ASO/siRNA/CRISPR-Cas9 vs. Antibodies for TTR Cardiac Amyloidosis

The Revolution in Pharmacotherapy:
From Herbs to Pills to Antibodies and Nucleic Acids

Mat Maurer, MD

February 1, 2024

ESC
European Society of Cardiology

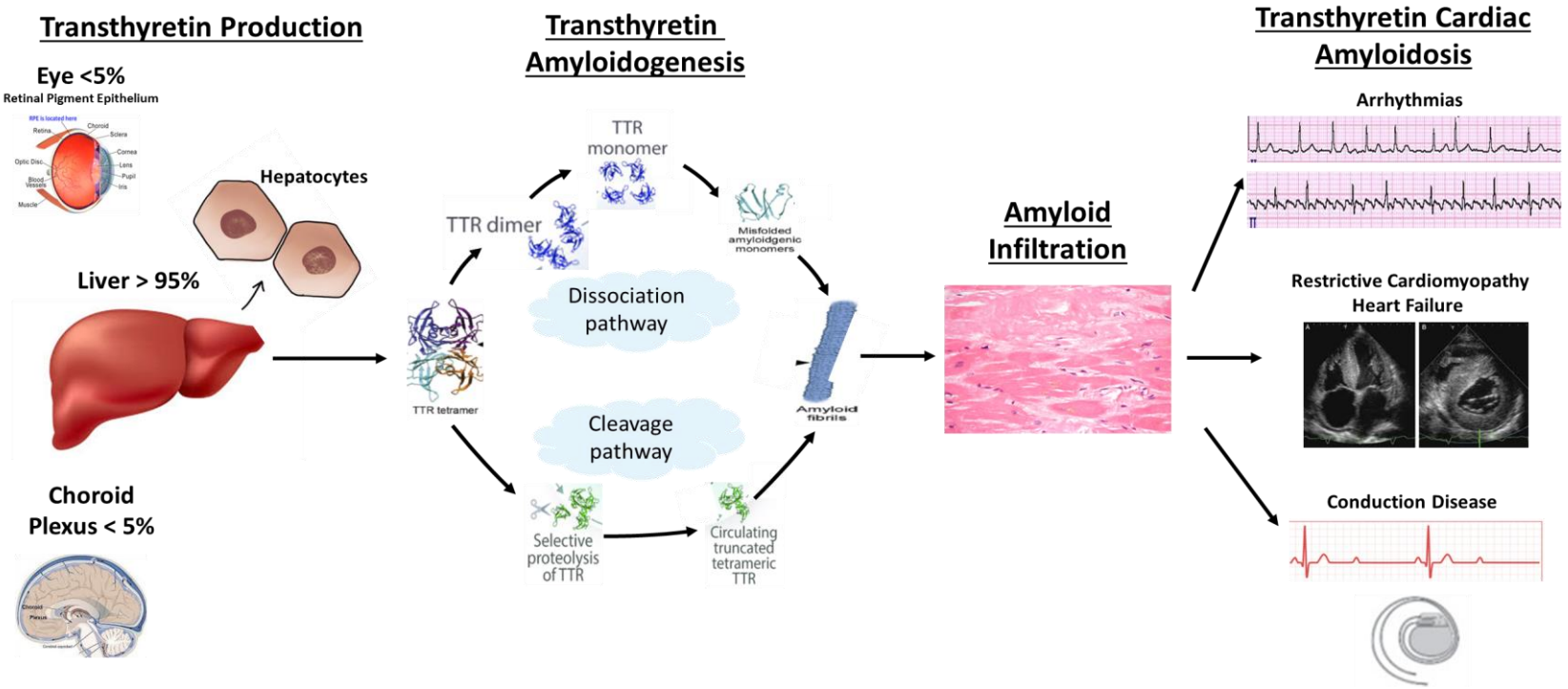
Disclosures

I am excited about all the progress in the arena of TTR amyloidosis but concerned about the high cost of therapy which is unsustainable.

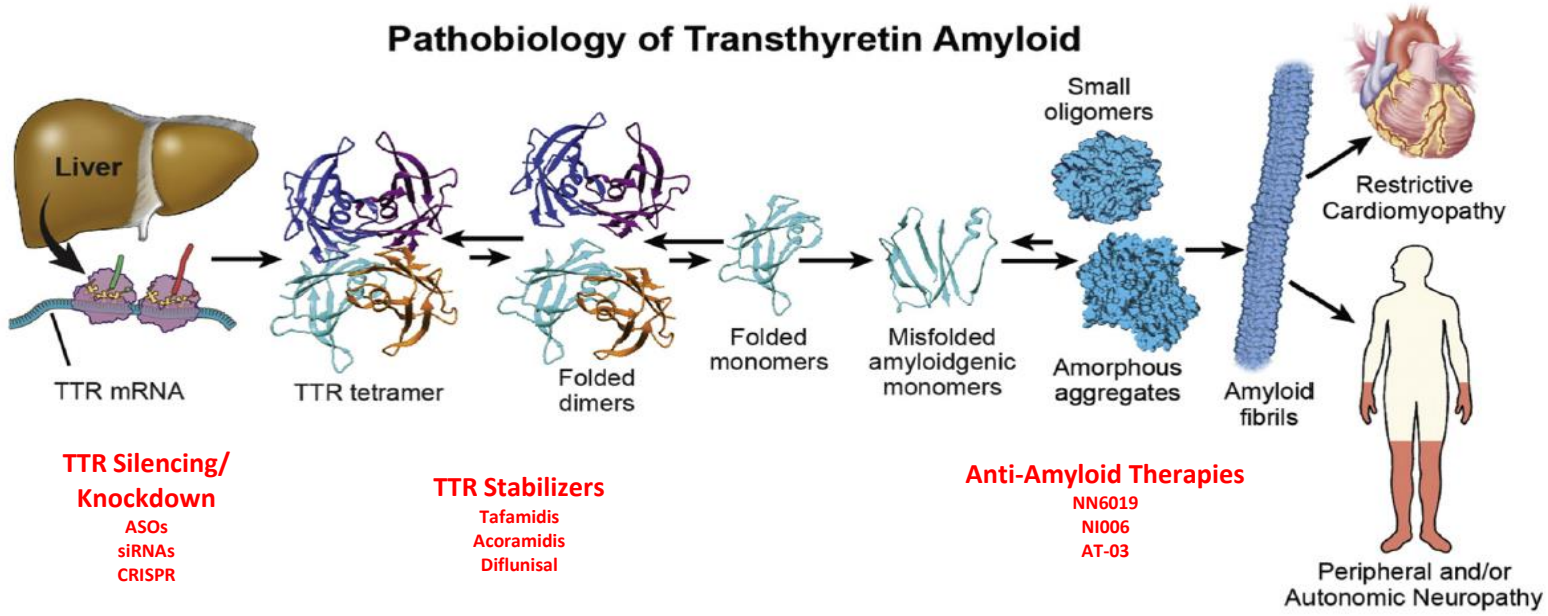
I have research and grant support from several pharmaceutical companies **:**

-NIH/NIA/NHLBI
-Intellia
-Attralus, Inc
-Alnylam, Inc
-Eidos
-Novo-Nordisk
-Ionis Pharmaceuticals
-Pfizer, Inc.

Biology Underlying Transthyretin Cardiac Amyloidosis



Therapies for transthyretin amyloidosis have emerged from elucidation of underlying biology

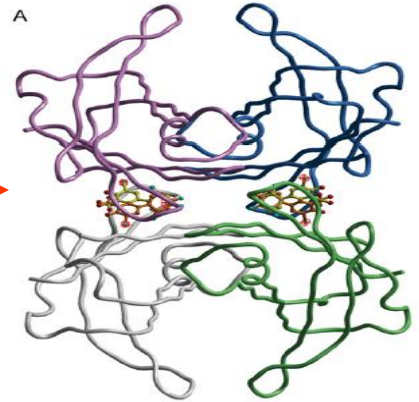


J Am Coll Cardiol. 2019;73:2872-91.

Tafamidis for Transthyretin Cardiac Amyloidosis

Tafamidis

Binds to TTR, stabilizes it an prevents amyloidogenesis.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

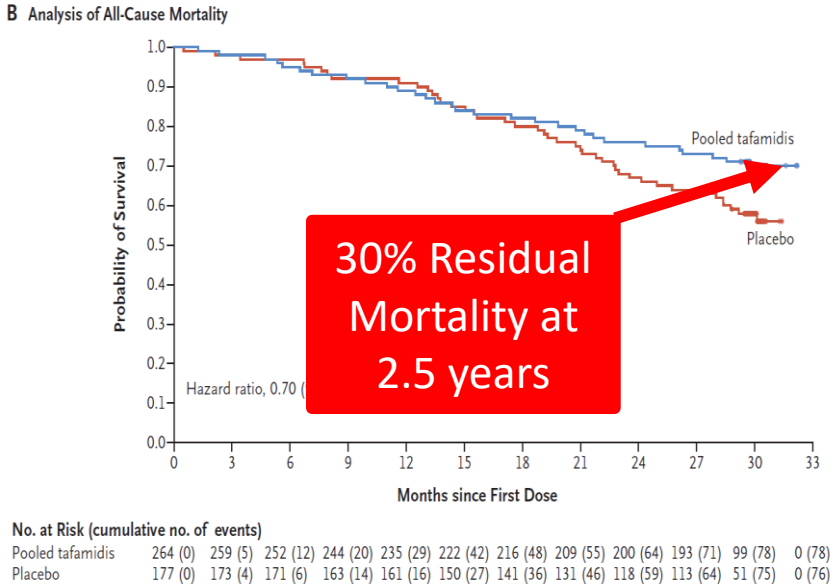
33% reduction in overall mortality – need to treat 7-8 patients to prevent one death over 2 ½ years

32% reduction in the rate of hospitalization with tafamidis compared with placebo – need to treat 4 patients to prevent 1 hospitalization per year.

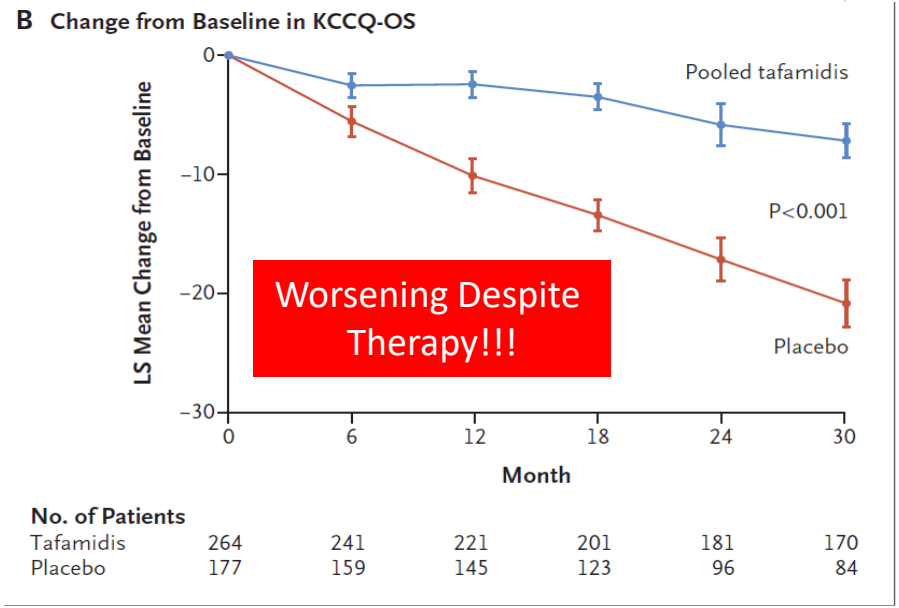
Amyloid. 2006 Dec;13(4):236-49
N Engl J Med. 2018 Sep 13;379(11):1007-1016.

Despite Efficacy –
Still high residual Mortality and Morbidity

Mortality

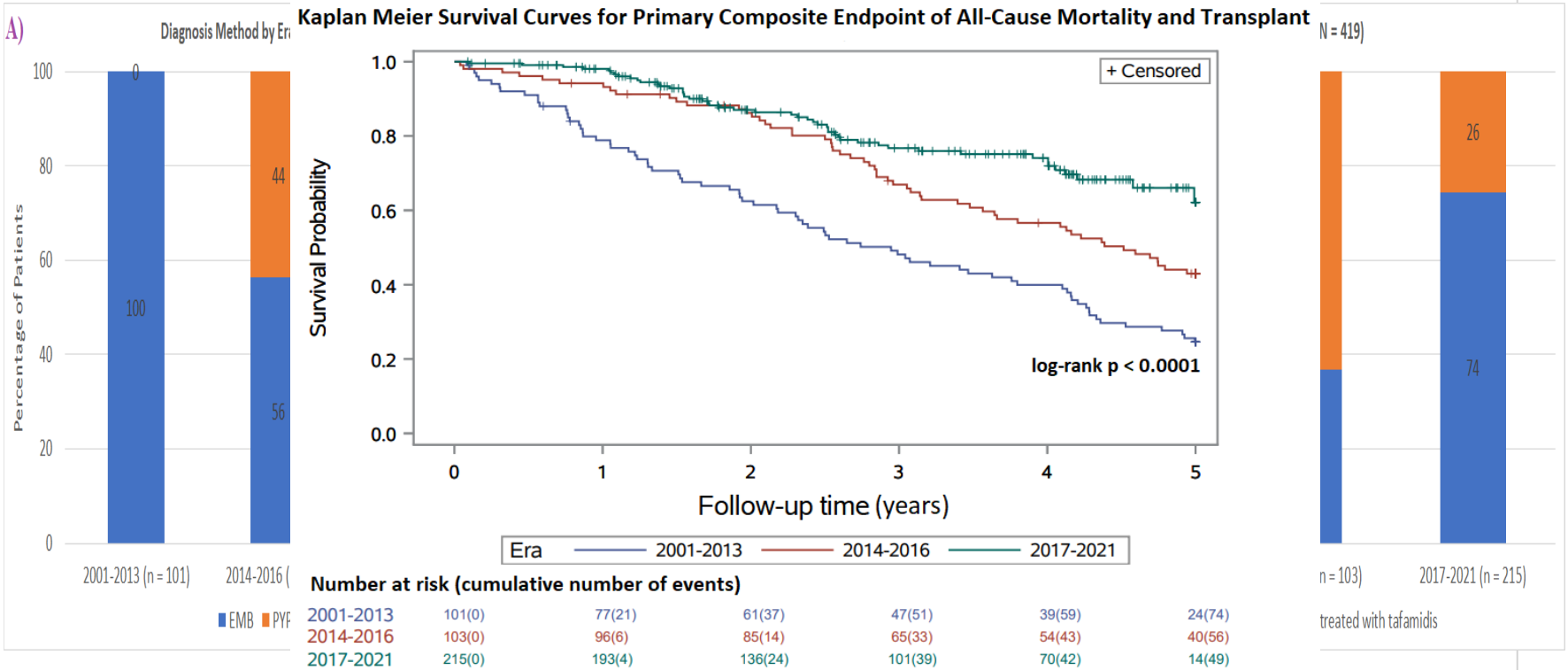


Morbidity



N Engl J Med. 2018 Sep 13;379(11):1007-1016

Improving Outcomes over Time: Attributable to Increasing Awareness, Early Diagnosis & Effective Therapy



