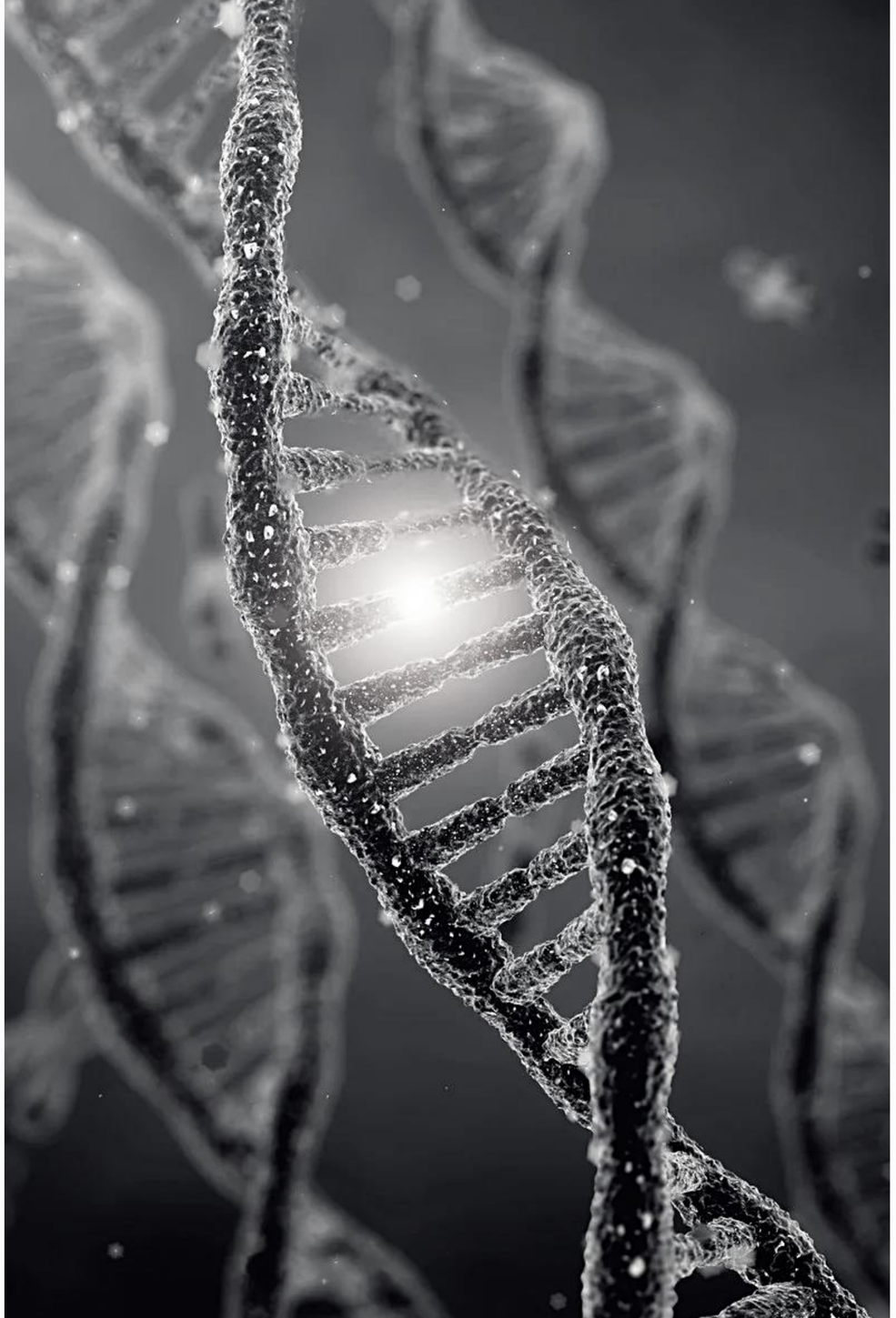

AMERICAN HEART ASSOCIATION'S
ATTR-CM WEBINAR SERIES:
WEBINAR #2

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.

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Meeting ID: 822 1919 2873
Passcode: 739461

Welcome & Introductions

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

Thank you to

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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

Disclosures

American Heart Association Statement

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

American Heart Association®

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/m^2
  - HR 68 bpm
  - BP 142/88 mm Hg
  - JVP 10 cm H_2O
  - 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 cm^2), 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 ~~31~~ 24 kg/m^2
  - HR 68 bpm
  - BP ~~142/88~~ 100/80 mm Hg
  - JVP ~~10~~ 14 cm H_2O
  - Lungs clear,
  - Heart regular with an S4 gallop
  - 2+ edema

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A. Cardiac amyloidosis

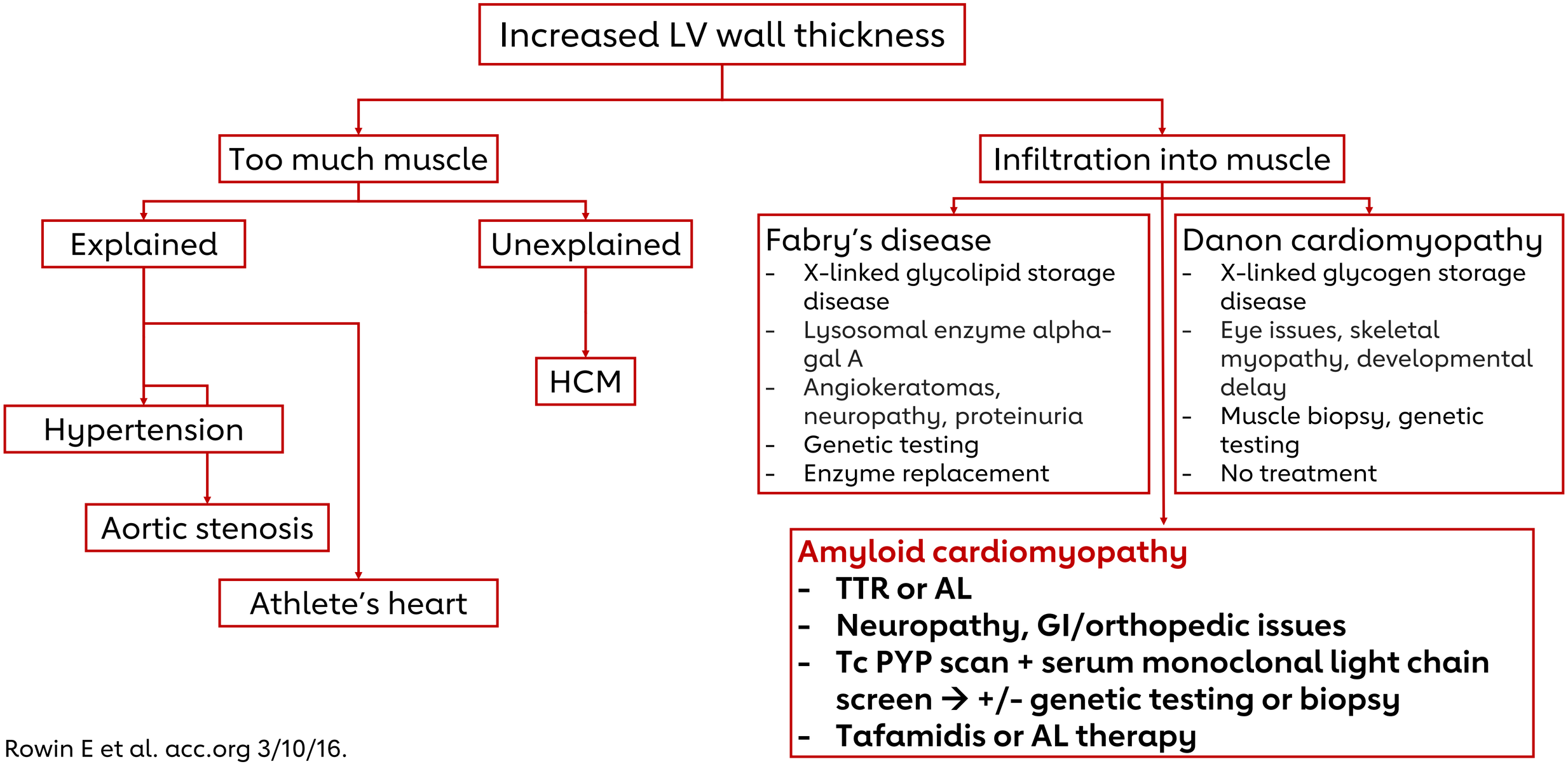
B. Heart failure with preserved ejection fraction

C. Hypertrophic cardiomyopathy

D. Aortic stenosis

E. Pulmonary arterial hypertension

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



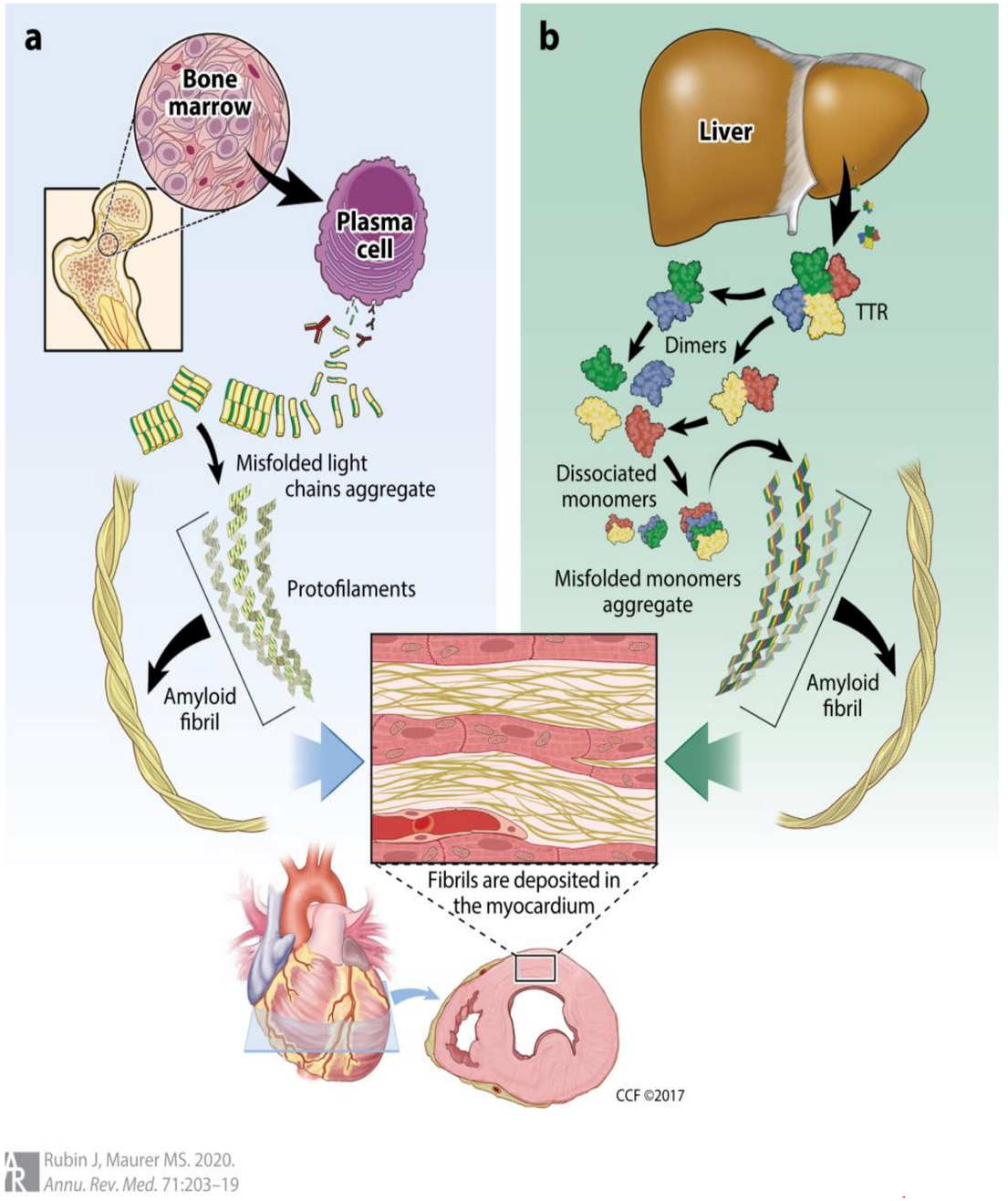
Rowin E et al. acc.org 3/10/16.

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis = protein infiltrates myocardium → restrictive cardiomyopathy

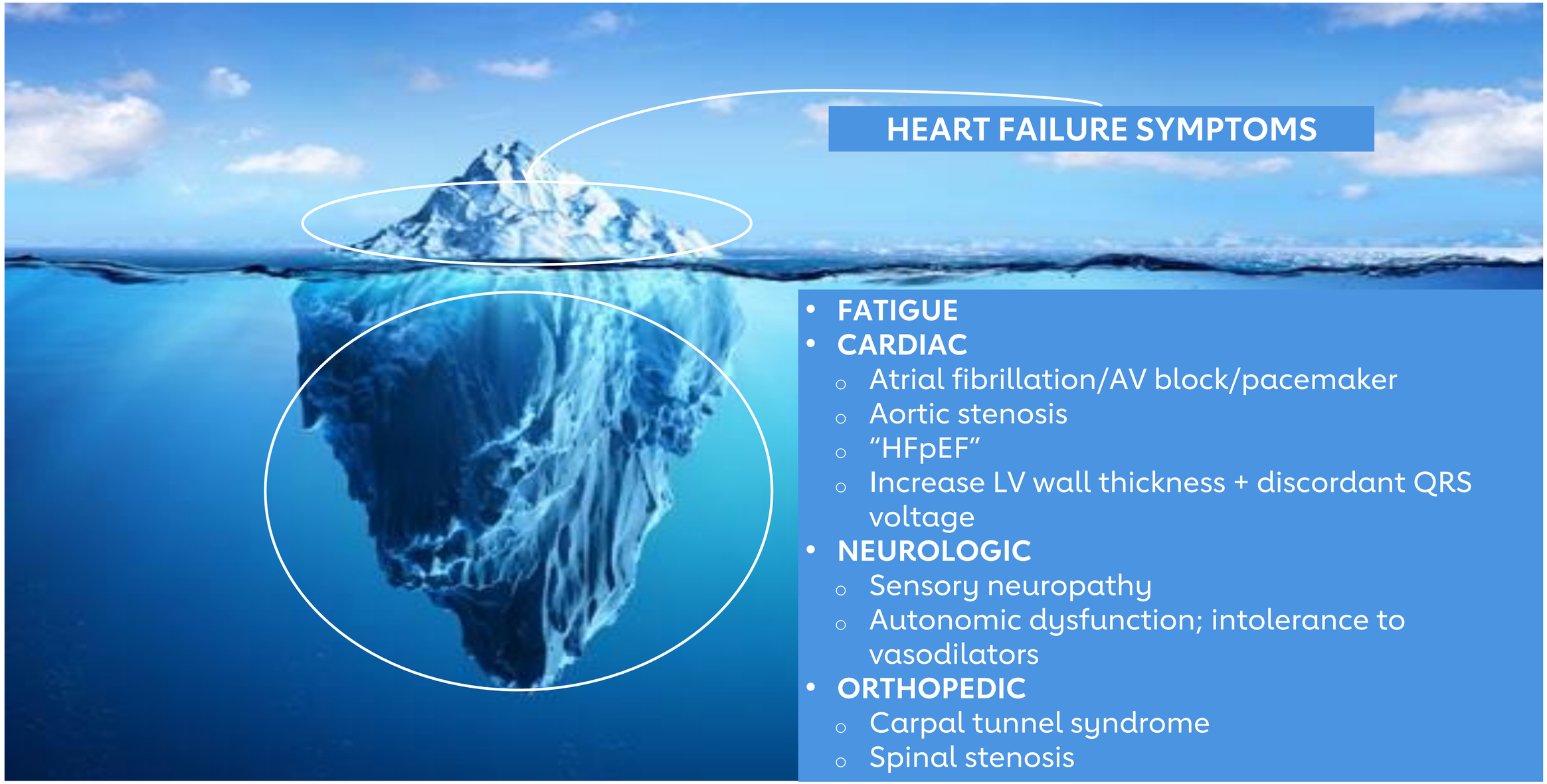
- Light chains → AL -CM
- TTR protein → ATTR-CM
  - Mutation in *TTR* gene: ATTRv-CM
  - Wild-type *TTR* gene: ATTRwt-CM

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

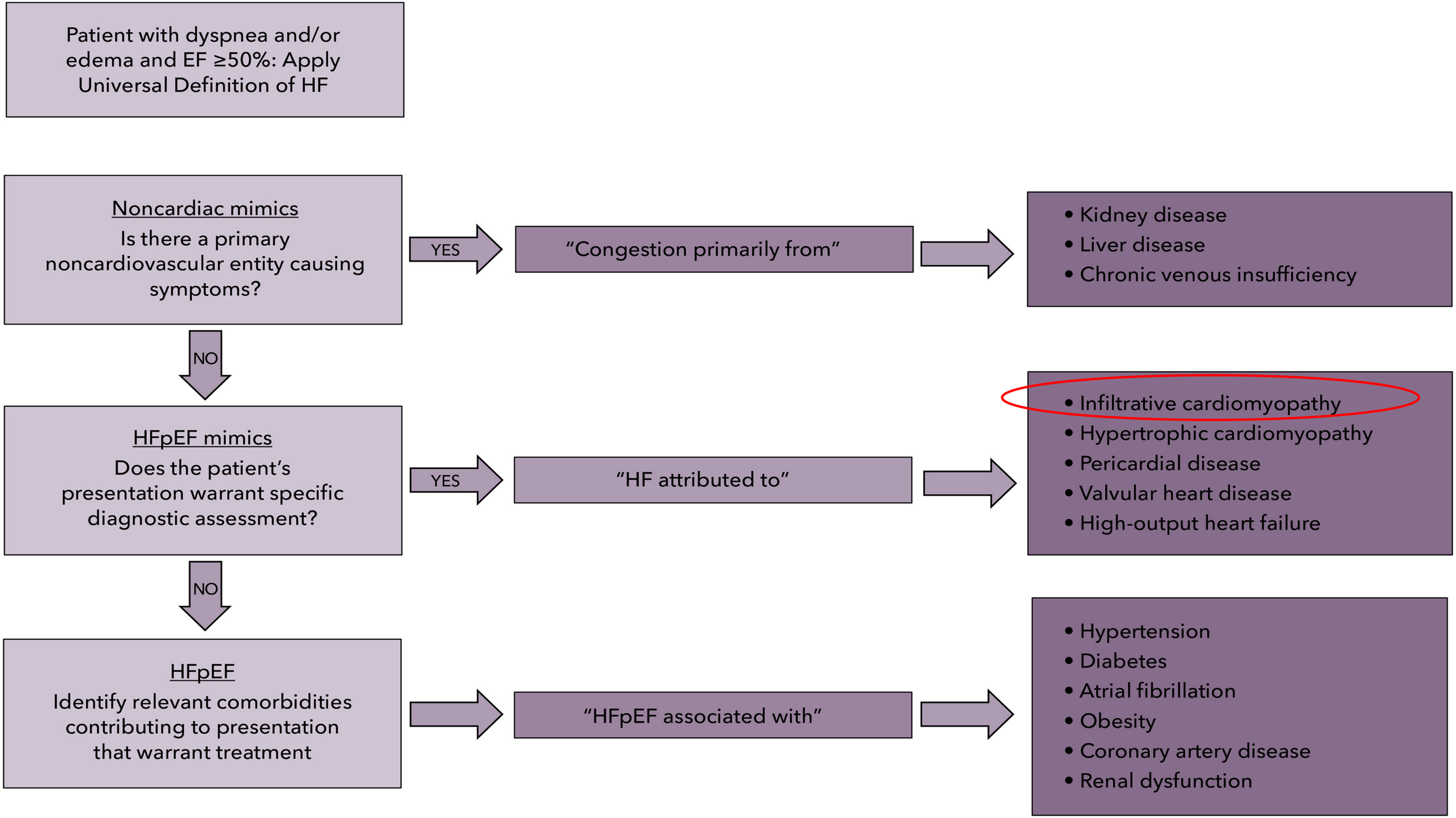


Rubin J, Maurer MS. 2020. *Annu. Rev. Med.* 71:203–19

AMYLOIDOSIS: HIGH INDEX OF SUSPICION



- **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



Kittleson et al. J Am Coll Cardiol. 2023 May, 81 (18) 1835–1878

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.**

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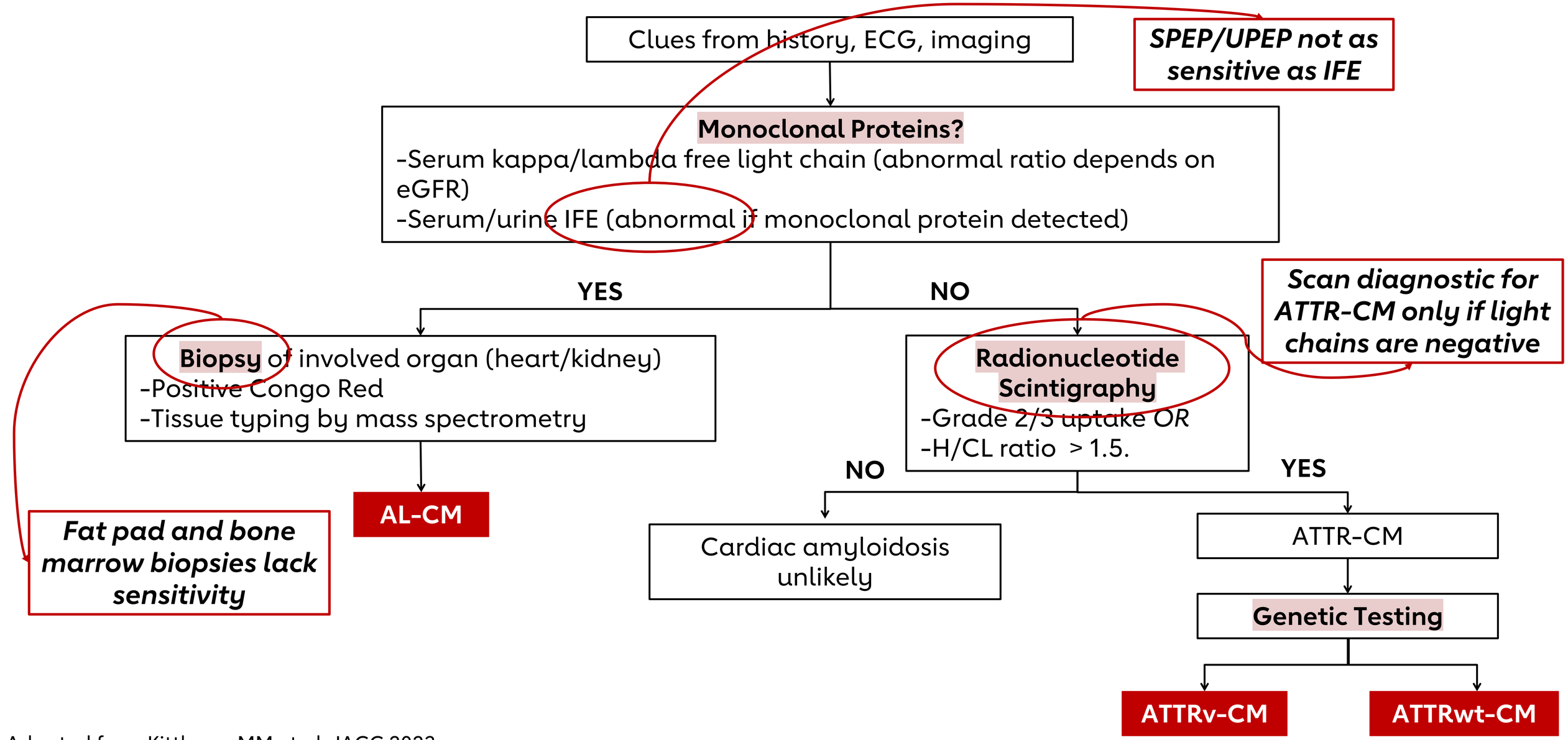
AMYLOIDOSIS: 3 (+/- 1) TESTS → 3 POSSIBLE DIAGNOSES



Adapted from Kittleson MM et al. JACC 2023.

AMYLOIDOS

GNOSES

Recommendations for Diagnosis of Cardiac Amyloidosis

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 *TTR* gene sequencing is recommended to differentiate hereditary variant from wild-type transthyretin cardiac amyloidosis.[8]

as
E

diagnostic for
-CM only if light
ns are negative

Biopsy of invo
-Positive Congo
-Tissue typing by

Fat pad and bone marrow biopsies lack sensitivity

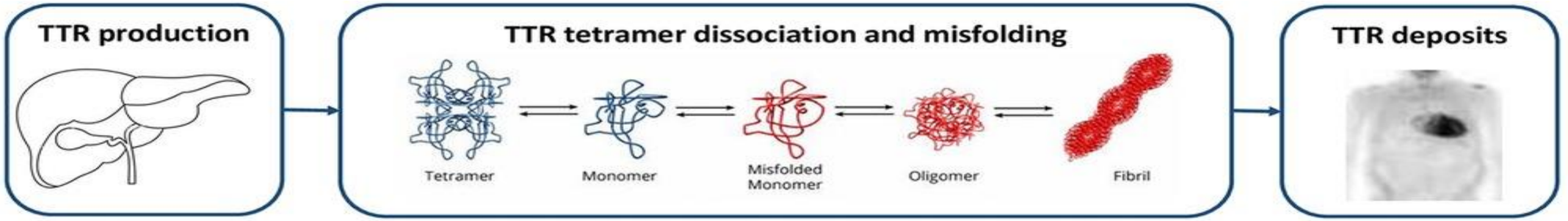
-CM

Testing

ATTRwt-CM

Adapted from Kittleson MM et al. JACC 2023.

