Current Diagnosis and Management of Cardiac Amyloidosis – Beyond the Biopsy

Marshall Hyden, MD

Nebraska Medicine

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Objectives:

1. **Review pathophysiology of amyloidosis**

2. **Understand role of cardiac imaging in cardiac amyloidosis**

3. **Treatment of ATTR amyloidosis**

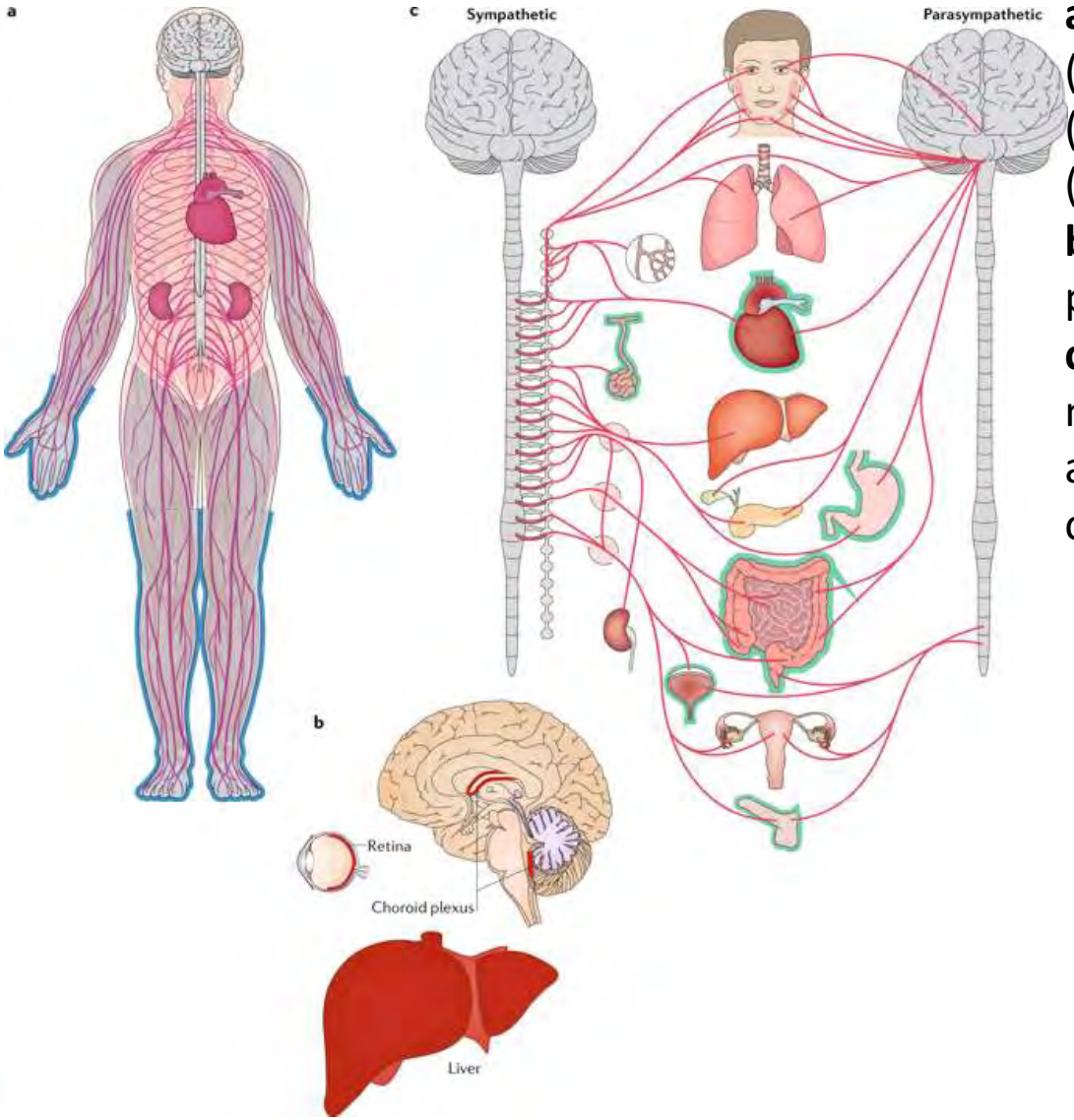
ATTR amyloidosis

Caused by mutation of the transthyretin protein which is encoded by the TTR gene.

TTR is a protein which is present in the serum and CSF. It is synthesized in the liver, choroid plexus and retinal and ciliary pigment epithelia of the eye.

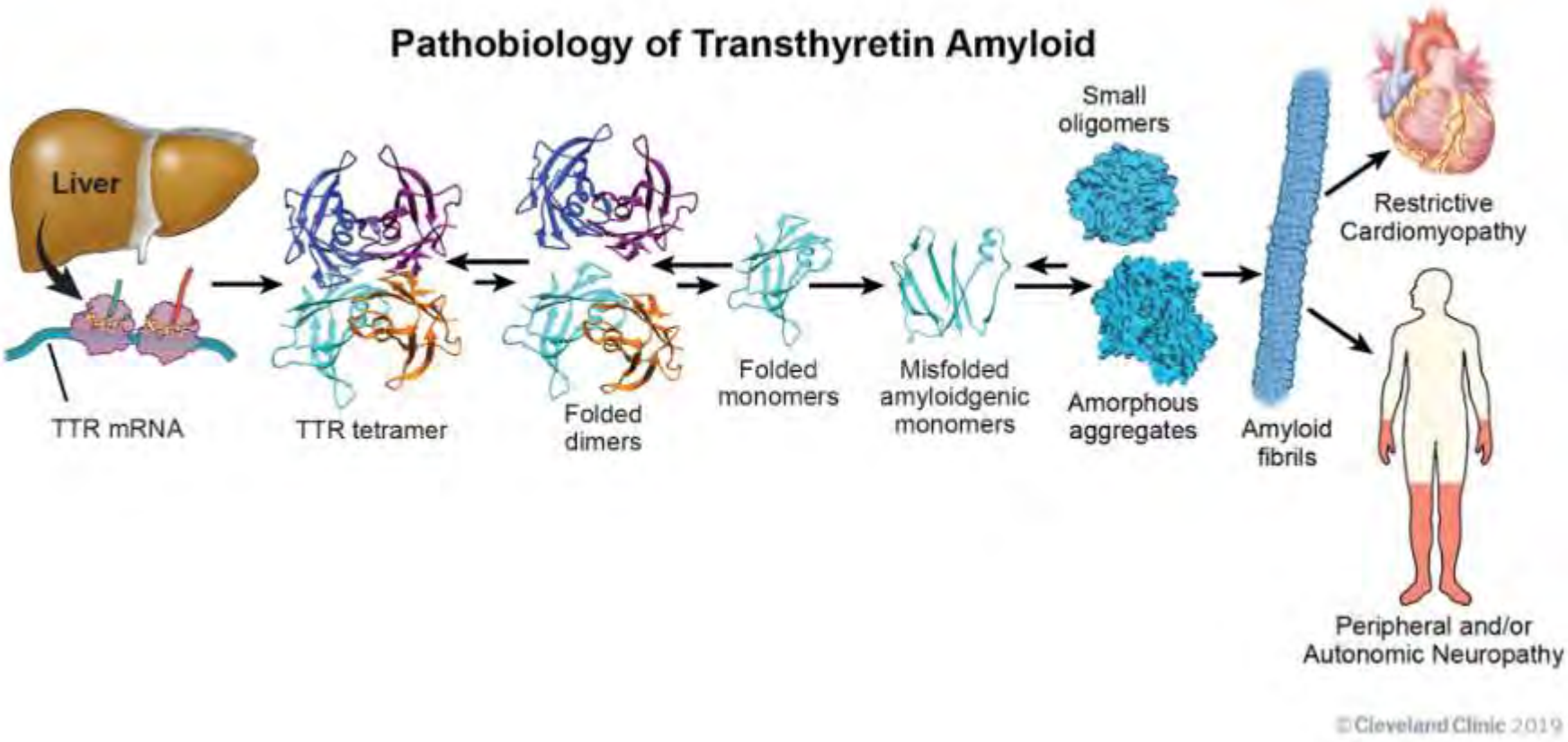
TTR is a tetrameric protein with four identical subunits with a central channel that contains two thyroxine binding sites.

ATTR amyloidosis is a protein misfolding disease. This is characterized by extracellular deposition of amyloid leading to organ dysfunction.



a | Sites of amyloid deposition (dark pink), sensory denervation (blue) and motor denervation (beige).
b | Sites of transthyretin production (red).
c | Organs affected by autonomic neuropathy and those affected by autonomic denervation (green outlines).

Adams, Koike, Slama, Coelho, **Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease**, Nature Review Neurology 15, 387-404 (2019)


Pathobiology of Transthyretin Amyloid
Liver
TTR mRNA
TTR tetramer
Folded dimers
Folded monomers
Misfolded amyloidgenic monomers
Small oligomers
Amorphous aggregates
Amyloid fibrils
Restrictive Cardiomyopathy
Peripheral and/or Autonomic Neuropathy
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Transthyretin amyloid cardiomyopathy (ATTR-CM)

Under-recognized cause of heart failure in older adults

Disease is classified by the sequence of the TTR gene either wild type or hereditary transthyretin amyloid

More than 120 pathogenic mutations in the TTR gene have been described, resulting in a variable phenotypic presentation, ranging from pure polyneuropathy with autonomic dysfunction, to mixed neurological and cardiac presentation, and to selective cardiac involvement

Prevalence has been reported in 16% of patients undergoing valve replacement for aortic stenosis, 13% among patients with heart failure with preserved EF and up to 5% of patients of patients carrying diagnosis of hypertrophic cardiomyopathy.