Chan N, …Maurer M. Journal of Cardiac Failure, accepted

Tafamidis with Earlier Diagnosis
Greater Efficacy Over Time in the Real World

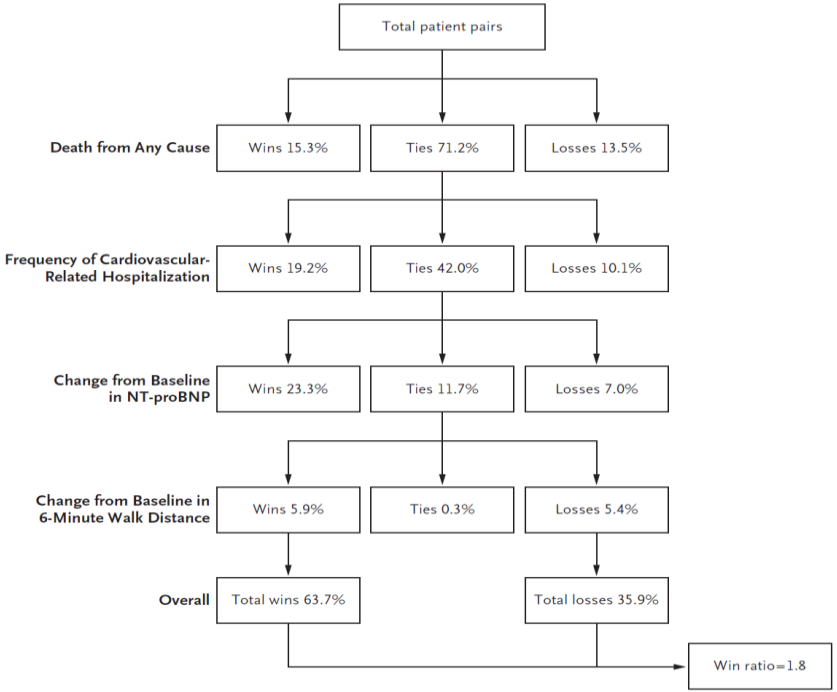
Variable	Tafamidis (n=201)			No Tafamidis (n=91)			Event rate ratio (95% CI)	p-value
	N	Total events	Events rate, per 100 person-years (95% CI)	N	Total events	Events rate, per 100 person-years (95% CI)		
Death	201	24	4.5 (3-6.7)	91	35	16 (11.4-22.4)	0.3 (0.2-0.5)	<.001
All Cause Hospitalization	201	372	70 (58.8-83.4)	91	229	112.5 (87.2-145.1)	0.6 (0.5-0.8)	0.003
CV Hospitalization	201	211	40.2 (32.3-50)	91	148	76 (55.8-103.6)	0.5 (0.4-0.8)	<.001
Non-CV Hospitalization	201	149	27.7 (22.3-34.4)	91	80	36.2 (26.4-49.5)	0.8 (0.5-1.1)	0.17

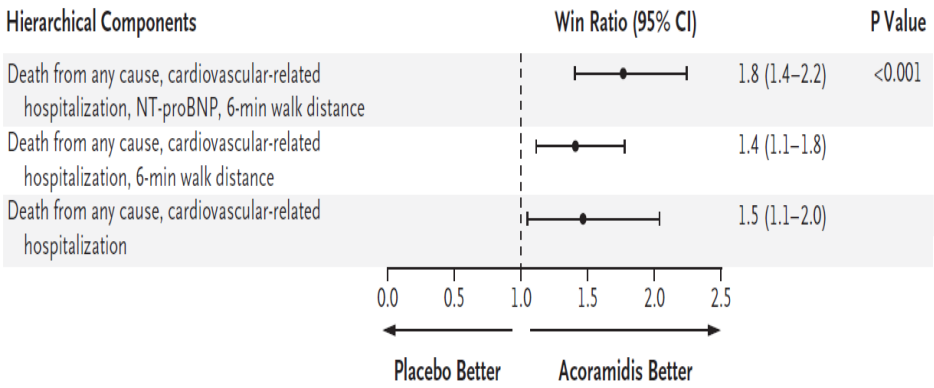
ATTRibute-CM and ATTR-ACT Trials

Parameter	ATTR-ACT (n=441)	ATTRibute-CM (n=632)
Age	74±7	77±7
Gender (% Male)	90.2%	90.2%
Race (% Black)	14.3%	4.7%
TTR genotype -ATTRwt -ATTRv	 76% 24%	 90.3% 9.7%
NYHA class Class I Class II Class III	 8.3% 59.6% 31.9%	 10.8% 72% 17.2%
NTproBNP (pg/ml)	3,078	2,325

N Engl J Med. 2018; 379(11):1007-1016, N Engl J Med 2024;390:132-42.

ATTRibute-CM Study of Acoramidis



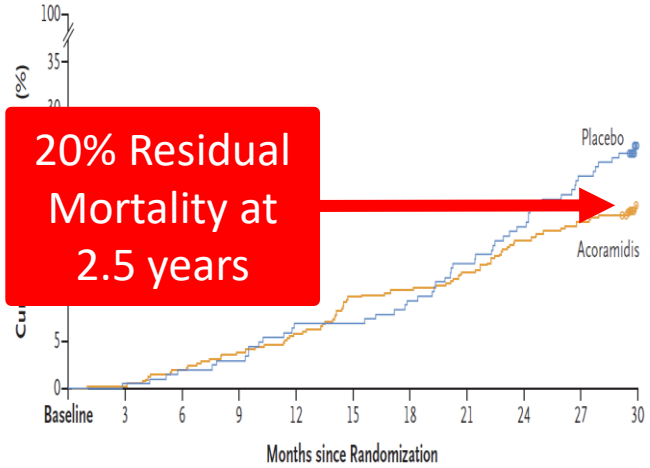


N Engl J Med 2024;390:132-42.

Still Unmet Needs – Even in Less Advanced Disease

Mortality

E Death from Any Cause



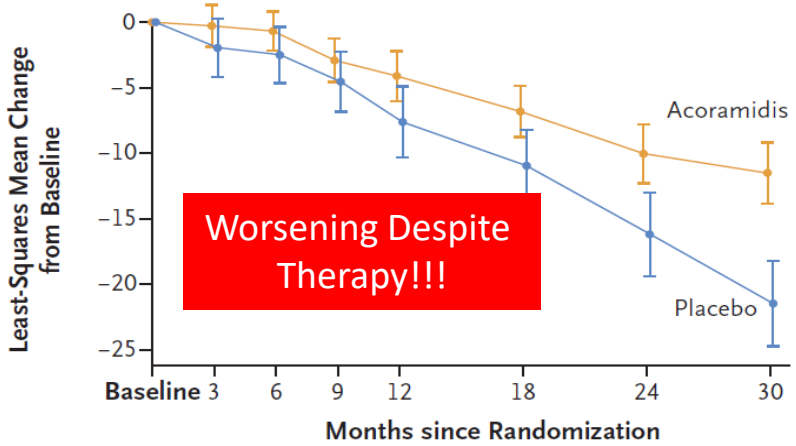
20% Residual Mortality at 2.5 years

No. at Risk (no. of events)

Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

Morbidity

C Change in Kansas City Cardiomyopathy Questionnaire–Overall Summary Score



Worsening Despite Therapy!!!

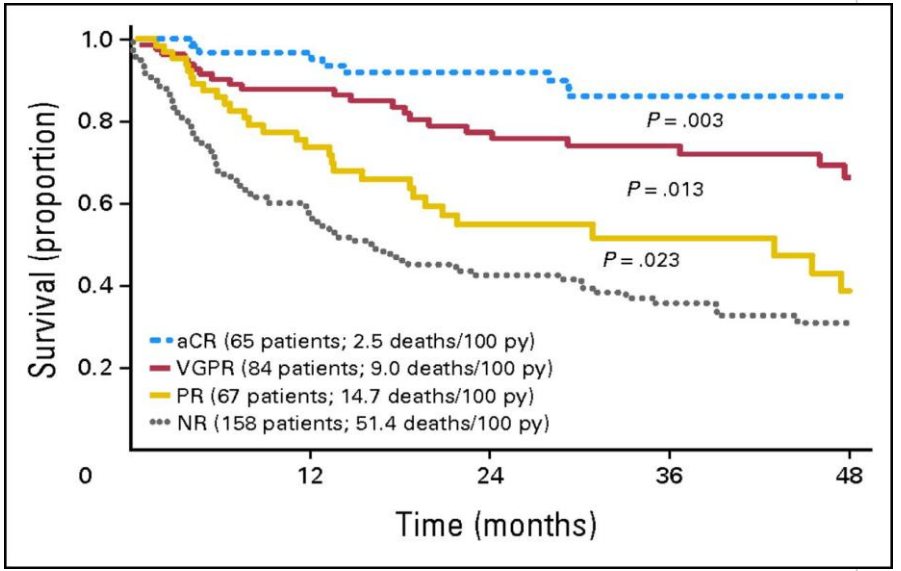
No. at Risk

Acoramidis	408	263	389	390	397	404	407	405
Placebo	202	134	192	194	196	199	201	201

Reductions in the Precursor Protein in other forms of Amyloidosis are key to therapeutic success

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

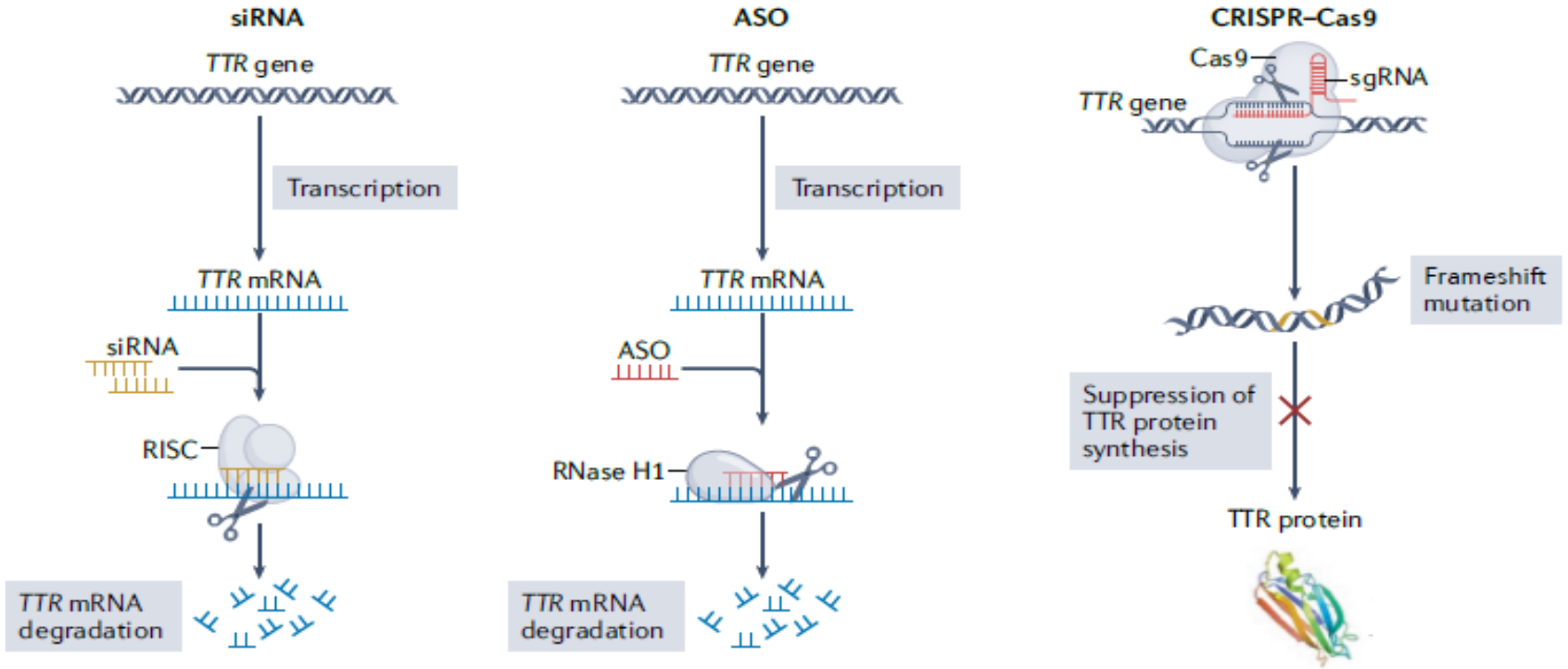


N Engl J Med. 2007 Jun 7;356(23):2361-71; J Clin Oncol. 2012 Dec 20;30(36):4541-9.

Unmet Needs and the Development of Additional therapies

Therapy	Trial	Mechanism	Route	N
Patisiran	APOLLO-B	Silencer (siRNA)	IV Q3 weeks	360
Vutrisiran	Helios-B	Silencer (siRNA)	SQ Q3 months	655
Eplontersen	Cardio TTRansform	Silencer (ASO)	SQ Q1 month	1,400
NTLA-2001	Magnitude	Gene Editing (CRISPR)	IV once	Initiated
ALX-ALXN2220	Depleter	Anti-amyloid Antibody	IV monthly	Phase 3 Initiation in Q1 2024
NN6019	Depleter	Anti-amyloid Antibody	IV monthly	Phase 2 Underway

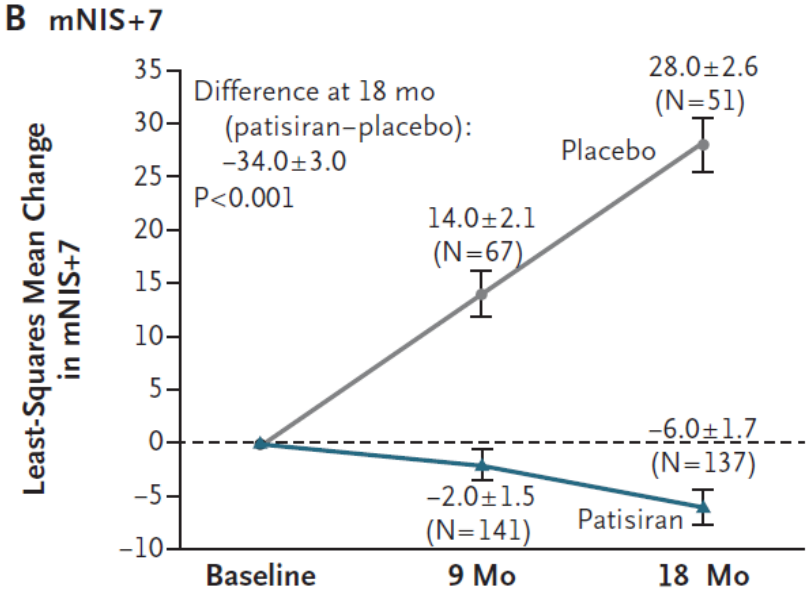
Approaches to Transthyretin Silencing (Knockdown)



Nat Rev Cardiol. 2022 Oct;19(10):655-667

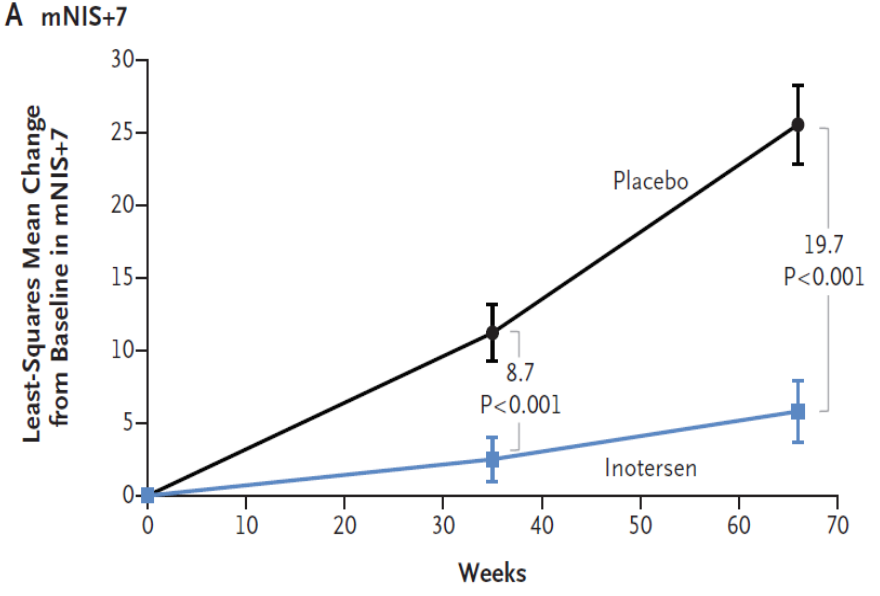
Efficacy of siRNA and ASO in ATTRv Amyloid Polyneuropathy

Patisiran (siRNA)



