

AMERICAN HEART ASSOCIATION'S
ATTR-CM WEBINAR SERIES:
WEBINAR #2

Breakthroughs in **ATTR-CM:** CRISPR-Cas9 and the Evolving Trial Landscape

OCTOBER 15, 2025



Meeting Reminders

Please Note:

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

Questions?

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

If you are having issue with audio, please call in using the appropriate number below.

Dial by your location:

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Passcode: 739461	





Welcome & Introductions

Devin Marie Keating

Director of Operations, Clinical Studies

American Heart Association



Thank you to
Intellia Therapeutics
for being a proud supporter of the
American Heart Association's
ATTR-CM Awareness and Education





AHA's ATTR-CM Educational Webinar Series

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

Educate | Elevate | Engage | Equip

Educational Objectives:

1. THERAPEUTIC APPROVALS & SILENCING ADVANCES

Review newly approved treatments for ATTR-CM and recent progress with TTR-silencing therapies.

2. PIPELINE OUTLOOK

Explore emerging therapies under investigation, including silencers, antibodies, and next-generation approaches.

3. CRISPR-Cas9 BREAKTHROUGHS

Examine findings from the November 2024 NEJM publication on nexiguran ziclumeran and their impact on ATTR-CM care.

4. TRIAL PROGRESS & FUTURE DIRECTIONS

Highlight ongoing clinical trial updates and introduce new educational tools designed to enhance patient identification and referral.



Welcome & Introductions

Michelle Kittleson, MD, PhD

Professor of Medicine

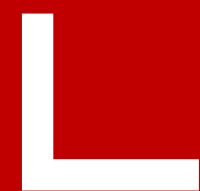
Smidt Heart Institute, Cedars Sinai Medical Center

Marianna Fontana, MD, PhD, FRCP

Professor of Cardiology, Hon. Consultant Cardiologist,

National Amyloidosis Centre,

University College London, United Kingdom



American Heart Association Statement

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

Michelle Kittleson, M.D., Ph.D

- No Disclosures

Marianna Fontana, M.D., Ph.D, FRCP

- Consultancy for Alnylam, Alexion/Caelum Biosciences, AstraZeneca, BridgBio/Eidos, Prothena, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Prothena, Pfizer, Novonordisk, Bayer, Mycardium.
- Research grants from: Alnylam, BridgBio, AstraZeneca, Pfizer.
- Share options in LexeoTherapeutics and shares in Mycardium.





Approach to Cardiac Amyloidosis

Michelle Kittleson, M.D., Ph.D

*Cardiology, Professor of Medicine, Director of
Education in Heart Failure and Transplantation,
Smidt Heart Institute, Cedars-Sinai Medical Center
Los Angeles, CA*



THE CASE:

- A 72-year-old woman presents with a 2-week history of shortness of breath. She has hypertension, paroxysmal atrial fibrillation, and osteoarthritis.
- Her medications include rivaroxaban 20 QD, chlorthalidone 25 QD, amlodipine 10 QD, and ibuprofen 400 QD as needed for knee pain.
- On examination:
 - BMI 31 kg/m²
 - HR 68 bpm
 - BP 142/88 mm Hg
 - JVP 10 cm H₂O
 - Lungs clear,
 - Heart regular with an S4 gallop
 - 2+ edema
- Echocardiogram with mild increased LV wall thickness (septum/posterior wall 1.2 cm), EF 60%, mild aortic stenosis (mean gradient 16 mm Hg, valve area 1.9 cm²), mild pulmonary hypertension (RVSP 40 mm Hg).





What's the most likely diagnosis?

- A. Cardiac amyloidosis
- B. Heart failure with preserved ejection fraction
- C. Hypertrophic cardiomyopathy
- D. Aortic stenosis
- E. Pulmonary arterial hypertension



WHAT ABOUT **THIS PATIENT:**

- A 72-year-old woman presents with a 2-week-month history of fatigue and shortness of breath. She has ~~hypertension~~, paroxysmal atrial fibrillation, ~~and osteoarthritis~~ bilateral carpal tunnel syndrome, spinal stenosis, and peripheral neuropathy.
- Her medications include rivaroxaban 20 QD, metoprolol XL 25 QD, and gabapentin 300 QHS. ~~chlorthalidone 25 QD, amlodipine 10 QD, and ibuprofen 400 QD as needed for knee pain~~.
- On examination:
 - BMI ~~34~~ 24 kg/m²
 - HR 68 bpm
 - BP ~~142/88~~ 100/80 mm Hg
 - JVP ~~10~~ 14 cm H₂O
 - Lungs clear,
 - Heart regular with an S4 gallop
 - 2+ edema
- Echocardiogram with mild increased LV wall thickness (septum/posterior wall 1.2 cm), EF 60%, mild aortic stenosis (mean gradient 16 mm Hg, valve area 1.9 cm²), mild pulmonary hypertension (RVSP 40 mm Hg).



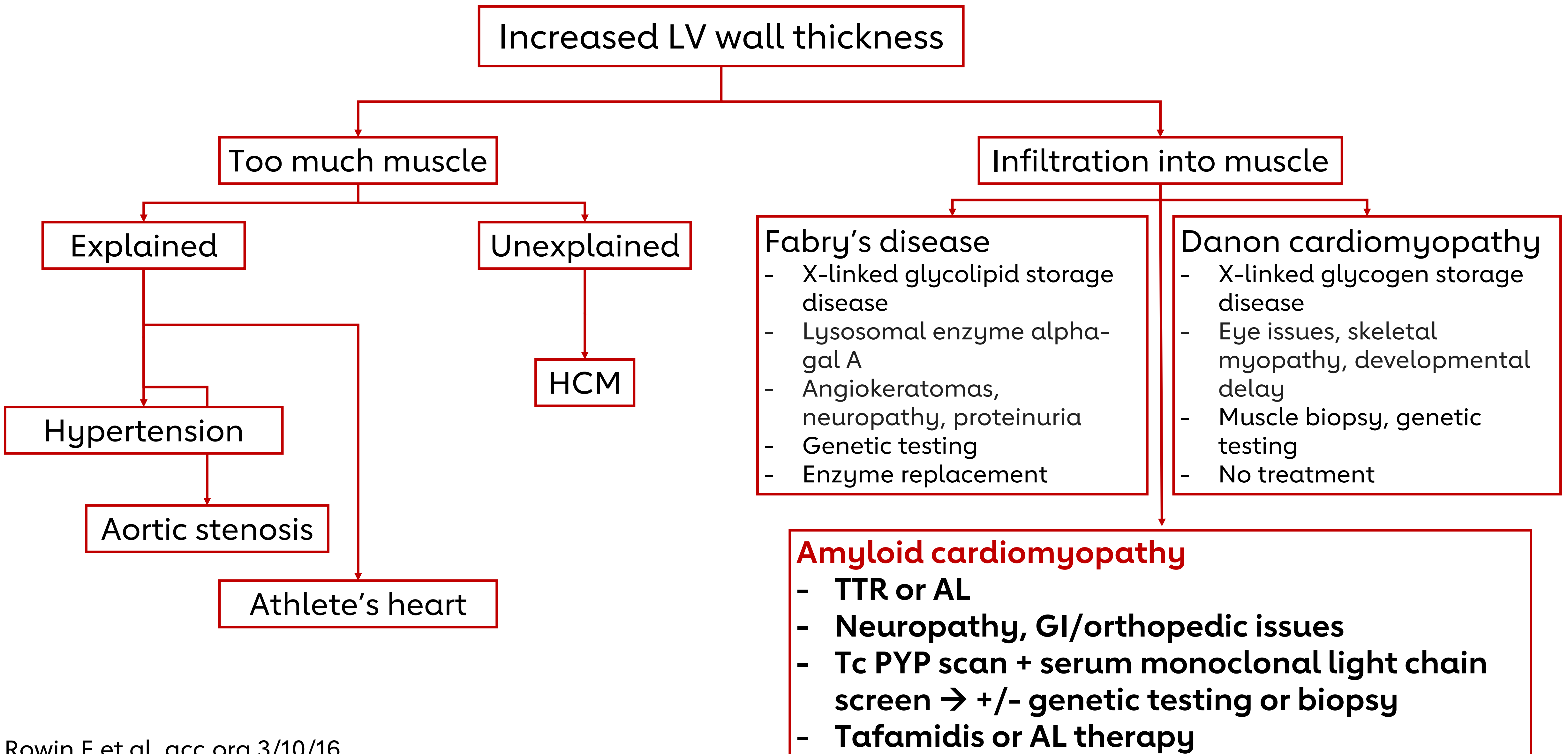


What's the most likely diagnosis?

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THICK HEART? It's not always "LVH"!



CARDIAC AMYLOIDOSIS

Cardiac amyloidosis = protein infiltrates myocardium → restrictive cardiomyopathy

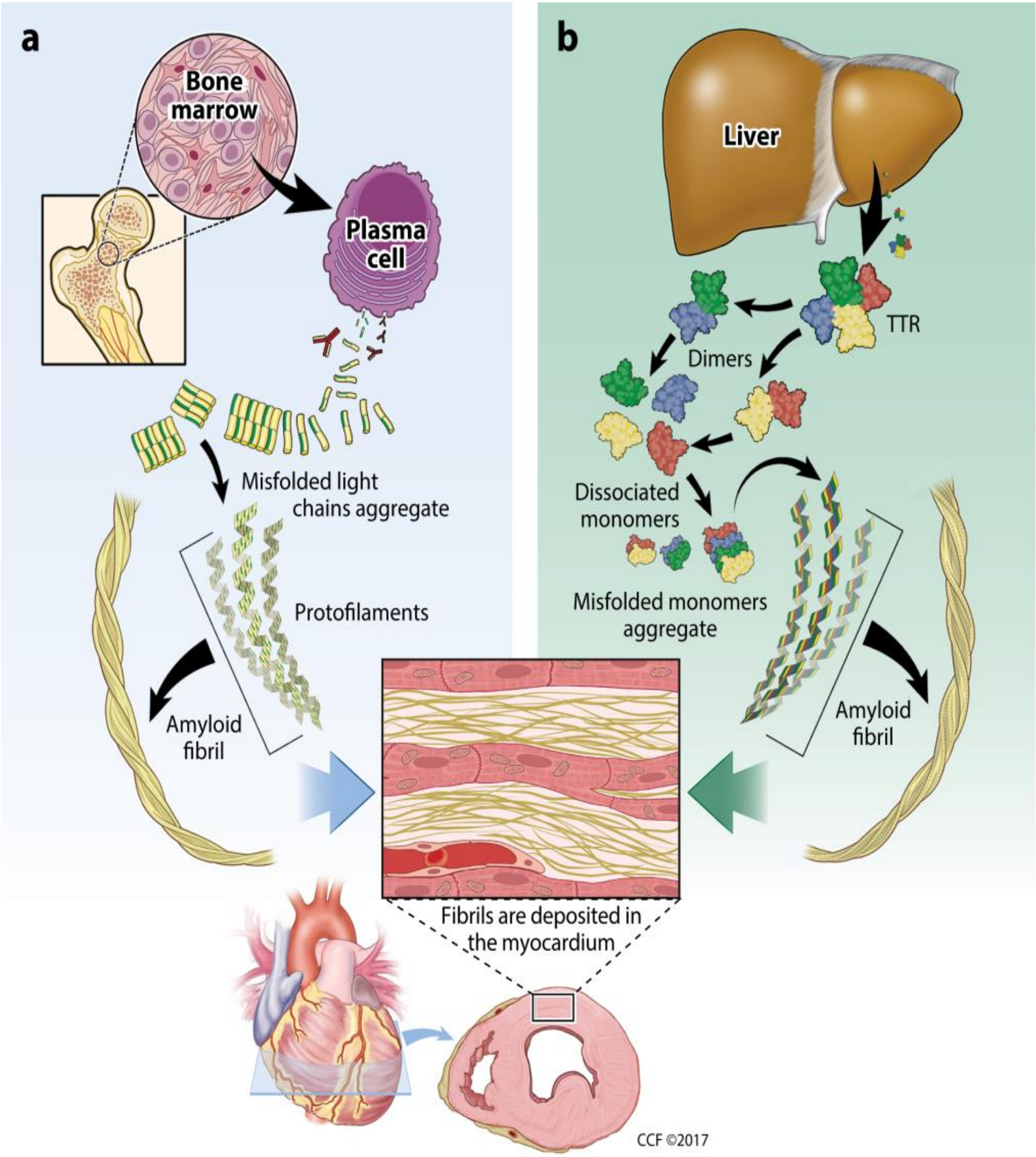
Light chains → AL-CM

TTR protein → ATTR-CM

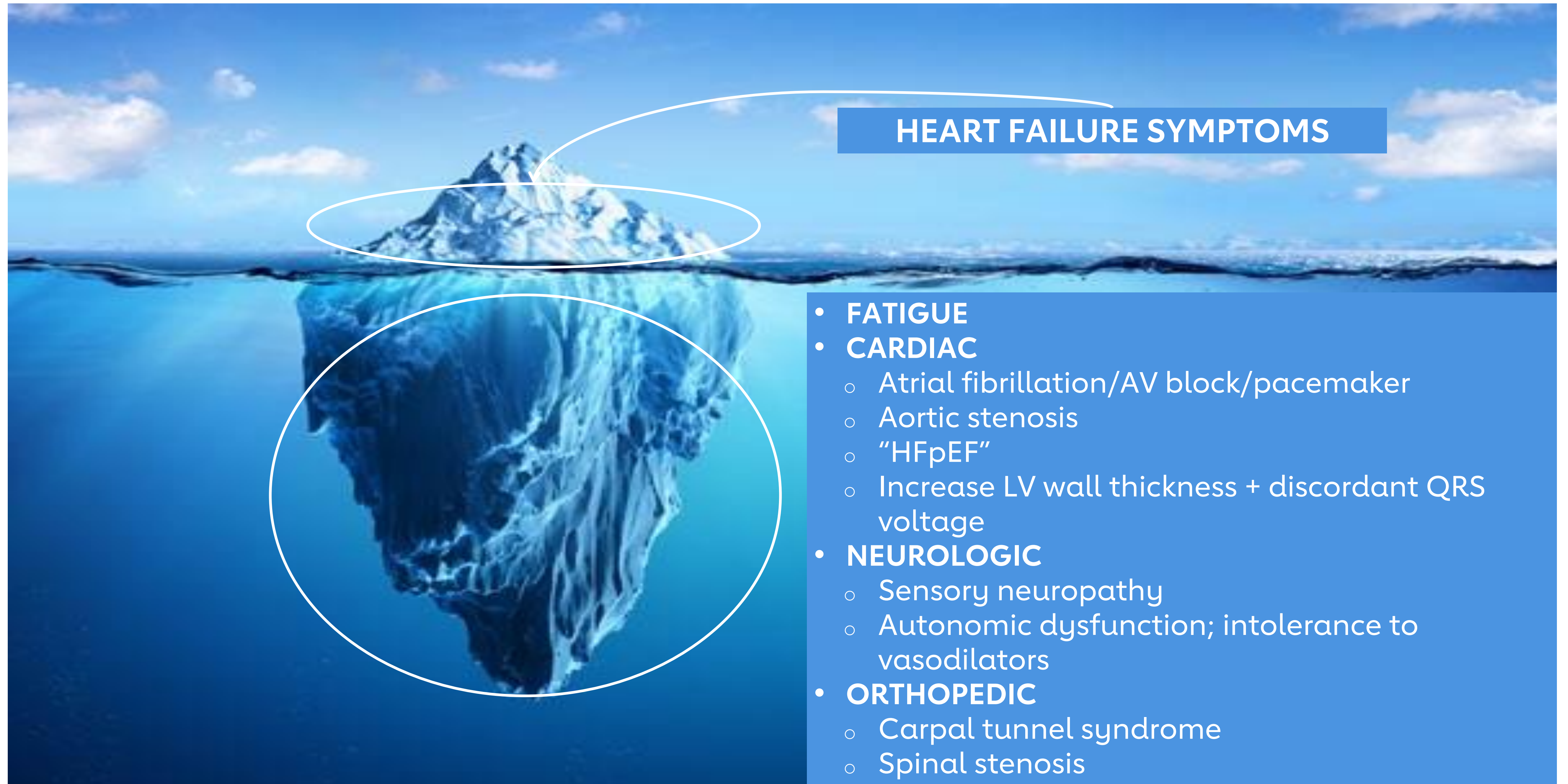
Mutation in *TTR* gene: ATTRv-CM

Wild-type *TTR* gene: ATTRwt-CM

	AL-CM	ATTRv-CM	ATTRwt-CM
Neuropathy	√	√√	√
Nephropathy	√		
GI involvement	√	√	√
Orthopedic issues		√	√√

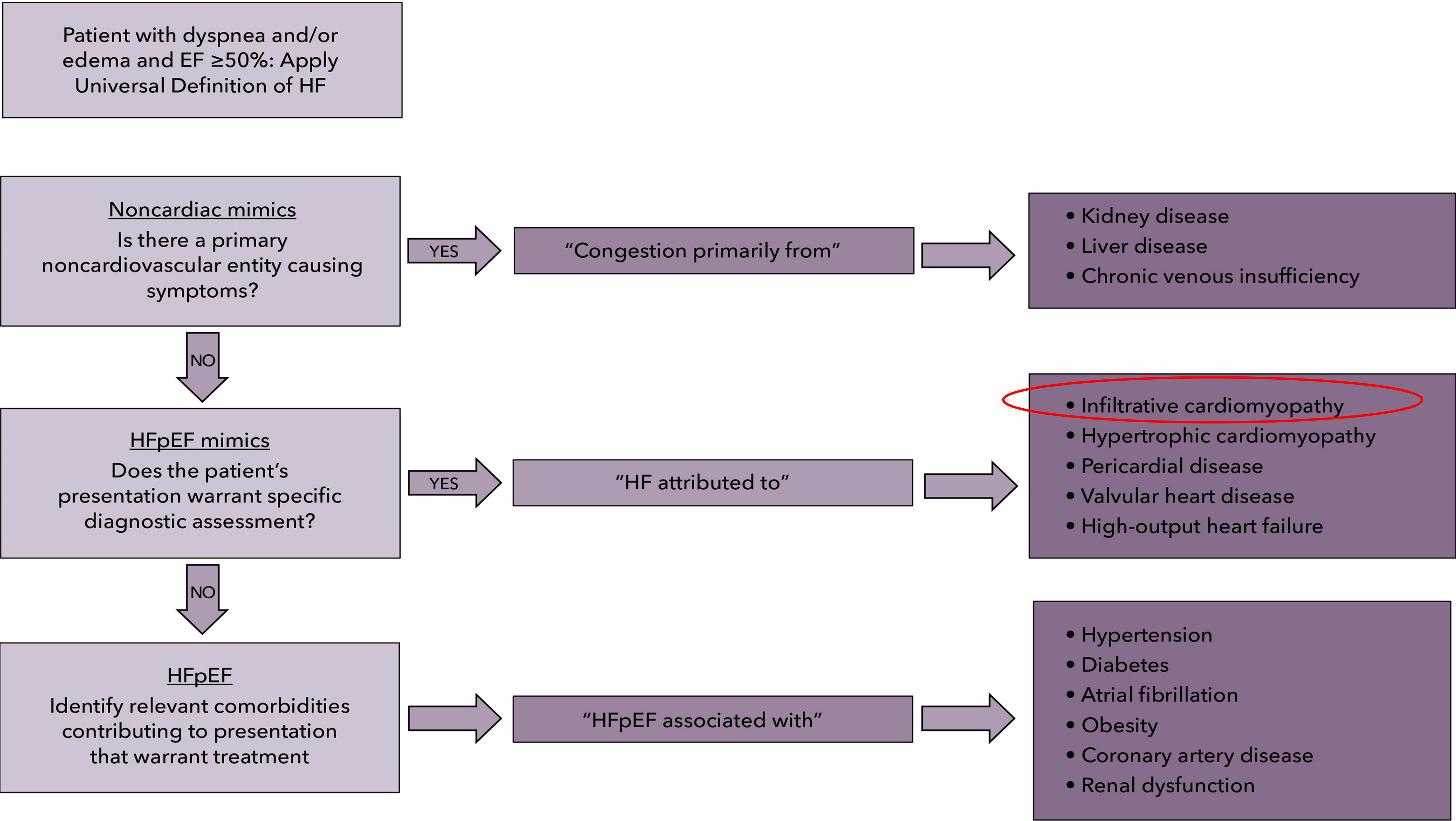


AMYLOIDOSIS: HIGH INDEX OF SUSPICION



HEART FAILURE SYMPTOMS

- **FATIGUE**
- **CARDIAC**
 - Atrial fibrillation/AV block/pacemaker
 - Aortic stenosis
 - "HFpEF"
 - Increase LV wall thickness + discordant QRS voltage
- **NEUROLOGIC**
 - Sensory neuropathy
 - Autonomic dysfunction; intolerance to vasodilators
- **ORTHOPEDIC**
 - Carpal tunnel syndrome
 - Spinal stenosis

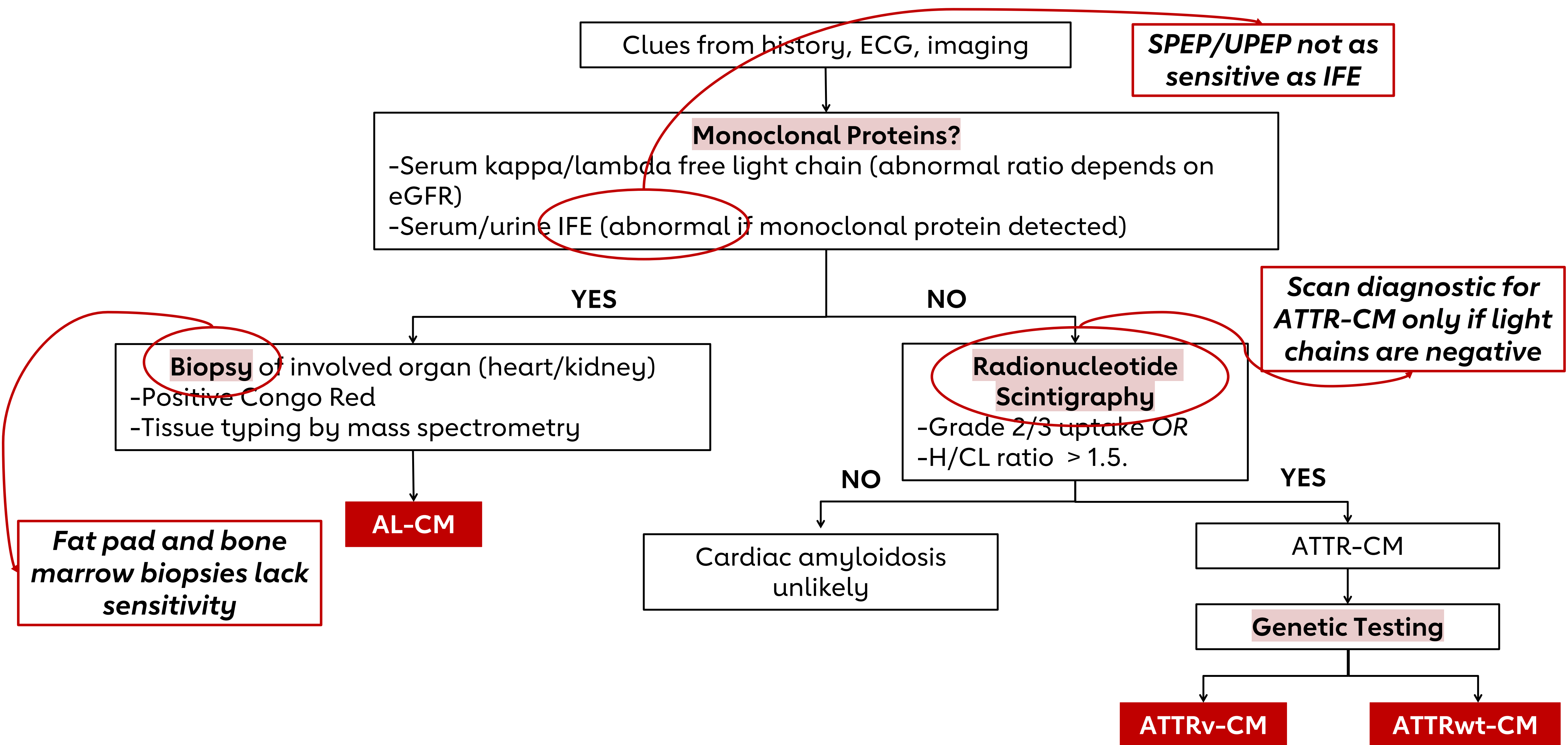


WHAT ABOUT THIS PATIENT:

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AMYLOIDOSIS: 3 (+/- 1) TESTS → 3 POSSIBLE DIAGNOSES



AMYLOIDOSIS

Recommendations for Diagnosis of Cardiac Amyloidosis

GNOSIS

COR	LOE	Recommendations
1	B-NR	1. Patients for whom there is a clinical suspicion for cardiac amyloidosis* ¹⁻⁵ should have screening for serum and urine monoclonal light chains with serum and urine immunofixation electrophoresis and serum free light chains. ⁶
1	B-NR	2. In patients with high clinical suspicion for cardiac amyloidosis, without evidence of serum or urine monoclonal light chains, bone scintigraphy should be performed to confirm the presence of transthyretin cardiac amyloidosis. ⁷
1	B-NR	3. In patients for whom a diagnosis of transthyretin cardiac amyloidosis is made, genetic testing with <i>TTR</i> gene sequencing is recommended to differentiate hereditary variant from wild-type transthyretin cardiac amyloidosis. ⁸

as
E

diagnostic for
CM only if light
chains are negative

-CM

Testing

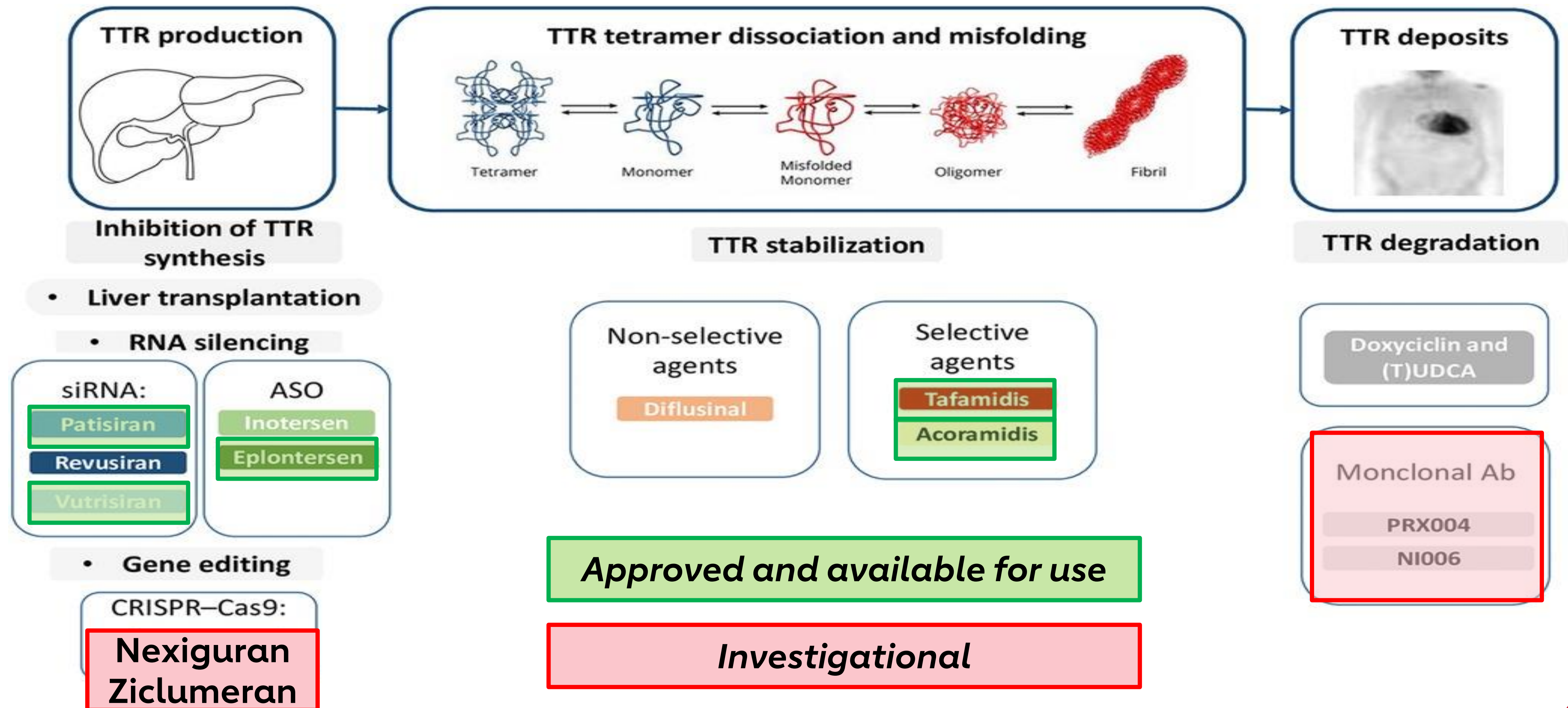
ATTRwt-CM

Biopsy of inv

- Positive Congo
- Tissue typing by

Fat pad and bone marrow biopsies lack sensitivity

THERAPIES FOR TRANSTHYRETIN AMYLOIDOSIS

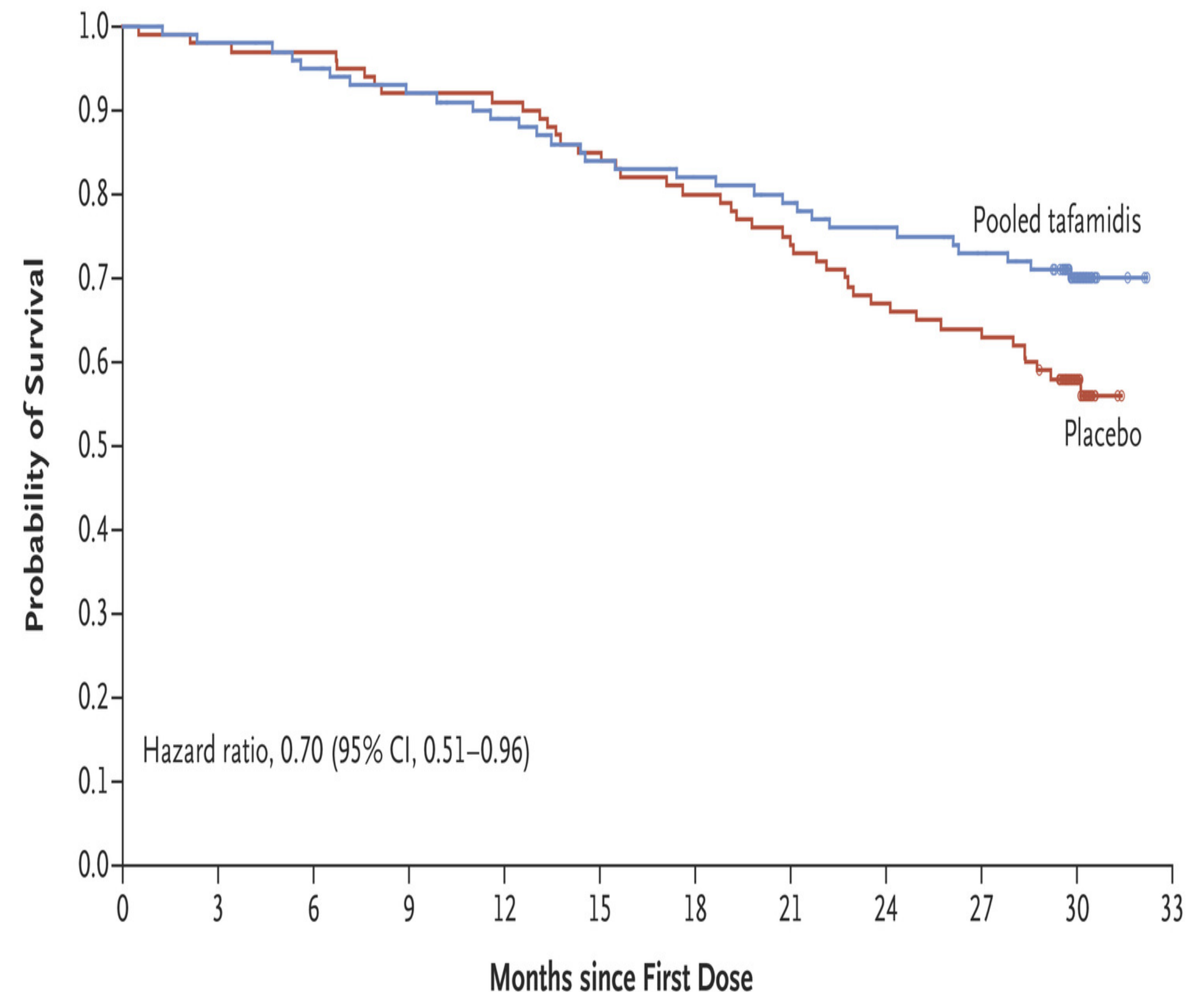


TTR Stabilizers: Tafamidis

- 441 pts with ATTR-CM NYHA I-III
- Tafamidis 80 vs 20 vs placebo
- 30 months
- Mortality: 43% → 30%
- Hospitalization: 0.7/yr → 0.48/yr
- NNT: 7.5 to prevent 1 death over 30 months

FDA Approval May 2019

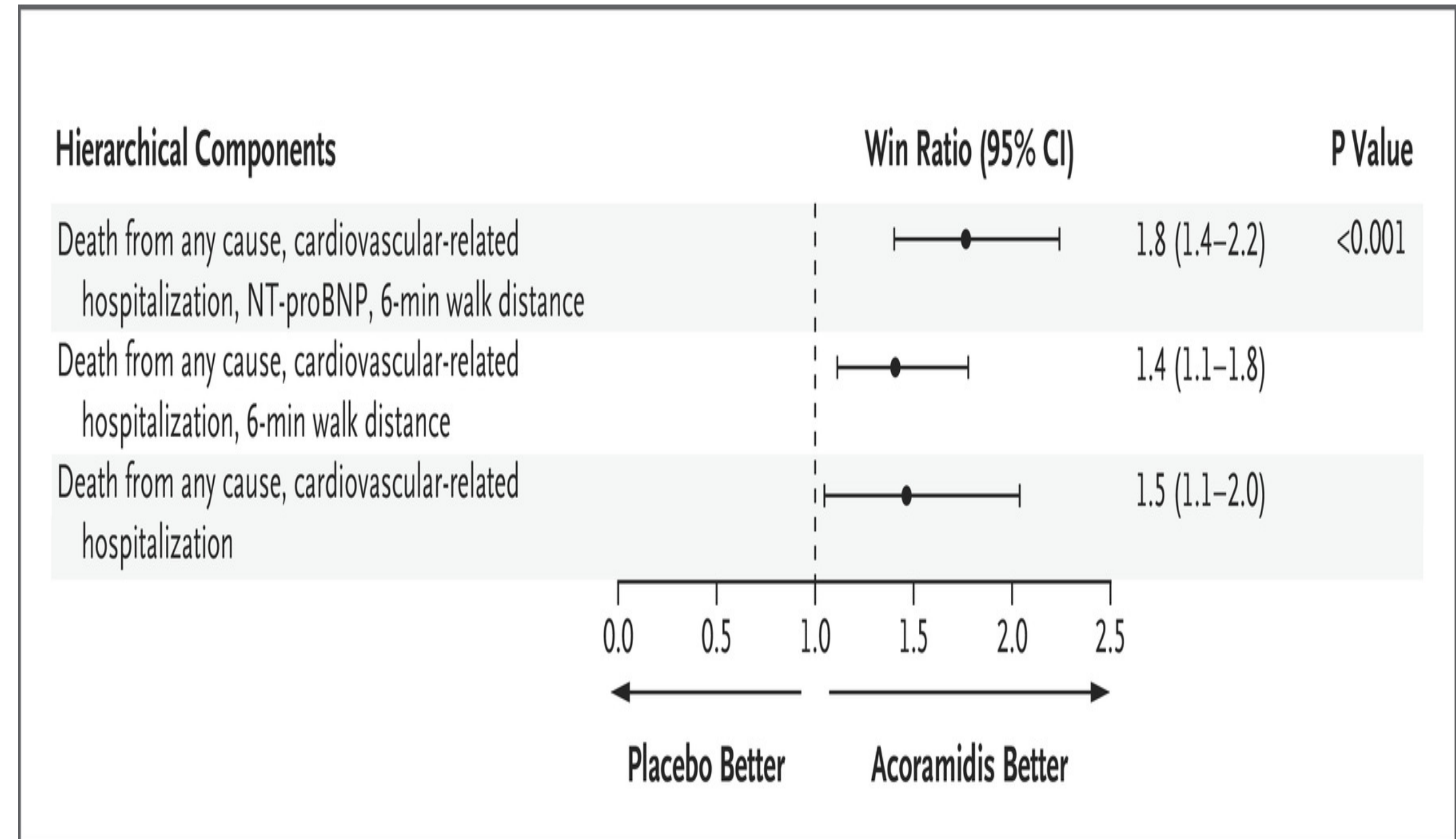
Analysis of All-Cause Mortality



TTR Stabilizers: Acoramidis

ATTRIBUTE-CM

- ATTR-CM
- Acoramidis 800 mg BID
- 632 patients
- Tafamidis allowed after 12m
 - (17% on tafamidis)
- Primary endpoint met



FDA Approval November 2024

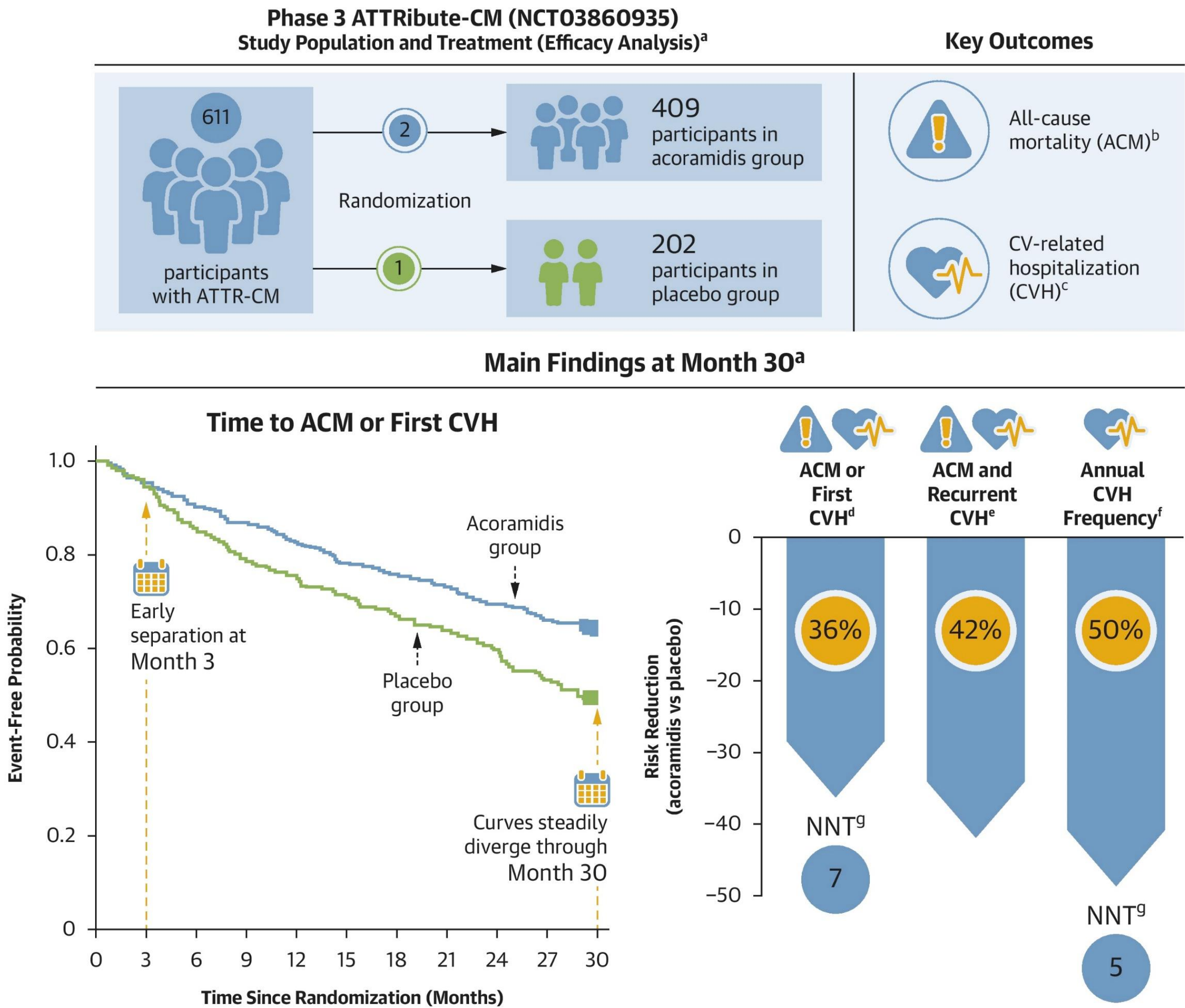


TTR Sta

- ATTR-CM
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FDA Appro

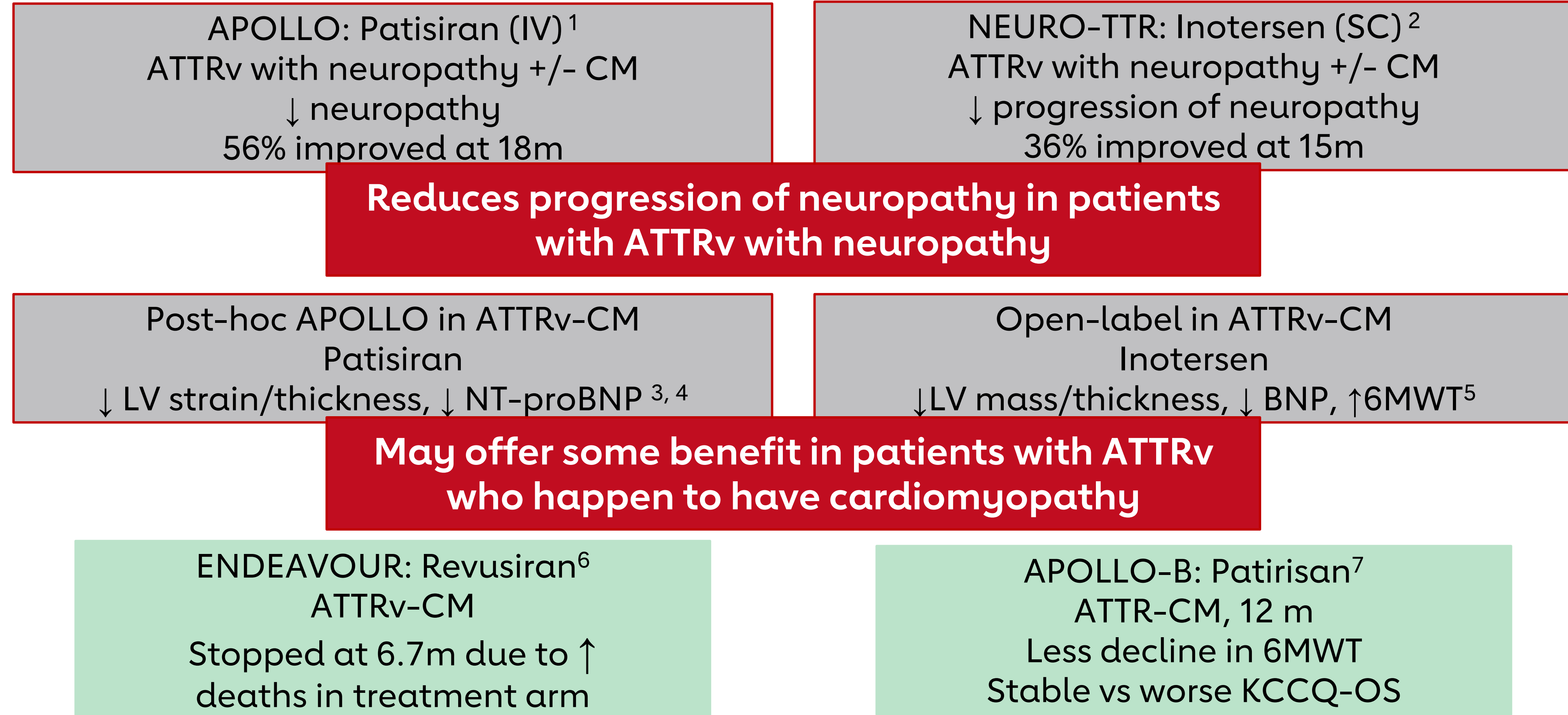
CENTRAL ILLUSTRATION: Early Benefits of Acoramidis on All-Cause Mortality and Cardiovascular-Related Hospitalization in Transthyretin Amyloid Cardiomyopathy



Judge DP, et al. JACC. 2025;85(10):1003-1014.



