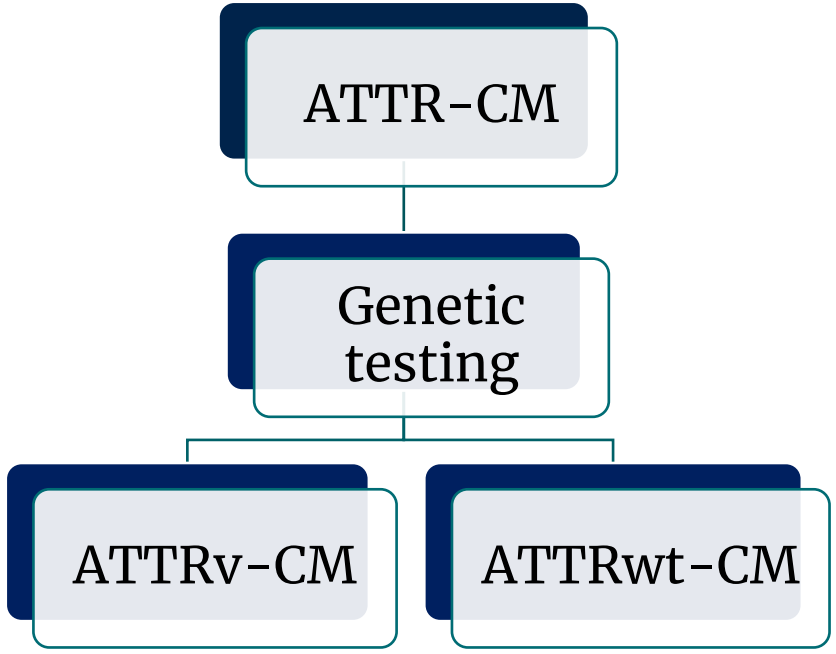
· Kittleson et al. J Am Coll Cardiol. 2025.

# Step 4: ATTR Subtyping




ATTRwt shows no mutation; ATTRv requires genetic counseling

Family members of ATTRv patients should undergo cascade screening

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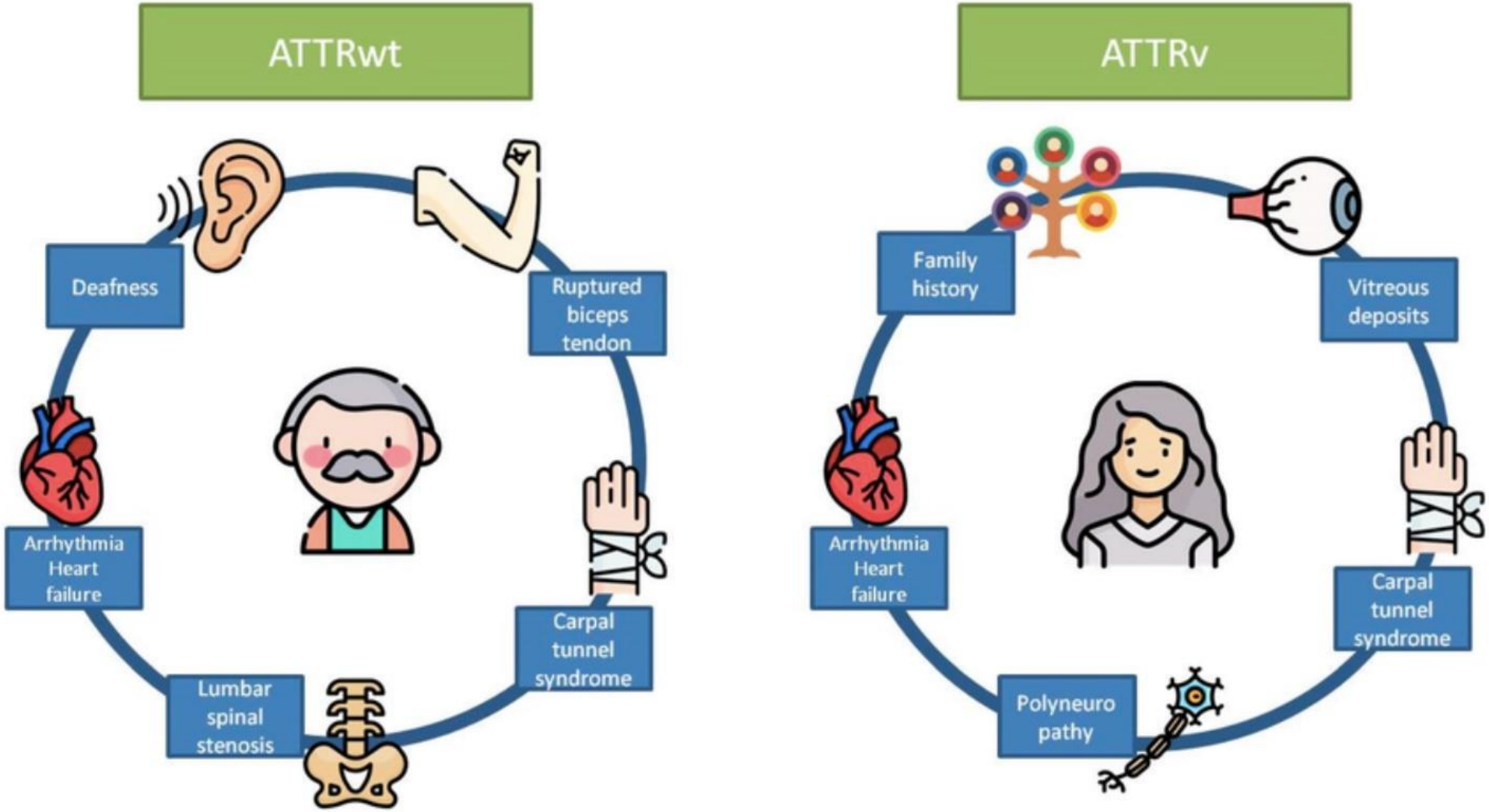
Kittleson et al. J Am Coll Cardiol. 2025.

