Neuropathy and Amyloidosis

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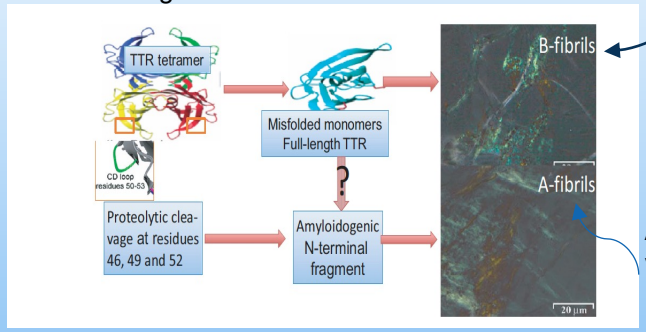
ARC

September 17, 2025

Disclosures

- Consultant to: Alnylum, Alexion, Astra-Zeneca, Bridge-Bio, Pfizer

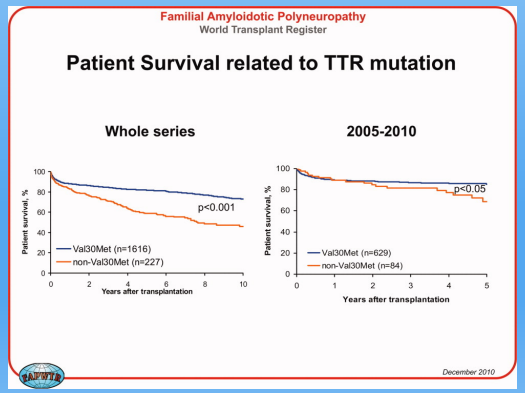
Amyloid A & B FIBRIL Fragments



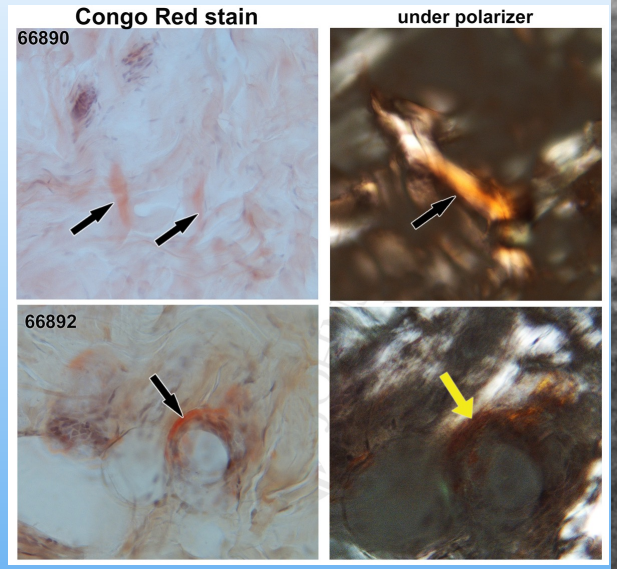
V30M

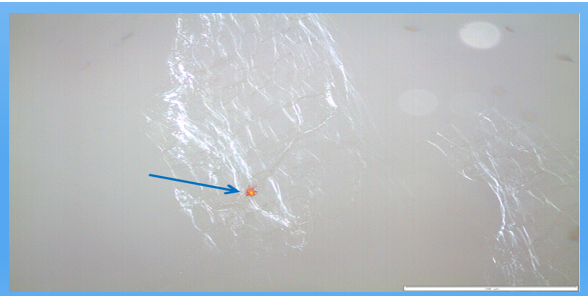
All other variants

Suhr OB, Lundgren E, Westermark. *J Intern Med*. 2017;281:337-347



Benson, M. *Muscle Nerve*. 2013;47(2):157-162





Journal of Internal Medicine, Volume: 281, Issue: 4, Pages: 337-347, First published: 17 January 2017, DOI: (10.1111/joim.12585)

Rudolph Virchow 1902

Frequency of Amyloid Types (N=16,175) 2008-2018

Type [a]	n	%	Age, y [b]	Sex (F/M/U)
AL	9542	58.99	64.4±11.3	3999/5463/80
ATTR	4600	28.44	74.4±8.7	661/3886/53
ALECT2	511	3.16	65.8±9.7	248/259/4
AA	463	2.86	57.5±14	221/239/3
AH	367	2.27	65.6±12.9	156/210/1
AIns	182	1.12	61.7±14	69/113/0
KRT5-14	94	0.58	60.9±14.4	51/42/1
AFib	71	0.44	62±10.5	23/48/0
AApoAIV	57	0.35	70.1±8.9	19/36/2
AApoAI	56	0.35	62.4±11.2	34/21/1
AANF	47	0.29	68.9±11.9	30/17/0
Aβ2M	38	0.23	66.5±12	14/23/1
ASem1	34	0.21	66.6±8.7	0/34/0
AGel	29	0.18	61.2±9.4	16/13/0
TGFBI	29	0.18	67.3±13.3	6/23/00
ALys	15	0.09	57.5±14.4	7/6/02
AIAPP	13	0.08	58.7±4.7	6/6/01
AApoCII	11	0.07	70.7±12.2	7/2/02
APro	8	0.05	44.5±11.4	3/3/02
AEnf	6	0.04	56.6±7.3	0/5/1
ACal	2	0.01	NA	0/2/0

41% non-immunoglobulin

Dasari et al Mayo Clinic Proceedings 2020; 95(9) 1852-64

THE CATEGORIES of AMYLOIDOSIS

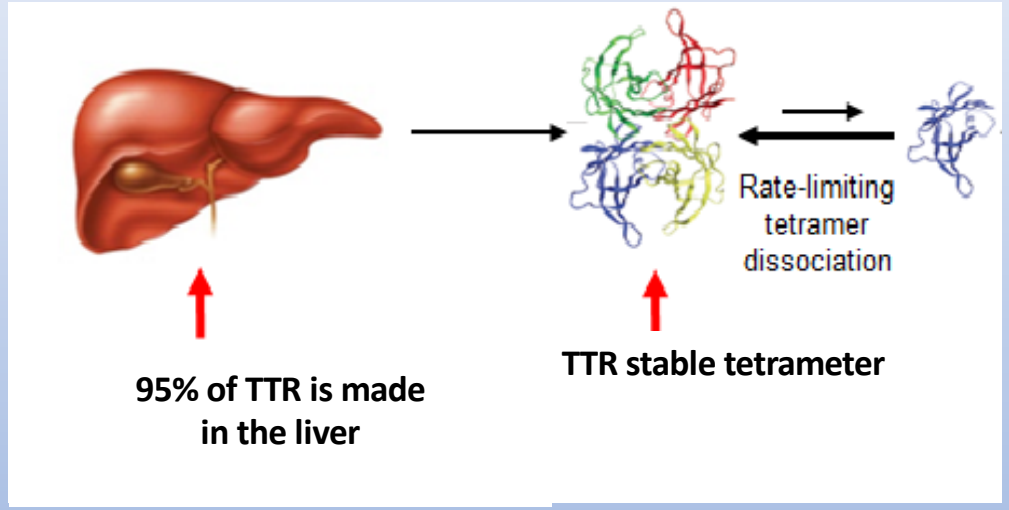
- HEREDITARY(VARIANT) – hATTR
  - FAMILIAL AMYLOID POLYNEUROPATHY (FAP)
  - FAMILIAL AMYLOID CARDIOMYOPATHY (FAC)
- ACQUIRED
  - AMYLOID WILD TYPE ~ ATTRwt
  - AMYLOID LIGHT CHAIN ~AL
  - SECONDARY AMYLOIDOSIS ~ RA (SERUM AMYLOID A PROTEINS [SAA])
  - MANY OTHER DISEASES ARE DUE TO AMYLOID PROTEINS

What Is Transthyretin?

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

1. Zhang KW et al. *JACC Basic Transl Sci*. 2019;4:438-448. 2. Robbins J. *Clin Chem Lab Med*. 2002;40:1183-1190.
3. Shetty NS et al. *Nat Commun*. 2024;15:6221. 4. Khella S et al. Low Transthyretin Level is Associated with Severe and Fatal Diseases: Insights from the UK Biobank Database. Presented at: 2025 Peripheral Nerve Society (PNS) Annual Meeting; May 17-20; Edinburgh, Scotland. P470.
5. https://www.uab.edu/news/research-innovation/uab-study-reveals-link-between-transthyretin-levels-and-heart-disease-risk

The Protein is Transthyretin (TTR)

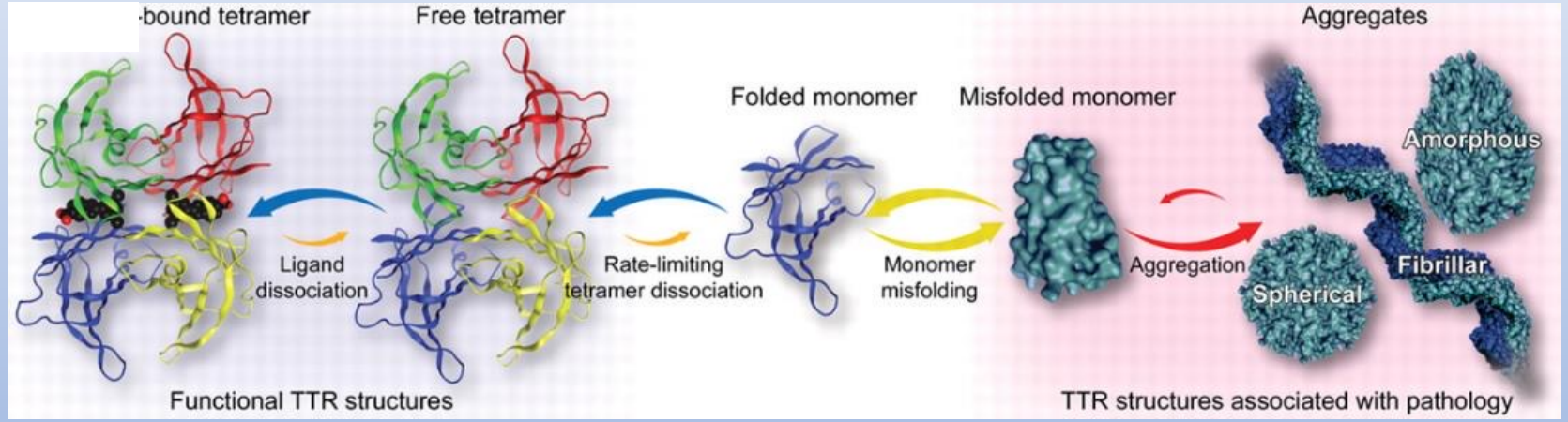


TTR carries vitamin A and Thyroxine hormone

Castano A et al. Emerging Therapies for Transthyretin Cardiac Amyloidosis Could Herald a New Era for the Treatment of HFPEF. Oct 14, 2015. https://www.acc.org/latest-in-cardiology/articles/2015/10/13/08/35/emerging-therapies-for-transthyretin-cardiac-amyloidosis. Accessed April 26, 2019.