THERAPIES FOR TRANSTHYRETIN AMYLOIDOSIS



Inhibition of TTR synthesis

- **Liver transplantation**
- **RNA silencing**

siRNA:
- Patisiran
- Revusiran
- Vutrisiran

ASO
- Inotersen
- Eplontersen

- **Gene editing**

CRISPR–Cas9:
- **Nexiguran Ziclumeran**

TTR stabilization

Non-selective agents
- Diflusinal

Selective agents
- Tafamidis
- Acoramidis

TTR degradation

- Doxyciclin and (T)UDCA

Monclonal Ab
- PRX004
- NI006

Approved and available for use

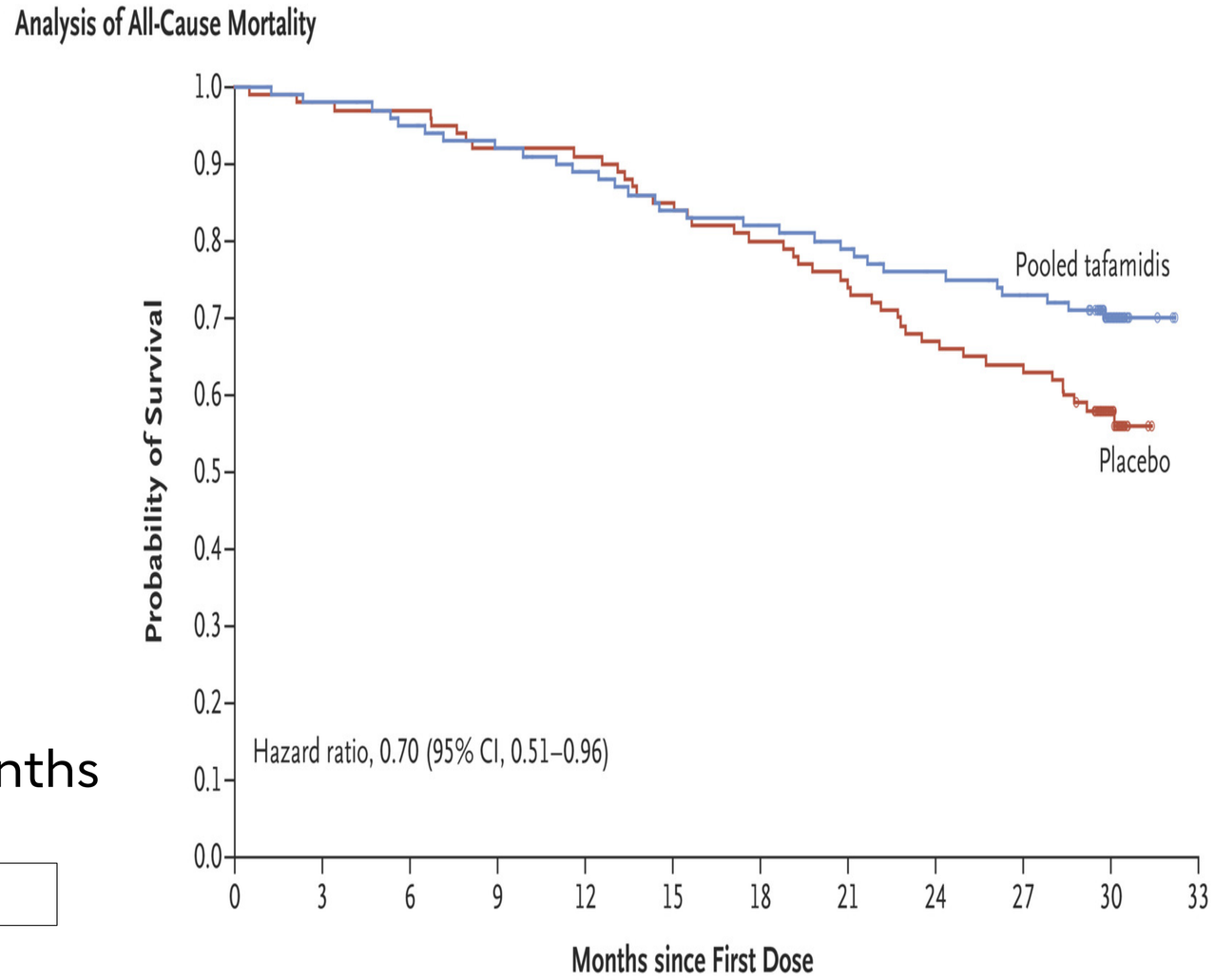
Investigational

Tomasoni D et al. Front. Cardiovasc. Med., 23 May 2023

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

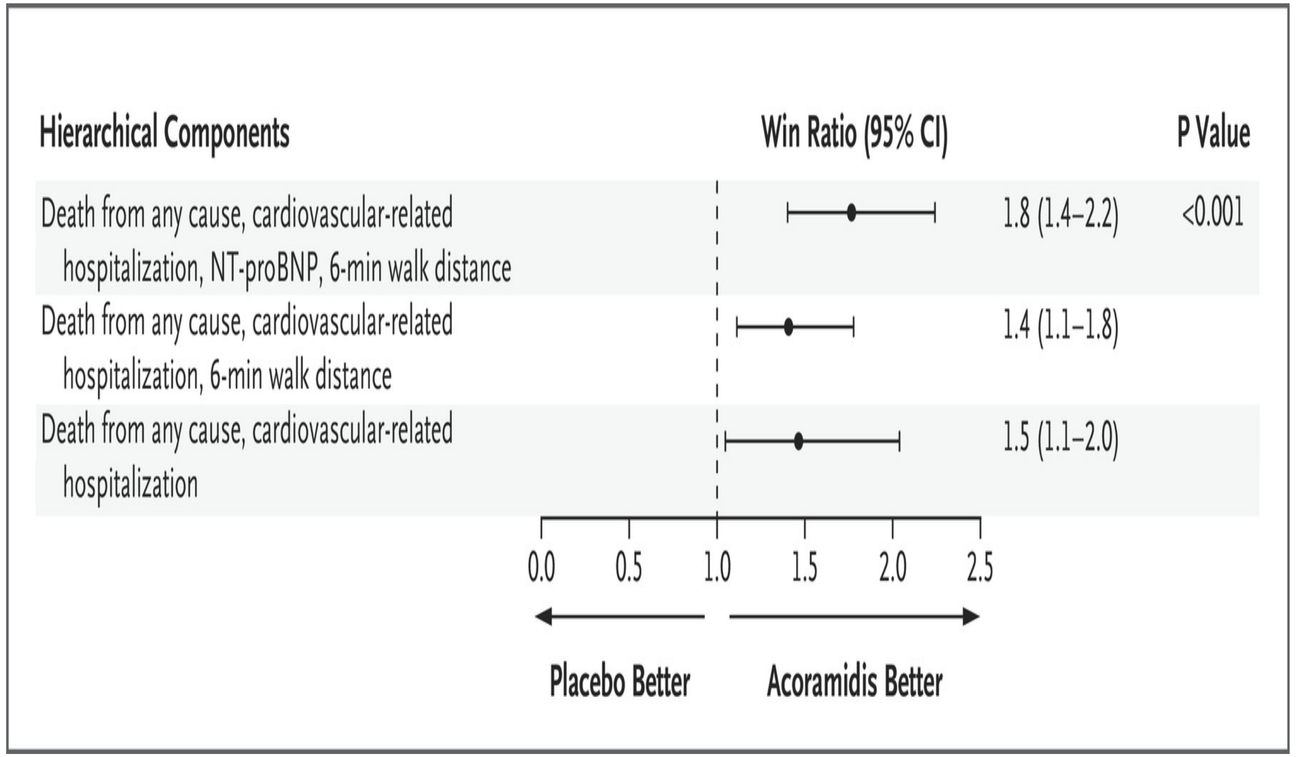


Maurer M et al. N Engl J Med. 2019;380:196-197; Maurer et al. NEJM 2018.

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

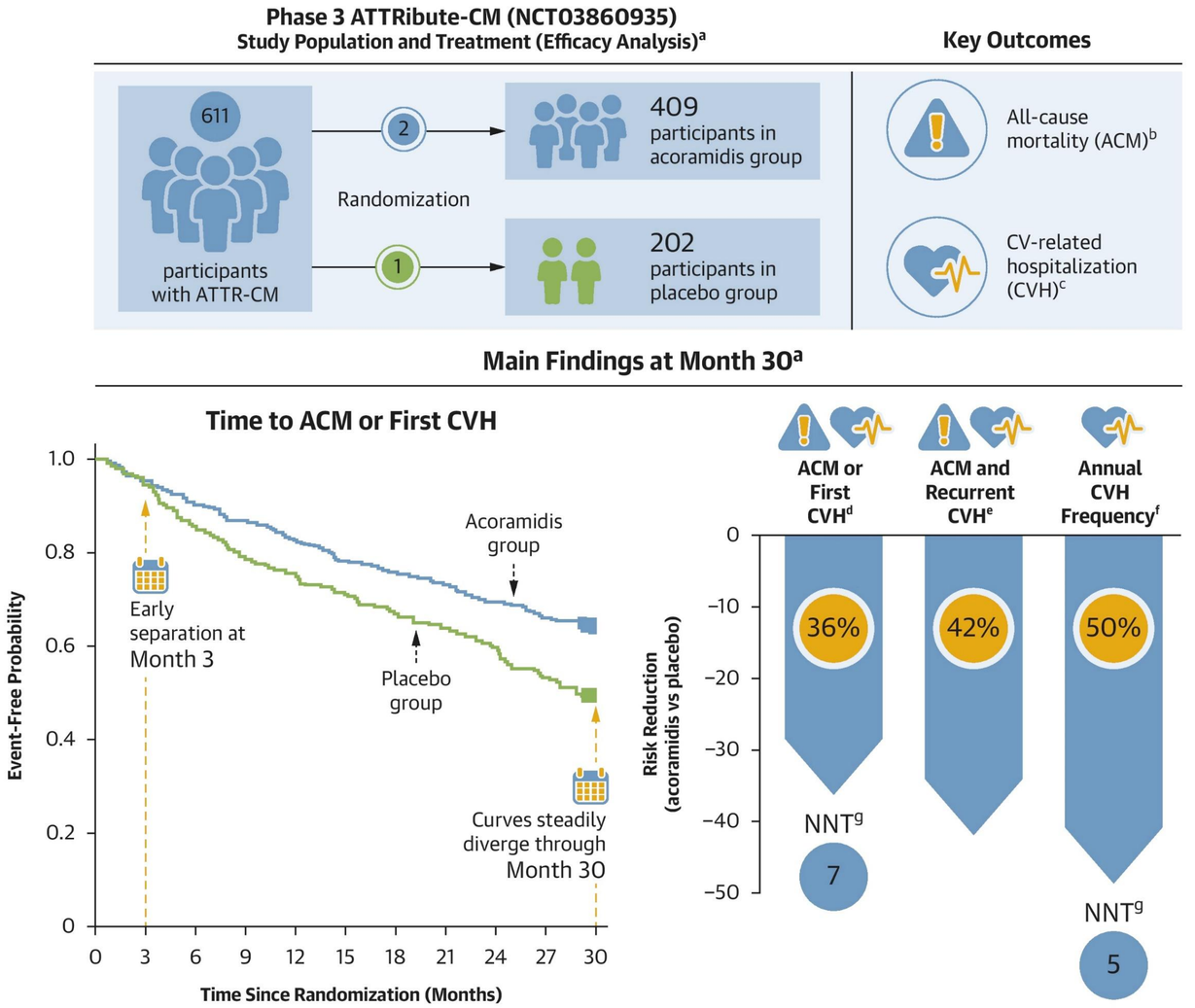
Gillmore J et al. N Engl J Med 2024; 390:132-142.
Judge D et al. JACC 2025 in press.

TTR Stab

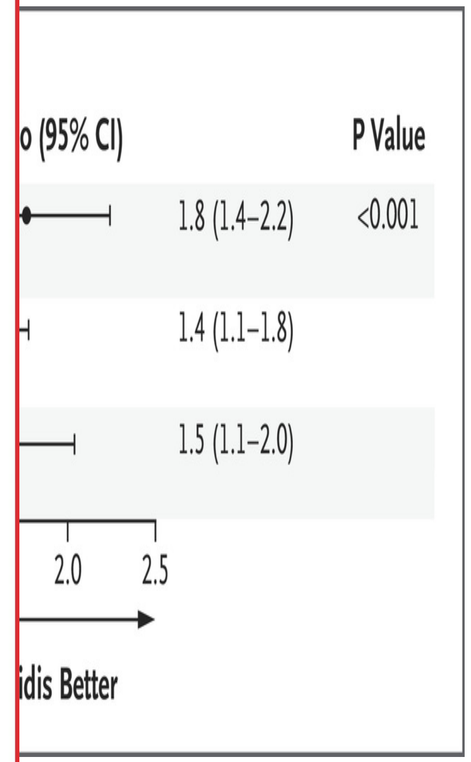
- ATTR-CM
- Acoramidis 800
- 632 patients
- Tafamidis allow
  - *(17% on tafar*
- Primary endpoi

FDA Approv

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.



Gillmore J et al. N Engl J Med 2024; 390:132-142.
Judge D et al. JACC 2025 in press.

TTR Silencers: Early Promise

APOLLO: Patisiran (IV) [1]
ATTRv with neuropathy +/- CM
↓ neuropathy
56% improved at 18m

NEURO-TTR: Inotersen (SC) [2]
ATTRv with neuropathy +/- CM
↓ progression of neuropathy
36% improved at 15m

Reduces progression of neuropathy in patients with ATTRv with neuropathy

Post-hoc APOLLO in ATTRv-CM
Patisiran
↓ LV strain/thickness, ↓ NT-proBNP [3, 4]

Open-label in ATTRv-CM
Inotersen
↓LV mass/thickness, ↓ BNP, ↑6MWT[5]

May offer some benefit in patients with ATTRv who happen to have cardiomyopathy

ENDEAVOUR: Revusiran[6]
ATTRv-CM
Stopped at 6.7m due to ↑ deaths in treatment arm

APOLLO-B: Patirisan[7]
ATTR-CM, 12 m
Less decline in 6MWT
Stable vs worse KCCQ-OS

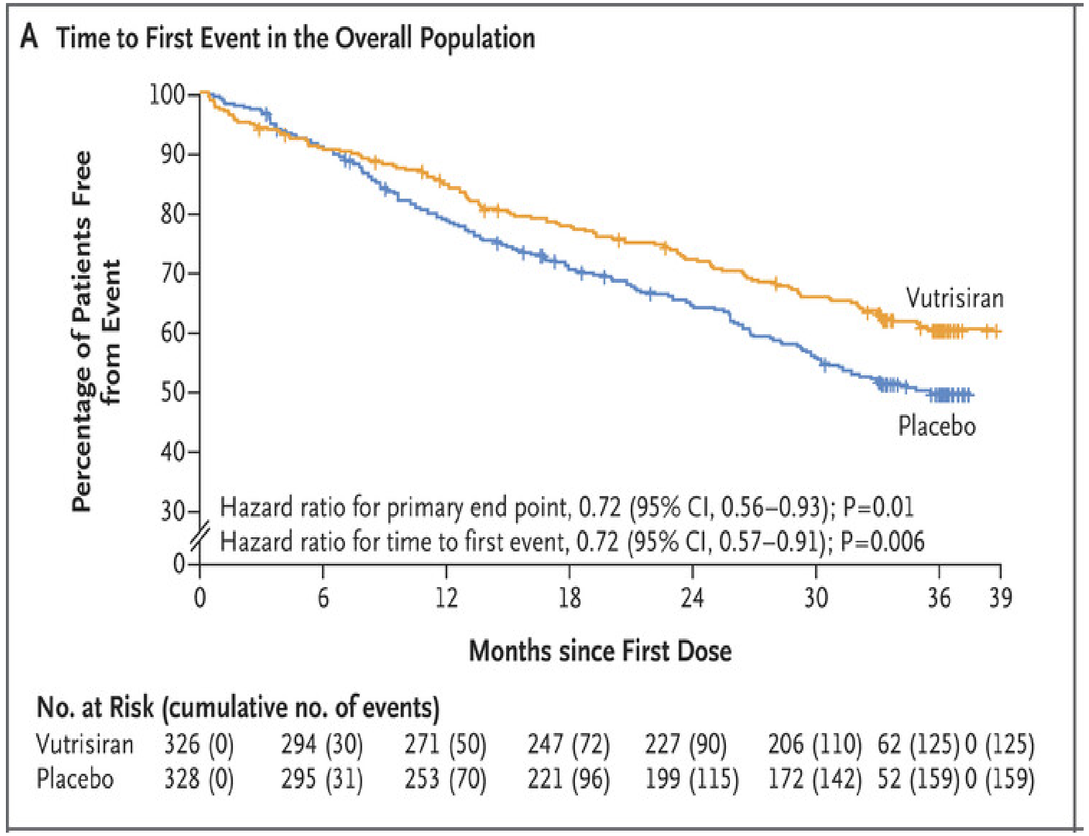
Early trials in patients with ATTR-CM: Not Exciting

[1]Adams et al. NEJM 2018
[2]Benson et al. NEJM 2018
[3]Solomon et al. Circulation 2019
[4]Minamisawa et al. JAMA Cardiol 2019
[5]Benson et al. Amyloid 2017
[6]Judge et al. Cardiovasc Drug Ther 2020
[7]Maurer 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

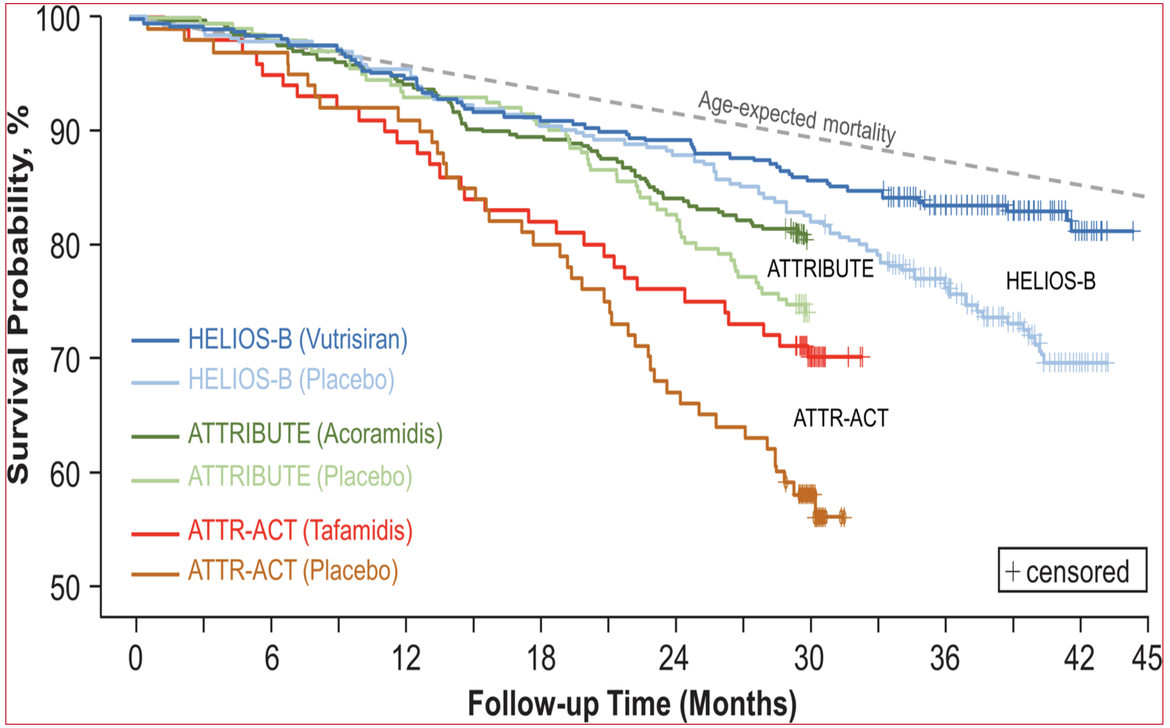
DOI: 10.1056/NEJMoa2409134


Which Medication
Should I Choose?

Can Trials Answer this Question? (No)

Table 3.2. Overview of Key Studies

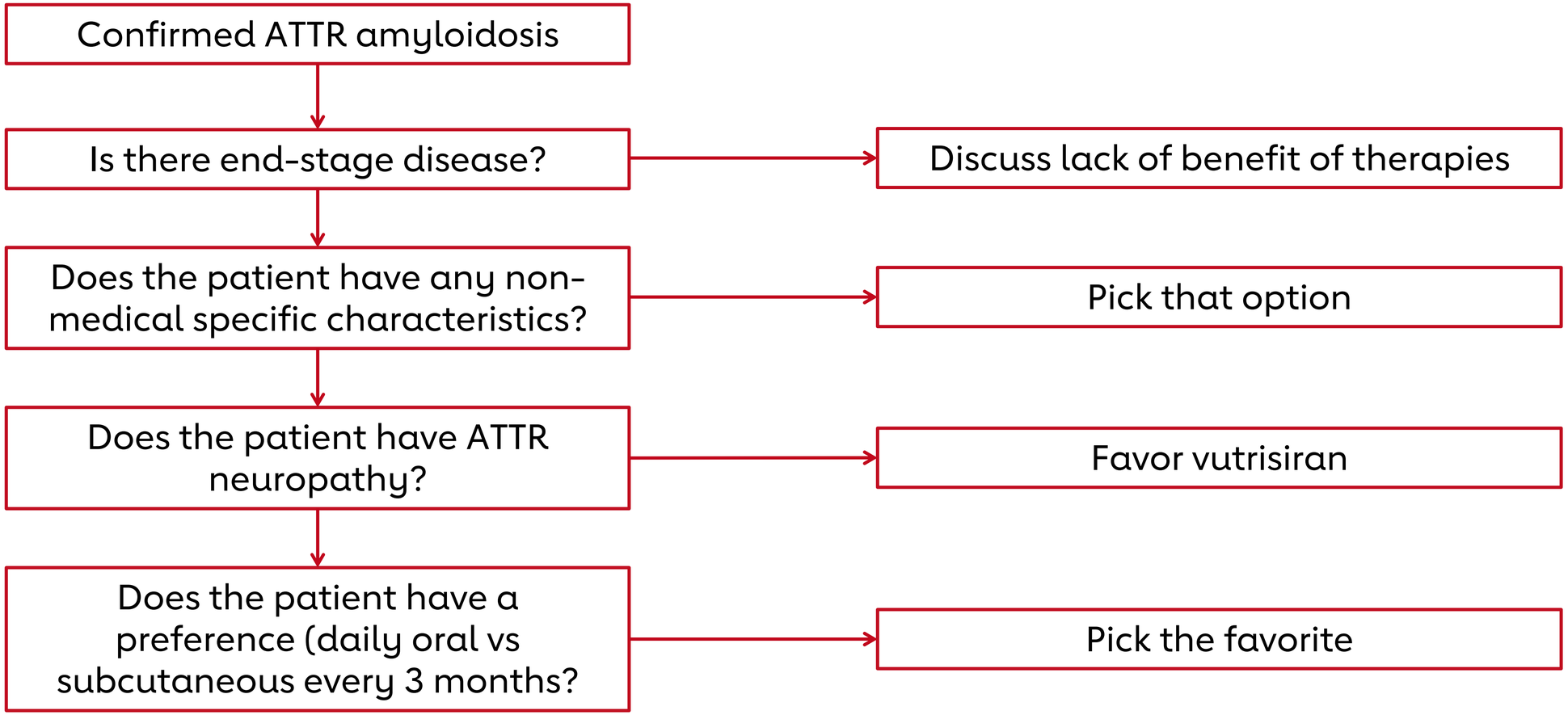
Trial		ATTR-ACT tafamidis 80 mg n=176 Placebo n=177	ATTRibute-CM acoramidis n=421 Placebo n=211	HELIOS-B vutrisiran n=326 Placebo n=328
N		353	632	654
Age, Years	Mean	74.3	77	77*
Sex, %	Male	90.2	90.2	92.5
	Female	9.8	9.8	7.5
Race, %	White	80.9	87.8	84.4
	Black	14.3	4.7	7.2
	Asian	3.9	2.1	5.7
	Other	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



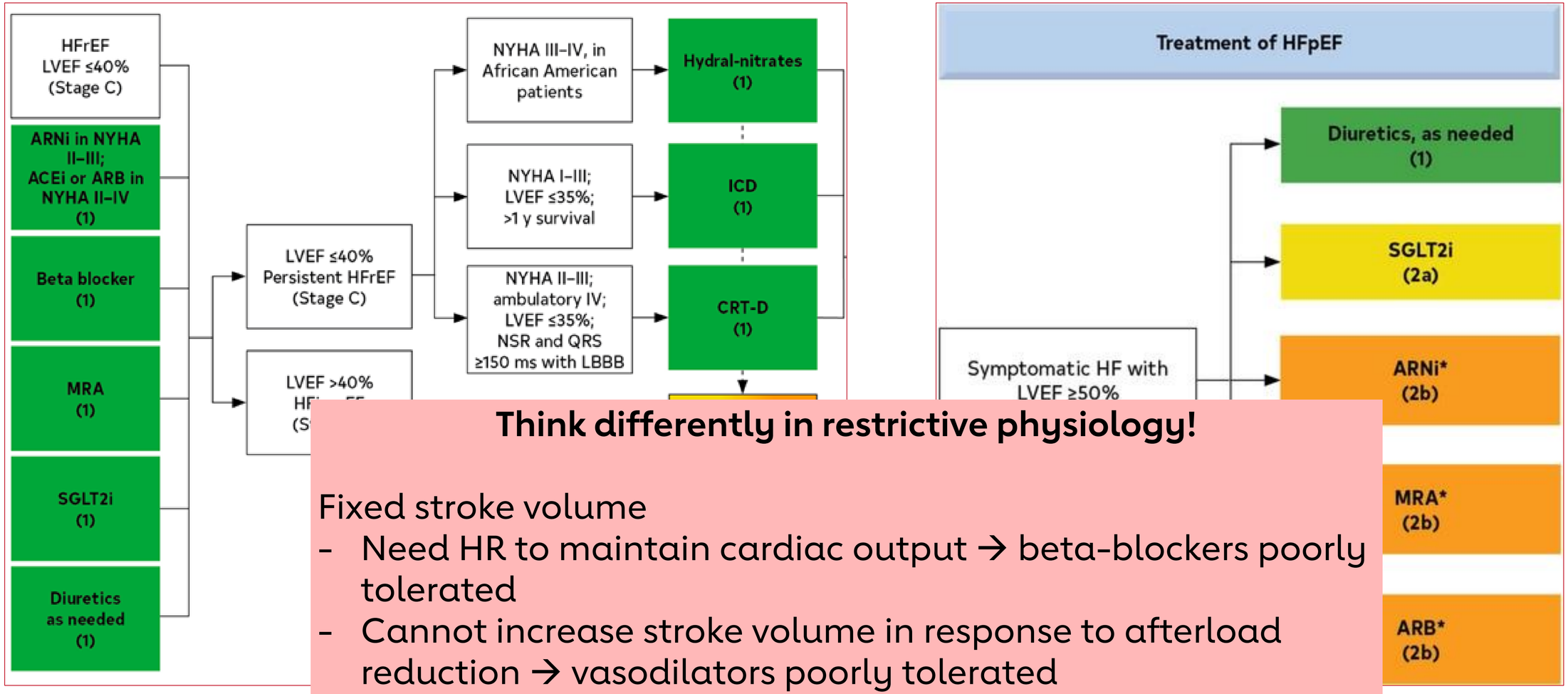
Wasfy JH et al. Disease Modifying Therapies for the Treatment of Transthyretin Amyloid Cardiomyopathy; Final Evidence Report. Institute for Clinical and Economic Review, October 21, 2024

Girard AA, Sperry BW. *Heart Fail Rev*. 2024 Oct 1. Epub ahead of print.