TTR Silencers: Early Promise



¹Adams et al. NEJM 2018

²Benson et al. NEJM 2018

³Solomon et al. Circulation 2019

⁴Minamisawa et al. JAMA Cardiol 2019

⁵Benson et al. Amyloid 2017

⁶Judge et al. Cardiovasc Drug Ther 2020

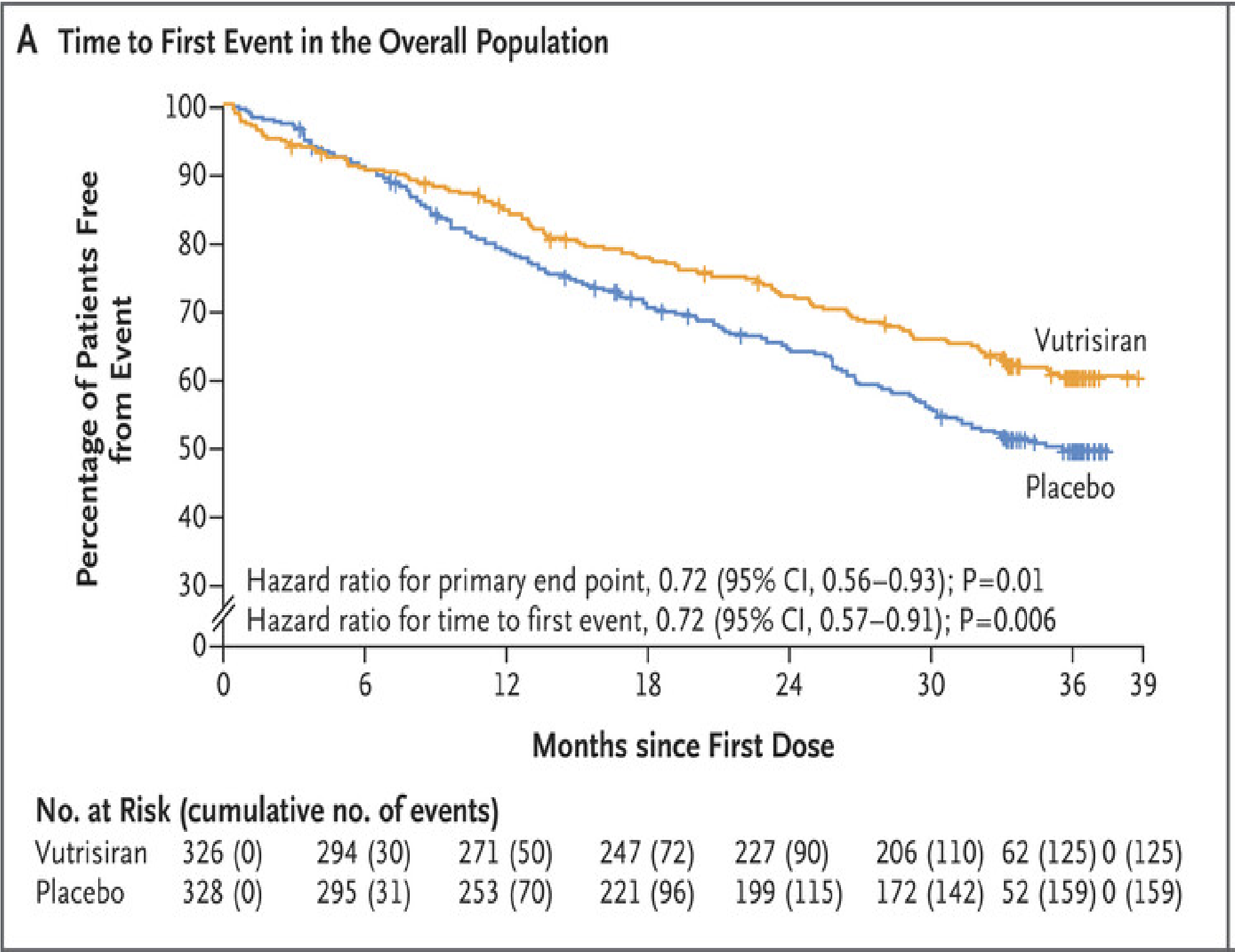
⁷Maurer et al. NEJM 2023



TTR Silencers: Vutrisiran

- HELIOS-B
- 655 patients with ATTR-CM, NYHA I-III
- Vutrisiran vs placebo for 36 months
- 40% of patients also on tafamidis at baseline and 20% started after enrollment
- Primary endpoint (death, CV hosp, HF urgent visits)
- Death: 26% → 18%
- CV events: 41% → 34%
- Preservation of 6MWD and QOL

FDA Approval March 2025



Stay tuned:
CARDIO-TTRansform: Eplontersen (death/CV hosp)
Study completion date: 2026



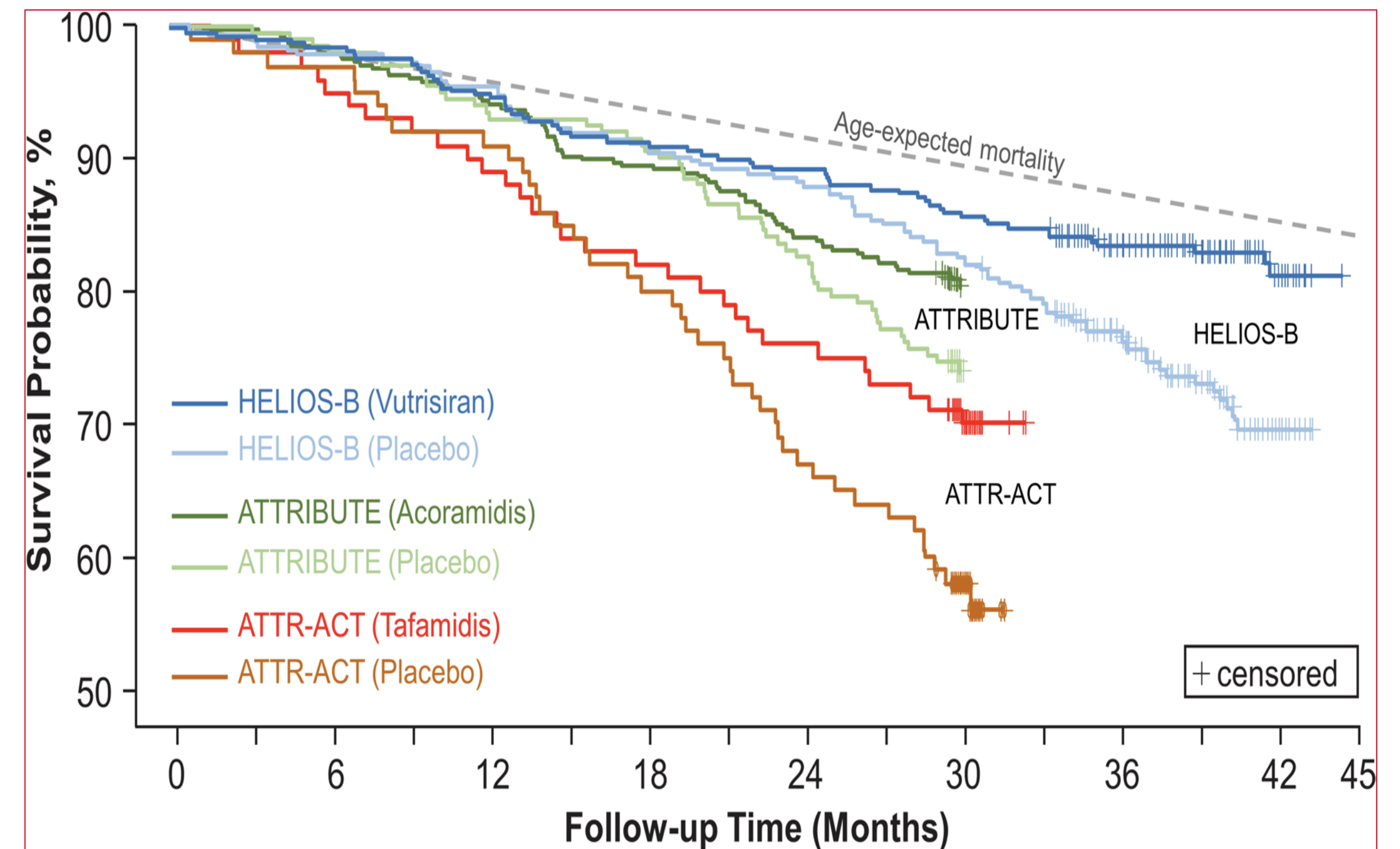
A still life photograph featuring a red apple and several slices of orange on a light-colored wooden surface. The apple is positioned in the center-right, with a small stem. To its left and in front are several slices of orange, some showing the green skin. The background is a soft-focus outdoor scene with green foliage and tree trunks. Overlaid on the image is the text "Which Medication Should I Choose?" in a large, white, sans-serif font.

**Which Medication
Should I Choose?**

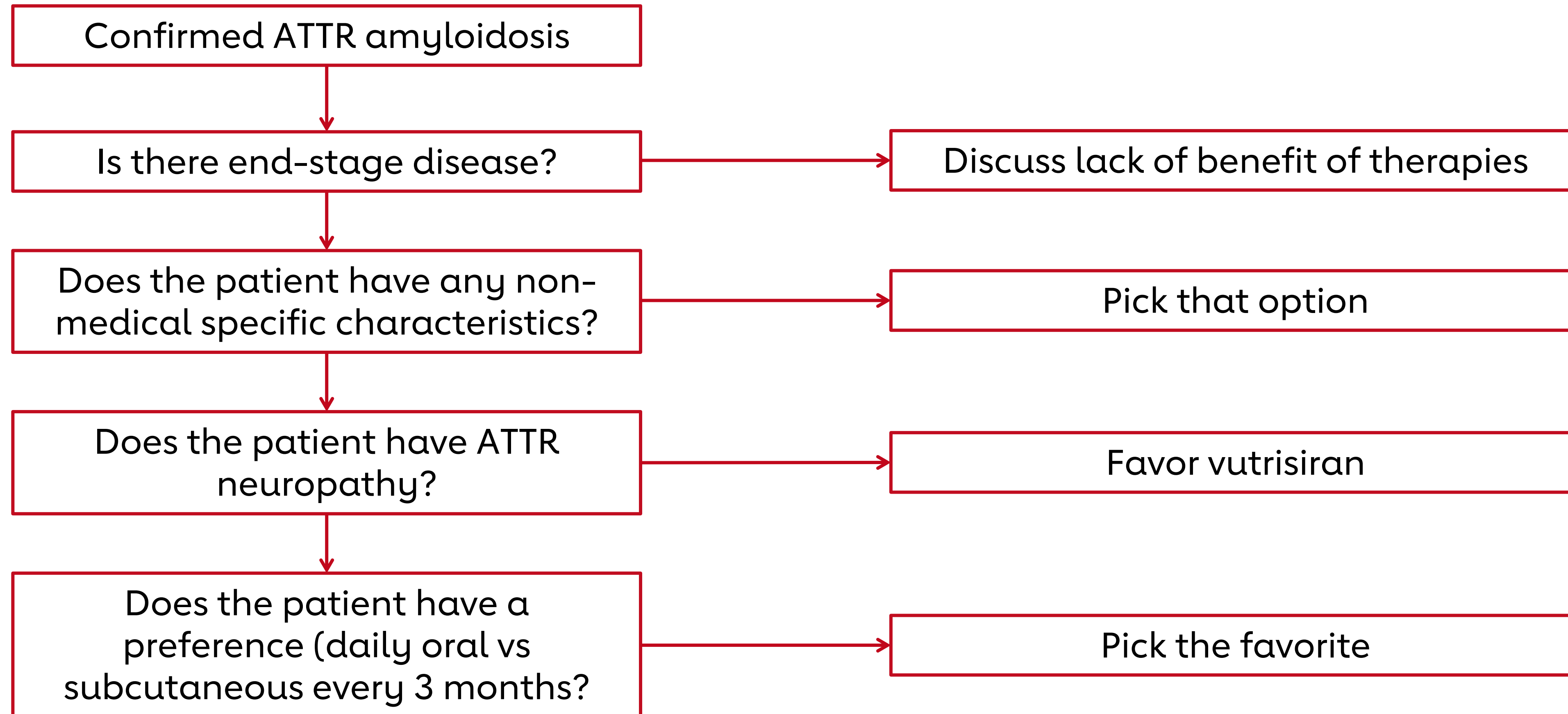
Can Trials Answer this Question? (No)

Table 3.2. Overview of Key Studies

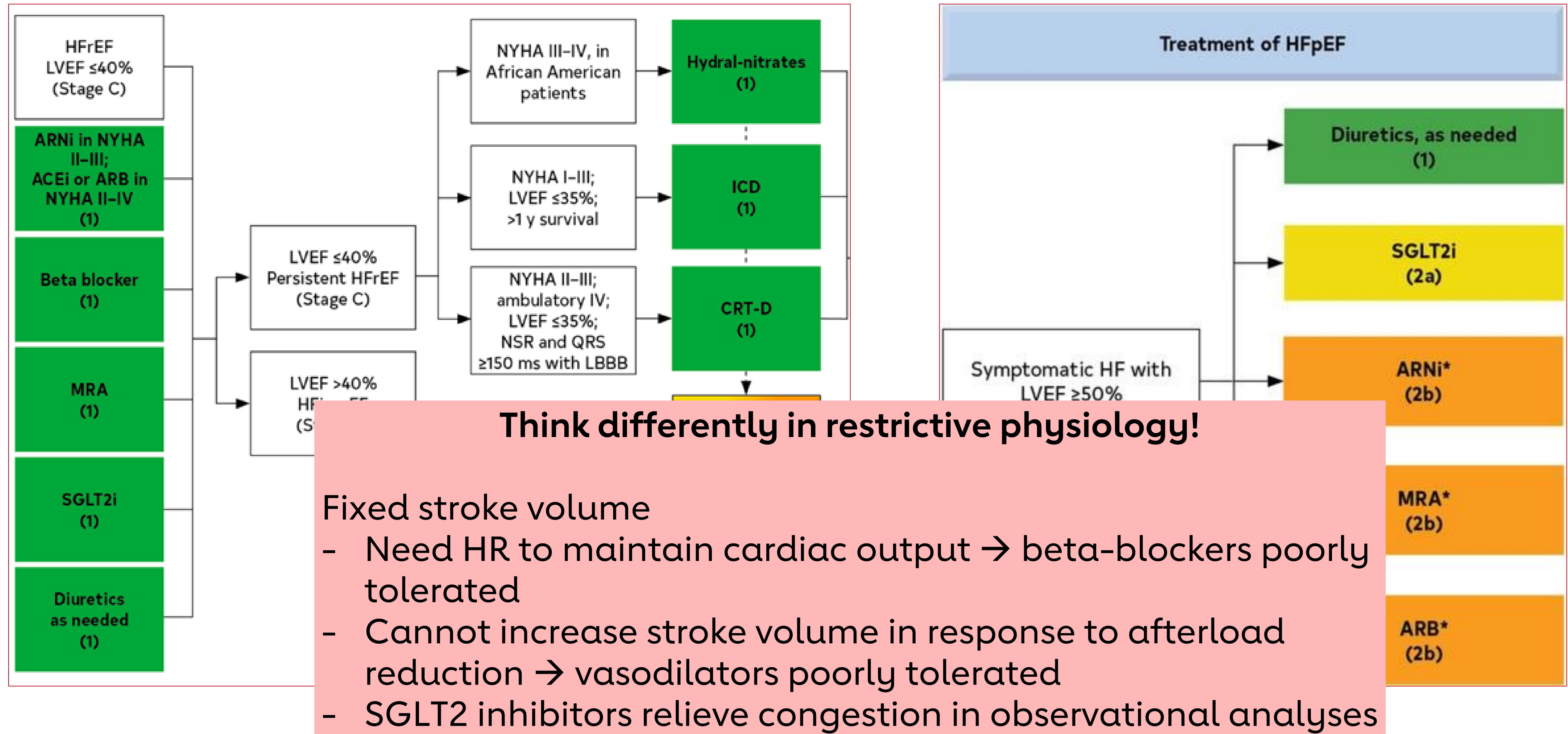
Trial		ATTR-ACT tafamidis 80 mg n=176 Placebo n=177	ATTRibute-CM acoramidis n=421 Placebo n=211	HELIO-B vutrisiran n=326 Placebo n=328
N		353	632	654
Age, Years	Mean	74.3	77	77*
Sex, %	Male	90.2	90.2	92.5
	Female	9.8	9.8	7.5
Race, %	White	80.9	87.8	84.4
	Black	14.3	4.7	7.2
	Asian	3.9	2.1	5.7
	Other	0.4	5.4	2.8
TTR Type, %	ATTRv	24	9.7	11.6
	ATTRwt	75.9	90.3	88.4
Transthyretin Variant, %	V122I	56.9	62.1†	64.5
	T60A	11.8	8.6†	10
NYHA Class, %	Class I	8.4	10.8	12.8
	Class II	59.6	72	77.7
	Class III	31.9	17.2	9.5
NT-proBNP, pg/mL	Median	2995.9‡	2326	1801#
Baseline Medications, %	Agents acting on renin-angiotensin system	26.5	NR	NR
	Beta Blockers	29.3	NR	NR
	Diuretics	67.6	NR	79.5
	Antithrombotic Agents	40.1	NR	NR
6MWT Distance, mean		351.9	354.8	374.5‡
KCCQ, mean	Overall Summary Score	66.6	70.9	72.65



My Take on the Upcoming Therapeutic Landscape



What about Guideline-Directed Medical Therapy for HF?



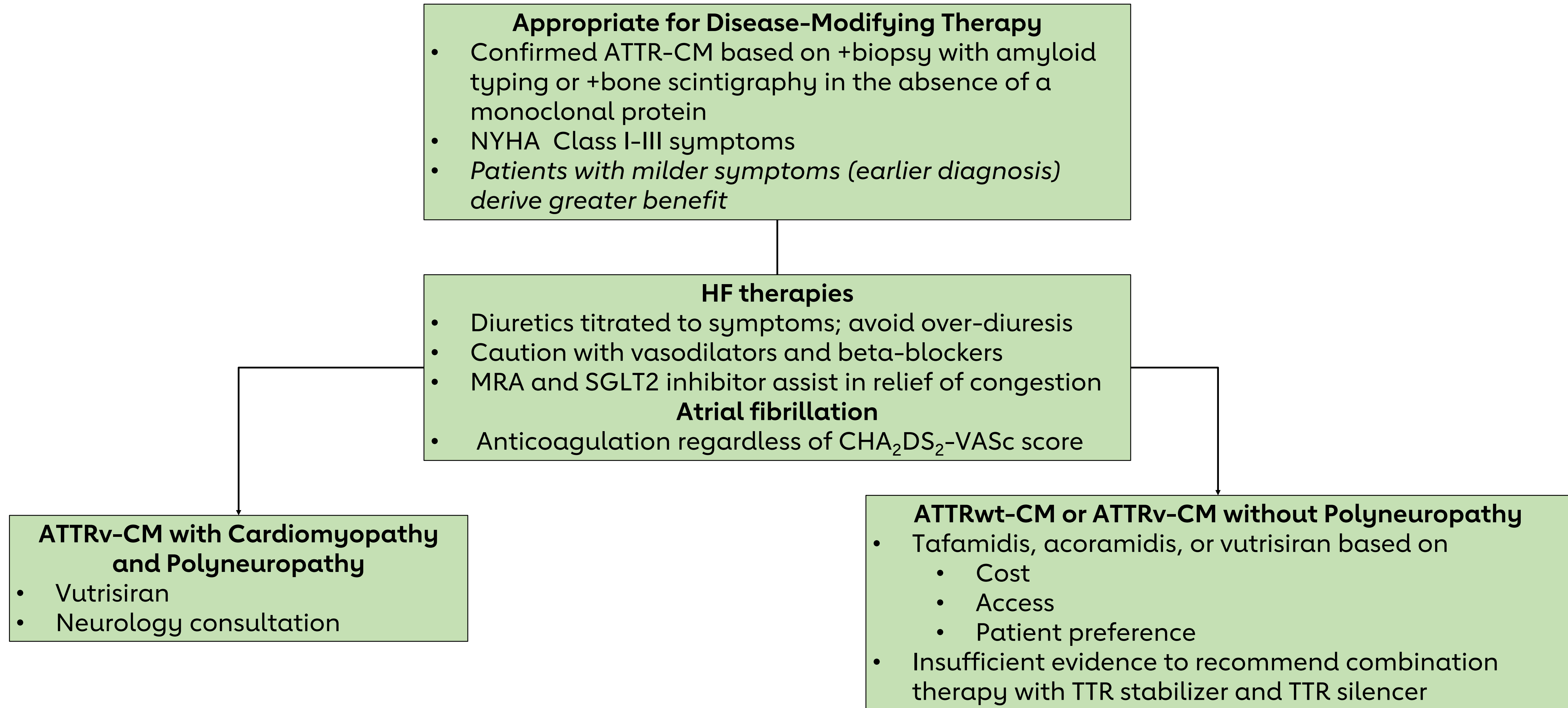
Think differently in restrictive physiology!

Fixed stroke volume

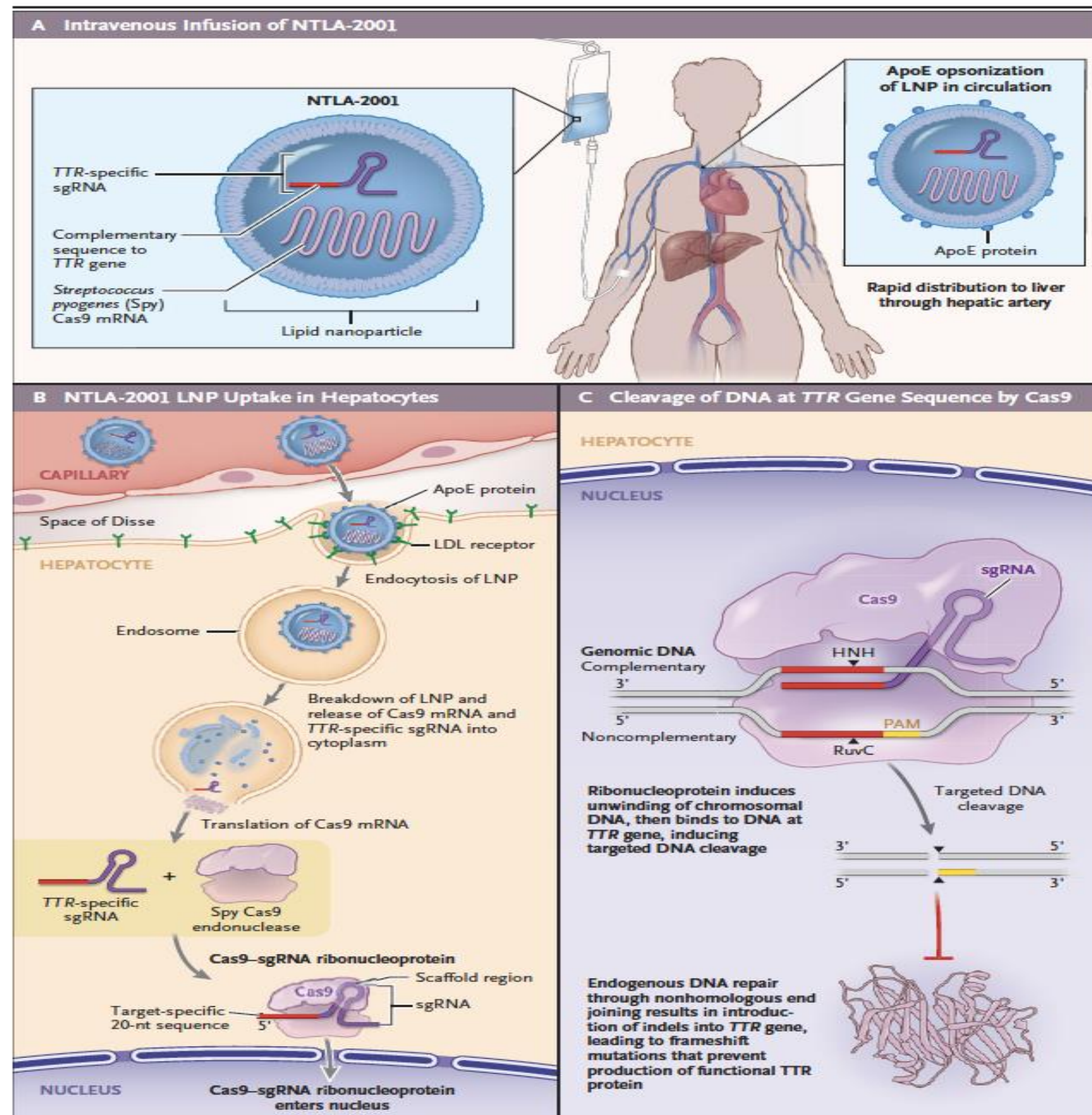
- Need HR to maintain cardiac output → beta-blockers poorly tolerated
- Cannot increase stroke volume in response to afterload reduction → vasodilators poorly tolerated
- SGLT2 inhibitors relieve congestion in observational analyses



Putting it All Together

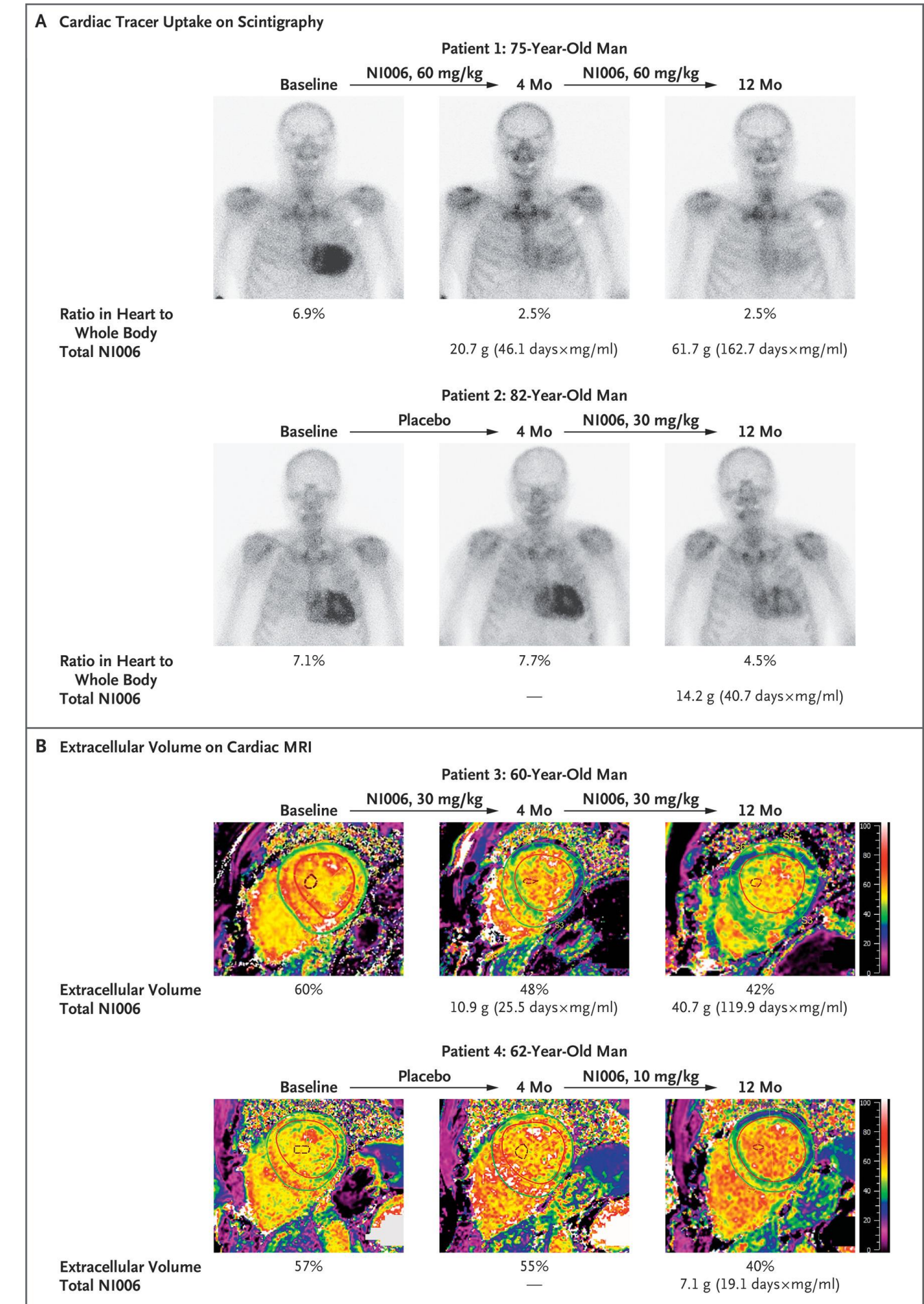


Glimpses into the Future



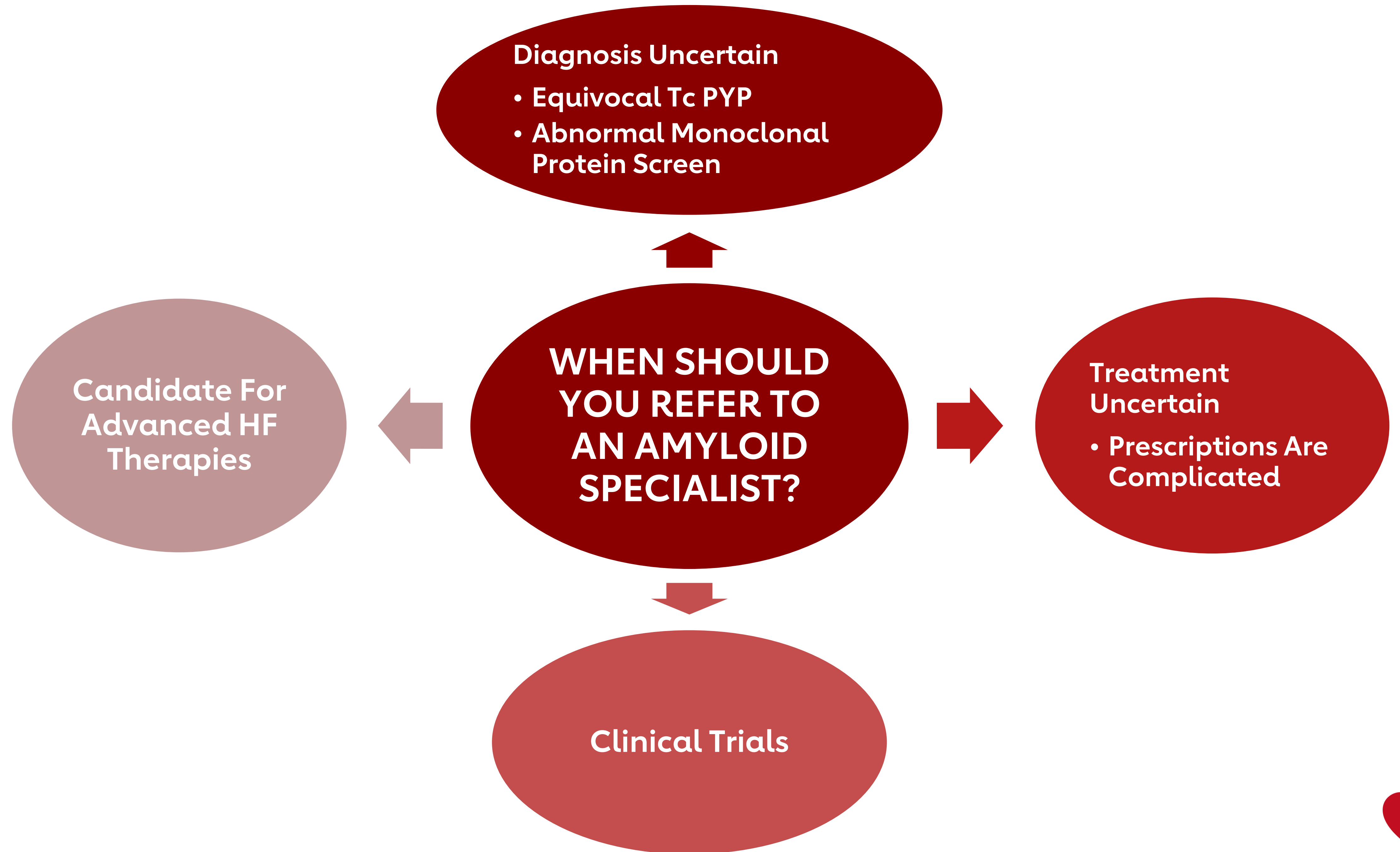
- Gene editing: Precisely target a predefined DNA sequence
- Permanently inactivate the TTR gene in the liver, the main source for circulating TTR
- 36 patients, 90% knockdown at 12 months, no change in 6MWD, KCCQ, NT-proBNP, troponin

Gillmore *NEJM* 2021, Fontana *NEJM* 2024



- Antibody depletion: mAb that binds only misfolded TTR amyloid fibrils → Ab-mediated phagocytosis and removal from tissues
- Potential to reverse ATTR-CM
- 40 patients, reduction in imaging-based surrogate markers of cardiac amyloid load

Garcia-Pavia et al. *NEJM* 2023



What We Know... And Still Need To Know

We Know:

- ATTR-CM is more common than you think: have a high index of suspicion in the face of clinical clues
- Noninvasive diagnosis is possible: a Tc PYP scan is diagnostic in the presence of a negative screen for monoclonal proteins
- Tafamidis, acoramidis, and vutrisiran are effective, evidence-based, and *FDA-approved* therapies for ATTR-CM

We Need To Know:

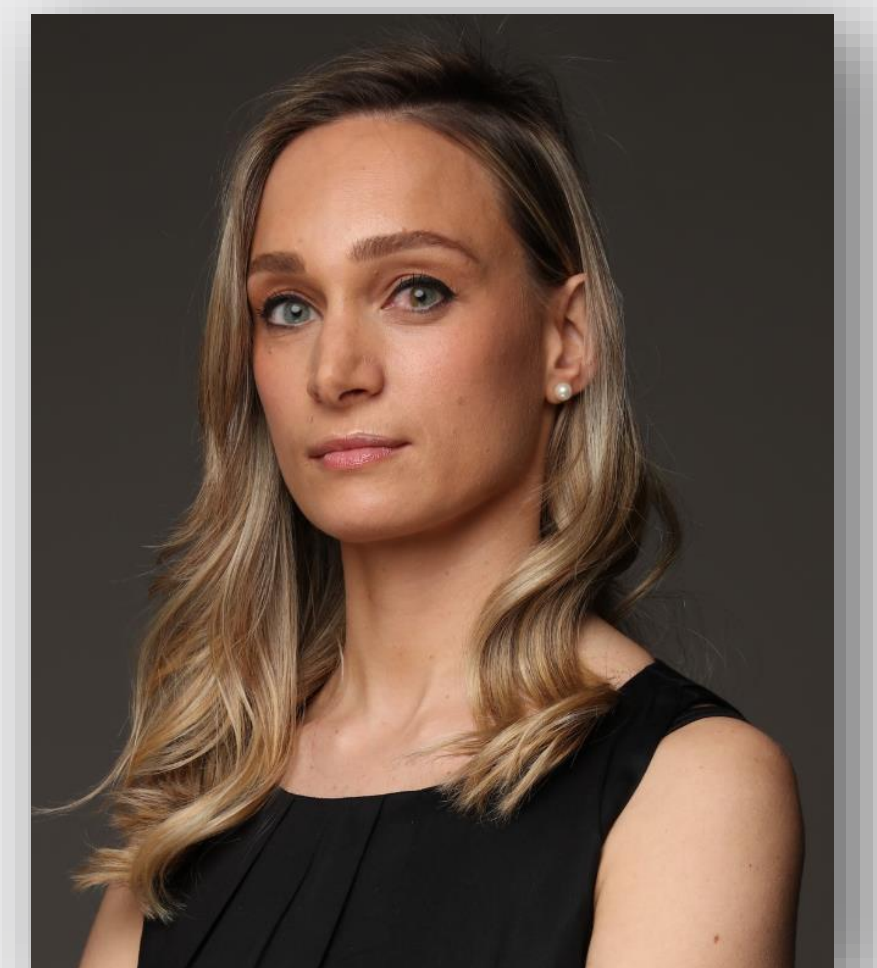
- What should standard of care be? TTR stabilizer? TTR silencer?
- How do you assess “response to therapy” and what do you do about “nonresponders”?
- What happens when we get too good at diagnosis → how should asymptomatic patients be managed?





CRISPR-Cas9 Deep Dive

Marianna Fontana, M.D., Ph.D, FRCP
Professor of Cardiology,
Hon. Consultant Cardiologist,
National Amyloidosis Centre,
University College London, United Kingdom

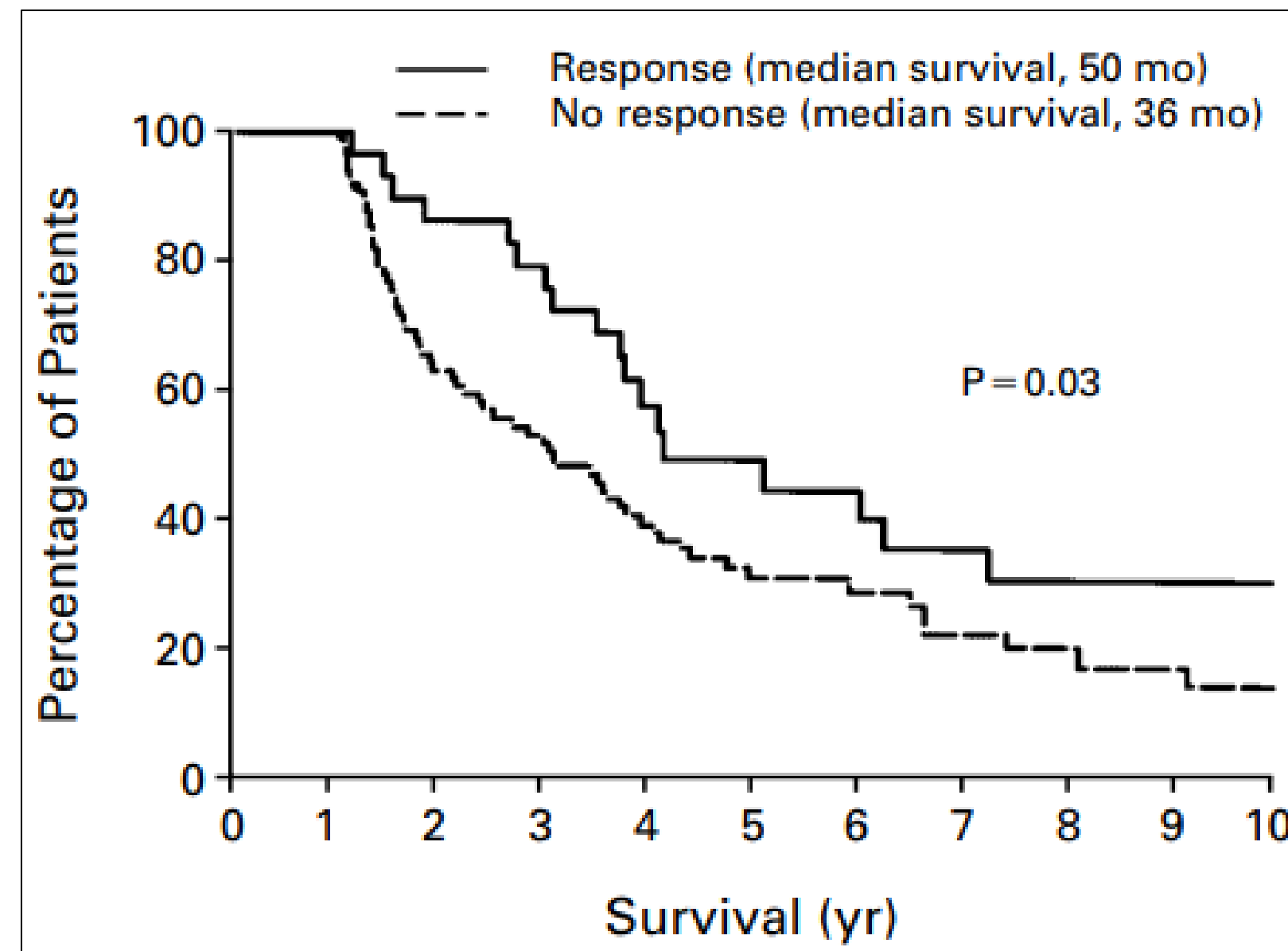


Treatment Of **Primary** (Systemic AL) Amyloidosis

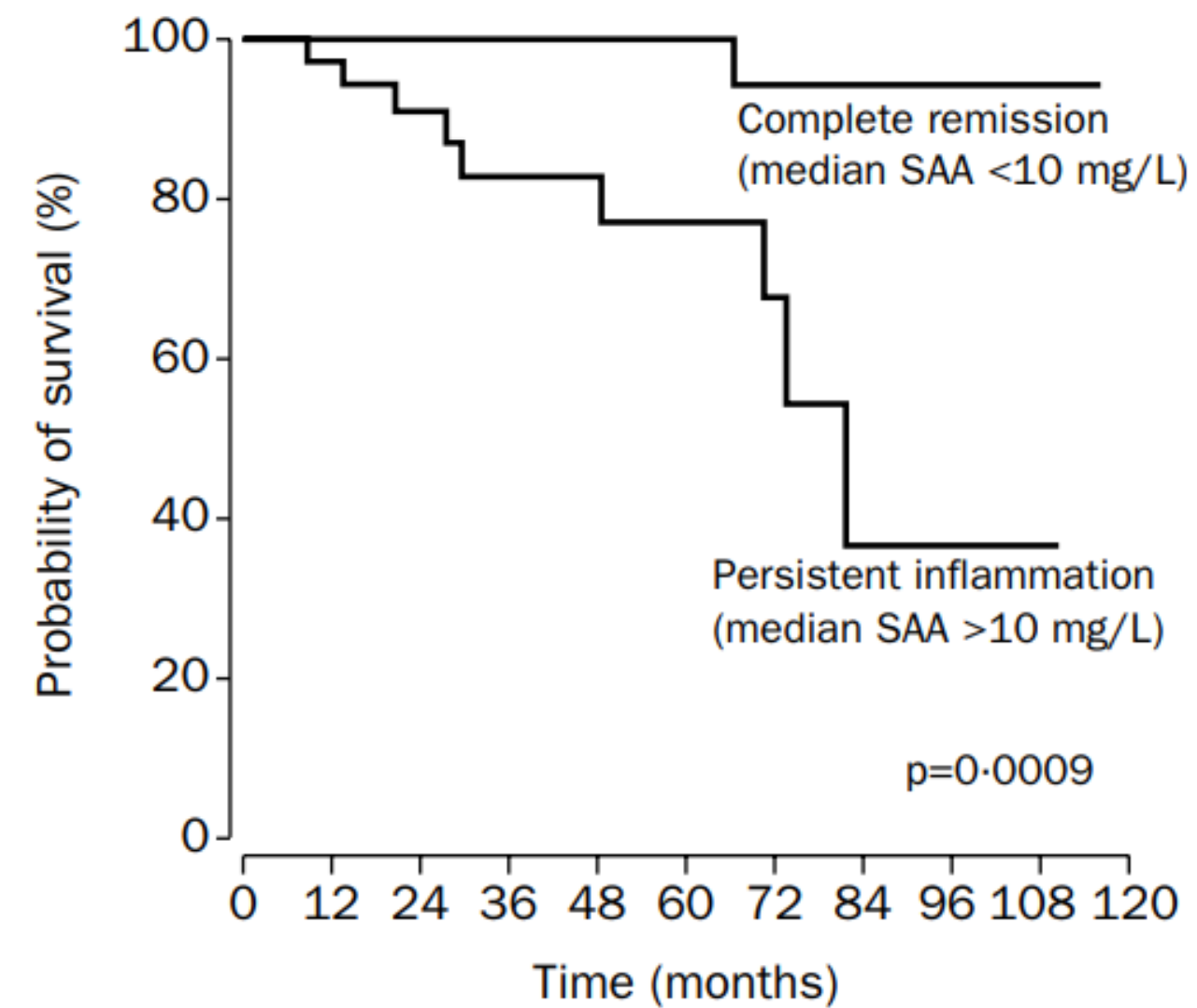
The New England Journal of Medicine

A TRIAL OF THREE REGIMENS FOR PRIMARY AMYLOIDOSIS: COLCHICINE ALONE, MELPHALAN AND PREDNISONE, AND MELPHALAN, PREDNISONE, AND COLCHICINE

ROBERT A. KYLE, M.D., MORIE A. GERTZ, M.D., PHILIP R. GREIPP, M.D., THOMAS E. WITZIG, M.D.,
JOHN A. LUST, M.D., PH.D., MARTHA Q. LACY, M.D., AND TERRY M. THERNEAU, PH.D.

