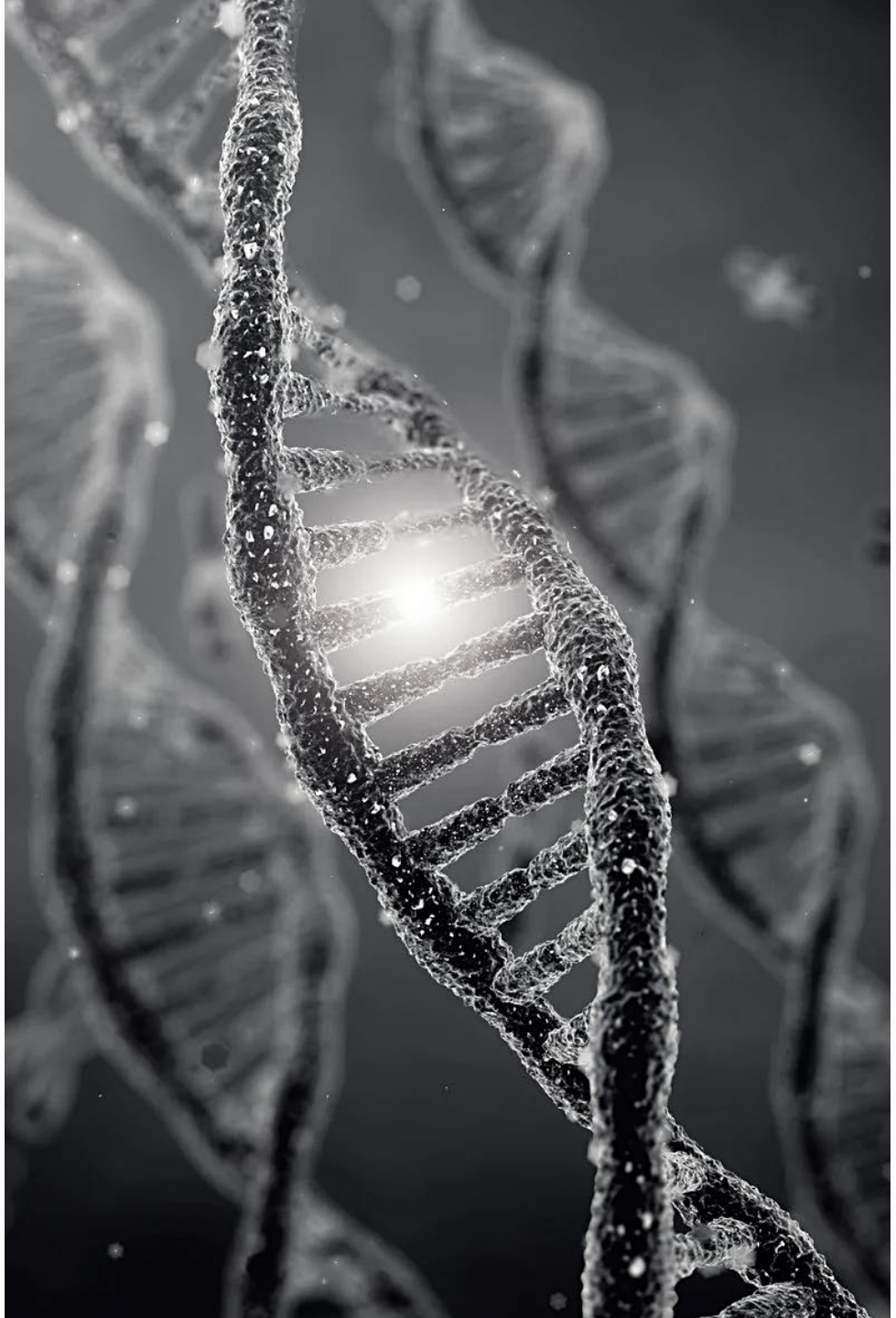

AMERICAN HEART ASSOCIATION'S
ATTR-CM WEBINAR SERIES:
WEBINAR #3

Cardiomyopathy in Focus: Recognizing and Managing Cardiac Amyloidosis

JUNE 16, 2026

Meeting Reminders

Please Note:

- This webinar is being recorded.
- All participants will be muted upon entry.
- Recordings of today's sessions will be enduring resources in a few weeks on www.heart.org

Questions?

- We encourage an open, conversational discussion, so please engage and share your thoughts!
- Q&A is scheduled at the end of the webinar.
- Submit your questions in the chat anytime—they will be addressed during the designated Q&A.

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Welcome & Introductions

Devin Marie Keating
Director of Operations, Clinical Studies
American Heart Association

Thank you to

Intellia Therapeutics

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American Heart Association's

ATTR-CM Awareness and Education

American Heart Association's ATTR-CM Educational Webinar Series

The ATTR-CM Educational Webinar Series is designed to advance awareness, early diagnosis, and equitable access to care for transthyretin amyloid cardiomyopathy (ATTR-CM). Through a series of expert-led sessions, the series aims to:

Educate | Elevate | Engage | Equip

Today's Speakers

Jan Griffin, MD

Associate Professor of Medicine
Director, MUSC Amyloidosis Center
Medical University of South Carolina
Charleston, SC

Janice Pieretti, MD

Associate Professor of Medicine
Medical Lead for Cardiac Amyloidosis
Hospital of the University of Pennsylvania
Philadelphia, PA

Yevgeniy Brailovsky, DO, MSc

Assistant Professor of Medicine
New York-Presbyterian/Columbia University
Irving Medical Center
New York, NY

Agenda:

1. **Cardiac Amyloidosis: Understanding The Heart And Beyond**
   Dr. Jan Griffin, MUSC

2. **Uncovering New Approaches In Cardiac Amyloidosis Care**
   Dr. Janice Pieretti, UPenn

3. **The Multidisciplinary Care Model In Cardiac Amyloidosis**
   Dr. Yevgeniy Brailovsky, NYP/Columbia

4. **Panel Discussion and Audience Q & A**

Disclosures

American Heart Association Statement

- The recommendations and opinions presented by our guest speakers may not represent the official position of the American Heart Association. The materials are for educational purposes only, and do not constitute an endorsement or instruction by the American Heart Association. The American Heart Association does not endorse any product or device.

Jan Griffin, MD

- Research grant from Pfizer and BridgeBio
- Advisory Board/Steering Committee/Speaker's Bureau for BridgeBio, AstraZeneca, Pfizer

Janice Pieretti, MD

- ATTR Medical Council, AstraZeneca

Yevgeniy Brailovsky, DO, MSc

- Advisory Board for Pfizer, Alnylam, AstraZeneca, and BridgeBio

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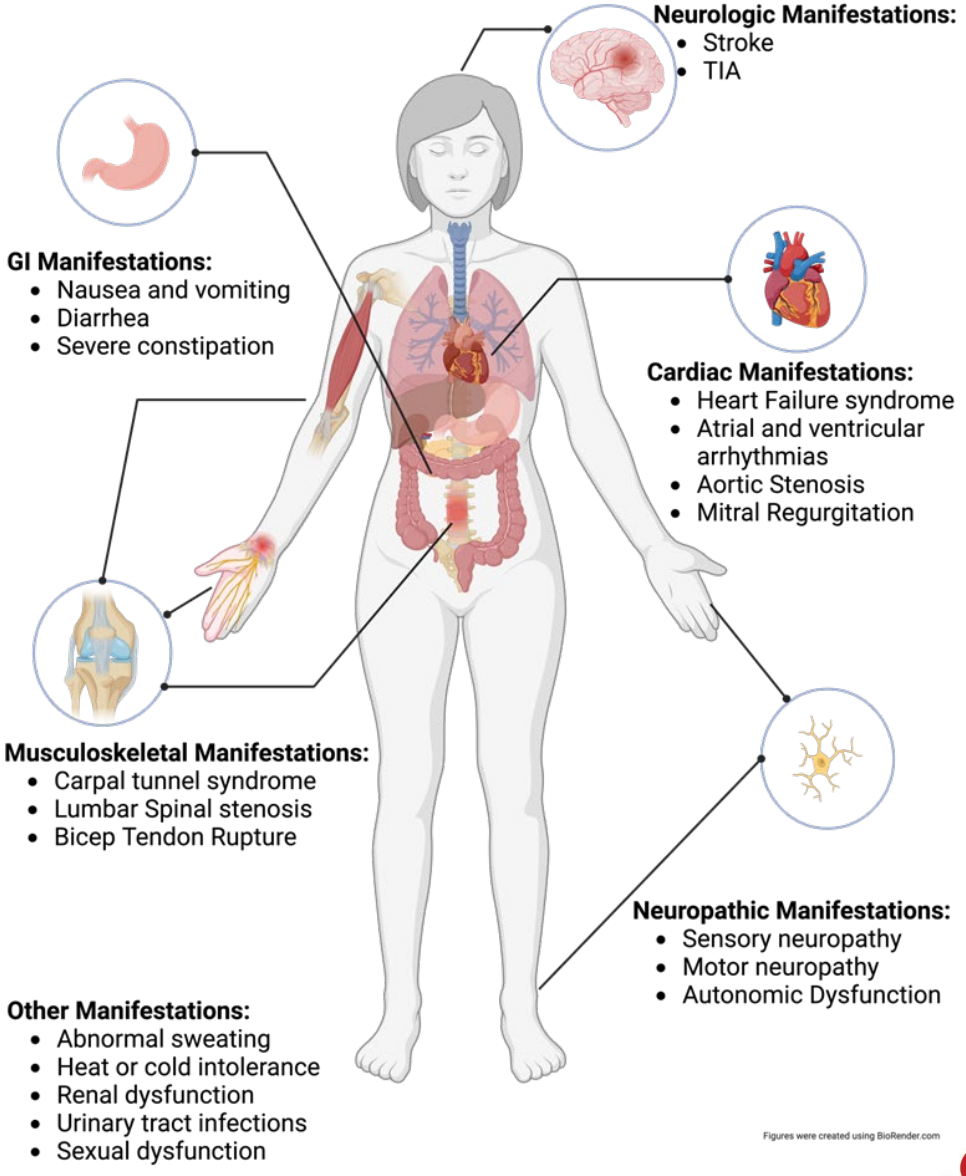
Cardiac Amyloidosis: Understanding the Heart and Beyond

Jan Griffin, MD
Associate Professor of Medicine
Director, MUSC Amyloidosis Center
Medical University of South Carolina
Charleston, SC

Amyloidosis

- Over 40 known amyloidogenic proteins
- Cardiac amyloidosis typically arises from either transthyretin (ATTR) or light-chain (AL) amyloid deposition
- Deposition in the myocardium → restrictive CM
- Deposition in the nerves → sensory, motor & autonomic neuropathy
- ATTR or AL cause > 95% of cardiac amyloidosis



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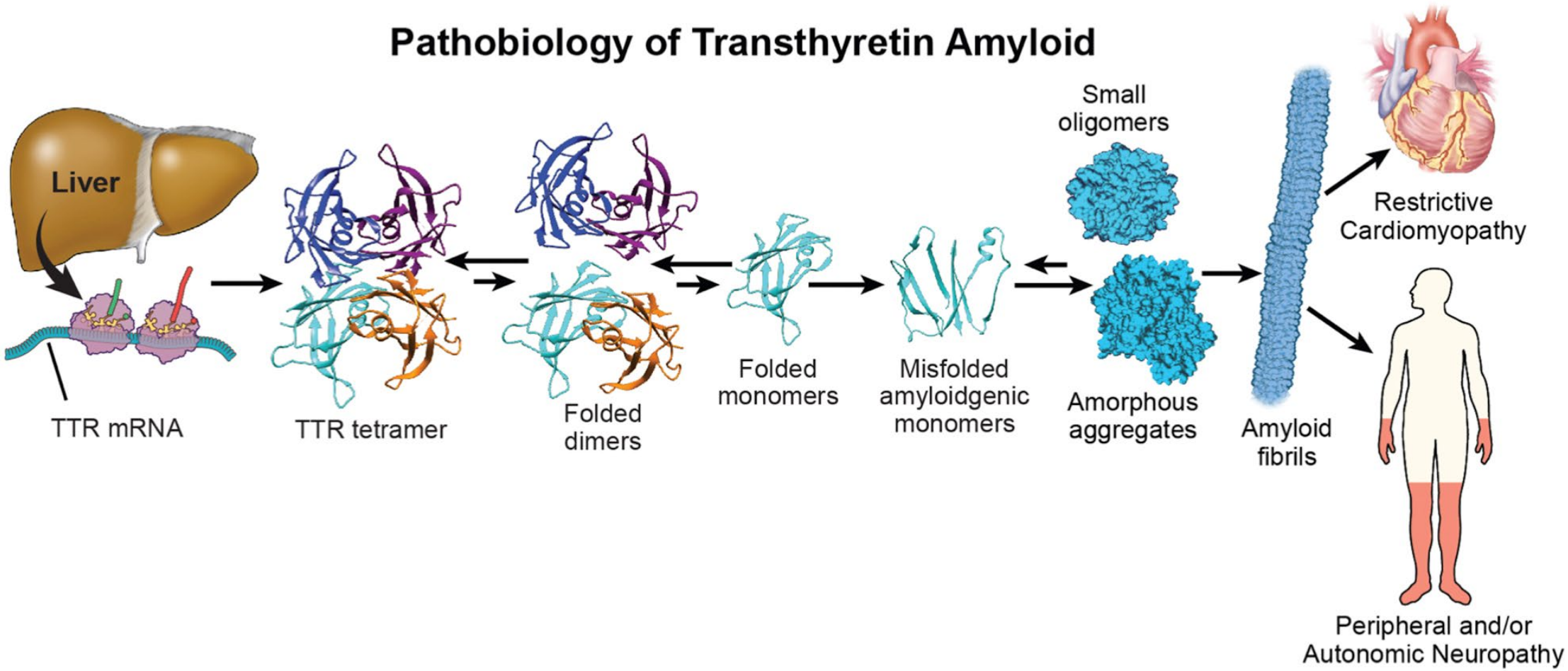
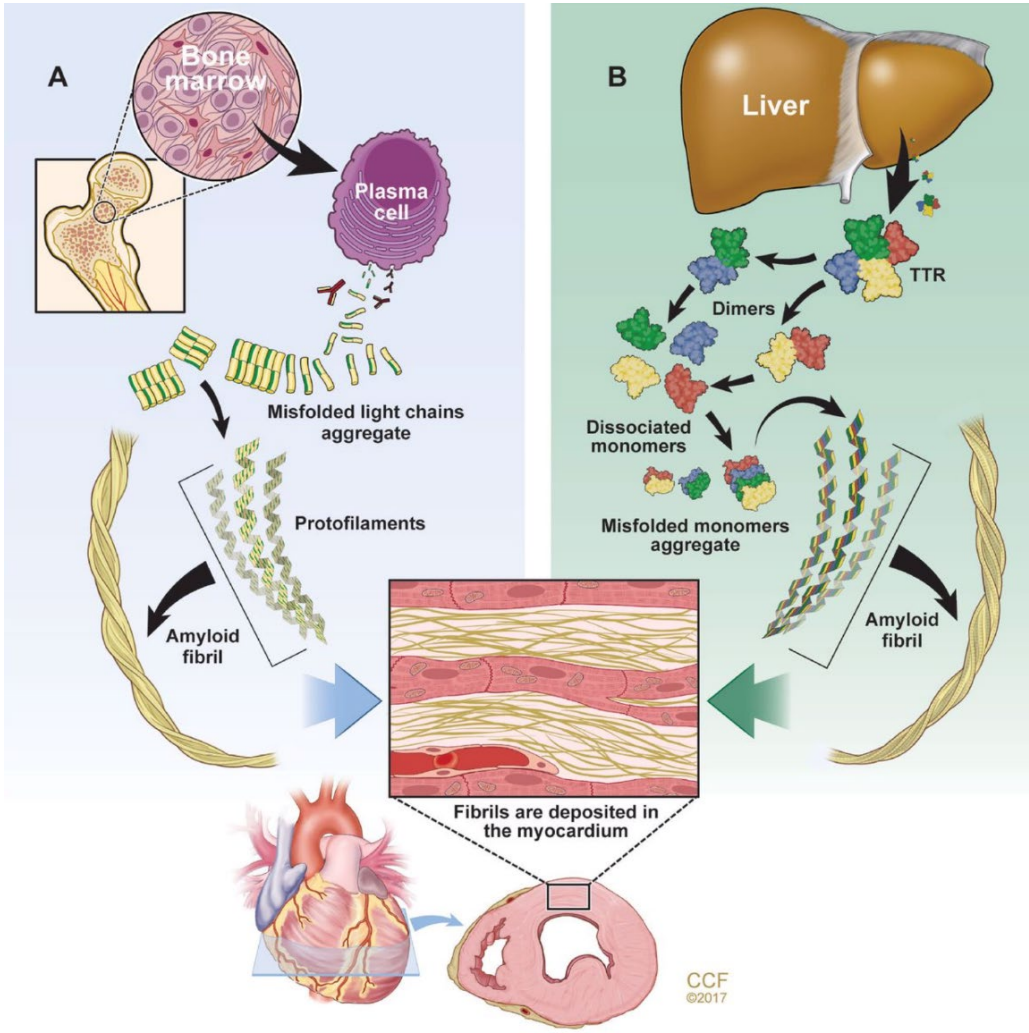
Biology of Transthyretin Amyloidosis



Ruberg et al. J Am Coll Cardiol. 2019

Biology of Light Chain Amyloidosis

- Age 50-80 yrs
- 50/50 male:female
- Overgrowth of clonal plasma cells in the bone marrow
- Monoclonal protein usually found in serum or urine
- Nerves, kidney, GI, liver, skin, soft tissues
- Cardiac involvement in ~ 70%



Madan et al. Blood. 2012;119(5):1117–22

Major Causes of Cardiac Amyloidosis

Features	Light chain cardiac amyloidosis (AL-CA)	Transthyretin cardiac amyloidosis	
		Wild type (ATTRwt-CA)	Variant/hereditary transthyretin (ATTRv-CA)
Age at diagnosis	Fifth to Ninth decade	Seventh to tenth decade	Third to eighth decade
Sex distribution	Roughly equal male:female	Very significant male predominance	Male predominance
Precursor protein	Light-chain	Transthyretin	Transthyretin
Genetic cause	None	None	Autosomal dominant inheritance
Genetic modifier to therapeutic efficacy	t(11,14) presence–poor response to bortezomib but responsive to venetoclax	None	None
Extracardiac involvement	Nerves, kidney, liver, gastrointestinal tract, skin, tongue/soft tissue	Carpal tunnel, lumbar spine, gastrointestinal tract	Nerves
Clinical manifestations	Multi-systemic disease with cardiac and renal involvement (60%–70%); liver (15%) and peripheral/autonomic neuropathy (10%)	Predominant cardiac phenotype with a restrictive cardiomyopathy, atrial and ventricular arrhythmias, and HFpEF	Depends on variant. Val122Ile predominately cardiac, Thr60Ala mixed and Val30Met predominately neuropathic
Prognosis after diagnosis	Depends on stage. Median survival 4–6 mo with advanced heart failure	Depends on stage. Median survival 2–6 y in the absence of treatment	Depends on mutation and stage. Median survival 3–12 y

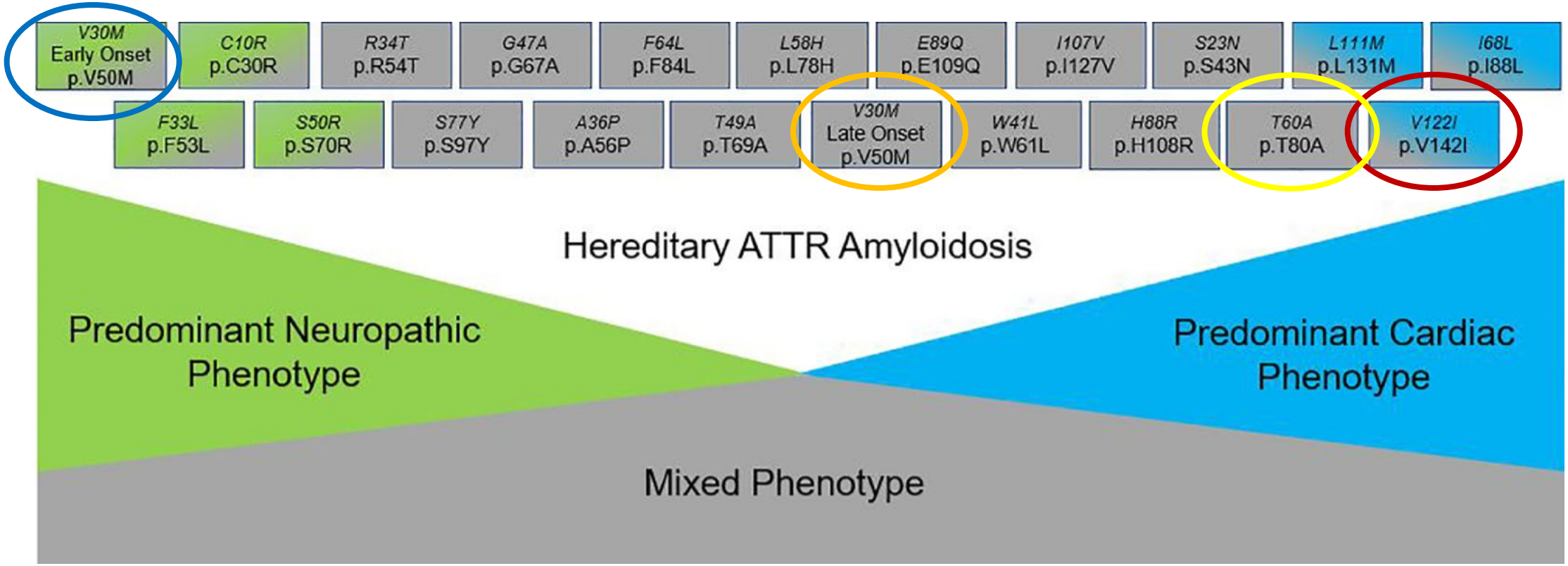
Griffin JM et al. Circ Res. 2021 May 14;128(10):1554-1575.

Etiology of ATTR Cardiac Amyloidosis

- Cause of wild type ATTR is unknown, thought to be related to the aging process
- Single amino acid mutation in the TTR gene leads to variant (hereditary of familial) ATTR
- Over 140 known pathogenic TTR mutations, resulting in variable phenotypic presentations

Buxbaum JN, et al. Amyloid. 2024;42(4):249-256

Genotype/Phenotype of Variant ATTR



Griffin, JM et al. Trends Cardiovasc Med. 2021

Geographic Distribution of ATTR Cardiac Amyloidosis

- Wild type ATTR is the most common form in the US
- V122I (p.V142I) is the most common mutation in the US
  - US, UK, Western Africa
  - ~3.5% of Black Americans, penetrance is unknown
- V30 (p.V50M) is the most common mutation worldwide
  - Portugal, Sweden, Japan
  - Early vs Late onset
- T60A (p.T80A)
  - US, UK, Northern part of the Republic of Ireland
  - ~1% of those of Irish descent

Mitchell J, al. et. JACC. 2025;85(12):1181.