Penn
University of Pennsylvania

Misfolded TTR: Making Amyloid



Penn
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Case example

- 74 AB yo F
- 2021 cold feet → now numb from knees to toes
- Was extremely active for 30 yrs, trouble walking 2023
- 2024 trouble going up steps → 2025 trouble going up a curb
- Using cane in October 2024 → unable to stand without assistance, bilateral foot drop
- Severe fatigue
- Diarrhea alternating with constipation
- Bp drops and gets light headed

Case continued

- EXAM

	ARM ABD	HIP FLEXORS	ANKLE D.FLEXORS	EXT HALLUCIS
	right/left	right/left	right/left	right/left
11/27/2024	4/ 4	4/4	2/2	
11/27/2024	4+/4+	4/4	4/4-	
4/22/2025	4/4+	4/4-	4/4-	3/3
7/14/2025	5/5	3/3	1/1	0/0

Data

Genetic Testing: c.250T>C (p.Phe84Leu)

NEGATIVE TESTS: FAT ASPIRATE
SKIN BIOPSY,

DATA

CARDIAC EVALUATION

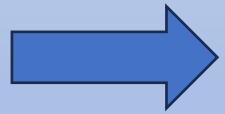
NT proBNP 3529 pg/ml

Troponin	2023	2025
	.02 (<0.04 ng/ml)	HS 36 (<14ng/ml)

2023 cardiac echo

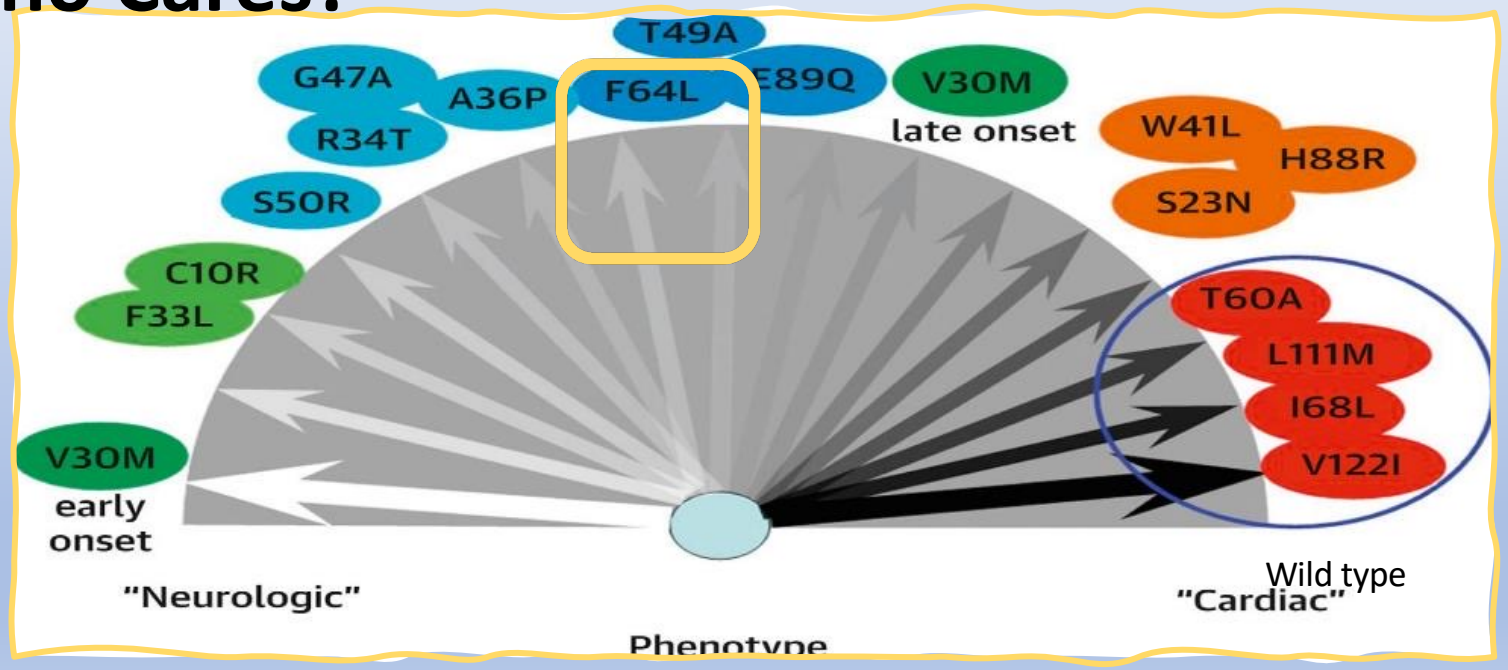
IVSd: 1.2 cm(nl 0.6-0.9 cm)

KAPPA QNT FREE LIGHT CHAINS	18.71
LAMBDA QNT FREE LIGHT CHAINS	10.98
K:L Ratio	1.70 High



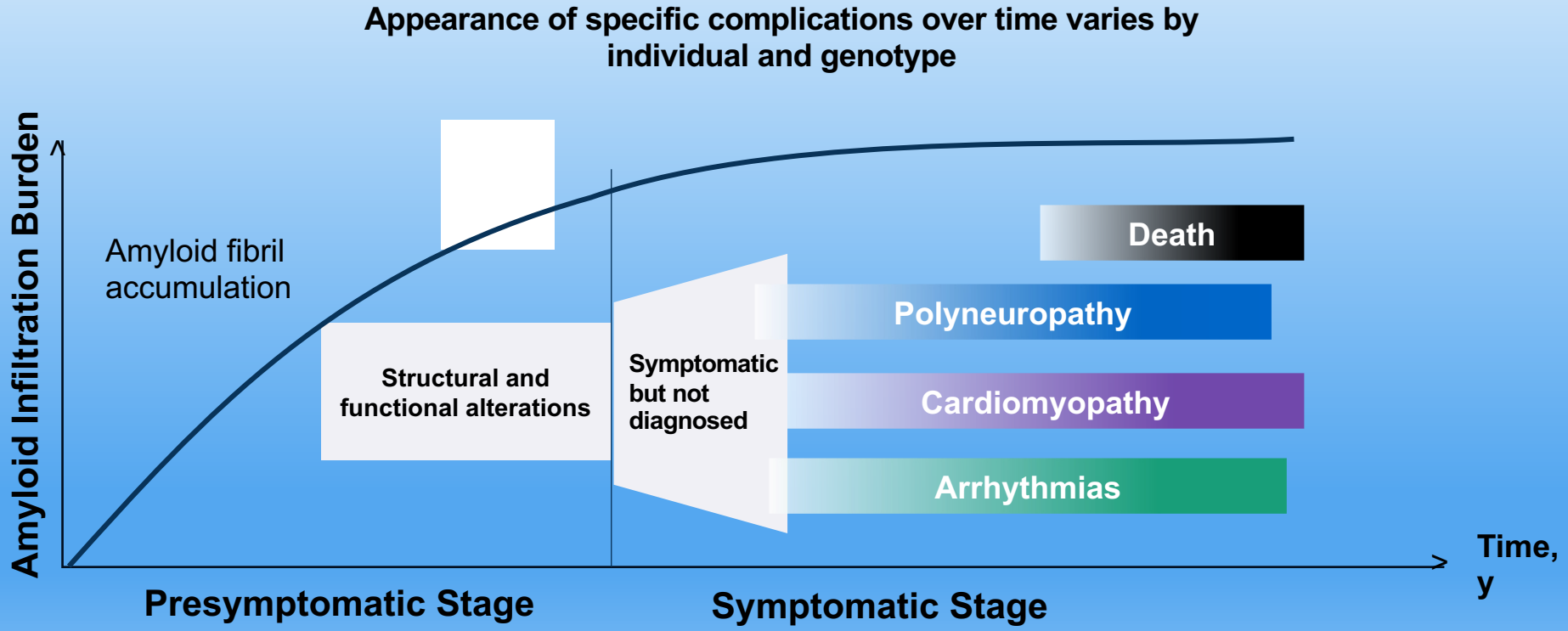
PYP SCAN

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



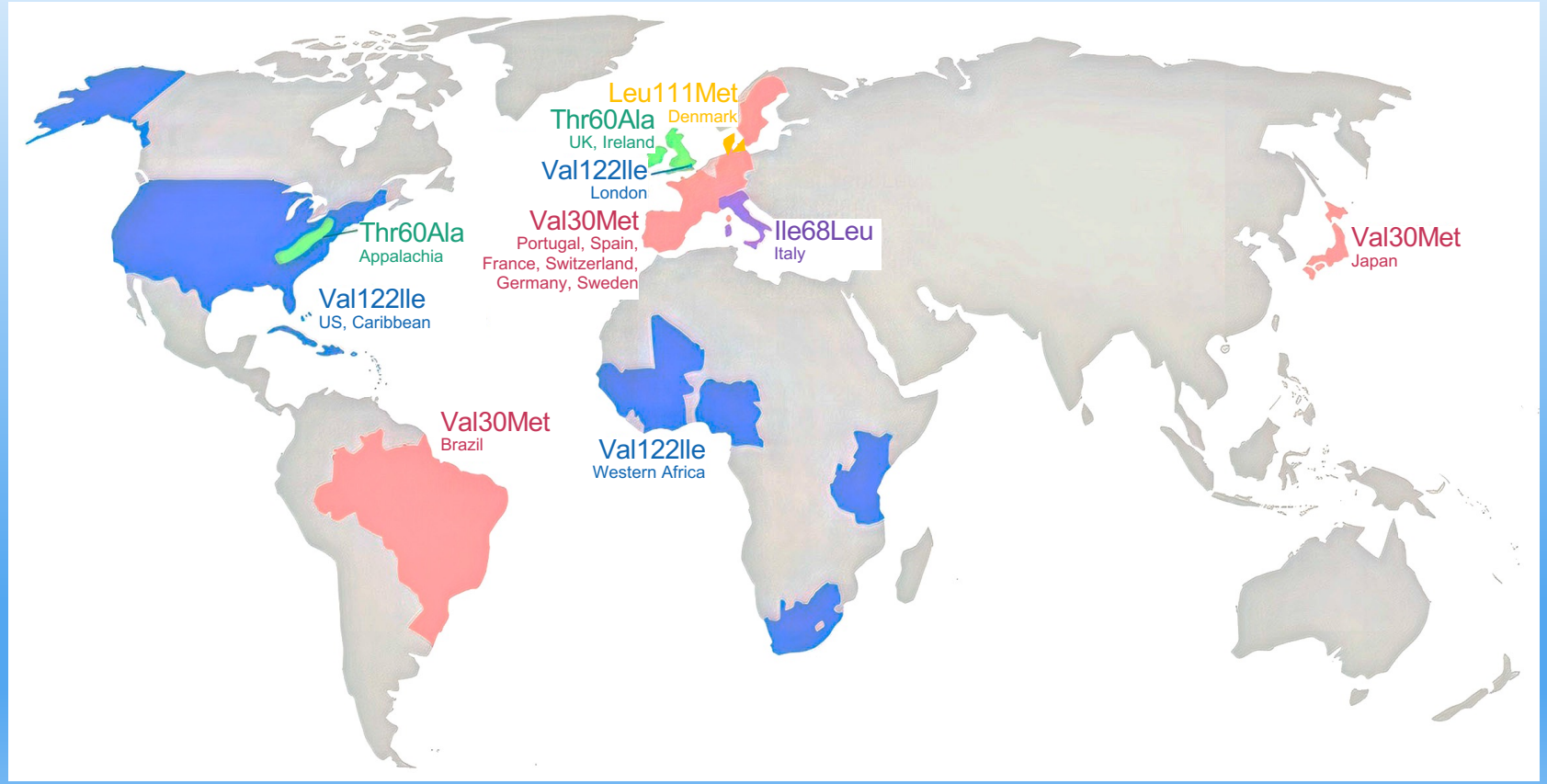
Rappezzi et al. *J Am Coll Cardiol.* 2015;66(21):2451-2466.

Natural History of ATTR[1-3]



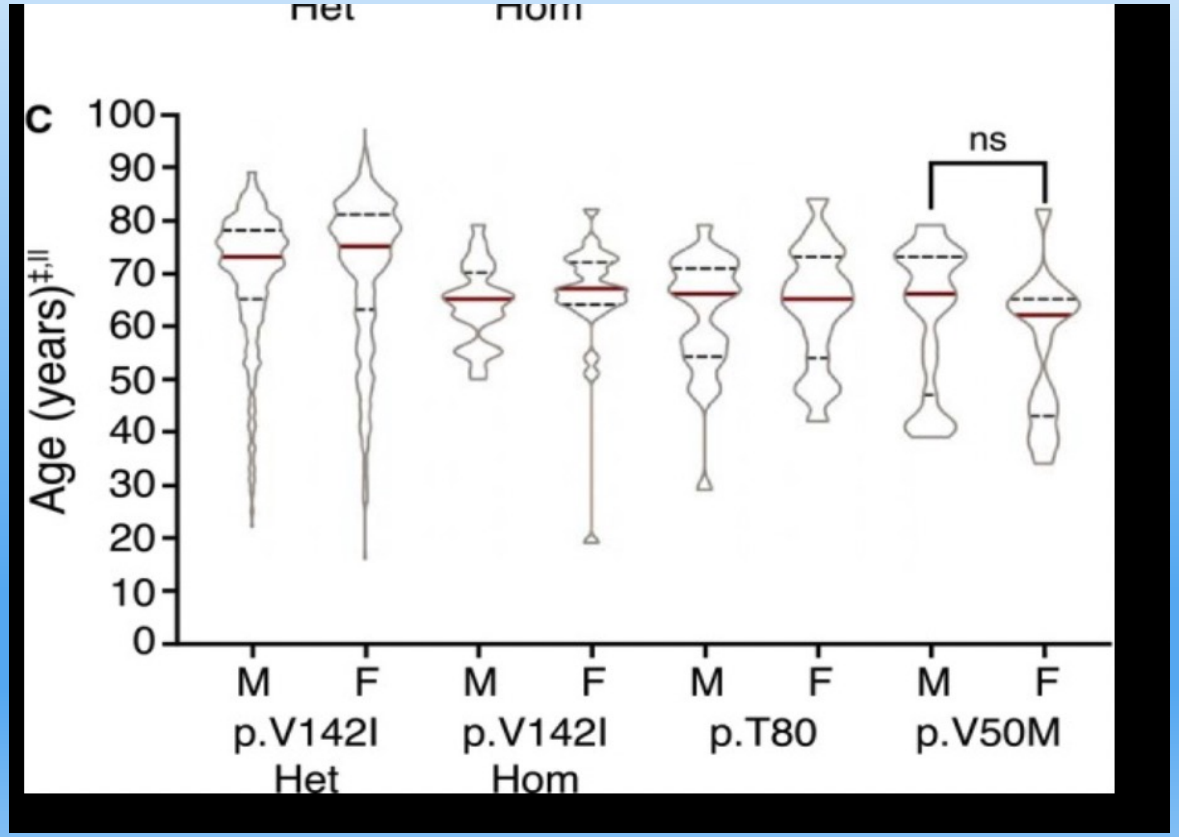
1. Aimo A et al. *Nat Rev Cardiol*. 2022;19:655-667. 2. Scirpa R et al. *Front Cardiovasc Med*. 2023;10:1151803.
3. Vera-Llonch M et al. *Orphanet J Rare Dis*. 2021;16:25.

