Case-Based Catalysts in ATTR Management:

Dynamic Discussions on the Latest Data and Current Clinical Challenges





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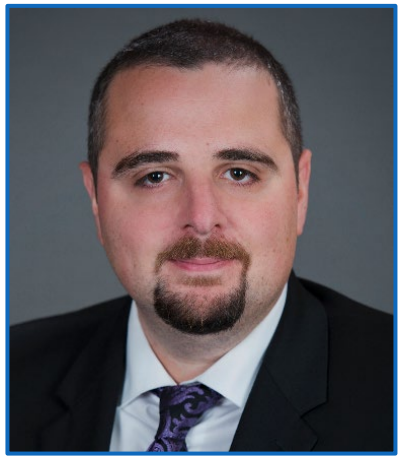
Faculty Information



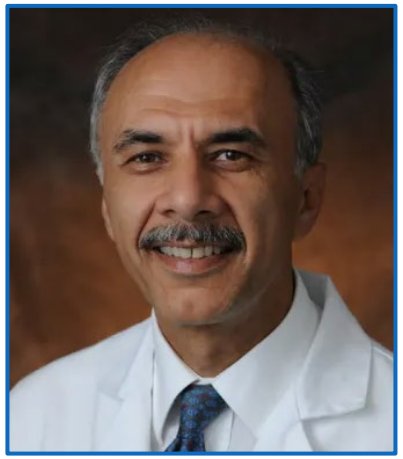
Morie Gertz, MD, MACP
Activity Chair
Roland Seidler Jr. Professor of Medicine
Chair, General Internal Medicine
Hematologist/Oncologist/Internist
Mayo Clinic
Rochester, MN



Jan Griffin, MD
Director, Cardiac Amyloidosis Program
Assistant Professor of Medicine
Beth Israel Deaconess Medical Center
New York, NY



Ahmad Masri, MD, MS
Director, Cardiac Amyloidosis Program
Assistant Professor of Medicine
Oregon Health & Science University
Portland, OR



Sami Khella, MD
Co-Founder
Penn Amyloidosis Center
Professor of Neurology
University of Pennsylvania
School of Medicine
Philadelphia, PA

Presented by

Pre-Test

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Support Statement

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Pre-Test

Faculty & Planner/Reviewer Disclosures

- **Sami Khella, MD**
  - **Advisory Board/Consultant:** Alnylam, AstraZeneca, Alexion, CSL Behring, BridgeBio
- **Ahmad Masri, MD, MS**
  - **Advisory Board/Consultant:** Cytokinetics, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Edgewise, Rocket, Lexeo, BioMarin, AstraZeneca, Avidity, Neurimmune
  - **Grant/Research Support:** Attralus, Bayer, Cytokinetics
- **Jan Griffin, MD**
  - **Advisory Board/Consultant:** BridgeBio, AstraZeneca, Pfizer
  - **Grant/Research Support:** Pfizer, BridgeBio
  - **Speaker's Bureau**: BridgeBio
- **Morie Gertz, MD, MACP**
  - **Advisory Board/Consultant:** AstraZeneca, Alnylam, Sanofi, Janssen, Johnson & Johnson, Recordati, Dava Oncology, Alexion
  - **Data Safety Monitoring Board:** AbbVie, Regeneron
- **Evangelos Oikonomou, MD, DPhil**
  - **Advisory Board/Consultant:** Cariso Diagnostics, Ltd, Ensight-AI
  - **Intellectual Property/Patents:** Caristo Diagnostics (through Oxford, UK)
- **Michael Chetrit, MD, FACC**
  - **Advisory Board/Consultant:** Alnylam, Pfizer, BMS
  - **Grant/Research Support:** Pfizer
- Clinical content has been reviewed for fair-balance and scientific objectivity, and all relevant relationships listed have been mitigated
- All planners and reviewers have no relevant relationships
- This educational activity will not review off-label utilization of currently available therapies in ATTR, but will review the prospective role and potential uses of investigational agents if and when they are FDA-approved.

Learning Objectives

Pre-Test

1. **Review** the epidemiology, pathophysiology, and clinical gravity of ATTR, with emphasis on the patient burden of illness across the phenotypic spectrum.
2. **Identify** hallmark features of ATTR clinical presentation and initiate best practice diagnostic pathways early in the disease natural history.
3. **Summarize** key therapeutic targets throughout the amyloidogenic cascade.
4. **Evaluate** the totality of emerging clinical trial evidence for novel therapeutics in ATTR, highlighting the latest data, regulatory milestones, ongoing pivotal studies, and impending readouts.
5. **Appraise** original ATTR research rationale, design, and data findings from work conducted by the Wiesman Award winners of the 2nd Annual ATTR Early-Career Research Forum.
6. **Develop** evidence-driven, patient-centric treatment plans that address the heterogeneous, multi-morbid nature of ATTR, with a focus on collaborative, multidisciplinary care.

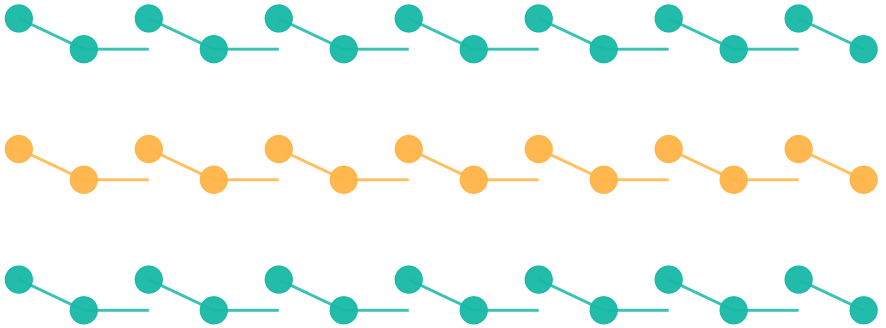


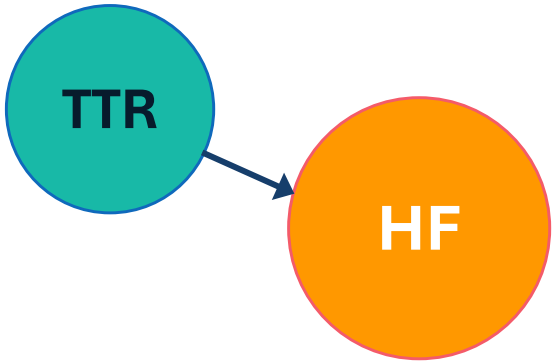
An ATTR Level-Set

Prevalence, Pathophysiology, and Multi-System Burden

ATTR Cardiac Amyloidosis

- Epidemiology
- Pathophysiology
- Clinical gravity across the phenotypic spectrum





Educational Design

Fundamentals → Clinical Pearls → Multidisciplinary Management

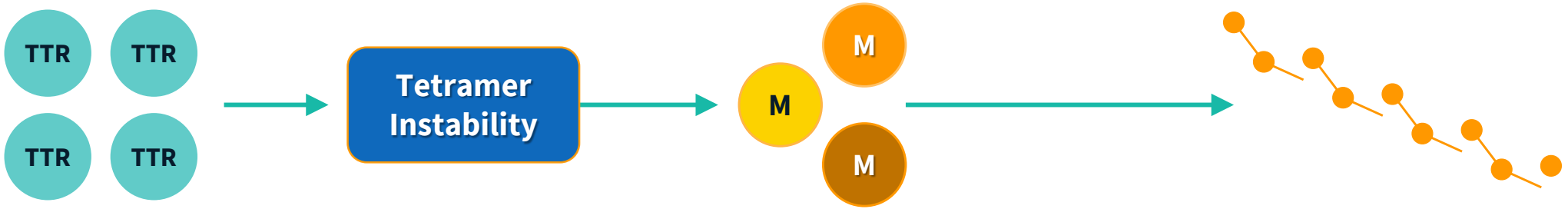
Hawkins P, et al. *Ann Med*. 2015; Suhr O, et al. *J Int Med*. 1994; Saraiva M. *FEBS Letter*. 2001; Ando Y, et al. *Orphanet Journal of Rare Diseases*. 2013; Coelho T, et al. *CMRO*. 2013.

ATTR Fundamentals: One Protein, Many Clinical Faces

ATTRwt: normal TTR, acquired/age-associated, usually cardiac-predominant

ATTRv: pathogenic TTR variant, inherited; phenotype may be cardiac, neurologic, or mixed

Mechanism is progressive protein misfolding + organ deposition



TTR Tetramer
(liver-derived transport protein)

Dissociation + Misfolding
Monomers / Fragments

Amyloid Fibrils
Deposit in Tissue

Heart
Stiff Ventricle, HF, AF, Conduction Disease

Peripheral + Autonomic Nerves
Pain, Numbness, Orthostasis, GI

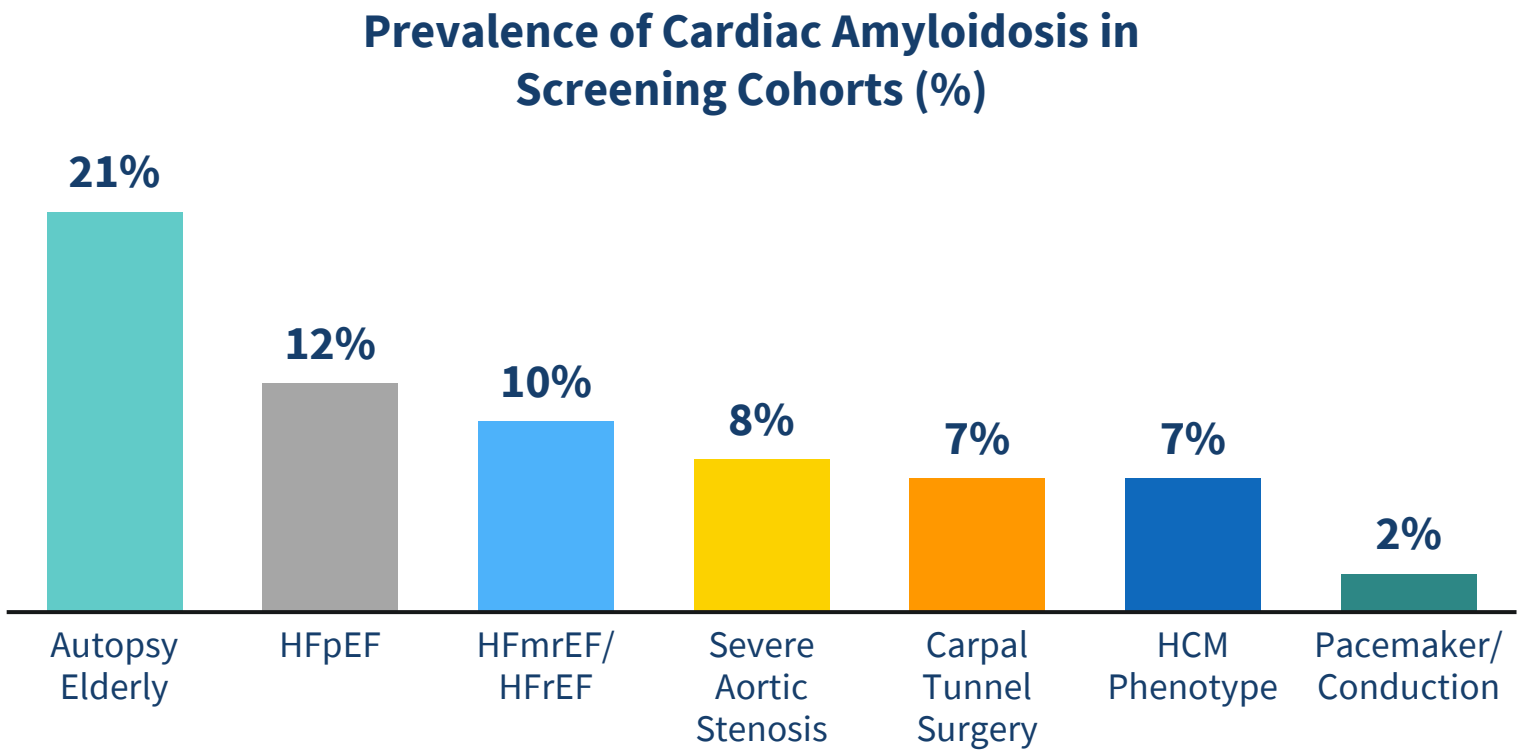
Musculoskeletal
CTS, Stenosis, Biceps Rupture, Trigger Finger

Renal / GI / Ocular
Proteinuria, Diarrhea/ Constipation, Vitreous

Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024; Garcia-Pavia P, et al. *Eur Heart J*. 2021.

Epidemiology: Enriched Clinical Windows, Not Random Screening

Active searching finds ATTR/CA in common HF practice scenarios.



Where to Raise Suspicion

- Older Patient With HFpEF or "HCM-Like" Wall Thickening
- Aortic Stenosis, AF / Conduction Disease, Elevated Biomarkers
- HF + CTS / Spinal Stenosis / Neuropathy = Multisystem Clue

Clinical Pearl

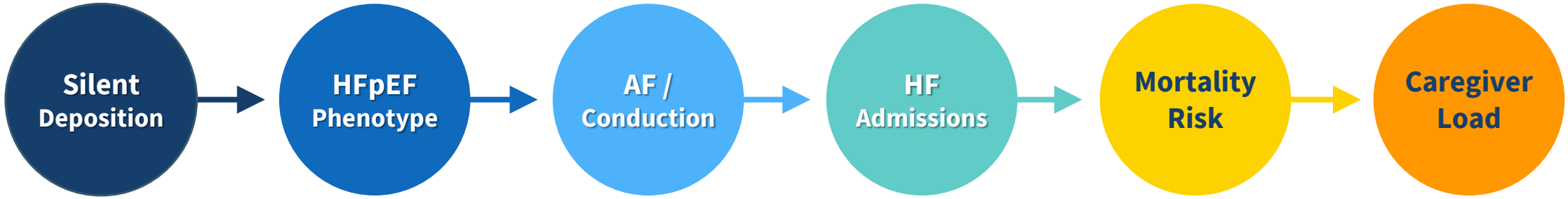
In enriched cohorts, ATTR/CA prevalence is high enough that missing it is now a workflow problem, not a "zebra" problem.

Aimo A, et al. *Eur J Heart Fail*. 2022; Brito D, et al. *Glob Heart*. 2023.

Clinical Gravity: Cardiac Progression + Lived Burden

Educational Emphasis
Clinical Gravity = Survival Risk + Function + Autonomy + Diagnostic Odyssey.

The patient burden is not captured by wall thickness alone.



~3.4 y

reported **median survival** in cardiomyopathy-predominant **untreated ATTRv.**

27 mo

median delay from presentation to confirmed amyloidosis diagnosis in a patient-impact study.

49%

patients reported breathlessness **before diagnosis** in a French daily-impact survey.

33%

reported tingling; pain and walking difficulty were each reported by 28%.

What patients experience before "the diagnosis":

Dyspnea, fatigue, edema, neuropathic pain, gait decline, orthostasis/GI symptoms, procedures for CTS/stenosis, repeated specialist visits, and uncertainty.

Brito D, et al. *Glob Heart*. 2023; Antonopoulos A, et al. *Eur J Heart Fail*. 2022; Damy T, et al. *Amyloid*. 2022; Karam C, et al. *Orphanet J Rare Dis*. 2024.

Phenotypic Spectrum: Cardiology Sees One Slice of a Systemic Disease

ATTRwt and ATTRv can present as cardiac, neurologic, or mixed disease.

Cardiac-Predominant ATTRwt

HFpEF, AS, AF, Conduction Disease, Wall Thickening

Mixed ATTRv

Cardiac + Sensorimotor/ Autonomic + GI/MSK Clues

Neuropathy-Predominant ATTRv

Progressive Small-Fiber Neuropathy, Pain, Numbness, Autonomic Dysfunction

Red-flag Constellation to Connect Across Specialties

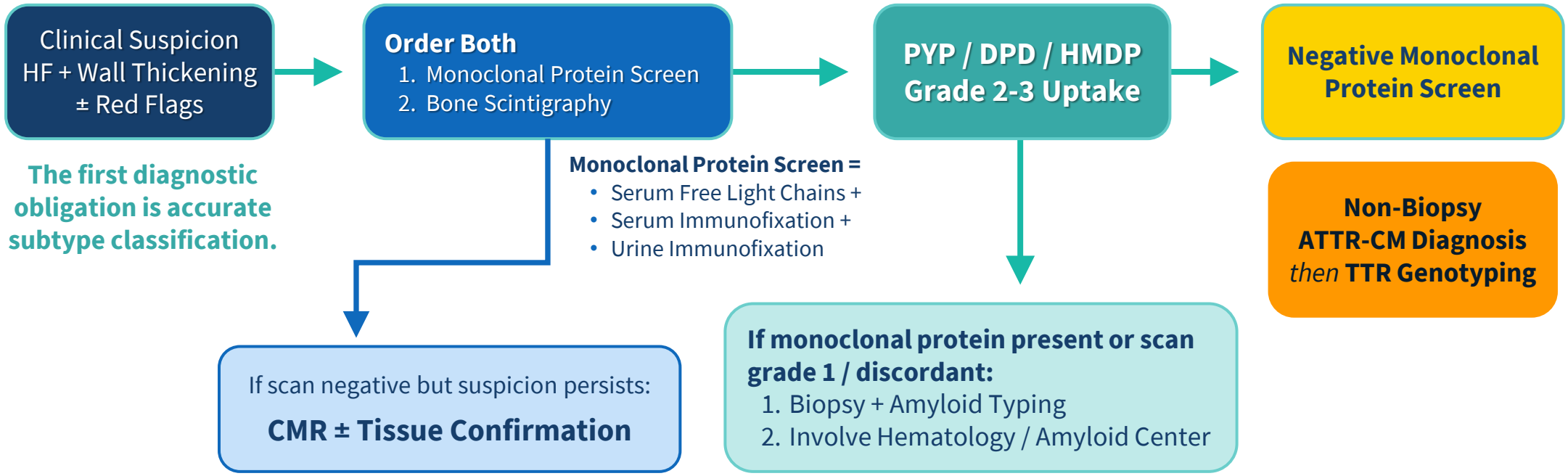
- Unexplained LV Wall Thickening
- Bilateral CTS / Trigger Finger
- Proteinuria / GI Dysmotility / Family History
- Lumbar Stenosis / Biceps Rupture
- AF / Conduction Disease
- Peripheral or Autonomic Neuropathy

Clinical Pearl

Low-voltage ECG is helpful when present, but it is not required; many amyloid patients do not have classic voltage-wall thickness discordance.

Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024.

Diagnose ATTR-CM Without Missing AL



Cardiology Clinical Pearl

Do not call ATTR on PYP alone. Grade 1 uptake is not diagnostic. Low voltage is not required.

Neurology Clinical Pearl

Progressive sensory/autonomic neuropathy + systemic clues/family history → TTR gene testing and cardiac screening.

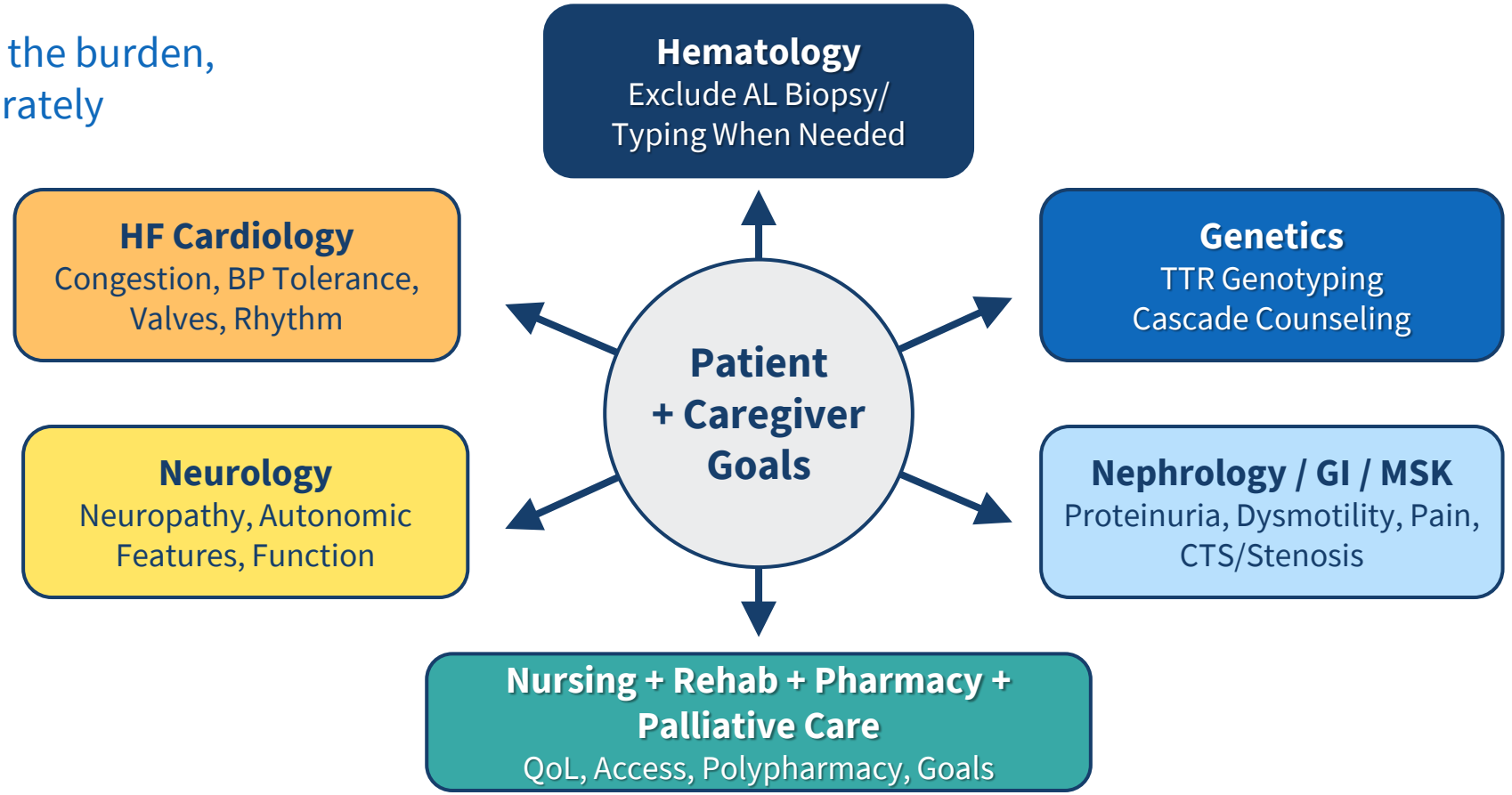
Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024; Garcia-Pavia P, et al. *Eur Heart J*. 2021.

Multidisciplinary Management: One Patient, Multiple Clocks

Treat the phenotype, track the burden, and coordinate care deliberately

Close With 3 Actions:

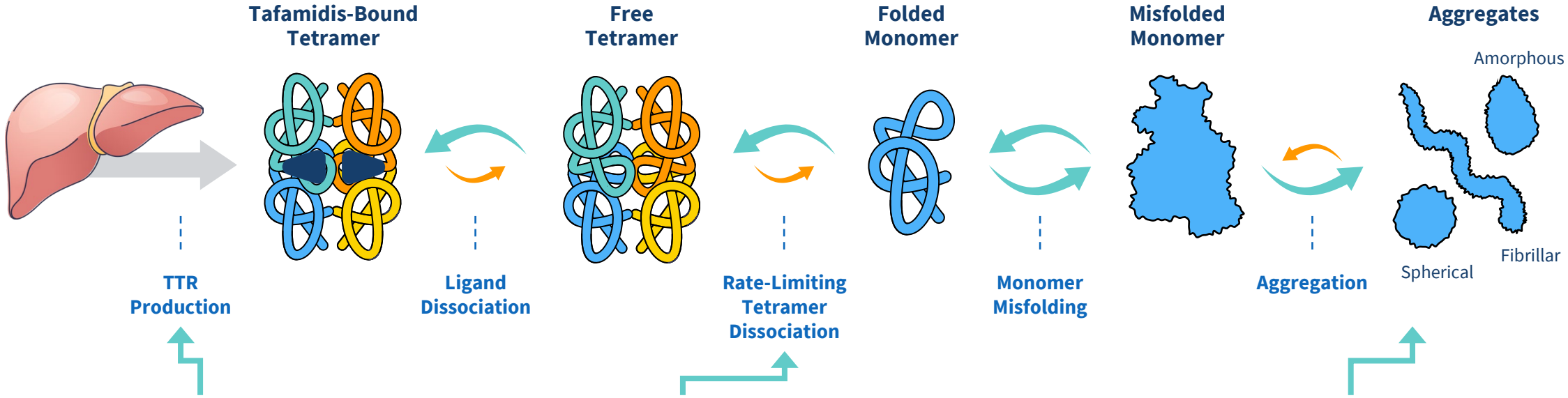
1. Screen enriched HF red-flag clusters.
2. Rule out AL before ATTR.
3. Manage cardiac + neurologic + functional burden together.



Kittleson M, et al. *JACC*. 2023; Maurer M, et al. *N Engl J Med*. 2018; FDA Prescribing Information.

Targeting the Amyloidogenic Cascade

Therapeutic Strategies and Mechanisms of Action



TTR mRNA Silencers

- ✶ Eplontersen (ASO)
- ✶ Patisiran (siRNA)
- ✶ ♥ Vutrisiran (siRNA)
- † Nucresiran
- † NTLA-2001 (gene therapy)

TTR Stabilizers

- ♥ Tafamidis
- ♥ Acoramidis
- Diflunisal[a]
- Tolcapone[a]

Anti-Fibril Agents

Monoclonal Antibodies

- † Coramitug (NNC6019-0001)
- † Cliramitug (ALXN2220)

♥ Indicated to treat ATTRwt-CA or ATTRv-CA. ✶ Indicated to treat ATTRv-PN. † Investigational. [a]Off-label use.

Adams D, et al. *Nat Rev Neurol*. 2019; Nativi-Nicolau J, et al. Cur*r Opin Cardiol*. 2018; Kadakia KT, et al. *J Am Coll Cardiol*. 2025; Berk JL, et al. *JAMA*. 2013; ClinicalTrials.gov; FDA Prescribing Information.

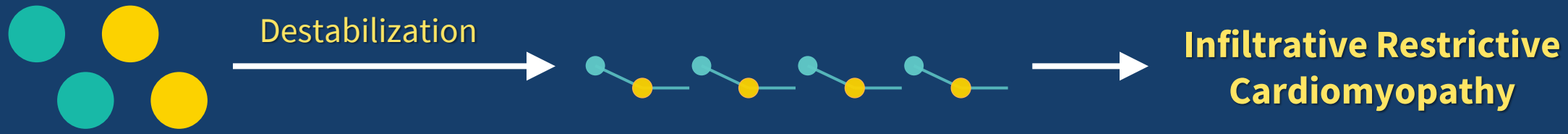
Emphasis on Early

Recognizing Red Flags and Achieving Timely ATTR Diagnosis in the Era of Disease-Modifying Therapeutics

Case 1: TTR Amyloidosis in HFpEF



- Spot the hallmark features and initiate the diagnostic pathway early.
- 76-year-old male with HFpEF
  - Reports **new tingling in hands/feet**
  - Has no known family history



Objective: Identify hallmark features of ATTR-CM, connect the clinical presentation to systemic red flags, and trigger best-practice diagnostic testing before late-stage restrictive physiology.

HFpEF + Neuropathy Is a Systemic Signal



- **Clinical Hinge:** The neurologic symptom shifts the question from "common HFpEF" to "multisystem amyloid until proven otherwise."
- **Why this patient is high-yield:** Older male with HFpEF, possible infiltrative physiology, and a new peripheral sensory compliant.

No family history does NOT close the door!

Late-onset ATTRv, incomplete penetrance, and unrecognized family disease make genetic testing essential after ATTR is confirmed.

AL remains the diagnosis to miss: Neuropathy can occur in AL and ATTRv. Rule out AL in parallel, not sequentially.