Prevalence of ATTR-CM

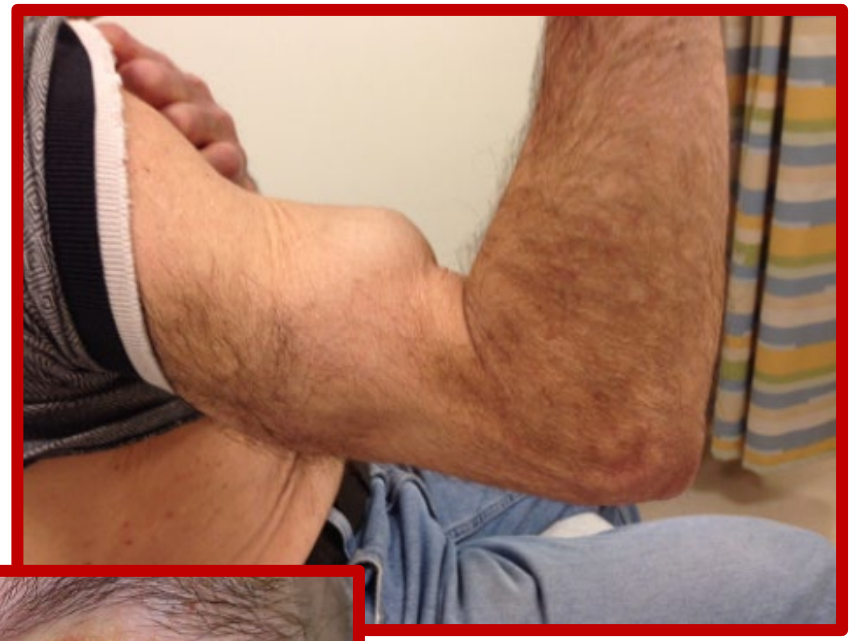
- 13% in patients with HFpEF and left ventricular wall thickness > 12mm
- 16% in patients with severe calcific aortic stenosis undergoing TAVR
- 5% among patients with presumed hypertrophic CM
- TTR amyloid deposits are found on autopsy in > 30% of HFpEF > 75 years old

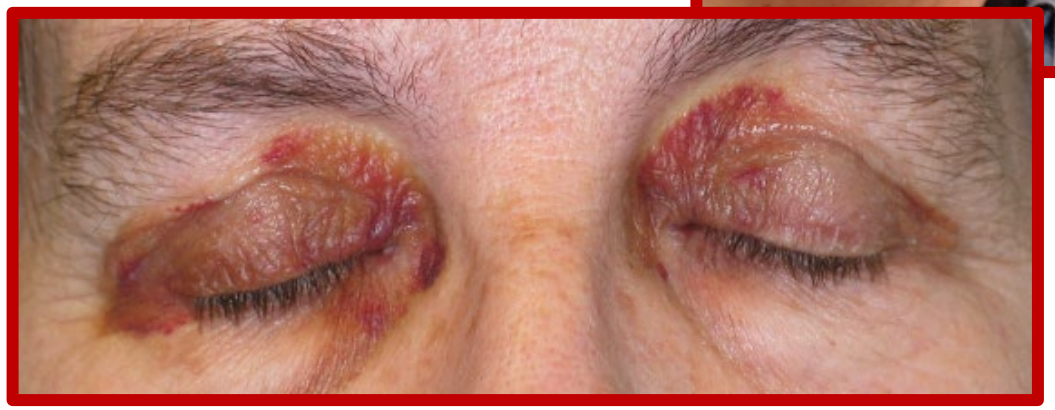
Gonzalez-Lopez et al. Eur Heart J. 2015 Oct 7;36(38):2585-94
Castano et al. Eur Heart J. 2017 Oct 7;38(38):2879-2887

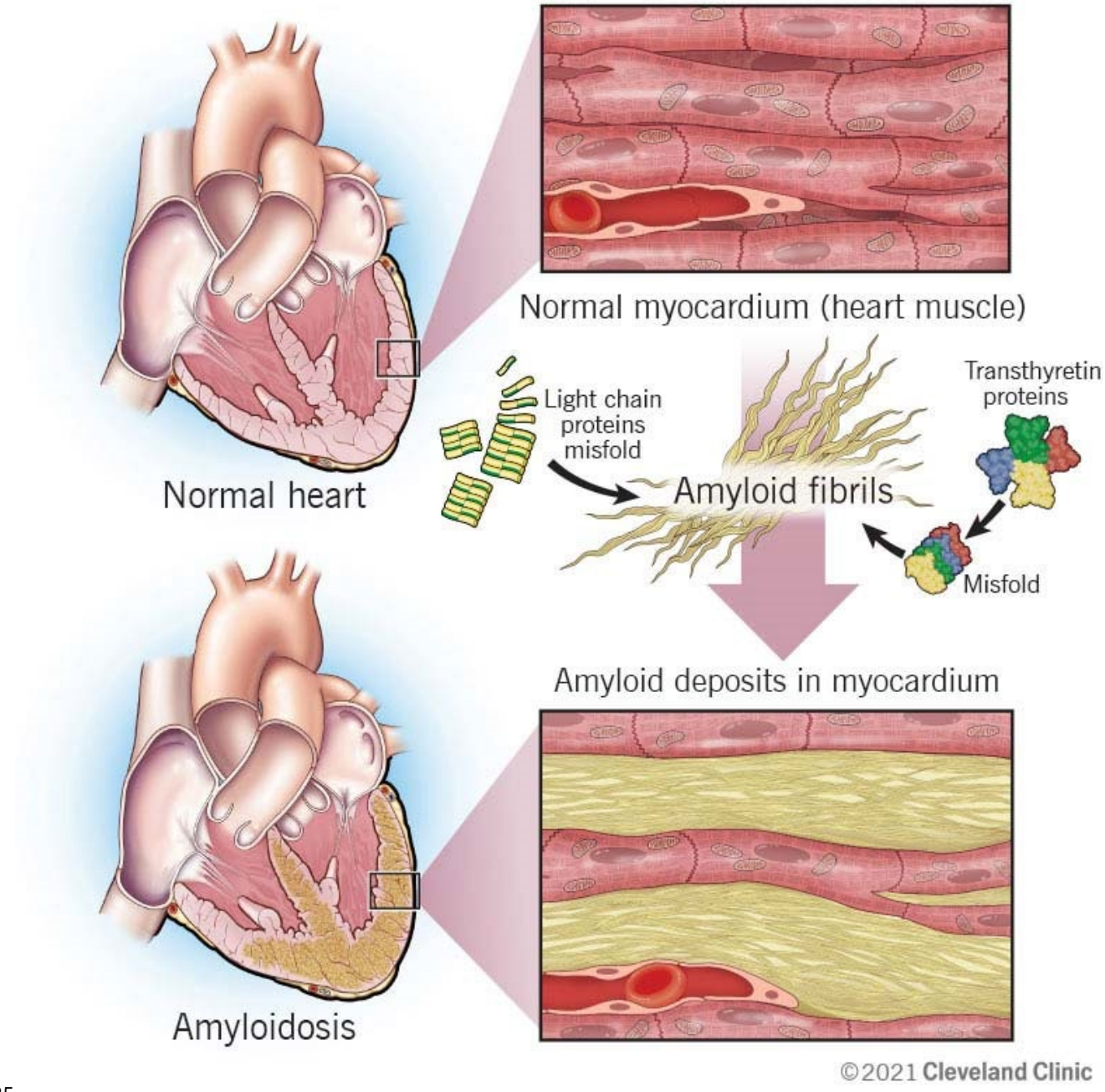
Morner et al. J Intern Med. 2005 Sep;258(3):225-30
Mohammed et al. JACC Heart Fail. 2014; 2:113–122

Amyloidosis – A Multisystem Disease

- Bilateral carpal tunnel syndrome (~50% in ATTRwt)
- Lumbar spine stenosis & orthopedic surgeries
- Biceps tendon rupture
- GI motility disorder (ATTRv)
- Peripheral neuropathy (ATTRv)
- Periorbital purpura (AL)
- Macroglossia (AL)

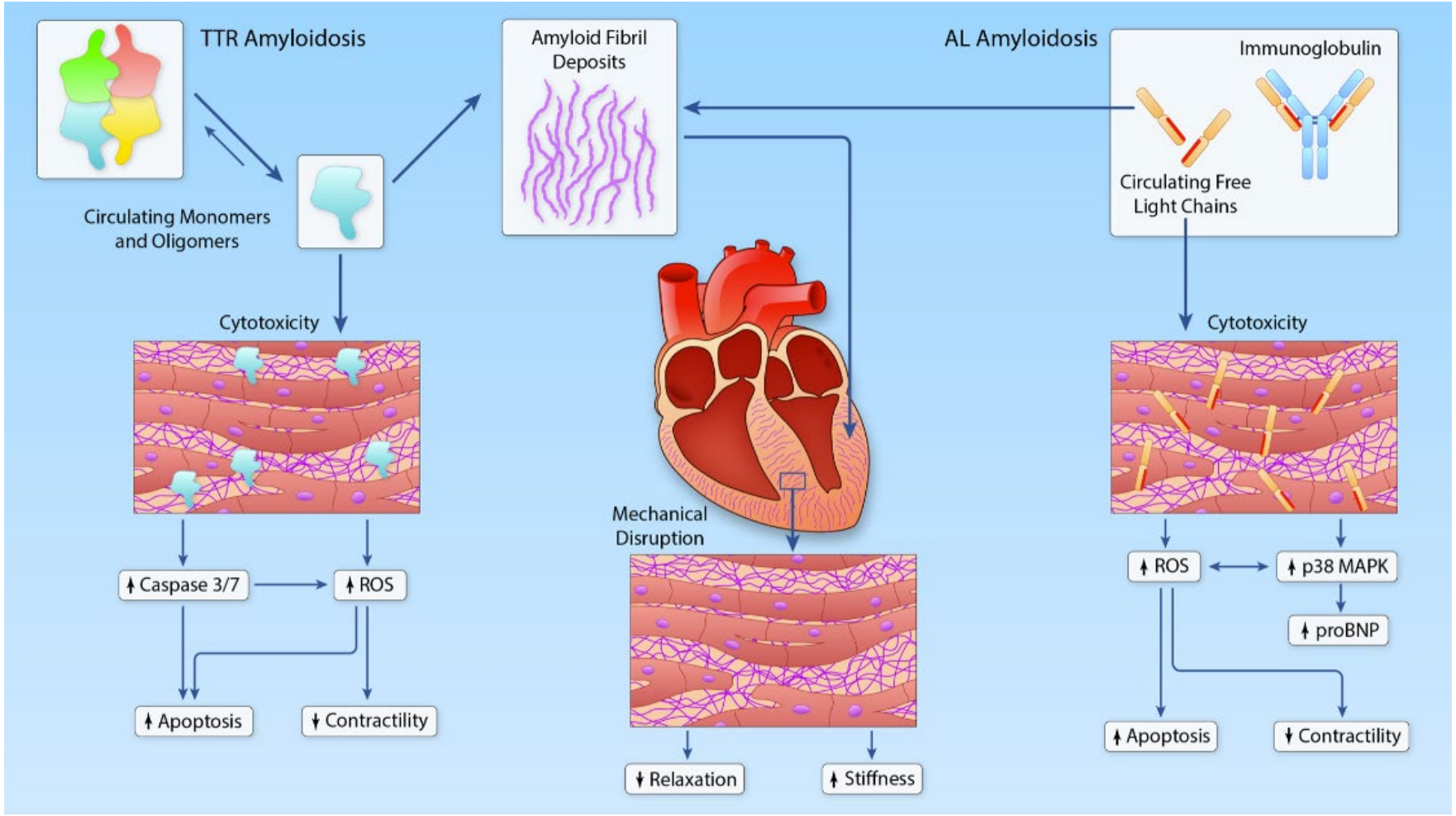






Cleveland Clinic. *Cardiac Amyloidosis.*; 2025.

Cardiac Amyloidosis causes a Restrictive Cardiomyopathy



Griffin JM et al. Circ Res. 2021 May 14;128(10):1554-1575.

Restrictive Physiology requires a tailored approach to HF management

- Reduced/relatively fixed stroke volume
- Decreased compliance
- Compromised cardiac output, HR dependent
- Preload dependent and afterload intolerant
  - Delicate balance between relieving congestion yet maintaining high enough filling pressures to maintain cardiac output
  - Prone to organ hypoperfusion – Acute Kidney Injury (AKI)

Griffin JM et al. J Am Coll CardioOnc. 2021;3(4):488-505

Atrial Arrhythmias

- Multifactorial mechanism
  - Fibril deposition/infiltration, impaired relaxation, restrictive filling
  - Elevated filling pressures → atrial dilation
  - Atrial amyloid deposition → myocardial fibrosis & remodeling

- Atrial fibrillation **prevalence 15-70%** across all CA subtypes

- Atrial fibrillation is the **most commonly encountered sustained arrhythmia** in ATTR-CA
  - More common in wild type than AL or variant ATTR

- **Up to 33% may develop LAA thrombus,** despite therapeutic anticoagulation

El-Am EA, et al. J Am Coll Cardiol. 2019;73:589–597
Donnellan E et al. J Am Coll Cardiol EP. 2019;5:1473–1474

Rate vs Rhythm Control for Afib/flutter

Rate: Challenging due to narrow heart rate range to optimize hemodynamics

- Recall – likely low relatively fixed stroke volume
- Require higher filling pressures to preserve SV
- Faster HR to maintain adequate cardiac output

Rhythm: Particularly effective for earlier stage disease

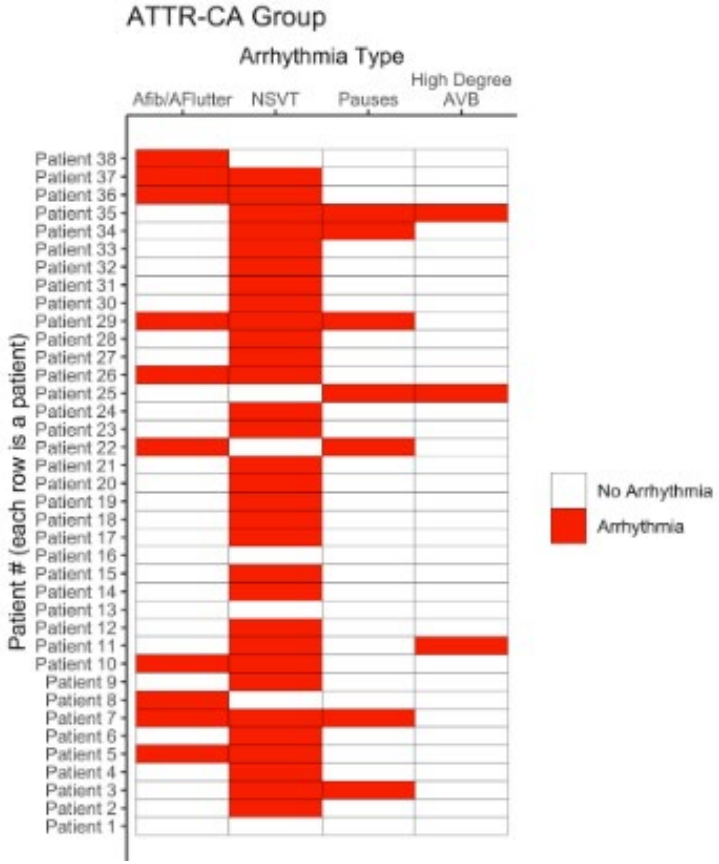
- No survival benefit for rhythm vs rate control
- TEE guided DCCV, 1-year recurrence risk is high (up to 70-80% reported)
- Afib ablation

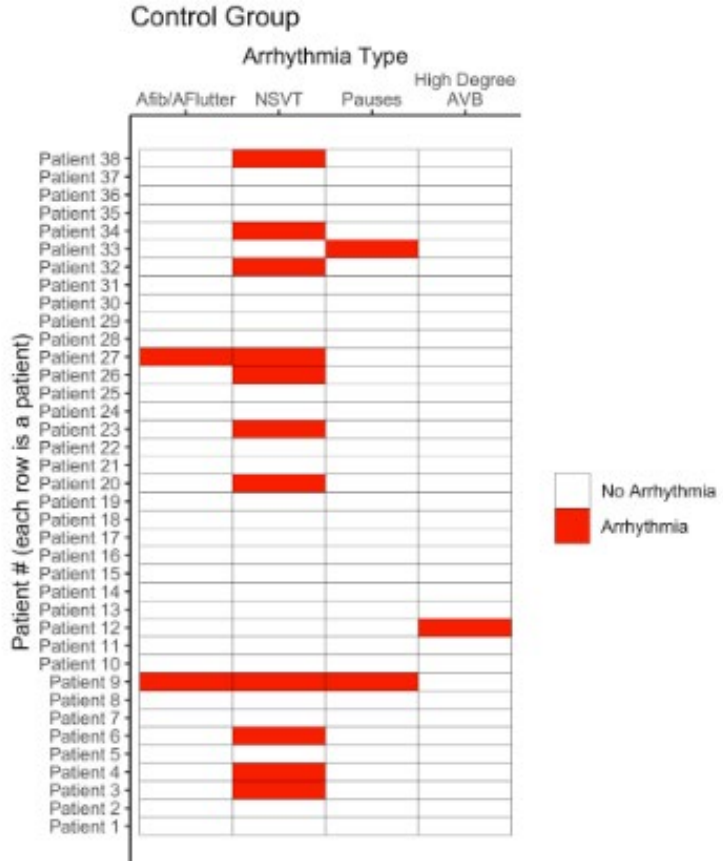
Mints YY et al. ESC Heart Fail. 2018;5:772–779
Donnellan E et al. J Am Coll Cardiol EP. 2020;6:1118–1127
Touboul O, et al. ESC Heart Fail, 9 (2022), pp. 3556-3564
Sanchis K, et al. Amyloid 2019;26:128-138
Loungani R, et al. Am Heart J, 222 (2020), pp. 26-29

Bradyarrhythmia and VT

- Conduction disease is common, prophylactic pacing has not been shown to improve outcomes

- Detection of NSVT is common
  - **81.6% (of 38 patients) of ATTR-CM had NSVT on remote patch monitors**
  - **Unclear association with SCD**





Giancaterino S, et al. JACC Clin Electrophysiol 2020; 6: pp. 351-361
Bruce SL, et al. Heart Rhythm O2 2024. 23;5:631-638

Sperry BW et al, Cureus 2023;15(1):e34107

Bradyarrhythmia and VT

- ICD placement is not well supported by expert guidelines
  - SCD in CA is thought to be due to primarily electromechanical dissociation → PEA arrest (controversial)
  - Some suggest higher defib threshold required for amyloid filled heart, refractory to ICD therapy
  - Poor prognosis if advanced heart failure

Giancaterino S, et al. JACC Clin Electrophysiol 2020; 6: pp. 351-361
Bruce SL, et al. Heart Rhythm O2 2024. 23;5:631-638
Sperry BW et al, Cureus 2023;15(1):e34107

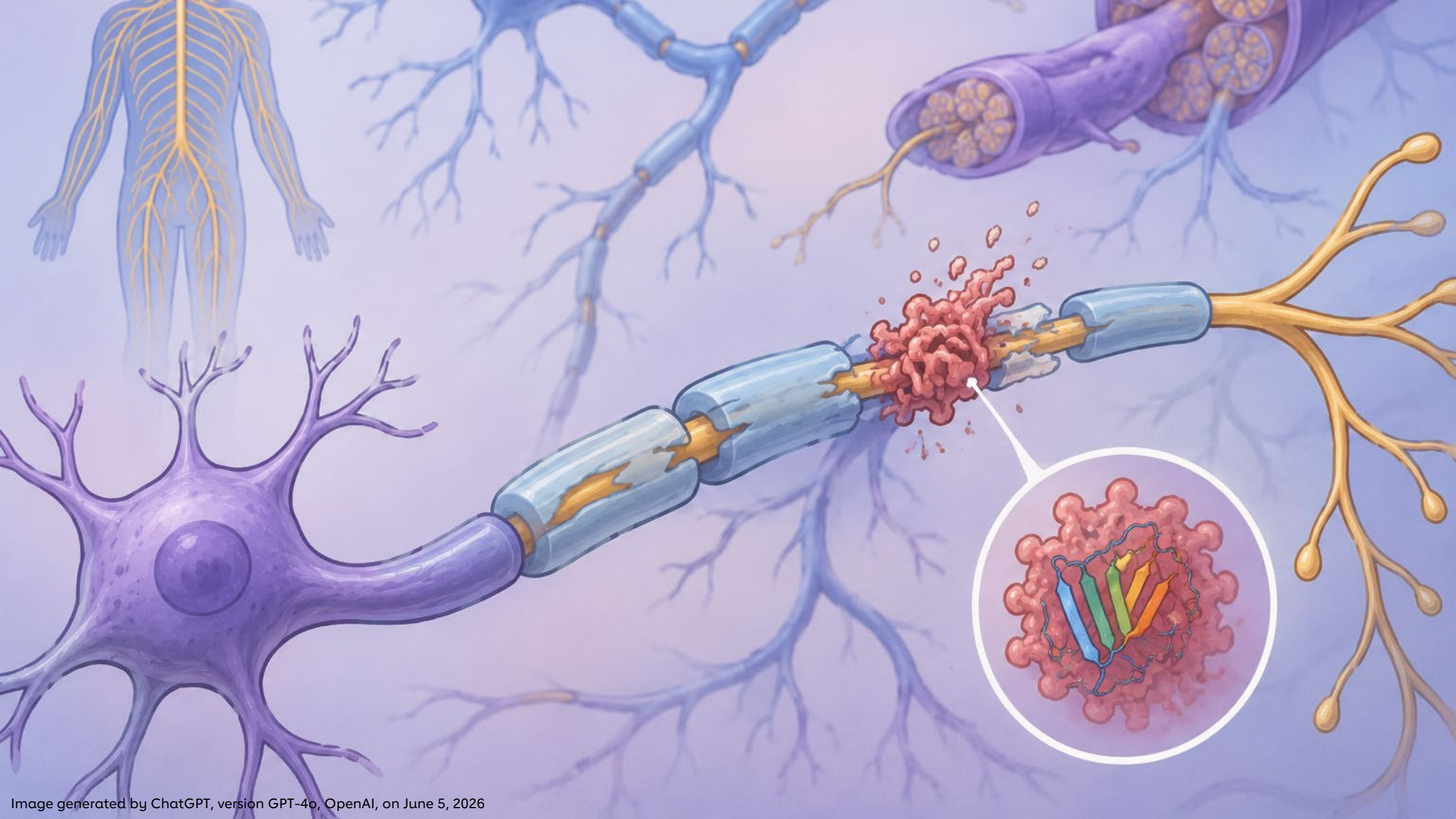


Image generated by ChatGPT, version GPT-4o, OpenAI, on June 5, 2026

Neuropathies in ATTR

- For individuals in the endemic regions of Portugal with the **p.Val50Met variant, >80% develop peripheral neuropathy** by **age 50** years.

