CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

@CanHFSociety #HFupdate

Update on Cardiac Amyloidosis

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Objectives

- Describe newer approaches for timely diagnosis of cardiac amyloid.
- Discuss the role of genetic testing for patients with cardiac amyloid.
- Know and be able to access current and upcoming treatments for cardiac ATTR.

Case 1: Mr. F

- 74-year-old man referred to Cardiac Amyloid Clinic with possible amyloid after presenting with new-onset HF and atrial flutter
- PMHx:
  - HFpEF; LVEF 50% on recent echo
  - Atypical atrial flutter/atrial fibrillation; previous DCCV
  - TIA vs. migraine
  - Bilateral CTS, status post-CTR x2
  - Lumbar spinal stenosis
  - BPH
  - OA
- Meds
  - Metoprolol 50 mg BID
  - Apixaban 5 mg BID
  - Furosemide 20 mg daily
  - Pantoprazole
- NYHA 3
- HR 62, BP 118/72
- JVP 8 cm ASA, mild edema

Steps toward earlier diagnosis

- Clinical decision aids
- Machine learning

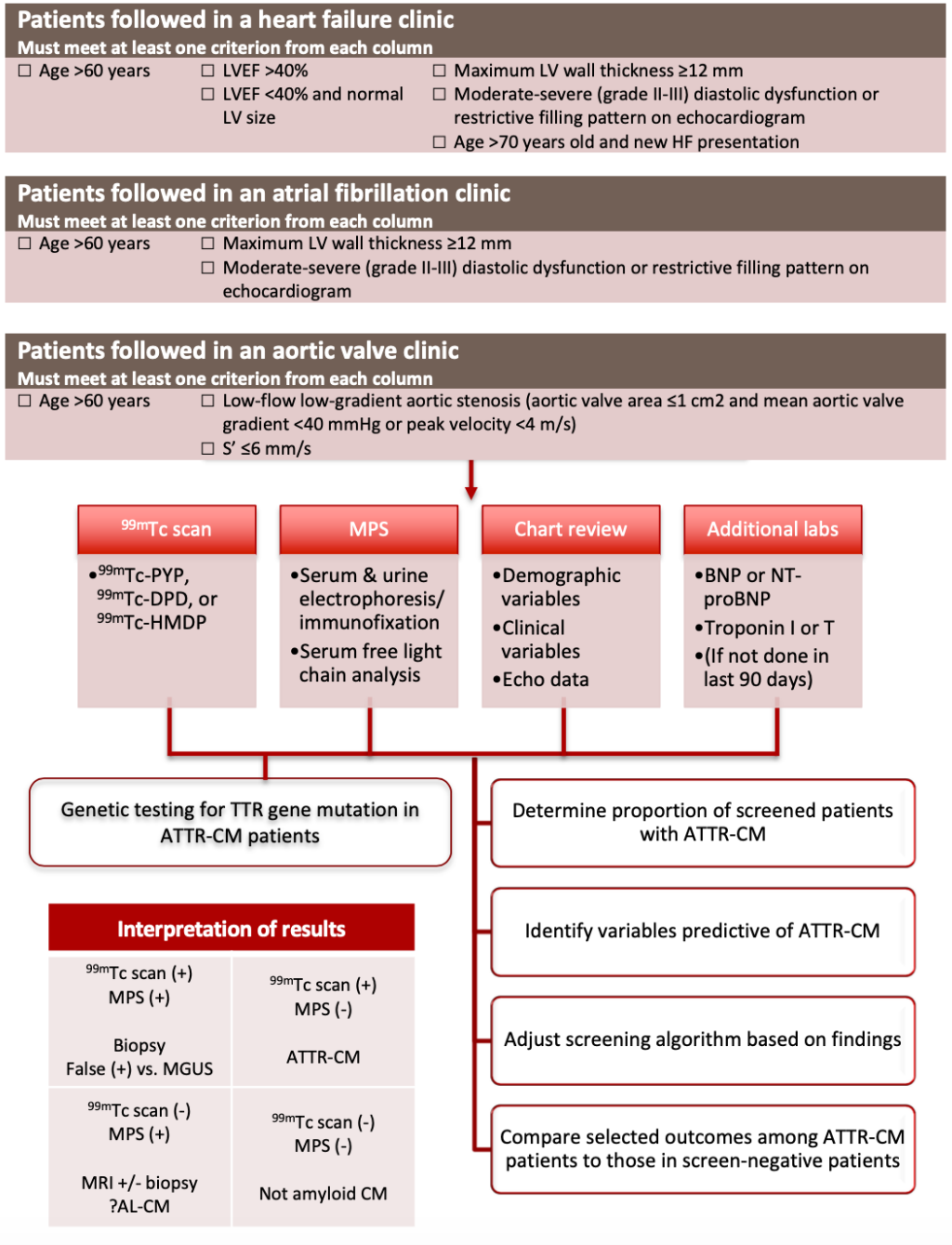
Transthyretin Amyloid Cardiomyopathy (ATTR-CM) Score

Clinical variable	Value	Points[a]
Age, y	If 60-69	+2
	If 70-79	+3
	If ≥80	+4
Sex	Male	+2
Hypertension diagnosis	Present	−1
Ejection fraction	<60%	+1
Posterior wall thickness	≥12 mm	+1
Relative wall thickness[b]	>0.57	+2

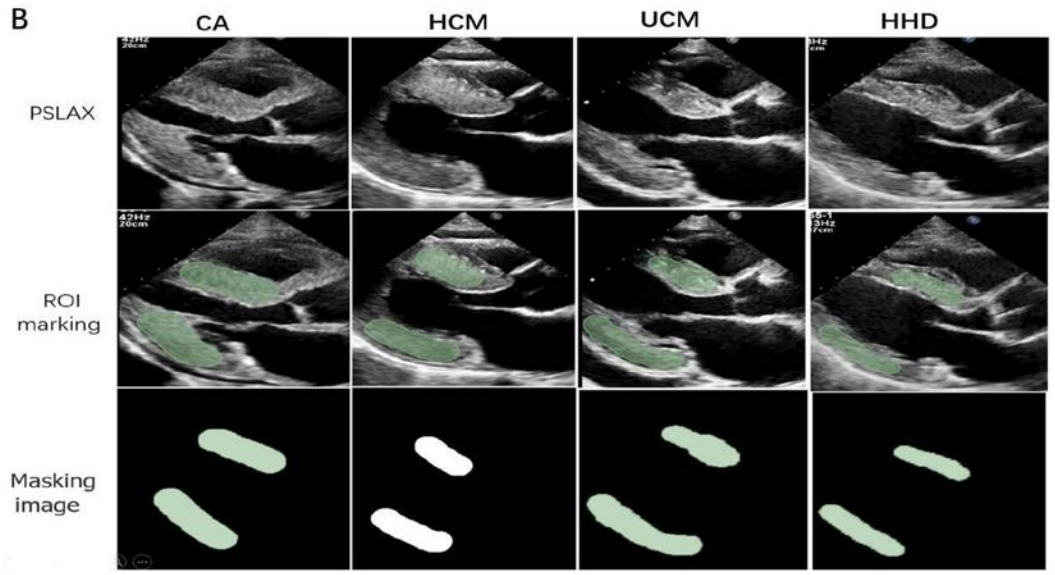
High-risk score ≥6

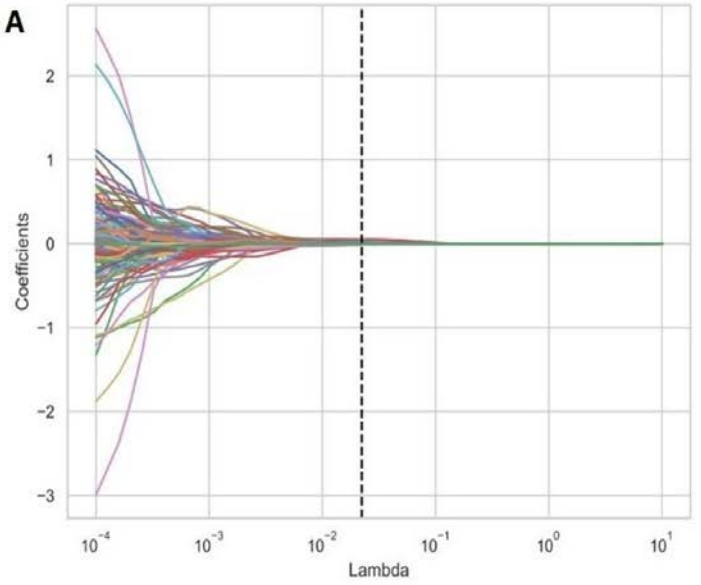
JAMA Cardiol. 2022;7(10):1036-1044.

