Amyloidosis Research Consortium

Emerging Treatment Strategies and Clinical Trials for Cardiac Amyloidosis

Presented by:

Jan M. Griffin, MD, FACC, FHFSA

Associate Professor of Medicine

Director, MUSC Amyloidosis Center

Advanced Heart Failure & Transplant Cardiology

Medical University of South Carolina

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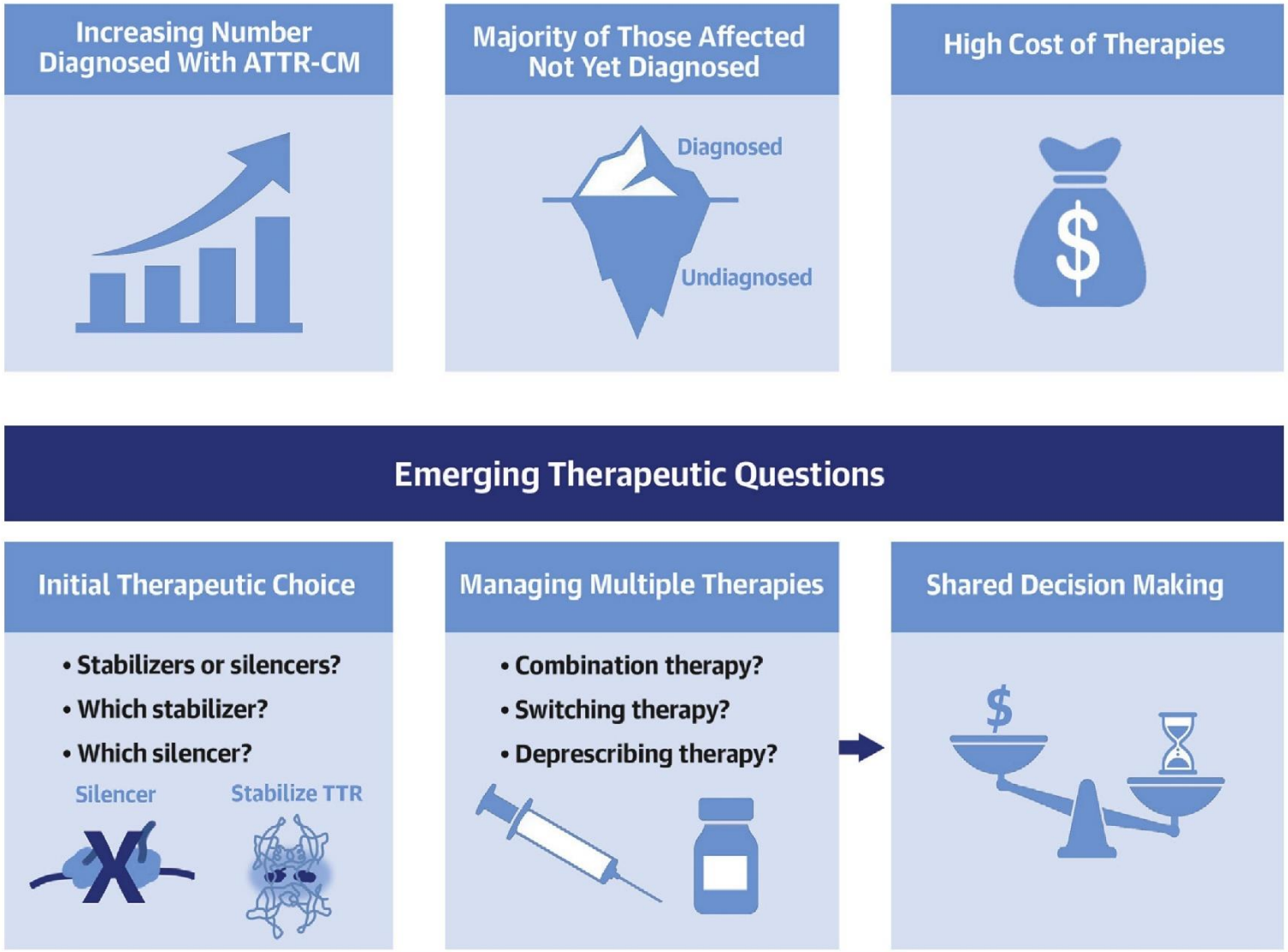
Disclosures

- Research Grants from Pfizer & BridgeBio
- Advisory board: Pfizer, BridgeBio, Astra Zeneca

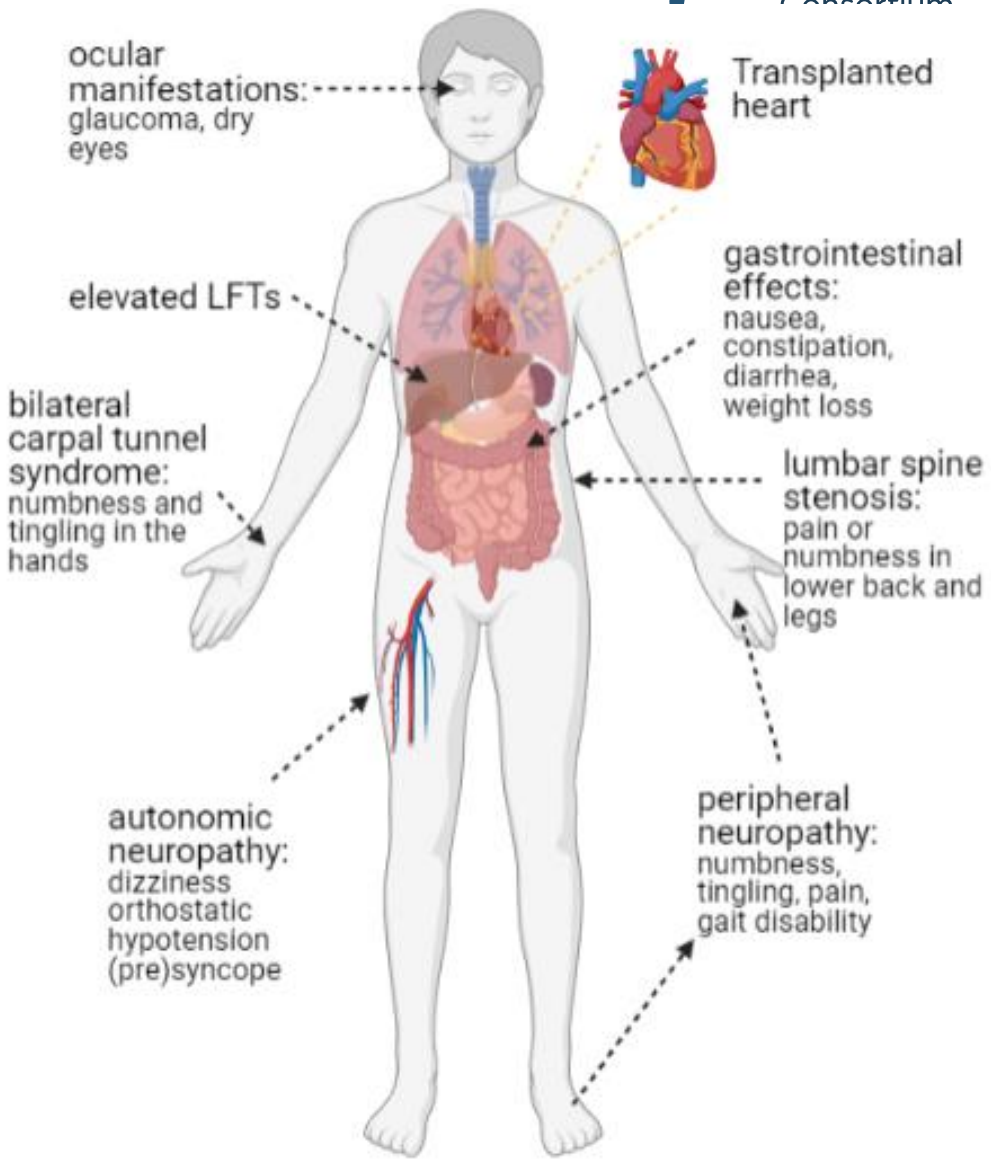
CENTRAL ILLUSTRATION: Evolving Landscape and Emerging Therapeutic Questions in ATTR-CM

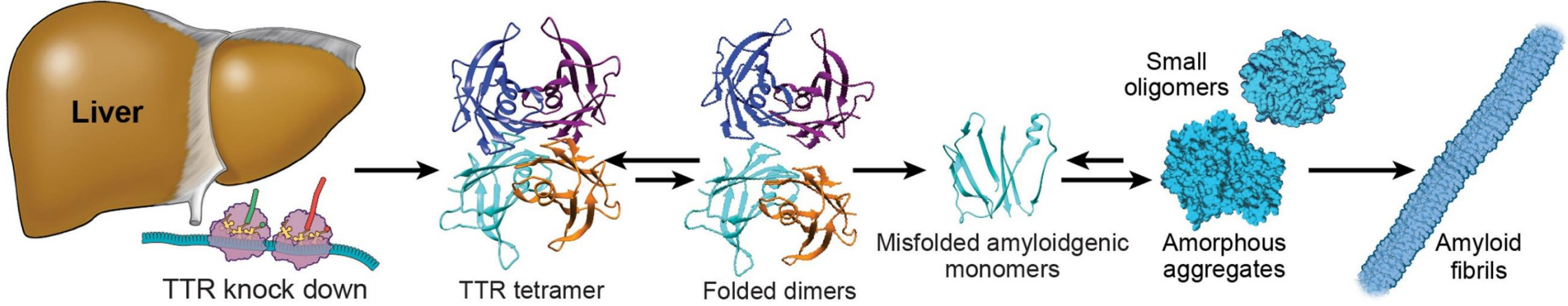


Griffin JM, et al. JACC Heart Fail. 2025;13(5):685-694.

Amyloidosis

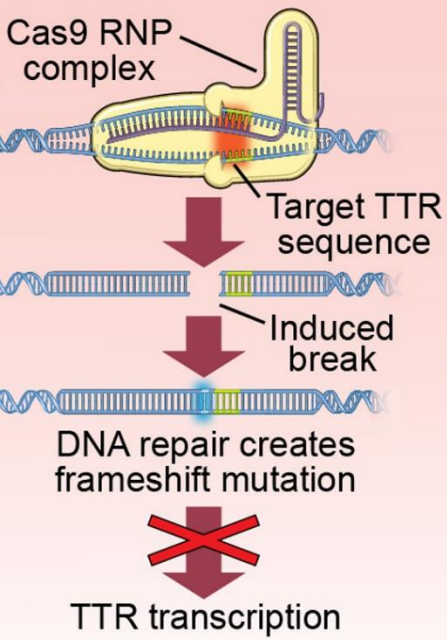
- Over 40 known amyloidogenic proteins
- Cardiac amyloidosis typically arises from either transthyretin (ATTR) or light-chain (AL) amyloid deposition
- Deposition in the myocardium → restrictive CM
- Deposition in the nerves → sensory, motor & autonomic neuropathy