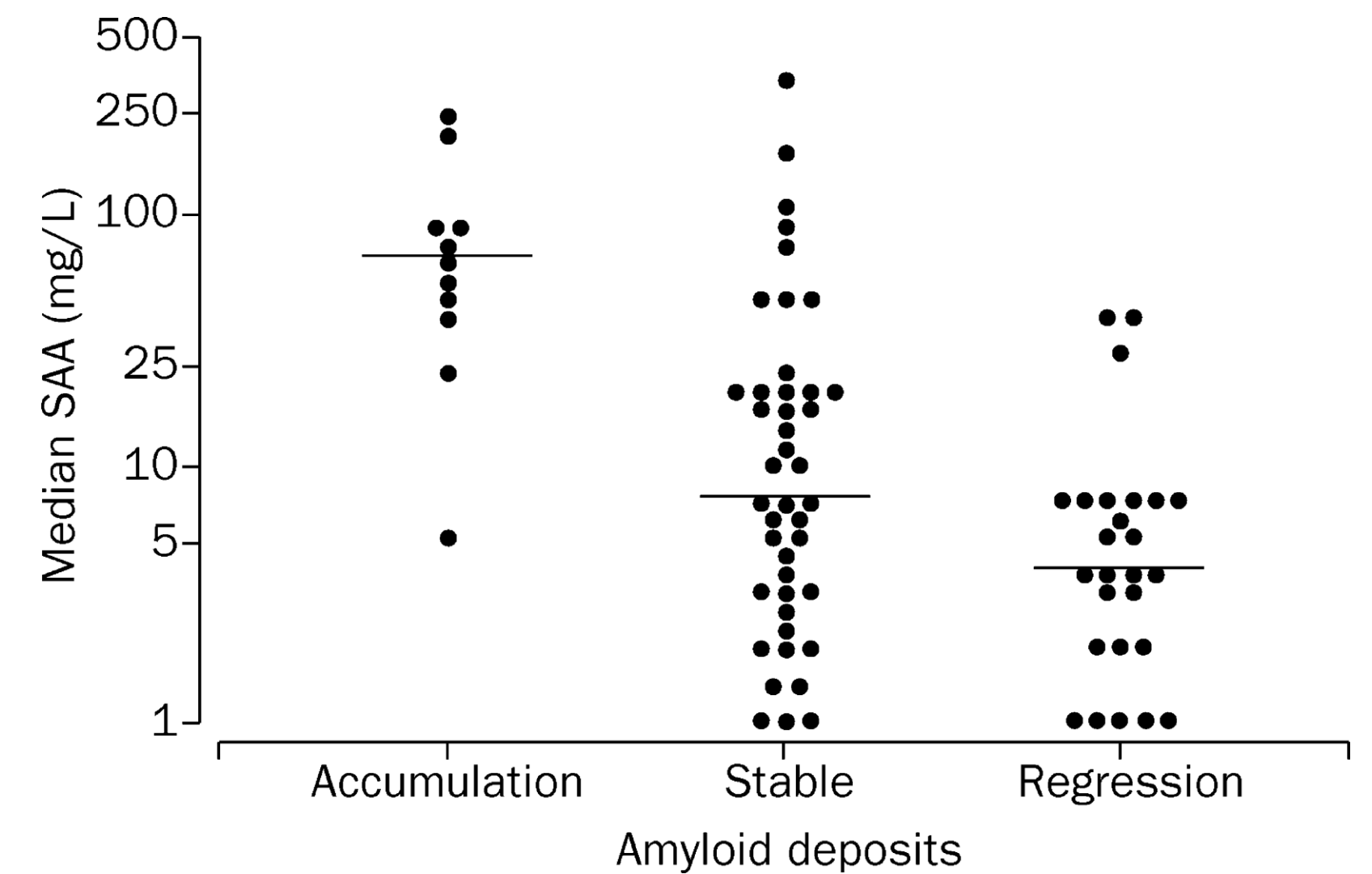
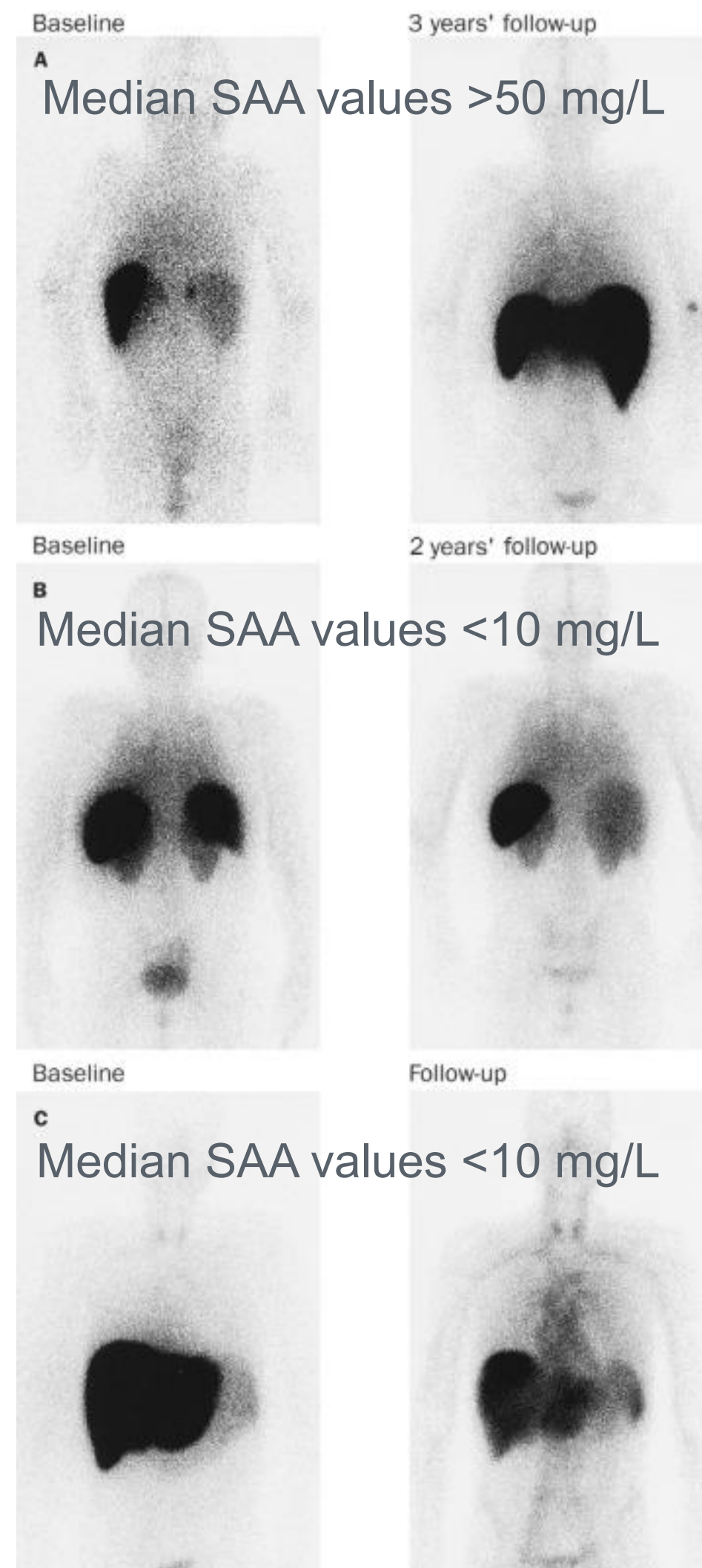


Treatment Of **Secondary** (Systemic AA) Amyloidosis

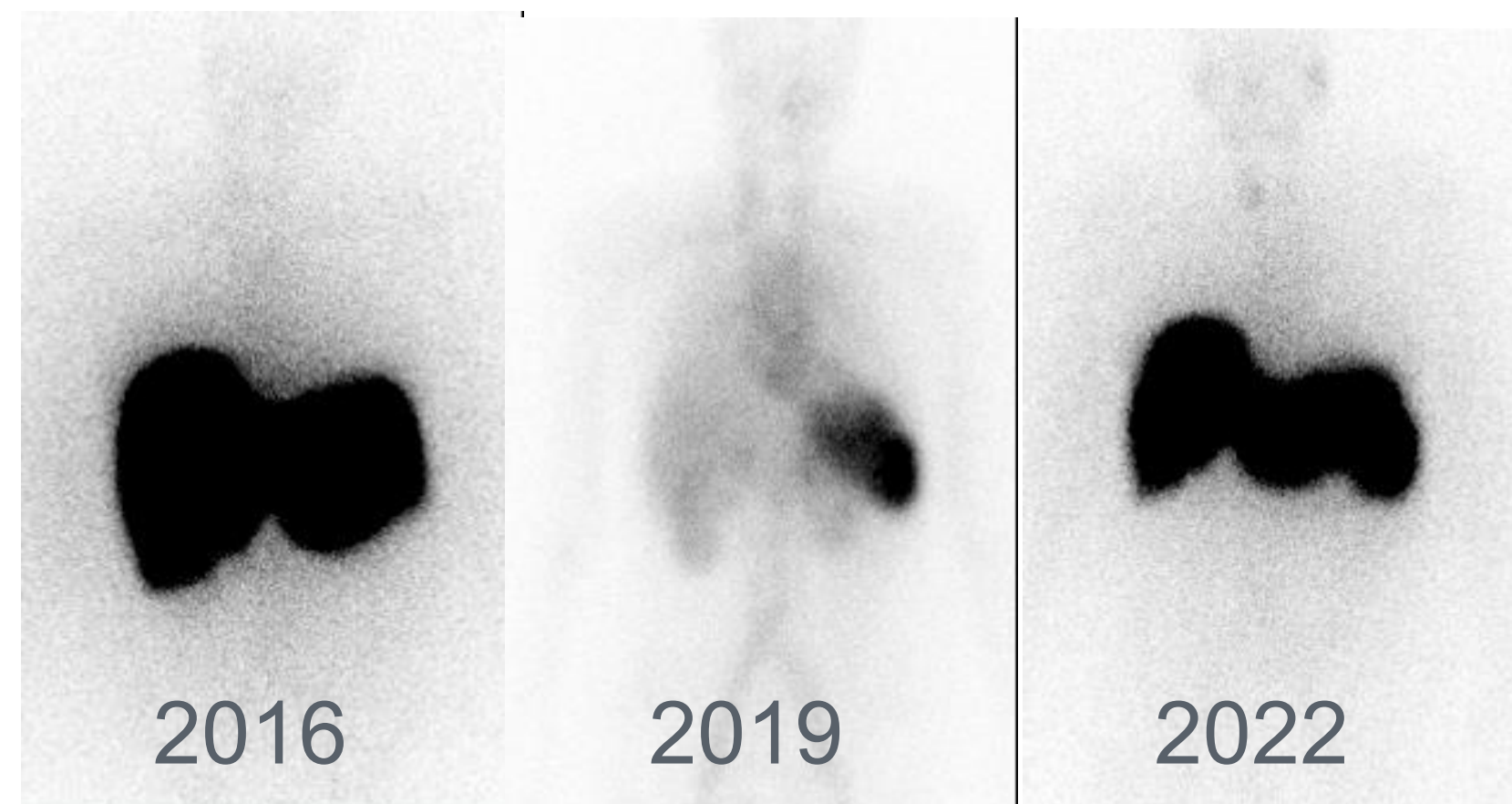
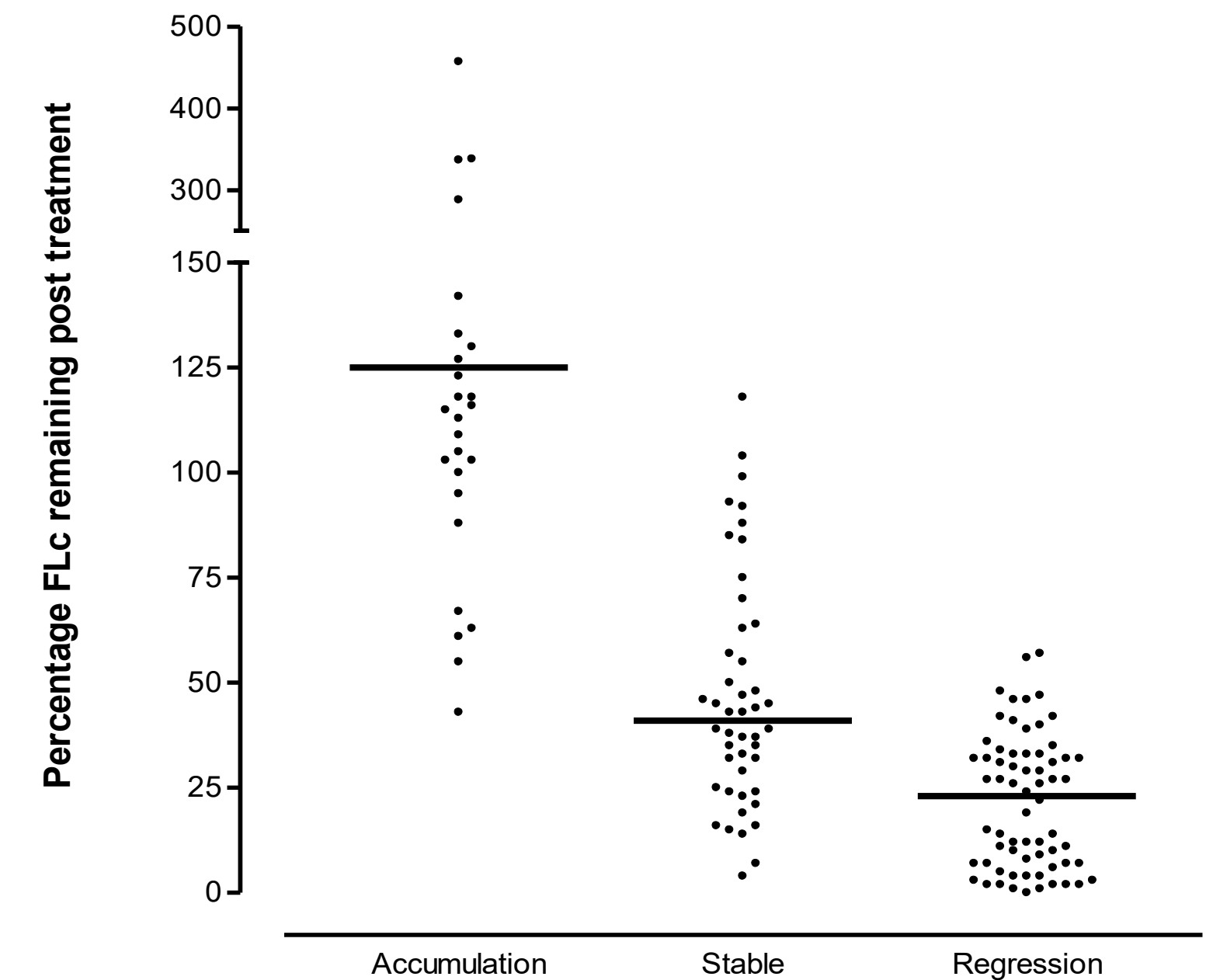
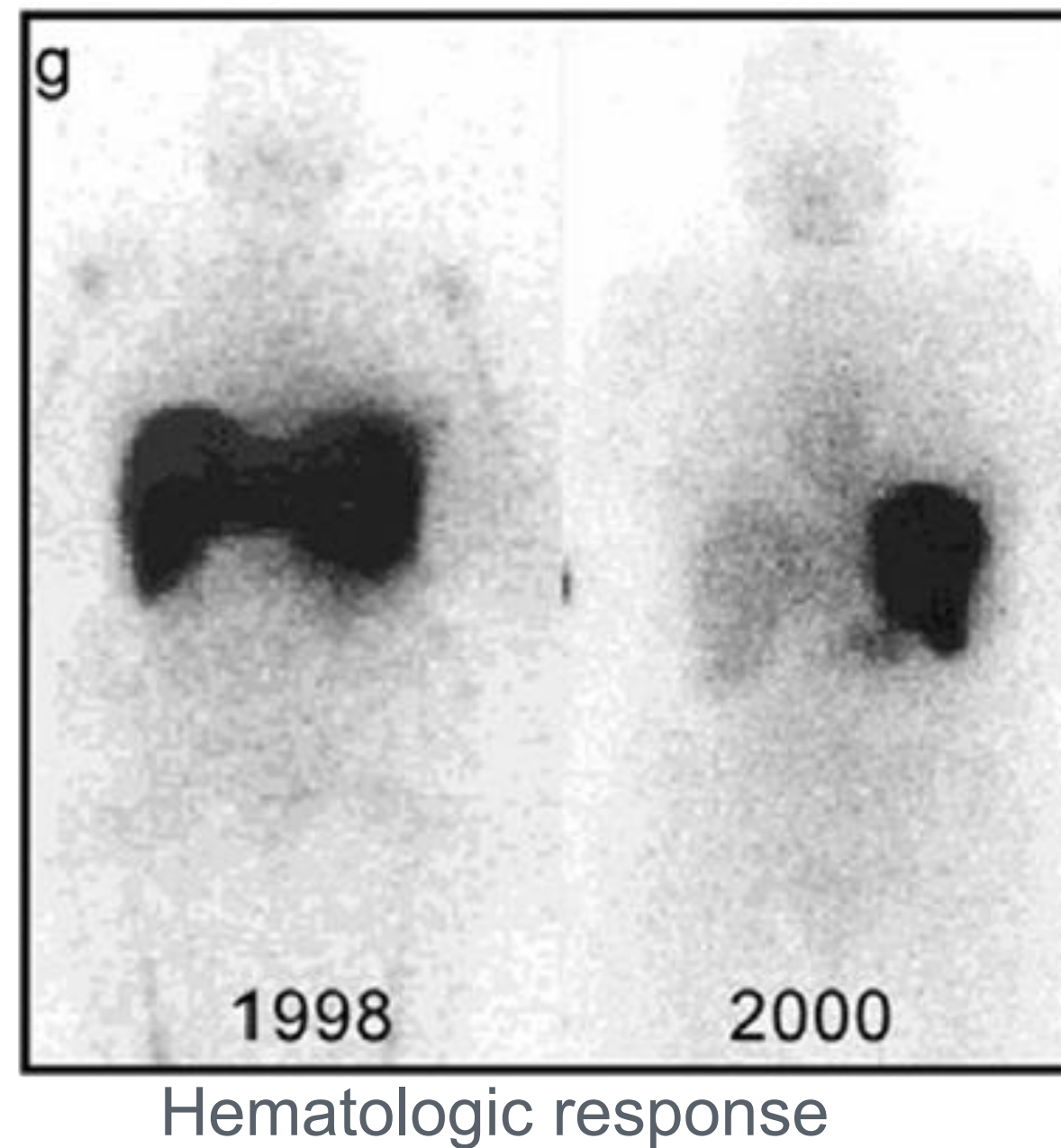
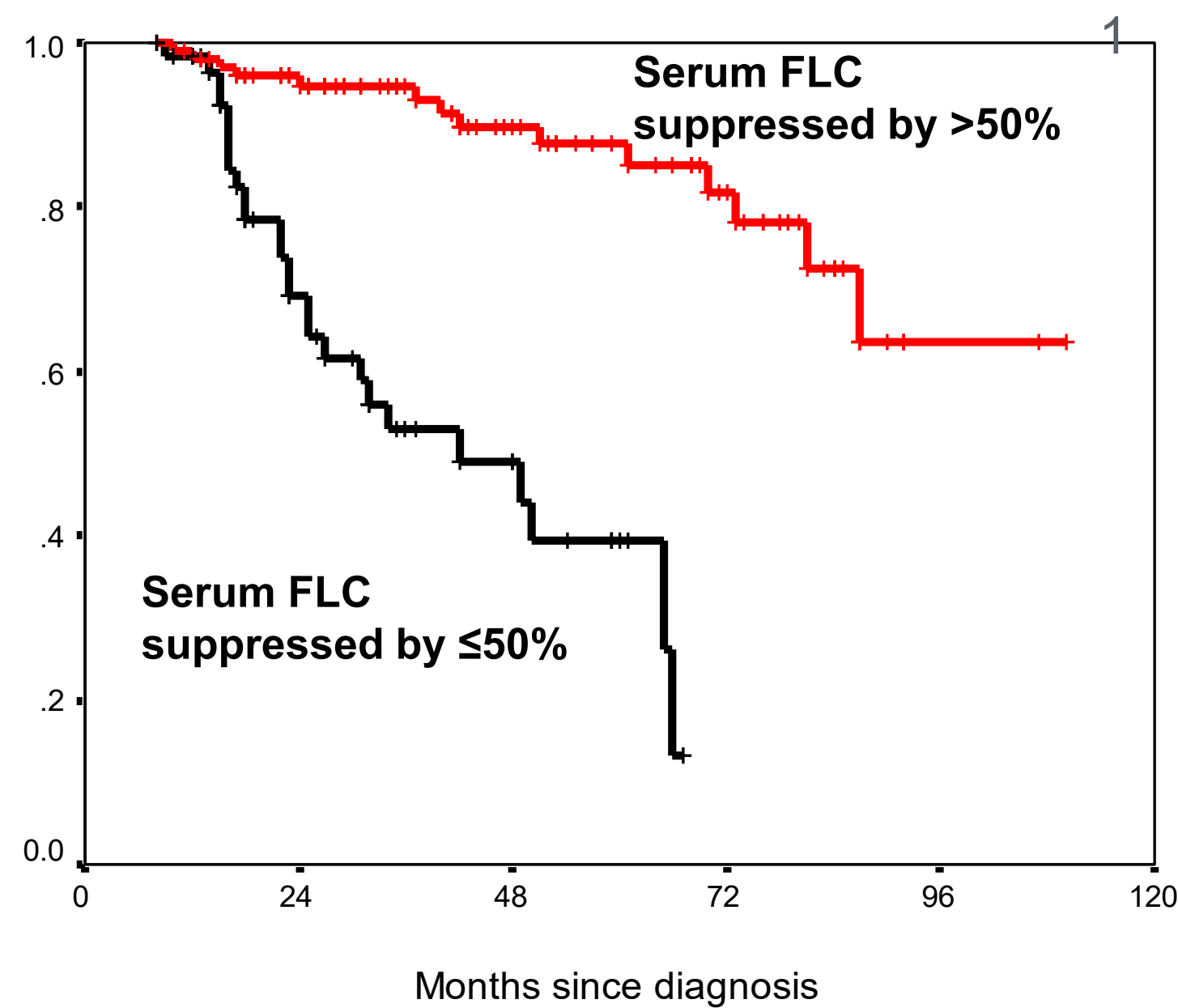


Number at risk

Complete remission	42	42	42	42	42	42	41	41	41	41
Persistent inflammation	38	37	35	33	33	32	31	29	29	29



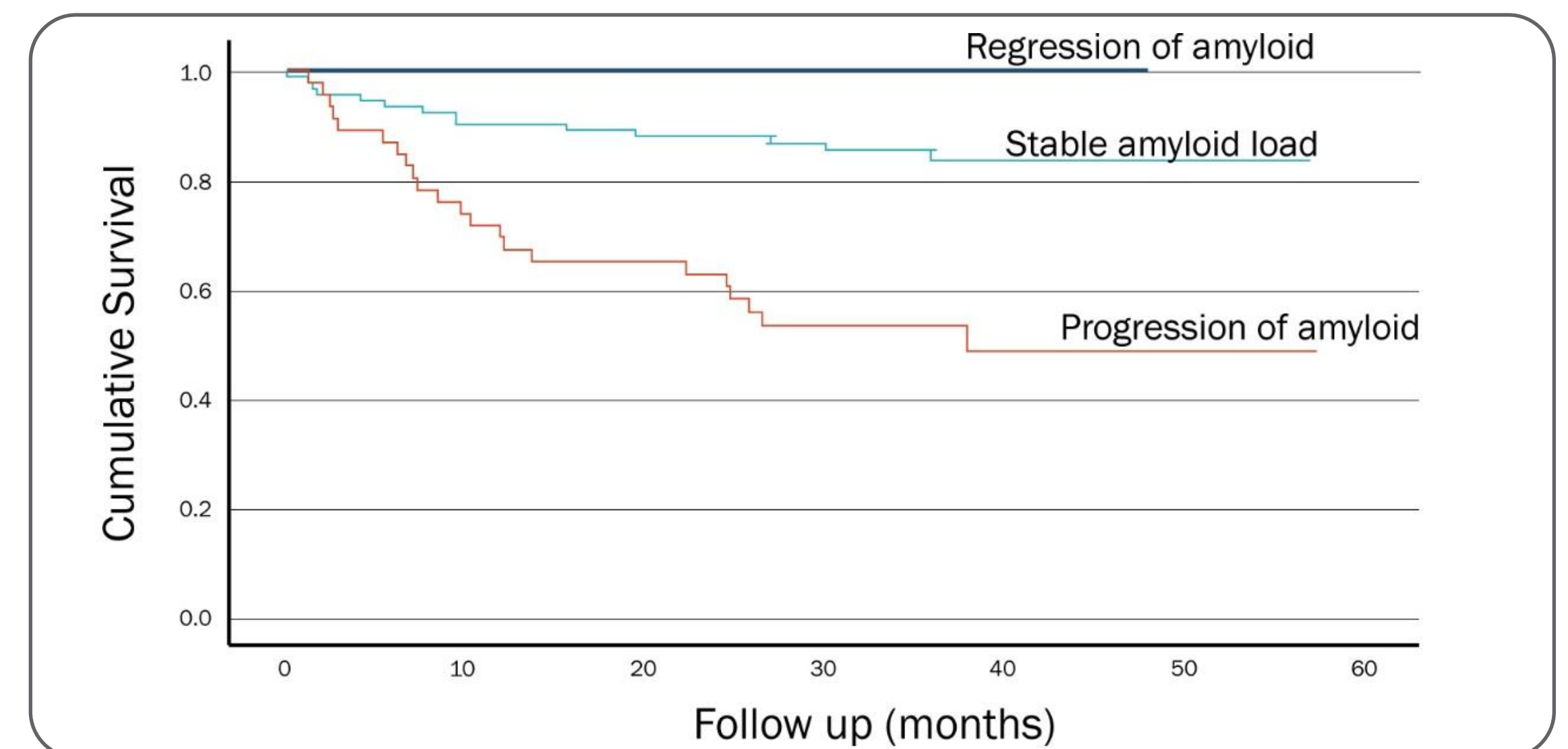
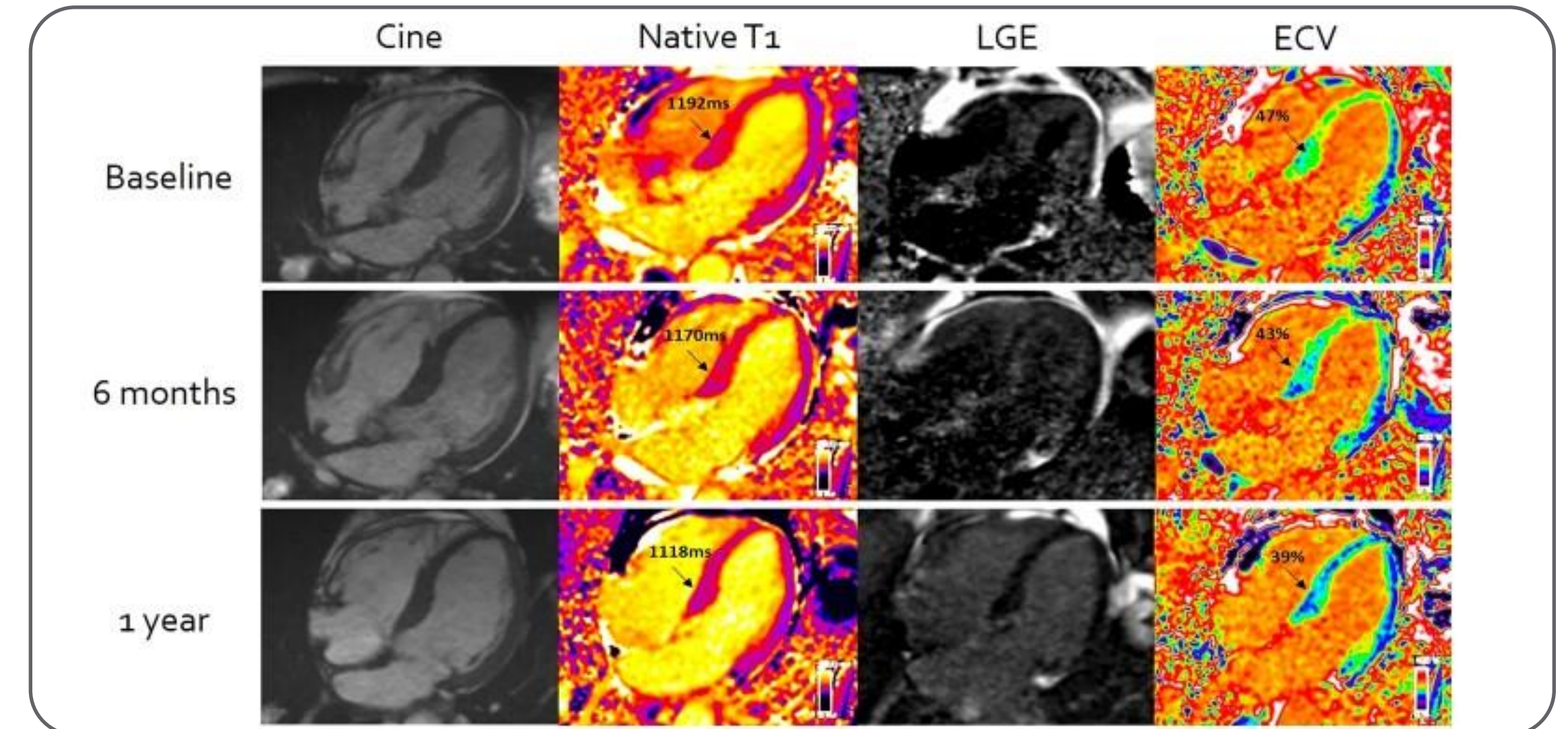
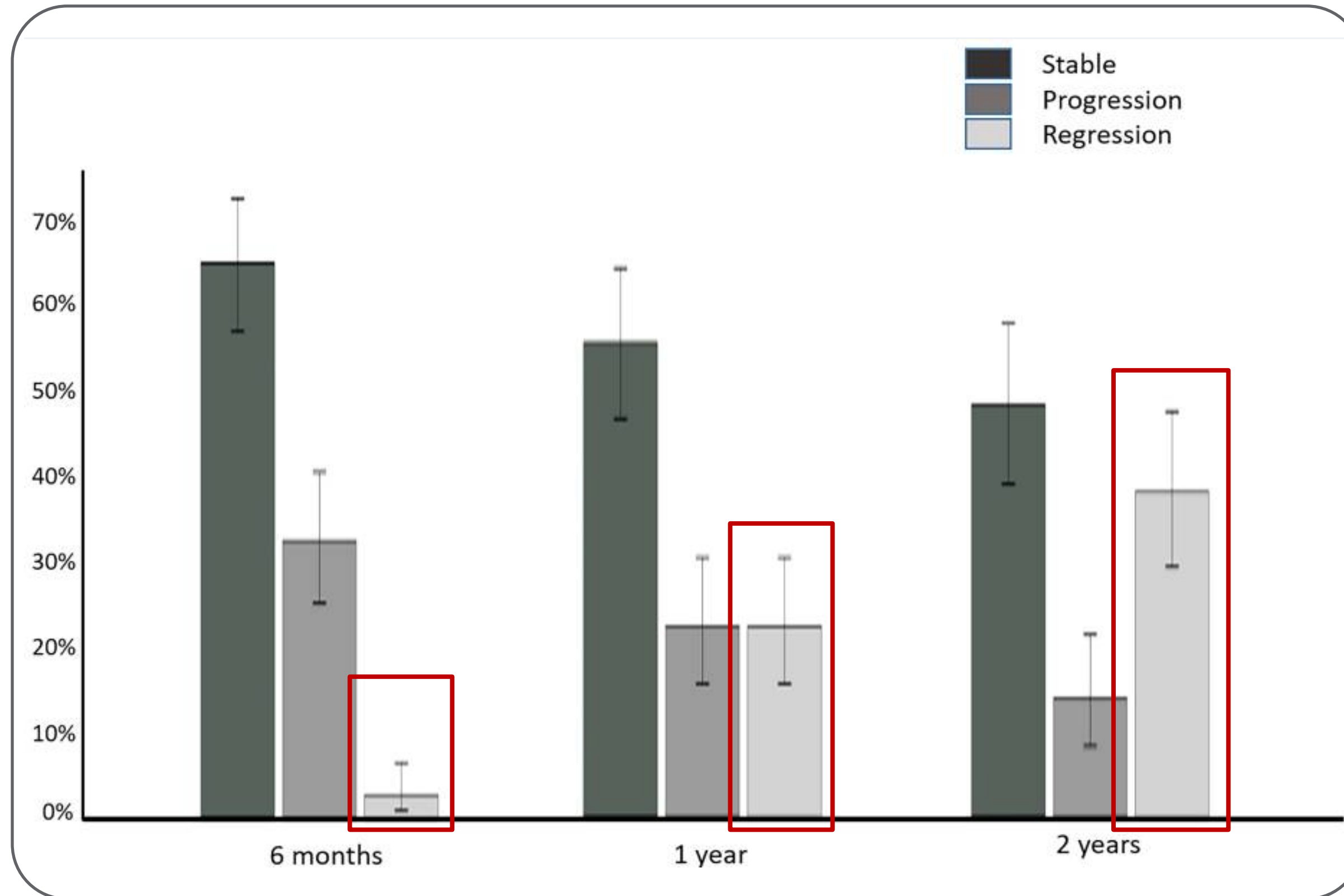
Treatment Of **Systemic** AL Amyloidosis



FLC, free light chain.
Lachmann HJ, et al. *Br J Haematol* 2003;122:78–84;
Pepys MB. *Annu Rev Med* 2006;57:223–241;
Martinez-Naharro A, et al. *Eur Heart J* 2022;43:4722–4735.



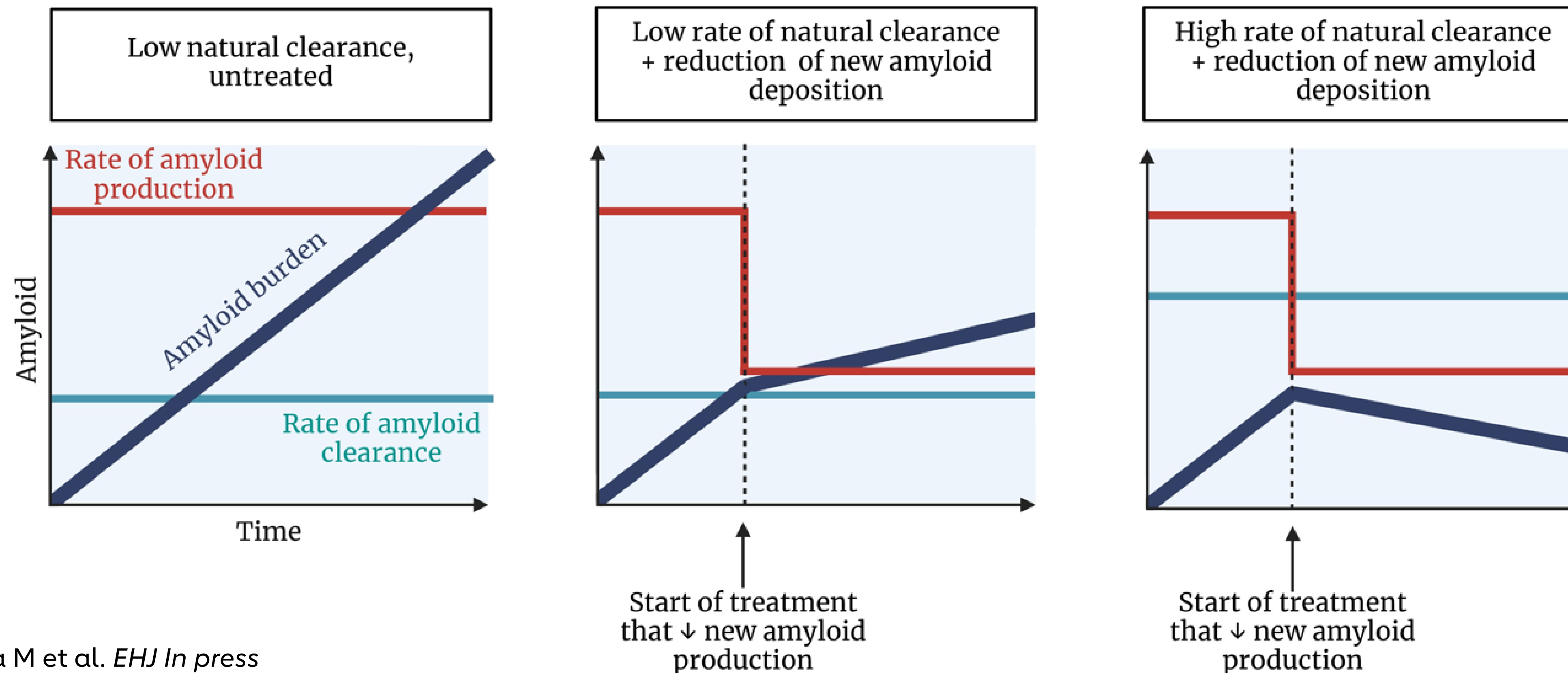
Cardiac Regression in AL Amyloidosis



AL, amyloid light chain; ECV, extracellular volume; LGE, late gadolinium enhancement.
Martinez-Naharro A, et al. *Eur Heart J* 2022;43:4722–4735.

Lessons From Imaging

- Unequivocal association between quantity of amyloid and organ function and outcome
 - Natural clearance of amyloid *in vivo* is invariably slow
- Clearance of amyloid occurs at different rates in different organs



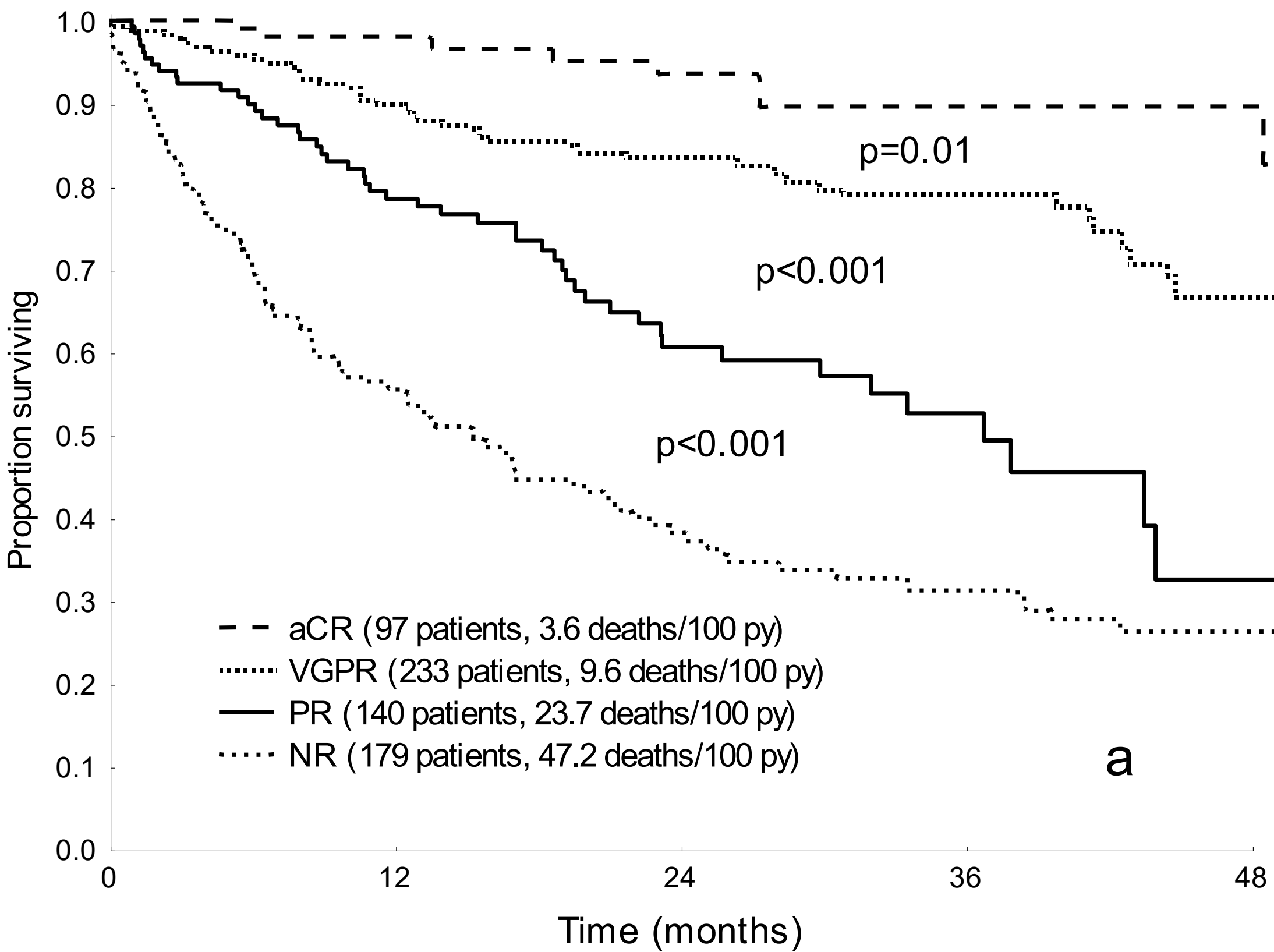
Importance Of Magnitude Of Knockdown Of Fibril Precursor Protein In Systemic Amyloidosis

AA Amyloidosis¹

Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*		
SAA Octile (mg/liter)	Relative Risk (95% CI)	P Value
<4	1.0	
≥4 to <9	3.9 (1.5–10.4)	0.007
≥9 to <16.7	5.1 (2.7–9.4)	0.003
≥16.7 to <28	7.0 (3.7–13.4)	0.07
≥28 to <45.6	9.1 (4.8–17.2)	0.008
≥45.6 to <87	12.1 (6.9–21.4)	<0.001
≥87 to <155	17.0 (8.6–33.8)	<0.001
≥155	17.7 (8.7–36.0)	<0.001

* The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.

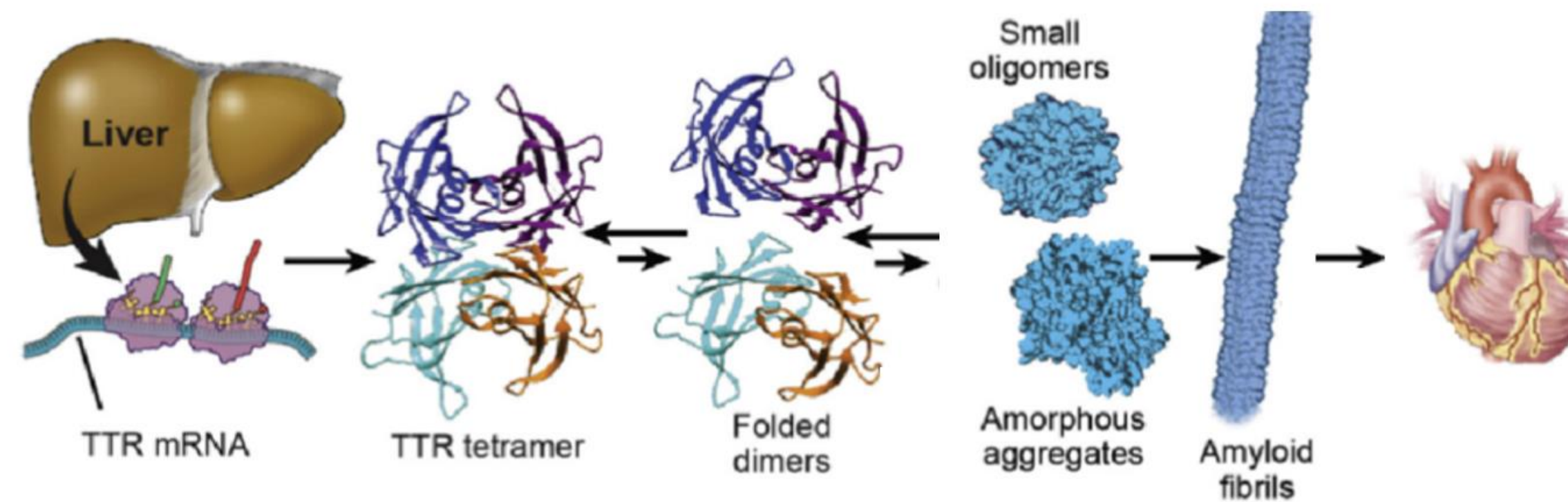
AL Amyloidosis²



aCR, amyloid complete response; NR, no response; PR, partial response; SAA, serum amyloid A protein; VGPR, very good partial response.
1. Lachmann HJ, et al. *N Engl J Med* 2007;356:2361–2371; 2. Palladini G, et al *J Clin Oncol* 2012;30:4541–4549.