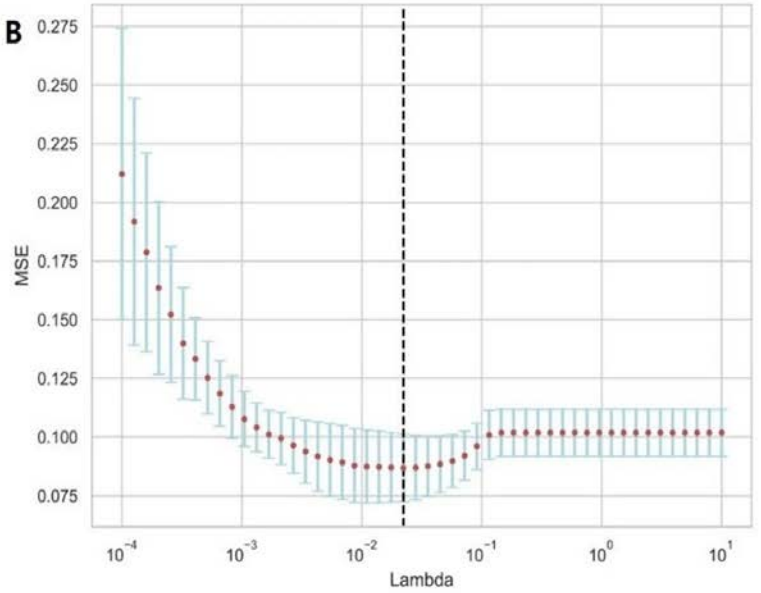
UBC ATTR-CM screening algorithm study

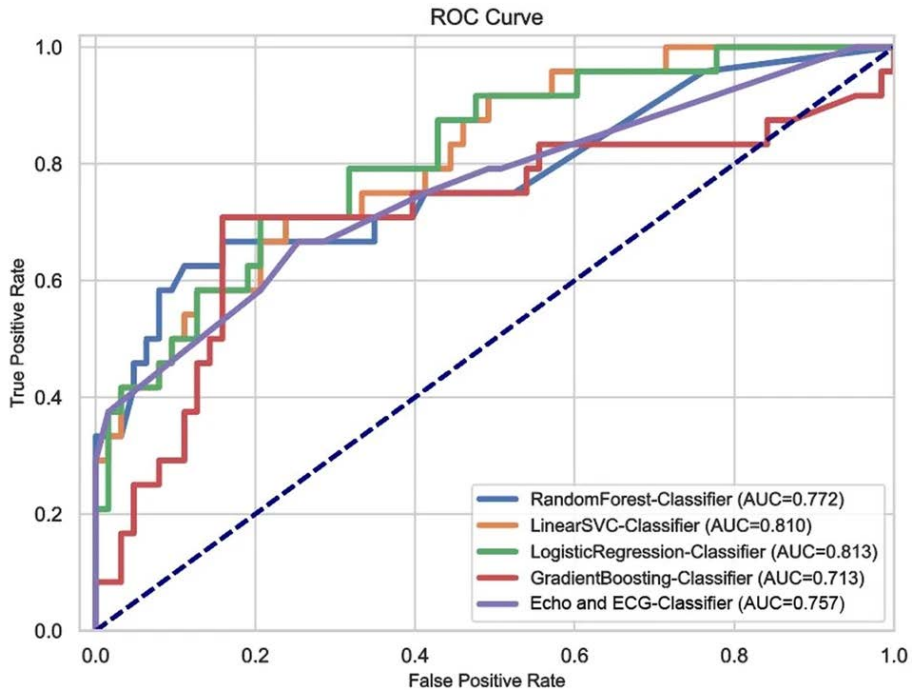


Machine learning



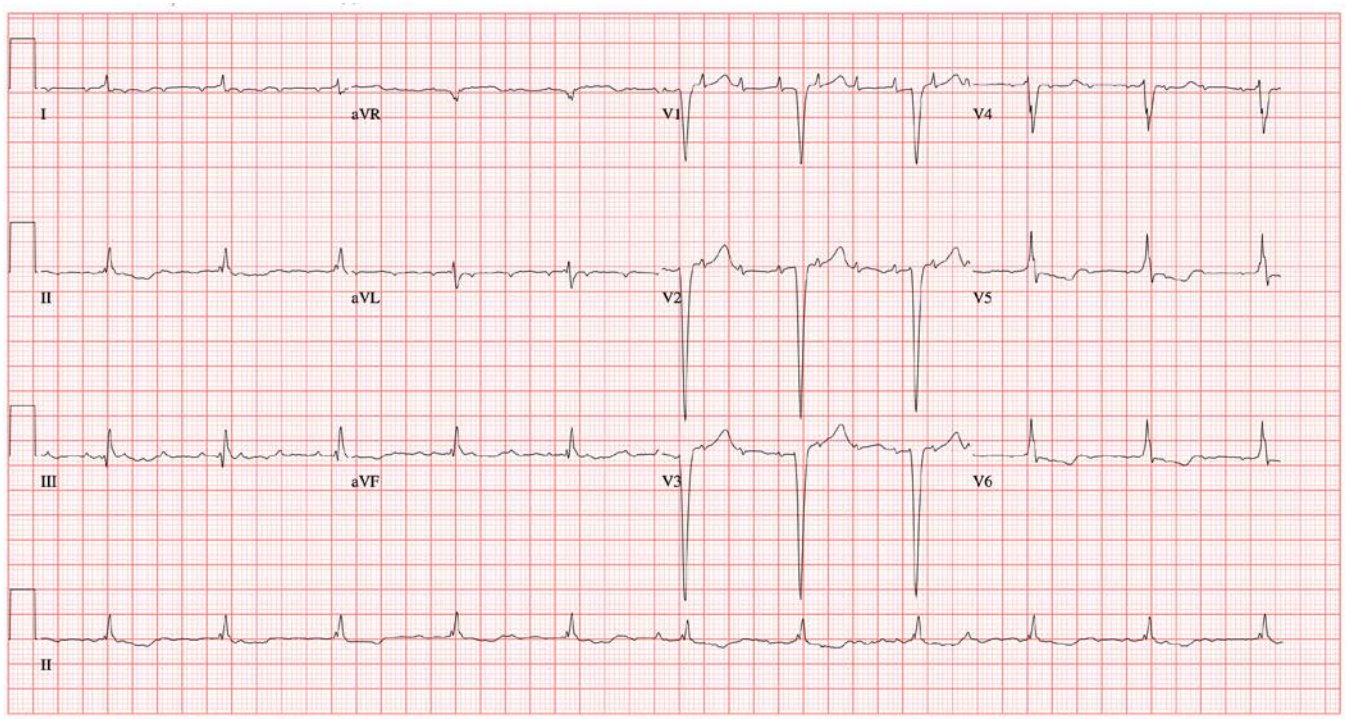






Investigations

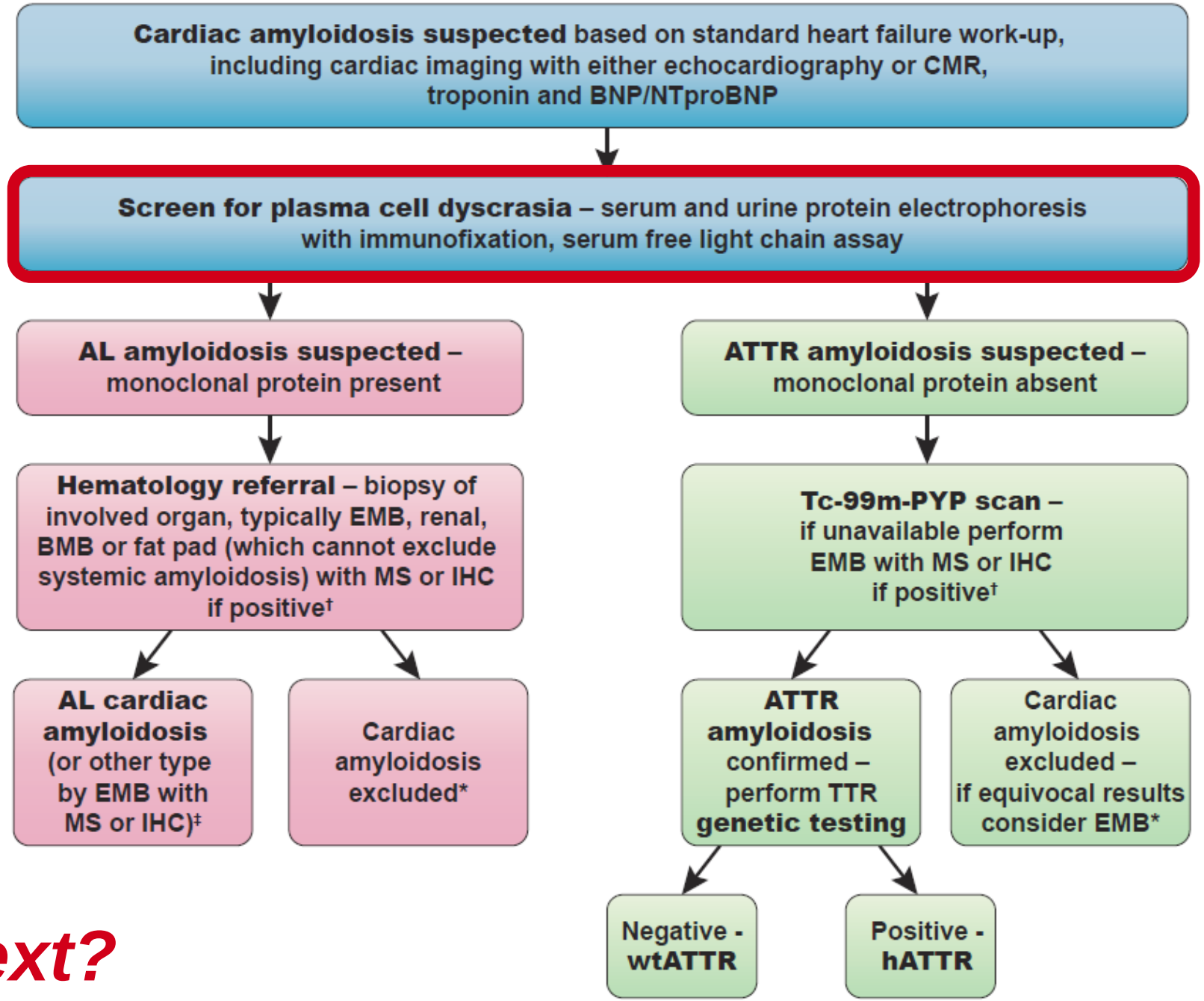
- Echo: normal LV size, thick walls (septum 16 mm), LVEF 50%. GLS -11% with ASP. Normal RV size and function, increased RVWT. Moderate TR, moderate AS.
- NT-proBNP 4000, TnT 43
- GFR 52



What tests should be ordered to confirm the diagnosis?

SPEP and UPEP with IFE normal

K 21.5 (*nml*)
L 11.3 (*nml*)
K/L ratio 1.9 (ULN 1.65)



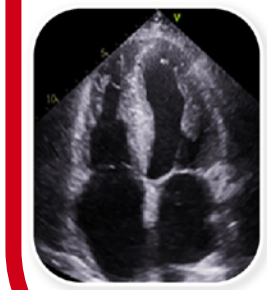
What next?

Validation of algorithm and refinement of FLC cutoffs

Non-biopsy diagnostic criteria of ATTR-CM; *Gillmore et al, 2016*

Clinical phenotype of heart failure +/- arrhythmias

+



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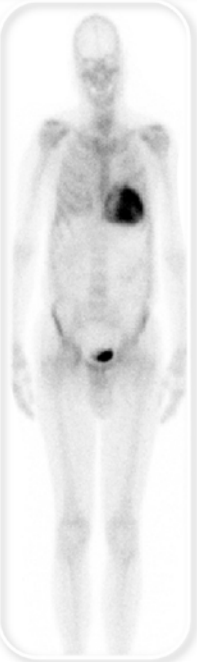

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Absence of MG

Monoclonal gammopathy (MG) is defined as a band on immunofixation of serum or urine or an abnormal FLC ratio on sFLC (κ/λ) assay

- Conventional κ/λ ratio 0.26–1.65 → Specificity of NBDC 97%
- Chronic Kidney disease: refined 'normal' κ/λ ratio according to

eGFR-eGFR >90ml/min-κ/λ 0.26–1.65
eGFR 60-90ml/min-κ/λ 0.26–2.00
eGFR 30-60ml/min-κ/λ 0.26–2.50
eGFR <30ml/min-κ/λ 0.26–3.10

→ Preserves specificity of NBDC 97%

Use of diagnostic algorithm in 3,354 patients with suspected CA

Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloid

Bone scintigraphy with ^{99m}Tc-DPD/HMDP (N=3354)

Grade 0 (N=1,091) | Grade 1 (N=183) | Grade 2 to 3 (N=2,080)

Serum immunofixation + urine immunofixation + serum-free light chain assay (Freelite). Monoclonal protein present?

No (N=498) | Yes (N=593) | Yes (N=122) | No (N=61) | Yes (N=444) | No (N=1,636)

Cardiac AL/ATTR amyloidosis unlikely ↔ Review/request CMR

CMR not suggestive (N=310) | CMR suggestive (N=283)

Need specialized assessment for diagnosis: histological confirmation and typing of amyloid

Cardiac ATTR amyloidosis (N=1,636)

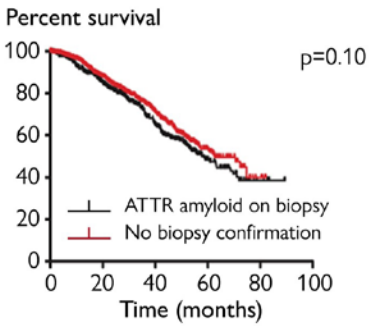
TTR genotyping

Cardiac amyloidosis (N=910)

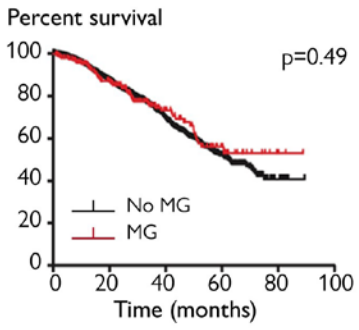
AL (N=434) | ATTR (N=467) | AApoAIV (N=8) | AApoAI (N=1)

Variant ATTR amyloidosis (N=340)

Wild-Type ATTR amyloidosis (N=1,296)



Survival comparison between patients fulfilling NBDC for ATTR-CM with and without corroborative amyloid histology



Survival in patients with ATTR-CM who do and don't have an incidental MG

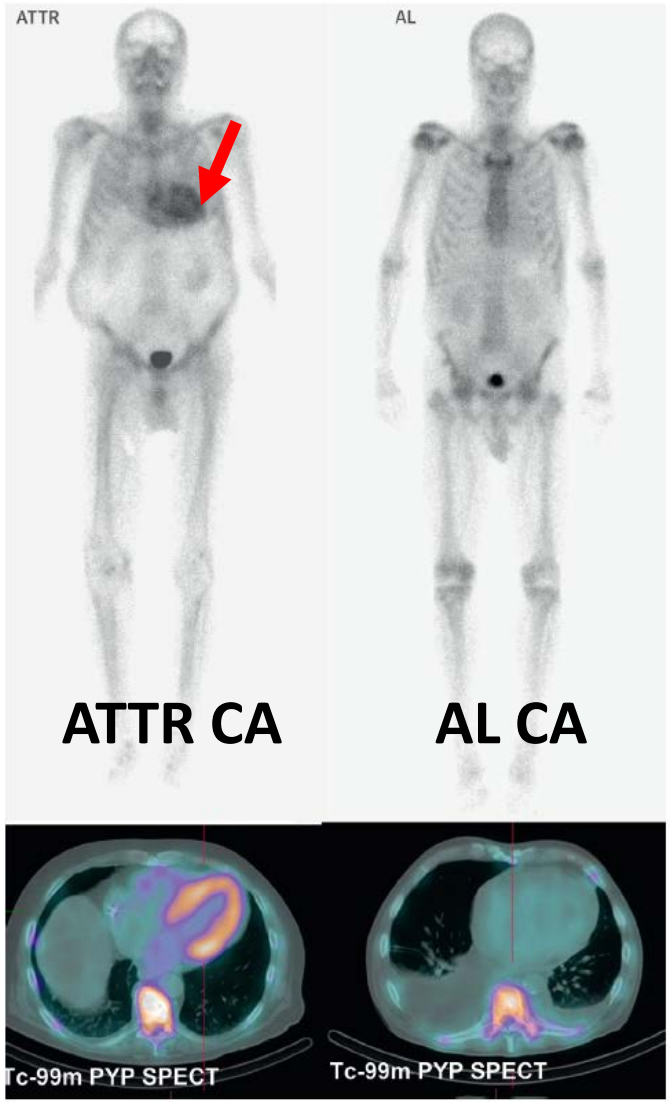
Rauf et al., Eur Heart J. 2023 Online ahead of print.