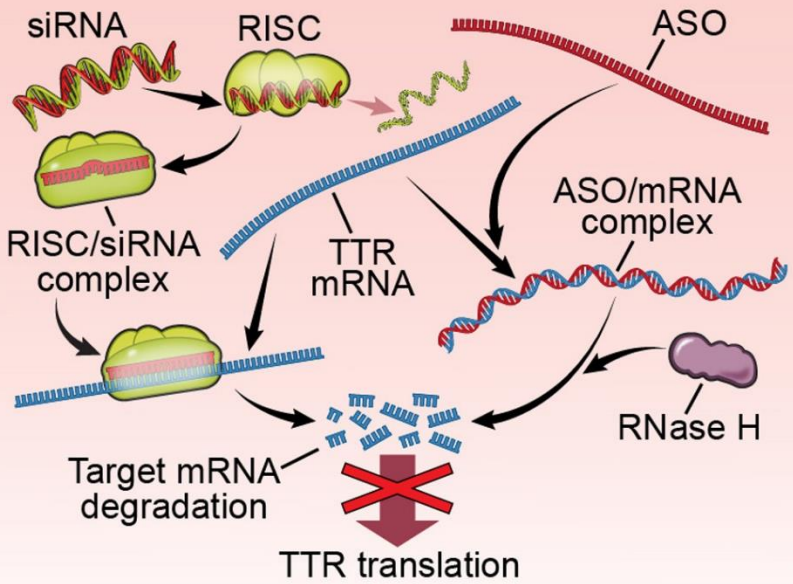
Gene Editing

- **Nex-z (NTLA-2001)**



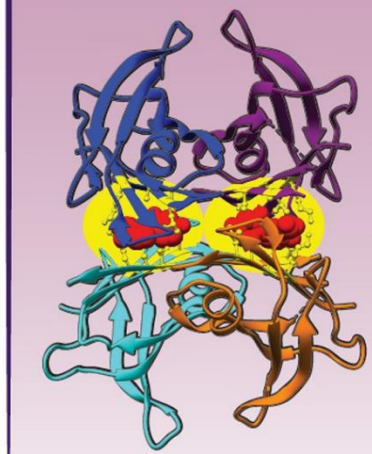
Block Protein Synthesis

- **Vutrisiran**
- **Patisiran**
- **Eplontersen**



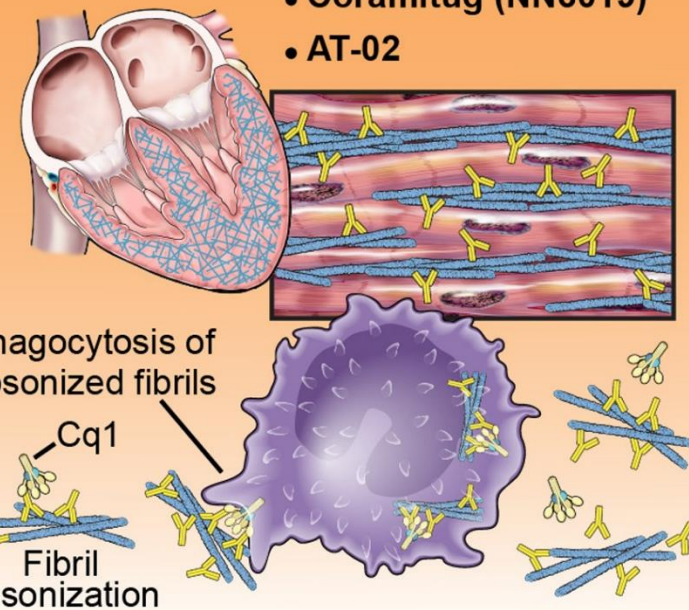
Stabilize Tetramer

- **Tafamidis**
- **Acoramidis**
- **Diflunisal***



Remove Amyloid Fibrils

- **ALXN 2220**
- **Coramitug (NN6019)**
- **AT-02**



Geographic Distribution of ATTR Cardiac Amyloidosis

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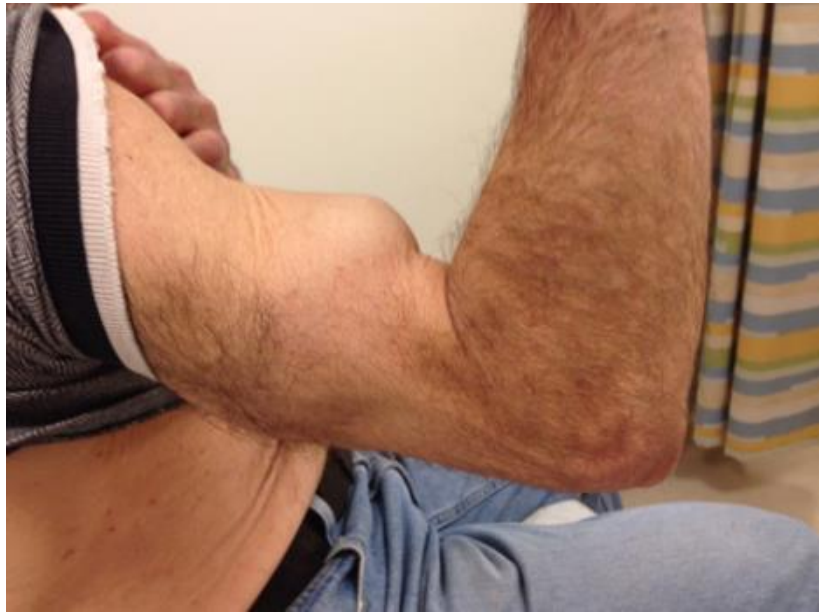
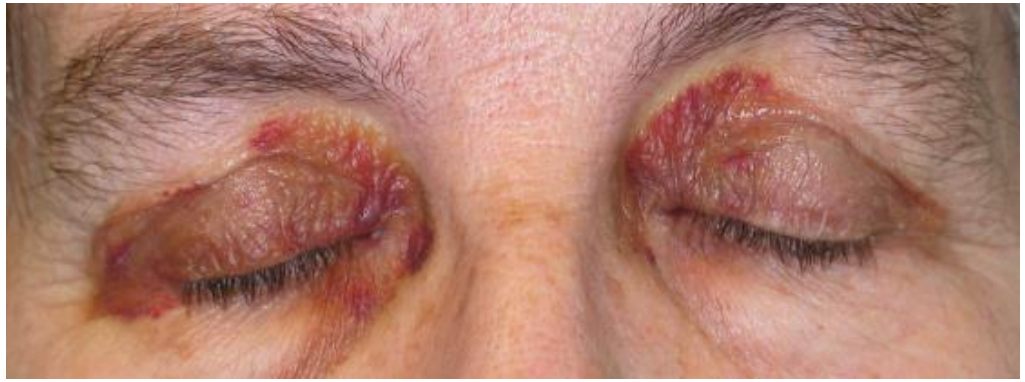
- Wild type ATTR is the most common form in the US
- V122I is the most common mutation in the US
  - US, UK, Western Africa
  - ~3.5% of Black Americans, penetrance is unknown
- V30M is the most common mutation worldwide
  - Portugal, Sweden, Japan
  - Early vs Late onset
- T60A
  - US, UK, Northern part of the Republic of Ireland
  - ~1% of those of Irish descent

Red Flags

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





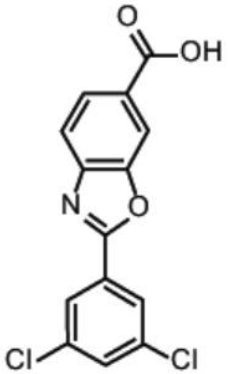
What we will cover

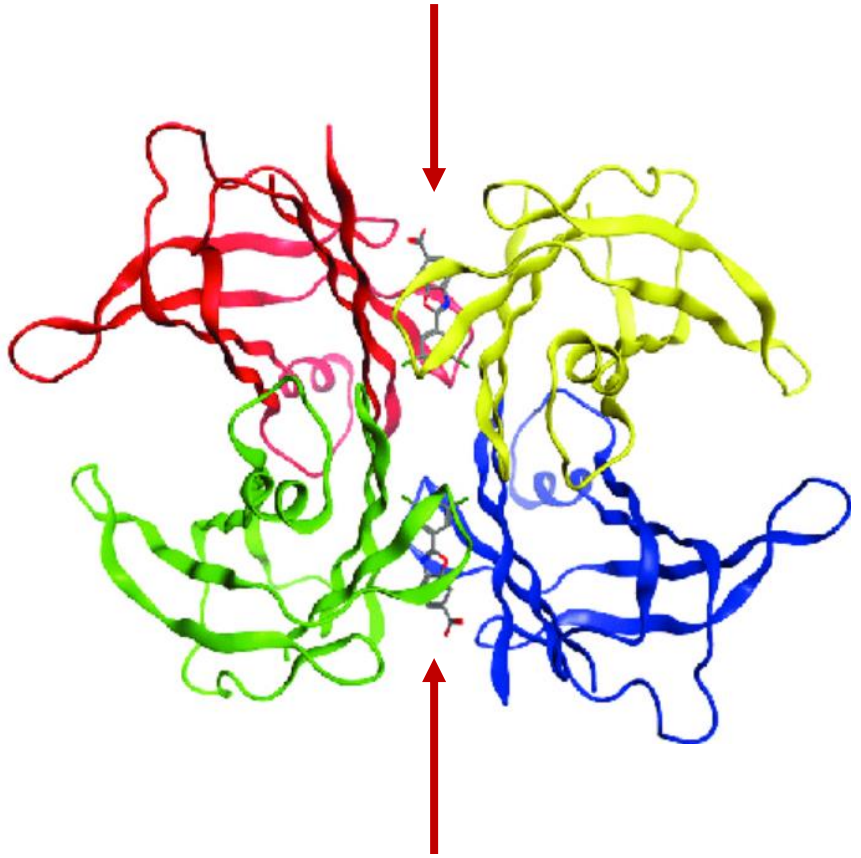
- TTR Stabilizing Therapies
- Silencing the TTR gene
- Gene editing with CRISPR
- TTR depleting agents in clinical trials
- Can we prevent TTR Amyloidosis?
- Is there a role for combination therapy?

TTR Stabilizers

Tafamidis : ATTR-ACT trial

- Benzoxazole derivative
- No safety signals of clinical concern
- Approved by the FDA in 2019 for ATTR cardiac amyloidosis





Maurer et al. NEJM 2018;379:1007-1016

ATTR-ACT

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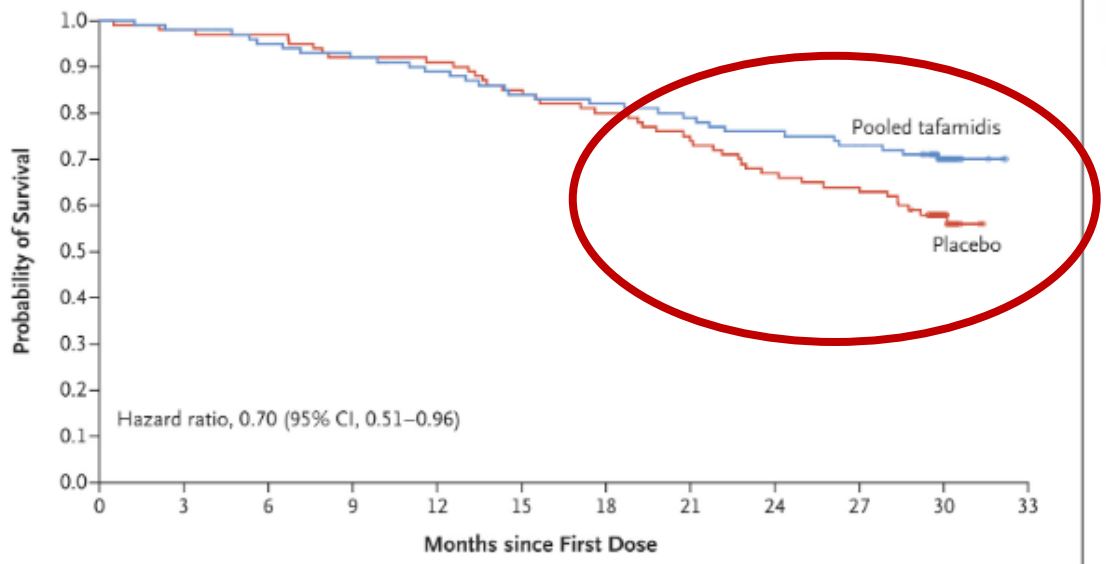
A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

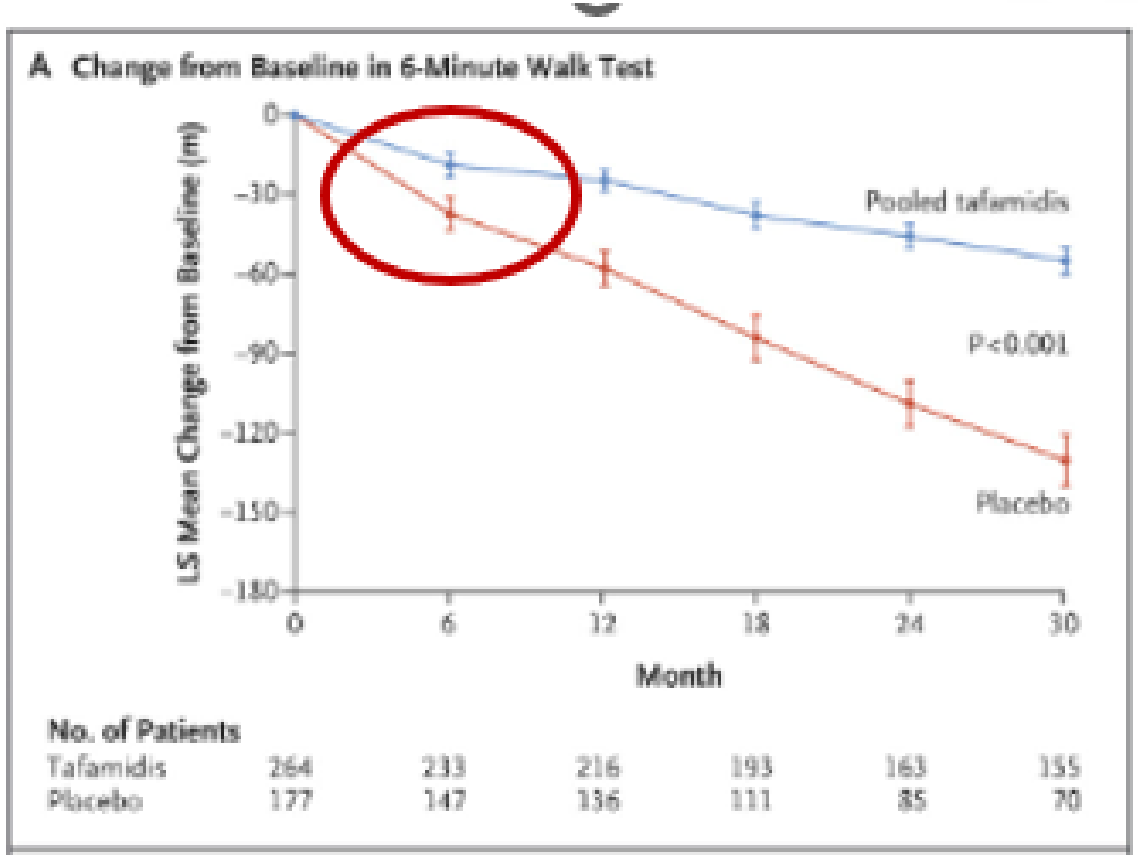
C Frequency of Cardiovascular-Related Hospitalizations