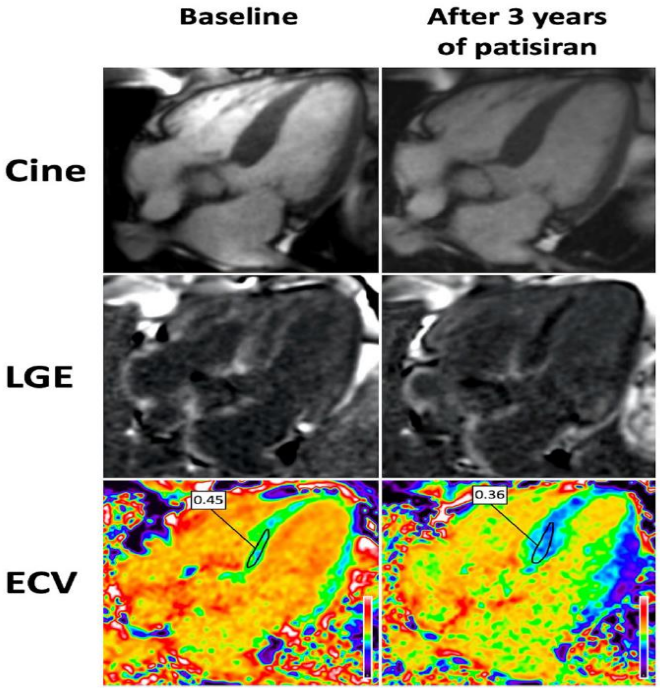
N Engl J Med 2018;379:11-21

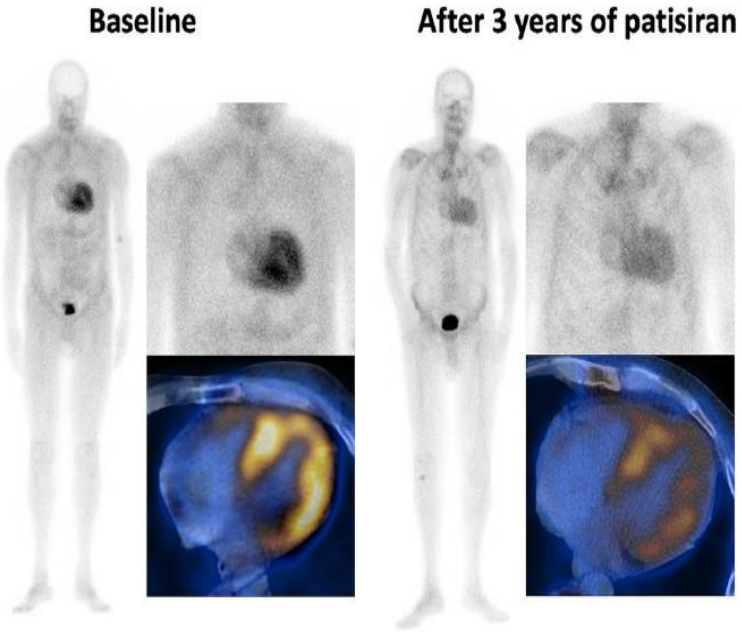
Inotersen (ASO)



N Engl J Med 2018;379:22-31..

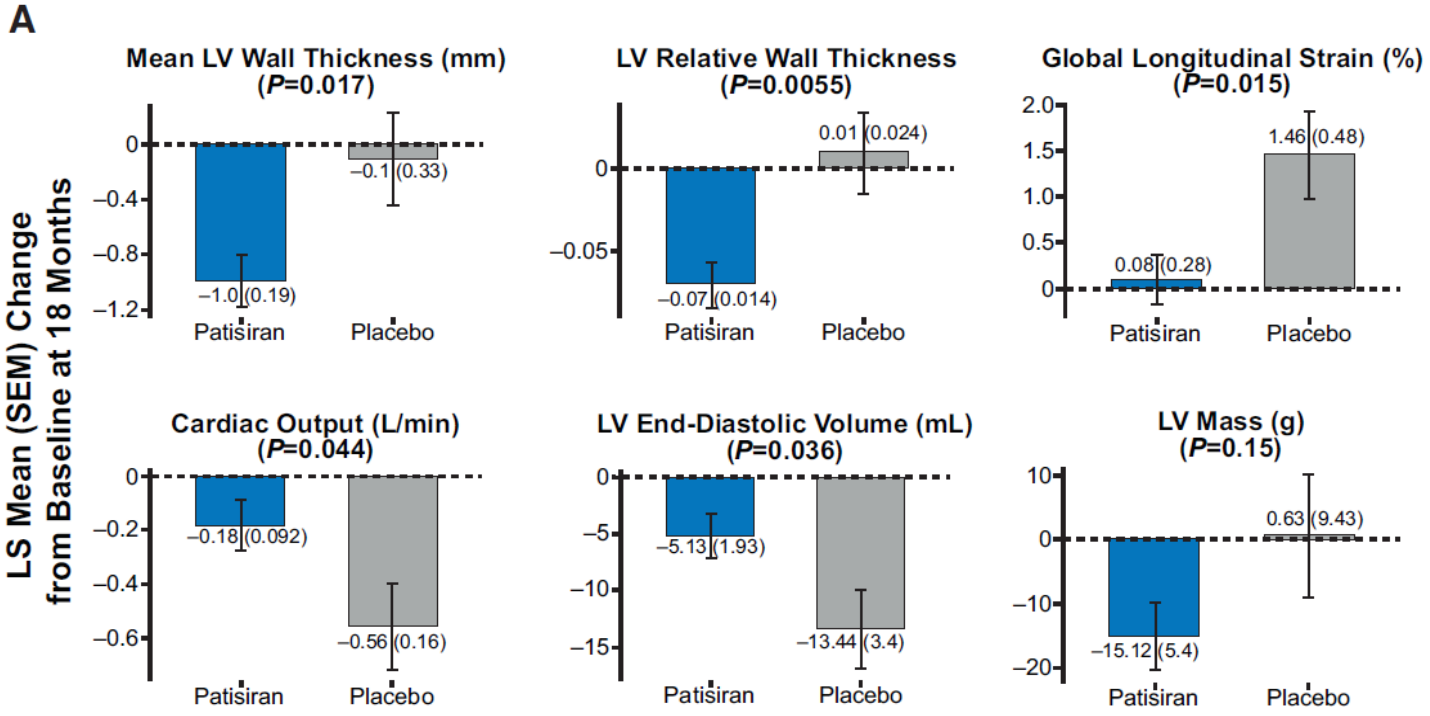
Efficacy of Patisiran, an siRNA, in ATTR-CA





BioDrugs. 2023 Mar;37(2):127-142

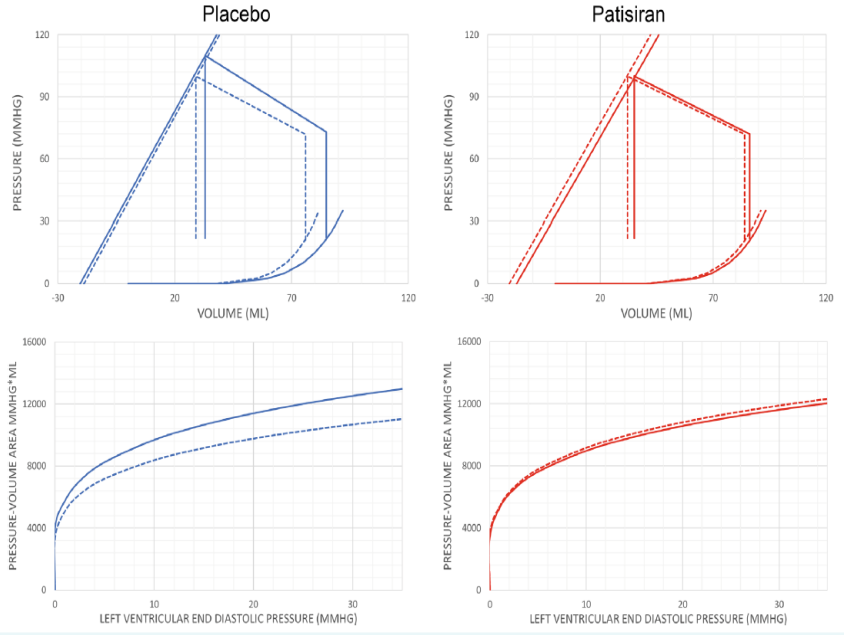
Patisiran, a siRNA, has favorable effects on Cardiac Parameters in Patients With ATTRv Amyloidosis



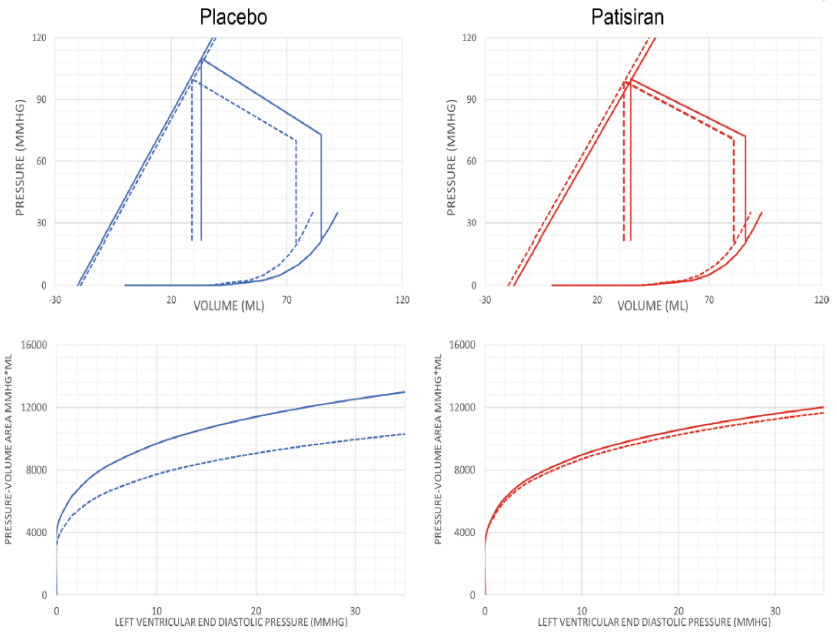
Circulation. 2019;139:431–443.

Patisiran in ATTRv Patients – Maintenance of Ventricular Capacitance

Changes after 9 Months



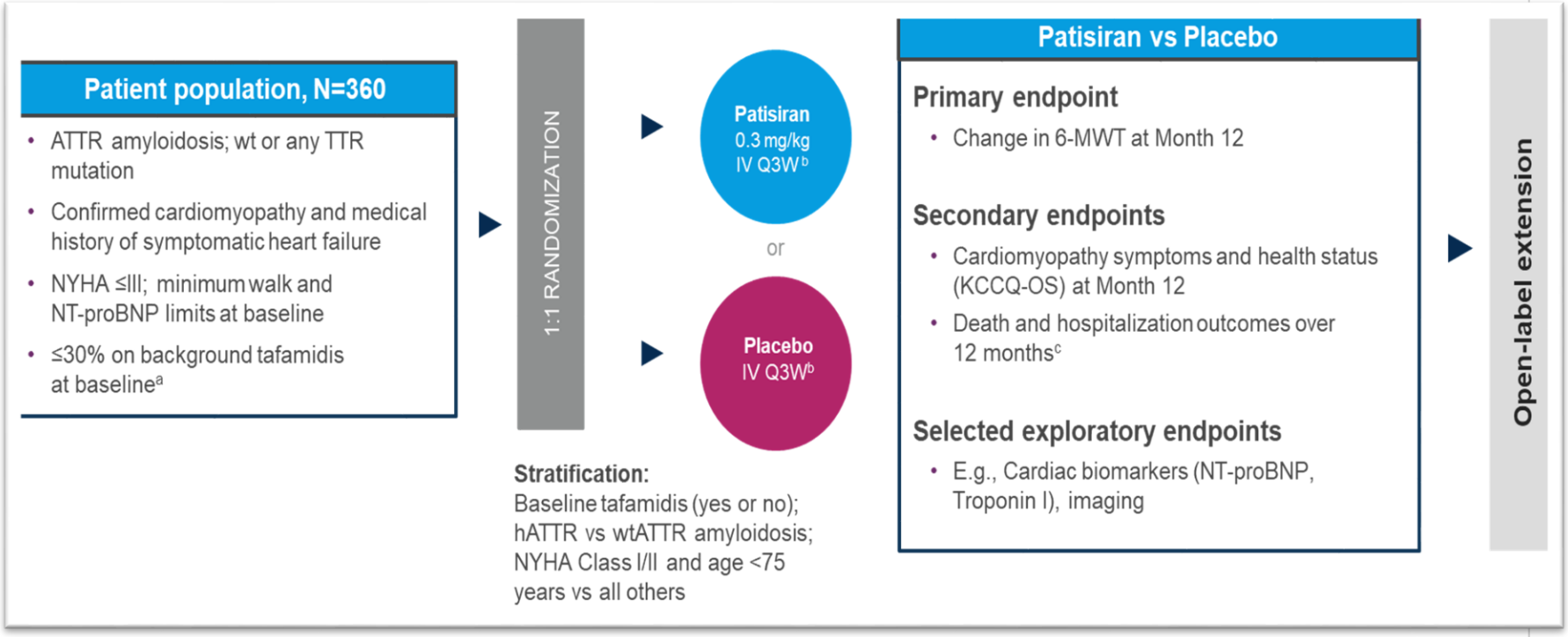
Changes after 18 Months



Eur J Heart Fail. 2023 May;25(5):727-736.

Study Design: Patisiran Phase 3 Study:

Randomized, Double-Blind, Placebo-Controlled Study in Patients with ATTR Amyloidosis with Cardiomyopathy



N Engl J Med. 2023 Oct 26;389(17):1553-1565

APOLLO-B: Baseline Demographics

	Patisiran N = 181	Placebo N = 178
Median Age at Screening, years (min, max)	**76** (47, 85)	**76** (41, 85)
≥ 75 years old	59%	57%
Male	89%	90%
Race		
White	76%	79%
Asian	13%	8%
Black or African American	9%	8%
Other or Not reported	2%	4%
Hispanic or Latino	12%	11%
Region		
North America	25%	29%
Western Europe	39%	38%
ROW	37%	33%

