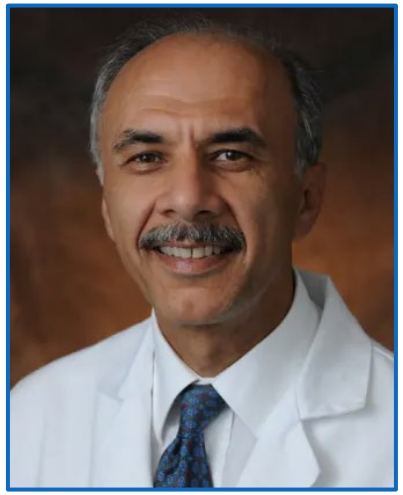
Faculty Information



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- **Ahmad Masri, MD, MS**
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- **Ani Nalbandian, MD, MPH**
  - **Reports no relevant disclosures**
- 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

- **Describe** the prevalence, multisystem pathophysiology, and heterogeneous clinical manifestations of ATTR, highlighting the clinical gravity of ATTR-CM, ATTR-PN, and ATTR of mixed phenotype.
- **Recognize** the imperative need for early and accurate diagnosis of ATTR, irrespective of phenotype, as a means of facilitating the initiation of evidence-based treatment earlier in the disease arc.
- **Examine** the novel pharmacologic mechanisms being investigated for ATTR, including inhibition of TTR synthesis, TTR stabilization, and TTR amyloid removal.
- **Evaluate** the totality of emerging clinical trial evidence for novel therapeutics in ATTR-CM and ATTR-PN, with a focus on recent readouts, ongoing pivotal studies, and regulatory updates.
- **Discuss** original ATTR research rationale, design, and data findings from work conducted by the Wiesman winners of the 1st Annual ATTR Early-Career Research Forum.
- **Design** individualized, evidence-driven treatment plans for patients with ATTR-CM and ATTR-PN, emphasizing cardiologist and neurologist roles in the multidisciplinary management of these conditions.

Activity Website

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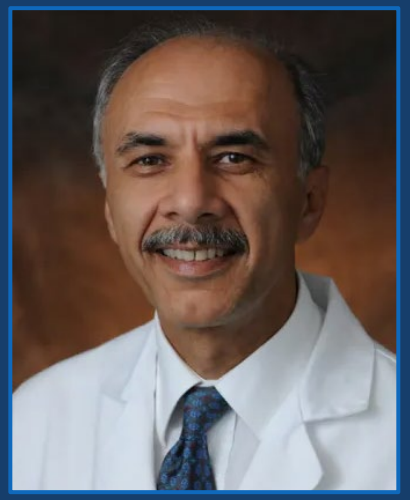


The Fundamentals of ATTR

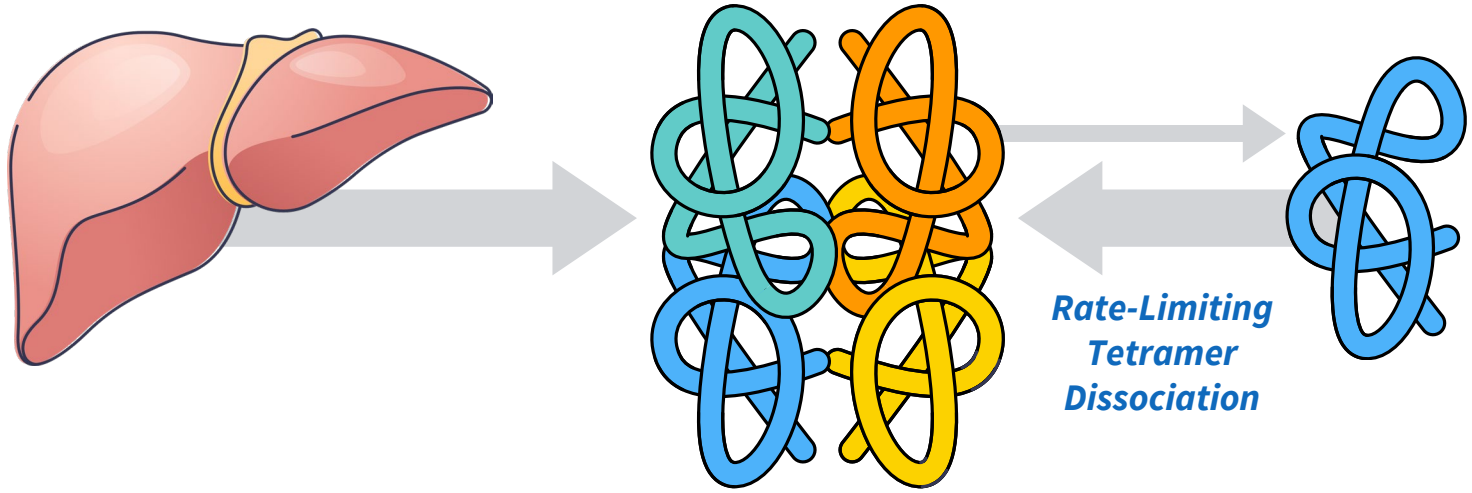
Epidemiology, Pathophysiology, and Heterogeneous Patient Burden

What Is Transthyretin?

- Transthyretin (TTR) is a **protein** primarily synthesized in the liver
- In the serum, it serves as the primary transport protein for Vitamin A via the retinol-binding protein and is a minor carrier for thyroxine[1,2]
- Low TTR levels are associated with many chronic diseases, including Alzheimer disease, heart failure, stroke, and rheumatoid arthritis[3-5]

1. Zhang KW, et al. *JACC Basic Transl Sci*. 2019. 2. Robbins J. *Clin Chem Lab Med*. 2002. 3. Shetty NS, et al. *Nat Commun*. 2024. 4. Khella S, et al. 2025 *Peripheral Nerve Society (PNS)* Annual Meeting; May 17-20; Edinburgh, Scotland. P470. 5. https://www.uab.edu/news/research-innovation/uab-study-reveals-link-between-transthyretin-levels-and-heart-disease-risk.

TTR Protein



TTR Carries:

- **Retinol**
- **Thyroxine Hormone**

Castaño A, et al. *Heart Fail Rev*. 2015.

Case: 72-Year-Old Female

- **Cardiac Evaluation**
  - NT proBNP: 3529 pg/mL
  - Troponin
    - **2023:** 0.02 (<0.04 ng/mL)
    - **2025:** HS 36 (<14ng/mL)
  - ECHO
    - **2023:** IVSd: 1.2 cm (nl 0.6-0.9 cm)
- **Genetic Testing:** c.250T>C (**p.Phe84Leu**)
- **Negative Tests**
  - Fat aspirate
  - Skin biopsy

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Kappa QNT Free Light Chains	18.71
Lambda QNT Free Light Chains	10.98
K:L Ratio	**1.70 (High)**

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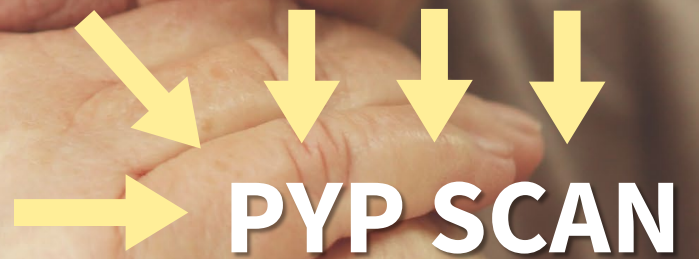


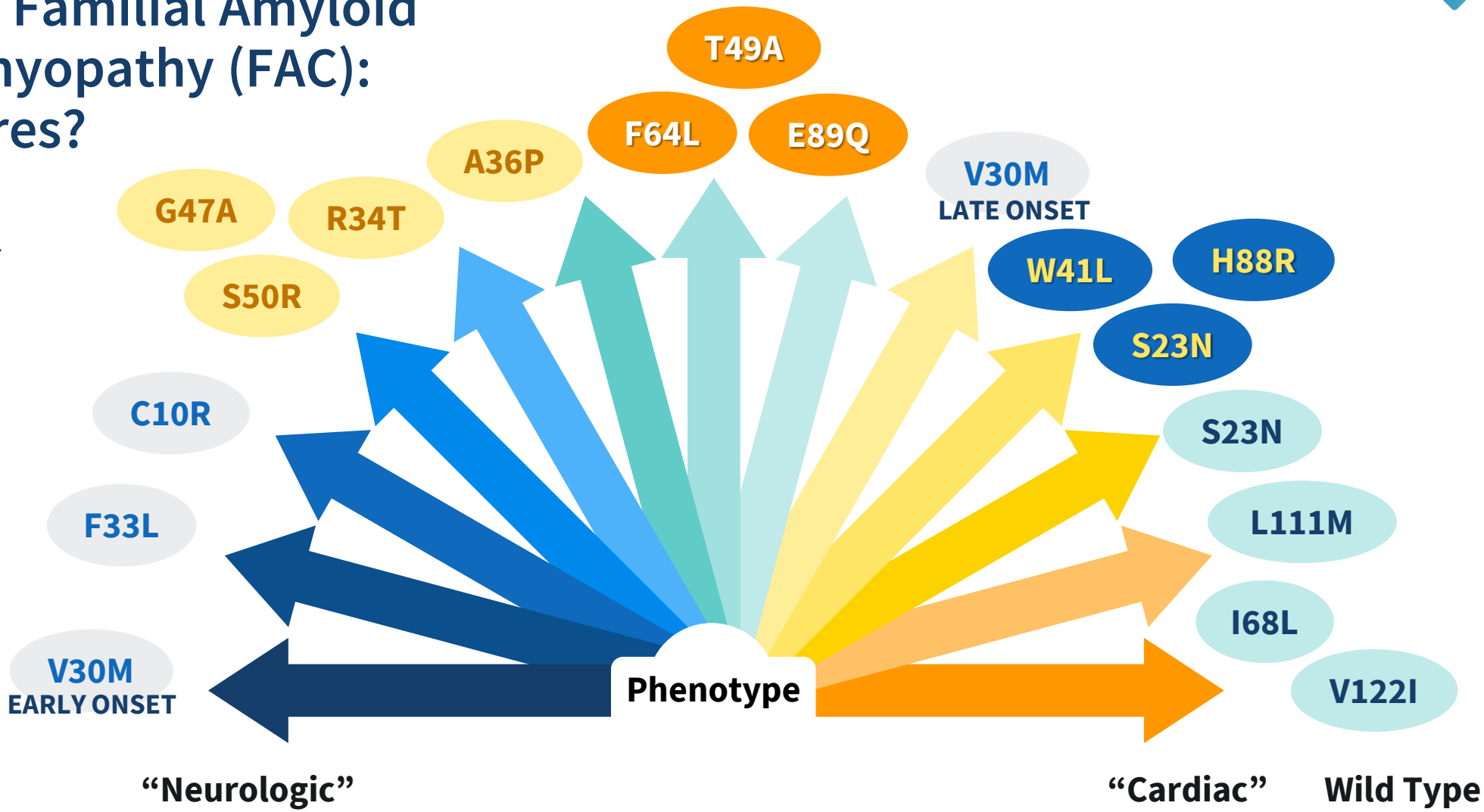
Case: 72-Year-Old Female

- **2021 cold feet** → now **numb from knees to toes**
- Was extremely active for 30 years, **trouble walking in 2023**
- **2024 trouble going up steps → 2025 trouble going up a curb**
- **Using cane in October 2024** → unable to stand without assistance, bilateral foot drop
- **Severe fatigue**
- Diarrhea alternating with constipation
- BP drops and gets lightheaded

Exam Date	Arm Abd Right/Left	Hip Flexors Right/Left	Ankle D. Flexors Right/Left	Ext Hallucis Right/Left
8/19/2024	4/4	4/4	2/2	-
11/27/2024	4+/4+	4/4	4/4-	-
4/22/2025	4/4+	4/4-	4/4-	3/3
7/14/2025	5/5	3/3	1/1	0/0

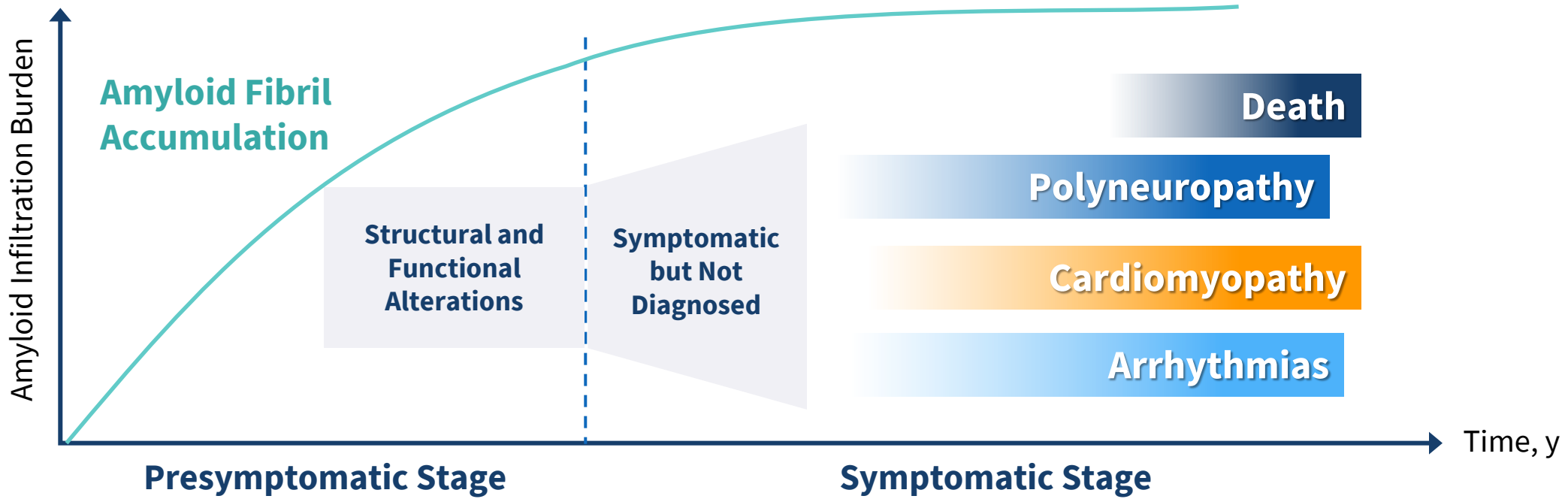
Familial Amyloid Polyneuropathy (FAP) or Familial Amyloid Cardiomyopathy (FAC): Who Cares?

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-CA 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

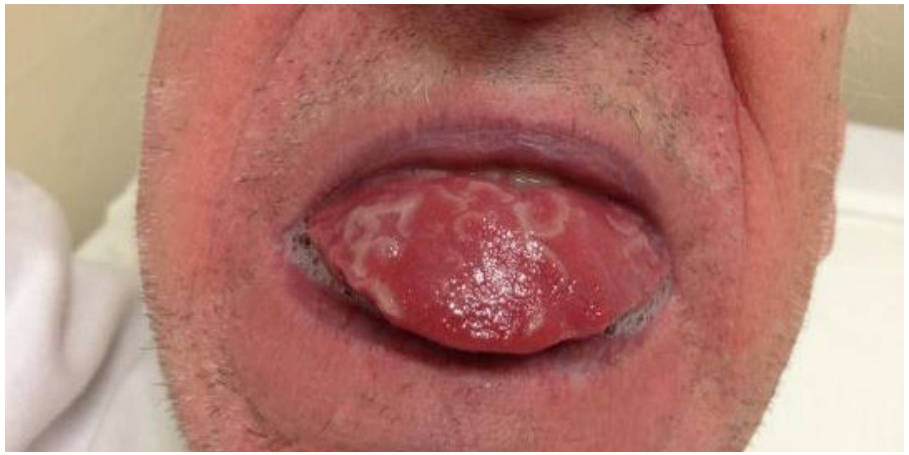
82 p.V142I

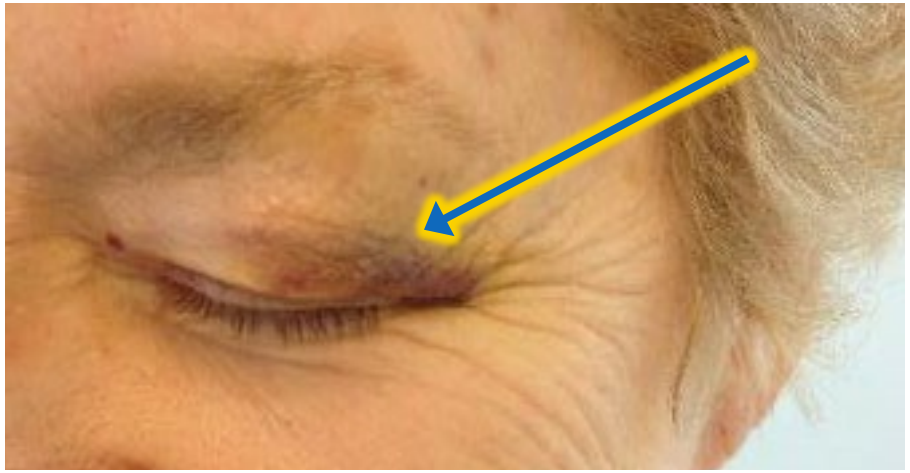
40% Neuropathy

13% from Amyloidosis – unpublished data

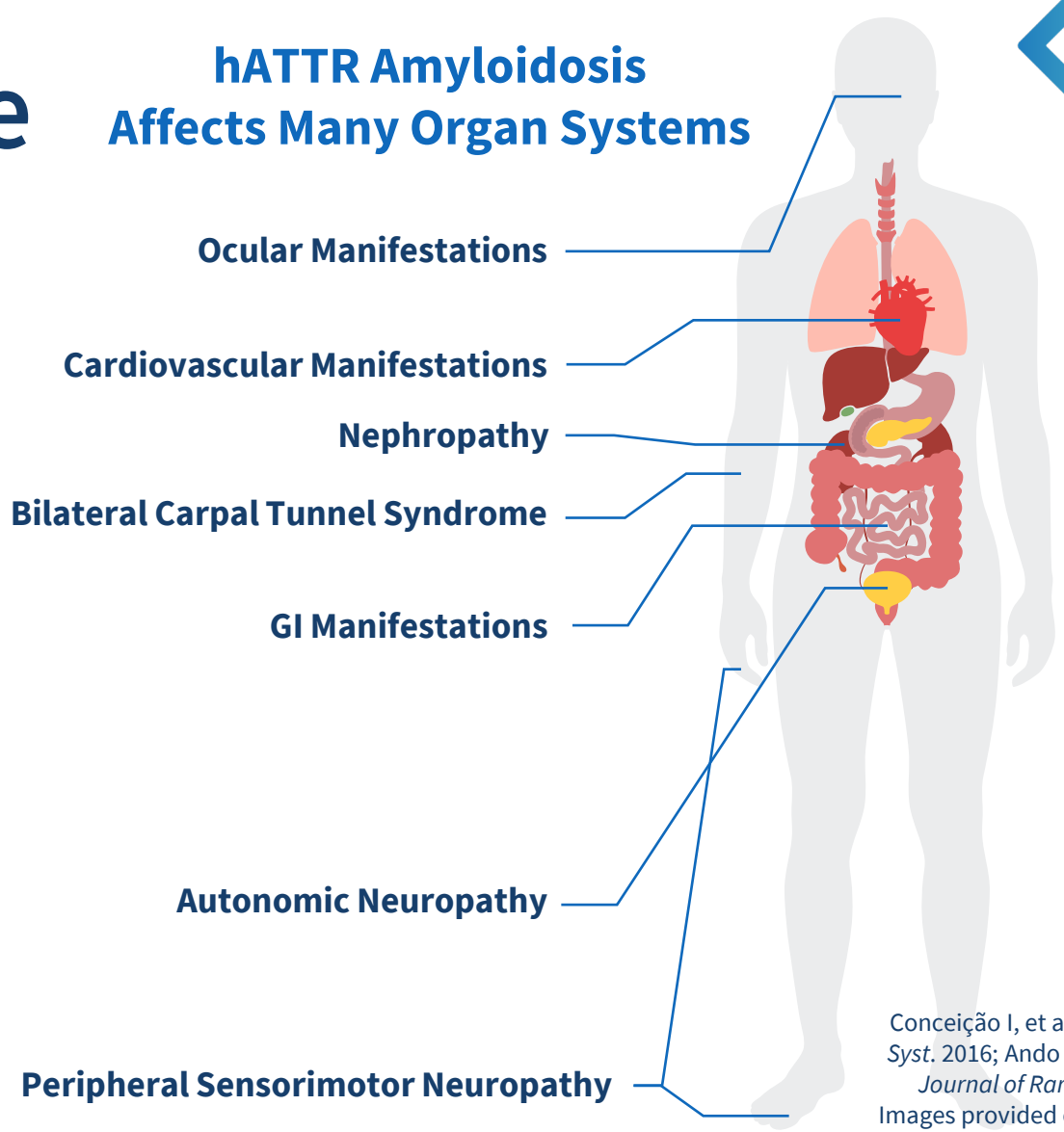
1. Selvaraj S et al. *JAMA*. 2024. 2. Kaniper S, et al. *J Pers Med*. 2024. 3. Lopes LR, et al. *Amyloid*. 2019. 4. Gentile L, et al. *PLoS One*. 2024. 5. Ekpo E, et al. *Amyloid.* 2024. 6. Gillmore JD, et al. *N Engl J Med*. 2024. 7. Fontana M, et al. *N Engl J Med*. 2025.