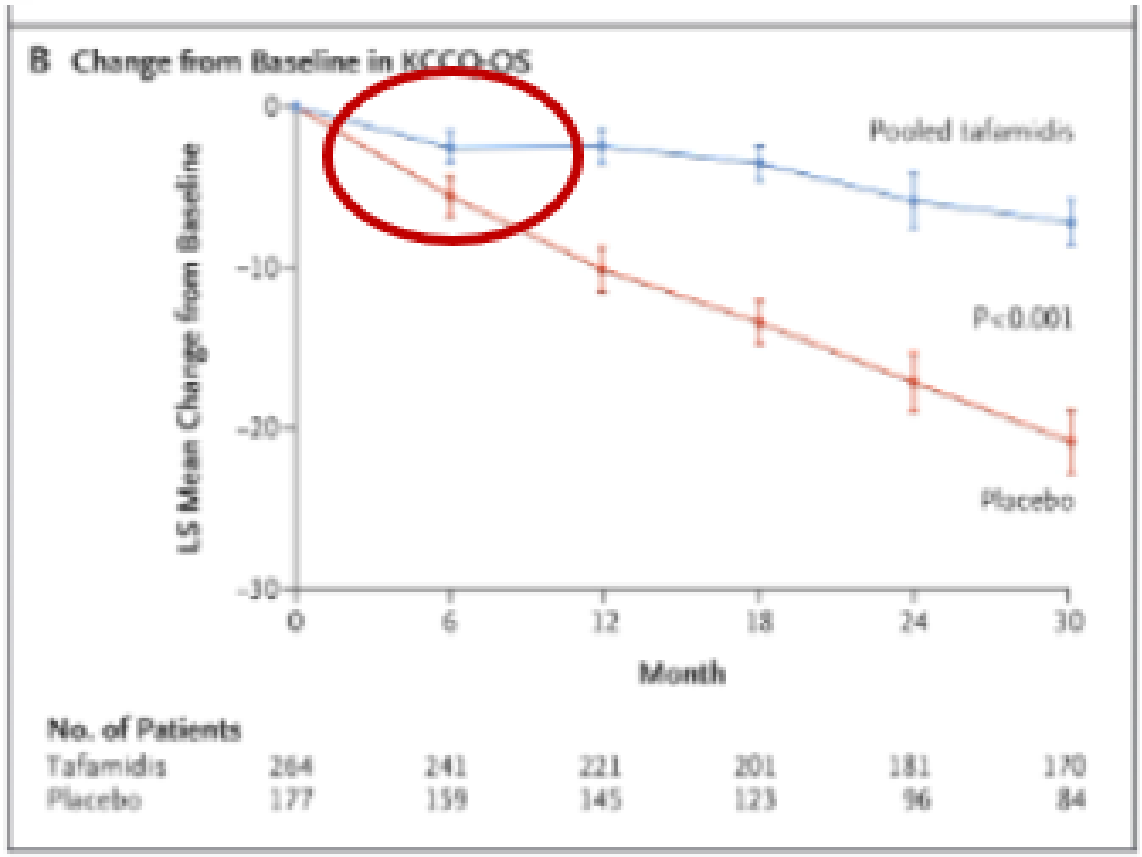
	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

- Primary outcome: 2-step hierarchical endpoint of death and CV related hospitalizations
- Tafamidis was superior to placebo
  - Win Ratio 1.7
- Pooled Tafamidis was associated with
  - 30% RRR in death (29.5% vs 42.9%)
  - 32% RRR in CV hospitalization

Maurer et al. NEJM 2018;379:1007-1016

Secondary Outcomes



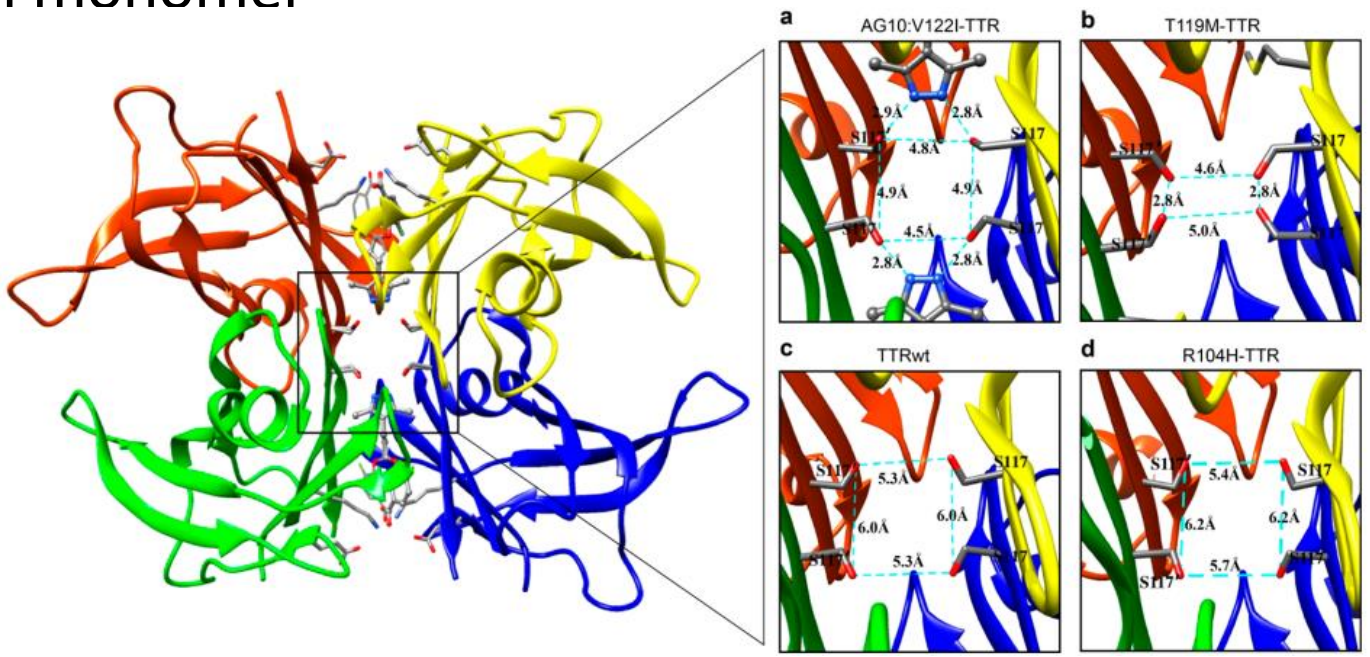


Exploratory Endpoint: Smaller increase in NT-proBNP for tafamidis at 30 months (−2180.54 [95% CI, −3326.14 to −1034.95])

Maurer et al. NEJM 2018;379:1007-1016

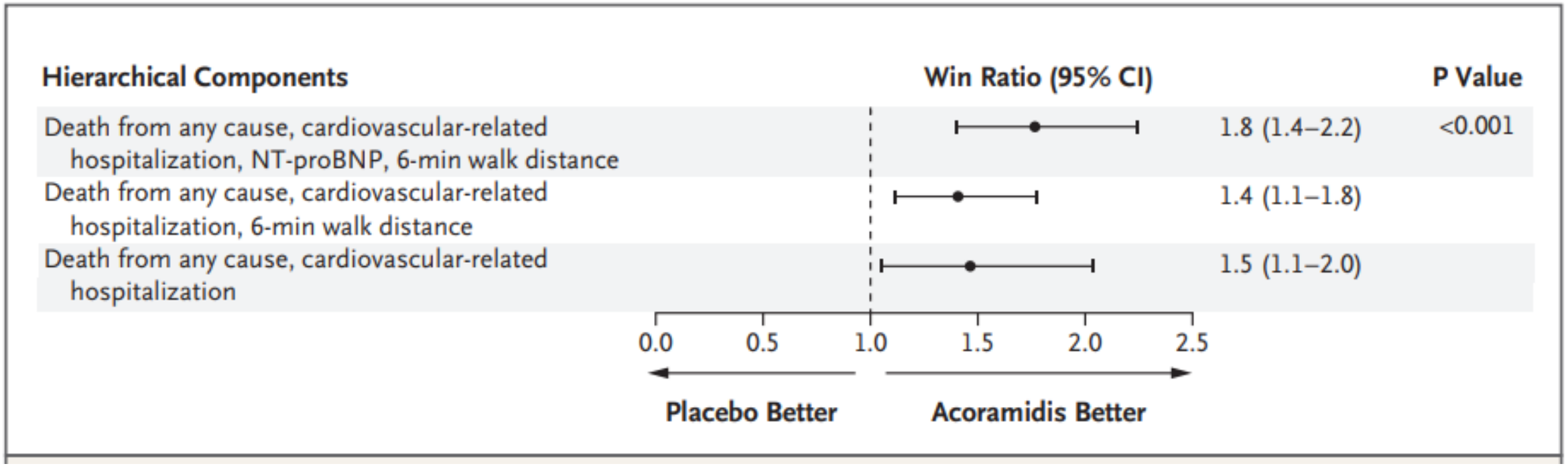
Acoramidis : ATTRibute-CM trial

- Mimics the super-stabilizing activity of Thr119Met (p.T139M)
  - Forms hydrogen bonds between neighboring serine residues at position 117 of each monomer
- Approved in November 2024 for ATTR-CM



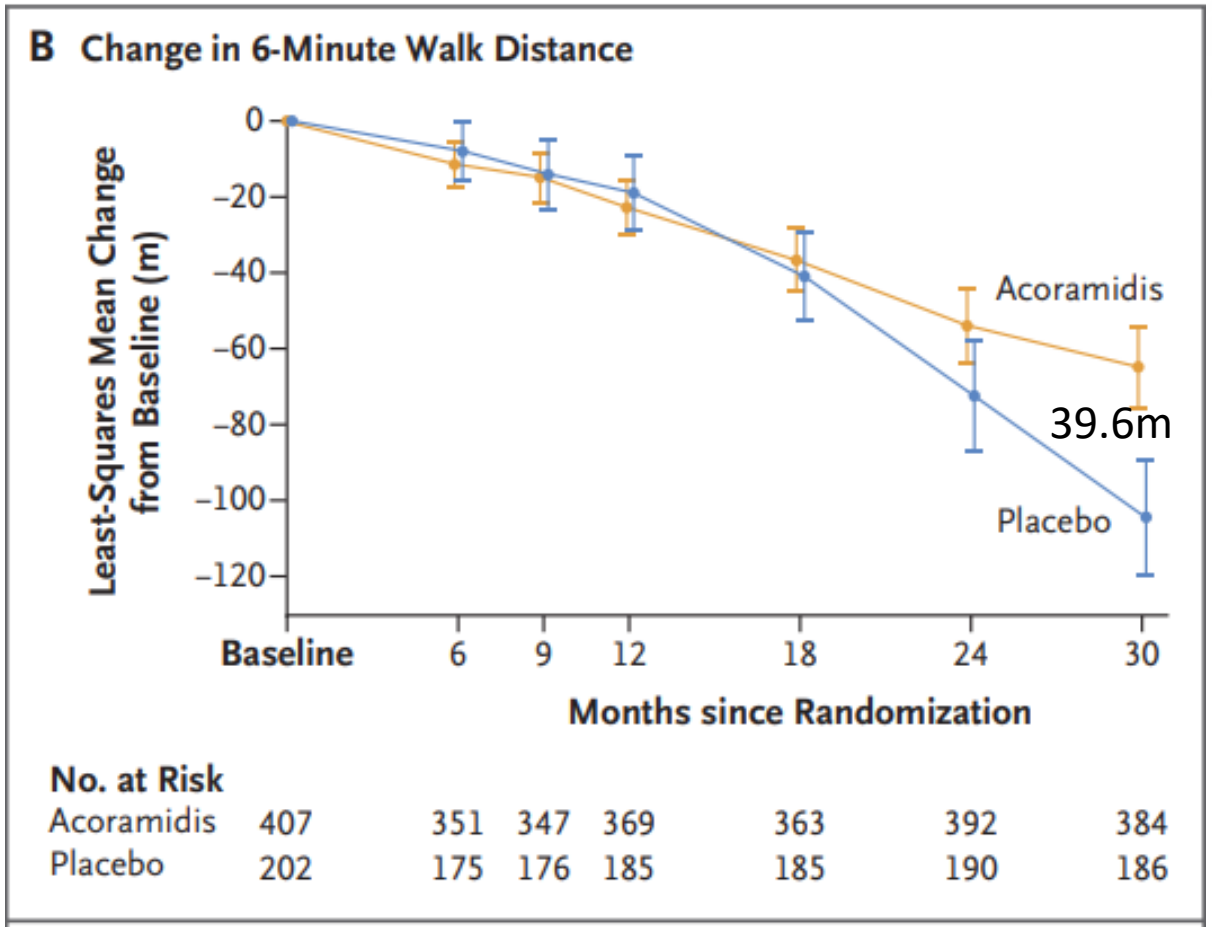
Miller et al. J med Chem 2018;61:7862-7876