# ATTRwt vs ATTRv

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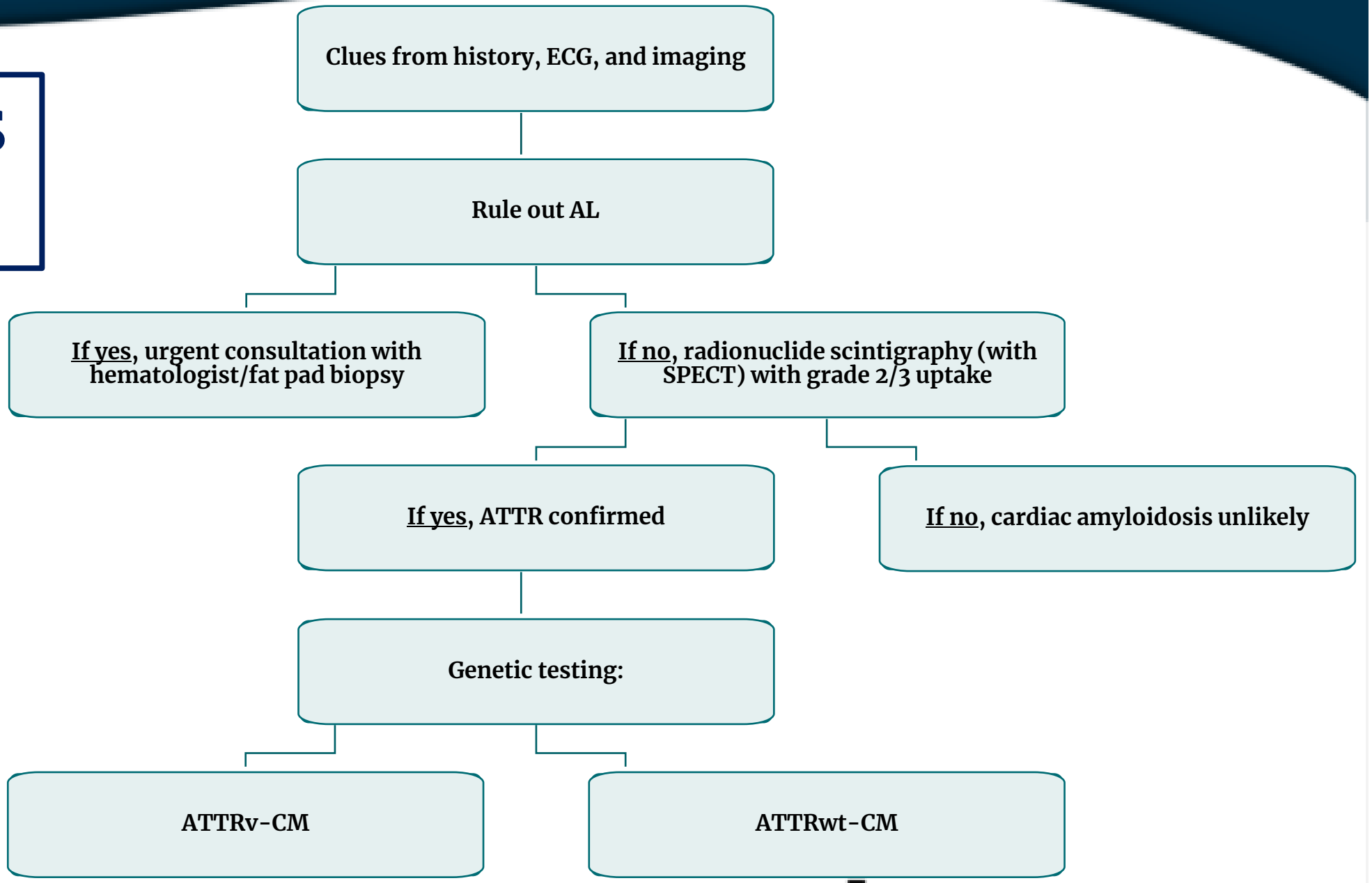
Merino-Merino et al. Biomedicines. 2024

# Diagnosis Pathway

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Kittleson et al. J Am Coll Cardiol. 2025.