Multi-System Disease





hATTR Amyloidosis Affects Many Organ Systems



Conceição I, et al. *J Peripher Nerv Syst*. 2016; Ando Y et al. *Orphanet Journal of Rare Diseases*. 2013; Images provided courtesy of Sami Khella, MD.

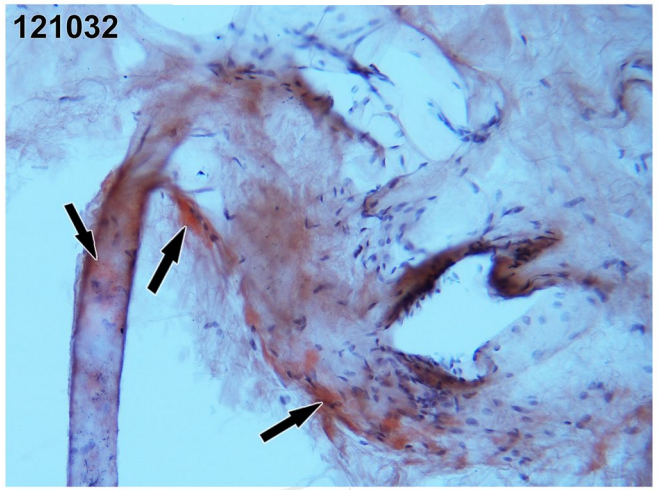
Flags Raising Suspicion of ATTRv in Patients Presenting With Neuropathy

- **Rapidly Progressive Neuropathy**
- **Heart Failure** With **Preserved EF**
- Prior History of **Carpal Tunnel Syndrome**
- **Autonomic Symptoms**
- **Refractory CIDP** (e.g., IVIg for CIDP)

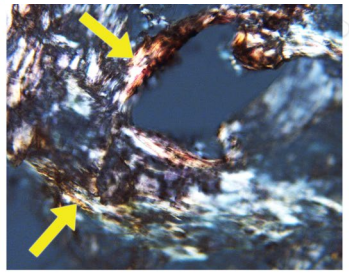
Karam C, et al. *Muscle Nerve*. 2024.

Diagnosis by Tissue Sampling or Cardiac Imaging

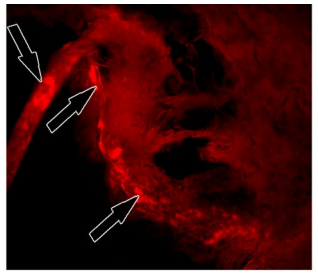
Congo Red Stain



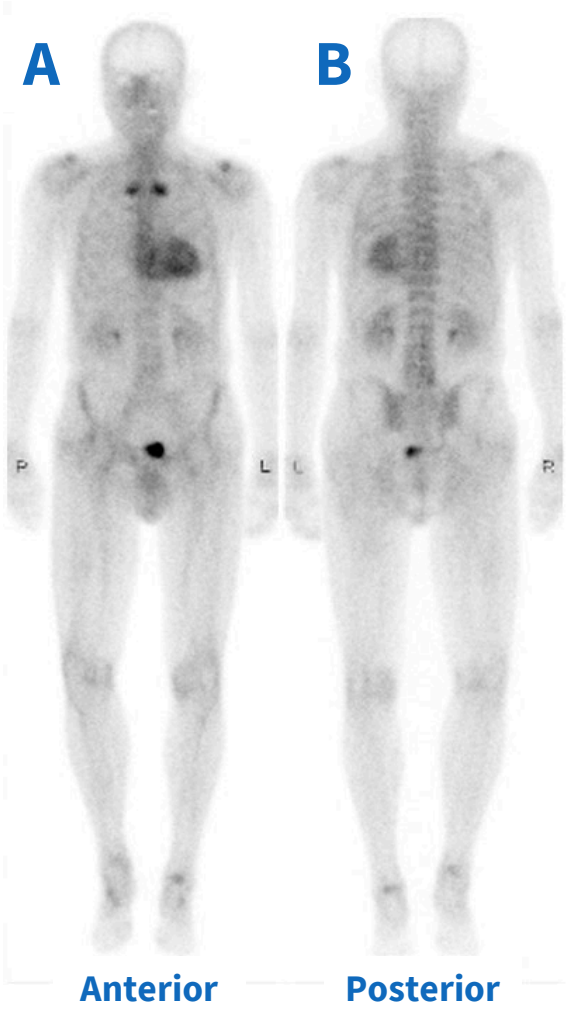
Under Polarizer

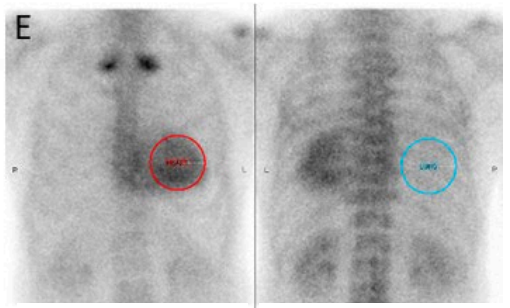


Fluorescence Microscopy



Mass spectroscopy is used to identify and type the protein





Anterior Heart-to-lung ratio 2.12

Posterior

A,B: Technetium-99m-pyrophosphate scintigraphy in hereditary transthyretin demonstrating cardiac uptake compared with surrounding tissues with a heart to contralateral lung ratio of 2.1 (normal <1.5).

Congo red stain images courtesy of Sami Khella, MD; Carroll A, et al. *J Neurol Neurosurg Psychiatry*. 2022.

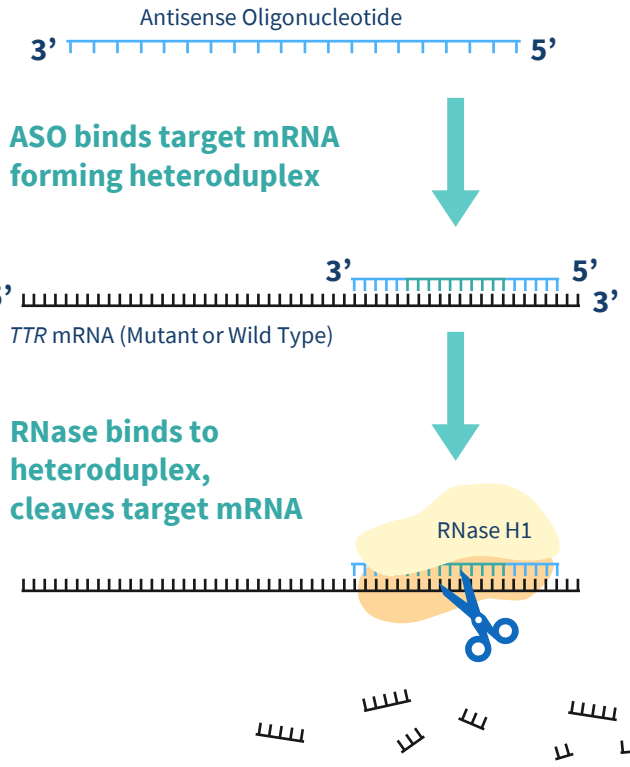
Evolving Approaches in ATTRv-PN Management

Laying the Groundwork for Drug Development in ATTR-CM

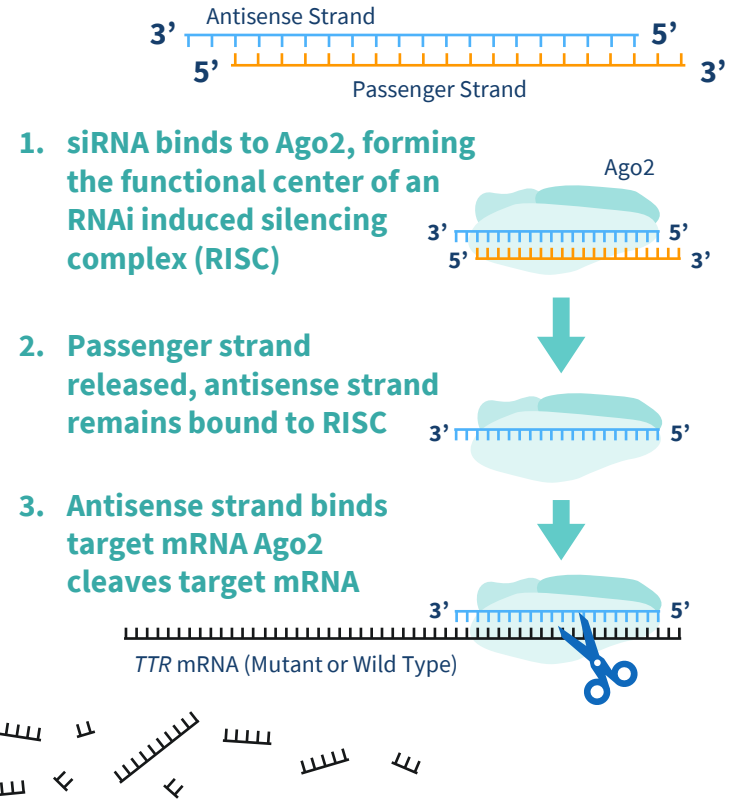
Less RNA = Less TTR Protein

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

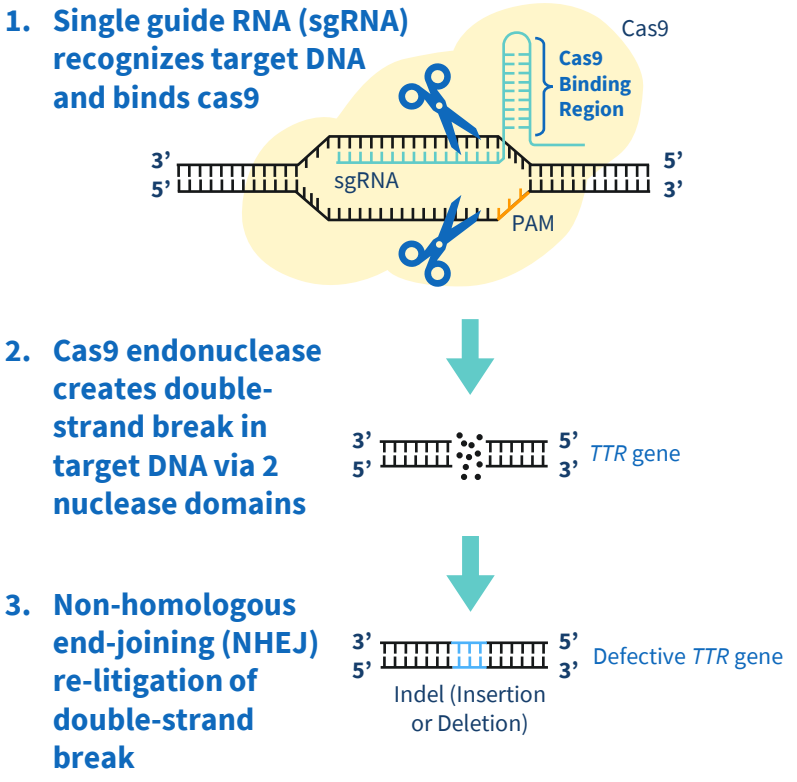
Antisense Oligonucleotide (ASO)



Small Interfering RNA (siRNA)



CRISPR-Cas9 Gene Editing



mRNA Degraded → Reduced Protein Levels

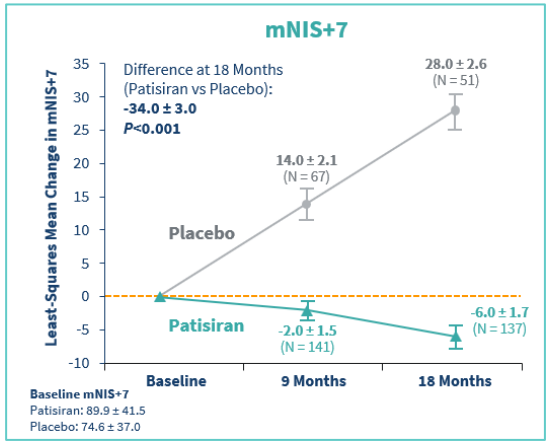
Gene Edited → Reduced Protein Levels

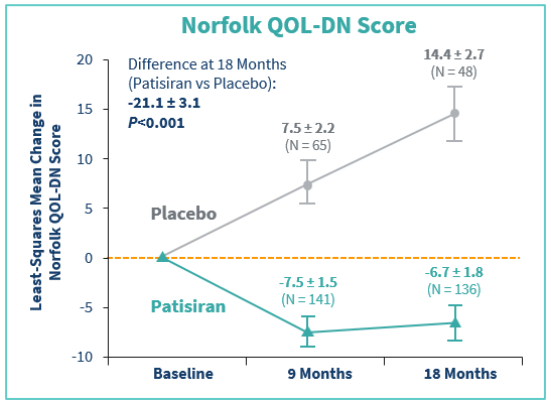
TTR Silencing Works for ATTRv-PN!

The Key Question - Could it also work for ATTR-CM?

Patisiran (APOLLO)

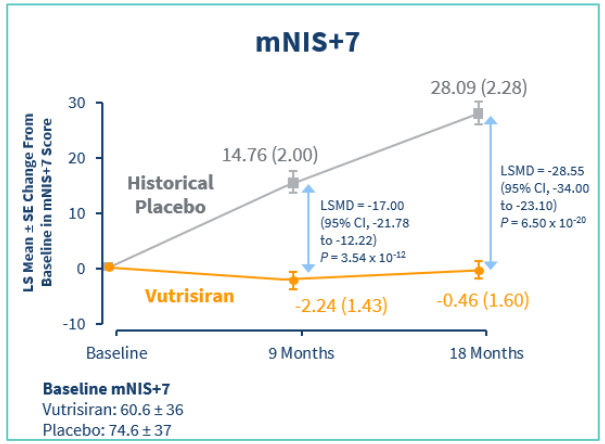
siRNA - FDA-approved

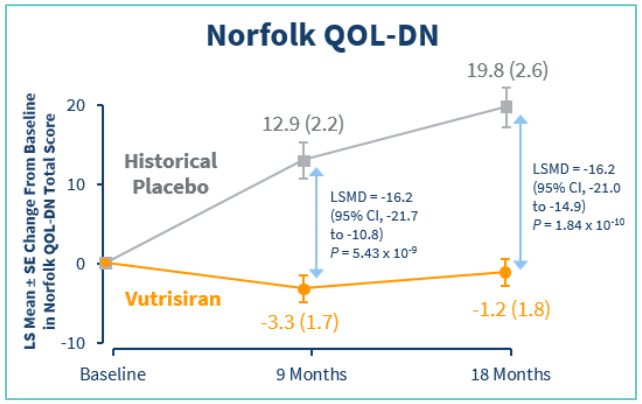




Vutrisiran (HELIOS-A)

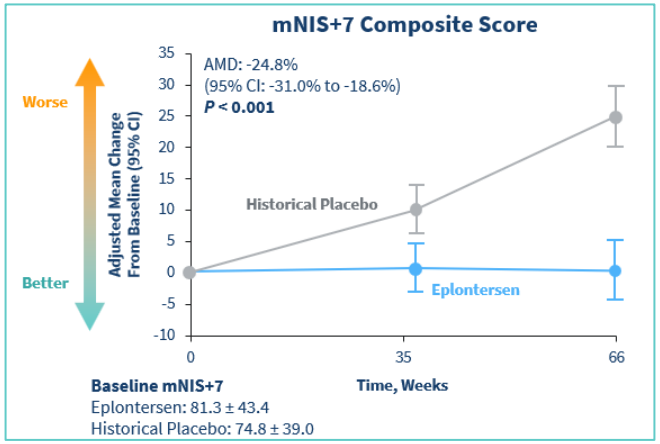
siRNA – FDA-approved

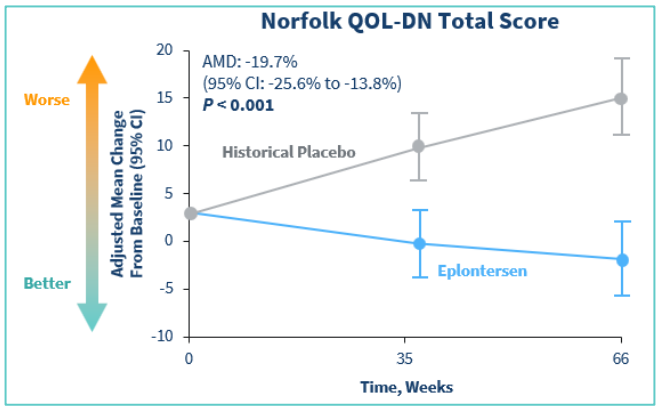




Eplontersen (NEURO-TTRansform)

ASO – FDA-approved





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	***FDA Fast Track***	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.

Managing GI Amyloidosis

Communication is Vital!

GI signs and symptoms: Pt won't mention them unless you ask!

Dietary Modifications	
Reflux and Nausea	• Small evening meal • Longer interval between evening meal and lying down
Malnutrition	Calorie-dense supplements and shakes
Cramping, Diarrhea, Bloating	FODMAP diet

Medications	
Nausea and Early Satiety	• Antiemetics: ondansetron, promethazine • Prokinetics: metoclopramide, prucalopride
Diarrhea	• **Opioid receptor agonists**: loperamide, diphenoxylate/atropine, tincture of opium • Antibiotics for SIBO • Bile acid sequestrants • Octreotide • **Aprepitant**
Constipation	• Laxatives: polyethylene glycol, magnesium-containing products, senna • Linaclotide, prucalopride

Kittleson M, et al. *J Am Coll Cardiol*. 2023.

Summary

- 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***

Strategies for Screening and Diagnosing ATTR Amyloidosis

Mitigating Diagnostic Odyssey and Streamlining Care

Amyloid Transthyretin (ATTR) Amyloidosis

- ATTR amyloidosis is a rare, progressive, and fatal disease characterized by deposition of amyloid fibrils in multiple organs and body systems (e.g., heart and nervous system)[1,2]
- In ATTR amyloidosis, transthyretin (TTR) is the protein responsible for forming amyloid fibrils[1,3]
- There are 2 types of ATTR amyloidosis[1,4,5]

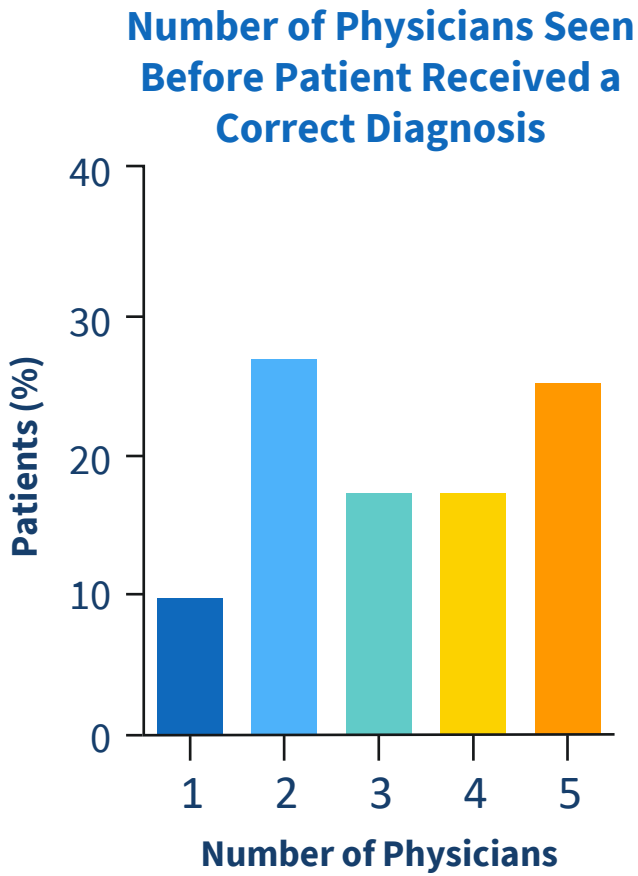
Wild-Type ATTR Amyloidosis, caused by deposition of wild-type TTR primarily in the heart of individuals >60 years old.

Hereditary ATTR Amyloidosis, caused by deposition of wild-type and mutant TTR throughout the body.

1.Hawkins P, et al. *Ann Med*. 2015. 2. Suhr O, et al. *J Int Med*. 1994. 3. Saraiva M. *FEBS Letter*. 2001. 4. Ando Y, et al. *Orphanet Journal of Rare Diseases*. 2013. 5. Coelho T, et al. *CMRO*. 2013.