TABLE 1 Clues Suggesting a Diagnosis of Cardiac Amyloidosis

Cardiac Manifestations	Extracardiac Manifestations
Clinical	**Musculoskeletal**
■ Fatigue	■ Bilateral carpal tunnel syndrome
■ Heart failure symptoms	■ Lumbar/cervical spinal stenosis
■ Family history of heart failure	■ Spontaneous biceps tendon rupture
Electrical	■ Hip or knee replacement
■ Conduction system disease/pacemaker	**Neurologic**
■ Atrial fibrillation	■ Peripheral neuropathy
■ Pseudoinfarct pattern	■ Family history of neuropathy
■ Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging	■ Autonomic dysfunction
Imaging	■ Intolerance to vasodilating antihypertensive medications
■ Increased left ventricular wall thickness	■ Orthostatic hypotension
■ Grade 2 or worse diastolic function	■ Gastroparesis
■ Abnormal longitudinal strain with apical sparing	■ Urinary incontinence
■ Diffuse subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging with increased extracellular volume fraction	■ Erectile dysfunction
Laboratories	**Renal**
■ Persistent low-level troponin elevation	■ Nephrotic syndrome
■ Elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide	

The following clinical clues, especially in combination, should raise suspicion for ATTR-CM and the need for further testing:

HFpEF heart failure with preserved ejection fraction in patients typically over 60[2,3]

INTOLERANCE to standard heart failure therapies (ACE inhibitors, angiotensin receptor blockers, and beta-blockers)[4]

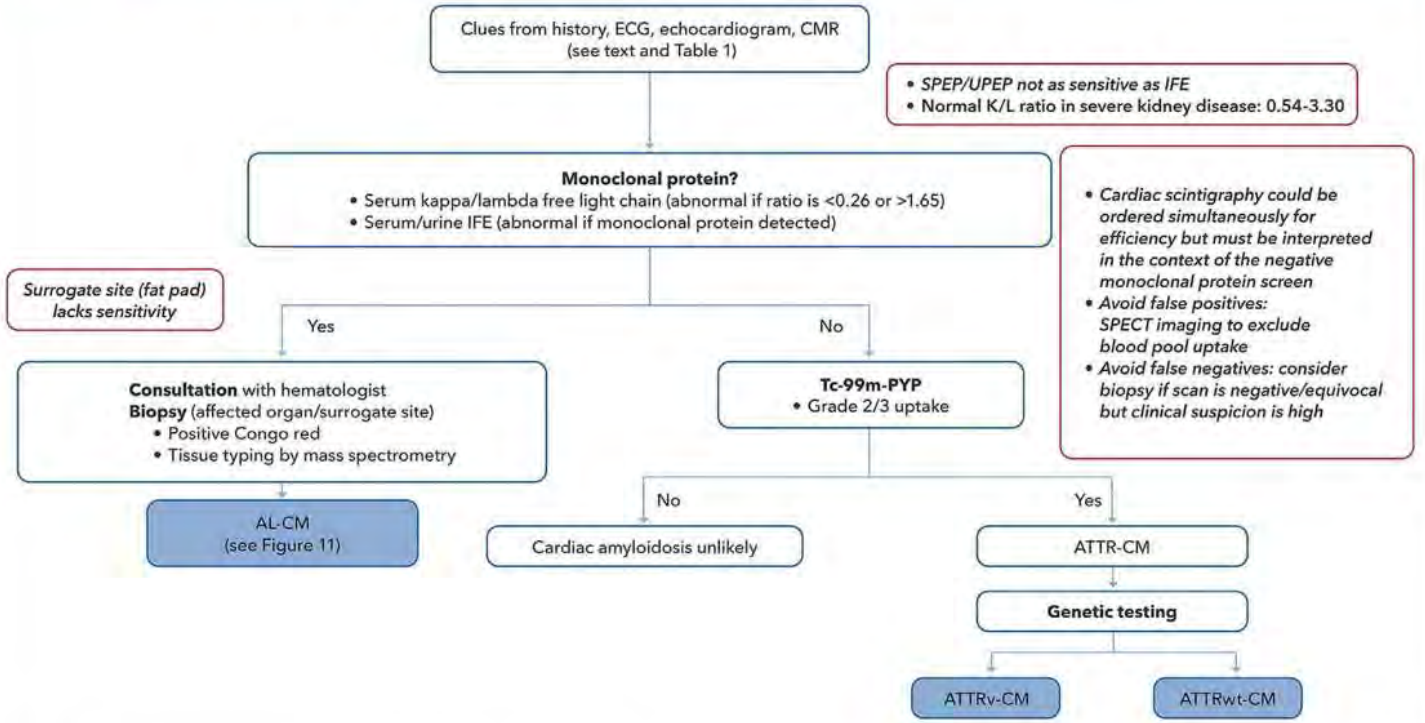
DISCORDANCE between QRS voltage and LV wall thickness[4]

DIAGNOSIS of carpal tunnel syndrome or lumbar spinal stenosis[4]

ECHO showing increased LV wall thickness[4]

NERVOUS SYSTEM autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss[4,5]

FIGURE 3 Diagnostic Algorithm for Cardiac Amyloidosis



AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM = amyloid transthyretin cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; IFE = immunofixation electrophoresis; K/L = kappa/lambda; PYP = pyrophosphate; SPECT = single-photon emission computed tomography; SPEP/UPEP = serum/urine protein electrophoresis.

Mayo clinic wtATTR-CM staging system

Stage I
Troponin T < 0.05 and N-Terminal pro-BNP < 3000

Stage II
Troponin T > 0.05 or N-Terminal pro-BNP > 3000

Stage III
Both markers above threshold

Median survival
Stage I – 66 months

Stage II - 42 months

Stage III – 20 months

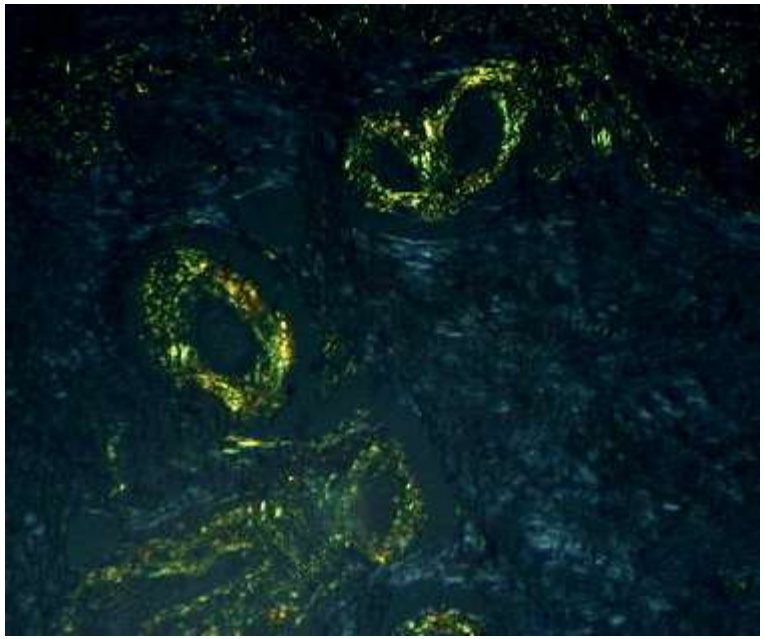
Wall thickness, LV mass, diastolic function have not been shown to be independent predictors of survival.

M. Grogan, C.G. Scott, R.A. Kyle, *et al.***Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system,** J Am Coll Cardiol, 68 (2016), pp. 1014-1020

Biopsy

Accumulation of amyloid proteins and fibers in extracellular space

Staining with Congo Red shows apple-green birefringence under cross-polarized light



M. Grogan, C.G. Scott, R.A. Kyle, *et al.***Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system,** J Am Coll Cardiol, 68 (2016), pp. 1014-1020

Imaging for diagnosis

1. Cardiac MRI

2. Nuclear scintigraphy by Tecnetium-99m pyrophosphate scan

Findings with Cardiac MRI

Typically, late gadolinium enhancement is present in a pattern of either subendocardial or transmural enhancement.