Tc99m-PYP SPECT in ATTR Cardiac Amyloidosis

Intense diffuse myocardial uptake in a patient with ATTR cardiac amyloidosis, grade 2-3 compared with bone

No/minimal myocardial uptake in a patient with AL cardiac amyloidosis, or other causes of LVH

Heart : Contralateral lung ratio >1.5 or grade 2-3 highly sensitive and specific for ATTR cardiac amyloidosis



Planar whole body scan

With SPECT

CAVEATS

Reported sensitivities and specificities are from experienced labs

Important to confirm myocardial uptake with SPECT imaging to differentiate from blood pool

Reported specificity only applies to patients with negative AL workup:

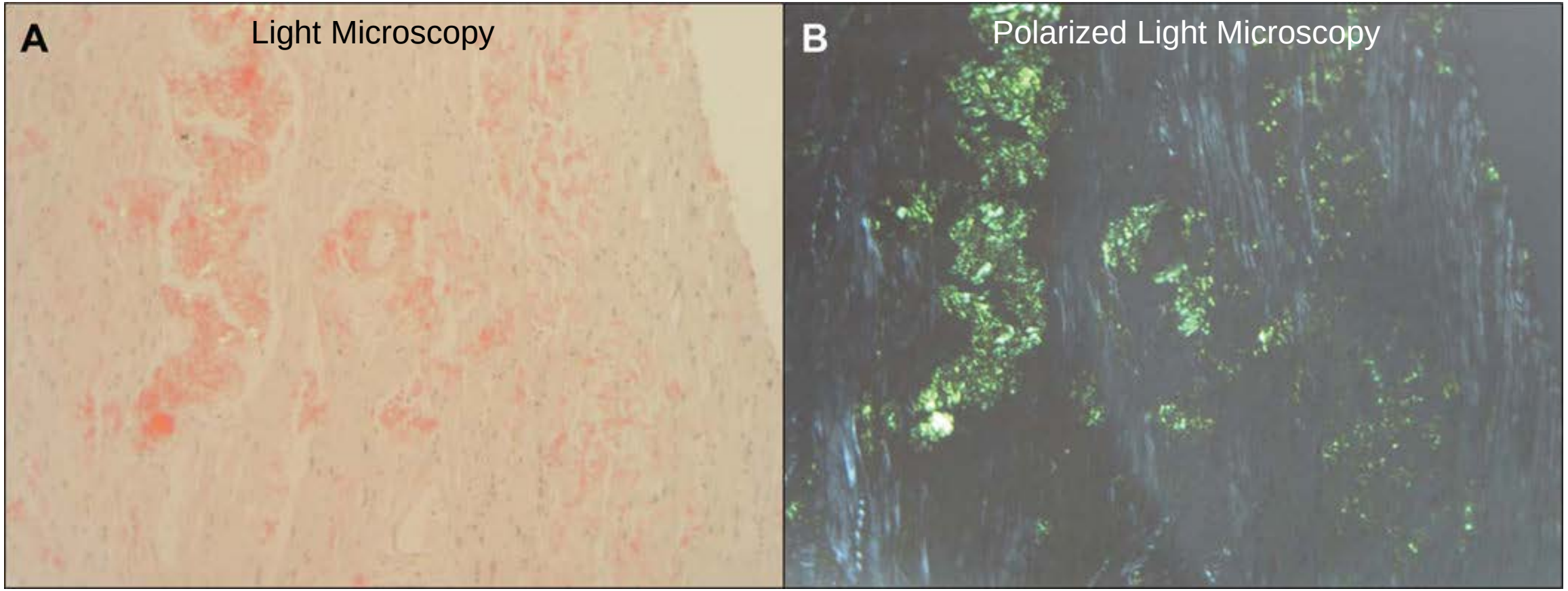
- SPEP/UPEP with IFE
- Serum FLC ratio

Must rule out AL in order to interpret test properly

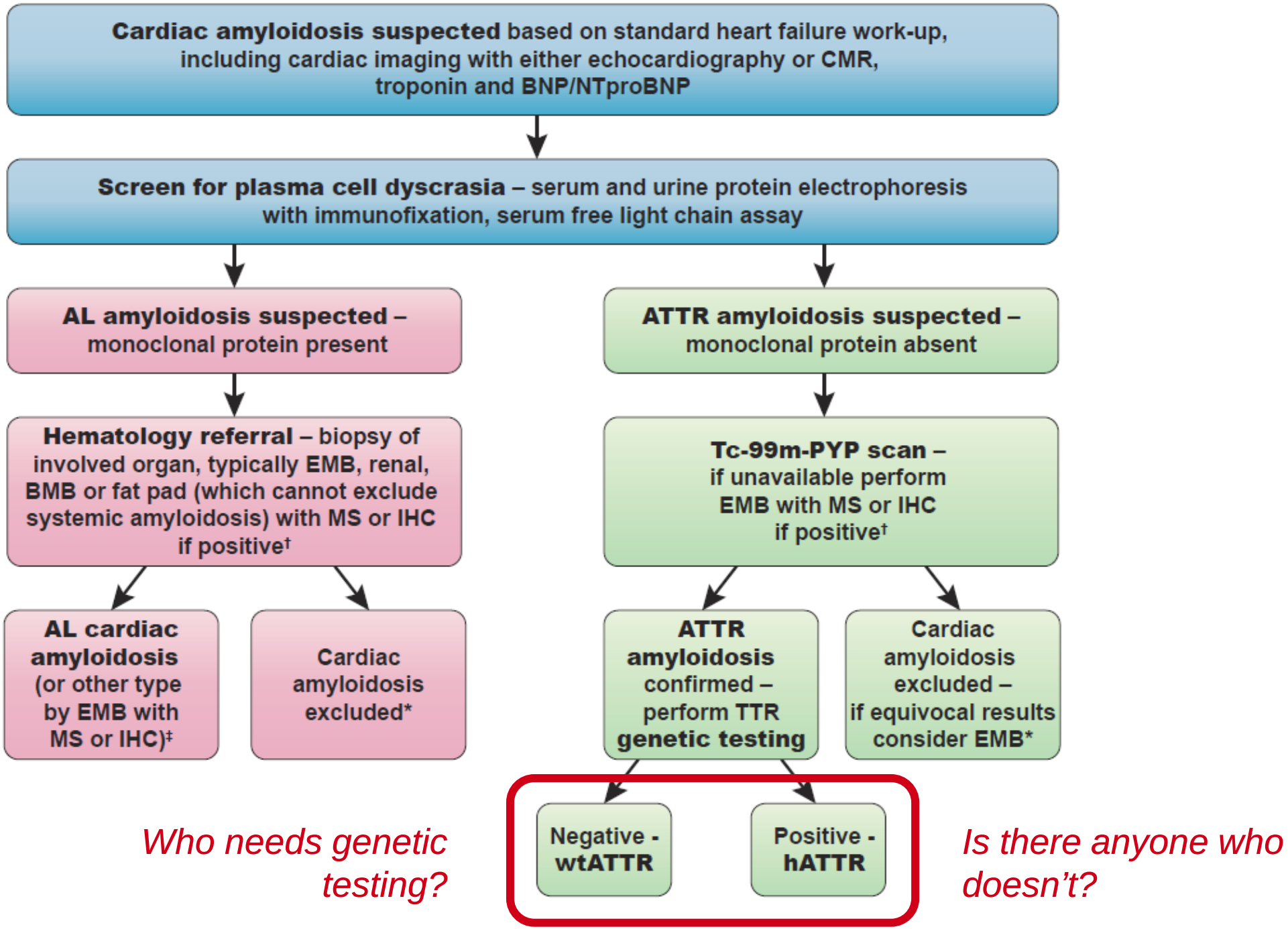
ATTR, transthyretin amyloidosis; SPECT, single photon emission computed tomographyTc99m-PYP, ^{99m}technetium pyrophosphate.

J Am Coll Cardiol, 68(12), Falk RH et al., 1323-1341, (2016)

Endomyocardial Biopsy in Cardiac Amyloidosis



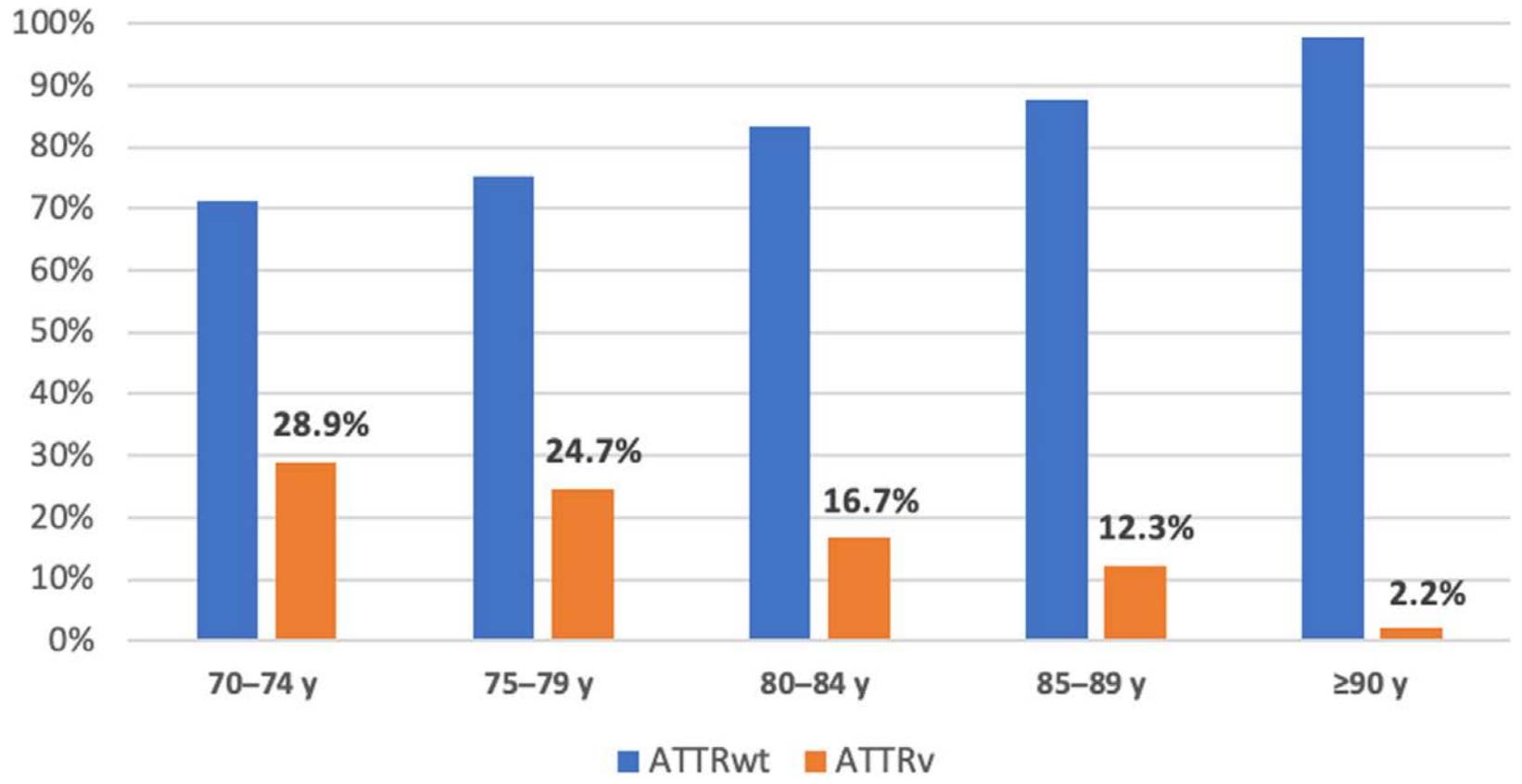
A) Light microscopy, and B) polarized light microscopy, 400X magnification.
Ruberg FL, Berk JL, Circulation 2012;126(10):1286-1300.