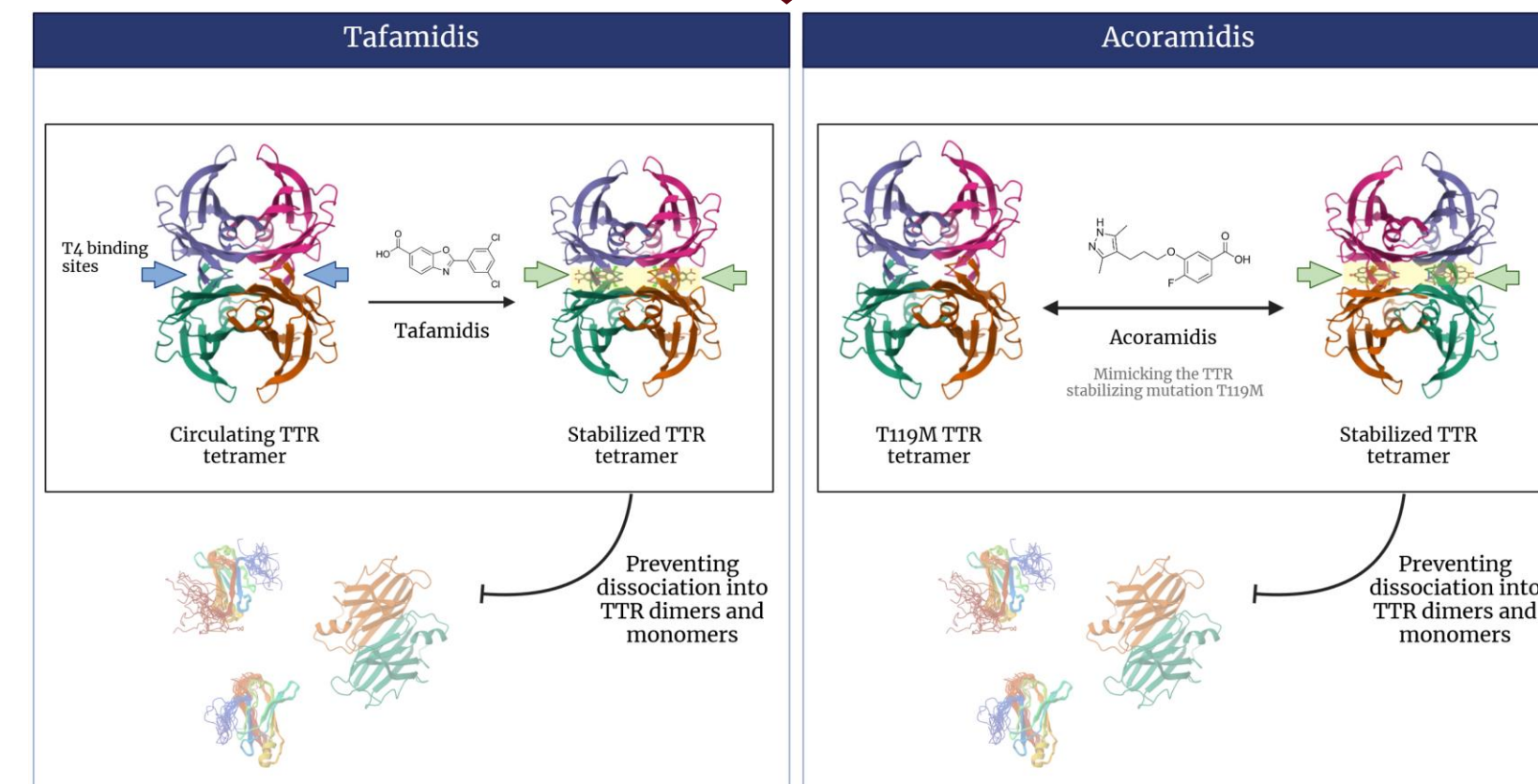
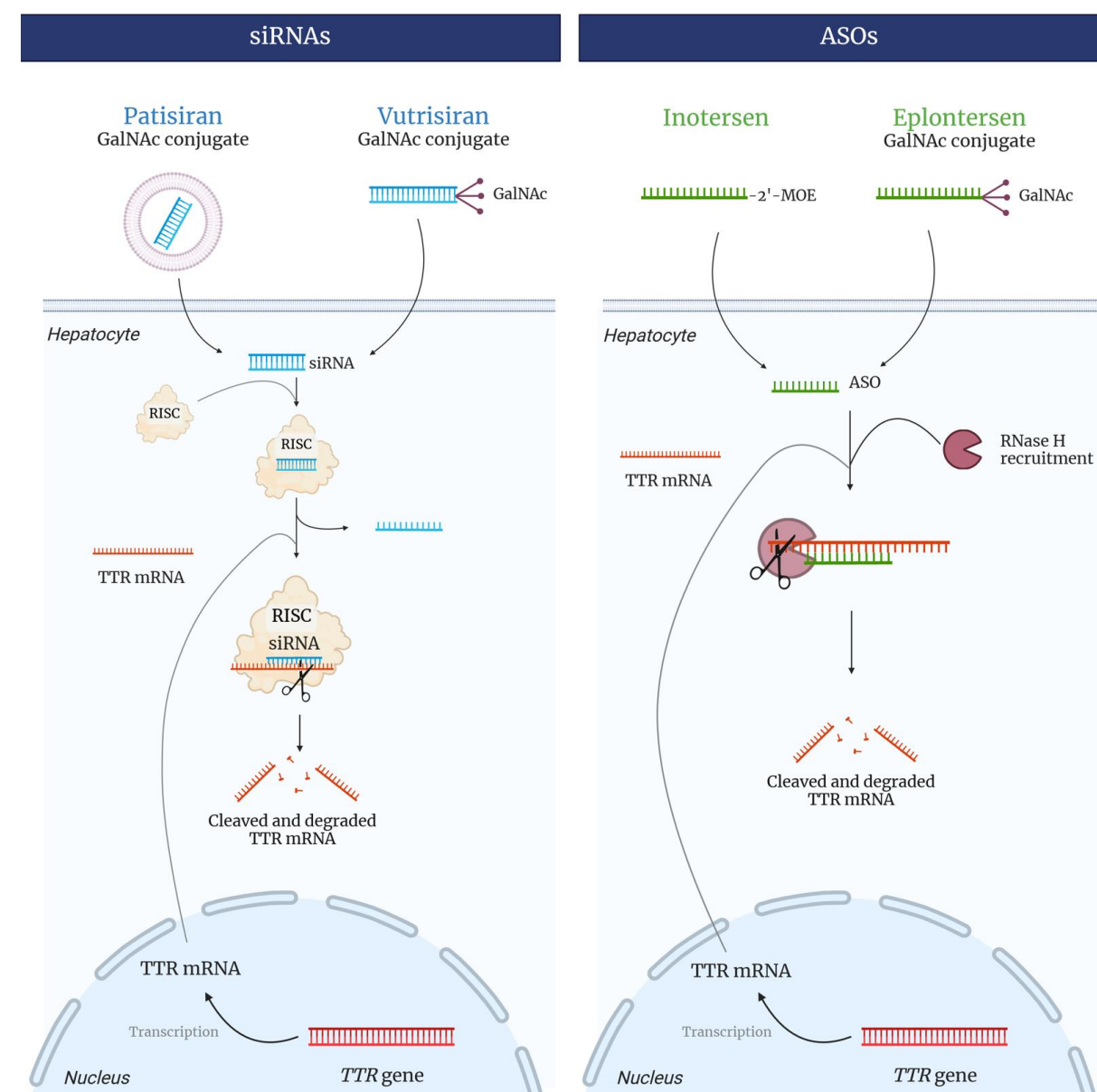


Treatment Of ATTR Amyloidosis: Silencers & Stabilizers

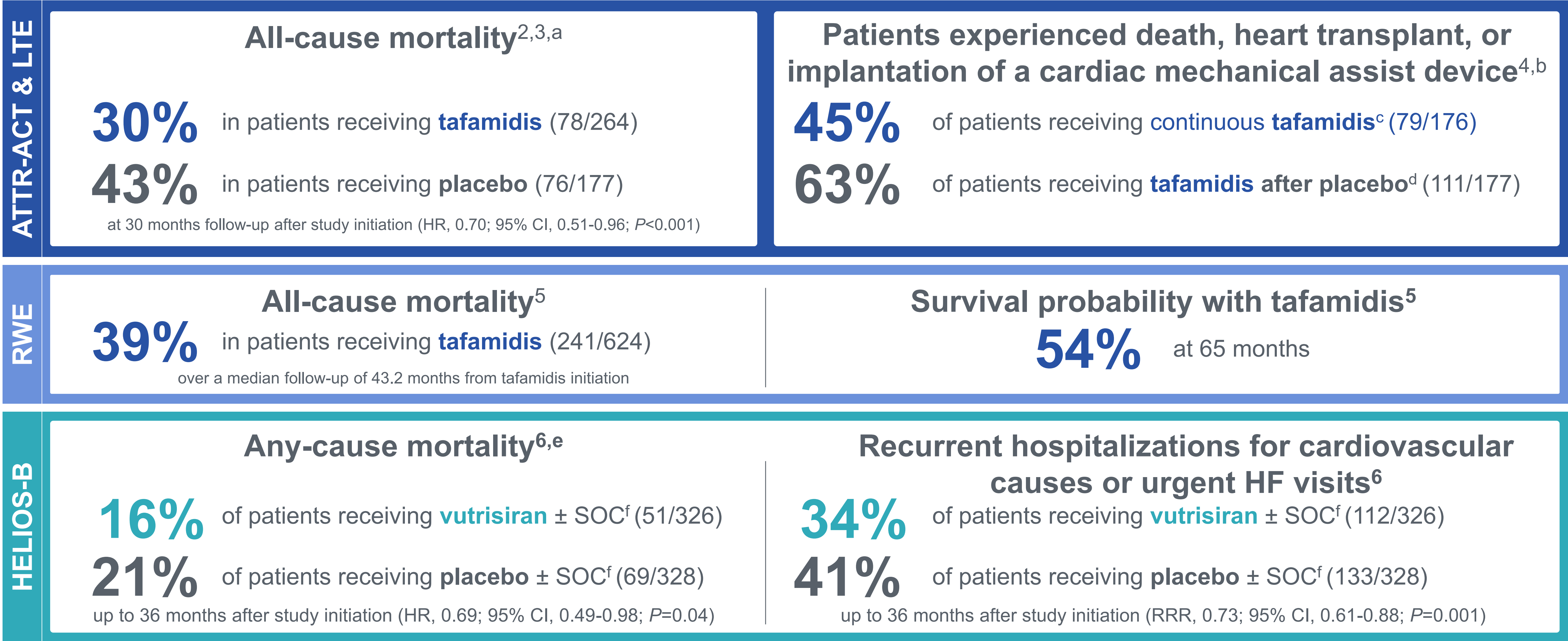


Reduction in TTR synthesis

TTR stabilization



Some patients with ATTR-CM do not respond to SOC treatment and continue to have an elevated risk for disease progression and mortality¹



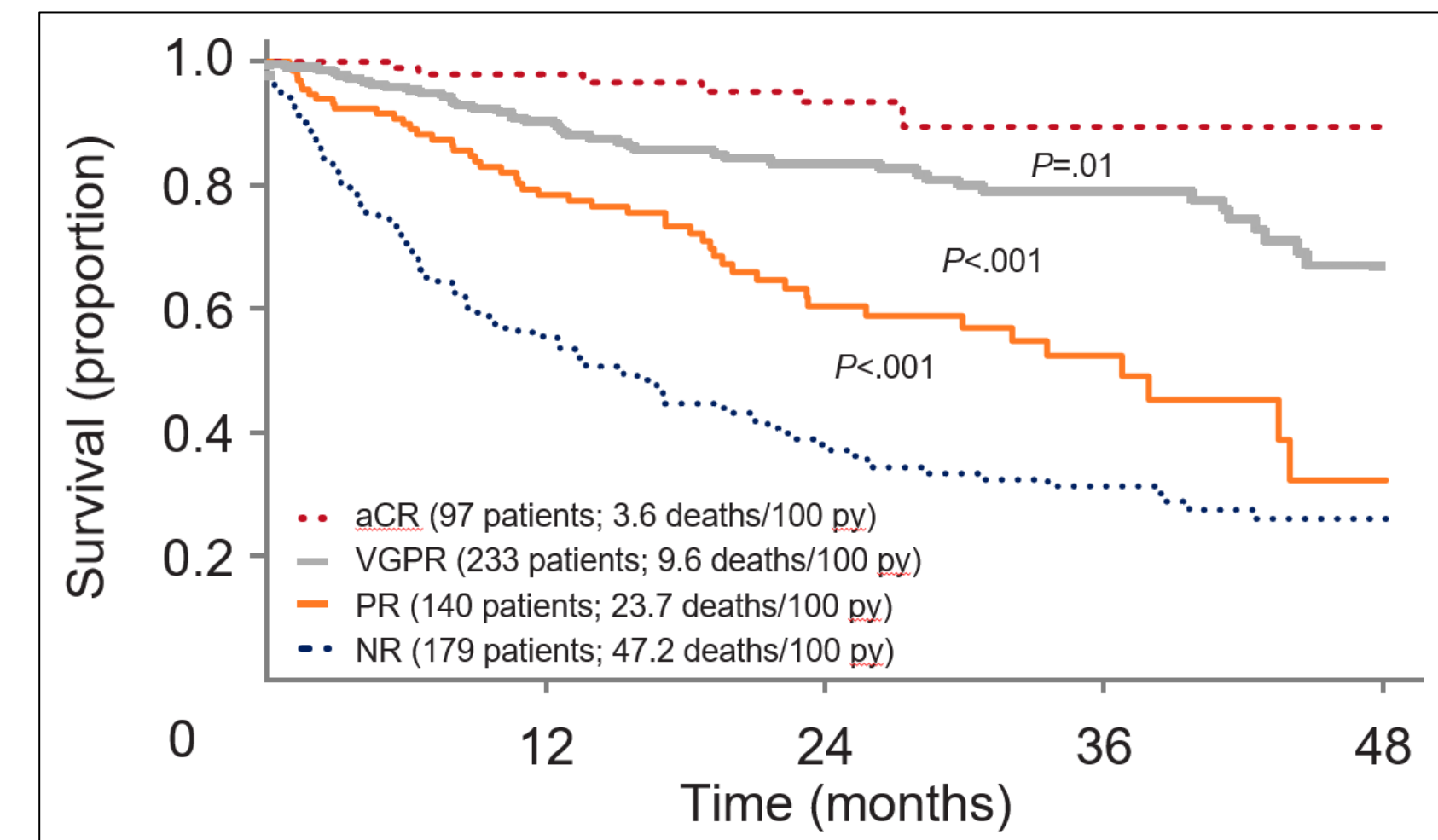
^aPatients who received either 80 mg or 20 mg tafamidis once daily during the study period. ^bPatients who completed 30 months of treatment in ATTR-ACT could enroll in the LTE. Patients who received tafamidis in ATTR-ACT continued at the same dose; patients who received placebo were randomized 2:1 to tafamidis 80 mg or 20 mg. ^cMedian follow-up of 58.5 months. ^dMedian follow-up of 57.1 months. ^eHeart transplantation and implantation of an LVAD were treated as deaths; 3 patients in the vutrisiran group and 4 in the placebo group had a heart transplantation. No patients had implantation of an LVAD. ^fSOC was tafamidis. ATTR-CM, ATTR amyloidosis with cardiomyopathy; HF, heart failure; HR, hazard ratio; LTE, long-term extension; LVAD, left ventricular assist device; RRR, relative risk ratio; RWE, real-world evidence; SOC, standard of care. 1. Kittleson MM, et al. *J Am Coll Cardiol.* 2023;81(11):1076-1126. 2. Vyndaqel (tafamidis). Prescribing information. Pfizer Inc; 2021. 3. Maurer MS, et al. *N Engl J Med.* 2018;379(11):1007-1016. 4. Elliott P, et al. *Circ Heart Fail.* 2022;15(1):e008193. 5. Masri A, et al. *JACC CardioOncol.* 2025;7(3):282-293. 6. Fontana M, et al. *N Engl J Med.* 2025;392(1):33-44.



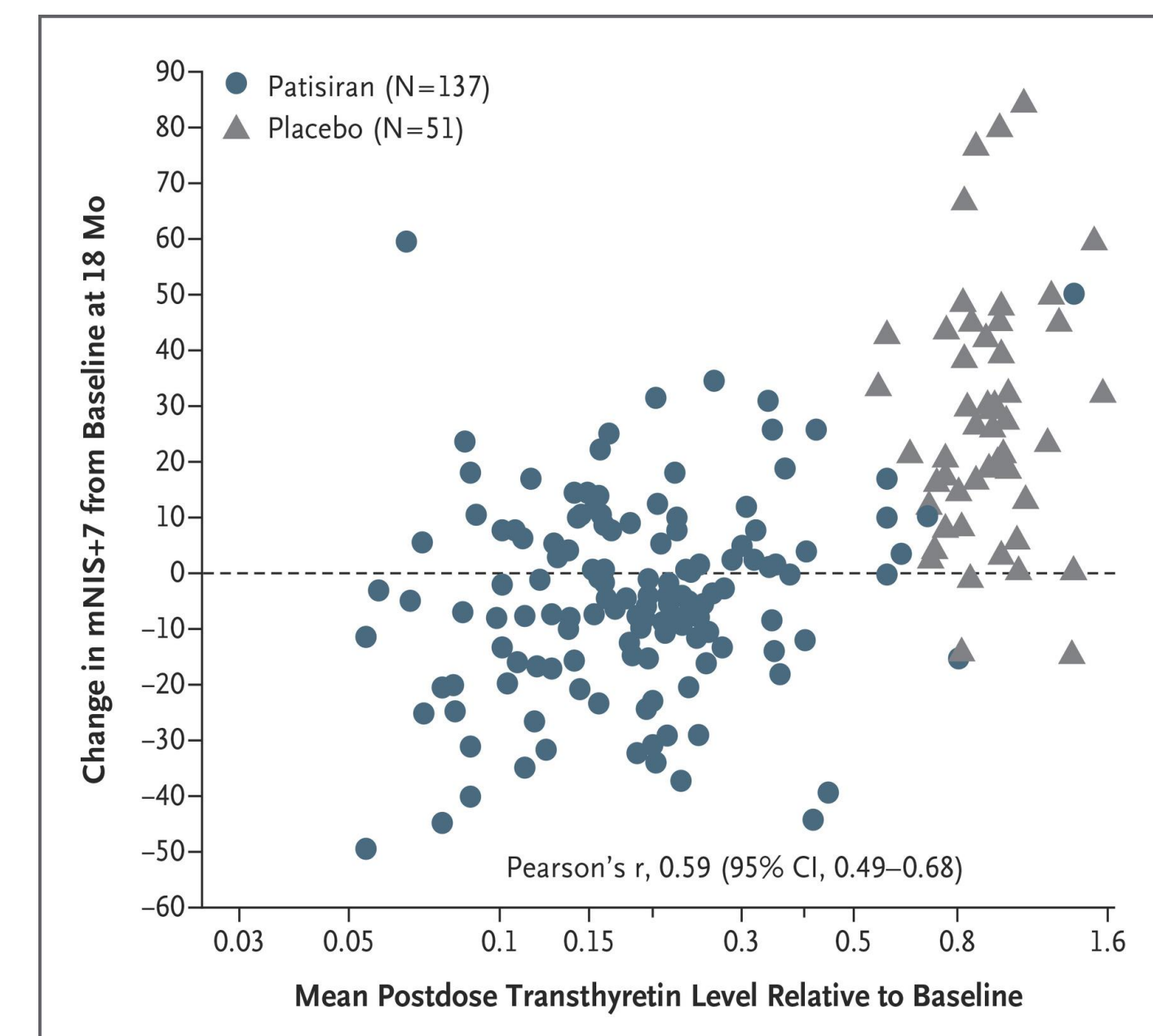
Reduction In New Amyloid Formation And Outcomes

- Achieving the lowest possible level of amyloid precursor protein is likely to be important to maximally impact disease progression in ATTR-CM
- Greater suppression in the amyloid precursor protein, in amyloid A protein (AA) and immunoglobulin light chain amyloidosis, is associated with better outcomes²⁻⁴
- Deeper reductions in TTR levels have been correlated with increased clinical benefit in patients with ATTRv-PN⁵

Survival Based on Hematologic Response in AL Amyloidosis⁴



Correlation of Reduction in TTR Levels With Change in mNIS+7 From Baseline to 18 Months⁵



aCR, amyloid complete response; AL, immunoglobulin light chain; CM, cardiomyopathy; CV, cardiovascular; mNIS, modified Neuropathy Impairment Score; NR, no response;

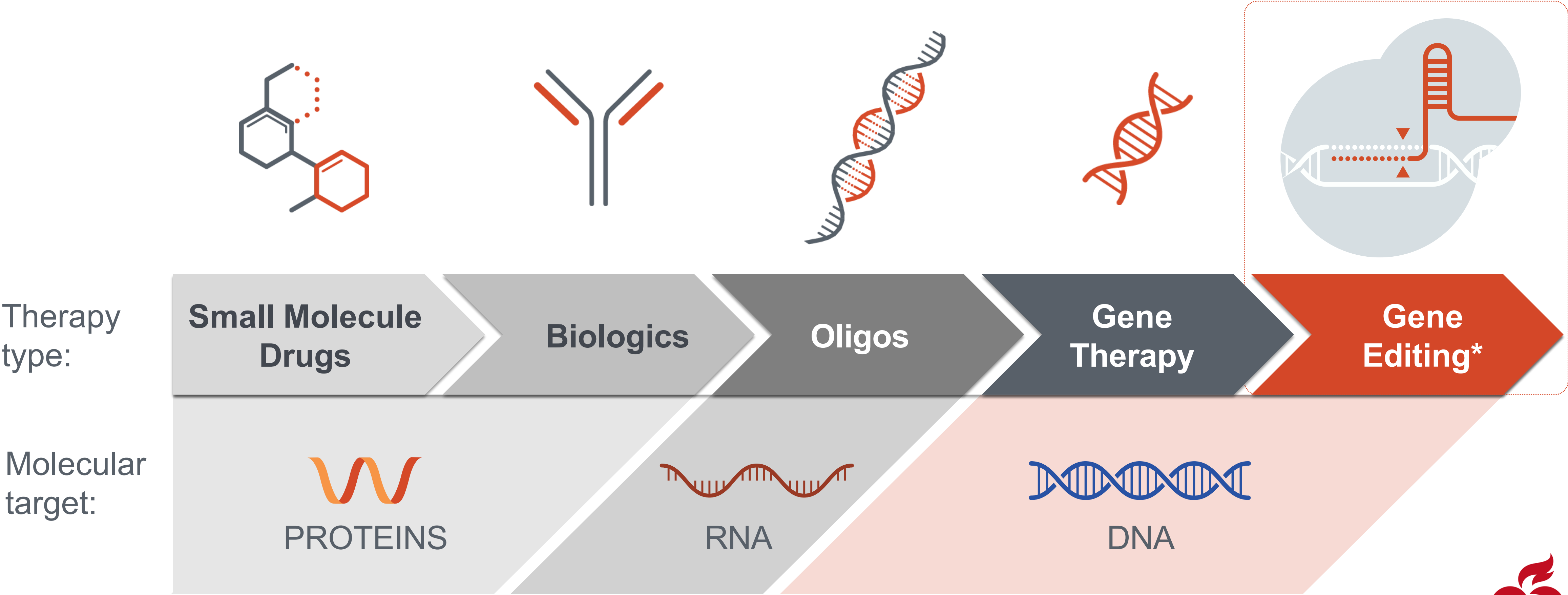
PR, partial response; PN, polyneuropathy; TTR, transthyretin; VGPR, very good partial response.

1. Fontana M, et al. *N Engl J Med*. 2024; DOI: 10.1056/NEJMoa2409134. 2. Gillmore JD, et al. *Lancet*. 2001;358(9275):24-29. 3. Lachmann HJ, et al. *Br J Haematol*. 2003;122(1):78-84. 4. Palladini G, et al. *J Clin Oncol*. 2012;30(36):4541-4549. 5. Adams D, et al. *N Engl J Med*. 2018;379(1):11-21.

Therapeutic and Investigational Strategies to Treat Life-Threatening Diseases Have Advanced Over Time¹⁻⁴

Therapeutic Innovation Over Time

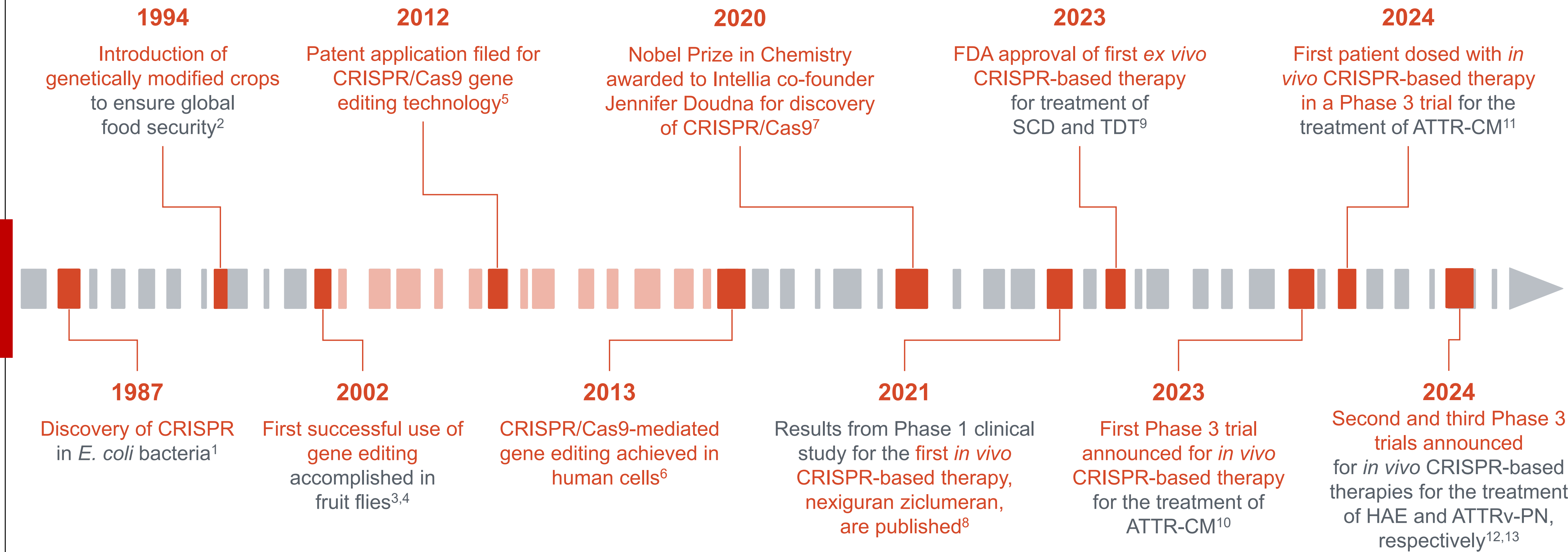
Past → Present



*Under investigation; not yet approved by any Health Authority. Oligo, oligonucleotide.
1. Stern LK, Patel J. *Methodist Debaque Cardiovasc J.* 2022;18(2):59-72. 2. Gertz MA. *Am J Manag Care.* 2017;23(7 suppl):S107-S112. 3. Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150.e3.
4. Smith TD, Riedl MA. *Ann Allergy Asthma Immunol.* 2024;S1081-1206(24)00275-8.



The Extensive History of Genomic Medicine Has Led to the First In Vivo Late-Stage Clinical Trials of a CRISPR-Based Therapy¹⁻¹³



ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; HAE, hereditary angioedema; FDA, US Food and Drug Administration; SCD, sickle cell disease; TDT, transfusion-dependent β -thalassemia.

1. Gostimskaya I. *Biochemistry (Mosc)*. 2022;87(8):777-788. 2. Ahmad A, et al. *Front Plant Sci*. 2023;14:1232938. 3. Bibikova M, et al. *Genetics*. 2002;161(3):1169-1175. 4. Carroll D. *Gene and Genome Editing*. 2021;1:100002. doi:10.1016/j.ggedit.2021.100002 5. Press release. Intellia Therapeutics. March 4, 2022. Accessed September 6, 2024. <https://ir.intelliatax.com/news-releases/news-release-details/intellia-therapeutics-statement-recent-us-patent-and-trademark-0> 6. Jinek M, et al. *Elife*. 2013;2:e00471. 7. Nobel Prize in Chemistry 2020. October 7, 2020. Accessed September 6, 2024. <https://www.nobelprize.org/uploads/2020/10/press-chemistryprize2020.pdf> 8. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 9. Casgevy. Prescribing information. Vertex Pharmaceuticals Inc; 2023. Accessed September 6, 2024. <https://www.fda.gov/media/174615/download> 10. Press release. Intellia Therapeutics. October 18, 2023. Accessed September 6, 2024. <https://ir.intelliatax.com/news-releases/news-release-details/intellia-therapeutics-announces-fda-clearance-investigational-0> 11. Press release. Intellia Therapeutics. March 18, 2024. Accessed September 6, 2024. <https://ir.intelliatax.com/news-releases/news-release-details/intellia-therapeutics-announces-first-patient-dosed-phase-3> 12. Press release. Intellia Therapeutics. October 7, 2024. <https://ir.intelliatax.com/news-releases/news-release-details/intellia-therapeutics-announces-initiation-haelo-phase-3-study> 13. Press release. Intellia Therapeutics. November 7, 2024. <https://ir.intelliatax.com/news-releases/news-release-details/intellia-therapeutics-announces-third-quarter-2024-financial>



CRISPR/Cas9 Technology Is Being Explored for Treatment Across a Wide Range of Disease States¹⁻¹²

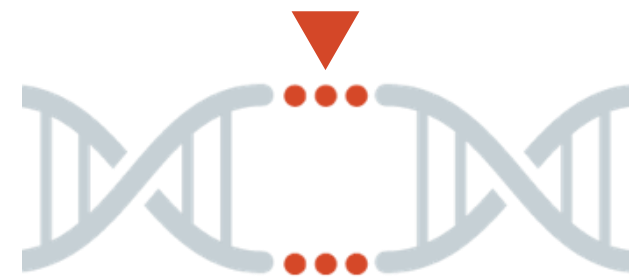
DISEASE AREA	COMPANY (PRODUCT)	APPROACH	DELIVERY SYSTEM	Early-Stage Clinical Trial	Late-Stage Clinical Trial	FDA-Approved
Sickle cell disease ¹	Vertex (CASGEVY®)	Ex vivo	Autologous HSCs			
Transfusion-dependent β-thalassemia ¹	Vertex (CASGEVY®)	Ex vivo	Autologous HSCs			
Transthyretin amyloidosis ²	Intellia (nexiguran ziclumeran)	In vivo	Proprietary LNP delivery system			
Hereditary angioedema ^{3,4}	Intellia (NTLA-2002)	In vivo	Proprietary LNP delivery system			
Cardiovascular disease ⁵⁻⁷	CRISPR Therapeutics (CTX310; CTX320) Verve Therapeutics (VERVE-101; VERVE-102)	In vivo	LNP			
Type 1 diabetes ⁸	CRISPR Therapeutics (CTX211)	Ex vivo	Allogeneic PECs			
Cancers ⁹⁻¹²	Beam Therapeutics (BEAM-201) Caribou Therapeutics (CB-012) CRISPR Therapeutics (CTX112; CTX131)	Ex vivo*	Allogeneic CAR T cells			

*CAR T-cell therapy is developed using CRISPR/Cas9 technology.⁹⁻¹²
CAR, chimeric antigen receptor; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; FDA, US Food and Drug Administration; HSC, hematopoietic stem cell; LNP, lipid nanoparticle; PEC, pancreatic endoderm cell.

1. Casgevy. Prescribing information. Vertex Pharmaceuticals Inc; 2023. Accessed October 15, 2024. https://pi.vrtx.com/files/uspi_exagamglogene_autotemcel.pdf 2. ClinicalTrials.gov identifier: NCT04601051. Updated September 8, 2023. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT04601051> 3. ClinicalTrials.gov identifier: NCT05120830. Updated July 11, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT05120830> 4. Press release. Intellia Therapeutics. October 7, 2024. Accessed October 7, 2024. <https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-initiation-haelo-phase-3-study> 5. Press release. CRISPR Therapeutics. Q4 2023. Accessed September 9, 2024. <https://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-provides-business-update-and-reports-third-4> 6. CRISPR Therapeutics. Pipeline. Accessed September 9, 2024. <https://crisprtx.com/pipeline> 7. Verve Therapeutics. Our PCSK9 Programs. Accessed September 9, 2024. <https://www.vervetx.com/our-programs/verve-101-102> 8. ClinicalTrials.gov identifier: NCT05565248. Updated May 23, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT05565248> 9. ClinicalTrials.gov identifier: NCT05885464. Updated June 3, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT05885464> 10. ClinicalTrials.gov identifier: NCT05643742. Updated August 28, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT05643742> 11. ClinicalTrials.gov identifier: NCT05795595 Updated June 25, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT05795595> 12. ClinicalTrials.gov identifier: NCT06128044. Updated April 26, 2024. Accessed September 9, 2024. <https://clinicaltrials.gov/study/NCT06128044>



CRISPR-Based Therapies Have the Potential to Change How Diseases Are Treated by Addressing the Underlying Mechanisms¹⁻³



Address the underlying mechanism of a variety of human diseases by **making precise edits** to certain genes that produce problematic proteins^{1,2}



Adaptable for the treatment of a **wide range of diseases**¹⁻³



Provide a single-dose treatment with the potential to have **permanent effects** on disease activity^{1,2,4}



Reduce healthcare and treatment burden over a patient's lifetime⁴

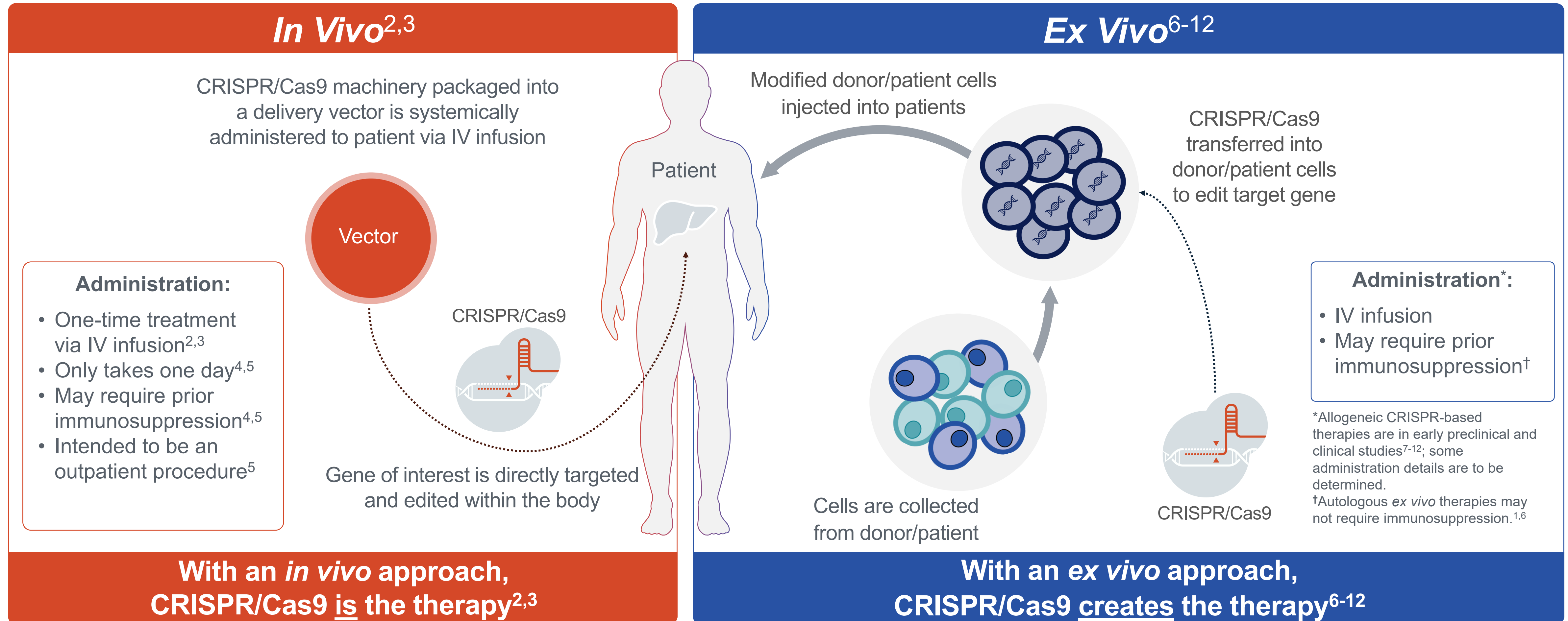
CRISPR, clustered regularly interspaced short palindromic repeats.

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 3. Abdelnour SA, et al. *Front Cell Dev Biol*. 2021;9:699597. 4. Intellia Corporate Overview. Intellia Therapeutics. February 2024. Accessed May 7, 2024. <https://ir.intelliatx.com/static-files/a57908a6-aaca-404d-9072-32471cd3d41e>



CRISPR/Cas9 Gene Editing Can Be Achieved Either *In Vivo* or *Ex Vivo*

The numerous uses of CRISPR/Cas9 technology allow for an expanded treatment toolbox¹

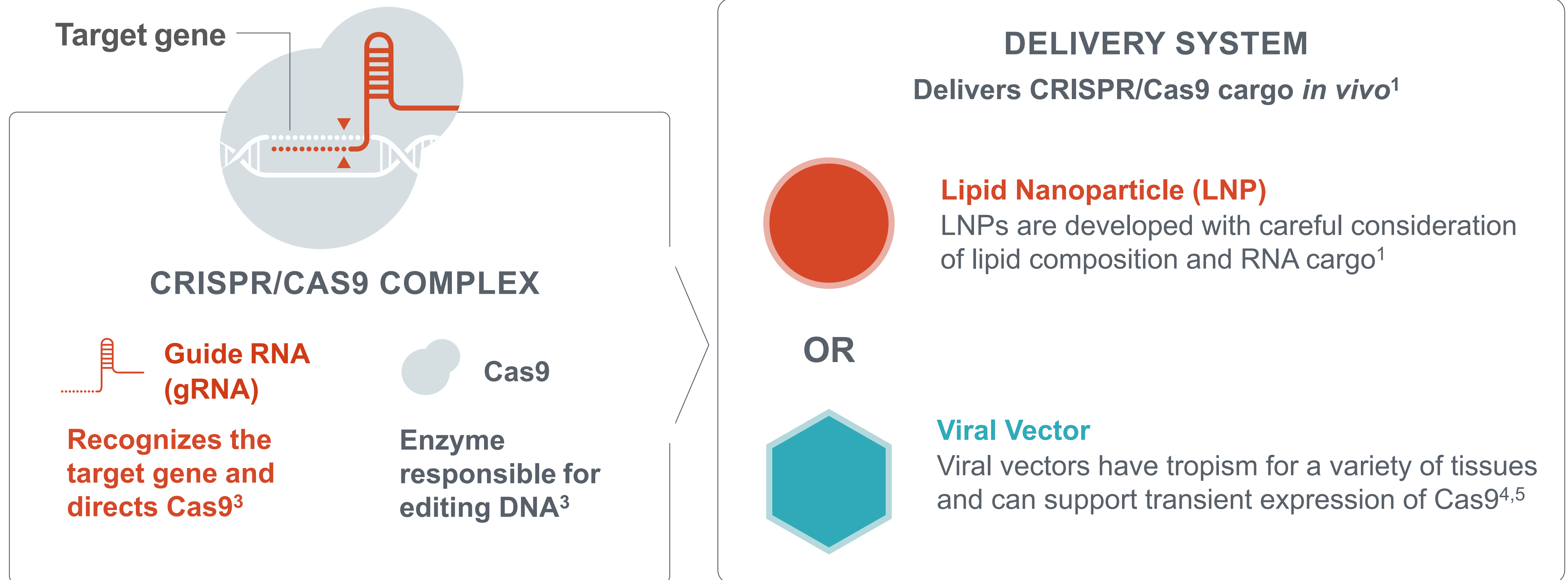


Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; IV, intravenous.

1. Li H, et al. *Signal Transduct Target Ther*. 2020;5(1):1-23. 2. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 3. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 4. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502 (Protocol). 5. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441 (Protocol.). 6. Casgevy. Prescribing information. Vertex Pharmaceuticals Inc; 2023. Accessed October 15, 2024. https://pi.vrtx.com/files/uspi_exagamglogene_autotemcel.pdf 7. ClinicalTrials.gov identifier: NCT05565248 Updated May 23, 2024. Accessed May 7, 2024. <https://clinicaltrials.gov/study/NCT05565248> 8. ClinicalTrials.gov identifier: NCT05885464. Updated June 3, 2024. Accessed June 11, 2024. <https://clinicaltrials.gov/study/NCT05885464> 9. ClinicalTrials.gov identifier: NCT05643742. Updated August 15, 2023. Accessed June 11, 2024. <https://clinicaltrials.gov/study/NCT05643742> 10. ClinicalTrials.gov identifier: NCT05795595. Updated April 2024. Accessed June 11, 2024. <https://clinicaltrials.gov/study/NCT05795595> 11. ClinicalTrials.gov identifier: NCT06128044. Updated April 26, 2024. Accessed June 11, 2024. <https://clinicaltrials.gov/study/NCT06128044> 12. Martínez Bedoya D, et al. *Front Immunol*. 2021;12:640082.



The Components of Investigational CRISPR-Based Therapies Are Designed for Transient Delivery to Target Cells^{1,2}



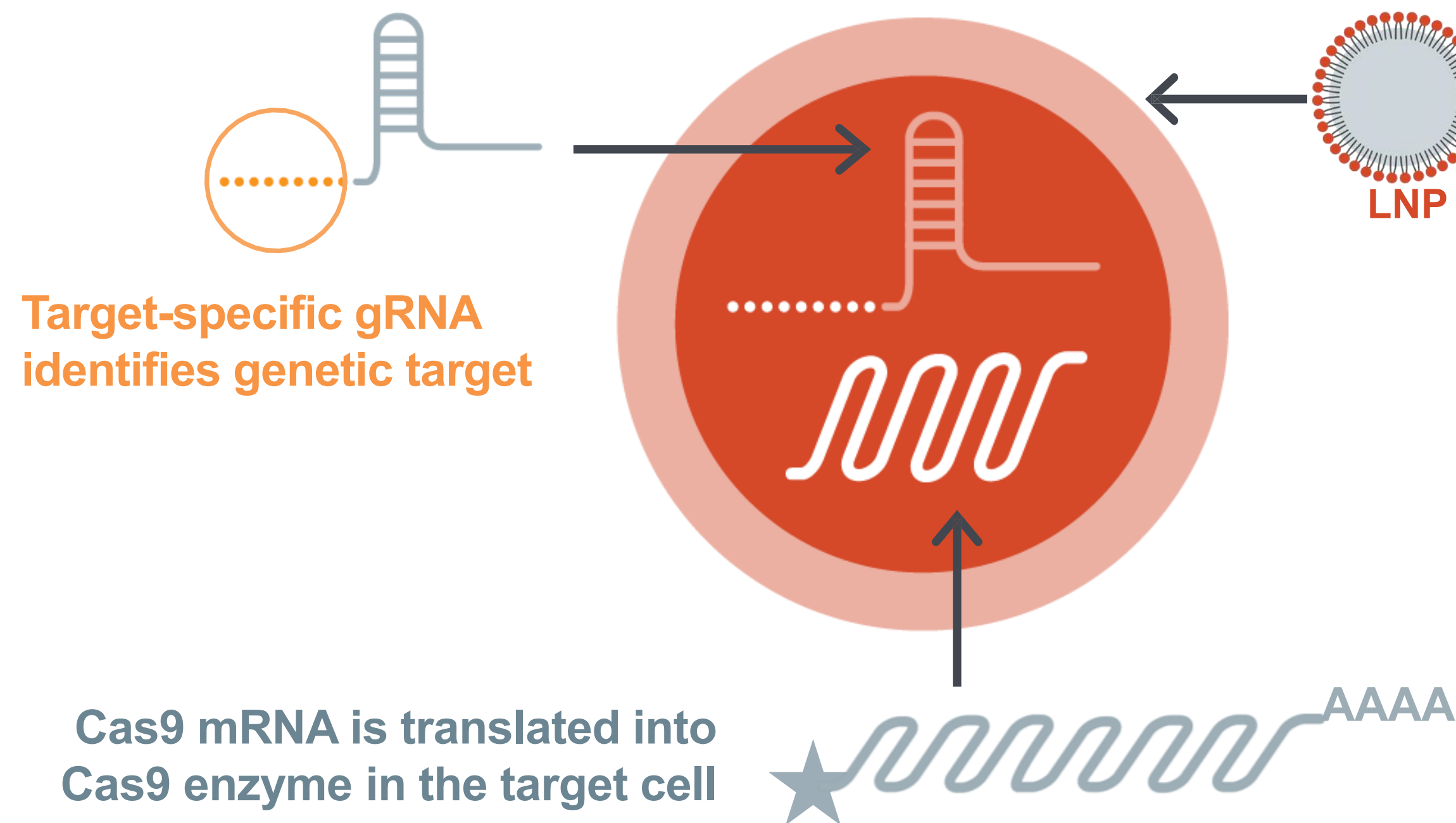
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats.

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Wood K, et al. Poster presented at: 2nd European Congress for ATTR Amyloidosis; September 1-3, 2019; Berlin, Germany.
3. Asmamaw M, Zawdie B. *Biologics*. 2021;15:353-361. 4. González Castro N, et al. *Int J Mol Sci*. 2021;22(19):10355. 5. Lee CS, et al. *Genes Dis*. 2017;4(2):43-63.