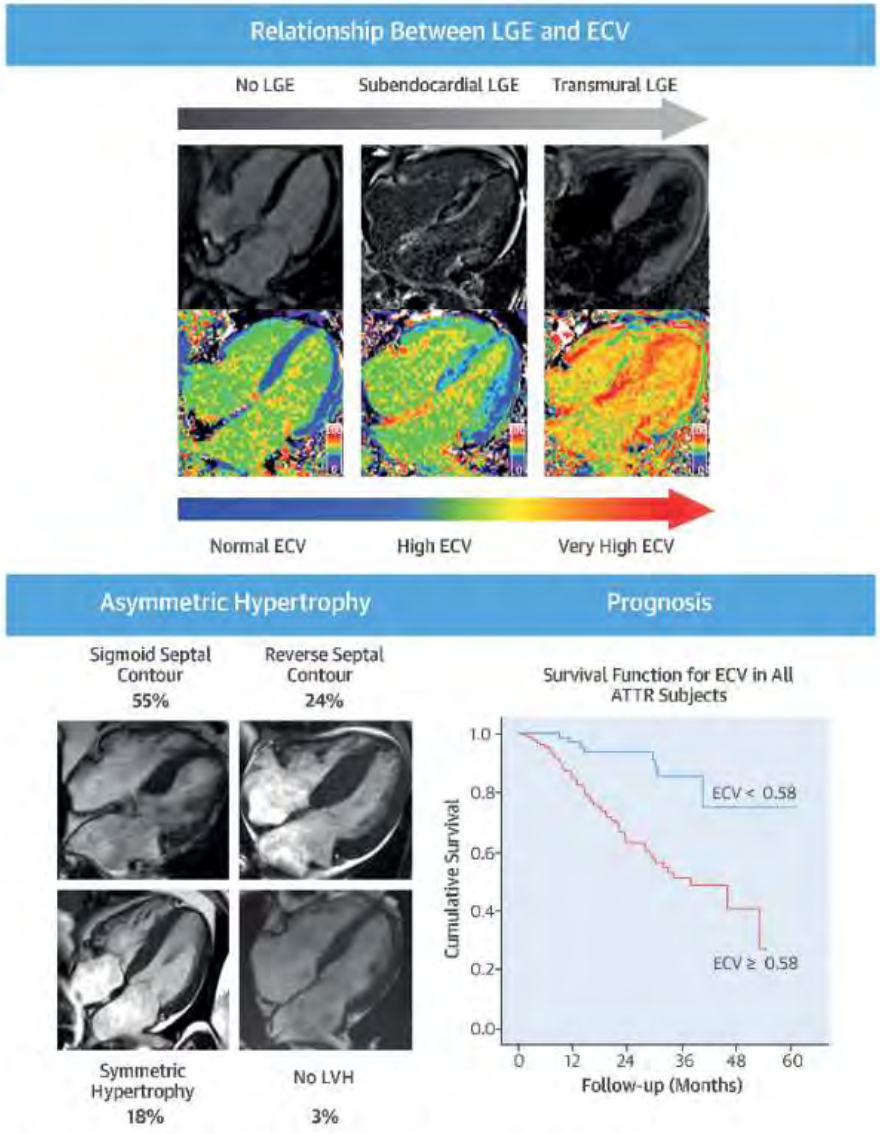
High diagnostic accuracy of late gadolinium enhancement imaging with sensitivity of 85% and specificity of 92%. (2)

False negative rate 12%, false positive rate 10% (3)

2) L. Zhao, Z. Tian, Q. Fang**Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis,** BMC Cardiovasc Disord, 16 (2016), p. 129

3) B.A. Austin, W.H. Tang, E.R. Rodriguez, *et al.***Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis,** JACC Cardiovasc Imaging, 2 (2009), pp. 1369-1377

CENTRAL ILLUSTRATION: CMR in ATTR



Martinez-Naharro, A. et al. J Am Coll Cardiol. 2017;70(4):466-77.

Nuclear scintigraphy using bone-avid radiotracers is the recommended imaging modality for diagnosis.

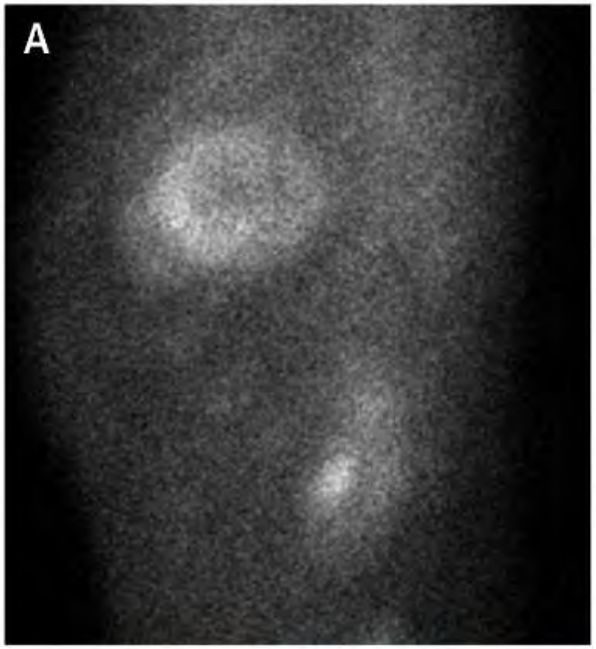
Three types have been evaluated for diagnosis of which only Tecnetium-99m pyrophosphate (Tc-99m-PYP) is used in the United States.

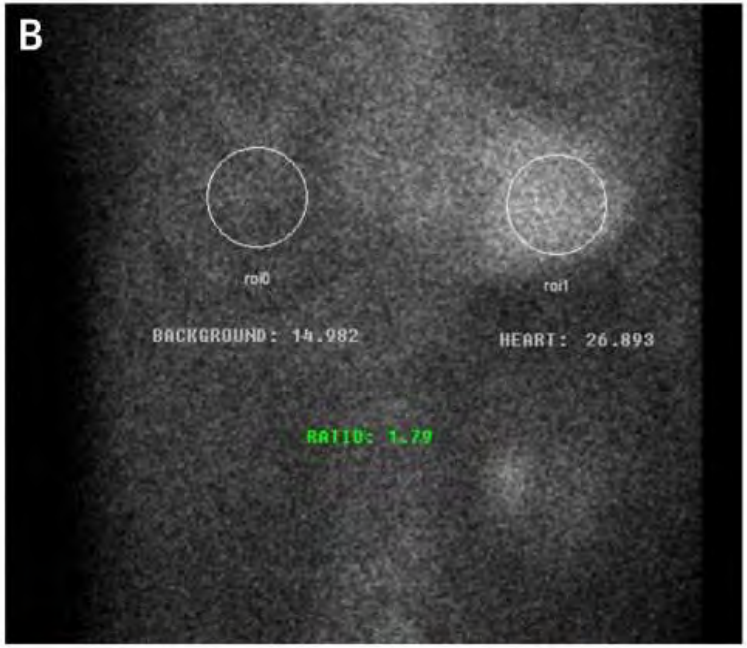
Uptake is compared with bone uptake of rib and graded from grade 0 which is no uptake to grade 3 where cardiac uptake exceeds rib uptake

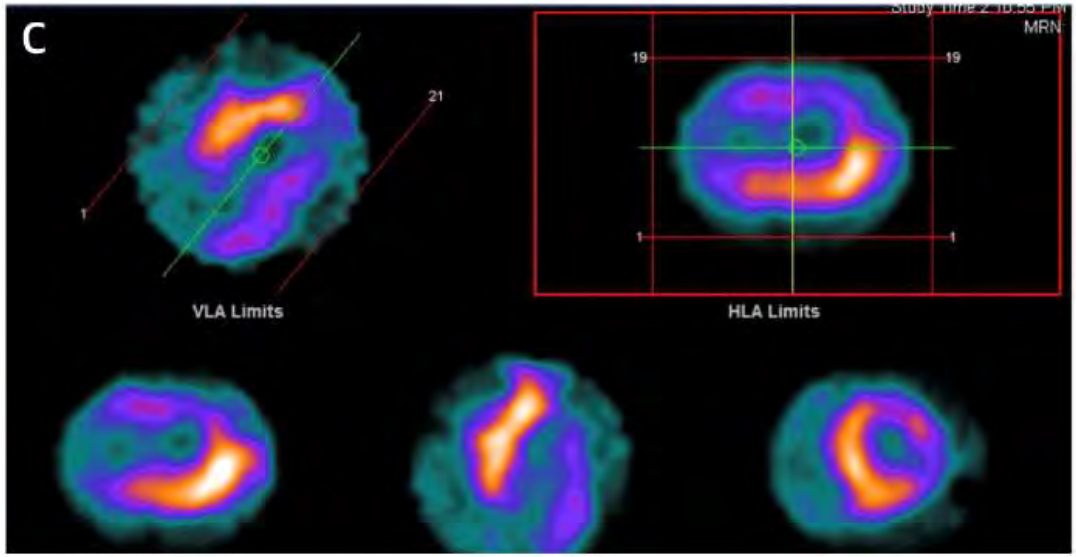
92% sensitivity, 95% specificity (1)

An international collaboration with a large cohort of endomyocardial biopsy proven cases of ATTR-CM concluded that these tests conferred 100% specificity for ATTR-CM when grade 2 or 3 uptake was seen in the absence of a monoclonal protein in patients with heart failure and typical echocardiography of cardiac MRI findings of amyloidosis. (2)

(1) G. Treglia, A. Glaudemans, F. Bertagna, *et al.***Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis,** Eur J Nucl Med Mol Imaging, 45 (2018), pp. 1945-1955
(2) J.D. Gillmore, M.S. Maurer, R.H. Falk, *et al.***Nonbiopsy diagnosis of cardiac transthyretin amyloidosis,** Circulation, 133 (2016), pp. 2404-2412