- By contrast, for patients with the **p.Val142Ile variant**, which is predominantly associated with cardiomyopathy, the prevalence of **polyneuropathy** is about **10%.**

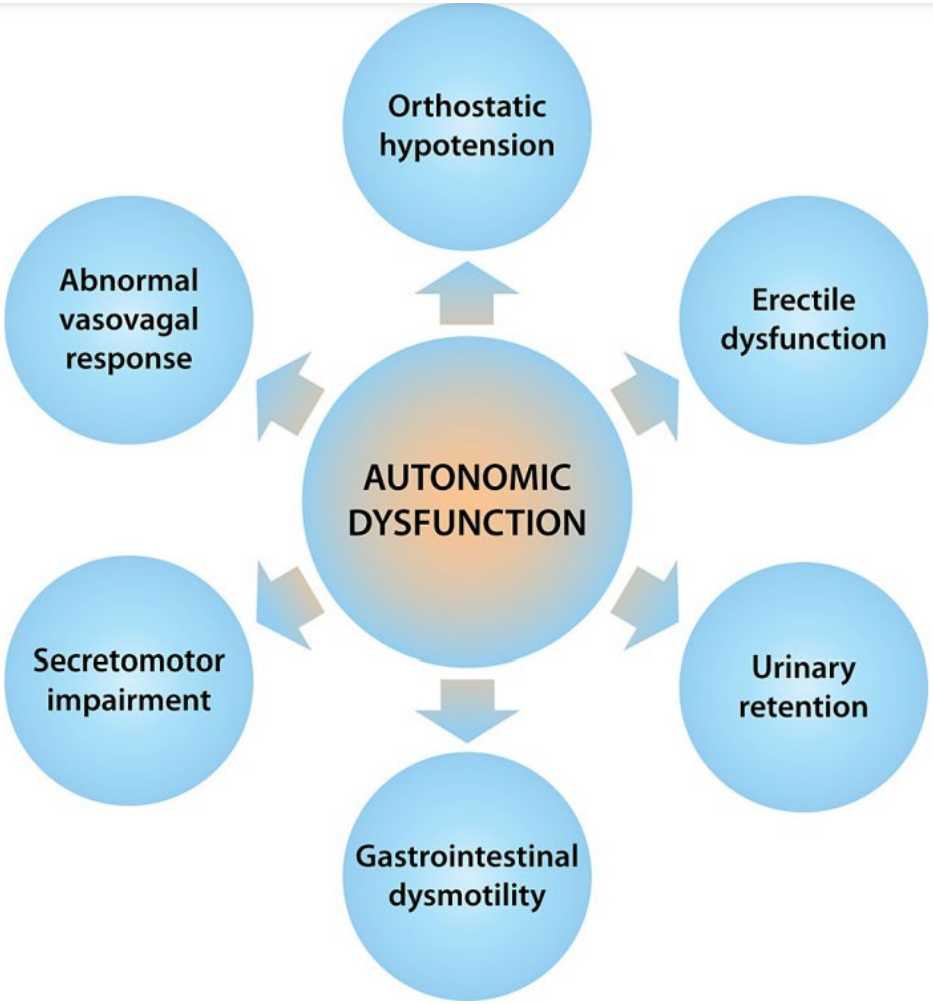
- **ATTRwt**, in turn, predominantly causes cardiomyopathy, while approximately **30%** of patients may have a **polyneuropathy** that may (or may not) be attributable to amyloidosis

Neuropathies in Amyloidosis

- Amyloid deposits in nerves are **unevenly distributed**
- Small or unmyelinated fibers are **selectively targeted**
- As they accumulate, they cause damage by
  - Mechanical compression
  - Direct blood vessel invasion
  - Likely direct toxic effects of amyloid fibrils

Neuropathies in Amyloidosis

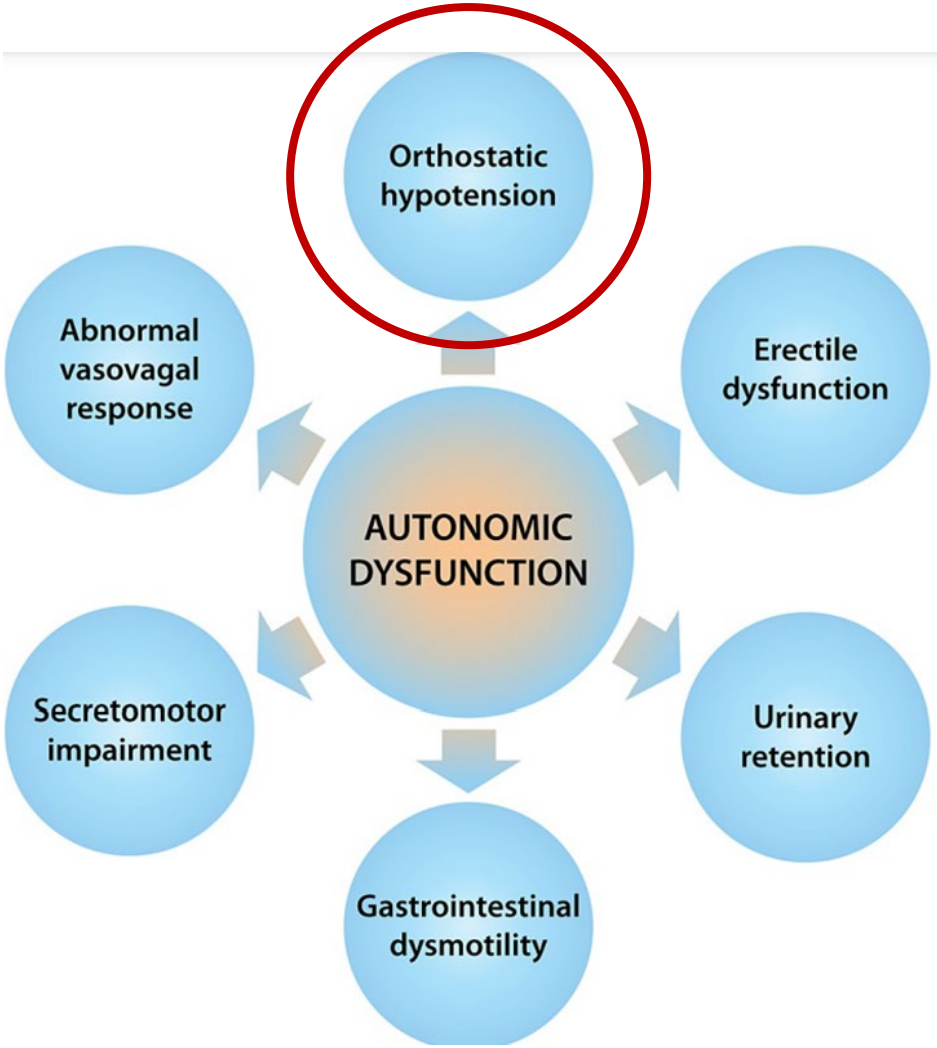
- **Focal Neuropathies**, such as carpal tunnel syndrome
- **Sensorimotor polyneuropathies**, affects small and then larger fibers
- **Autonomic Dysfunction** *aka* Dysautonomia *aka* Autonomic Neuropathy



Sperry B W. Cureus 15(1): e34107

Autonomic Dysfunction

- Common in early onset familial amyloid polyneuropathy (neuropathic ATTRv in endemic areas)
- Less common in late onset ATTRv
- AL amyloidosis
  - 17% have peripheral neuropathy
  - 65% with autonomic NS involved



Sperry B W. Cureus 15(1): e34107
Shin, SC. Mt Sinai J Med. 2012
Gertz MA et al. Hematol Oncol Clin North Am. 1999

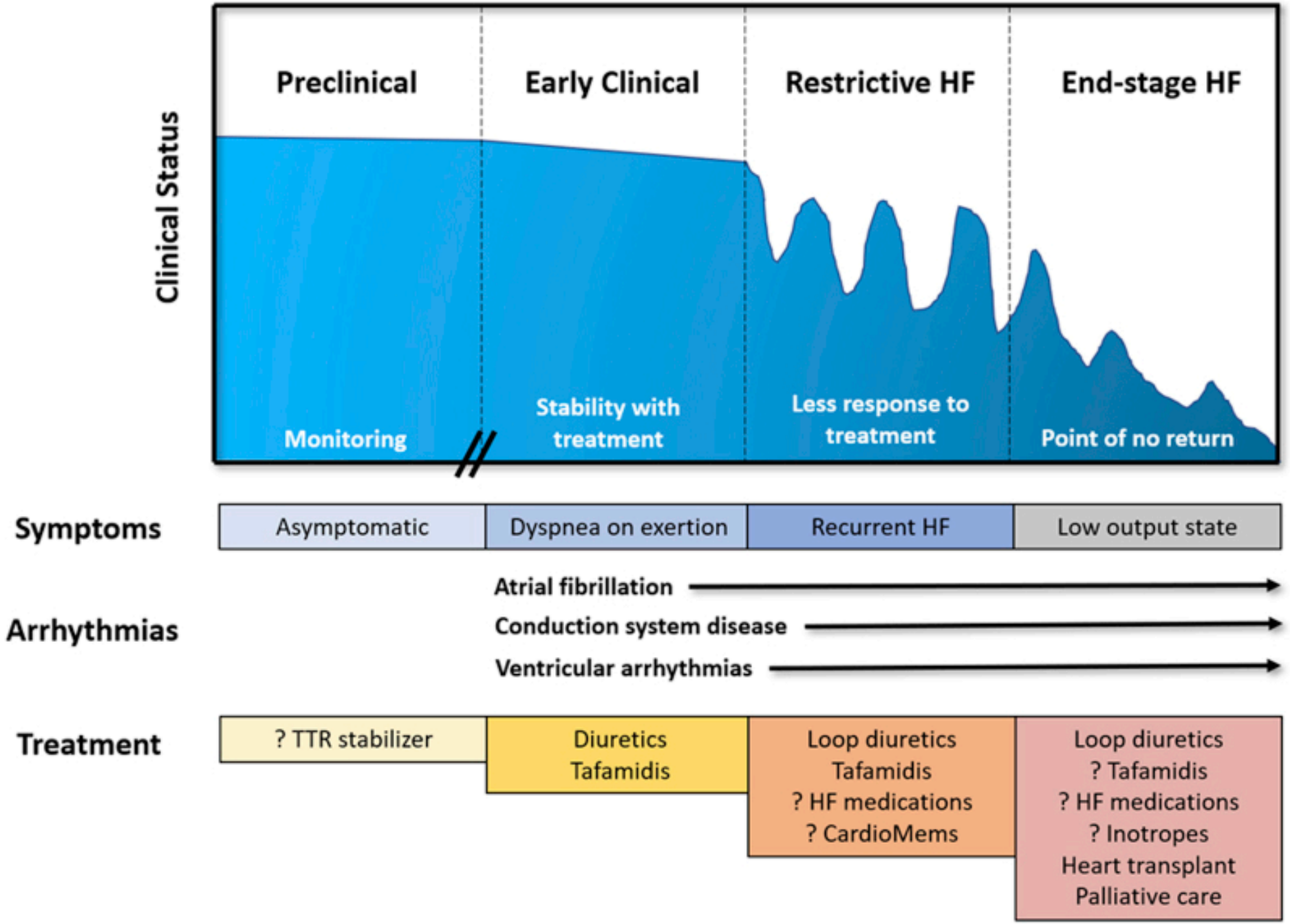
Diagnostic Delays

- **~80% with ATTR-CM have preceding orthopedic interventions** of the shoulder, hip, or knee; carpal tunnel syndrome; spinal stenosis; trigger finger; or biceps tendon rupture
  - *Identified an average of **4 to 10 years prior to cardiac symptom development***

- Transthyretin deposition in the ligamentum flavum has been reported in up to one-third of older individuals undergoing surgery for lumbar spinal stenosis

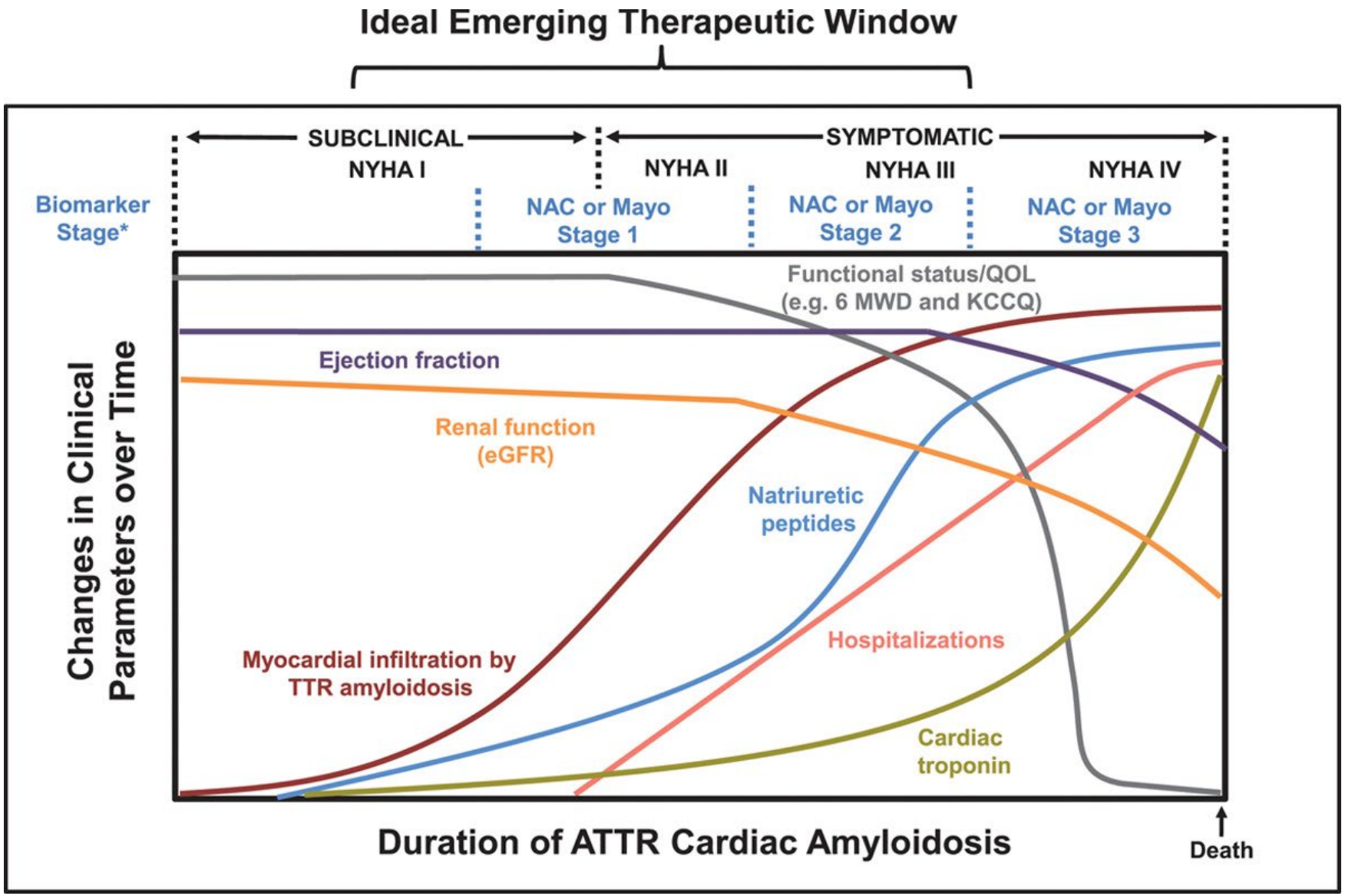
- **Spontaneous biceps tendon rupture** may occur a median of **5 years prior** to the HF diagnosis, while **carpal tunnel syndrome** can manifest **5 to 10 years prior**

Kittleson MM et al. J Am Coll Cardiol. 2026;87(5):549-65
Zhang D, et al. J Am Acad Orthop Surg. 2021;29(10):e488-e96.



Griffin JM et al. J Am Coll CardioOnc. 2021;3(4):488-505

Early Recognition is Essential



Griffin JM et al. Circ Res. 2021 May 14;128(10):1554-1575.

American Heart Association®

Uncovering New Approaches in Cardiac Amyloidosis Care

Janice Pieretti, MD
Associate Professor of Medicine
Medical Lead for Cardiac Amyloidosis
Hospital of the University of Pennsylvania
Philadelphia, PA

Suspect Cardiac Amyloidosis Based on…

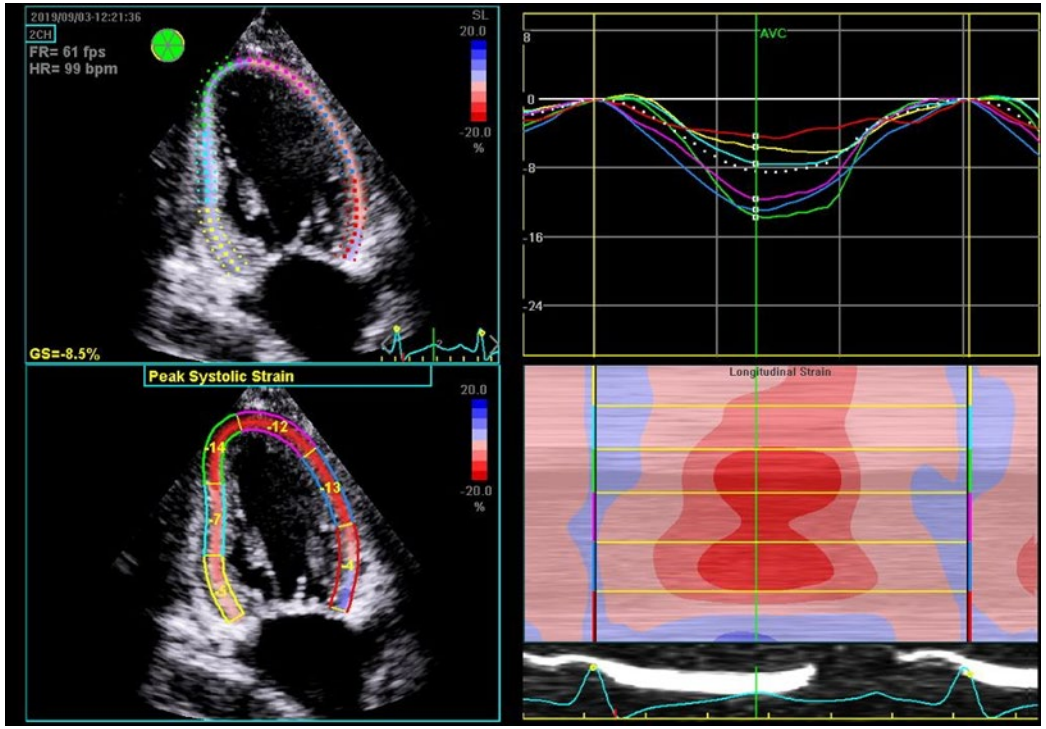
- Clinical Clues
- **Echocardiogram**
- **ECG**
- **MRI:** *not needed to initiate workup if above is strongly suggestive*

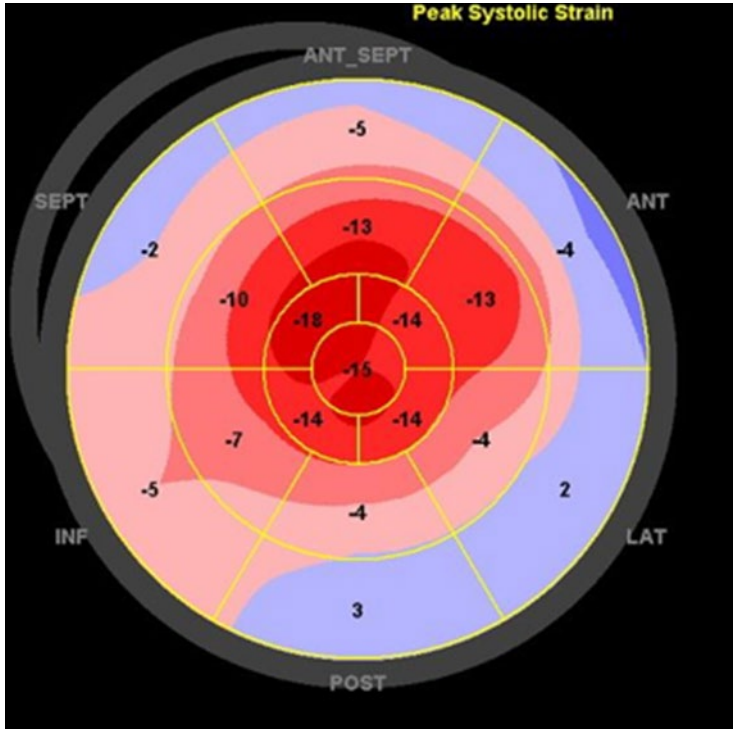
Echo Findings

- Increased LV wall thickness and everything else - RV wall, valve leaflets, and atrial septum
- "Sparkling or speckled appearance" – (not as specific due to modern tissue harmonic imaging)
- Low ventricular volume/low stroke volume
- Diastolic dysfunction – restrictive pattern in more advanced disease

Echo Findings

- Dilated Atria – may have atrial thrombi
- Pleural and Pericardial Effusions
- Decreased Global Longitudinal Strain (GLS)
- Apical sparing pattern on LV strain imaging





Decreased global longitudinal strain

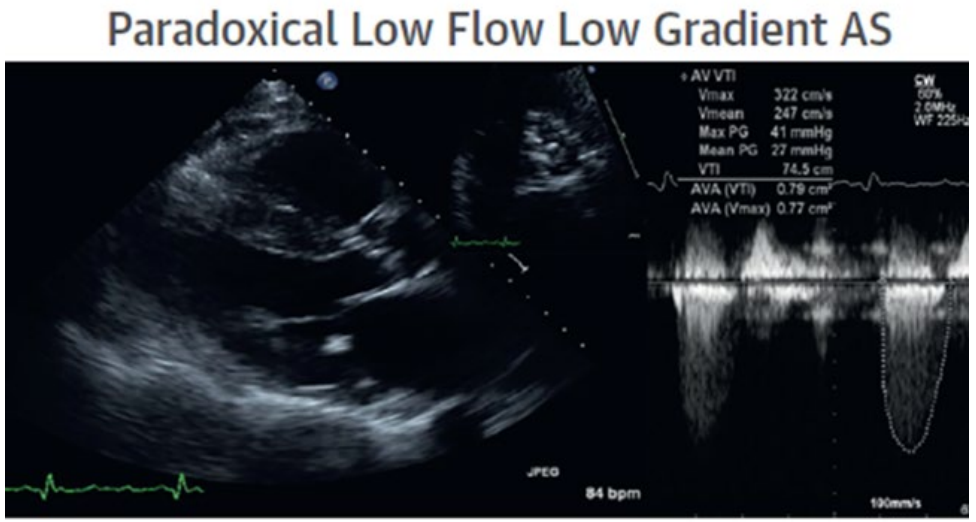
Characteristic apical sparing pattern of the LV apex

GLS decreased early in disease when LVEF is normal

93% sensitivity and 82% specificity to distinguish amyloidosis from LVH

Phelan D, et al. *J Am Coll Cardiol.* 2012;59(10):870–878.