Diagnosis of ATTR Amyloidosis

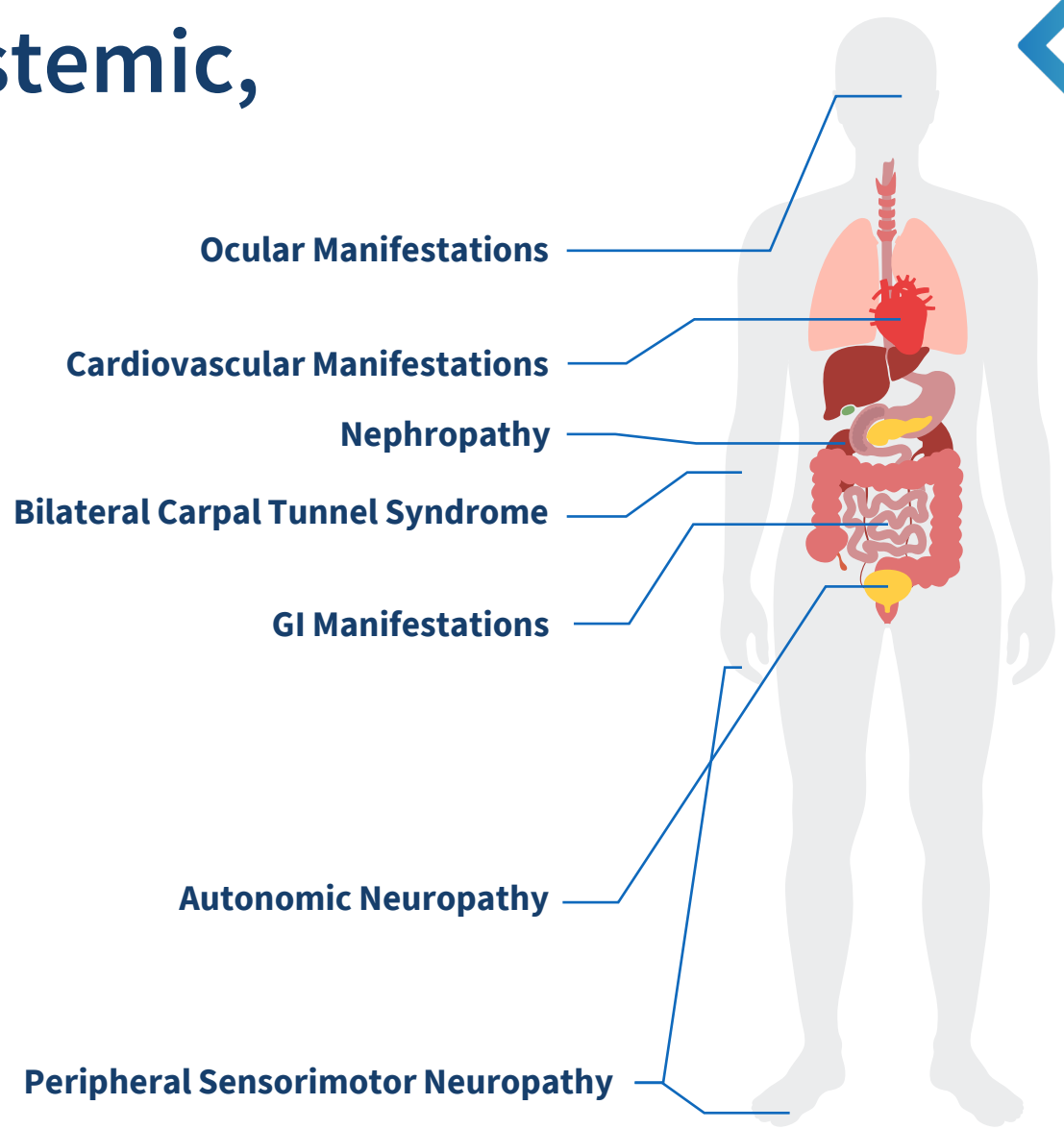
- Tissue biopsy is **not required** for diagnostic confirmation[1-3]
- **Congo red staining of amyloid is the gold standard for diagnosis** but not required for confirmation[1,2]
- A diagnostic algorithm proposed by Gillmore et al. based on myocardial radiotracer uptake on bone scintigraphy has been developed for use in patients with cardiac ATTR amyloidosis[4]
- **Amyloid typing** may be achieved using a variety of techniques[1,2]
  - Immunohistochemistry and immunofluorescence
  - Proteomics can be utilized for amyloidosis typing
  - **Mass spectrometry the gold-standard**



1. Ando Y, et al. *Orphanet Journal of Rare Diseases*. 2013. 2. Leung N, et al. *Blood*. 2012. 3. Castaño A, et al. *J Nucl Cardiol.* 2016. 4. Gillmore JD, et al. *Circulation.* 2016.

ATTR Amyloidosis is a Systemic, Multi-organ Disease

- Symptoms are multi-systemic involving multiple tissues and organs
- Nonspecific symptoms overlap with more common disorders and hinder recognition of amyloidosis
- Low index of clinical suspicion coupled with disease unawareness impede early and accurate diagnosis



Conceição I, et al. *J Peripher Nerv Syst*. 2016; Ando Y, et al. *Orphanet Journal of Rare Diseases*. 2013.

Clinical Tests and Findings Potentially Suggestive of ATTR Amyloidosis

Heart	
ECG	Normal or low ECG voltage often discrepant from ECHO findings, pseudo-infarct pattern, atrioventricular block, bundle branch block
ECHO	Increased left and/or right ventricular wall thickness, increased atrial septal thickness, impaired longitudinal strain, apical sparing pattern by longitudinal strain, thickened valve leaflets , increased LV filling pressures, pericardial effusion
CMR	Increased bioventricular wall thickness , increased LV mass, diffuse subendocardial or transmural late gadolinium enhancement, increased native noncontrast T1 and ECV
99m Tc Bone Scintigraphy (DPD/PYP/HMDP)	Grade 2/3 myocardial uptake; note, this test should always be ordered with serum FLC/serum and urine immunofixation electrophoresis to rule out the presence of a monoclonal protein. If any of these are abnormal, endomyocardial biopsy with typing of amyloid fibril may be necessary for an accurate diagnosis
Serum Cardiac biomarkers	Increased BNP or NT-proBNP levels, increased troponin T or troponin I levels
Peripheral Nerves	
Nerve Conduction Study	Axonal sensorimotor neuropathy, CTS
Neuro MRI	Swelling of dorsal ganglia
Autonomic Nerves	
Schellong Test	Neurologic orthostatic hypotension
CVRR	Decreased CVRR
Sweat Test Laser Doppler Flowmetry	Anhidrosis, hypohidrosis

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

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.

Diagnostic Flowchart

Patient With Symptoms Suspicious for Amyloidosis

Light Chain Abnormality

Referral to Hematology

Cardiac Symptoms

- Orthopnea, paroxysmal nocturnal dyspnea, fatigue, exercise intolerance, dizziness/syncope, palpitations, atrial fibrillation, thromboembolism, and fluid retention
- **Other Systemic Manifestations:**
  - Unexplained peripheral neuropathy
  - Gastrointestinal symptoms (e.g., early satiety, nausea, vomiting , and/or altered bowel habits)
  - History of surgically corrected bilateral CTS and/or lumbar stenosis

ECHO and ECG
Cardiac MRI
^{99m}Tc-PYP/^{99m}Tc-DPD

Referral to Cardiology

Peripheral Neuropathy Symptoms

- Progressive sensory polyneuropathy , autonomic dysfunction (e.g., chronic or alternating diarrhea and/or constipation , erectile dysfunction and postural hypotension), pain in the hands or feet and gait disorders
- **Other Systemic Signs:**
  - Unexplained weight loss
  - Cardiac symptoms
  - Ocular manifestations
  - Renal abnormalities
  - History of surgically corrected bilateral CTS and/or lumbar stenosis

***TTR* Genetic Testing**

Referral to Neurology and Genetic Counseling

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

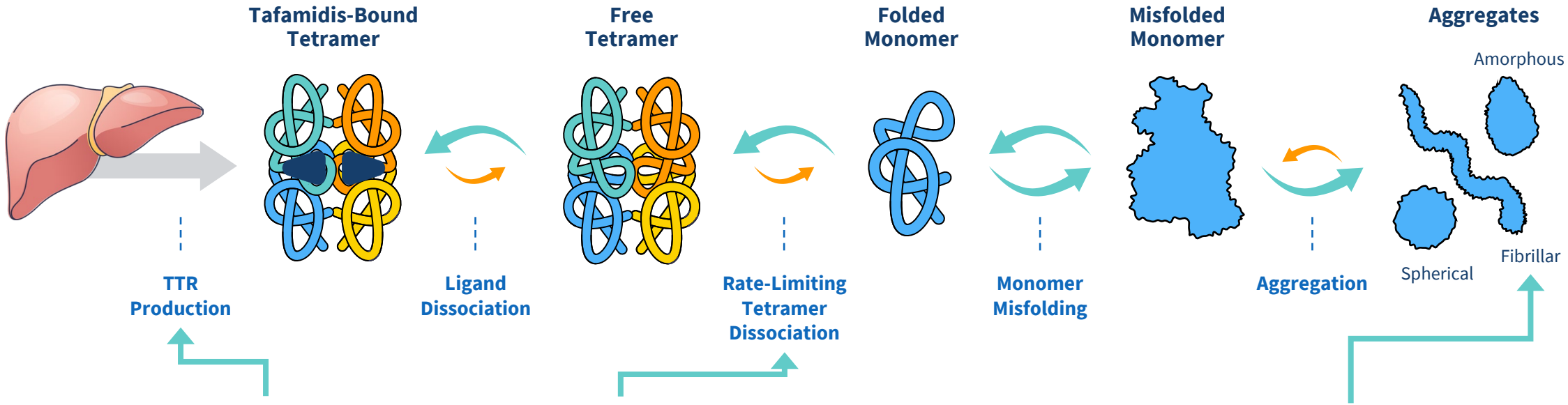
Embracing a New Era in ATTR Disease Modification

Established and Evolving Evidence for Novel Therapeutics

At the Leading Edge in ATTR-CM

Lessons Learned from Tafamidis

Targeting the Amyloidogenic Cascade



Therapeutic Strategies and Mechanisms of Action

♥ 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.

ATTR-ACT Study

- Mauer MS, et al. **Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy**. *N Engl J Med*. 2018.

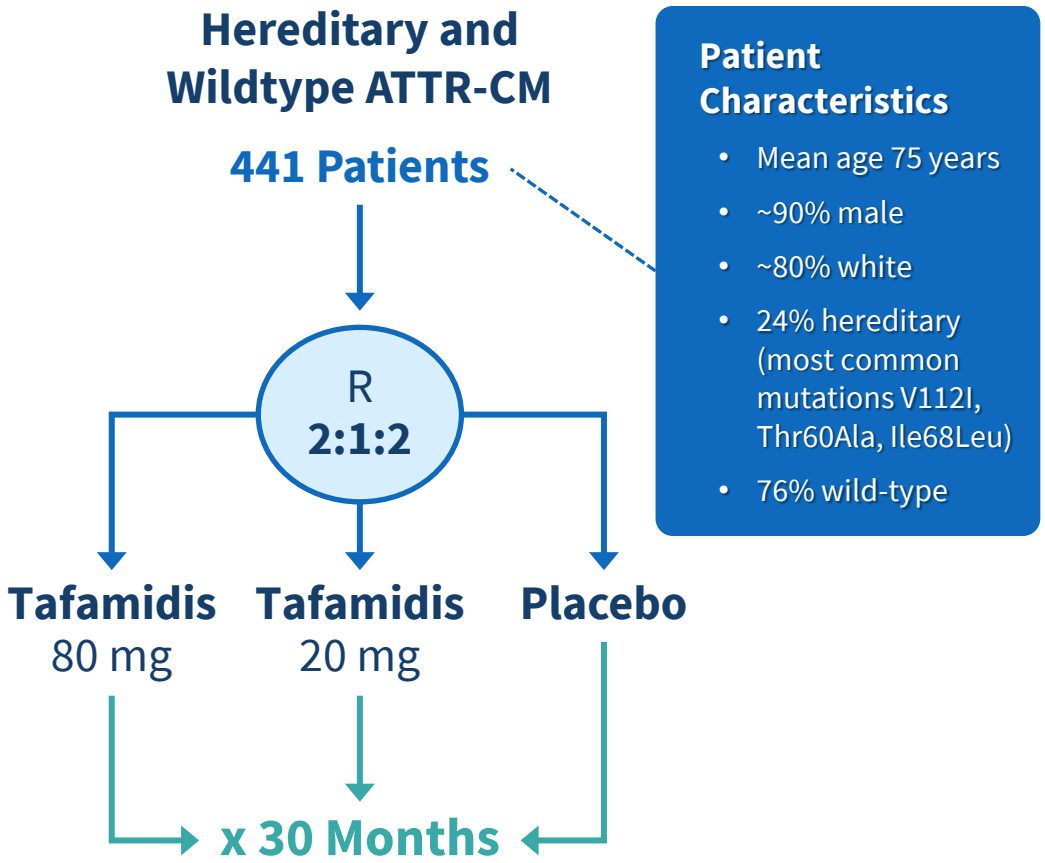
Inclusion Criteria

- **Patients 18-90 years** with amyloid confirmed on biopsy confirmed by immunohistochemistry, mass spectrometry or scintigraphy
- **Cardiac involvement: IVS >12 mm**, **history of heart failure** with at least one hospitalization or clinical evidence of heart failure without hospitalization requiring diuretics, **NT-pro BNP ≥ 600 pg/ml**, and **6-MWT distance >100 m**.

Exclusion Criteria

- **NYHA IV**
- Light chain **amyloidosis**
- Heart/liver **transplant**
- Cardiac assist **device**
- **Prior tafamidis treatment**
- GFR <25 ml/min/1.73m^2
- **Severe malnutrition** with mBMI < 600 (serum albumin (g/L) x BMI (wt (kg)/ht (m2))
- **Treatment with** NSAIDs, TUDCA, doxycycline, calcium channel blockers, or digitalis.

ATTR-ACT Study



Primary Endpoint

- Hierarchically assessed **All-Cause Mortality** followed by **CV-Related Hospitalization** with Finkelstein-Shonenfeld Method

Secondary Endpoints

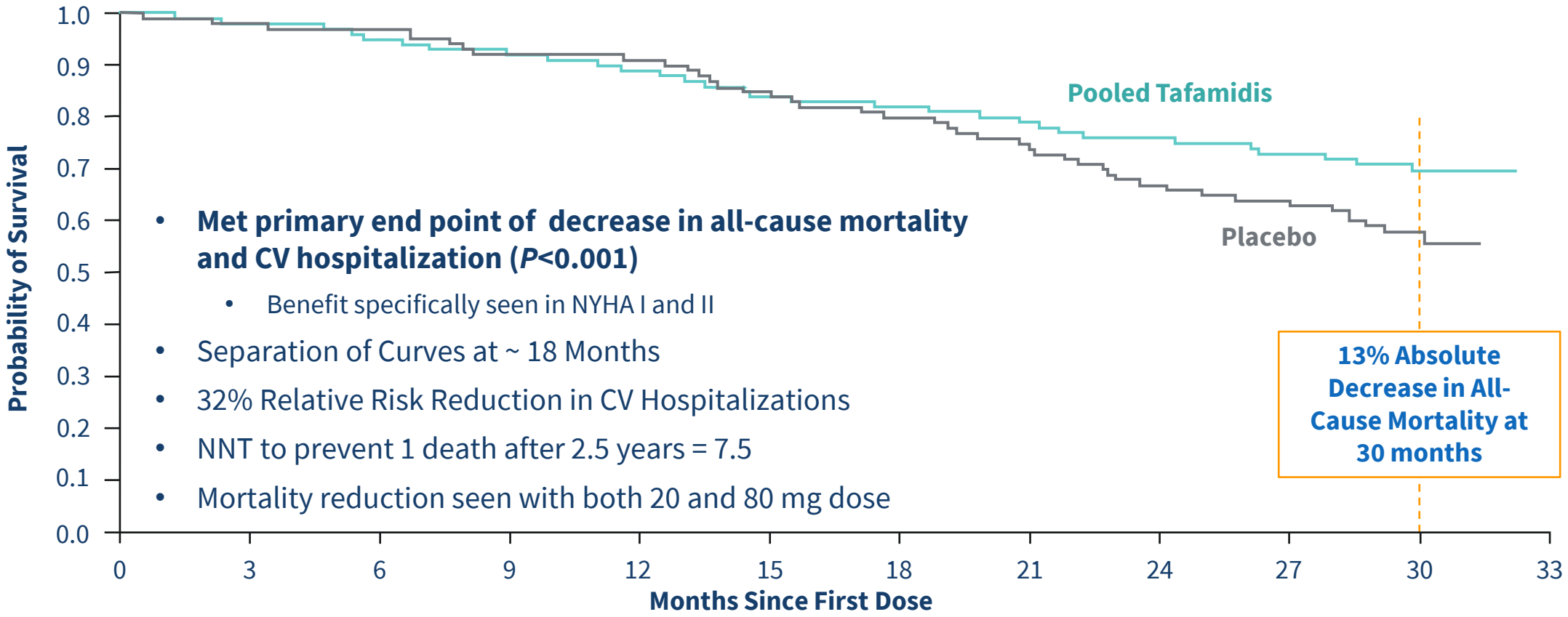
Change from Baseline:

- 6MWT
- Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS)

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

ATTR-ACT Results

Primary Endpoint: All Cause Mortality

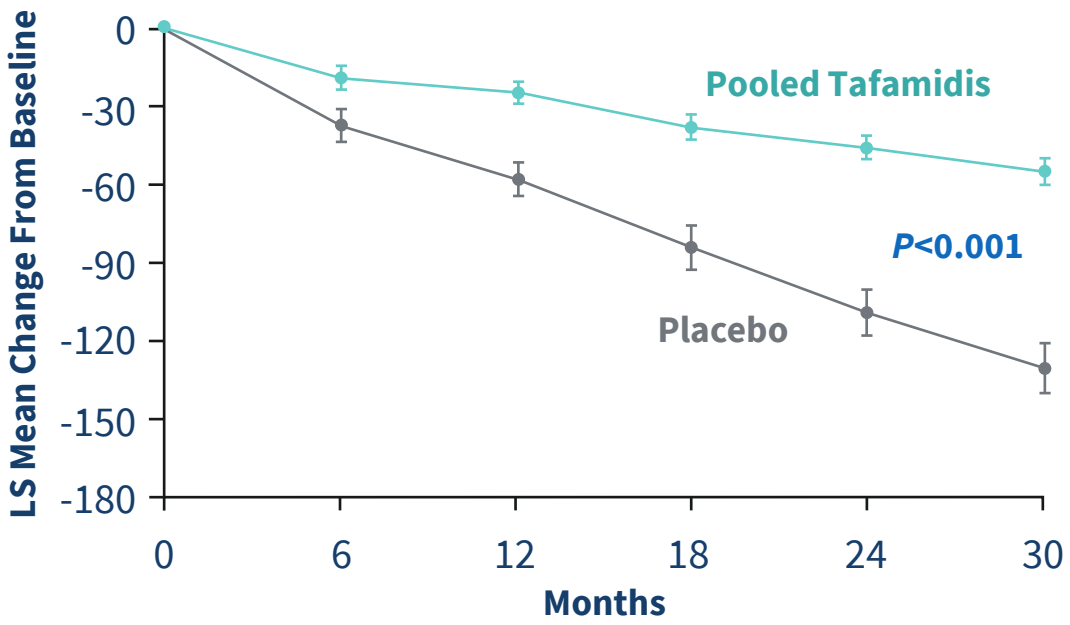


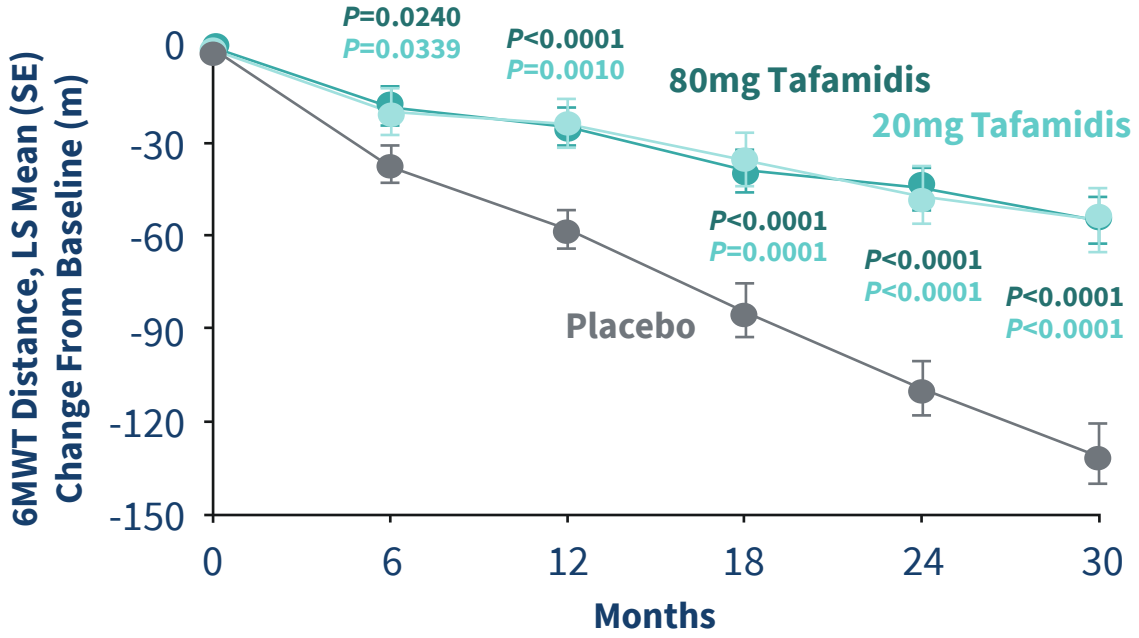
- **Met primary end point of decrease in all-cause mortality and CV hospitalization (*P*<0.001)**
  - Benefit specifically seen in NYHA I and II
- Separation of Curves at ~ 18 Months
- 32% Relative Risk Reduction in CV Hospitalizations
- NNT to prevent 1 death after 2.5 years = 7.5
- Mortality reduction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