Who needs genetic testing?

Is there anyone who doesn't?

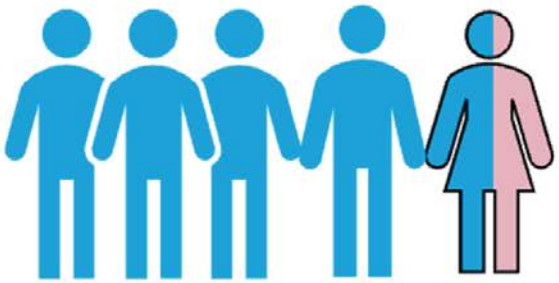
Trends in diagnosis of ATTRv-CM according to age ranges at diagnosis



Eur J Heart Fail. 2023 Jan 16. doi: 10.1002/ejhf.2776. Online ahead of print.

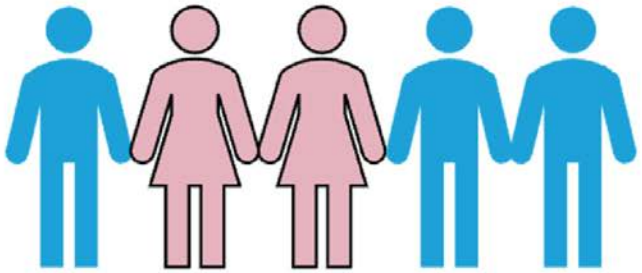
Clinical Profile of Patients with Wild-Type and Hereditary ATTR-CM

ATTRwt-CM



Age ≥ 80 years
♂
Caucasian Ethnicity
No Autonomic Neuropathy
No Peripheral Neuropathy
Atrial Fibrillation
Ischaemic Heart Disease

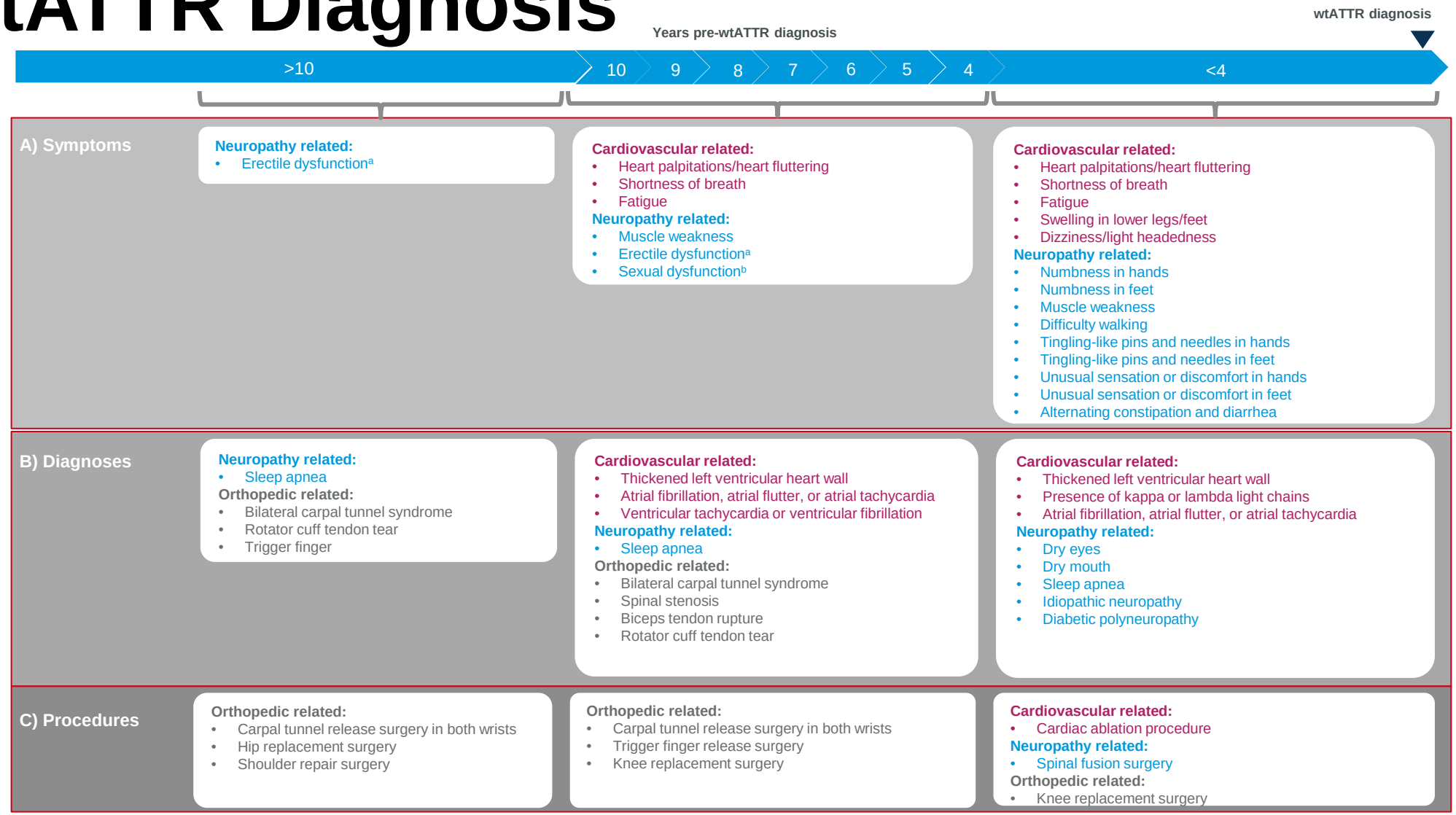
ATTRv-CM



Age < 80 years
♀
Afro-Caribbean Ethnicity
Orthostatic Hypotension
Peripheral Neuropathy
Sinus Rhythm
No Ischaemic Heart Disease

Eur J Heart Fail. 2023 Jan 16. doi: 10.1002/ejhf.2776. Online ahead of print.

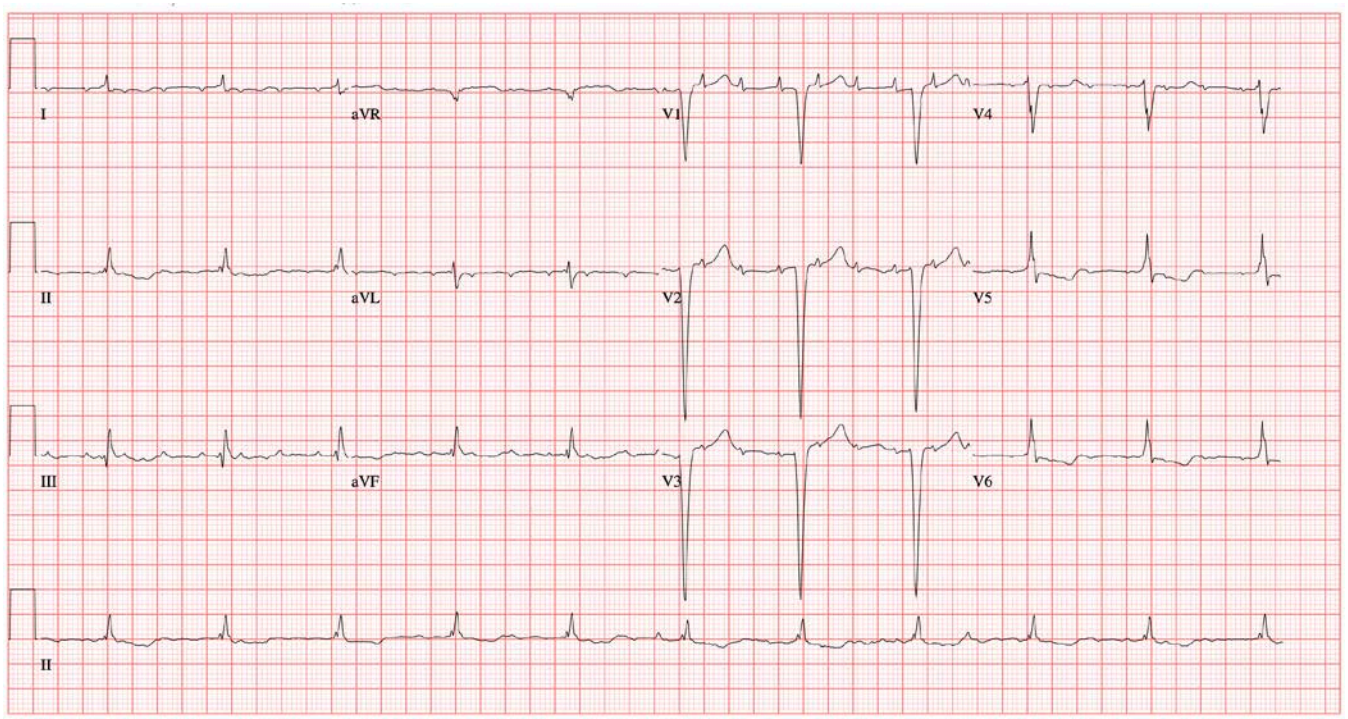
Comorbidities in ≥10% of Patients Prior to wtATTR Diagnosis



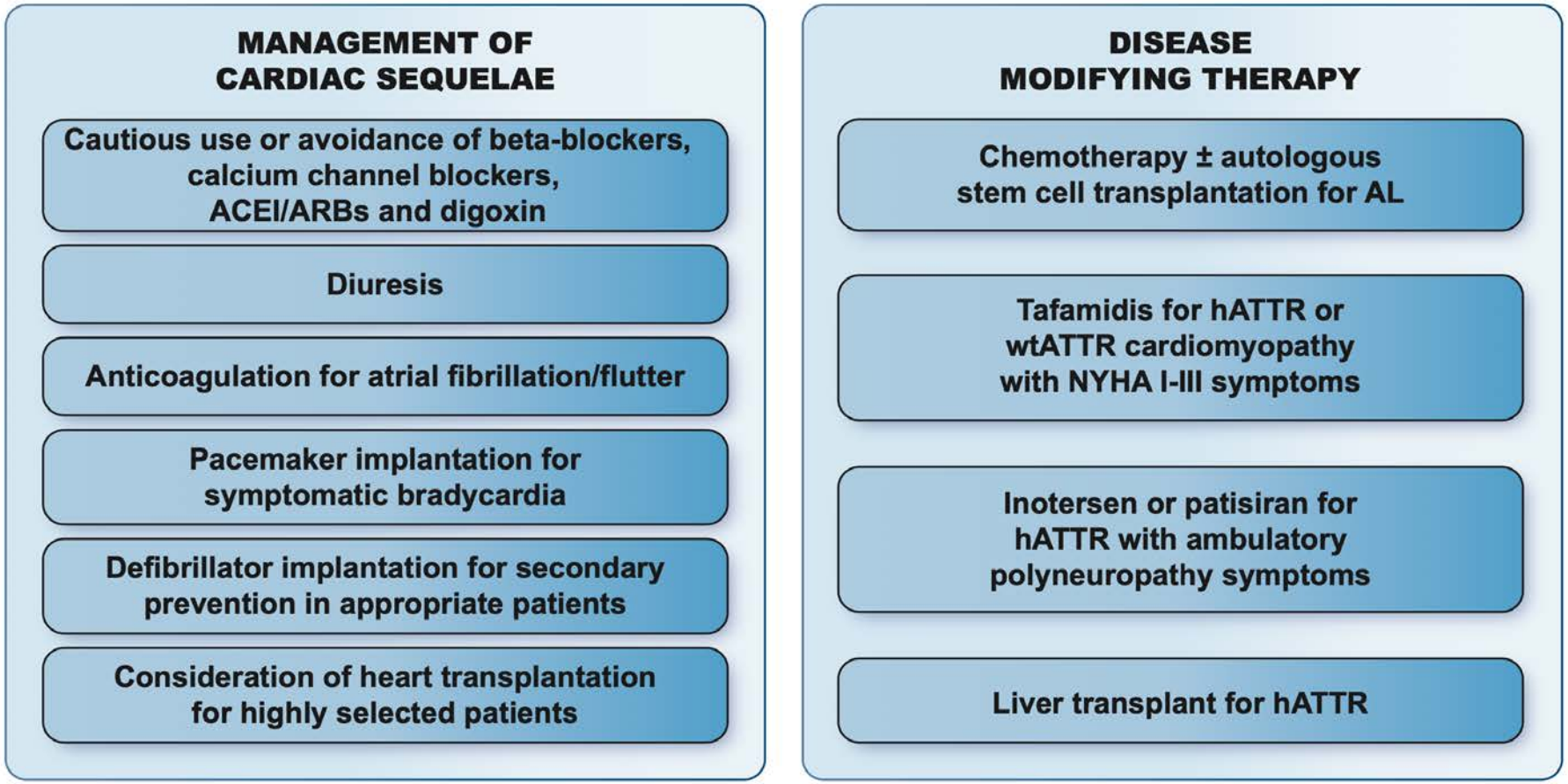
Karam et al., HFSA ASM 2022

Investigations

- Echo: normal LV size, thick walls (septum 16 mm), LVEF 50%. GLS -11% with ASP. Normal RV size and function, increased RVWT. Moderate TR, moderate AS.
- NT-proBNP 4000, TnT 43
- GFR 52
- **SPEP/UPEP/IFE/SFLC normal *for GFR***
- **PYP: grade 3**
- **Genetic testing: no mutation in *TTR***



So, he has ATTRwt… Now what?