N Engl J Med. 2023 Oct 26;389(17):1553-1565

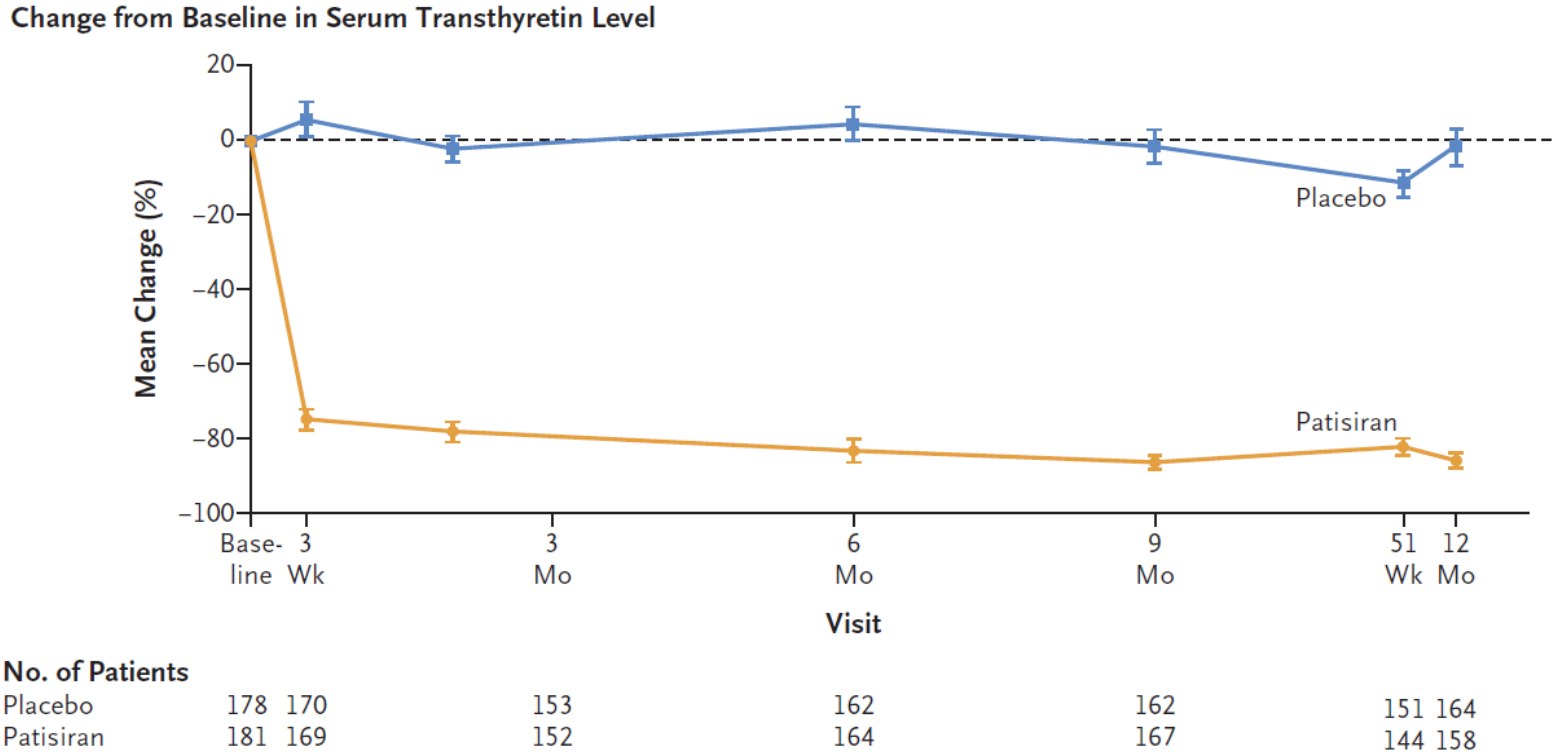
APOLLO-B: Clinical Characteristics at Baseline

		Patisiran N = 181	Placebo N = 178
ATTR amyloidosis type	wtATTR	80%	81%
	hATTR	20%	19%
Median time since diagnosis, years (min, max)		0.8 (0, 6)	0.4 (0, 10)
Baseline tafamidis use		25%	25%
NYHA class	I	6%	8%
	II	86%	84%
	III	8%	7%
Median NT-proBNP, ng/L (Q1, Q3)		2008 (1135, 2921)	1813 (952, 3079)
Median baseline 6MWT, meters (Q1, Q3)		358 (295, 420)	368 (300, 444)
Mean baseline KCCQ-OS Score (SEM)		69.8 (1.6)	70.3 (1.6)

N Engl J Med. 2023 Oct 26;389(17):1553-1565

Rapid and Sustained Serum TTR Reduction:

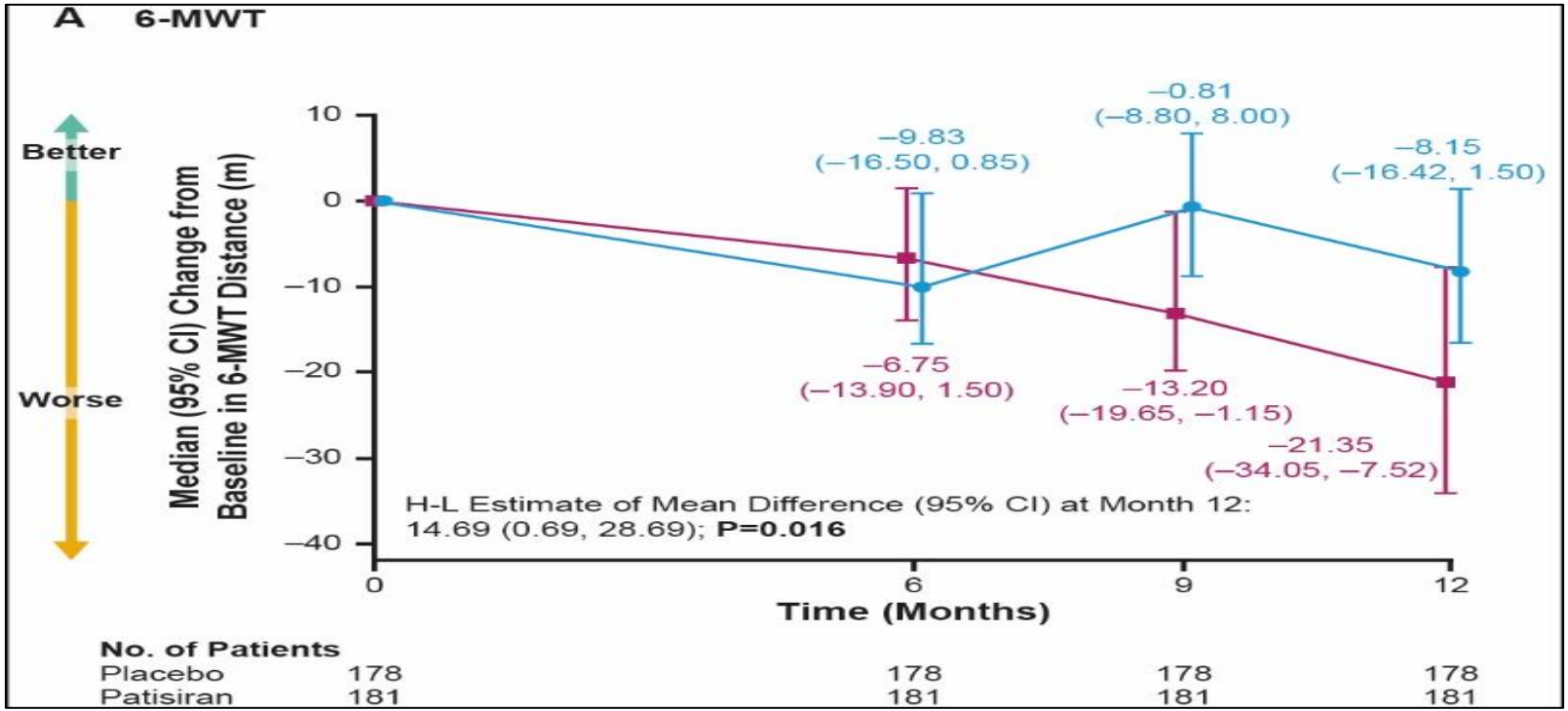
Patisiran achieved a mean (SD) percent reduction in serum TTR of 86.8% (13.6) at Month 12



N Engl J Med. 2023 Oct 26;389(17):1553-1565

Primary Endpoint:

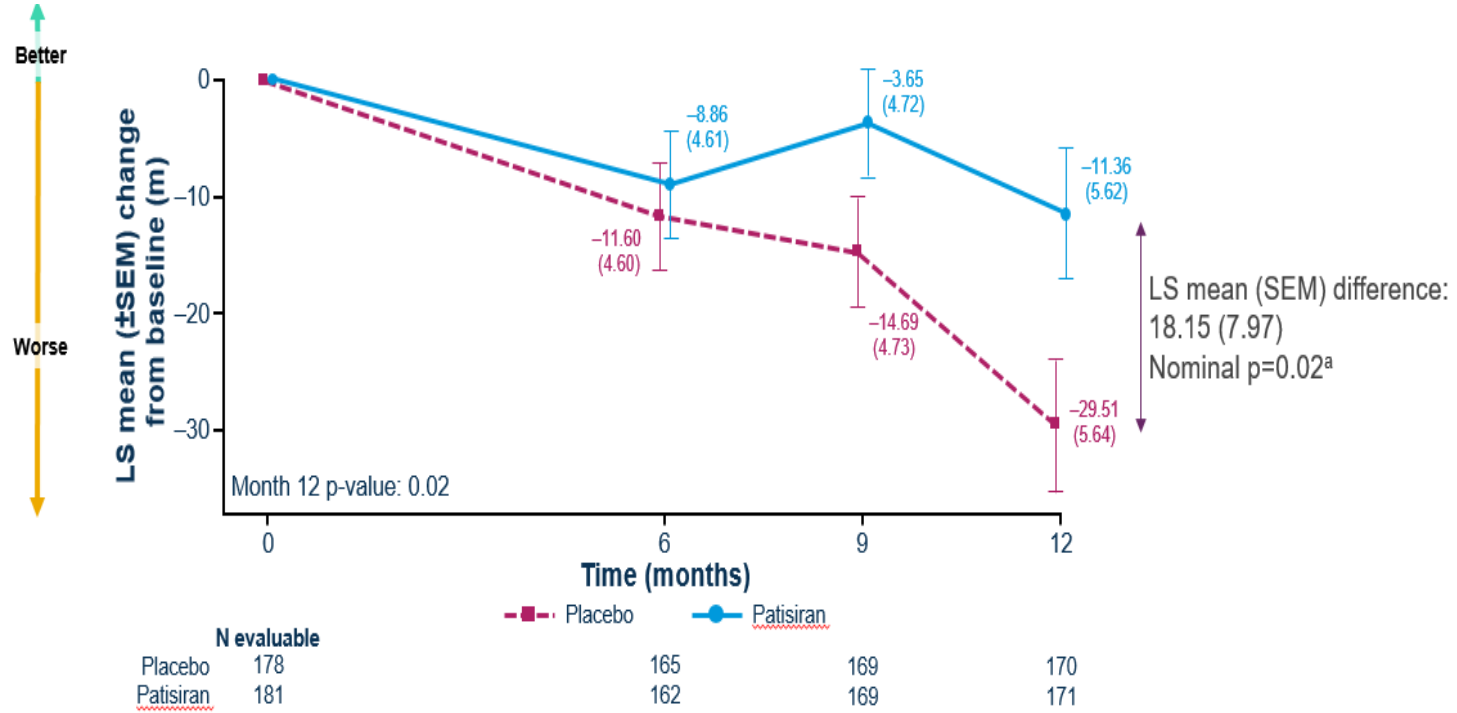
Patisiran Demonstrated Significant Benefit in Functional Capacity (6-MWT) Compared to Placebo at Month 12



N Engl J Med. 2023 Oct 26;389(17):1553-1565

Sensitivity Analysis:

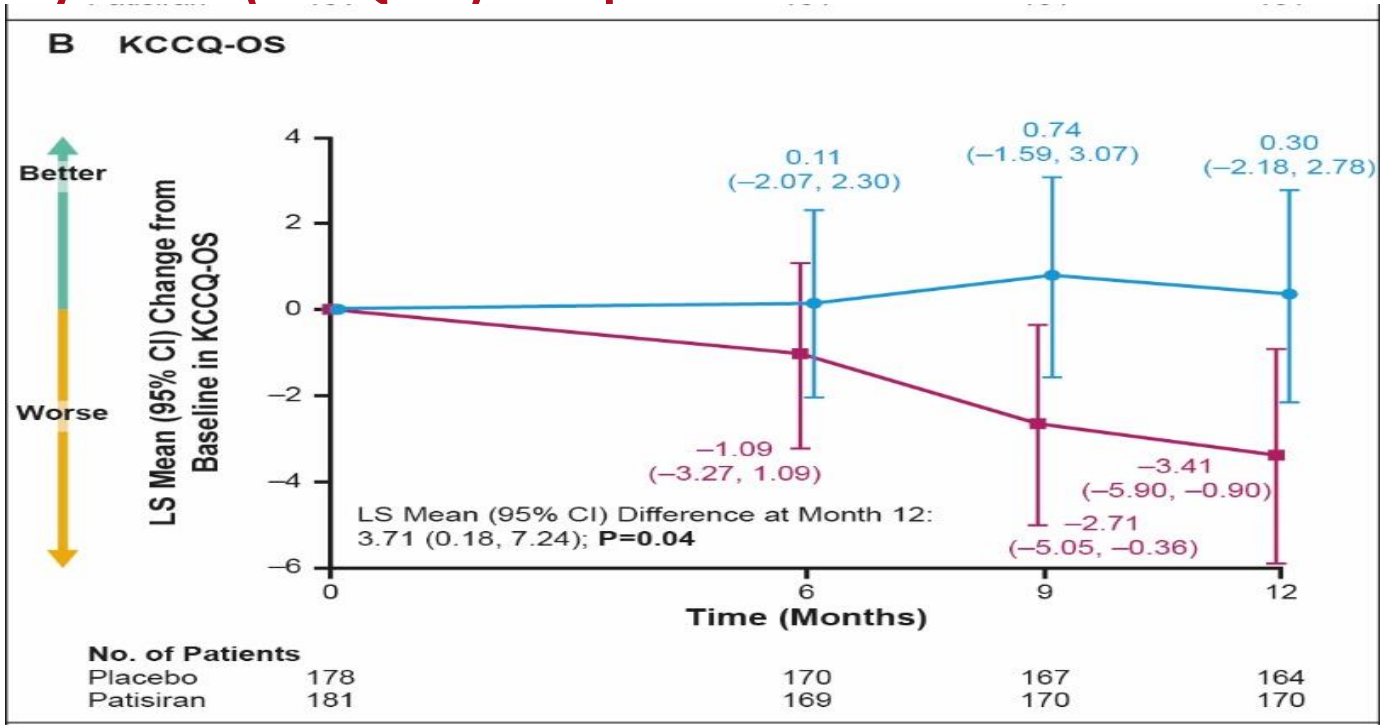
Confirms Robustness of the Observed Benefit in 6-MWT with Patisiran Compared to Placebo



N Engl J Med. 2023 Oct 26;389(17):1553-1565

Secondary Endpoint:

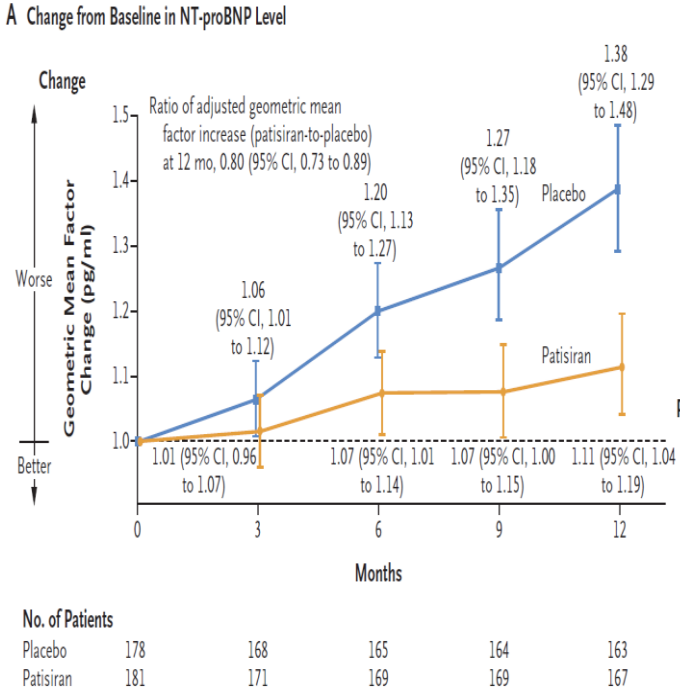
Patisiran Demonstrated Significant Clinical Benefit in Health Status and Quality of Life (KCCQ-OS) Compared to Placebo at Month 12



N Engl J Med. 2023 Oct 26;389(17):1553-1565

Exploratory Endpoint:

Patisiran Demonstrated Benefit in NT-proBNP and Troponin Change from Baseline Compared to Placebo at Month 12