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

ATTR-ACT Results

Secondary Endpoints: 6MWD

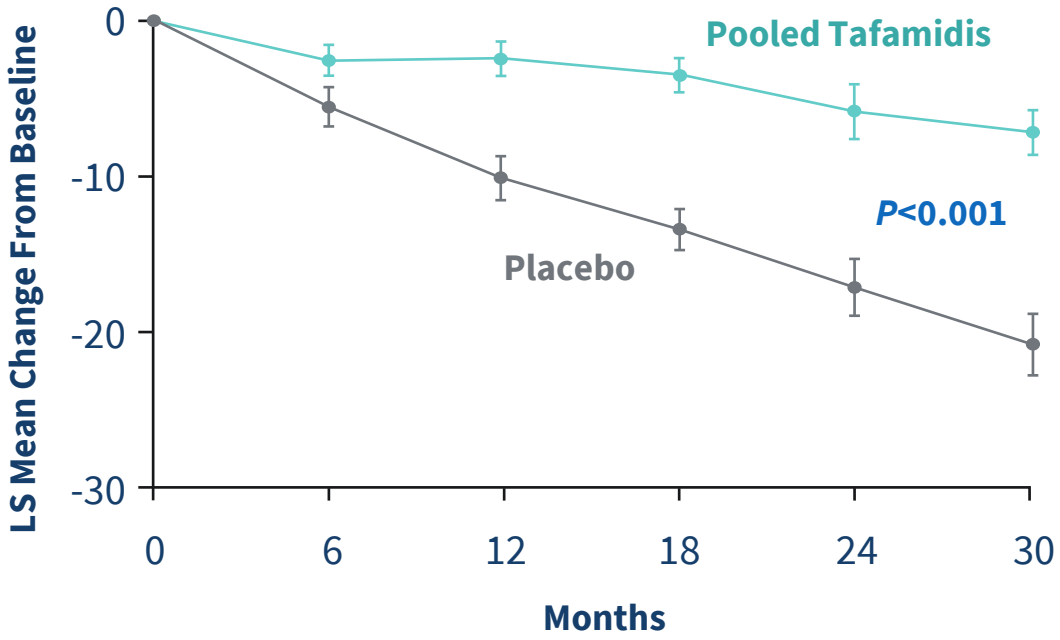


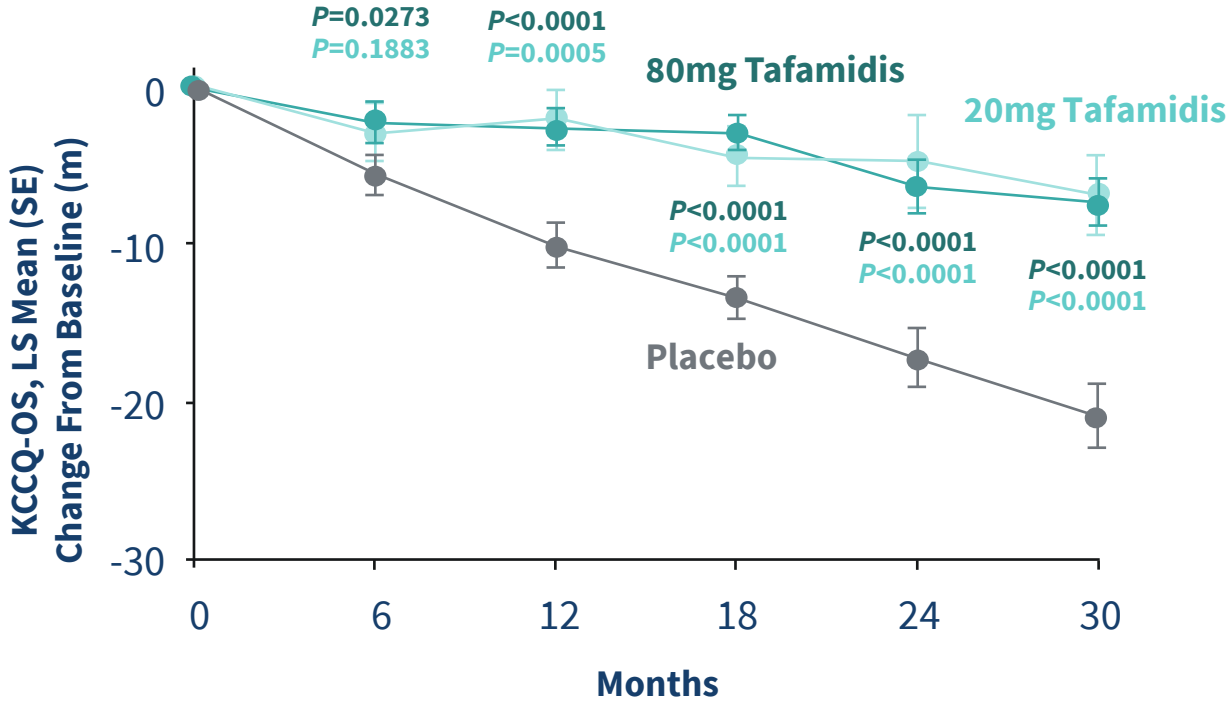


Maurer MS, et al. *N Engl J Med.* 2018; Sperry BW, et al. *JAMA Cardiol*. 2023.

ATTR-ACT Results

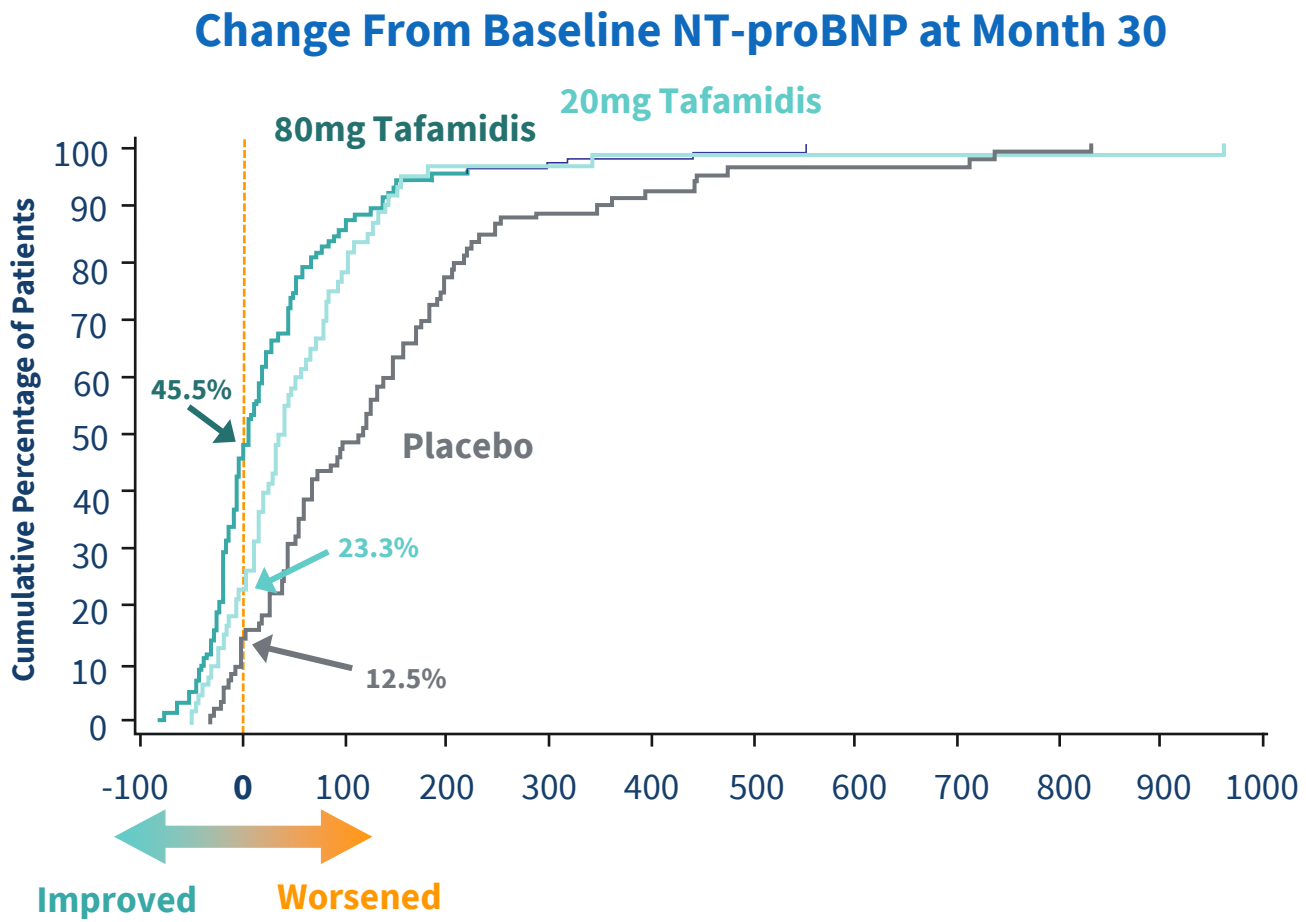
Secondary Endpoints: KCCQ-OS

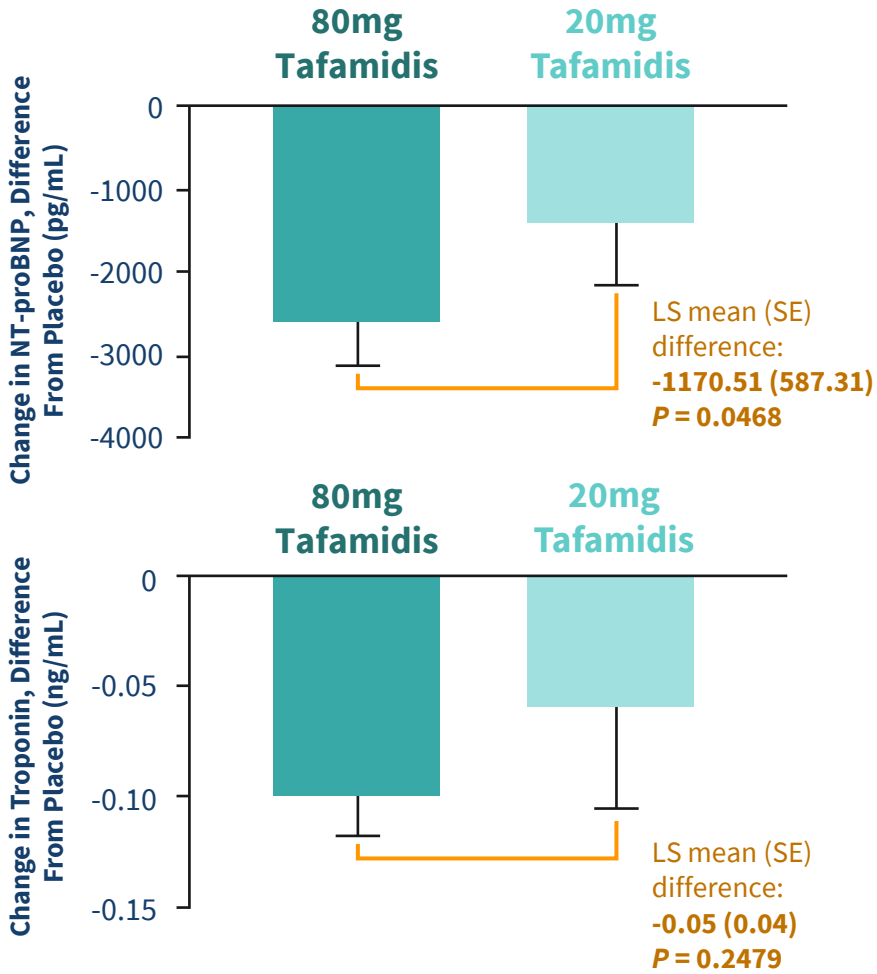




Maurer MS, et al. *N Engl J Med.* 2018; Sperry BW, et al. *JAMA Cardiol*. 2023.

Tafamidis Dosing: 80 mg Favored Over 20 mg





Damy T, et al. *Eur J Heart Fail*. 2021.

ATTR-ACT Results

Summary

- **Mortality and hospitalizations decreased in patients with baseline NYHA I and II** *but not NYHA III* patients who had more hospitalizations than the placebo group.
- Although not powered to assess outcomes with baseline NYHA III: Post-hoc Analysis by Sperry et al 2023 in JAMA showed that **patients with baseline NYHA III had worse overall outcomes** but a trend toward improvement in survival and KCCQ compared to placebo
- Side effects similar to placebo
- **Dosing:** Favored 80 mg dose compared to 20 mg for survival, change in 6MWT distance, KCCQ-OS, and NT-proBNP compared to placebo at 30 months

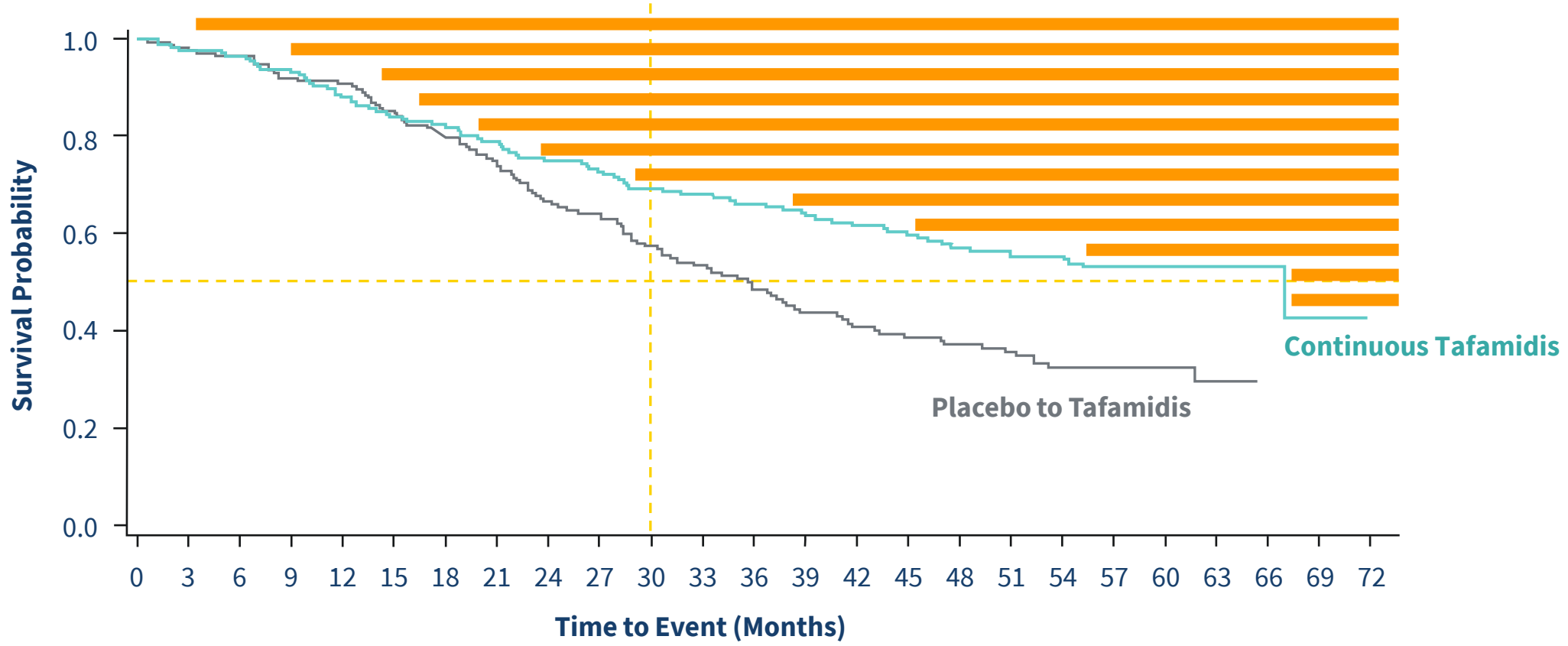
Approved by the FDA on May 3, 2019, for the **Treatment of ATTR-CM** (Hereditary and Wild-Type)

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

Trials and Tribulations in Transthyretin Amyloidosis

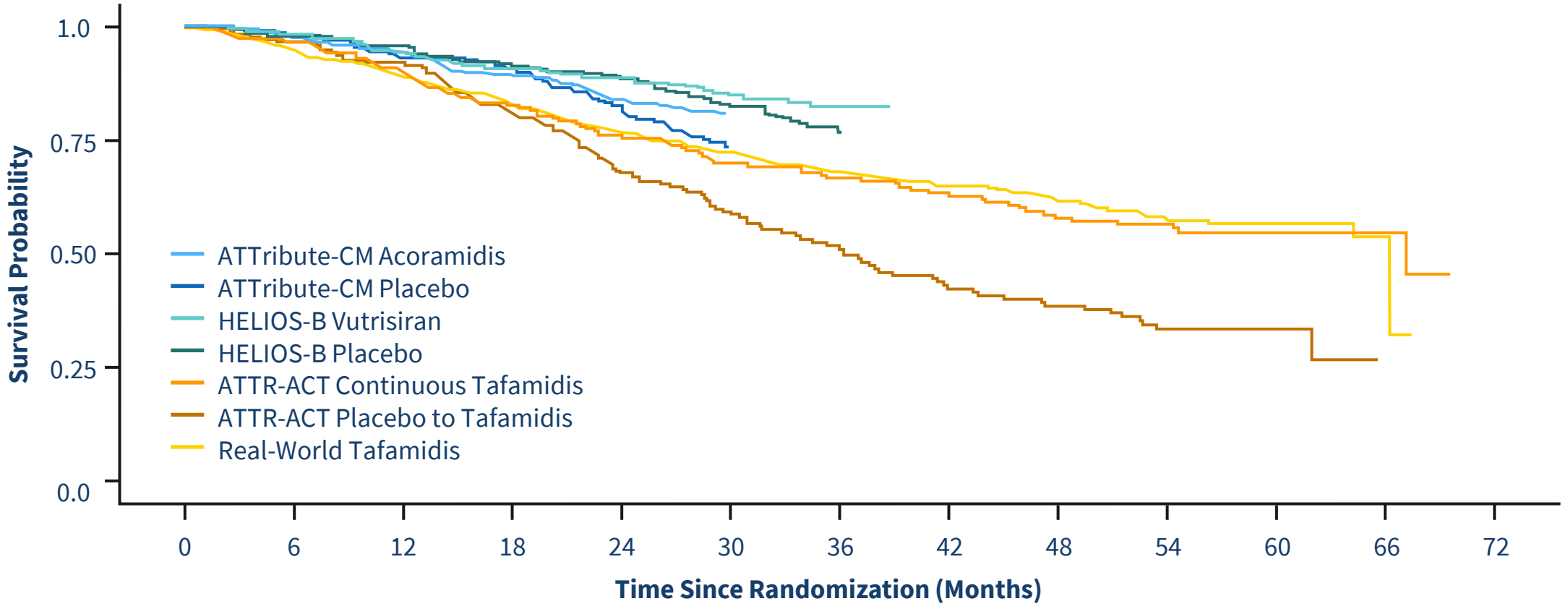
A Closer Look at the Ongoing Evolution of Evidence in ATTR-CM

Unmet Need on Tafamidis



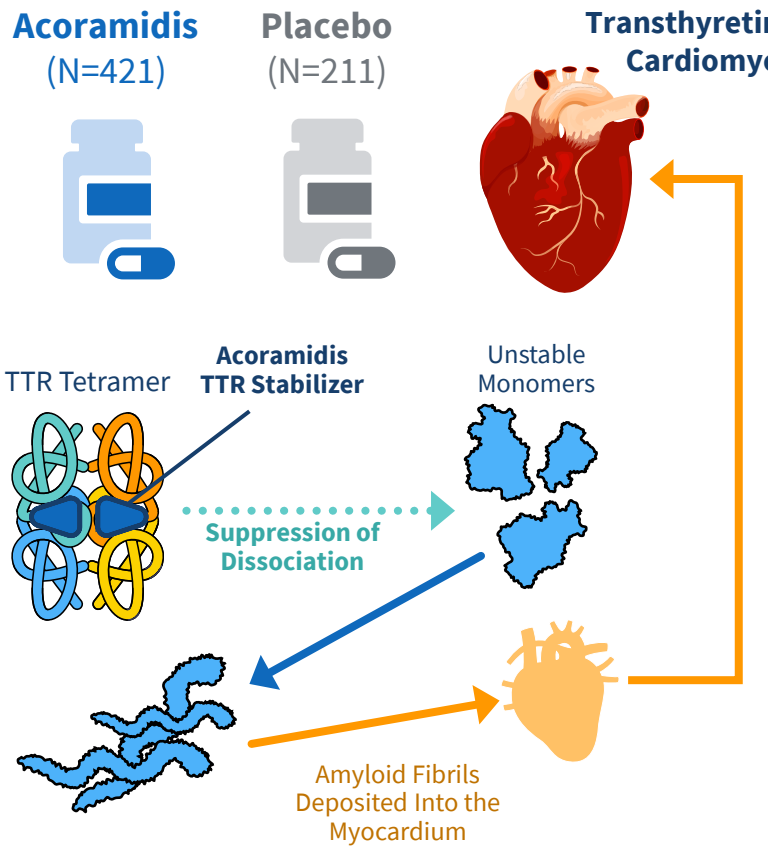
Elliott P, et al. *Circ Heart Fail*. 2022.