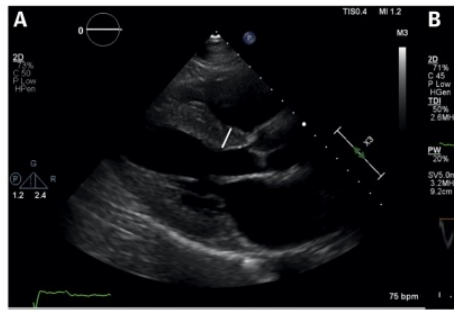


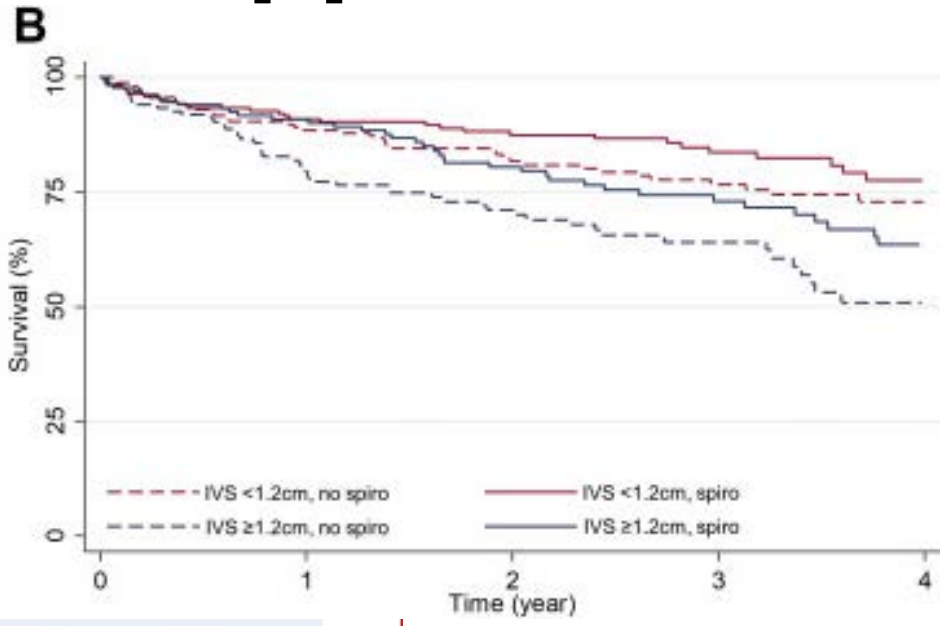
How can we optimize his supportive management?

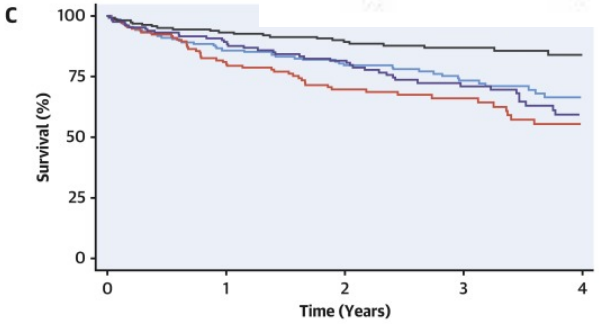
MANAGEMENT OF CARDIAC SEQUELAE

- Cautious use or avoidance of beta-blockers, calcium channel blockers, ACEI/ARBs and digoxin
- Diuresis
- Anticoagulation for atrial fibrillation/flutter
- Pacemaker implantation for symptomatic bradycardia
- Defibrillator implantation for secondary prevention in appropriate patients
- Consideration of heart transplantation for highly selected patients

CENTRAL ILLUSTRATION: Example of Cardiac Amyloidosis







Number at risk

s' velocity ≤6 cm/s, IVS <1.2 cm	157	131	104	69	37
s' velocity ≤6 cm/s, IVS ≥1.2 cm	135	105	70	41	19
s' velocity >6 cm/s, IVS <1.2 cm	165	152	121	77	42
s' velocity >6 cm/s, IVS ≥1.2 cm	133	113	84	53	27

Sperry, B.W. et al. J Am Coll Cardiol HF. 2021;9(11):795-802.

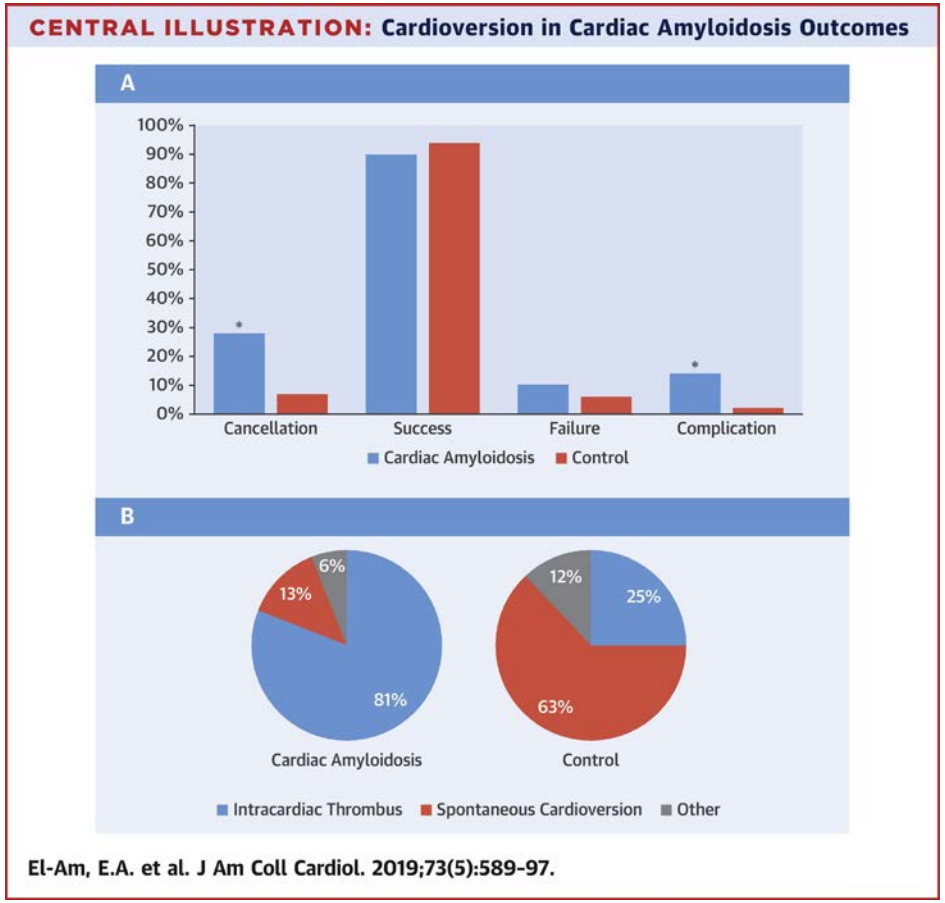
Supportive management

- Metoprolol reduced to 25 BID, HR 89
- Furosemide increased to 40 mg BID, spironolactone 12.5 mg daily added
- He feels better!
- GFR stable, NT-proBNP 2300

- Metoprolol stopped, average HR on Holter now 115 bpm
- What should we do now?

Back to Mr. F

- He is loaded with oral amiodarone followed by 100 mg daily maintenance
- HR improved to 80
- TEE-guided cardioversion successful
- Continues on apixaban
- NYHA 2



What about the other parallel track?

Would you offer disease-modifying therapy to Mr. F?

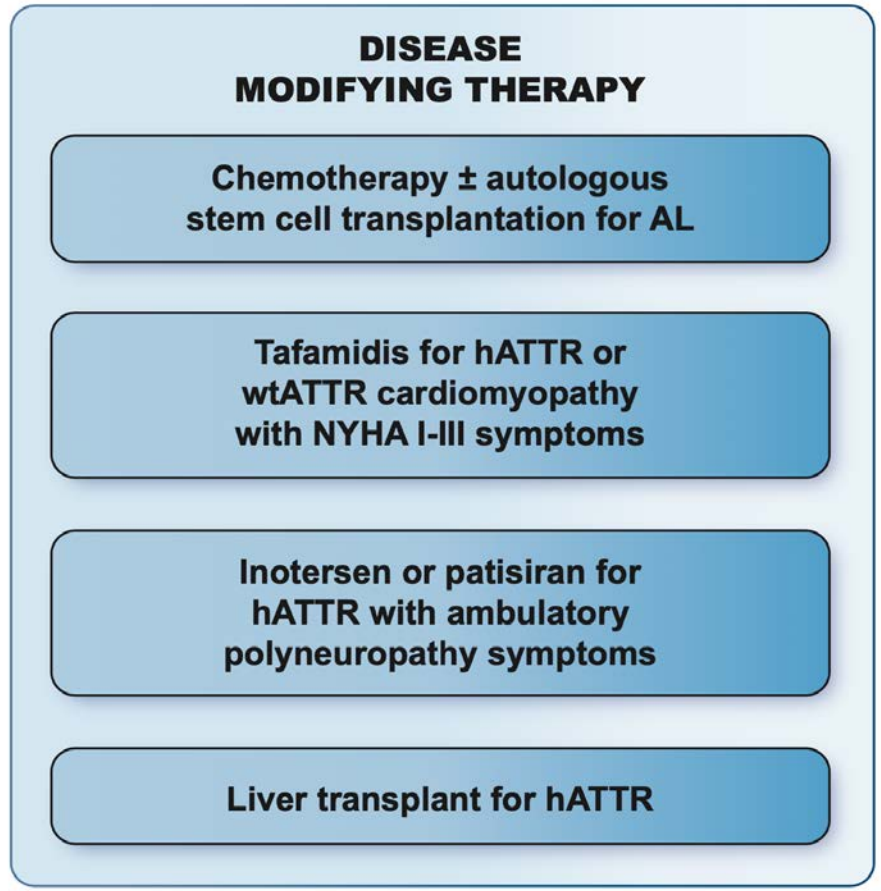


TABLE 5 Recommendations About Disease-Modifying Drugs for ATTRv or ATTRwt Amyloidosis