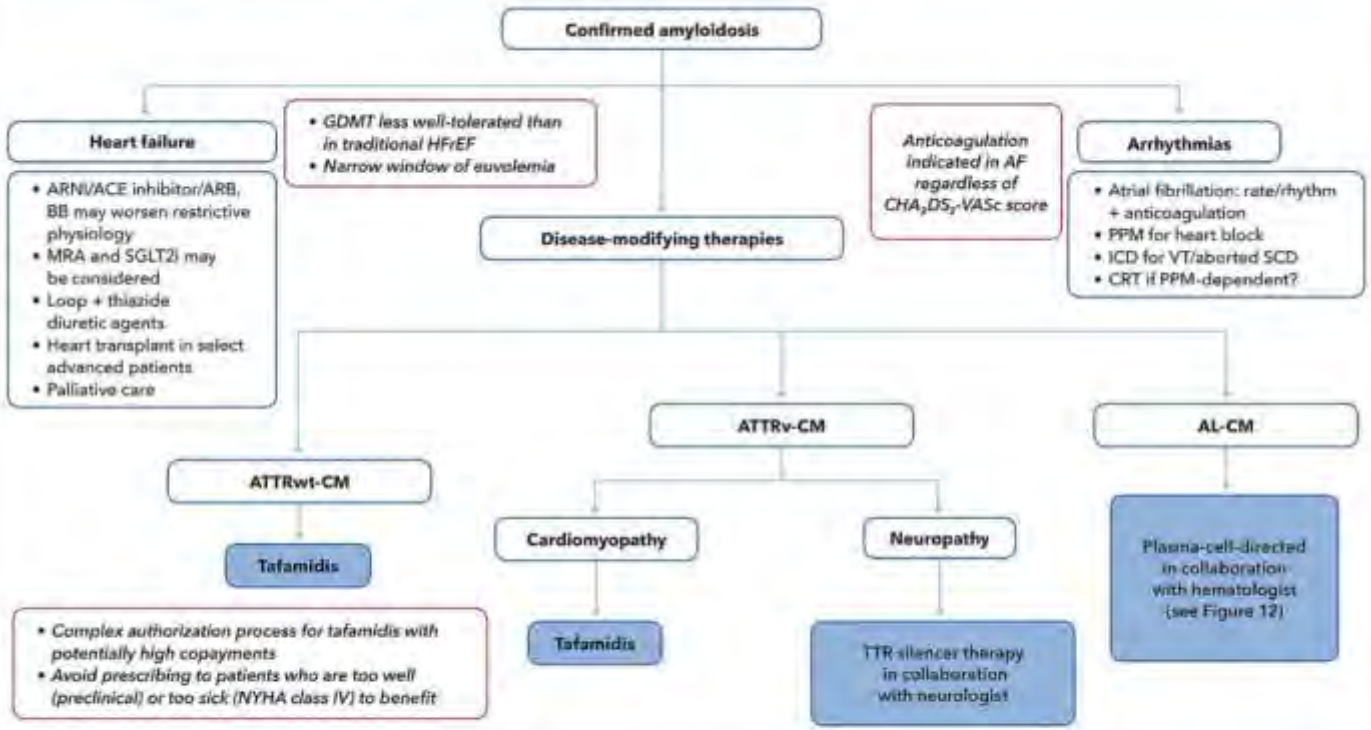




(A) A typical patient with ATTR-CM is depicted with grade 3 tracer uptake on planar imaging.
(B) Increased heart to contralateral chest ratio of 1.79
(C) multiplanar single-photon emission computed tomography showing myocardial (and not blood pool) tracer uptake, with some heterogeneity in uptake intensity.

Ruberg, F, Ggrogan, M, Hanna, M, Kelly, J, Maurer, M, Transthyretin Amyloid Cardiomyopaty: JACC State-of-the-Art Review, Journal of the American College of Cardiology, 72, 22, 11June2019, 2872-2891

FIGURE 4 Overview of Management of Cardiac Amyloidosis



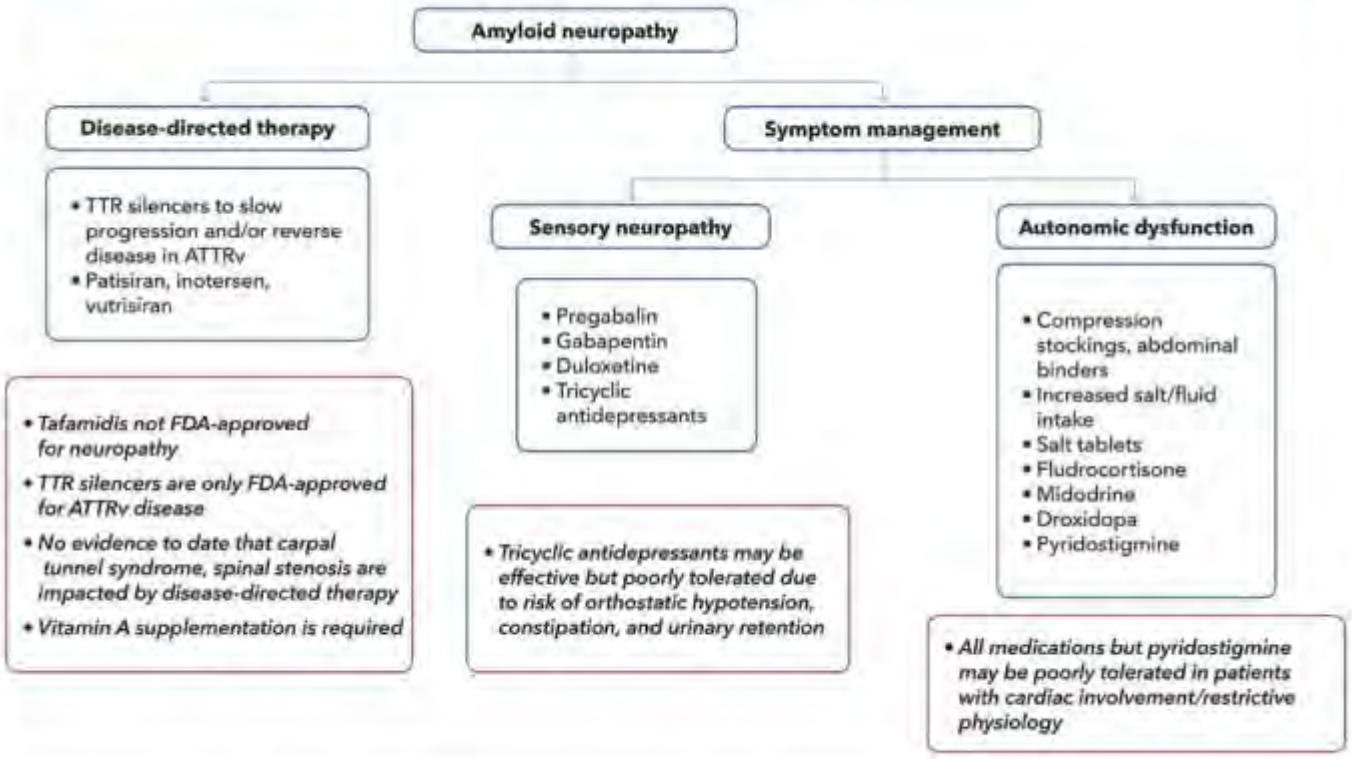
AF = atrial fibrillation; ARNI/ACE inhibitor/ARB = renin-angiotensin system inhibitors; AL-CM = amyloid monoclonal immunoglobulin light chain; ATTR = amyloid transthyretin; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; BB = beta-blocker; CRT = cardiac resynchronization therapy; HFrEF = heart failure with reduced ejection fraction; GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association; PPM = permanent pacemaker; SCD = sudden cardiac death; SGLT2i = sodium glucose cotransporter 2 inhibitor; TTR = transthyretin; VT = ventricular tachycardia.

TABLE 2 Phase 3 Clinical Trials in ATTR-CM

Trial Name	Intervention	Endpoints	Study Progress
ATTRIBUTE-CM NCT03860935	Acoramidis (TTR stabilizer)	Hierarchical combination of all-cause mortality, frequency of CV-related hospitalization, and change from baseline to month 30 of treatment in the total distance walked in 6 min	Enrollment completed November 2020 Did not meet primary 12-mo endpoint of change in 6-min walk distance; 30-mo endpoint of all-cause mortality and CV-related hospitalization is ongoing
CARDIO-TTRansform NCT04136171	Eplontersen (TTR silencer, antisense oligonucleotide)	Composite of CV mortality and recurrent CV clinical events up to week 140	Enrollment completed mid-2022
HELIOS-B NCT04153149	Vutrisiran (TTR silencer, small interfering RNA)	Composite of all-cause mortality recurrent CV events (CV hospitalizations and urgent HF visits) at 30-36 mo	Enrollment completed August 2021
APOLLO-B NCT03997383	Patisiran (TTR silencer, small interfering RNA)	6-min walk distance at 12 mo	Met 12-mo primary endpoint: improvement in 6-min walk test Met 12-mo first secondary endpoint: improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary No difference in secondary composite endpoint: win ratio for change in 6-min walk test, death, and CV hospitalization at 12 mo

APOLLO-B = A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy; ATTRIBUTE-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; CARDIO-TTRansform = A Study to Evaluate the Efficacy and Safety of Eplontersen in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy; CV = cardiovascular; HELIOS-B = A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; HF = heart failure; TTR = transthyretin.

FIGURE 8 Management of Amyloid Neuropathy



ATTRv = variant transthyretin amyloidosis; FDA = U.S. Food and Drug Administration; TTR = transthyretin.

ATTR-ACT

Phase 3 multicenter international placebo-controlled, double blind randomized trial. Randomized patients with ATTR confirmed by biopsy to tafamidis 20mg, tafamidis 80mg or placebo.

Inclusion: Confirmed cardiac involvement with echo (septal wall thickness greater than 12mm, history of heart failure with at least 1 prior hospitalization for heart failure or clinical evidence of heart failure, nt pro-BNP > 600pg/ml, 6 MWDT > 100m.