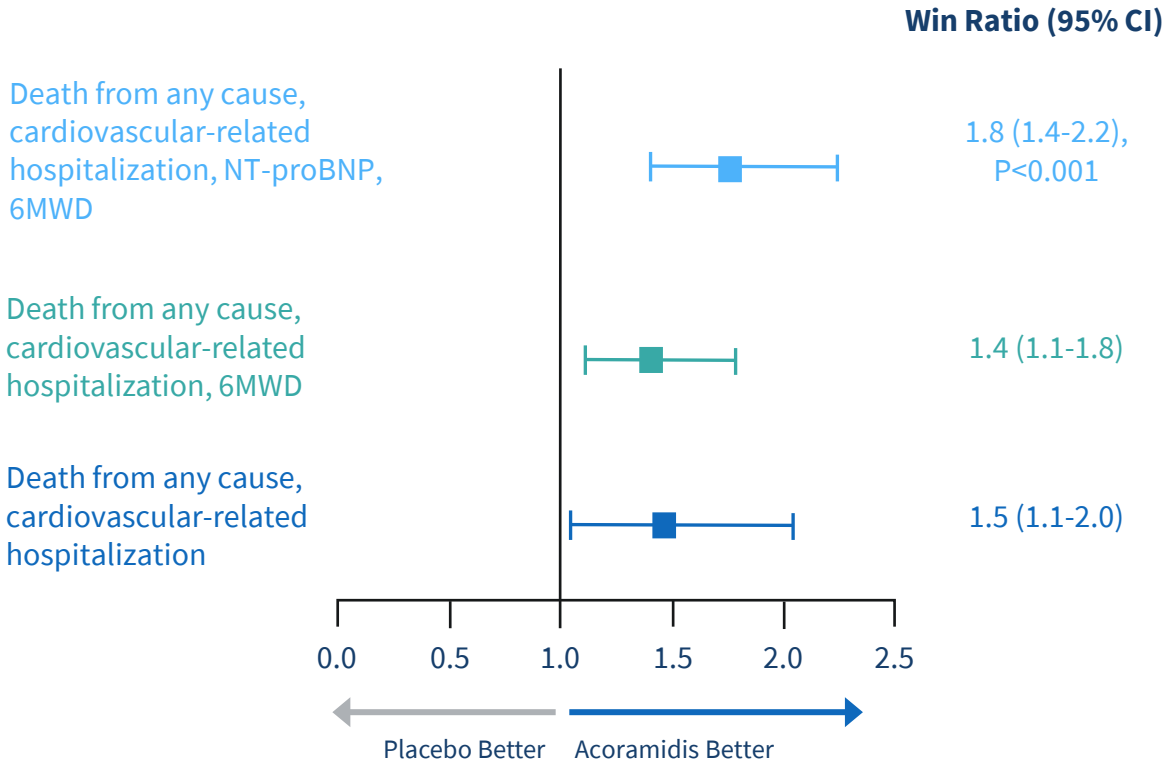
Natural History is Rapidly Changing



Masri A, et al. *JACC CardioOncol*. 2025.

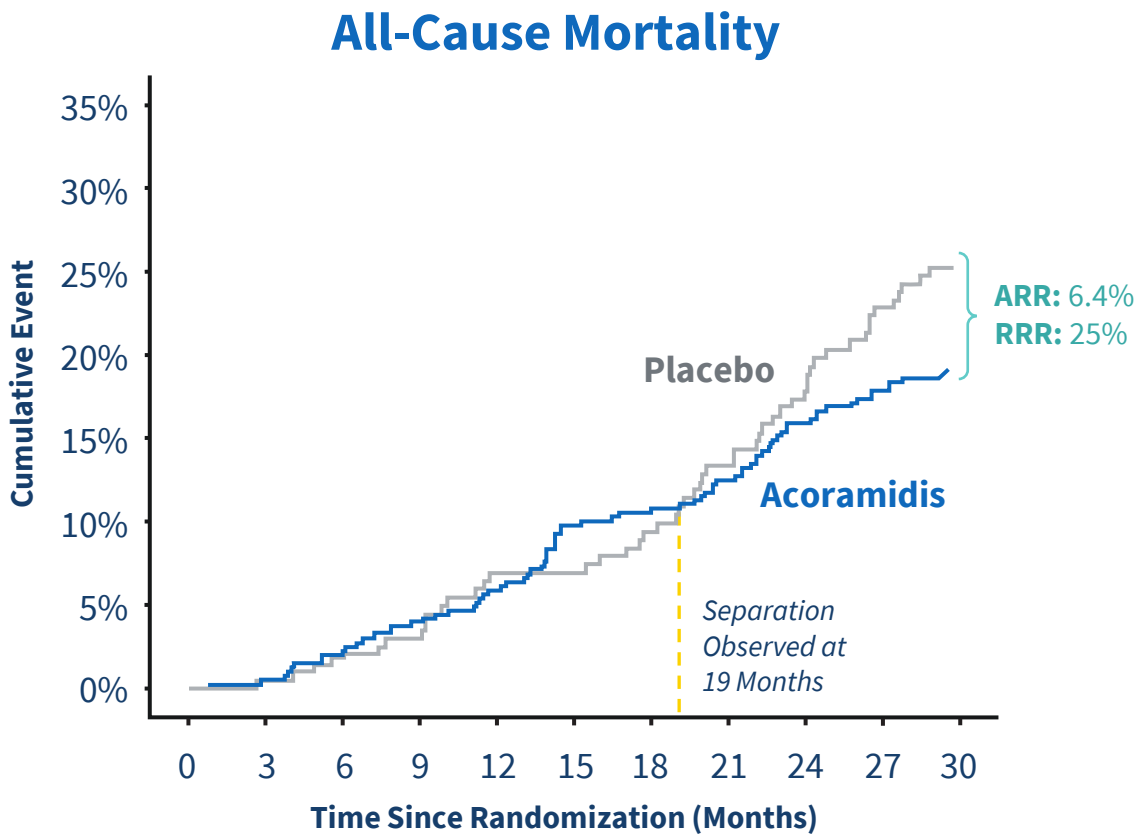
ATTRibute-CM: Acoramidis in ATTR-CM



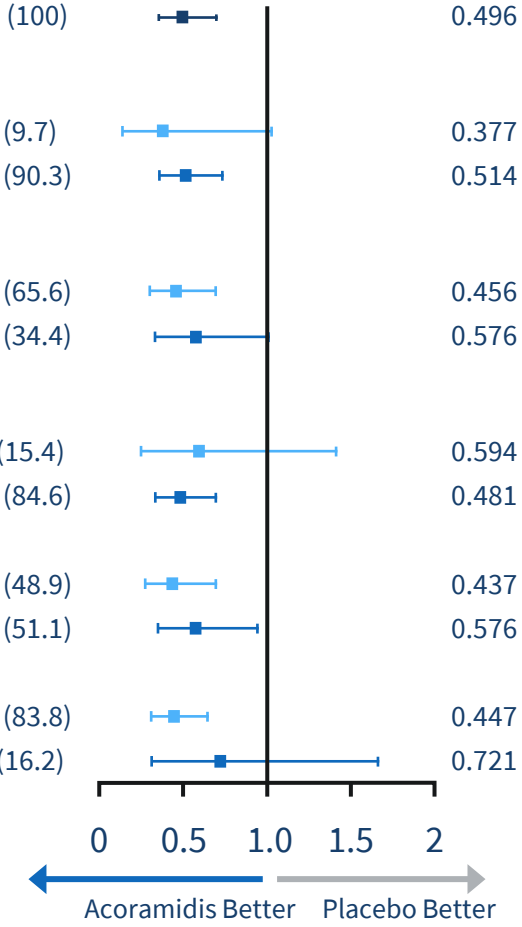


Gillmore J, et al. *N Engl J Med*. 2024.

ATTRibute-CM: Acoramidis in ATTR-CM



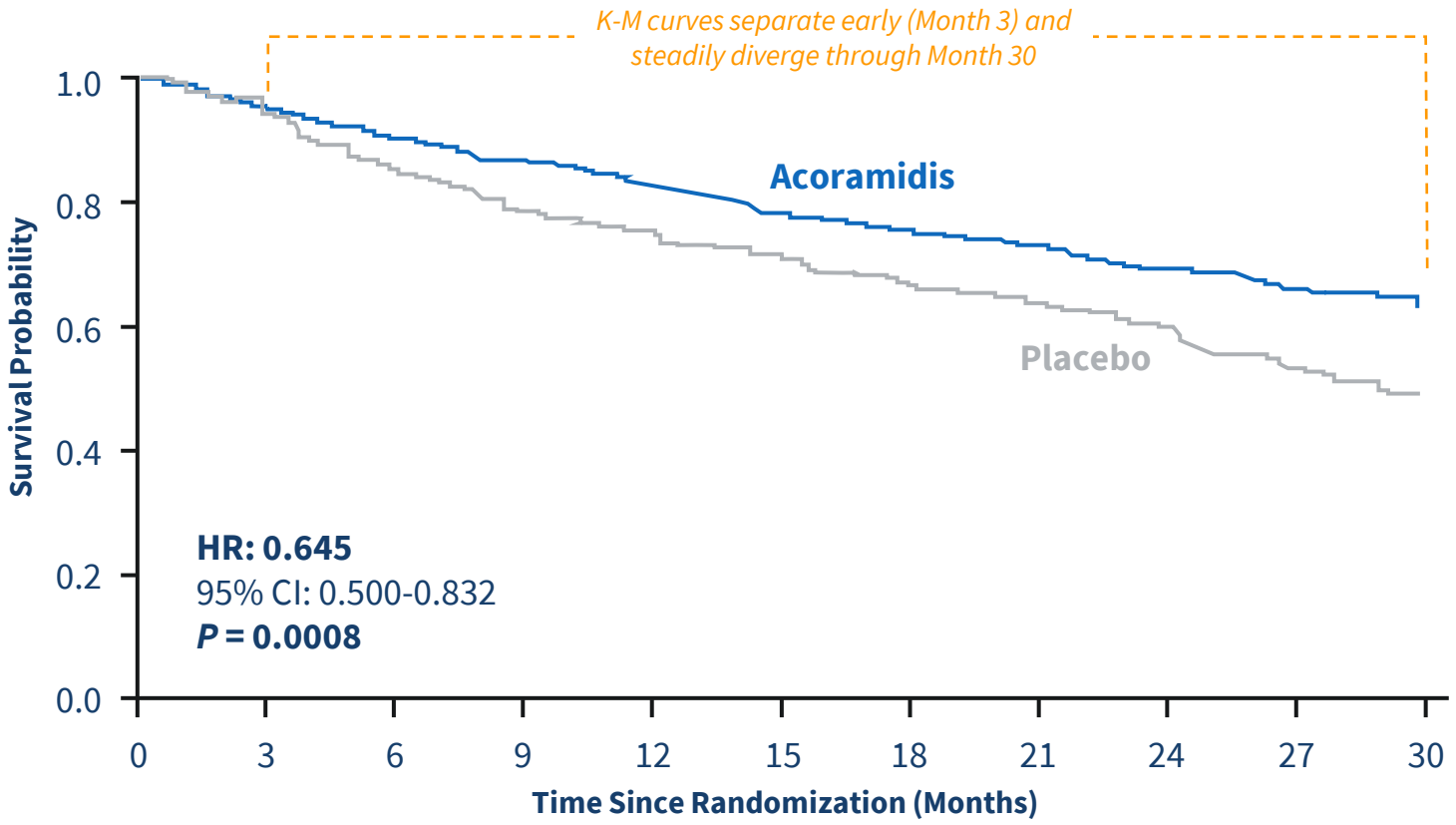
Subgroup	N (%)	RR (95% CI)
Overall	611 (100)	0.496 (0.355-0.695)
ATTR-CM Genotype		
ATTRm-CM	59 (9.7)	0.377 (0.139-1.027)
ATTRwt-CM	552 (90.3)	0.514 (0.360-0.734)
NT-proBNP (pg/mL)		
≤3000	401 (65.6)	0.456 (0.299-0.695)
>3000	210 (34.4)	0.576 (0.330-1.003)
eGFR (mL/min/1.73m^2)		
<45	94 (15.4)	0.594 (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.

Composite ACM/CVH

Time-to-First Event and F-S Test



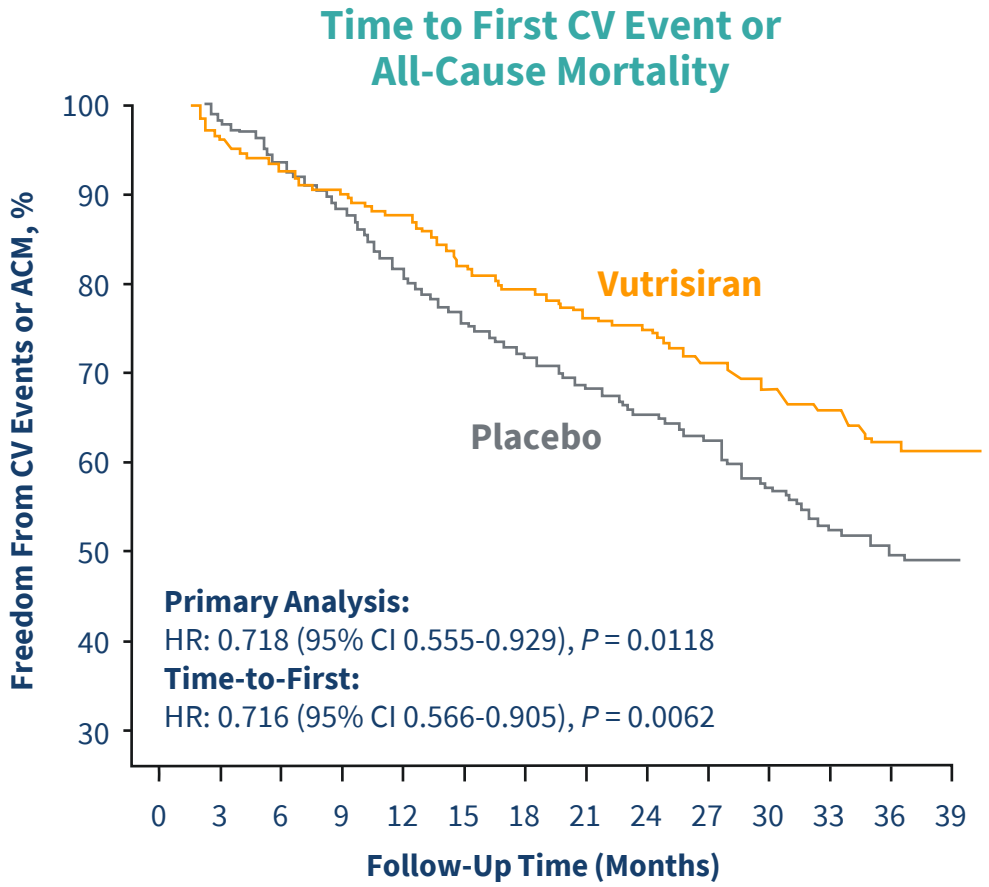
2-Component F-S Test
(ACM, CVH)

Favors Acoramidis
Over Placebo
***P* = 0.0162**

Judge D, et al. *J Am Coll Cardiol.* 2025.

HELIOS-B

Vutrisiran vs Placebo

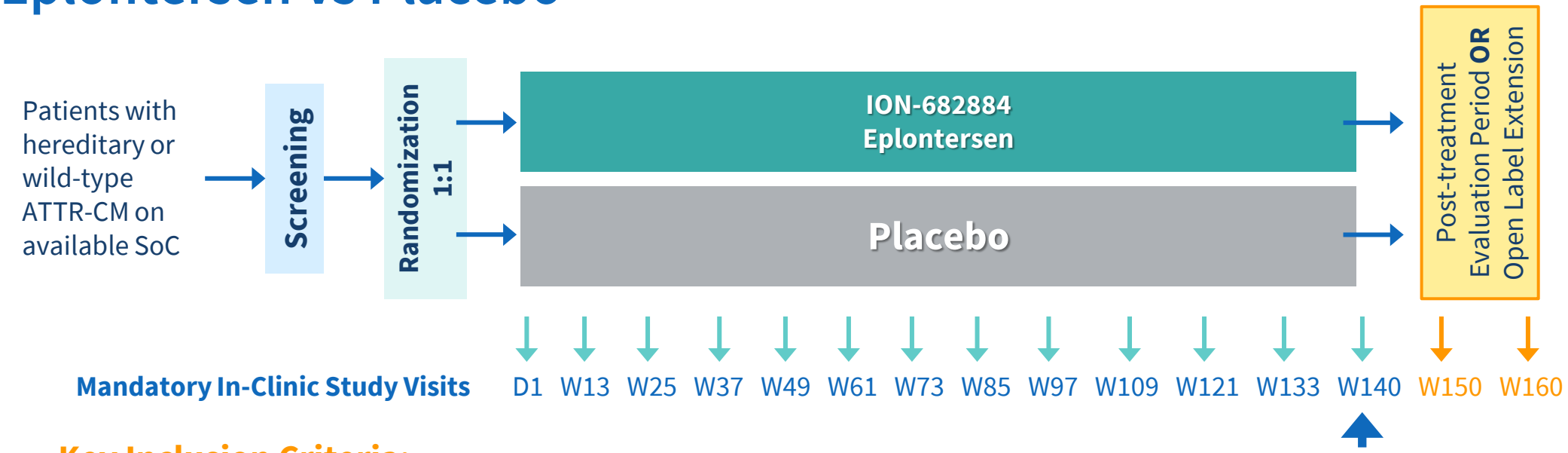


Endpoint	Tx Effect Est.	Overall Population (N=654)		Monotherapy Population (N=395)	
		Tx Effect	P-Value	Tx Effect	P-Value
Primary Endpoints: Composite Outcome of All-Cause Mortality and Recurrent CV Events	Hazard Ratio	0.718	0.0118	0.672	0.0162
Secondary Endpoints:					
6-MWT Change at Month 30	LS Mean 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.