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

Heidenreich P… Kittleson MM et al. 2022 HF Guidelines.

Putting it All Together

Appropriate for Disease-Modifying Therapy

- Confirmed ATTR-CM based on +biopsy with amyloid typing or +bone scintigraphy in the absence of a monoclonal protein
- NYHA Class I-III symptoms
- *Patients with milder symptoms (earlier diagnosis) derive greater benefit*

HF therapies

- Diuretics titrated to symptoms; avoid over-diuresis
- Caution with vasodilators and beta-blockers
- MRA and SGLT2 inhibitor assist in relief of congestion

Atrial fibrillation

- Anticoagulation regardless of CHA_2DS_2-VASc score

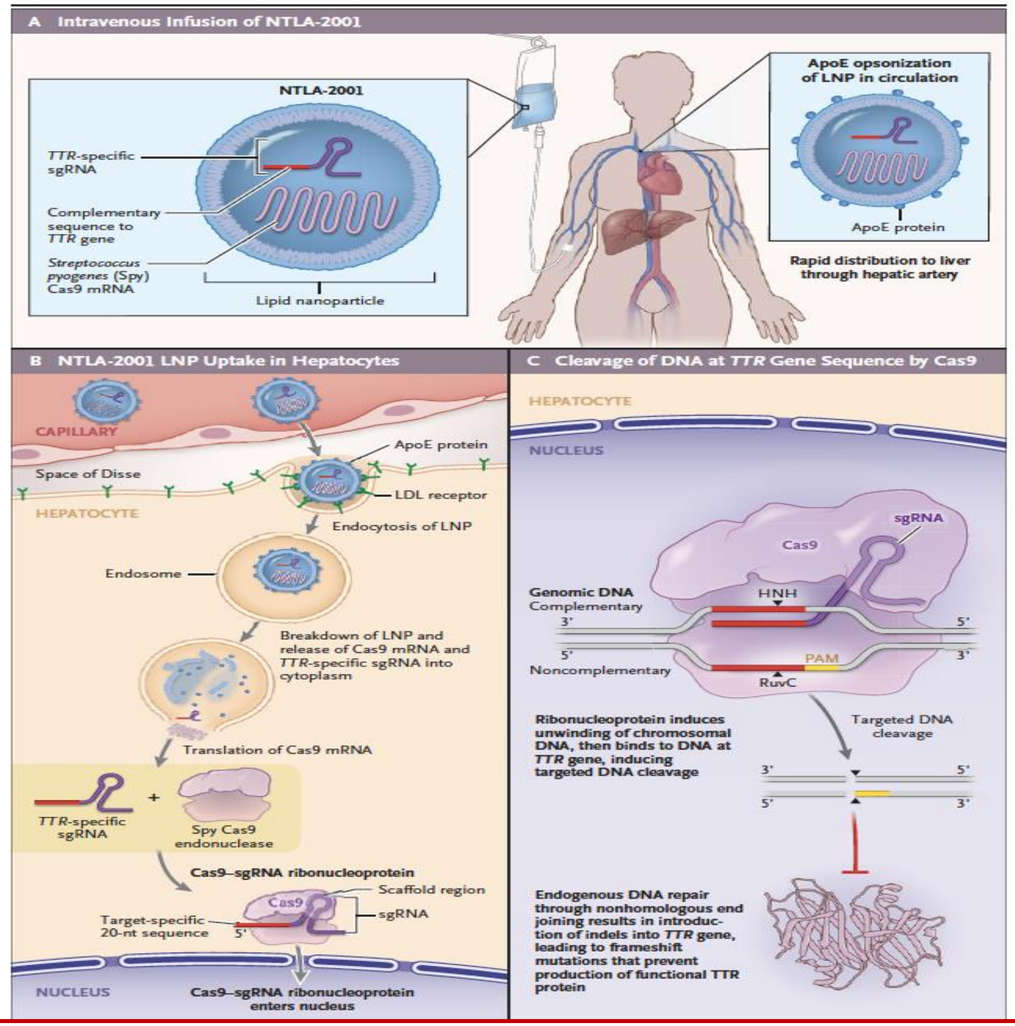
ATTRv-CM with Cardiomyopathy and Polyneuropathy

- Vutrisiran
- Neurology consultation

ATTRwt-CM or ATTRv-CM without Polyneuropathy

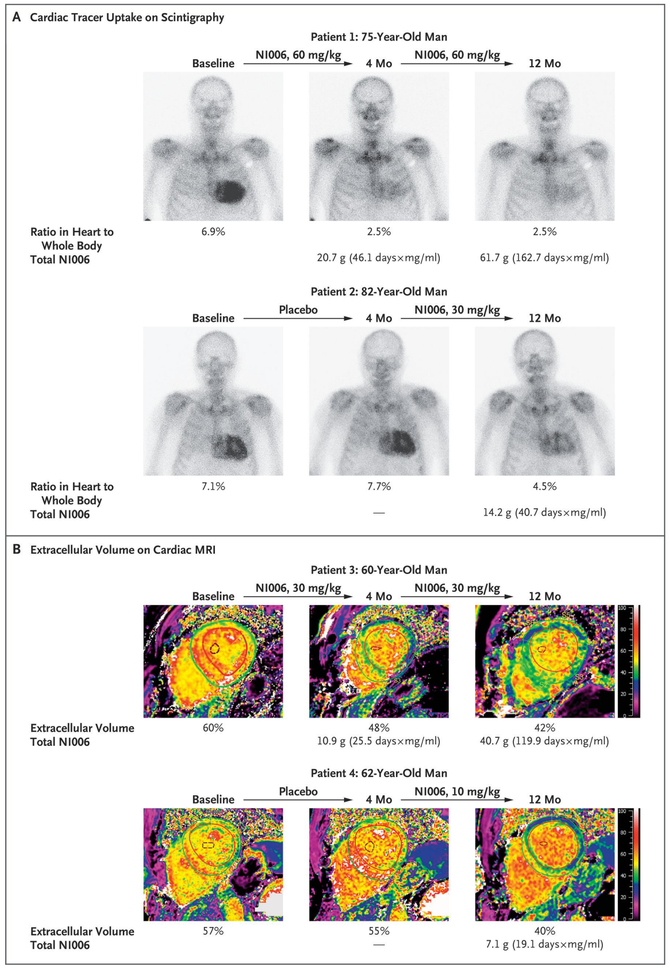
- Tafamidis, acoramidis, or vutrisiran based on
  - Cost
  - Access
  - Patient preference
- Insufficient evidence to recommend combination therapy with TTR stabilizer and TTR silencer

Glimpses into the Future



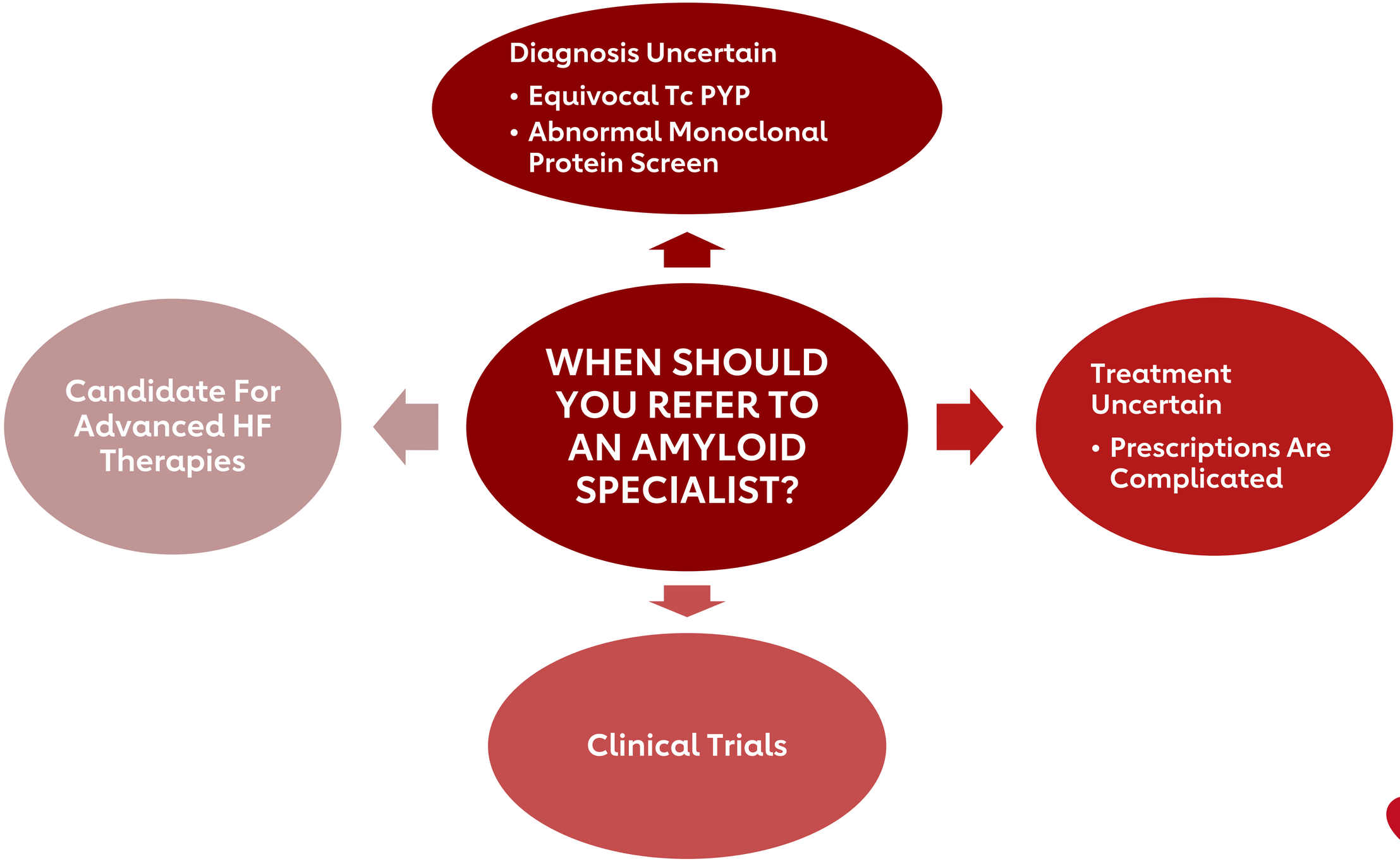
- Gene editing: Precisely target a predefined DNA sequence
- Permanently inactivate the TTR gene in the liver, the main source for circulating TTR
- 36 patients, 90% knockdown at 12 months, no change in 6MWD, KCCQ, NT-proBNP, troponin

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


Diagnosis Uncertain
• Equivocal Tc PYP
• Abnormal Monoclonal Protein Screen
Candidate For Advanced HF Therapies
WHEN SHOULD YOU REFER TO AN AMYLOID SPECIALIST?
Treatment Uncertain
• Prescriptions Are Complicated
Clinical Trials

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?

American Heart Association®

CRISPR-Cas9 Deep Dive

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

Professor of Cardiology,

Hon. Consultant Cardiologist,

National Amyloidosis Centre,

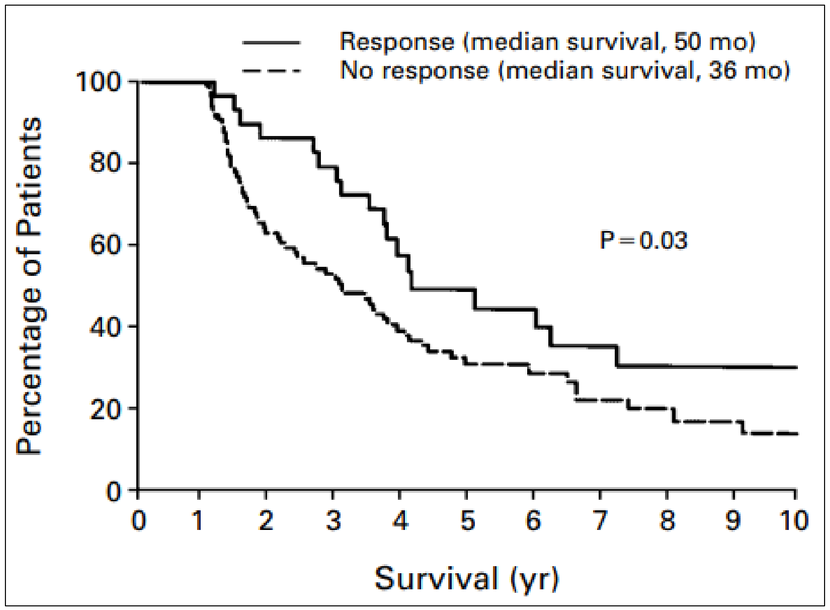
University College London, United Kingdom

Treatment Of Primary (Systemic AL) Amyloidosis

The New England Journal of Medicine

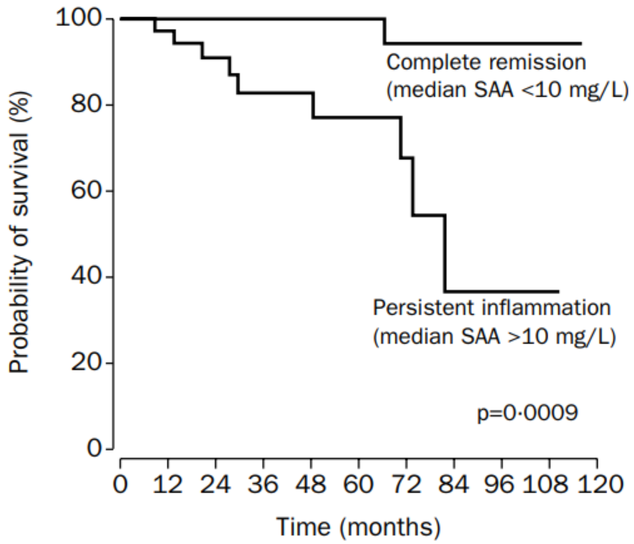
A TRIAL OF THREE REGIMENS FOR PRIMARY AMYLOIDOSIS: COLCHICINE ALONE, MELPHALAN AND PREDNISONE, AND MELPHALAN, PREDNISONE, AND COLCHICINE

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.



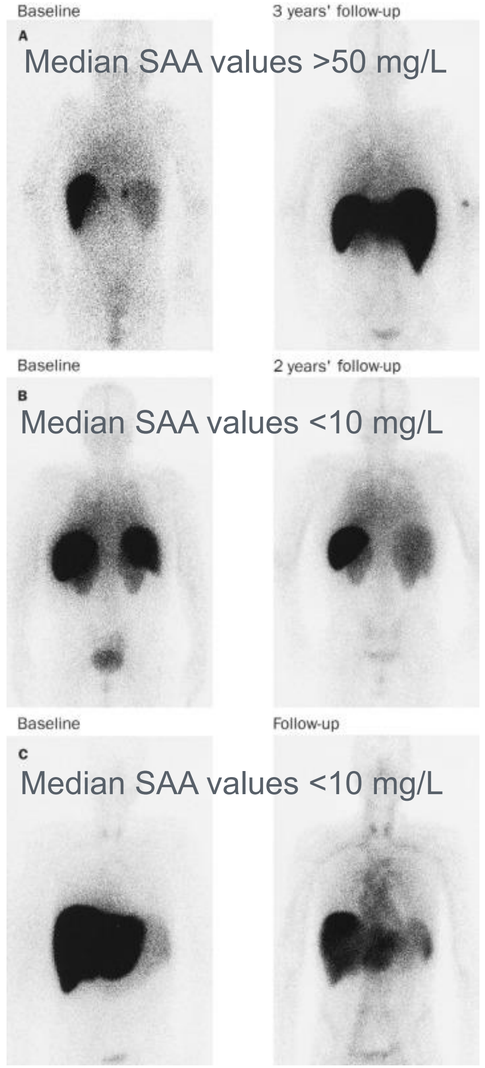
Kyle RA, et al. *N Engl J Med* 1997;336:1202–1207.

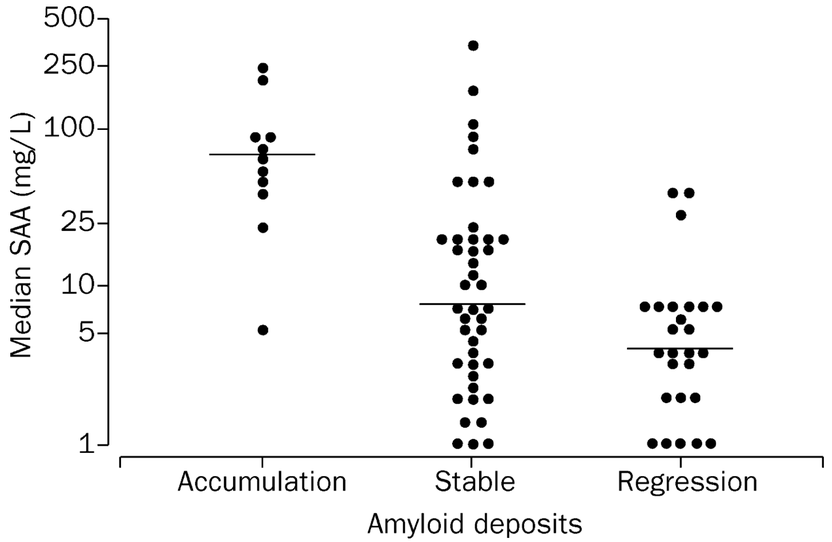
Treatment Of Secondary (Systemic AA) Amyloidosis



Number at risk

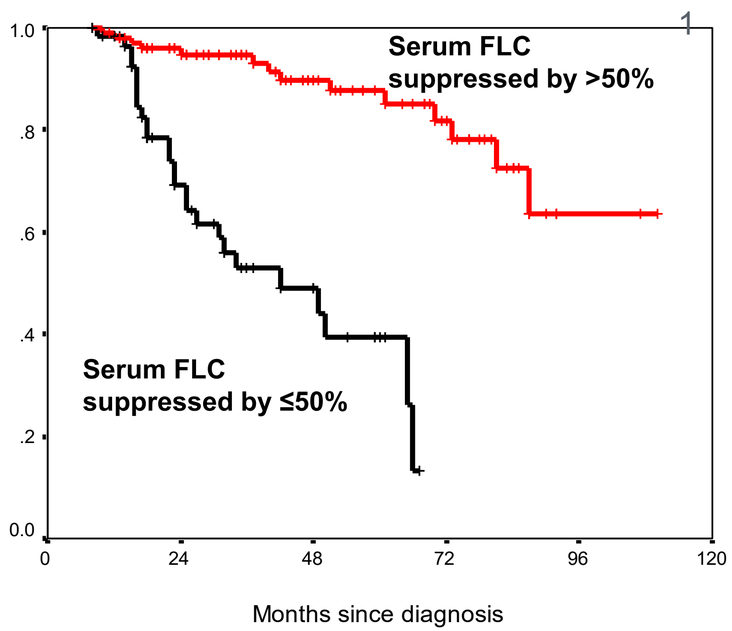
Complete remission	42	42	42	42	42	42	41	41	41	41	41
Persistent inflammation	38	37	35	33	33	32	31	29	29	29	29

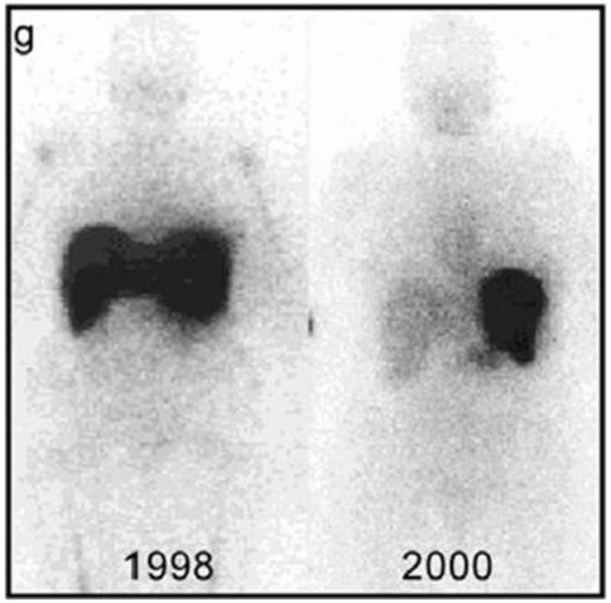




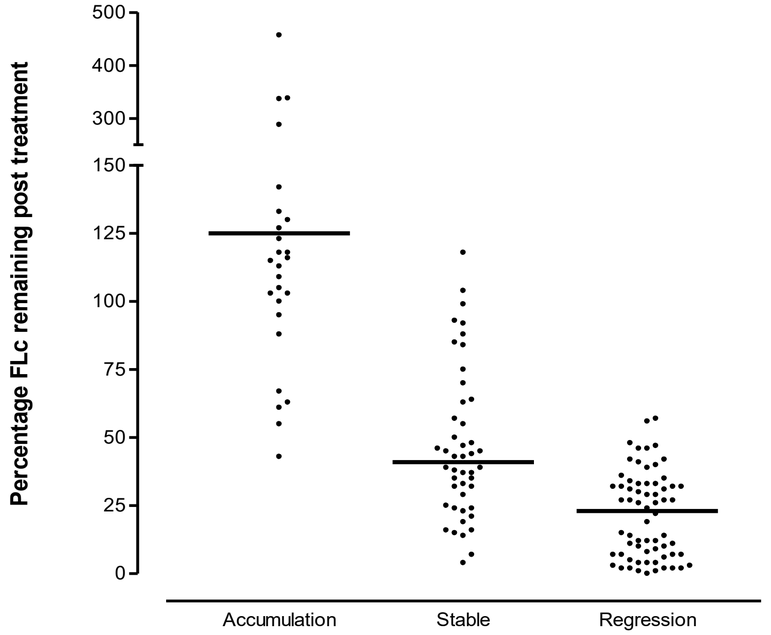
Gillmore JD, et al. *Lancet* 2001;358:24–29.