# of ATTRv-CA Genotypes s[1]



1. Obi CA et al. *Methodist deBakey Cardiovasc J*. 2022;18:17-26.

Males and Females nearly equally affected



N=22,886 tested

V122I = 1,263

62.4% no family history

Bhatt K et al. *J Am Heart Assoc*. 2024;13:e033
Khella S et al *Neurology Journal 94 (15 S) 20*

Some ATTR Variants Are Not Rare in the United States[1-4]

The p.V142I (V122I) variant is the most common cause of ATTR-CA in the United States, but are underrepresented in clinical trials[5-7]

U.S. 3.2% of Blacks carry ATTRv p.V142I

- 23,338 self-identified Black individual4 cohorts
- 754 p.V142I carriers
- Variable penetrance

University of Pennsylvania Cohort 2020-2025

TTR 153

82 p.V142I

40% neuropathy

13% from Amyloidosis – upublished data

1. Selvaraj S et al. *JAMA*. 2024;331:1824-1833. 2. Kaniper S et al. *J Pers Med*. 2024;14:271. 3. Lopes LR et al. *Amyloid*. 2019;26:243-247.
4. Gentile L et al. *PLoS One*. 19:e0292435. 5. Ekpo E et al. *Amyloid*. 2024;31(Suppl 1):S141-S142. Abstract 343. 6. Gillmore JD et al. *N Engl J Med*. 2024;390:132-142.
7. Fontana et al. *N Engl J Med*. 2025;392:33-44.

Amyloid Neuropathy In p.V142I patients @ U. of Pennsylvania

Characteristic	p.V142I N = 82	non-p.V142I N = 71	p-value[1]	Overall N = 153
Age in years	63 (54,72)	60 (46,67)	0.067	61 (51,69)
Female	44 (54)	33 (46)	0.4	77 (50)
Race			**<0.001**	
African Descent	68 (83)	1 (1.4)		69 (45)
Caucasian	4 (4.9)	65 (92)		69 (45)
Asian	0 (0)	3 (4.2)		3 (2.0)
Other	3 (3.7)	0 (0)		3 (2.0)
Unknown	7 (8.5)	2 (2.8)		9 (5.9)
TTR targeted therapy	33 (40)	52 (73)	**<0.001**	85 (56)
Stabilizer	33 (40)	43 (61)	**0.022**	76 (50)
Silencer	16 (20)	36 (51)	**<0.001**	52 (34)
Mortality	6 (7.3)	5 (7.0)	>0.9	11 (7.2)
Comorbidities	48 (59)	19 (27)	**<0.001**	67 (44)
Diabetes	23 (28)	4 (5.7)	**<0.001**	27 (18)
History of B12 Deficiency	9 (11)	3 (4.3)	0.2	12 (7.9)
Alcohol Heavy Use or Abuse	4 (4.9)	2 (2.9)	0.7	6 (4.0)
Chronic Kidney Disease	28 (34)	9 (13)	**0.005**	37 (24)
Monoclonal Gammopathy (MGUS)	7 (13)	3 (6.3)	0.4	10 (9.7)
Nerve-toxic medications	12 (15)	2 (2.9)	**0.022**	14 (9.2)

[1] Wilcoxon rank sum test, Pearson's Chi-squared test, or Fisher's exact test with FDR correction for multiple testing

Dvorak, Row, Khella et al

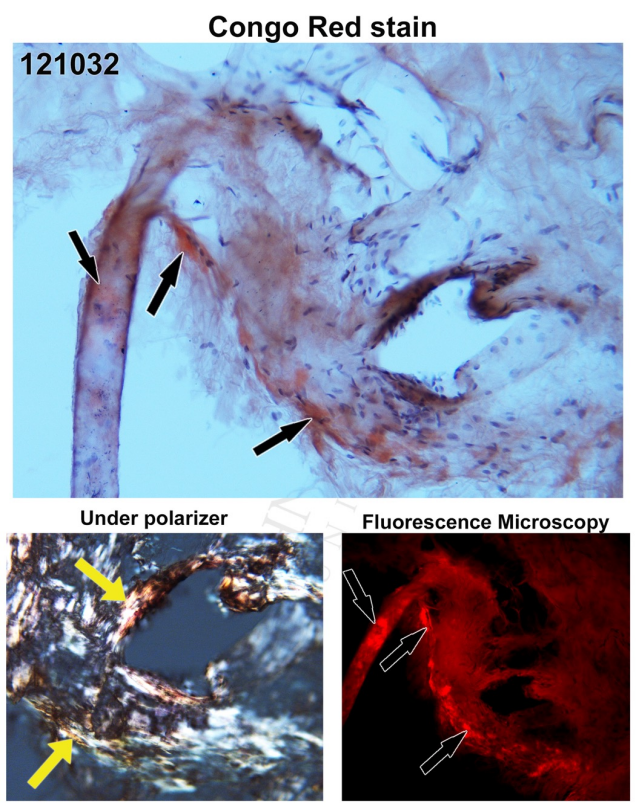
Unpublished data 2025

Red-Flag Signs/Symptoms/Medical History Raising Suspicion of ATTRv in Patients Presenting With Neuropathy[1]

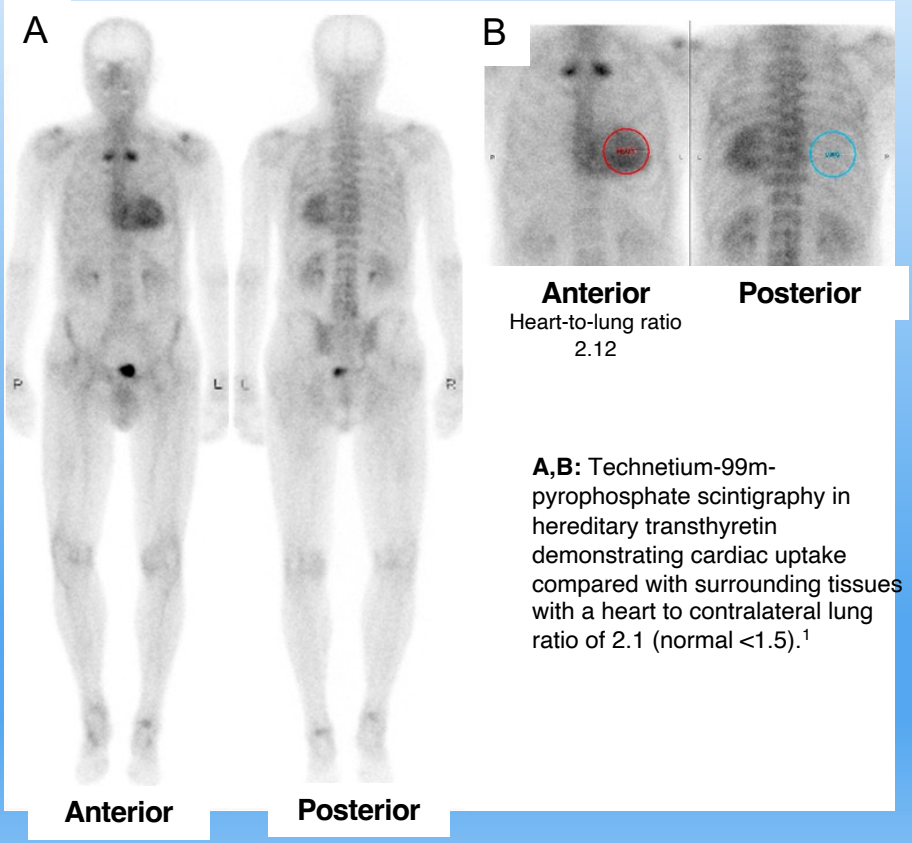
- Rapidly Progressive Neuropathy
- Heart Failure with preserved EF
- Prior history of Carpal Tunnel Syndrome
- Autonomic Symptoms
- Refractory CIDP (eg, IVIg for CIDP)

1. Karam C et al. *Muscle Nerve*. 2024;69:273-287.

DIAGNOSIS BY TISSUE SAMPLING OR CARDIAC IMAGING



Mass spectroscopy is used to identify and type the protein



Heart-to-lung ratio
2.12

A,B: Technetium-99m-pyrophosphate scintigraphy in hereditary transthyretin demonstrating cardiac uptake compared with surrounding tissues with a heart to contralateral lung ratio of 2.1 (normal <1.5).[1]

Congo red stain images courtesy of Sami Khella, MD.

1. Carroll A et al. *J Neurol Neurosurg Psychiatry*. 2022;93:668-678.

Is it Amyloid Neuropathy?

Characteristic	All p.V142I N = 82[1]	Cardiac Amyloidosis N = 31[1]	No Cardiac Amyloidosis N = 51[1]	p-value[2,3]
Evidence for Polyneuropathy	34 (41)	17 (55)	17 (33)	0.083
Possible Polyneuropathy	7 (8.5)	0 (0)	7 (14)	0.082
Probable Polyneuropathy	3 (3.7)	0 (0)	3 (5.9)	0.3
Probable subclinical	1 (1.2)	0 (0)	1 (2.0)	>0.9
Definite Polyneuropathy	24 (29)	17 (55)	7 (14)	**<0.001**
Definite subclinical	9 (11)	7 (23)	2 (3.9)	0.070

[1] n (%)
[2] False discovery rate correction for multiple testing
[3] Pearson's Chi-squared test or Fisher's exact test

Dvorak, Row, Khella et al

Unpublished data 2025

Definite – nerve bx + congo red stain

Probable Attribution – no other explanation

Possible Attribution – 1 comorbidity

AMYLOID VS CHRONIC INFLAMMATORY DEMYELINATING NEUROPATHY

AMYLOID NEUROPATHY

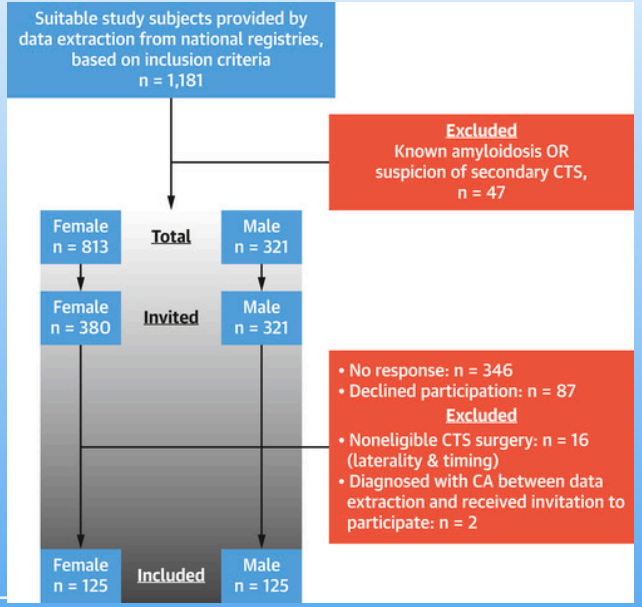
- DISTAL SYMMETRIC SENS-MOTOR
- PROXIMAL WEAKNESS
- DYSAUTONOMIA
- WEIGHT LOSS
- CHF WITH PRESERVED EF
- NO RESPONSE IVIG

CIDP

- DISTAL SYMMETRIC SENS-MOTOR
- PROXIMAL WEAKNESS
- NO AUTONOMIC SYMPTOMS
- NO WEIGHT LOSS
- NO CHF
- RAPID RESPONSE TO IVIG

Screening for Cardiac Amyloidosis 5 to 15 Years After Surgery for Bilateral Carpal Tunnel Syndrome

	CA (n = 12) (4.8 %)	Non-CA (n=238)	*P* Value
Demographics			
Age, y	80.9 (75.9-84.8)	69.8 (64.7-74.2)	<0.0001
Male	91.7	47.9	0.003
Years since CTS surgery	7.1 (6.4-8.1)	9.4 (7.6-11.6)	0.0006
Ruptured bicep tendon	41.7(17%)	6.7	0.001
Lumbar spinal stenosis	16.7	13.9	0.29



Oscar Westin et al. *J Am Coll Cardiol* 2022; 80:967-977.