CARDIO-TTRansform

Eplontersen vs Placebo



Key Inclusion Criteria:

- NT-proBNP ≥ 600 pg/mL
- 6MWT ≥ 150 meters
- IVS > 12 mm
- Positive PYP/DPD/HMDP scan
- Biopsy if MGUS/FLCR altered
- NYHA class I-III

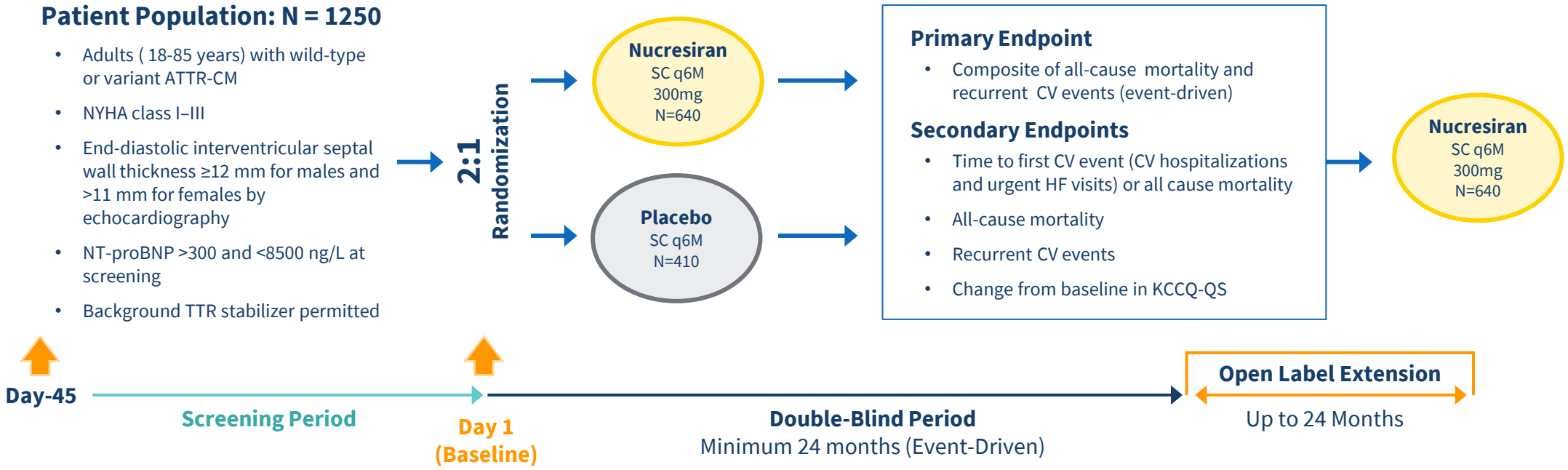
Substudies:

- CMR Substudy
- Nuclear Substudy

ClinicalTrials.gov; Fontana M, et al. *Eur Heart J.* 2024; Masri A, et al. *J Card Fail*. 2024.

TRITON-CM

Nucresiran vs Placebo

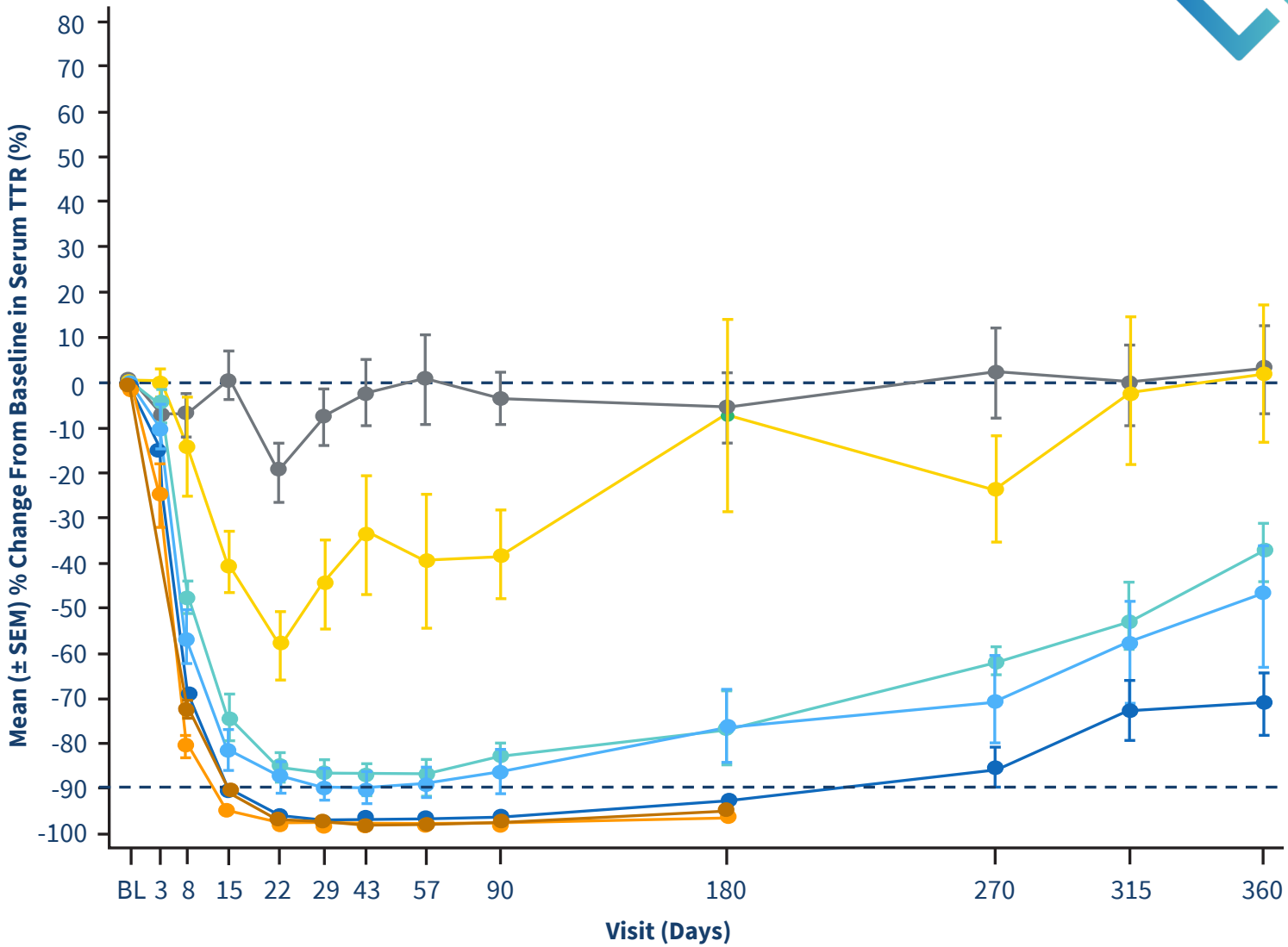


ClinicalTrials.gov; Fontana M, et al. Poster Presented at ESC HFA. 2025.

TRITON-CM

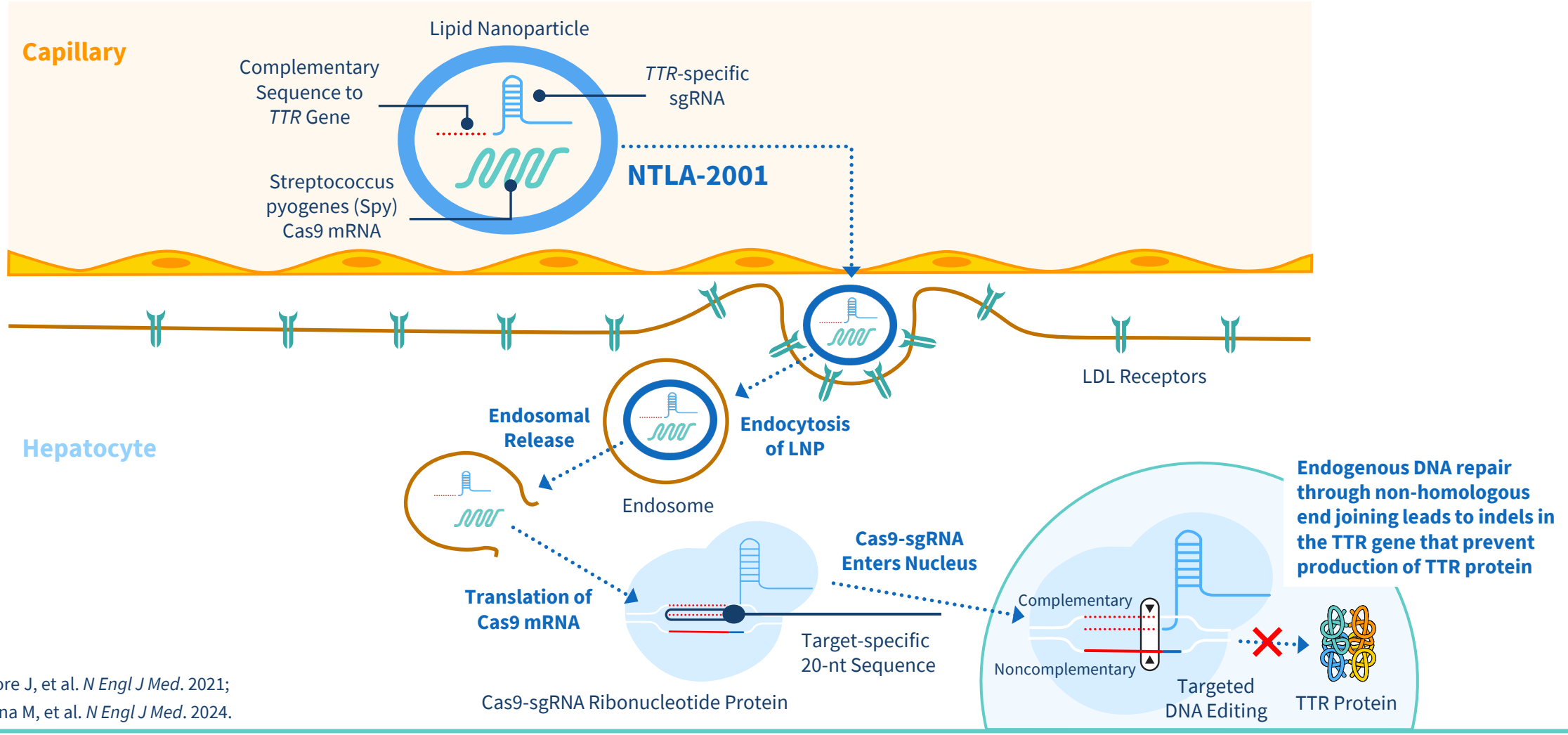
Nucresiran vs Placebo

- Placebo (N=12)
- Nucresiran 5 mg (N=6)
- Nucresiran 25 mg (N=6)
- Nucresiran 100 mg (N=6)
- Nucresiran 300 mg (N=6)
- Nucresiran 600 mg (N=6)
- Nucresiran 900 mg (N=6)



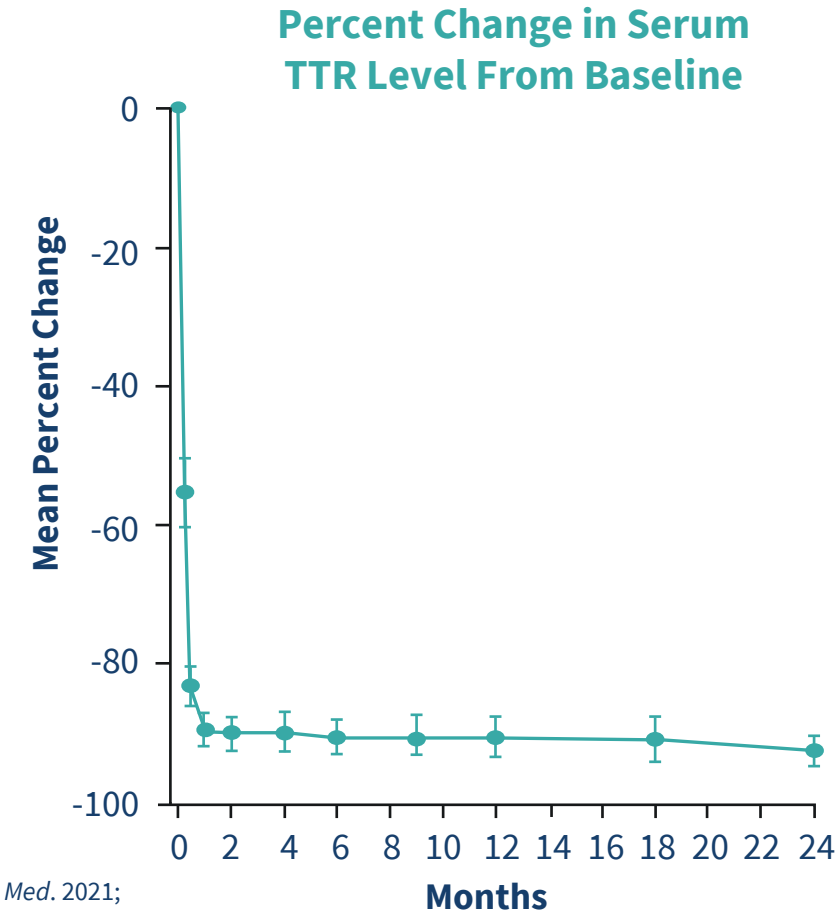
ClinicalTrials.gov; Fontana M, et al. Poster Presented at ESC HFA. 2025.

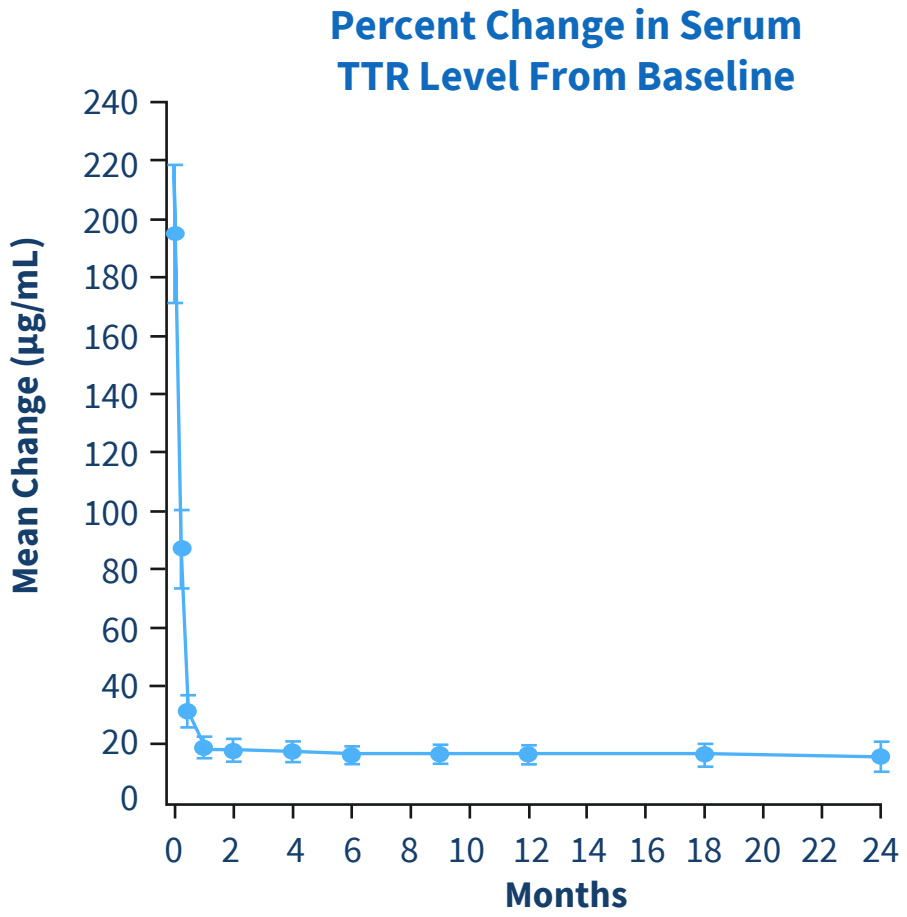
Silencing the TTR Gene By Gene Editing



Gillmore J, et al. *N Engl J Med*. 2021;
Fontana M, et al. *N Engl J Med*. 2024.

Silencing the TTR Gene By Gene Editing

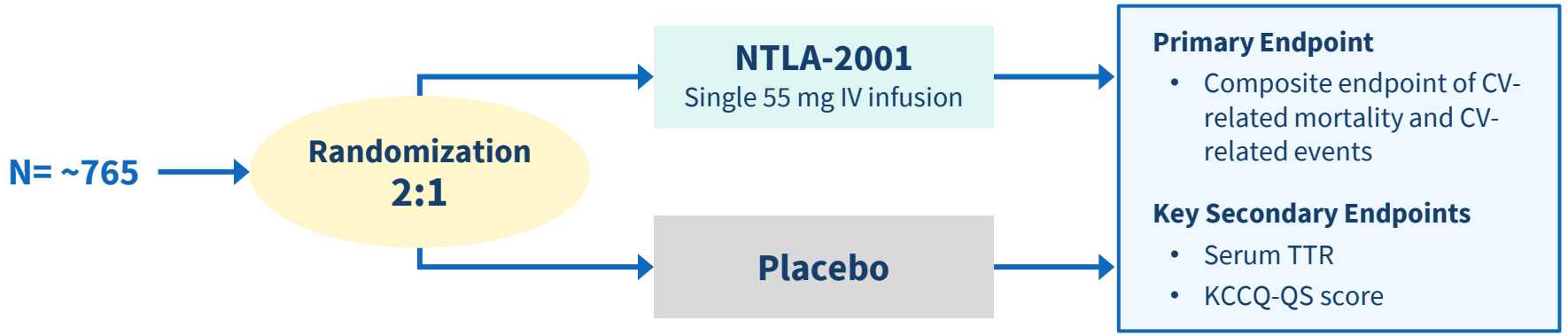




Gillmore J, et al. *N Engl J Med*. 2021;
Fontana M, et al. *N Engl J Med*. 2024.

MAGNITUDE

TTR Gene Editing Phase III Trial



Key **Eligibility** Criteria

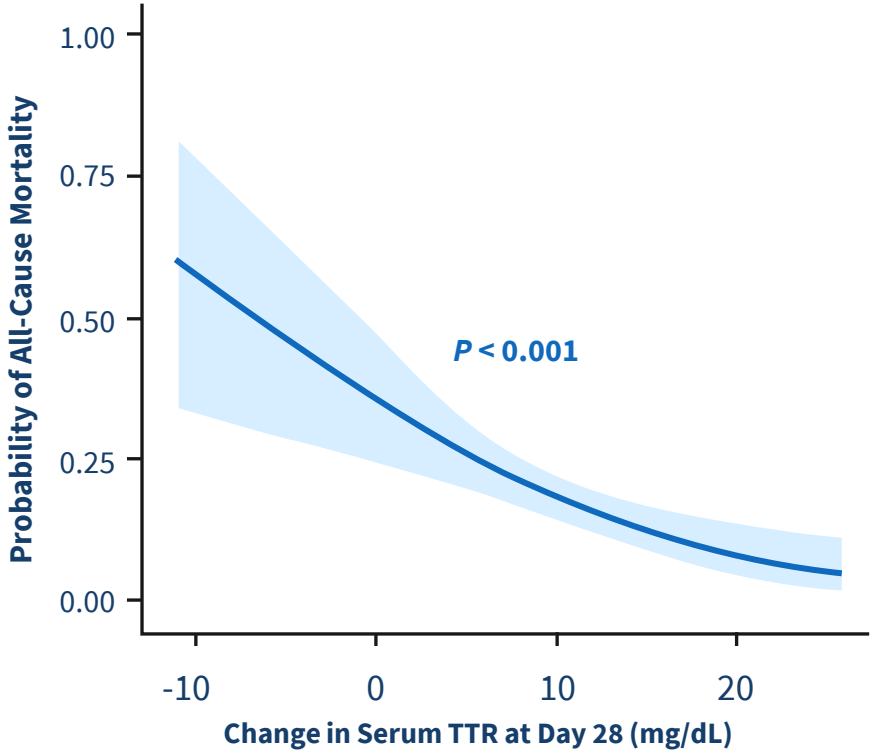
- Adult patients with diagnosis of hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/ml
- Other criteria apply