# Question 2: What nuclear imaging study can noninvasively diagnose ATTR-CM?

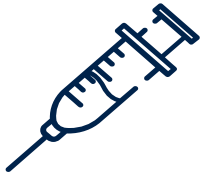
A. PET myocardial perfusion scan

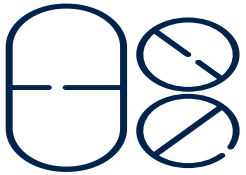
B. Cardiac CT angiography

C. Technetium-99m pyrophosphate (PYP) scan

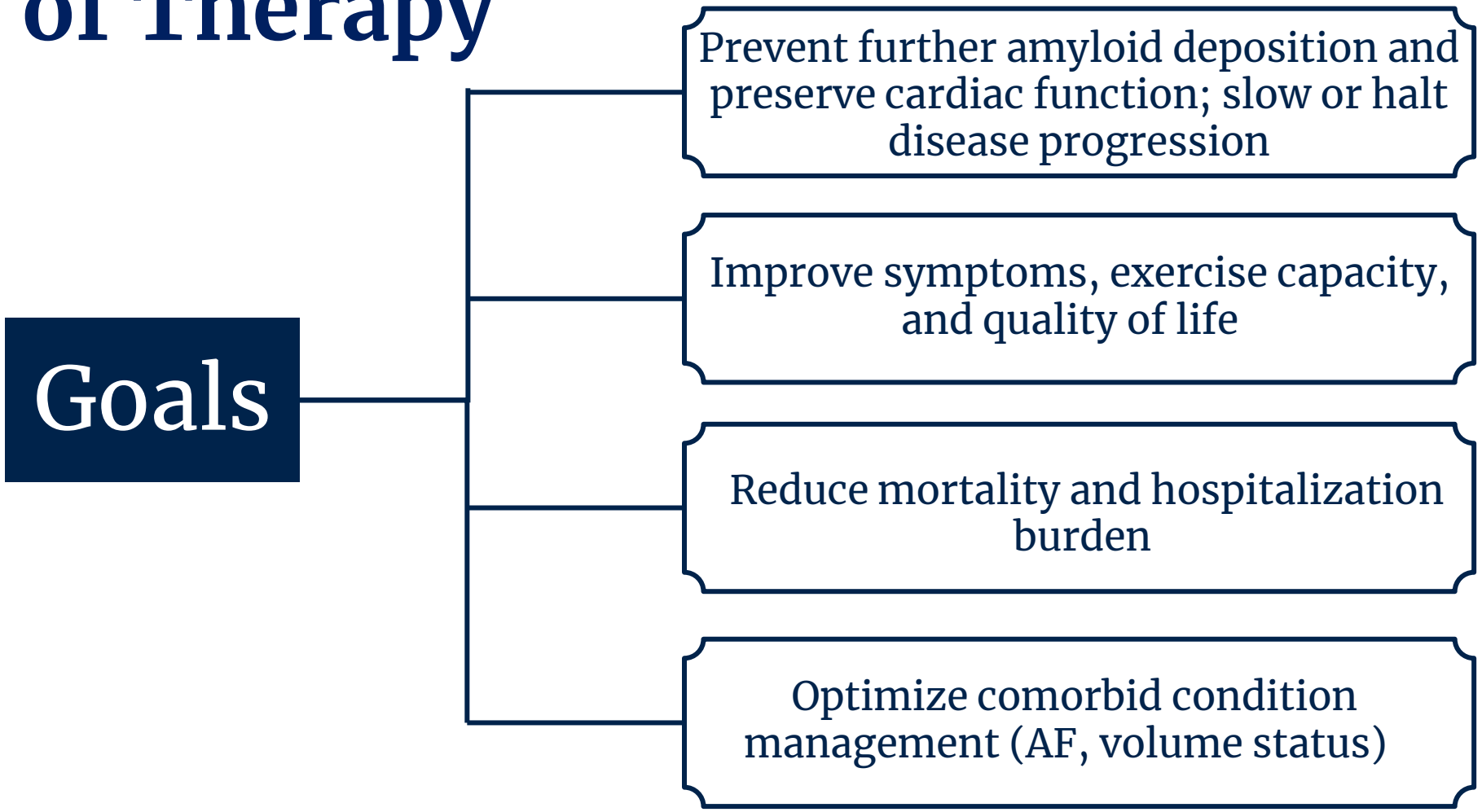
D. Ventilation-perfusion scan

# Treatment





# Goals of Therapy

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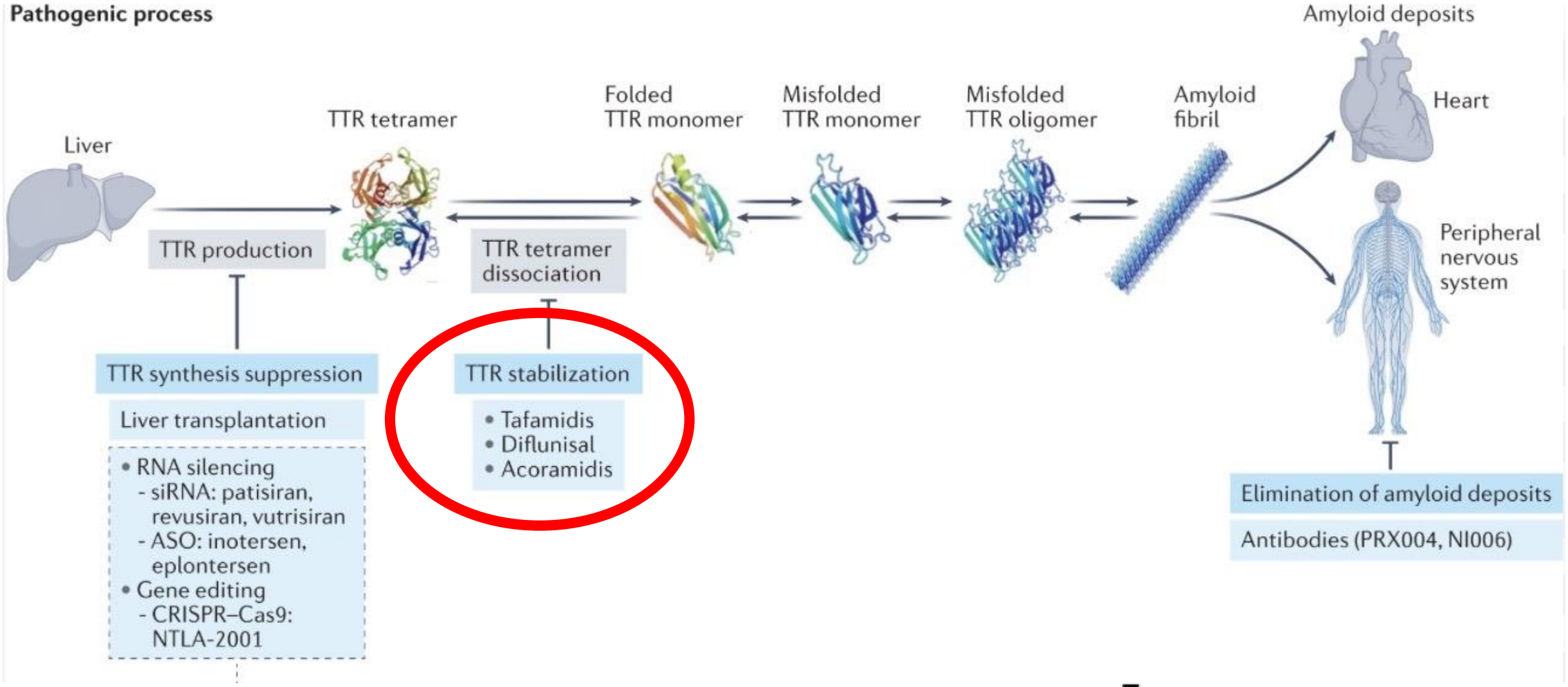
Kittleson et al. J Am Coll Cardiol. 2025.

# Treatment Options

| TTR Stabilizers | TTR Gene Silencers |
| --- | --- |
| Tafamidis | Vutrisiran |
| Acoramidis | Patisiran |
| | Eplontersen |

# TTR Stabilizers

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Wu & Chen. Heart Fail Rev. 2024.

| | tafamidis | acoramidis |
|---|---|---|
| **Mechanism of Action** | Binds thyroxine-binding sites on TTR tetramer | Mimics protective T119M mutation with higher binding affinity |
| **Dosing** | 61 mg PO once daily (free acid); bioequivalent to 80 mg meglumine | 712 mg PO twice daily regimen |
| **Formulation** | Soft capsule, oral | Tablet, oral |