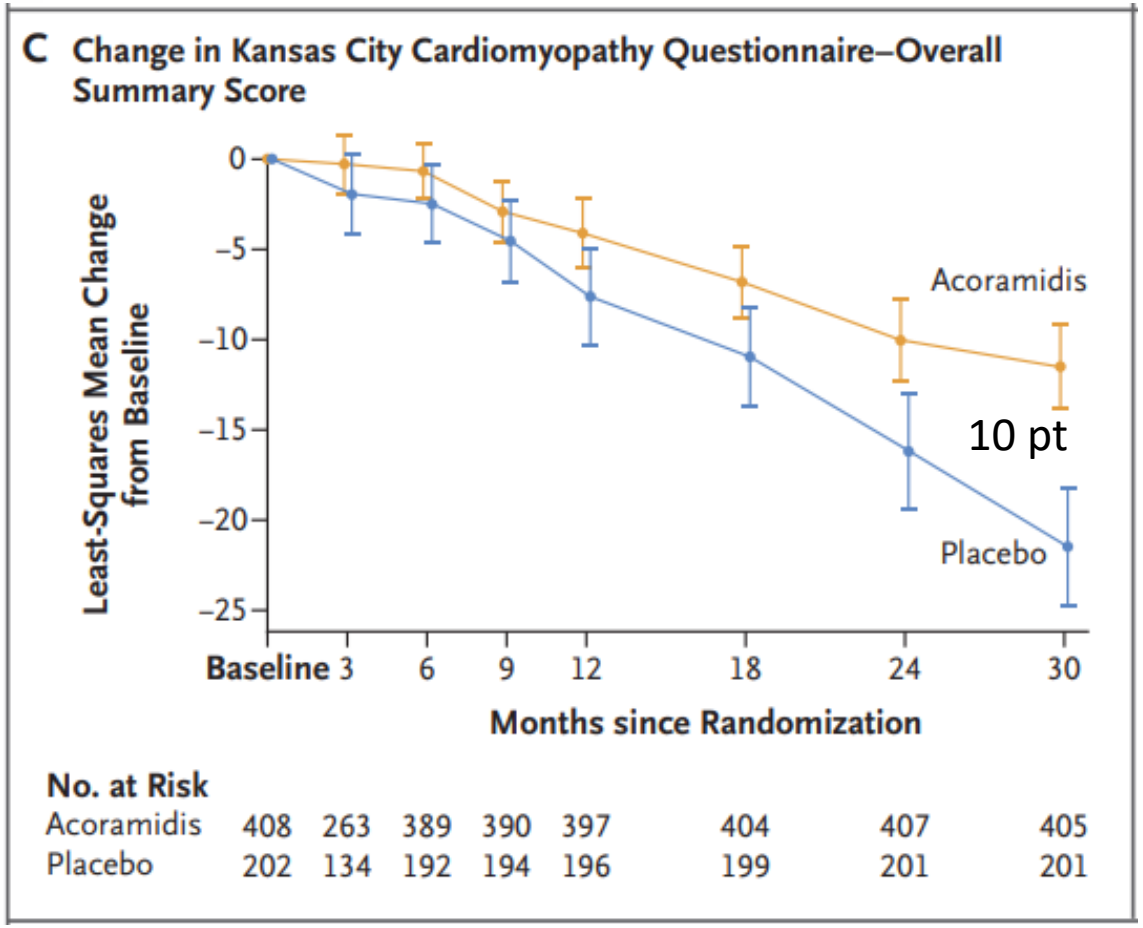
Hierarchical Efficacy Analyses



Gillmore et al. NEJM 2024;390:132-14

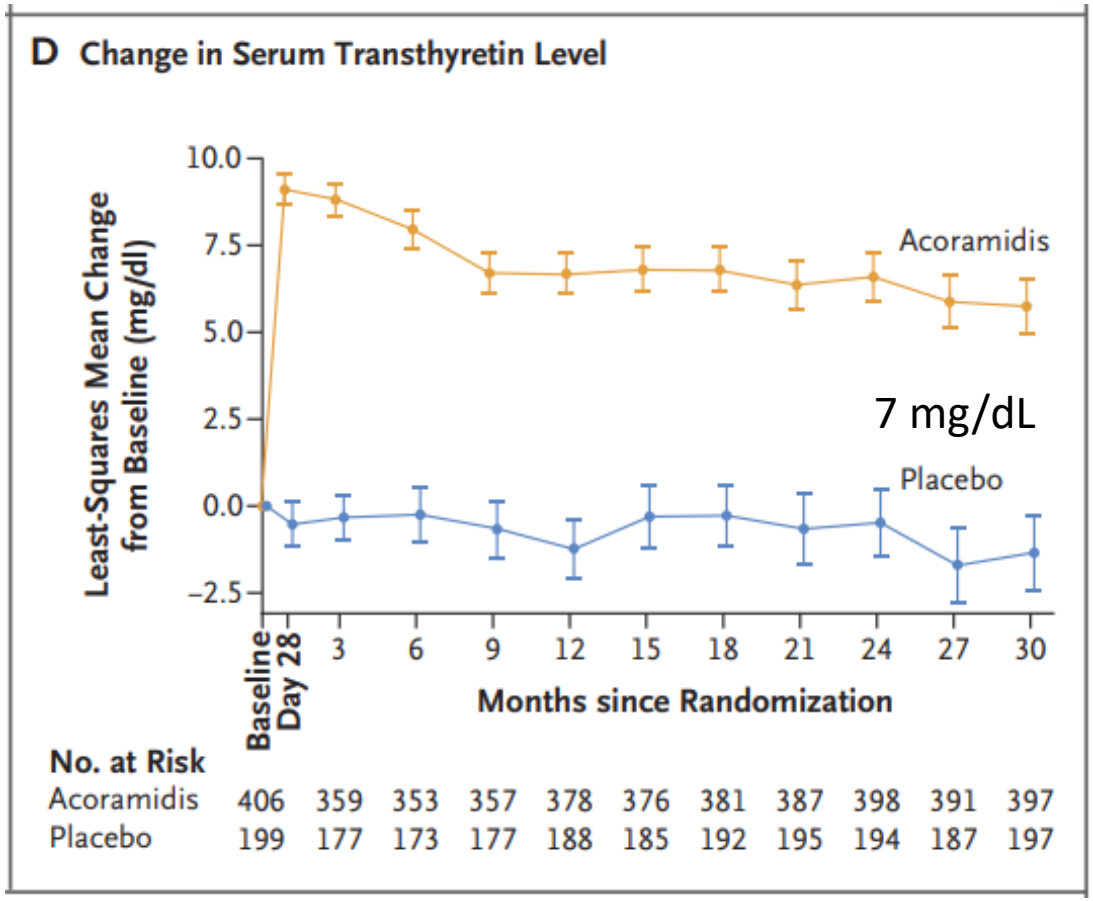
Key Secondary Endpoints – Functional and QoL Components

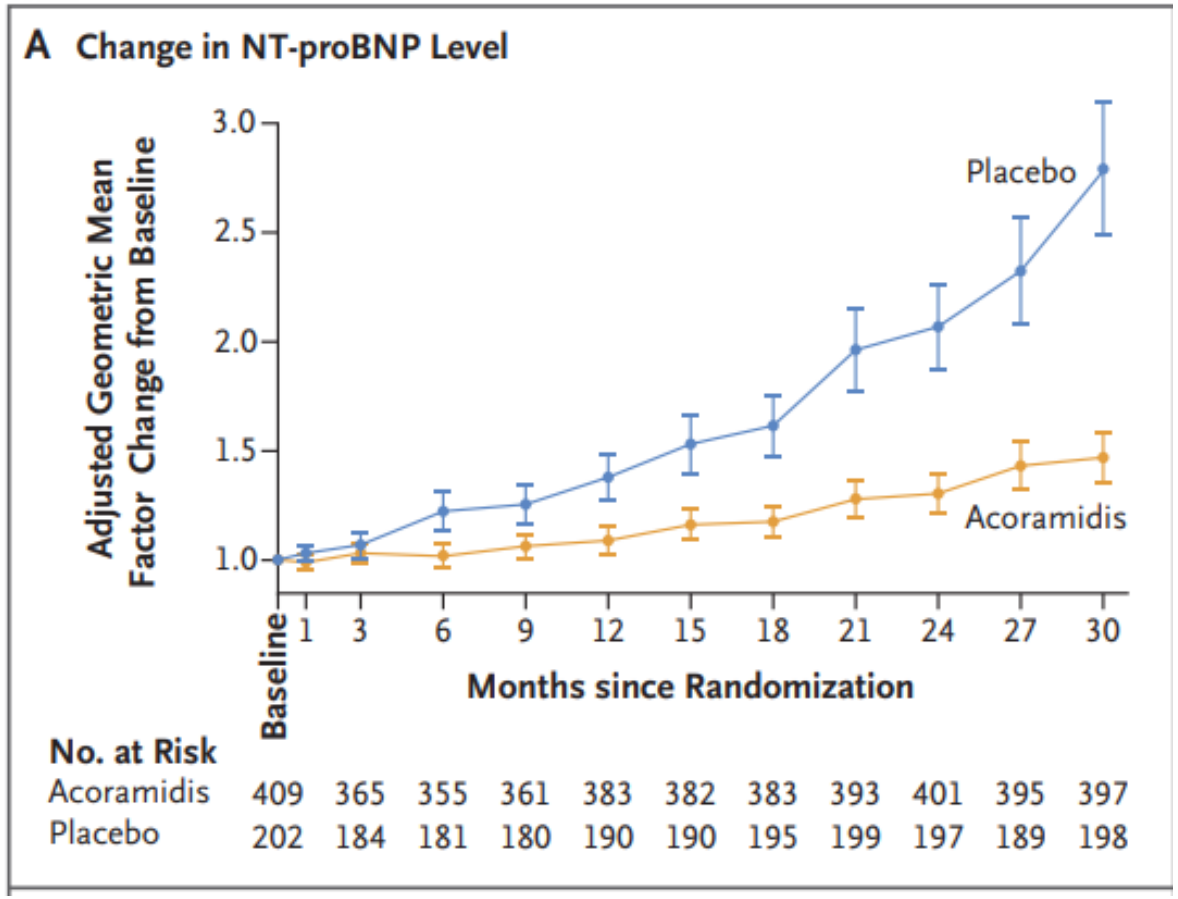




Gillmore et al. NEJM 2024;390:132-14

Serum Biomarkers





Gillmore et al. NEJM 2024;390:132-14

TTR Silencers

Silencing Agents

- Small interfering RNA molecules (siRNA)
  - Vutrisiran (HELIOS-B [NCT04153149])
- Antisense oligonucleotide (ASO)
  - Eplontersen (Cardio-TTRansform [NCT04136171])

Gillmore et al. N Engl J Med 2021;385:493-502

HELIOS-B: Vutrisiran

- Dose is 25mg SC every 3 months (no premedication)
- Lifelong vitamin A supplementation
- Reduction in circulating TTR by 80-90%

- 655 patients, 1:1 randomization
- Monotherapy group and overall group
- Highly pretreated population, 40% on tafamidis at baseline
  - 20% of the remaining initiated tafamidis after randomization

Fontana et al. NEJM 2024

Primary and Secondary Endpoints

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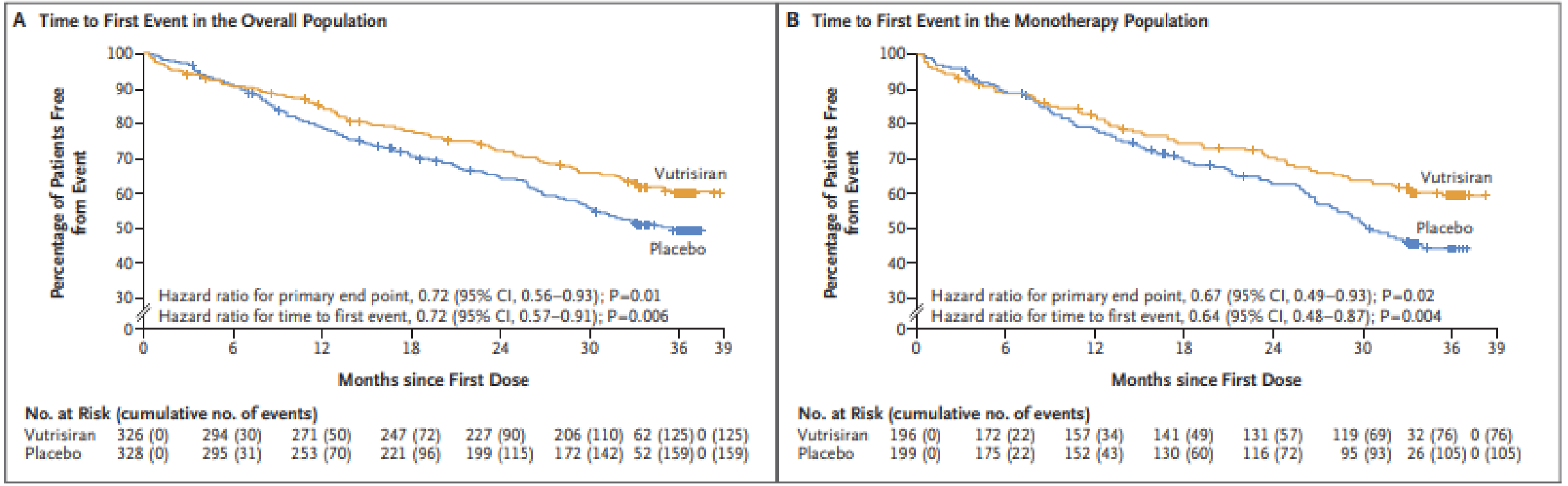
		Treatment Effect	Overall Population (N=654)	Monotherapy Population (N=395)
Primary Endpoint	Composite of ACM and recurrent CV events	Hazard Ratio	0.72, p=0.01	0.67, p=0.02
Secondary Endpoints	ACM at 42M	Hazard Ratio	0.65, p=0.01	0.66, p=0.045
	Change in KCCQ-OS at 30M	LS mean diff	5.8, p<0.001	8.7, p<0001
	Change in 6MWT at 30M	LS mean diff	26.5, P<0.001	32.1, p<0.001
	NYHA class stable or improved at 30M	% difference	8.7, p=0.02	12.5, p=0.01