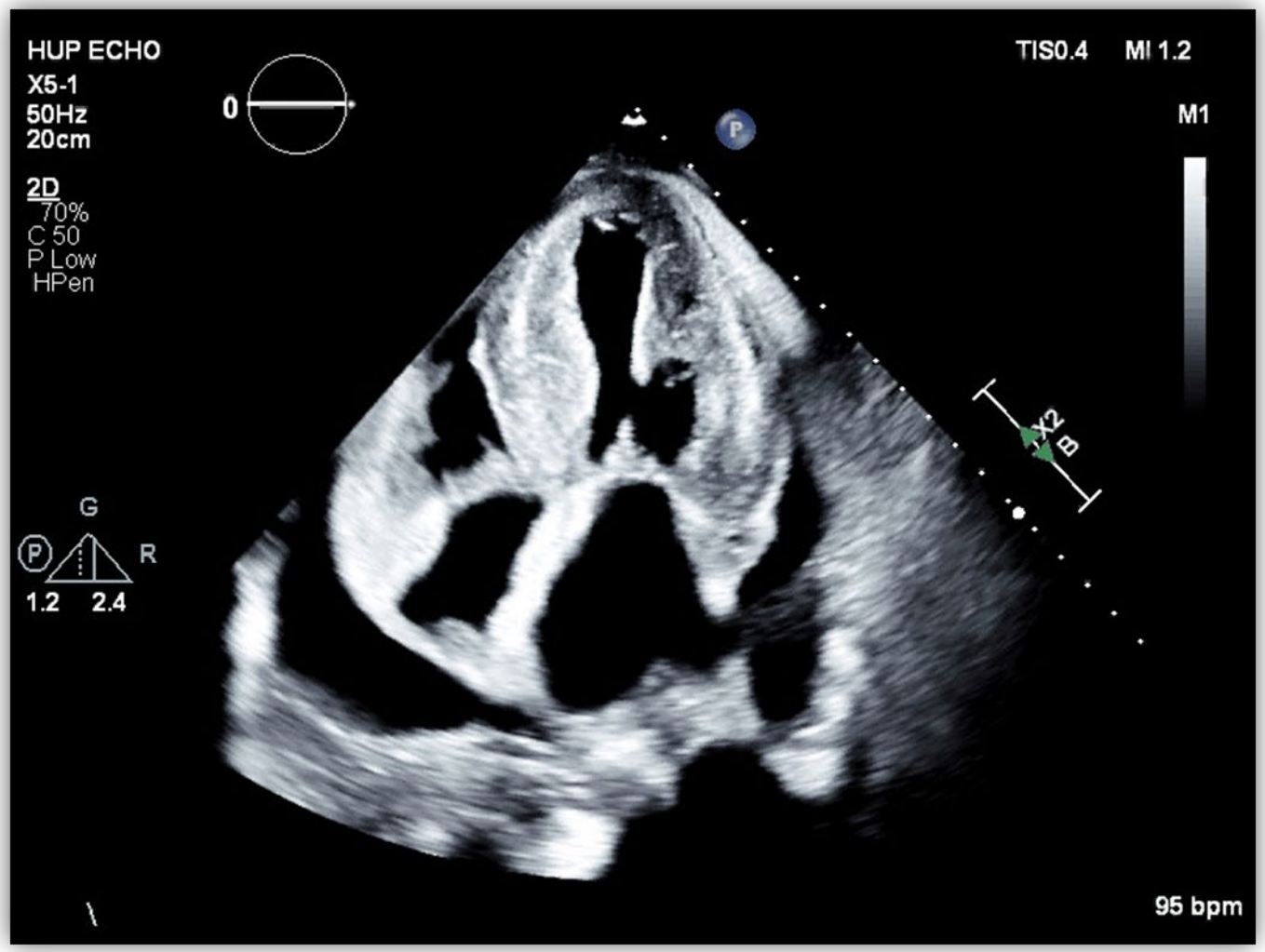
ATTR and Aortic Stenosis



10% of patients with low flow-low gradient aortic stenosis have ATTR-CM

TAVR/transcatheter valve replacement improves symptoms

Galat et al, Eur heart J. 2016; 37:3525-3531


HUP ECHO
X5-1
50Hz
20cm
2D
70%
C 50
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TIS0.4 MI 1.2
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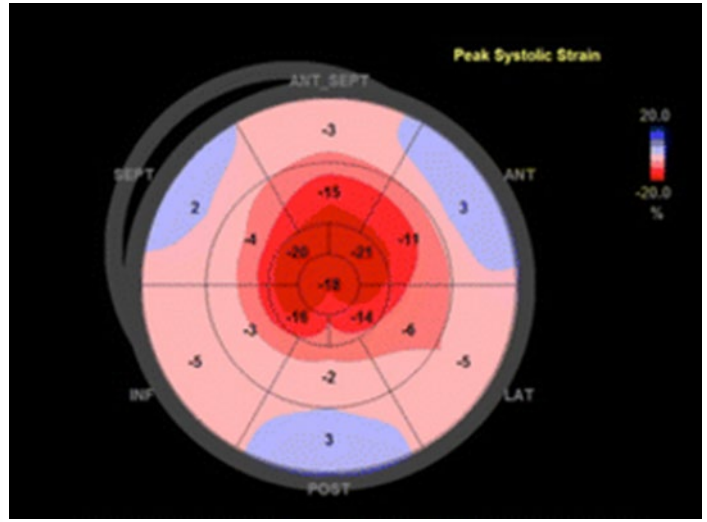
1.2 2.4
95 bpm


Peak Systolic Strain
ANT_SEPT
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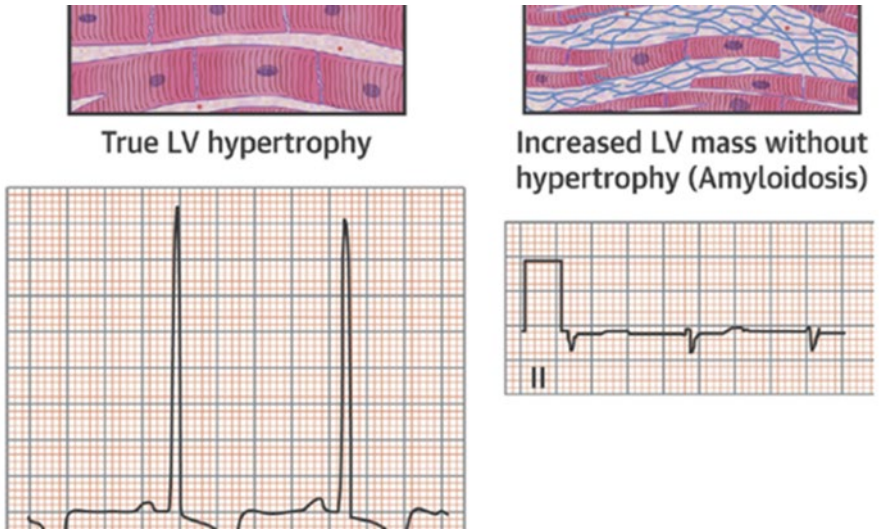
ECG Findings



Classic feature is low voltage in limb leads

Depends on extent and duration of disease

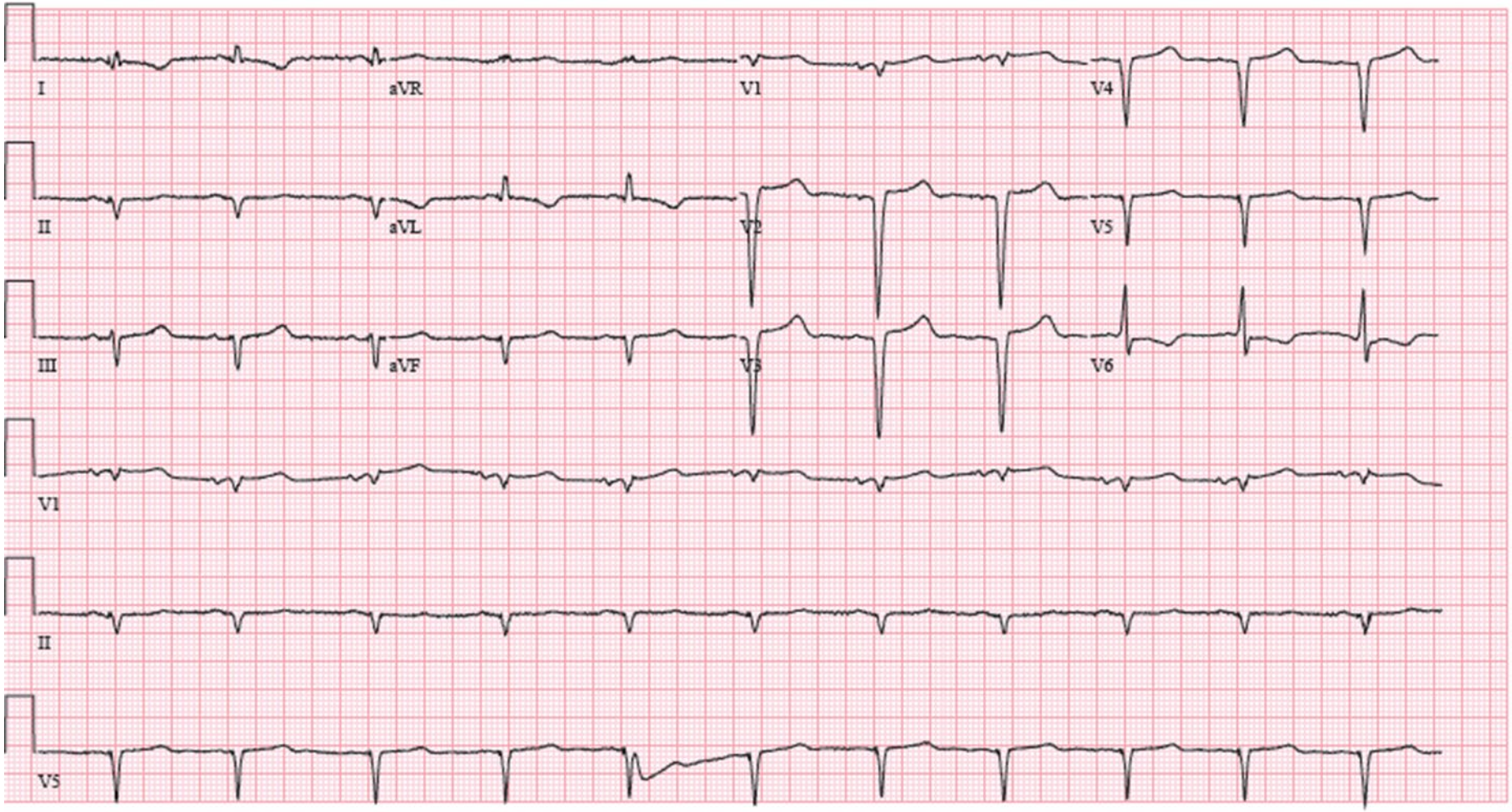
More commonly seen in AL amyloid than TTR

Low voltage to mass ratio is more specific

Siddiqi OK, Ruberg FL. *Circulation*. 2017;135:1357–1377

ECG Findings

- Pseudo-infarct pattern
- Conduction disease – first degree AV block, interventricular block, fascicular block
- Atrial fibrillation, atrial flutter
- Poor heart rate variability – chronotropic incompetence



Siddiqi OK, Ruberg FL. *Circulation*. 2017;135:1357–1377

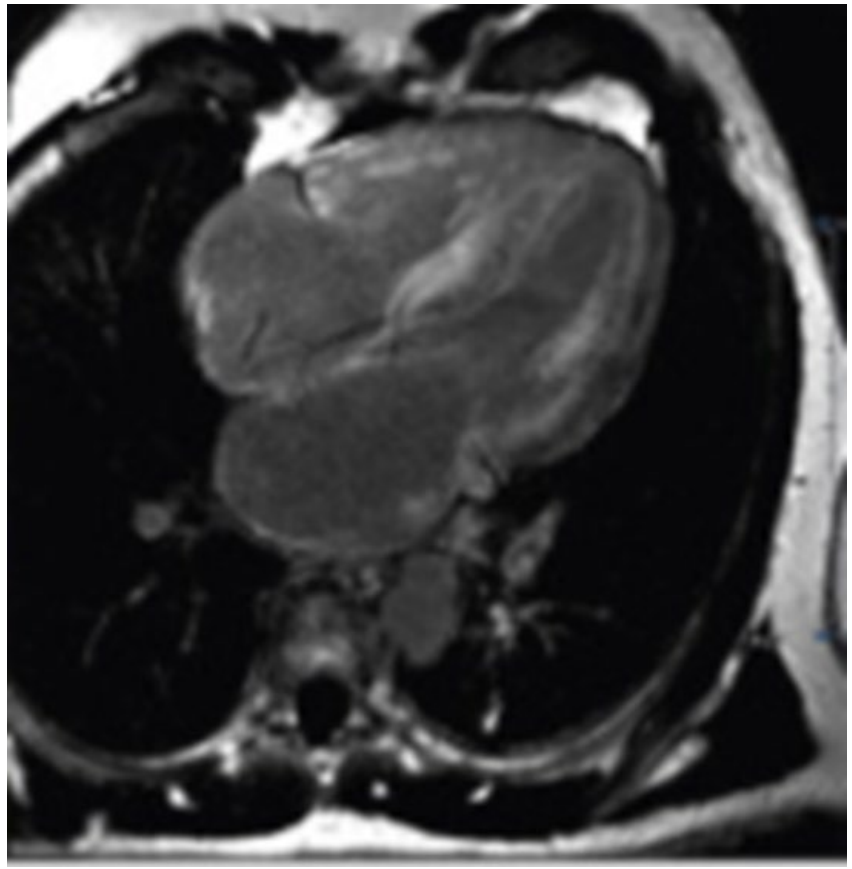
MRI

LGE

- Interstitial expansion from amyloid deposit avidly pick up and retain gadolinium

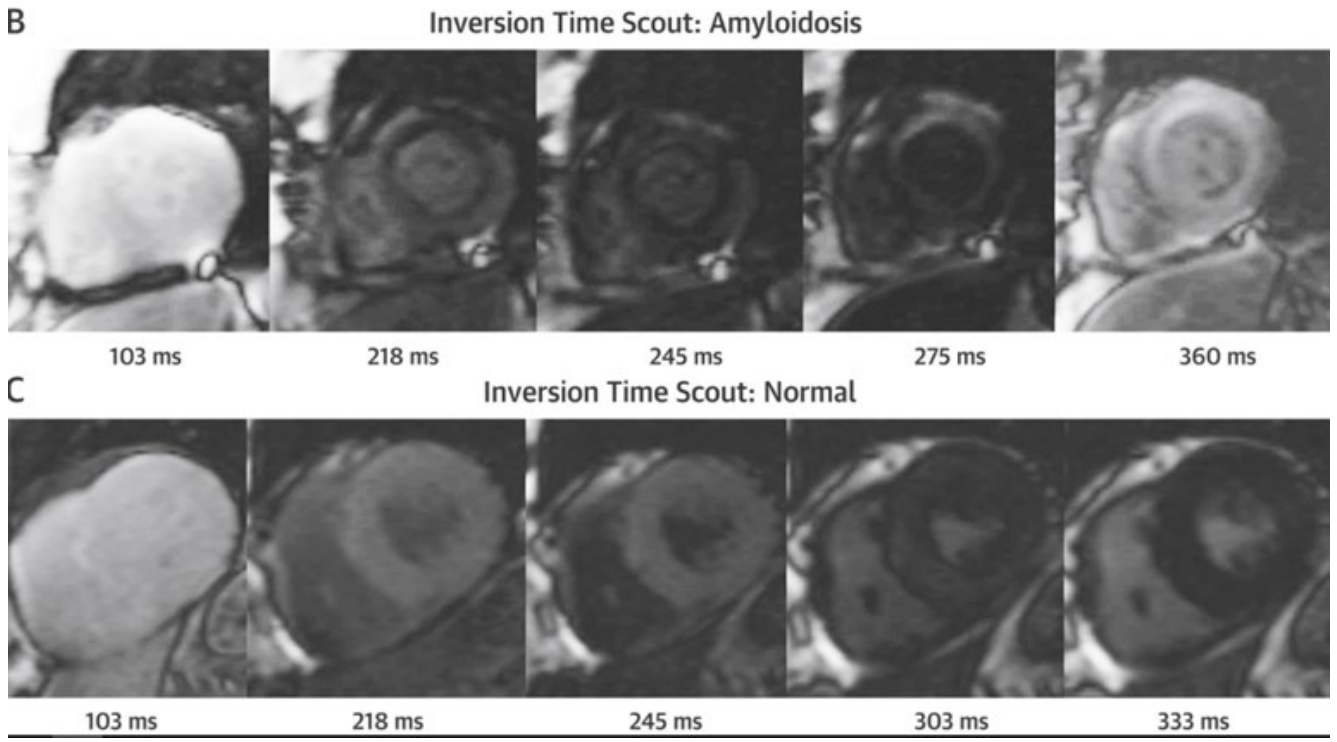
- Global transmural or diffuse subendocardial LGE can detect disease before increased LV wall thickness occurs

- LGE has sensitivity of 88% & specificity of 95%



Maceira AM, et al. *Circulation*. 2005;111:186–193

MRI



Operator determined null point - the inversion recovery time at which the normal myocardium appears black or "nulled"

"Difficulty nulling the myocardium" - Sensitivity 100%

Maceira AM, et al. *Circulation*. 2005;111:186–193.

MRI

- Quantitative T1 mapping - measure of fibrosis: Markedly increased – 92% sensitivity and 91% specificity
- Increased extracellular volume fraction (ECV) measurement – usually markedly elevated
- ECV <30% excludes, ≥40% confirms cardiac involvement, 30% to 39% indicates early infiltration

Sheik A, et al. JACC 2026;87(5):505-518

Diagnostic Workflow

First Rule out AL

- Serum kappa/lambda free light chain quant with ratio (abnormal if ratio <0.26 or > 1.65)
- SPEP with immunofixation (abnormal if monoclonal protein is detected)
- UPEP with immunofixation (abnormal if monoclonal protein is detected)

*** 24 Hour Urine NOT random sample***

Why Immunofixation?

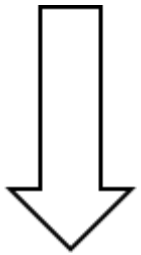
- SPEP and UPEP tell us **how much** monoclonal protein
- Immunofixation tells us the **type** of monoclonal protein – Monospecific anti sera against IgA, M, G, Kappa and Lambda
- ***Must do immunofixation as a monoclonal protein may be missed on protein electrophoresis***

What if AL lab screen is abnormal?

- **Differential:**
  - MGUS – diagnosis of exclusion
  - Multiple Myeloma
  - Light Chain Amyloidosis

MGUS - prevalence increases with age

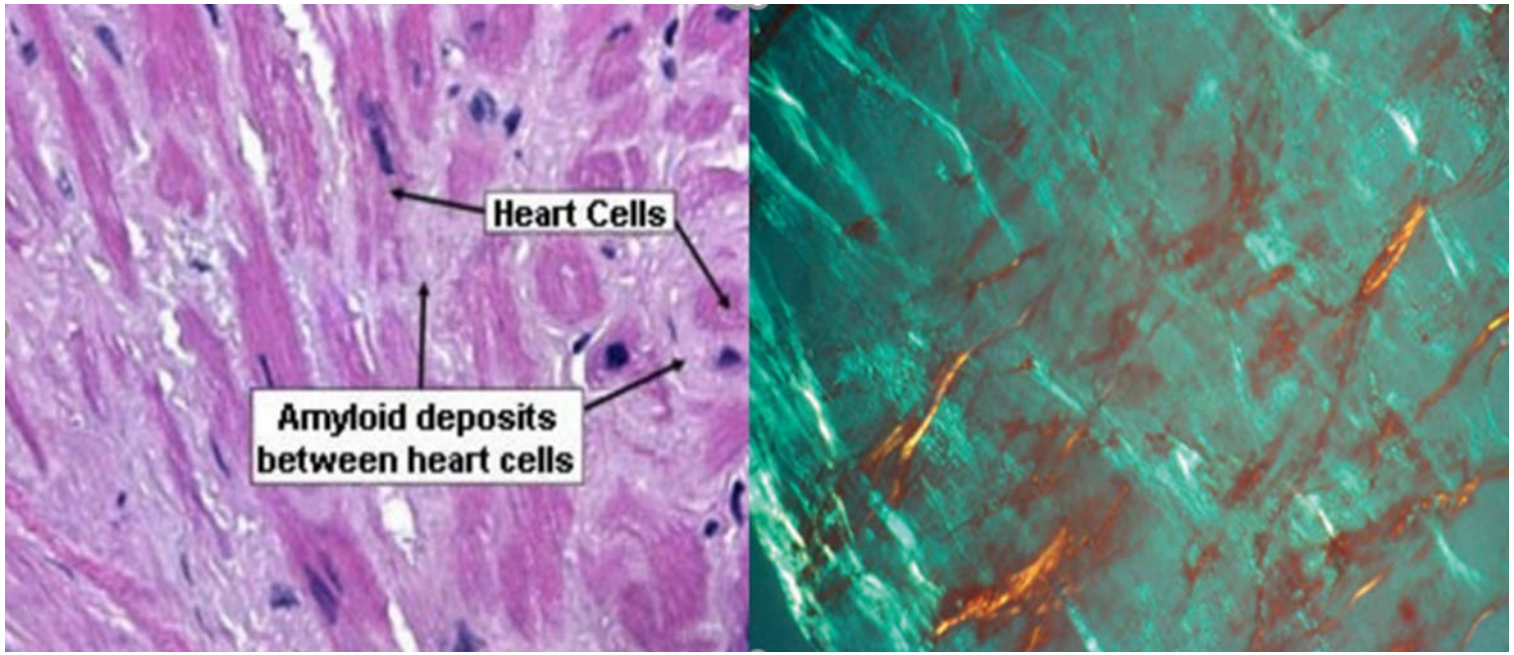
Estimated **20-40%** of patients with **ATTR** amyloidosis also have a monoclonal gammopathy!