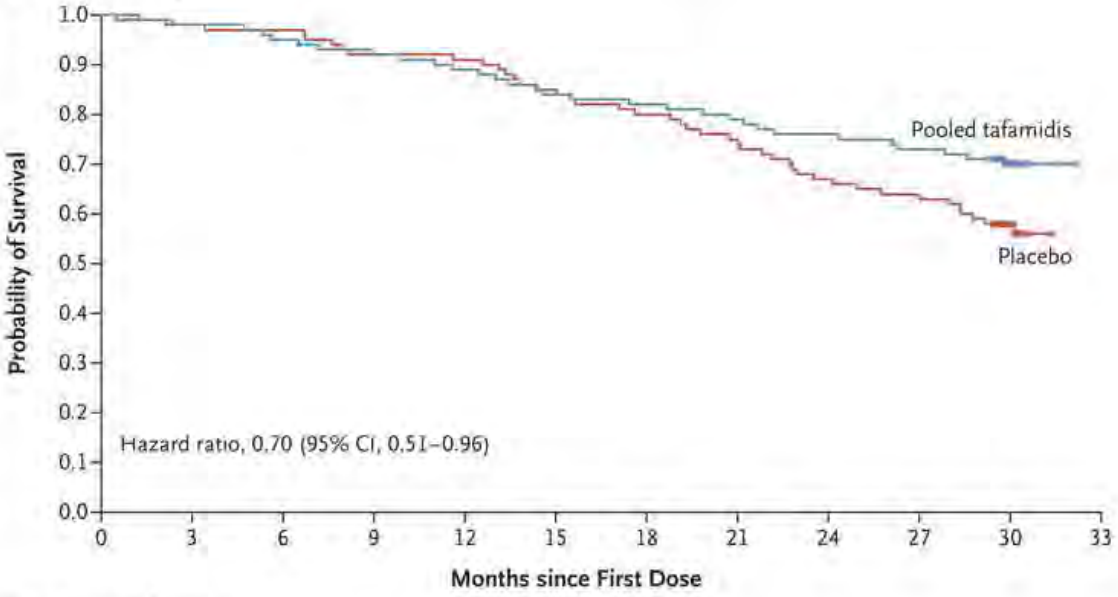
Exclusion: heart failure not due to ATTR, NYHA class IV heart failure, AL amyloidosis, history of liver or heart transplantation, implanted cardiac device, eGFR < 25, liver transaminases > 2 x upper limit of normal range, severe malnutrition

(1) Maurer, Schwartz, Gundapneni et al. **Tafamidis Treatment for Patients with Tranthyretin Amyloid Cardiomyopathy, N Engl J Med**, 2018, 379: 1007-1016

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	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*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

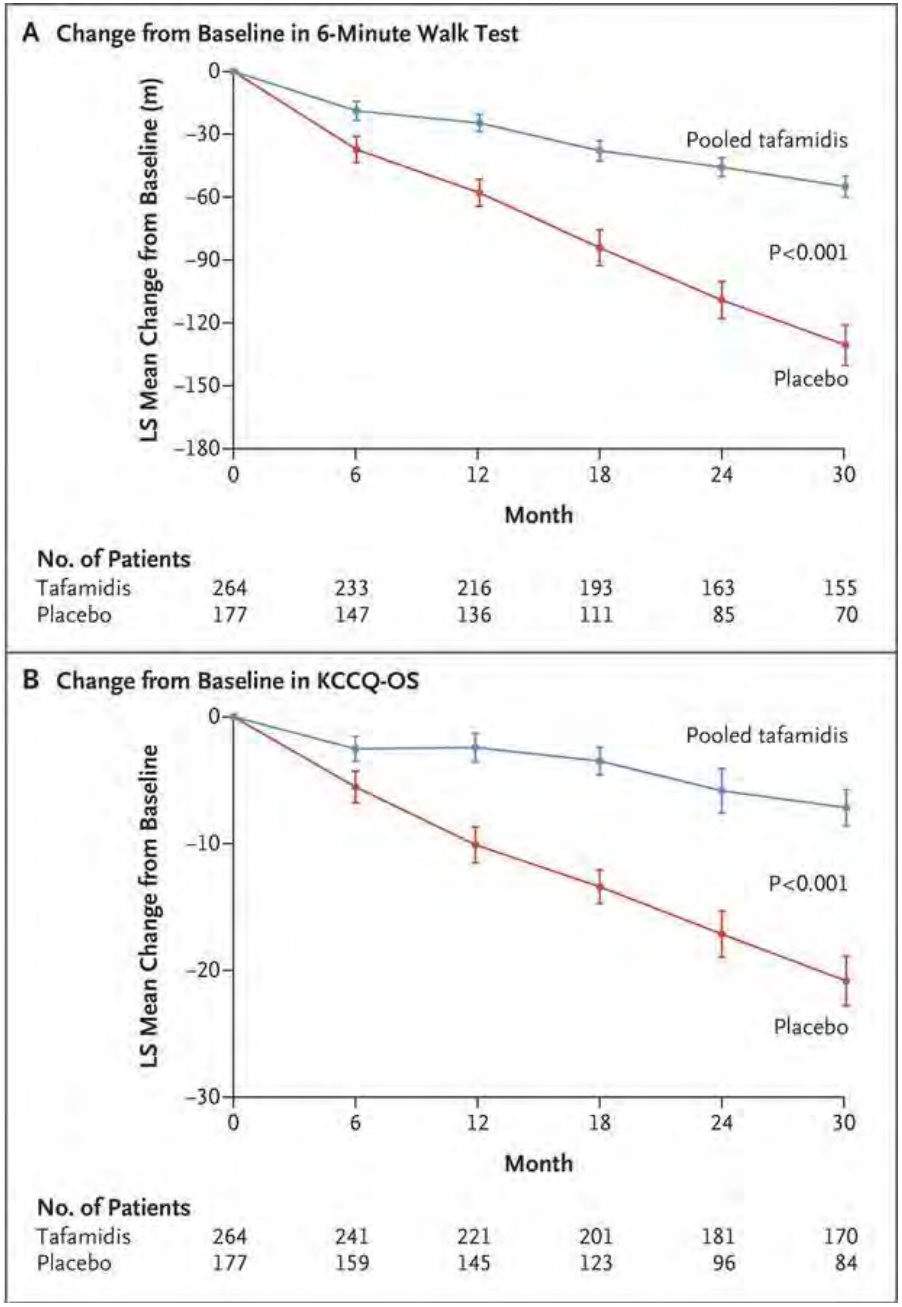


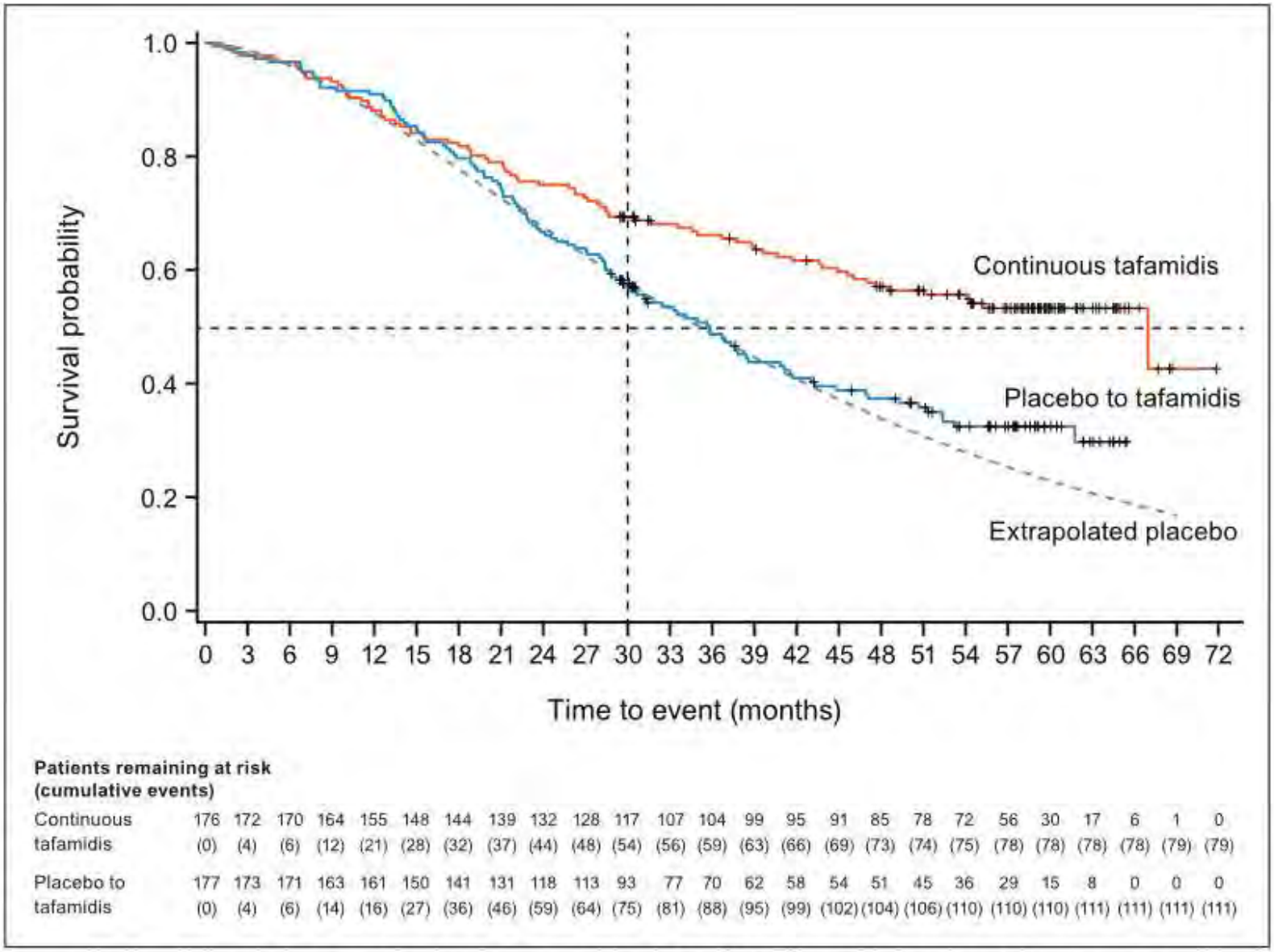
No. at Risk (cumulative no. of events)

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	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*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	


A Change from Baseline in 6-Minute Walk Test
LS Mean Change from Baseline (m)
0
−30
−60
−90
−120
−150
−180
Pooled tafamidis
P<0.001
Placebo
0
6
12
18
24
30
Month
No. of Patients
Tafamidis 264 233 216 193 163 155
Placebo 177 147 136 111 85 70
B Change from Baseline in KCCQ-OS
LS Mean Change from Baseline
0
−10
−20
−30
Pooled tafamidis
P<0.001
Placebo
0
6
12
18
24
30
Month
No. of Patients
Tafamidis 264 241 221 201 181 170
Placebo 177 159 145 123 96 84