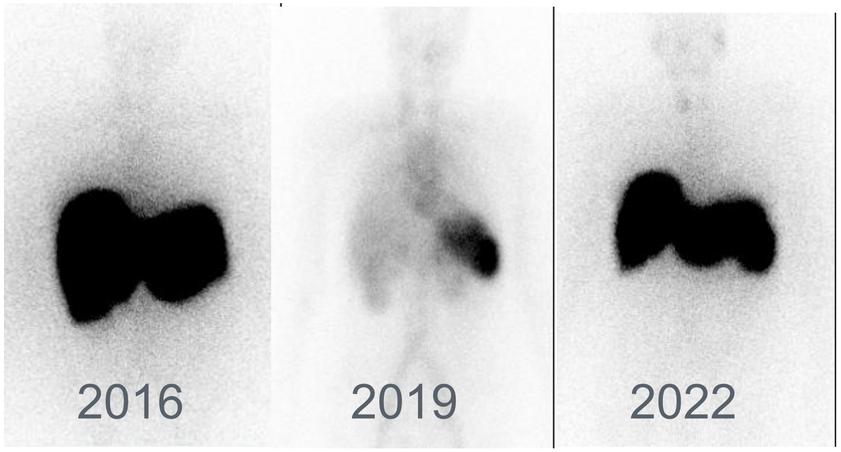
Treatment Of Systemic AL Amyloidosis





Hematologic response

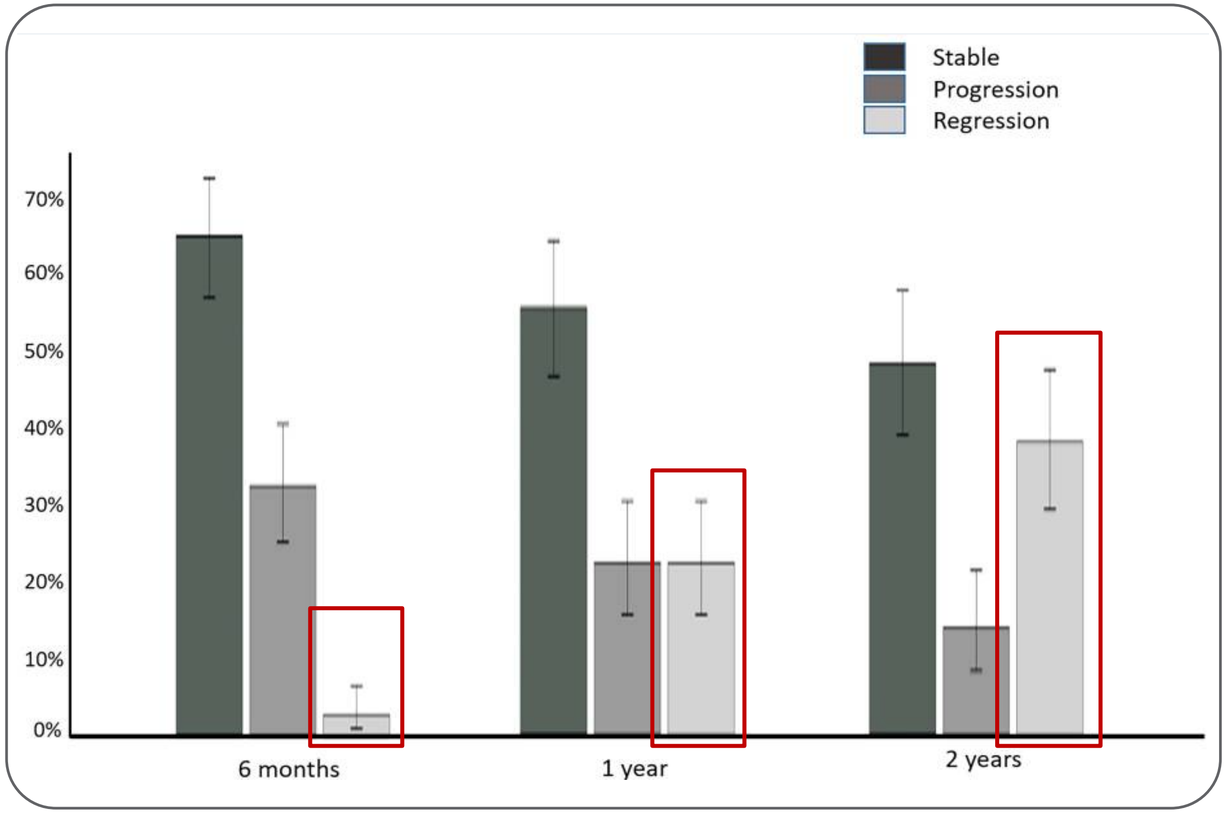


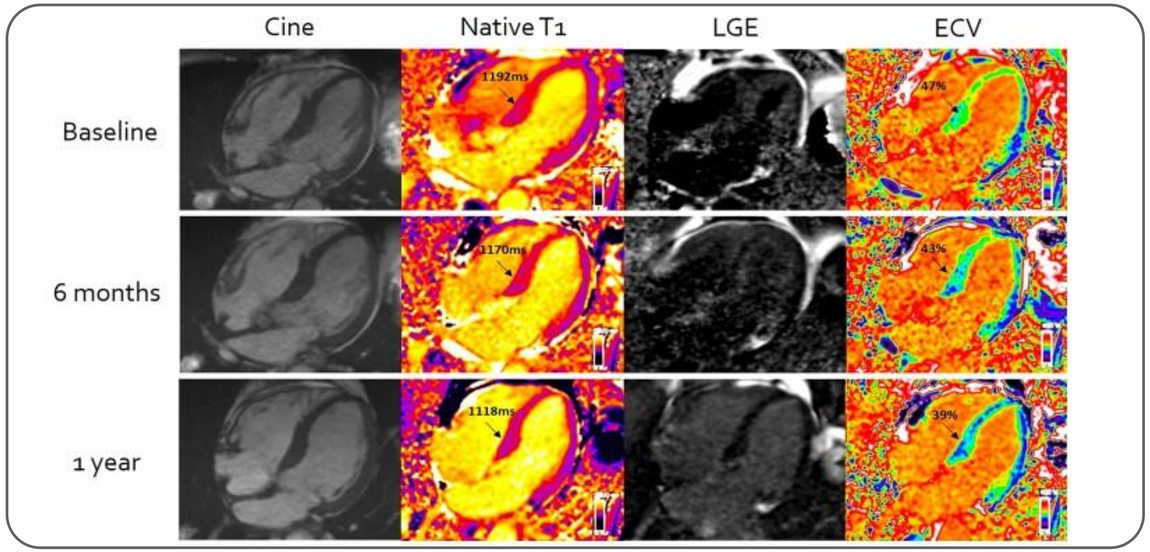


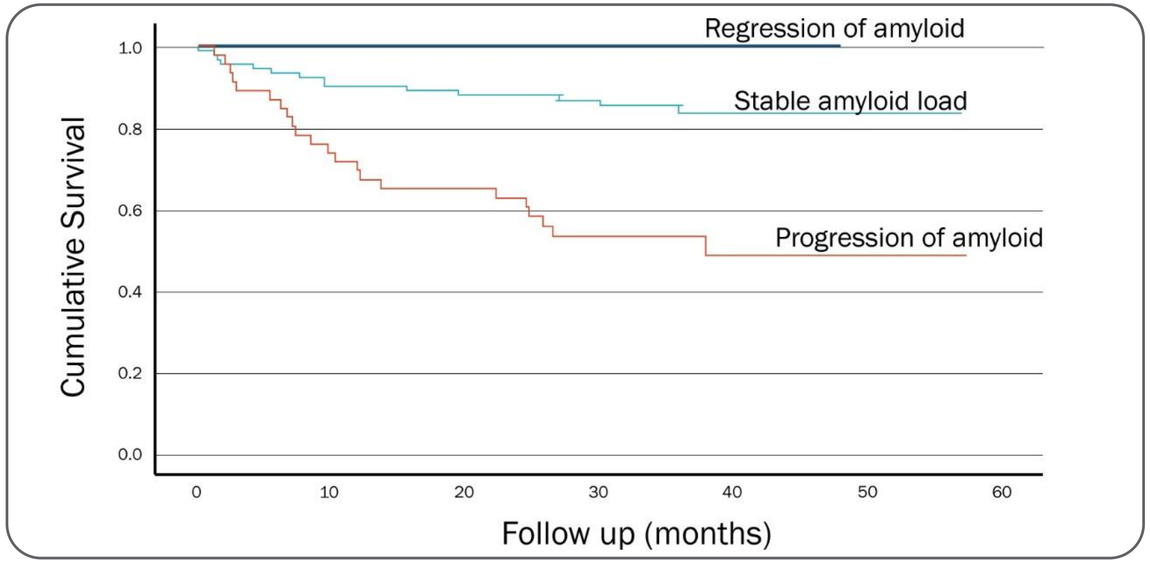
FLC, free light chain.

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



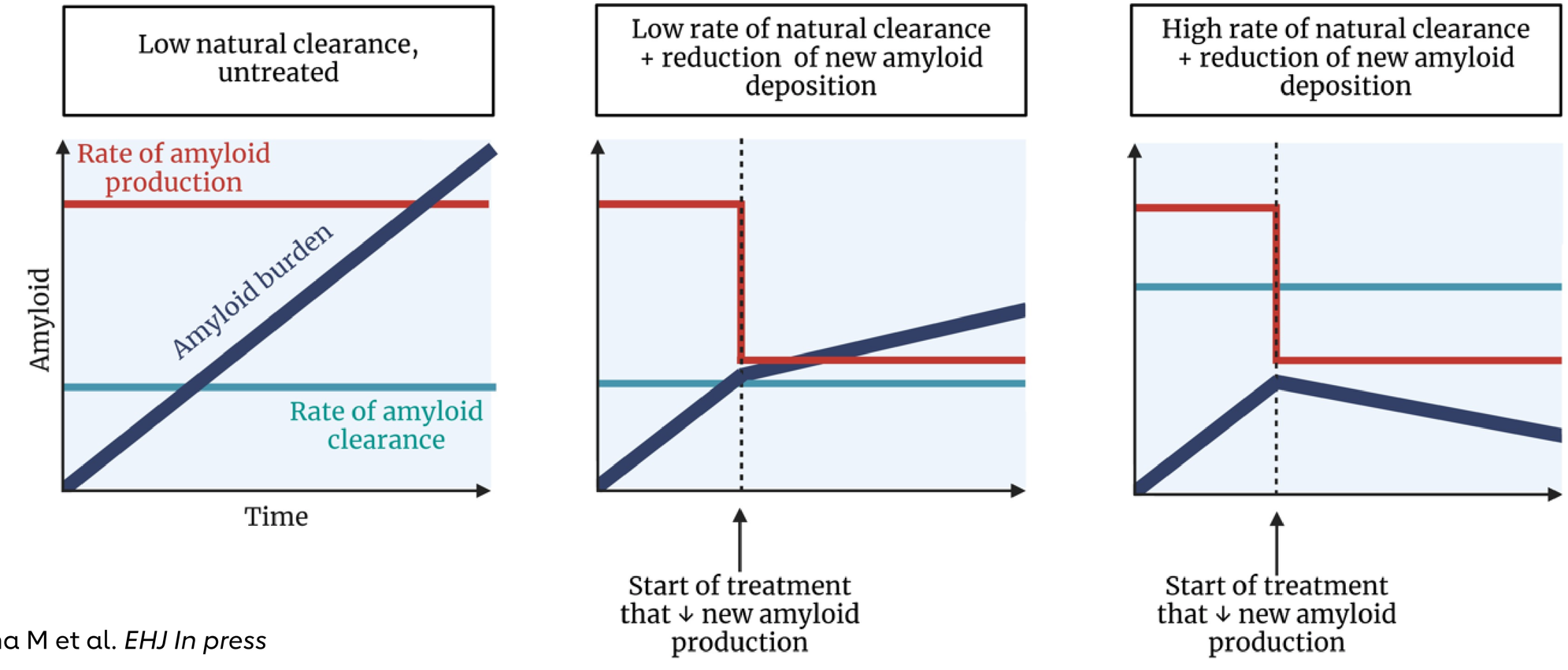




AL, amyloid light chain; ECV, extracellular volume; LGE, late gadolinium enhancement.
Martinez-Naharro A, et al. *Eur Heart J* 2022;43:4722–4735.

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



Fontana M et al. *EHJ In press*

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

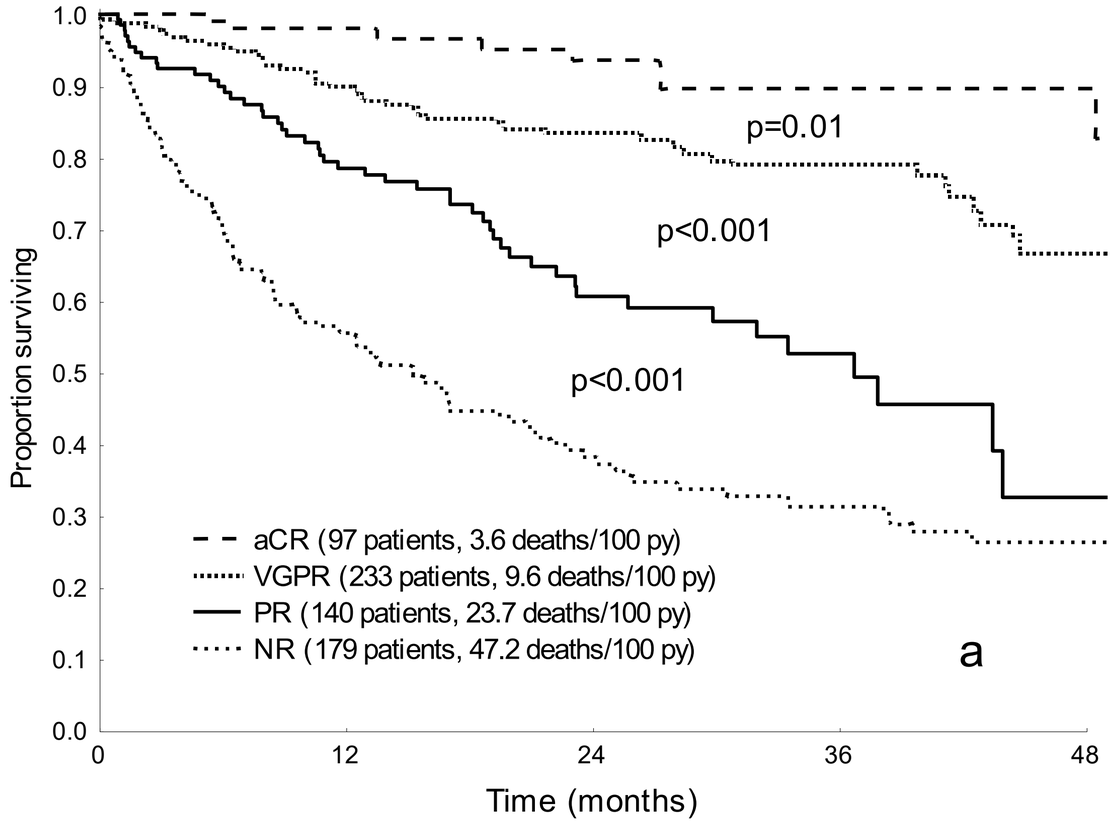
AA Amyloidosis[1]

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.

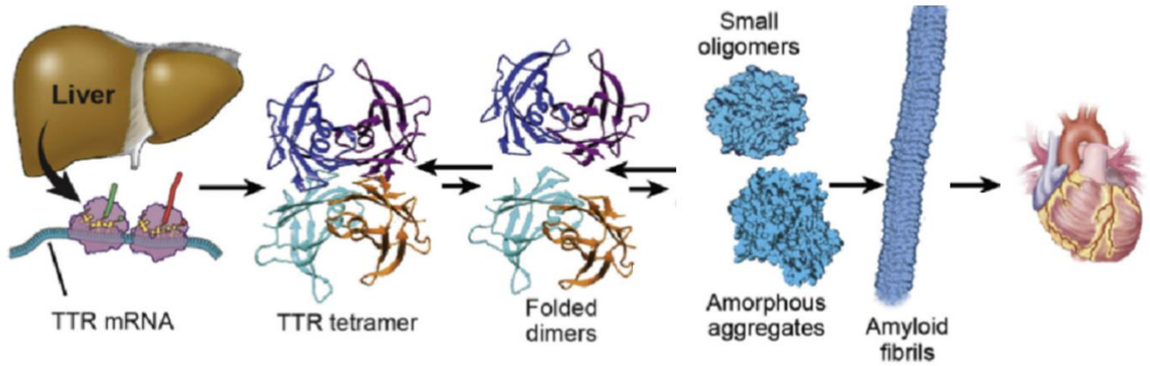
AL Amyloidosis[2]



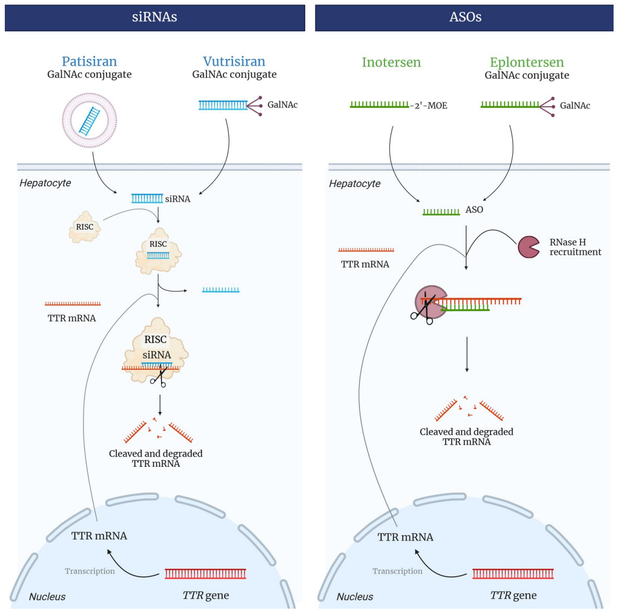
aCR, amyloid complete response; NR, no response; PR, partial response; SAA, serum amyloid A protein; VGPR, very good partial response.

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.

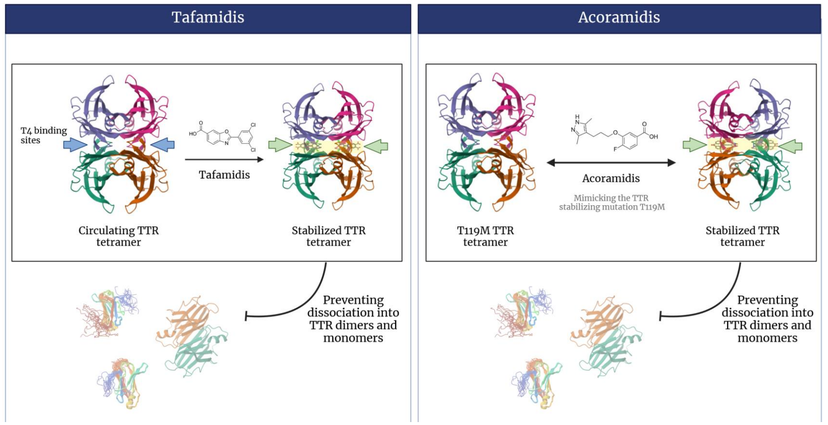
Treatment Of ATTR Amyloidosis: Silencers & Stabilizers



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 mortality[1]

ATTR-ACT & LTE

All-cause mortality[2,3,a]

30% in patients receiving **tafamidis** (78/264)

43% in patients receiving **placebo** (76/177)

at 30 months follow-up after study initiation (HR, 0.70; 95% CI, 0.51-0.96; *P*<0.001)

Patients experienced death, heart transplant, or implantation of a cardiac mechanical assist device[4,b]

45% of patients receiving continuous **tafamidis**[c] (79/176)

63% of patients receiving **tafamidis after placebo**[d] (111/177)

RWE

All-cause mortality[5]

39% in patients receiving **tafamidis** (241/624)

over a median follow-up of 43.2 months from tafamidis initiation

Survival probability with tafamidis[5]

54% at 65 months

HELIOS-B

Any-cause mortality[6,e]

16% of patients receiving **vutrisiran** ± SOC[f] (51/326)

21% of patients receiving **placebo** ± SOC[f] (69/328)

up to 36 months after study initiation (HR, 0.69; 95% CI, 0.49-0.98; *P*=0.04)

Recurrent hospitalizations for cardiovascular causes or urgent HF visits[6]

34% of patients receiving **vutrisiran** ± SOC[f] (112/326)

41% of patients receiving **placebo** ± SOC[f] (133/328)

up to 36 months after study initiation (RRR, 0.73; 95% CI, 0.61-0.88; *P*=0.001)

[a]Patients who received either 80 mg or 20 mg tafamidis once daily during the study period. [b]Patients 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. [c]Median follow-up of 58.5 months. [d]Median follow-up of 57.1 months. [e]Heart 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. [f]SOC was tafamidis.

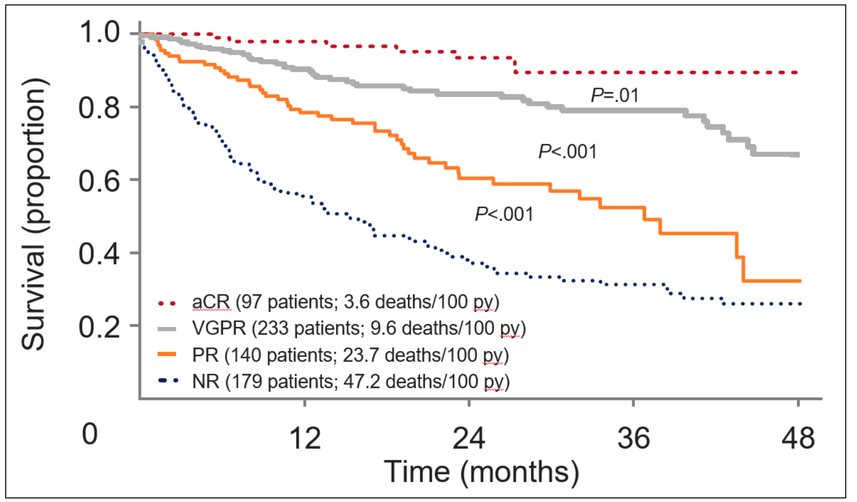
ATTR-CM, ATTR amyloidosis with cardiomyopathy; HF, heart failure; HR, hazard ratio; LTE, long-term extension; LVAD, left ventricular assist device; RRR, relative risk ratio; RWE, real-world evidence; SOC, standard of care.

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.

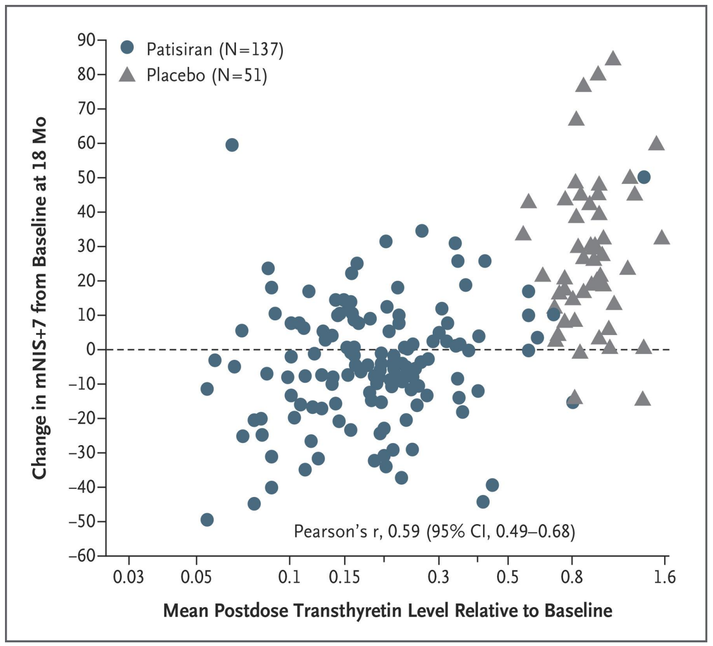
Reduction In New Amyloid Formation And Outcomes

- 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 outcomes[2-4]
  - Deeper reductions in TTR levels have been correlated with increased clinical benefit in patients with ATTRv-PN[5]

Survival Based on Hematologic Response in AL Amyloidosis[4]



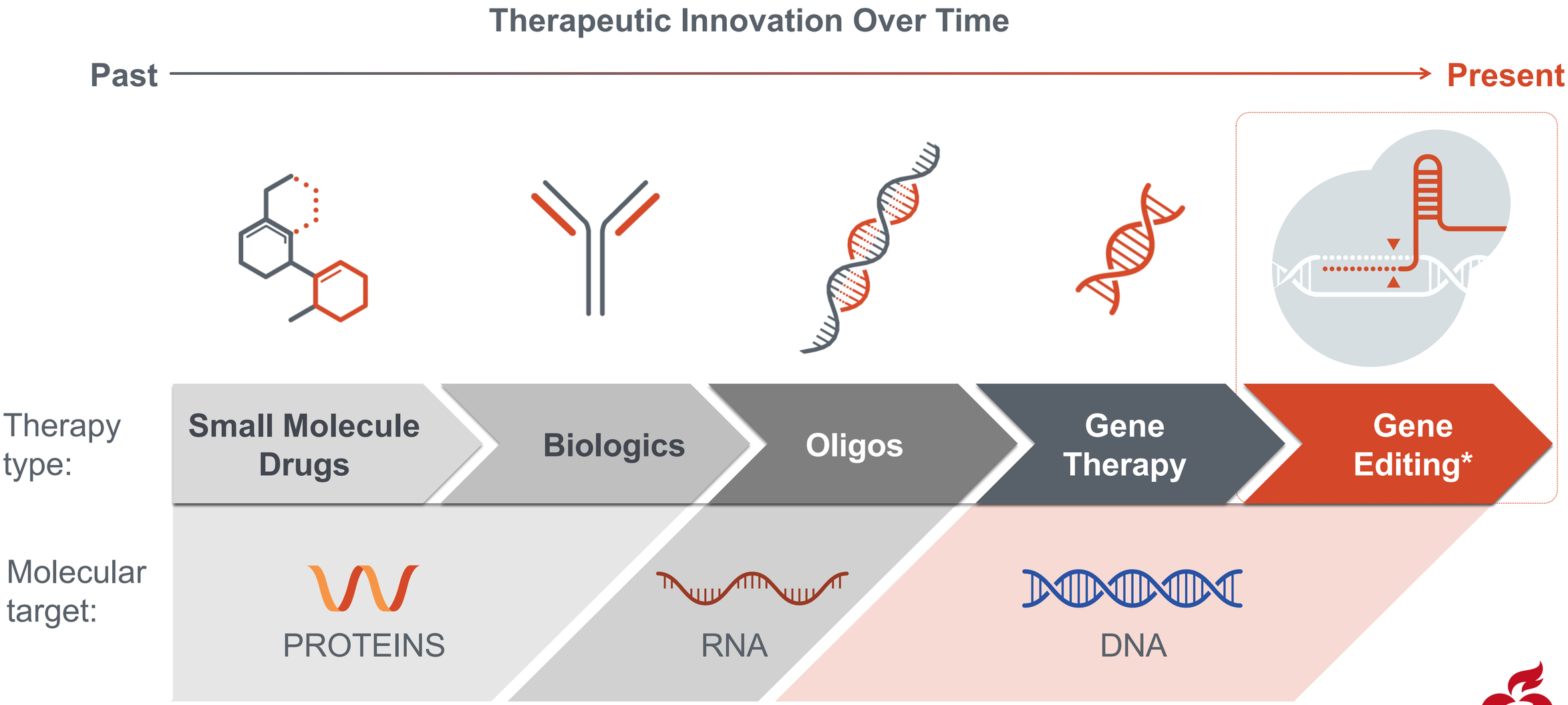
Correlation of Reduction in TTR Levels With Change in mNIS+7 From Baseline to 18 Months[5]



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.