Biopsy & Refer to Heme/Onc

Biopsy

- **Congo Red** staining identifies amyloid fibrils
- **Mass spectrometry** identifies protein – light chain vs TTR; TTR gene sequencing if present



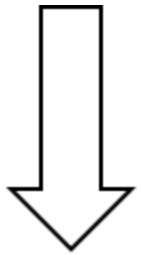
Siddiqi OK, Ruberg FL. *Circulation*. 2017;135:1357–1377

Utility of Fat Pad Aspirate

- Congo red only, no protein ID
- If negative, you are not done! Only helpful when positive
- Fat pad aspirate sensitivity in 15-45% in TTR and 84% AL

99mTc Radionuclide Scintigraphy

If all 3 AL screening tests are normal

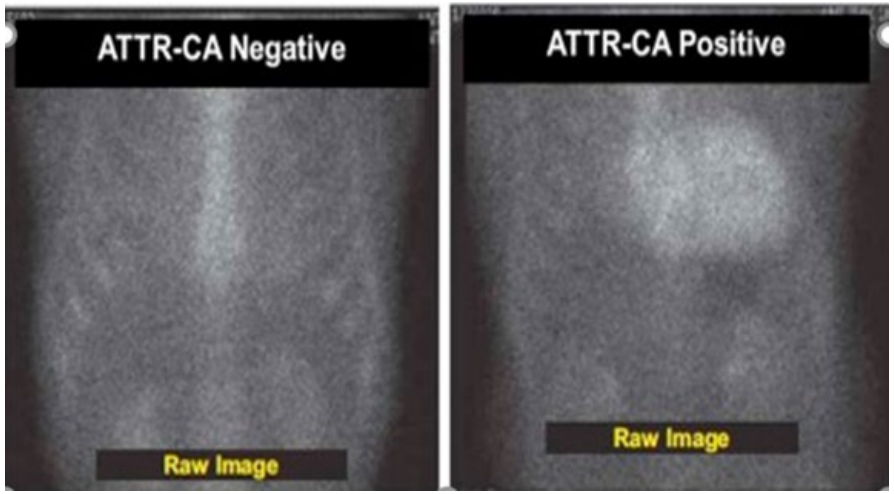


Radionuclide Scintigraphy

PPV 100% for ATTR with grade 2 or 3 myocardial uptake
AND absence of monoclonal protein in serum and urine

Tc-99m Radionuclide Scintigraphy

- Bone avid radiotracers (Tc-99m PYP/DPD/HMDP) have changed clinical practice
- Able to diagnose ATTR without endomyocardial biopsy
- High sensitivity for detecting TTR even in subclinical or early phase of disease
- 10% of AL patients may have uptake



Visual Score Grade ≥ 2

Grade 0: no myocardial uptake
Grade 1: Myocardial uptake less than rib uptake
Grade 2: Myocardial uptake equal to rib uptake
Grade 3: Myocardial uptake greater than rib uptake

Bokhari S, et al. *Circ Cardiovasc Imaging*. 2013;6:195–201. Figure 1 (p. 197)

ATTR-CM Treatment

- Management of heart failure symptoms
  - Interventions to improve symptoms and functional status

- Treatment of underlying pathology with disease modifying therapies
  - Current therapies slow progression of disease
  - Emerging therapies exploring reversal of cardiomyopathy

Management of HF Symptoms

- **Diuresis mainstay of therapy:** careful titration, over-diuresis can cause low blood pressure
  - **Loop diuretics (furosemide, torsemide, bumetanide) -** torsemide or bumetanide preferred due to better absorption/bioavailability in cases of bowel edema
  - **Spironolactone:** Potassium-sparing effect. Subgroup analysis of the TOPCAT trial showed patients with echocardiographic features of cardiac amyloidosis benefited from spironolactone, showing reduced adverse clinical outcomes
  - Sequential nephron blockade with thiazide diuretics (metolazone) if needed

Sperry, et al. *JACC. Heart failure* vol. 9,11 (2021): 795-802

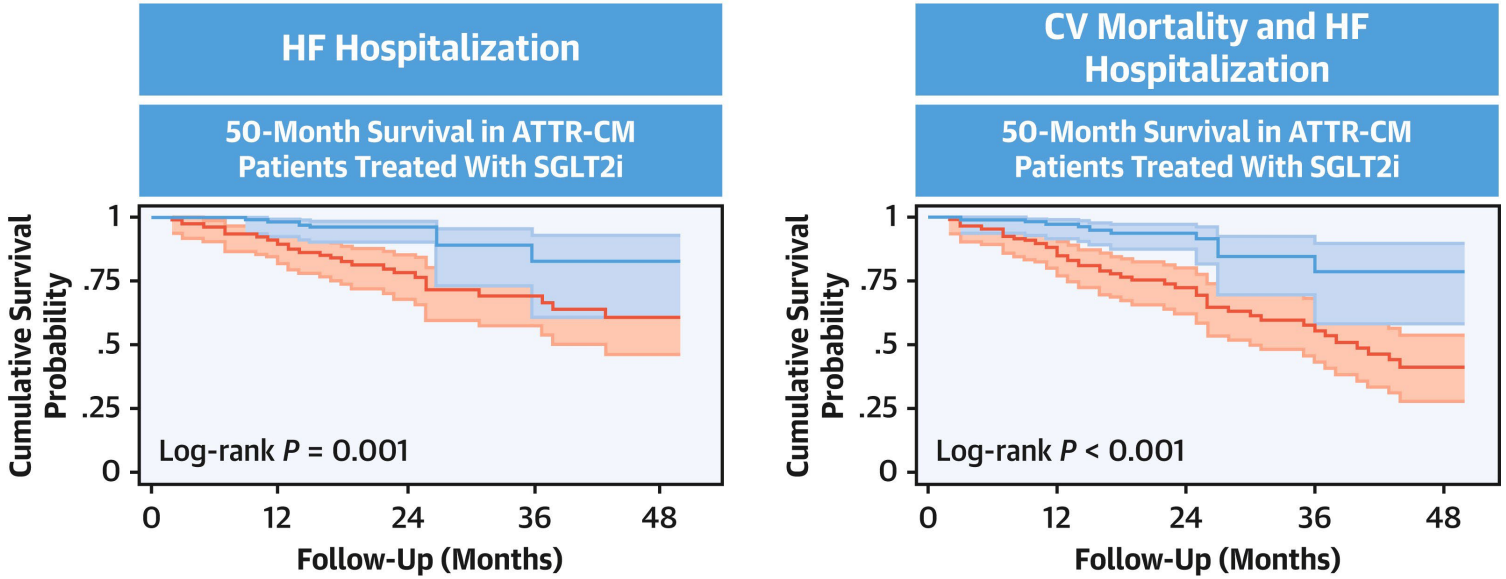
Management of HF Symptoms

- Beta blockers: with caution as can worsen symptoms
- ACE-I, ARB, ARNI, nitrates: may be poorly tolerated
  - Post Hoc analysis of PARADIGM-HF (Entresto versus ACE-I) showed benefit in patients who may have had amyloidosis
- Digoxin and non-dihydropyridine CCB binds amyloid fibrils: concern for toxicity

McMurray JJV. et. Al. NEJM. 2014;371(11):993-1004.

Management of HF Symptoms

- SGLT2i (dapagliflozin, empagliflozin): Helps to relieve congestion, more studies needed to determine additional benefits
  - Treatment with SGLT2i was associated with a reduced risk of all-cause mortality, HF hospitalization, and CV mortality These findings were consistent across TTR genotype



Porcari A, Cappelli F, Nitsche C, et al. JACC. 2024;83(24):2411–2422

Arrhythmia & Conduction Disease

- Rhythm management for atrial fibrillation and atrial flutter may improve symptoms

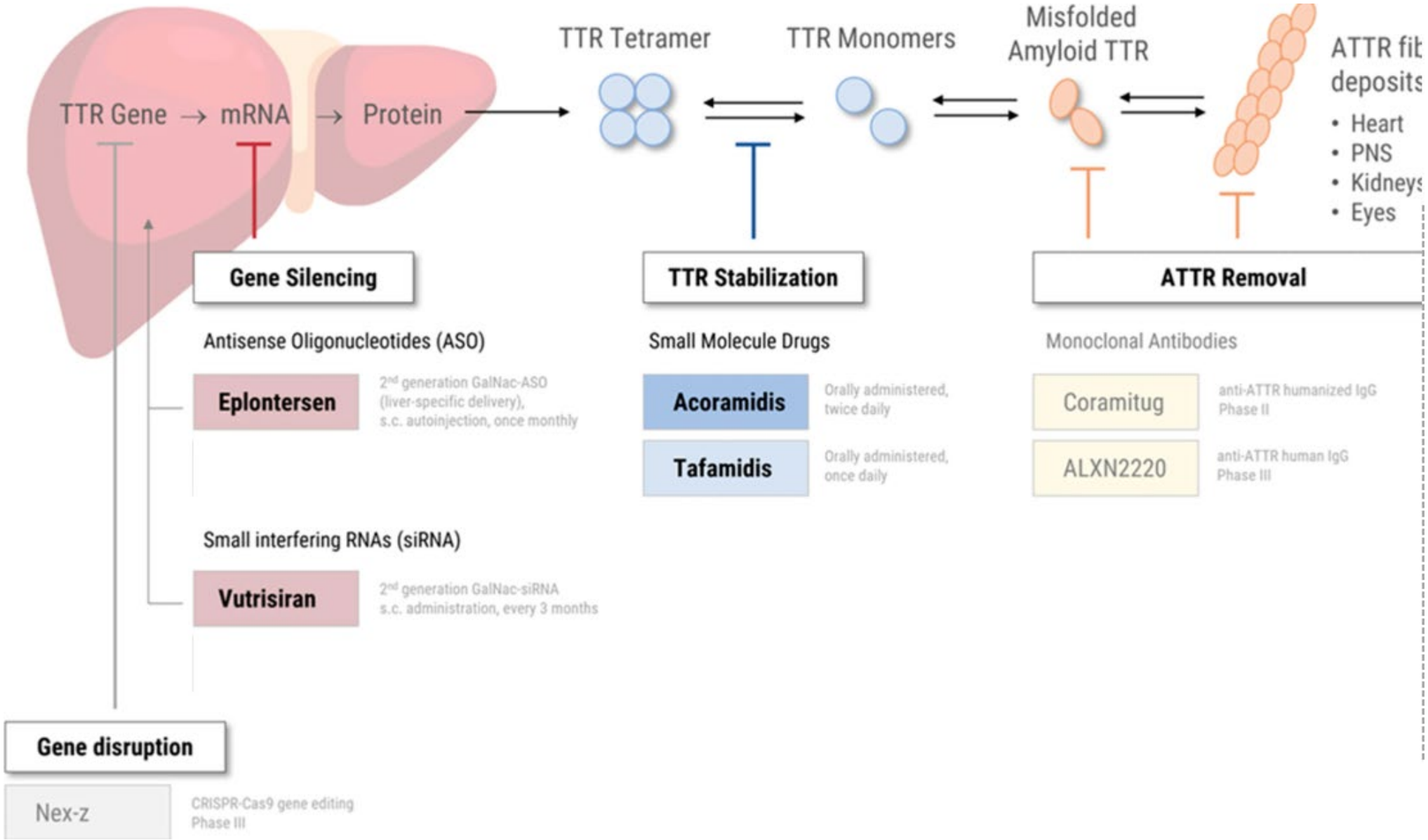
  - Ablation: associated with reduced mortality in ATTR CA and is most effective when performed earlier during the disease process, preferred management
  - Cardioversion (TEE to rule out thrombus)
  - Antiarrhythmic drug (AAD) therapy: amiodarone and dofetilide
  - AV nodal ablation with pacing may be needed for refractory cases

Always anticoagulate for atrial fibrillation/flutter

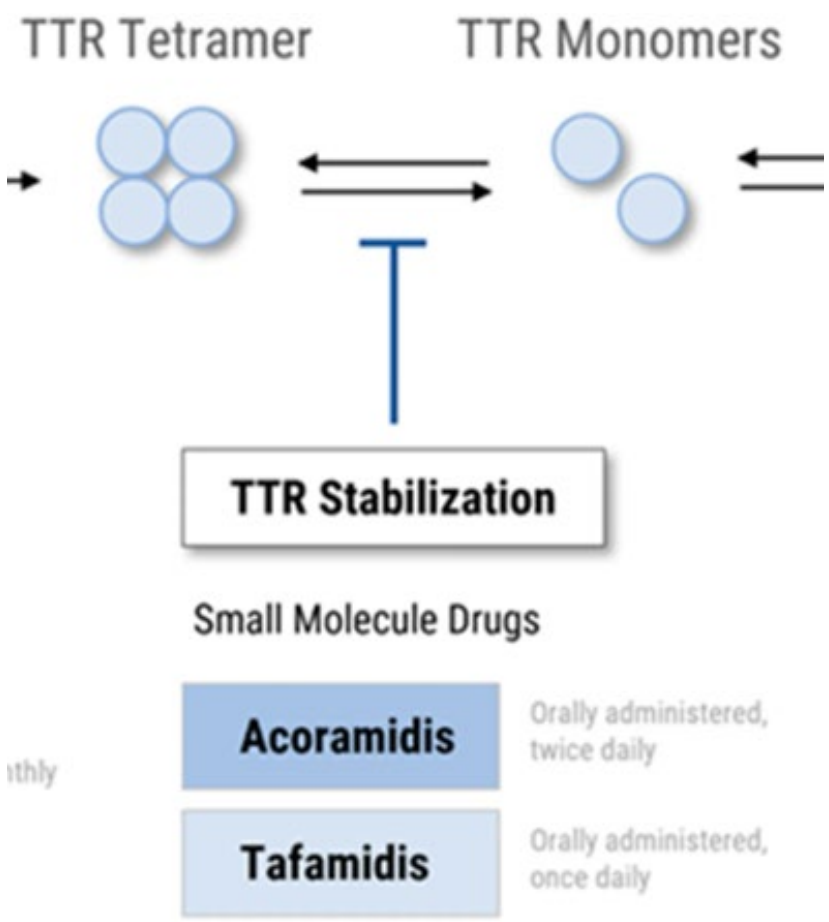
Arrhythmia & Conduction Disease

- Pacemaker (cardiac resynchronization therapy/CRT-P) for conduction disease
- Implantable Cardioverter-Defibrillators (ICDs)
  - Aborted sudden cardiac death with >1yr expected survival
  - Significant ventricular arrhythmias
  - Indication for primary prevention not well established
    - Can consider MRI to assess extent of fibrosis
    - Can consider EP study
    - Can consider implantable loop recorder for surveillance

TTR Directed Therapy



Margolin E, et al. J Clin Med. 2025;14(18):6202



TAFAMIDIS:

ATTR-ACT: FDA approved in 2019 for ATTR-CM

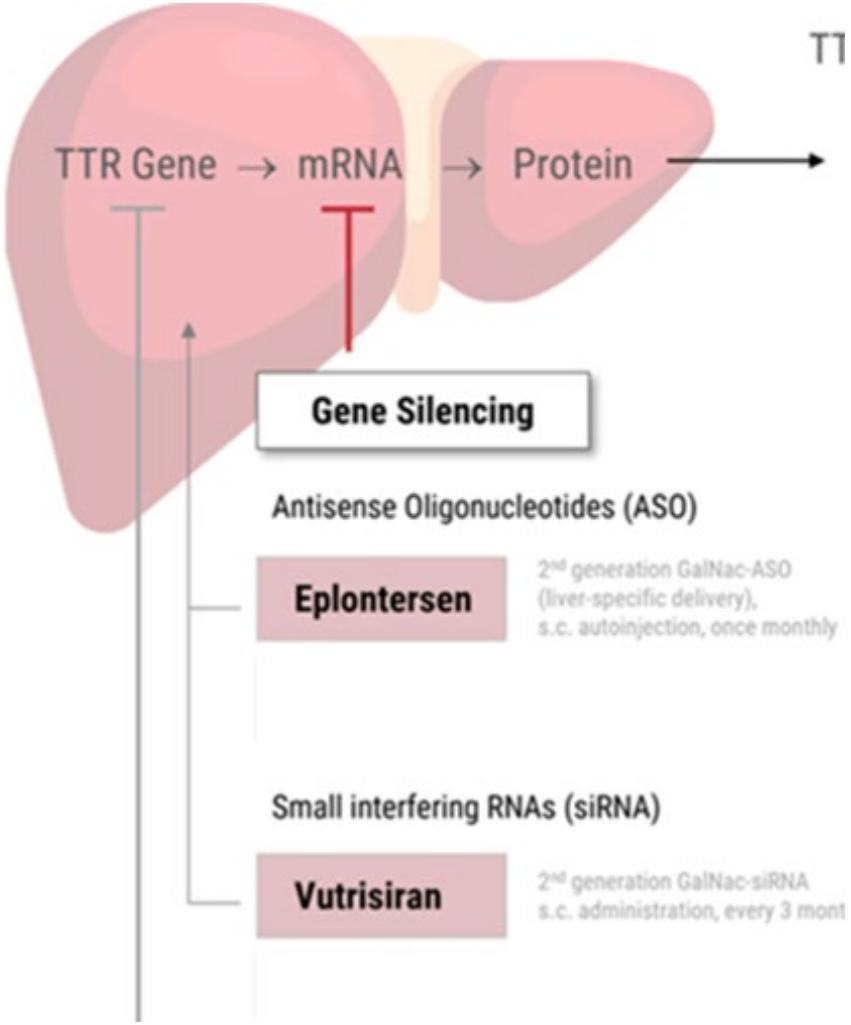
- 30% RRR in death and 32% RRR in CVH, slowed decline in 6MWD, and decline in KCCQ-OSS over time.
- Lower NYHA functional class had a greater degree of benefit.

ACORAMIDIS:

ATTRibute-CM: FDA approved 2024 for ATTR-CM

- Confers nearly complete stabilization
- Superior to placebo for primary outcome of death, CVH, change from baseline NT-proBNP, and change from baseline in 6MWD
- OLE after 42 months, showed a 36% RRR in mortality
- Reduction of CVH appears as early as 3 months after initiation
- Within 28 days, significant early rise in TTR is sustained, higher early ΔTTR significantly associated with improved all cause mortality

Margolin E, et al. J Clin Med. 2025;14(18):6202
Maurer MS, et. al. NEJM. 2018;379(11):1007-1016.
Gillmore JD, et. al. NEJM. 2024;390(2):132-142.



VUTRISIRAN:

- **Helios-A: FDA approved for ATTRv polyneuropathy in 2022**
- **Helios-B: FDA approved for ATTR-CM in 2025**
  - 40% on tafamidis at baseline, 60% monotherapy group and 20% initiated tafamidis after randomization at a median of ~17 months.
  - Serum TTR reduction was 81% at 36 months.
  - 28% RRR in all-cause mortality and recurrent cardiovascular (CV) events for the overall population
  - 33% RRR in the monotherapy population compared with placebo
  - Preserved functional capacity and quality of life and slowed the progression of HF
  - Not powered to compare vutrisiran monotherapy and combination therapy with tafamidis

Margolin E, et. al. J Clin Med. 2025;14(18):6202
Fontana M, et. al. NEJM. 2024;392(1).

ATTR-CM Treatment Choice

- No comparative evidence available to ascertain superiority between stabilizers and silencers
- In ATTRv polyneuropathy, silencers recommended as first line as more data with effects on neurologic progression
- Consider cost, payor preference, and individual patient preference
- No evidence supporting combination therapy

ATTR-CM: The Path Forward

- **Gene Silencing**: Decrease dosing frequency, achieve higher TTR knockdown
- **Gene Editing:** Permanent TTR knockdown – who needs TTR anyway!
- **Fibril Depleters**: Can we reverse cardiomyopathy?
- **Prevention:** Stop disease onset
- **Enhance** detection, progression, and response to therapy

Cardio-TTRansform Trial (N ≈ 1,400)

TRIAL DESIGN

- Phase 3 randomized double-blind
- ATTR-CM (wt &variant)
- **EPLONTERSEN** vs placebo
- SC q4 weeks; tafamidis allowed

PRIMARY ENDPOINT

- All-cause mortality
- Recurrent CV hospitalizations

SECONDARY ENDPOINTS

- NT-proBNP, 6MWT, KCCQ
- Troponin / biomarkers
- Functional status

140-WEEK TREATMENT PERIOD

INCLUSION

- NYHA I–III
- NT-proBNP ≥600
- 6MWT ≥150 m
- IVS ≥12 mm

EXCLUSION

- NYHA IV
- Severe renal impairment

Closed, Awaiting Results - Soon!

CARDIO-TTRansform (ION-682884-CS2; NCT04136171). *A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Eplontersen (ION-682884) in Patients With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM).* ClinicalTrials.gov; Ionis Pharmaceuticals.

TRITON-CM Trial: Nucresiran in ATTR-CM (N≈1,250)

TRIAL DESIGN

- Phase 3, global, randomized, double-blind,
- ATTR-CM: wild-type or variant
- 2:1 randomization:
  NUCRESIRAN 300 mg SC q6M vs placebo SC
- Open-label extension: nucresiran up to 24 months
- Background TTR stabilizer permitted

PRIMARY ENDPOINT

- Composite of all-cause mortality and recurrent CV events

MINIMUM 24-MONTH DOUBLE-BLIND PERIOD

INCLUSION

- Adults 18–85 years
- NYHA class I–III
- IVS thickness >12 mm *(male)* or >11 mm *(female)*
- NT-proBNP >300 and <8500 ng/L – AF: >600 and <8500 ng/L
- HF history: prior HF hospitalization or diuretic-treated HF

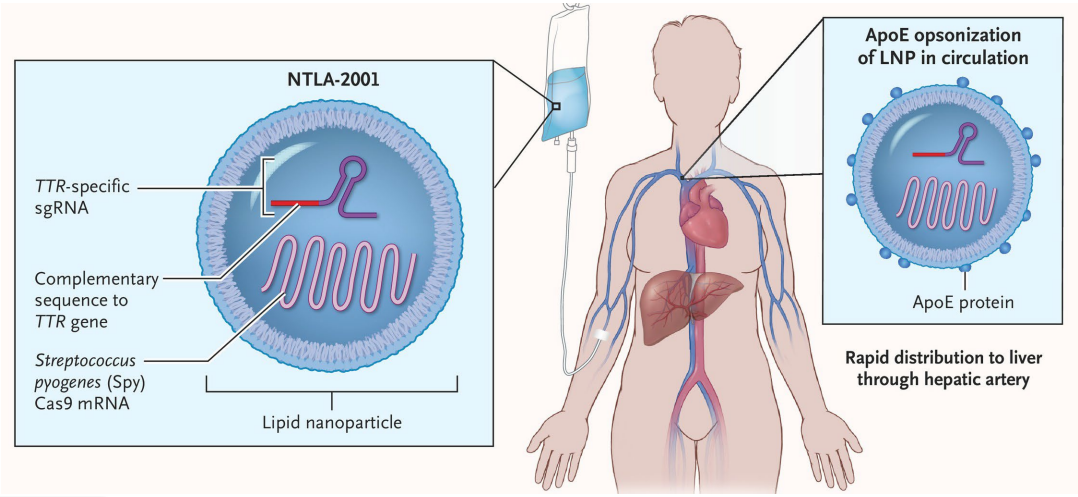
EXCLUSION

- NYHA class IV HF
- NYHA class III HF + ATTR Amyloidosis Disease Stage 3
- PND score ≥IIIa
- eGFR <30 mL/min/1.73 m^2

Actively Enrolling

TRITON-CM (ALN-TTRSC04-003; NCT07052903). *A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Nucresiran in Patients With Transthyretin-Mediated Amyloidosis With Cardiomyopathy (ATTR-CM).* ClinicalTrials.gov; Alnylam Pharmaceuticals.