Patients remaining at risk (cumulative events)

Continuous tafamidis	176 (0)	172 (4)	170 (6)	164 (12)	155 (21)	148 (28)	144 (32)	139 (37)	132 (44)	128 (48)	117 (54)	107 (56)	104 (59)	99 (63)	95 (66)	91 (69)	85 (73)	78 (74)	72 (75)	56 (78)	30 (78)	17 (78)	6 (78)	1 (79)	0 (79)
Placebo to tafamidis	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	93 (75)	77 (81)	70 (88)	62 (95)	58 (99)	54 (102)	51 (104)	45 (106)	36 (110)	29 (110)	15 (110)	8 (111)	0 (111)	0 (111)	0 (111)

Figure 2. Kaplan–Meier plot of observed time to all-cause mortality in ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) and the long-term extension (LTE) and compared with model-based extrapolation of time to all-cause mortality with placebo. Time to all-cause mortality (with heart transplant and implantation of a cardiac mechanical assist device treated as death) shown for all patients treated with tafamidis 80 mg in ATTR-ACT continuing with tafamidis 80 mg, then tafamidis free acid 61 mg in the LTE (continuous tafamidis) compared with patients treated with placebo in ATTR-ACT continuing with tafamidis (20, 80, or 61 mg) in the LTE (placebo to tafamidis). The extrapolated placebo curve (dotted line) is a model-based extrapolation of survival in placebo-treated patients in ATTR-ACT beyond 30 months.[18] Data cutoff: March 20, 2020.

Patisiran, an RNAi Therapeutic for Hereditary Transthyretin Amyloidosis

RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

Inclusion: Documented pathogenic variant in TTR, a diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, with Neuropathy Impariment Score (NIS) of 5 to 130 with higher score indicating more-impairment, adequate liver and renal function, a polyneuropathy disability score of IIIb or lower.

Exclusion: History of liver transplantation, NYHA class III or IV heart failure

(1) Adams, Gonzalez-Duarte, O'Riordan et al. **Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis, N Engl J Med**, 2018, 379: 11-21

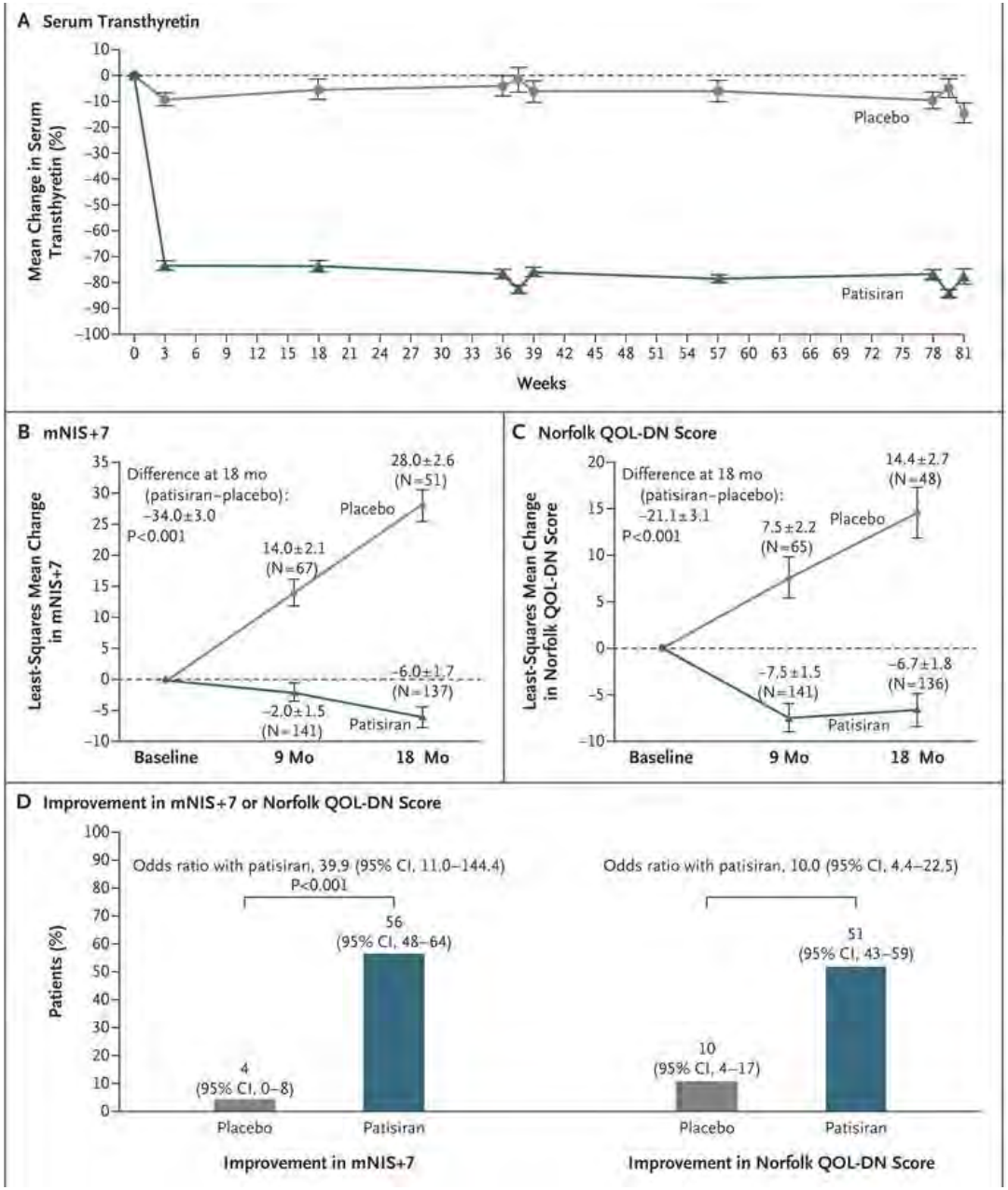
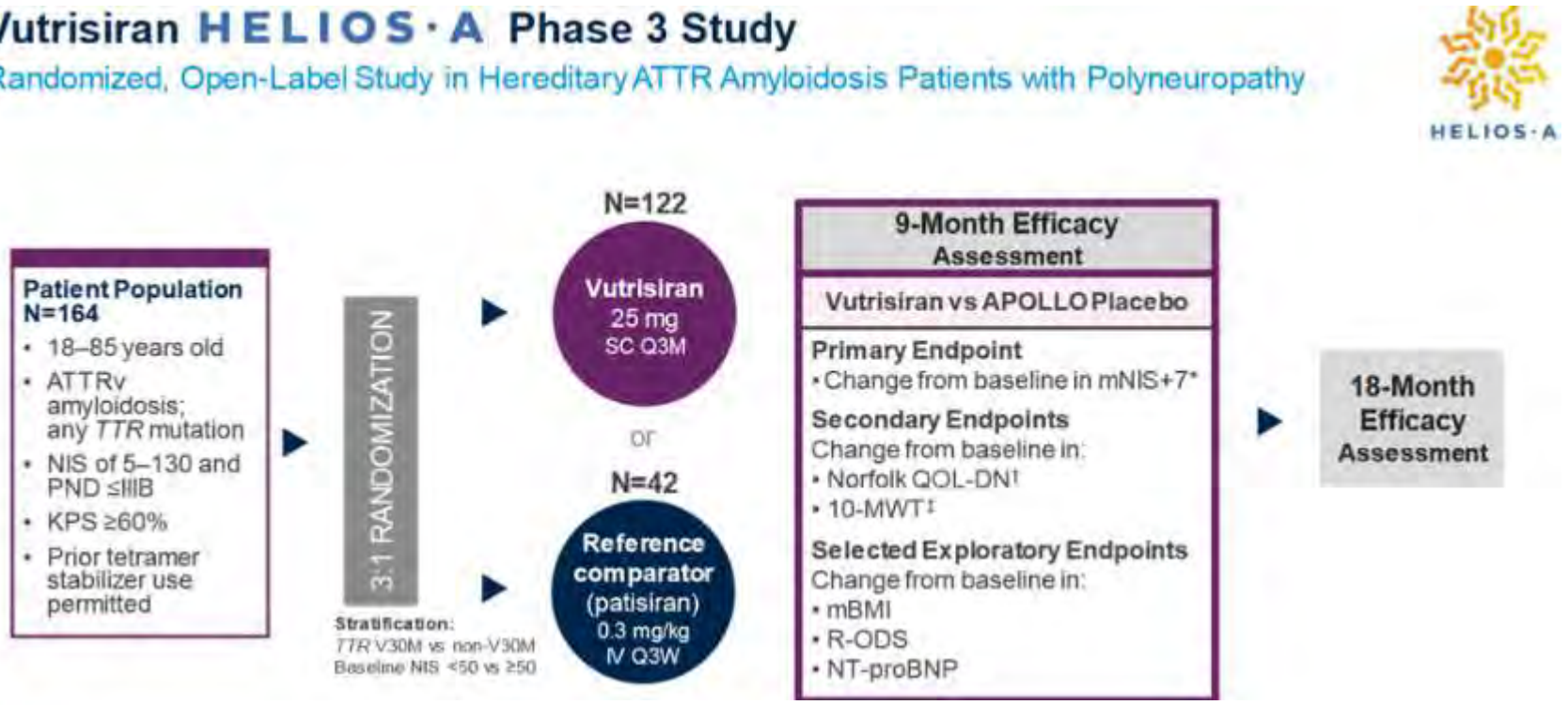

A Serum Transthyretin
Mean Change in Serum Transthyretin (%)
Placebo
Patisiran
Weeks
B mNIS+7
Least-Squares Mean Change in mNIS+7
Difference at 18 mo (patisiran–placebo): −34.0±3.0
P<0.001
28.0±2.6 (N=51)
Placebo
14.0±2.1 (N=67)
−6.0±1.7 (N=137)
−2.0±1.5 (N=141)
Patisiran
Baseline
9 Mo
18 Mo
C Norfolk QOL-DN Score
Least-Squares Mean Change in Norfolk QOL-DN Score
Difference at 18 mo (patisiran–placebo): −21.1±3.1
P<0.001
14.4±2.7 (N=48)
Placebo
7.5±2.2 (N=65)
−7.5±1.5 (N=141)
−6.7±1.8 (N=136)
Patisiran
Baseline
9 Mo
18 Mo
D Improvement in mNIS+7 or Norfolk QOL-DN Score
Patients (%)
Odds ratio with patisiran, 39.9 (95% CI, 11.0–144.4)
P<0.001
56 (95% CI, 48–64)
4 (95% CI, 0–8)
Placebo
Patisiran
Improvement in mNIS+7
Odds ratio with patisiran, 10.0 (95% CI, 4.4–22.5)
51 (95% CI, 43–59)
10 (95% CI, 4–17)
Placebo
Patisiran
Improvement in Norfolk QOL-DN Score

Table 2. Secondary and Exploratory End Points.