Intellia Developed a Proprietary LNP Delivery System That Enables Efficient Delivery of the CRISPR/Cas9 System to the Specific Cells Underlying a Disease^{1,2}

LNP Delivery System^{1,2}



Unique attributes of the LNP delivery system

- Clinically proven delivery to liver via active endocytosis through the LDL receptor¹
- Transient expression³
- Low immunogenicity (non-viral)⁴
- Well-tolerated^{5,6}
- Potentially tunable to other tissues⁷

Intellia's proprietary LNP delivery system was designed to help maximize the efficacy of CRISPR-mediated gene editing while minimizing systemic toxic effects¹

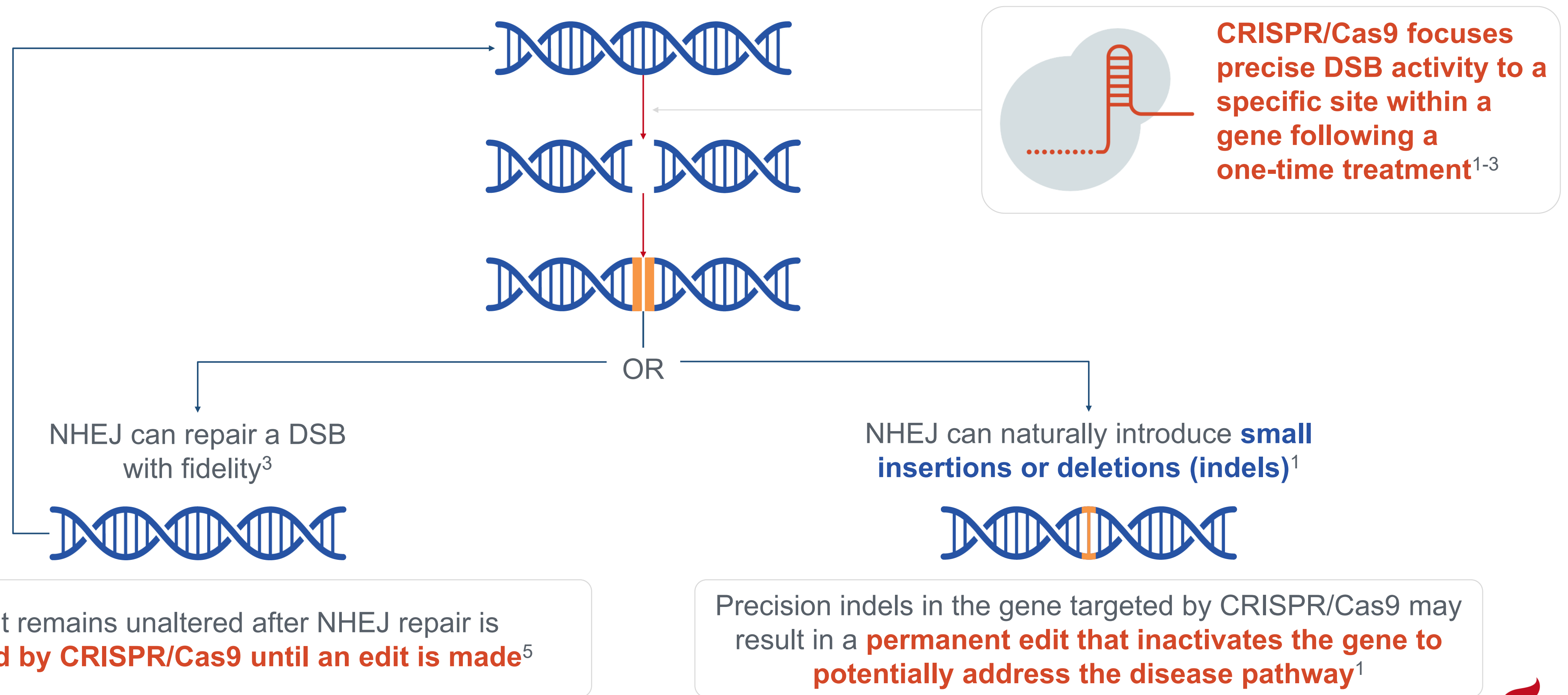
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; LDL, low-density lipoprotein receptor; mRNA, messenger RNA.

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 3. Wood K, et al. Poster presented at: 2nd European Congress for ATTR Amyloidosis; September 1-3, 2019; Berlin, Germany. 4. Kenjo E, et al. *Nat Commun*. 2021;12(1):7101. 5. Gillmore JD, et al. Paper presented at: 4th International ATTR Amyloidosis Meeting for Patients and Doctors; November 2-3, 2023; Madrid, Spain. 6. Longhurst HJ, et al. Paper presented at: European Academy of Allergy & Clinical Immunology Congress 2024; May 31-June 3, 2024; Valencia, Spain. 7. Swetha K, et al. *Vaccines (Basel)*. 2023;11(3):658.



CRISPR-Based Therapies Take Advantage of the Cell's Natural Repair Process to Genetically Address the Underlying Cause of a Disease¹⁻³

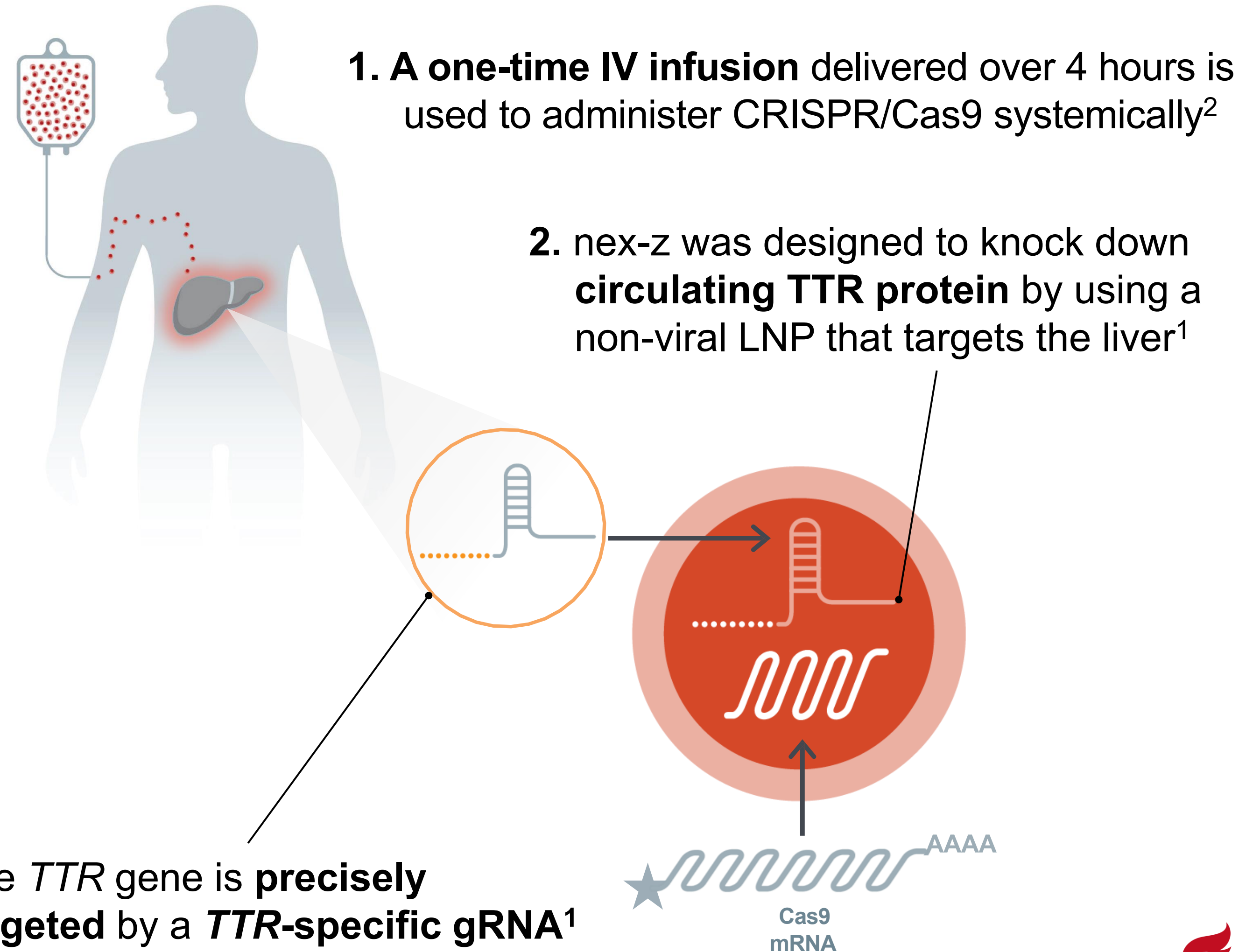
Spontaneous double-stranded breaks (DSBs) can randomly occur in mammalian cells and are resolved naturally by a process known as non-homologous end joining (NHEJ)⁴



Nexiguran ziclumeran (nex-z), Targets *TTR* in the Liver to Reduce Serum TTR Levels With a One-Time IV Infusion¹

ATTR amyloidosis¹:

- **Monogenic disease** caused by misfolded TTR
- **>99% of circulating TTR is synthesized by the liver**—a single location targetable by LNP
- An ideal application to investigate CRISPR/Cas9 gene editing therapy



ATTR, transthyretin amyloidosis; gRNA, guide RNA; IV, intravenous; LNP, lipid nanoparticle; mRNA, messenger RNA; TTR, transthyretin.

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Intellia Therapeutics. Data on file.

This slide is for Reactive Use Only. nex-z is an investigational product that has not been approved by FDA or received marketing authorization by any Health Authority.



Rigorous Research has been conducted to Identify gRNA Sequences With High Specificity for Genes of Interest^{1,2*}

Key Attributes for Identifying Therapeutic gRNAs³



High Precision:

- Edits genome at intended target site
- Genomic edit results in intended therapeutic outcome
- Target site in gene is conserved across patient population
- Has high potency



High Accuracy:

- Avoids validated unintended edits
- Avoids DNA structural variants associated with toxicity or transformation
- Wide genotoxicity safety window compared with expected therapeutic exposure

Comprehensive gRNA specificity assessment is conducted prior to the development of the CRISPR-based therapy¹⁻³



Discovery of potential off-target edits in the genome

Assess risk of biological impact of gRNA due to inadvertent indel formation at each site³

Functional Region

Risk of impacting genomic function

Sequence Identity

Risk of creating an indel in the DNA

Role in Cell

Risk of impacting target cell function

*Intellia's extensive pre-clinical work supports the initiation of our clinical trials to assess the safety and efficacy in humans.

CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; indel, insertion or deletion.

1. O'Connell DJ. Paper presented at: 24th Annual Meeting of the American Society of Gene and Cell Therapy; May 11-14, 2021 (Virtual). 2. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 3. Intellia Therapeutics. Data on file.



Rigorous Comprehensive, Computational, and Empirical Testing to Help Ensure Precise On-Target Editing^{1,2}

- 1 Identify potential loci for knockout¹
- 2 Characterize gRNA candidates off-target activity across the human genome^{1,*}
- 3 Validate gRNA with high specificity activity to the targeted DNA^{1,2}
nexiguran ziclumeran (nex-z) demonstrated a lack of detectable off-target edits at therapeutically-relevant doses[†]

Clinical trials are planned or underway to establish the safety and efficacy of nex-z administered as a one-time IV infusion in patients with ATTR-CM and ATTR-PN^{3,4}

*Approaches used include Cas-OFFinder, GUIDE-Seq, and SITE-Seq. [†]The study was conducted in primary human hepatocytes.¹

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTR-PN, transthyretin amyloidosis with polyneuropathy; gRNA, guide RNA; IV, intravenous.

1. O'Connell DJ. Paper presented at: 24th Annual Meeting of the American Society of Gene and Cell Therapy; May 10, 2021 (virtual). 2. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502.

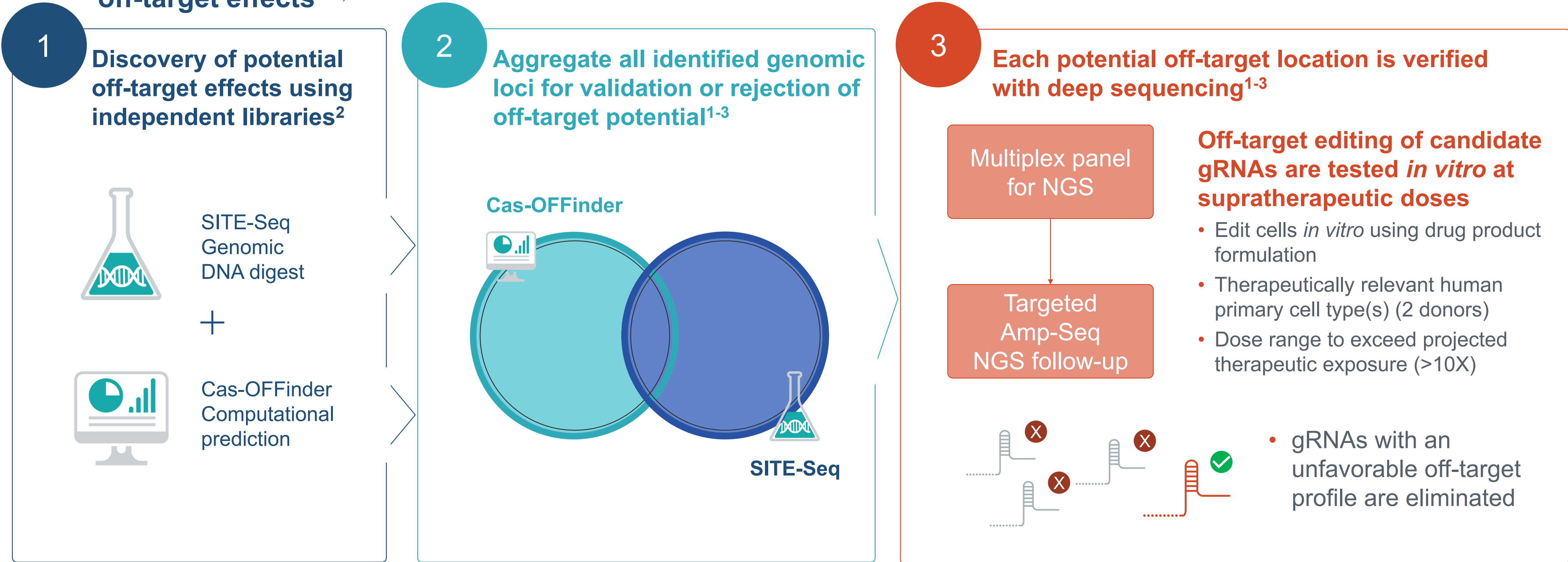
3. ClinicalTrials.gov identifier: NCT06128629. Updated May 2, 2024. Accessed May 7, 2024. <https://clinicaltrials.gov/study/NCT06128629>. 4. ClinicalTrials.gov Identifier: NCT04601051. Updated September 8, 2023. Accessed August 27, 2024. <https://clinicaltrials.gov/study/NCT04601051>

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The Comprehensive Computational and Empirical Testing Help Maximize Precise On-Target Editing of Their **Investigational CRISPR-Based Therapies**¹⁻³

Off-target characterization workflow: Combining NGS with Cas-OFFinder and SITE-Seq libraries helps ensure Intellia's investigational CRISPR-based therapies **target the gene of interest with high specificity while minimizing off-target effects**^{1-3,*}



*The risk of unintended, off-target editing cannot be ruled out. The clinical significance of potential off-target editing is unknown.

CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; NGS, next-generation sequencing.

1. O'Connell DJ. Paper presented at: 24th Annual Meeting of the American Society of Gene and Cell Therapy; May 11-14, 2021 (Virtual). 2. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502.

3. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441.



Results Following a **Single Dose of nex-z** in Preclinical Models¹

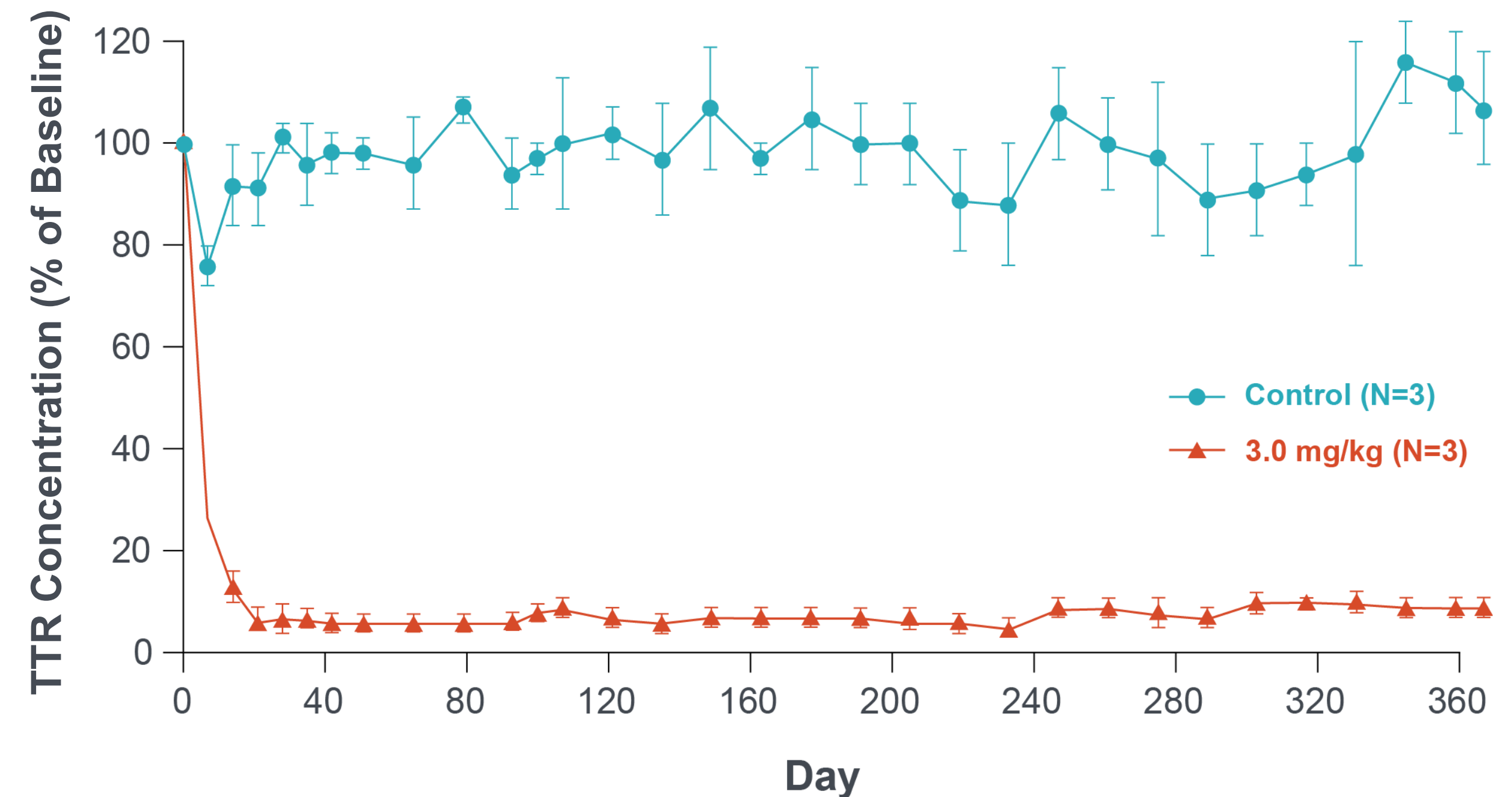
Following treatment with the nonhuman primate surrogate of nex-z in cynomolgus monkeys¹:

73% gene editing across the whole liver

>94% reduction in serum TTR protein sustained for 12 months

0 AEs after a single infusion of the therapy

In vivo pharmacologic properties of the nonhuman primate surrogate of nex-z¹



**nex-z appeared to be cleared from circulation after 5 days.
TTR knockdown was observed over a period of 12 months^{1,2}**

AE, adverse event; nex-z, nexiguran ziclumeran; TTR, transthyretin.

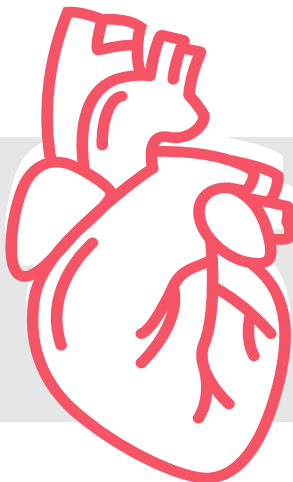
1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Wood K, et al. Poster presented at: 2nd European Congress for ATTR Amyloidosis; September 1-3, 2019; Berlin, Germany.

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Two-Part, Open-Label Study in Adults With ATTR-CM

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I-III



Intervention:
Single dose administered via an IV infusion



PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg NYHA Class I/II (n=3)
- 0.7 mg/kg NYHA Class I-III (n=9)

PART II
Dose Expansion

- 55 mg NYHA Class I-III (n=24)

PRIMARY OBJECTIVES

- Evaluate safety, tolerability, and PD
- Measure serum TTR levels

SECONDARY OBJECTIVES

- Evaluate efficacy on clinical measures of cardiac disease
- Biomarkers of disease progression including NT-proBNP, hs-Troponin T, and 6MWT, cardiopulmonary exercise test, cardiac imaging, and KCCQ score



Demographics and Baseline Characteristics

Characteristic	All patients (N=36)
Age, median (min, max), y	78.0 (46, 90)
Sex, male, n (%)	35 (97)
Black or African descent	8 (22)
White or Caucasian	28 (78)
NT-proBNP, median (min, max), ng/L	2052 (851, 19624)
hs-Troponin T, median (min, max), ng/L	56 (15, 204)
eGFR, median (min, max), mL/min/1.73 m ²	65.1 (32.7, 96.3)
6-Minute Walk Test distance, median (min, max), m	331 (178, 580)
Peak VO ₂ , median (min, max), mL/kg/min	12.7 (7.8, 28.4)
CMR extracellular volume, median (min, max), %	58 (45, 71)

Characteristic	All patients (N=36)
TTR genotype, n (%)	
Wild type	25 (69)
p.V142I ^a	7 (19)
Other mutations	4 (11)
NYHA class, n (%)	
I	3 (8)
II	15 (42)
III	18 (50)
Tafamidis use at baseline, n (%)	0 (0)

Population representative of ATTR-CM, including patients with advanced disease

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.

^aIncludes 2 homozygous patients.

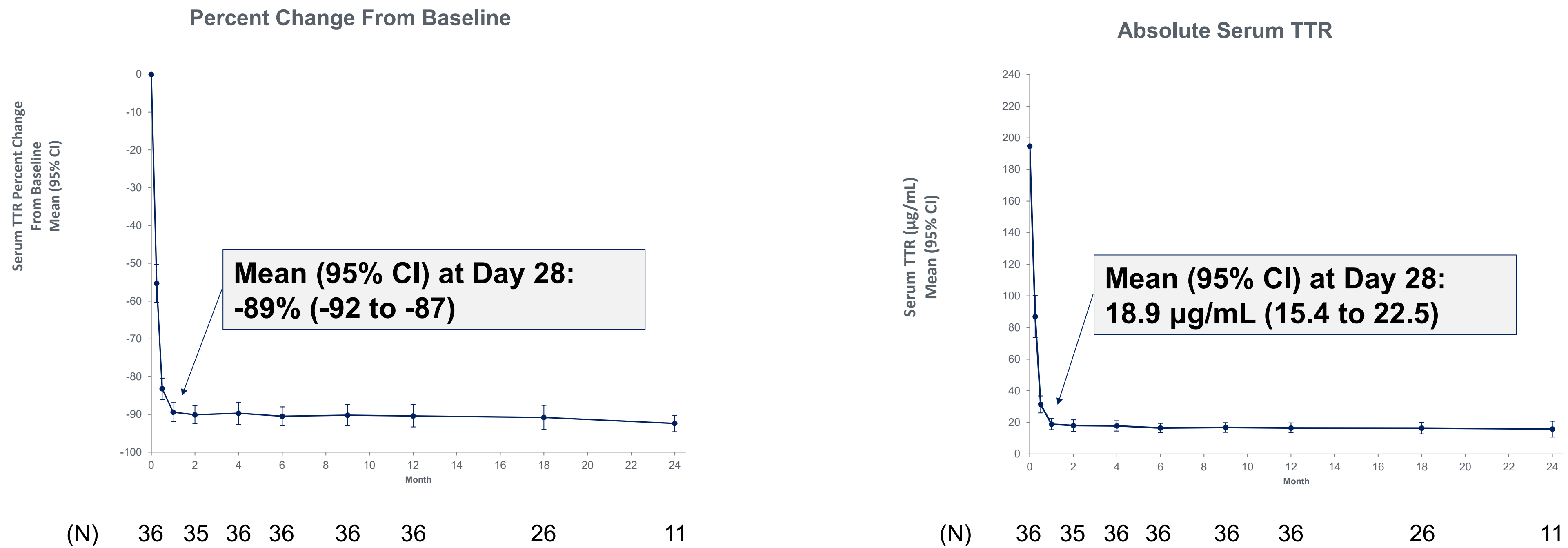
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; VO₂, oxygen consumption.

Fontana M et al. *NEJM* 2024



Nex-z Led to **Deep, Rapid, and Durable Reductions** in Absolute Serum TTR in Every Patient Following a Single Dose

Change in Serum TTR Levels Through Month 24



Similar serum TTR reductions were observed in every patient, regardless of baseline TTR level or genotype. Mean absolute serum levels of 18.9 µg/mL achieved at Day 28, with levels remaining virtually unchanged through 24 months.

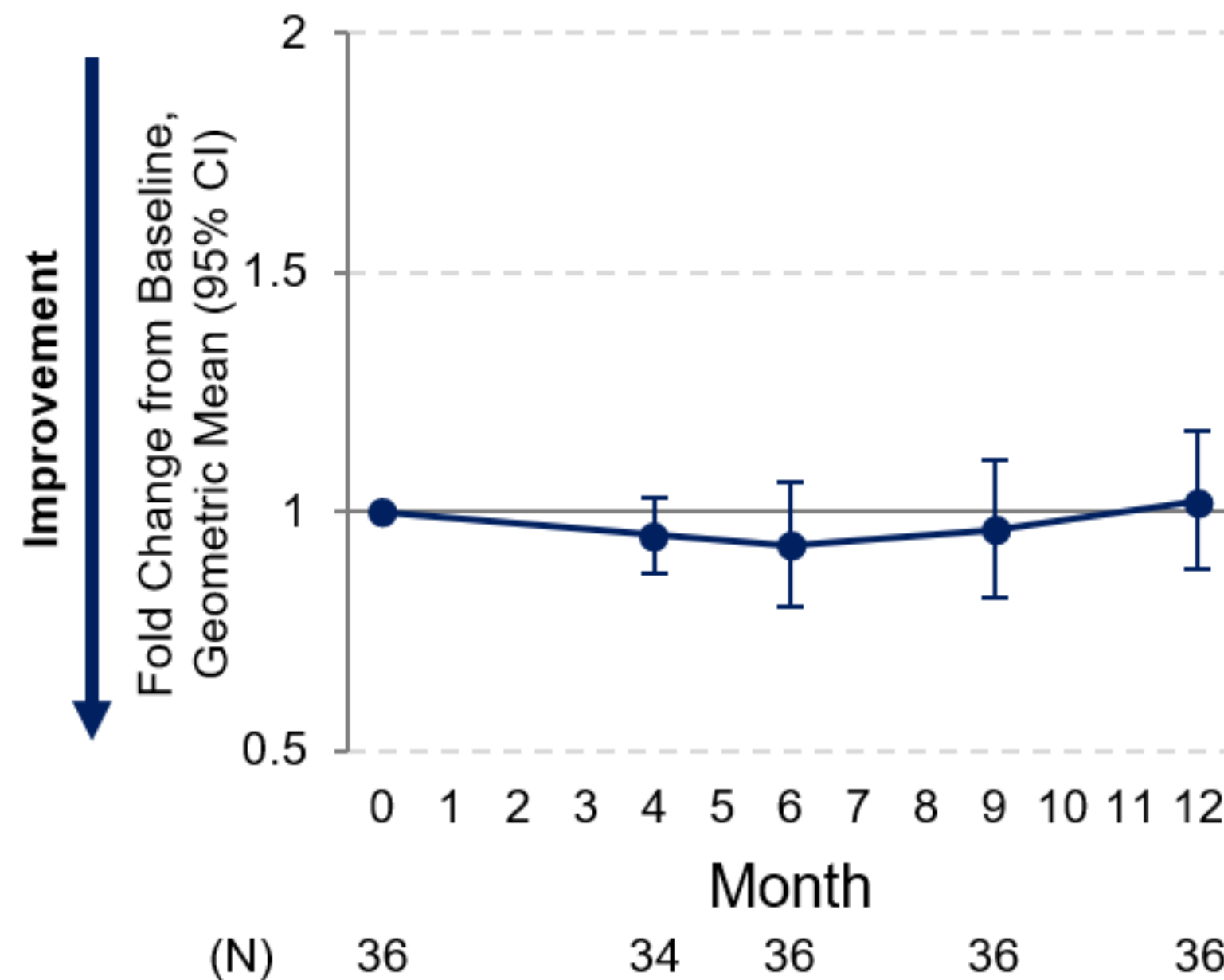
Data cutoff August 21, 2024.
TTR, transthyretin.



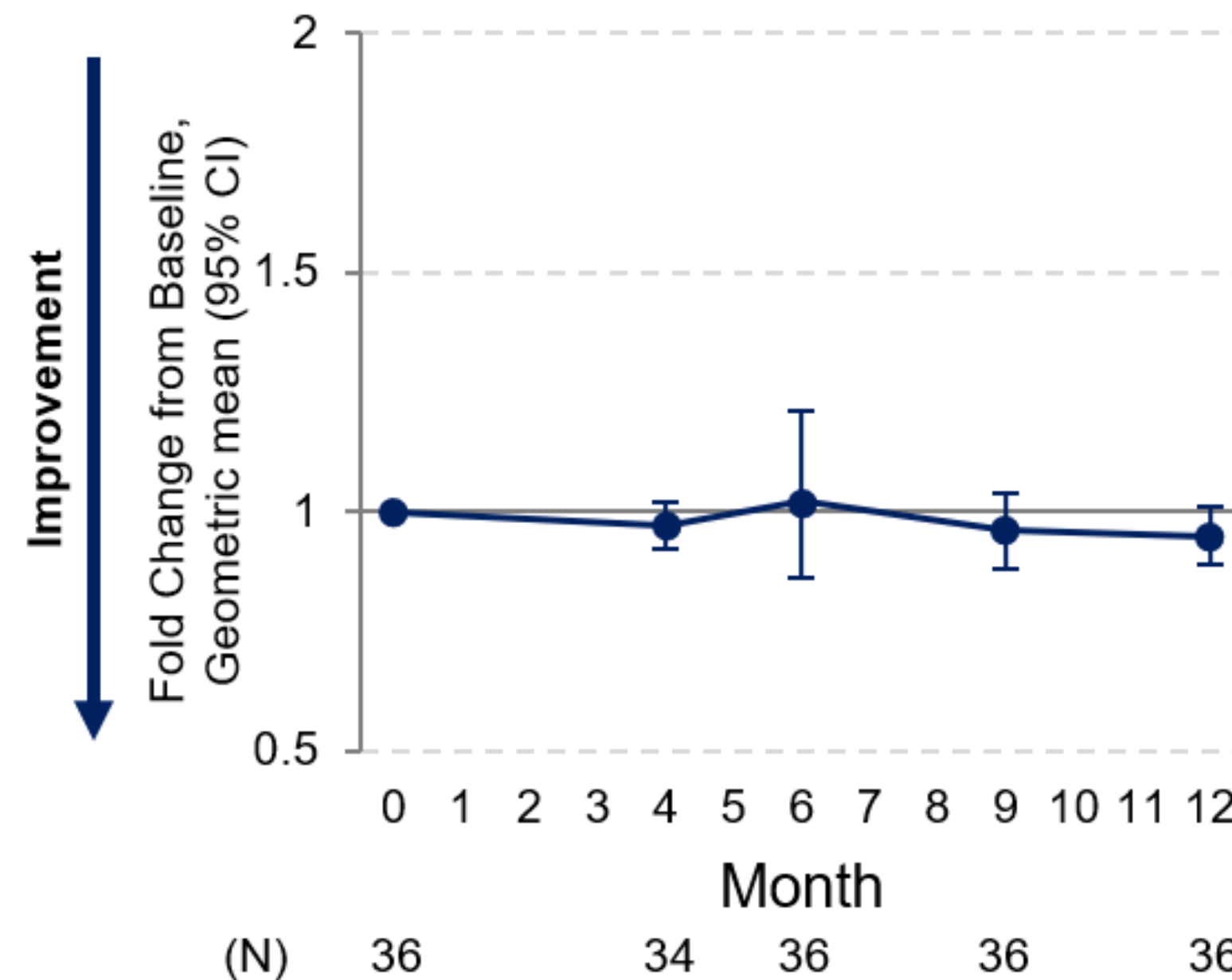
Nex-z Treatment Led to Stability of NT-proBNP, hs-Troponin T, and 6MWT Over 12 Months

Markers of Disease Progression¹

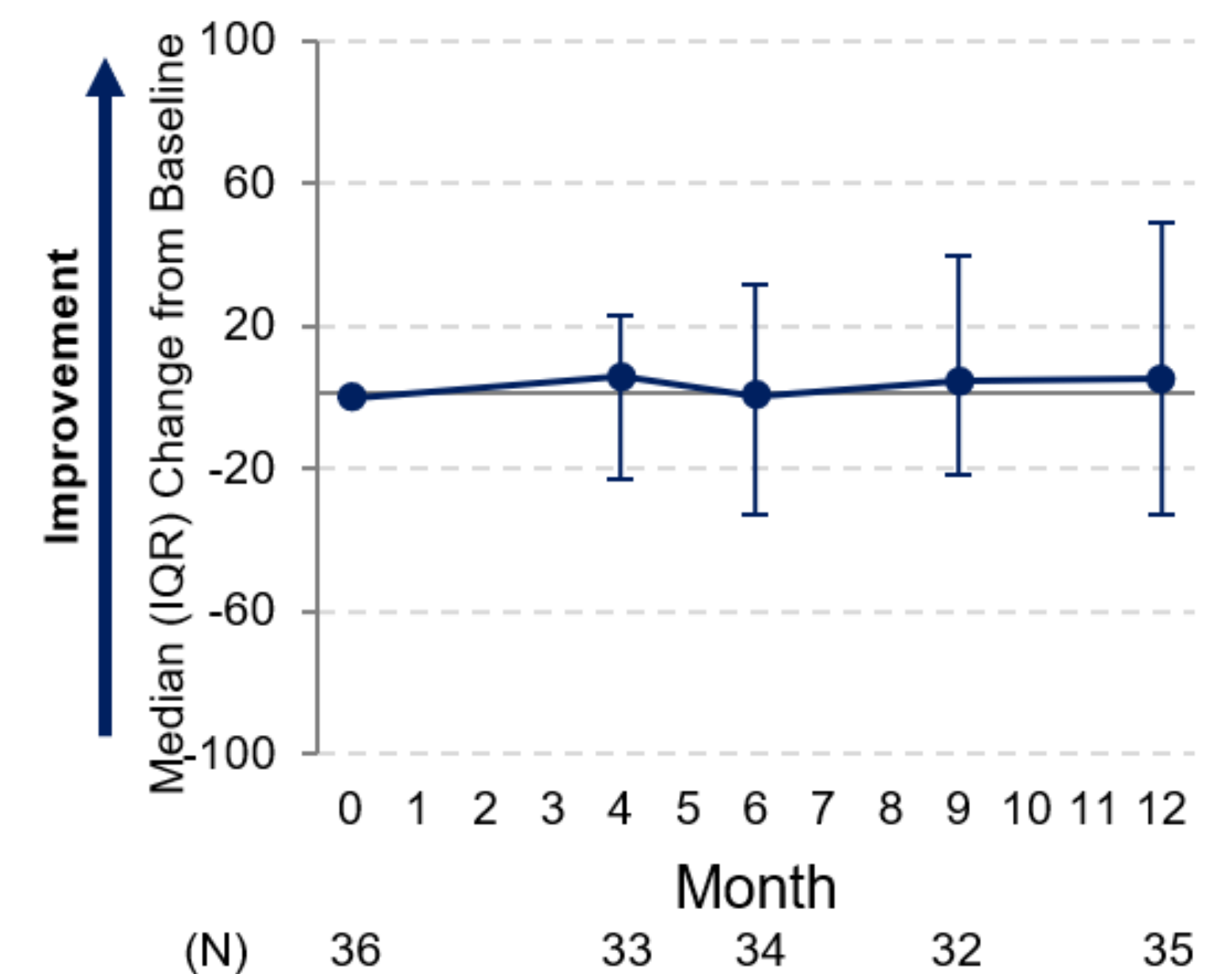
NT-proBNP



hs-Troponin T



6MWT Distance (meters)



Data cutoff August 21, 2024.

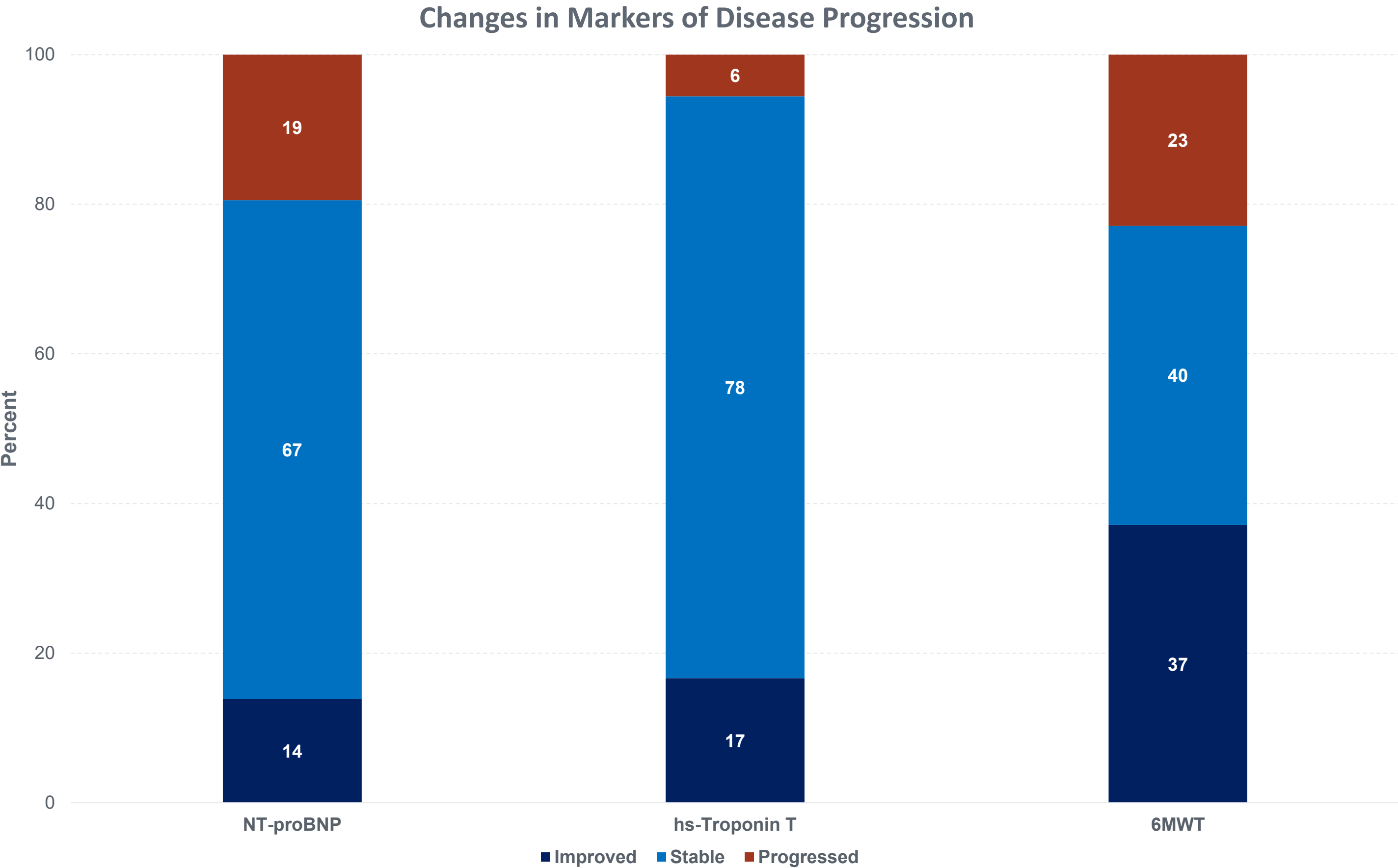
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

1. Ioannou A. et al. *J Am Coll Cardiol*. 2024;83(14):1276-1291.



Fontana M et al. *NEJM* 2024

Nearly 80% of Patients Demonstrated Stability or Improvement in Markers of Disease Progression



Disease Progression Criteria^{1,2}:

- NT-proBNP: an increase of >700 ng/L and >30%
- hs-Troponin T: an increase of >10 ng/mL and >20%
- 6MWT: an absolute reduction of >35 m in 6MWT distance

Improvement was defined as the equivalent counter criteria

83% of NYHA class I/II patients and 47% of NYHA class III patients had no worsening in any marker at 12 months

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
1. Ioannou A. et al. *J Am Coll Cardiol.* 2024;83(14):1276-1291. 2. Ioannou A. et al. *J Am Coll Cardiol.* 2024;84(1):43-58.



Evidence of Stability or Improvement in Symptoms and QOL in Most Patients Following nex-z Treatment

Endpoint	Overall (N=36)	NYHA Class I/II (n=18)	NYHA Class III (n=18)
KCCQ Overall Score at Month 12			
Median change (IQR)	7.8 (-0.5, 15.4)	5.2 (-3.6, 10.9)	9.0 (0.8, 18.8)
Change in NYHA Class at Month 12 ^a			
Improved, n (%)	17 (47)	4 (22)	13 (72)
No change, n (%)	16 (44)	11 (61)	5 (28)
Worsened, n (%)	3 (8)	3 (17)	0 (0)

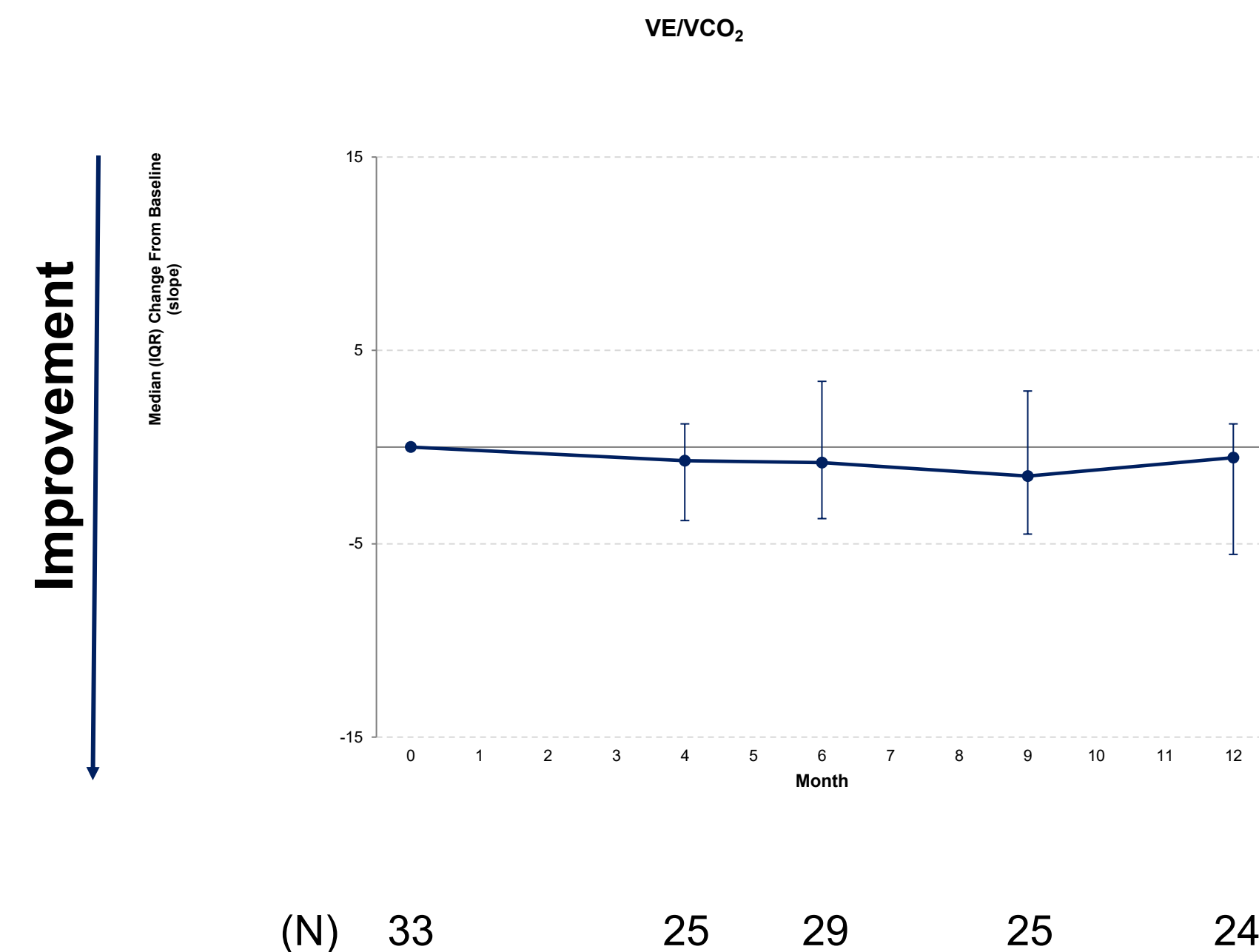
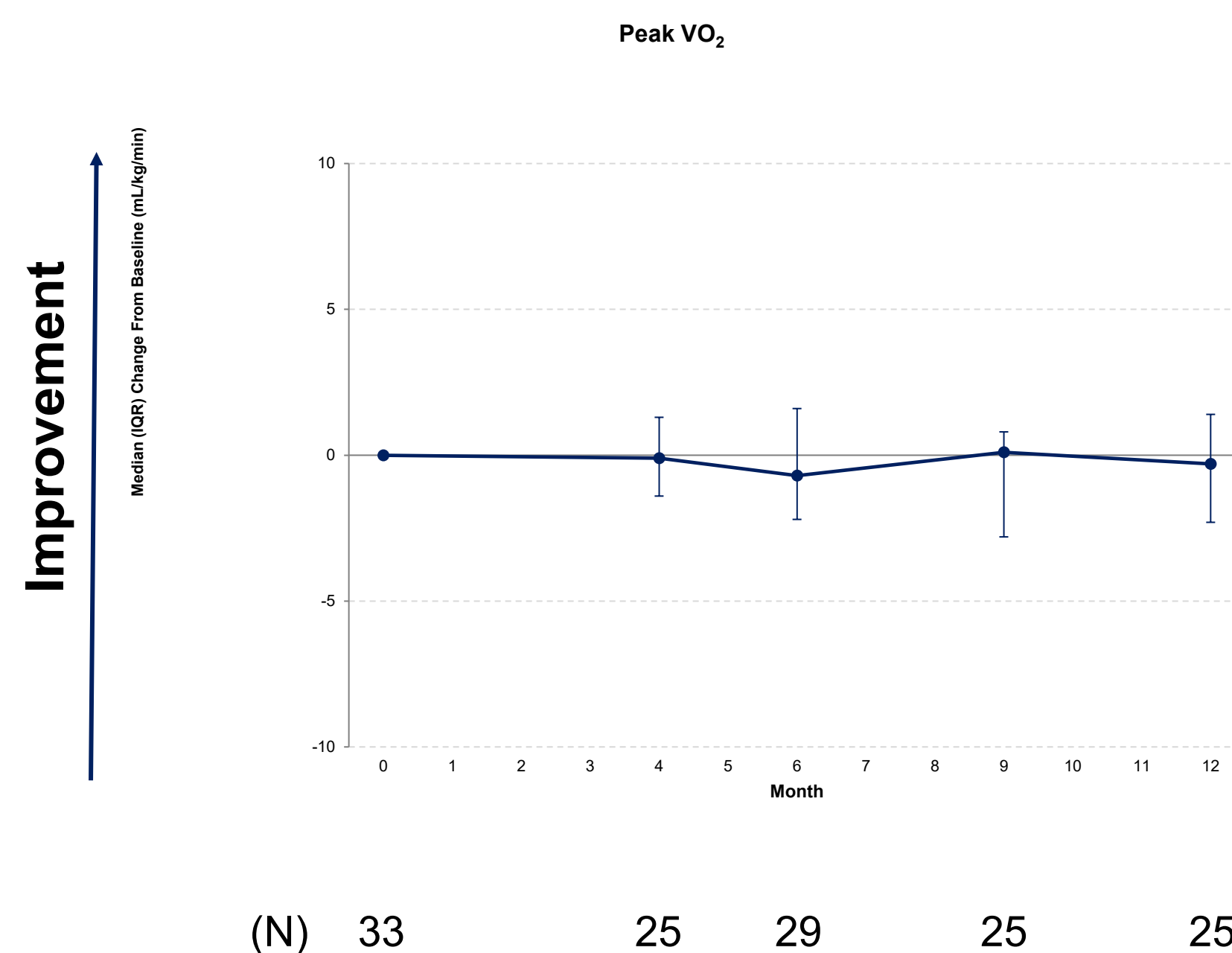
92% of patients demonstrated either no change or improvement in NYHA class at 12 months, including improvement in 72% of patients with NYHA class III

^aValues represent a change of at least one level in NYHA class.
IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; QOL, quality of life.