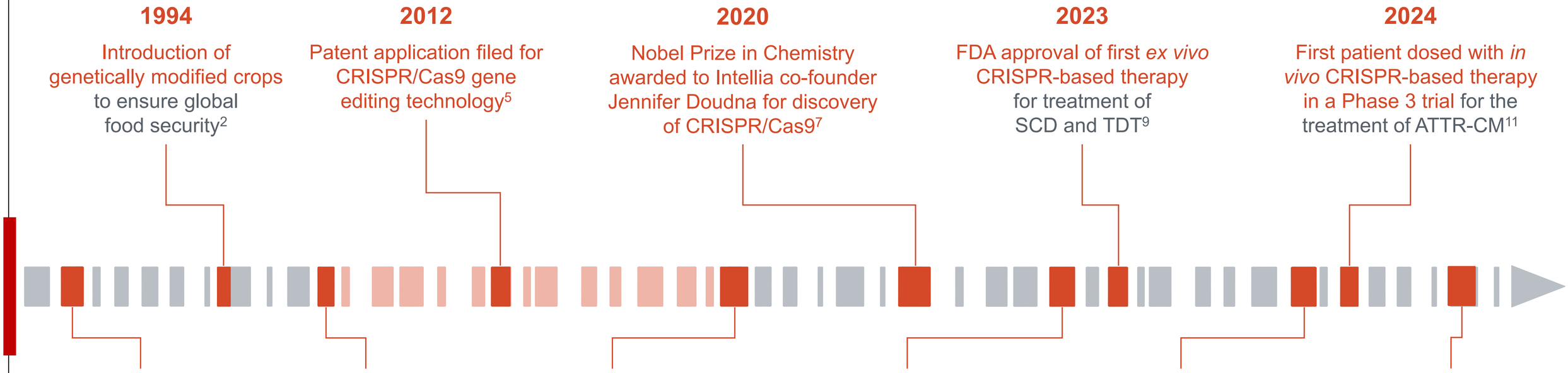
Therapeutic and Investigational Strategies to Treat Life-Threatening Diseases Have Advanced Over Time[1-4]



*Under investigation; not yet approved by any Health Authority. Oligo, oligonucleotide.

1. Stern LK, Patel J. *Methodist Debakey 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 Therapy[1-13]



1987
Discovery of CRISPR in *E. coli* bacteria[1]

1994
Introduction of genetically modified crops to ensure global food security[2]

2002
First successful use of gene editing accomplished in fruit flies[3,4]

2012
Patent application filed for CRISPR/Cas9 gene editing technology[5]

2013
CRISPR/Cas9-mediated gene editing achieved in human cells[6]

2020
Nobel Prize in Chemistry awarded to Intellia co-founder Jennifer Doudna for discovery of CRISPR/Cas9[7]

2021
Results from Phase 1 clinical study for the first *in vivo* CRISPR-based therapy, nexiguran ziclumeran, are published[8]

2023
FDA approval of first *ex vivo* CRISPR-based therapy for treatment of SCD and TDT[9]

2023
First Phase 3 trial announced for *in vivo* CRISPR-based therapy for the treatment of ATTR-CM[10]

2024
First patient dosed with *in vivo* CRISPR-based therapy in a Phase 3 trial for the treatment of ATTR-CM[11]

2024
Second and third Phase 3 trials announced for *in vivo* CRISPR-based therapies for the treatment of HAE and ATTRv-PN, respectively[12,13]

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.intelliatx.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.intelliatx.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.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-first-patient-dosed-phase-3 12. Press release. Intellia Therapeutics. October 7, 2024. https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-initiation-haelo-phase-3-study 13. Press release. Intellia Therapeutics. November 7, 2024. https://ir.intelliatx.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 States[1-12]

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 Mechanisms[1-3]

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 lifetime[4]

CRISPR, clustered regularly interspaced short palindromic repeats.

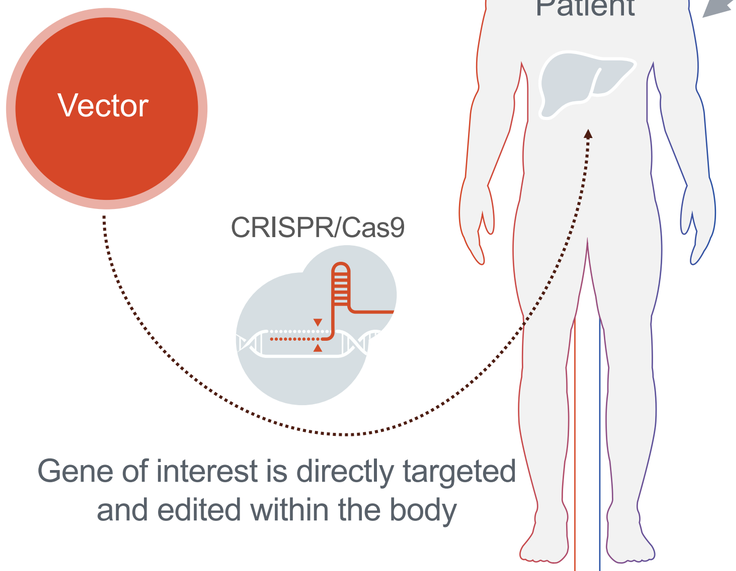
1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 3. Abdelnour SA, et al. *Front Cell Dev Biol*. 2021;9:699597. 4. Intellia Corporate Overview. Intellia Therapeutics. February 2024. Accessed May 7, 2024. https://ir.intelliatx.com/static-files/a57908a6-aaca-404d-9072-32471cd3d41e

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 toolbox[1]

In Vivo[2,3]

CRISPR/Cas9 machinery packaged into a delivery vector is systemically administered to patient via IV infusion

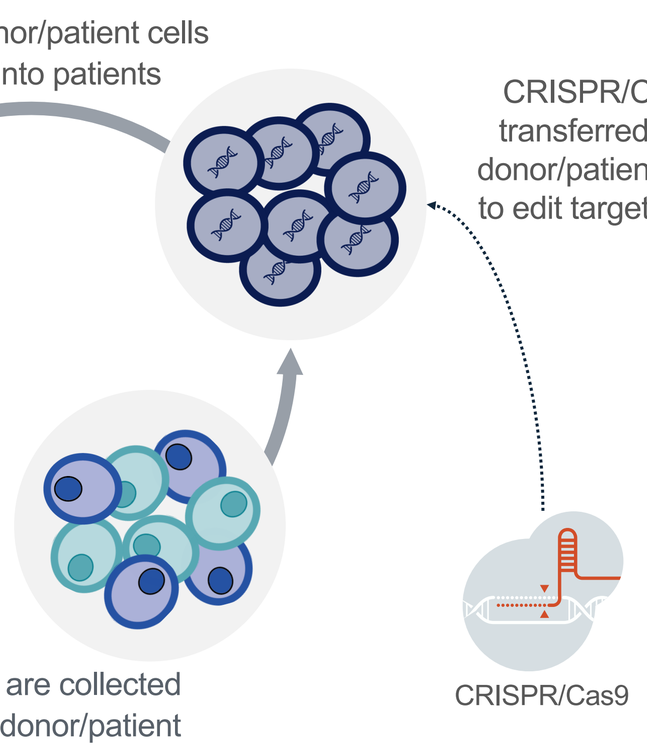


Administration:

- One-time treatment via IV infusion[2,3]
- Only takes one day[4,5]
- May require prior immunosuppression[4,5]
- Intended to be an outpatient procedure[5]

With an *in vivo* approach, CRISPR/Cas9 is the therapy[2,3]

Ex Vivo[6-12]



Administration*:

- IV infusion
- May require prior immunosuppression†

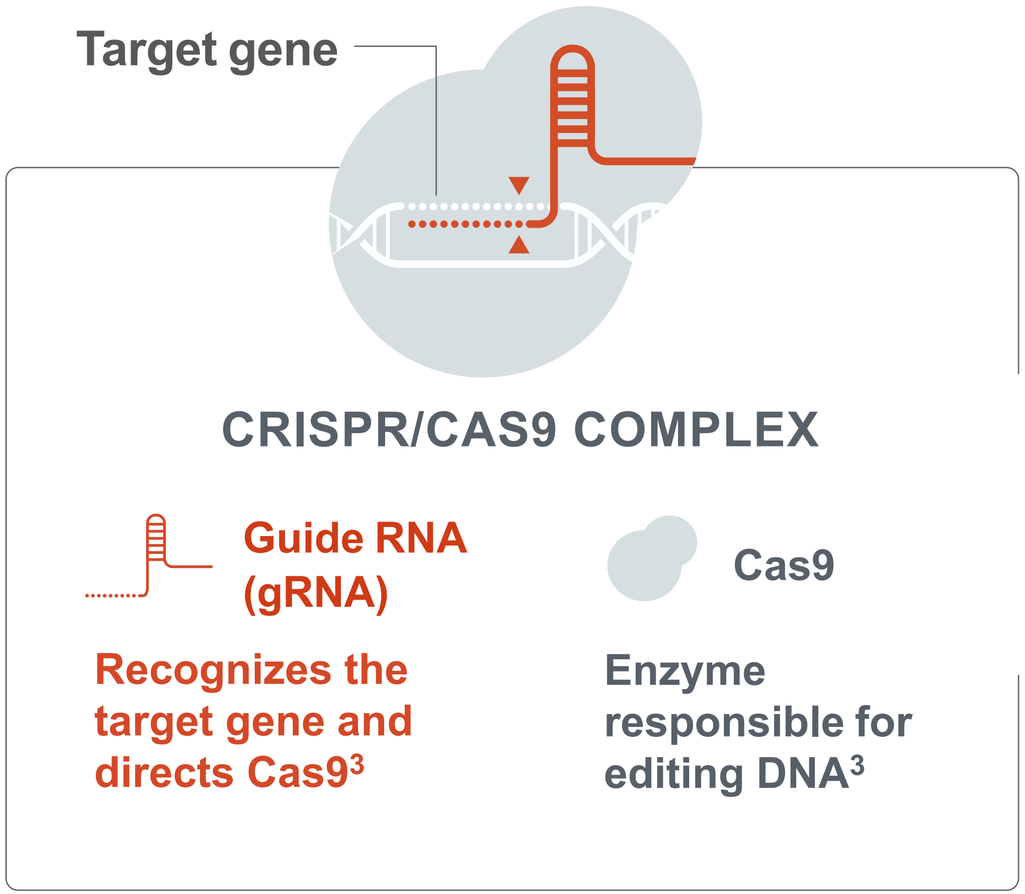
*Allogeneic CRISPR-based therapies are in early preclinical and clinical studies[7-12]; some administration details are to be determined.
†Autologous *ex vivo* therapies may not require immunosuppression.[1,6]

With an *ex vivo* approach, CRISPR/Cas9 creates the therapy[6-12]

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]



DELIVERY SYSTEM

Delivers CRISPR/Cas9 cargo *in vivo*[1]

Lipid Nanoparticle (LNP)

LNPs are developed with careful consideration of lipid composition and RNA cargo[1]

OR

Viral Vector

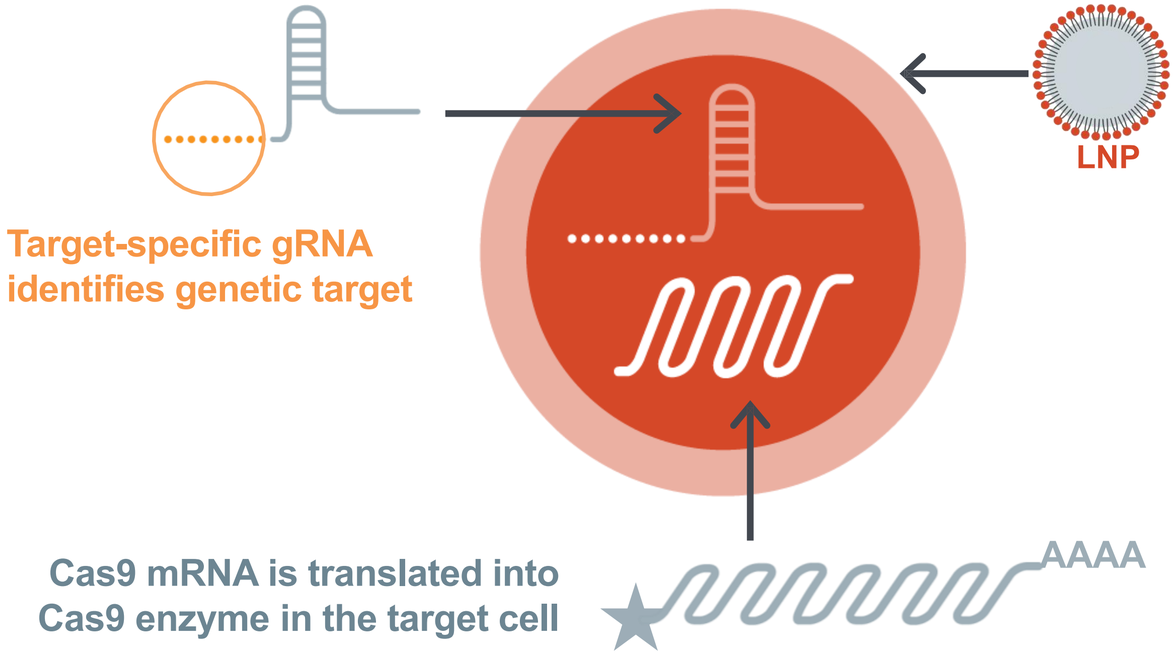
Viral vectors have tropism for a variety of tissues and can support transient expression of Cas9[4,5]

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 receptor[1]
- Transient expression[3]
- Low immunogenicity (non-viral)[4]
- Well-tolerated[5,6]
- Potentially tunable to other tissues[7]

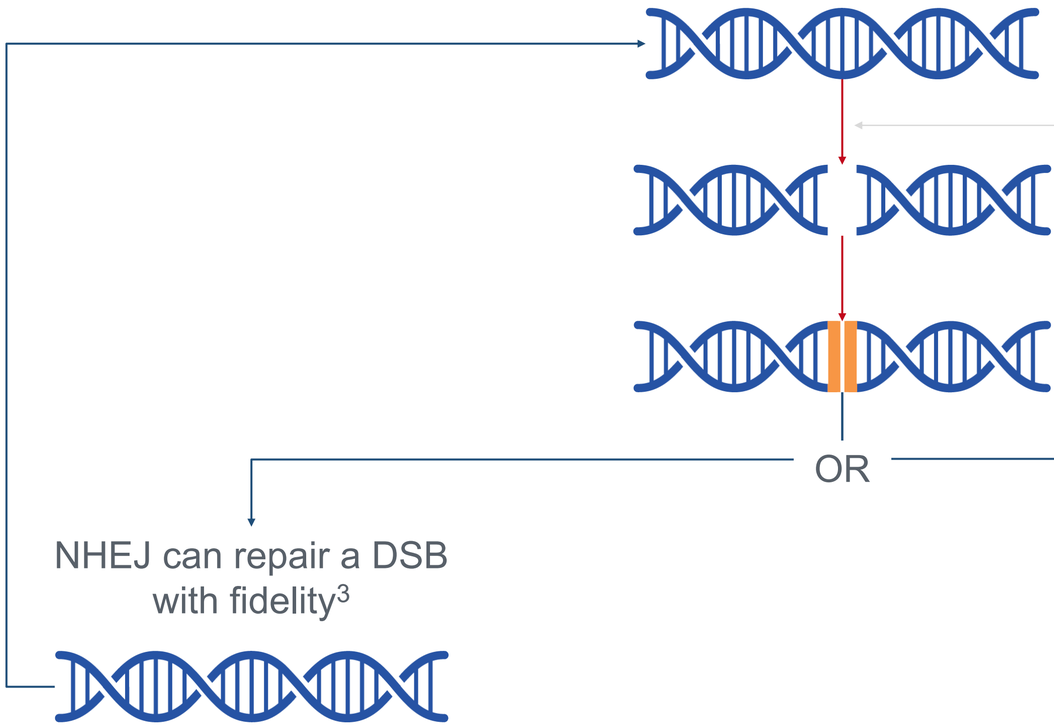
Intellia's proprietary LNP delivery system was designed to help maximize the efficacy of CRISPR-mediated gene editing while minimizing systemic toxic effects[1]

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 Disease[1-3]

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]



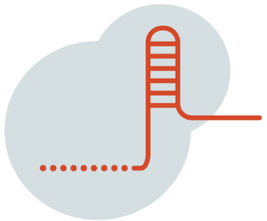
OR

NHEJ can repair a DSB with fidelity[3]

DNA that remains unaltered after NHEJ repair is **re-targeted by CRISPR/Cas9 until an edit is made**[5]

NHEJ can naturally introduce **small insertions or deletions (indels)**[1]

Precision indels in the gene targeted by CRISPR/Cas9 may result in a **permanent edit that inactivates the gene to potentially address the disease pathway**[1]



CRISPR/Cas9 focuses precise DSB activity to a specific site within a gene following a one-time treatment[1-3]

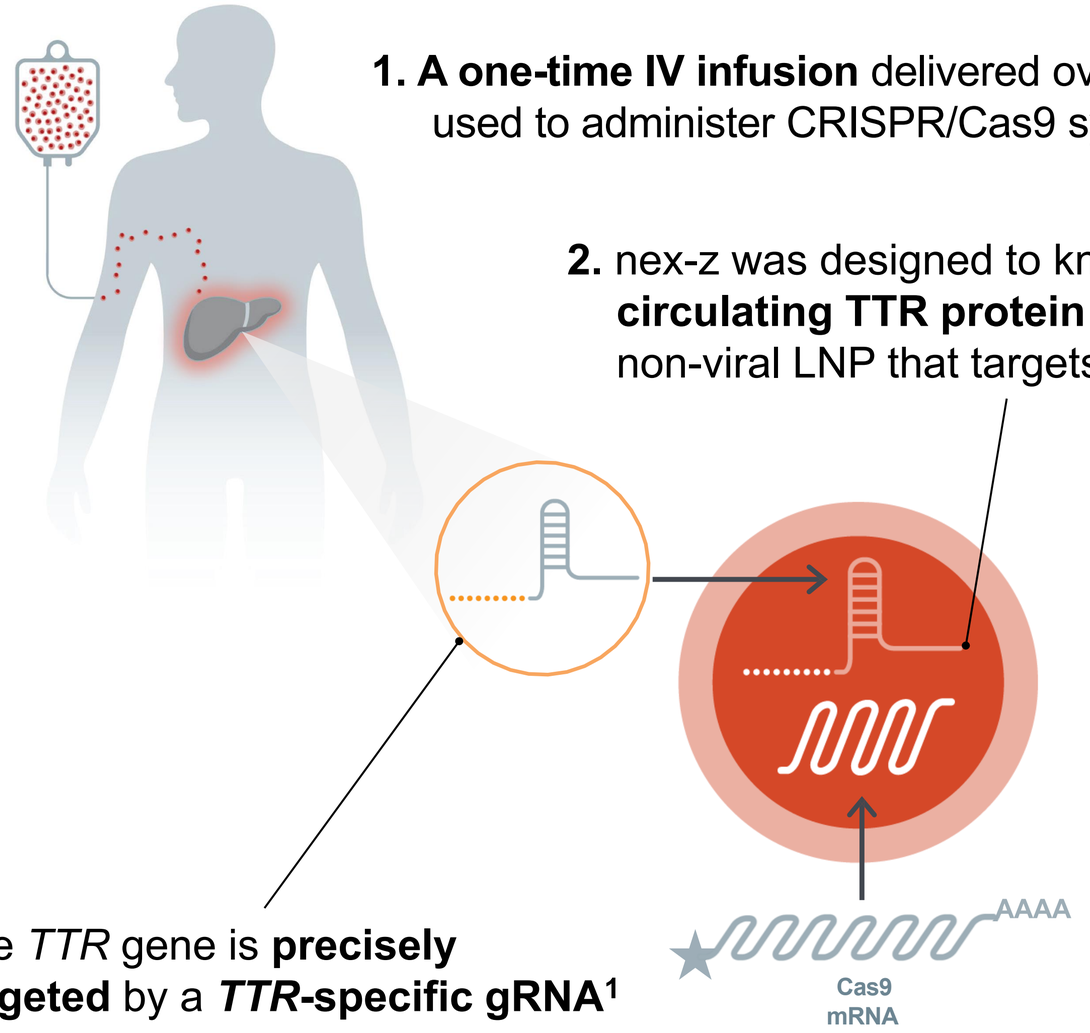
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; DSB, double-strand break; NHEJ, non-homologous end joining.

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. Stinson BM, Loparo JJ. *Annu Rev Biochem*. 2021;90:137-164. 4. Cannan WJ, Pederson DS. *J Cell Physiol*. 2016;231(1):3-14. 5. Li T, et al. *Signal Transduct Target Ther*. 2023;8(1):36.

Nexiguran ziclumeran (nex-z), Targets *TTR* in the Liver to Reduce Serum TTR Levels With a One-Time IV Infusion[1]

ATTR amyloidosis[1]:

- **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



1. A one-time IV infusion delivered over 4 hours is used to administer CRISPR/Cas9 systemically[2]

2. nex-z was designed to knock down **circulating TTR protein** by using a non-viral LNP that targets the liver[1]

3. The *TTR* gene is **precisely targeted** by a ***TTR*-specific gRNA[1]**

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.

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

Key Attributes for Identifying Therapeutic gRNAs[3]

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 therapy[1-3]

Discovery of potential off-target edits in the genome

Assess risk of biological impact of gRNA due to inadvertent indel formation at each site[3]

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 knockout[1]
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

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,*]

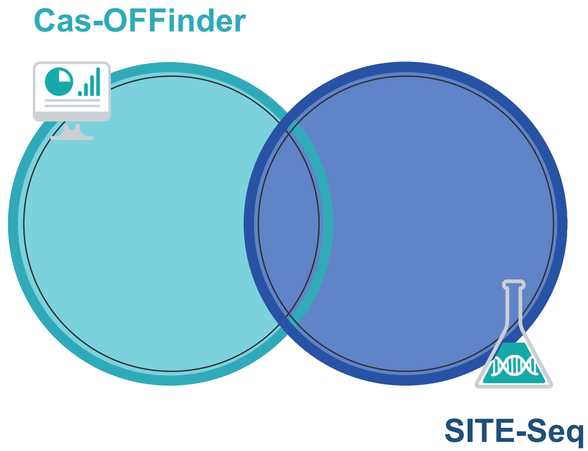
1 Discovery of potential off-target effects using independent libraries[2]

SITE-Seq
Genomic
DNA digest

+

Cas-OFFinder
Computational
prediction

2 Aggregate all identified genomic loci for validation or rejection of off-target potential[1-3]



3 Each potential off-target location is verified with deep sequencing[1-3]

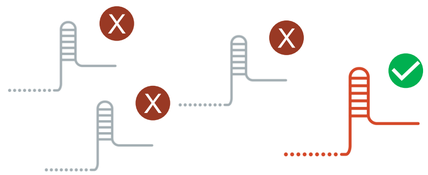
Multiplex panel for NGS

↓

Targeted Amp-Seq NGS follow-up

Off-target editing of candidate gRNAs are tested *in vitro* at supratherapeutic doses

- Edit cells *in vitro* using drug product formulation
- Therapeutically relevant human primary cell type(s) (2 donors)
- Dose range to exceed projected therapeutic exposure (>10X)



- gRNAs with an unfavorable off-target profile are eliminated

*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 Models[1]

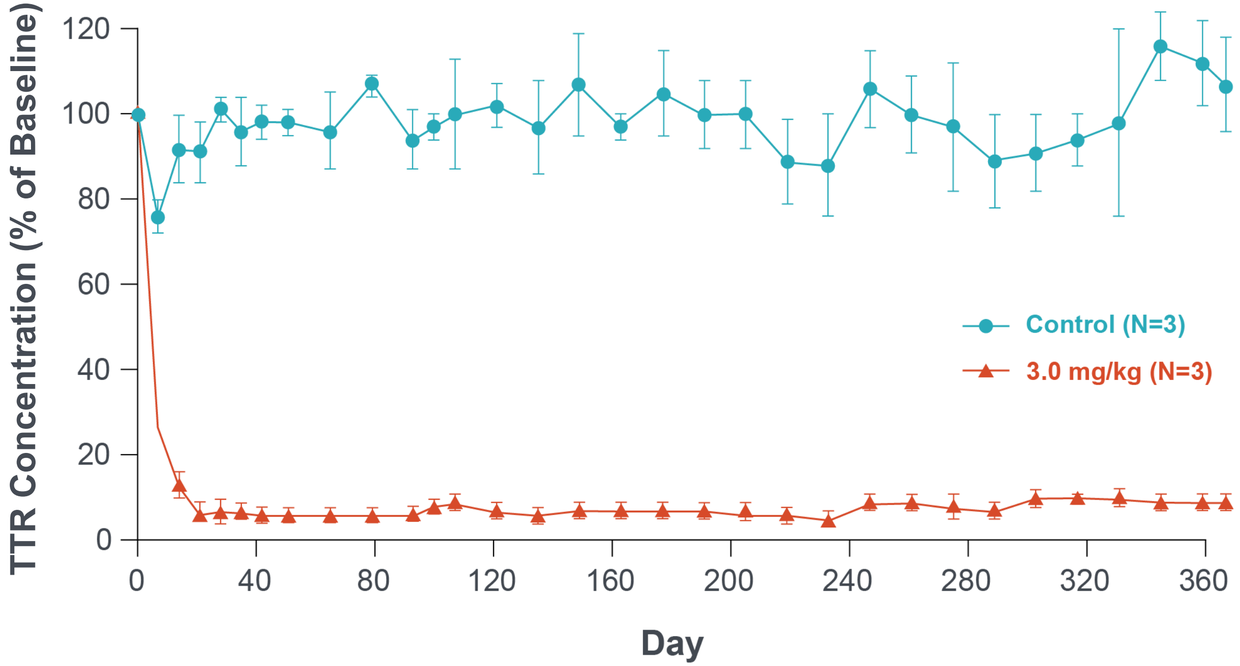
Following treatment with the nonhuman primate surrogate of nex-z in cynomolgus monkeys[1]:

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-z[1]**



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.