CLINICAL PRESENTATION ATTR AMYLOIDOSIS

- (MOST VARIANTS & WT)
- EFFECT ON PENETRANCE/ANTICIPATION??
- LATE ONSET (JAPAN/SWEEDEN/PORTUGAL)
- SEVERE CARDIOMYOPATHY##
- PAINFUL SENSORY/MOTOR NEUROPATHY
- CARPAL TUNNEL
- SPINAL STENOSIS (ESPECIALLY IN WT?)

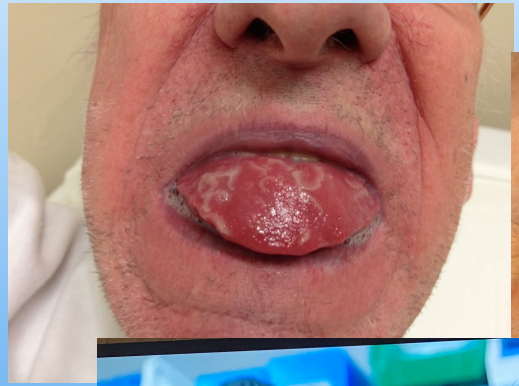
- (V30M)
- EFFECT ON PENETRANCE/ANTICIPATION??
- EARLY ONSET W/ NEUROPATHY (SWEEDEN/PORTUGAL)
- CARDIAC ARRHYTHMIA RATHER THAN ENLARGEMENT*
- DYSAUTONOMIA - NAUSEA/VOMITING/DIARRHEA&&
- ORTHOSTASIS

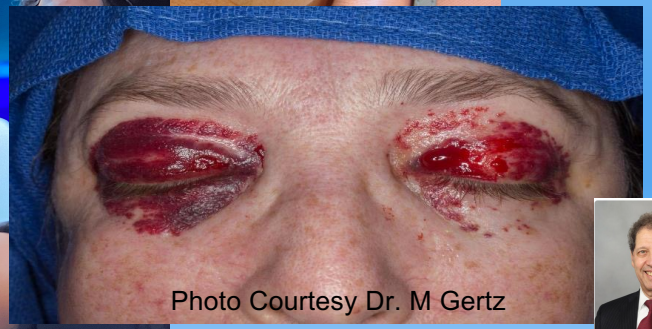
*Amyloid 2010; **17**: 63–8.

&&*Neurogastroenterol Motil* 2012; **24**: 1111–e568.

Amyloid 2006; **13**: 154–9.

Amyloidosis
Multisystem Disease





Ocular Findings

Cardiac Abnormalities

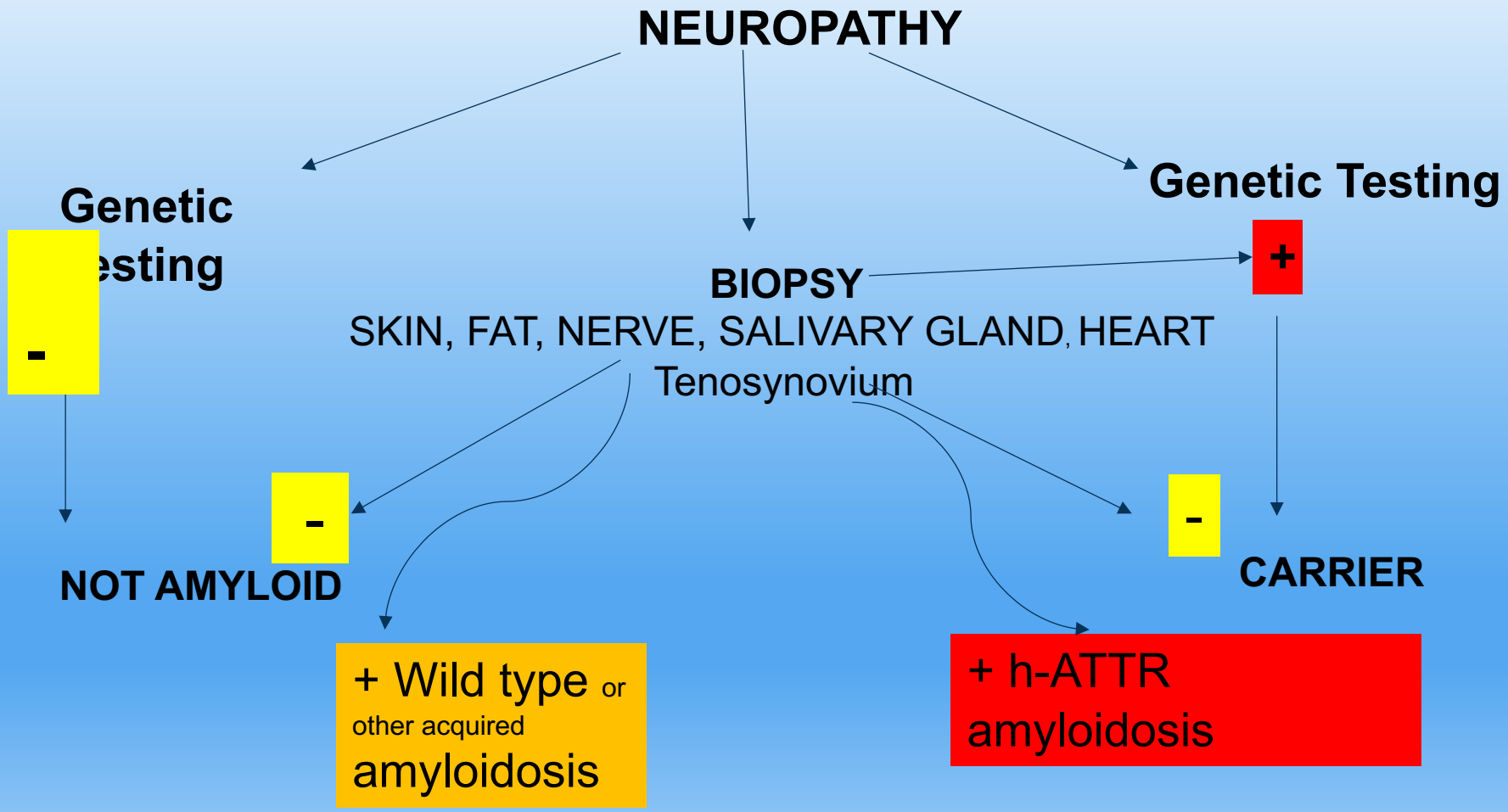
GI symptoms

Bilateral Carpal Tunnel Syndrome

Tendinopathies –biceps rupture

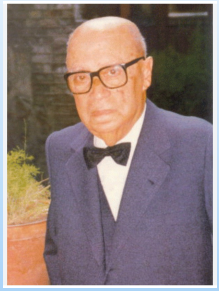
Autonomic Neuropathy

Peripheral Neuropathy


NEUROPATHY
Genetic
esting
-
NOT AMYLOID
BIOPSY
SKIN, FAT, NERVE, SALIVARY GLAND, HEART
Tenosynovium
-
+ Wild type or other acquired amyloidosis
Genetic Testing
+
-
CARRIER
+ h-ATTR amyloidosis