Gamification Question

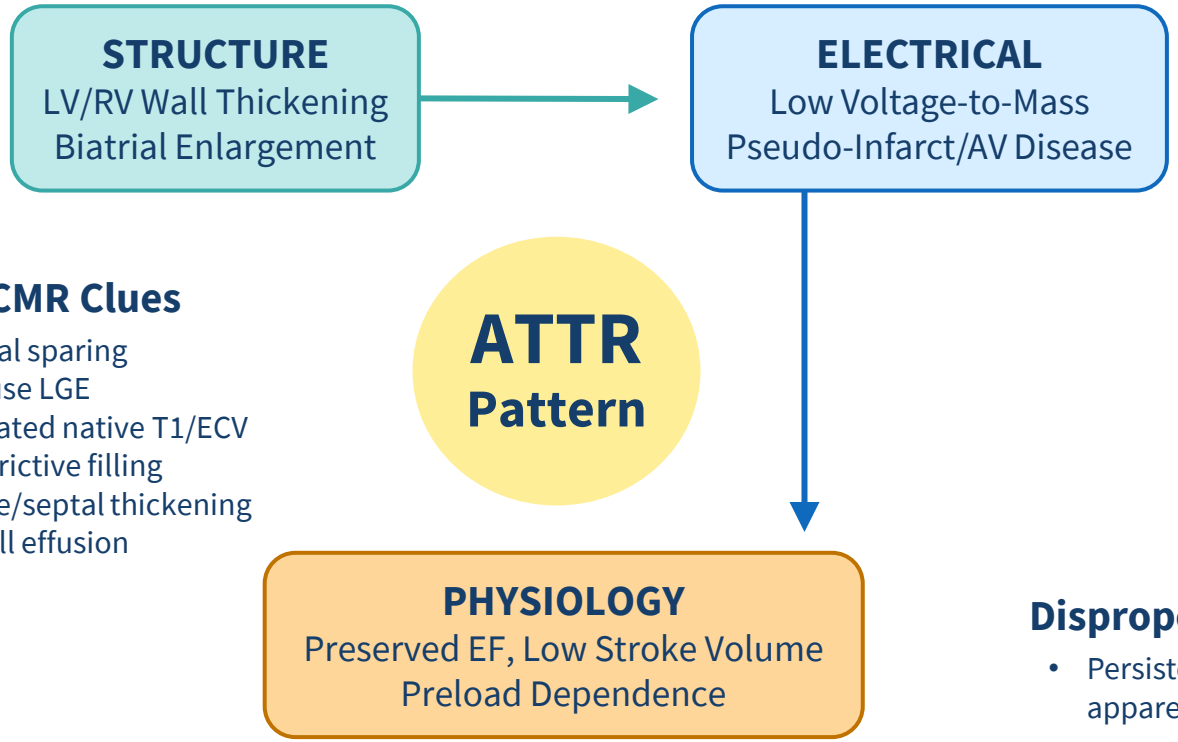


What is the most important clinical clue that this patient has TTR amyloidosis?

A. His age of 76 years is very consistent with “senile cardiac amyloid,” now referred to as ATTR cardiomyopathy
B. The presentation of HFpEF with normal valves argues against an ischemic etiology
C. The neuropathy suggests there is an underlying systemic disorder
D. The absence of edema, hypertension, and male sex strongly suggests an infiltrative cardiomyopathy

Hallmark ATTR-CM: Discordance Is the Clue

Wall thickness, voltage, and biomarkers and output do not match.



Echo/CMR Clues

- Apical sparing
- Diffuse LGE
- Elevated native T1/ECV
- Restrictive filling
- Valve/septal thickening
- Small effusion

Systemic Red Flags

- **Carpal Tunnel**
- **Lumbar/Cervical Stenosis**
- **Spontaneous Biceps Rupture**
- **Sensory or Autonomic Neuropathy**
- **Orthopedic Procedures**
- **Proteinuria or Purpura → Think AL**

Disproportionate Biomarkers

- Persistent troponin/elevated NT-proBNP out of proportion to apparent congestion can be a red flag.

Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024; Garcia-Pavia P, et al. *Eur Heart J*. 2021.

Common Misdiagnoses of Disturbances Caused by ATTR Amyloidosis

Common Misdiagnosis	ATTR Symptoms Contradicting Given Diagnosis
Cardiac	
Hypertrophic cardiomyopathy	Discordant voltage to mass ratio
Hypertensive heart disease	Discordant voltage to mass ratio; intolerance to beta blockers: waning need for antihypertensives
Undifferentiated HF with preserved EF	Nondilated hypertrophic LV
Uncomplicated degenerative aortic stenosis	Reduced longitudinal strain frequent low-flow, low-gradient paradoxical pattern thickened atrioventricular valves

Common Misdiagnosis	ATTR Symptoms Contradicting Given Diagnosis
Neurologic	
Chronic inflammatory demyelinating polyneuropathy	Pain in the limbs, dysautonomia (erectile dysfunction , OH) symmetric polyneuropathy in upper limbs
Monoclonal gammopathy-associated neuropathy	Autonomic dysfunction (erectile dysfunction , OH)
Idiopathic and polyneuropathy	Dysautonomia (erectile dysfunction , OH) walking difficulties
CTS	Worsening of upper limb symptoms despite CTS surgery
Lumbar spinal stenosis	Failure to relieve symptoms in spite of spine surgery
Diabetic neuropathy	Walking difficulties
Amyotrophic lateral sclerosis	No upper motor neuron syndrome Reduction of amplitude of SNAP
Motor neuropathy	Reduction of amplitude of SNAP

Common Misdiagnosis	ATTR Symptoms Contradicting Given Diagnosis
Gastrointestinal	
Inflammatory bowel syndrome	Absence of inflammation
Irritable bowel syndrome	Absence of or only minor abdominal pain; weight loss
Idiopathic diarrhea idiopathic bile acid malabsorption	Weight loss
Pseudo-obstruction	Absence of or only minor abdominal pain or radiologic findings of intestinal obstruction

Gertz M, et al. *BMC Fam Pract*. 2020.

Phenotype Triage: ATTRwt, ATTRv, AL

Tingling widens the differential; AL must be excluded early.



Older male HFpEF phenotype; Musculoskeletal deposition may predate HF by years. Family history is often absent.

High Pre-Test Probability



Peripheral sensory/autonomic symptoms make ATTRv plausible. No known family history does not exclude a pathogenic variant.

Genotype All ATTR



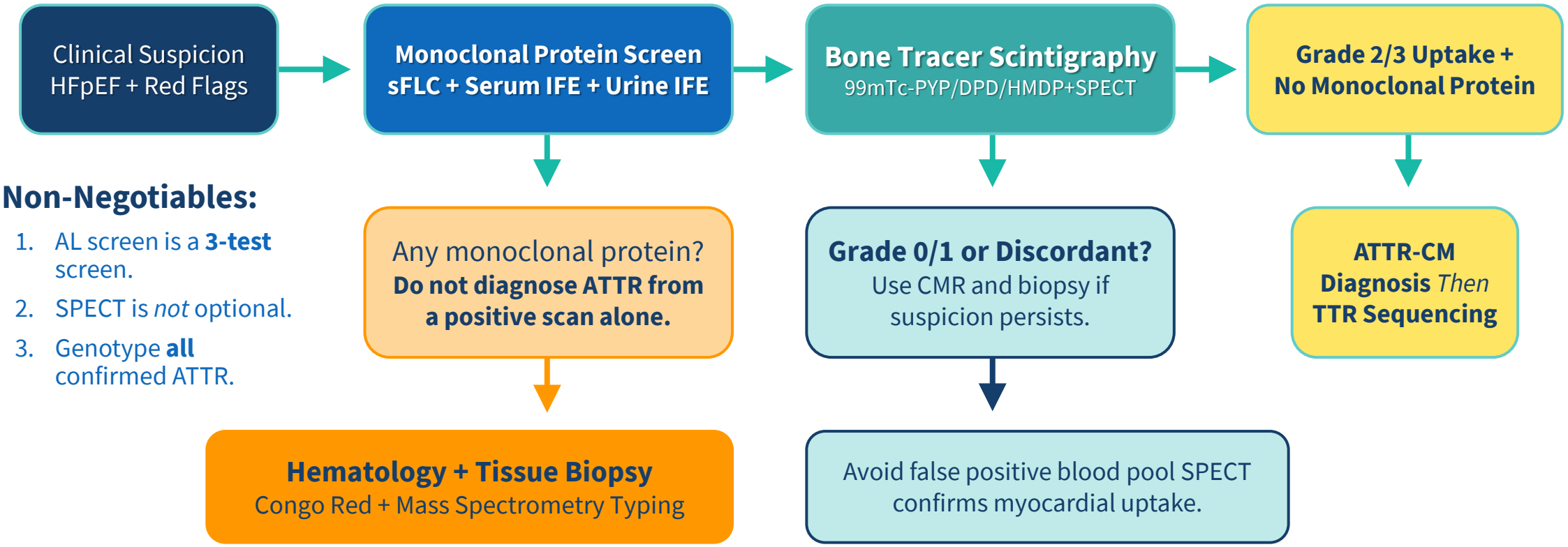
Neuropathy, proteinuria, macroglossia, purpura or rapidly progressive HF should accelerate hematology involvement and tissue typing.

Rule Out First

Case Synthesis: a 76-year-old man with HFpEF fits ATTRwt, but new distal paresthesias means ATTRv and AL remain live possibilities until the pathway separates them.

Diagnostic Pathway: Exclude AL While Localizing Amyloid

The monoclonal screen determines what a positive bone scan means.



Non-Negotiables:

1. AL screen is a **3-test** screen.
2. SPECT is *not* optional.
3. Genotype **all** confirmed ATTR.

Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024; Garcia-Pavia P, et al. *Eur Heart J*. 2021; Gertz M, et al. *BMC Fam Pract*. 2020.

Order Set + Pitfalls for Tomorrow Morning

The diagnostic pathway works when the tests are ordered together and interpreted together.

Parallel Orders

1. **Phenotype Review**
   ECG + Echo Re-Review; Add strain if absent; check LVWT, stroke volume, AF/AV disease.
2. **AL Screen**
   sFLC Ratio + Serum IFE + Urine IFE. Add CBC/CMP, eGFR, Urine Protein, NT-proBNP/troponin.
3. **Localize Amyloid**
   99mTc-PYP/DPD/HMDP with SPECT; CMR if scan is equivocal or alternate infiltrative disease remains likely.
4. **Type and Stage**
   If ATTR: TTR sequencing, amyloid clinic/neurology, functional and biomarker baseline. **If monoclonal:** tissue biopsy + mass spec.

Pitfalls That Delay Diagnosis

- **SPEP/UPEP Alone:** Insufficient for AL exclusion; use immunofixation + sFLC.
- **Positive PYP + MGUS:** Not diagnostic of ATTR; biopsy and type amyloid.
- **H/CL Ratio Alone:** Quantitation is adjunctive; SPECT confirms myocardial uptake.
- **Negative or Grade 1 Scan:** Does not end the work-up if phenotype is compelling.
- **Family History Absent:** Do not skip sequencing once ATTR is confirmed.

Case Action: order a 3-test AL screen and PYP SPECT now; do not wait for overt restrictive physiology.

Kittleson M, et al. *JACC*. 2023; Karam C, et al. *Muscle Nerve*. 2024; Garcia-Pavia P, et al. *Eur Heart J*. 2021; Gertz M, et al. *BMC Fam Pract*. 2020.

Take-Home: Complete the ATTR-CM Pathway

The diagnostic win is moving from “consider amyloid” to “complete the pathway.”



Older HFpEF + unexplained wall thickening, low voltage-to-mass, AF/AV disease, disproportionate biomarkers, or systemic red flags.

Order sFLC, serum IFE, and urine IFE immediately; neuropathy keeps AL and ATTRv in the frame.

Grade 2/3 bone-tracer myocardial uptake with negative monoclonal screen → ATTR-CM; then sequence TTR.

Why Early Matters

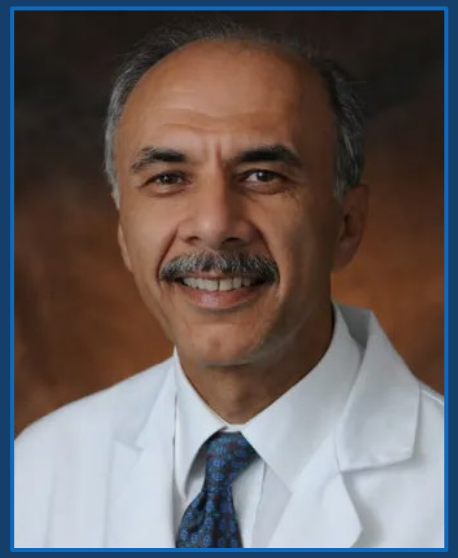
Current disease-modifying therapy is disease-slowing, not organ-restoring. A 76-year-old with HFpEF and new distal paresthesias deserves the pathway before irreversible functional loss.

“In HFpEF, amyloid is not the last diagnosis after everything else fails; it is a parallel diagnostic pathway triggered by the first red flag.”

Kittleson M, et al. *JACC*. 2023; Gertz M, et al. *BMC Fam Pract*. 2020.

Taking Aim at the Amyloidogenic Cascade

Evidence, Best Practices, and Impending Landscape Shifts in ATTR Treatment



Case and Therapeutic Targets

A Neurologist's Perspective

Case 2: 63-year-old female with p. V142I and polyneuropathy worsening fatigue and dyspnea

- Neuropathic pain in LE worsening
- Increasing bilateral hand numbness and tingling with nocturnal awakening
- New pedal edema
- New 3 pillow orthopnea



- **PMH:** Diabetes type 2, anemia.
- **SH:** 1ppd, 2 glasses wine daily.
- **Meds:** Eplontersen monthly x 1 year and gabapentin 600mg TID (neuropathic pain).

Examination and Labs

- In mild distress
- New S3 and S4 with 2 cm jvp
- Bilateral pitting pedal edema
- 4/5 hip flexion weakness and 3/5 ankle dorsiflexion weakness
- Graded sensory loss to pinprick and temperature with vibratory sensory loss to the knees
- Ankle and knee jerk areflexia
- Walks with a cane

- BS 200 mg/dL
- BUN 45 Crt 2.01
- Hb 10.5 g/dL
- NT proBnP 2000 pg/mL
- KLC 95 mg/L, LLC 25 mg/L ratio K:L 3.8
- EMG/NCS : fiber length dependent axonal neuropathy unchanged compared to 2 years prior

Gamification Question

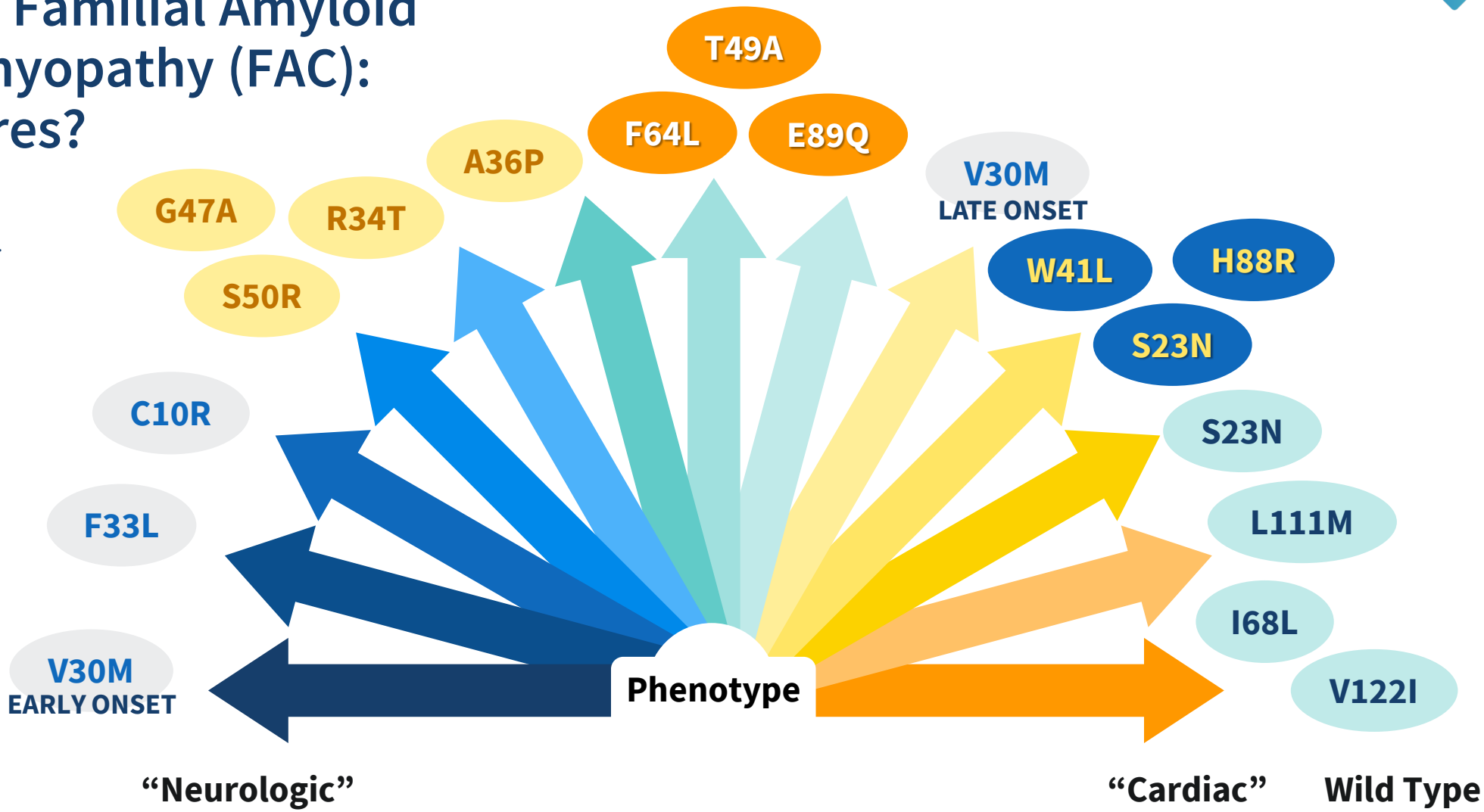


Which of the following is the most appropriate next step?

A. Start silencer therapy for amyloid polyneuropathy
B. Neuropathy may have another etiology; get neurology consult
C. Switch treatment to acoramidis
D. Order a nerve biopsy

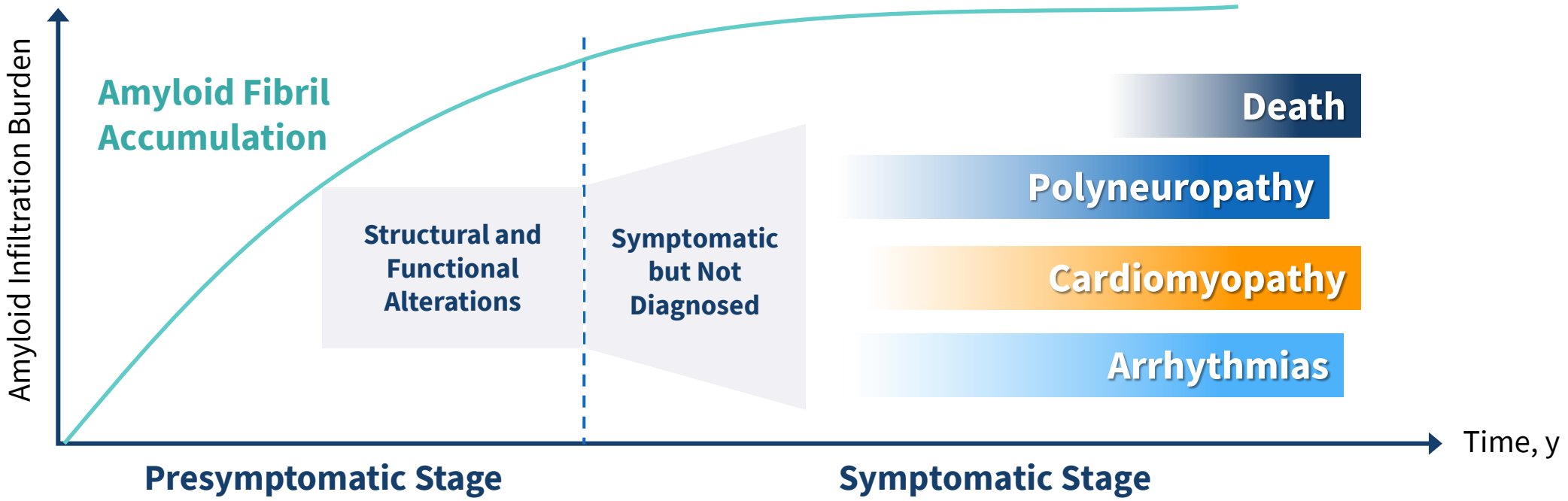
Familial Amyloid Polyneuropathy (FAP) or Familial Amyloid Cardiomyopathy (FAC): Who Cares?

Gertz M, et al.
J Am Coll Cardiol.
2015;66(21):2451-2466.



Natural History of ATTR

Appearance of Specific Complications Over Time Varies by Individual and Genotype



Aimo A, et al. *Nat Rev Cardiol*. 2022; Scirpa R, et al. *Front Cardiovasc Med*. 2023; Vera-Llonch M, et al. *Orphanet J Rare Dis*. 2021.

Some ATTR Variants Are Not Rare in the United States[1-4]

The p.V142I (V122I) variant is the most common cause of ATTR-CM in the United States, but are underrepresented in clinical trials[5-7]

3.2% of Black Americans carry **ATTRv p.V142I**

- **23,338** self-identified Black individuals, 4 cohorts
- 754 p.V142I carriers
- Variable penetrance

University of Pennsylvania Cohort 2020-2025

TTR 153

82 p.V142I

20-40% comorbid neuropathy

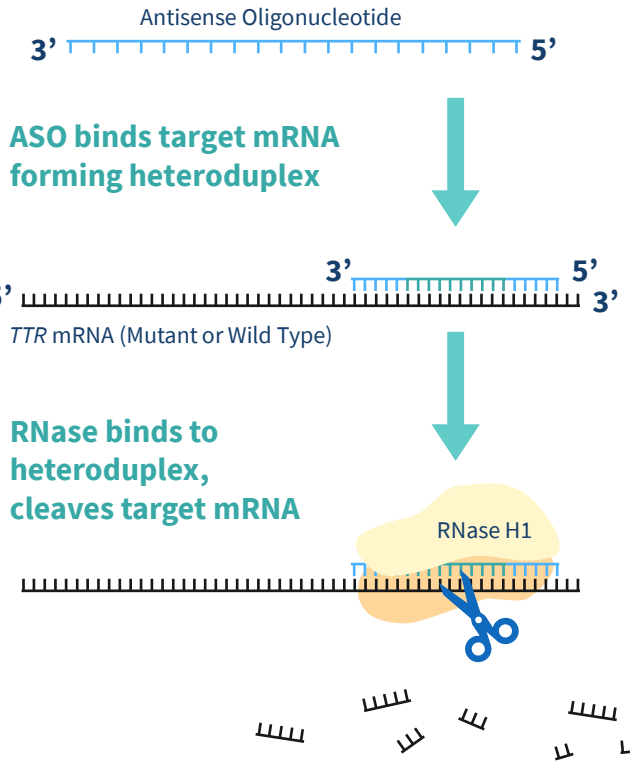
13% from Amyloidosis – unpublished data

1. Selvaraj S et al. *JAMA*. 2024. 2. Kaniper S, et al. *J Pers Med*. 2024. 3. Lopes LR, et al. *Amyloid*. 2019. 4. Gentile L, et al. *PLoS One*. 2024. 5. Ekpo E, et al. *Amyloid.* 2024. 6. Gillmore JD, et al. *N Engl J Med*. 2024. 7. Fontana M, et al. *N Engl J Med*. 2025.

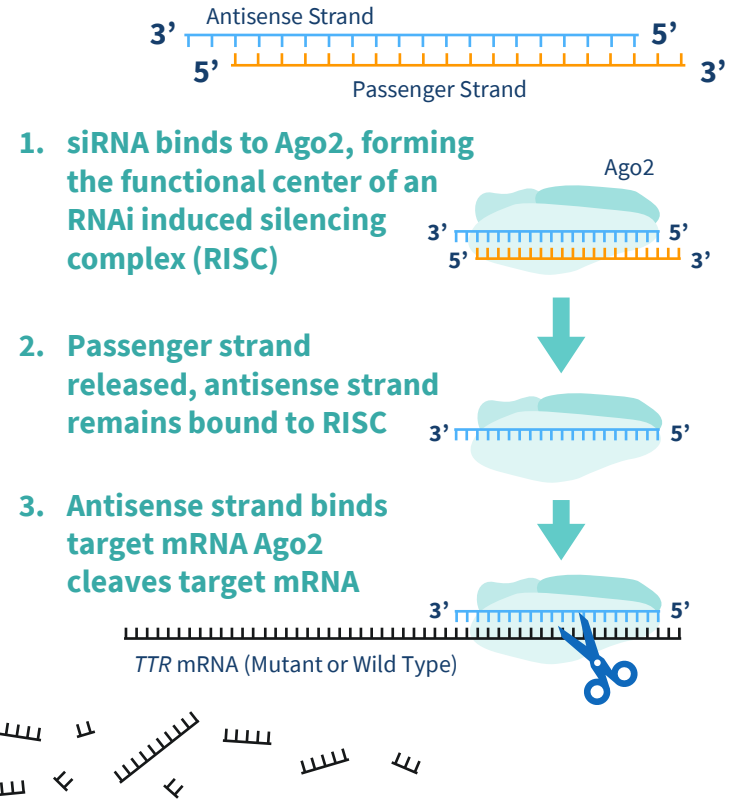
Less RNA = Less TTR Protein

Brannagan TH, et al. *JPNS.* 2022.

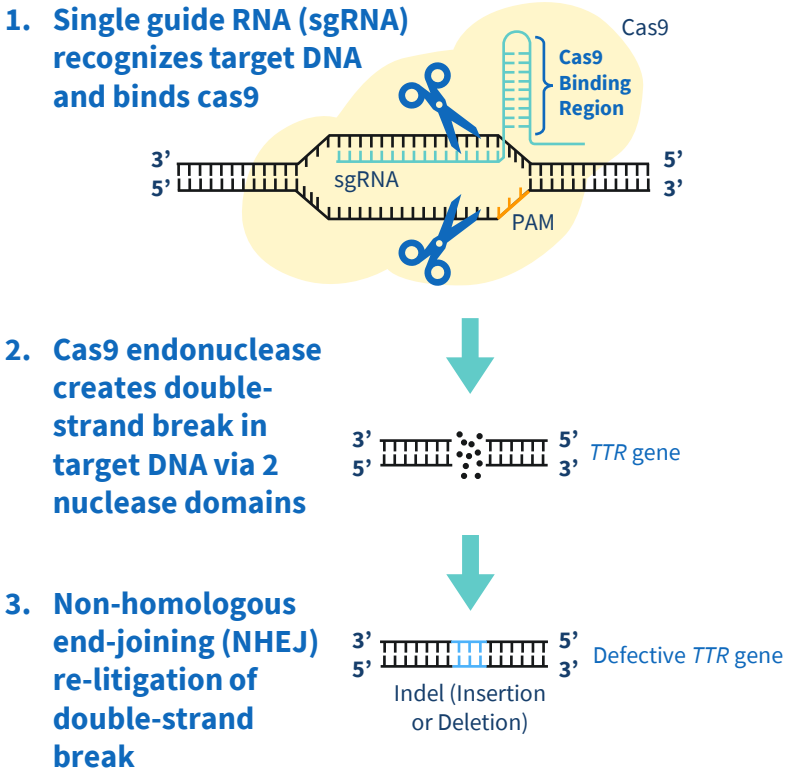
Antisense Oligonucleotide (ASO)



Small Interfering RNA (siRNA)



CRISPR-Cas9 Gene Editing



mRNA Degraded → Reduced Protein Levels

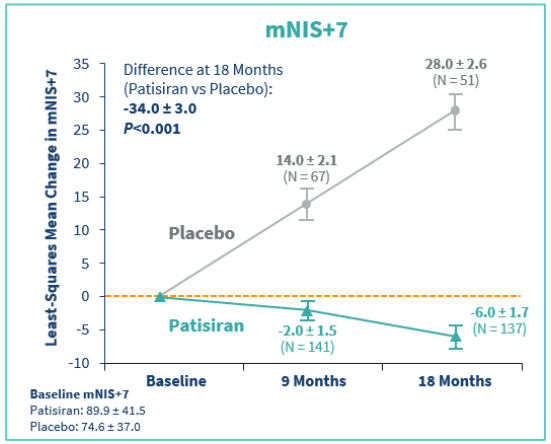
Gene Edited → Reduced Protein Levels

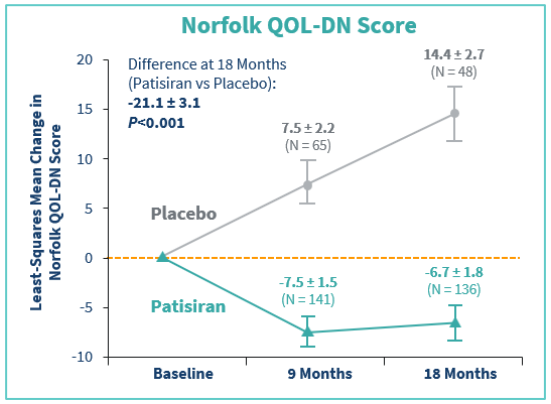
TTR Silencing Works for ATTRv-PN!