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*

Clinicaltrials.gov ID: NCT04601051

Fontana M et al. *NEJM 2024*

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)

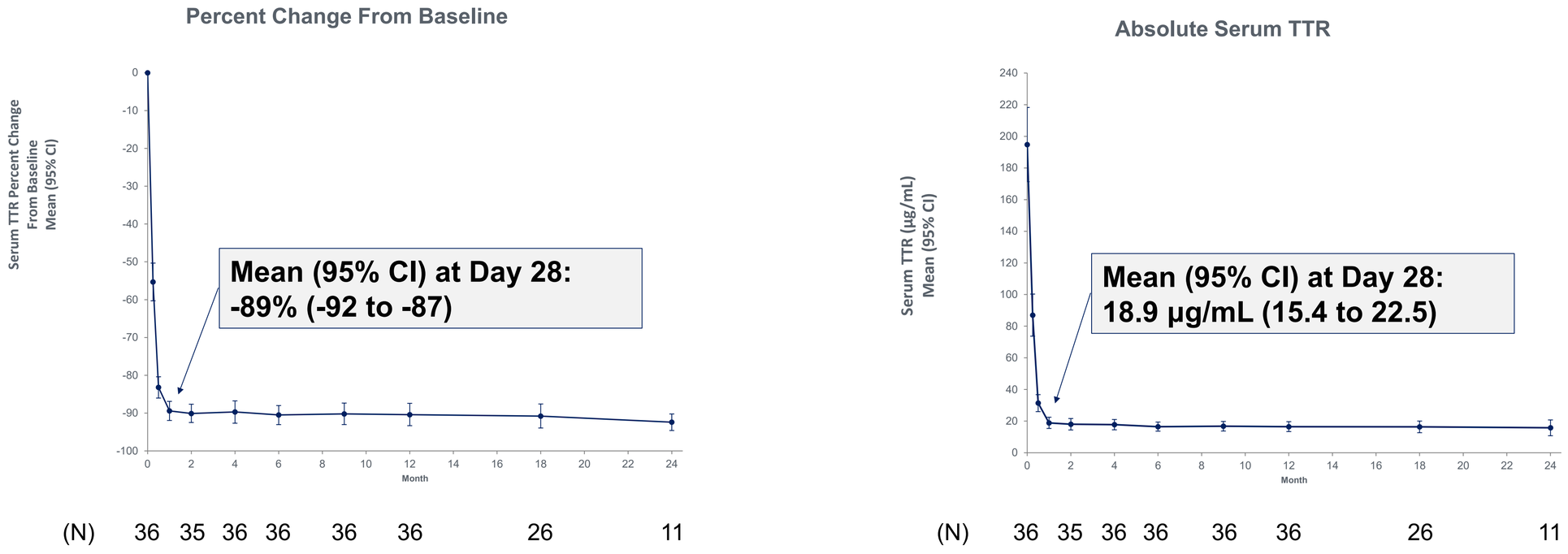
Population representative of ATTR-CM, including patients with advanced disease

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
[a]Includes 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; VO_2, 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



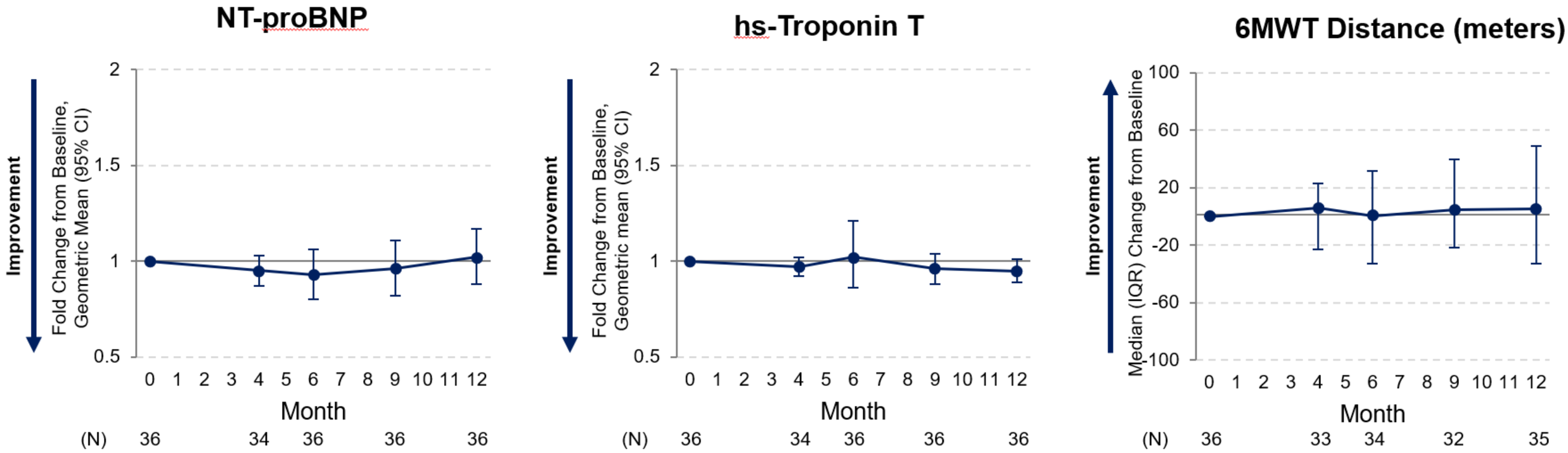
Similar serum TTR reductions were observed in every patient, regardless of baseline TTR level or genotype. Mean absolute serum levels of 18.9 µg/mL achieved at Day 28, with levels remaining virtually unchanged through 24 months.

Data cutoff August 21, 2024.
TTR, transthyretin.

Fontana M et al. *NEJM 2024*

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

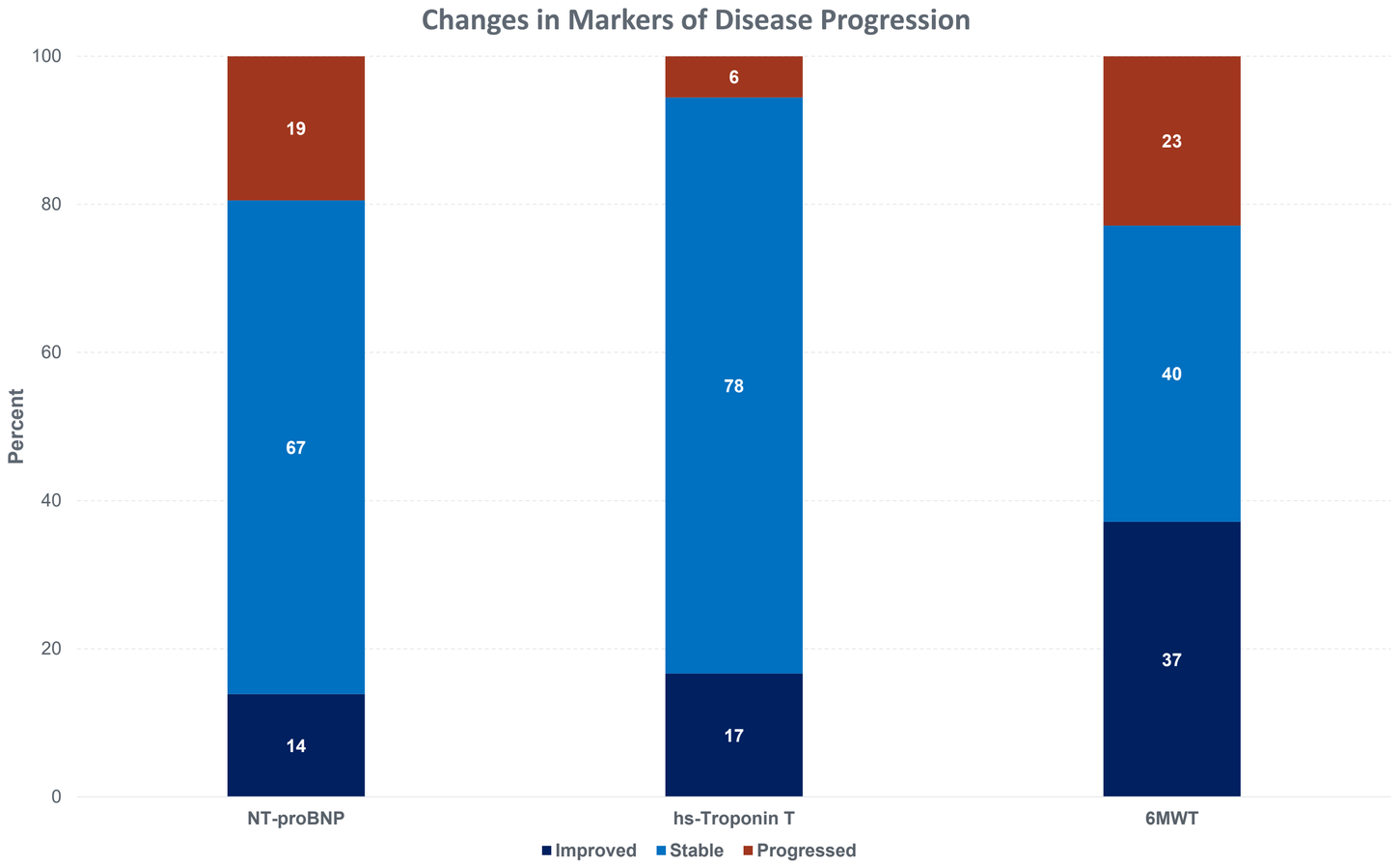
Markers of Disease Progression[1]



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.

Fontana M et al. *NEJM 2024*

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)

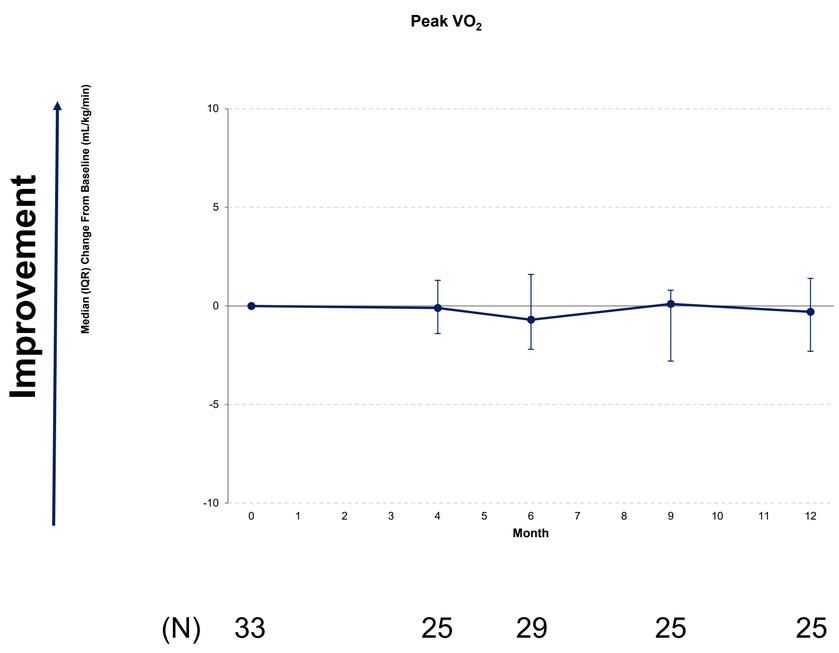
92% of patients demonstrated either no change or improvement in NYHA class at 12 months, including improvement in 72% of patients with NYHA class III

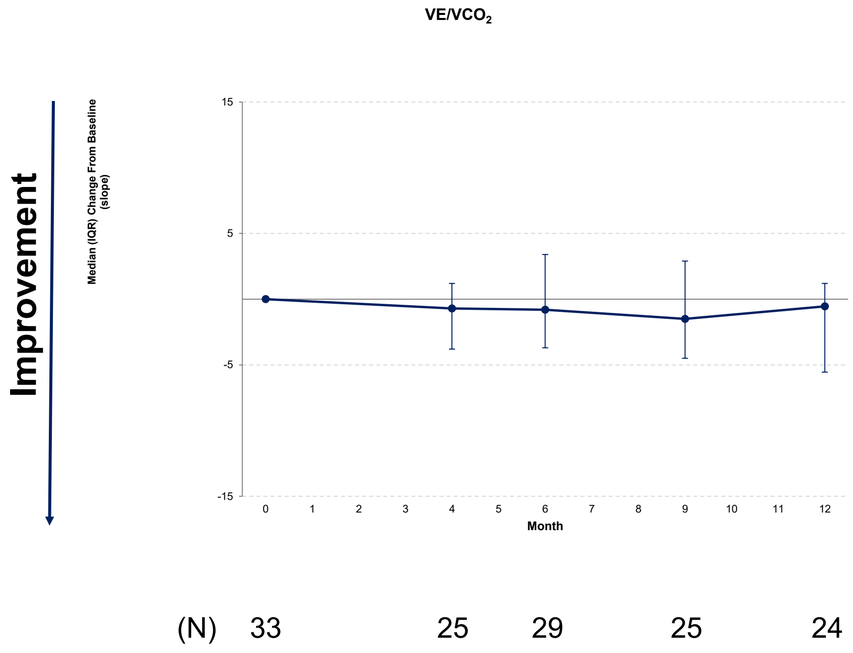
[a]Values represent a change of at least one level in NYHA class.
IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; QOL, quality of life.

Fontana M et al. *NEJM 2024*

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

Cardiopulmonary Exercise Test



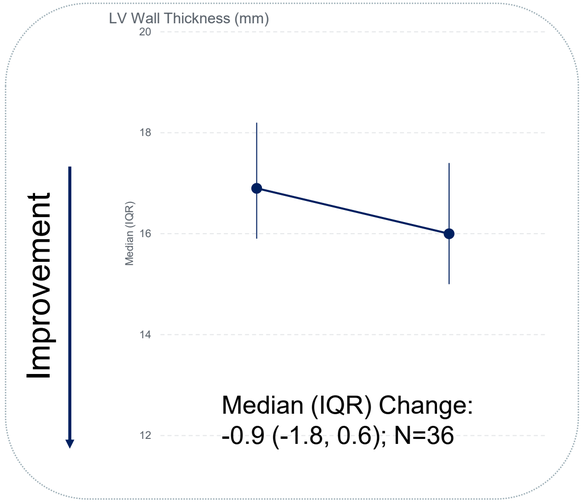


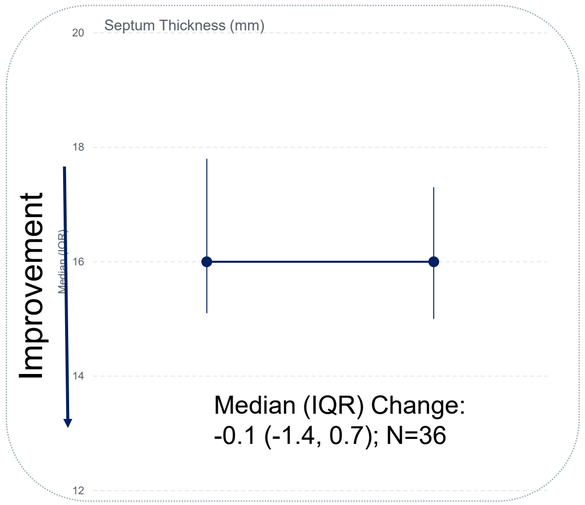
Peak VO_2 and VE/VCO_2 slope are strong prognostic markers[1] and deteriorate rapidly in ATTR-CM[2]

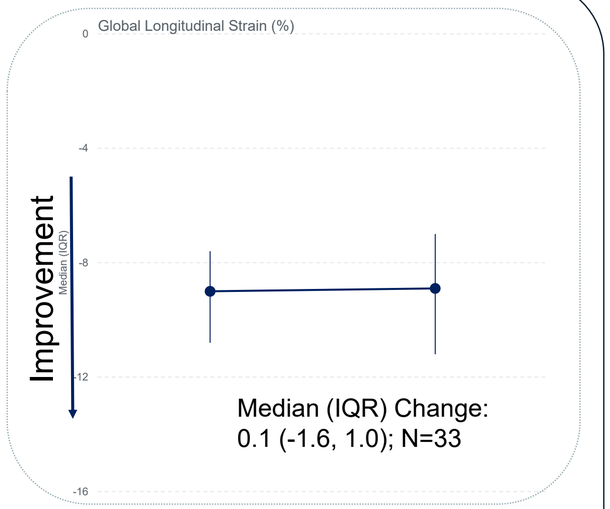
Data cutoff August 21, 2024.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; IQR, interquartile range; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.
1. Patel RK, et al. *JAMA Cardiol*. 2024;9(4):367-376. 2. Argirò A, et al. *Can J Cardiol*. 2024;40(3):364-369.

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

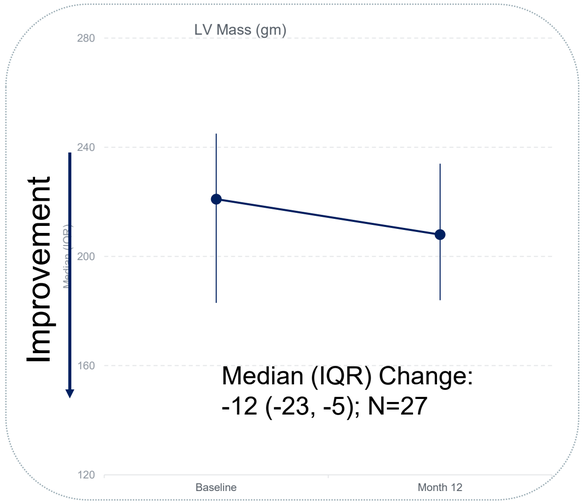
Echo

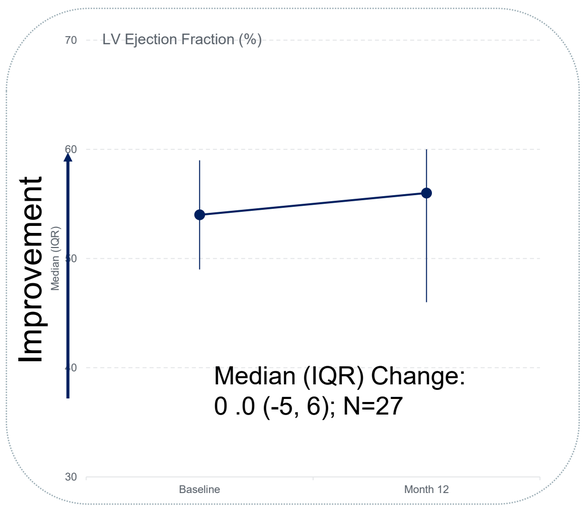


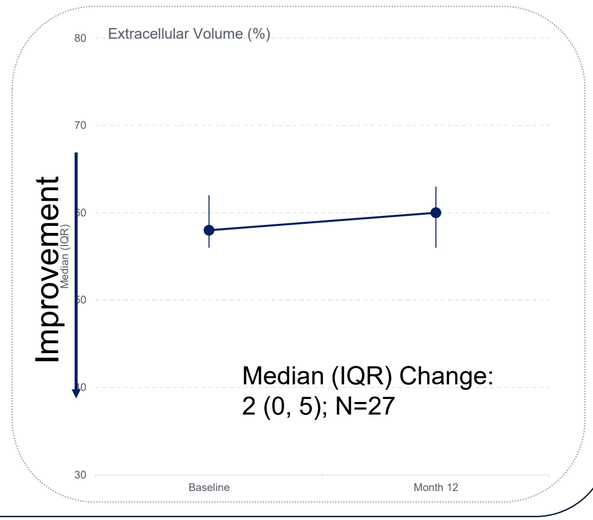




CMR



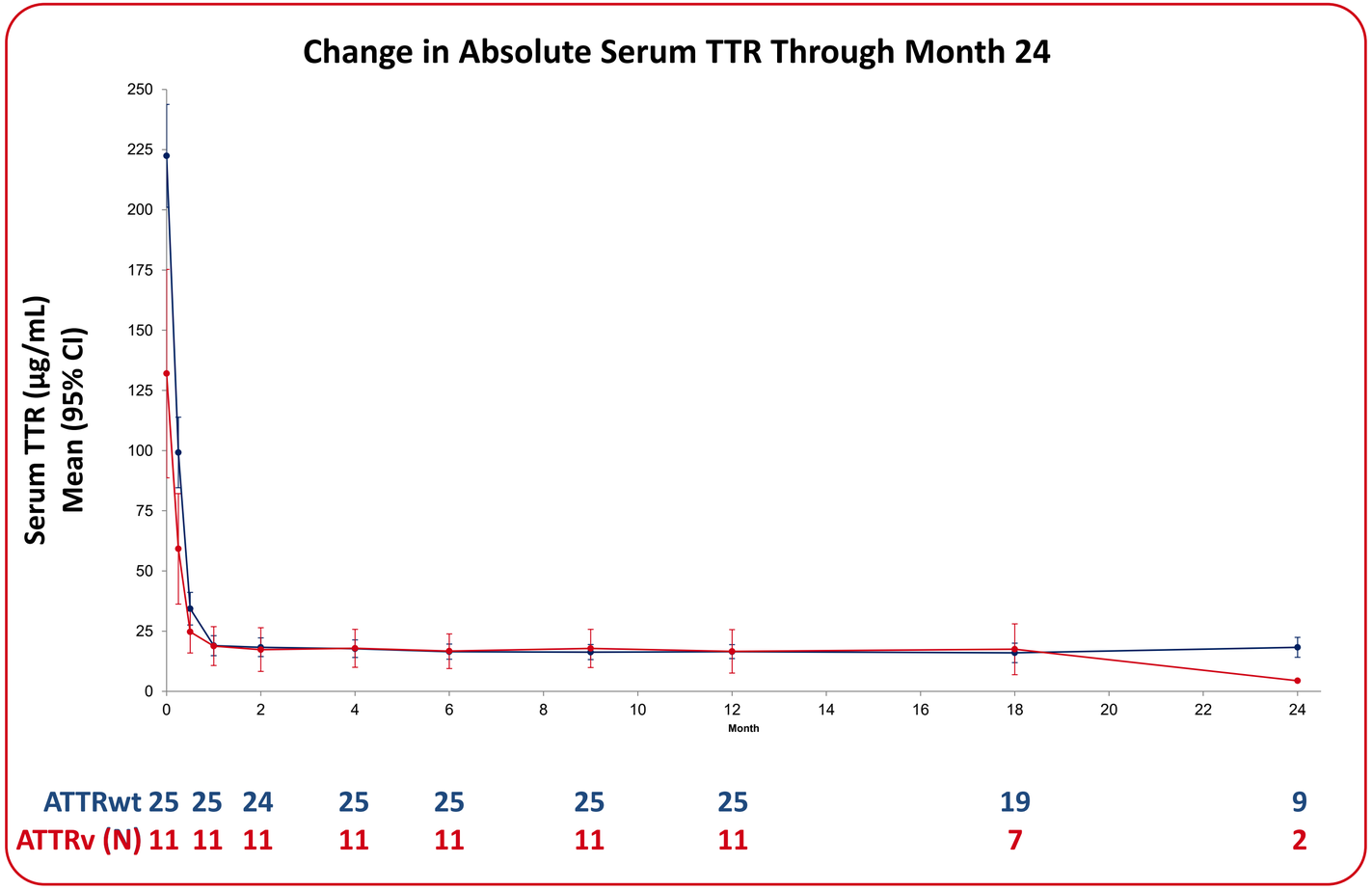




Data cutoff August 21, 2024.
CMR, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricular.