| **Adverse Effects** | **Mild:** fatigue, diarrhea, urinary tract infections | **Mild:** diarrhea/abdominal pain, increase in serum creatinine/decrease in eGFR |
| **Drug Interactions** | Moderate BCRP inhibition (e.g., rosuvastatin) | UGT/CYP3A inducers; monitor CYP2C9 substrates (e.g., warfarin) |
| **Contraindications** | Avoid in pregnancy | |
| **Clinical Pearls** | First disease-modifying ATTR-CM therapy; benefit greatest if started early | Higher binding affinity than tafamidis; similar disease-modifying goal |

Mayo Clinic. Acoramidis. 2026.
Mayo Clinic. Tafamidis. 2024.

| | tafamidis | acoramidis |
|---|---|---|
| **FDA Approval** | FDA approved 2019 | FDA approved 2025 |
| **Clinical Benefit** | ↓ mortality + ↓ CV hospitalizations | |
| **Annual List Price** | ~$225,000 | ~$244,000 |
| **Formulary Status** | Not currently on formulary at Advocate Health | |
| **Access Challenges** | Significant financial barriers, especially for Medicare beneficiaries | |

Krumholz et al. J Am Coll Cardiol. 2025.
Pfizer. VYNDAQEL®/VYNDAMAX™ FDA approval. 2019
FDA. Transthyretin-mediated amyloidosis drug approval. 2024.