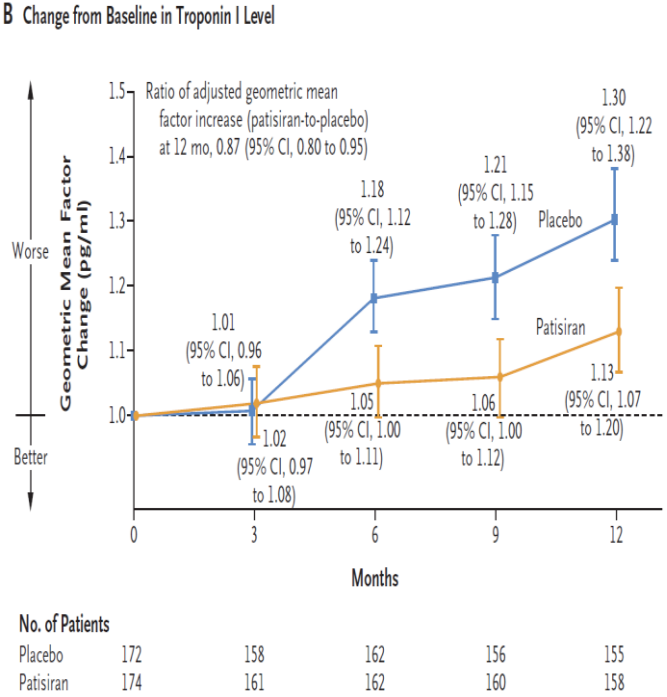


Median NT-proBNP Level

	Baseline	Month 12	Change from baseline
	pg/ml (IQR)		
Placebo	1813 (952 to 3079)	2299 (1180 to 4364)	518 (51 to 1544)
Patisiran	2008 (1135 to 2921)	1944 (1158 to 3726)	131 (−280 to 817)

No. of Patients

Placebo	178	168	165	164	163
Patisiran	181	171	169	169	167



Median Troponin I Level

	Baseline	Month 12	Change from baseline
	pg/ml (IQR)		
Placebo	60.20 (38.15 to 103.10)	72.10 (45.60 to 127.35)	14.50 (0.00 to 32.20)
Patisiran	64.00 (38.60 to 92.00)	67.75 (37.40 to 114.10)	3.75 (−7.10 to 19.90)

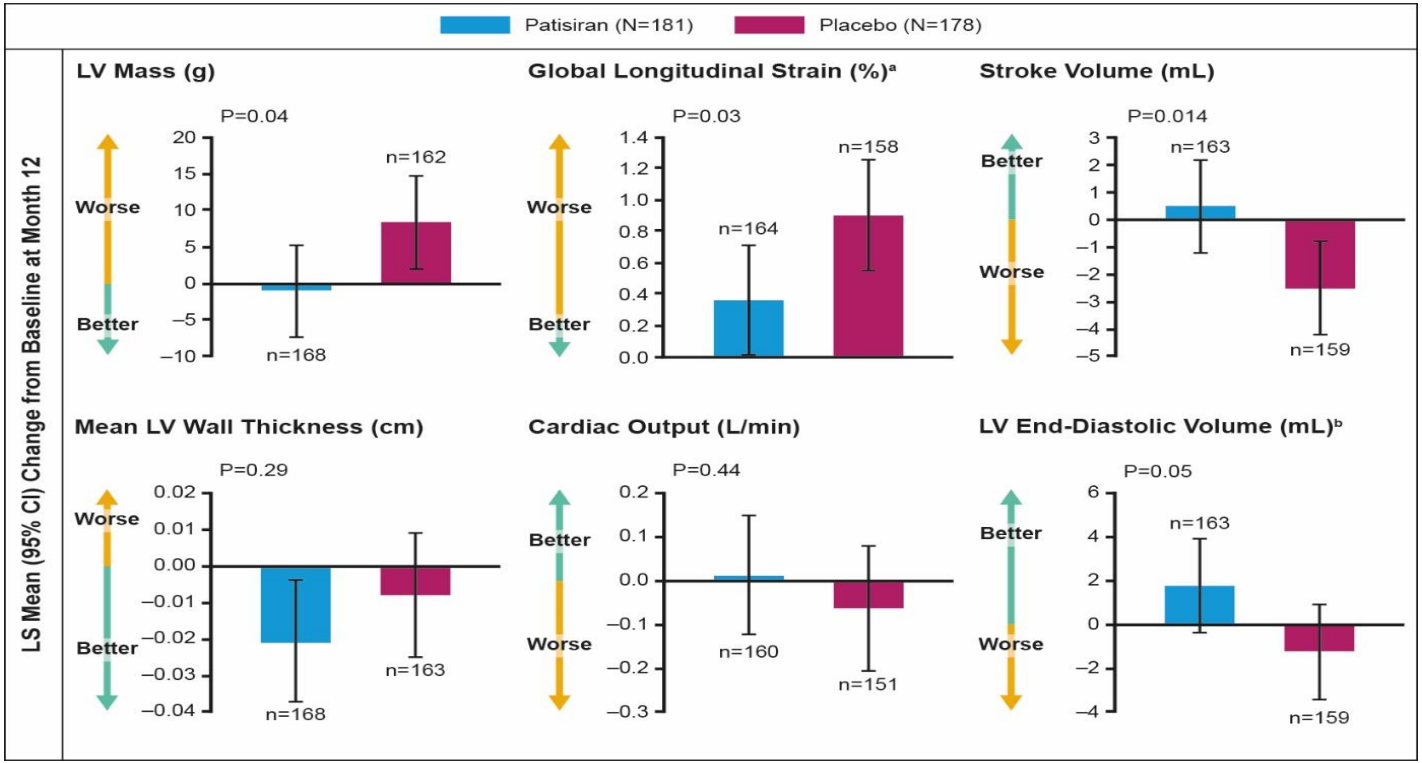
No. of Patients

Placebo	172	158	162	156	155
Patisiran	174	161	162	160	158

N Engl J Med. 2023 Oct 26;389(17):1553-1565

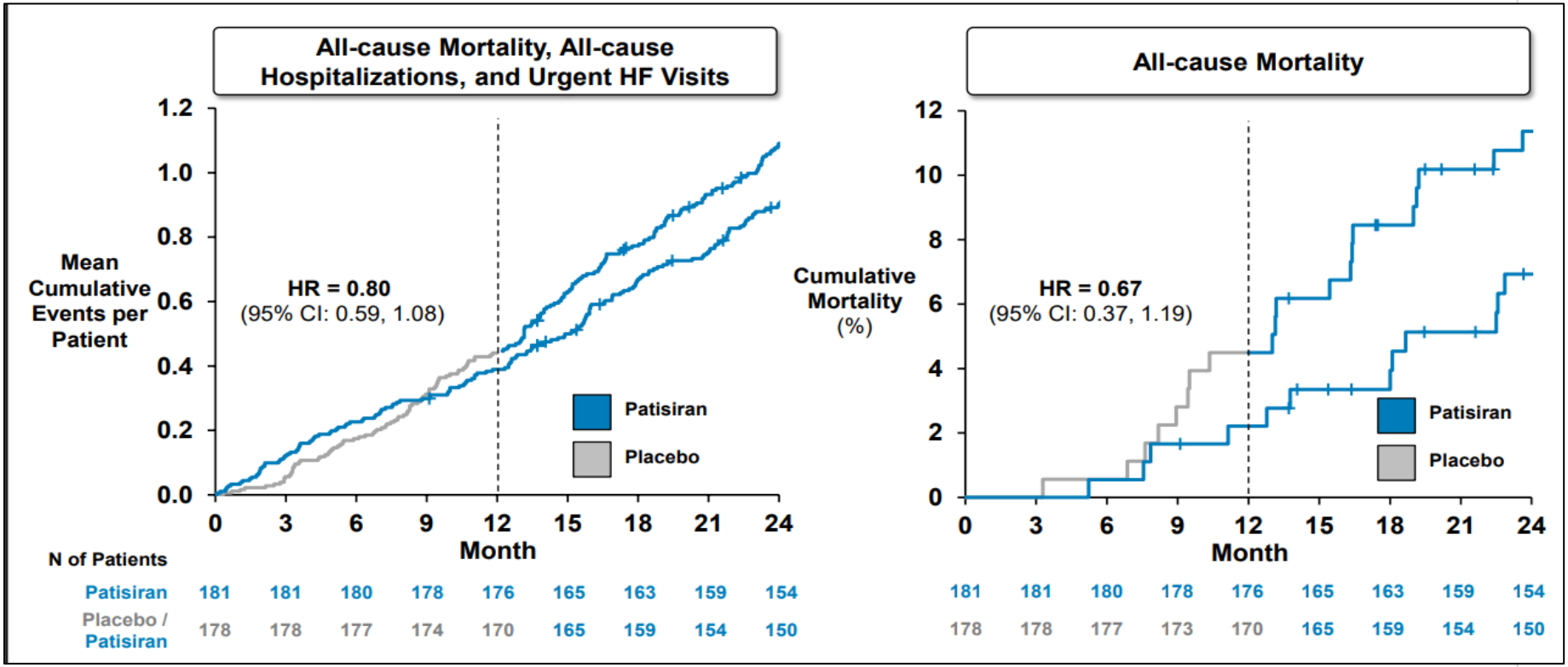
Exploratory Endpoints:

Patisiran Demonstrated Evidence of Favorable Changes from Baseline of Most Echocardiographic Parameters Compared to Placebo at Month 12



N Engl J Med. 2023 Oct 26;389(17):1553-1565

Fewer Events in Patisiran Arm in APOLLO-B through 24 months



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APOLLLO-B: 24 months data Functional Capacity, and Health Status and QOL

Figure 2. Mean Change from Baseline in 6MWT over 24 Months

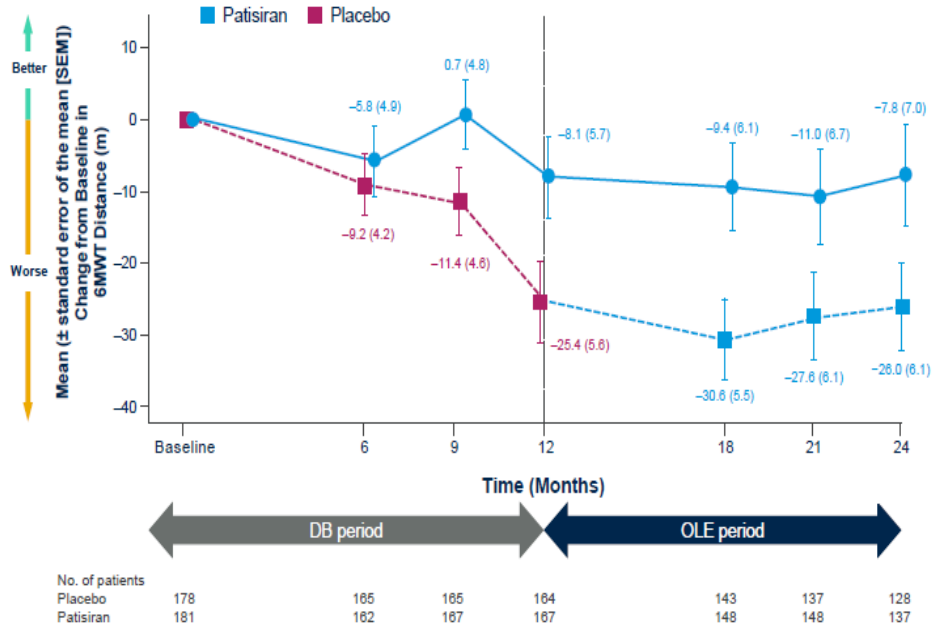
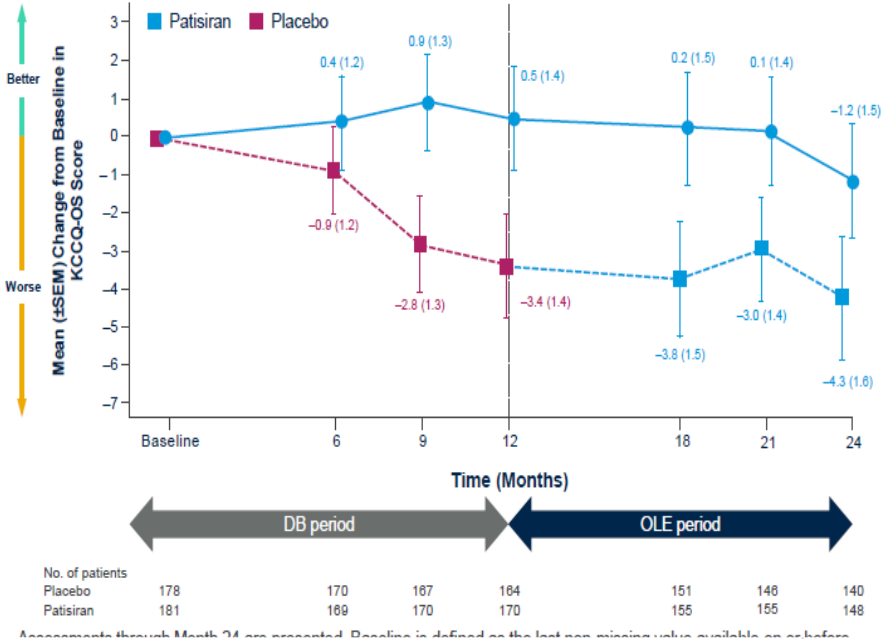


Figure 3. Mean Change from Baseline in KCCQ-OS over 24 Months



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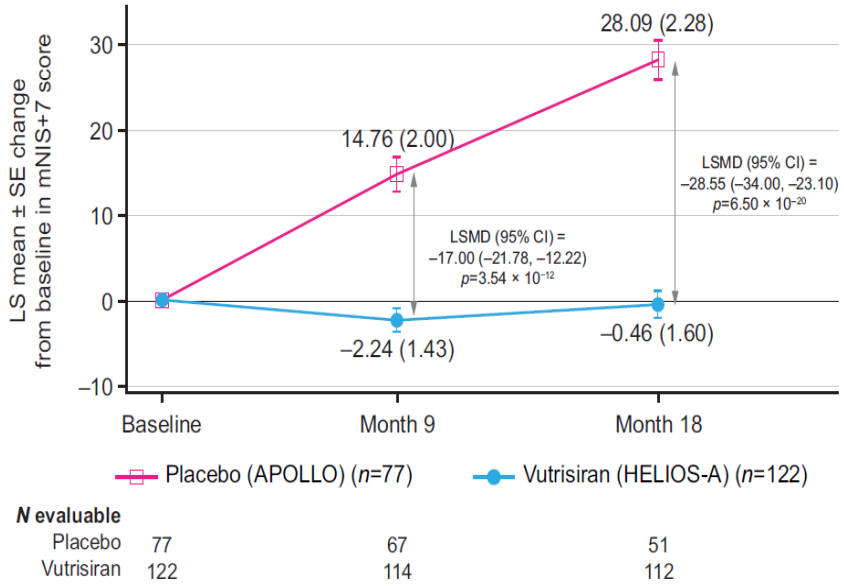
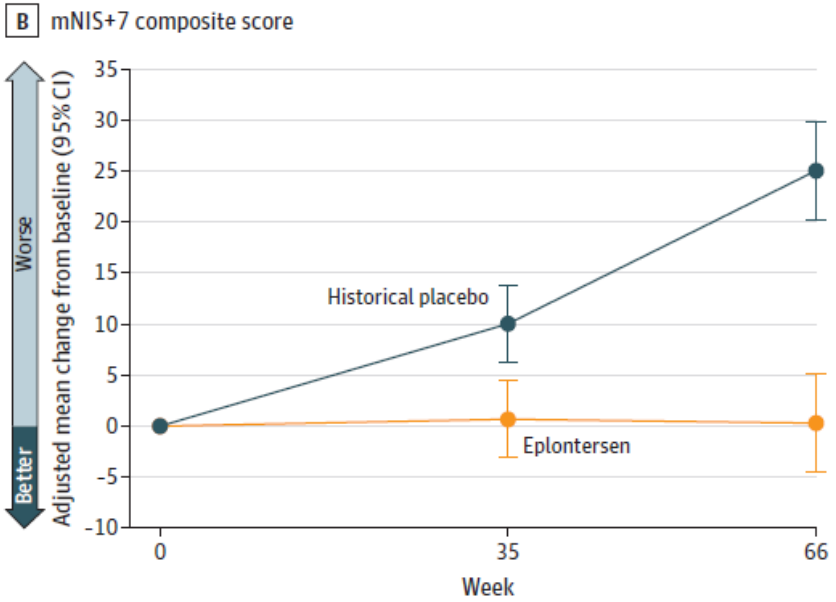
Next Generation Silencers –
Vutrisiran and Eplontersen