Fontana M et al. *NEJM 2024*

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)

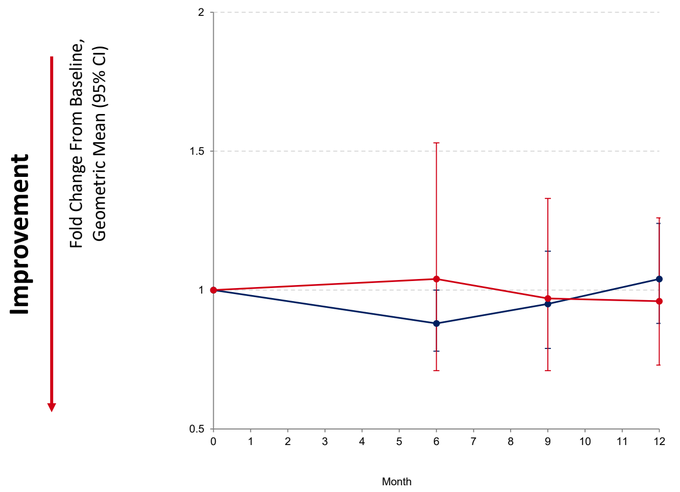
Data cutoff August 21, 2024.
ATTRv-CM, variant ATTR amyloidosis with cardiomyopathy; ATTRwt-CM, wild-type ATTR amyloidosis with cardiomyopathy; TTR, transthyretin.

Fontana M et al. *HFA 2025*

Disease Progression Is Favorably Impacted With nex-z Treatment

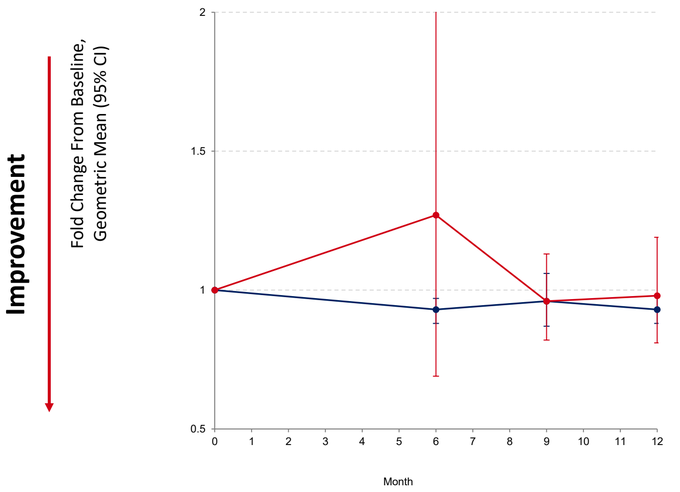
Markers of Disease Progression[1,2]

NT-proBNP



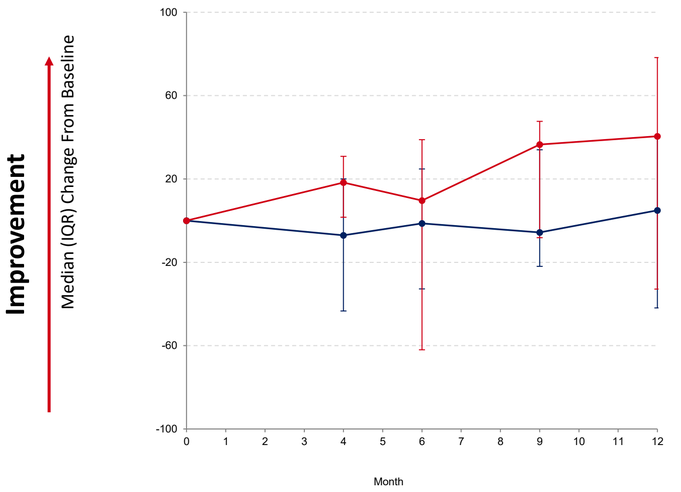
ATTRwt (N)	25	25	25	25	
ATTRv (N)	11	11	11	11	

hs-Troponin T



ATTRwt (N)	25	25	25	25	
ATTRv (N)	11	11	11	11	

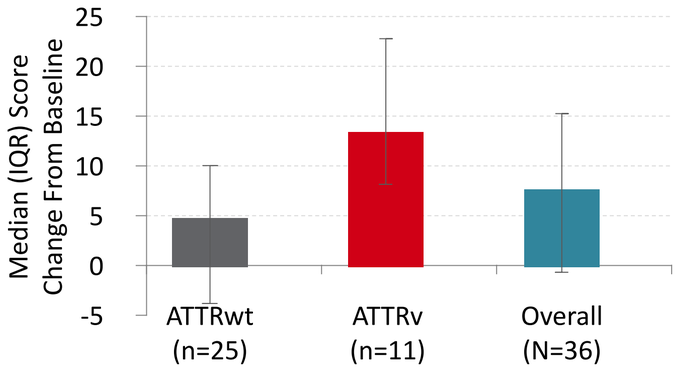
6MWT Distance (meters)



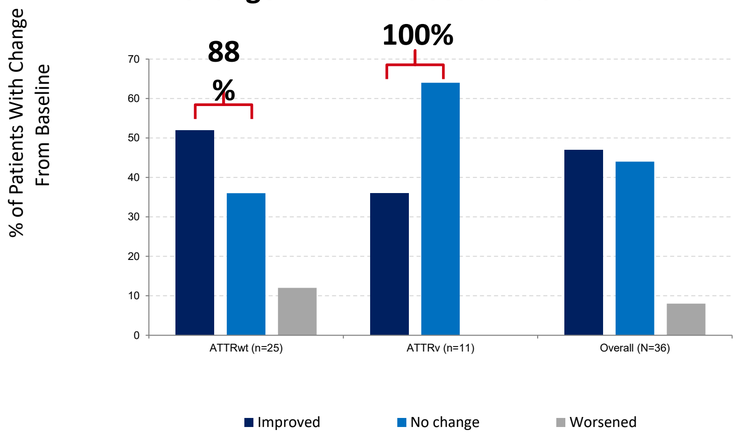
ATTRwt (N)	25	22	23	23	24
ATTRv (N)	11	11	11	9	11

Evidence of Stability or Improvement in Symptoms and QOL

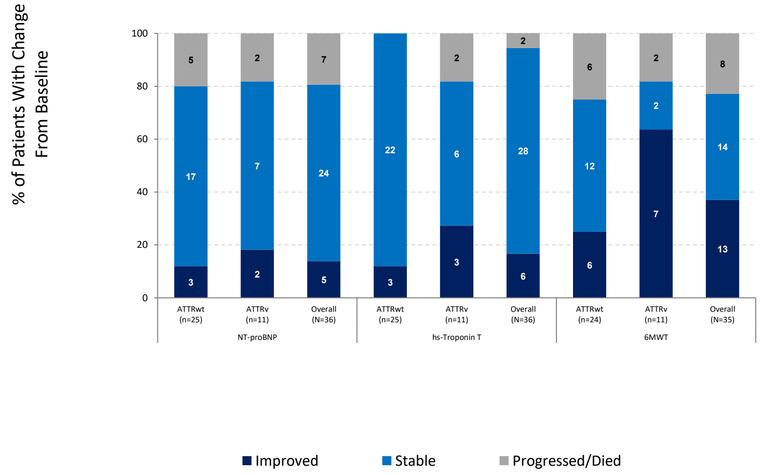
KCCQ-OS at Month 12



Change in NYHA Class at Month 12[a]



Changes in Markers of Disease Progression at Month 12[1,2]



Data cutoff August 21, 2024. [a]Values 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.

Fontana M et al. *HFA 2025*

Summary of Safety

Event	n (%)
At least one AE	34 (94)
AEs occurring in ≥15% of patients	
Cardiac failure	13 (36)
COVID-19	7 (19)
Upper respiratory tract infection	7 (19)
Atrial fibrillation	6 (17)
Urinary tract infection	6 (17)
Treatment-related AEs in ≥5% of patients	
Infusion-related reaction	5 (14)
Aspartate aminotransferase increased	2 (6)
Any AE leading to treatment discontinuation	0
Any event leading to death[a]	1 (3)

Event	n (%)
Any SAE	14 (39)
SAEs occurring in ≥5% of patients	
Cardiac failure	5 (14)
Acute myocardial infarction	3 (8)
Urinary tract infection	3 (8)
Atrial flutter	2 (6)
Pneumonia	2 (6)
SAEs of heart failure or arrhythmia	7 (19)
Cardiac failure	5 (14)
Arrhythmia[b]	3 (8)
CV hospitalization rate[c] (n/pt/yr, 95% CI)	0.16 (0.08 to 0.36)

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. [a]Only one death occurred (ischemic heart disease) on Day 506 after dosing; unrelated to treatment.
[b]Arrhythmia events included SAEs of atrial flutter and atrioventricular block complete, with one patient experiencing both cardiac failure and arrhythmia on the same day. [c]Includes hospitalizations for cardiac failure, arrhythmia, or stroke. AE, adverse event; CV, cardiovascular; SAE, serious AE.

Fontana M et al. *NEJM 2024*

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

Single-dose nex-z IV infusion administered over 4 hours

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

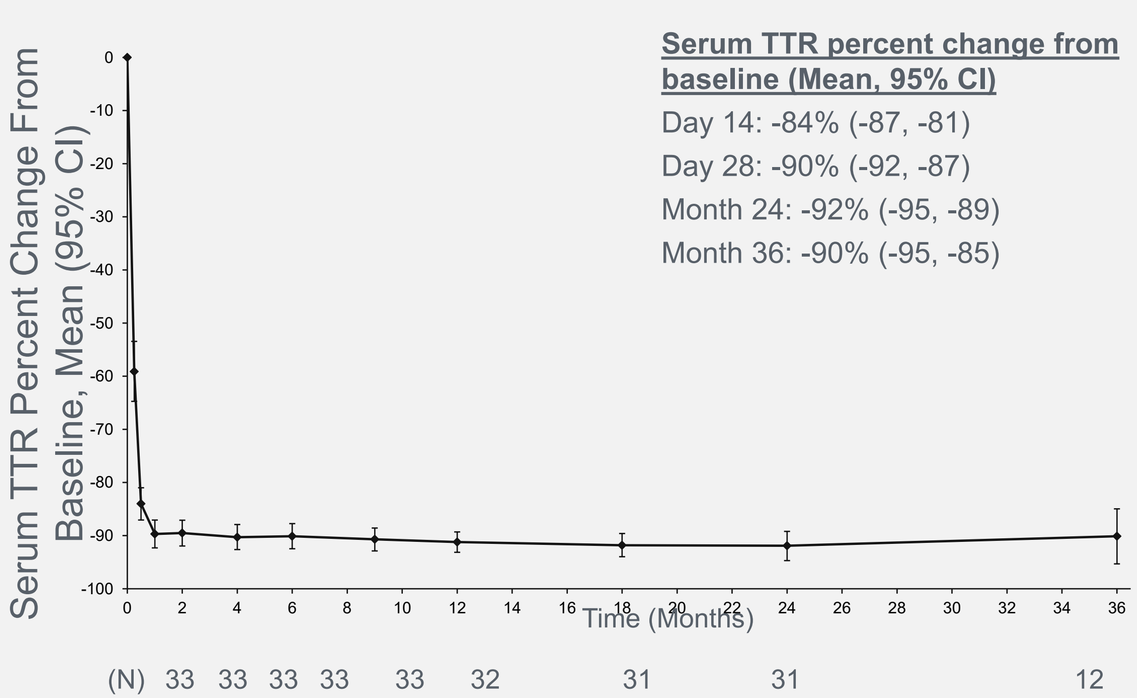
Phase 1 (NCT04601051); Long-term follow-up study (NCT05697861). Data cutoff April 11, 2025.

[a]Patients 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



Serum TTR percent change from baseline (Mean, 95% CI)

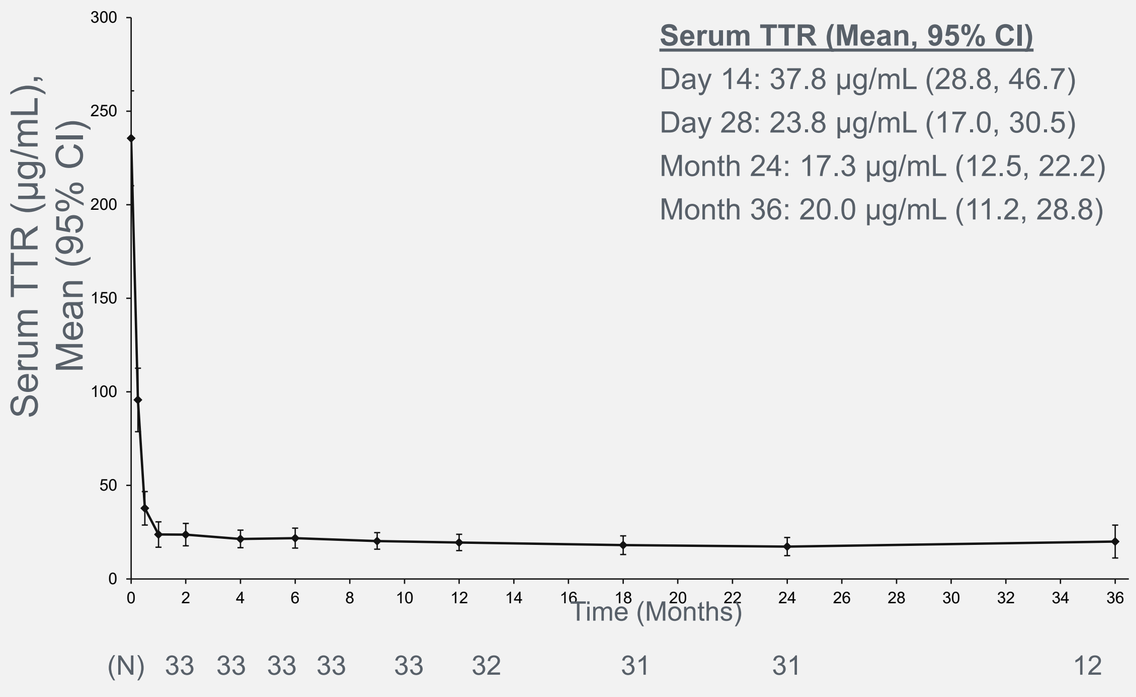
Day 14: -84% (-87, -81)

Day 28: -90% (-92, -87)

Month 24: -92% (-95, -89)

Month 36: -90% (-95, -85)

Absolute Serum TTR Concentration



Serum TTR (Mean, 95% CI)

Day 14: 37.8 µg/mL (28.8, 46.7)

Day 28: 23.8 µg/mL (17.0, 30.5)

Month 24: 17.3 µg/mL (12.5, 22.2)

Month 36: 20.0 µg/mL (11.2, 28.8)

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

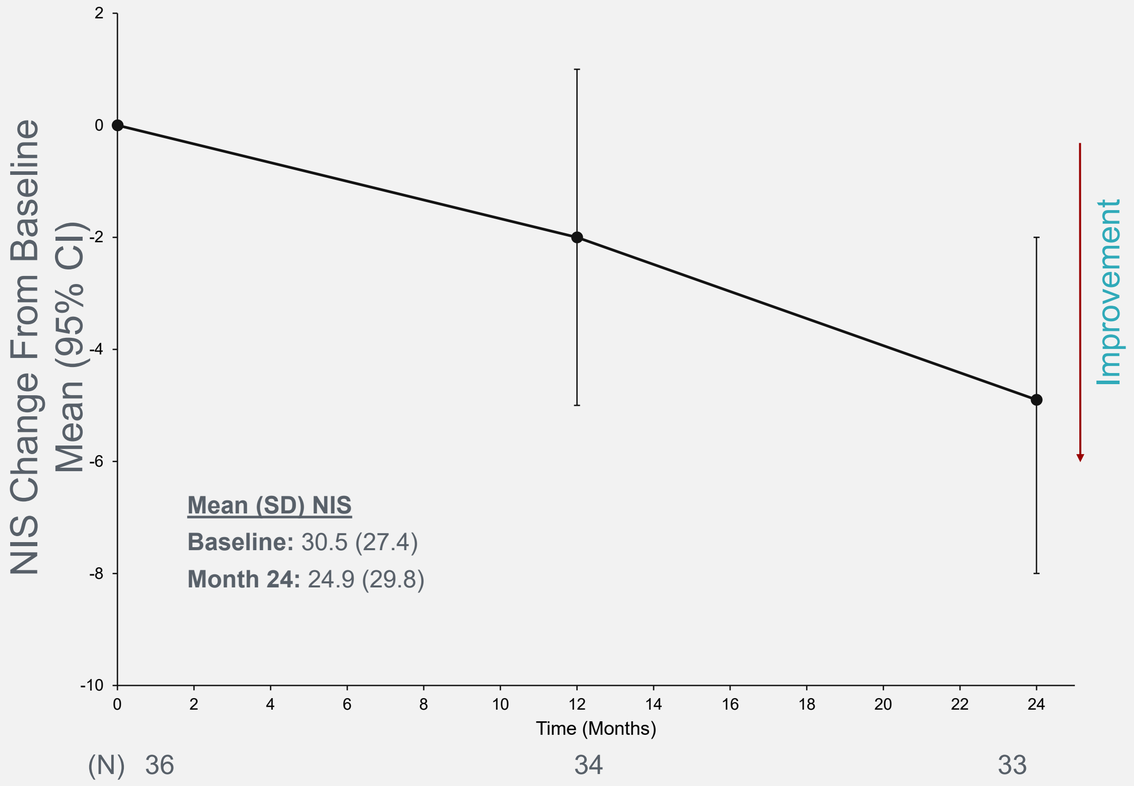
Data cutoff April 11, 2025. Data regarding the serum TTR level at month 36 were collected from patients who entered the long-term follow-up safety monitoring study (data-cutoff date, April 16, 2025).

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.

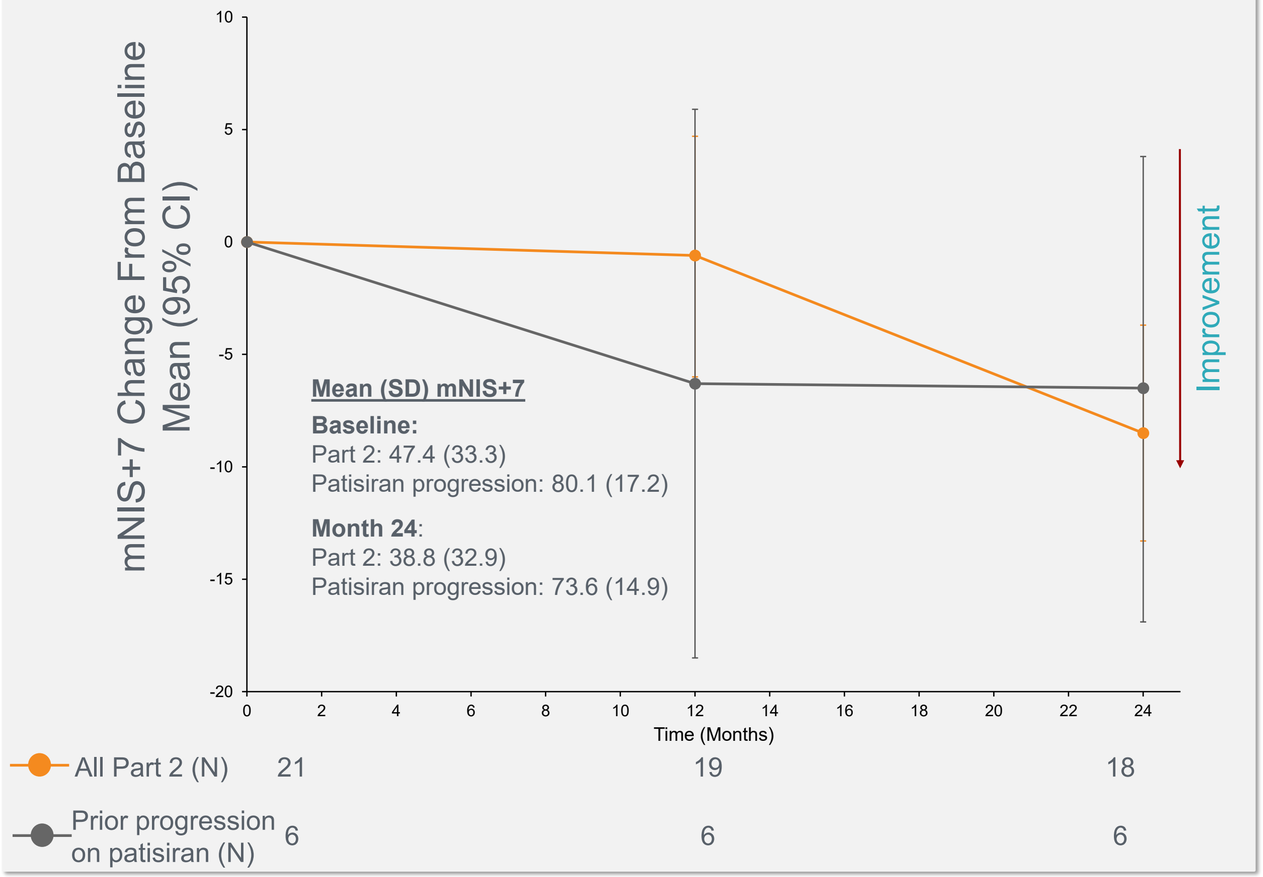
TTR, transthyretin.

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

NIS Change from Baseline

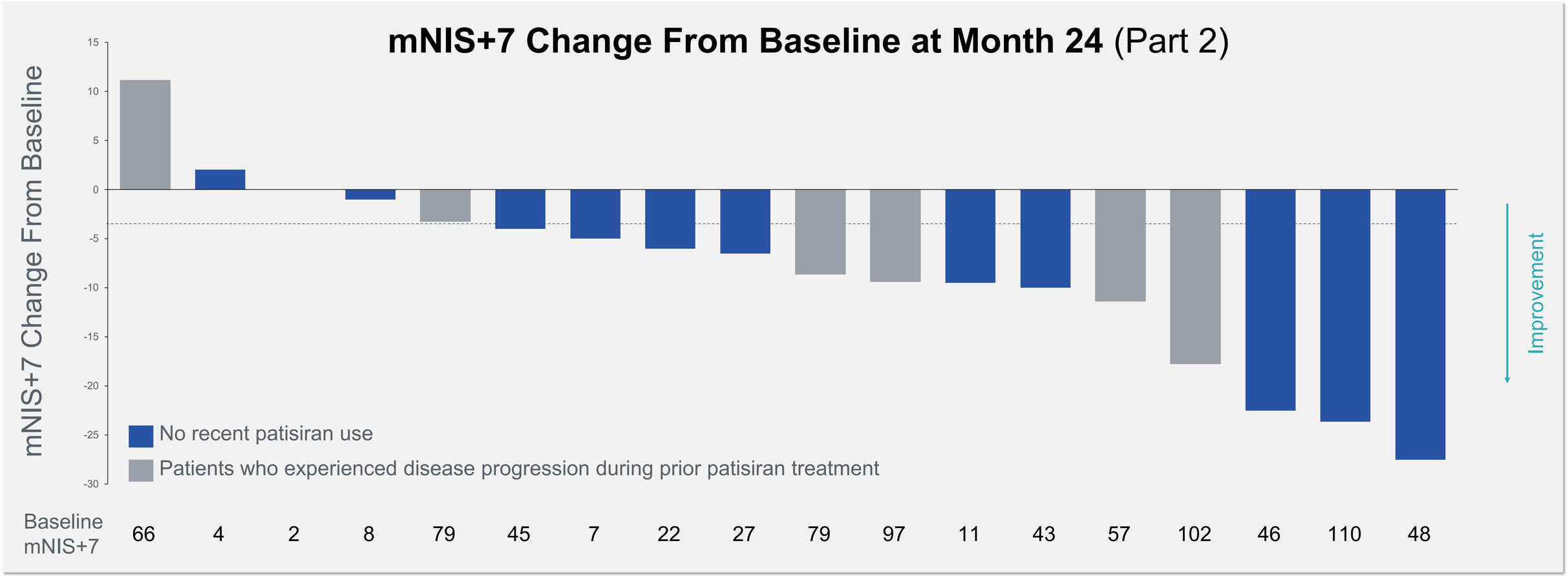


mNIS+7 Change from Baseline (Part 2)



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.