The Key Question İ Could it also work for ATTRİCM‡

Patisiran (APOLLO)

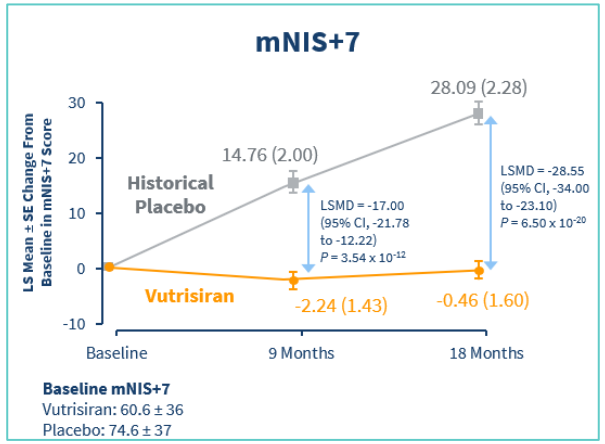
siRNA - FDA-approved ✓

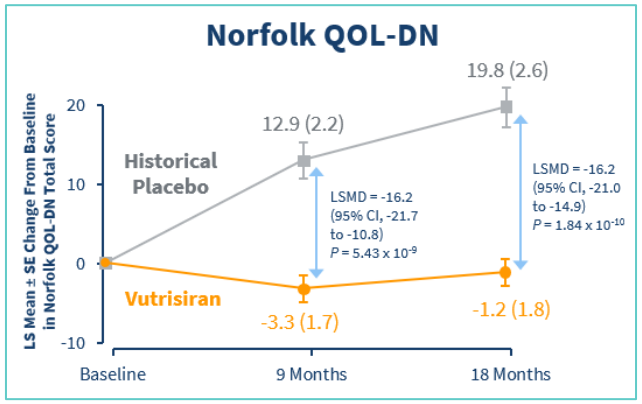




Vutrisiran (HELIOS-A)

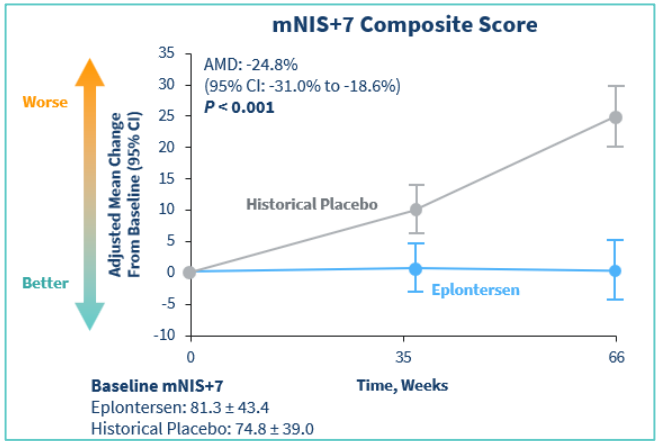
siRNA – FDA-approved ✓

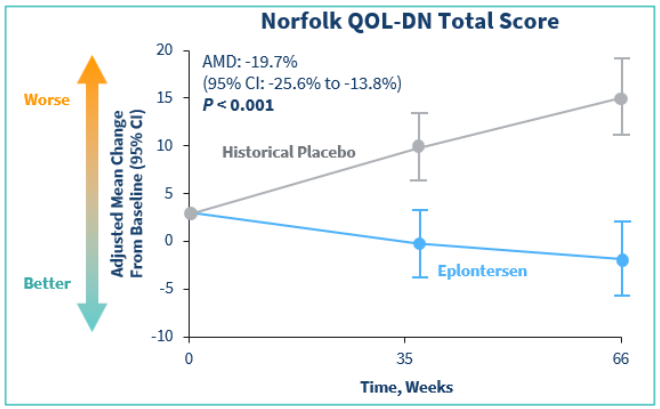




Eplontersen (NEURO-TTRansform)

ASO – FDA-approved ✓





AACME® AMERICAN ACADEMY OF CME, INC.

Adams D, et al. *N Engl J Med*. 2018; Adams D, et al. *JAMA Neurol*. 2025; Adams D, et al. *Amyloid*. 2023; Luigetti M, et al. *Neurol Ther*. 2024; Coelho T, et al. *JAMA*. 2023; Wixner J, et al. *Amyloid*. 2025.

Individualizing Current Targeted Treatments for ATTRv-PN

	Agent	Administration and Route	Vitamin A Supplement Needed?	Cardio-myopathy indication?	Neuropathy Indication?	Most Common AEs in Clinical Trials
Silencers	Eplontersen	SC injection once monthly via autoinjector	Yes	**No**	Yes	↓Vitamin A, vomiting
	Patisiran	Lipid complex injection via IV infusion every 3 weeks; premedication needed	Yes	**No**	Yes	Upper respiratory tract infection, infusion-related reactions
	Vutrisiran	SC injection, every 3 months at infusion clinic; no premedication needed	Yes	**Yes**	Yes	Pain in extremity, arthralgia, dyspnea, ↓Vitamin A

FDA Prescribing Information.

Key Takeaways

- Amyloid neuropathy is **progressive**
- Carpal tunnel syndrome may precede it by several years
- Look for **congestive HFpEF**
- Look for **dysautonomia**
- Document presence of amyloid
- ***Treat as early as possible***
  - ***3 TTR silencers are currently FDA-approved (and available in the US) for ATTR-PN***



Trials and Tribulations

A Cardiologist's Perspective on the Ongoing Evolution in ATTR-CM

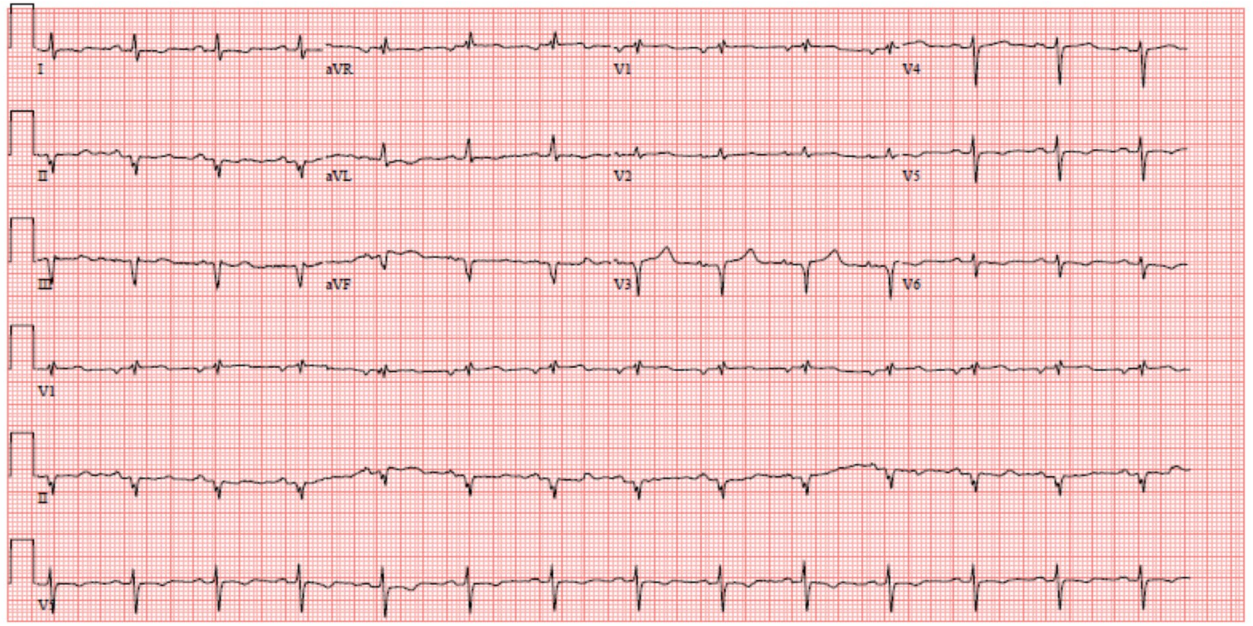
Case 3: “I am Short of Breath”

- 74-year-old Black man with strong family history of deaths due heart failure.
- History of Hypertension
  - Initially required 4 meds but under good control.
  - In the last 3 years stopped 3 of them but remained on hydrochlorothiazide.
- Progressive dyspnea over 3 years, leg swelling
- Dizziness with standing and changing position.
  - Almost passed out 2-3 times over 6 months.
- Alternating diarrhea and constipation but diarrhea has been extremely bothersome.
- Erectile dysfunction that started 2-3 years ago.

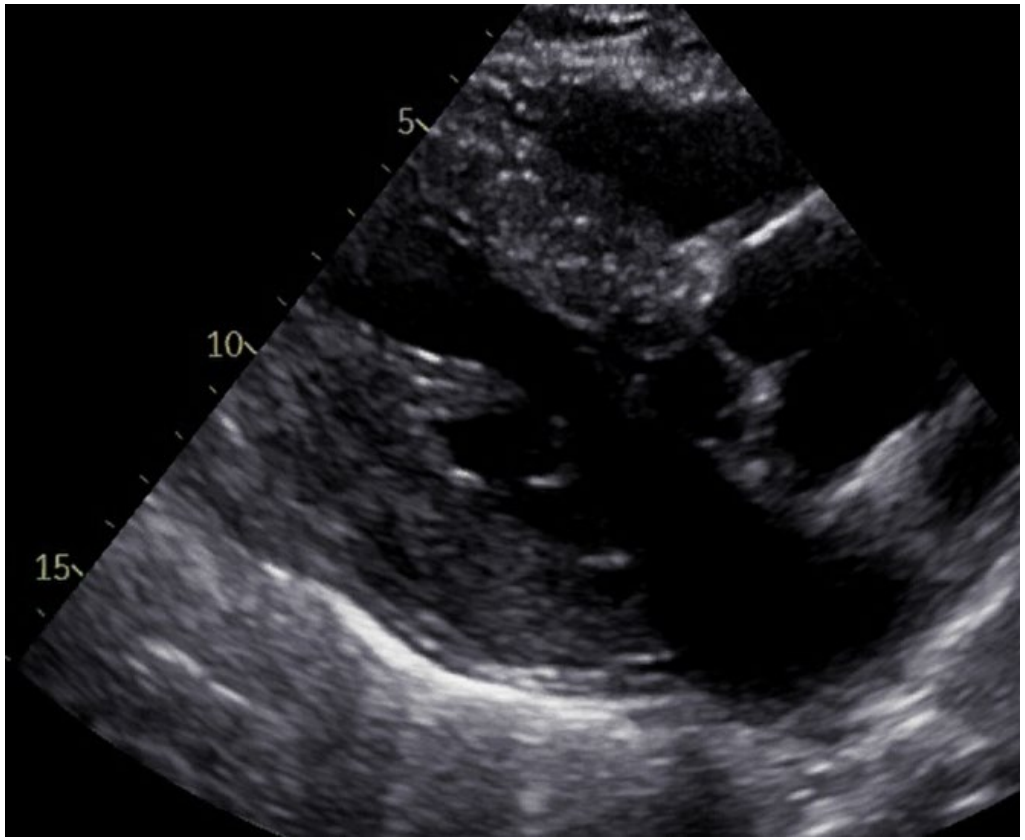


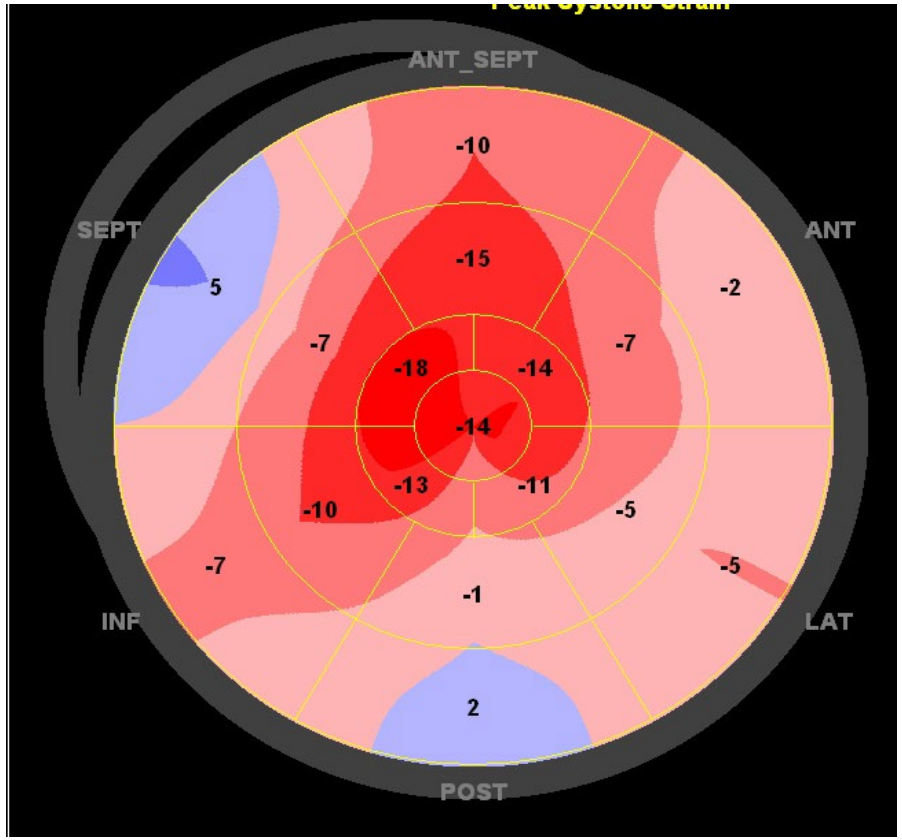
Electrocardiogram

- Hgb 12.8 g/dl
- Creatinine 1.3 mg/dl
- NTproBNP 1,320 pg/ml
- hsTnI 42 ng/L
- Prealbumin (TTR) 14 mg/dl
- Normal Lambda and Kappa LC levels, negative urine and serum IFE

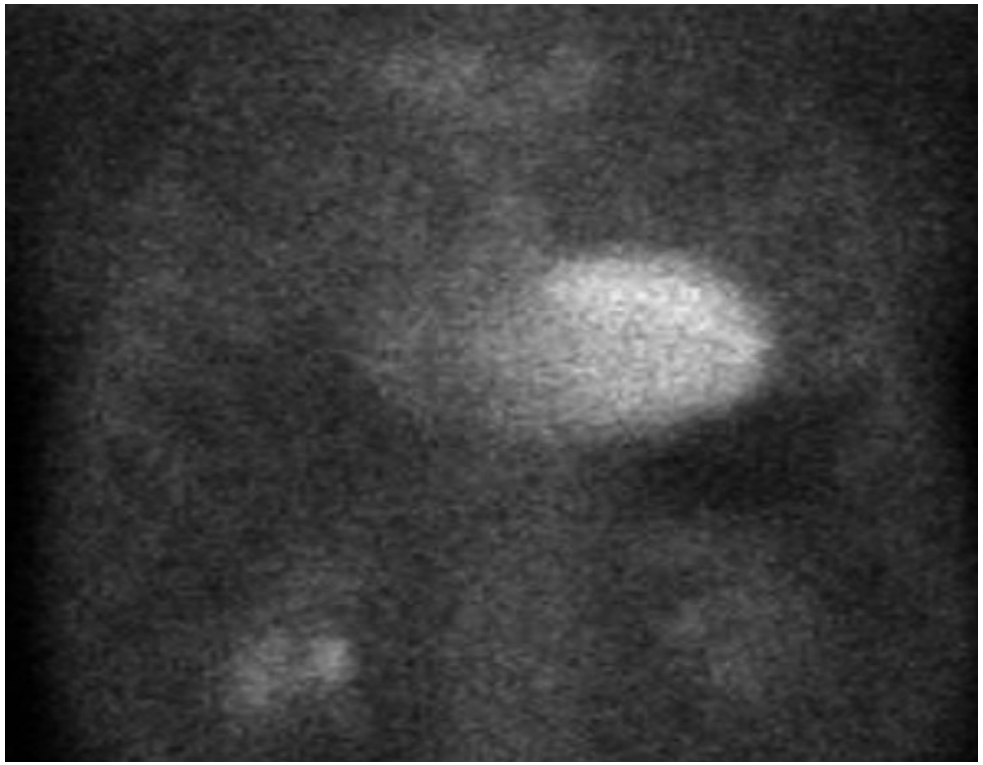


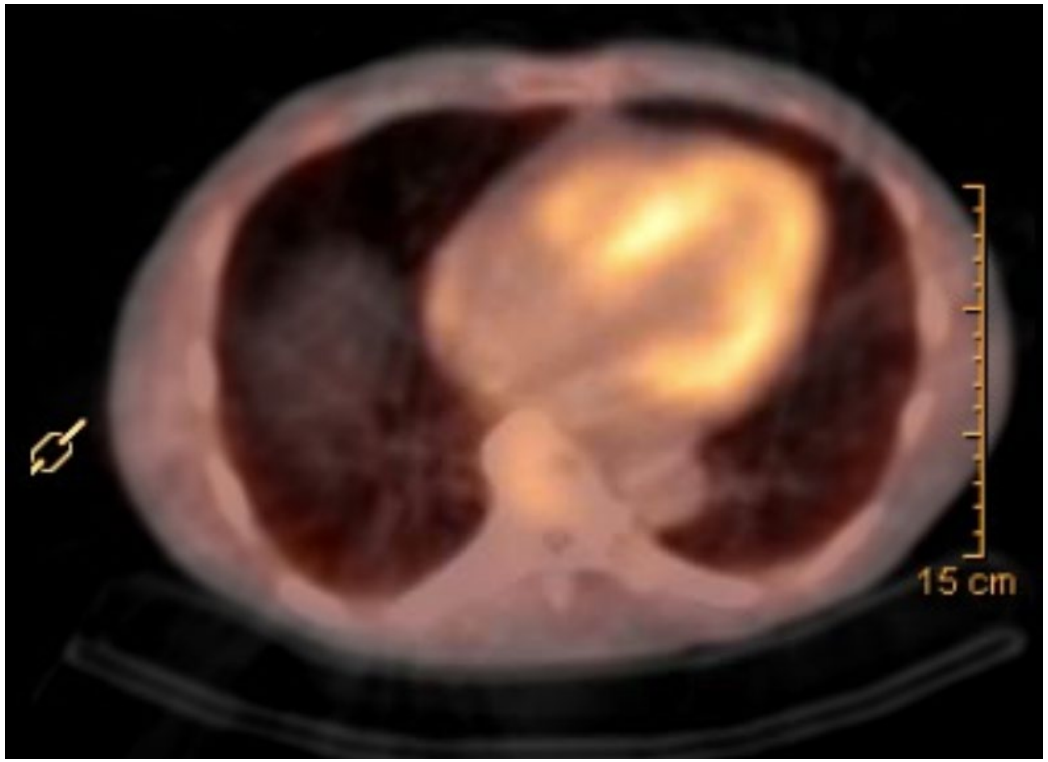
Echocardiogram





Tc-99m Pyrophosphate Scintigraphy





TTR Gene Sequencing

- Val122Ile

Gamification Question



What is the next step in work-up for this patient?

A. No additional testing is needed
B. Cardiac MRI
C. Neurological evaluation
D. Expanded genetic panel testing

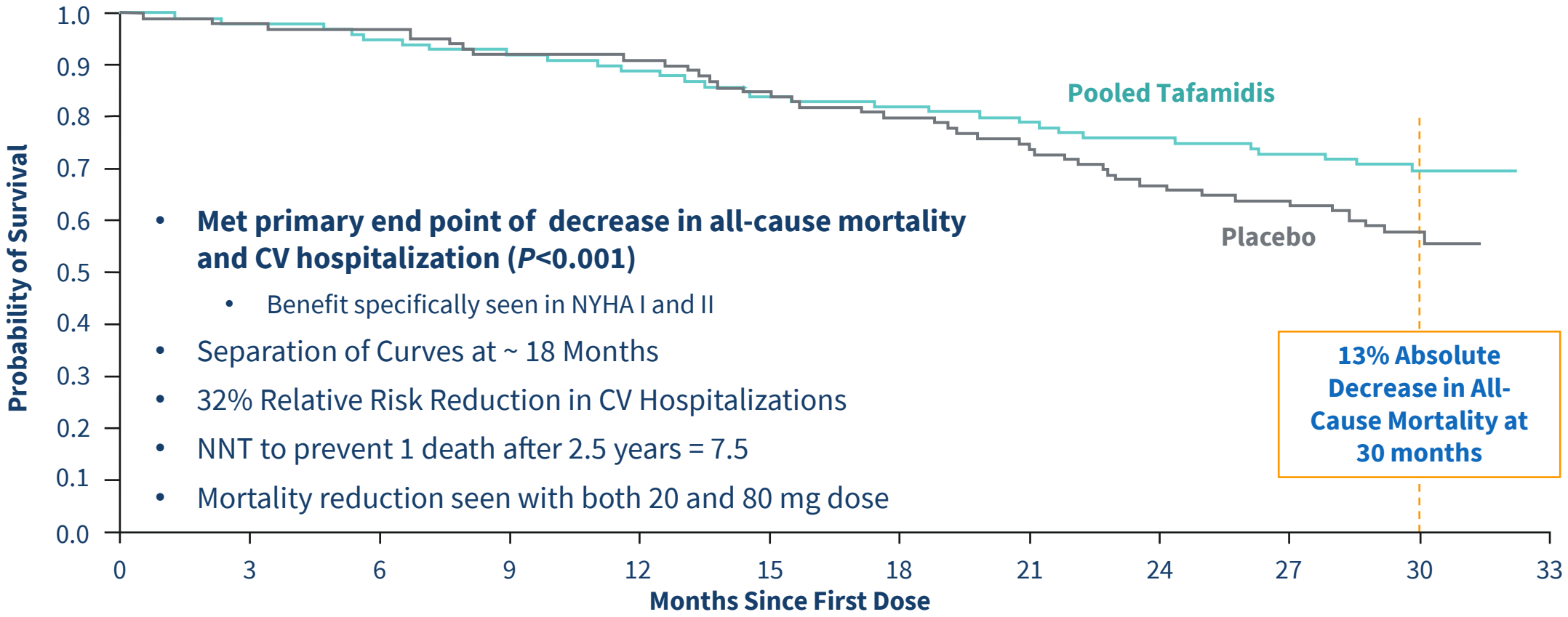
Treatment Options in the US



FDA Prescribing Information.

ATTR-ACT Results

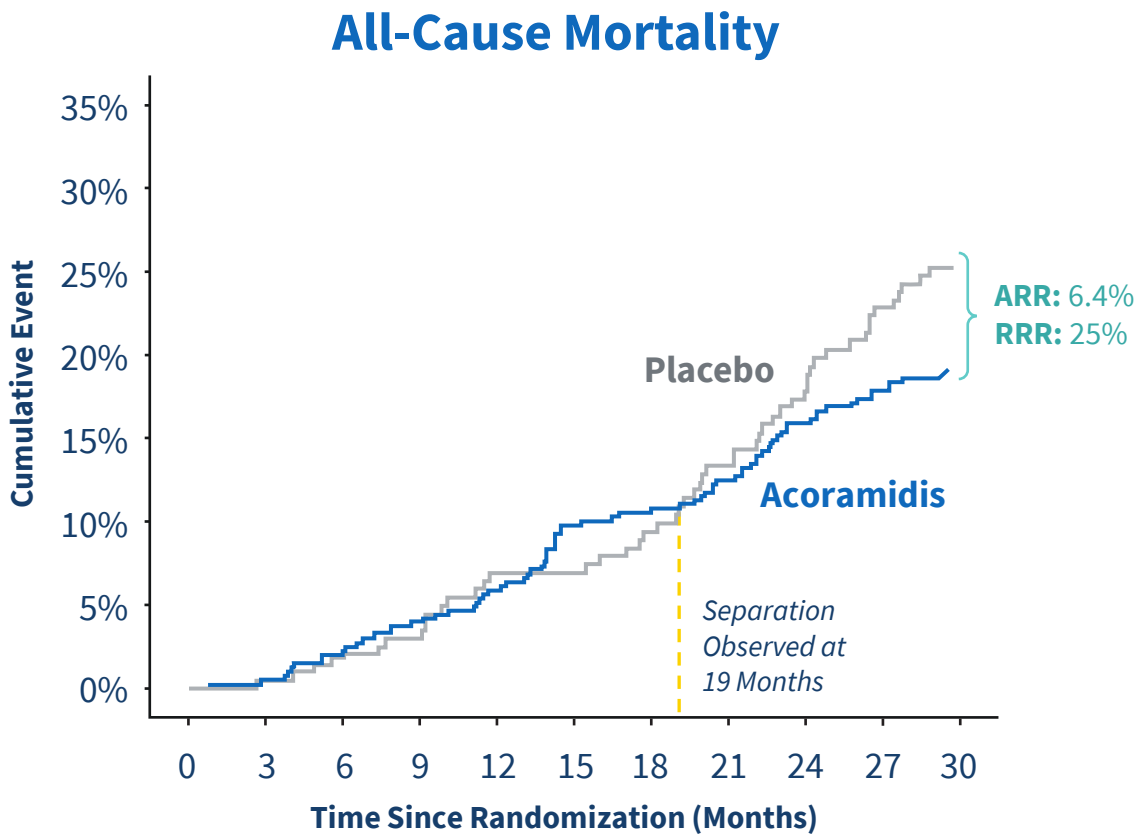
Primary Endpoint: All Cause Mortality



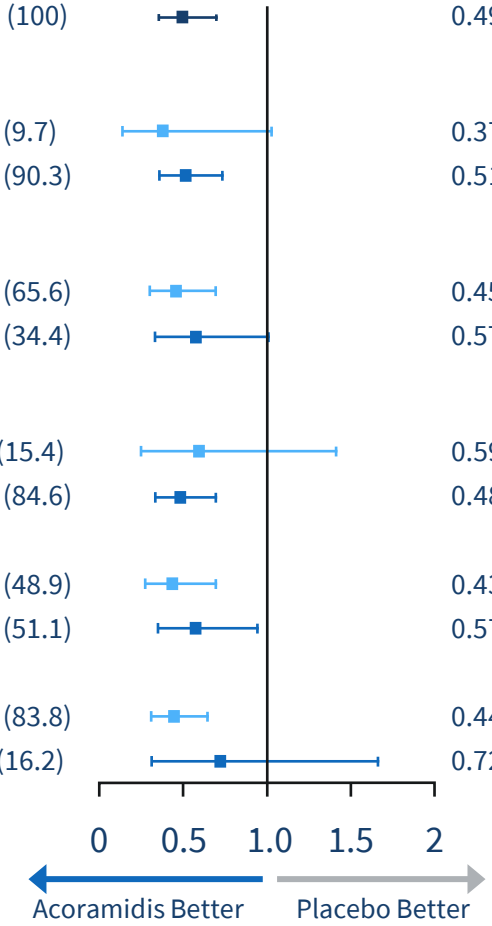
- **Met primary end point of decrease in all-cause mortality and CV hospitalization (*P*<0.001)**
  - Benefit specifically seen in NYHA I and II
- Separation of Curves at ~ 18 Months
- 32% Relative Risk Reduction in CV Hospitalizations
- NNT to prevent 1 death after 2.5 years = 7.5
- Mortality reduction seen with both 20 and 80 mg dose

Maurer MS, et al. *N Engl J Med.* 2018; Sperry BW, et al. *JAMA Cardiol*. 2023.