NTLA-2001 Mechanism of Action (CRISPR Gene Editing)



1. Delivery

IV LNP delivers Cas9 mRNA + sgRNA

Targets liver via ApoE

2. Cell Entry

LDL receptor uptake → endosome

LNP releases RNA cargo

3. Cas9 Production

mRNA → Cas9 protein

Combines with sgRNA

4. Targeting

Complex enters nucleus

Finds TTR gene (PAM site)

5. Gene Editing

Cas9 cuts TTR DNA

Activates repair

6. DNA Repair & Effect

DNA repair ligates cut ends

Indels disrupt TTR gene

↓ TTR production

Gillmore JD, Gane E, Taubel J, et al. N Engl J Med. 2021;385:493–502

NTLA-2001 (Nexiguran Ziclumeran or "Nex-Z") Phase 1

STUDY DESIGN

- First-in-human, open-label
- Dose-escalation study
- ATTRv-PN and ATTR-CM
- Single-dose IV infusion
- CRISPR/Cas9 gene editing

SAFETY

- Generally well tolerated
- Mild infusion reactions
- No dose-limiting toxicities

KEY FINDINGS

- ~85–90% TTR reduction
- Rapid and durable effect

PK/PD

- Supports one-time dosing
- Transient drug exposure

≈90% TTR REDUCTION WITH SINGLE DOSE

Fontana M, et al. N Engl J Med. 2024;391:2231-2241

MAGNITUDE Trial (Nex-Z/NTLA-2001) N≈1,200)

TRIAL DESIGN

- Phase 3, randomized, double-blind
- ATTR-CM (wild-type & variant)
- 2:1: NTLA-2001 vs placebo
- Single-dose IV infusion

PRIMARY ENDPOINT

- CV mortality + recurrent CV events

SECONDARY ENDPOINTS

- TTR
- KCCQ score

INCLUSION

- NYHA I–III
- IVS thickness ≥12 mm
- NT-proBNP ≥ 600pg/mL (≥2000 pg/mL if AF)
- HF requiring a diuretic AND HF hospitalization within 12 mo OR clinical evidence of HF
- 6MWT ≥100 m

EXCLUSION

- NYHA IV HF
- eGFR <30 mL/min/1.73 m^2
- Significant non-ATTR cardiomyopathy

Actively Enrolling

MAGNITUDE (ITL-2001-CL-301; NCT06128629). *A Phase 3, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NTLA-2001 (Nexiguran Ziclumeran) in Participants With Transthyretin Amyloidosis With Cardiomyopathy (ATTR-CM).* ClinicalTrials.gov; Intellia Therapeutics.

Antibody-Associated Reversal of ATTR-CM

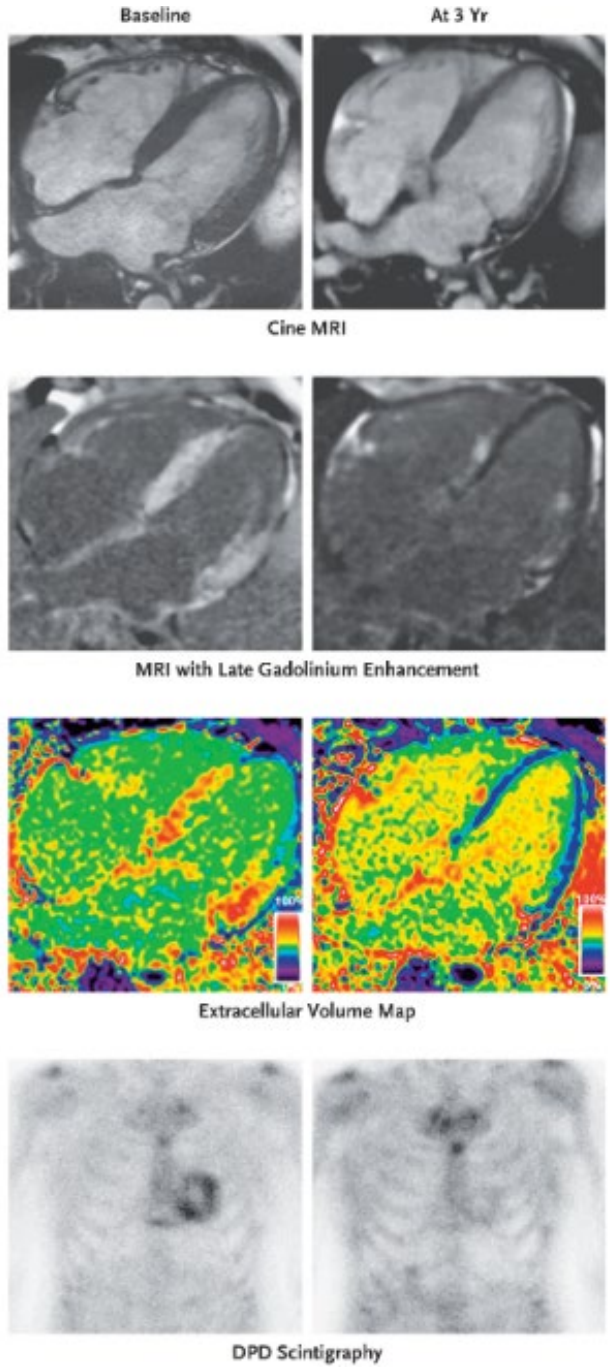
- Patients with endogenous anti-TTR antibodies
- No disease-modifying therapy

KEY FINDINGS

- Clinical improvement over time
- Reduction in cardiac amyloid burden
- Imaging evidence of regression

MECHANISM

- Antibodies bind amyloid fibrils
- Promote clearance of deposits



Reduction in myocardial amyloid burden over time

Fontana M, et al.. N Engl J Med. 2023;388:2199–2201

Monoclonal Antibody Amyloid Depleter

ALXN2220 – Mechanism

- Binds deposited ATTR amyloid fibrils
- No binding to circulating TTR
- Opsonization of amyloid deposits
- Macrophage-mediated phagocytosis
- Promotes fibril clearance

ALXN2220 – Clinical Data

PHASE 1 (first-in-human)

- No major safety signals
- Evidence of target engagement

PHASE 2

- Cardiac amyloid reduction on imaging (ECV ↓ reported)
- NT-proBNP: stabilization or ↓ trends
- Early signals of functional improvement (6MWT/KCCQ)

Michalon et al. *Nat Commun*. 2021;12:3142;
Garcia-Pavia et al. *N Engl J Med*. 2023;389:239–250.

ALXN2220 (DepleTTR-CM) Phase 3 Trial

TRIAL DESIGN

- Phase 3, randomized, double-blind
- ATTR-CM (wt & variant)
- ALXN2220 vs placebo
- IV infusion every 4 weeks
- Event-driven (24–48 months)

PRIMARY ENDPOINT

- All-cause mortality
- CV clinical events

SECONDARY ENDPOINTS

- NT-proBNP change
- 6-minute walk distance (6MWT)
- KCCQ score
- Imaging: ECV / amyloid burden

INCLUSION

- IVS ≥12 mm
- NT-proBNP >2000 pg/mL
- Loop diuretic ≥30 days
- NYHA II–IV
- Age 18–90

EXCLUSION

- LVEF <30%
- eGFR <20 or dialysis
- Uncontrolled arrhythmias
- Advanced neuropathy (PND IV)

Closed, Awaiting Results!

DepleTTR-CM (ALXN2220-ATTRCM-301; NCT06183931). *A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Amyloid Depleter ALXN2220 in Adult Participants With Transthyretin Amyloid Cardiomyopathy (ATTR-CM).* ClinicalTrials.gov. Sponsor: Alexion Pharmaceuticals, Inc.

Monoclonal Antibody Amyloid Depleter

PRX004 (Coramitug) Mechanism

- Selectively binds misfolded TTR
- No binding to native tetramer
- Targets soluble aggregates + fibrils
- Promotes immune-mediated clearance
- Reduces toxic species

PRX004 (Coramitug) – Clinical Data

PHASE 1

- Well tolerated across doses
- Stabilization of neuropathy scores (mNIS+7)
- Cardiac: NT-proBNP stabilization trends

PHASE 2

- Signals of disease stabilization
- Continued favorable safety profile

Suhr OB, et al. *Amyloid*. 2025;32(1):1–10

CLEOPATTRA Phase 3 Trial (PRX004/Coramitug)

TRIAL DESIGN

- Phase 3, randomized, double-blind
- ATTR-CM (wild-type & variant)
- Investigational therapy vs placebo
- Background standard of care allowed
- Event-driven outcomes study

PRIMARY ENDPOINT

- All-cause mortality
- Cardiovascular events / hospitalizations

SECONDARY ENDPOINTS

- NT-proBNP change
- 6-minute walk distance (6MWT)
- KCCQ score
- Imaging (ECV / amyloid burden)

INCLUSION

- IVS ≥12 mm
- NYHA Class I–IV
- Loop diuretic therapy
- ≥1 HF hospitalization
- History of clinical HF

EXCLUSION

- NYHA Class IV unstable HF
- Severe renal impairment
- Recent major CV events

Actively Enrolling

ClinicalTrials.gov. NCT07207811. *CLEOPATTRA: A Research Study to Look at the Effects of Treatment With Coramitug (NNC6019-0001) in People With Heart Failure Due to Transthyretin Amyloid (ATTR) Amyloidosis.* Sponsor: Novo Nordisk A/S.

ACT-EARLY Trial (Acoramidis): Primary Prevention in ATTRv

TRIAL DESIGN

- Phase 3, randomized, multicenter, double-blind
- Population: asymptomatic carriers of a pathogenic TTR variant
- ~582–600 participants; 1:1 randomization
- Acoramidis 712 mg orally BID vs placebo
- Event-driven prevention study; long follow-up

PRIMARY ENDPOINT

- Time to development of ATTR-CM and/or ATTR-PN

SECONDARY / EXPLORATORY ENDPOINTS

- Safety and tolerability
- Cardiac imaging parameters
- Plasma TTR concentration
- Nerve conduction and neurofilament light chain

INCLUSION

- Age ≥18 to ≤75 years
- Established pathogenic TTR variant genotype (heterozygous or homozygous; central lab confirmed)
- Asymptomatic / no ATTR-CM or ATTR-PN
- Age ≤10 years younger than predicted age of disease onset (PADO)

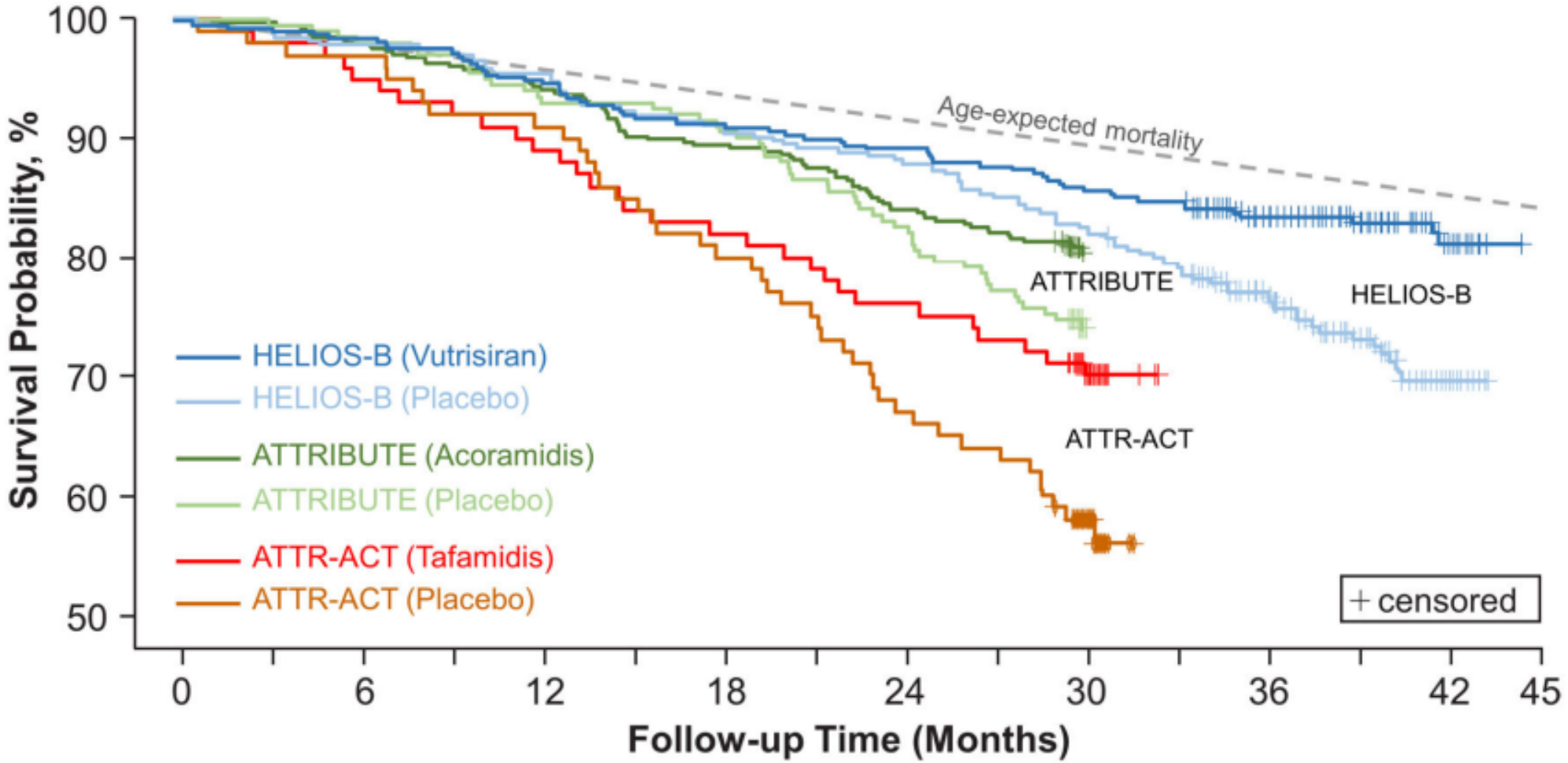
EXCLUSION

- Evidence of ATTR-CM or ATTR-PN
- Phenotypically protective TTR variant *(e.g., T119M, R104H)*
- Current or prior TTR-modifying therapy
- Major kidney, liver, heart, or neuropathy disorder

Actively Enrolling

ClinicalTrials.gov. NCT06563895. *Acoramidis Transthyretin Amyloidosis Prevention Trial in the Young (ACT-EARLY Study) in Asymptomatic Carriers of a Pathogenic TTR Variant (AG10-501).*
Sponsor: Eidos Therapeutics, BridgeBio

How Are ATTR-CM Patients Doing?



Girard AA, Sperry BW. Heart Fail Rev. 2025;30(1):69–73

Key Points

- **Look for it!!** Clinical History, Echo, ECG, and MRI
- **Treat Early for Best Outcomes!!**
- Ongoing development of novel therapeutics

The Multidisciplinary Care Model in Cardiac Amyloidosis

Yevgeniy Brailovsky, DO, MSc

Assistant Professor of Medicine

New York-Presbyterian/Columbia University Irving Medical Center

New York, NY

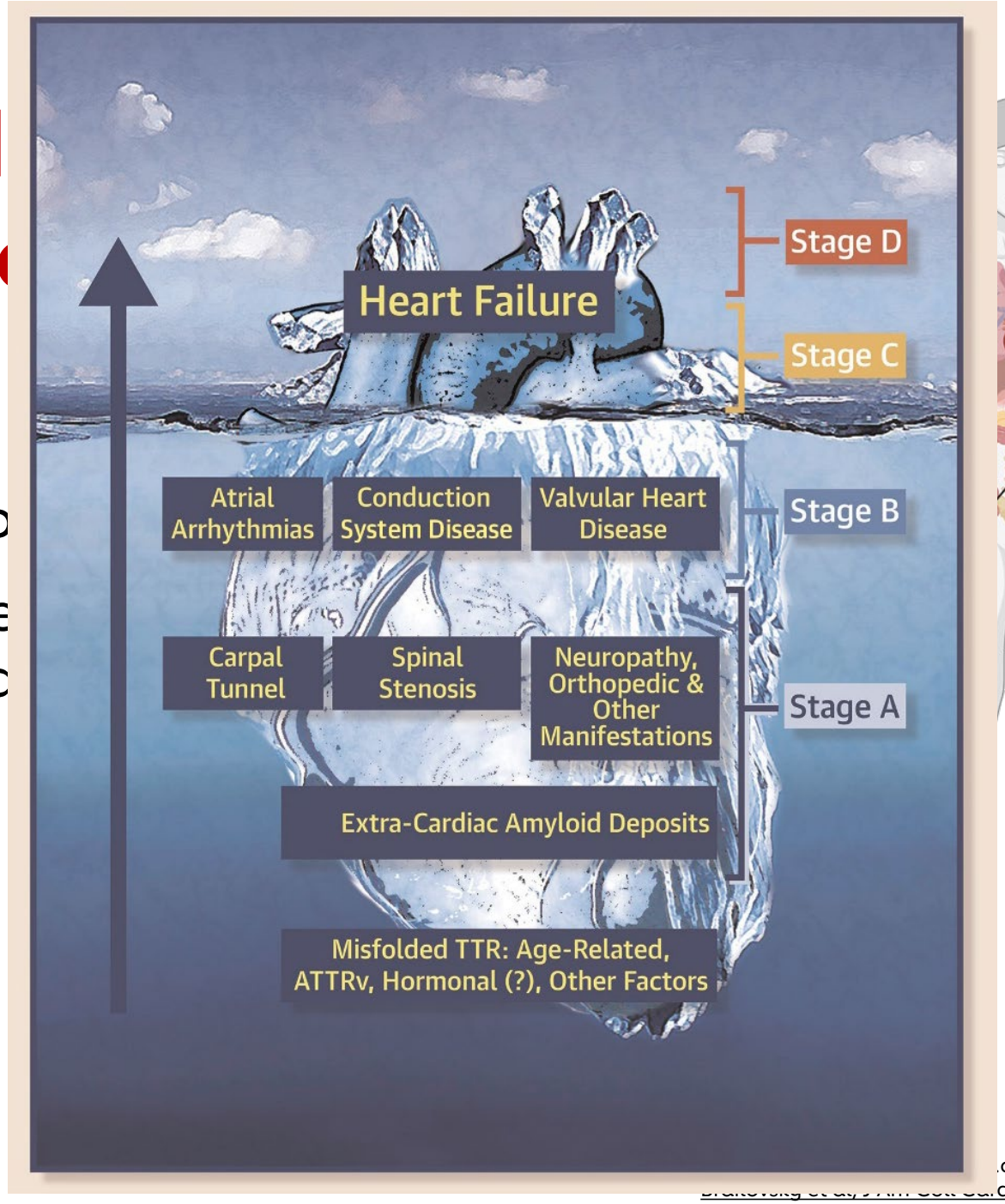
Evolving Field

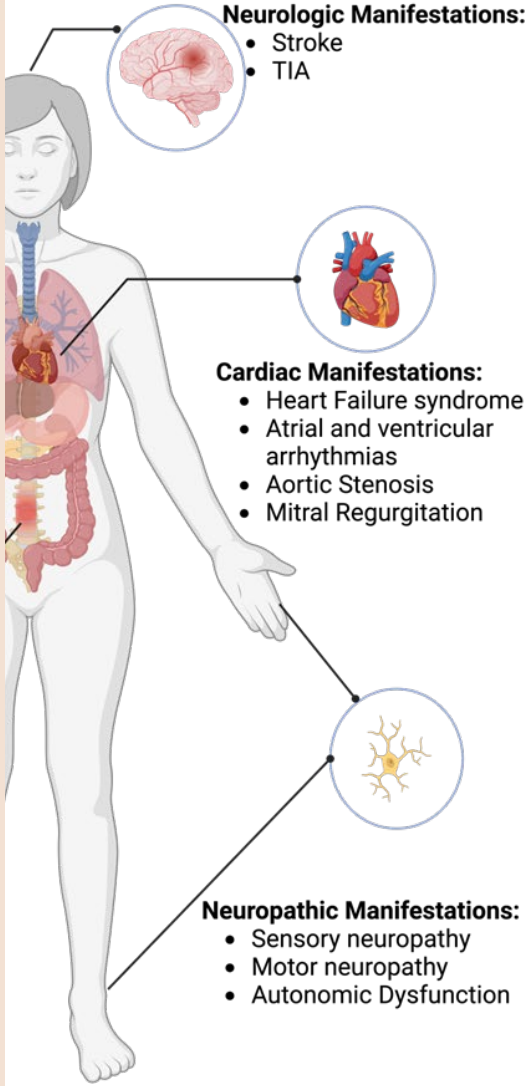
The field of amyloidosis is **rapidly evolving**, fueled by advancement in:

1. Disease awareness
2. Diagnostics
3. Disease targeted therapeutics

Systemic M
of Amyloid

- Systemic sympto
- Need a multi-spe
  for diagnosis anc





JACC CardioOncol . 2021 Oct 19;3(4):488-505.