Evolving Approaches in ATTRv-PN Management

THERAPIES FOR HEREDITARY AMYLOID CARDIOMYOPATHY AND POLYNEUROPATHY



1952 Disease described
Corino Andrade

1990

Orthotopic
FAP
Liver transplantation

2008
j Kelley

Stabilize TTR

2012 2013
Tafamadis Diflunisal

European Patent
EP1988397A1

2018
FDA
Breakthrough
therapy

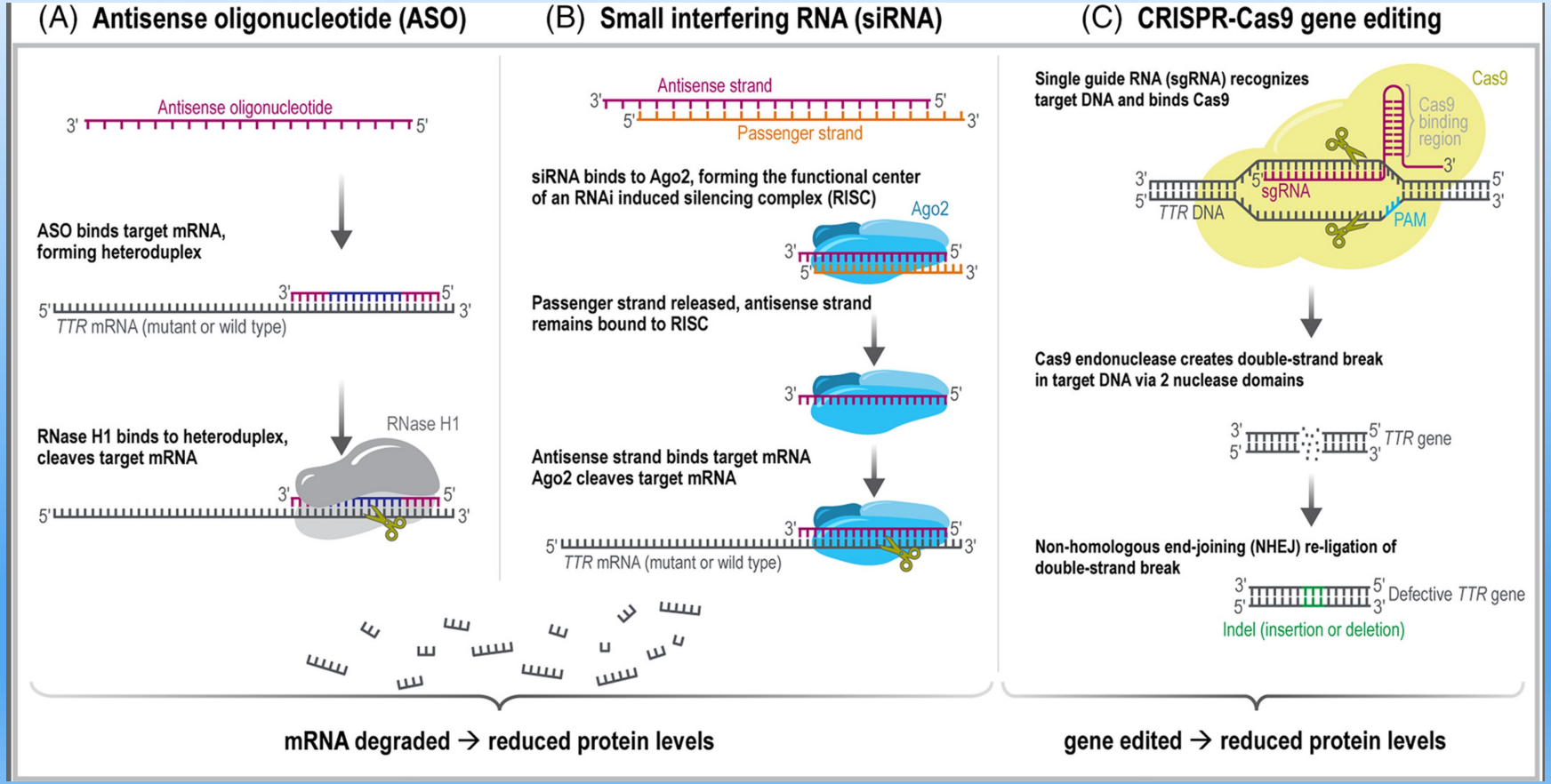
Europe FAP + 1°US
endpoint

Tafamadis FAC

FDA approval
Inotersen & Patiseran

2022 2023
Vutrisiran Eplontersen

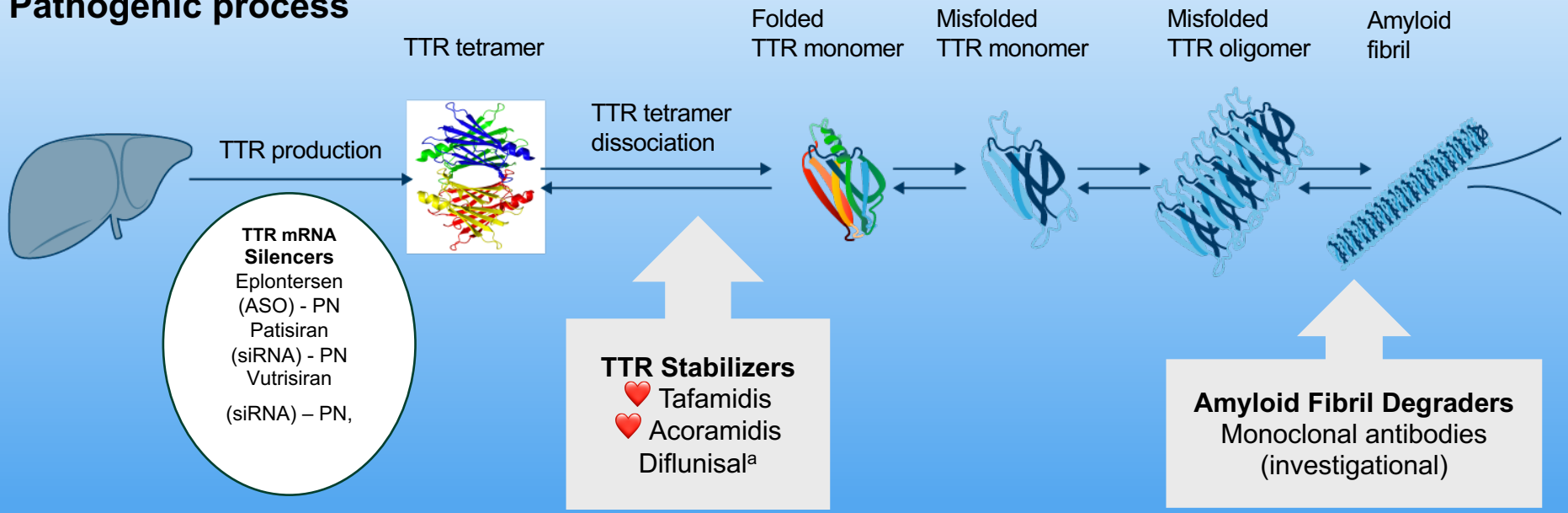
LESS RNA = LESS TTR PROTEIN



Brannagan TH et al. JPNS 2022; 27: 228-237

Therapies Targeting the Amyloidogenic Cascade[1-4]

Pathogenic process



Therapeutic Strategies and Mechanisms of Action

❤️ Indicated to treat ATTRwt-CA or ATTRv-CA. ✷ Indicated to treat ATTRv-PN. a Off-label use.

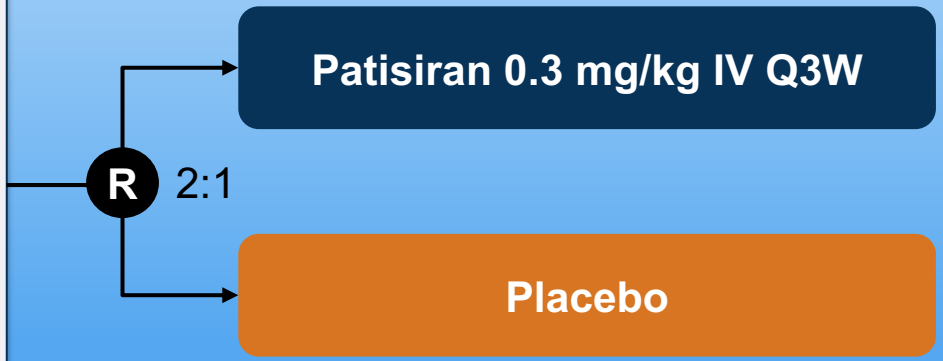
1. Adams D et al. *Nat Rev Neurol*. 2019;15:387-404. 2. Nativi-Nicolau et al. *Curr Opin Cardiol*. 2018;33:571-579.
3. Kadakia KT et al. *J Am Coll Cardiol*. 2025;85:1907-1910. 4. Berk JL et al. *JAMA*. 2013;310:2658-2667.

APOLLO: Design[1]

- Phase 3 RCT investigating change in neuropathy impairment on mNIS+7 (primary endpoint)
- Change in Norfolk QOL-DN, 10-m walk test, mBMI (secondary endpoints)

- Adults aged 18-85 y (62 y, median)
  - 21% North American
- Documented *TTR* variant
  - 1.4 y since diagnosis, median
  - 43% V30M
  - 0.9% V122I
- NIS 5 to 130
- Polyneuropathy Disability ≤ IIIb

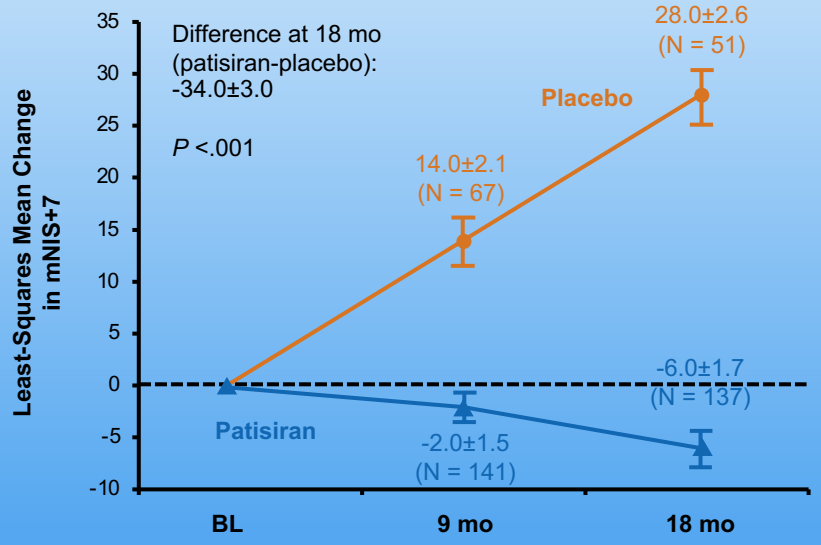
N = 225



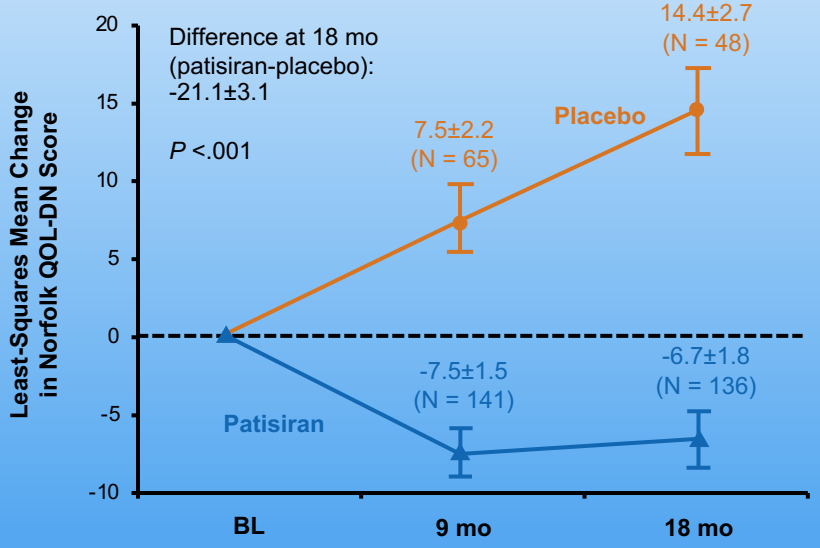
1. Adams D et al. *N Engl J Med*. 2018;379:11-21.

APOLLO: Primary and Secondary Endpoints[1]

mNIS+7



Norfolk QOL-DN Score



Baseline mNIS+7: 89.9 ± 41.5 patisiran
74.6 ± 37.0 placebo

Patisiran was statistically significantly better than placebo on all endpoints

1. Adams D et al. *N Engl J Med*. 2018;379:11-21.

APOLLO: Safety[1]

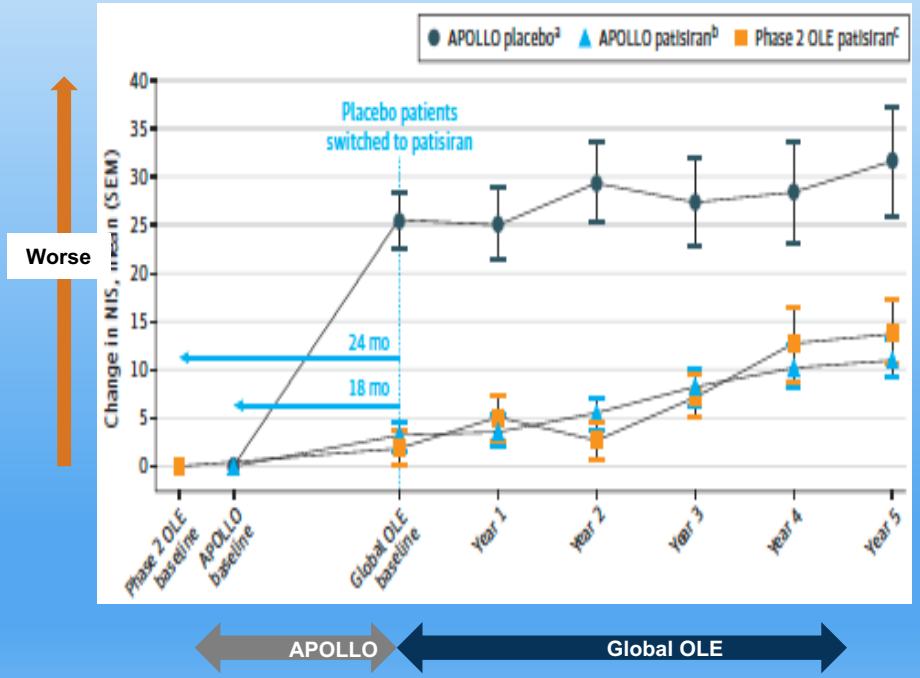
Event, n (%)	Placebo (n = 77)	Patisiran (n = 148)
Any AE	75 (97)	143 (97)
AEs occurring in ≥10% of patients in either group		
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	44 (30)
Fall	22 (29)	25 (17)
Nausea	16 (21)	22 (15)
Infusion-related reaction	7 (9)	28 (19)
Constipation	13 (17)	22 (15)
UTI	14 (18)	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	11 (14)	5 (3)
Anemia	8 (10)	3 (2)
Syncope	8 (10)	3 (2)

Event, n (%)	Placebo (n = 77)	Patisiran (n = 148)
AE leading to discontinuation of the trial regimen	11 (14)	7 (5)
AE leading to withdrawal from the trial	9 (12)	7 (5)
Death	6 (8)	7 (5)
Any serious AE	31 (40)	54 (36)
Any severe AE	28 (36)	42 (28)

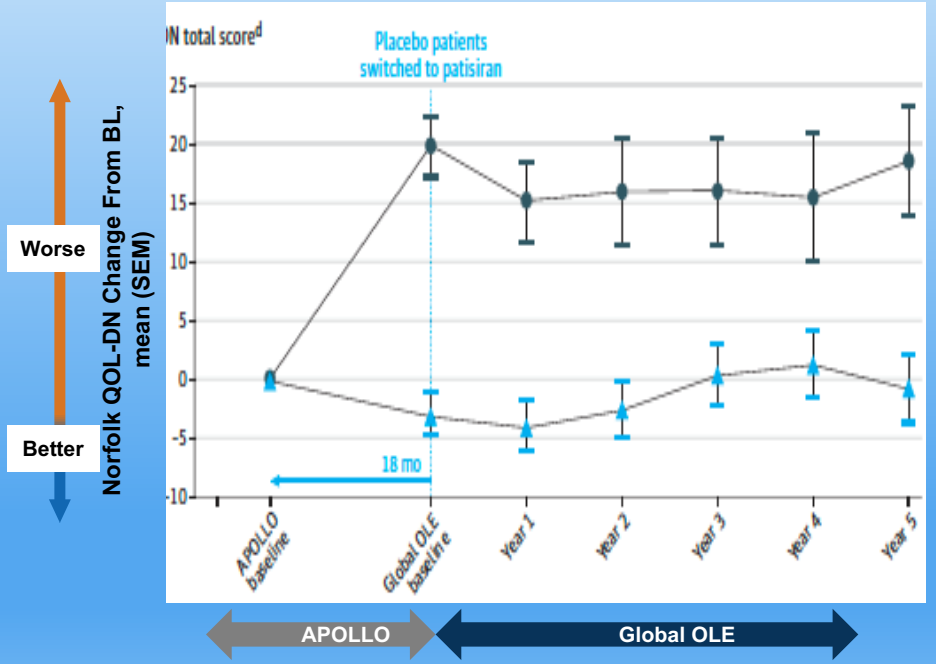
1. Adams D et al. *N Engl J Med*. 2018;379:11-21.