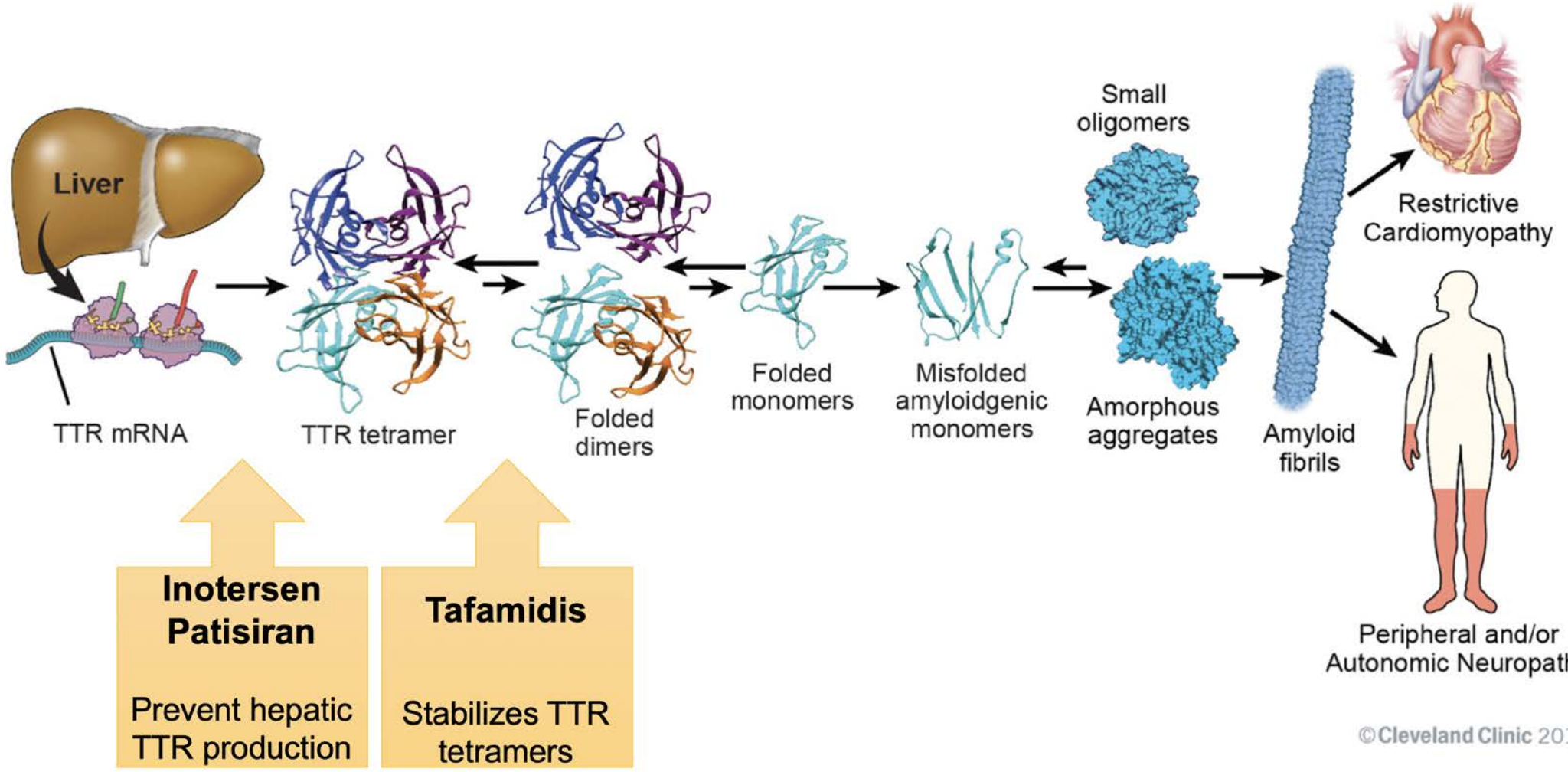
Rapezzi C, et al. J Am Coll Cardiol. 2022;79(13):1288–1303.

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Tafamidis	ATTRwt-CA or ATTRv-CA (recommended)[a] ATTRv-CA + PN (stage 1) (recommended) ATTRv PN (stage 1) (recommended)[b]	ATTRwt-CA or ATTRv-CA (recommended)[a]	Recommended for patients with ATTR-CA and NYHA functional class I-III symptoms[a]	Patients with predominantly cardiac disease from ATTRv or ATTRwt, NYHA functional class I to III symptoms (recommended)[a]	• ATTRwt-CA with NYHA functional class I-II symptoms (recommended) • ATTRwt-CA with NYHA functional class III symptoms (recommended) • ATTRv-PN and CA with NYHA functional class I-II symptoms (recommended) • ATTRv-PN and CA with NYHA functional class III symptoms (recommended)[b]
Notes	ESC HF guidelines recommendations: • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) Reasonable expected survival	ATTR-ACT inclusion and exclusion criteria should be met Case-by-case decision is needed when NYHA functional class III symptoms	ATTR-ACT inclusion (NT-proBNP >600 ng/L) and exclusion criteria (NYHA functional class IV, severe functional disability, 6MWD <100 m) should be considered when determining eligibility for treatment The expected benefit is greater in patients with NYHA functional class I-II symptoms	Benefit of tafamidis not observed in patients with NYHA functional class IV, severe aortic stenosis, or eGFR <25 mL/min/1.73 m^2	Need for histological documentation of ATTR amyloid deposits in the heart or peripheral tissue Tafamidis doses: 20 mg PN, 80 mg CA
Patisiran	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]
	ATTRv PN (stage 1-2) + CA (recommended)[b]	No sufficient data about ATTRv PN (stage 1-2) + CA	No sufficient data about ATTRv PN + CA	–	No sufficient data about ATTRv PN + CA
Inotersen	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	Not approved in Japan

Disease modifying therapy for Mr. F?

- Does he meet criteria for tafamidis?
  - ATTR-CM with septum >12 mm
  - ATTRwt or ATTRv
  - NYHA I-III
- What if he had ATTRv, V122I mutation, minimal polyneuropathy symptoms?
- What if he had ATTRv, T60A mutation, symptomatic but ambulatory polyneuropathy?

Therapeutic Targets of the Amyloidogenic TTR Cascade



The NEW ENGLAND JOURNAL of MEDICINE

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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*

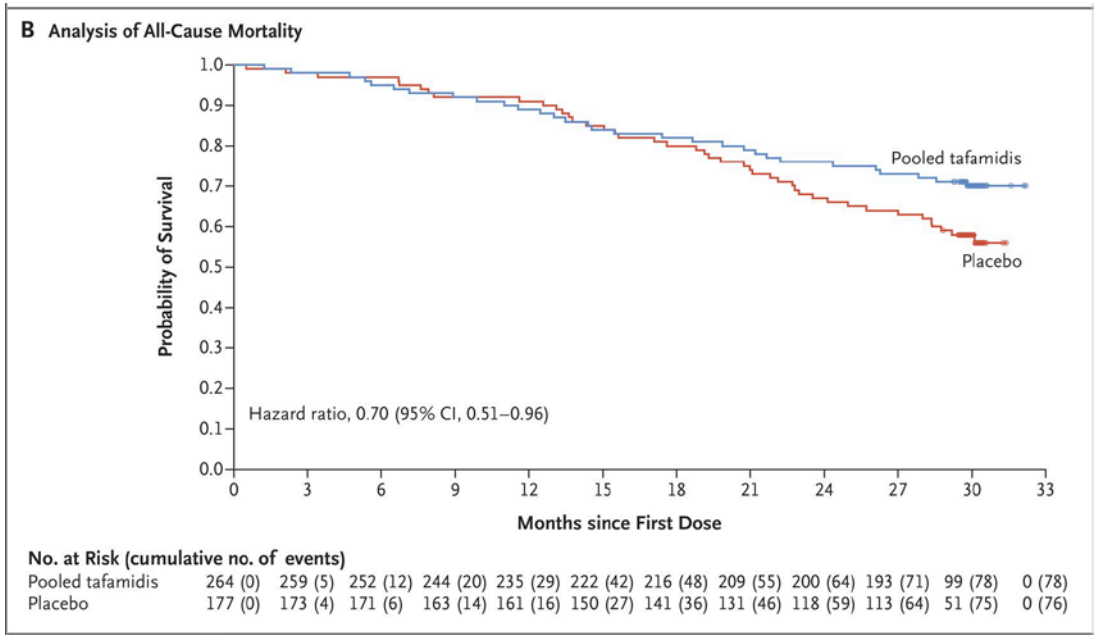
ATTR-ACT Primary outcome and components

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

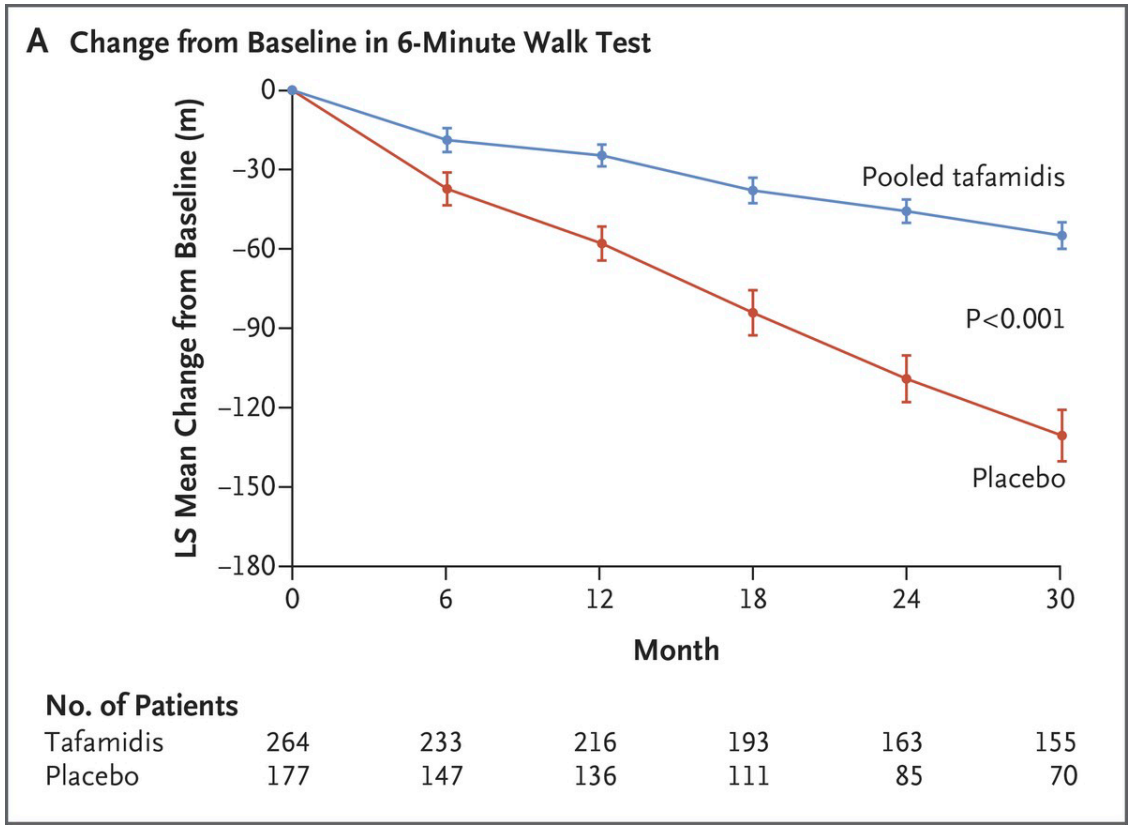
C Frequency of Cardiovascular-Related Hospitalizations

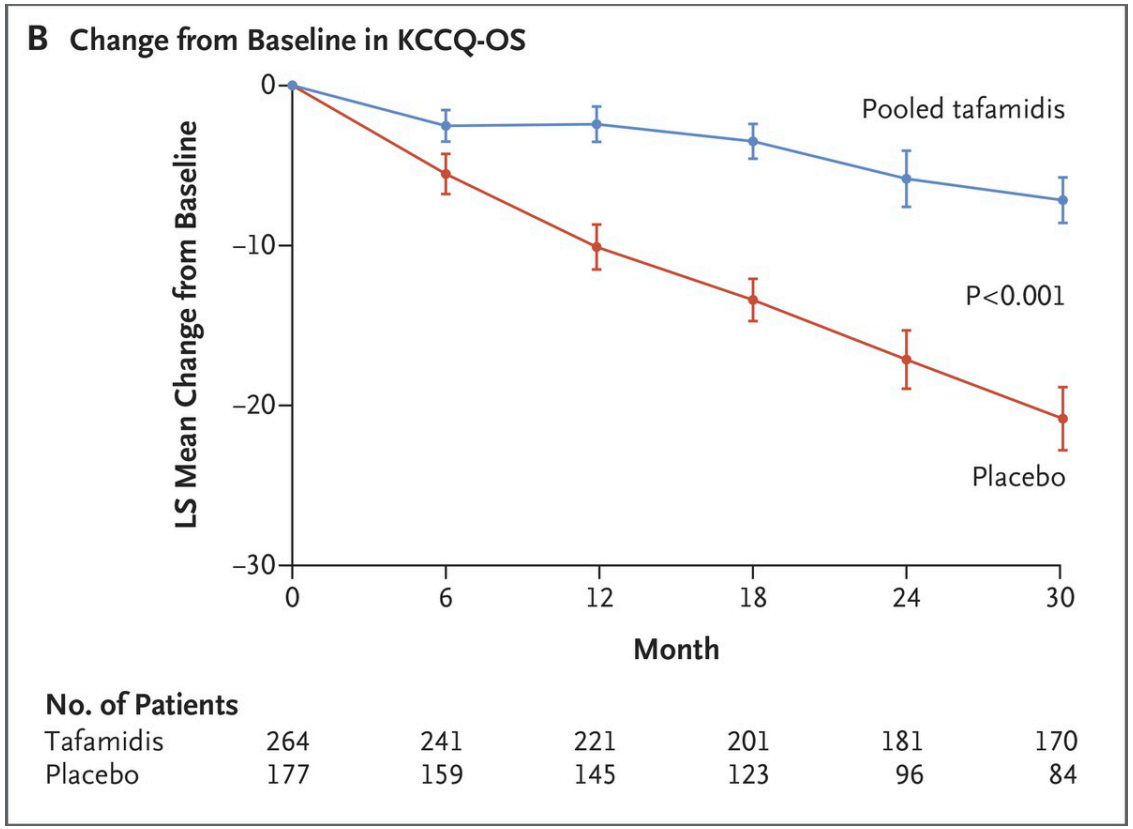
	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)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