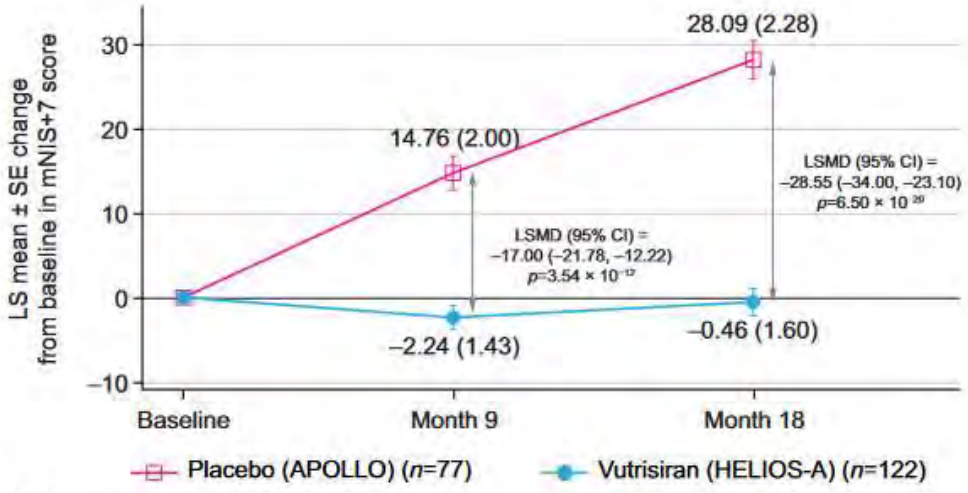
End Point	Placebo	Patisiran	Least-Squares Mean Difference (Patisiran – Placebo)	P Value
Secondary end points in the modified ITT population*				
No. of patients	77	148		
Neuropathy Impairment Score–weakness†				
Mean (±SD) baseline score	29.0±23.0	32.7±25.2		
Least-squares mean (±SE) change from baseline at 18 mo	17.9±2.0	0.1±1.3	−17.9±2.3	<0.001
Score on the Rasch-built Overall Disability Scale‡				
Mean (±SD) baseline score	29.8±10.8	29.7±11.5		
Least-squares mean (±SE) change from baseline at 18 mo	−8.9±0.9	0.0±0.6	9.0±1.0	<0.001
10-m walk test — m/sec§				
Mean (±SD) baseline value	0.79±0.32	0.80±0.40		
Least-squares mean (±SE) change from baseline at 18 mo	−0.24±0.04	0.08±0.02	0.31±0.04	<0.001
Modified BMI¶				
Mean (±SD) baseline value	989.9±214.2	969.7±210.5		
Least-squares mean (±SE) change from baseline at 18 mo	−119.4±14.5	−3.7±9.6	115.7±16.9	<0.001
Composite Autonomic Symptom Score 31‖				
Mean (±SD) baseline score	30.3±16.4	30.6±17.6		
Least-squares mean (±SE) change from baseline at 18 mo	2.2±1.9	−5.3±1.3	−7.5±2.2	<0.001
Exploratory end points in the cardiac subpopulation**				
No. of patients	36	90		
Left ventricular wall thickness — mm				
Mean (±SD) baseline value	16.4±2.1	16.8±2.6		
Least-squares mean (±SE) change from baseline at 18 mo	−0.1±0.3	−1.0±0.2	−0.9±0.4	0.02
Left ventricular longitudinal strain — %				
Mean (±SD) baseline value	−15.66±3.51	−15.13±3.41		
Least-squares mean (±SE) change from baseline at 18 mo	1.46±0.48	0.08±0.28	−1.37±0.56	0.02
NT-proBNP††				
Baseline value				
Geometric mean — pg/ml	711.1	726.9		
Coefficient of variation — %	190.8	220.3		
Ratio to baseline at 18 mo‡‡	1.97	0.89	0.45§§	<0.001

Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidsosi with polyneuropathy: a randomized clinical trial



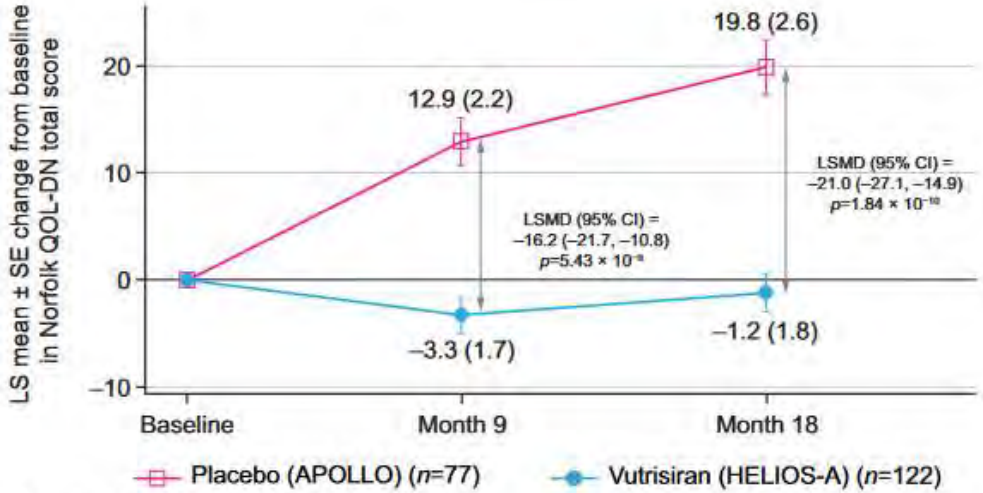
Adams, D., Tournev, I. L., Taylor, M. S., Coelho, T., Planté-Bordeneuve, V., … Berk, J. L. (2022). Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*, *30*(1), 18–26. https://doi.org/10.1080/13506129.2022.2091985

(A) mNIS+7*



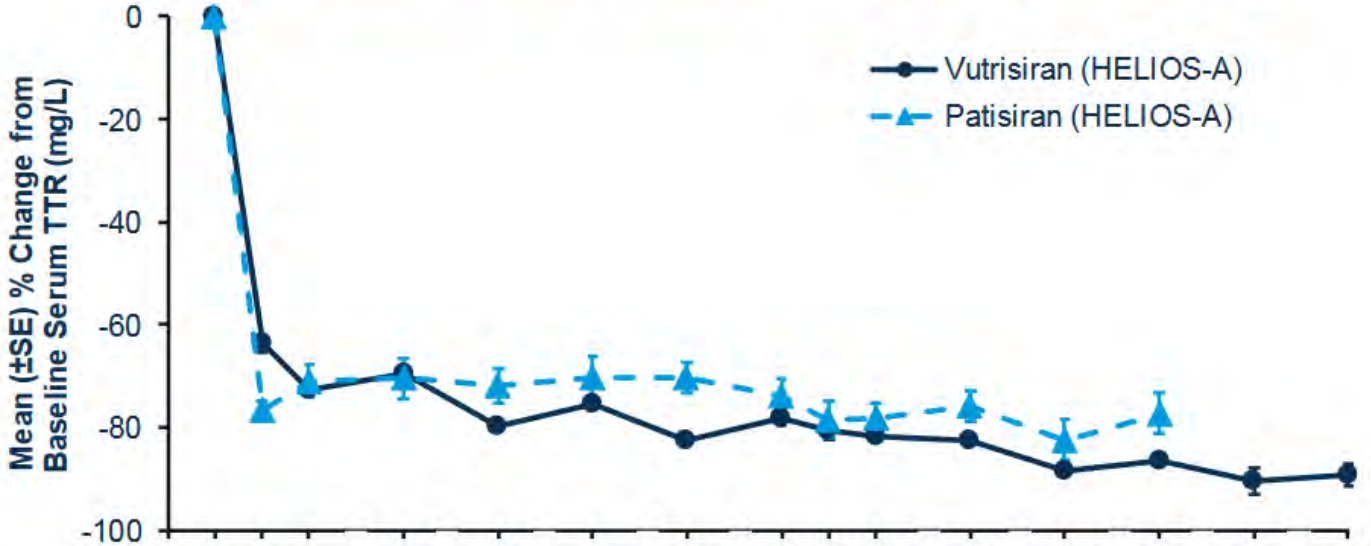
N evaluable	Baseline	Month 9	Month 18
Placebo	77	67	51
Vutrisiran	122	114	112