APOLLO OLE: Efficacy at 5 Years[1]

Total NIS[a]



Norfolk QOL-DN



[a] mNIS=7, primary endpoint.

1. Adams D et al. *JAMA Neurol*. 2025;82:228-236.

HELIOS-A: Design[1]

- 18-month RCT study investigating change in neuropathy impairment on mNIS+7
- Primary endpoint assessed at 9 months; all patients eligible to receive vutrisiran after 18 mo

- Adults aged 18-85 y (60 y, median)
  - ~17.6% North American
- Documented *TTR* variant
  - 2.2 y since diagnosis, median
  - 45.1% V30M
  - 4.3% V122I
- NIS 5 to 130
- Polyneuropathy Disability ≤IIIb
- Karnofsky Performance Status score ≥60%

N = 164

R 3:1

Vutrisiran 25 mg SC Q3M

Patisiran 0.3 mg/kg IV Q3W

Premedication 60 min prior to infusion

- Historical controls from APOLLO
- Similar eligibility and endpoints

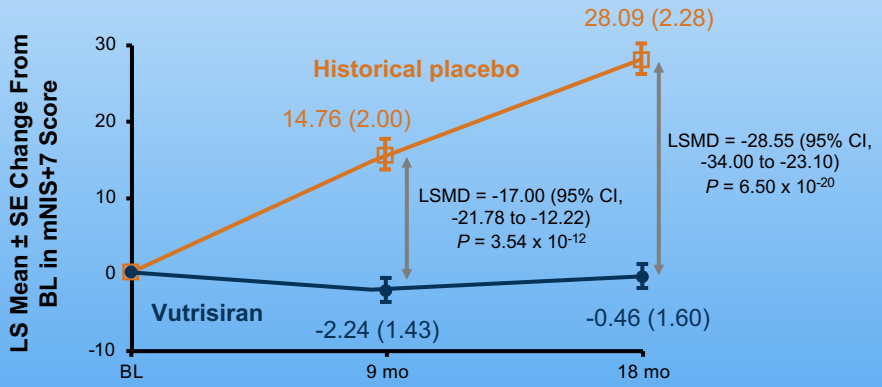
N = 77

Historical placebo

1. Adams D et al. *Amyloid*. 2023;30:1-9.

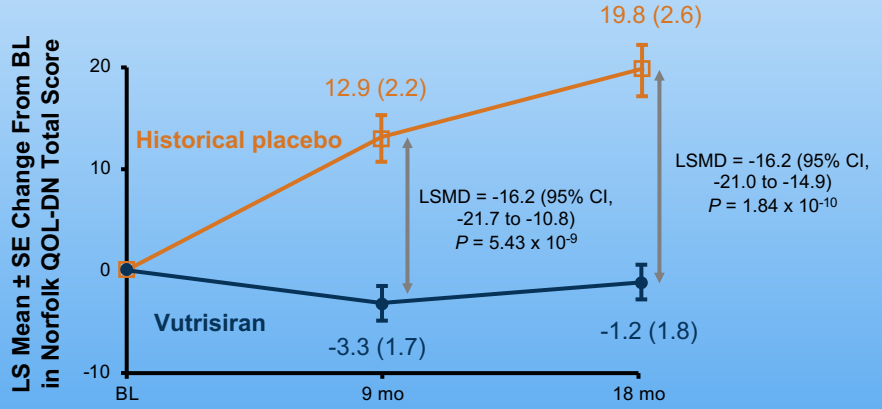
HELIOS-A: Primary and Secondary Endpoints[1]

mNIS+7



No. at Risk			
Vutrisiran	122	114	112
Historical placebo	77	67	51

Norfolk QOL-DN



No. at Risk			
Vutrisiran	121	114	111
Historical placebo	76	65	48

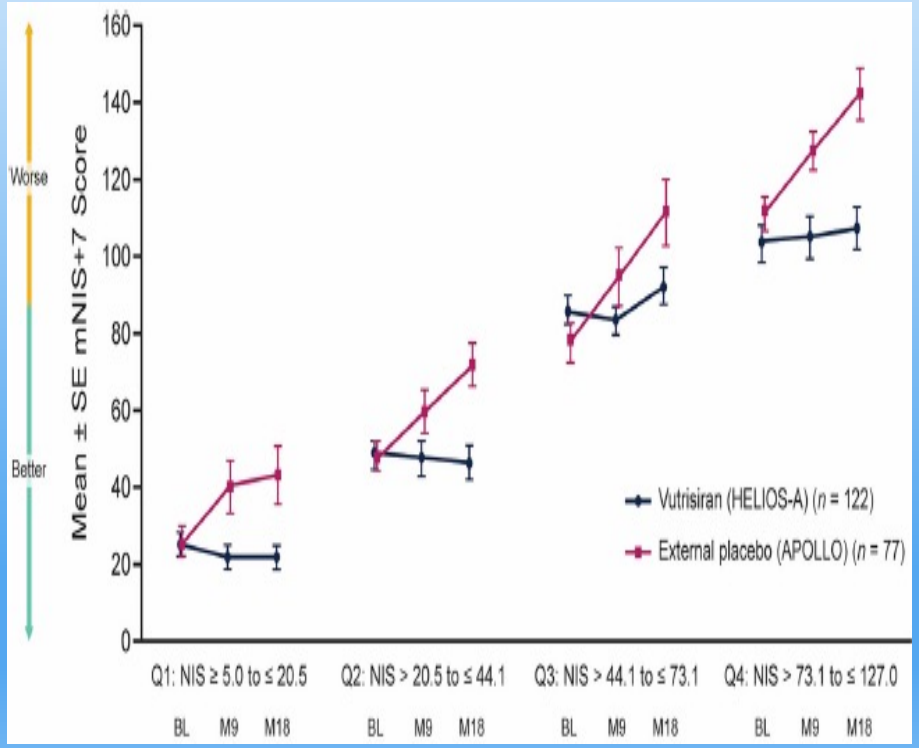
Baseline

- 60.6 ± 36 vutrisiran
- 74.6 ± 37 placebo

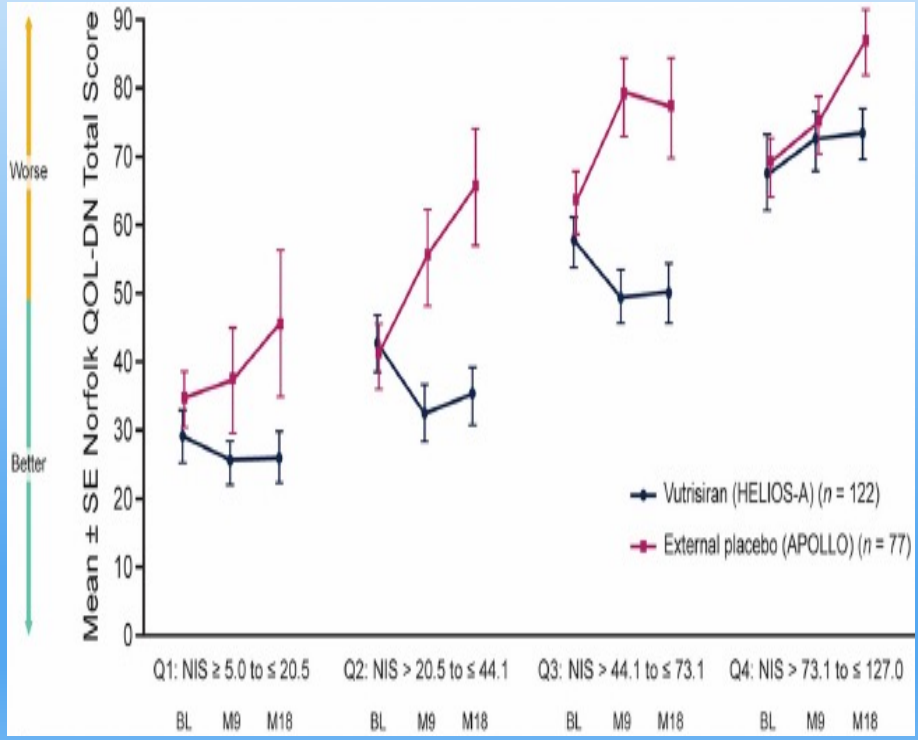
1. Adams D et al. *Amyloid*. 2023;30:1-9.

HELIOS-A: Primary and Secondary Endpoints Stratified by Baseline Neuropathy Severity[1]

mNIS+7



Norfolk QOL-DN



1. Luigetti M et al. *Neurol Ther*. 2024;13:625-639.

HELIOS-A: Safety[1]

At Least One Event, n (%)	APOLLO	HELIOS-A	
	Placebo (n = 77)	Vutrisiran (n = 122)	Patisiran (n = 42)
Summary of AEs			
Any AE	75 (97.4)	119 (97.5)	41 (97.6)
Serious AEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)
AEs occurring in ≥10% in vutrisiran-treated patients			
Fall	22 (28.6)	22 (18.0)	6 (14.3)
Pain in extremity	8 (10.4)	18 (14.8)	3 (7.1)
Diarrhea	29 (37.7)	17 (13.9)	7 (16.7)
Edema peripheral	17 (22.1)	16 (13.1)	4 (9.5)
UTI	14 (18.2)	16 (13.1)	8 (19.0)
Arthralgia	0	13 (10.7)	4 (9.5)
Dizziness	11 (14.3)	13 (10.7)	0

1. Adams D et al. *Amyloid*. 2023;30:1-9.

NEURO-TTRansform Trial Design[1,a]

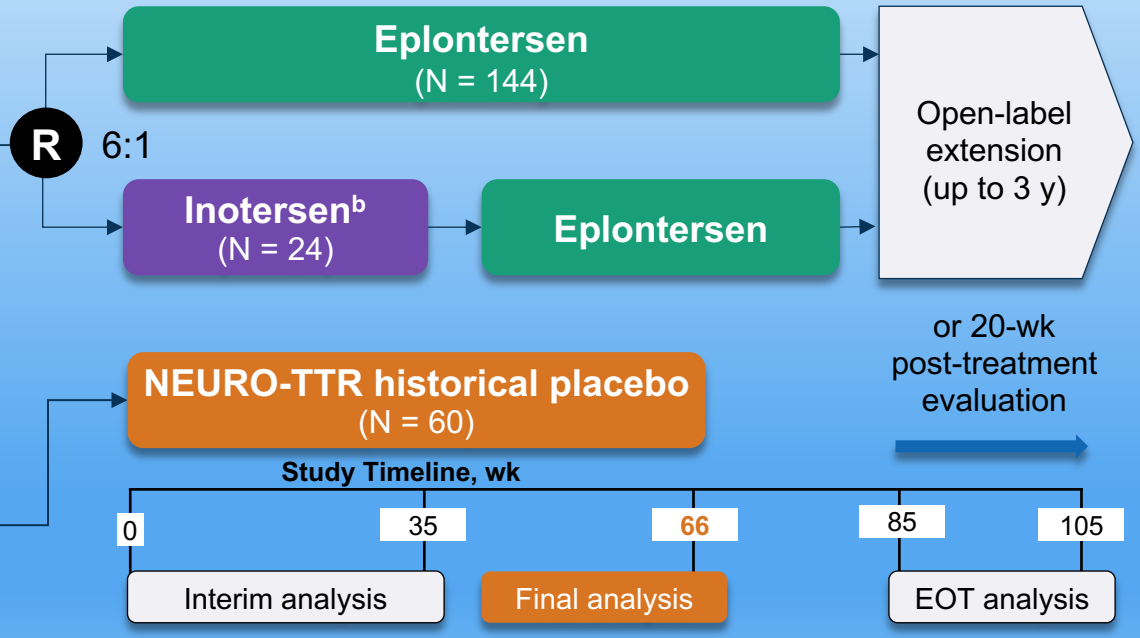
Phase 3 study evaluating eplontersen in ATTRv-PN compared with historical placebo