Fontana et al. NEJM 2024

Time to First CV event or ACM

Not powered to compare vutrisiran monotherapy and combination therapy with tafamidis

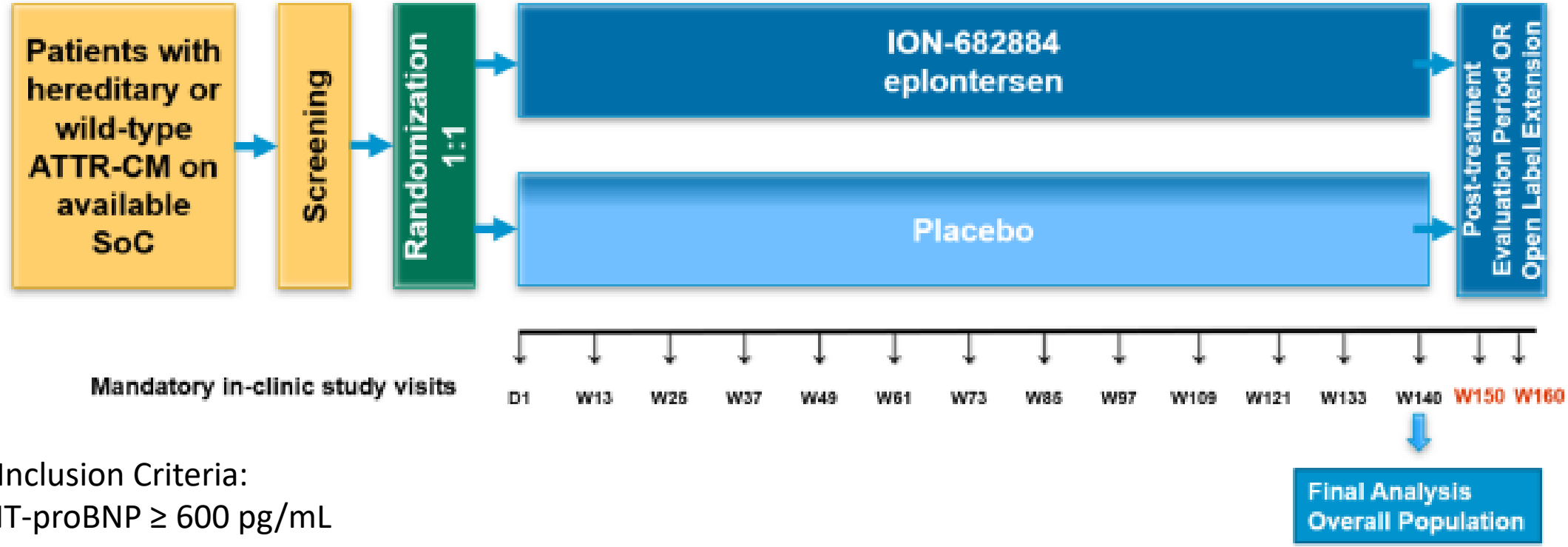


Fontana et al. NEJM 2024

Eplontersen

- Dose 45mg monthly via self SC injection
- Neuro-TTRansform (ATTR-PN) demonstrated efficacy, mean reduction in serum TTR of 81.7% at 66 weeks
- Cardio-TTRansform Trial – fully enrolled
- Primary endpoint is a composite of CV mortality and recurrent CV clinical events at 140 weeks
- Estimated completion early 2026

CARDIO-TTRansform : Eplontersen

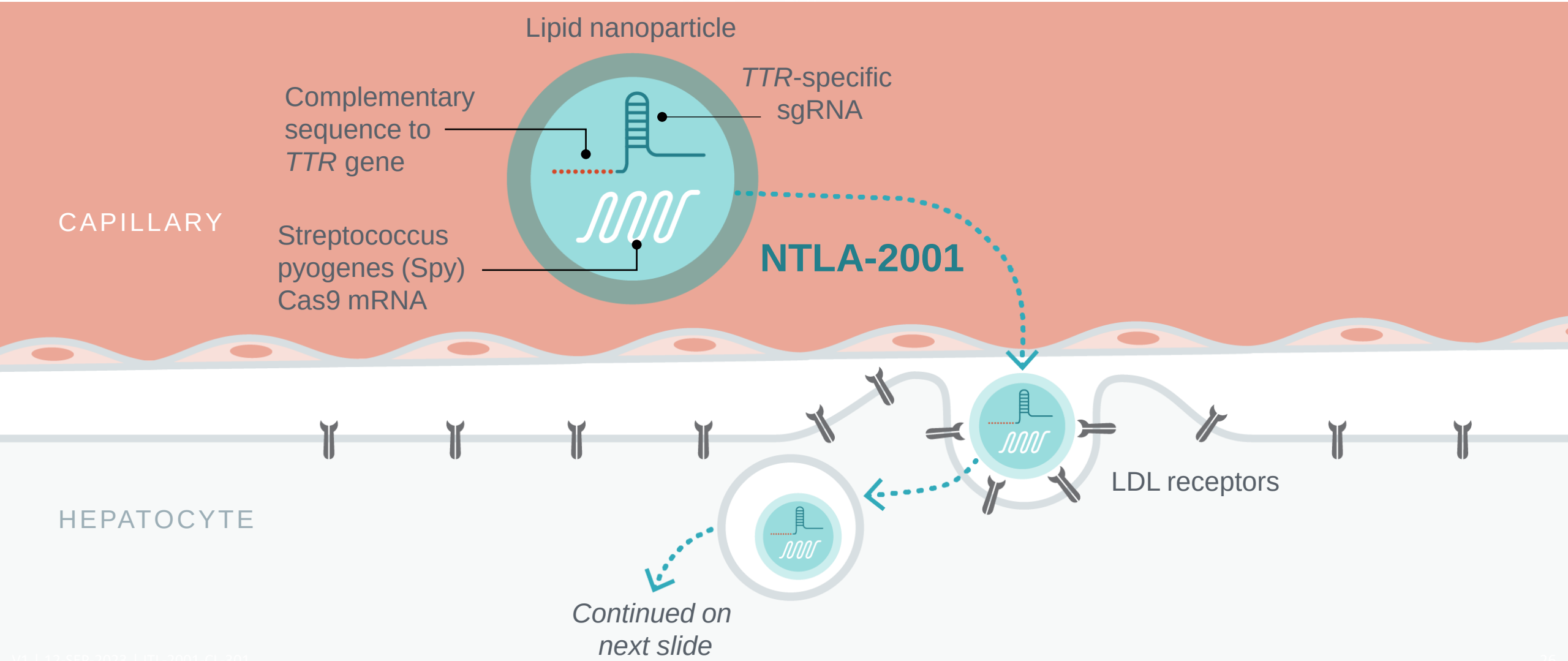


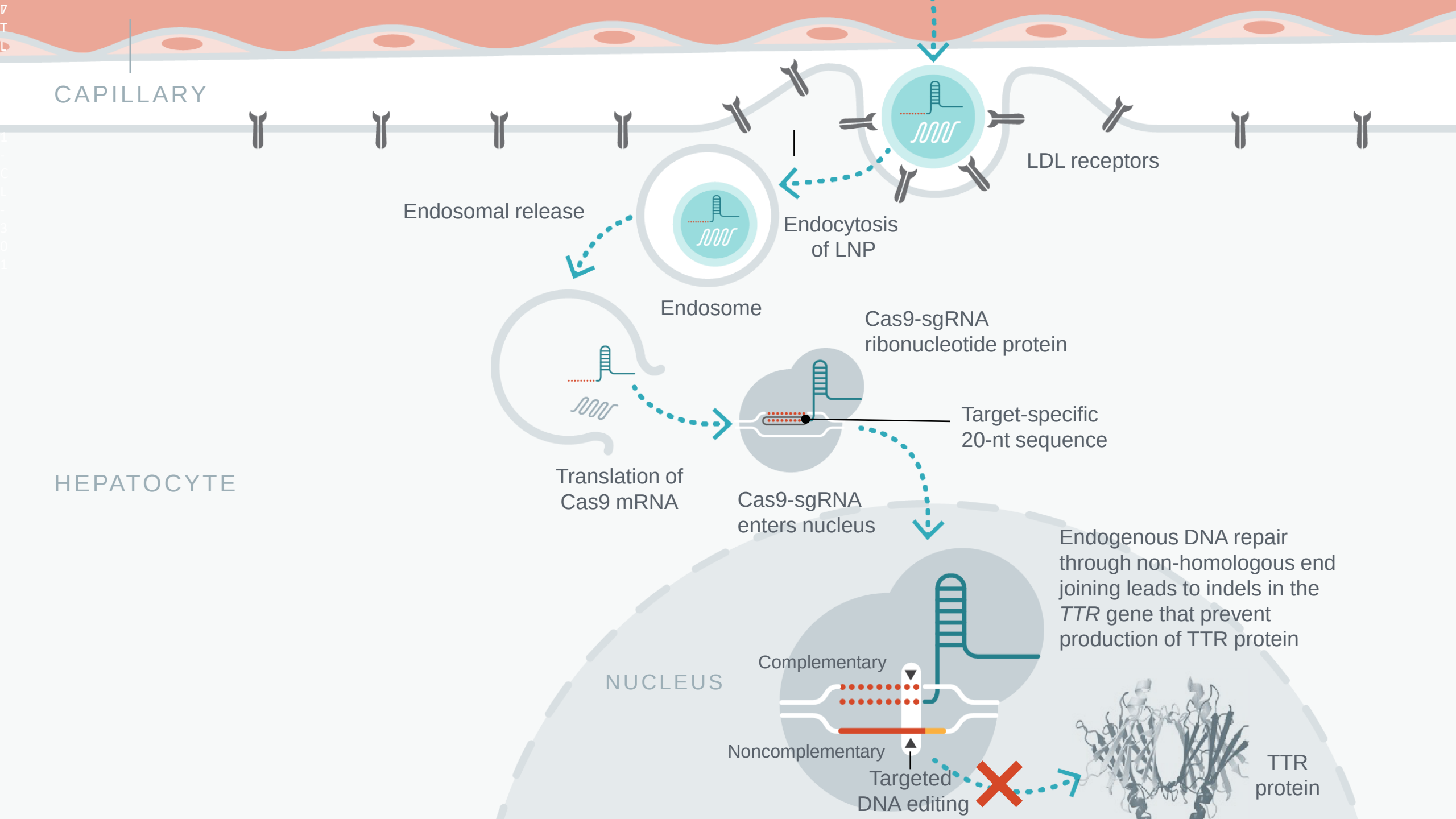
Key Inclusion Criteria:

- NT-proBNP ≥ 600 pg/mL
- 6MWT ≥ 150 m
- IVS > 12 mm
- Positive nuclear scintigraphy or biopsy if MGUS
- NYHA I - III

Gene Editing with CRISPR

NTLA-2001


Lipid nanoparticle
Complementary sequence to *TTR* gene
TTR-specific sgRNA
Streptococcus pyogenes (Spy) Cas9 mRNA
NTLA-2001
CAPILLARY
HEPATOCYTE
LDL receptors
Continued on next slide


CAPILLARY
LDL receptors
Endosomal release
Endocytosis
of LNP
Endosome
Cas9-sgRNA
ribonucleotide protein
Target-specific
20-nt sequence
HEPATOCYTE
Translation of
Cas9 mRNA
Cas9-sgRNA
enters nucleus
Endogenous DNA repair
through non-homologous end
joining leads to indels in the
TTR gene that prevent
production of TTR protein
NUCLEUS
Complementary
Noncomplementary
Targeted
DNA editing
TTR
protein

NTLA 2001, nexiguran ziclumeran (nex-z)

- Clustered Regularly Interspaced Short Palindromic Repeats and associated Cas9 endonuclease (CRISPR-Cas9 system)
- Gene-editing approach, permanently modify or repair target DNA
- Aim is to produce a single administration, curative treatment for ATTR amyloidosis
- NTLA-2001 Phase 1
  - 36 patients with ATTR-CM
  - 12 months of follow up
  - 50% NYHA III
  - 31% ATTRv

Gillmore, J et al. N Engl J Med 2021;385:493-502
Fontana et al. N Engl J Med 2024;391:2231-41