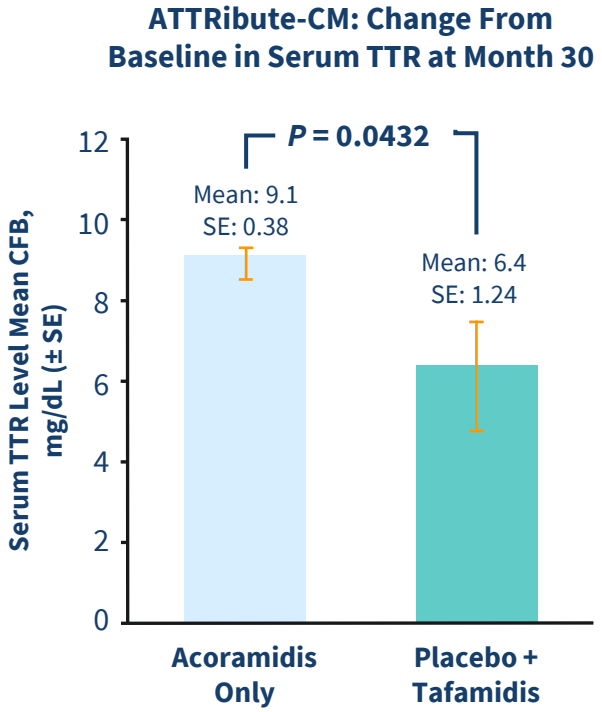
Key **Exclusion** Criteria

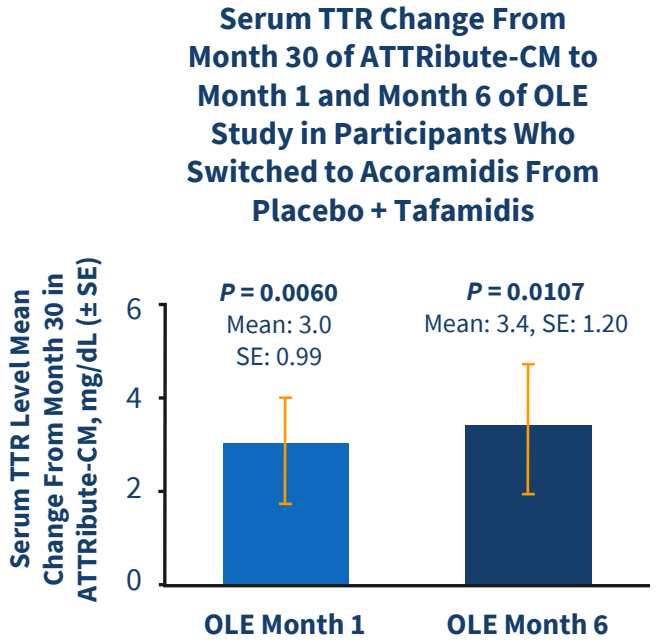
- RNA silencer therapy (patisiran, inotersen and/or eplontersen) within 12 month prior to dosing. Any prior vutrisiran use is not allowed.
- Other criteria apply

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

More Stabilization is Better - Whether Applies Across Drugs Remains to Be Seen

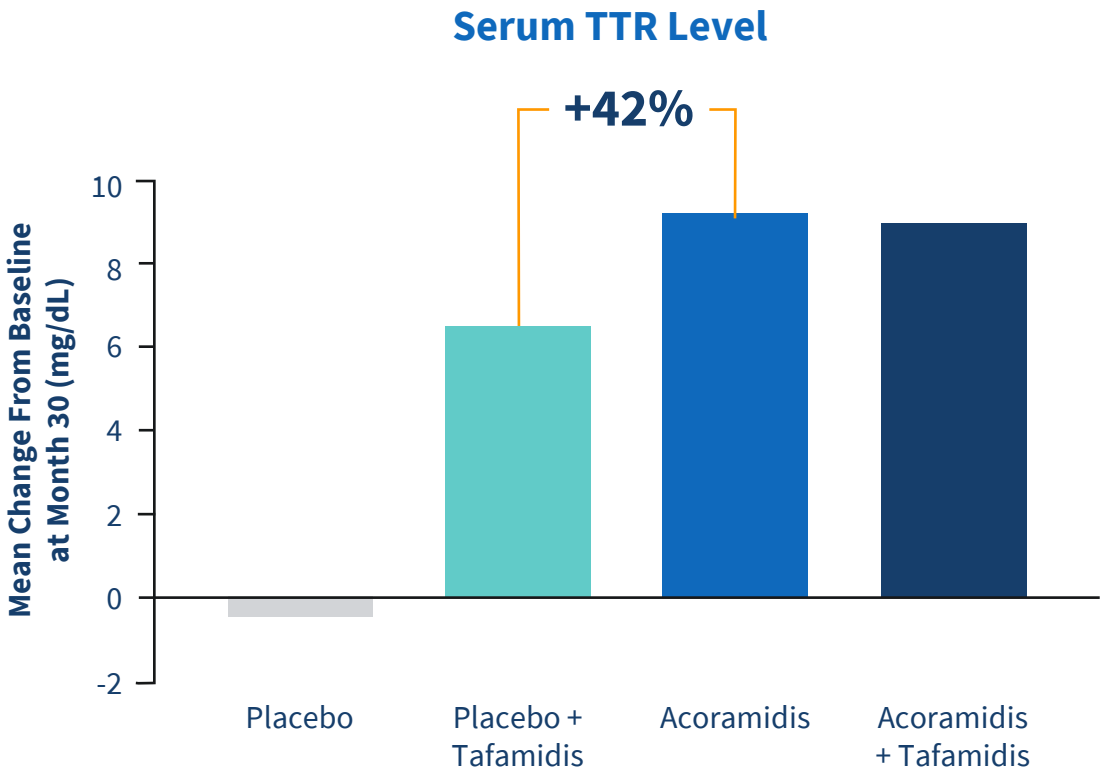


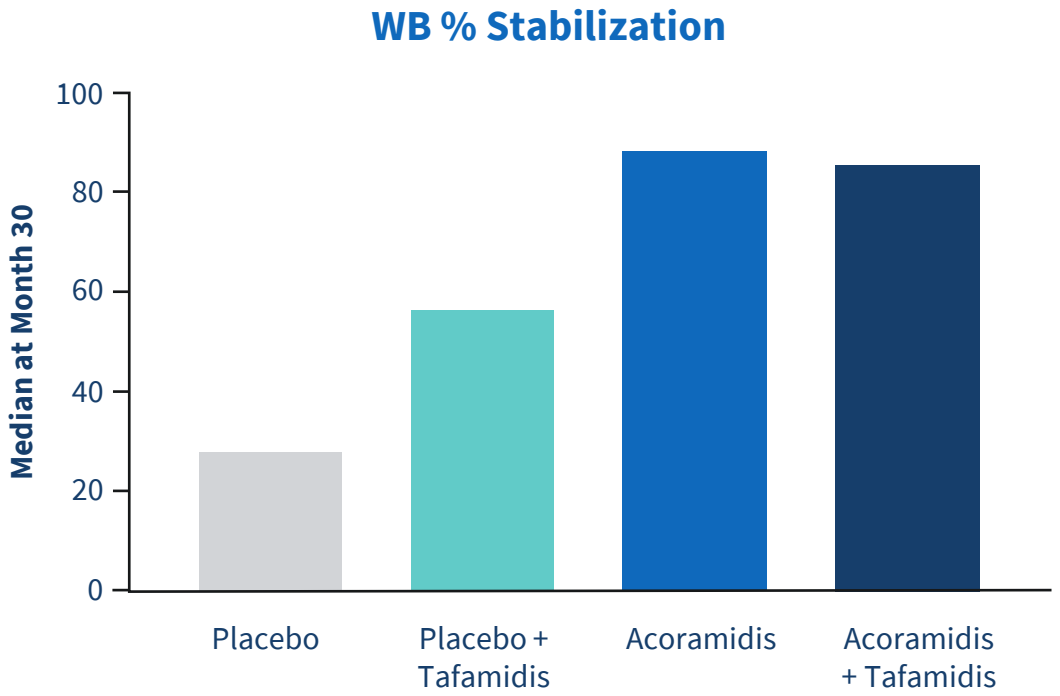




Maurer M, et al. *Eur Heart J*. 2024; Maurer M, et al. *J Am Coll Cardiol*. 2025.

More Stabilization is Better - Whether Applies Across Drugs Remains to Be Seen

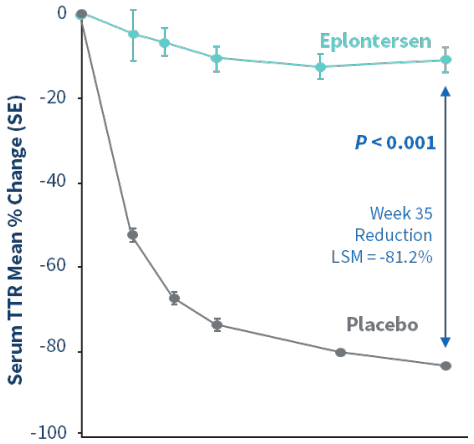




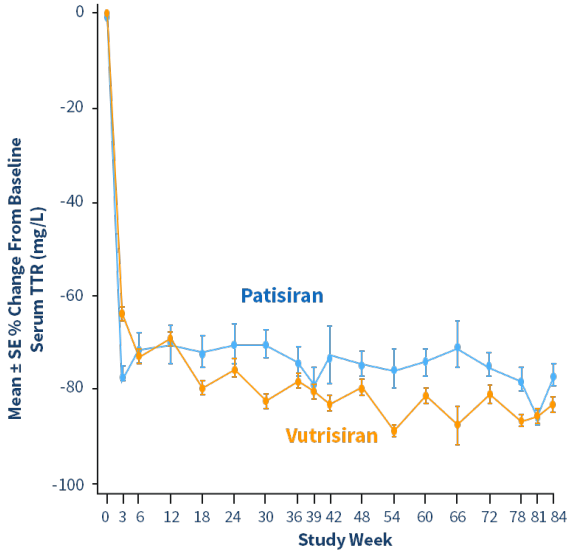
Maurer M, et al. *Eur Heart J*. 2024; Maurer M, et al. *J Am Coll Cardiol*. 2025.

Is Lower TTR Always Better?

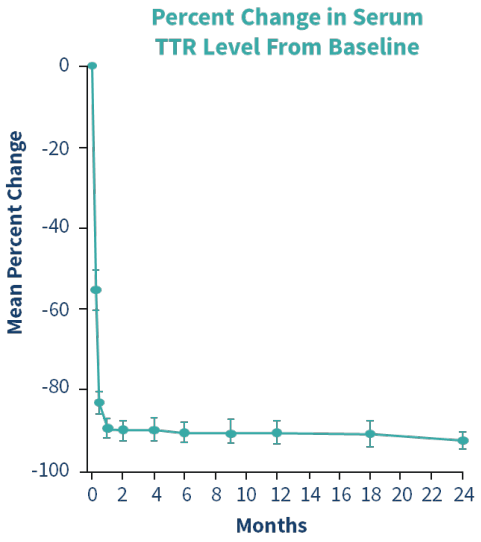
Eplontersen



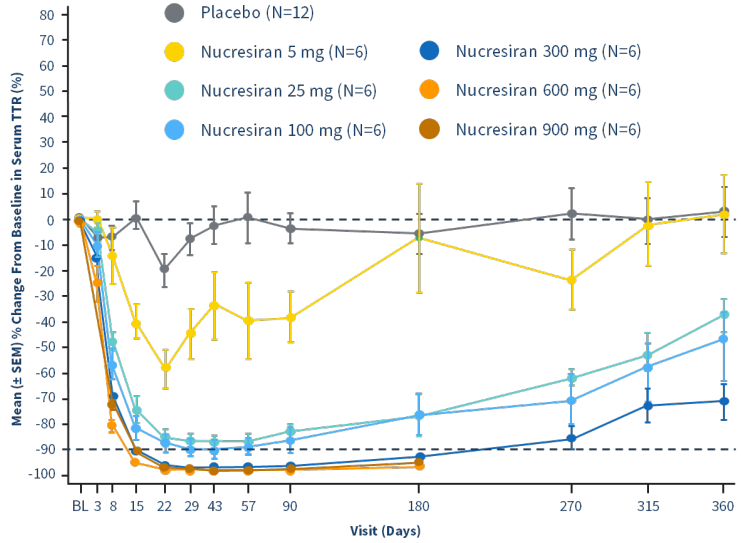
Vutrisiran



NTLA-2001



Nucresiran



Coelho T, et al. *JAMA*. 2023; Adams D, et al. *Amyloid*. 2023; Fontana M, et al. *N Engl J Med*. 2024; Murad A, et al. *Circulation*. 2024: Abstract 4135443.

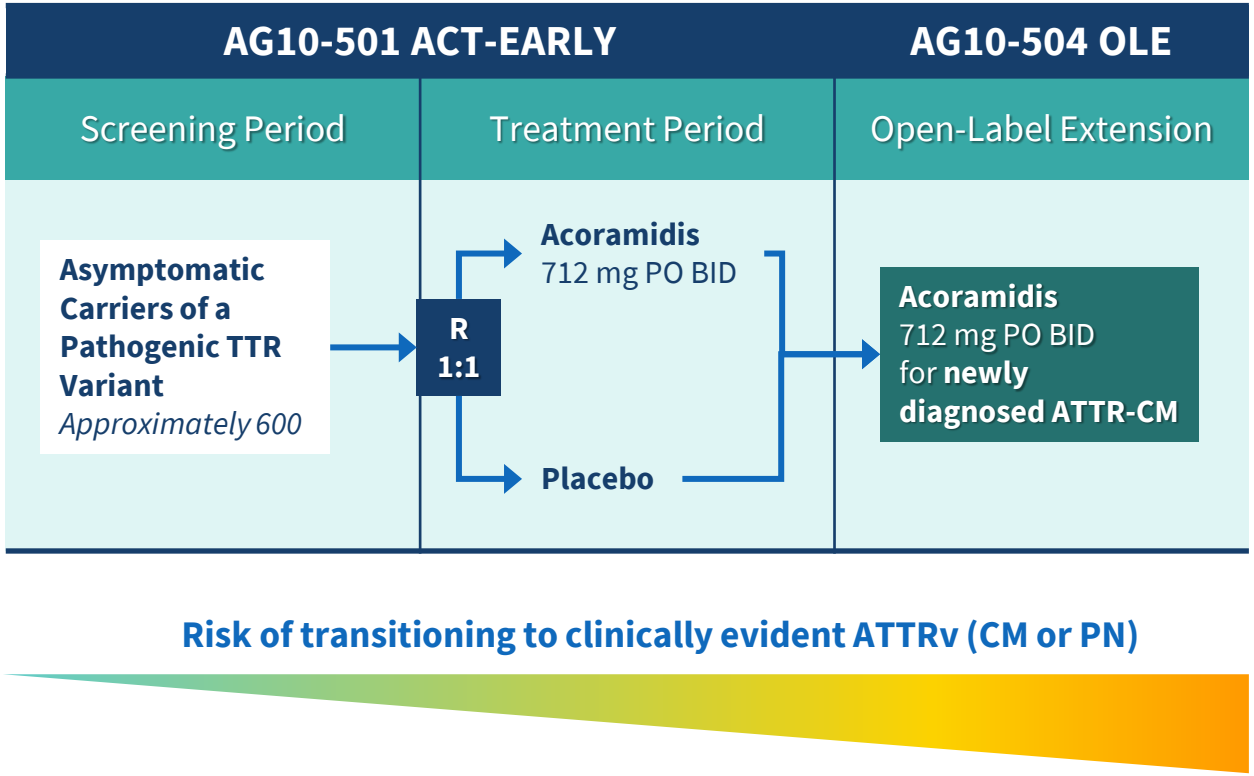
Fibril Depleters

Name of Drug	Type of Amyloidosis	Phase of Study	Sponsor	Outcome
NEOD001 (Birtamimab)	AL	3	Prothena	Negative
CAEL-101 (Anselamimab)	AL	3	Alexion	Primary negative
NNC6019 / PRX004	ATTR	2	Novo-Nordisk	Pending but phase III is starting
NI006 / ALXN2220	ATTR	3	Alexion	Pending
AT-02	AL, ATTR, others	1	Attralus	Pending

ClinicalTrials.gov; Griffin J, et al. *JACC Heart Failure*. 2025.

Is Variant ATTR Prevention Possible?

1. We can **reliably identify** genotype positive **phenotype negative** individuals.
2. We are reasonably good at **predicting approximate age of onset** based on variant and/or family history.
3. We are reasonably good at **identifying disease development** (established phenotypes not very early ones).
4. Treatment is **non-toxic**.



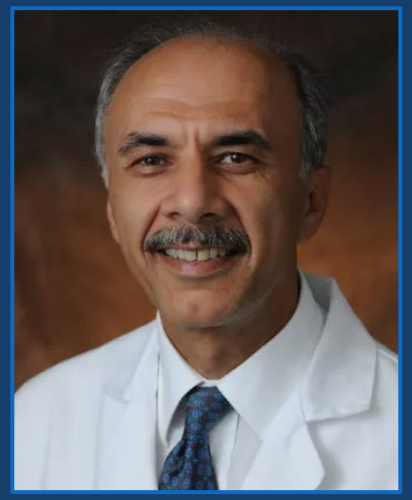
ClinicalTrials.gov; Garcia-Pavia P, et al. Presented at ISA. 2024; Griffin J, et al. *JACC Heart Failure*. 2025; Margolin E, et al. *Cardiol Ther.* 2025.

Summary

- Tremendous therapeutic development is happening in ATTR
- Clinical trials results and design should be interpreted within the framework of changing natural history of ATTR-CM.
- Tafamidis, acoramidis, and vutrisiran are all now FDA-approved for the treatment of ATTR-CM
- New silencers, preventative strategies, and a new class of anti-fibril therapies (depleters) are currently under investigation.

A Promising Glimpse of the Future

Emerging ATTR Research from the 1st Annual ATTR Early-Career Research Forum



Wiesman Award Presentation

Winners from the 1st Annual ATTR Early-Career Research Forum

Presented in Honor of Dr. Janice Wiesman

Senthil Selvaraj, MD, MS, MA

Advanced Heart Failure Specialist,
Cardiologist
Assistant Professor of Medicine,
Duke University School of Medicine
Durham, NC

Cardiovascular Burden of the Amyloidogenic V142I Transthyretin Variant in Black Americans

Ani Nalbandian, MD, MPH

Cardiology Critical Care Fellow
Columbia University Irving Medical Center
New York, NY

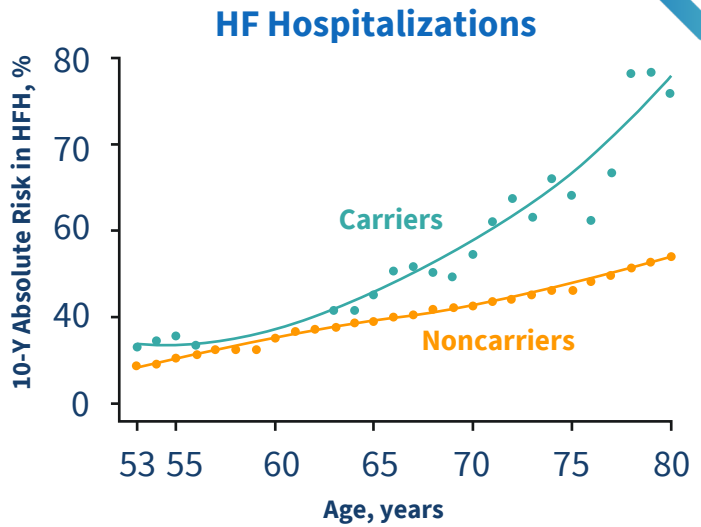
Sodium-glucose Cotransporter-2 (SGLT2) Inhibitor Therapy and Body Composition Analysis in Transthyretin Amyloid Cardiomyopathy

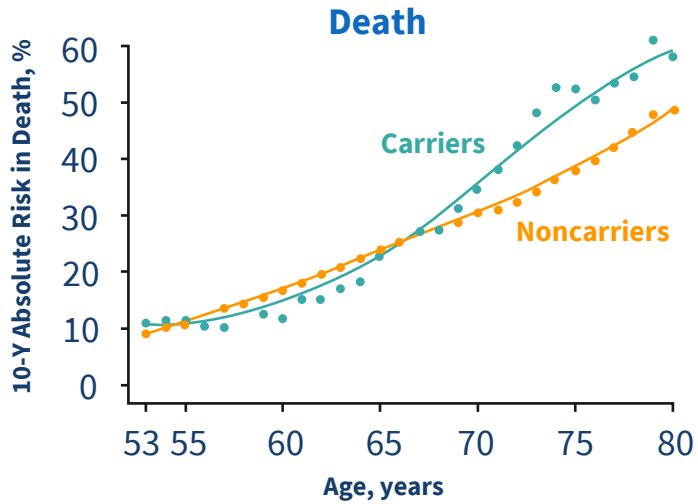
Echocardiographic Effects of the Amyloidogenic p.V142I Transthyretin Variant in Late Life

Senthil Selvaraj, MD, MS, MA

Introduction

- p.V142I (V122I) transthyretin variant is common (**3.4% of self-identified Black Americans**)
  - **Most common inherited form of cardiac amyloidosis in the US**
  - Recently classified as reportable by ACMG
  - Age-dependent anatomic penetrance
- Targeted treatments are available with greater efficacy in early disease
- The natural echocardiographic history and progression of the variant in late life, when differences may be more pronounced, remains unknown



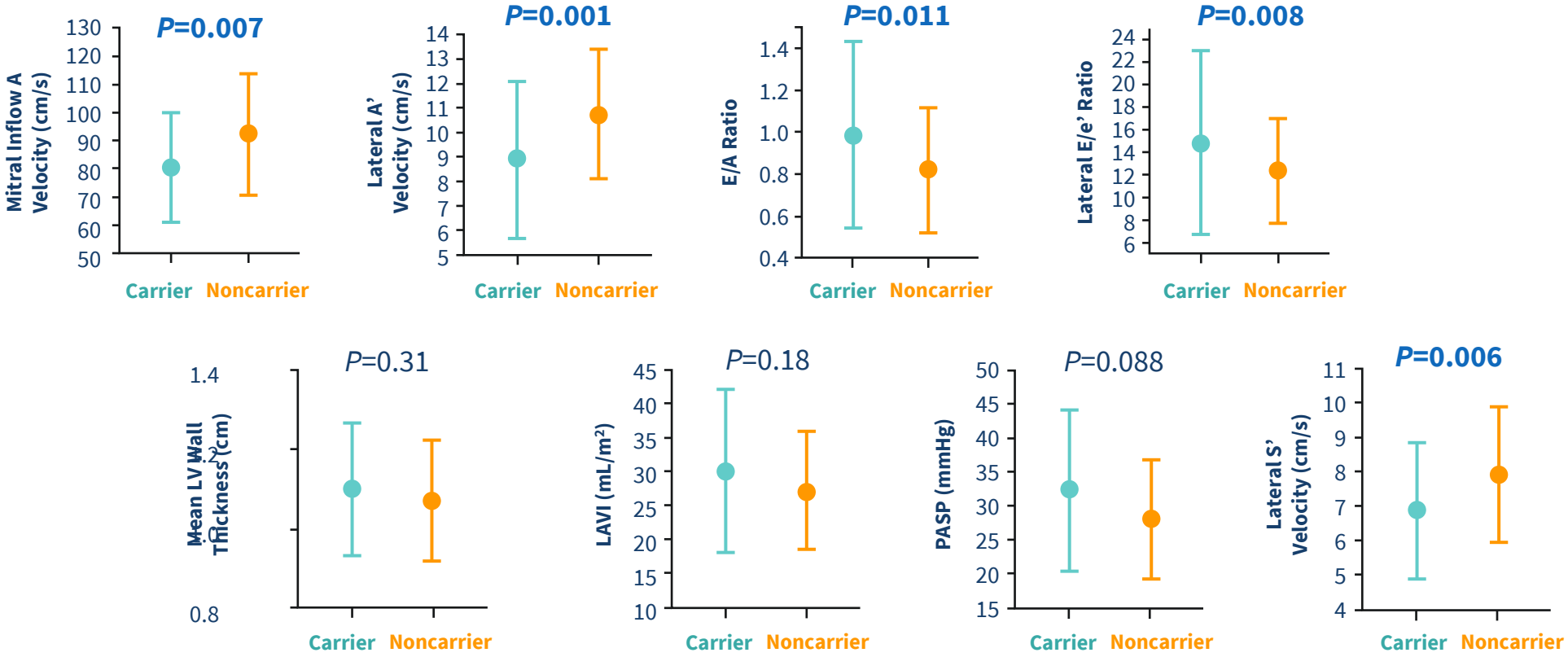


Regan J, et al. *JAMA Cardiol*. 2024; Regan J, et al. *J Card Fail*. 2024; Selvaraj S, et al. *JAMA Cardiol*. 2023; Chandrashekar P, et al. *Circ Genom Precis Med*. 2021.