Functional Capacity Remained Stable Through 12 Months Following nex-z Treatment

Cardiopulmonary Exercise Test



Peak VO₂ and VE/VCO₂ slope are strong prognostic markers¹ and deteriorate rapidly in ATTR-CM²

Data cutoff August 21, 2024.

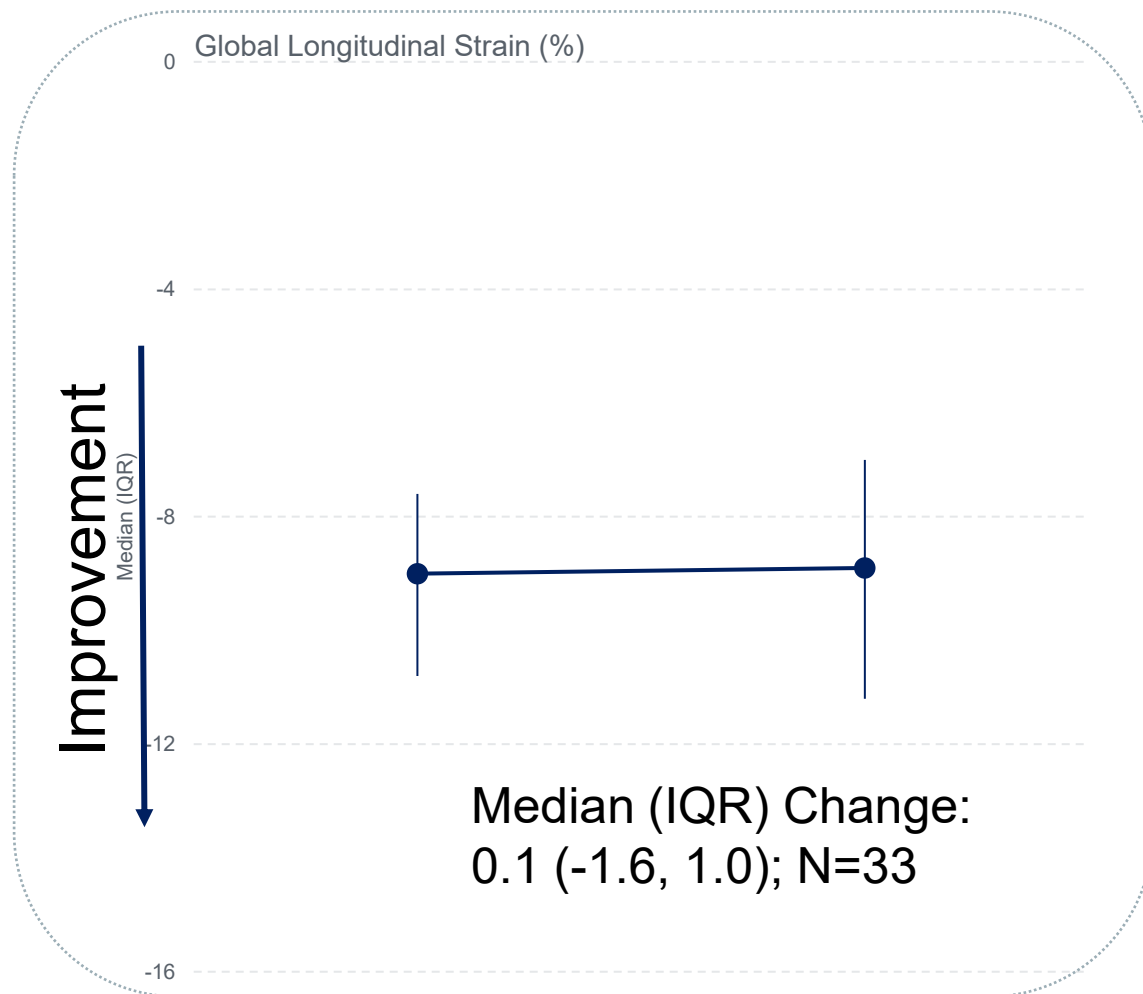
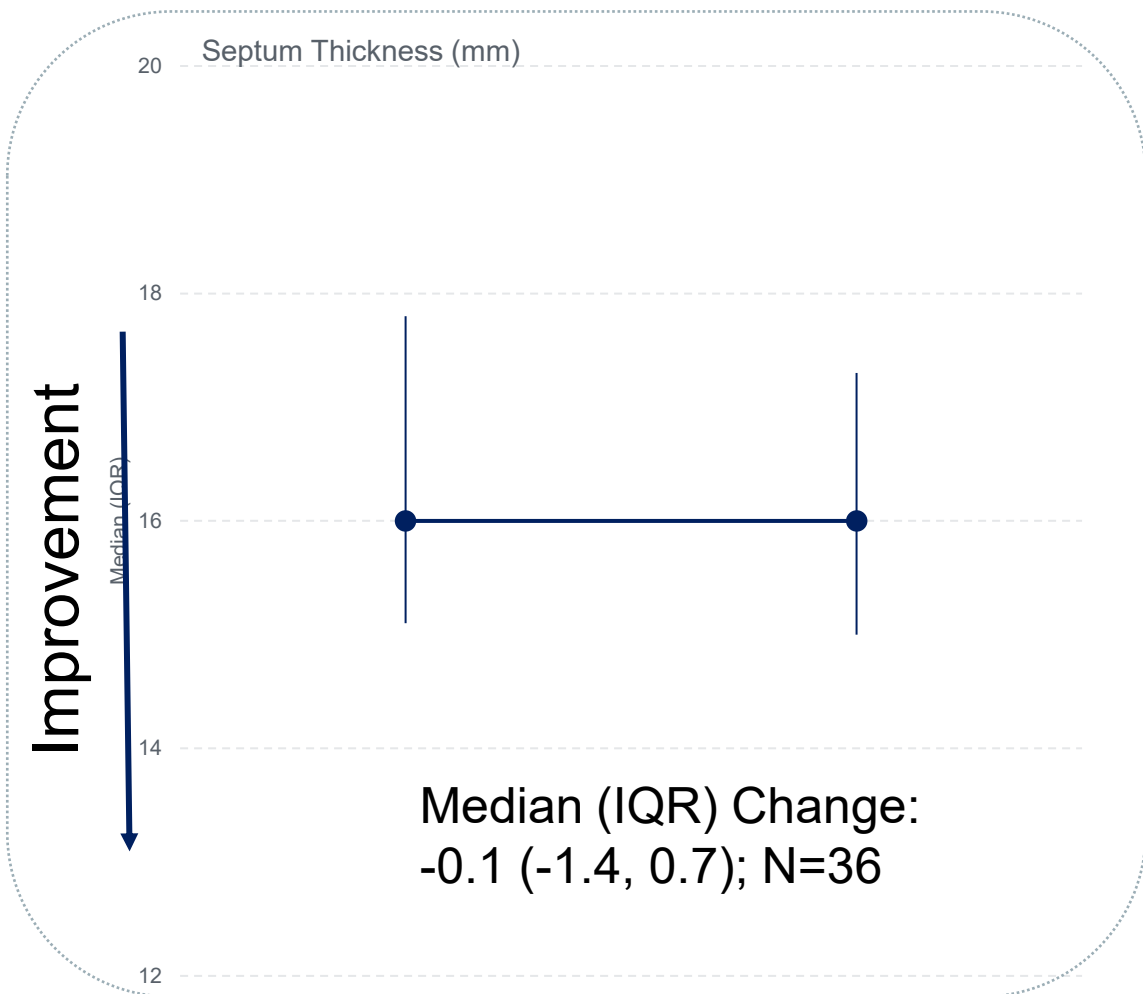
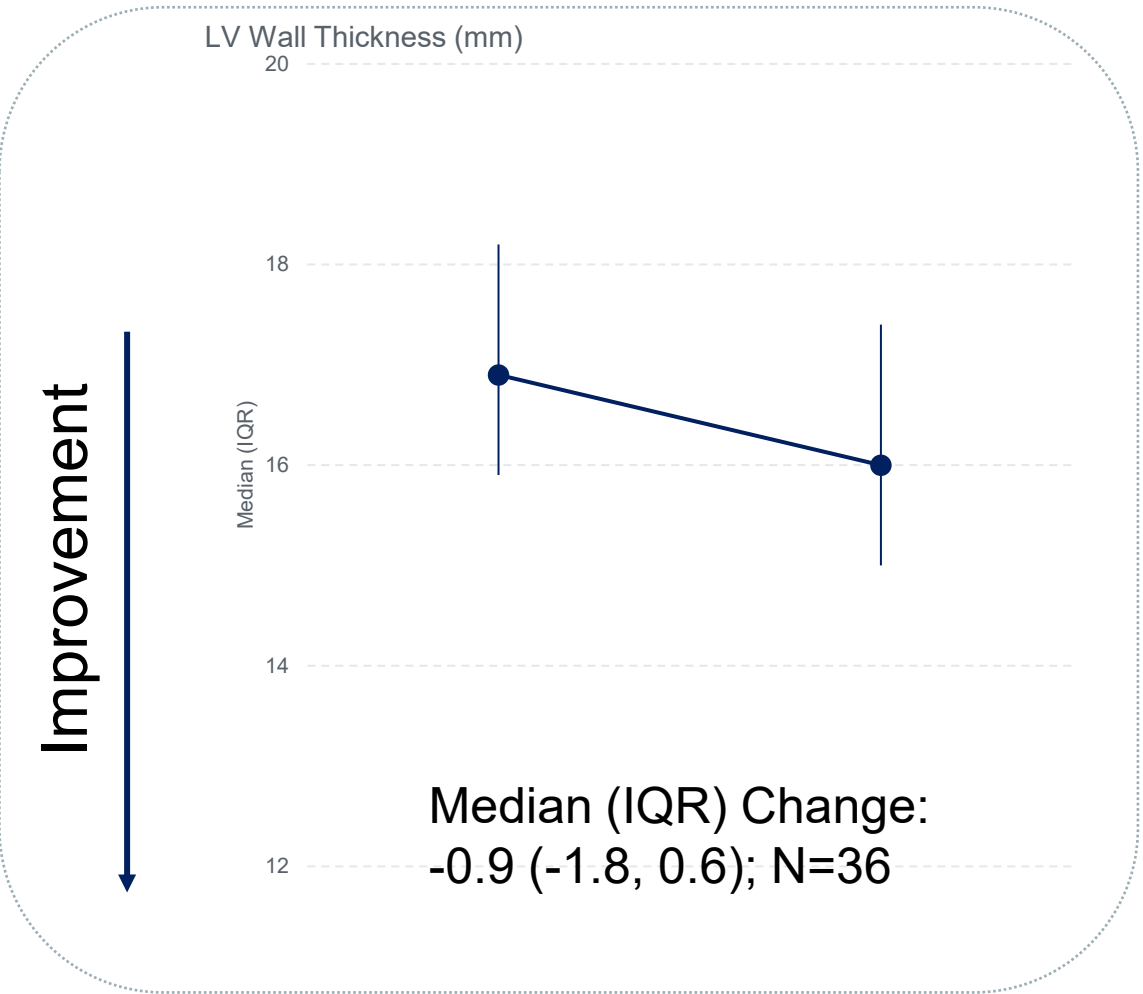
ATTR-CM, ATTR amyloidosis with cardiomyopathy; IQR, interquartile range; VE/VCO₂, ventilatory efficiency; VO₂, oxygen consumption.

1. Patel RK, et al. *JAMA Cardiol.* 2024;9(4):367-376. 2. Argirò A, et al. *Can J Cardiol.* 2024;40(3):364-369.

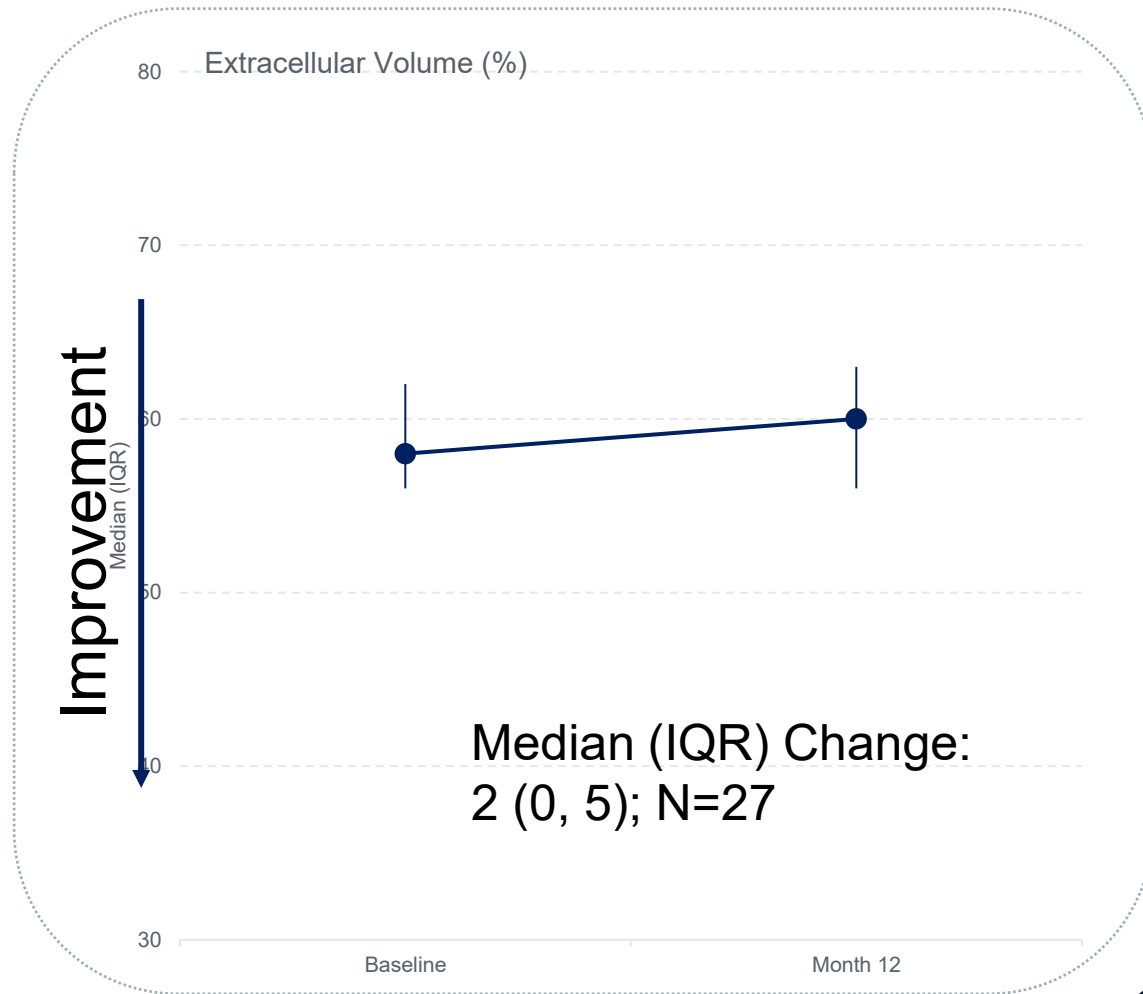
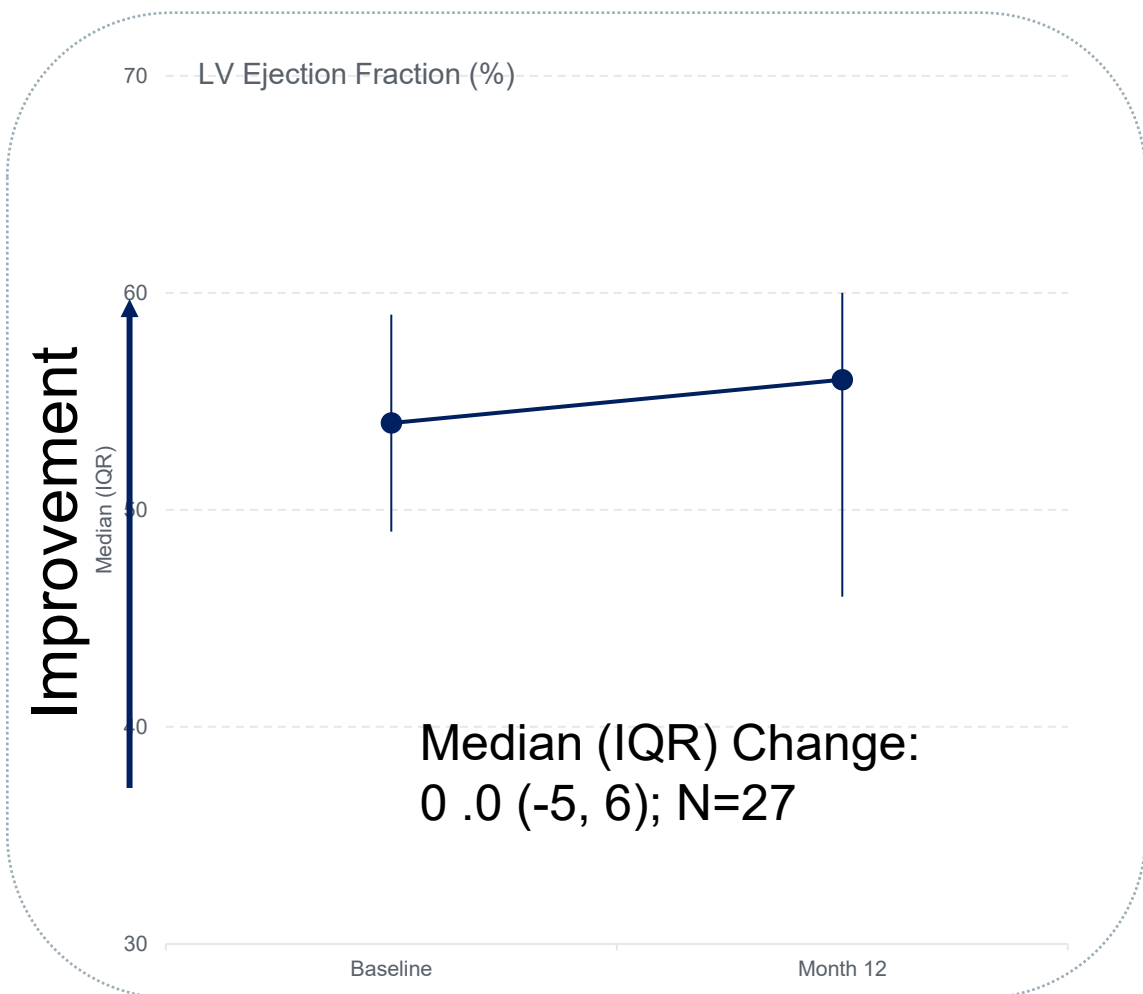
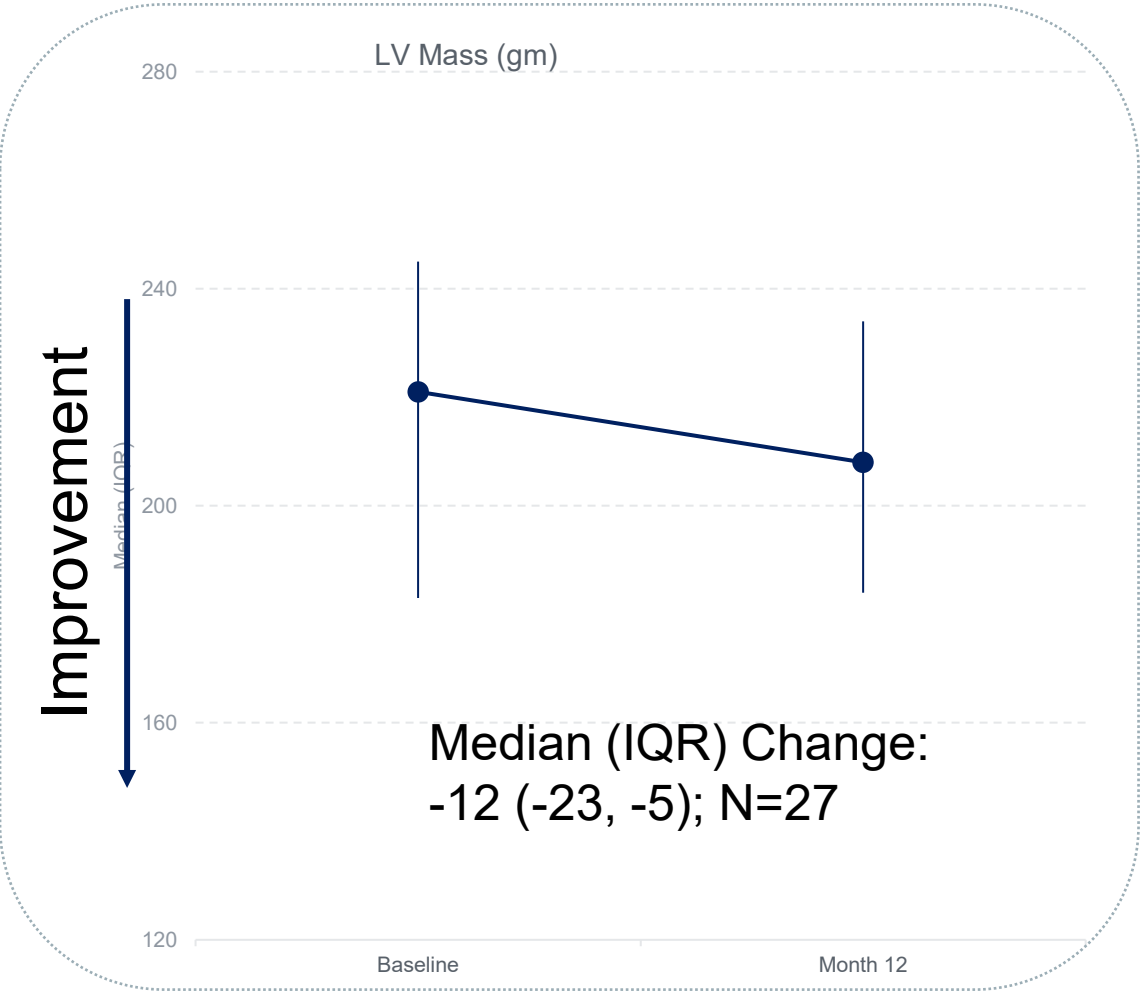


Imaging Assessments of Cardiac Remodeling Showed a Similar Pattern of Stability Following nex-z Treatment

Echo



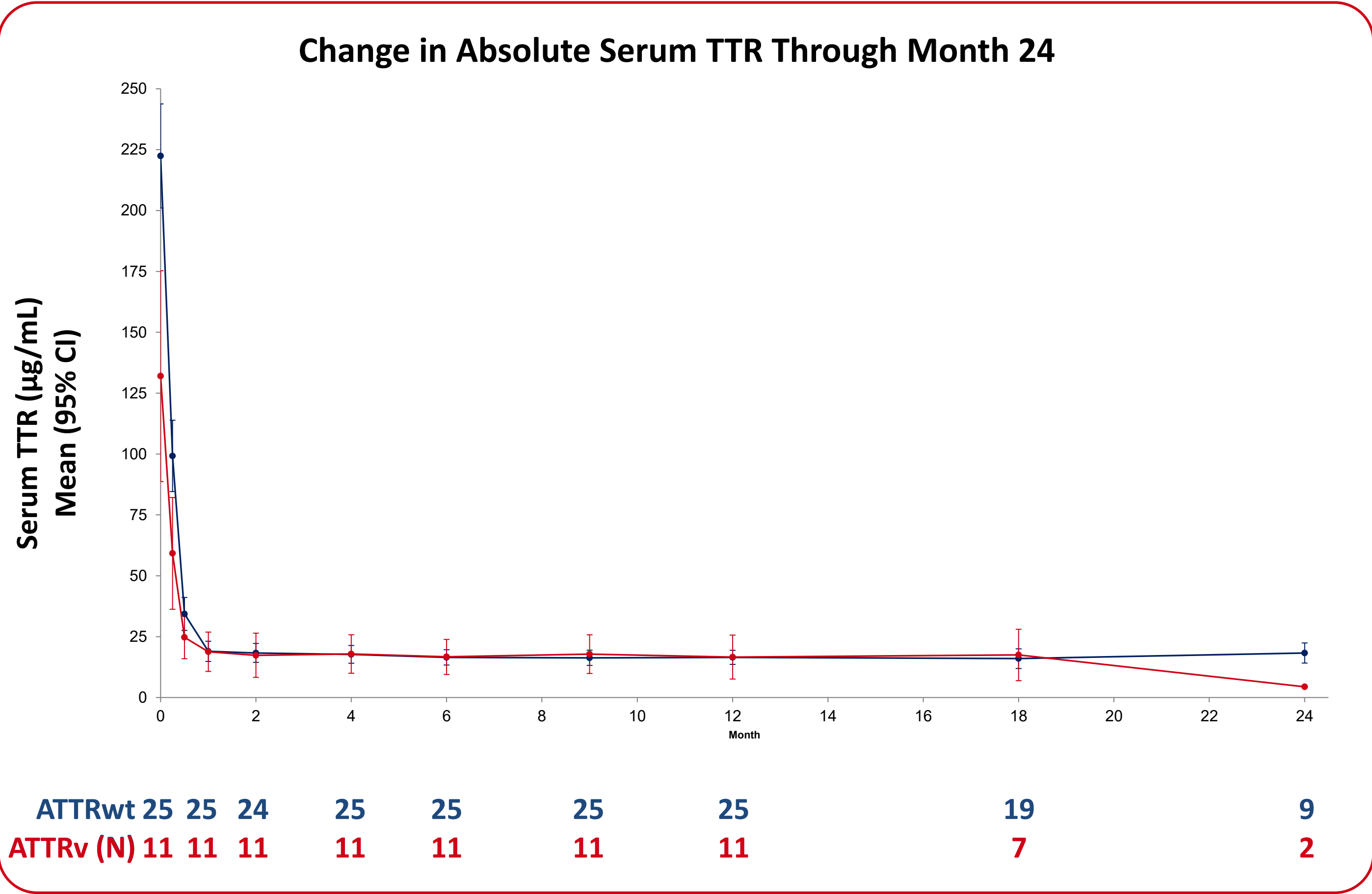
CMR



Data cutoff August 21, 2024.
CMR, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricular.



A Single Dose of nex-z Was Associated With Consistent Deep, Rapid, and Durable Reductions in Serum TTR in Both Wild-Type and Variant Disease

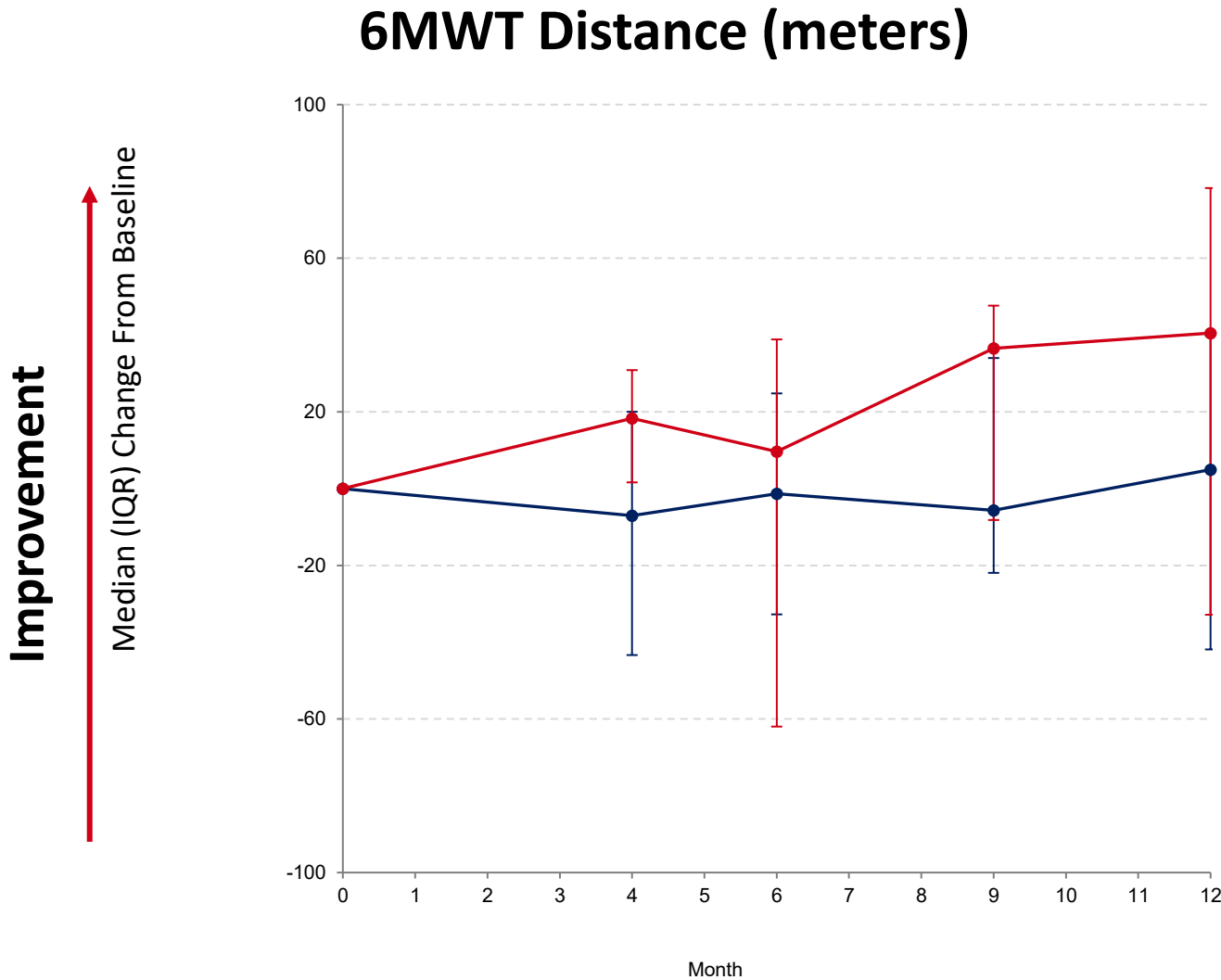
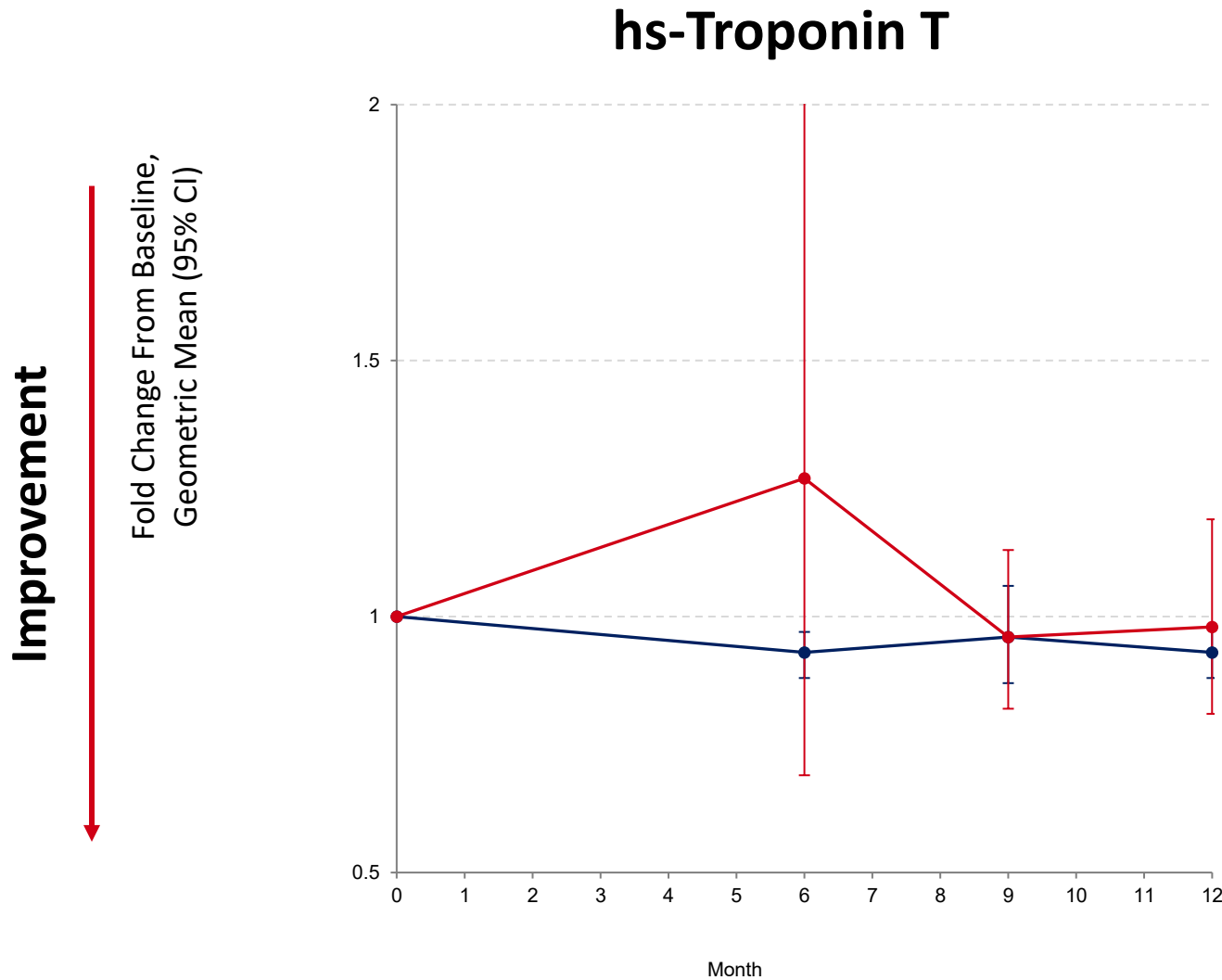
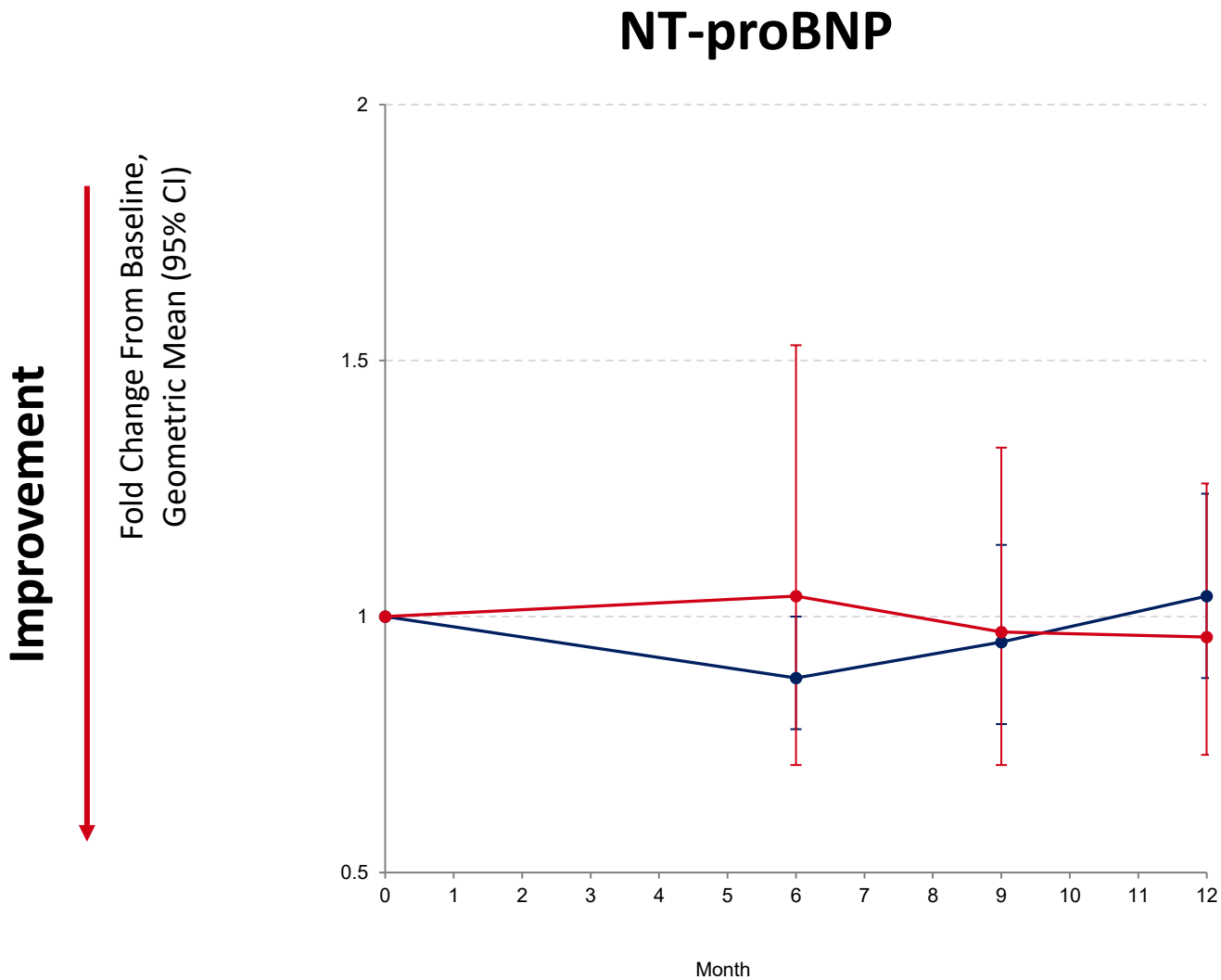


	ATTRwt	ATTRv
Absolute serum TTR (µg/mL), mean (95% CI)		
Baseline	222.4 (201.1, 243.8)	132.0 (88.7, 175.3)
Month 12	16.5 (13.6, 19.4)	16.6 (7.6, 25.6)
Percent change from baseline, mean (95% CI)		
Month 12	-92.5 (-93.7, -91.4)	-85.4 (-95.2, -75.7)

Data cutoff August 21, 2024.
ATTRv-CM, variant ATTR amyloidosis with cardiomyopathy; ATTRwt-CM, wild-type ATTR amyloidosis with cardiomyopathy; TTR, transthyretin.