Reduction in Serum TTR level at 12 months

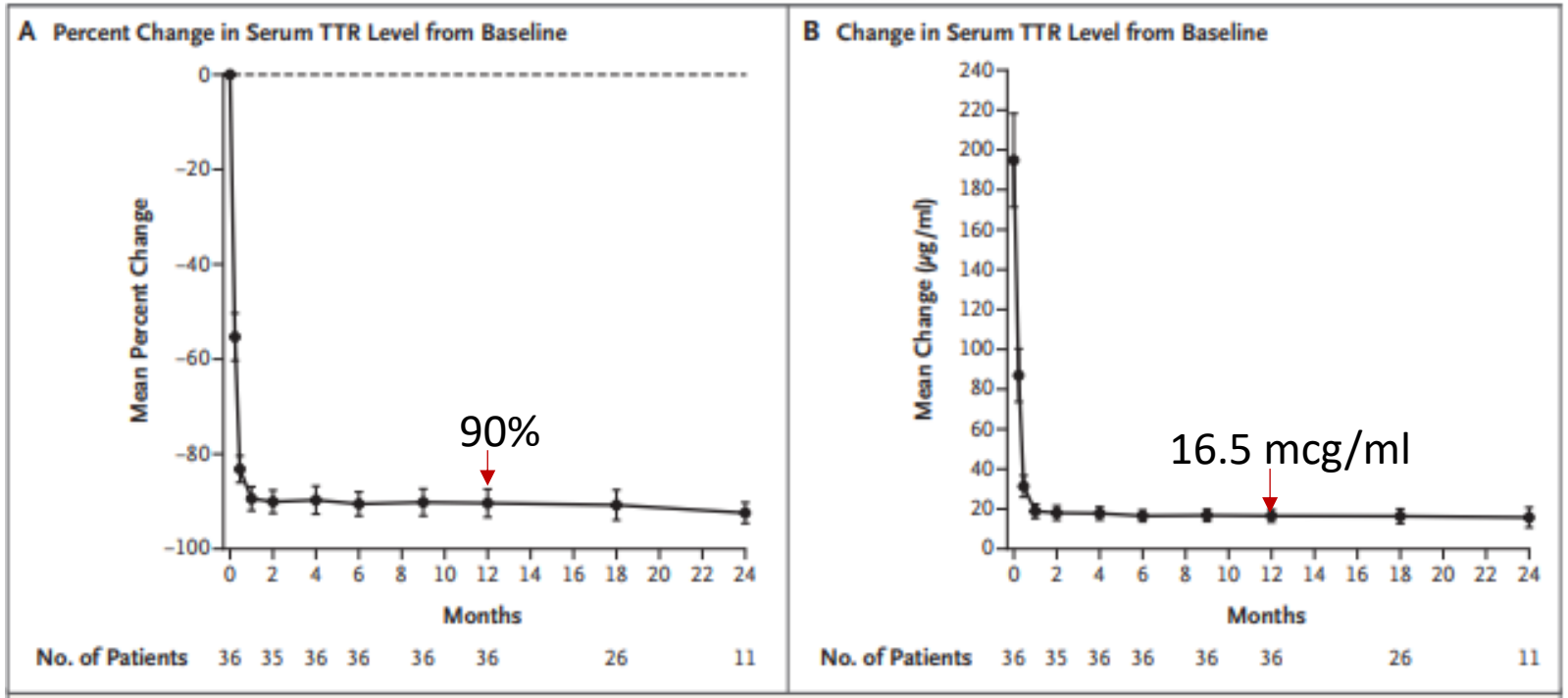


Figure 1. Reduction in Serum Transthyretin Level.

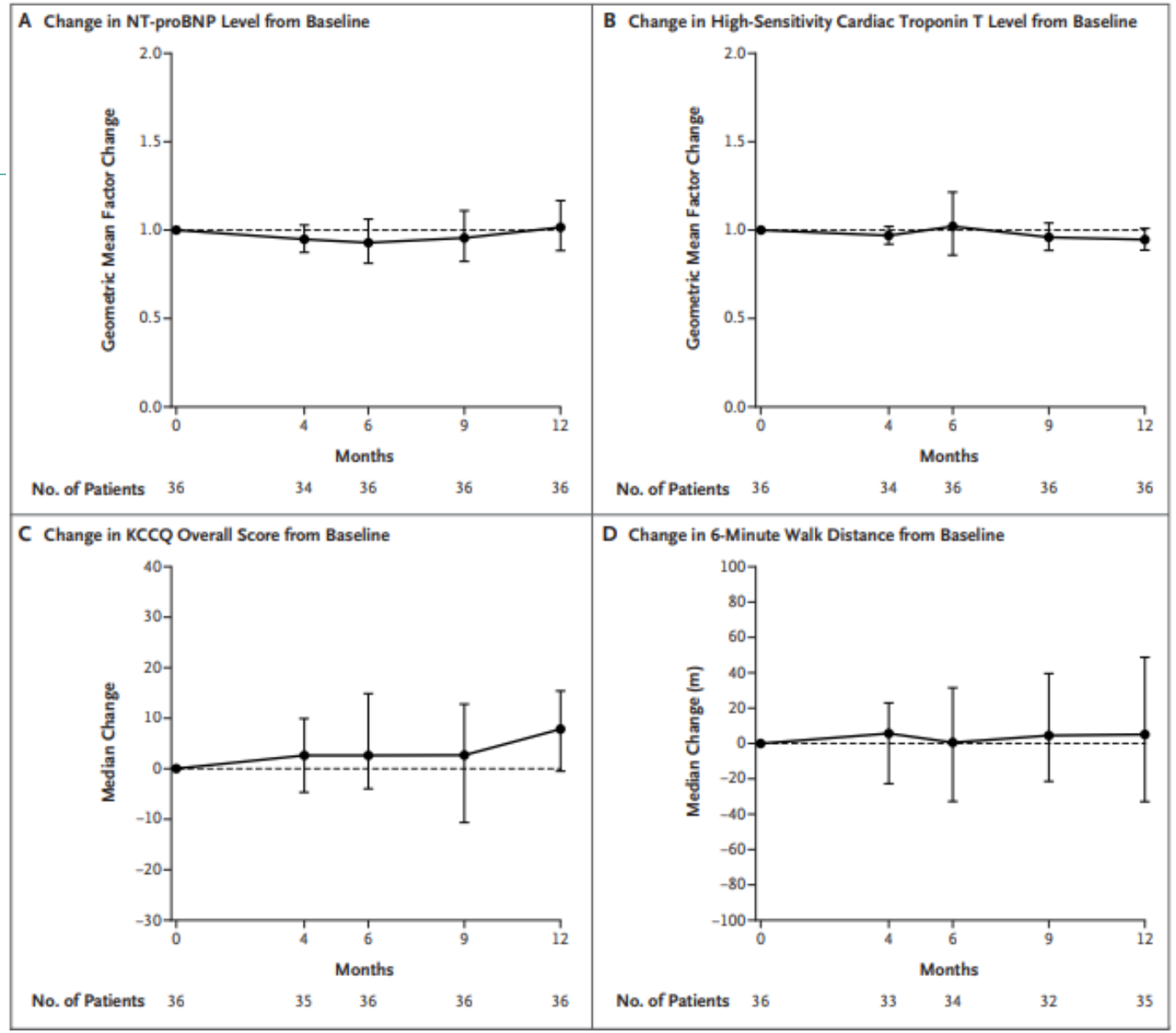
Panel A shows the mean percent change in the transthyretin (TTR) level after a single intravenous infusion of nexiguran ziclumeran (nex-z) through 24 months. The mean change was –83% at 14 days, –89% at 28 days, and –90% at 12 months. Panel B shows the corresponding mean absolute serum TTR levels of 31.4 μg per milliliter at 14 days, 18.9 μg per milliliter at 28 days, and 16.5 μg per milliliter at 12 months. The I bars indicate 95% confidence intervals, which have not been adjusted for multiplicity.

Observed reduction in serum TTR was sustained at 24 months in all 11 patients who had 2 years of follow up

Fontana et al. N Engl J Med 2024;391:2231-41

Secondary Endpoints

- NT-proBNP and Tn remained stable at 12 months
- Median change in the overall KCCQ score was 8 points
- Median change from baseline to month 12 in the 6-MWD was an increase of 5 m.



Fontana et al. N Engl J Med 2024;391:2231-41

Phase 3 MAGNITUDE Study (NCT06128629)

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- NTLA-2001, 55mg by intravenous infusion, **single dose**
- Randomization 2 : 1, NTLA-2001 or placebo
- ~ 765 participants, age 18-90 years
- Currently enrolling

- <u>Key Exclusion Criteria:</u>

- Treatment with patisiran, vutrisiran, inotersen or eplontersen (silencing drugs)
- Initiation of tafamidis or acoramidis within 56 days prior to dose
- NT-proBNP < 600

Depleting TTR/Knockdown

Amyloid depleting agents – ALXN2220

- ALXN2220 (formerly NI006)
  - Recombinant IgG1 human monoclonal antibody
  - Intravenous infusion **every 4 weeks**
  - Targets misfolded and aggregated forms of ATTRwt and ATTRv

- Phase 1 study (dose escalation)
  - 40 patients with ATTRwt or ATTRv
  - 4% female
  - 85% wild type

Garcia-Pavia, P et al. NEJM 2023;389:239-250

NI006/ALXN2220

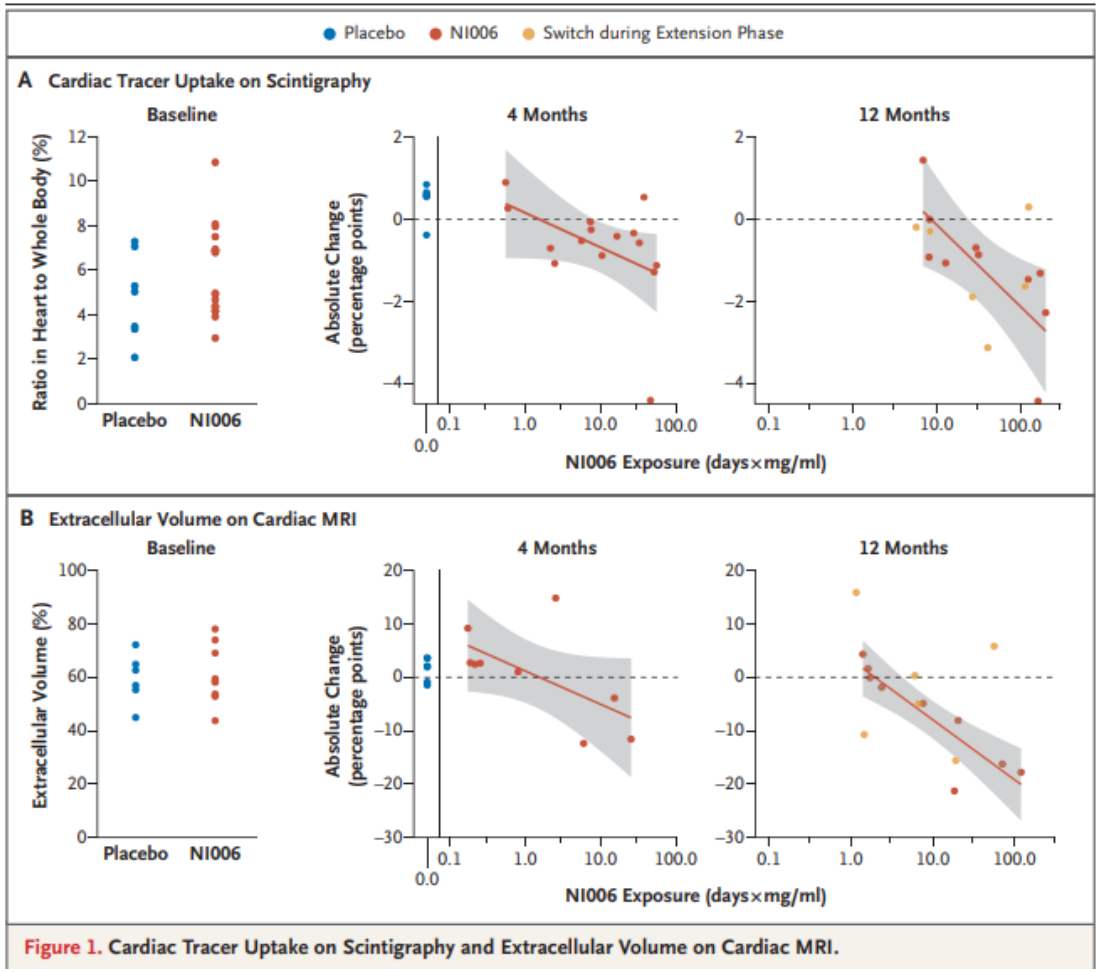
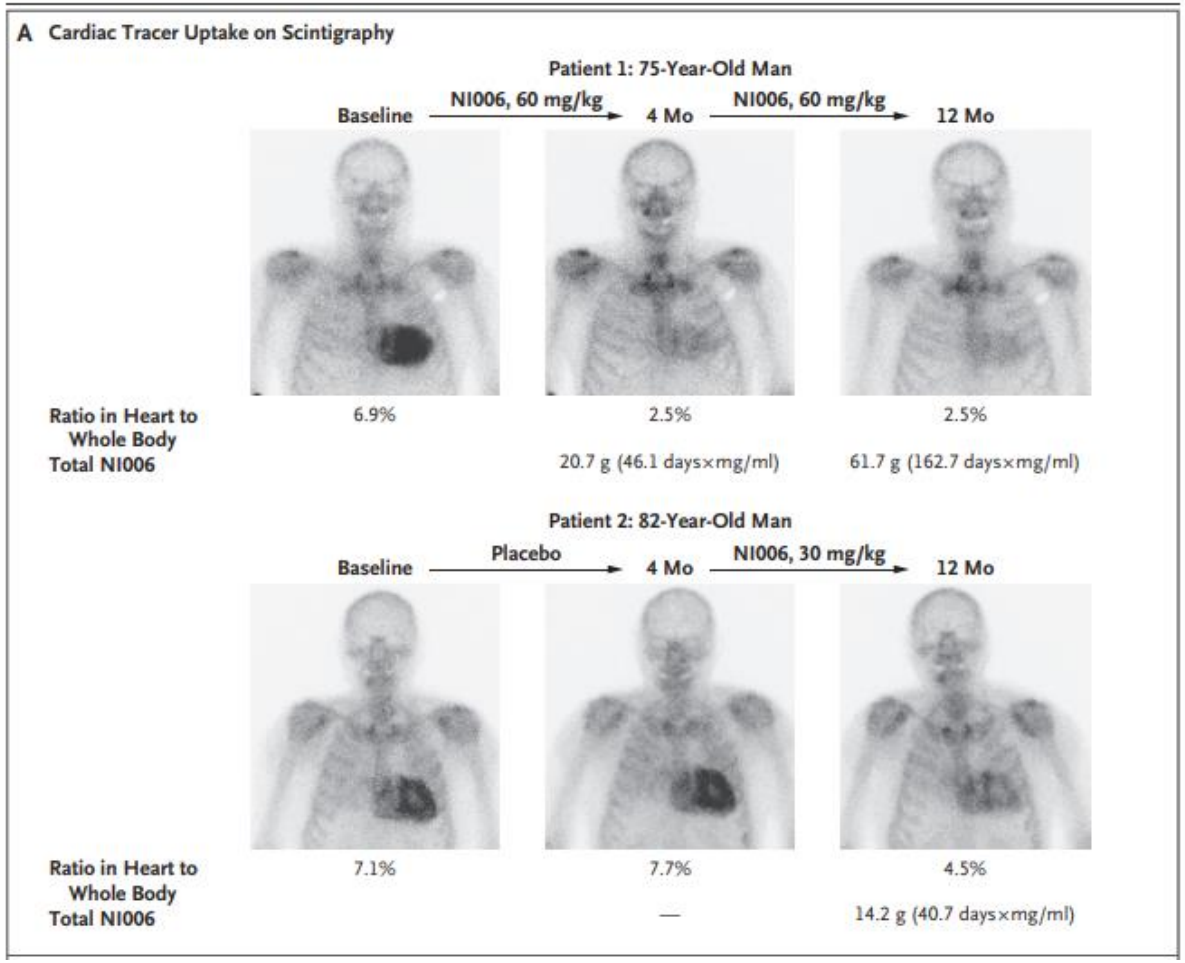