- Adults aged 18-82 years
  - 53 y, mean
  - 15% North American
- ATTRv-PN with documented sequence variant
  - 2.5 y since diagnosis, mean
  - 59% V30M, 3% V122I
- NIS 10-130 points
- Coutinho stage 1 or 2[a]

N = 168

- Historical controls
- Placebo group from week 66 endpoint of phase 3 RCT (NEURO-TTR)

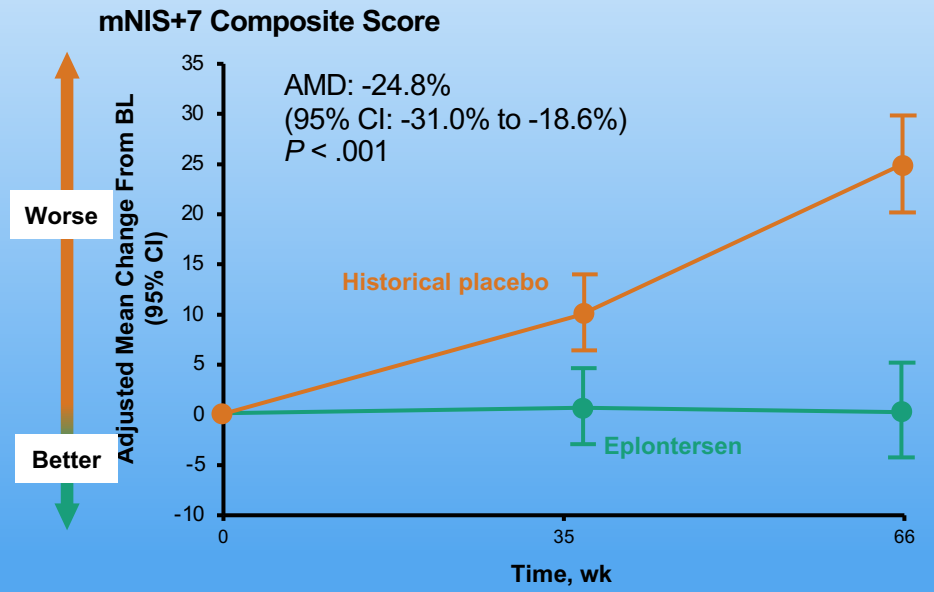
N = 60

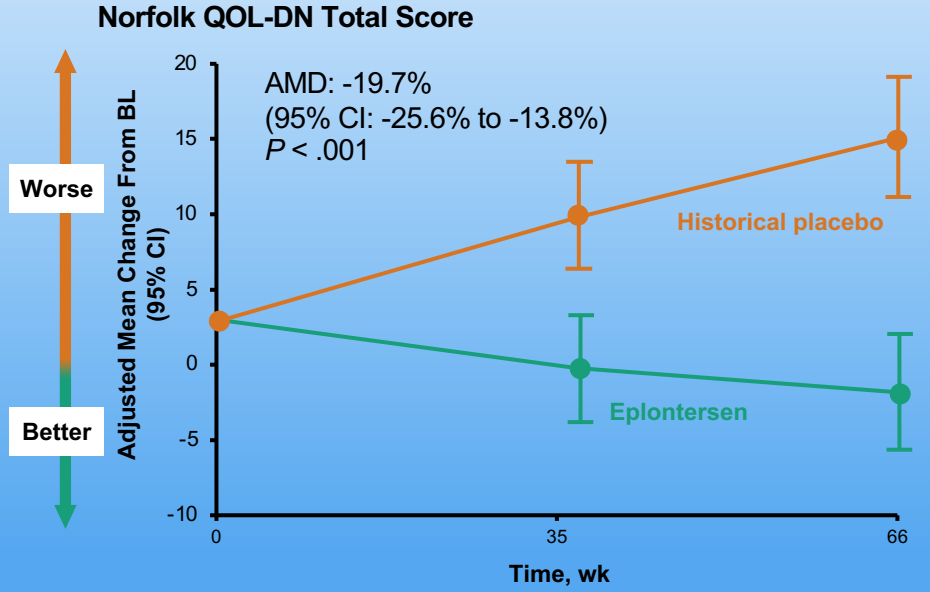


[a] Coutinho stage 1, ambulatory without assistance; Coutinho stage 2, ambulatory with assistance; NIS, Neuropathy Impairment Score, score range 0-244, higher values indicate poorer function. [b] Inotersen is no longer available in the United States.

1. Coelho T et al. *JAMA*. 2023;330:1448-1458.

NEURO-TTRansform: Primary Endpoints at 66 Weeks[1]





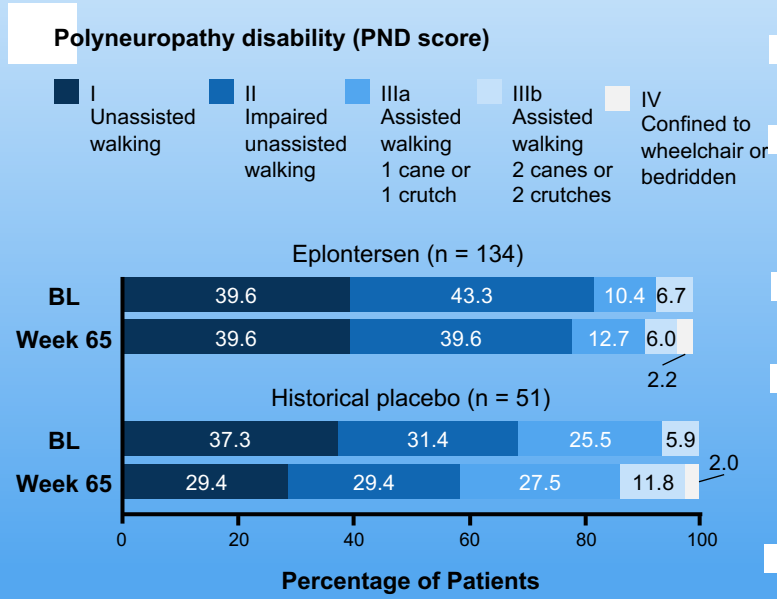
Baseline mNIS+7

- 81.3 ± 43.4 eplontersen
- 74.8 ± 39.0 historical placebo

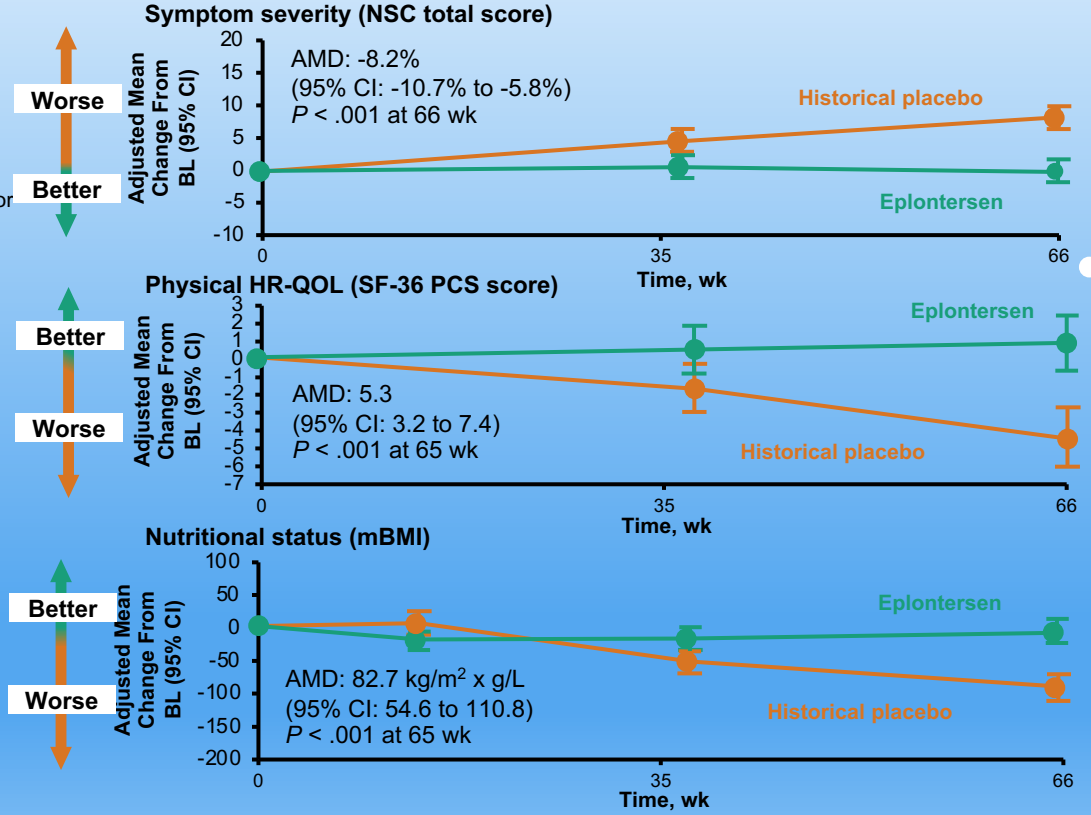
Means, filled circles; medians, open diamonds, first/third quartiles, lower and upper ends of whiskers; AMD, adjusted mean difference.

1. Coelho T et al. *JAMA*. 2023;330:1448-1458.

NEURO-TTRansform: Secondary Endpoints at 65-66 Weeks[1]



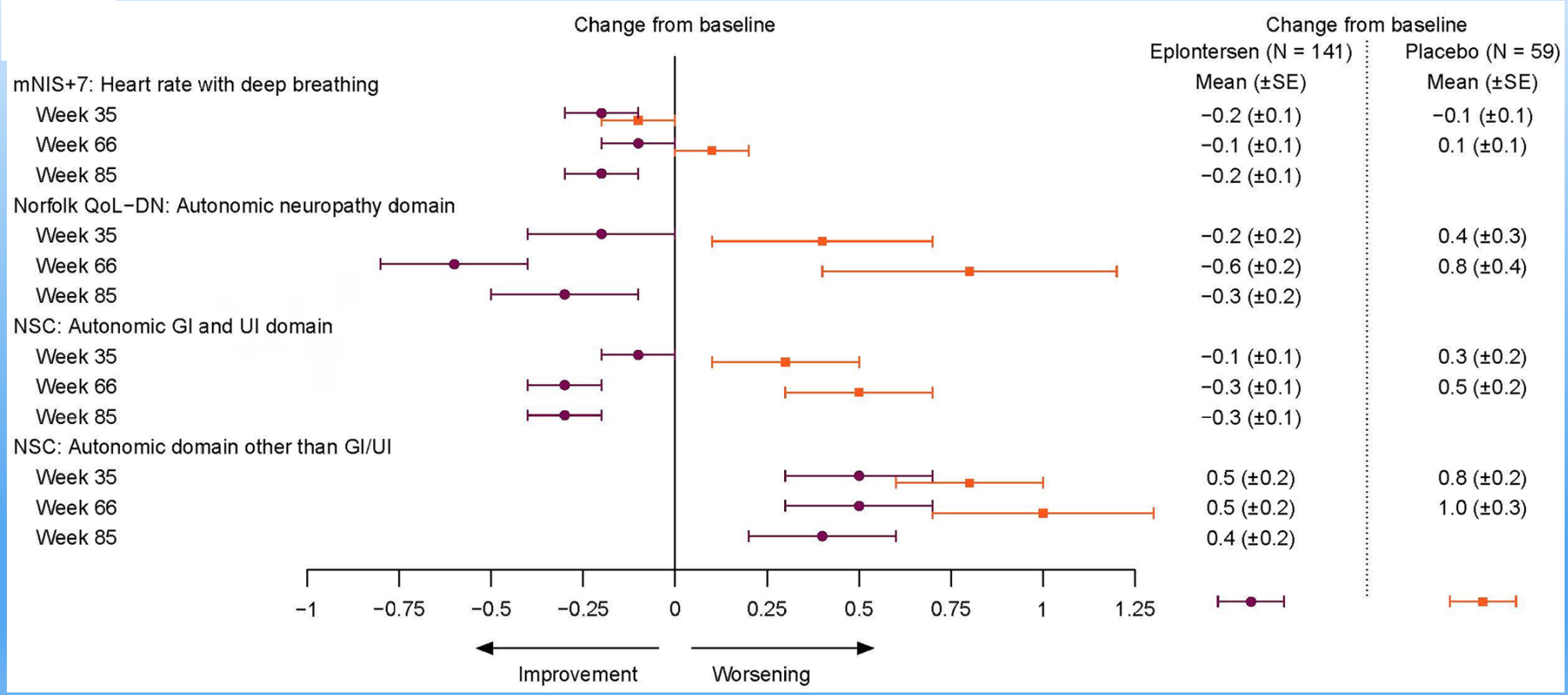
Eplontersen vs historical controls, *P* < .05 at week 65



Means, filled circles; medians, open diamonds, first/third quartiles, lower and upper ends of whiskers; AMD, adjusted mean difference.