Disease Progression Is Favorably Impacted With nex-z Treatment

Markers of Disease Progression^{1,2}

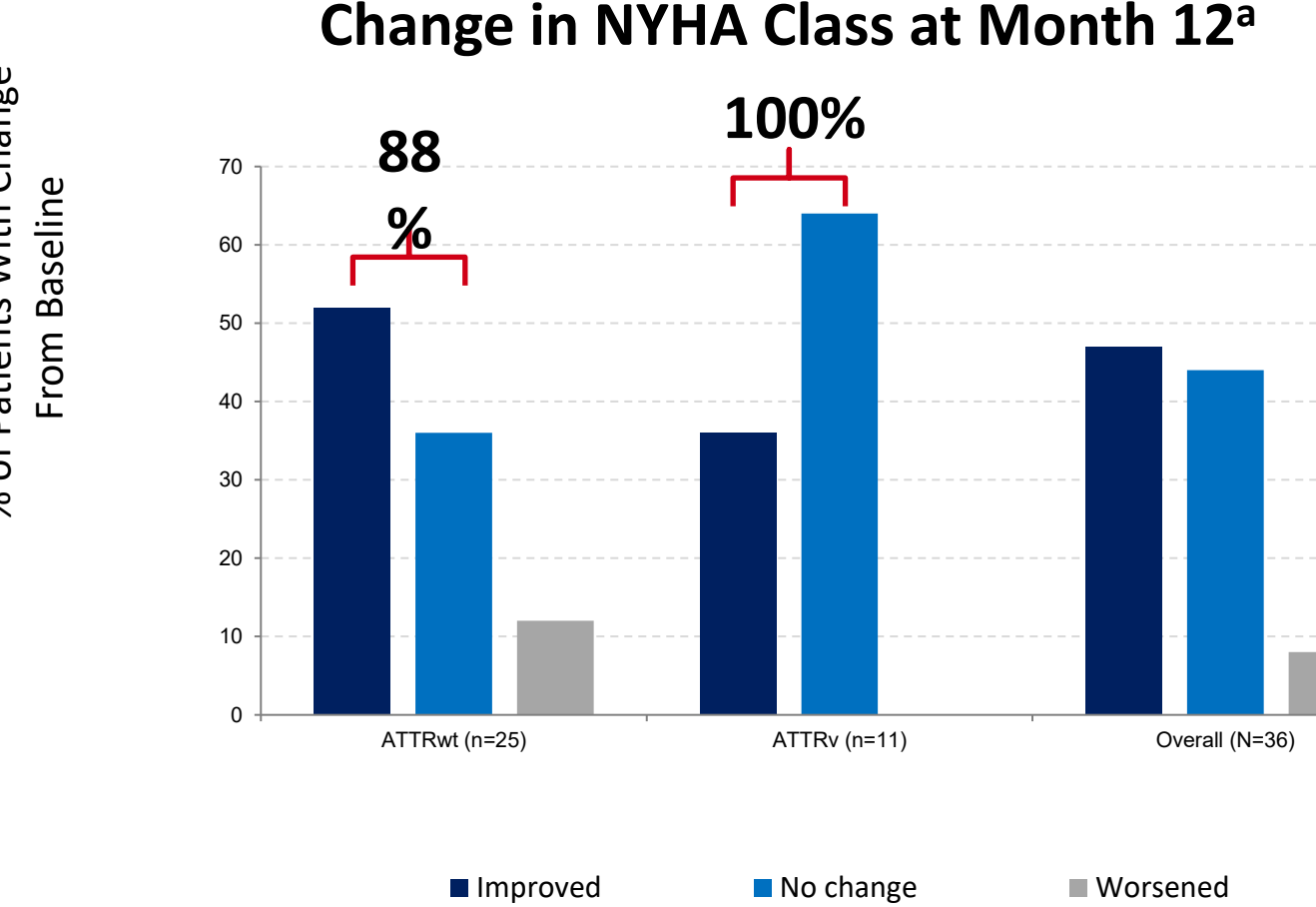
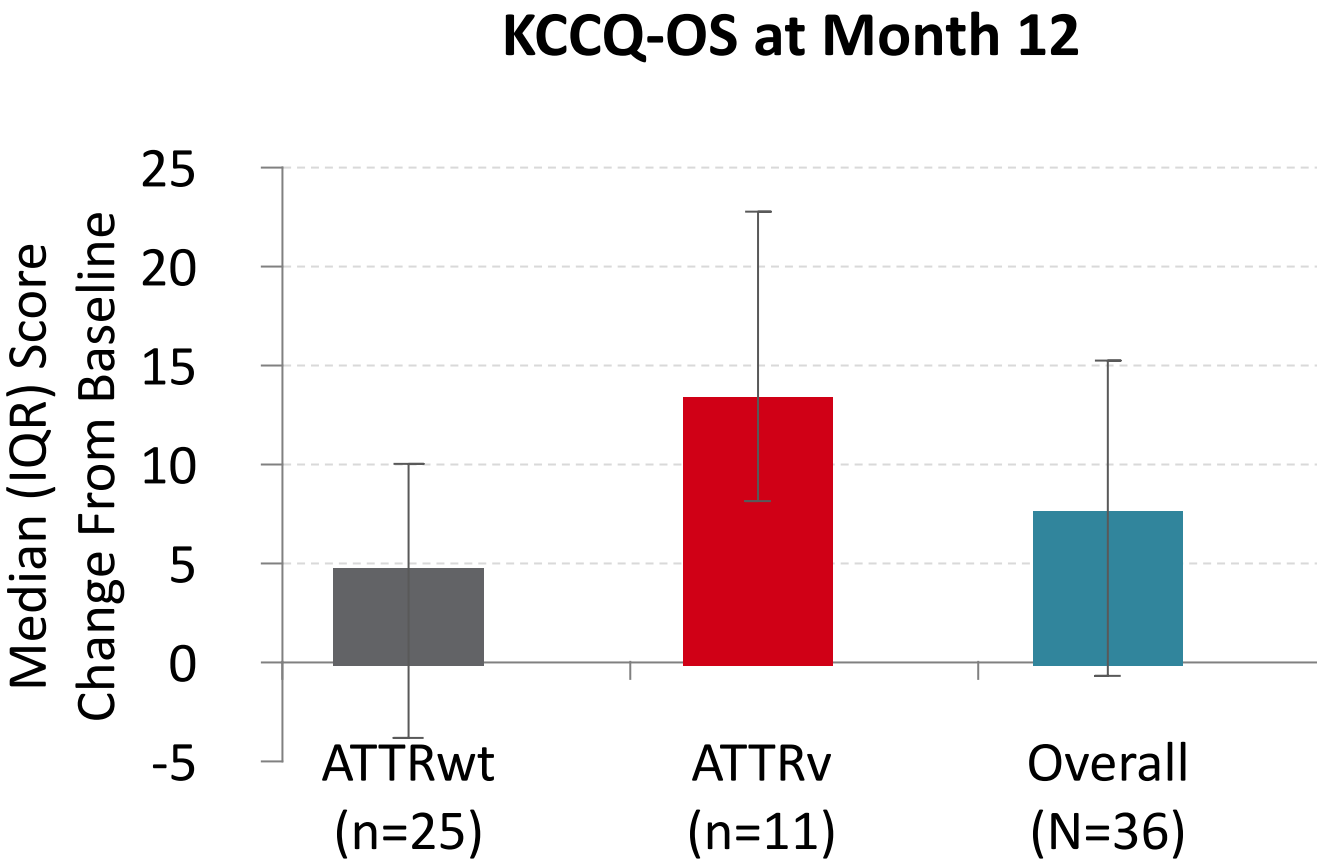


ATTRwt (N) 25
ATTRv (N) 11

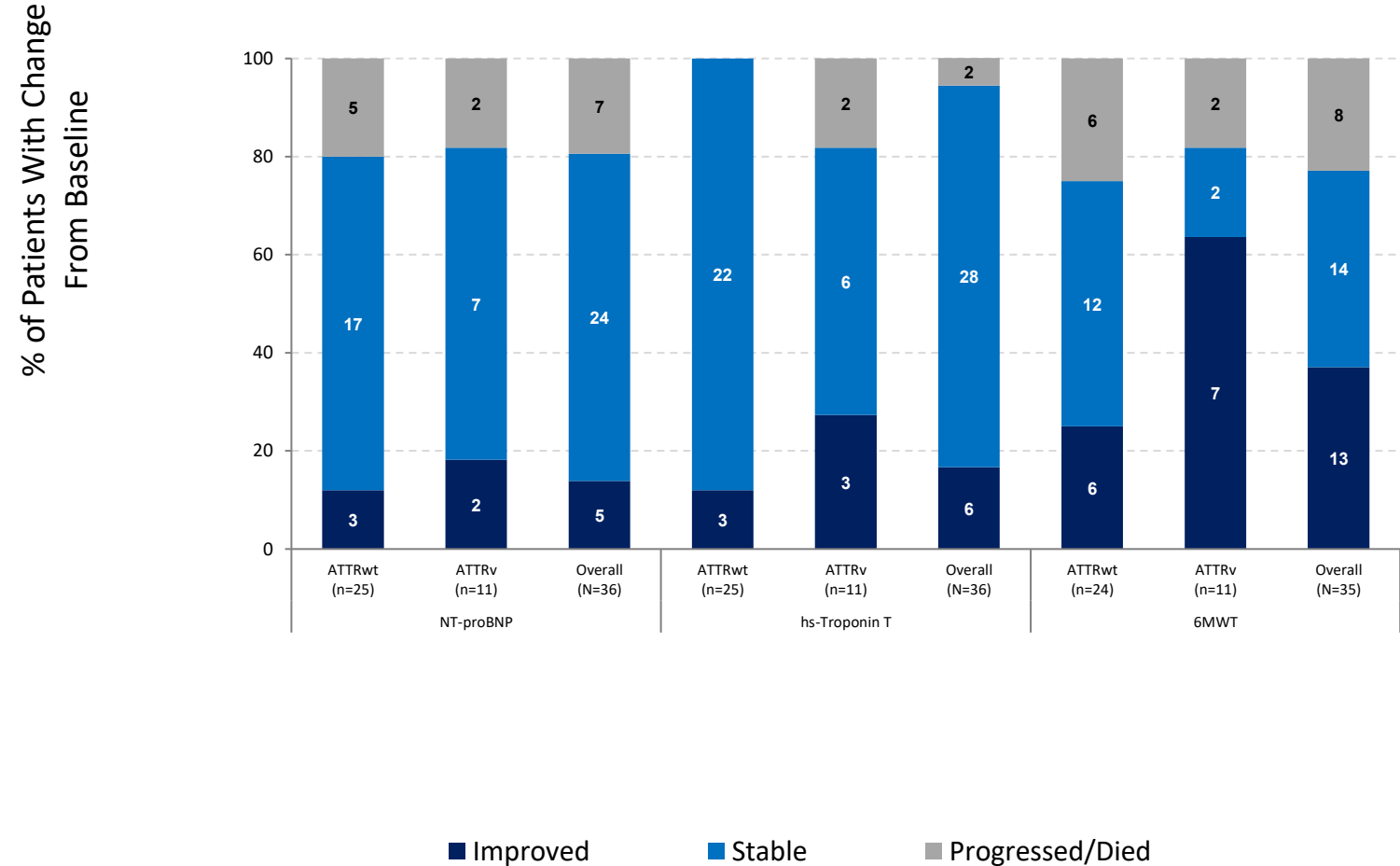
ATTRwt (N) 25
ATTRv (N) 11

ATTRwt (N) 25
ATTRv (N) 11

Evidence of Stability or Improvement in Symptoms and QOL



Changes in Markers of Disease Progression at Month 12^{1,2}



Data cutoff August 21, 2024. ^aValues represent a change of at least one level in NYHA class.
6MWT, 6-Minute Walk Test; ATTRv, variant ATTR amyloidosis; ATTRwt, wild-type ATTR amyloidosis; hs, high sensitivity; IQR, interquartile range; KCCQ OS, Kansas City Cardiomyopathy Questionnaire Overall Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QOL, quality of life.
1. Ioannou A, et al. *J Am Coll Cardiol.* 2024;83(14):1276-1291. 2. Ioannou A, et al. *J Am Coll Cardiol.* 2024;84(1):43-58.

Summary of Safety

Event	n (%)	Event	n (%)
At least one AE	34 (94)	Any SAE	14 (39)
AEs occurring in ≥15% of patients		SAEs occurring in ≥5% of patients	
Cardiac failure	13 (36)	Cardiac failure	5 (14)
COVID-19	7 (19)	Acute myocardial infarction	3 (8)
Upper respiratory tract infection	7 (19)	Urinary tract infection	3 (8)
Atrial fibrillation	6 (17)	Atrial flutter	2 (6)
Urinary tract infection	6 (17)	Pneumonia	2 (6)
Treatment-related AEs in ≥5% of patients		SAEs of heart failure or arrhythmia	7 (19)
Infusion-related reaction	5 (14)	Cardiac failure	5 (14)
Aspartate aminotransferase increased	2 (6)	Arrhythmia ^b	3 (8)
Any AE leading to treatment discontinuation	0	CV hospitalization rate ^c (n/pt/yr, 95% CI)	0.16 (0.08 to 0.36)
Any event leading to death ^a	1 (3)		

Data cutoff August 21, 2024. Median (min, max) follow-up for safety was 18 months (12, 27). For each preferred term, subjects reporting more than one adverse event are counted only once. Liver enzyme elevations were transient, generally mild, and not indicative of liver injury. ^aOnly one death occurred (ischemic heart disease) on Day 506 after dosing; unrelated to treatment. ^bArrhythmia events included SAEs of atrial flutter and atrioventricular block complete, with one patient experiencing both cardiac failure and arrhythmia on the same day. ^cIncludes hospitalizations for cardiac failure, arrhythmia, or stroke. AE, adverse event; CV, cardiovascular; SAE, serious AE.



Phase 1, two-part, open-label, multicenter study of nex-z in patients with ATTRv-PN

Adults (aged 18-80 years) with ATTRv-PN, including patients who had previously progressed on patisiran



PART 1: Single-Ascending Dose

N=15

0.1 mg/kg (n=3)^a

0.3 mg/kg (n=3)

0.7 mg/kg (n=3)

1.0 mg/kg (n=6)

PART 2: Dose Expansion

N=21

55 mg (n=16)

80 mg (n=5)

PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- Measure serum TTR levels

SELECT SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- Changes from baseline in NIS, mNIS+7 (Part 2 only), mBMI, Norfolk QoL-DN, NfL, and PND

Mean (range) follow-up: 27 (9 - 44) months

Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>

Phase 1 (NCT04601051); Long-term follow-up study (NCT05697861). Data cutoff April 11, 2025.

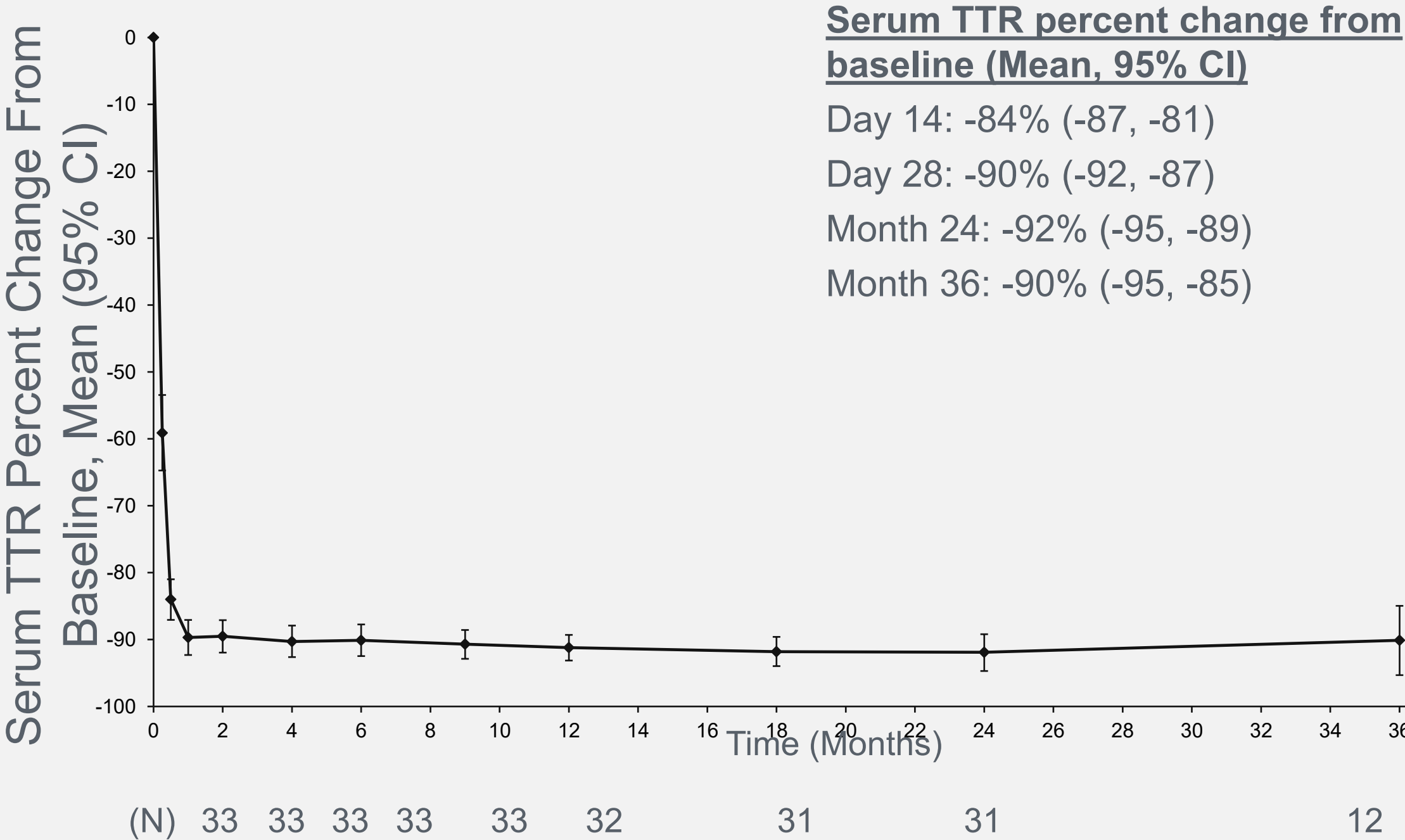
^aPatients who received the 0.1 mg/kg dose were redosed with 55 mg after completing 24 months of follow-up.

AL, light chain; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; FAP, Familial Amyloid Polyneuropathy, IV, intravenous; mNIS+7, modified Neuropathy Impairment Score +7; mBMI, modified body mass index; NfL, neurofilament light chain; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PD, pharmacodynamics; PND, Polyneuropathy Disability; TTR, transthyretin.

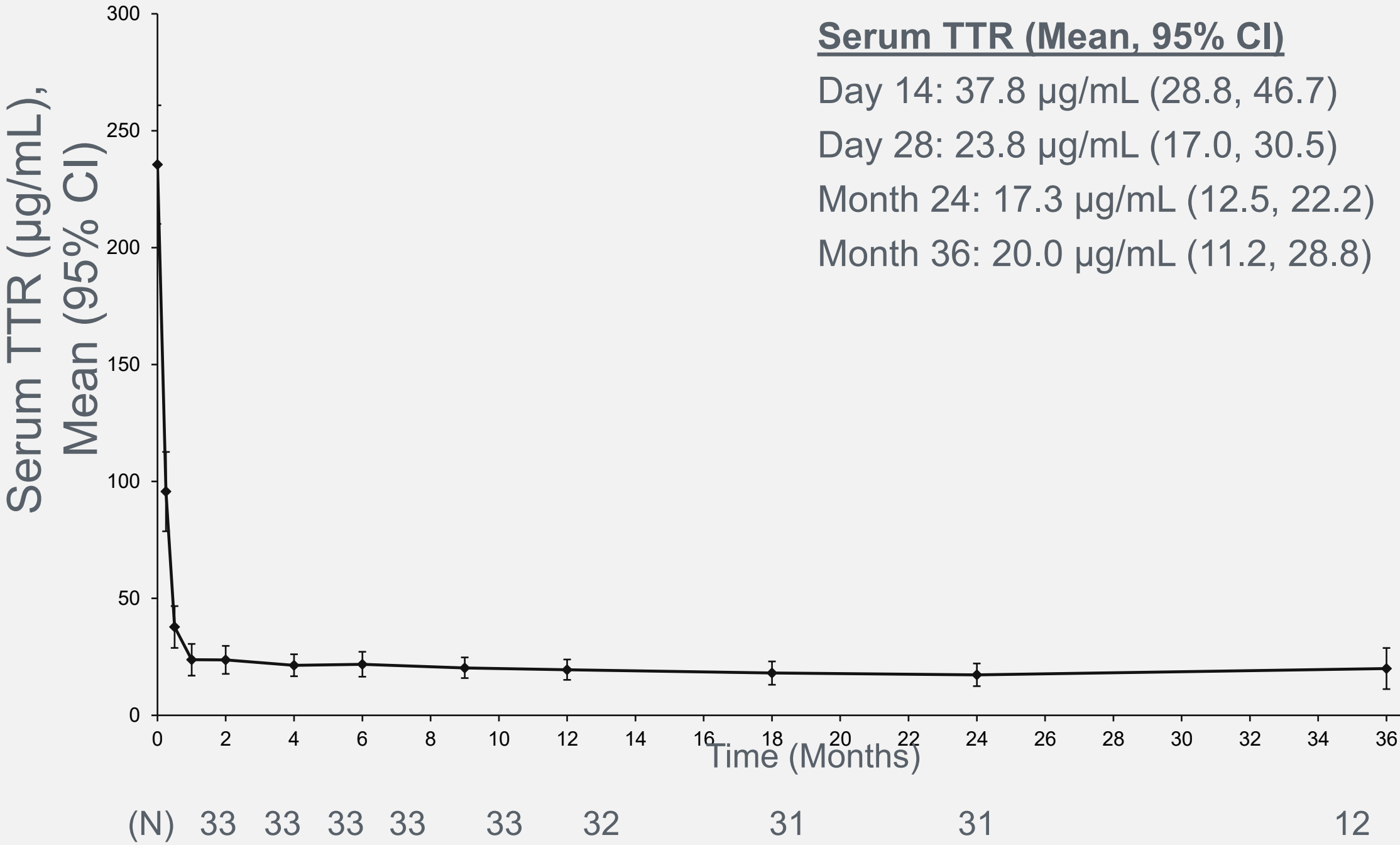


One-time treatment with nex-z led to rapid, deep, consistent, and durable reductions in serum TTR levels with low variability

Serum TTR Percent Change from Baseline



Absolute Serum TTR Concentration

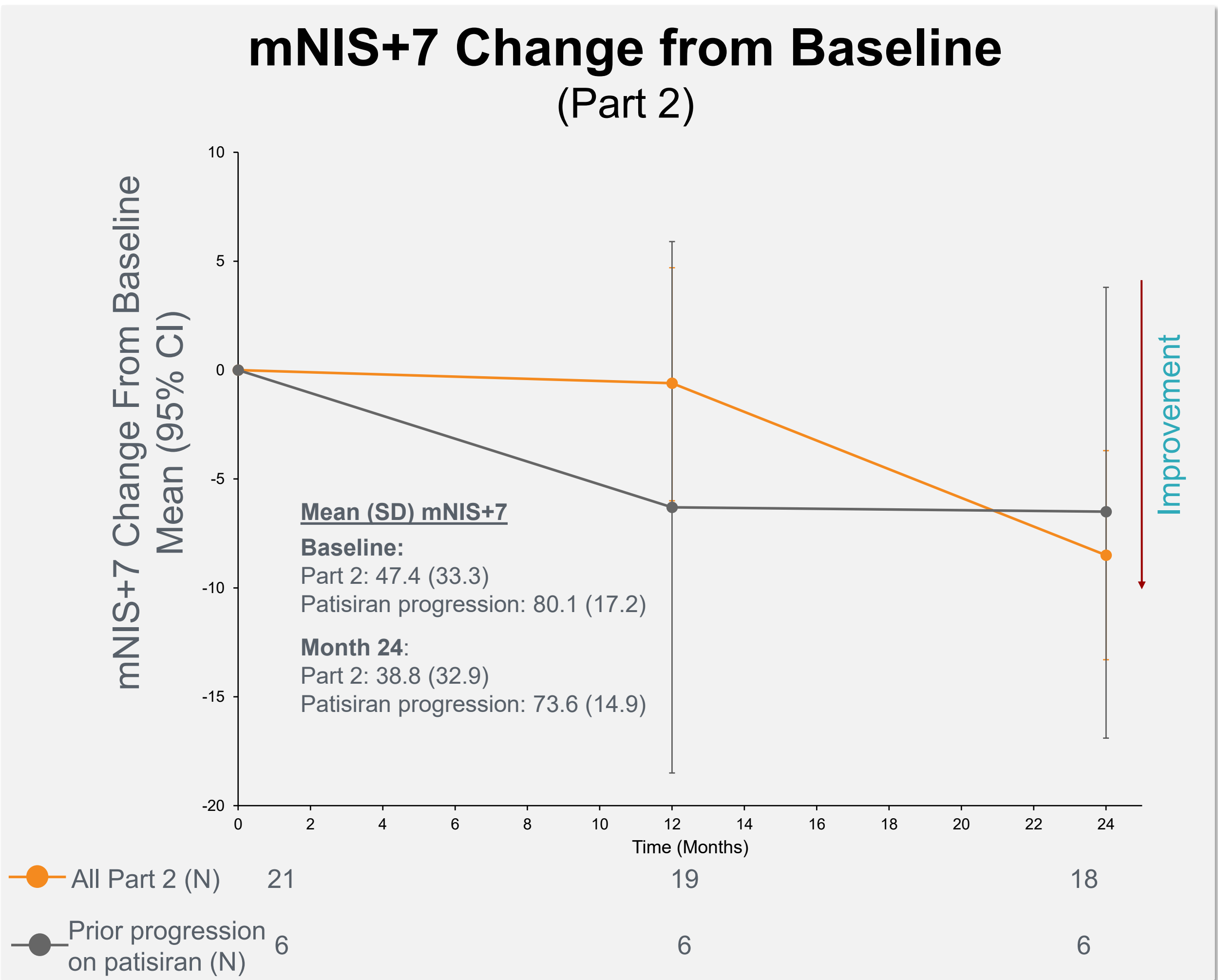
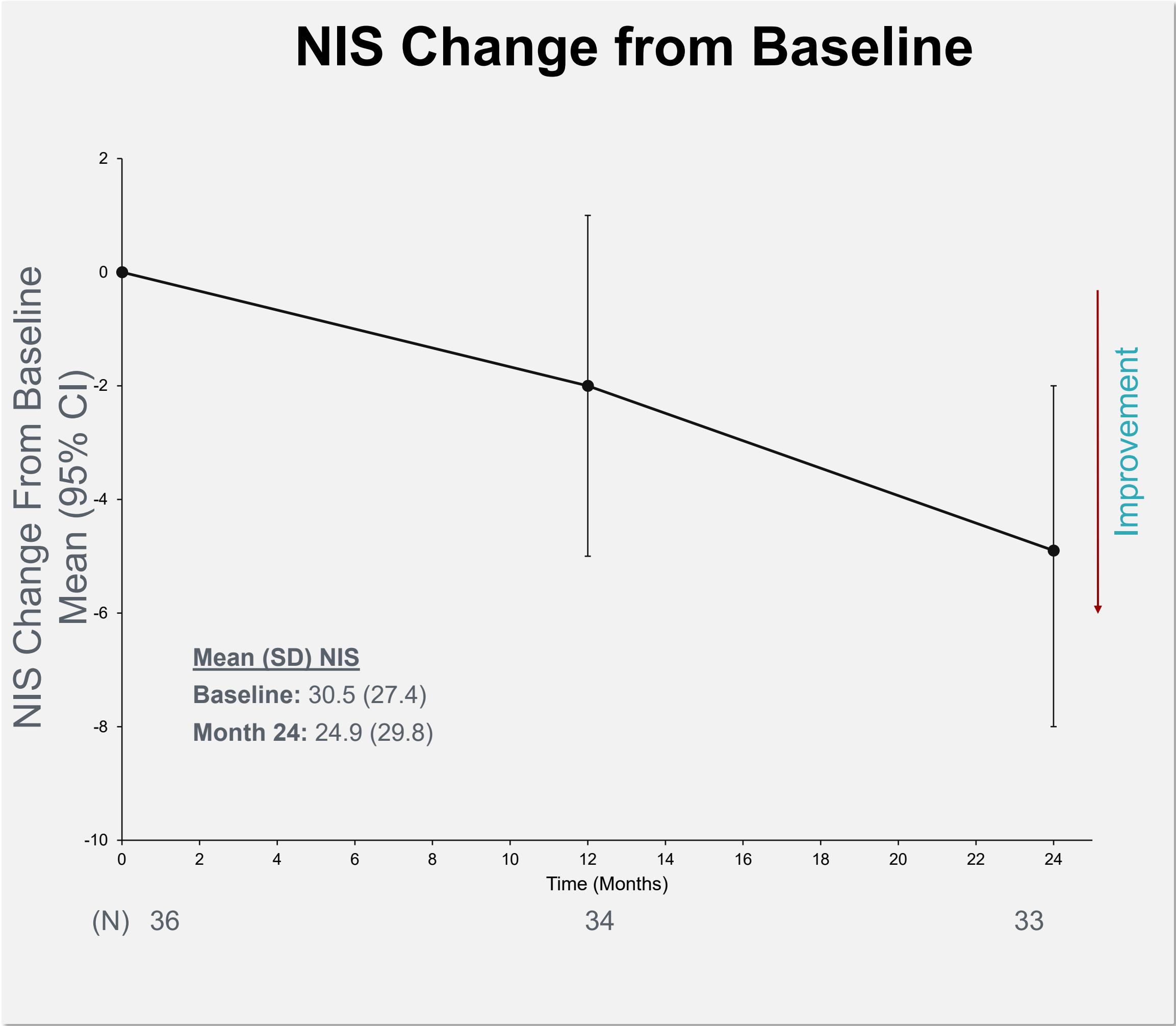


94% (29/31) of patients achieved serum TTR levels <50 µg/mL and 90% (28/31) achieved levels <30 µg/mL at Month 24

Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>
Data cutoff April 11, 2025. Data regarding the serum TTR level at month 36 were collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date, April 16, 2025).
Data presented exclude the 0.1 mg/kg cohort. The 3 patients in the 0.1 mg/kg cohort have been redosed at 55 mg.
TTR, transthyretin.

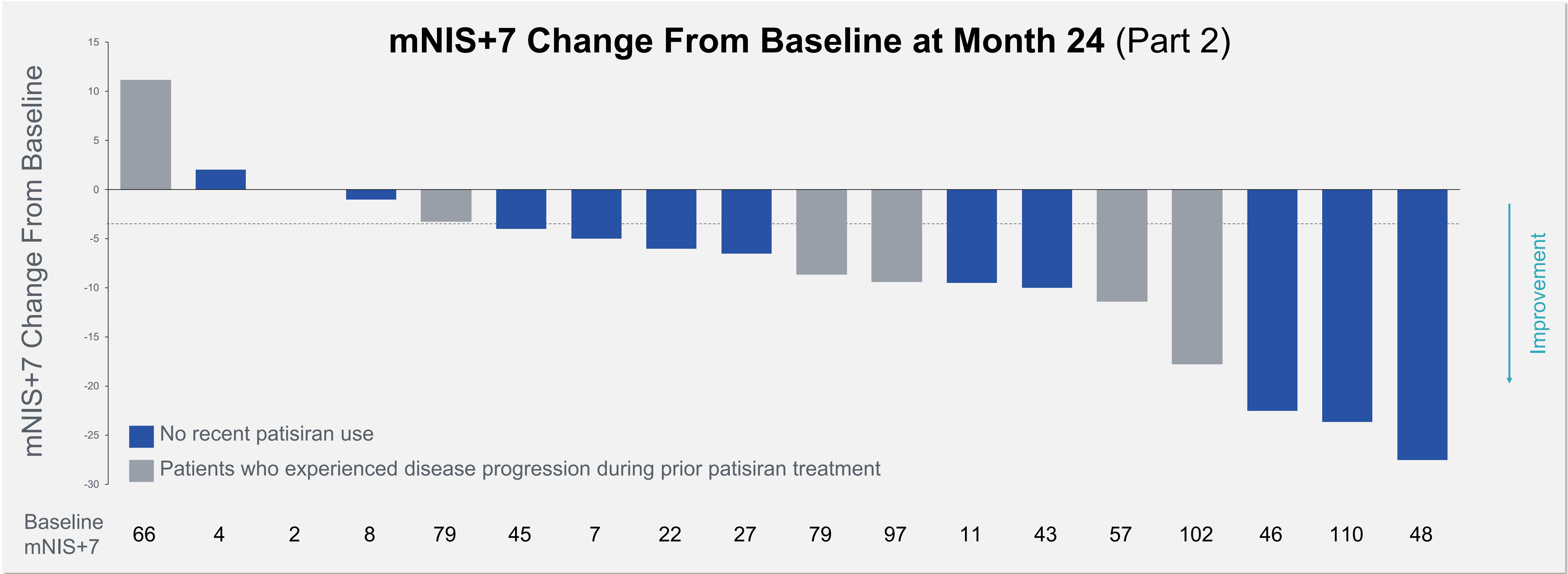


Improvements in NIS and mNIS+7 were observed following a one-time treatment with nex-z



Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>
Data cutoff April 11, 2025.
NIS ranges from 0 to 244 and mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment.
mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score.

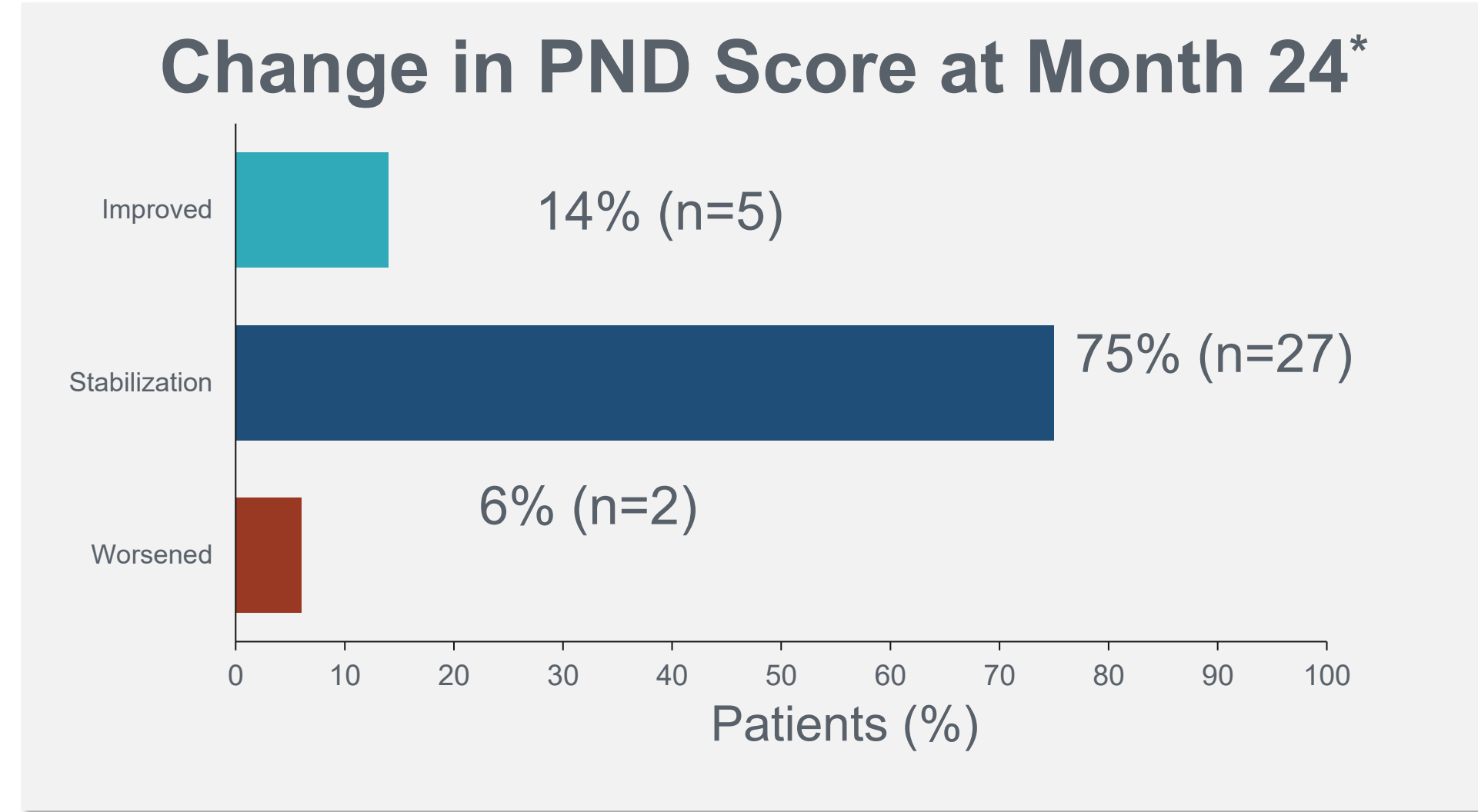
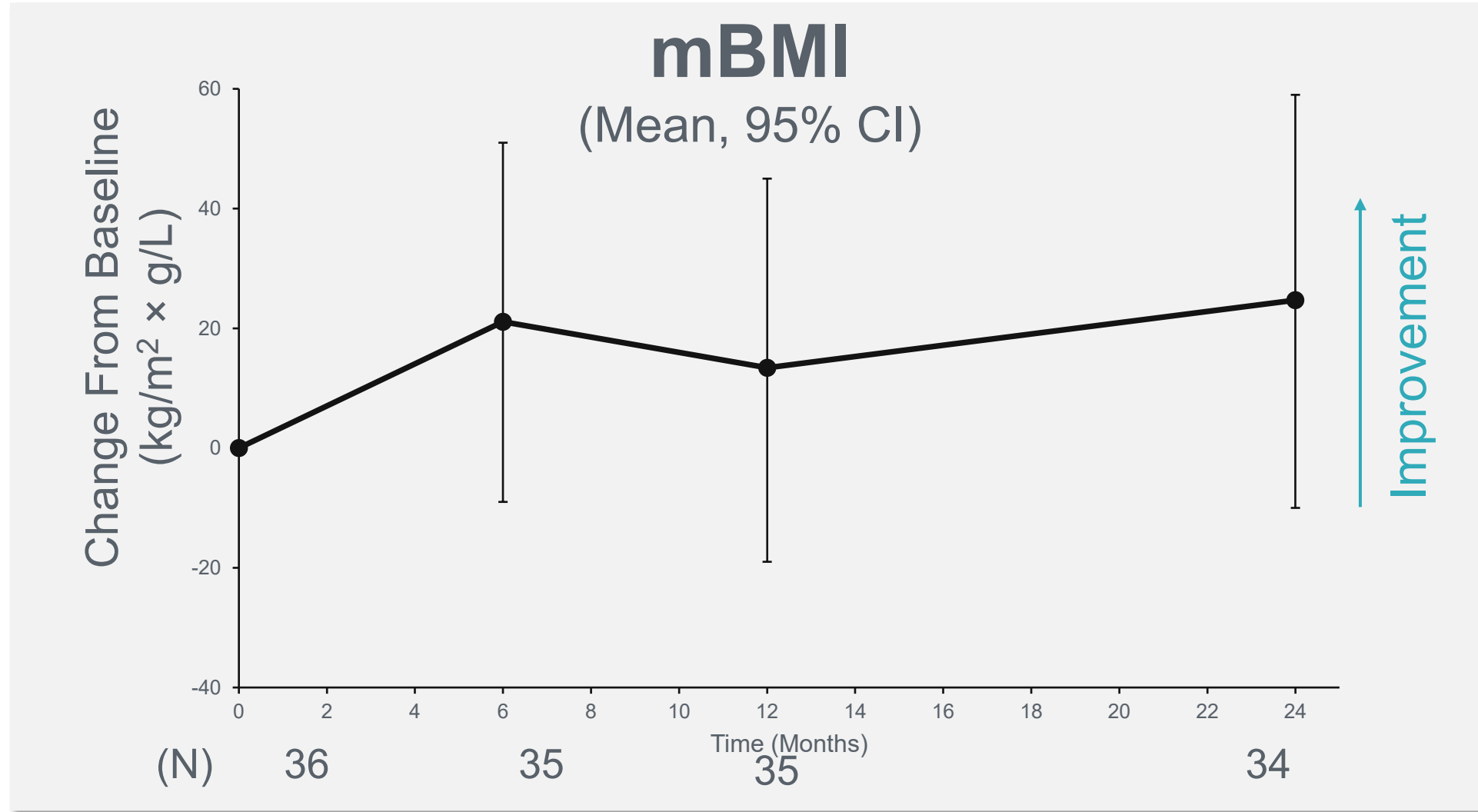
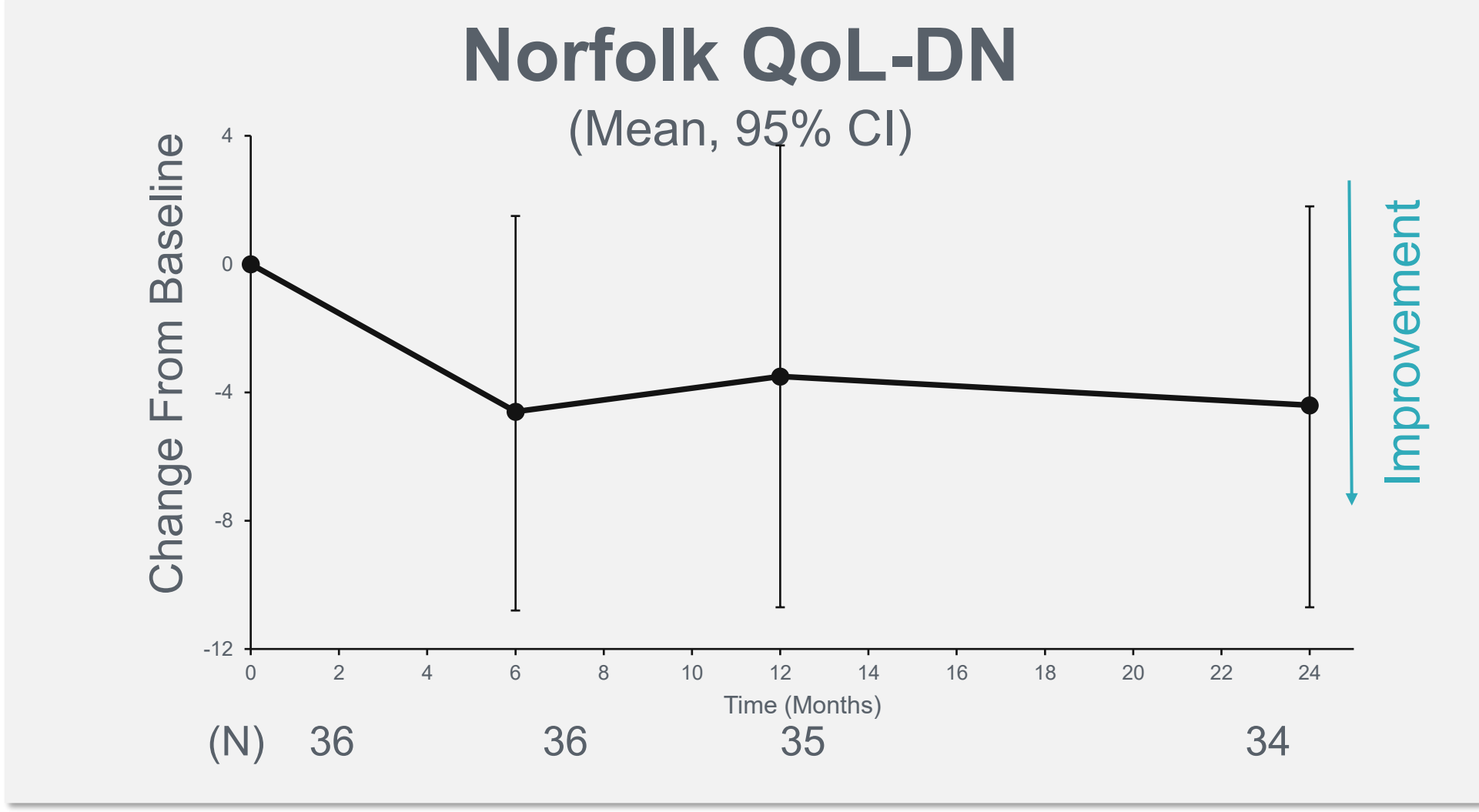
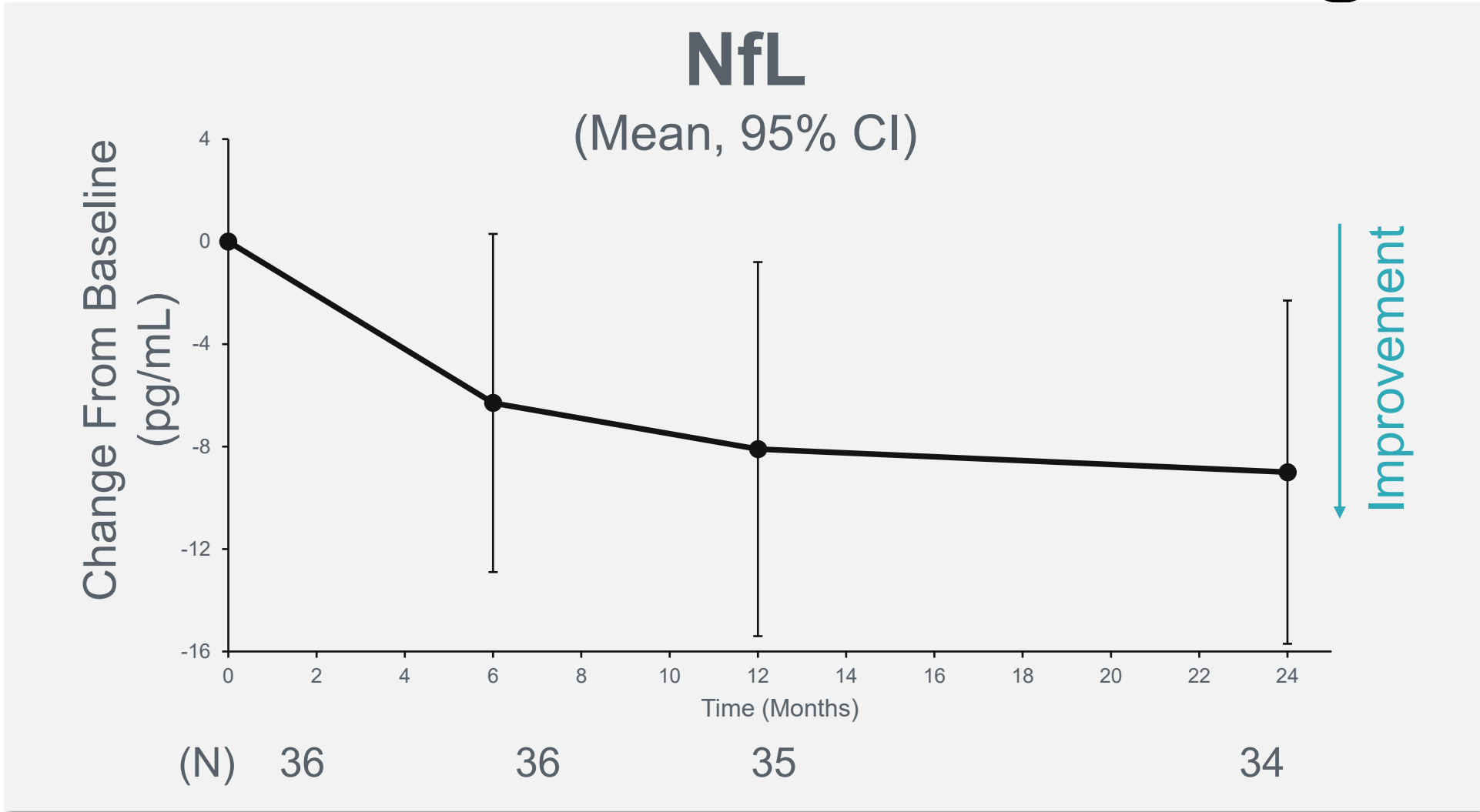
At Month 24, the majority of patients experienced improvements in mNIS+7



- The mean change in mNIS+7 at Month 24 was -8.5 points
- 13/18 (72%) patients had improvements in mNIS+7 which exceeded the clinically meaningful threshold of a ≥ 4 -point reduction¹

Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>
Data cutoff April 11, 2025.
Dotted line indicates cutoff for clinically meaningful improvement (Folkvaljon F, et al. *Muscle Nerve*. 2025;71(1):96-107.)
mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment.
mNIS+7, modified Neuropathy Impairment Score +7.