Helios A - Vutrisiran



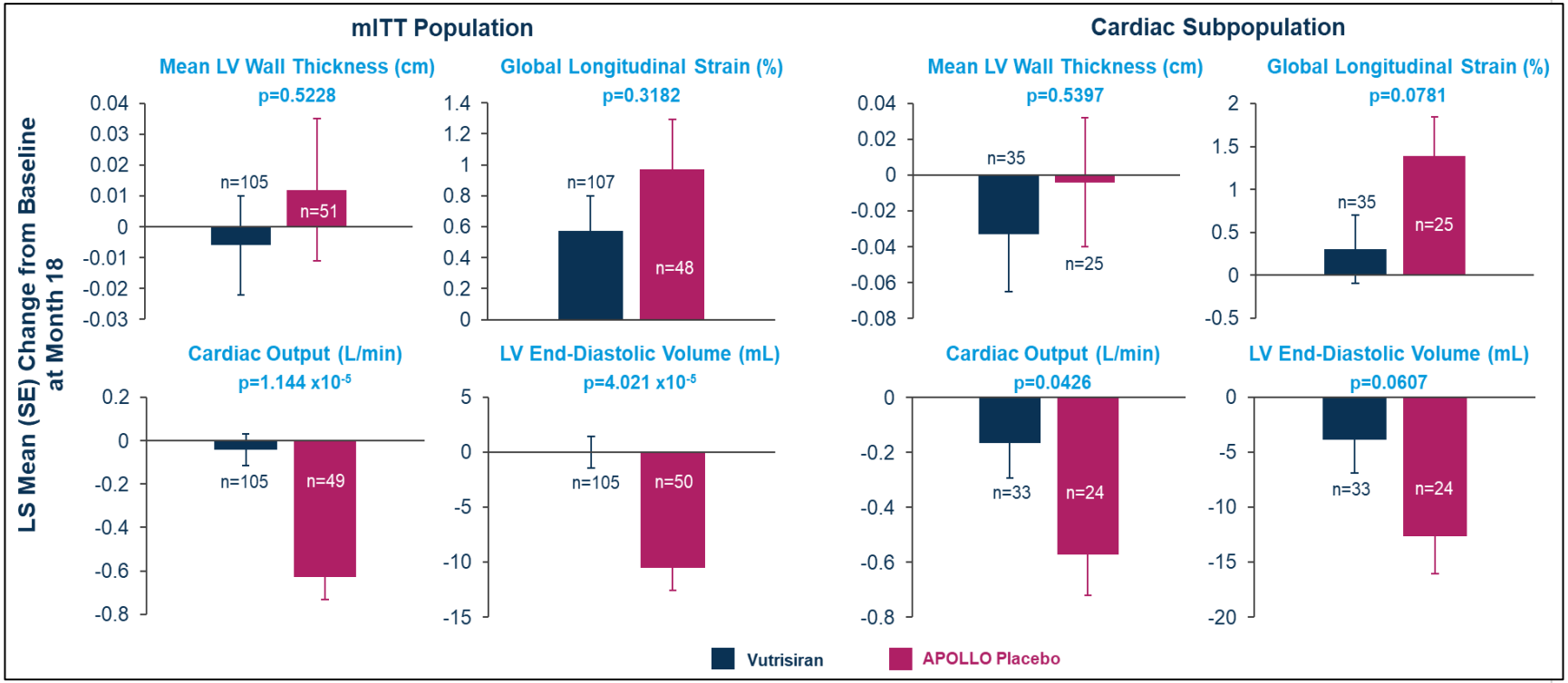
NEURO-TTRansform - Eplontersen



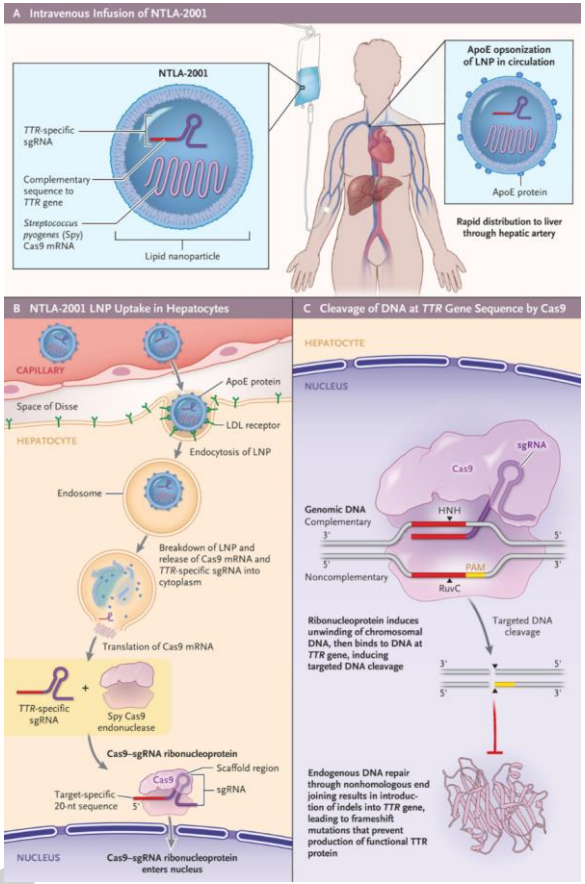
Amyloid. 2023 Mar;30(1):1-9.

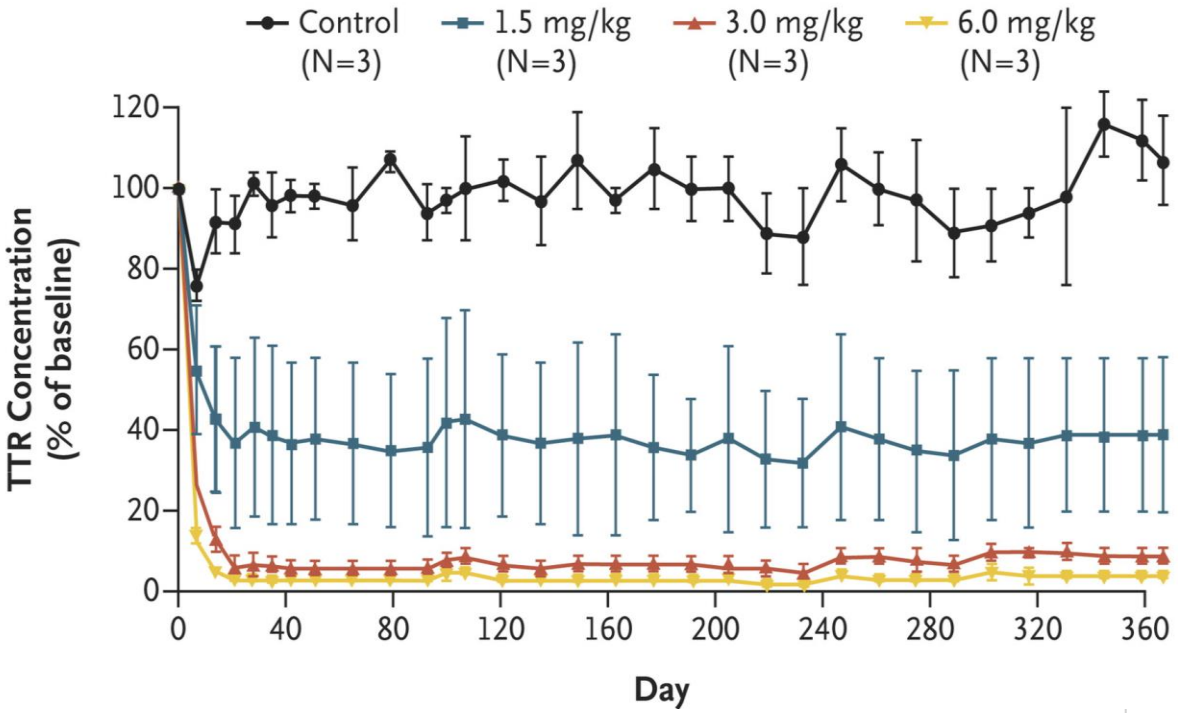
JAMA. 2023;330(15):1448-1458

Effects of Vutrisiran on Cardiac Parameters in ATTRv Amyloidosis



TTR Gene Editing via CRISPR-Cas9





N Engl J Med 2021;385:493-502

TTR Gene Editing via CRISPR-Cas9
Phase 1 Patients

Characteristic		PN Patients (N=36)	CM Patients (N=29)	All Patients (N=65)
Age, years	Median (min, max)	61 (19, 75)	78 (46, 86)	68 (19, 86)
Sex, n (%)	Male	26 (72)	28 (97)	54 (83)
Weight, kg	Median (min, max)	77 (55, 117)	82 (63, 115)	81 (55, 117)
***TTR* genotype, n (%)**	p.V50M	11 (31)	0	11 (17)
	p.V142I	1 (3)	6 (21)	7 (11)
	p.T80A	7 (19)	1 (3)	8 (12)
	p.S97Y	7 (19)	0	7 (11)
	p.E62D	4 (11)	0	4 (6)
	Other	6 (17)	2 (7)	8 (12)
	WT	0	20 (69)	20 (31)
NYHA Class, n (%)	No diagnosis of heart failure	12 (33)	0	12 (18)
	I	19 (53)	3 (10)	22 (34)
	II	5 (14)	14 (48)	19 (29)
	III	0	12 (41)	12 (18)
NT-proBNP, ng/L	Median (min, max)	127 (<50, 1878)	1845 (851, 19,624)	757 (<50, 19,624)

TTR Gene Editing via CRISPR-Cas9
Phase 1 – Adverse Events

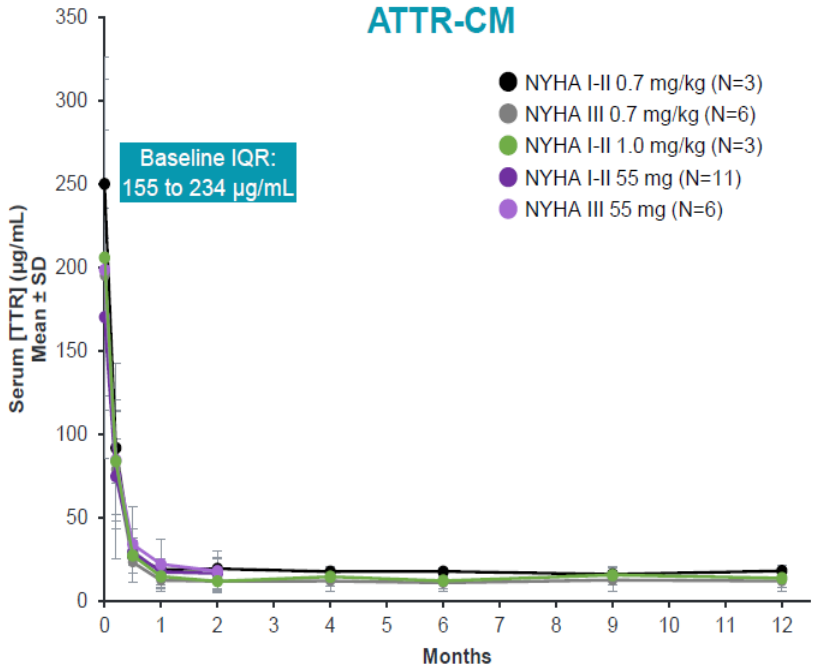
TEAEs by Maximum Toxicity Grade and Preferred Term Reported in >5% of All ATTRv-PN and ATTR-CM Patients (N=65)

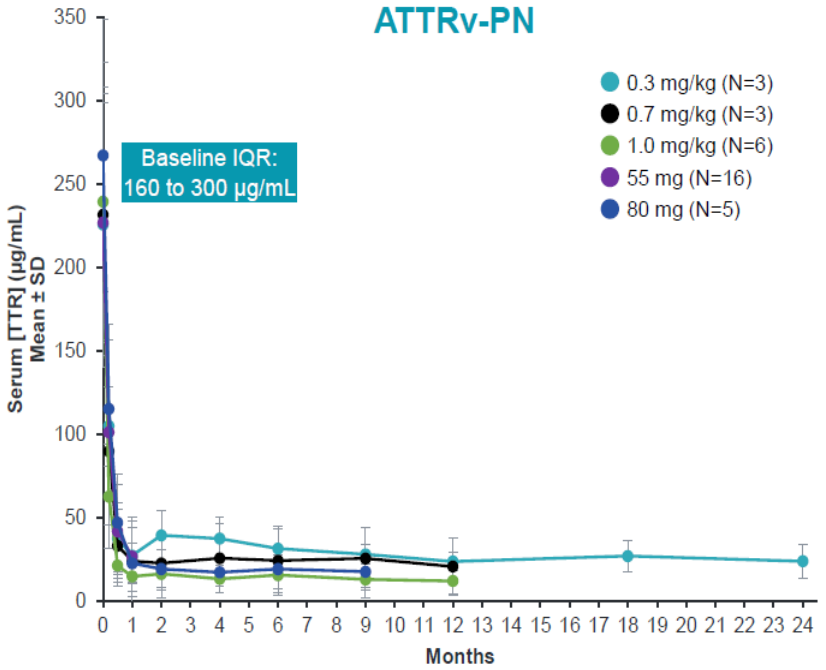
AE, Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3
Infusion-related reaction	25 (38)	10 (15)	14 (22)	1 (2)
Headache	12 (18)	12 (18)		
Diarrhea	11 (17)	10 (15)	1 (2)	
Back pain	7 (11)	7 (11)		
COVID-19 infection	6 (9)	5 (8)	1 (2)	
Cardiac failure	6 (9)	2 (3)	2 (3)	2 (3)
Upper respiratory tract infection	6 (9)	6 (9)		
AST increased	5 (8)	3 (5)	1 (2)	1 (2)
Dizziness	5 (8)	5 (8)		
Fatigue	5 (8)	5 (8)		
Muscle spasms	5 (8)	4 (6)	1 (2)	
Vision blurred	5 (8)	5 (8)		
Atrial flutter	4 (6)		1 (2)	3 (5)
Constipation	4 (6)	2 (3)	2 (3)	
Rash	4 (6)	4 (6)		

Data cutoff May 11, 2023.