.com
diol Case Rep. 2023 Mar, 10 101759

95% of Cardiac Amyloidosis is Caused by Two Types of Amyloidosis: *Transthyretin (ATTR) and Light chain (AL)*

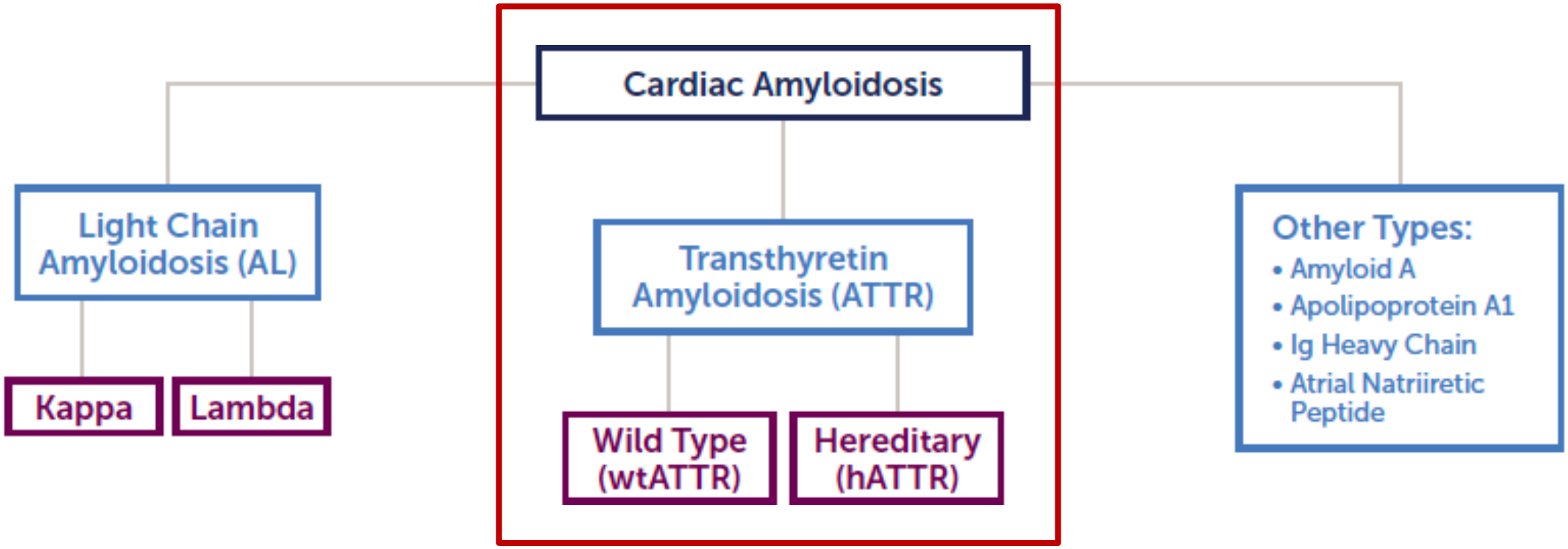


Figure created with Biorender.com @YevgeniyBr

Pathophysiology of Amyloidosis

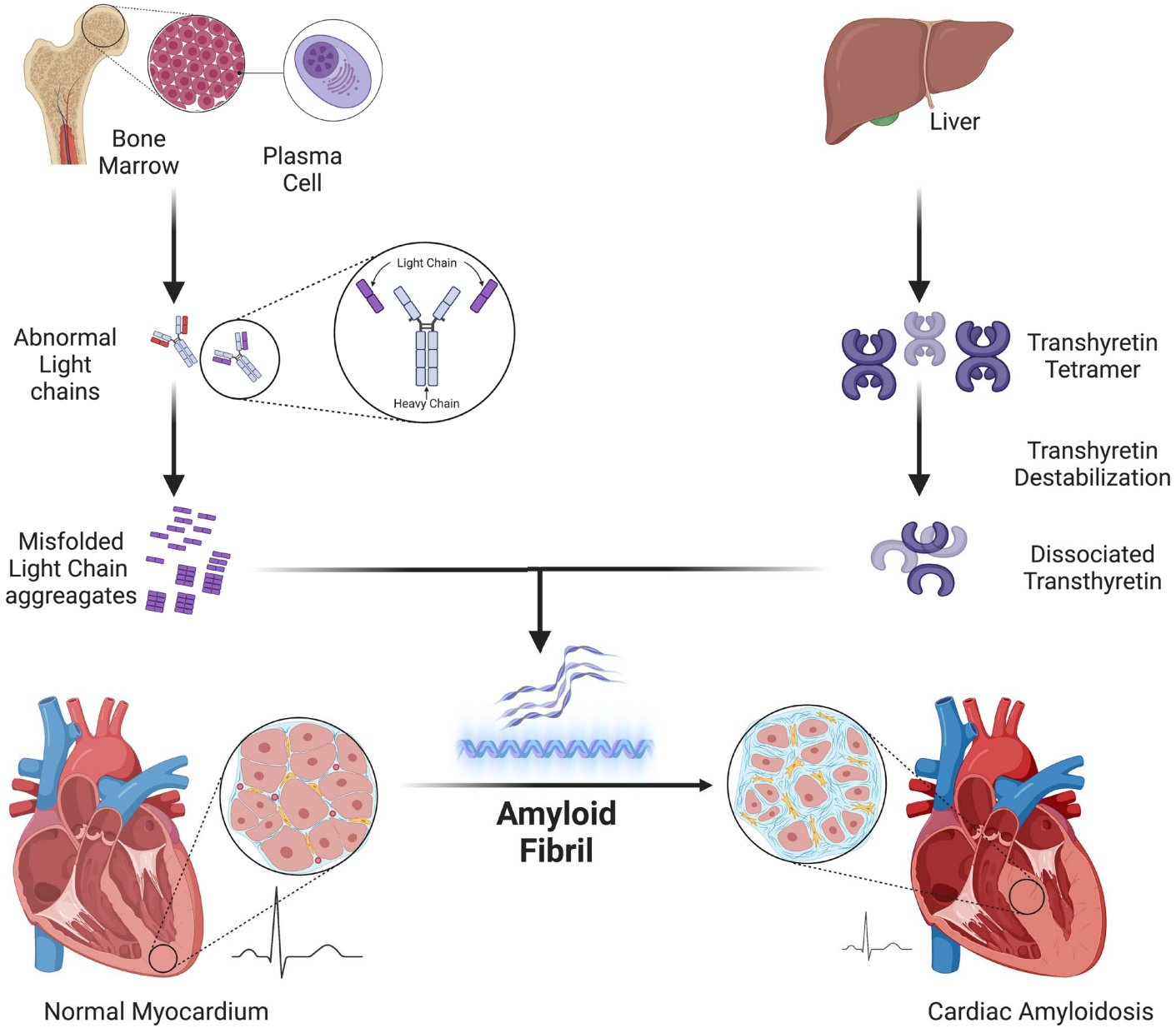
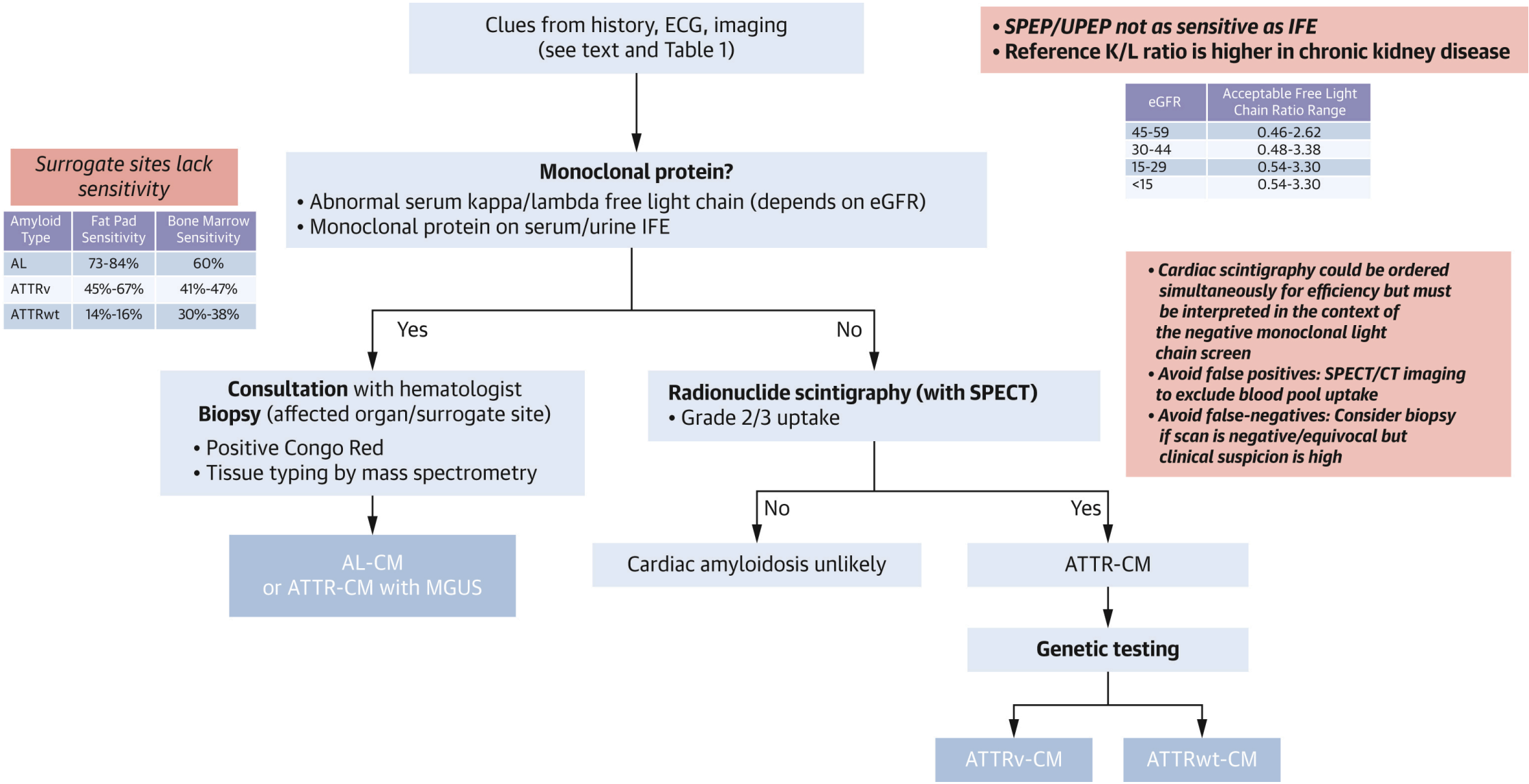


Figure created with Biorender.com
@YevgeniyBr

Nuance of Diagnostic Approach



Surrogate sites lack sensitivity

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

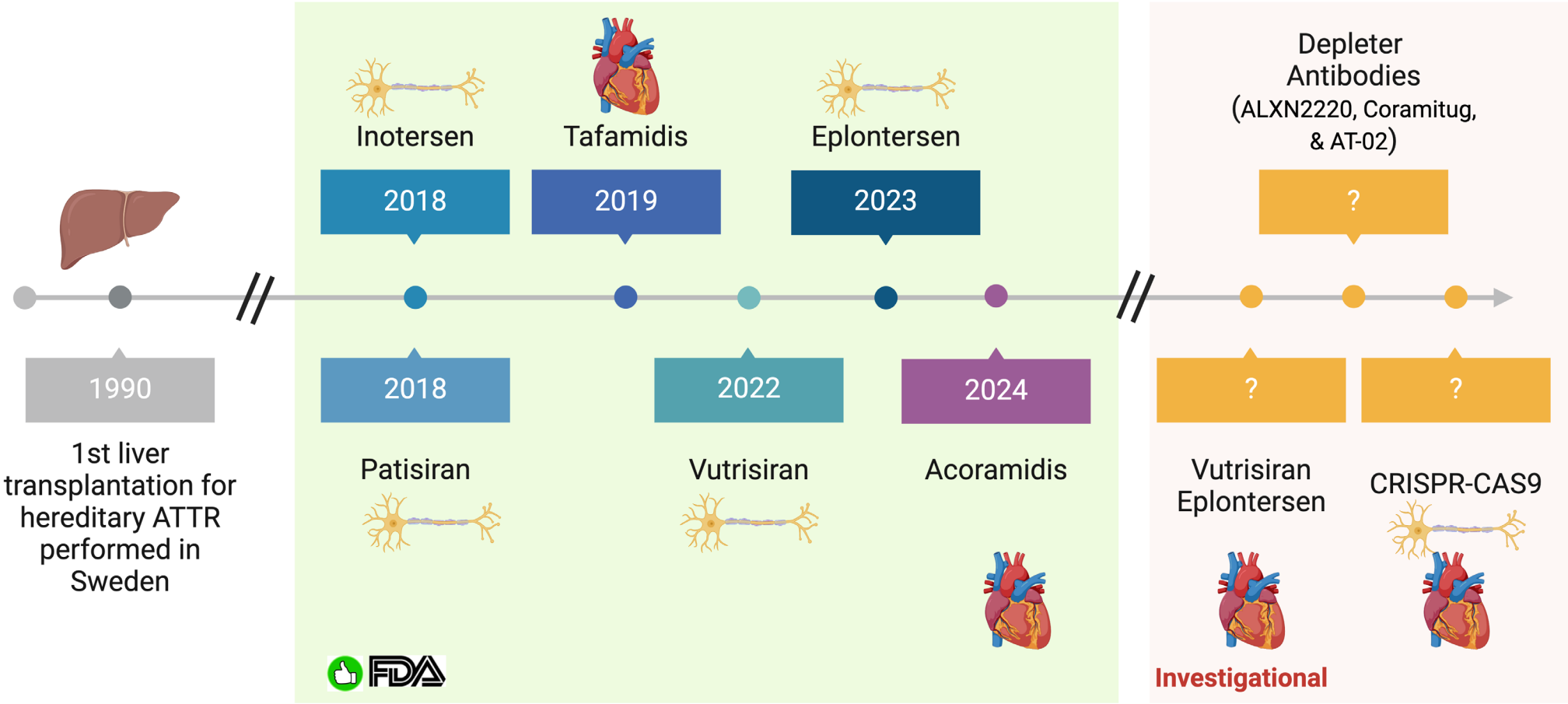
- ***SPEP/UPEP not as sensitive as IFE***
- **Reference K/L ratio is higher in chronic kidney disease**

eGFR	Acceptable Free Light Chain Ratio Range
45-59	0.46-2.62
30-44	0.48-3.38
15-29	0.54-3.30
<15	0.54-3.30

- ***Cardiac scintigraphy could be ordered simultaneously for efficiency but must be interpreted in the context of the negative monoclonal light chain screen***
- ***Avoid false positives: SPECT/CT imaging to exclude blood pool uptake***
- ***Avoid false-negatives: Consider biopsy if scan is negative/equivocal but clinical suspicion is high***

Kittleson et al, Am Coll Cardiol. 2025 Oct 31

Progress in Therapeutic Arena of ATTR-CM

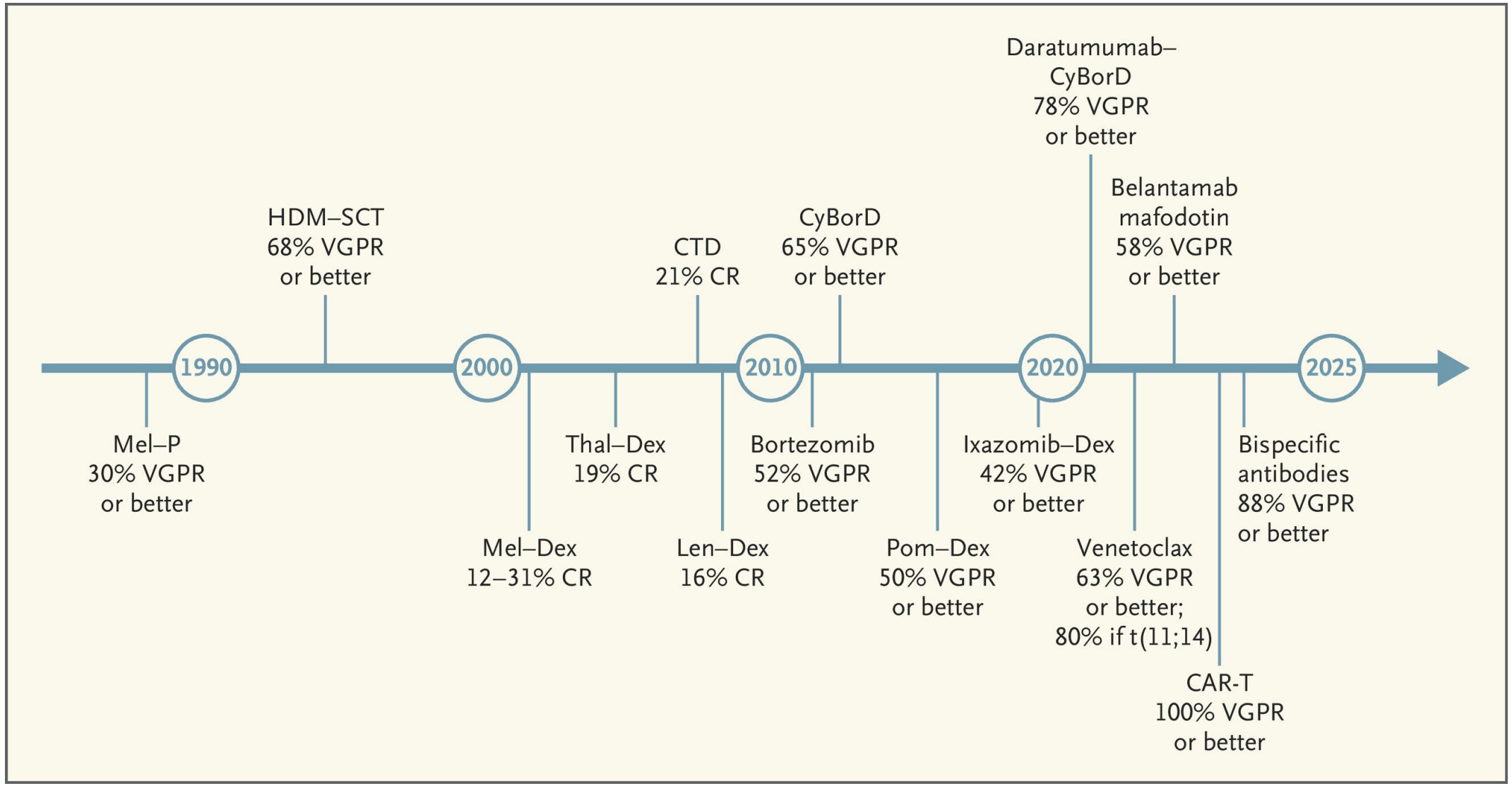


$$$*

*** Specialty Pharmacy is an invaluable resource**

Figure created with Biorender.com @YevgeniyBr

Progress in Therapeutic Arena of AL



N Engl J Med 2024;390:2295-2307

Amyloidosis is a Team Sport

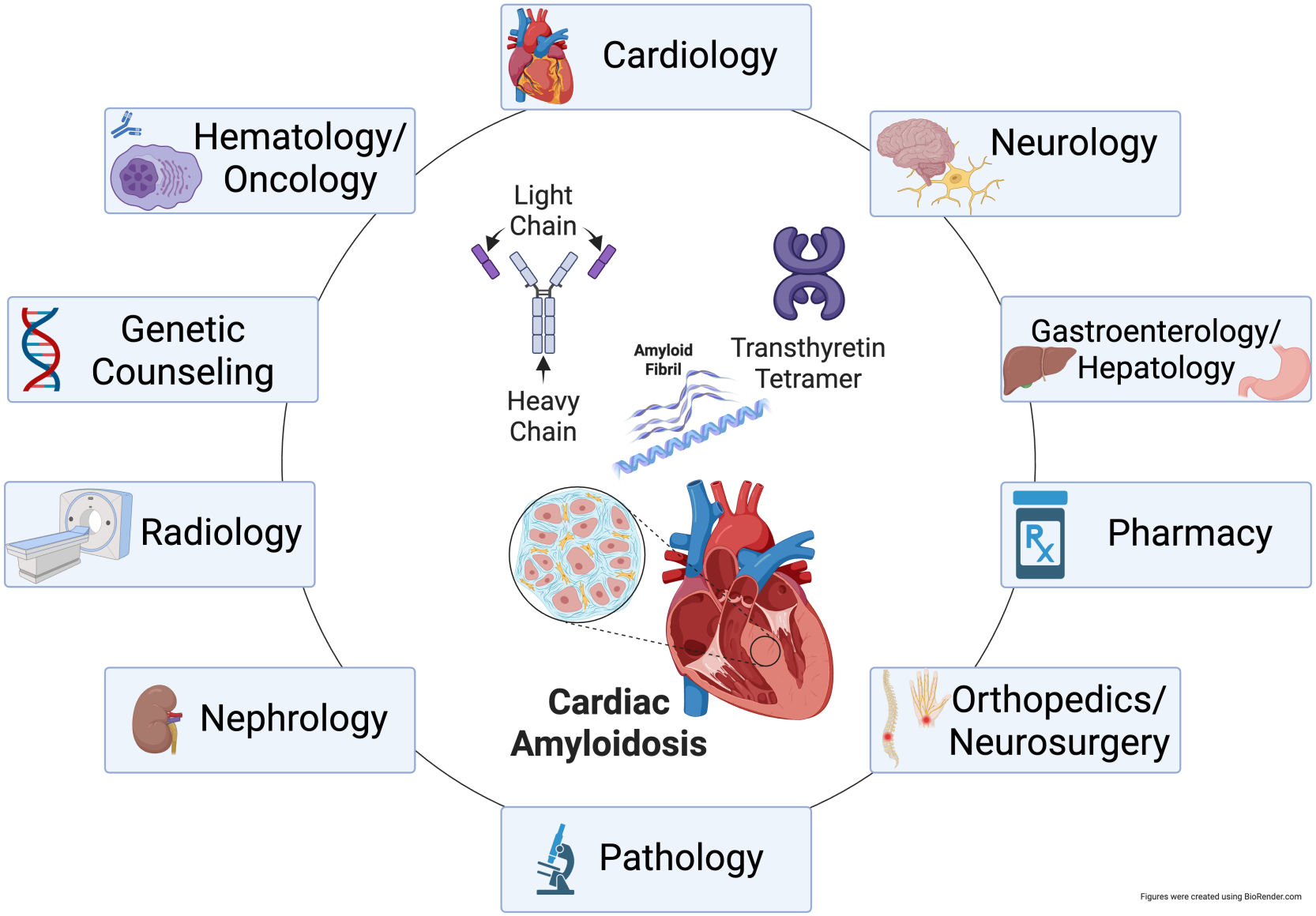


Figure created with Biorender.com

Brailovsky et al, J Am Coll Cardiol Case Rep. 2023 Mar, 10 101759

What is an Amyloidosis Center of Excellence?