Figure 1. Cardiac Tracer Uptake on Scintigraphy and Extracellular Volume on Cardiac MRI.



Garcia-Pavia, P et al. NEJM 2023;389:239-250

ALXN2220

Cardiac Biomarker Response

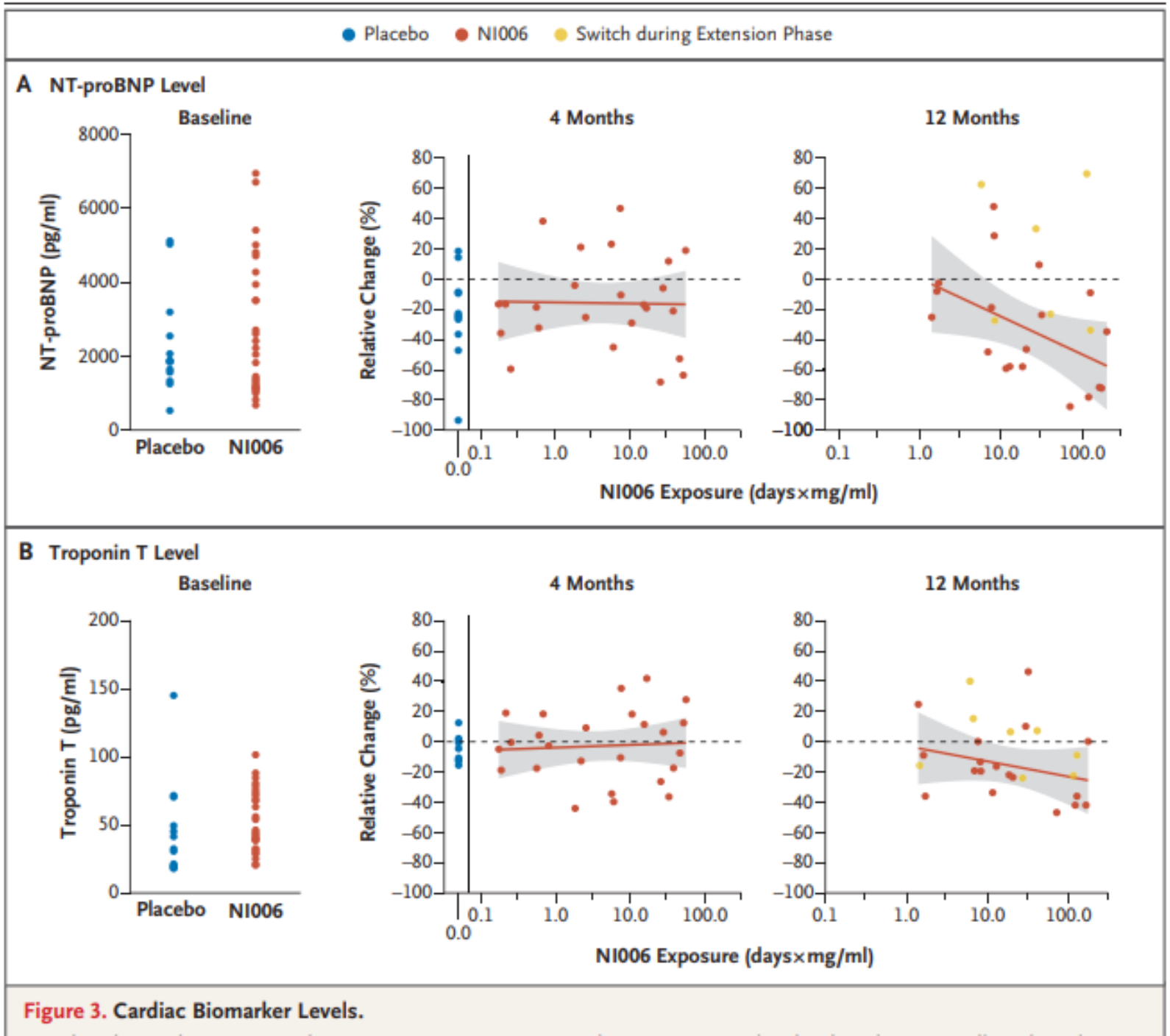


Figure 3. Cardiac Biomarker Levels.

Garcia-Pavia, P et al. NEJM 2023;389:239-250

DepleTTR-CM (NCT06183931)

- Phase 3 study
- Purpose of the study is to determine if ALXN2220 improves life expectancy and overall quality of life
- Blinded treatment period is a minimum of 24 months (max 48 months)
- Randomized ALXN2220 or placebo, 2:1
- Current stabilizer or silencer therapy is allowed
- Fully enrolled

Coramitug (NNC6019/PRX004)

- IgG1 monoclonal antibody binds to soluble aggregate and misfolded TTR but not to native TTR
- Phase 1 in 21 ATTRv patients, well tolerated

- Phase 2 (NCT05442047)
  - 99 patients with ATTRwt or ATTRv, fully enrolled
  - NYHA II or III
  - Infusion every 4 weeks x 52 weeks
  - Primary endpoints: Change in 6MWT and NTproBNP at 1 year
  - Results expected late 2025

- A phase 3 trial is being planned

Fontana, M et al. Eur Heart J 2022;43(2)

Prevention?

- There is no approved drug for the PREVENTION of ATTR cardiomyopathy or polyneuropathy
- There are no guidelines for the management of asymptomatic carriers of a TTR mutation
- We know that early treatment is better
- This study is targeted at **ASYMPTOMATIC CARRIERS** of a TTR mutation

ACT-EARLY Trial – currently enrolling

Amyloidosis Research Consortium

- Purpose is to determine if patients with no clinical evidence of ATTR, who have a known mutation, will benefit from early treatment with acoramidis
- Participants aged 18-75 years
- Enrolled within 10 years of predicted age of onset of disease
- Randomized 1:1, acoramidis or placebo
- Study duration of at least 5-7 years
- Patients who developed ATTR-CM or –PN will be placed on standard of care therapies

Summary of Therapeutic Agents

Amyloidosis Research Consortium

- Approved for ATTR-CM
  - Tafamidis, Acoramidis, Vutrisiran
- Silencer in Clinical Trial for ATTR-CM – results due early 2026
  - Eplontersen (approved for ATTR-PN)
- MAGNITUDE (NCT06128629)
  - CRISPR, gene editing
- DepleTTR-CM (NCT06183931) – closed to enrollment
  - ALXN2220, amyloid removal agent
- ACT-EARLY
  - Prevention study for ATTRv carriers with acoramidis

Is there a role for combination therapy?

ATTR-CM as a paradigm for advancing precision medicine

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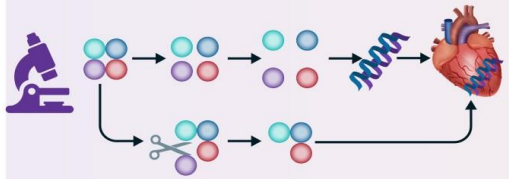
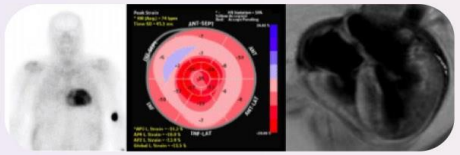
Transthyretin cardiac amyloidosis as an example of precision medicine in cardiology

Elucidation of underlying disease mechanisms

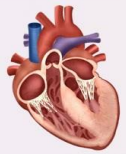


Advances in imaging techniques: **Non-invasive diagnosis possible**



Precise data of the epidemiology: **High prevalence of the disease in common clinical scenarios**

- Heart failure
- Aortic stenosis
- LVH/HCM



New specific therapies acting at different steps of the TTR amyloidogenic cascade

Suppressors

- Gene editing (NTLA-2001)
- Gene silencers:
  - Patisiran
  - Inotersen
  - Vutrisiran
  - Eplontersen

Stabilizers

- Tafamidis
- Diflunisal
- Acoramidis

Removers

- ALX2220/NI006
- Coramitug
- AT-02

Pending questions

- Initial therapy according to patient's profile
- Assessing response to therapy
- Switching from one agent to another
- Deprescribing treatment
- Long-term safety of TTR depletion
- Treatment of pre-symptomatic patients and ATTRv gene carriers