ATTRibute-CM: Acoramidis in ATTR-CM

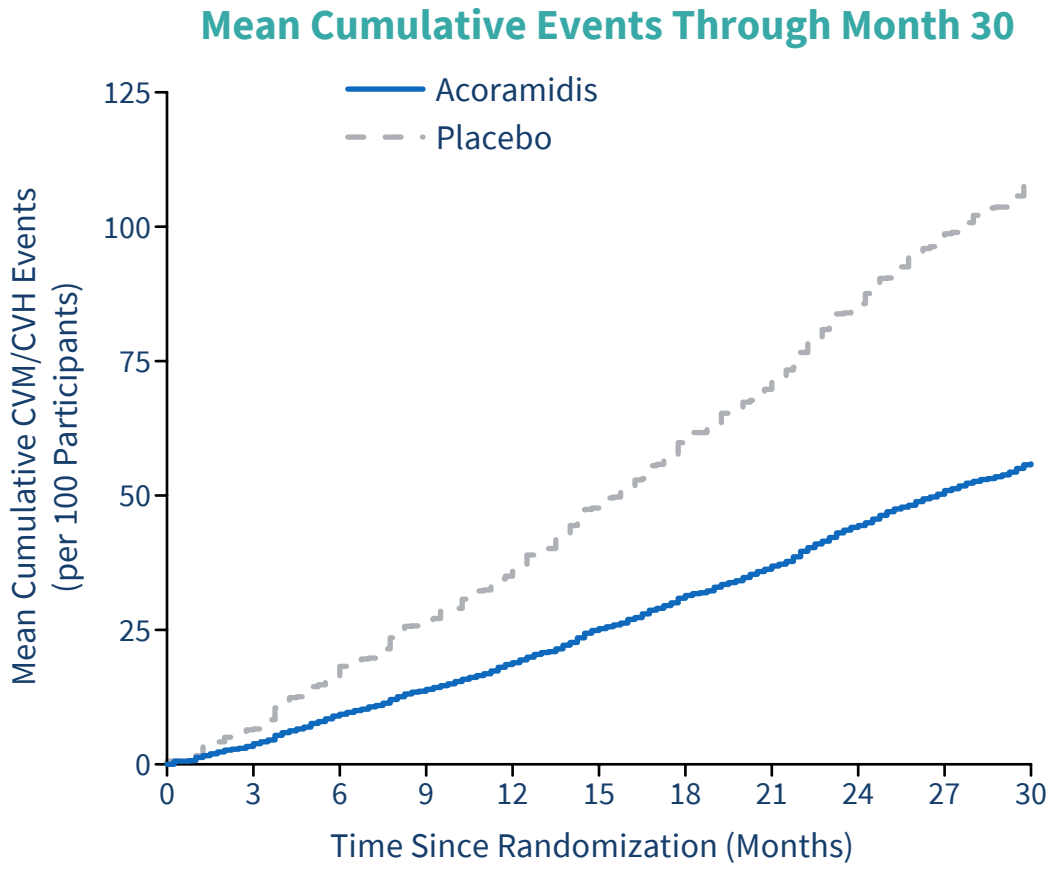


Subgroup	N (%)	RR (95% CI)
Overall	611 (100)	0.496 (0.355-0.695)
ATTR-CM Genotype		
ATTRm-CM	59 (9.7)	0.377 (0.139-1.027)
ATTRwt-CM	552 (90.3)	0.514 (0.360-0.734)
NT-proBNP (pg/mL)		
≤3000	401 (65.6)	0.456 (0.299-0.695)
>3000	210 (34.4)	0.576 (0.330-1.003)
eGFR (mL/min/1.73m^2)		
<45	94 (15.4)	0.594 (0.250-1.415)
≥45	517 (84.6)	0.481 (0.334-0.692)
Age (Years)		
<78	299 (48.9)	0.437 (0.275-0.696)
≥78	312 (51.1)	0.576 (0.353-0.940)
NYHA Class		
I, II	512 (83.8)	0.447 (0.310-0.645)
III	99 (16.2)	0.721 (0.313-1.660)



Gillmore J, et al. *N Engl J Med*. 2024.

Acoramidis Reduced CVM/CVH Events by 49%

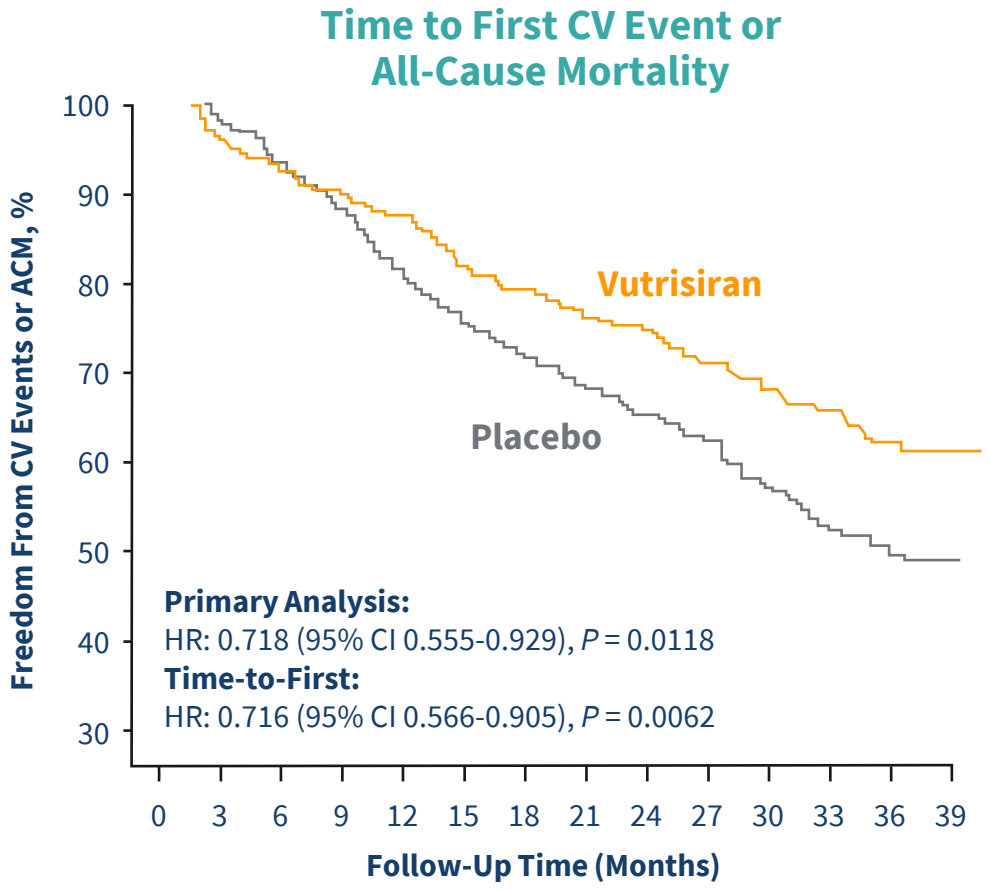


Outcome	Acoramidis (n = 409)	Placebo (n = 202)
Participants With CVM or Recurrent CVH, n (%)	136 (33.3)	98 (48.5)
Hazard Ratio (95% CI)	0.51 (0.43, 0.62)	
P-Value	**<0.0001**	

Masri A, et al. *JACC*. 2026.

HELIOS-B

Vutrisiran vs Placebo

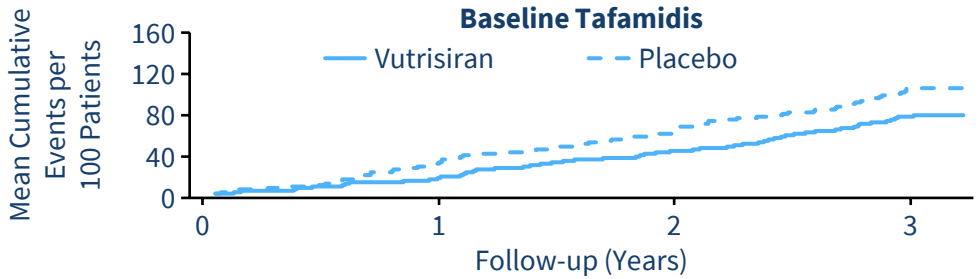


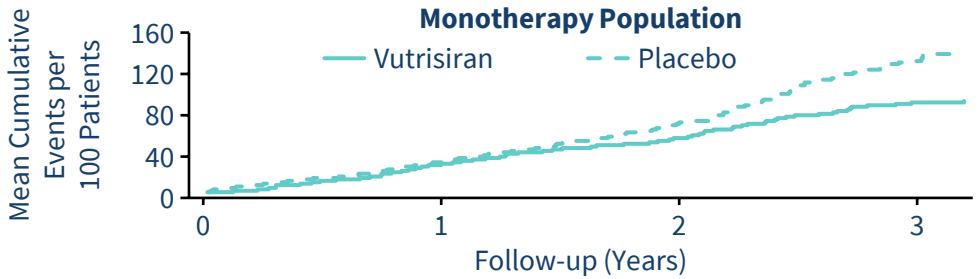
Endpoint	Tx Effect Est.	Overall Population (N=654)		Monotherapy Population (N=395)	
		Tx Effect	P-Value	Tx Effect	P-Value
Primary Endpoints: Composite Outcome of All-Cause Mortality and Recurrent CV Events	Hazard Ratio	0.718	0.0118	0.672	0.0162
Secondary Endpoints:					
6-MWT Change at Month 30	LS Mean Difference	26.46	0.00008	32.09	0.0005
KCCQ-OS Change at Month 30	LS Mean Difference	5.80	0.0008	8.69	0.0003
All-Cause Mortality Through Month 42	Hazard Ratio	0.645	0.0098	0.655	0.0454
NYHA Class % Stable or Improved at Month 30	Adjusted % Difference	8.7%	0.0217	12.5%	0.0121

Fontana M, et al. *N Engl J Med*. 2025; Witteles R, et al. *J Am Coll Cardiol*. 2025.

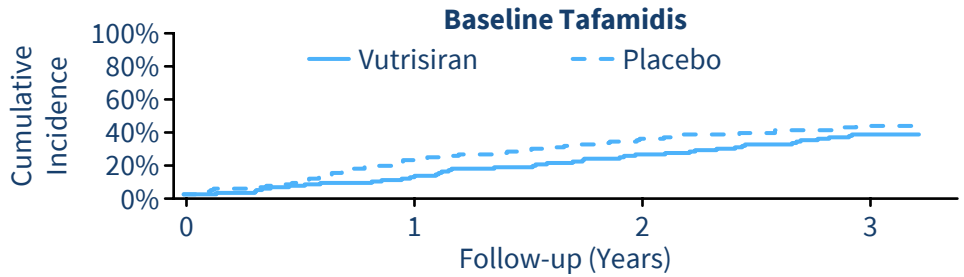
Outcomes Based on Tafamidis Use in Helios-B

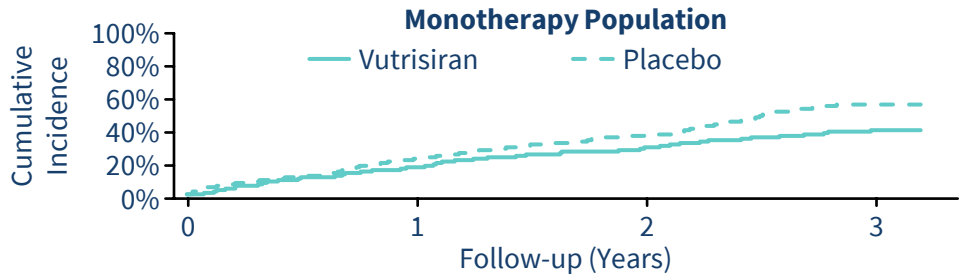
All-Cause Death and Recurrent CV Events



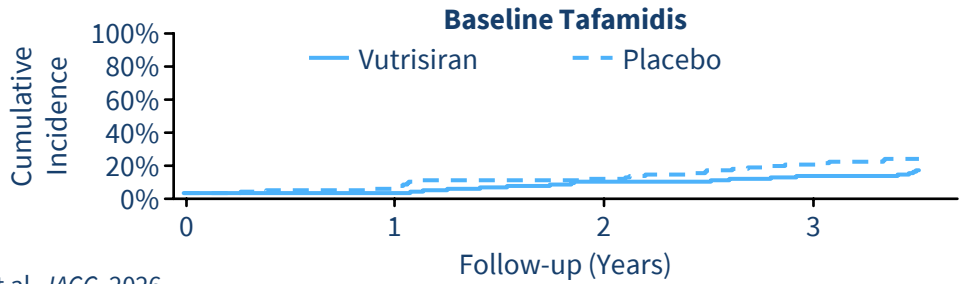


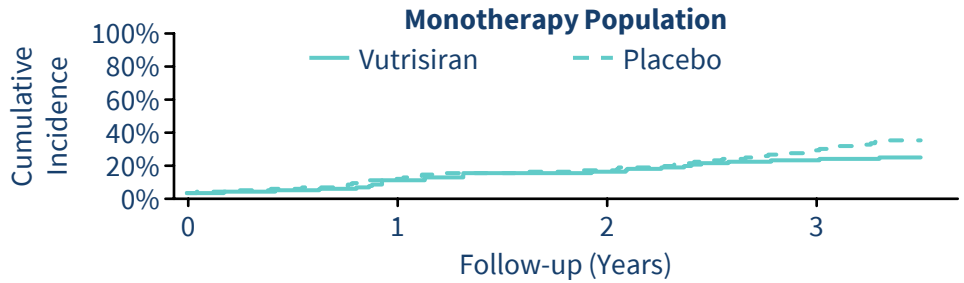
Time to First All-Cause Death or CV Events





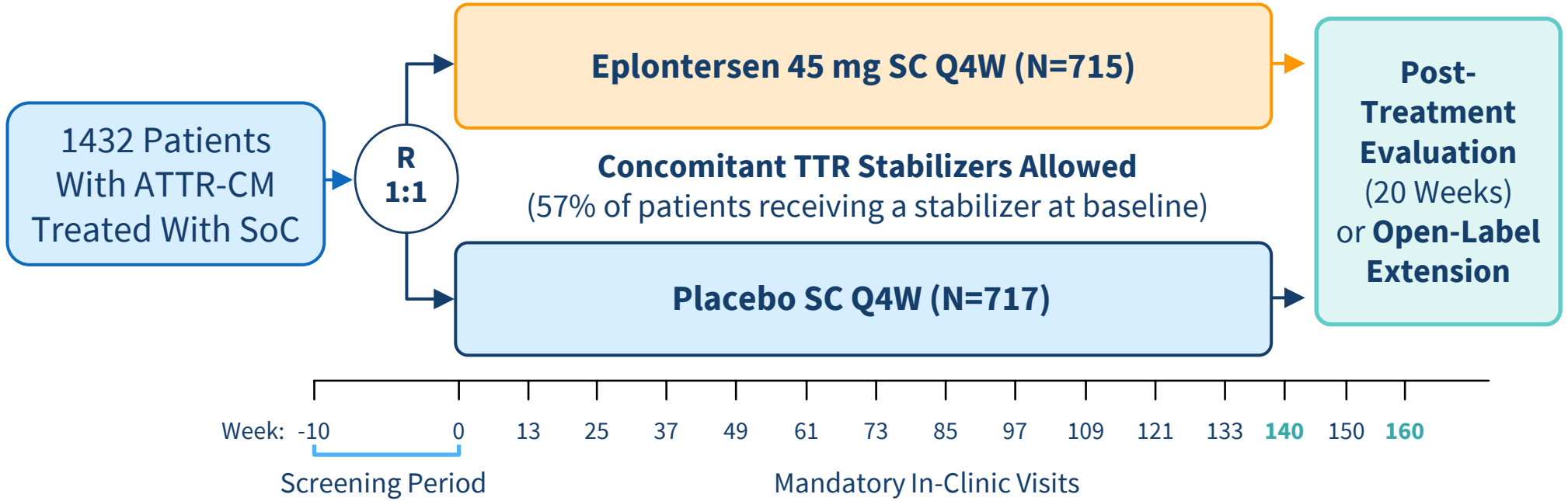
All-Cause Death Up to 42 Months





Hamatani Y, et al. *JACC*. 2026.

CARDIO-TTRansform: Study Design



Primary Endpoint:

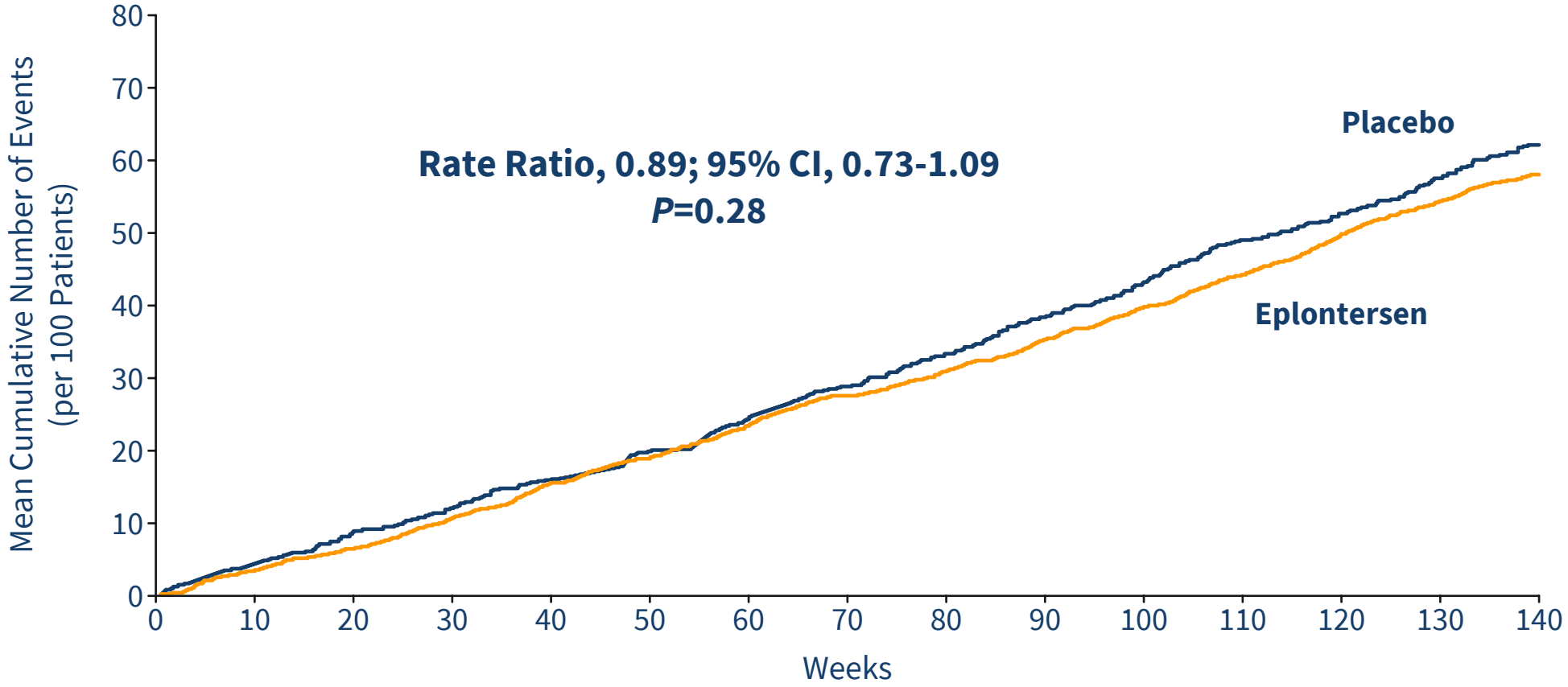
Composite of CV mortality and recurrent CV clinical events up to week 140

Secondary Endpoints (in Hierarchical Order):

- Change in 6MWT distance at week 140
- Change in KCCQ-OS score at week 140
- Total recurrent CV clinical events up to week 140
- All-cause mortality up to weeks 160 and 140
- Primary endpoint in patients receiving stabilizer at baseline up to week 140
- CV mortality up to weeks 160 and 140

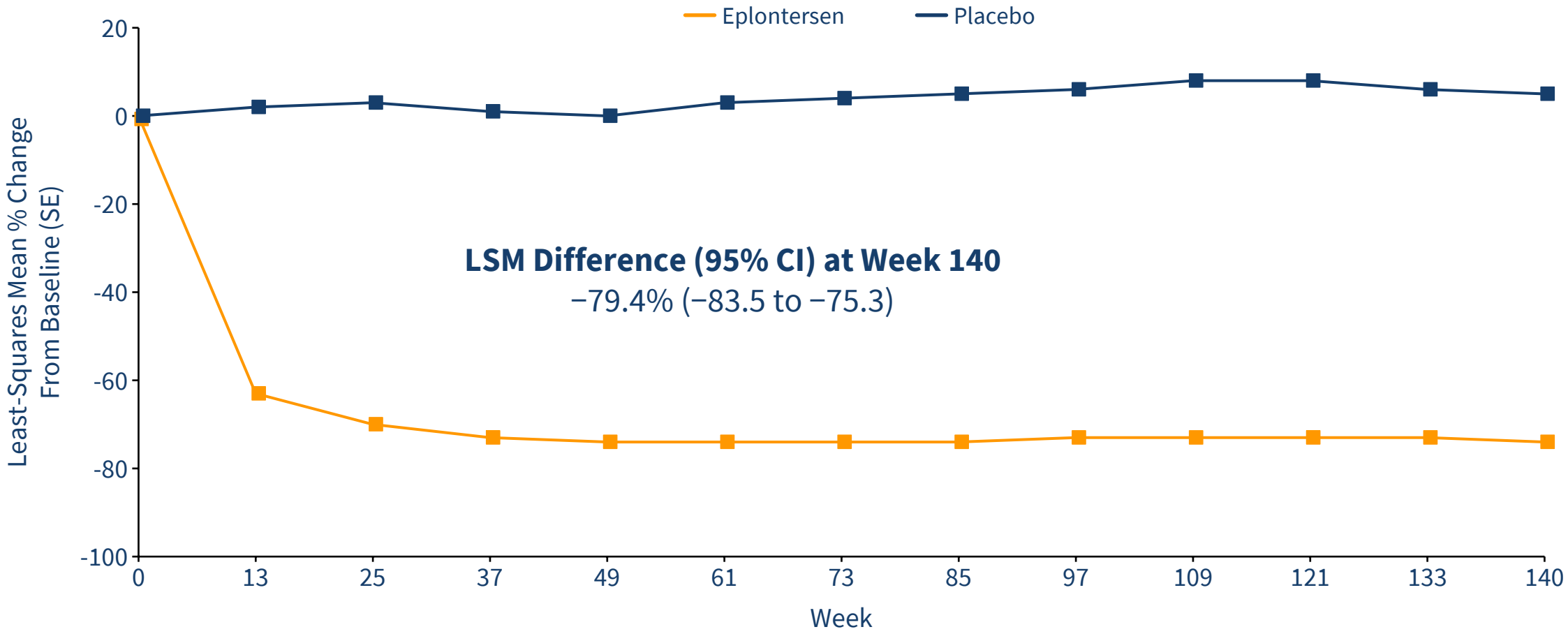
Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

CARDIO-TTRansform: Eplontersen vs Placebo



Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

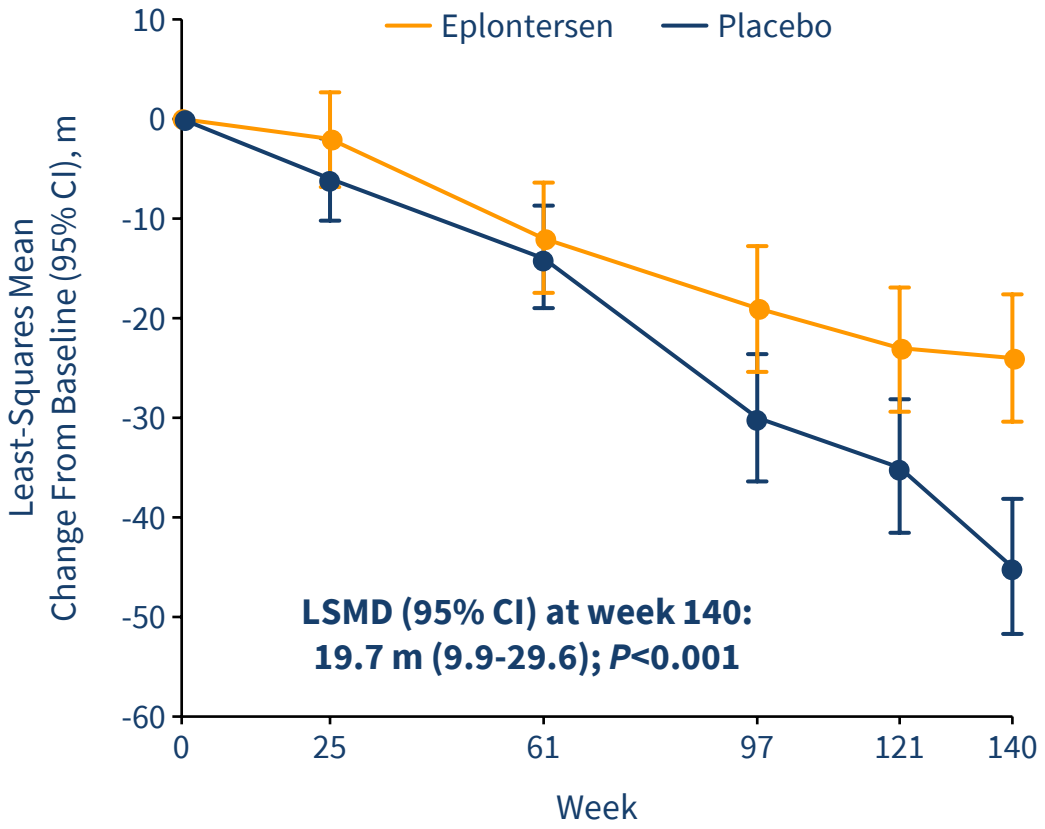
CARDIO-TTRansform: Serum TTR



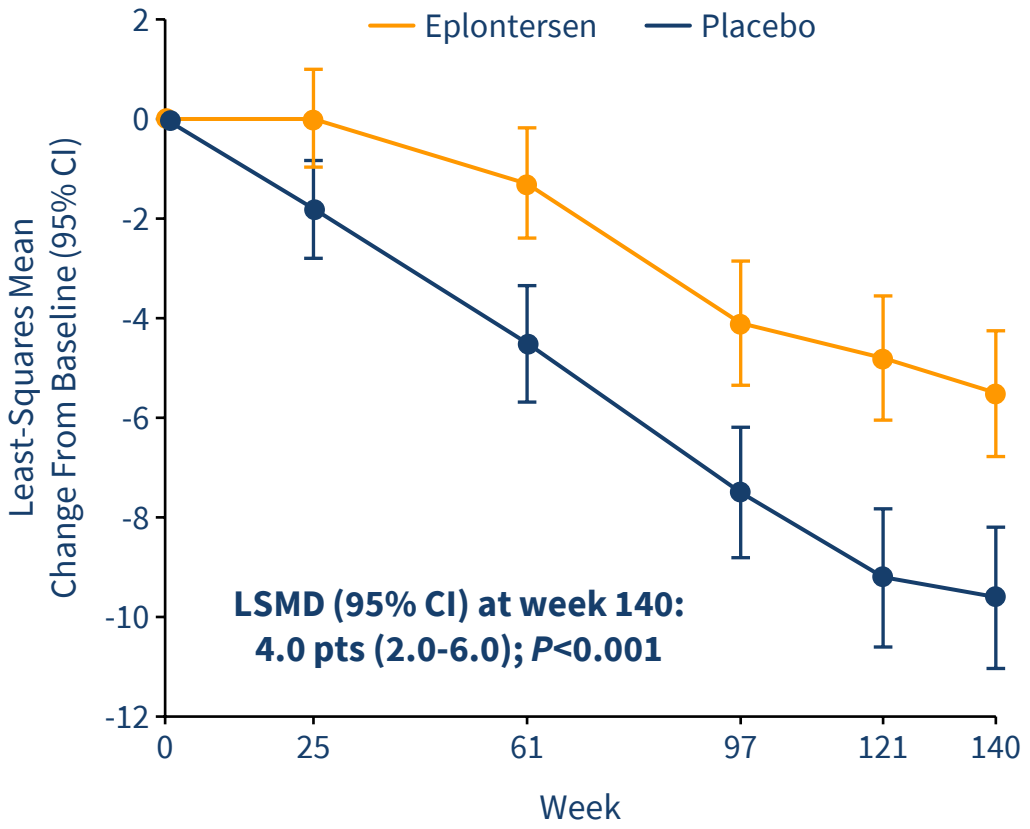
Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