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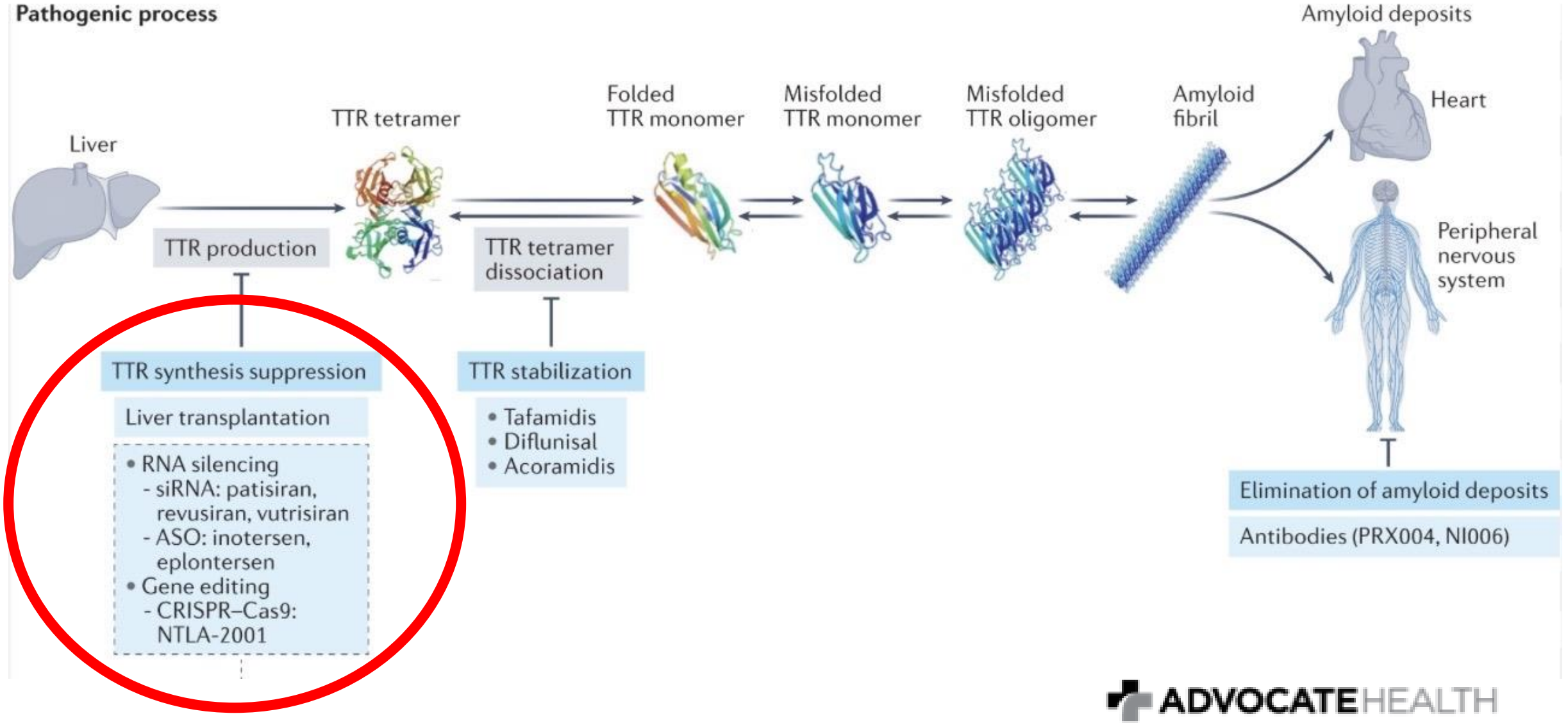
# TTR Gene Silencers

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Wu & Chen. Heart Fail Rev. 2024.

| | vutrisiran | patisiran | eplontersen |
|---|---|---|---|
| **Mechanism of Action** | siRNA → ↓ TTR mRNA (GalNAc-mediated hepatocyte uptake) | siRNA → ↓ TTR mRNA (LNP-based) | Antisense oligonucleotide → ↓ TTR mRNA |
| **Indications** | ATTR-CM (wild-type & variant); hATTR amyloidosis with polyneuropathy | hATTR amyloidosis with polyneuropathy | hATTR amyloidosis with polyneuropathy |
| **Dosing** | 25 mg SQ every 3 months (by a healthcare professional) | 0.3 mg/kg IV every 3 weeks (by a healthcare professional) | 45 mg SQ monthly (by a healthcare professional) |
| **Premedication** | None | Required (steroid + H1 + APAP) | None |
| **Adverse Effects** | Injection-site reactions, arthralgia | Infusion reactions, edema, arthralgia | GI intolerance |
| **Contraindications** | None | Hypersensitivity to lipid formulation | None |
| **Clinical Pearls** | Vitamin A Supplementation | | |

AstraZeneca. WAINUA® (eplontersen) HCP. 2025.
Alnylam Pharmaceuticals. ONPATTRO® (patisiran) Treatment Brochure. 2022.
Alnylam Pharmaceuticals. AMVUTTRA® (vutrisiran) HCP. 2022.

# Question 3: Tafamidis works primarily by:

A. Silencing TTR production in the liver

B. Stabilizing the TTR tetramer to prevent misfolding

C. Breaking down existing amyloid deposits

D. Increasing diuresis to relieve symptoms

# Literature

# ATTR-ACT Trial:
## Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Maurer MS, et al. N Engl J Med. 2018.

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# ATTR-ACT Methods

## Purpose

To evaluate tafamidis efficacy in treating transthyretin amyloid cardiomyopathy

## Methods

International

Double-blind

Multicenter

Placebo-controlled

Phase 3

## Patients

441 patients with ATTRwt or ATTRv

NYHA class I-III

Mean NT-proBNP ~3,000 pg/mL

Mean 6MWD~350 m

## Treatment Arms

Randomized (2:1:2) to receive tafamidis 80 mg daily, tafamidis 20 mg daily, placebo daily

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Maurer MS, et al. N Engl J Med. 2018.