Maurer MS et al. N Engl J Med 2018;379:1007-1016

ATTR-ACT Secondary outcomes

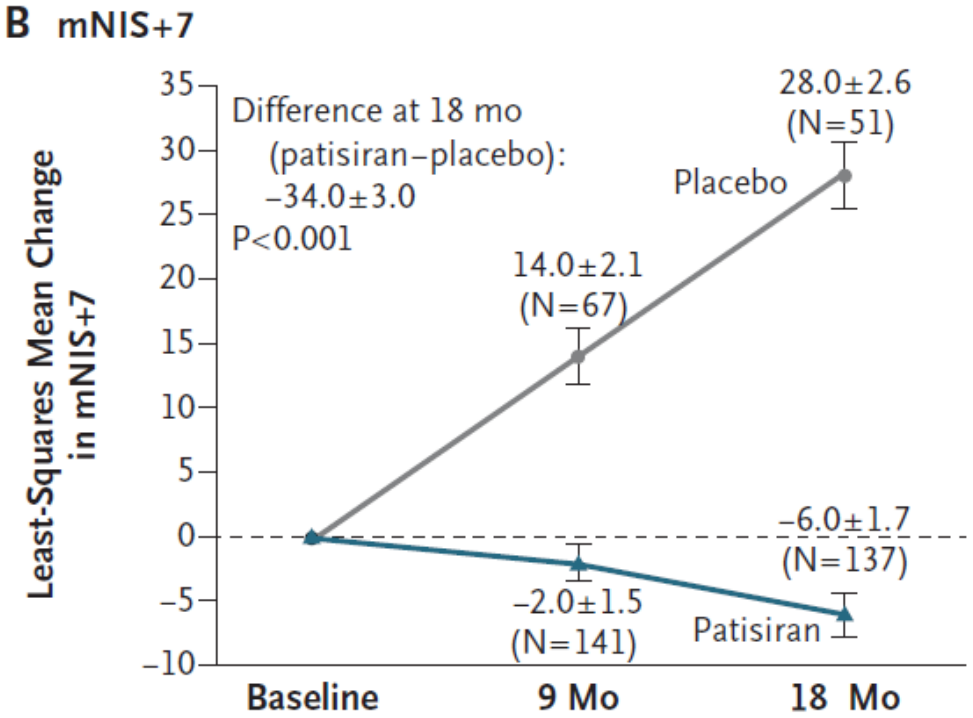




Maurer MS et al. N Engl J Med 2018;379:1007-1016

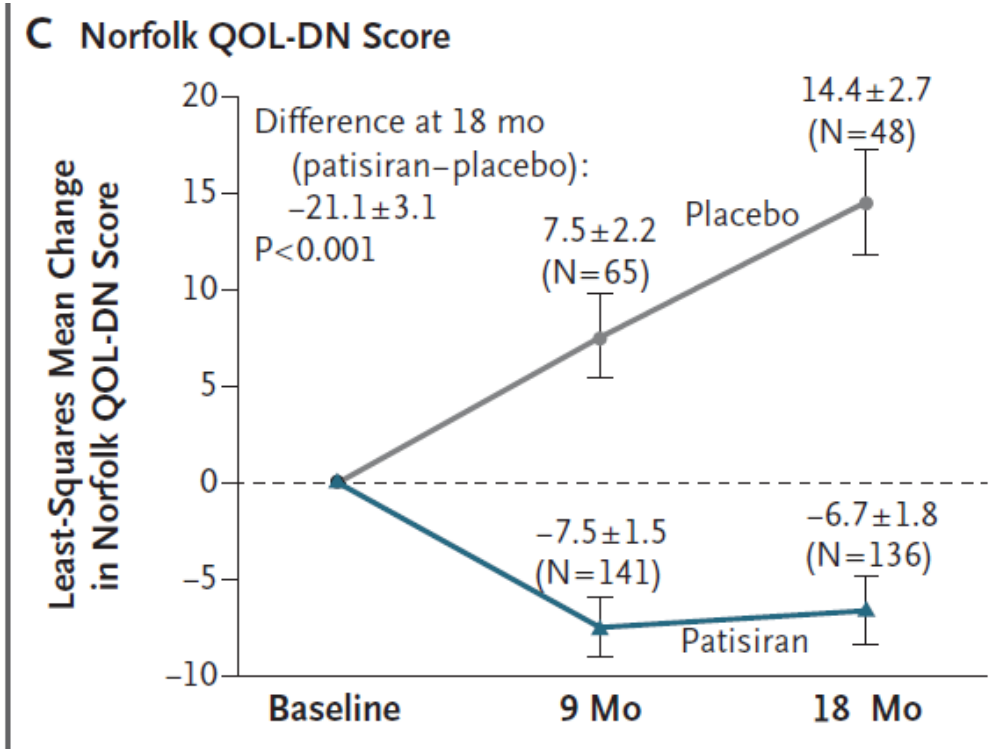
APOLLO A: Patisiran in HATTR-PN

mNIS+7



The higher the score, the poorer the function. A decrease in score indicates an improvement in function.

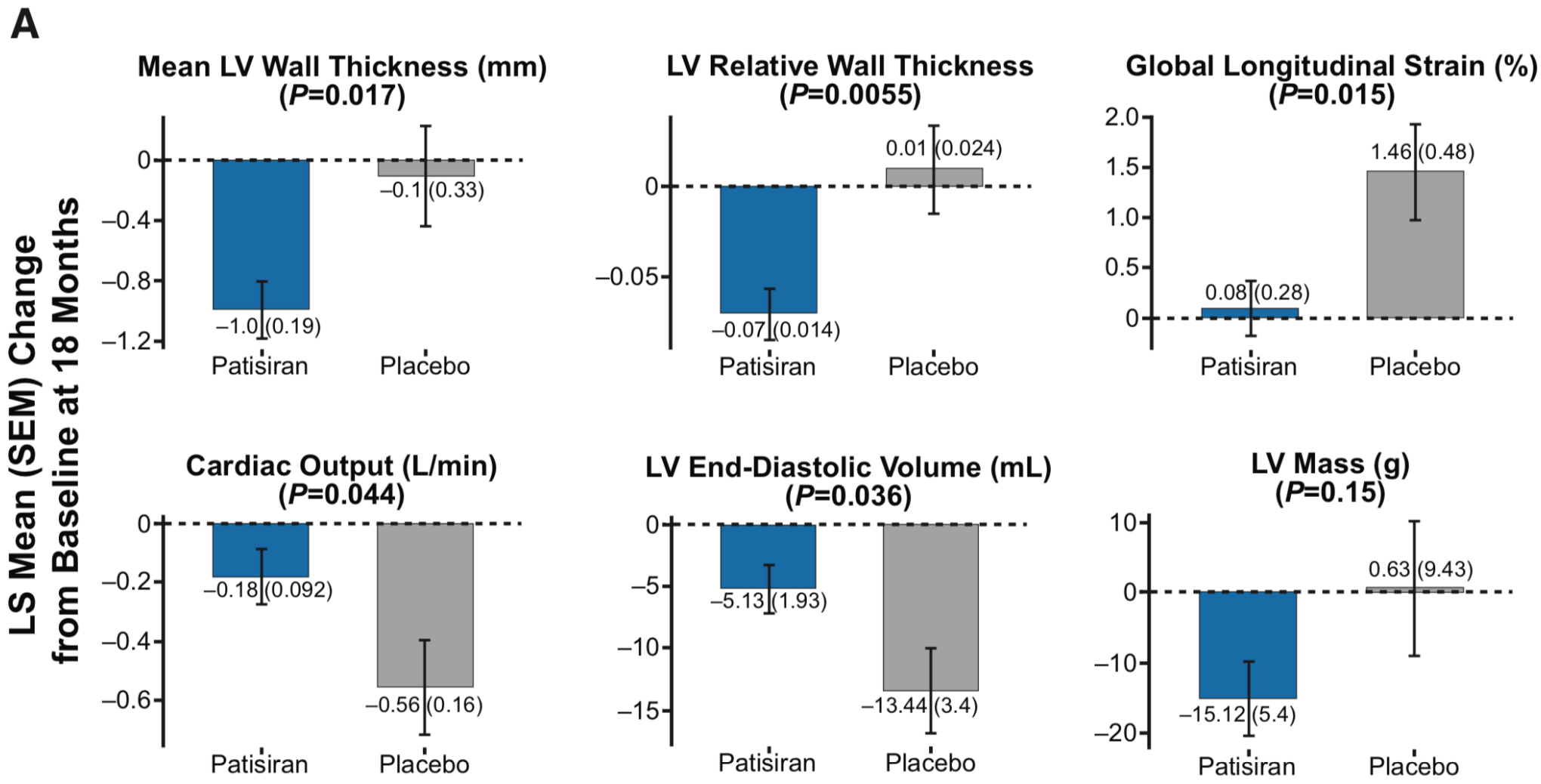
Norfolk QOL-DN



The higher the score, the poorer the QoL. A decrease in score indicates an improvement in QoL.

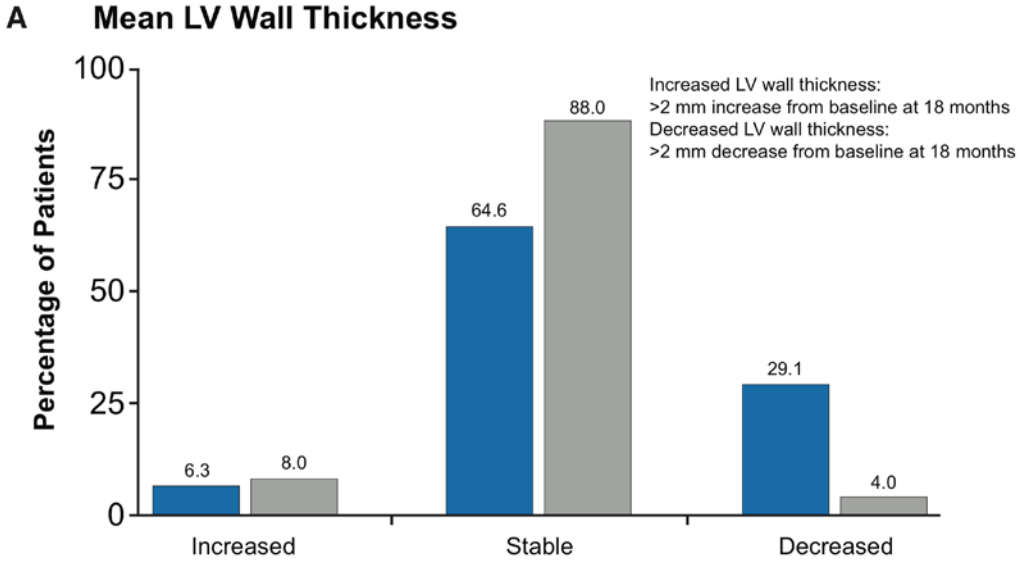
Adapted from Adam D et al. N Engl J Med 2018;379(1):11-21.