CARDIO-TTRansform: Functional Outcomes

6MWT

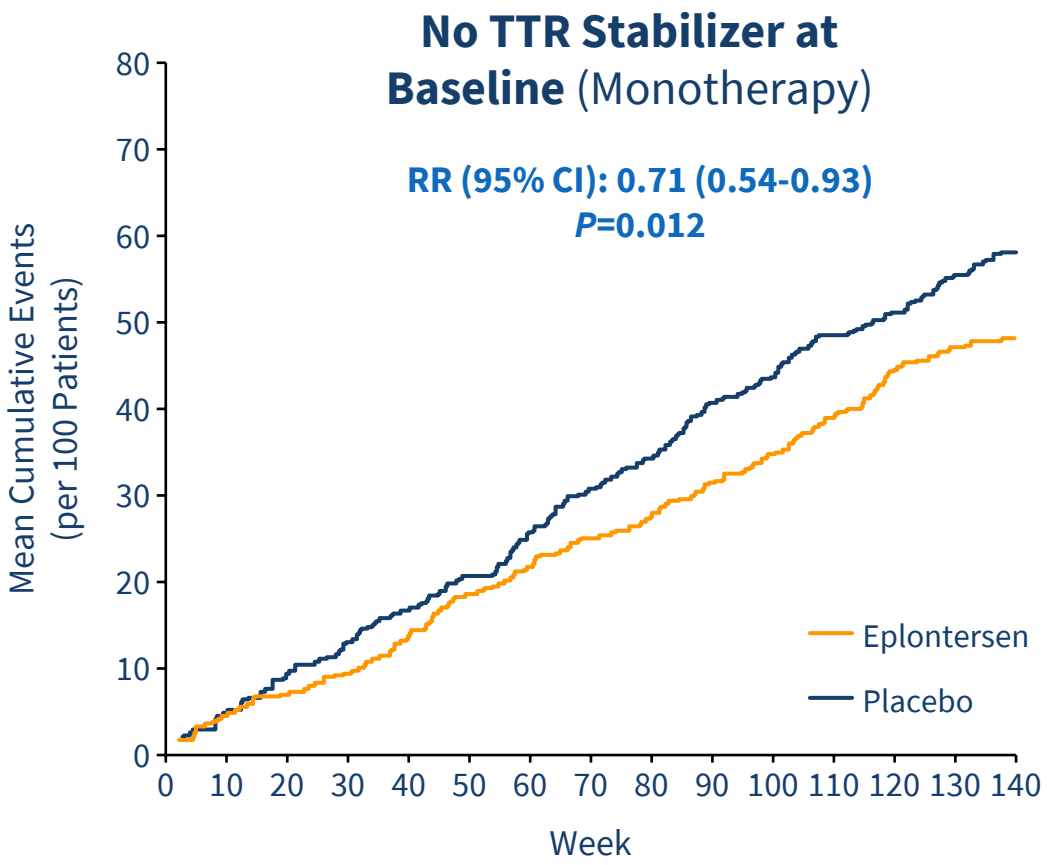


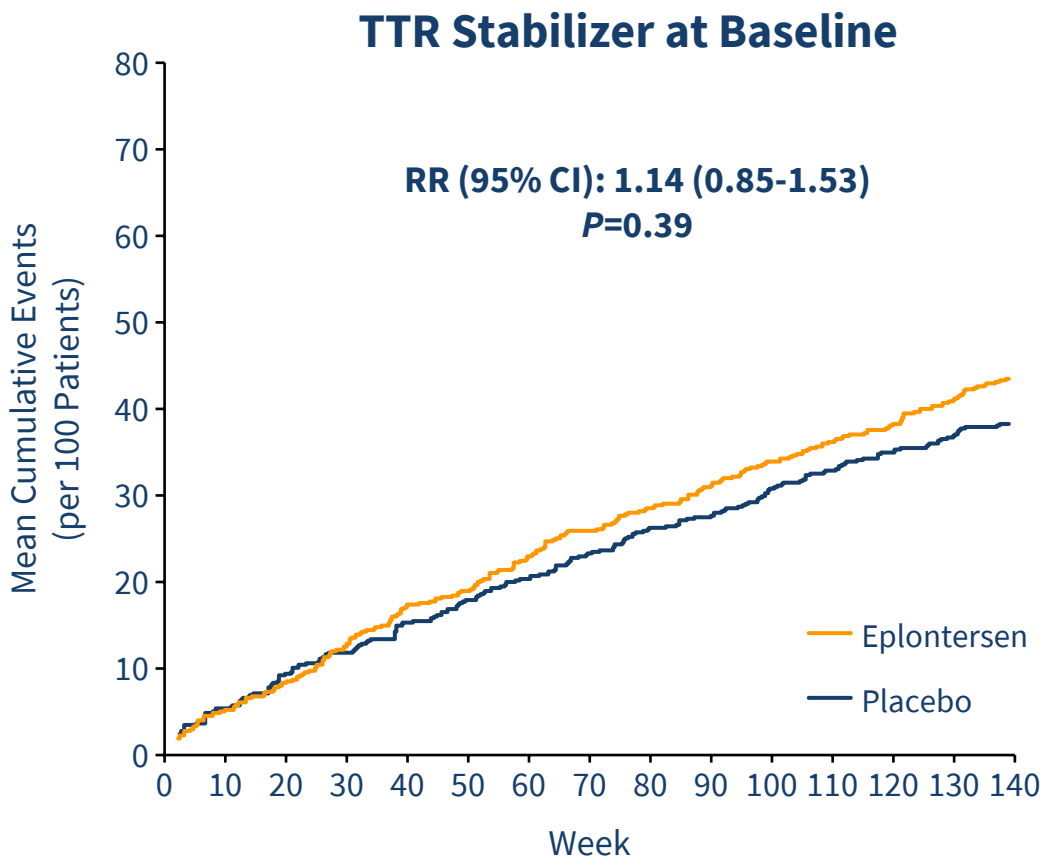
KCCQ-OS Score



Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

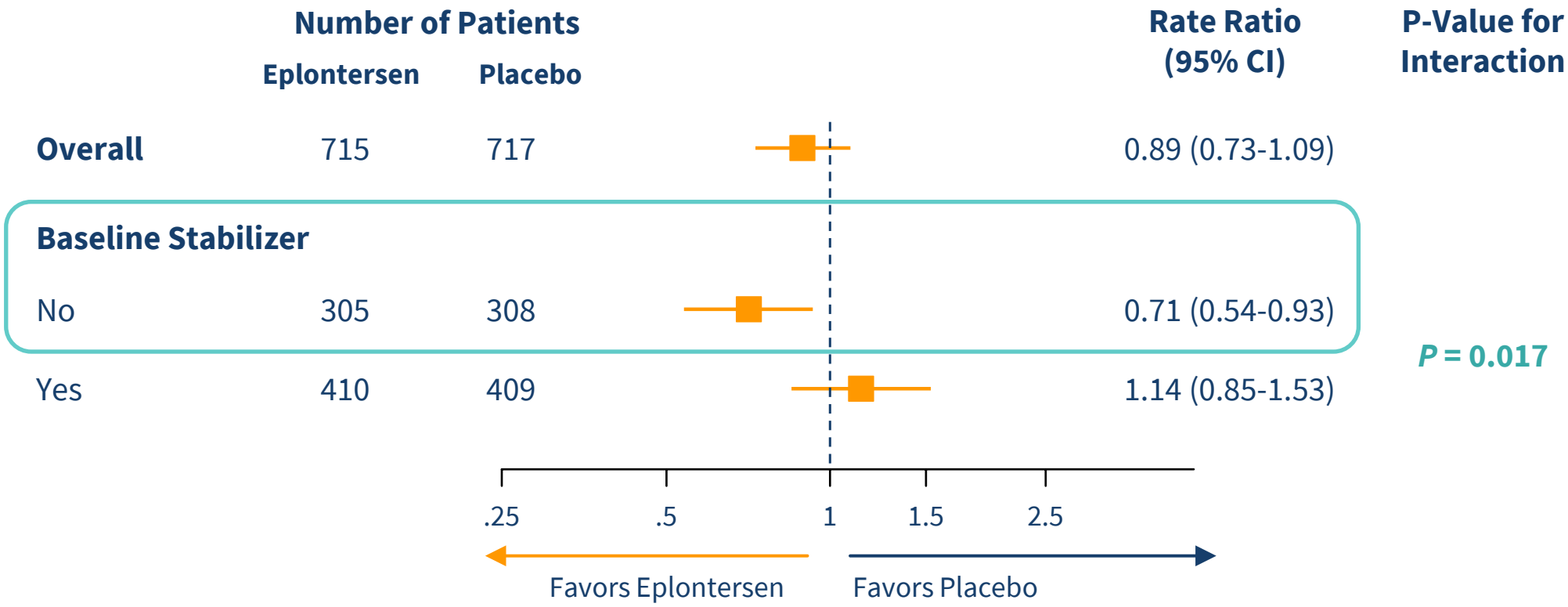
CARDIO-TTRansform: Baseline TTR Stabilizer Use





Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

CARDIO-TTRansform: Baseline Stabilizer Subgroups



Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

Clinical Benefit With Eplontersen in the Monotherapy Subgroup

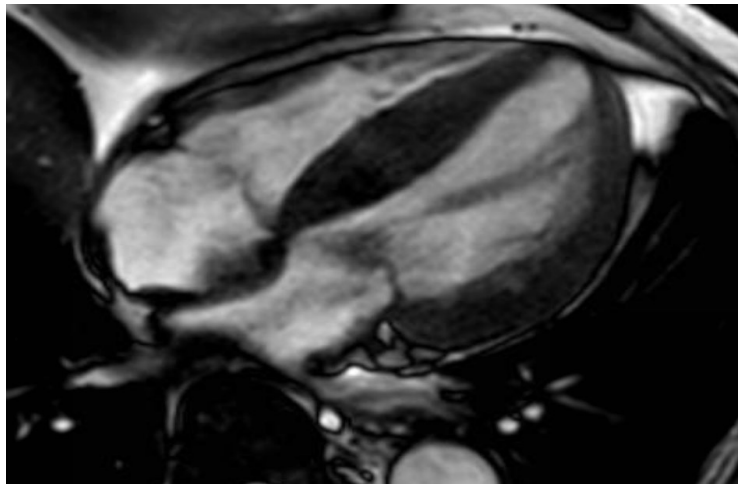
Prespecified Endpoints	**No TTR Stabilizer at Baseline** (N = 613) (Monotherapy)		**TTR Stabilizer at Baseline** (N = 819)	
	Efficacy vs Placebo (95% CI)	**P-Value**	**Efficacy vs Placebo** (95% CI)	**P-Value**
Primary Endpoint	RR: 0.71 (0.54-0.93)	0.012	RR: 1.14 (0.85-1.53)	0.39
Δ 6MWT (m)	LSMD: 29.90 (14.3-45.5)	<0.001	LSMD: 12.00 (-1.0 to 25.0)	0.07
Δ KCCQ-OS (points)	LSMD: 7.6 (4.2-11.0)	<0.001	LSMD: 1.1 (-1.3 to 3.6)	0.37
Recurrent CV Events	RR: 0.67 (0.50-0.90)	0.008	RR: 1.16 (0.85-1.58)	0.35
All-Cause Death	HR: 0.85 (0.62-1.16)	0.30	HR: 0.70 (0.49-1.01)	0.06
CV Death	HR: 0.90 (0.61-1.32)	0.59	HR: 0.83 (0.55-1.25)	0.37

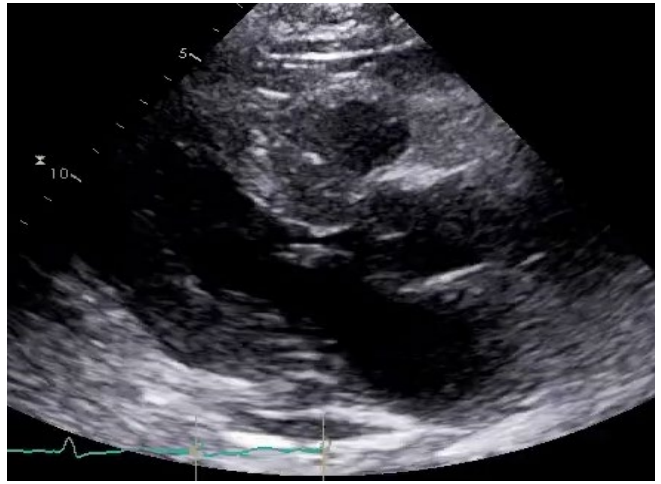
Fontana A, et al. *N Engl J Med*. 2026; Masri A, et al. *Circ Heart Fail*. 2026; Garcia-Pavia P, et al. *Nature Med*. 2026.

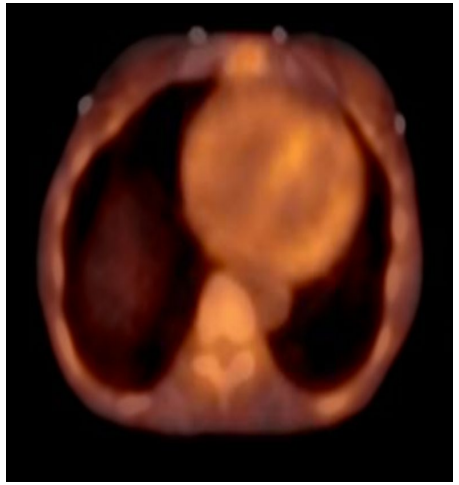
How Do We Monitor Patients?

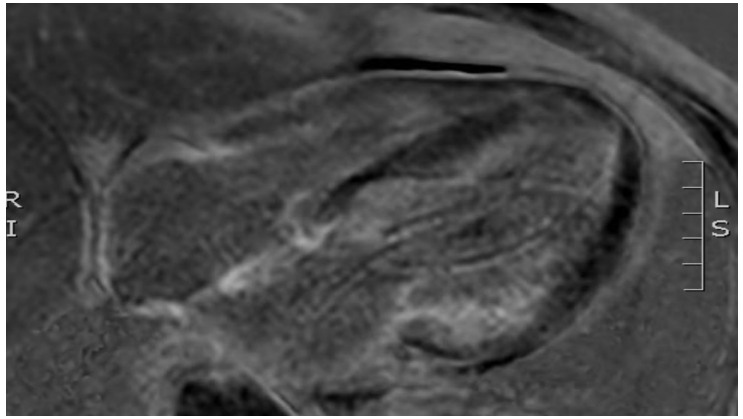
Deposition/Infiltration ⟷ Heart Failure

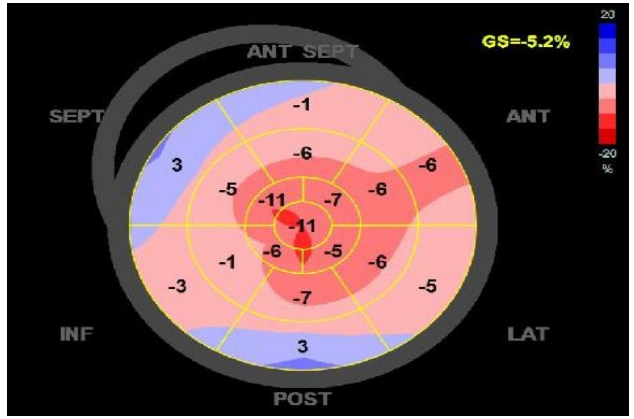








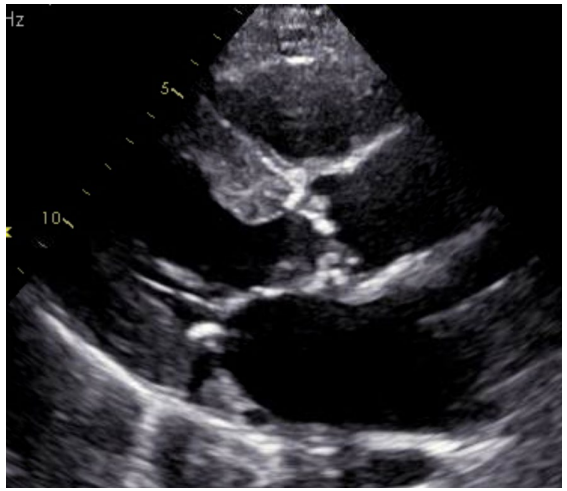


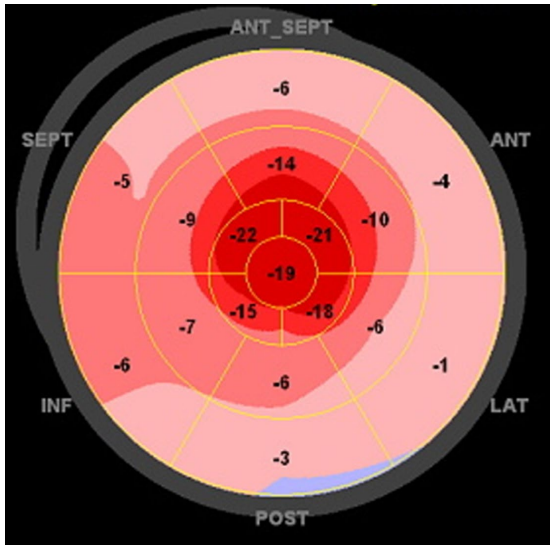


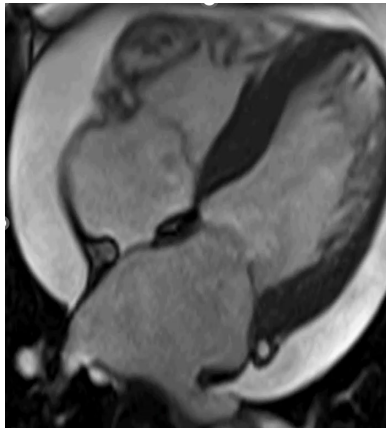
Mortality
CV Hospitalizations
Urgent Visits
Diuretics Intensification
Neuropathy

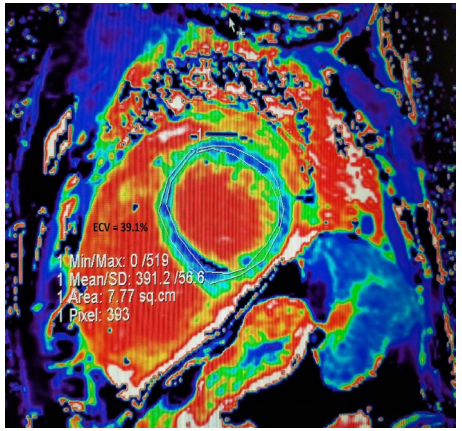
KCCQ
NYHA class
6MWT

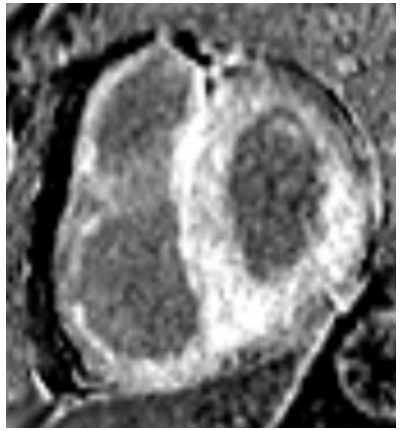
NT-proBNP
Troponin
TTR level

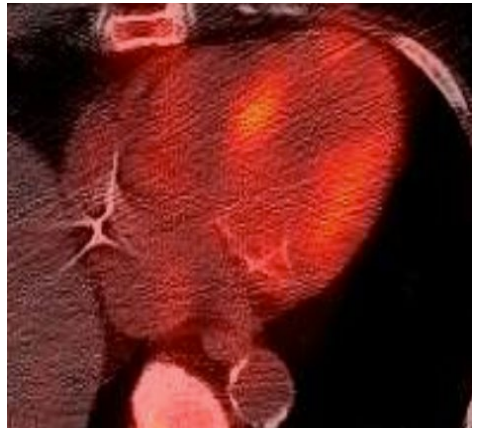


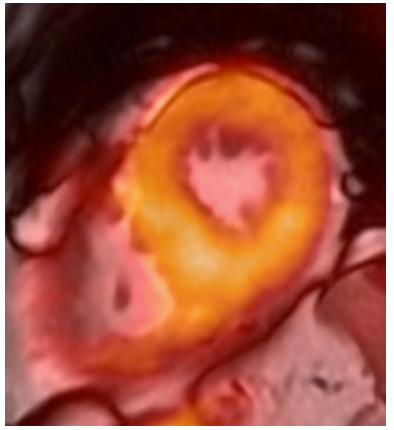








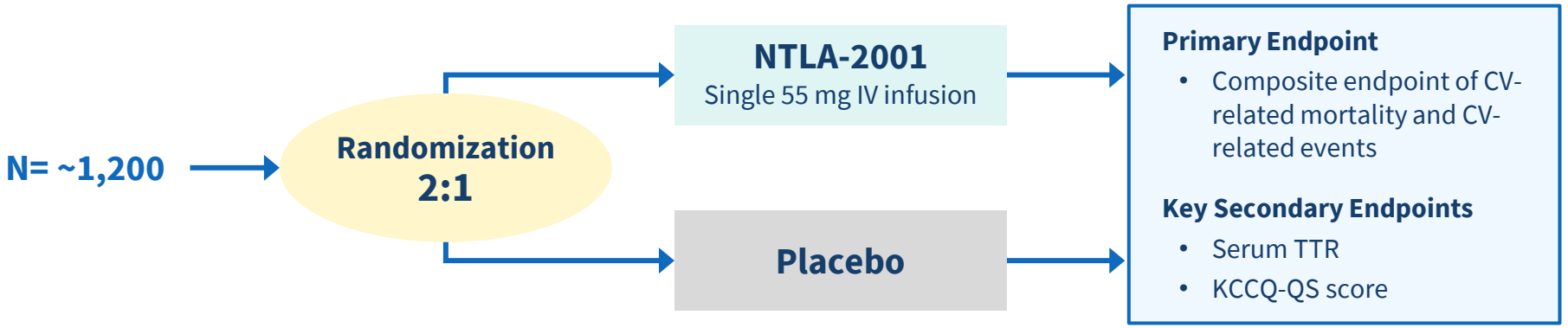




Ongoing Trials

MAGNITUDE

TTR Gene Editing Phase III Trial



*Restarted after liver injury risk mitigation strategies were implemented

Key **Eligibility** Criteria

- Adult patients with diagnosis of hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/ml
- Other criteria apply

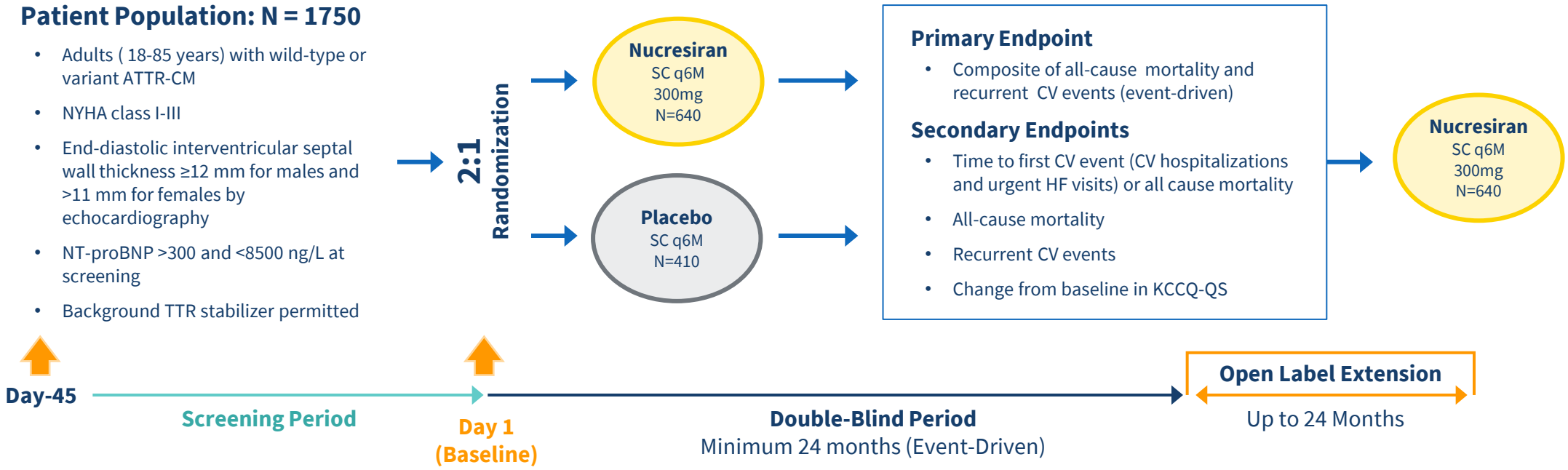
Key **Exclusion** Criteria

- RNA silencer therapy (patisiran, inotersen and/or eplontersen) within 12 month prior to dosing. Any prior vutrisiran use is not allowed.
- Other criteria apply

ClinicalTrials.gov; Gillmore J, et al. Presented at EU ATTR. 2023.

TRITON-CM

Nucresiran vs Placebo



ClinicalTrials.gov; Fontana M, et al. Poster Presented at ESC HFA. 2025.

Fibril Depleters

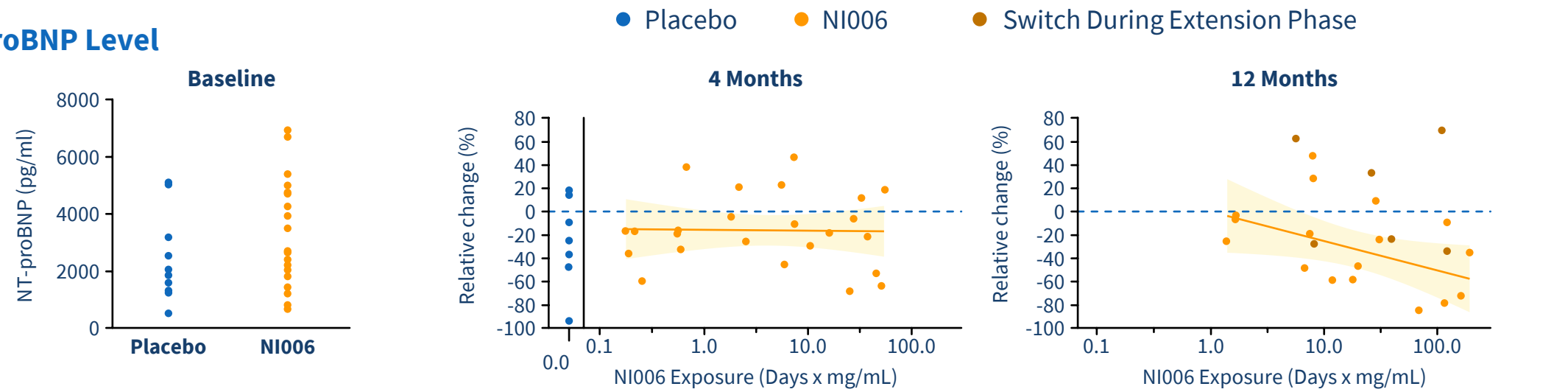
Name of Drug	Type of Amyloidosis	Phase of Study	Sponsor	Outcome
NNC6019 / PRX004 (Coramitug)	ATTR	2 3 (CleopATTRA)	Novo-Nordisk	+ NT-proBNP change Pending
NI006 / ALXN2220 (Cliramitug)	ATTR	3 (DepleTTR-CM)	AstraZeneca	Total occurrences of ACM and CV events Pending
AT-02	AL, ATTR, others	1	Attralus	Pending for ATTR-CM + findings from small AL cohort

ClinicalTrials.gov.