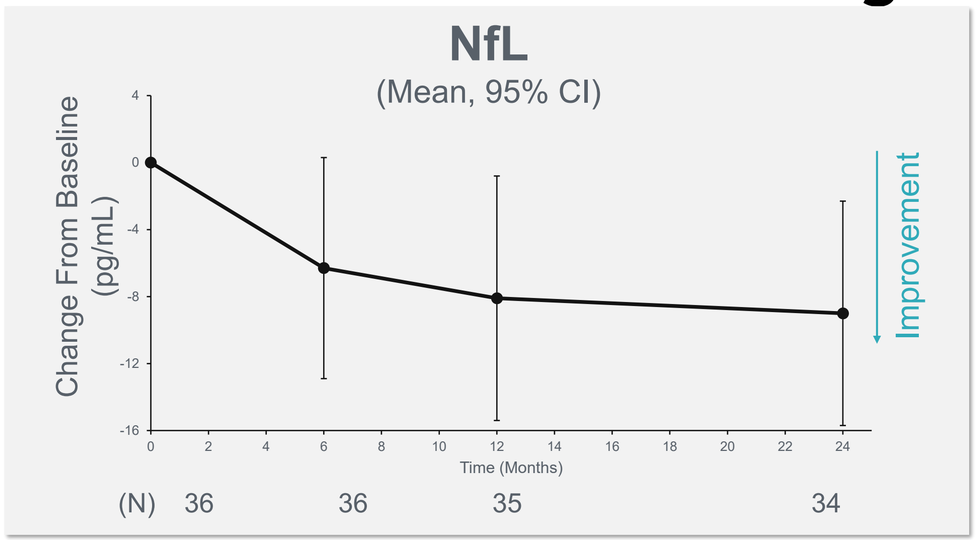
At Month 24, the majority of patients experienced improvements in mNIS+7

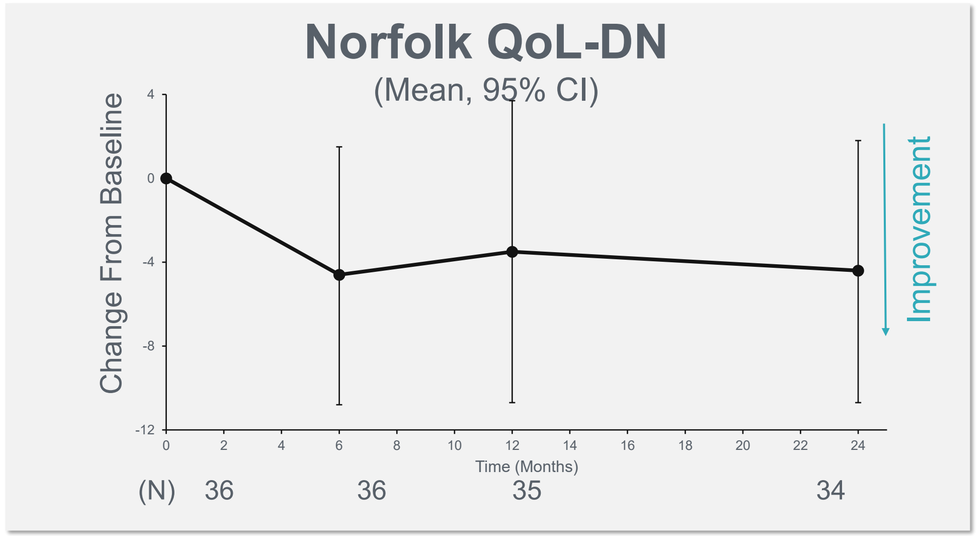


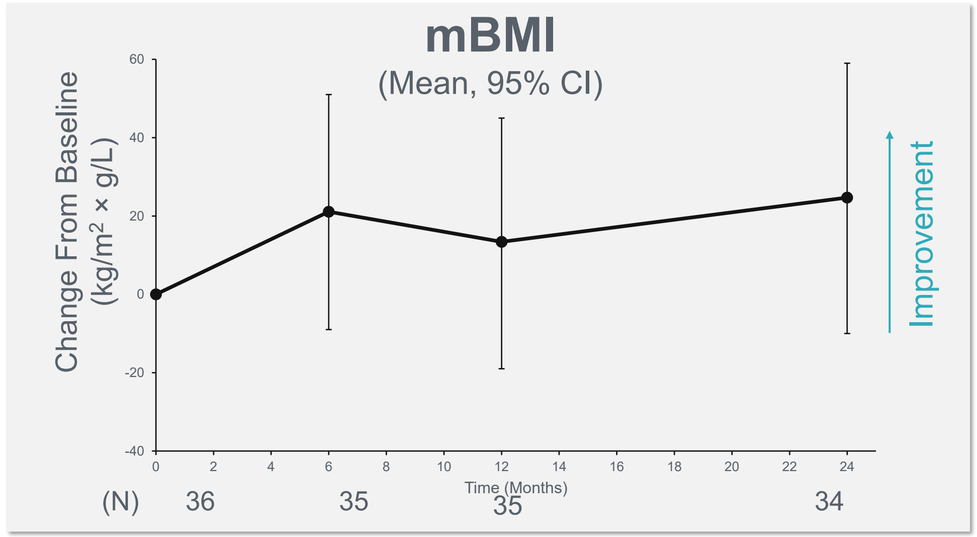
- **The mean change in mNIS+7 at Month 24 was -8.5 points**
- **13/18 (72%) patients had improvements in mNIS+7 which exceeded the clinically meaningful threshold of a ≥4-point reduction[1]**

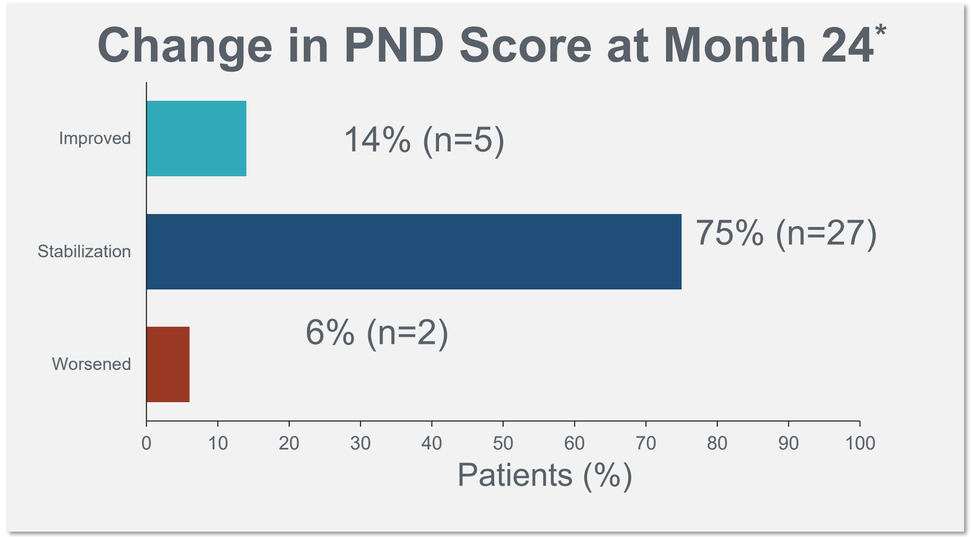
Gillmore, J. D., et al. (2025). *Nexiguran Ziclumeran gene editing in hereditary ATTR. The New England Journal of Medicine, 393*(15), 1375–1386. https://doi.org/10.1056/NEJMoa2510209
Data cutoff April 11, 2025.
Dotted line indicates cutoff for clinically meaningful improvement (Folkvaljon F, et al. *Muscle 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

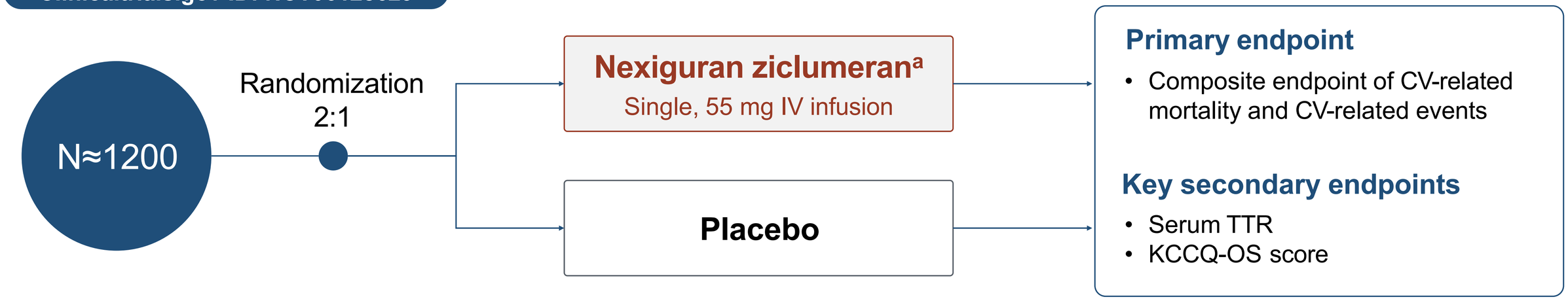
Gillmore, J. D., et al. (2025). *Nexiguran Ziclumeran gene editing in hereditary ATTR. The New England Journal of Medicine, 393*(15), 1375–1386. https://doi.org/10.1056/NEJMoa2510209
Data cutoff April 11, 2025.
[a]Not accompanied by thyroid-stimulating hormone elevation or symptoms of hypothyroidism. No patient had clinical hypothyroidism or TSH elevation. [b]3 patients had Grade ≥3 liver enzyme elevations. [c]One 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 [d]One 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]

MAGNITUDE CLINICAL TRIAL

Recruiting

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.

[a]NTLA-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]

MAGNITUDE CLINICAL TRIAL

Recruiting

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.**

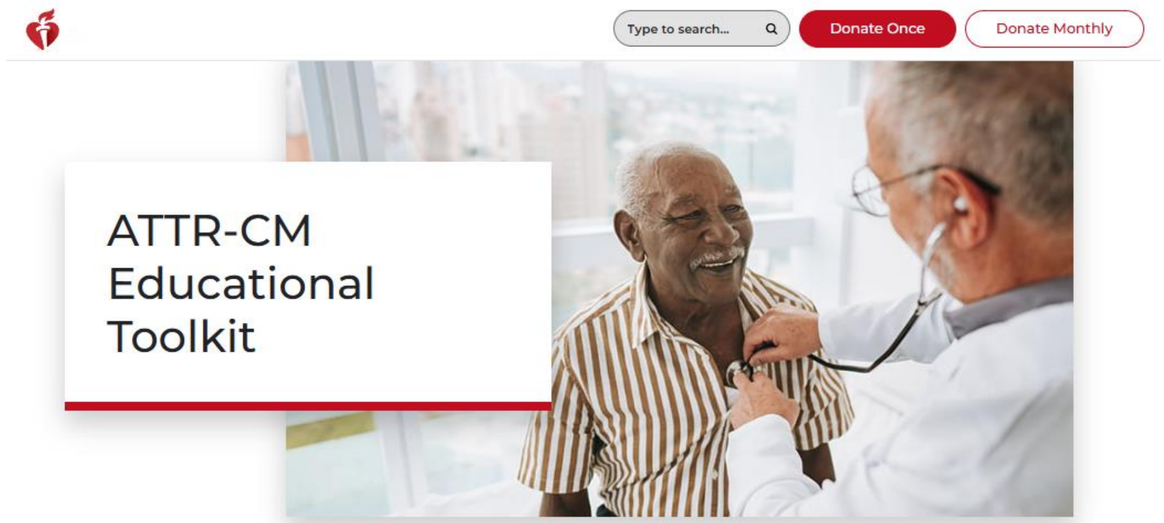
- The effects of nex-z on clinical outcomes are being evaluated in MAGNITUDE[a], a phase 3, global, randomized, placebo-controlled trial in patients with ATTR-CM.

ATTR-CM Educational Toolkit

Kellie Lavender

National Program Lead,
Patient Education and Support,
American Heart Association

ATTR-CM Educational Toolkit



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

Scan the QR code to Learn More!

www.heart.org/ATTR-CM

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:

1 Learning about the trial

- Ask your doctor to explain the trial and what it involves
- Your doctor will check if the trial is a good fit
- You can say no at any point

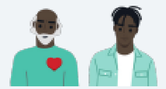
2 Screening and consent

- Doctors will ask about your health and do some tests (like blood work) to see if the trial is right for you
- You'll review a form that explains any risks and benefits
- The care team will explain how they will keep you safe during the trial

3 Treatment and monitoring

- You may get a treatment or a placebo—it depends on the trial
- You'll have check-ins to see how you're doing and talk through any concerns
- You can still leave the trial at any time, even during treatment

4 After the trial



- Your care team may keep checking in with you to see how you are doing
- You might hear how the trial helped others or led to new learning
- You may keep getting care or be connected to other helpful options

Who to ask about clinical trial participation

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

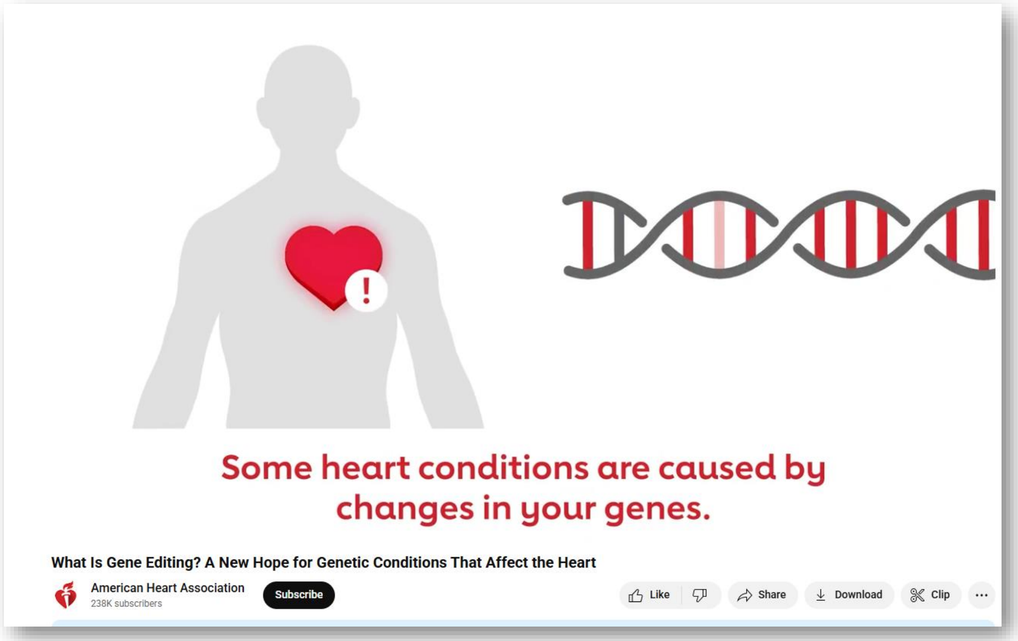
What questions do you or your family/caregiver have for your doctor?

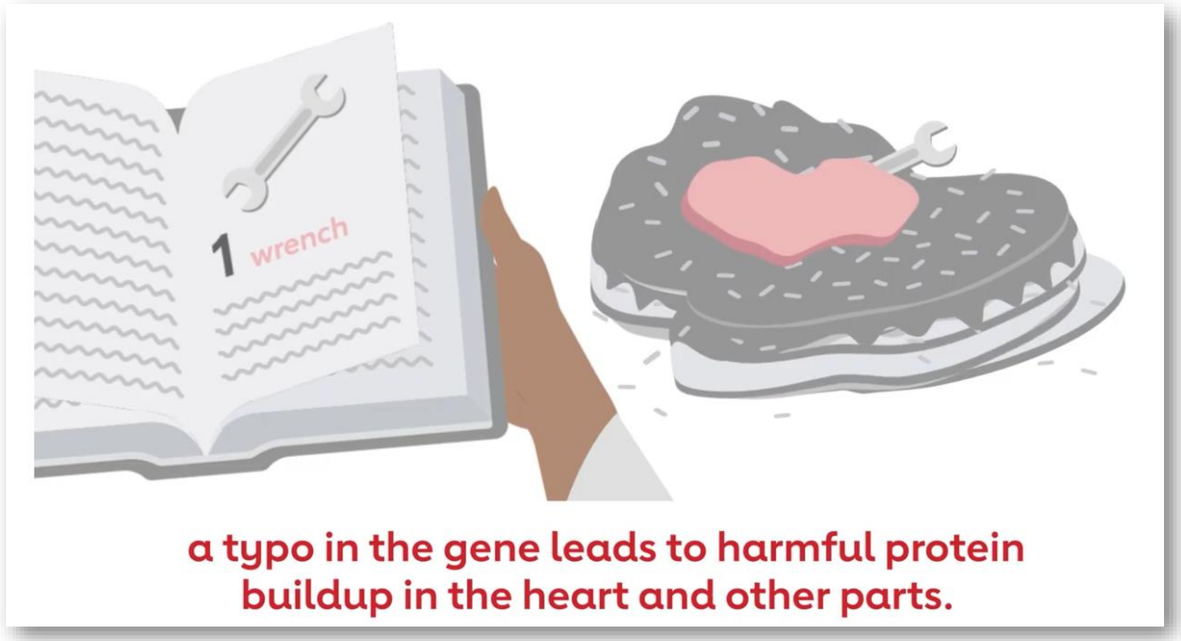
You can find information at www.heart.org/ATTR-CM

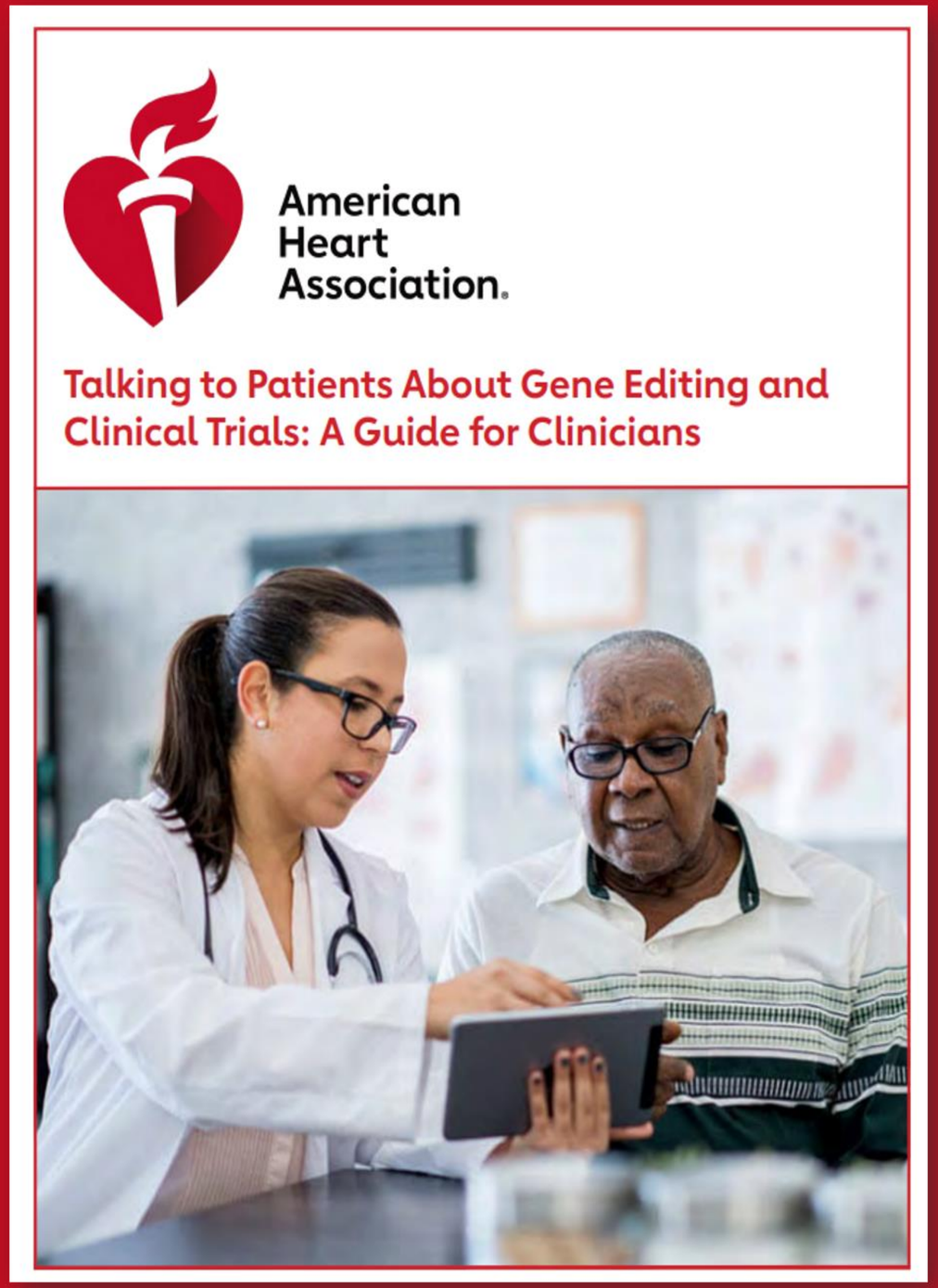
Intellia Therapeutics is proud to support the American Heart Association's Gene Therapy Awareness and Education resources.

This information is based on recommendations from the American Heart Association.

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







www.heart.org/ATTR-CM

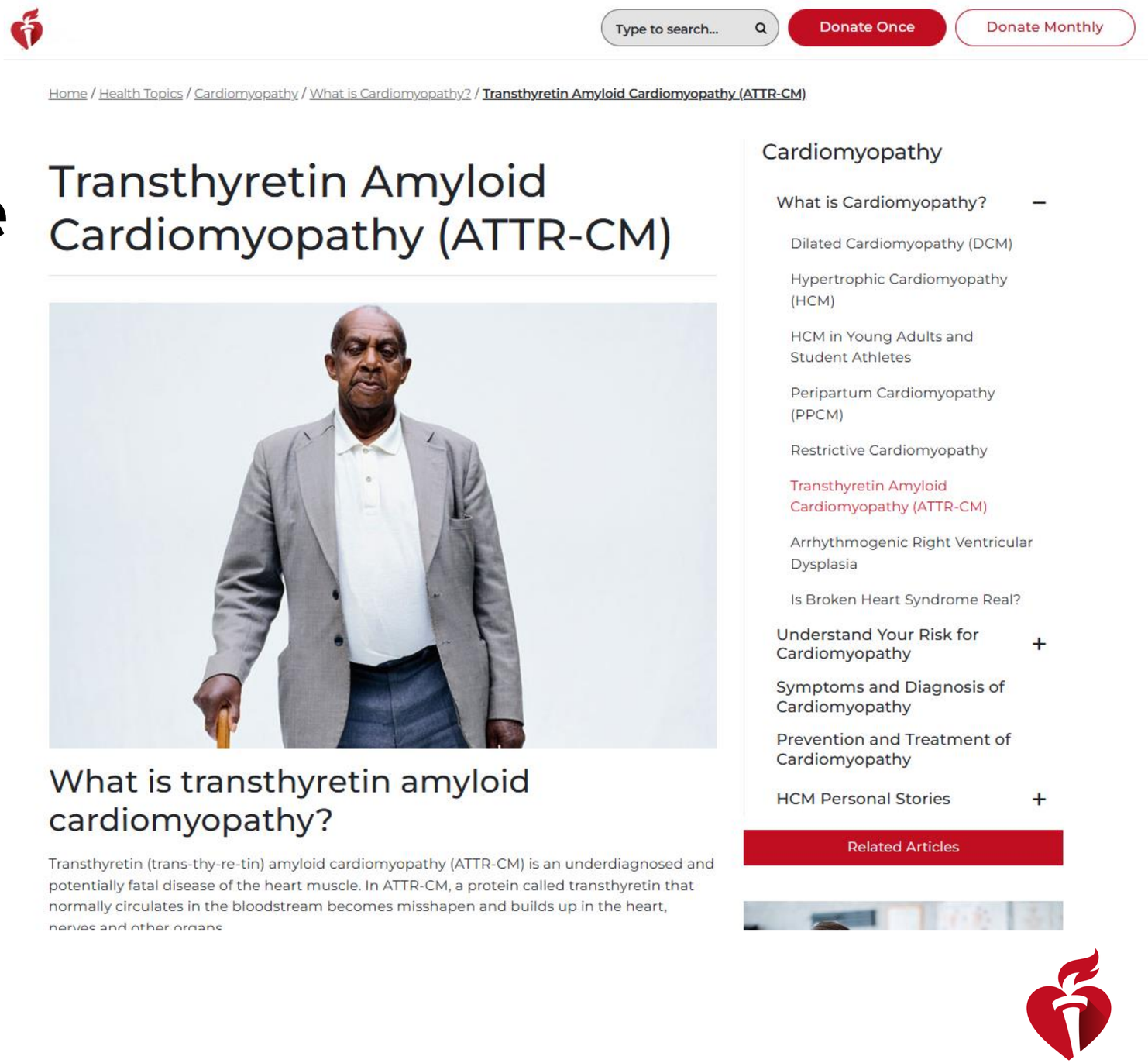
Scan the QR code
to Learn More!

ATTR-CM Resources Available

Health Topics:
What is ATTR-CM?

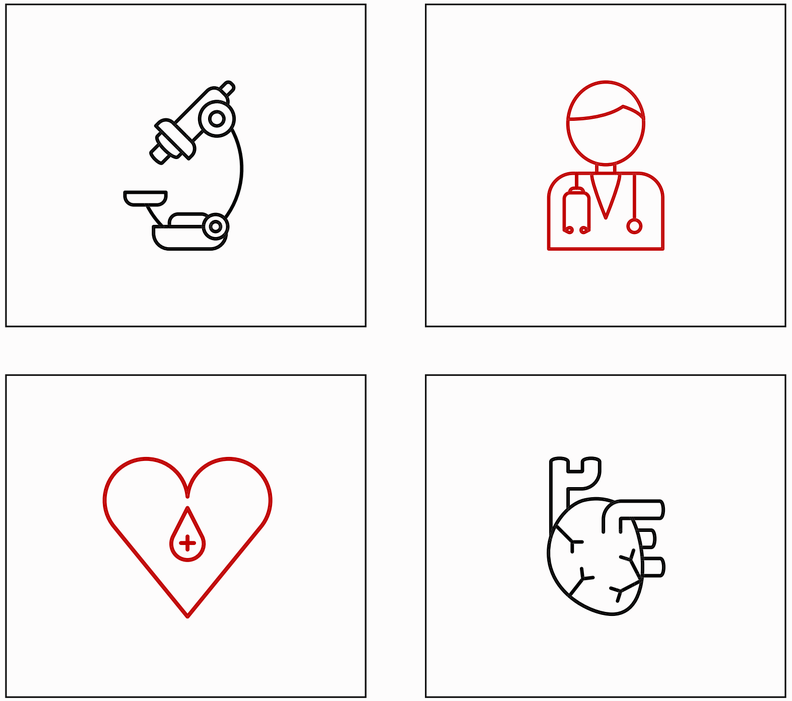
Health Topics:
Genetic Testing and Counseling for hATTR

Health Topics:
A Guide to Understanding Clinical Trials



Q & A

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

American Heart Association®

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

Connect with Us! Scan to email ClinicalStudies@heart.org