# ATTR-ACT Results

| Endpoint (Tafamidis vs Placebo) | Result | P Value |
|---|---|---|
| **All-Cause Mortality** | 29.5% vs 42.9%<br>(HR 0.70; 95% CI 0.51–0.96)<br>NNT ≈ 7–8 over 30 months | 0.025 |
| **Cardiovascular Hospitalizations** | 0.48 vs 0.70 events/year<br>(RR 0.68; 95% CI 0.56–0.81) | <0.001 |
| **6MWD** | Significantly less decline; separation by 6 months | <0.001 |
| **KCCQ-Overall Score** | Slower decline; sustained benefit through 30 months | <0.001 |

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Maurer MS, et al. N Engl J Med. 2018.

# ATTRibute-CM Trial:
## Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

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Fontana M, et al. N Engl J Med. 2024.

# ATTRibute-CM Methods

## Purpose

To evaluate the efficacy and safety of acoramidis in patients with transthyretin amyloid cardiomyopathy

## Methods

International

Double-blind

Multicenter

Placebo-controlled

Phase 3

## Patients

632 patients with ATTRwt or ATTRv

NYHA class I-III

Mean NT-proBNP ~2,300-2,400 pg pg/mL

Mean 6MWD~350 m

## Treatment Arms

Randomized (2:1) to receive acoramidis hydrochloride 800 mg BID (712 mg acoramidis) or placebo BID

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Fontana M, et al. N Engl J Med. 2024.

# ATTRibute-CM Results

| Endpoint (Acoramidis vs Placebo) | Result | P Value |
|---|---|---|
| **Primary Hierarchical Endpoint** | Win ratio 1.8 (95% CI 1.4–2.2) | <0.001 |
| **All-Cause Mortality or First CV Hospitalization** | 35.9% vs 50.5% (HR 0.64; 95% CI 0.50–0.83) | 0.0008 |
| **Cardiovascular Hospitalizations** | 0.22 vs 0.45 events/year (~50% reduction) | <0.0001 |
| **6MWD** | +34.4 m (wild-type); +86.7 m (variant) vs placebo | <0.001 |
| **NT-proBNP** | Stable vs progressive increase with placebo | <0.001 |
| **KCCQ-Overall Score** | Better preserved vs progressive decline | <0.001 |
| **Serum Transthyretin Level** | +9.1 mg/dL by day 28; sustained | <0.001 |

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Fontana M, et al. N Engl J Med. 2024.

# ATTR-ACT vs ATTRibute-CM

| Baseline Characteristic | ATTR-ACT (Tafamidis) | ATTRibute-CM (Acoramidis) |
|---|---|---|
| **Total patients** | 441 | 632 |
| **ATTR type** | ATTRwt + ATTRv | ATTRwt + ATTRv |
| **NYHA class** | I–III (more II–III) | I–III (more class I–II) |
| **Mean NT-proBNP** | ~3,000 pg/mL | ~2,300–2,400 pg/mL |
| **Mean 6MWD** | ~350 m | ~350 m |
| **Disease stage** | More advanced | Earlier stage ATTR-CM |

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# APOLLO-B Trial:
# Patisiran, an RNAi Therapeutic, for Transthyretin Amyloidosis

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Maurer MS et al., NEJM 2023

# APOLLO-B Methods

## Purpose

To evaluate whether patisiran could slow functional decline and improve quality of life in patients with transthyretin amyloid cardiomyopathy

## Methods

International

Double-blind

Multicenter

Placebo-controlled

Phase 3

## Patients

360 patients with ATTRwt or ATTRv

NYHA class I-II

Polyneuropathy disability score ≤II

Mean 6MWD ≥150 m

## Treatment Arms

Randomized (1:1) to patisiran 0.3 mg/kg IV every 3 weeks or placebo every 3 weeks

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Maurer MS et al., NEJM 2023

# APOLLO-B Results

| Endpoint (Patisiran vs Placebo) | Result | P Value |
|---|---|---|
| 6MWD | −8.2 m vs −21.4 m Δ +14.7 m (95% CI 0.7–28.7) | 0.02 |
| KCCQ-Overall Score | −0.3 vs −3.4 points Δ +3.7 points | 0.04 |
| NT-proBNP | Median +131 vs +518 pg/mL Geometric mean ratio 0.80 | <0.001 |
| Troponin I | Ratio 0.87 vs placebo | <0.01 |
| LV Mass | −9.5 g vs placebo | — |
| Global Longitudinal Strain | Preserved vs worsening | — |
| Stroke Volume | +3.0 mL vs placebo | — |
| Composite: Death + CV Events + 6MWD | Win ratio 1.27 (95% CI 0.99–1.61) | NS |
| Serum Transthyretin Reduction | −86.8% at 12 months | — |

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Maurer MS et al., NEJM 2023

# HELIOS-B Trial:
# Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

ADVOCATEHEALTH

Fontana M, et al. N Engl J Med. 2025.