- This includes all reported events, including those unrelated to NTLA-2001 (e.g., atrial flutter and cardiac failure hospitalizations)
- Infusion-related reactions were most common; nearly all were considered mild and resolved without sequelae, and all patients received the complete, planned dose
- Any liver enzyme elevations resolved spontaneously, were asymptomatic, and required no intervention (e.g., steroids) or hospitalization

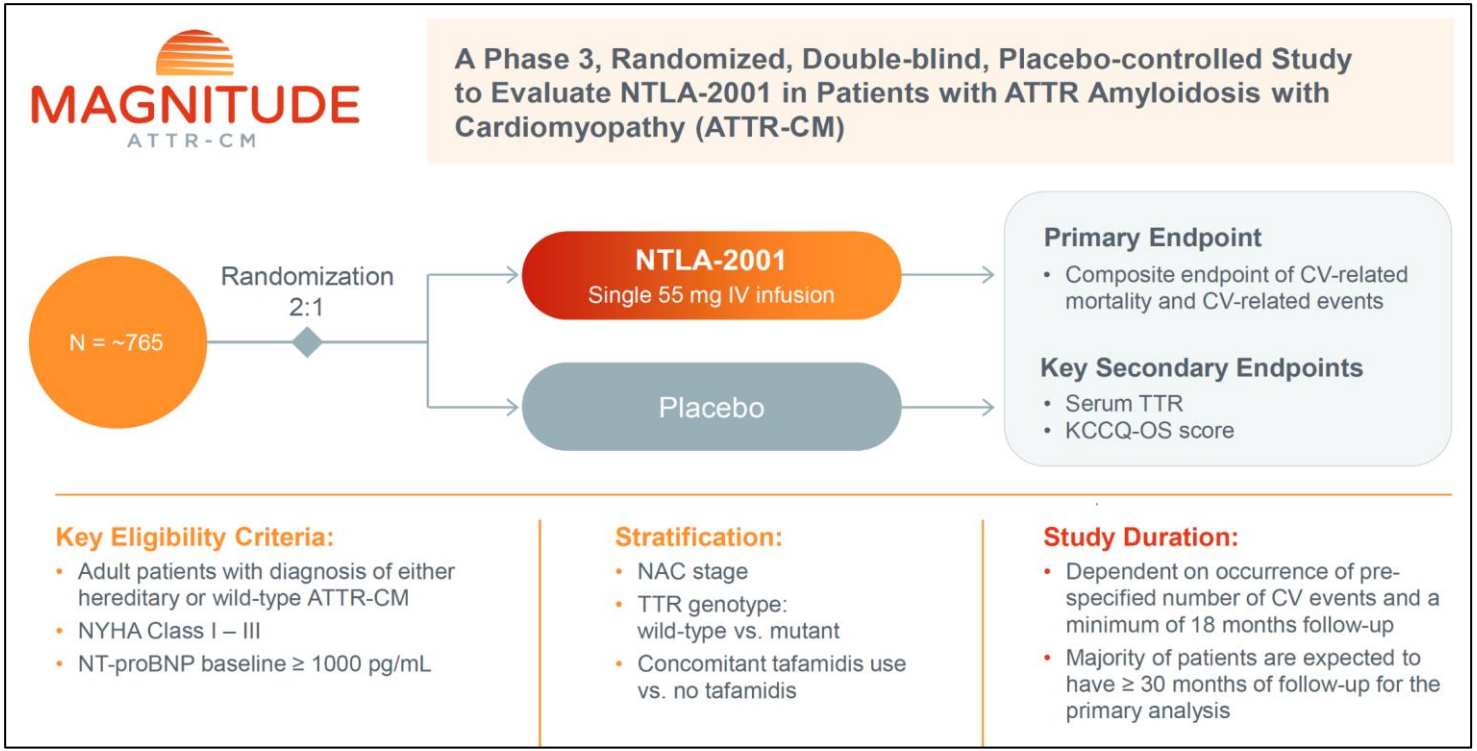
TTR Gene Editing via CRISPR-Cas9
Phase 1 – Sustained TTR Knockdown



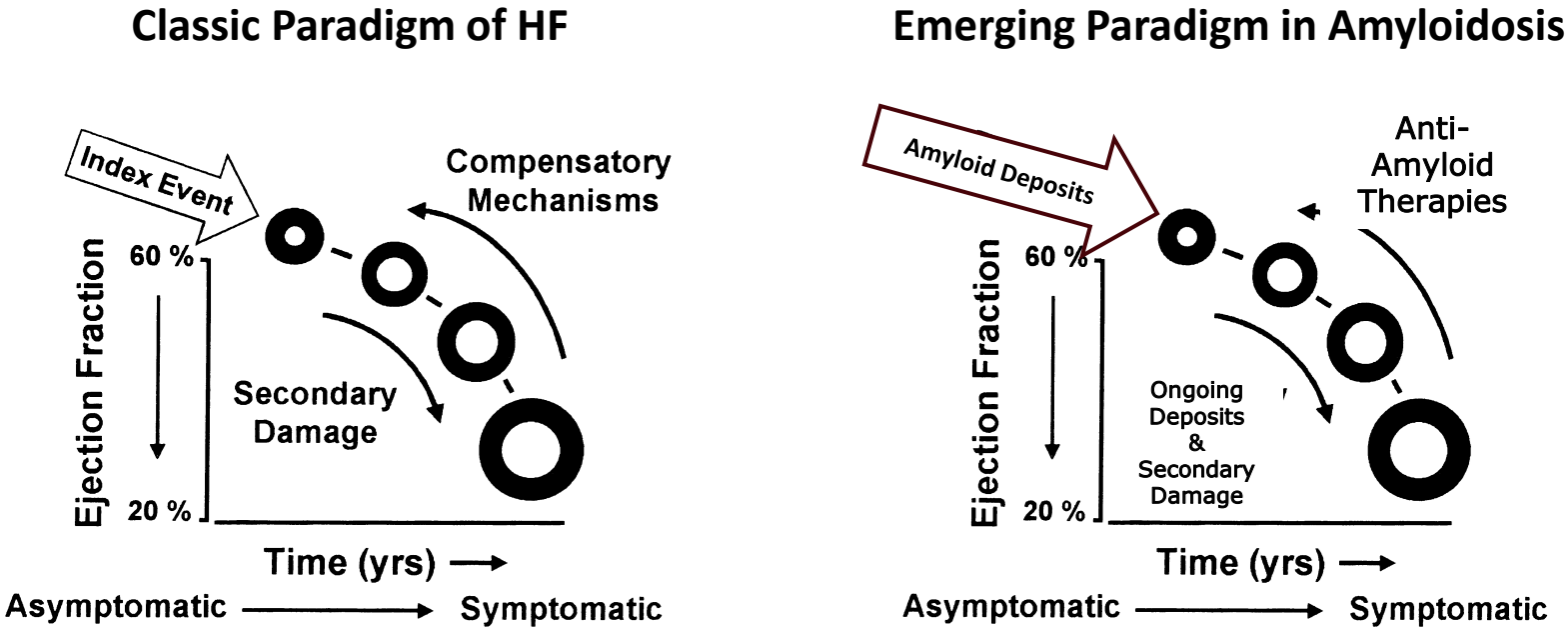


Median (IQR) Serum [TTR] at Day 28 (n=62)	Residual absolute TTR concentration at day 28	17 µg/mL (11 to 24)
	% Change from baseline in serum TTR at day 28	-91% (-88 to -94)

Magnitude – Phase 3 Trial of CRISPR in ATTR-CA



Progression of HF in Cardiac Amyloidosis:
Potential Role of Anti-Amyloid Therapy



Modified from Mann DL et al. Circulation 1999;100:999-1008

Antibody-Associated Reversal of ATTR-CA

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ATTR-CA

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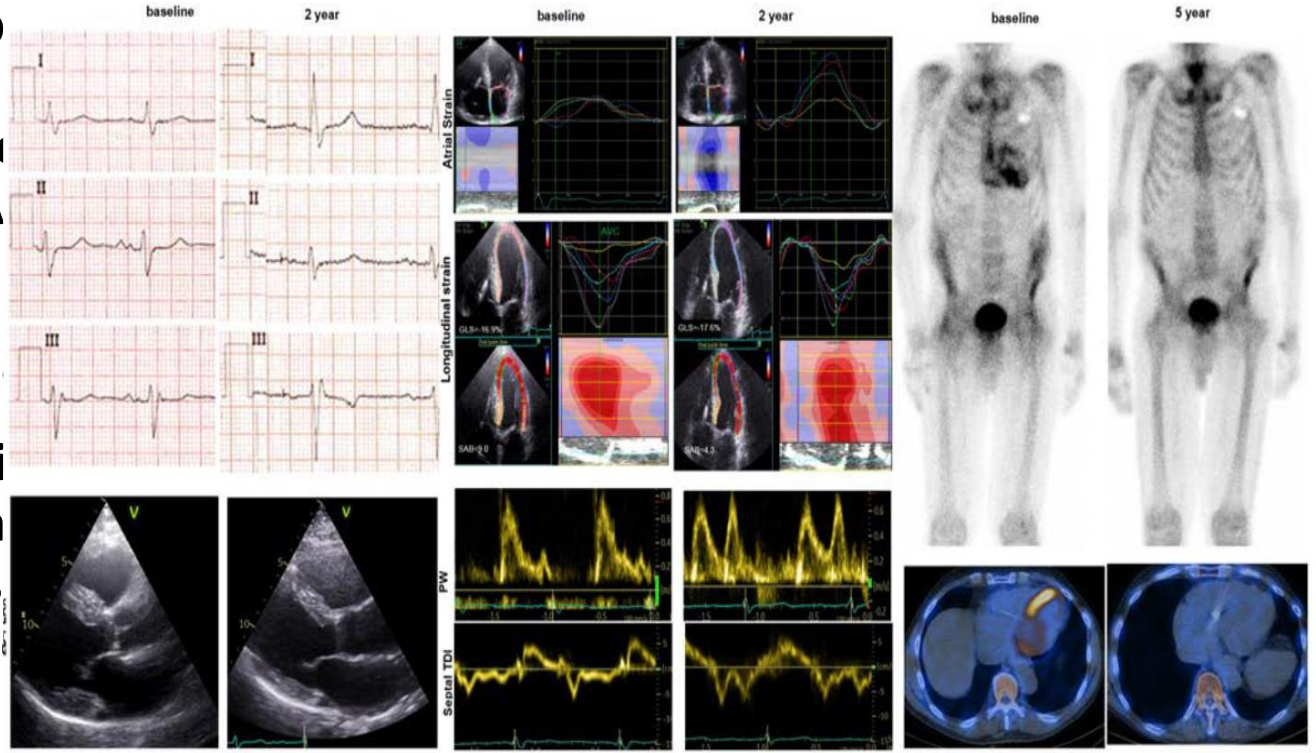


N Engl J Med. 2023 Jun 8;388(23):2199-2201.

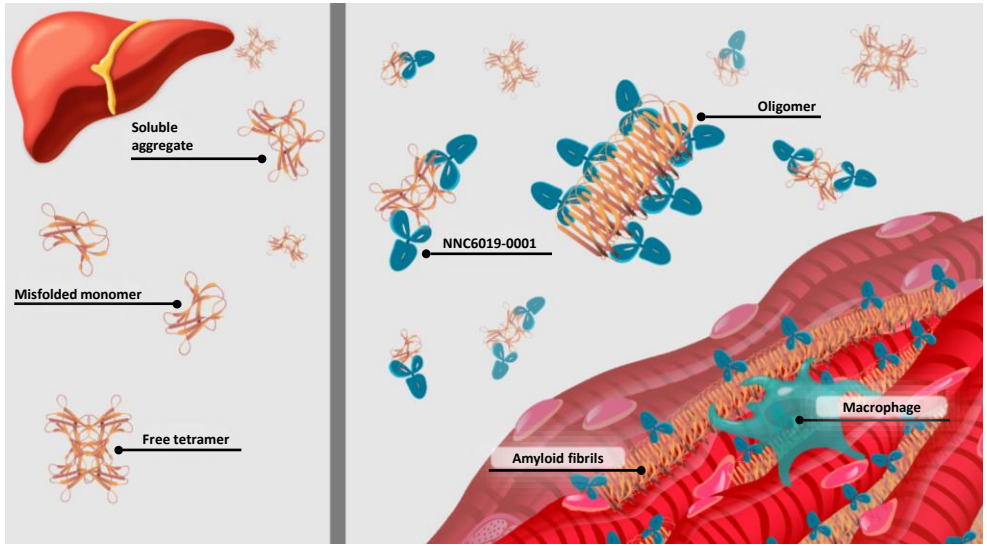
Anti-Amyloid Therapies

Name of Drug	Type of Amyloidosis	Phase of Study	Sponsor
NEOD001 (Birtamimab)	AL	3	Prothena
CAEL-101 (Anselamimab)	AL	3	Alexion
NNC6019 (PRX004)	ATTR	2	Novo-Nordisk
ALX2220 (NI006)	ATTR	3	Alexion
AT-02	AL, ATTR, others	1	Attralus

NNC6019-0001 (formerly PRX004)
Mechanism of action

- **NNC6019-0001 is a a humanized monoclonal antibody that targets an epitope of TTR that is exposed on monomeric, misfolded and aggregated forms of TTR, but hidden in native TTR tetramers.**

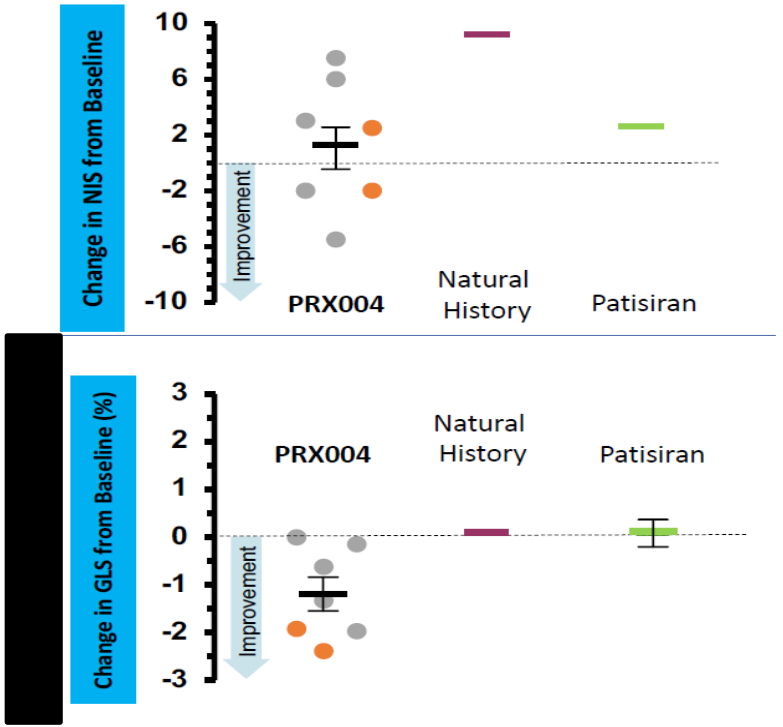
- **Through antibody-mediated phagocytosis, NNC6019-0001 depletes TTR amyloid deposits. In addition, it may prevent TTR amyloid formation.**



Higaki JN et al. Amyloid 2016;23:86–97

NNC6019-0001 (Novo Nordisk) (PRX004; Prothena): A monoclonal antibody that targets misfolded TTR

- Showed neurologic and cardiac benefit in a small phase 1 study in patients with ATTR amyloidosis .
- At 9 months, neuropathy progression (measured by NIS) slowed in 7/7 evaluable patients compared with natural history
- Cardiac systolic function (measured by GLS) improved in 7/7 evaluable patients compared with untreated patients
- Phase 2 trial underway



https://s201.q4cdn.com/351053094/files/doc_presentations/2021/04/1/AAN-PRX004-Ph1_20March21-FINAL.pdf

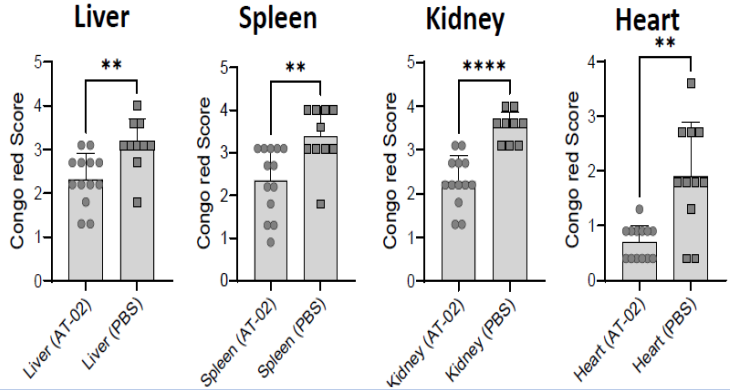
AT-02: IgG1-peptide fusion with pan-amyloid reactivity
Binds to all types of amyloid

A humanized IgG1-peptide fusion reagent

The pan-amyloid reactive peptide p5R, which binds to amyloid fibrils by electrostatic interactions, is fused to the C-terminal of the light chain

Designed to be capable of:

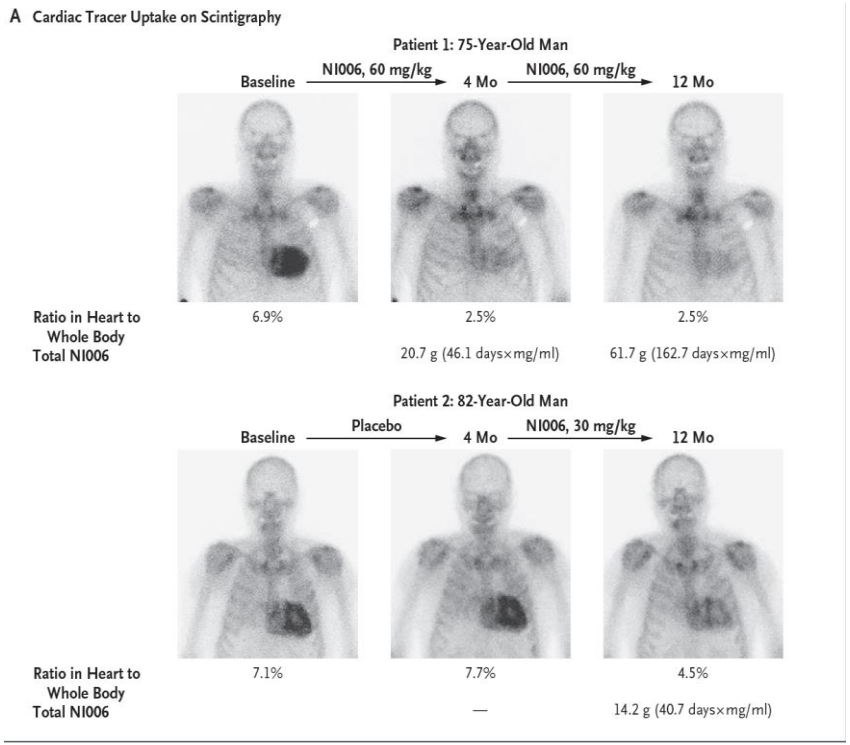
- Binding to all types of amyloid deposits
- Opsonizing the deposits and promoting macrophage-mediated amyloid clearance
- Binding complement to enhance phagocytosis of amyloid

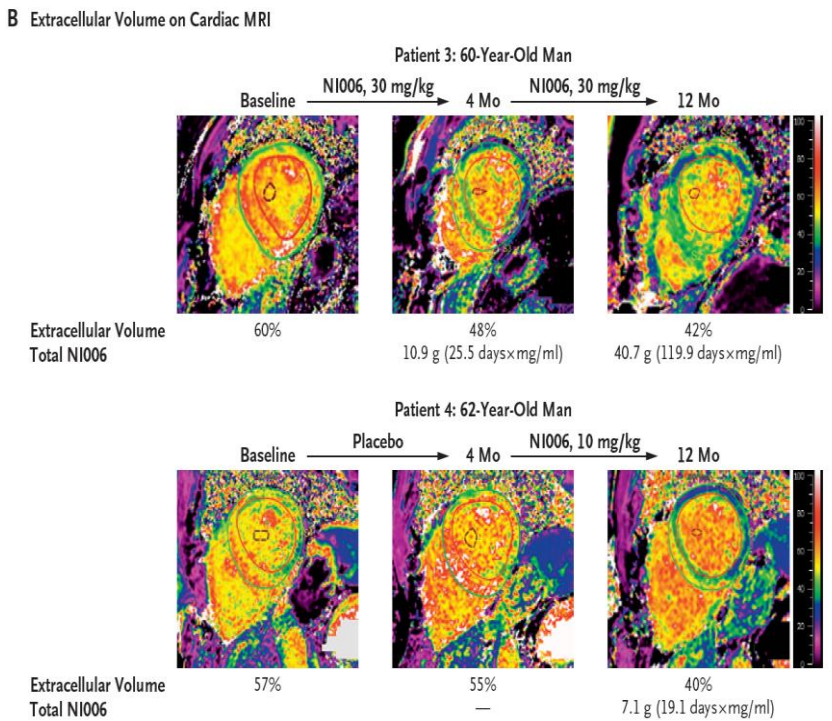


Organ	AT-02 median (n)	PBS median (n)	Mann- Whitney Sig.
Liver	2.2 (*n*=13)	3.1 (*n*=10)	p=0.0029
Spleen	2.7 (*n*=13)	3.35 (*n*=10)	p=0.0023
Kidney	2.2 (*n*=13)	3.6 (*n*=9)	p<0.0001
Heart	0.9 (*n*=13)	1.8 (*n*=11)	p=0.0017

Wall et al. *ISA* 2022

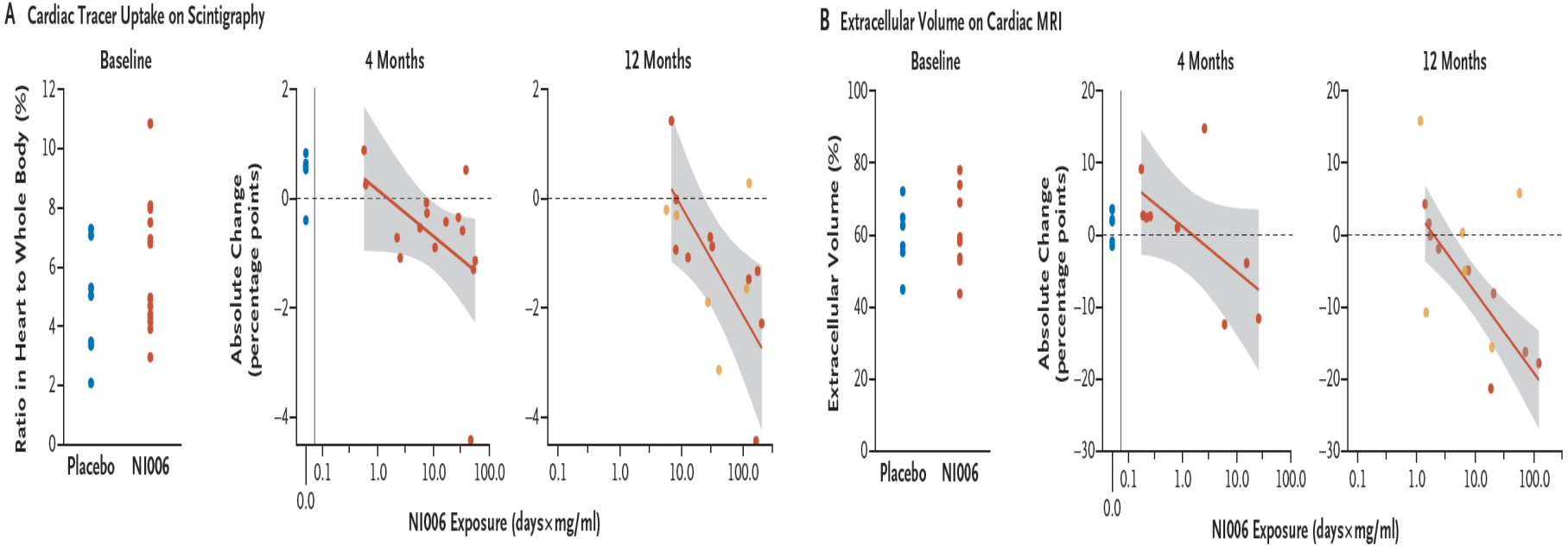
Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid





N Engl J Med. 2023 Jul 20;389(3):239-250

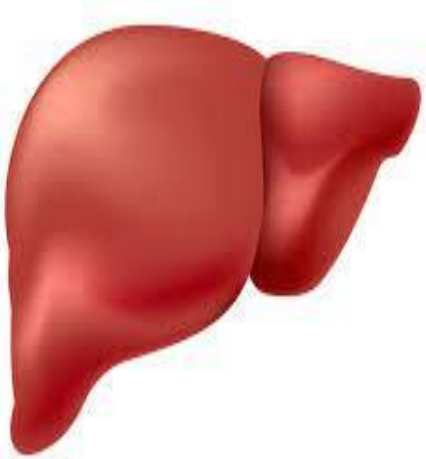
Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid



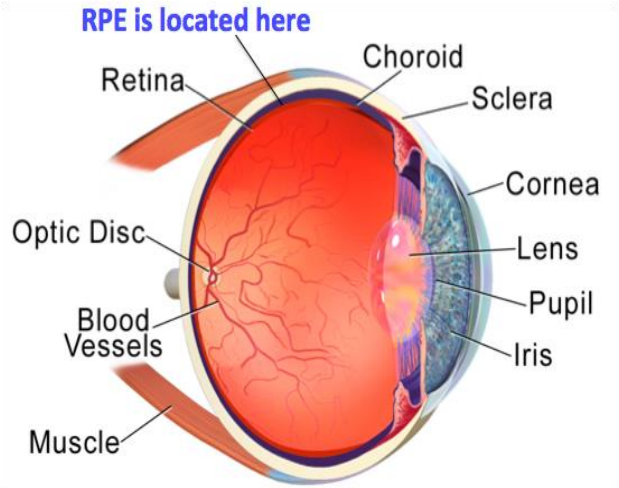
N Engl J Med. 2023 Jul 20;389(3):239-250

Sources of TTR Production

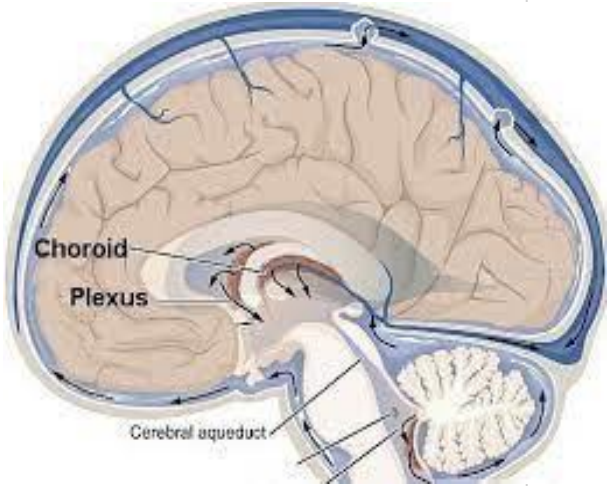
Liver



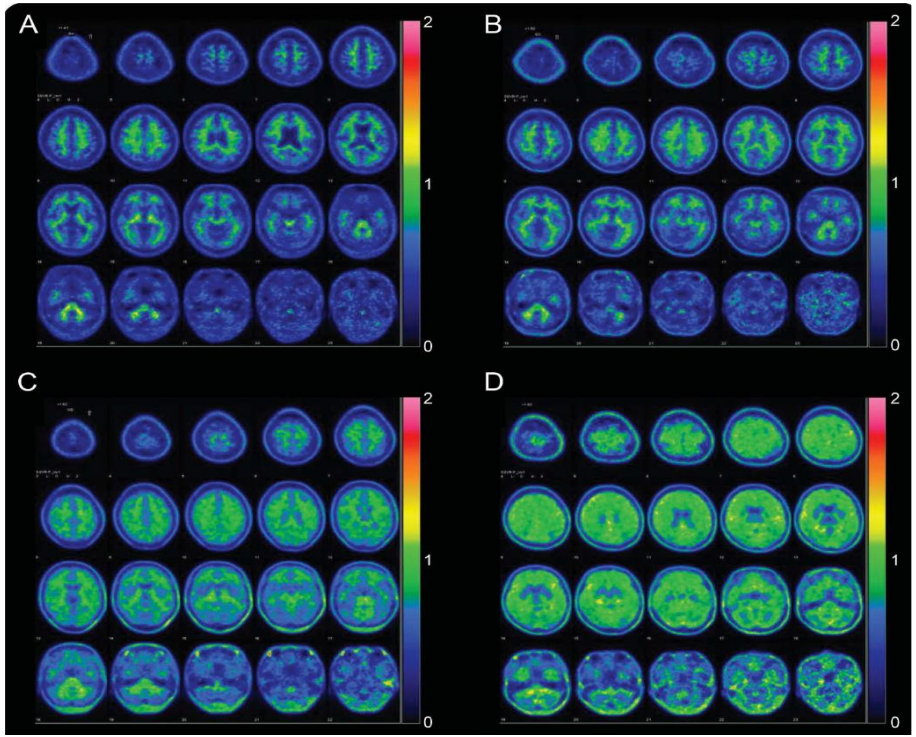
Eye:
Retinal Pigment



Choroid Plexus



Will an emerging phenotype in the CNS influence our choice of therapies?



Drug	Crosses Blood Brain Barrier
Diflunisal	Very little
Tafamidis	Yes
Acoramidis	No
Patisiran	No
Vutrisiran	No
Eplontersen	No

Neurology 2016;87:773–781

Risk of subdural hematoma in cardiac amyloidosis

	Cardiac Amyloidosis (n=515)	Without Cardiac Amyloidosis (n=1,912,760)
Subdural Hematoma	15 (3.1%)	6389 (0.33%)
No Subdural Hematoma	500 (96.9%)	1,906,371 (99.7%)

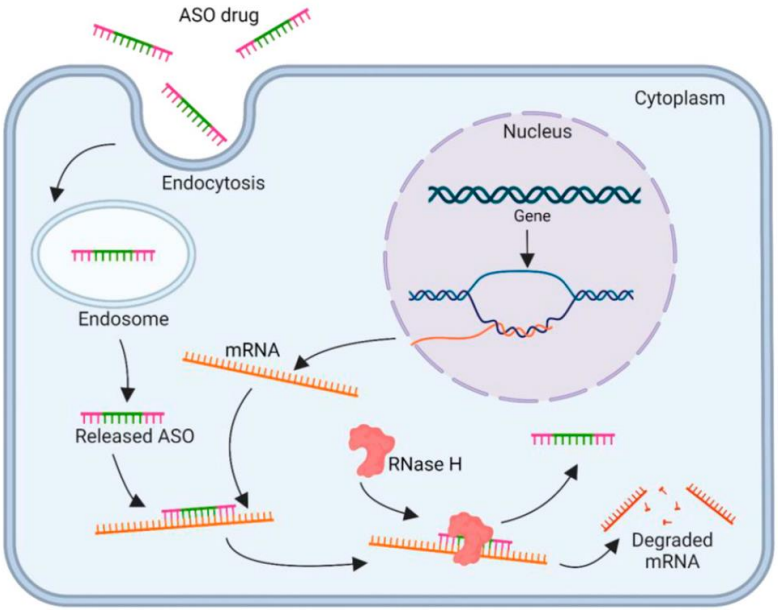
Presence of cardiac amyloidosis was associated with a **9.6-fold higher risk** of SDH (OR 9.6, 95% confidence interval 5.8-15.7).

Summary

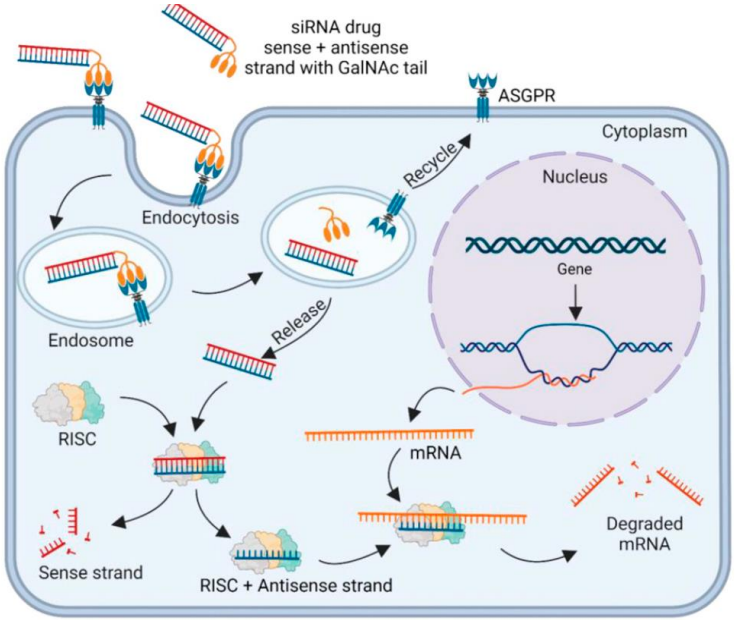
- Elucidation of the biology mechanism of disease development has led to several effective therapies for transthyretin amyloidosis.
- Ongoing clinical trials will provide invaluable insights in the safety and efficacy of novel agents for ATTR-CA.
- Providers and patients will be in an enviable position of choosing among available therapies, unfortunately without much data to guide selection.
- Neurologic and ocular manifestations of ATTR amyloidosis are the next frontier for therapeutic drug development.

Anti-Sense Oligonucleotides (ASO) and small Interfering RNA (siRNA) mediated TTR mRNA degradation.

ASO



siRNA



Pharmacol Rev. 2023 Dec 15;76(1):49-89.