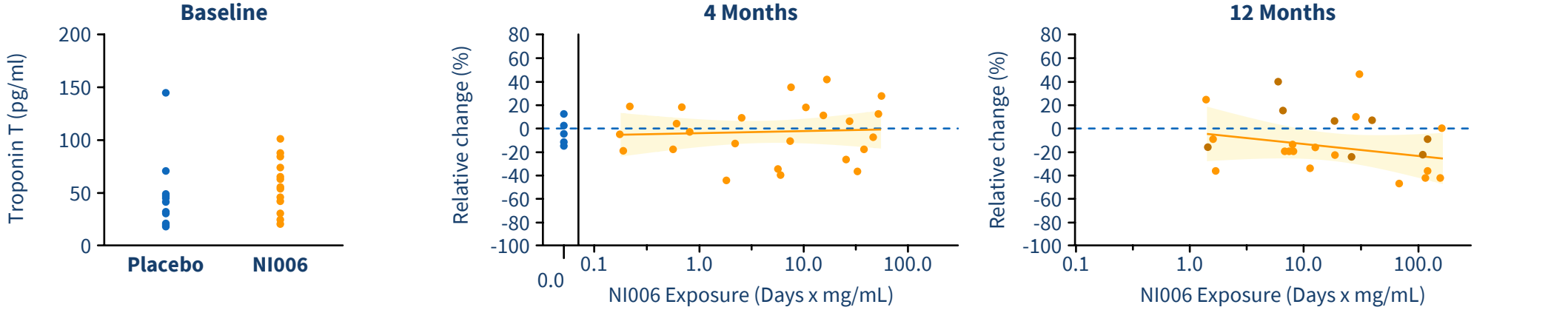
ALXN2220/Cliramitug Fibril Depleter Phase I



NT-proBNP Level



Troponin T Level

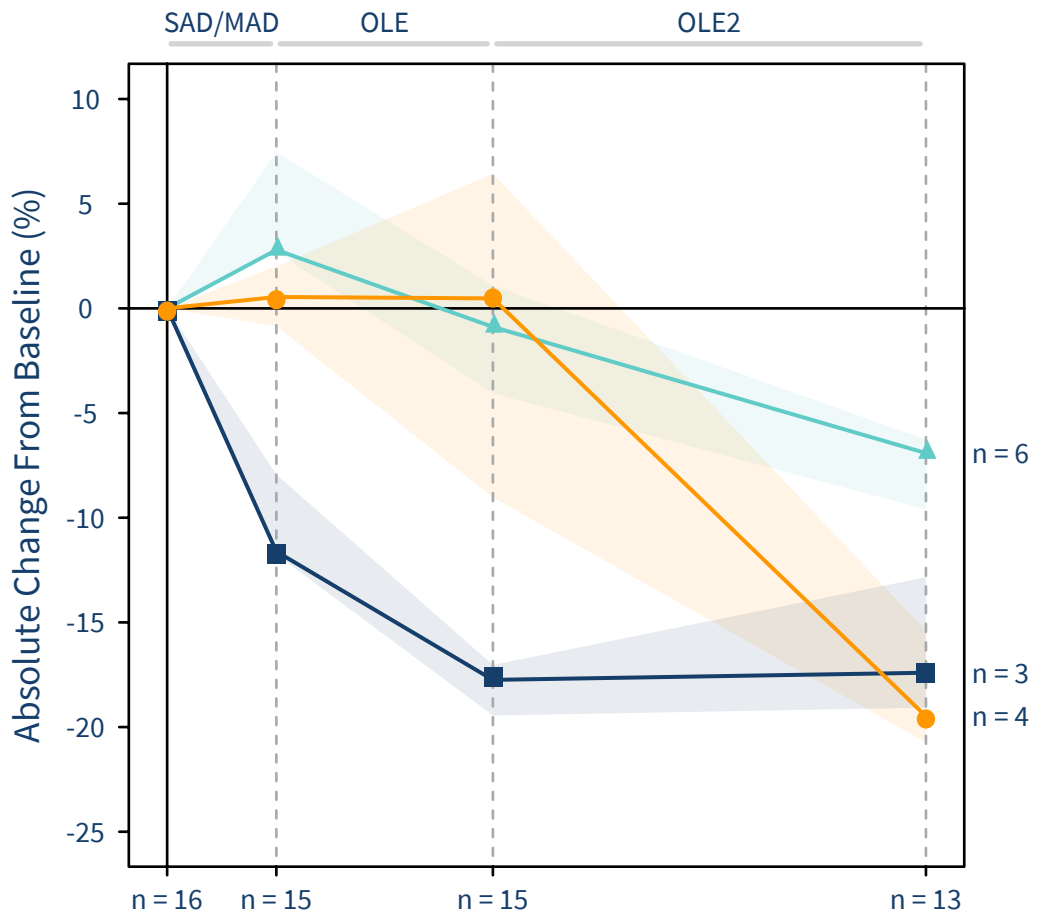


Garcia-Pavia P, et al. *N Engl J Med*. 2023.

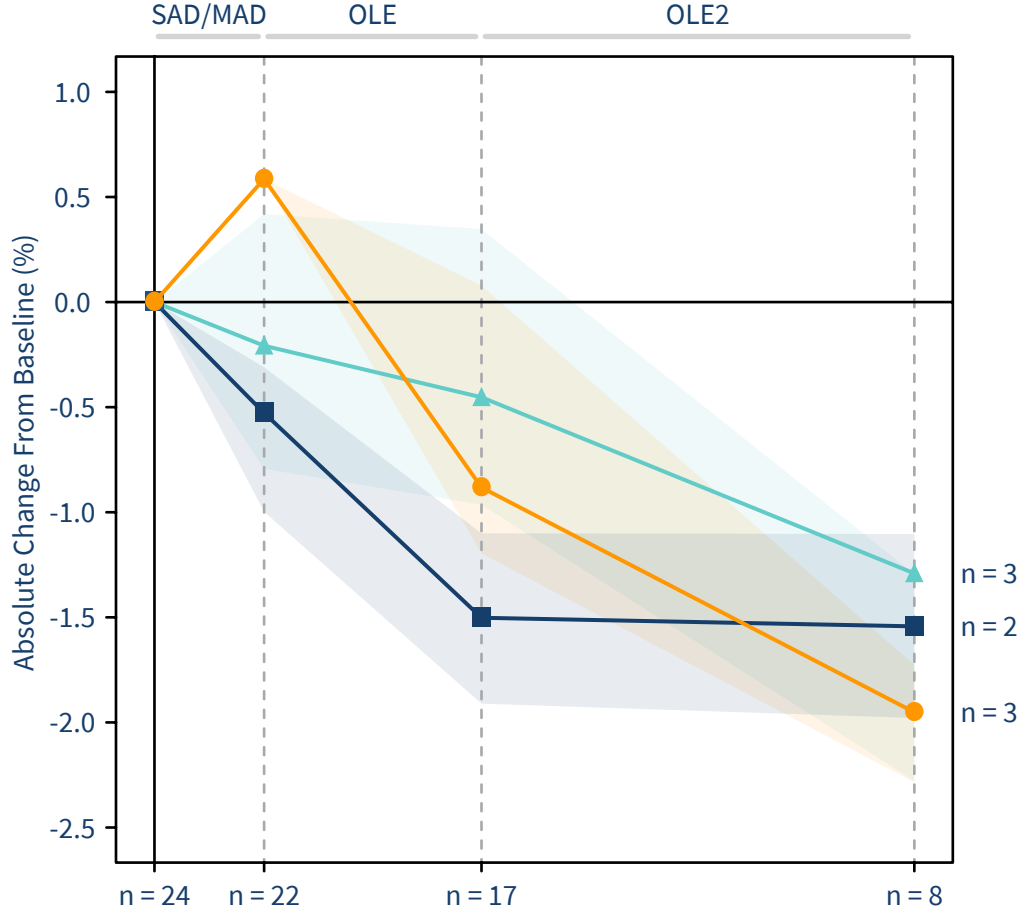
Longer Term Follow-up

Cliramitug Low Starting Dose
Cliramitug High Starting Dose
Placebo/Cliramitug Mixed Dose Levels

ECV on Cardiac MRI

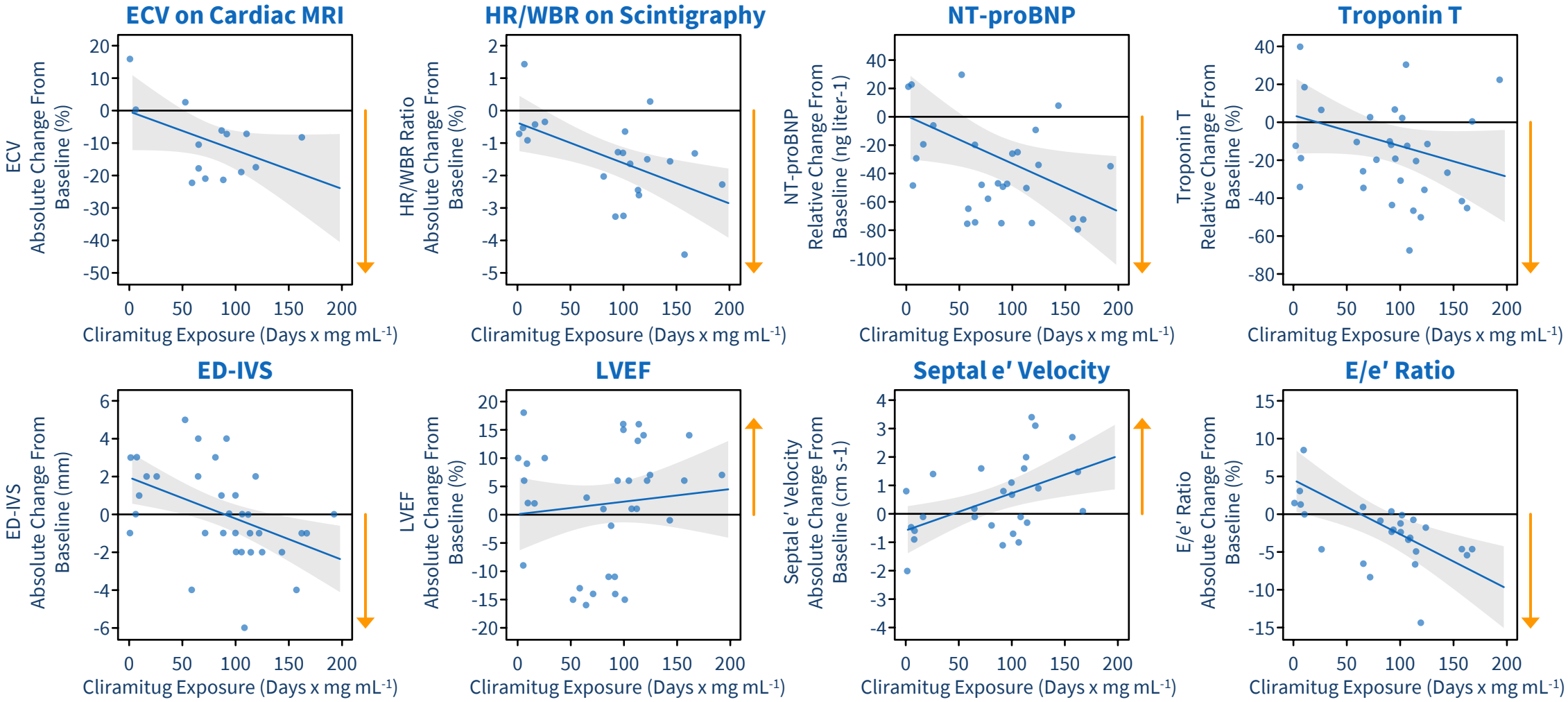


HR/WBR on Bisphosphonate Scintigraphy



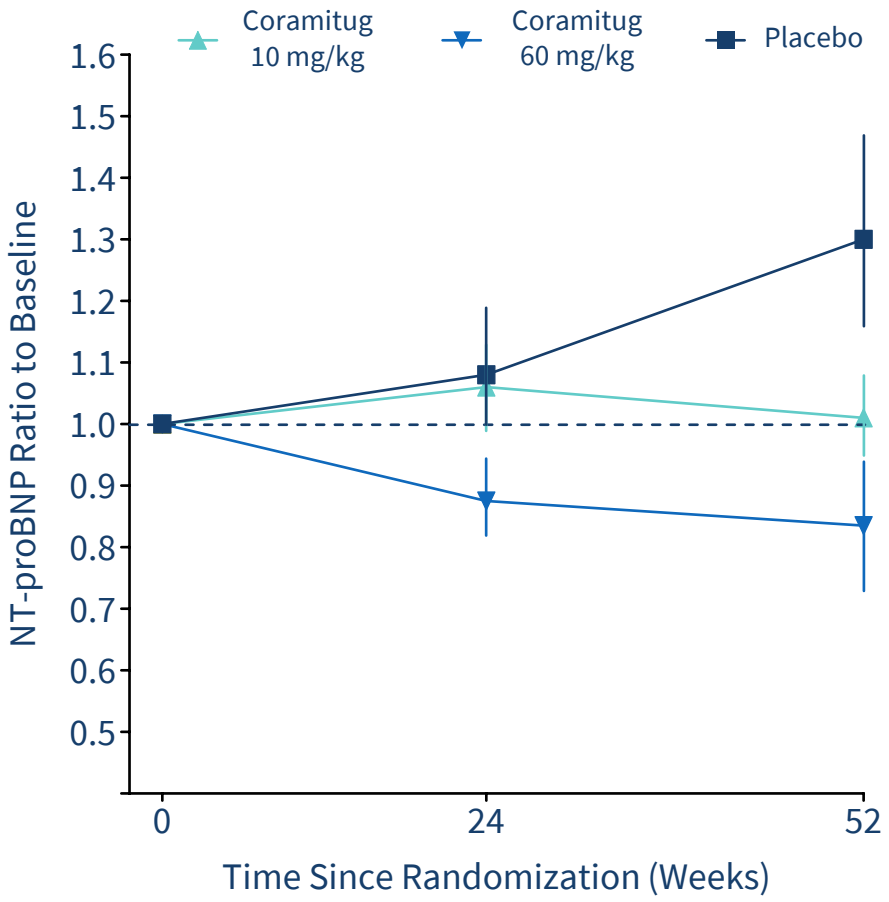
Kahr P, et al. *Nature Med*. 2026.

Longer Term Follow-up



Kahr P, et al. *Nature Med*. 2026.

PRX004/Coramitug



Event	Placebo (n = 35)		Coramitug 10 mg/kg (n = 34)		Coramitug 60 mg/kg (n = 35)	
	No. (%)	Events	No. (%)	Events	No. (%)	Events
Any Adverse Event*	33 (94.3)	316	32 (94.1)	266	33 (94.3)	224
Adverse Event Occurring in >15% of Participants in Any Group, n (%)						
Dyspnea	5 (14.3)	10	7 (20.6)	10	2 (5.7)	2
Cardiac Failure	8 (22.9)	12	4 (11.8)	8	8 (22.9)	9
Adverse Events of Special Interest, n (%)						
Thrombocytopenia	0	0	0	0	0	0
Arthralgias	0	0	3 (8.8)	3	3 (8.6)	4
Cardiac Arrhythmia	8 (22.9)	11	9 (26.5)	15	15 (42.9)	16
Infusion Reactions	4 (11.4)	4	2 (5.9)	2	6 (17.1)	6
Serious Adverse Event	13 (37.1)	35	9 (26.5)	23	12 (31.4)	16
Adverse Event Leading to Discontinuation of Study	3 (8.6)	3	3 (8.8)	3	2 (5.7)	2

Fontana M, et al. *Circulation*. 2026.

CleopATTRA: Depleter in ATTR-CM

Study Overview

Condition	**Transthyretin Amyloid Cardiomyopathy (ATTR-CM)**
Treatment	NNC6019-0001 or Matched Placebo
Study Type	Interventional
Trial Duration	Oct 2, 2025–Jun 29, 2029
Participants	1,280
Phase	III

Arms and Interventions

Group	Intervention
Experimental: NNC6019-0001 Participants receive NNC6019-0001 IV and may continue standard of care as recommended by their clinician.	NNC6019-0001 Administered IV
Placebo Comparator Participants receive matched placebo IV and may continue standard of care as recommended by their clinician.	Matched Placebo Administered IV

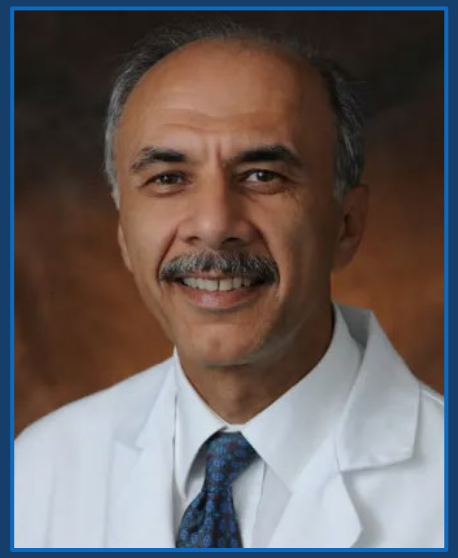
Primary Outcome Measure: Number of occurrences of the composite endpoint of cardiovascular deaths and recurrent CV events (CV hospitalizations and urgent heart failure visits).

- Measured as a count of events from baseline (week 0) to end of study (up to approximately 4 years).

ClinicalTrials.gov.

Conclusions

- Tremendous development is happening in ATTR-CM.
- Different mechanisms are being investigated.
- Earlier recognition and improved standard of care have shifted the outcomes of patients.
- ***Clinical trial results must be viewed within the context of their design and the population enrolled.***



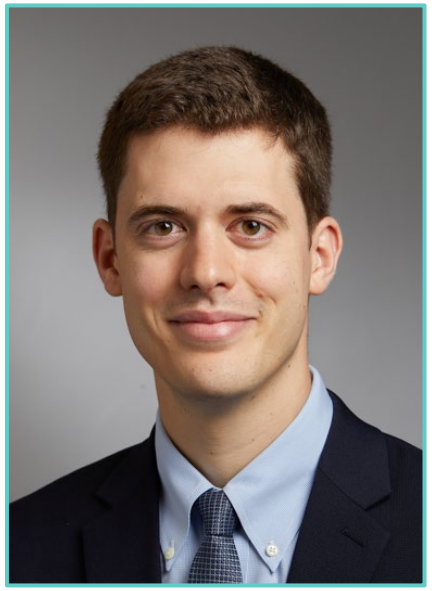
The Wiesman Moment

Emerging ATTR Research from the 2nd Annual ATTR Early-Career Research Forum

Presented in Honor of Dr. Janice Wiesman



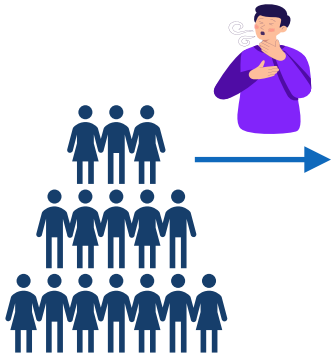
Integrating AI-ECG With Deep Learning From Electronic Health Records and POCUS for Precision Screening of ATTR-CM



Evangelos K. Oikonomou, MD, DPhil

- Assistant Professor of Medicine (Cardiology), Yale School of Medicine
- Associate Director, Yale Cardiovascular Data Science Lab
- Deputy Editor, European Heart Journal
- @ekoikonomou

Can We Build a Digital End-to-End ATTR-CM Screening Pathway?



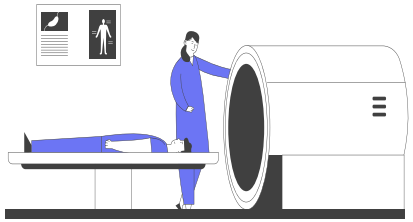
Population



ECG
(Croon PM et al.
JAMA 2026)



Echo
(Oikonomou EK et al.
Eur Heart J & Lancet Digit Health 2025)



Targeted Cardiac Amyloid Screening



Targeted Therapy
(Stabilizers, Silencers, Depleters)



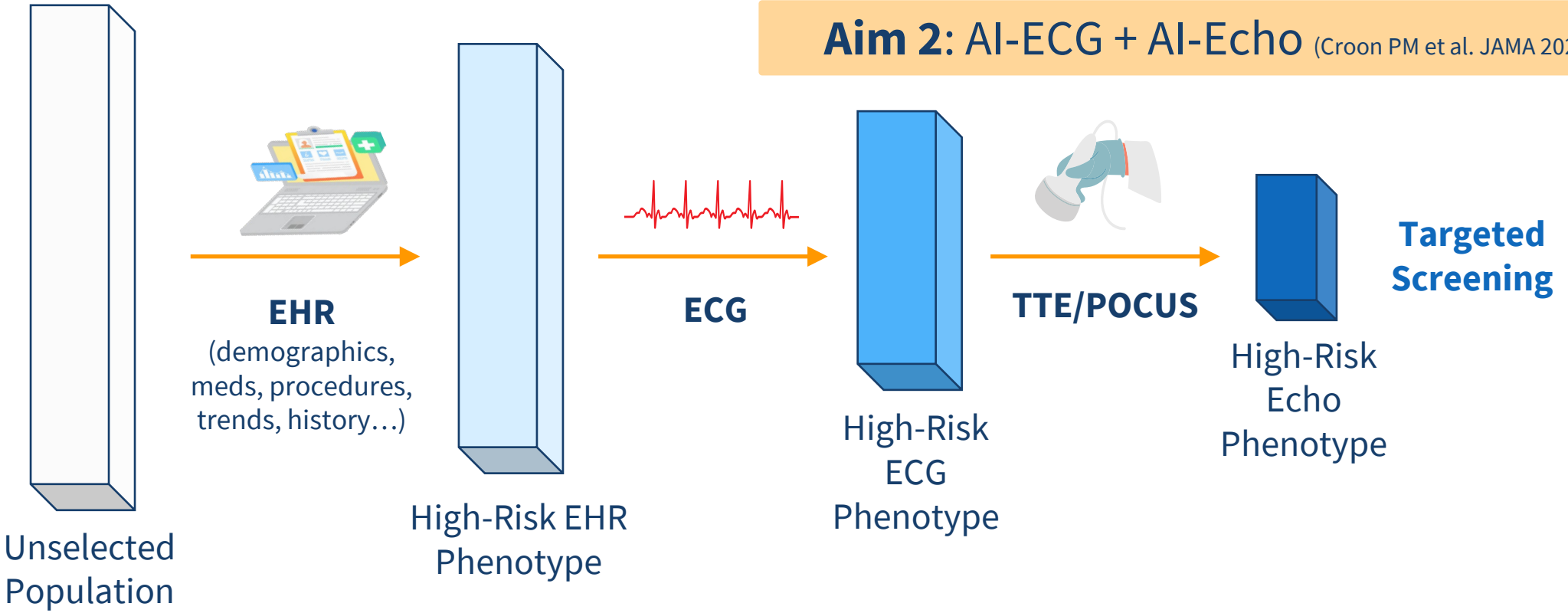
Screening for earlier phenotypes increases false discovery.

Diagnosis

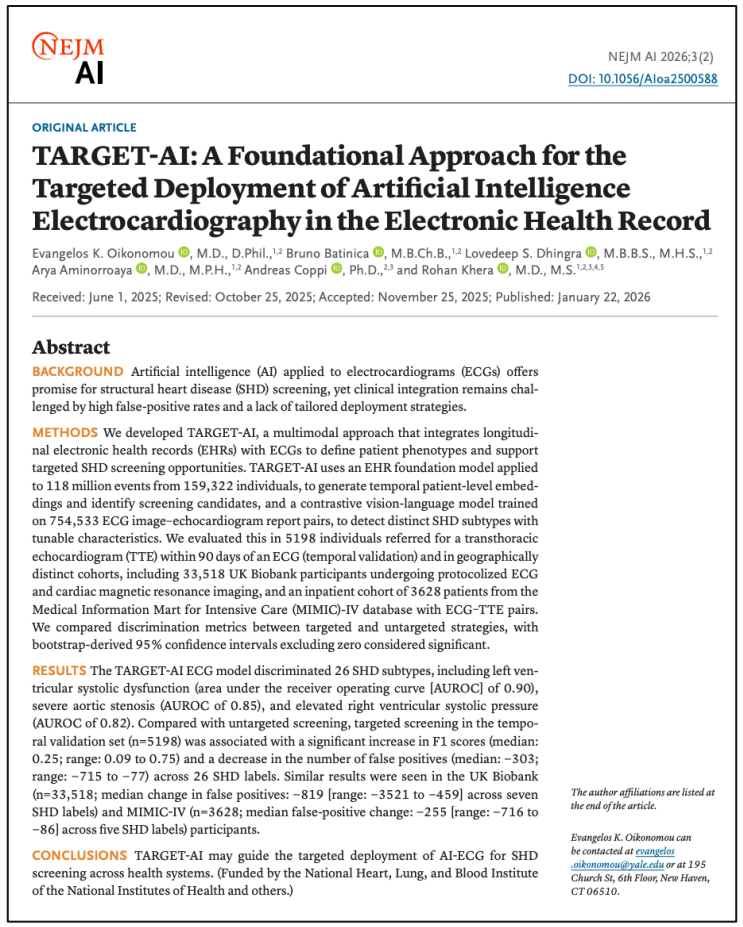
How Will We Achieve This?

Aim 1: EHR → AI-ECG (Oikonomou EK et al. NEJM AI 2026)

Aim 2: AI-ECG + AI-Echo (Croon PM et al. JAMA 2026)



Aim 1: AI to Interpret the EHR and Guide AI-ECG



NEJM AI

NEJM AI 2026;3(2)
DOI: 10.1056/AIoa2500588

ORIGINAL ARTICLE

TARGET-AI: A Foundational Approach for the Targeted Deployment of Artificial Intelligence Electrocardiography in the Electronic Health Record

Evangelos K. Oikonomou, M.D., D.Phil.,[1,2] Bruno Batinica, M.B.Ch.B.,[1,2] Lovedeep S. Dhingra, M.B.B.S., M.H.S.,[1,2] Arya Aminorroaya, M.D., M.P.H.,[1,2] Andreas Coppi, Ph.D.,[2,3] and Rohan Khera, M.D., M.S.[1,2,3,4,5]

Received: June 1, 2025; Revised: October 25, 2025; Accepted: November 25, 2025; Published: January 22, 2026

Abstract

BACKGROUND Artificial intelligence (AI) applied to electrocardiograms (ECGs) offers promise for structural heart disease (SHD) screening, yet clinical integration remains challenged by high false-positive rates and a lack of tailored deployment strategies.

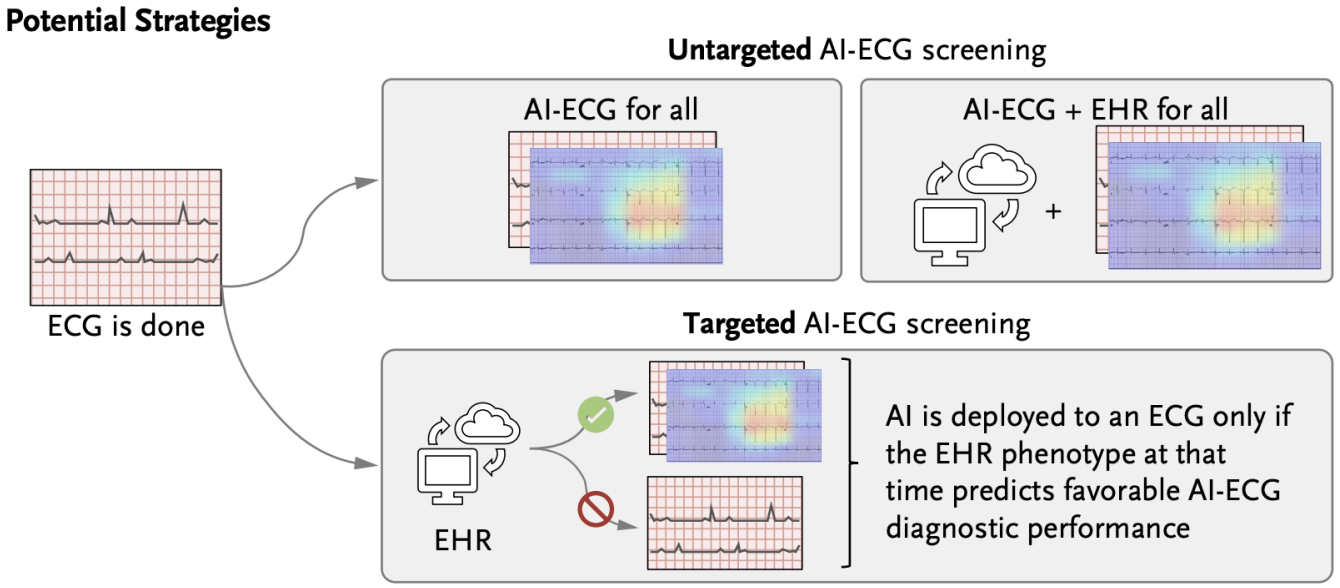
METHODS We developed TARGET-AI, a multimodal approach that integrates longitudinal electronic health records (EHRs) with ECGs to define patient phenotypes and support targeted SHD screening opportunities. TARGET-AI uses an EHR foundation model applied to 118 million events from 159,322 individuals, to generate temporal patient-level embeddings and identify screening candidates, and a contrastive vision-language model trained on 754,533 ECG image–echocardiogram report pairs, to detect distinct SHD subtypes with tunable characteristics. We evaluated this in 5198 individuals referred for a transthoracic echocardiogram (TTE) within 90 days of an ECG (temporal validation) and in geographically distinct cohorts, including 33,518 UK Biobank participants undergoing protocolized ECG and cardiac magnetic resonance imaging, and an inpatient cohort of 3628 patients from the Medical Information Mart for Intensive Care (MIMIC)-IV database with ECG–TTE pairs. We compared discrimination metrics between targeted and untargeted strategies, with bootstrap-derived 95% confidence intervals excluding zero considered significant.