Study Design

- **Population**
  - 699 self-identified Black ARIC participants with echocardiographic data at Visit 7 (2018-2019), including 27 carriers (3.9%)
- Paired echocardiographic data at Visit 5 (2011-2013) in 629 participants
- Mean difference in age between visits 6.5±0.6 years
- **Laboratory Testing**
  - NT-proBNP at Visits 5 and Visits 7
- **Statistical Analysis**
  - Linear regression for echo data among carriers vs. non-carriers, adjusting for age, sex, and the first 10 PCs of ancestry
  - Among echo parameters affected by carrier status at Visit 7, linear regression used to assess progression of echocardiographic data between Visits 5 and 7
  - Interaction splines
    - Outcome: change in NT-proBNP
    - Predictor: changes in echo parameters
    - Interaction term: (carrier) x (change in echocardiographic parameter)

Select Echocardiographic Parameters at Visit 7 by V142I Carrier Status



Echo Analysis at Visit 7 by Carrier Status

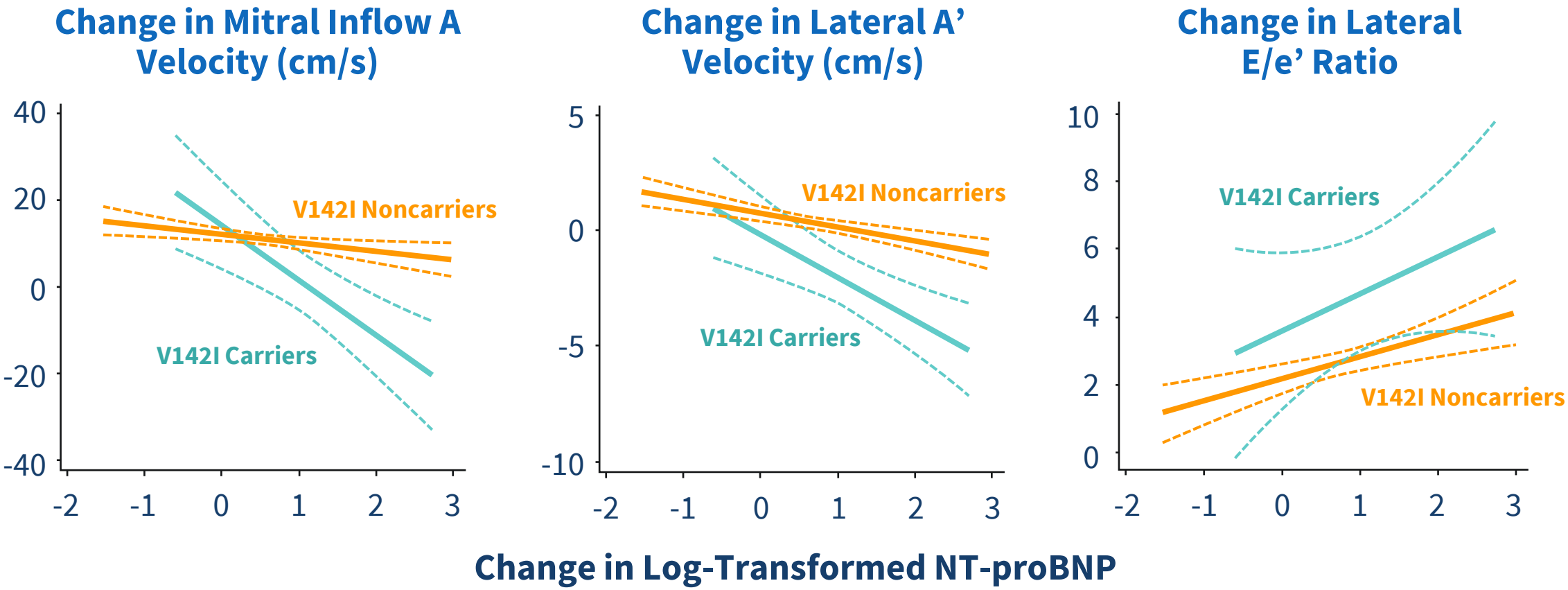
	p.V142I Noncarrier (N=672)	p.V142I Carrier (N=27)	P-Value
IVS, cm	1.15 ± 0.19	1.17 ± 0.19	0.44
EDV, mL	86 ± 25	87 ± 27	0.71
ESV, mL	32 ± 17	35 ± 25	0.40
LVMI, g/m^2	81 ± 21	87 ± 24	0.25
LVEF, %	63.9 ± 8.3	62.7 ± 11.3	0.48
Mean GLS, %	-17.3 ± 2.9	-16.6 ± 3.2	0.20
Mean GCS, %	-27.5 ± 3.7	-26.1 ± 5.4	0.11
Lateral S' velocity, cm/s	**7.9 ± 2.0**	**6.9 ± 2.0**	**0.006**
LVOT VTI, cm	22.0 ± 4.9	21.1 ± 6.1	0.27

	p.V142I Noncarrier (N=672)	p.V142I Carrier (N=27)	P-Value
LAVI, mL/m^2	27.2 ± 8.6	30.1 ± 12.0	0.18
E velocity, cm/s	73 ± 19	75 ± 17	0.72
A velocity, cm/s	**92 ± 21**	**81 ± 19**	**0.007**
E/A ratio	**0.8 ± 0.3**	**1.0 ± 0.4**	**0.011**
Lateral E' velocity, cm/s	6.4 ± 2.0	5.8 ± 2.0	0.12
Lateral A' velocity, cm/s	**10.7 ± 2.6**	**8.9 ± 3.2**	**0.001**
Lateral E/E' ratio	**12.4 ± 4.6**	**14.8 ± 8.1**	**0.008**
TR velocity, cm/s	262 ± 39	281 ± 48	0.10

Change in Echocardiographic Parameters between Visits 5 and 7 by Carrier Status

	V142I Noncarrier (N=606)	V142I Carrier (N=23)	Difference (95% CI)	P-Value
Lateral S' velocity, cm/s	0.6 ± 2.1	-0.2 ± 1.9	-0.8 (-1.7, 0.1)	0.075
Peak A wave velocity, cm/s	**11.2 ± 15.0**	**0.1 ± 23.8**	**-10.7 (-17.5, -3.9)**	**0.002**
E/A ratio	0.00 ± 0.27	0.11 ± 0.39	0.11 (-0.01, 0.23)	0.066
Lateral A' velocity, cm/s	**0.3 ± 2.6**	**-1.8 ± 3.8**	**-2.1 (-3.3, -1.0)**	**<0.001**
Lateral E/E' ratio	**2.6 ± 4.0**	**4.9 ± 7.1**	**2.2 (0.5, 4.0)**	**0.011**

Individual & Population Impact of V142I on Death



Discussion

- p.V142I carriers in 8th decade of life had worse LA function, diastolic function, and S' velocity
- **Findings worsened from 6.5 years earlier**, highlighting echocardiographic age-dependent penetrance, supporting the large clinical risk apparent at this time
- Declines in indices of LA function were more strongly related to NT-proBNP worsening in carriers
- Echo characteristics of atrial myopathy may be a specific marker of worsening ATTRv-CA that can be followed for disease trajectory and facilitate early identification of carriers at risk for ATTRv-CA.
- **Limitations:**
  1. Attendance and survivorship bias, potentially underestimating the echocardiographic differences between carriers and noncarriers
  2. Modest number of carriers presenting in late life
- Data may guide discussions regarding the initiation or results of genetic screening, while arming clinicians with data to share with carriers on expected disease trajectory.

Thank you!

- Study participants
- Sponsors (NIH, DHHS)
- Collaborators

Late-Life Echocardiographic Effects of the Amyloidogenic p.V142I Transthyretin Variant

Vishal N. Rao, Brian L. Claggett, Michel G. Khouri, Amil M. Shah, Scott D. Solomon, and Senthil Selvaraj | AUTHOR INFO & AFFILIATIONS

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Rao V, et al. *Circ Heart Fail*. 2025.

Prevalence, Characterization, and Prognosis of Pulmonary Disease in ATTR Cardiac Amyloidosis

Ani Nalbandian, MD,MS

Disclosure

- **1st Annual Wiesman Award for Excellence in Early-Career ATTR Research**, Cornerstone Medical Education

Clinical Background

- **1-year Critical Care Fellowship** (following Cardiology Fellowship)
  - Thoracentesis, Lung ultrasound, Bronchoscopy, Intubation
- **1st Annual Wiesman Award for Excellence in Early-Career ATTR Research**

Pulmonary Involvement in ATTR Cardiac Amyloidosis: Patterns & Prognosis?

- Objectives:
  - Assess prevalence of pulmonary disease in ATTR cardiac amyloidosis
  - Identify clinical and radiographic features of pulmonary involvement in ATTR cardiac amyloidosis
  - Characterize prognostic implications of pulmonary involvement, and ATTR treatment impact on pulmonary disease

Pulmonary Amyloidosis: Subtypes

1. Nodular Pulmonary Amyloidosis
2. Diffuse Alveolar-Septal Amyloidosis
3. Tracheobronchial Amyloidosis
4. Amyloidosis of the Pleura; Pleural Effusions

Non-Cardiogenic Mechanism(s) for: Pleural Effusions, Respiratory Symptoms

Methods

- ATTR Cardiac Amyloidosis Registry: Comprehensive Retrospective Review
  - PFTs
  - CPET
  - Radiographic Imaging: CXR, CT chest
  - TTE or Lung U/S
  - 6MWT

Future Directions:

- Comprehensive Prospective Cardiopulmonary Assessment at Diagnosis, **Annually**
- **Clinical Implications**
  - PFTs, radiographic imaging, CPET assessment
  - Differences in pulmonary disease burden / progression in subtypes of ATTR who may benefit from tailored therapies / management (e.g. Pulmonology)

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Kristin Burkart, MD MSc
Director of Pulmonary and Critical Care Fellowship Training Program
Professor of Medicine
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Empowering ATTR Outcomes Optimization at the Cardiology-Neurology Nexus

A Case-Driven Practicum

Case: 74-Year-Old Male

- Worsening heart failure signs/symptoms
- **CC:** Palpitations and increasing dyspnea on exertion 3 months
- **ROS:** Increased fatigue with routine activities of daily living; occasional lightheadedness; mild pain in wrists and shoulders
- **Labs:** Over the past year NT-proBNP rose from 575 pg/mL to 974 pg/mL
- **Medication:** Lisinopril

Case: 74-Year-Old Male

- Ekg nsR 1◦ av BLOCK Low limb lead voltage LBBB

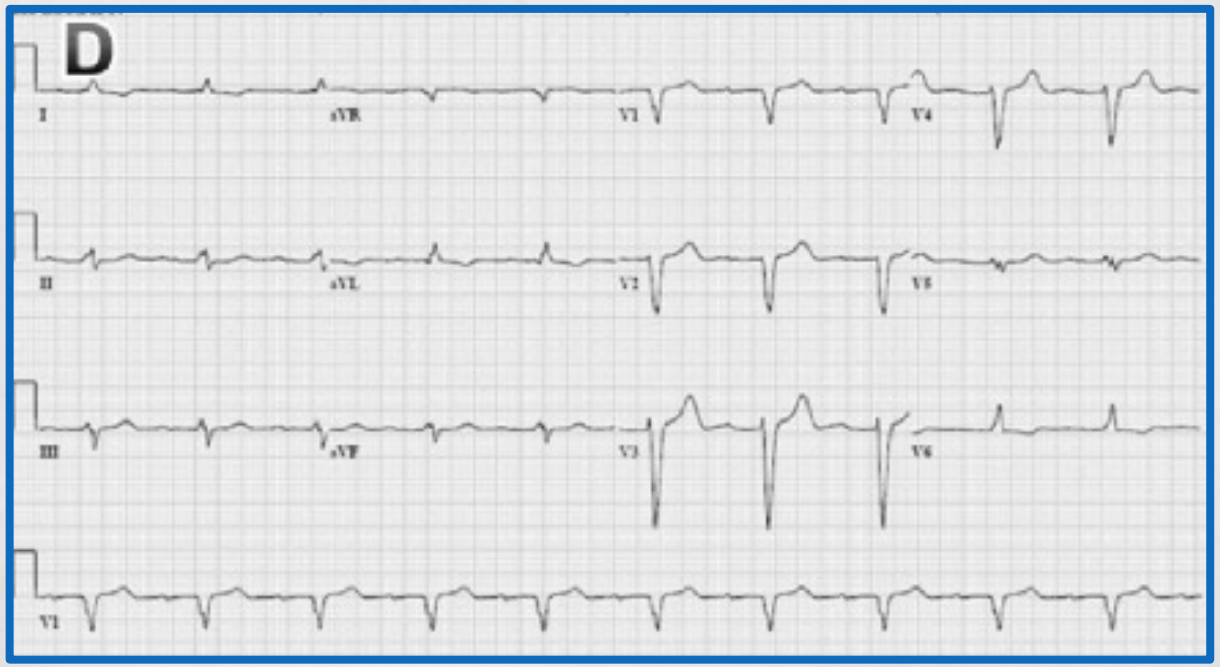

Image provided courtesy of Dr. Morie Gertz.

Case: 74-Year-Old Male

- **ECHO:** Concentric LVH EF 55%
  Thick AV valves

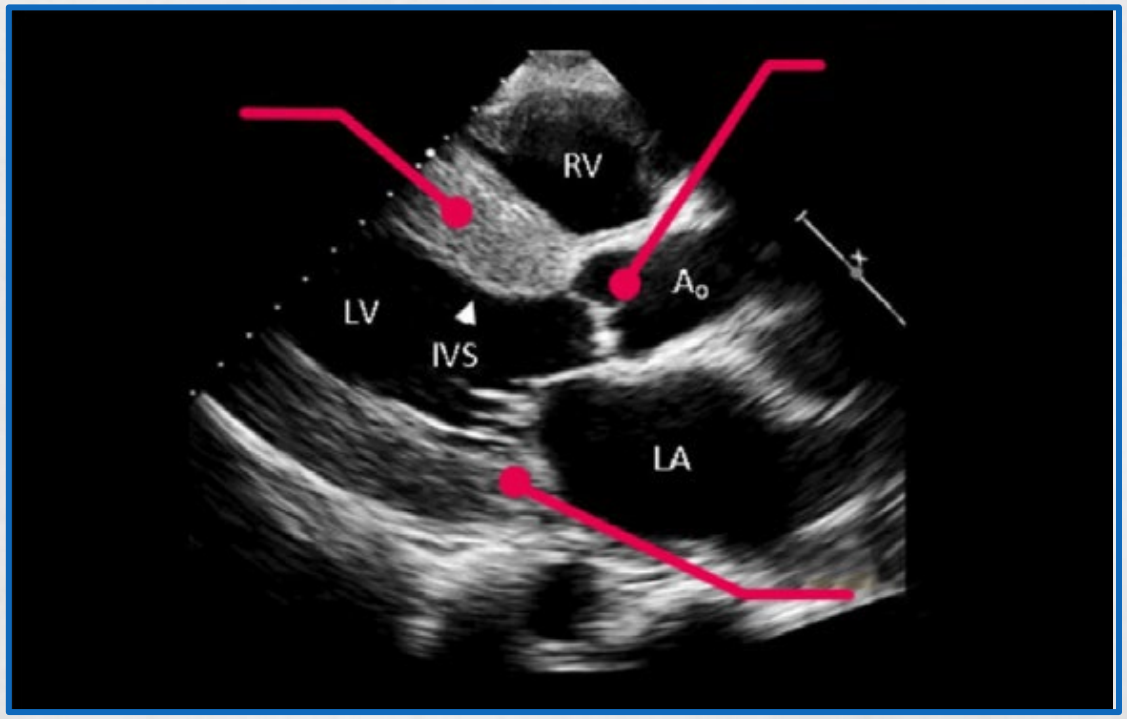

Image provided courtesy of Dr. Morie Gertz.

Case: 74-Year-Old Male

- Serum immunofixation and immunoglobulin free light chains negative
- PYP scan ordered
- Genetic testing of TTR negative

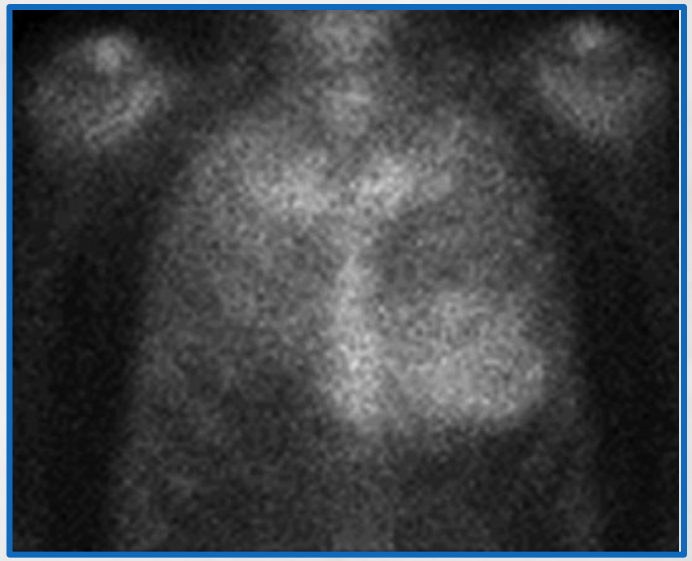

Image provided courtesy of Dr. Morie Gertz.

Case: 67-Year-Old Female

- **CC:** Fatigue and DOE
- Tingling hands and feet
- **PE:** Edema LE
- Occasional diarrhea unexplained
- Over 1 year NT-proBNP 1008 to 1544 pg/mL
- Exam atrial fibrillation + tinels bilaterally
- **Medications:** metformin, torsemide, lisinopril, apixaban
- **Family history:** father died age 85 “heart” no other details

Case: 67-Year-Old Female

- **Diagnostics**
  - Echo ? of HOCM
  - EMG axonal PN with bilateral median neuropathy at the wrist
  - Light chains normal serum immunofixation normal
  - PYP imaging 3+
  - TTR gene sequencing + V142I

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