1. Coelho T et al. *JAMA*. 2023;330:1448-1458.

NEURO-TTRansform: Effects of Eplontersen on Symptoms of Autonomic Neuropathy[1]



1. Wixner J et al. *Amyloid*. 2025;32:29-38.

NEURO-TTRansform: Safety[1]

n (%)	Eplontersen (n = 144)	Historical Placebo (n = 60)
Any TEAE	140 (97)	60 (100)
Leading to study drug discontinuation	6 (4)	2 (3)
Maximum severity of TEAEs		
Mild	74 (51)	7 (12)
Moderate	53 (37)	40 (67)
Severe	13 (9)	13 (22)
AEs of special interest	41 (29)	12 (20)
Vitamin A deficiency/decreased/abnormal	23 (16)	NR
Ocular events potentially related to vitamin A deficiency	24 (17)	9 (15)
Thrombocytopenia	3 (2)	1 (2)
Glomerulonephritis	0	2 93)
Leading to study drug discontinuation	0	0
Injection-site reactions	12 (8)	7 (12)
Flu-like symptoms	0	2 (3)
Abnormal liver function	9 (6)	4 (7)
Any serious TEAE	21 (15)	12 (20)
Related to study drug	0	1 (2)
Death	2(1)	0
Death due to study drug	0	0

1. Coelho T et al. *JAMA*. 2023;330:1448-1458.

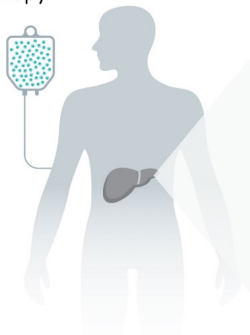
Individualizing Current Targeted Treatments for ATTRv-PN[1]

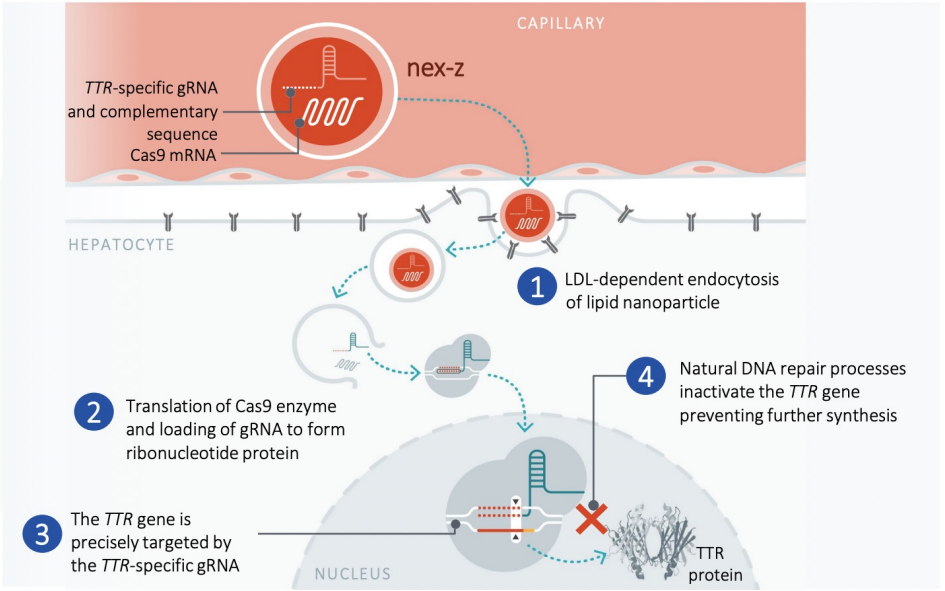
	Agent	Administration and Route	Vitamin A Supplement Needed?	Cardio-myopathy indication?	Neuropathy Indication?	Most Common AEs in Clinical Trials
Silencers	Eplontersen	SC injection once monthly via autoinjector	Yes	FDA Fast Track	Yes	↓Vitamin A, vomiting
	Patisiran	Lipid complex injection via IV infusion every 3 weeks; premedication needed	Yes	No	Yes	Upper respiratory tract infection, infusion-related reactions
	Vutrisiran[3]	SC injection, every 3 months at infusion clinic; no premedication needed	Yes	Yes	Yes	Pain in extremity, arthralgia, dyspnea, ↓Vitamin A

1. Wainua PI
2. Onpattro PI
3. Amvuttra (vutrisiran) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215515s006lbl.pdf.

Nex-z, an *In Vivo* Investigational CRISPR/Cas9 Therapy, Inactivates the *TTR* Gene, Whether Wild-Type or Variant, With a One-Time Treatment[1,2]

A one-time IV infusion delivered over 4 hours is used to administer nex-z, a CRISPR/Cas9 gene editing therapy





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

1. Gillmore JD, et al. *N Engl J Med*. 2021;385(6):493-502. 2. Fontana M, et al. *N Engl J Med.* 2024;391(23):2231-2241.

Two-Part, Open-Label, Multicenter Phase 1 Study

Adults (aged 18-80 years) with hereditary ATTR amyloidosis with polyneuropathy (ATTRv-PN)[a] including patients previously progressing on patisiran[b]

INTERVENTION
Single-dose nex-z administered via an IV infusion

PART 1: Single-Ascending Dose

- 0.1 mg/kg (n=3)
- 0.3 mg/kg (n=3)
- 0.7 mg/kg (n=3)
- 1.0 mg/kg (n=6)

N=15

PART 2: Dose Expansion

- 55 mg (n=16)
- 80 mg (n=5)

N=21

PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- *Measure serum TTR levels*

SELECT SECONDARY OBJECTIVES

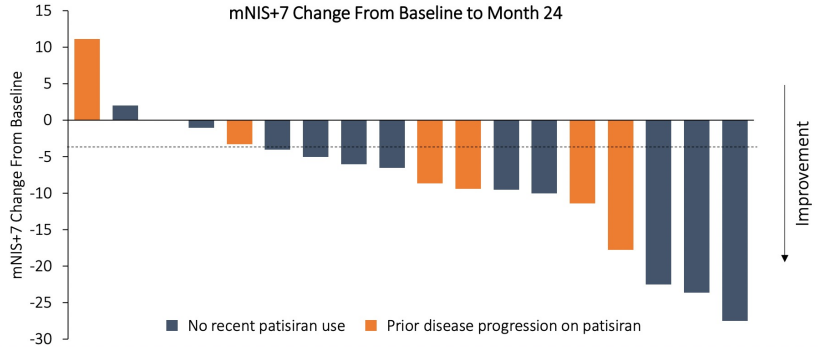
Evaluate efficacy on clinical measures of:

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

[a]Other inclusion criteria included body weight of ≥45 kg at screening visit, lack of access to approved ATTR and/or progression of ATTRv-PN despite use of approved treatments for the disease. Exclusion criteria included amyloidosis attributable to non-TTR protein (eg, AL amyloidosis), known leptomeningeal ATTR, and use of TTR-directed therapy for ATTR within a certain timeframe (ie, patisiran, inotersen, vutrisiran, tafamidis, diflunisal, doxycycline, tauroursodeoxycholic acid, or any other investigational agent for the treatment of ATTR-PN).
[b]Disease progression on patisiran per investigator assessment and criteria established per protocol.
AL, light chain; 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; TTR, transthyretin.
Clinicaltrials.gov. Accessed May 9, 2025. https://clinicaltrials.gov/study/NCT04601051.

CRISPER phase I results

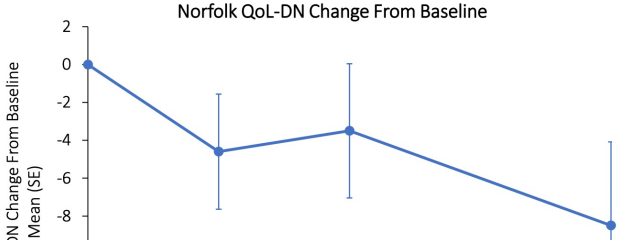
At Month 24, the Majority of Patients Experienced Improvements in mNIS+7 After a Single Dose of Nex-z



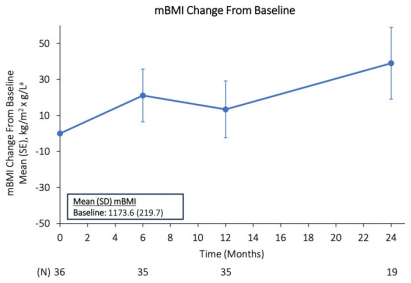
72% of patients treated with nex-z experienced a clinically meaningful improvement (reduction of ≥4 points[1]) in mNIS+7

Dotted line indicates cutoff for clinically meaningful improvement.[1]

Reductions in Norfolk QoL-DN Scores Demonstrate Improvement in Patient QoL



Increases in mBMI Over 2 Years Indicative of Disease Stability or Improvement



cutoff August 21, 2024.
[a] is calculated as BMI (kg/m²) × albumin (g/L).
%, modified body mass index.

CRISPER Safety

Summary of Safety

Event, n (%)	N=36
≥1 AE	36 (100)
AEs occurring in ≥15% of participants	
Infusion-related reaction	21 (58)
Headache	10 (28)
Diarrhea	8 (22)
Thyroxine decreased[a]	8 (22)
AST increased[b]	6 (17)
TRAEs occurring in ≥10% of participants	
Infusion-related reaction	21 (58)
Thyroxine decreased	8 (22)
Headache	4 (11)
Any AE leading to treatment discontinuation	0
Any AE leading to death	1[c] (3)
Any SAE	10 (28)
SAEs occurring in ≥5% of participants	0

- Infusion-related reactions were the most common AE—all were considered mild to moderate in severity and resolved without sequelae. All participants received the completed planned dose
- Any liver enzyme elevations resolved spontaneously, were asymptomatic, not considered serious, and required no intervention (eg, steroids) or hospitalization[b]
- Safety in patients who had switched from patisiran to nex-z is comparable to the overall study population

No vitamin A data

Data cutoff August 21, 2024. Median (min, max) follow-up for safety was 24 months (9, 38). AEs are presented by preferred term and were coded using *Medical Dictionary for Regulatory Activities*, version 26.0. For each preferred term, participants reporting ≥1 AE are counted only once. [a]Not accompanied by thyroid-stimulating hormone elevation or symptoms of hypothyroidism. [b]The AE summary includes an AST elevation that was identified following the data extract. Three participants had Grade ≥3 liver enzyme elevations (one 55 mg dose and two 80 mg dose participants). [c]Death due to ATTR-CM on Day 273. Pathogenic variant: p.S97Y [S77Y; Ser77Tyr; p.Ser97Tyr; c.290C>A].
AE, adverse event; AST, aspartate aminotransferase; ATTR-CM, ATTR amyloidosis with cardiomyopathy; SAE, serious adverse event; TRAE, treatment-related adverse event.

More About the Management of GI Amyloidosis[1]

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

Dietary Modifications	
For reflux and nausea	• Small evening meal • Longer interval between evening meal and lying down
For malnutrition	Calorie-dense supplements and shakes
For cramping, diarrhea, bloating	FODMAP diet

Medications	
For nausea and early satiety	• Antiemetics: ondansetron, promethazine • Prokinetics: metoclopramide, prucalopride
For diarrhea	• Opioid receptor agonists: loperamide, diphenoxylate/atropine, tincture of opium • Antibiotics for SIBO • Bile acid sequestrants • Octreotide • Aprepitant
For constipation	• Laxatives: polyethylene glycol, magnesium-containing products, senna • Linaclotide, prucalopride

1. Kittleson et al. *J Am Coll Cardiol*. 2023;81:1835-1878.

Summary

- Amyloid neuropathy is **progressive**
- Carpal tunnel syndrome may precede it by several years
- Look for CHFpEF
- Look for dysautonomia
- Document presence of amyloid
- Treat as early as possible