RESULTS The TARGET-AI ECG model discriminated 26 SHD subtypes, including left ventricular systolic dysfunction (area under the receiver operating curve [AUROC] of 0.90), severe aortic stenosis (AUROC of 0.85), and elevated right ventricular systolic pressure (AUROC of 0.82). Compared with untargeted screening, targeted screening in the temporal validation set (n=5198) was associated with a significant increase in F1 scores (median: 0.25; range: 0.09 to 0.75) and a decrease in the number of false positives (median: −303; range: −715 to −77) across 26 SHD labels. Similar results were seen in the UK Biobank (n=33,518; median change in false positives: −819 [range: −3521 to −459] across seven SHD labels) and MIMIC-IV (n=3628; median false-positive change: −255 [range: −716 to −86] across five SHD labels) participants.

CONCLUSIONS TARGET-AI may guide the targeted deployment of AI-ECG for SHD screening across health systems. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health and others.)

The author affiliations are listed at the end of the article.

Evangelos K. Oikonomou can be contacted at evangelos.oikonomou@yale.edu or at 195 Church St, 6th Floor, New Haven, CT 06510.



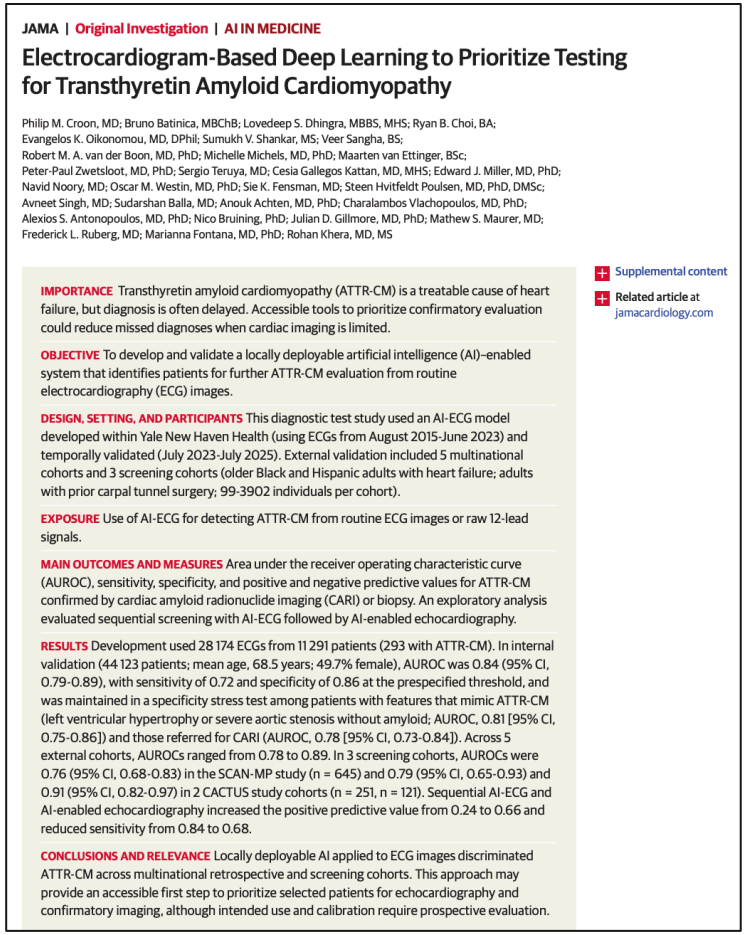
False positives decrease by

87.8%

AI-ECG tests run **decrease by up to 53%** to detect the **same number of cases**.

Oikonomou EK et al. NEJM AI 2026.

Aim 2: Multimodal ECG/TTE Interpretation for Increased Precision



JAMA | Original Investigation | AI IN MEDICINE

Electrocardiogram-Based Deep Learning to Prioritize Testing for Transthyretin Amyloid Cardiomyopathy

Philip M. Croon, MD; Bruno Batinica, MBChB; Lovedeep S. Dhingra, MBBS, MHS; Ryan B. Choi, BA; Evangelos K. Oikonomou, MD, DPhil; Sumukh V. Shankar, MS; Veer Sangha, BS; Robert M. A. van der Boon, MD, PhD; Michelle Michels, MD, PhD; Maarten van Ettinger, BSc; Peter-Paul Zwetsloot, MD, PhD; Sergio Teruya, MD; Cesia Gallegos Kattan, MD, MHS; Edward J. Miller, MD, PhD; Navid Noory, MD; Oscar M. Westin, MD, PhD; Sie K. Fensman, MD; Steen Hvitfeldt Poulsen, MD, PhD, DMSc; Avneet Singh, MD; Sudarshan Balla, MD; Anouk Achten, MD, PhD; Charalambos Vlachopoulos, MD, PhD; Alexios S. Antonopoulos, MD, PhD; Nico Bruining, PhD; Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Frederick L. Ruberg, MD; Marianna Fontana, MD, PhD; Rohan Khera, MD, MS

IMPORTANCE Transthyretin amyloid cardiomyopathy (ATTR-CM) is a treatable cause of heart failure, but diagnosis is often delayed. Accessible tools to prioritize confirmatory evaluation could reduce missed diagnoses when cardiac imaging is limited.

OBJECTIVE To develop and validate a locally deployable artificial intelligence (AI)–enabled system that identifies patients for further ATTR-CM evaluation from routine electrocardiography (ECG) images.

DESIGN, SETTING, AND PARTICIPANTS This diagnostic test study used an AI-ECG model developed within Yale New Haven Health (using ECGs from August 2015-June 2023) and temporally validated (July 2023-July 2025). External validation included 5 multinational cohorts and 3 screening cohorts (older Black and Hispanic adults with heart failure; adults with prior carpal tunnel surgery; 99-3902 individuals per cohort).

EXPOSURE Use of AI-ECG for detecting ATTR-CM from routine ECG images or raw 12-lead signals.

MAIN OUTCOMES AND MEASURES Area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, and positive and negative predictive values for ATTR-CM confirmed by cardiac amyloid radionuclide imaging (CARI) or biopsy. An exploratory analysis evaluated sequential screening with AI-ECG followed by AI-enabled echocardiography.

RESULTS Development used 28 174 ECGs from 11 291 patients (293 with ATTR-CM). In internal validation (44 123 patients; mean age, 68.5 years; 49.7% female), AUROC was 0.84 (95% CI, 0.79-0.89), with sensitivity of 0.72 and specificity of 0.86 at the prespecified threshold, and was maintained in a specificity stress test among patients with features that mimic ATTR-CM (left ventricular hypertrophy or severe aortic stenosis without amyloid; AUROC, 0.81 [95% CI, 0.75-0.86]) and those referred for CARI (AUROC, 0.78 [95% CI, 0.73-0.84]). Across 5 external cohorts, AUROCs ranged from 0.78 to 0.89. In 3 screening cohorts, AUROCs were 0.76 (95% CI, 0.68-0.83) in the SCAN-MP study (n = 645) and 0.79 (95% CI, 0.65-0.93) and 0.91 (95% CI, 0.82-0.97) in 2 CACTUS study cohorts (n = 251, n = 121). Sequential AI-ECG and AI-enabled echocardiography increased the positive predictive value from 0.24 to 0.66 and reduced sensitivity from 0.84 to 0.68.

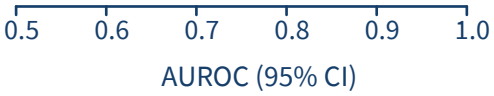
CONCLUSIONS AND RELEVANCE Locally deployable AI applied to ECG images discriminated ATTR-CM across multinational retrospective and screening cohorts. This approach may provide an accessible first step to prioritize selected patients for echocardiography and confirmatory imaging, although intended use and calibration require prospective evaluation.

Supplemental content

Related article at jamacardiology.com

Croon PM et al. JAMA 2026.

External-Europe		
National Amyloidosis Center (UCL)		
AI-ECG Score	3902 (2595)	0.89 (0.87-0.90)
AI-ECG With Age and Sex	3902 (2595)	0.88 (0.87-0.89)
Hippokration Hospital (Greece)		
AI-ECG Score	99 (49)	0.82 (0.70-0.91)
AI-ECG With Age and Sex	99 (49)	0.77 (0.65-0.87)
Erasmus		
AI-ECG Score	516 (174)	0.78 (0.73-0.83)
AI-ECG With Age and Sex	516 (174)	0.71 (0.66-0.77)
External-US		
Northwell		
AI-ECG Score	140 (70)	0.82 (0.73-0.90)
AI-ECG With Age and Sex	140 (70)	0.78 (0.70-0.86)
West Virginia University		
AI-ECG Score	126 (66)	0.83 (0.74-0.91)
AI-ECG With Age and Sex	126 (66)	0.82 (0.73-0.89)
Prospective		
SCAN-MP (Ruberg et al,[28] 2025)		
AI-ECG Score	645 (43)	0.76 (0.68-0.83)
AI-ECG With Age and Sex	645 (43)	0.78 (0.71-0.85)
CACTUS (Westin et al,[25] 2022)		
AI-ECG Score	251 (13)	0.79 (0.65-0.93)
AI-ECG With Age and Sex	251 (13)	0.91 (0.82-0.98)
CACTUS (Ladefoged et al,[26] 2023)		
AI-ECG Score	121 (10)	0.91 (0.82-0.97)
AI-ECG With Age and Sex	121 (10)	0.90 (0.79-0.98)



- ***Referring only double-positive*** patients for confirmatory imaging yielded a PPV of 0.66 (95% CI, 0.56- 0.76) and 1.5 CARI scans per true diagnosis.
- ***Concordant double-negative*** results had an NPV of 0.98 (95% CI, 0.96-0.99).

What's Next

- End-to-end integration of EHR data, opportunistic ECG, POCUS, and/or TTE to identify optimal multimodal intersections for targeted prompts recommending evaluation for cardiac amyloidosis and ATTR-CM → **interoperable screening platform.**
- **Longitudinal assessment of temporal validity** as ATTR-CM epidemiology evolves with earlier screening and detection.
- Development of a deployable end-to-end package to facilitate implementation and **adoption across health systems**.

Acknowledgements

Funding Acknowledgements:

- **Wiesman Award for Excellence in Early-Career ATTR Research (AstraZeneca & Ionis Pharmaceuticals)**
- NHLBI (NIH): K23HL181318
- American Heart Association: 26CDA1612298
- Robert A. Winn Excellence in Clinical Trials Career Development Award
- NIA (NIH) through the Yale Pepper Center: P30AG021342

Please reach out:

evangelos.oikonomou@yale.edu

X: @ekoikonomou





CarDS Lab

Rohan Khera
Lovedeep Dhingra
Andreas Coppi
Caitlin Malicki
Aline Pedroso
Arya Aminorroaya
Sumukh Vasisht Shankar
Philip Croon
Bruno Batinica
Phyllis Thangaraj
Alejandra Hagewood
Doris Yang
Ryan Choi
Favour Olushola
Brian Ram
Mohanad Elchouemi
Wendy Luo

Yale University

Eric J Velazquez
Harlan M Krumholz
Erica S Spatz
Robert L McNamara
Edward J Miller
Norrisa A Haynes
Thomas M Gill

University of Texas, Austin

Atlas Wang
Gregory Holste

Houston Methodist

Sadeer Al-Kindi
Khurram Nasir

Mount Sinai, NY

Girish N. Nadkarni

Utility of Non-Invasive MRI Assessment of Tenosynovial Amyloidosis for Early Detection of Cardiac Amyloidosis: UNRAVEL, A Pilot Study



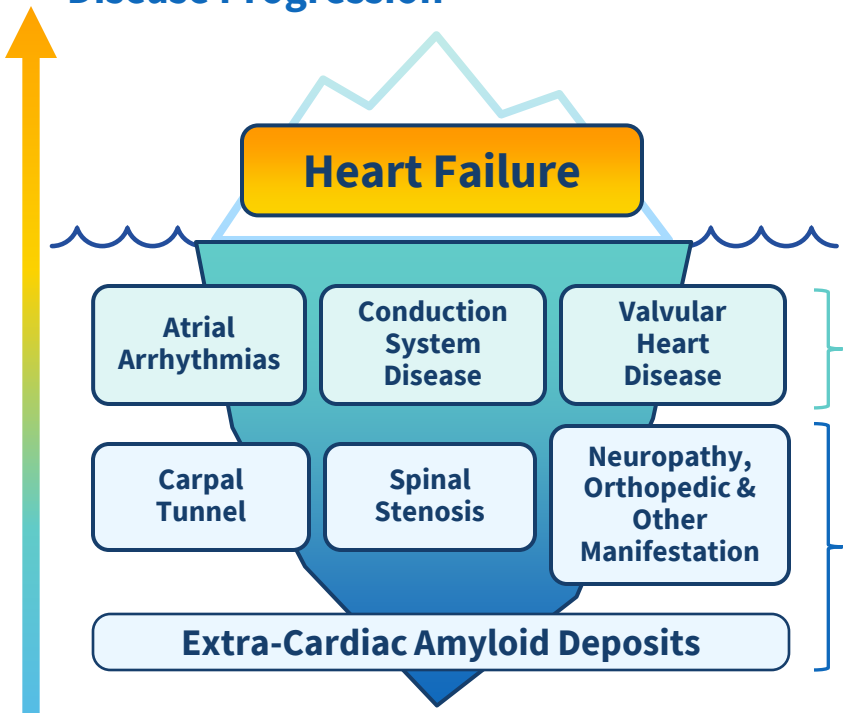
Michael Chetrit, MD, FRCPC, FACC

- Assistant Professor of Medicine, McGill University,
- Co-Directors, Cardiac Imaging, Department of Radiology, McGill University
- Cardiologist, McGill University Health Centre
- Site Director, Echocardiography lab, Montreal General Hospital
- Director, McGill Amyloidosis Project
- Clinical Director, Courtois Cardiac MRI Program
- President, Canadian Society of Cardiac MRI

Carpal Tunnel Syndrome as an Early Manifestation of CA

CTS is an early extracardiac manifestation of CA, often appearing 4–10 years before cardiac symptoms.

Disease Progression



Misfolded TTR: Age-Related, ATTRv, Hormonal (?), Other Factors

Stage Treatments and Clinical Course

Stage D	• Palliative care • Advanced heart failure therapy	→ **Death due to progressive HF**
Stage C	• TTR stabilizer • Clinical trials of TTR therapy in progress	→ **Slowly progressive HF;** death likely due to other causes
Stage B	• Consider TTR stabilizer • Clinical trials needed	→ **Near normal;** minimal cardiac symptoms
Stage A	• Benefit of Rx unknown • Consider TTR stabilizer • Clinical trials needed	→ **Normal life expectancy**

Goals of Therapy in ATTR: Slow progression of disease (proven) and prevent heart failure and/or remove amyloid (hypothesis).

Goal and Objectives

Pilot: Primary Objectives

1. To identify anatomical changes in the carpal tunnel using T1-weighted and proton density imaging.
2. To evaluate amyloid-related macromolecular changes through MTR attenuation.

Overarching Goal

To determine if MRI can accurately detect the **presence of amyloid** as a **cause of carpal tunnel syndrome (CTS)** to enable the early detection of systemic amyloidosis.

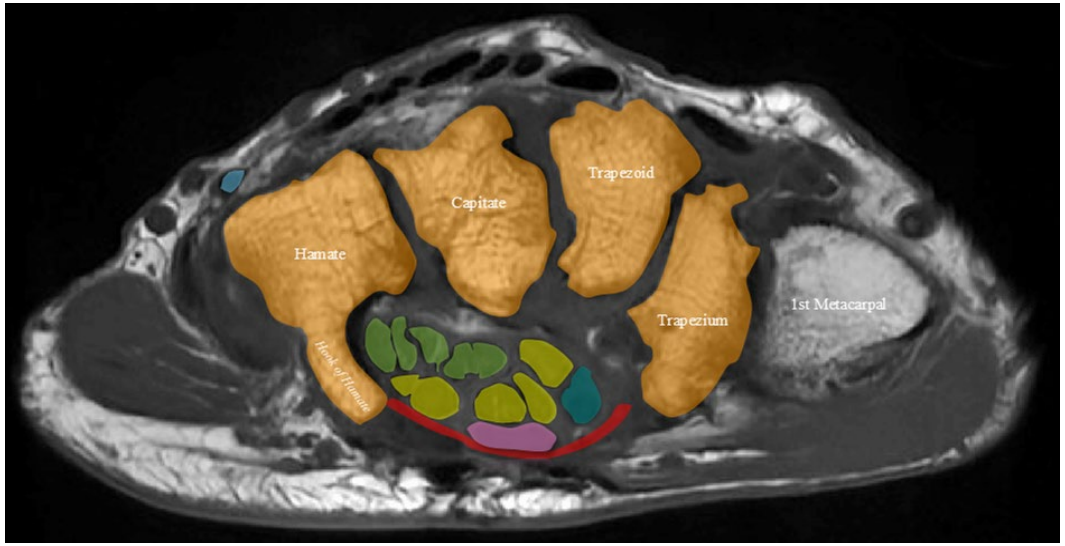
Methods: Study Population Criteria

Pilot: 12 Patients (6/6)

Recruitment From Hand/ Amyloid Clinics

Moderate to Severe CTS
Males ≥50, Females ≥60
Bx Confirmed Amyloid+ or Amyloid-

12 Cases Total
6 Amyloid+, Mean Age 73, 4 Females
6 Amyloid-, Mean Age 67, 2 Females



Wrist MRI → **T1**, **PD**, **MTR** → **ROI Analysis**

Carpal Bones, Flexor Retinaculum, Tendons, Median Nerve, Tenosynovium

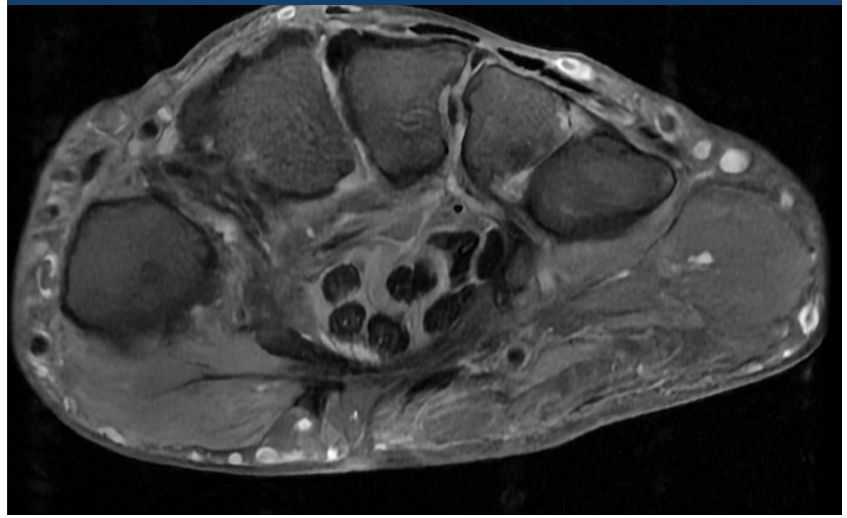
Results: Baseline Measurements of CTS Patients by Amyloid Type

	Amyloid + (N=6) % or Mean (SD)	Amyloid - (N=6) % or Mean (SD)	*F or t*	Significance
Age (Years)	73.3 (6.0)	66.7 (6.6)	0.13	ns
Male (Percentage)	33%	67%	0.57	ns
Height (cm)	167.0 (7.9)	168.3 (10.3)	0.82	ns
Weight (kg)	80.7 (15.2)	84.0 (24.1)	0.80	ns
BMI	28.9 (5.3)	29.1 (5.5)	0.96	ns
Bilateral CTS	100%	100%		
Amyloid Type				
wtATTR	66%	N/A		
AL	33%	N/A		
Symptoms				
Numbness	100%	100%		
Pain	33%	33%		
Tingling	33%	0%		

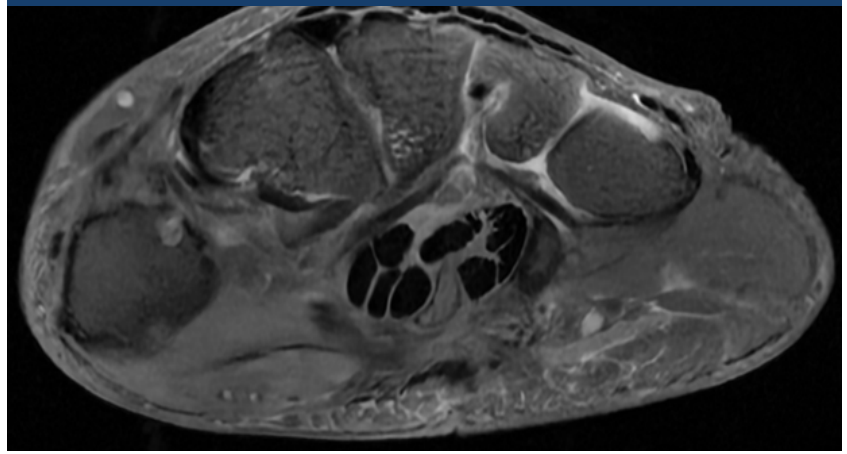
Results: Proton Weighted

- Flattened and thickened median nerve fascicles
- Thickened tenosynovial tissue
- Marked thickening of flexor tendons

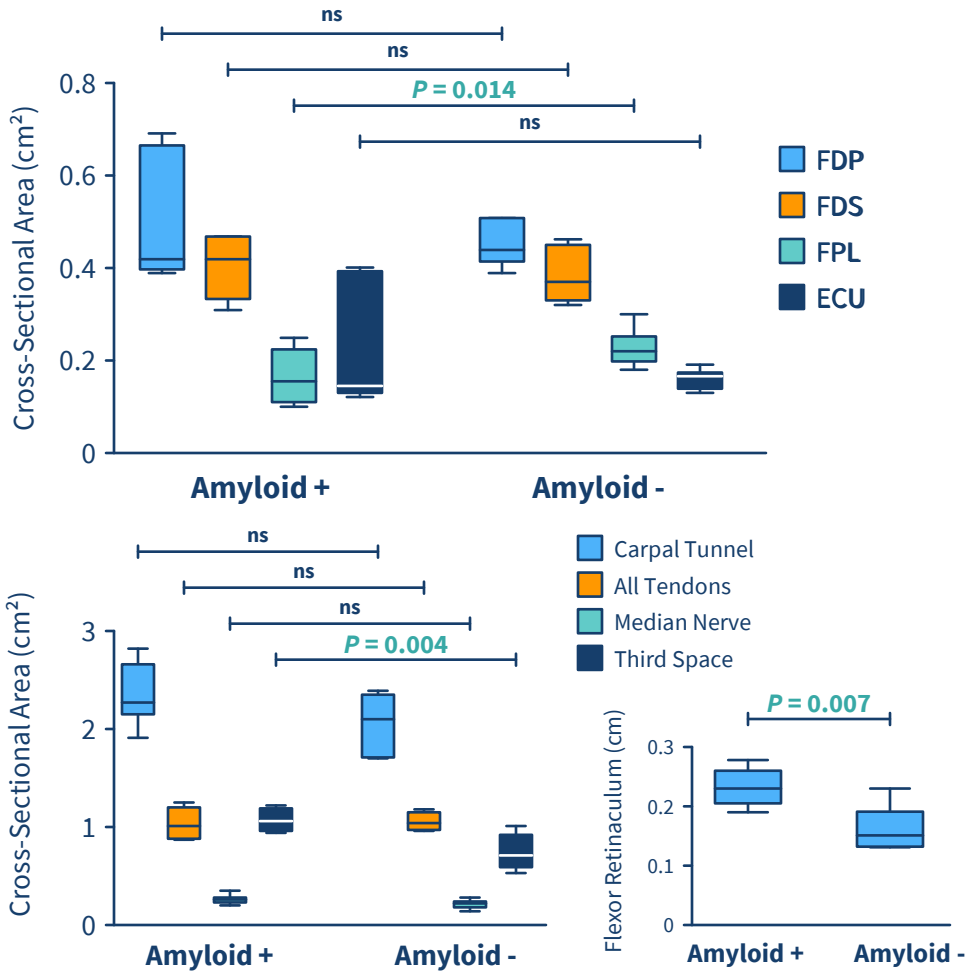
65M with severe CTS, bx confirmed wtATTR