(B) Norfolk QOL-DN†



N evaluable	Baseline	Month 9	Month 18
Placebo	76	65	48
Vutrisiran	121	114	111

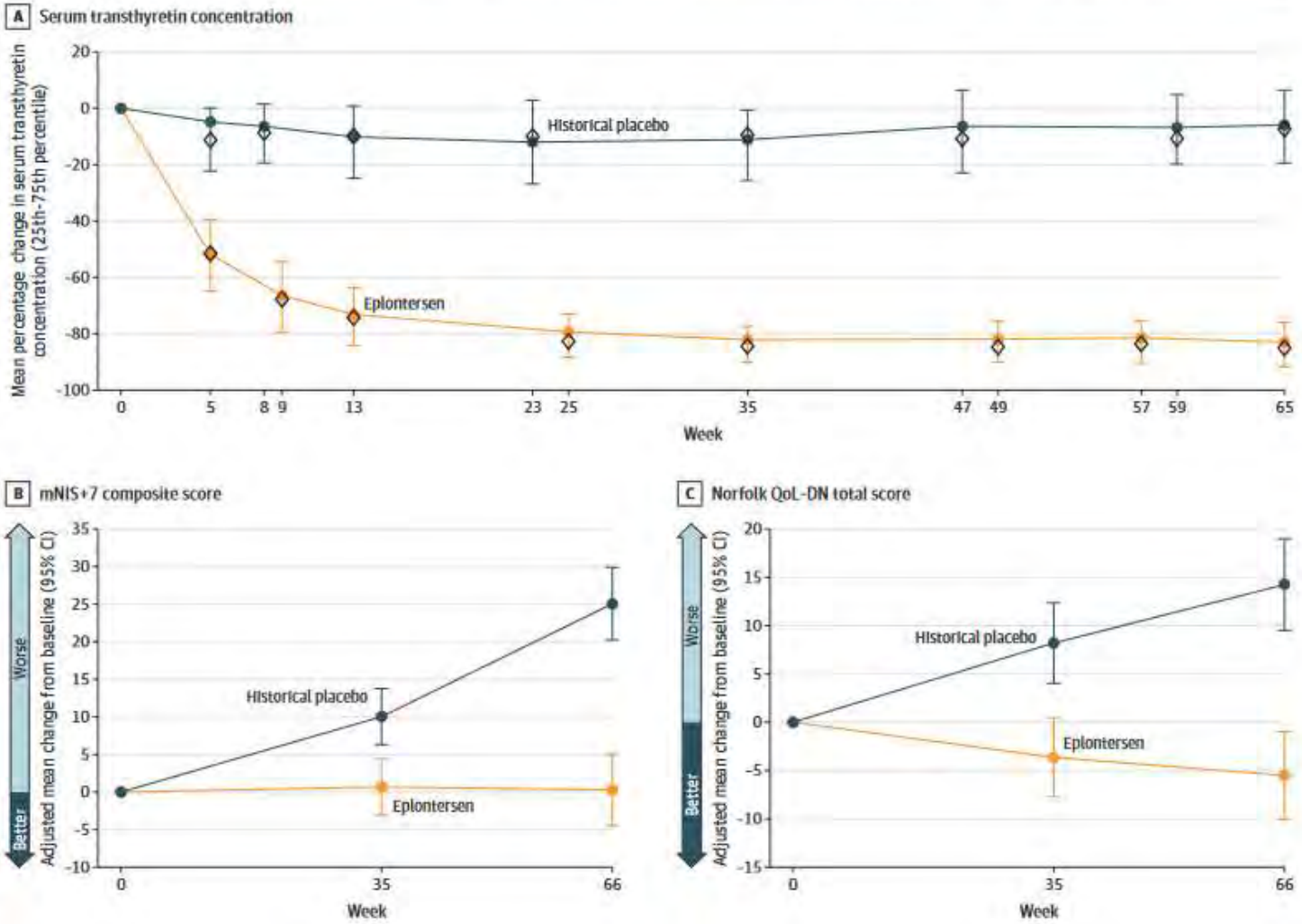
Percent Change from Baseline in Serum TTR Levels



N evaluable															
Vutrisiran	122	114	109	119	105	117	91	118	113	51	85	35	41	8	11
Patisiran	42	42	41	41	37	38	39	34	37	22	27	14	12		

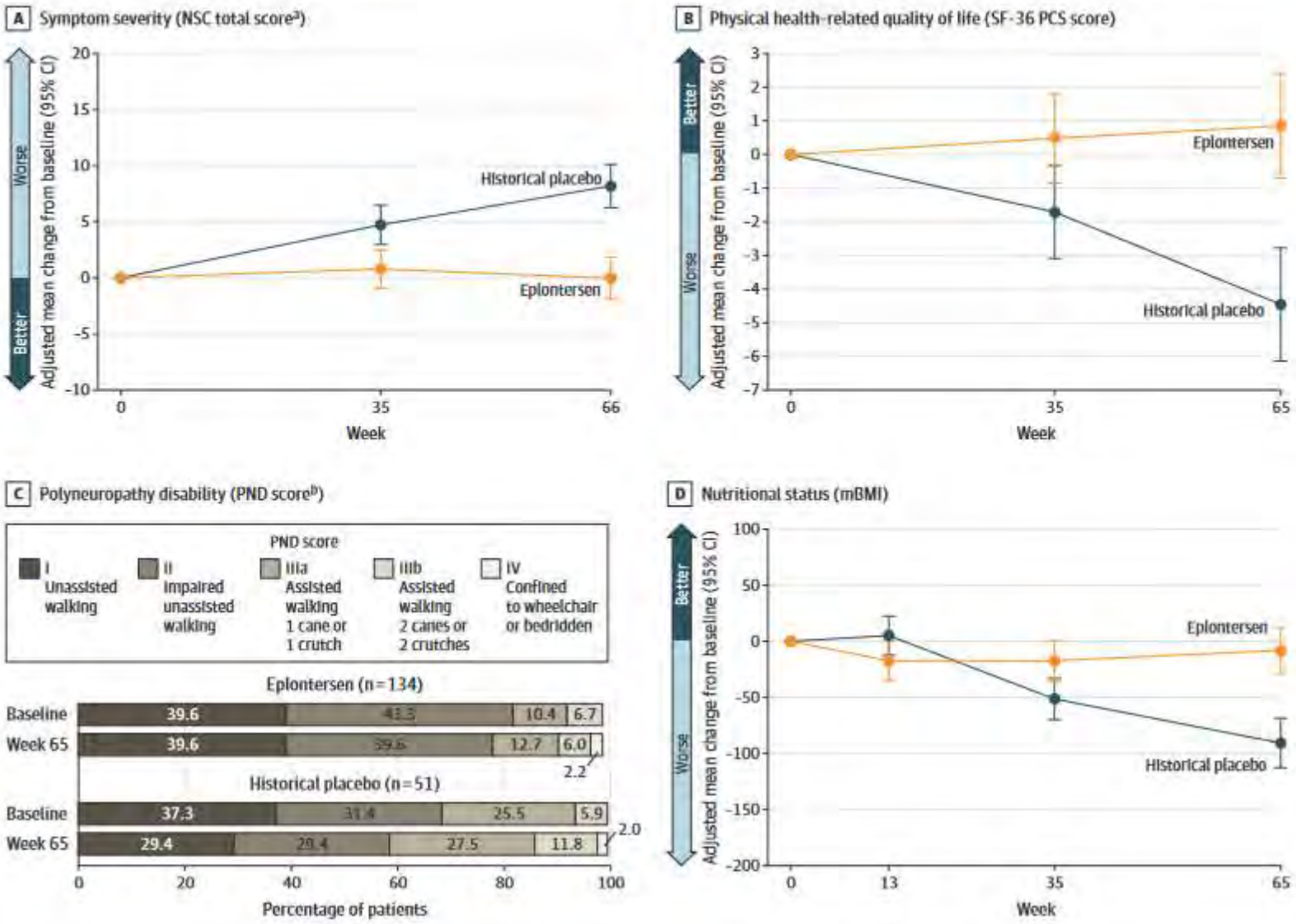
Eplontersen for Hereditary Transthyretin Amyloidosis with Polyneuropathy

Figure 2. Change From Baseline in Primary End Points (Serum Transthyretin Concentration, mNIS+7 Composite Score, Norfolk QoL-DN Total Score)



Coelho T, Marques W Jr, Dasgupta NR, Chao CC, Parman Y, França MC Jr, Guo YC, Wixner J, Ro LS, Calandra CR, Kowacs PA, Berk JL, Obici L, Barroso FA, Weiler M, Conceição I, Jung SW, Buchele G, Brambatti M, Chen J, Hughes SG, Schneider E, Viney NJ, Masri A, Gertz MR, Ando Y, Gillmore JD, Khella S, Dyck PJB, Waddington Cruz M; NEURO-TTRansform Investigators. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. JAMA. 2023 Oct 17;330(15):1448-1458. doi: 10.1001/jama.2023.18688. PMID: 37768671; PMCID: PMC10540057.

Figure 3. Change From Baseline in Secondary End Points (NSC Total Score, SF-36 PCS Score, Distribution of Polyneuropathy Disability Scores at Baseline and Week 65, mBMI)



AL amyloidosis Case

PMHx of HTN, BPH and smoldering multiple myeloma

In his usual state of health until about 1.5 years ago when he noticed new shortness of breath with exertion when walking from parking lot into his workplace. About a half a year ago when his shortness of breath worsened.

He also has lower extremity edema which he feels has not improved and worsens throughout the day before slight improvement overnight while sleeping. He reports some lightheadedness when he stands quickly. Denies chest pain. Reports orthopnea, PND, abdominal bloating. Has chronic cough productive of foamy white sputum.

He underwent evaluation with echocardiogram showing normal LV and RV systolic function, severe bi-atrial dilatation and speckling concerning for possible amyloidosis.

Kappa light chain	17.1
Lambda light chain	1090.3