Multiple disease related clinical measures show stability or improvement though Month 24



Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>

Data cutoff April 11, 2025.

Norfolk QoL-DN total score ranges from -4 to 136, with lower scores indicating better QoL.

*Improvement, No Change, or Worsened in PND score is relative to the measurement at baseline. PND score were missing for 2 patients at Month 24. In the patient who died and the patient who discontinued, PND score remained unchanged from baseline at the last available assessment, Month 6 and Month 12, respectively.

mBMI, modified body mass index; NfL, neurofilament light chain; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PND, Polyneuropathy Disability; QoL, quality of life.



Safety summary in patients with ATTRv-PN treated with nex-z

Safety Events	All Patients (N=36) n (%)
At least 1 AE	36 (100)
AEs occurring in ≥15% of patients	
IRR	21 (58)
Headache	10 (28)
Diarrhea	8 (22)
Thyroxine decreased	8 (22) ^a
AST increased	6 (17) ^b
Any serious AE	11 (31)
Treatment-related SAEs	3 (8) ^c
Death	1 (3) ^d

- All patients received the intended dose of nex-z
- All IRRs were Grade ≤2 and resolved
- Three patients had ALT and/or AST elevations >5× ULN
 - No symptoms, changes in hepatic synthetic function, prolonged prothrombin time, or clinical sequelae; Hy’s Law criteria were not met
 - Onset occurred 24 to 35 days following infusion and all returned to normal levels without intervention within 31 to 58 days
 - Two patients received a 80mg dose and one patient received a 55 mg dose (selected as the Phase 3 dose)
- The safety profile in patients with prior disease progression on patisiran was comparable to the overall study population

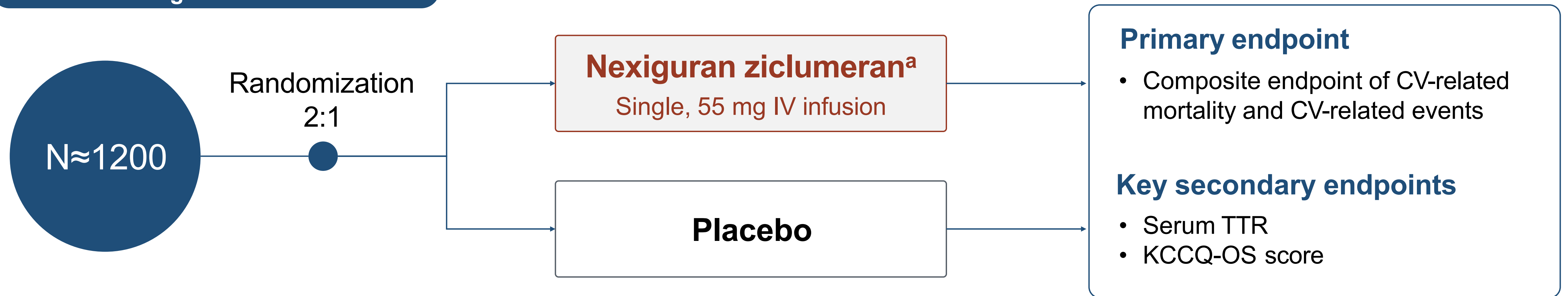
Gillmore, J. D., et al. (2025). Nexiguran Ziclumeran gene editing in hereditary ATTR. *The New England Journal of Medicine*, 393(15), 1375–1386. <https://doi.org/10.1056/NEJMoa2510209>
Data cutoff April 11, 2025.
^aNot accompanied by thyroid-stimulating hormone elevation or symptoms of hypothyroidism. No patient had clinical hypothyroidism or TSH elevation. ^b3 patients had Grade ≥3 liver enzyme elevations. ^cOne patient had grade 3 vomiting lasting 12 days, another had grade 2 ileus (Days 2–4), and the third patient had esophageal adenocarcinoma (Day 513) and prostate cancer (Day 610). This third patient had multiple risk factors for esophageal adenocarcinoma, including older age of 73 years, occupational chemical exposure including asbestos, a long history (>15 years) of smoking, heavy alcohol use, gastroesophageal reflux and recently diagnosed Barrett’s esophagus ^dOne patient died from sudden cardiac death associated with cardiac amyloidosis at Month 9, not considered treatment-related.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATTRv-PN, hereditary ATTR amyloidosis with polyneuropathy; IRR, infusion-related reaction; ULN, upper limit of normal.



MAGNITUDE: a Phase 3, randomized, double-blind, placebo-controlled study to evaluate nexiguran ziclumeran^a in patients with ATTR-CM^{1,2}



Clinicaltrials.gov ID: NCT06128629



Stratification:

- NAC stage
- *TTR* genotype: wild-type vs mutant
- Concomitant tafamidis or acoramidis use vs no tafamidis or acoramidis

Study duration:

- Dependent on occurrence of prespecified number of CV events and a minimum of 18 months of follow-up
- Majority of patients are expected to have ≥33 months of follow-up for the primary analysis

Nexiguran ziclumeran is an investigational product that has not been approved by FDA or received marketing authorization by any Health Authority.

^aNTLA-2001 is now known as nexiguran ziclumeran (nex-z).

ATTR-CM, ATTR amyloidosis with cardiomyopathy; CV, cardiovascular; FDA, U.S. Food and Drug Administration; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-overall summary;

NAC, National Amyloidosis Centre; TTR, transthyretin.

1. NIH. Accessed Jun 18, 2025. <https://clinicaltrials.gov/study/NCT06128629>. 2. Maurer MS, et al. Presented at: ESC Heart Failure; May 11-14, 2024; Lisbon, Portugal.



Select Eligibility Criteria for MAGNITUDE^{1,2}



INCLUSION CRITERIA

- 18 to 90 years of age
- Documented diagnosis of ATTR-CM
- Medical history of HF
- Symptoms of HF are optimally managed and clinically stable within 28 days prior to administration of study intervention
- Screening NT-proBNP, a blood marker of HF severity, greater than or equal to 600 pg/mL and less than 10000 pg/mL
- Able to complete distance of greater than or equal to 100 meters on the 6MWT at screening



EXCLUSION CRITERIA

- Amyloidosis (non-TTR protein/primary/leptomeningeal amyloidosis)
- NYHA Class IV HF at screening
- History of MI, unstable angina, severe aortic stenosis, CVA or TIA, symptomatic PAD, pulmonary emboli, or DVT within 3 months of study
- Polyneuropathy Disability score of IV (confined to wheelchair or bed)
- Initiation of tafamidis or acoramidis within 56 days prior to study dosing
- RNA silencer therapy (patisiran, inotersen and/or eplontersen) within 12 months prior to dosing. Any prior vutrisiran use is not allowed
- Any of the following within 28 days of study dosing:
 - Implantation of an electronic cardiac device, except loop recorders
 - Start or change in antiarrhythmic medication
 - CV hospitalization or invasive procedure
- History of cirrhosis
- AST, ALT, or total bilirubin >2 x ULN
 - >3.0 x ULN for patients with history of Gilbert's syndrome
- Prior liver, heart, or other solid organ transplant, bone marrow transplant; or anticipated transplant within 1 year of screening

6MWT, 6-minute walk test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; CVA, cerebral vascular accident; DVT, deep vein thrombosis; HF, heart failure; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; TIA, transient ischemic attack; TTR, transthyretin; ULN, upper limit of normal.

1. Maurer MS, et al. Poster presented at: European Society of Cardiology Heart Failure 2024 Congress; May 11-14, 2024; Lisbon, Portugal. 2. ClinicalTrials.gov identifier: NCT06128629. Updated August 29, 2025. Accessed Sept 7, 2025. <https://clinicaltrials.gov/study/NCT06128629>

Nex-z is an investigational product that has not been approved by FDA or received marketing authorization by any Health Authority.



Summary

- A **single dose of nex-z demonstrated favorable safety and tolerability** and resulted in deep, rapid, and durable **reductions in serum TTR** with very low variability among all patients with ATTR-CM and patients with ATTR-PN.
- Reductions in TTR were accompanied by stability or **improvement of several disease markers in an ATTR-CM population with advanced disease** who are expected to have rapid disease progression and high mortality rates.
- In patients with ATTR-PN, nex-z **favorably impacted multiple disease-relevant measures** with stability or improvements in most parameters.
- The effects of nex-z observed in this ongoing phase 1, single arm, open-label study will need to be confirmed in randomized controlled trials.



Conclusions

- These results represent the **first clinical evidence of *in vivo* CRISPR/Cas9 gene editing** showing that targeted inactivation of the *TTR* gene may favorably impact disease progression in ATTR-CM and ATTR-PN.
- These results also support the hypothesis that **rapid, deep, and durable reductions in serum TTR result in meaningful clinical benefits.**
- The effects of nex-z on clinical outcomes are being evaluated in MAGNITUDE^a, a phase 3, global, randomized, placebo-controlled trial in patients with ATTR-CM.



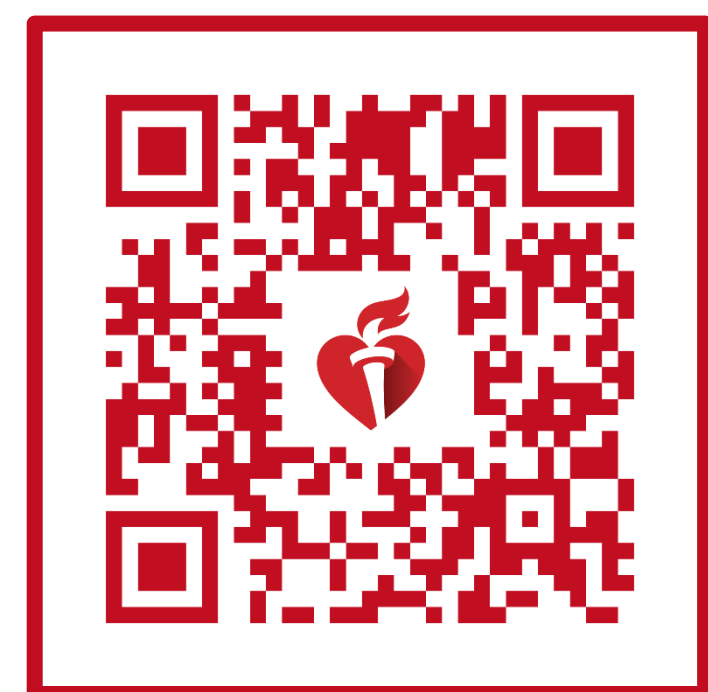
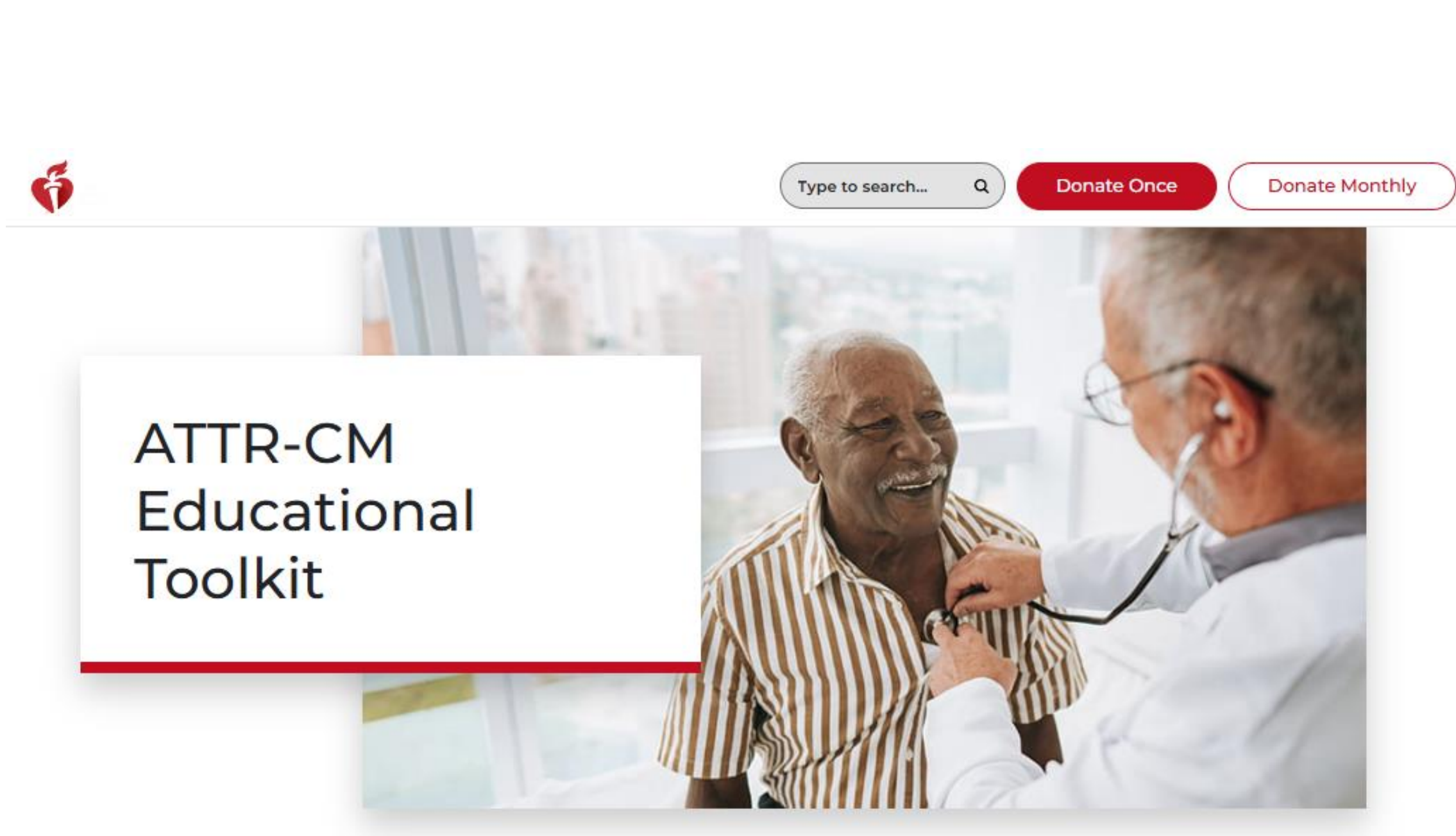


ATTR-CM Educational Toolkit

Kellie Lavender
*National Program Lead,
Patient Education and Support,
American Heart Association*



ATTR-CM Educational Toolkit



Scan the QR code
to Learn More!

www.heart.org/ATTR-CM

ATTR-CM Educational Materials

Health Care Provider Toolkit

This resource helps clinicians engage patients with conditions like transthyretin amyloid cardiomyopathy (ATTR-CM) in conversations about emerging therapies and research opportunities.

- **Clear explanations** – Breaks down the differences between gene editing and gene therapy in simple, relatable terms.
- **Patient support** – Offers guidance to address common concerns and foster shared decision-making.
- **Clinical trial insights** – Outlines the process, protections, risks, and benefits of participation.
- **Trusted resources** – Provides links to AHA guides, ClinicalTrials.gov, and genetic counseling directories for further support.

By combining clear communication with reliable tools, this toolkit empowers patients and caregivers to make informed decisions about their care.

Download Toolkit

Patient & Caregiver Guide

This guide gives patients and caregivers clear, supportive information about genetic heart conditions like transthyretin amyloid cardiomyopathy (ATTR-CM) and emerging treatments.

- **Easy-to-understand explanations** – Breaks down genetic conditions, gene editing, and gene therapy using simple examples.
- **Clinical trial basics** – Explains what trials are, how they work, and what to expect during participation.
- **Decision support** – Helps patients reflect on personal values and goals when considering trial options.
- **Caregiver resources** – Offers guidance for supporting loved ones emotionally, practically, and in conversations with doctors.
- **Trusted tools** – Connects readers to AHA resources, ClinicalTrials.gov, and genetic counseling services.

This guide empowers patients and families to feel informed, ask the right questions, and move forward with confidence in their care.

Download Guide

Understanding Clinical Trials

This infographic gives patients and families a clear overview of what clinical trials are and what to expect if you join one.

- **What trials do** – Explain how treatments are tested for safety and effectiveness.
- **Step-by-step process** – Covers learning about the trial, screening and consent, treatment and monitoring, and what happens afterward.
- **Patient choice** – Reinforces that participation is voluntary, and you can leave at any time.
- **Support system** – Highlights the role of cardiologists, genetic counselors, and trial coordinators in guiding you through the process.
- **Trusted source** – Based on recommendations from the American Heart Association.

This resource helps patients and caregivers feel prepared, informed, and supported when considering trial participation.

Download Clinical Trial Infographic



Health Care Professional Toolkit

2. Tips for Discussion With Your Patients

Introducing the concept: The recipe book metaphor^{1,2}

Gene editing and gene therapy can be explained using the metaphor of a recipe book.



Imagine the human genome as a recipe book containing instructions for how the body functions. Each recipe (gene) contributes to the body's health. Sometimes, a recipe has a mistake that leads to problems.



Gene editing is like fixing the recipe directly in the book. It removes or corrects the faulty instruction so future batches (cell replications) are made correctly.



Gene therapy is like adding a missing ingredient or replacing a faulty recipe with a new one. It doesn't change the recipe book itself but supplements it to restore balance.

Tips for addressing patient concerns

Your patients are likely to be nervous or concerned when considering these types of treatments. You can anticipate common worries and respond with clarity and compassion:

"This feels overwhelming."

That's totally natural. We're here to help you understand every step.

"Will this change all my genes?"

No—it only targets the specific gene causing the issue. It's like fixing one recipe, not the whole book.^{2,3}

"I don't trust clinical trials."

We understand your concerns. Today's trials follow strict ethical guidelines with informed consent and safety checks.¹¹⁻¹³

"How does this affect my family or future children?"

These treatments affect only the targeted cells, not reproductive cells, so they won't pass on changes to children.³

"Will I be treated differently because of my race, gender, or religion?"

This treatment is available to all eligible patients, and we're committed to ensuring everyone has equal access to care.¹¹⁻¹³

Reinforce transparency and shared decision-making:

Let's talk through the risks and benefits together. You can opt out of participation at any time. This is your decision.¹⁴

Whether at diagnosis, during genetic counseling, or at the time of choosing a path forward, balancing optimism with realism fosters trust. This encourages informed decision-making and ensures your patients feel supported throughout their care journey.



3. Explaining Clinical Trial Participation Clearly and Transparently

Demystifying clinical trial participation

Clinical trials are a vital part of advancing medical research, and discussing them with your patients and their caregivers requires clarity, empathy, and transparency. Below are some tips to help you guide these conversations effectively.¹⁴



Clinical trials are an important part of scientific research.

Key aspects of clinical trials



Purpose

Trials aim to test new treatments, improve existing ones, or explore innovative approaches to care. Participation contributes to medical advancements while prioritizing patient safety.^{11,14}



Process Overview

Trial participation involves a sequence of screening, doctor visits, procedures, and follow-ups. They are highly structured and include ongoing support throughout the process.^{12,14}



Patient Protections

Safety measures include informed consent, ethical oversight, and patient monitoring. Patient privacy and well-being are top priorities.¹¹⁻¹⁴



Benefits and Risks

There are potential benefits (e.g., access to cutting-edge treatments) and risks (e.g., side effects or uncertainty of outcomes), and both must be considered on balance.^{11,13,14}



Values-Based Decision-Making

Patients should be encouraged to reflect on their personal values, goals, and preferences when considering trial participation.



Patient & Caregiver Guide

2. What Is a Genetic Condition That Affects the Heart?

Genes affect how your body works

DNA is a tiny chemical structure in all of your cells that carries the instructions your body needs. DNA tells the body how to grow, work, and repair itself. Genes are sections of your DNA. Genes give instructions to your cells to make the proteins that build and maintain your body. Some heart conditions are caused by changes in your genes.

Your DNA comes from your parents. It determines traits like eye color, height, and even your risk for certain diseases. Scientists study DNA to better understand how changes in genes' instructions can affect health and to develop new treatments for genetic conditions.

Your DNA recipe:



Think of DNA as a recipe book. Each gene is like a specific recipe or page in that book.



If one of the pages in your recipe book has a typo, your body might make a protein that doesn't work right.



That can lead to problems, like harmful protein buildup in your heart.

DIGGING DEEPER: Types of genetic conditions that affect the heart

ATTR-CM (transthyretin amyloid cardiomyopathy):

This happens when a protein in your body called transthyretin breaks down and forms deposits in the heart. These buildups, or amyloids, can make it harder for your heart to pump blood properly. There are two types—one that is hereditary and one that is not.

Familial hypercholesterolemia (FH):

This causes very high cholesterol. Cholesterol is a waxy substance in your blood that helps build healthy cells. Too much can cause fatty buildup in your blood vessels, raising your risk of heart disease.

Hypertrophic cardiomyopathy (HCM):

This makes the walls of your heart muscle thicker than normal. It can block blood flow and make your heart work harder than it should.

Long QT syndrome (LQTS):

This affects your heart's rhythm. It can cause your heart to beat abnormally.

Finding out that you have a heart condition can feel overwhelming. Learning about it is an important first step toward getting the care and support you need.

How to ask about clinical trial participation

If you're thinking about joining a gene editing trial, here are the people who can help you understand what it means and what to ask:

- **Your cardiologist** (heart doctor) can tell you if a trial might be right for you and how it fits into your care. You can ask about the risks, possible benefits, and what to expect
- **A genetic counselor** can explain how your genes and family history affect your health. They can also help you understand gene editing in simple words
- **A trial coordinator** can help with questions about signing up, scheduling, and support during the trial. They make sure you know what joining a trial means

Questions to help you talk with your doctor about a clinical trial

What to ask or consider	Notes section
What are the short- and long-term risks I should know about before participating in this trial?	
What kind of support (transport, caregiver help, communication) will I receive?	
Where do I need to go, and how often will I need to go there?	
What will happen during those visits?	
What happens if I miss or stop a treatment?	
What happens when the trial is over? Will I still get care?	
What do I have to pay for during the trial?	
Will I keep taking my regular medicine during the trial?	
Do I need to do anything on my own like keep a journal or fill out surveys or questionnaires?	
Will I need to have internet access or an app on my phone?	



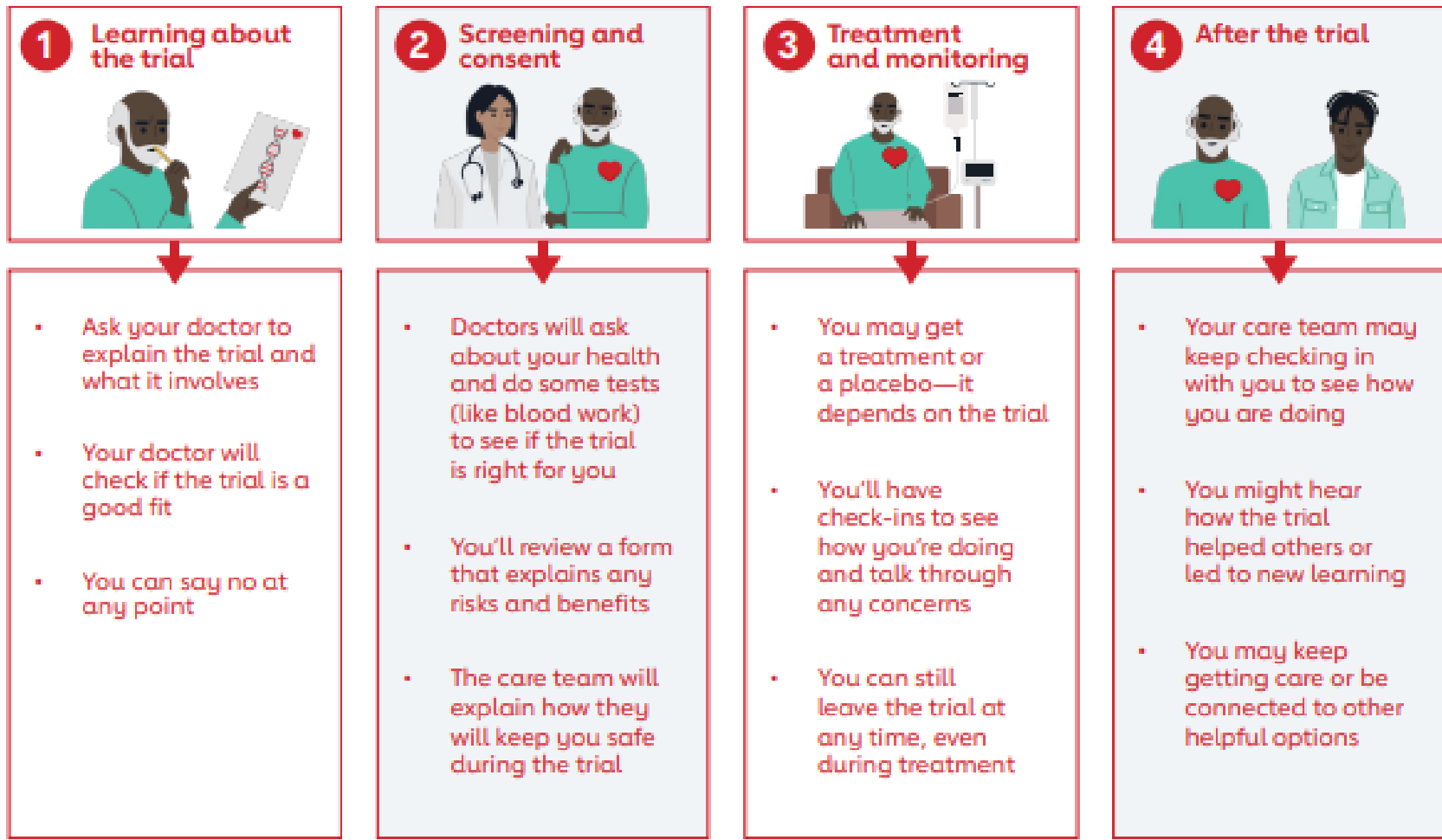
Clinical Trial Infographic

What Is a Clinical Trial?



Clinical trials help doctors test treatments to see if they are safe and helpful. If you join a trial, you become part of a team working to improve care for yourself and others.

Every clinical trial differs based on what is being studied. Here's what to expect:



Who to ask about clinical trial participation

- Your cardiologist (heart doctor)
- A genetic counselor
- A trial coordinator

What questions do you or your family/caregiver have for your doctor?



You can find information at www.heart.org/ATTR-CM

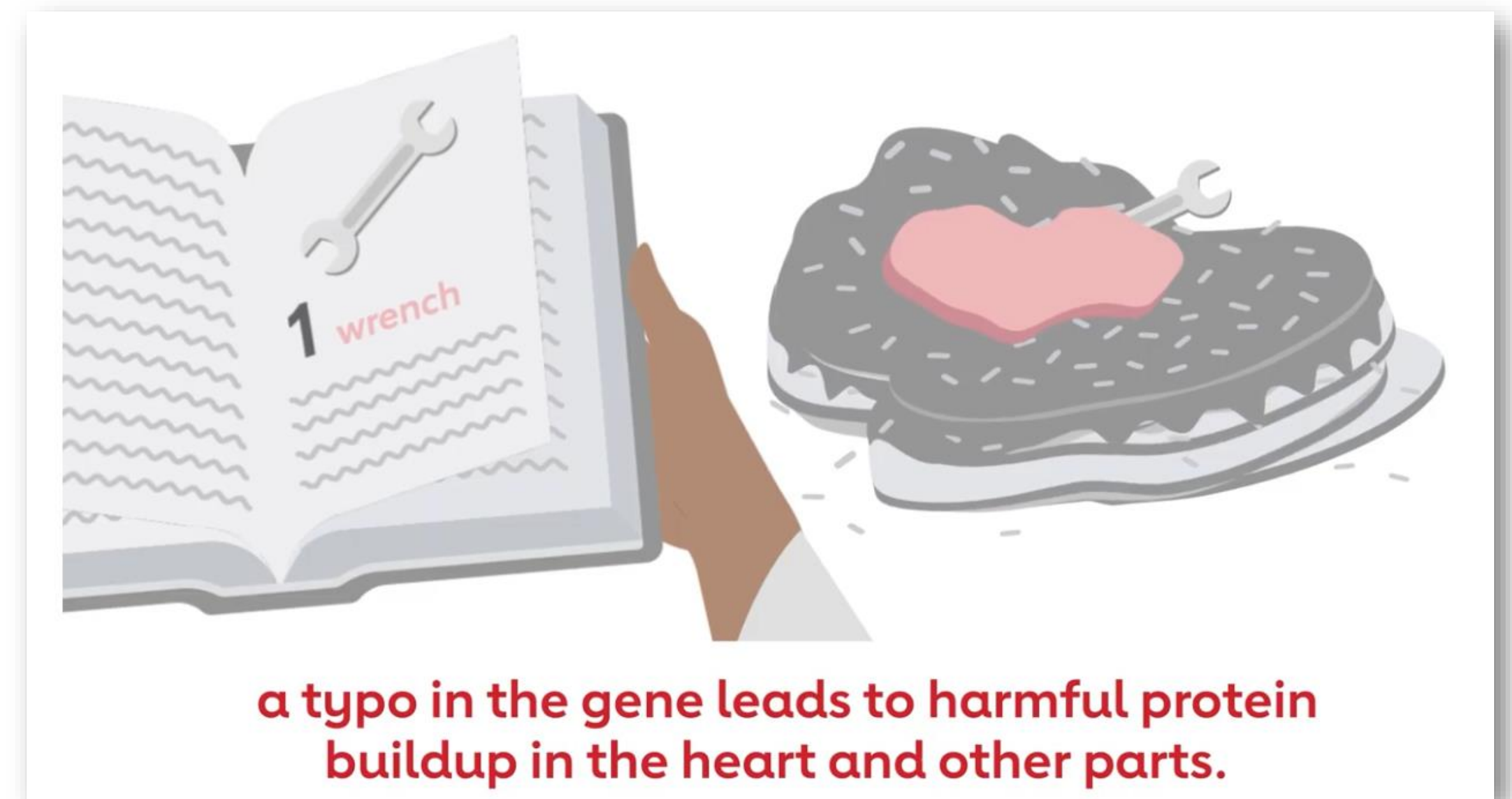
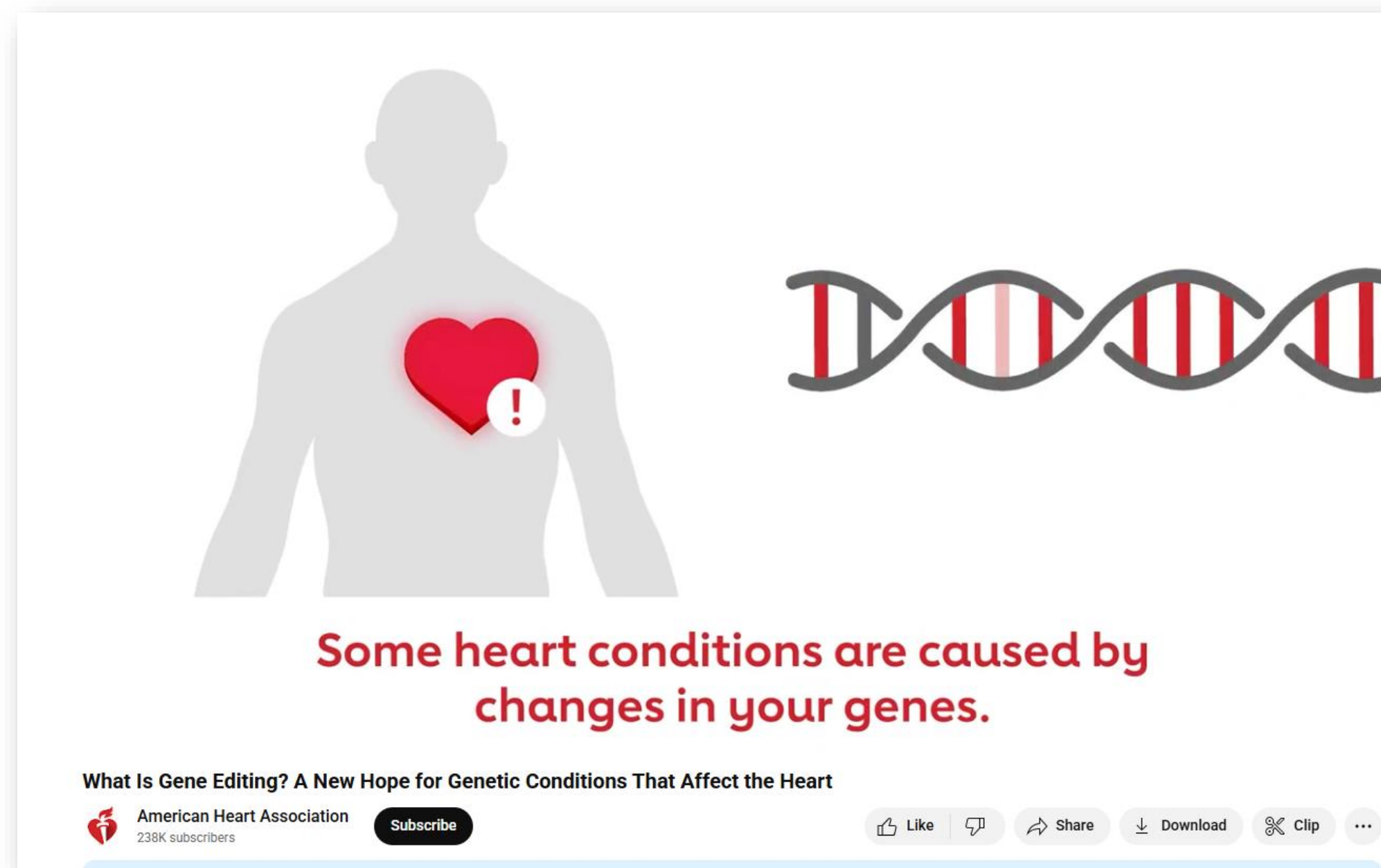
Intellia Therapeutics is proud to support the American Heart Association's Gene Therapy Awareness and Education resources. This information is based on recommendations from the American Heart Association.

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Video:

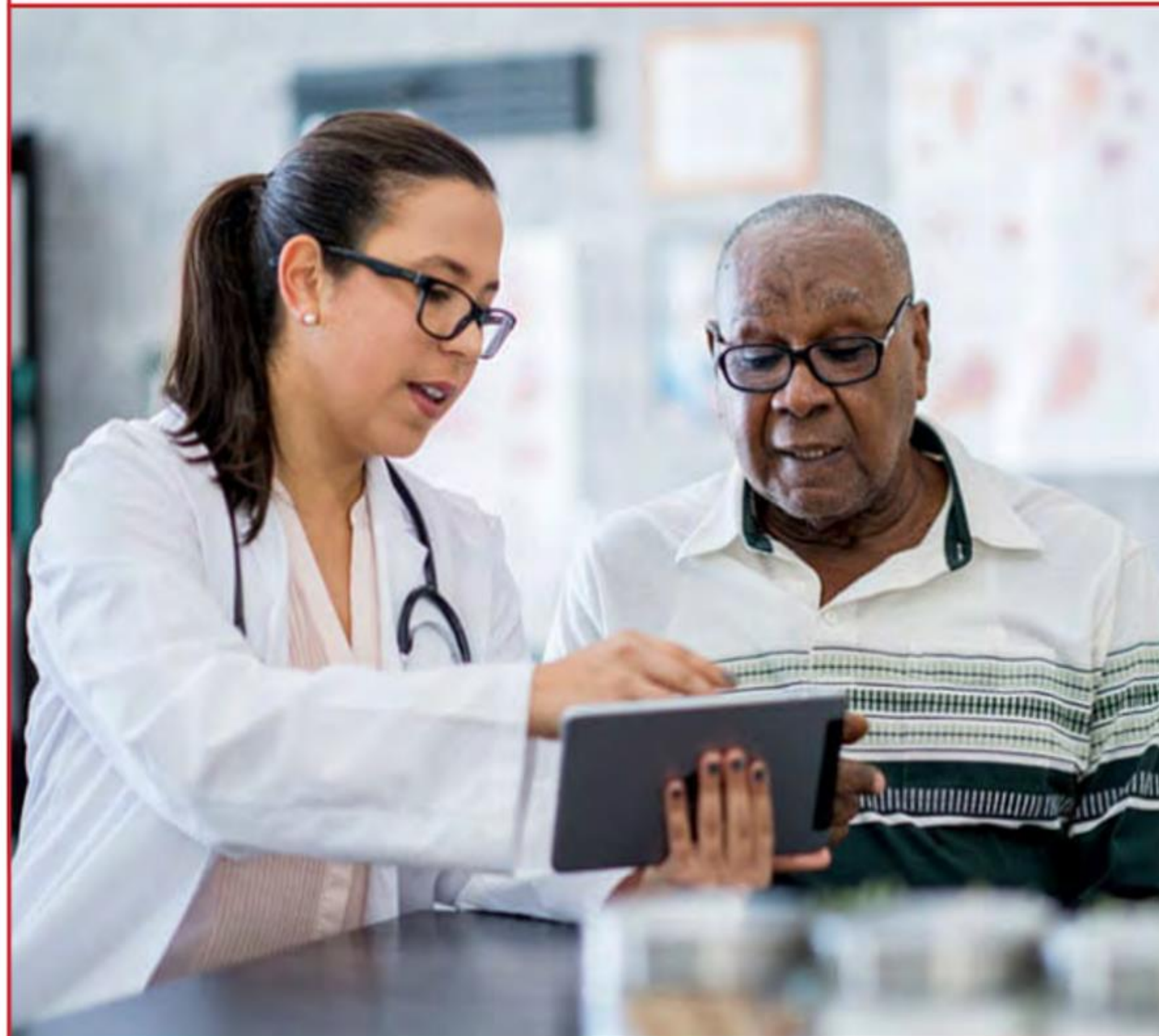
What Is Gene Editing? A New Hope for Genetic Conditions That Affect the Heart





American
Heart
Association.

Talking to Patients About Gene Editing and
Clinical Trials: A Guide for Clinicians



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ATTR-CM Resources Available



Health Topics:
What is ATTR-CM?



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Health Topics:
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Transthyretin Amyloid Cardiomyopathy (ATTR-CM)



What is transthyretin amyloid cardiomyopathy?

Transthyretin (trans-thy-re-tin) amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed and potentially fatal disease of the heart muscle. In ATTR-CM, a protein called transthyretin that normally circulates in the bloodstream becomes misshapen and builds up in the heart, nerves and other organs.

Cardiomyopathy

What is Cardiomyopathy? —

Dilated Cardiomyopathy (DCM)

Hypertrophic Cardiomyopathy (HCM)

HCM in Young Adults and Student Athletes

Peripartum Cardiomyopathy (PPCM)

Restrictive Cardiomyopathy

Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Arrhythmogenic Right Ventricular Dysplasia

Is Broken Heart Syndrome Real?

Understand Your Risk for Cardiomyopathy +

Symptoms and Diagnosis of Cardiomyopathy

Prevention and Treatment of Cardiomyopathy

HCM Personal Stories +

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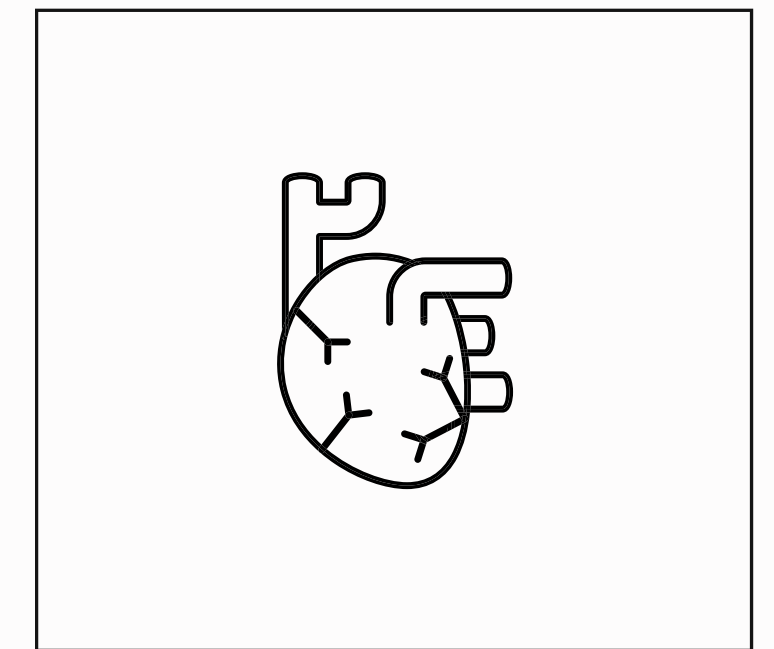
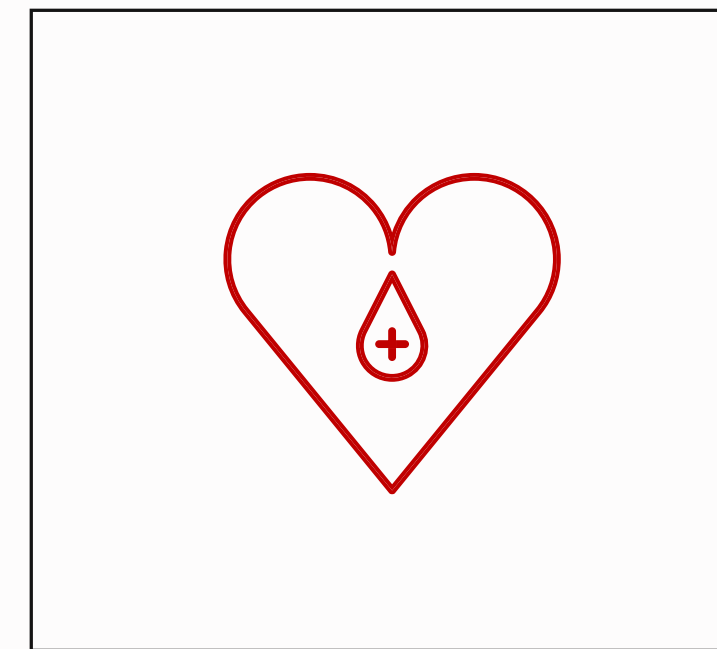
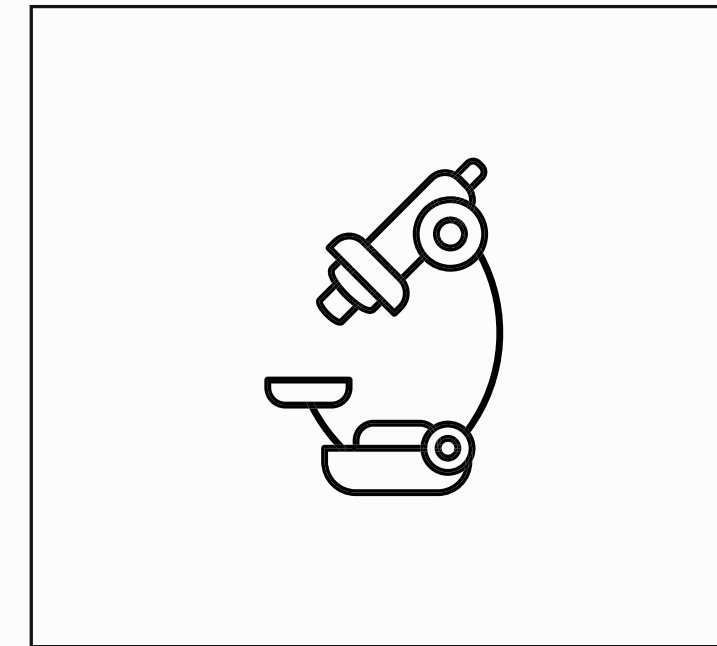


Q & A

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Continuing the Conversation



Webinar #3 – December 2025

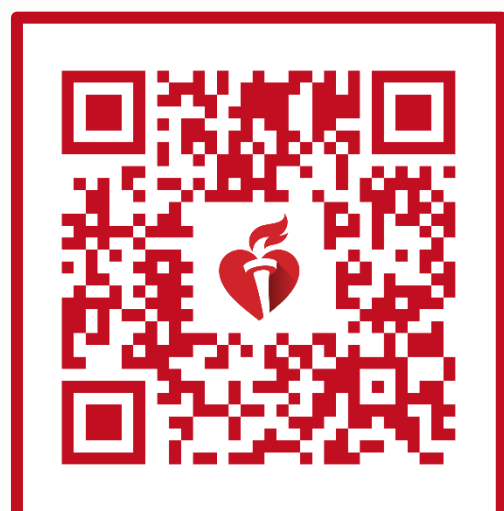
ATTR-CM in Practice: New Therapies & Precision Approaches

Webinar #4 – February 2026

Multidisciplinary Care & Future Directions in Amyloidosis

STAY TUNED!

Invitation and registration details for upcoming webinars will be shared in the coming weeks!



Scan the QR code to Learn More! Or visit: www.heart.org/ATTR-CM





Thank you for joining us today!

Recordings of today's sessions will be enduring resources in a few weeks on

www.heart.org/ATTR-CM



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