76M with moderate-severe CTS, amyloid negative bx

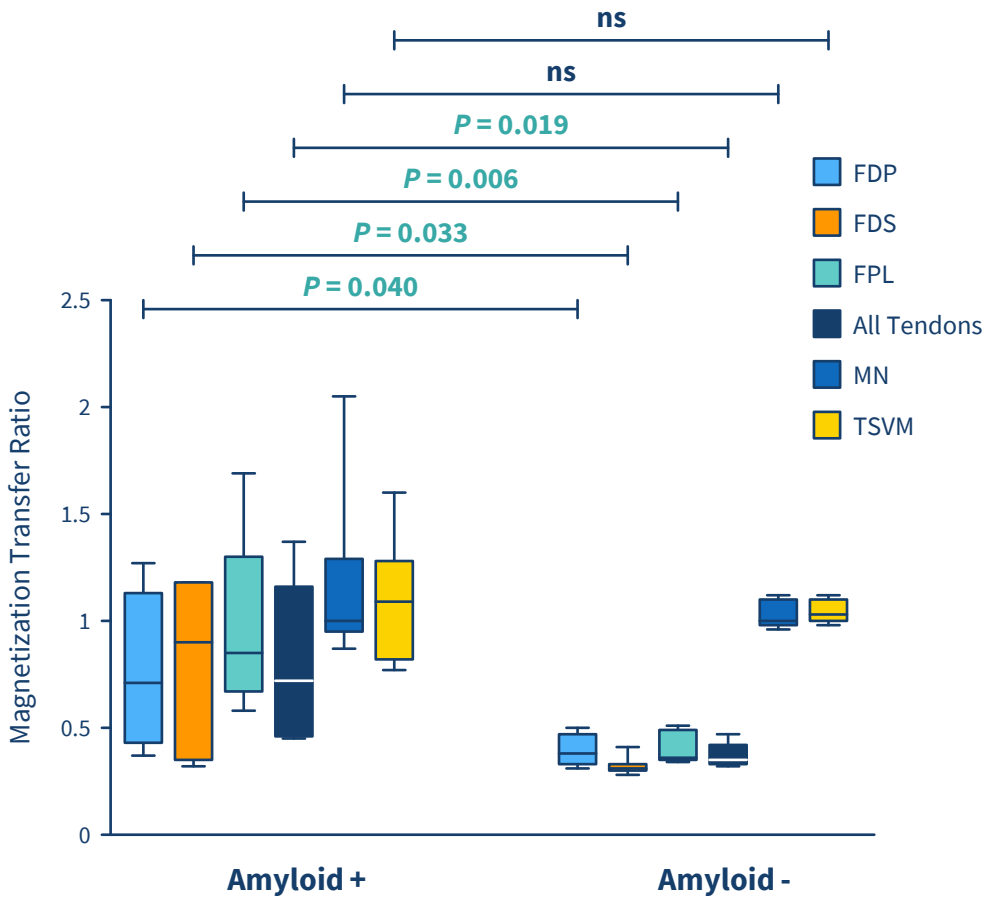


Tendon Involvement in Amyloidosis-Related CTS

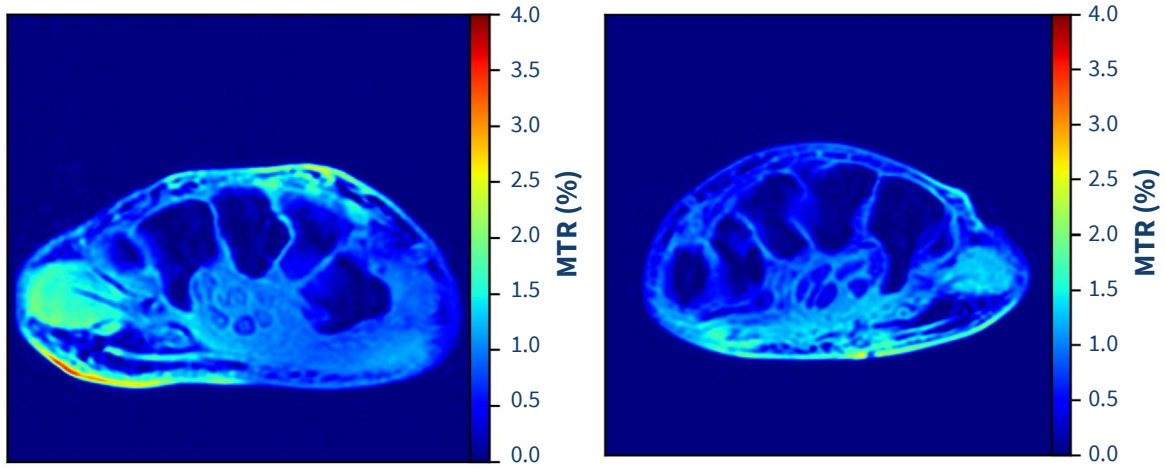


MRI Parameter	Amyloid (+) Mean	Amyloid (-) Mean	% Difference
CSA of FDP (cm^2)	0.50	0.45	**+11%** (↑ in flexor digitorum profundus)
CSA of FDS (cm^2)	0.41	0.38	**+8%** (↑ in flexor digitorum superficialis)
CSA of FPL (cm^2)	0.17	0.23	**-26%** (↓ in flexor pollicis longus)
CSA of ECU (cm^2)	0.22	0.16	**+38%** (↑ in extensor carpi ulnaris)
Third Space (cm^2)	1.05	0.77	**+36%** (↑ thickening in amyloid-positive)
Flexor Retinaculum Thickness (cm)	0.23	0.16	**+44%** (↑ thickening in amyloid-positive)

MTR Quantifies Molecular Changes in CTS



MRI Parameter	Amyloid (+) Mean	Amyloid (-) Mean	% Difference
FDP (%)	0.77	0.4	**+94%** (↑ in amyloid-positive)
FDS (%)	0.69	0.32	**+119%** (↑ in amyloid-positive)
FPL (%)	0.97	0.40	**+142%** (↑ in amyloid-positive)
All Tendons (%)	0.81	0.37	**+118%** (↑ in amyloid-positive)
MN (%)	1.15	1.03	**+12%** (↑ in amyloid-positive)
TSVM (%)	1.09	1.05	**+4%** (↑ in amyloid-positive)

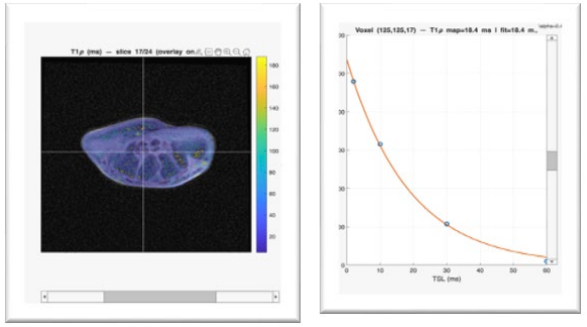


Conclusions and Future Directions

This pilot study demonstrates the potential of non-invasive wrist MRI as an early detection tool for amyloidosis.

Enlarged carpal tunnel structures, selective tissue involvement, and macromolecular alterations in amyloid-positive patients support MRI-based detection of amyloid deposition.

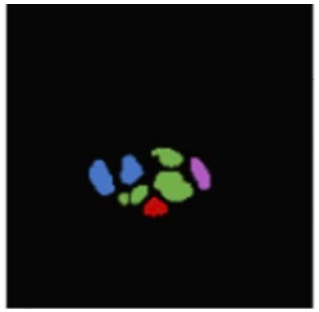
T1 Rho



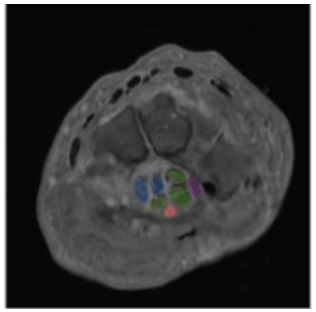
T1ρ Map and Decay Fit

AI

Prediction

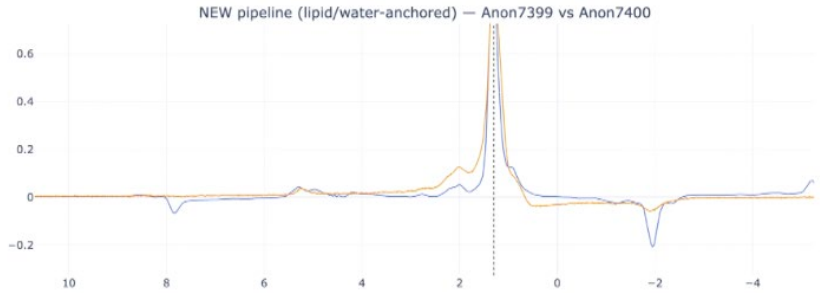


Overlay



AI Segmentation

H-MRS



Spectroscopy

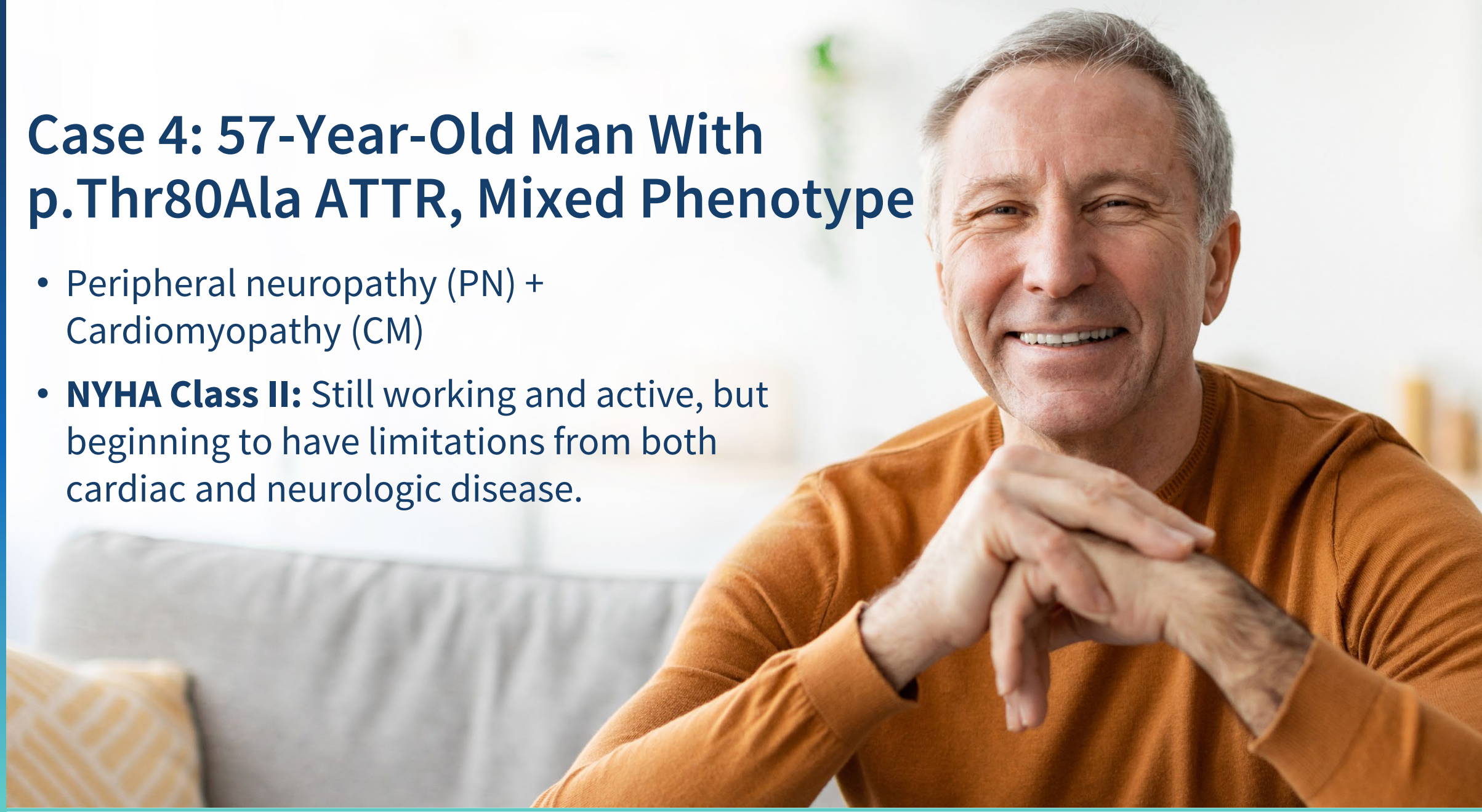


Realizing Collaborative Synergies in ATTR: Real World Strategies for Meeting Multi-System Needs with the MDT

A Case-Driven Practicum

Case 4: 57-Year-Old Man With p.Thr80Ala ATTR, Mixed Phenotype

- Peripheral neuropathy (PN) + Cardiomyopathy (CM)
- **NYHA Class II:** Still working and active, but beginning to have limitations from both cardiac and neurologic disease.



What Do You See?

- If you're the cardiologist, you may see relatively compensated heart failure.
- If you're the neurologist, you may see progressive neuropathy.
- But if you ask the patient what is happening, *the answer is much more complicated*.



Gamification Question



Given mixed phenotype, which aspect of ATTR management should take priority for this patient?

A. Cardiomyopathy
B. Peripheral neuropathy
C. Diagnostic confirmation
D. Patient-centered communication

When We Think About ATTR

- **How we frame it:** We often think in terms of phenotype: cardiac ATTR, neuropathic ATTR, or mixed phenotype.
- **How patients experience it:** But our patients don't experience ATTR as separate phenotypes. They experience it as **one disease** affecting multiple aspects of their lives.

The Right Question

How do we treat cardiac ATTR? How do we treat ATTR polyneuropathy?

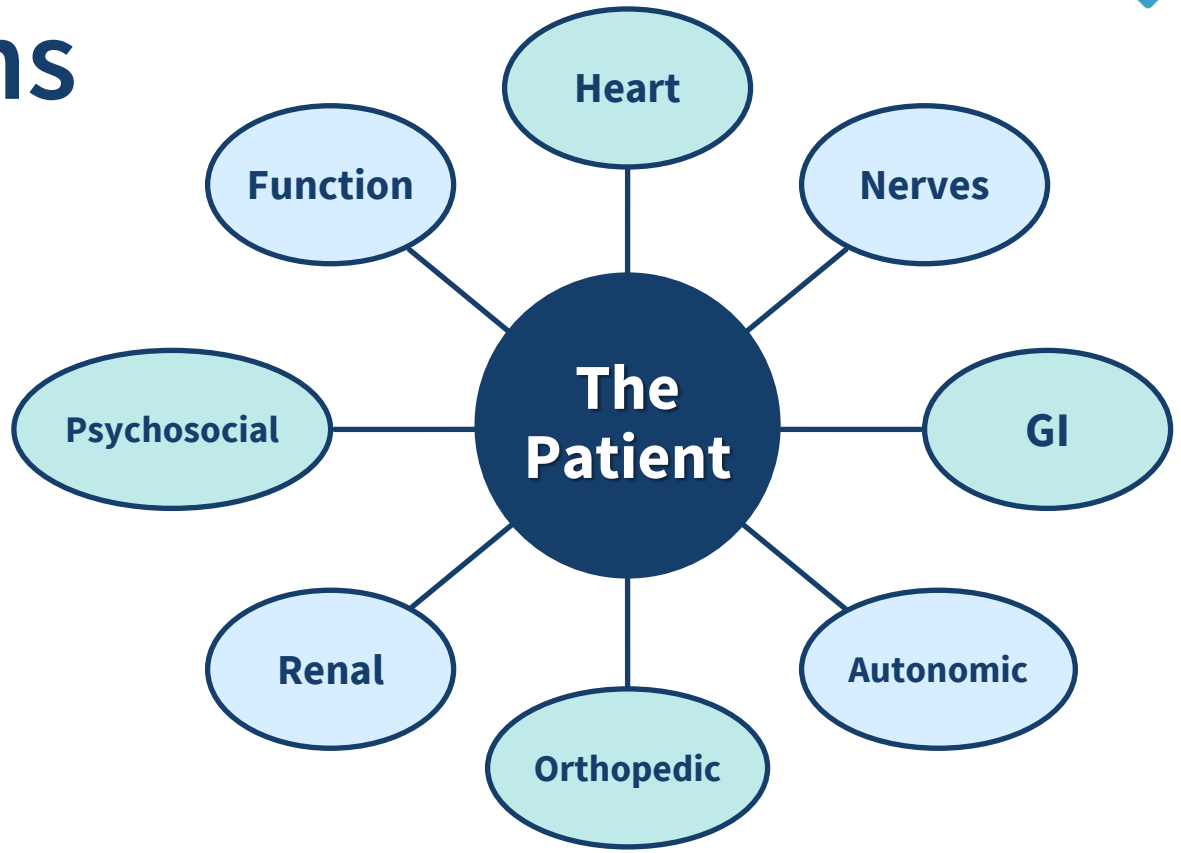
*How do we build **one treatment plan** for **one patient** when **ATTR is affecting multiple organ systems** at the same time?*

Sperry B, et al. *Cureus*. 2023; Griffin J, et al. *JACC CardioOncol*. 2021.

The ATTR Patient Does Not Live in Organ Systems

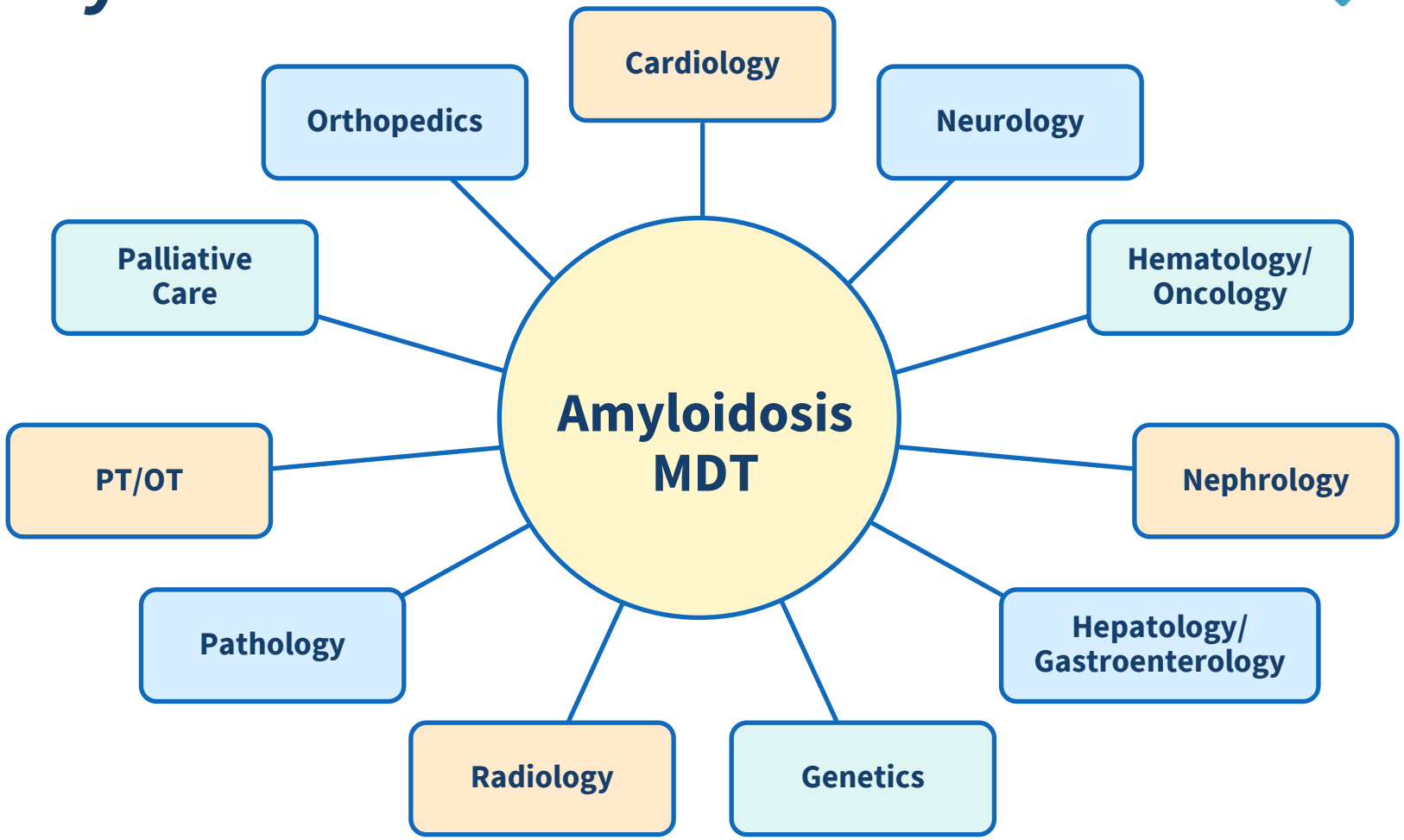
Which of These Is Most Important?

The answer is the one that is *most important to the patient*.



Our traditional healthcare system is organized around specialties. ***ATTR is not.*** The disease crosses boundaries that we've created in the healthcare system.

Multidisciplinary Specialties in Amyloid Care



Sperry B, et al. *Heart Fail Rev*. 2022.

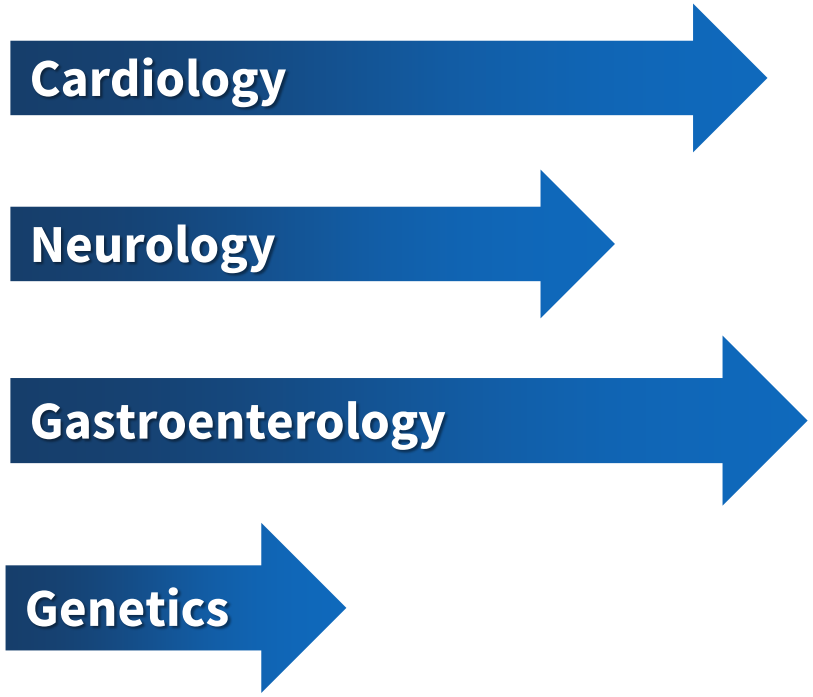
The First Multidisciplinary Question

- What matters most to the patient?
- Need to establish a **shared definition** of the problem
- Instead of asking what 'stage' they are, **ASK…**
  - What can you no longer do?
  - Do you fall?
  - Can you walk a mile/climb stairs?
  - Is dyspnea or neuropathy the dominant limitation?
  - What do you want to preserve?

What Does Collaboration Actually Mean?

Not This

A patient can see six specialists and still receive fragmented care.



But This

True multidisciplinary care means a common understanding of the disease, common goals, and a mechanism for communicating decisions back to the patient.

The Team

The ATTR Multidisciplinary Team and Critically: **the Patient and Family**



Cardiology

- Cardiac phenotype
- HF & arrhythmias
- Disease trajectory



Neurology

- Neuropathy phenotype
- Functional progression
- Neuropathic symptoms



Genetics

- Variant interpretation
- Family testing
- Cascade screening



Nursing / Navigator

- Coordination
- Education
- Follow-up



Pharmacy

- Treatment selection
- Drug interactions
- Access & adherence



PT / OT

- Mobility & falls
- Strength
- Adaptive strategies



Nutrition / GI

- Weight loss
- GI & autonomic symptoms

Sperry B, et al. *Heart Fail Rev*. 2022.

Where Multidisciplinary Care Changes Decisions

Example: Patient has ATTR-CM + ATTR-PN.

Cardiology says:

"His cardiac disease is relatively stable."

Neurology says:

"His neuropathy is progressing."

Patient says:

"I don't care that my echo is stable. **I'm falling and I'm worried I'm going to lose my independence!**"

Treatment success cannot be defined by cardiac outcomes alone. **All three statements can be true**, and that is exactly why the team matters.

Evidence-Driven Doesn’t Mean Evidence-Only

- Think about treatment decisions through **three lenses**:

1. Disease

- What phenotype is present?
- How advanced is it?
- What is the trajectory?

2. Evidence

- What therapies have demonstrated benefit?
- Which manifestations are expected to respond?
- What are the limitations of the evidence?

3. Patient

- What matters most?
- What risks are acceptable?
- What is feasible?
- What are the patient's goals?

*Evidence tells us what a treatment **can** do. It doesn't tell us what is most important to **this particular patient.***

The Shared Treatment Plan

- Build **one plan**, *not separate plans*
  - Disease-modifying therapy
  - Cardiac management
  - Neuropathy management
  - Rehabilitation
  - Nutrition
  - Genetic counseling
  - Palliative care
  - Monitoring and patient goals

Someone needs to "own" the overall plan!

Make the Collaboration Visible

Practical Tools for Structured Multidisciplinary Care

1 → 2 → 3

Before the Visit

- Shared Clinical Data
- Cardiac + Neurologic Assessment
- Medication Review
- Patient-Reported Priorities

During the Visit

- Common Assessment
- Agree on Treatment Goals
- Identify Conflicts

After the Visit

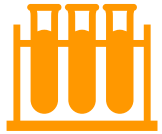
- One Documented Plan
- Clear Responsibilities
- Follow-up Timeline

Multidisciplinary care is a ***process***, not a room full of people.

Back to Our Case: What is the Most Important Outcome for This Patient?



Improvement in LV Function



Reduction in NT-proBNP



Stabilization of Neuropathy



Improved Walking Ability



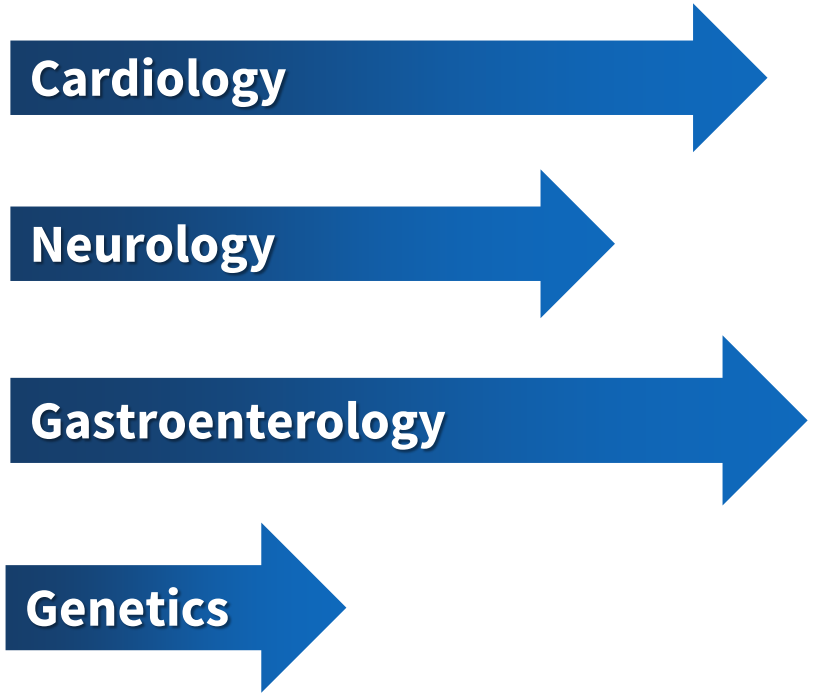
Remaining Independent and Able to Work

- There *may not* be one correct answer.
- The answer depends on what matters most to the patient.
- That is **why we need the team.**

Collaborative Care

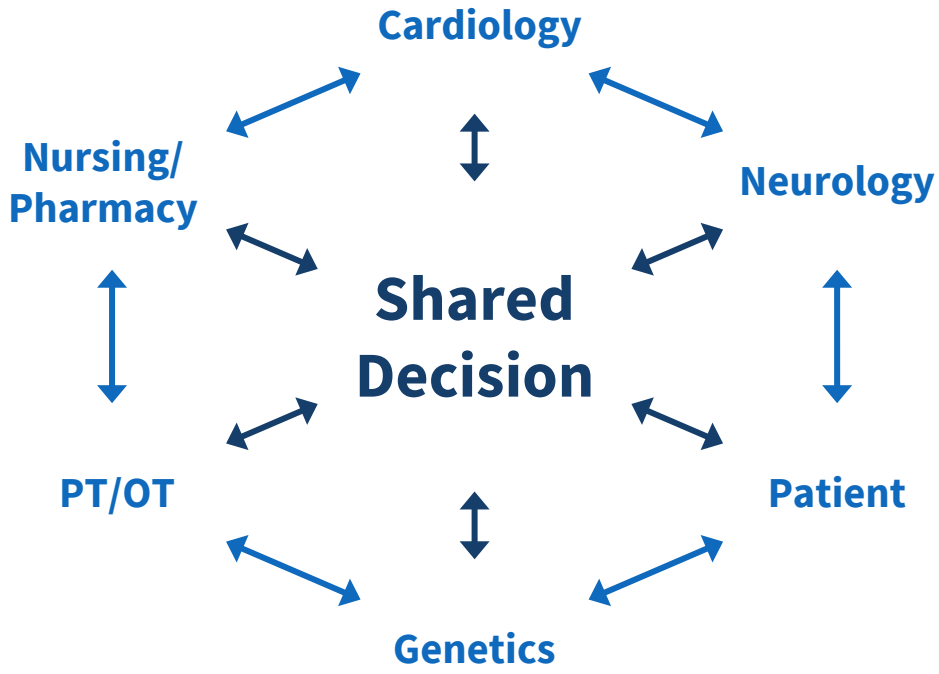
Side-By-Side Care

Each specialist produces a recommendation. No shared decision.



Head-to-Head Collaborative Care

Specialists work together. This is where the real value of an ATTR center lies.



The Three Take-Home Messages

1. **ATTR is a multisystem disease.**
   - Don’t organize the patient’s care around our specialties
2. **Multidisciplinary care must be integrated.**
   - Multiple specialists do not automatically equal multidisciplinary care
3. **The patient’s goals are the organizing principle.**
   - The endpoint isn’t simply stabilization of a biomarker, an echo, or a nerve study. It is preserving the life the patient wants to live