# HELIOS-B Methods

## Purpose

To evaluate vutrisiran efficacy and safety in patients with ATTRwt or ATTRv

## Methods

International

Double-blind

Multicenter

Placebo-controlled

Phase 3

## Patients

655 patients with ATTRwt or ATTRv

NYHA class I-III

NT-proBNP 300-8,500 pg/mL

Mean 6MWD ≥150 m

## Treatment Arms

Randomized (1:1) to vutrisiran 25 mg SC every 3 months vs placebo every 3 months

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Fontana M, et al. N Engl J Med. 2025.

# HELIOS-B Results

| Endpoint (Vutrisiran vs Placebo) | Result | P Value |
|---|---|---|
| All-Cause Death + Recurrent CV Events | HR 0.72 (95% CI 0.56–0.93)<br>38% vs 48% with ≥1 event | 0.01 |
| Monotherapy Population (Death + CV Events) | HR 0.67 (95% CI 0.49–0.93)<br>39% vs 53% with ≥1 event | 0.02 |
| All-Cause Mortality | 18% vs 26% deaths HR 0.65 (overall);<br>HR 0.66(monotherapy) | 0.01 |
| 6MWD | -45.4 m vs -71.9 m Δ +26.5 m | <0.001 |
| KCCQ-Overall Score | -9.7 vs -15.5 points Δ +5.8 points | <0.001 |
| NYHA Class | Improved or stable 68% vs 61% | 0.02 |
| Serum Transthyretin Reduction | 81%, rapid and sustained | — |

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Fontana M, et al. N Engl J Med. 2025.

# CARDIO-TTRansform

## Eplontersen in Patients with Transthyretin Amyloidosis with Cardiomyopathy

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Fontana M, et al. Eur Heart J. 2024.

# Cardio-TTRansform Methods

## Purpose

To evaluate the efficacy and safety of eplontersen in patients with transthyretin amyloid cardiomyopathy

## Methods

International

Double-blind

Multicenter

Placebo-controlled

Phase 3

## Patients

More than 1,400 patients with ATTRwt or ATTRv

## Treatment Arms

Randomized to eplontersen 45 mg SC every month or placebo every month

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Fontana M, et al. Eur Heart J. 2024.

# CARDIO-TTRansform Trial

- Although the full results are not yet published, the therapy has been granted FDA Fast Track status (2024) based on promising early data showing robust TTR reduction and improved tolerability compared to older agents.

- Preliminary data show eplontersen reduces serum TTR by ~80%, improves LVEF and stroke volume in early cardiomyopathy sub-analyses, and is being evaluated in the largest ATTR-CM outcomes trial to date (≈1,400 pts) with CV death + recurrent events as primary endpoint; FDA has fast tracked the agent for ATTR-CM.

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Fontana M, et al. Eur Heart J. 2024.

# Question 4: In ATTR-ACT, tafamidis mainly showed benefit by:

A. Reducing all-cause mortality and CV-related hospitalizations

B. Improving 6-Minute Walk Test

C. Reducing BNP and improving Quality of Life

D. Reversing amyloid build up

# Supportive Care

# Supportive Care in Cardiac Amyloidosis

**Volume management:**
Gentle loop diuretics for congestion; avoid over-diuresis
Maintain adequate preload to prevent low output

**Arrhythmia management:**
Amiodarone preferred for rate/rhythm control
Anticoagulate all with atrial fibrillation or atrial standstill

**Drugs to Avoid/Use Caution:**
Digoxin – binds amyloid fibrils → toxicity risk
Non-DHP CCBs (verapamil, diltiazem) – cause severe hypotension
Beta-blockers – poorly tolerated due to fixed stroke volume
ACEi/ARBs – often limited by hypotension

**Device therapy:**
Pacemaker for advanced conduction disease
ICDs rarely prevent sudden death (electromechanical dissociation)

# So What Next???

Who to Consult:

- HF Team
  - Volume strategy, medication adjustments
  - Guidance on suspected or confirmed amyloidosis

- HF / Amyloidosis Pharmacist
  - Review existing amyloid therapies (e.g., tafamidis, silencers)
  - Provide counseling on medication safety/tolerance

Communicate diagnosis to all team members

Document clearly in discharge summary

Arrange outpatient follow-up with:

- HF cardiology
- Amyloidosis specialty clinic

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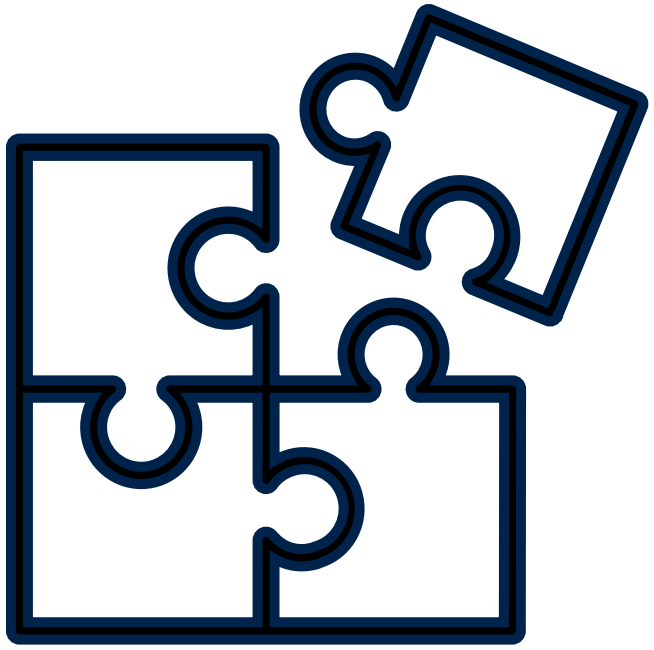
# Patient Case:

*am*



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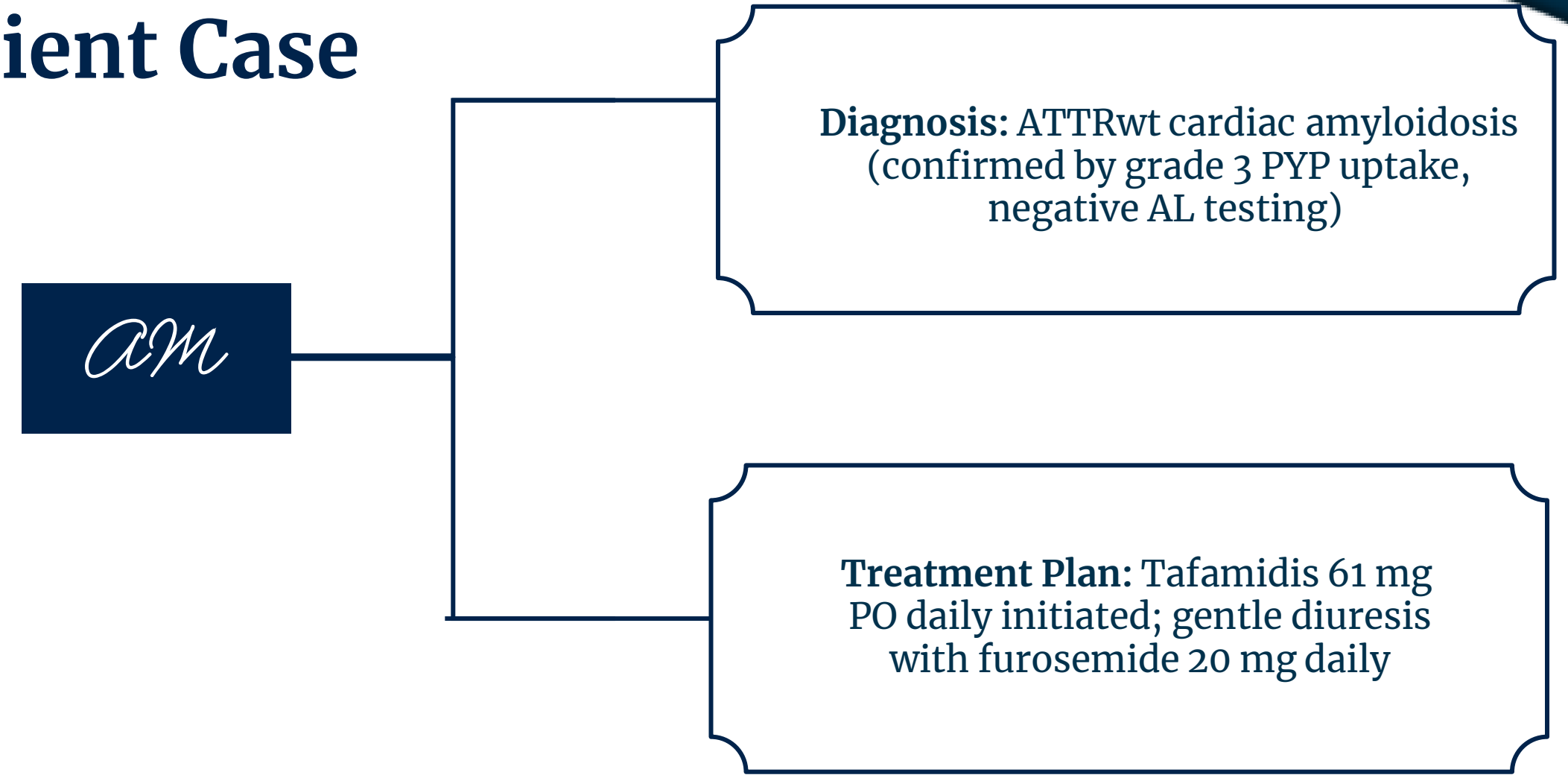
# Patient Case

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# Patient Case

*am*

**3–6 month Follow-Up:**

NYHA class: Mostly stable, with possible slight improvement after gentle diuresis

NT-proBNP: May decrease mildly with improved volume status

6MWD: Generally stable (tafamidis prevents decline, it does not restore function)

# Summary

ATTR-CM is a protein misfolding disease that is often underdiagnosed.

Diagnosis is a stepwise approach.

TTR stabilizers and gene silencers modify disease

Supportive care differs from standard HF GDMT

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# The Misfolding Mechanism:

## Understanding and Treating ATTR Cardiac Amyloidosis

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