Provide care for patients with suspected and confirmed diagnosis of Amyloidosis across the entire spectrum of disease

1. Deliver rapid, multidisciplinary approach to diagnosis
   - Labs, imaging, biopsy capabilities

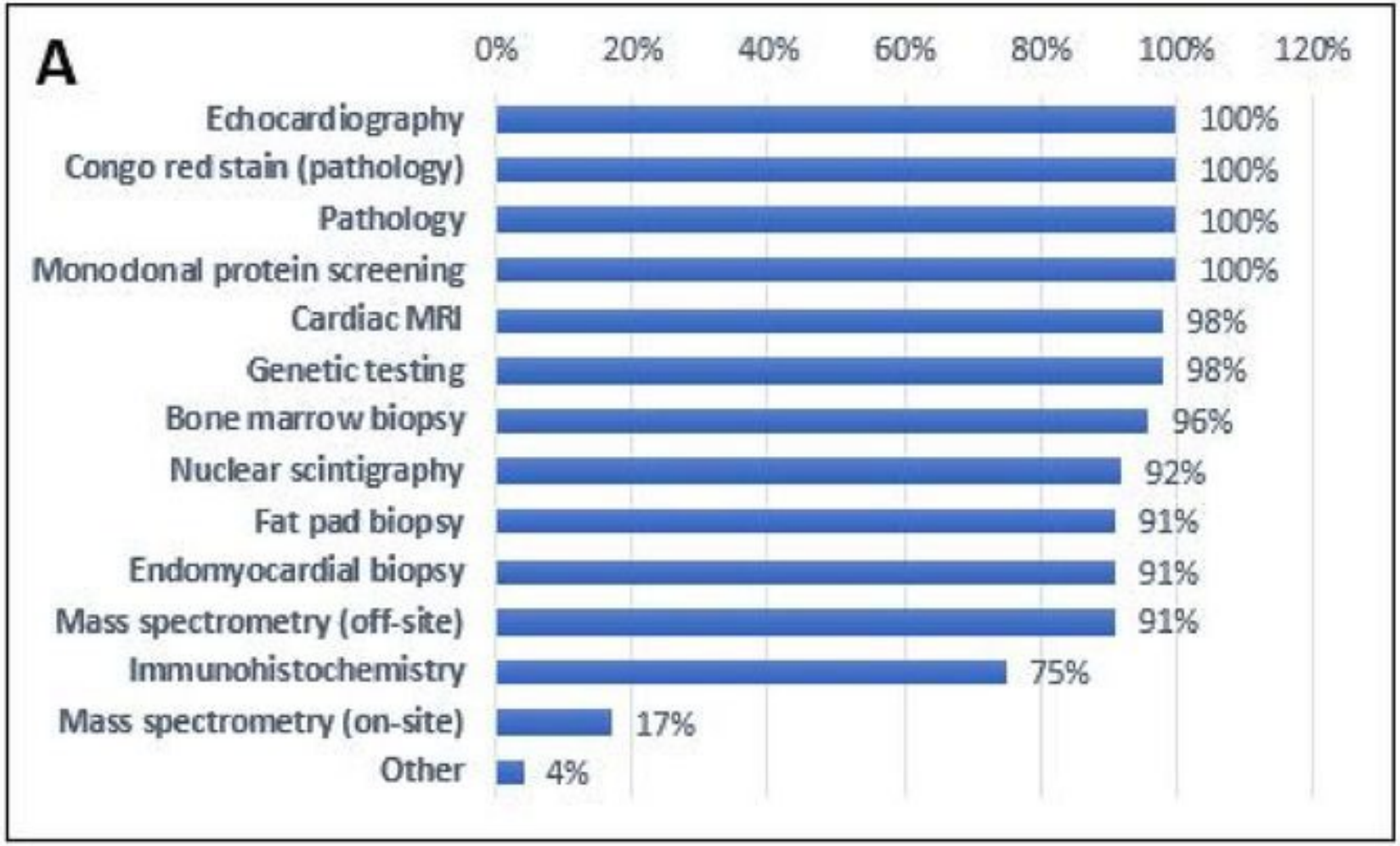
2. Initiate state-of-the art therapies (Specialty Pharmacy)
   1. **ATTR:** TTR stabilizers, RNA silencers
   2. **AL:** CyBorD-Dara, Autologous Stem Cell transplant, CAR-T, Bi-specifics,…
   3. Heart transplant in selected patients

3. Provide access to available clinical trials in this rapidly evolving field

4. Provide educational resources and access to support groups

5. Partner with community

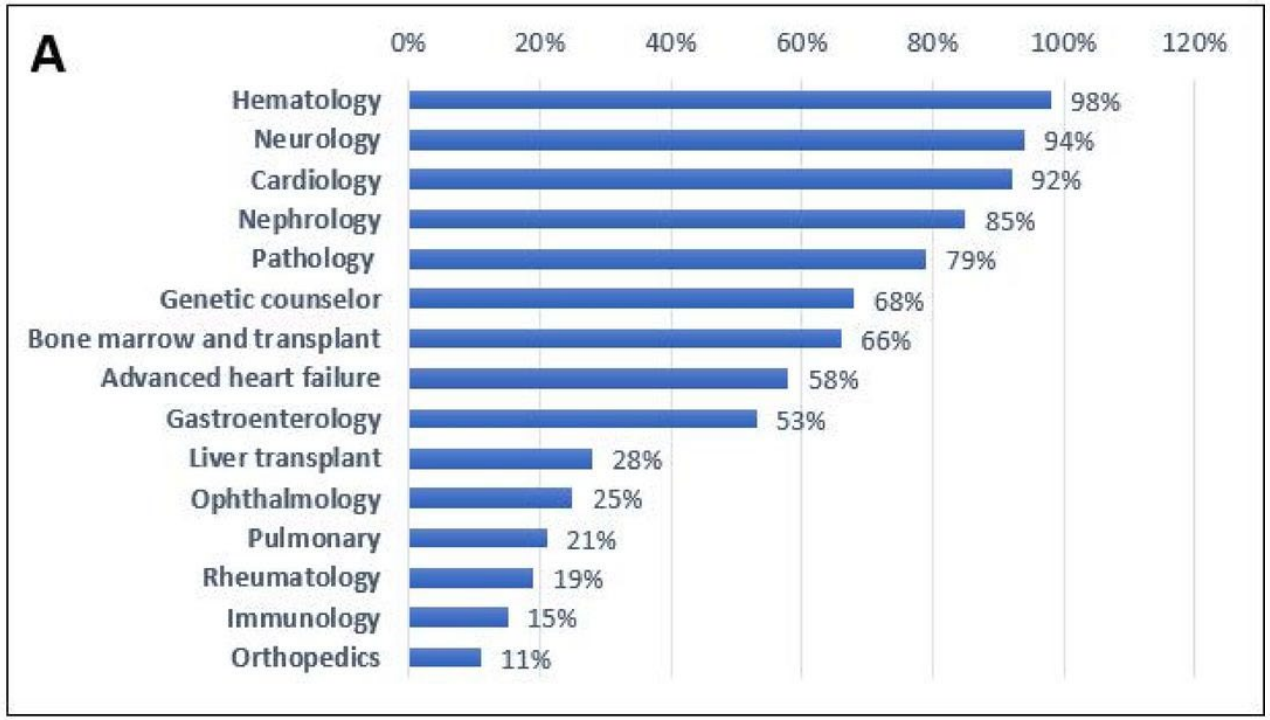
Is there a minimum requirement for diagnostic capabilities?

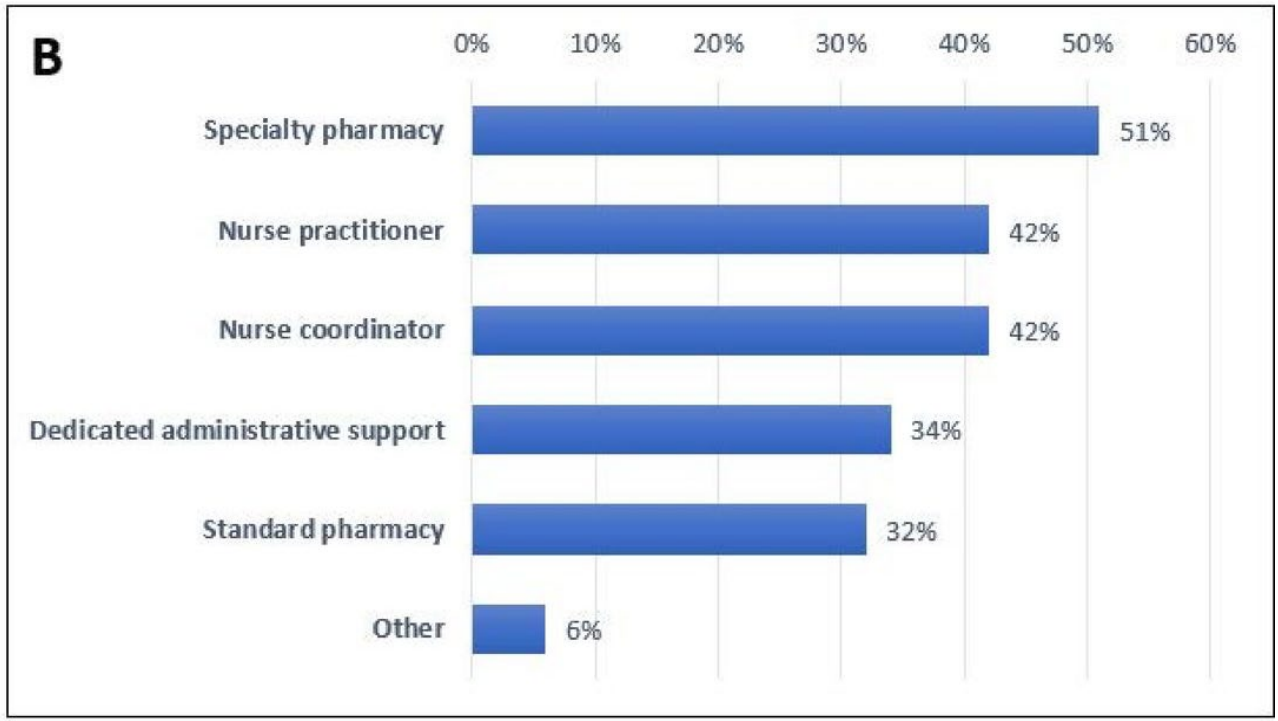


Cheng R, et al. Heart 2024;110:823–830.

Teams will vary by institution.

Is there a minimum requirement?





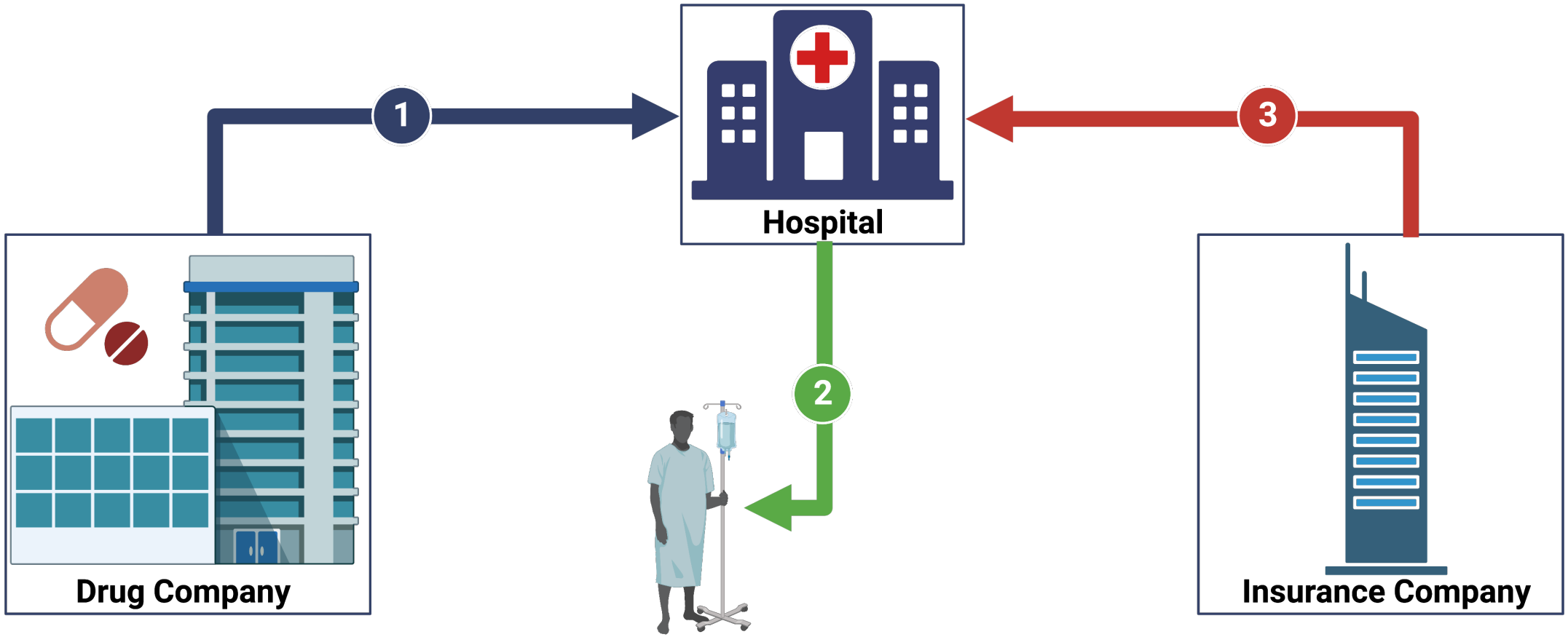
Cheng R, et al. Heart 2024;110:823–830.

Amyloid Center of Excellence Designations

	Bronze	Silver	Gold
Diagnosis of amyloidosis			
Identify clinical red flags to initiate diagnostic evaluation	X	X	X
Order monoclonal protein screens	X	X	X
Interpret abnormal monoclonal protein screen	X	X	X
Refer for bone scintigraphy	X	X	X
Perform and interpret bone scintigraphy		X	X
Arrange amyloid typing (eg, mass spectrometry)	X	X	X
Perform and interpret cardiac MRI		X	X
Refer for genetic testing	X	X	X
Perform and interpret genetic testing for amyloidosis, offer counselling		X	X
Surrogate site biopsy (such as fat pad biopsy)	X	X	X
Affected organ biopsy		X	X
Treatment of amyloidosis			
Prescribe tafamidis*	X	X	X
Prescribe and administer patisiran/vutrisiran*		X	X
Administer anti-plasma cell therapy*		X	X
Clinical trial access—at least one type of amyloidosis*		X	X
Clinical trial access—more than one type of amyloidosis*			X
Access to stem cell transplantation*			X
Access to solid organ transplantation*			X
Access to palliative care services (particularly for light chain amyloidosis)		X	X
Education and outreach			
Community and professional education	X	X	X

Cheng R, et al. Heart 2024;110:823–830.

Specialty Pharmacy – 340B



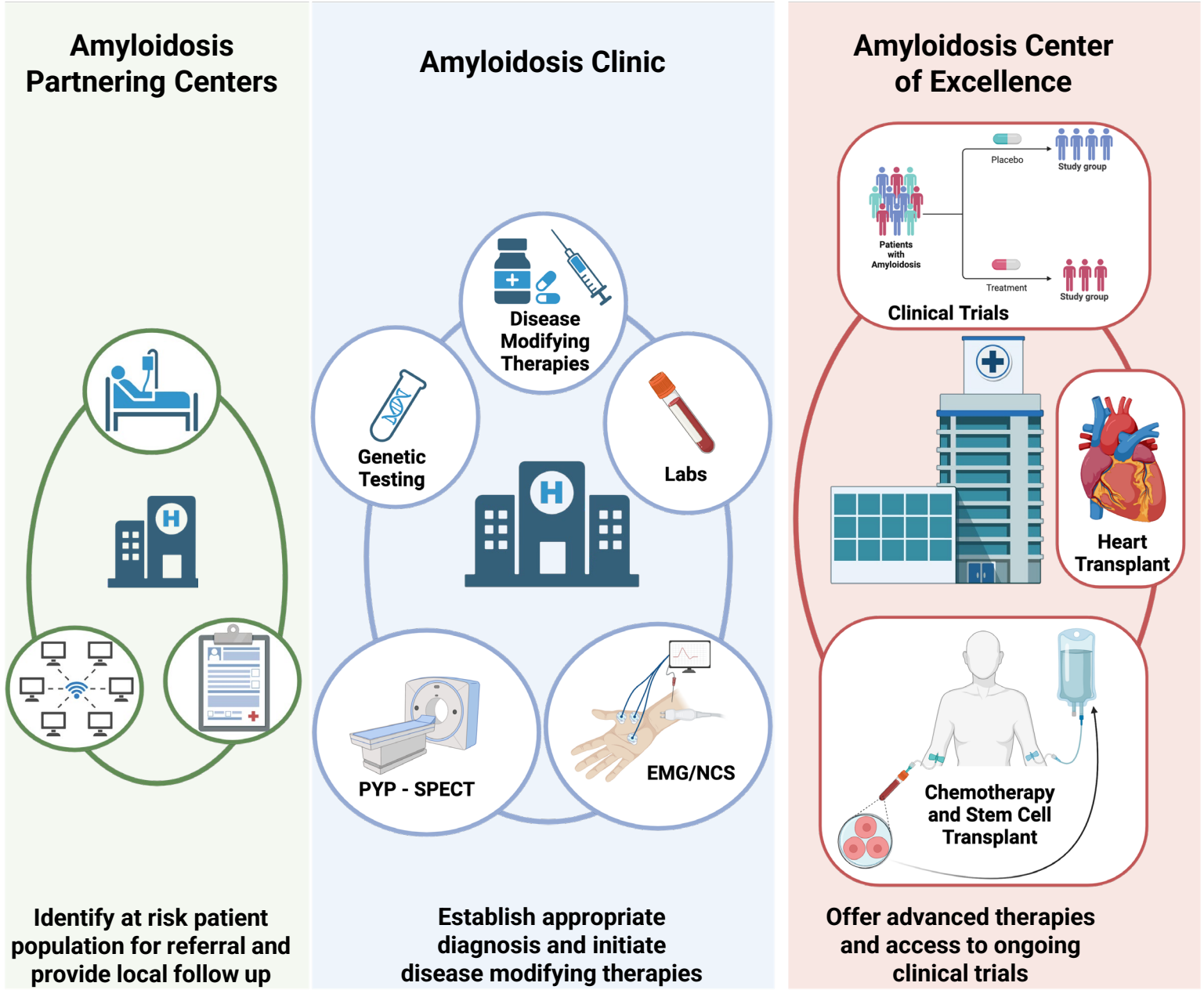
1. Drug manufacturer provides discounted medications to a 340B hospital
2. 340B hospital provides medications to patients with insurance who can and cannot afford full price
3. Insurance company reimburses the 340B hospital with a full negotiated price and keeps the difference as profit

Figure created with Biorender.com @YevgeniyBr

Specialty Pharmacy – 340B

- Take care of prior authorizations
- Can provide financial assistance for patients who qualify
- Ship medications directly to patients
- Increase compliance

Partner with the Community



Brailovsky Y et al. ACC Magazine. 2025

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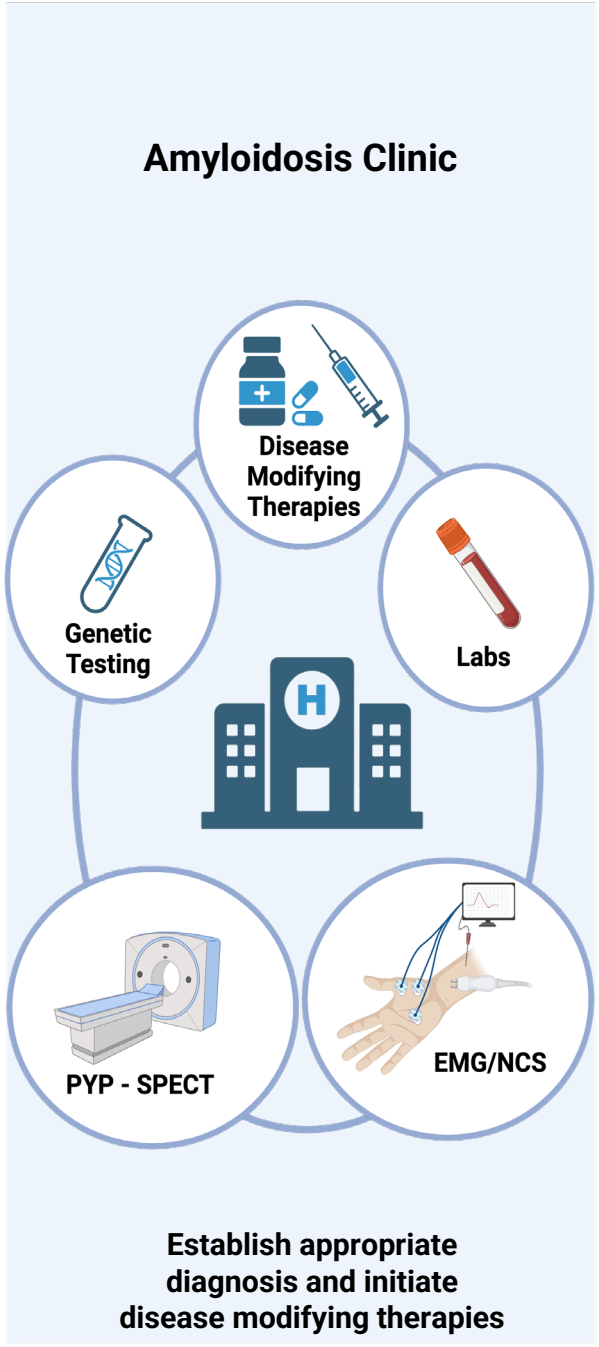
Amyloidosis Partnering Centers

Identify at risk patient population for referral and provide local follow up

Find the Patients

- Majority of patients with amyloidosis are likely outside of large centers
- Develop practices to identify patients with early signs of amyloidosis
- Identify systems for expedited referral to amyloidosis clinics/centers of excellence
- Feedback loop to continue local follow up and promote clinician education

Brailovsky Y et al. ACC Magazine. 2025

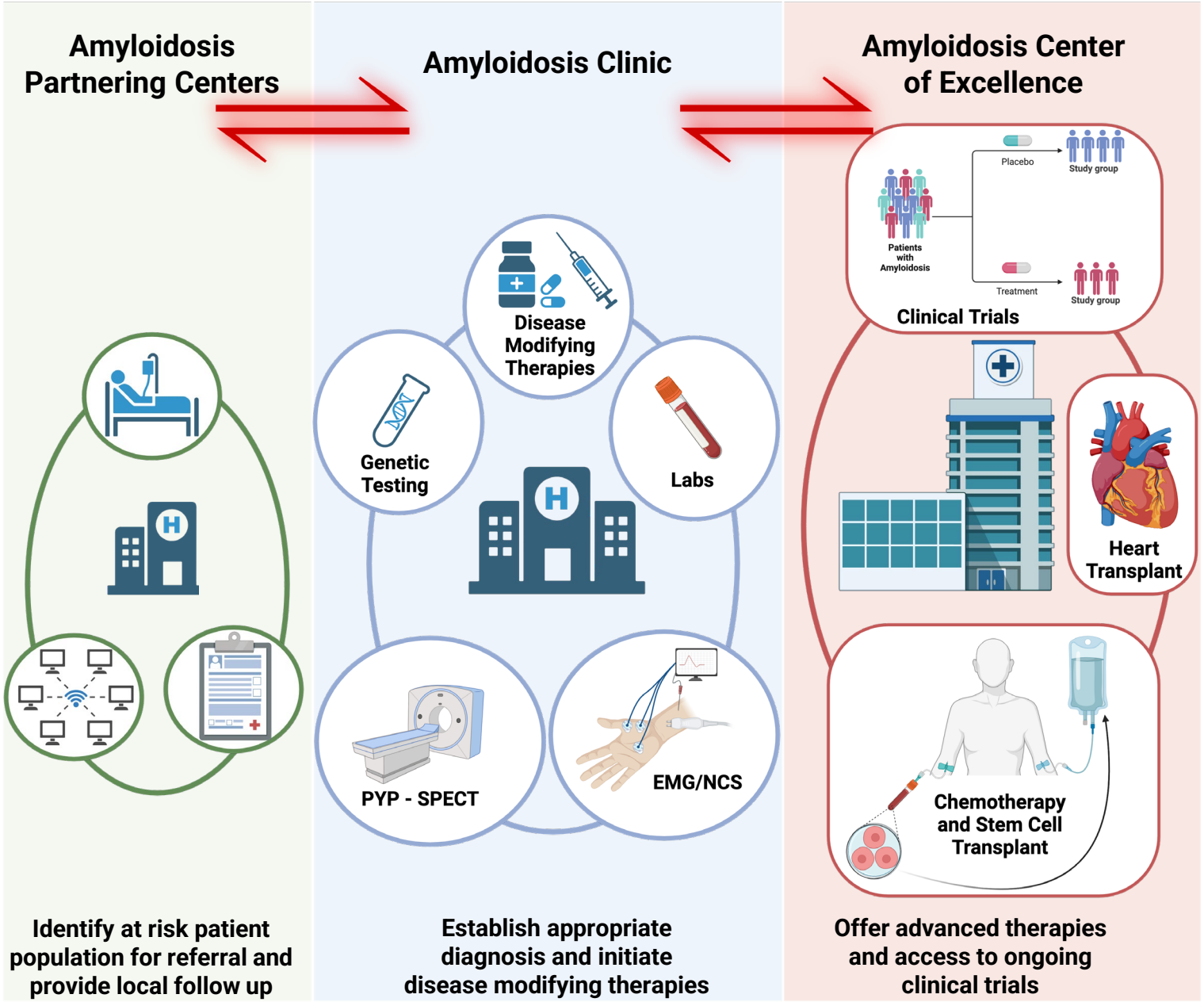


Establish the Diagnosis and Initiate Approved Therapies

- Multiple state of the art therapies are available
- The cost of therapy is still high
- Specialty pharmacy is key
- Identify patients who may be eligible/interested in clinical trials
- Refer patients for advanced therapies (Heart transplant, ASCT)

Brailovsky Y et al. ACC Magazine. 2025

Partner with the Community



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Brailovsky Y et al. ACC Magazine. 2025

Q & A

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