Eur Heart J, 2025;46(11):999–1013

We Cannot Compare Drugs

Amyloidosis Research Consortium

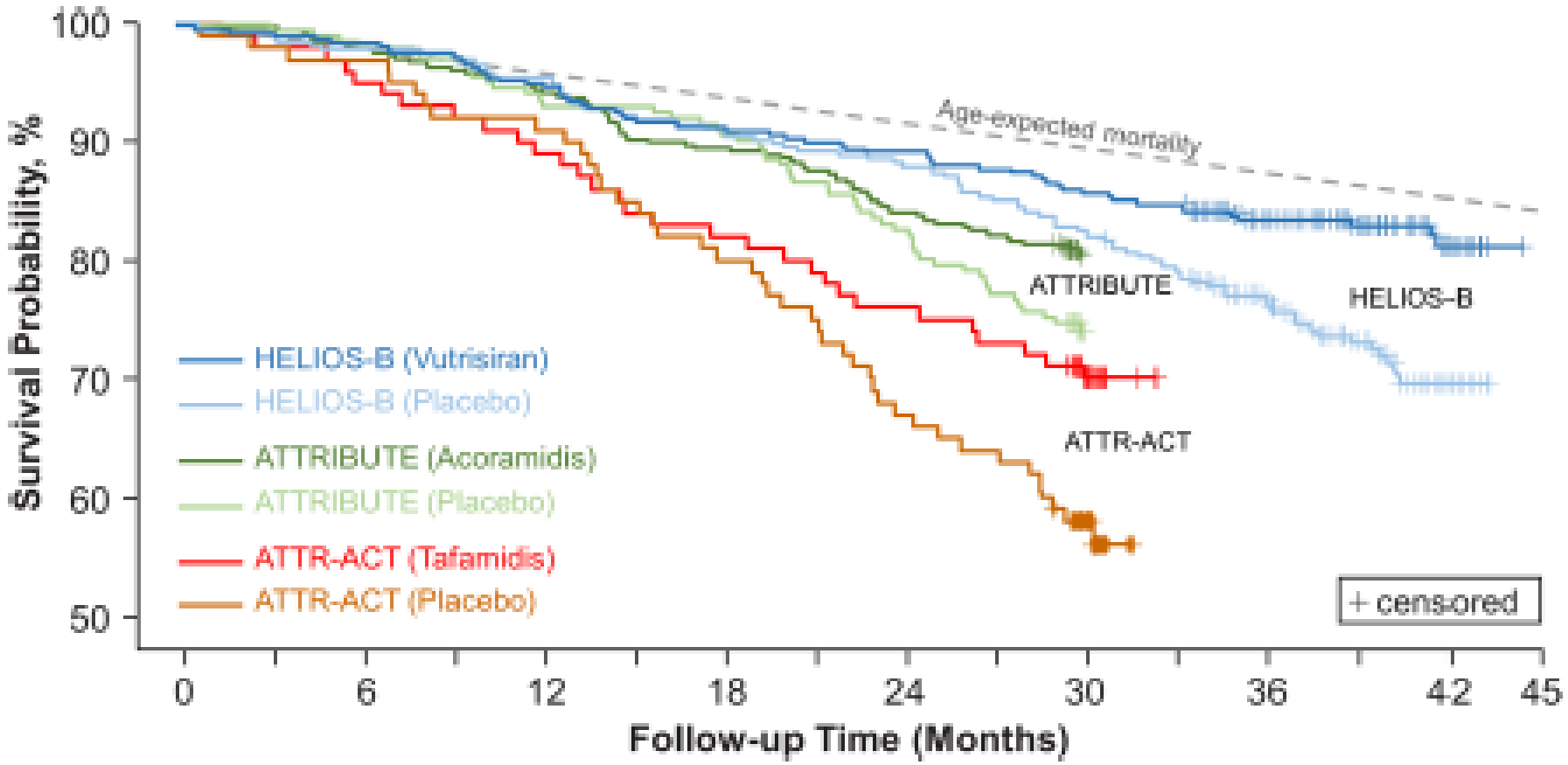
	ATTR-ACT	ATTRibute-CM	HELIOS-B
Era	2013-2018	2019-2023	2019-2024
NYHA class (I/II vs III)	68% vs 32%	83% vs 17%	91% vs 9%
Median NTproBNP (pg/ml)	3,078	2,134	1,911
ATTRv	24%	9%	12%
Placebo mortality	30%	26%	18%
Placebo CV event rate/year	0.70	0.45	0.288
HR in mortality *	0.70 (0.51 to 0.96)	0.77 (0.54 to 1.10)	0.69 (0.49-0.98)*
% increase in TTR	33%	39%	-
TTR stabilization % TTR occupancy with FPE assay Tetramer Dissociation assay	 ~65% >96% at 28µm	 96.6 ± 2.1% >96% at 11µm	-
Cost	$267,908	$225,108	$477,404

* Survival at 42 months

Griffin et al. JACC:Heart Failure 2025

We Cannot Compare Trials

Amyloidosis Research Consortium



Heart Fail Rev. 2025 Jan;30(1):69-73

How to Choose Initial Therapy

- There are no comparative effectiveness studies, so:
- Mode of administration
  - Oral vs Injection
  - Daily vs twice daily vs every 1 or 3 months
  - Location of administration – home or infusion clinic
- Cost
  - Monotherapy (~ 250k-450k per year) vs combination therapy (~ 700k per year)
- Wild type or Variant

There are no data to support combined therapy

Amyloidosis Research Consortium

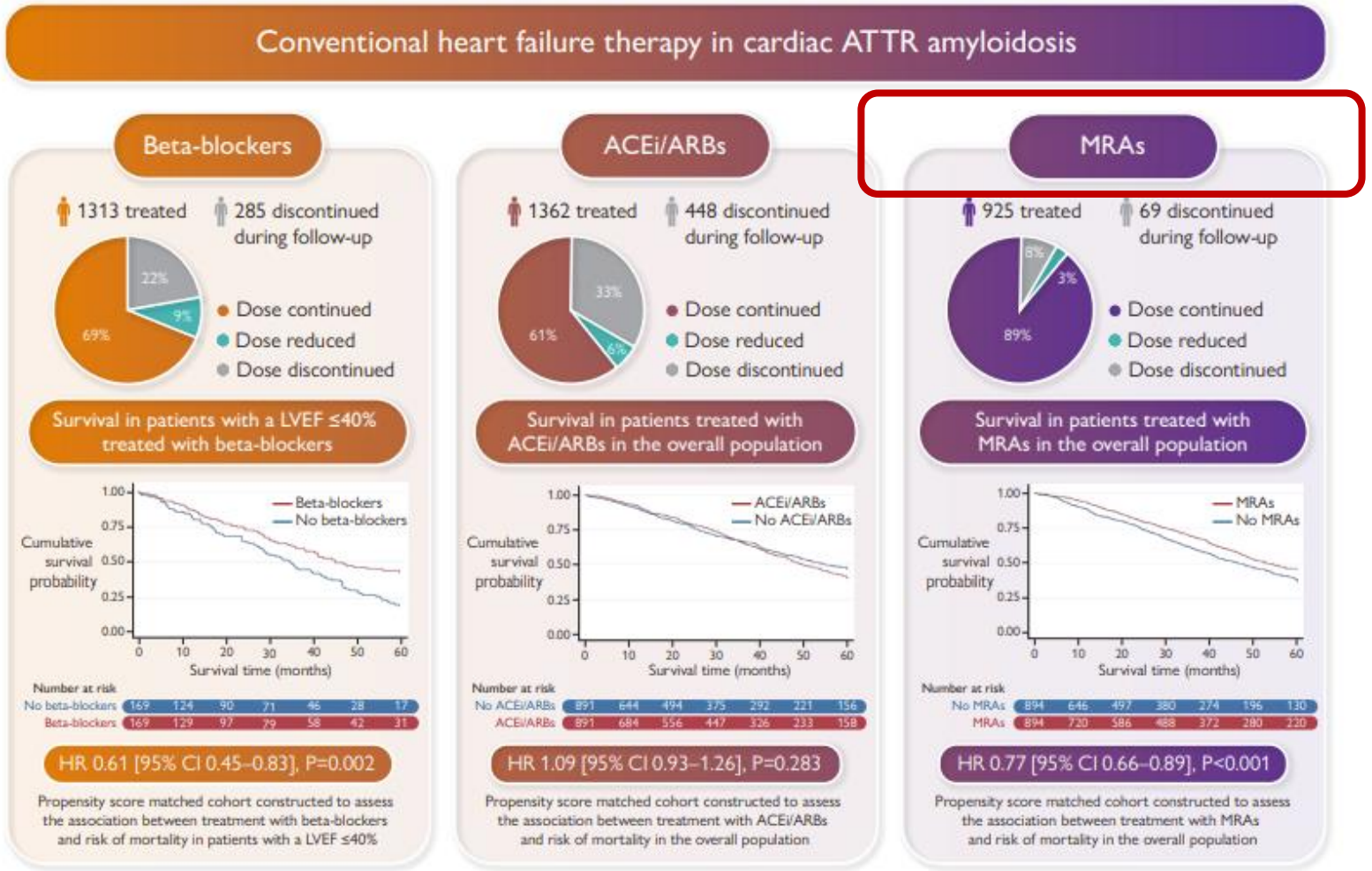
- APOLLO-B (patisiran)
  - Patisiran was NOT superior to placebo in 91 patients who received tafamidis at baseline when assessing 6MWT and KCCQ (at 12 months)
- ATTRIBUTE-CM (acoramidis)
  - 15% of participants initiated tafamidis after 12 months, no evidence to support combination of stabilizers
- HELIOS-B (vutrisiran)
  - 40% of participants on tafamidis at baseline and a further 22% in the vutrisiran only group started tafamidis during follow up
  - Not powered or designed to show a difference according to tafamidis use
- Cardio-TTRansform (eplontersen)
  - Still waiting for results, though may have enough patients to perform a subgroup analysis

Maurer et al. J Card Fail 2023;29:550
Gillmore et al. *N Engl J Med* 2024;390:132–42
Fontana et al. *N Engl J Med* 2024

Adjunctive Therapies for Heart Failure

Management of Heart Failure

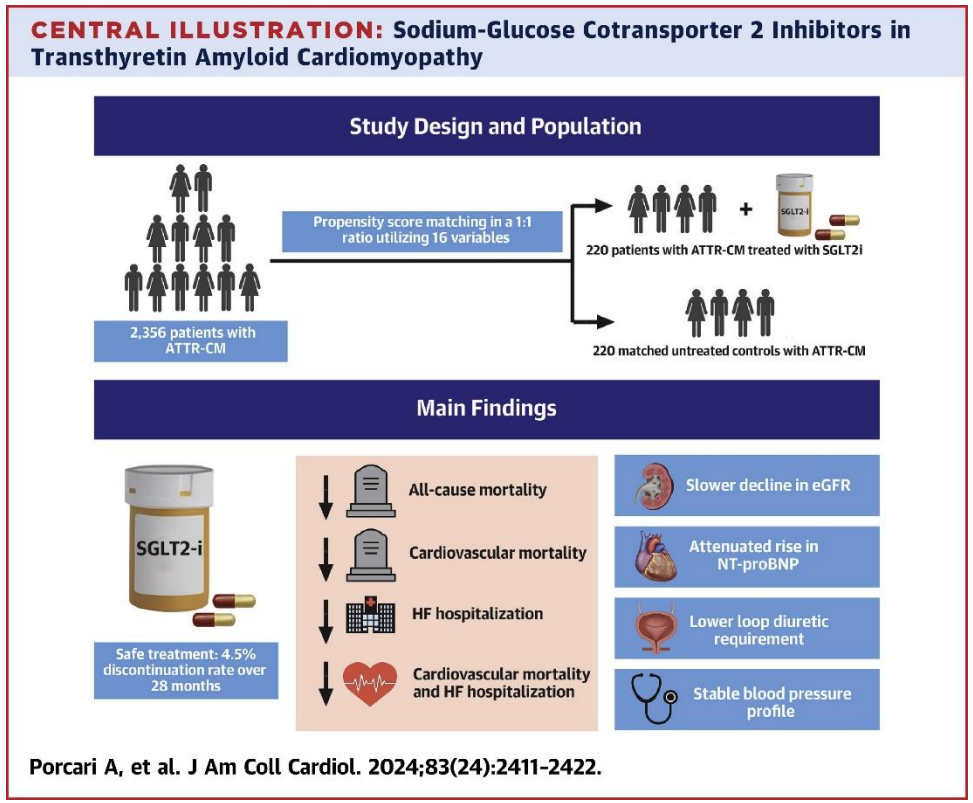
- Mineralocorticoid receptor antagonists (MRA) are a/w lower risk of mortality irrespective of EF
- Spironolactone or Eplerenone

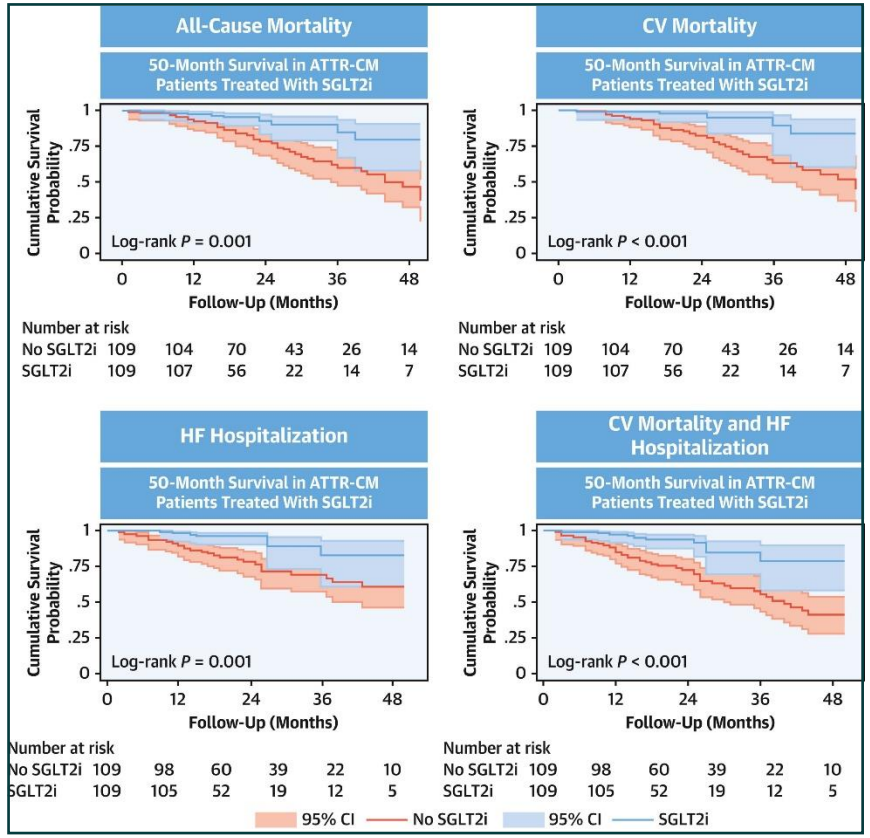


Ioannou A, et al. *Eur Heart J*. 2023;44(31):2893-2907

SGLT2 inhibitors

- Well tolerated, enhance natriuresis, no effect on blood pressure, safe to use in CKD (eGFR > 20)





Dobner et al. ESC Heart Fail 2023;10(1):397-404
Porcari et al. J Am Coll Cardiol. 2024;83(24):2411-2422