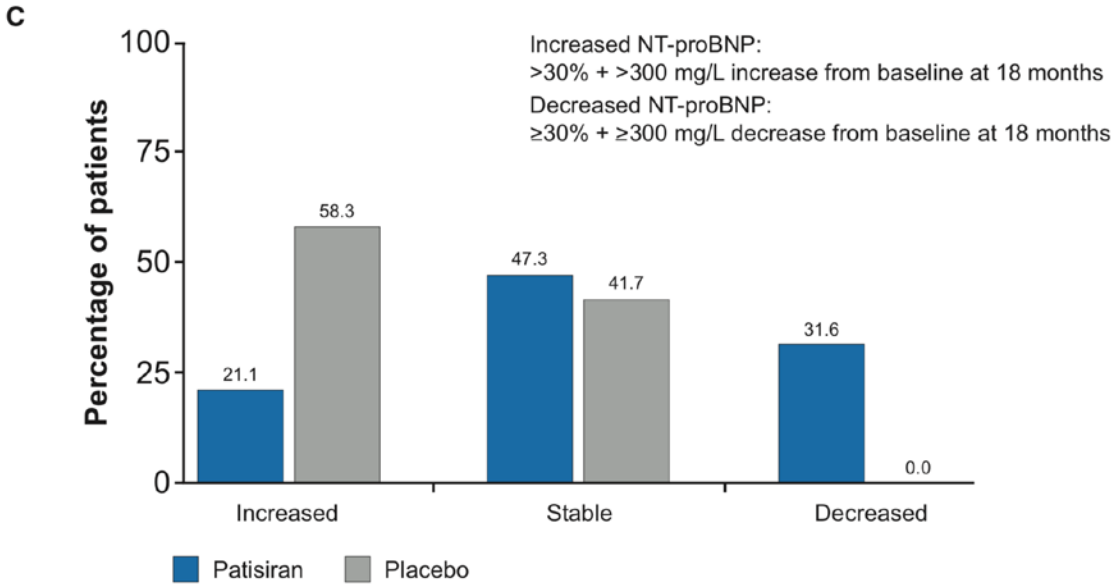
Patisiran: Cardiac Endpoints (post-hoc)



Circulation. 2019;139:431–443

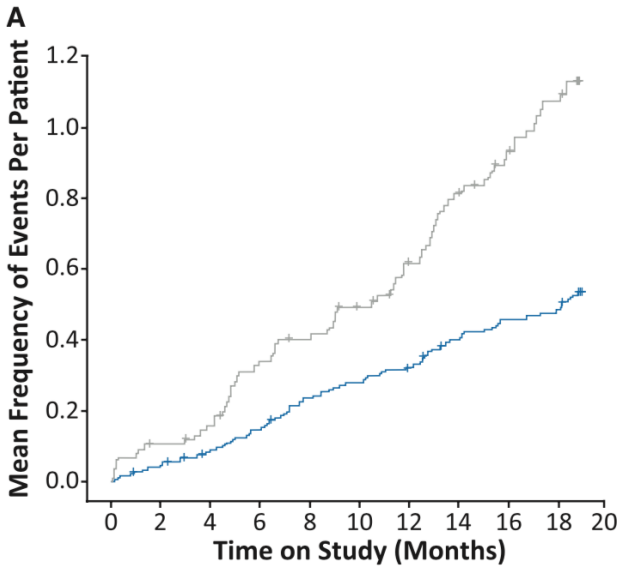
Patisiran: Cardiac and Clinical Outcomes (post-hoc)



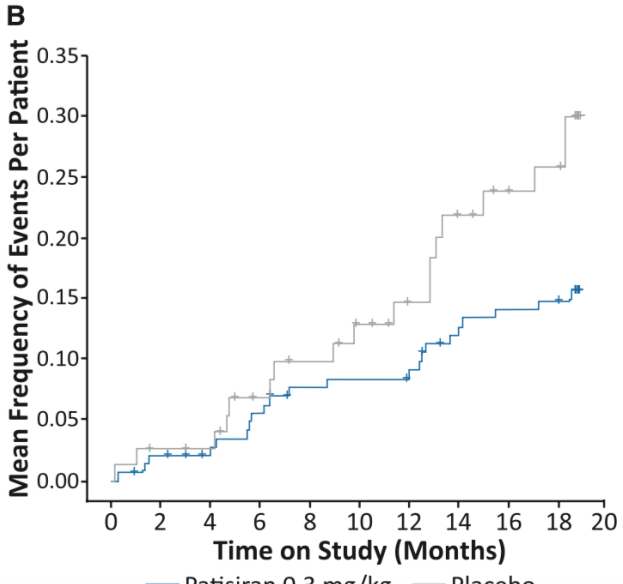


Circulation. 2019;139:431–443

All-cause hospitalization and mortality



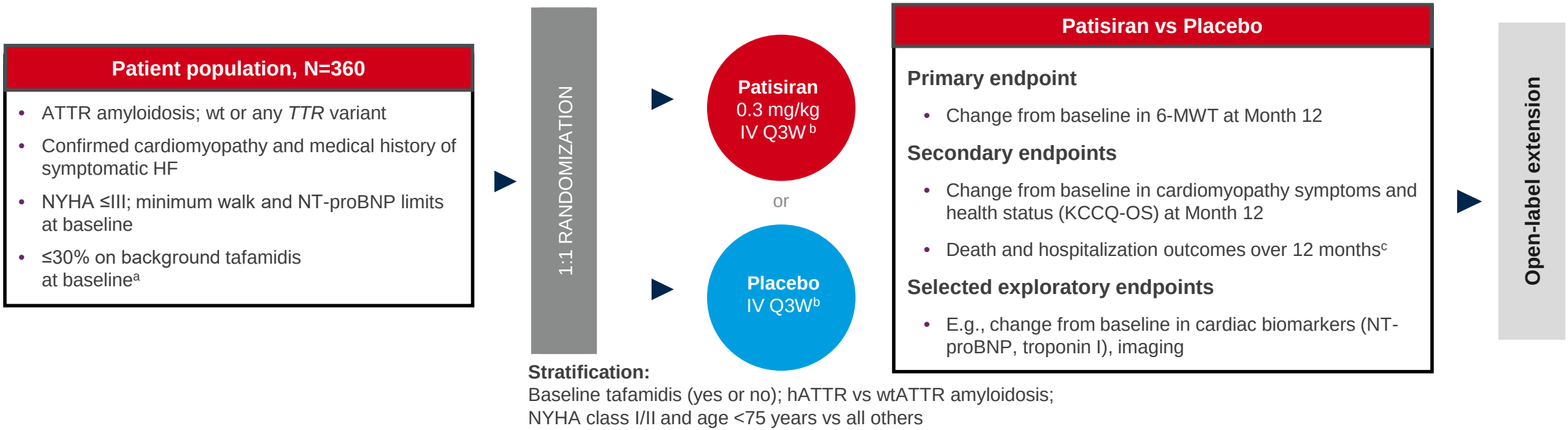
Cardiac hospitalization and all-cause mortality



Patisiran Phase 3 APOLLO-B Study

- Randomized, double-blind, placebo-controlled study in patients with ATTR amyloidosis with cardiomyopathy

Study Design: Patisiran Phase 3 APOLLO-B Study



Stratification:
Baseline tafamidis (yes or no); hATTR vs wtATTR amyloidosis;
NYHA class I/II and age <75 years vs all others

- [a]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [b]To reduce likelihood of infusion-related reactions, patients receive following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. [c]Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; composite all-cause mortality, frequency of all-cause hospitalizations, and urgent HF visits in patients not on tafamidis at baseline; composite all-cause mortality, frequency of all-cause hospitalizations, and urgent HF visits in overall population.
- **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CV, cardiovascular; hATTR, hereditary transthyretin-mediated; HF, heart failure; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q3W, once every 3 weeks; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated

Results

Baseline Biomarker and Echocardiographic Parameters

- Baseline patient demographics and characteristics,[1] including cardiac parameters, were comparable between the patisiran and placebo arms

Baseline Characteristics

Characteristic	Patisiran (n=181)	Placebo (n=178)
NT-proBNP level, ng/L, median (IQR)	2008 (1135–2921)	1813 (952–3079)
Troponin I level, ng/L, median (IQR)	64.00 (38.60–92.00)	60.20 (38.15–103.10)
Echocardiographic parameters, mean (SD)		
Mean LV wall thickness (cm)	1.781 (0.248)	1.786 (0.238)
LV relative wall thickness	0.835 (0.194)	0.855 (0.190)
LV mass (g)	335.485 (91.390)	326.445 (79.385)
LV end-diastolic volume (mL)	89.550 (24.600)	92.903 (26.246)
Global longitudinal strain (%)	–10.89 (3.36)	–11.19 (3.01)
Cardiac output (L/min)	3.442 (0.976)	3.519 (0.971)
LV ejection fraction (%)	55.604 (13.031)	56.219 (13.156)

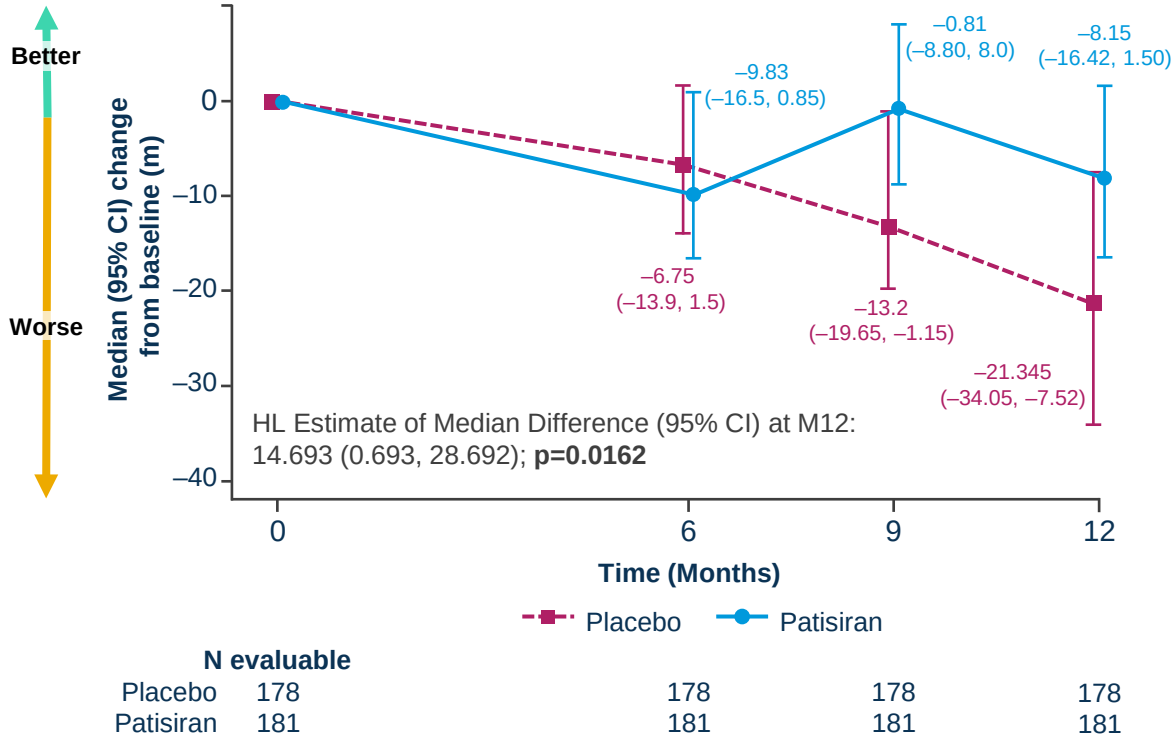
- **Abbreviations:** IQR, interquartile range; LV, left ventricular; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; SD, standard deviation. **Reference:** 1. Maurer et al. *International Symposium on Amyloidosis (ISA)* 2022.

Results

Primary Analysis: Functional Capacity

- Patisiran demonstrated significant clinical benefit in functional capacity (6-MWT) compared with placebo at Month 12 (p=0.0162)[a]
  - Decline in 6-MWT with patisiran was similar to typical age-related decline seen in healthy adults[1–7]
- Prespecified sensitivity analysis (MMRM) confirmed robustness of the observed benefit in 6-MWT with patisiran vs placebo; LS mean (SEM) difference: 18.146 m (7.967), nominal p=0.0234[b]

Change from Baseline in 6-MWT at Month 12[a]



N evaluable

Placebo	178	178	178	178
Patisiran	181	181	181	181

• [a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values is based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline is averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis were imputed as the worst 10th percentile change observed across all patients in the double-blind period, capped by the worst possible change for the patient (i.e., 0 minus the patient's baseline 6-MWT). Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. At baseline, the median (IQR) 6-MWT was 358.00 (295.00, 420.00) in the patisiran group and 367.74 (300.00, 444.25) in the placebo group. [b]LS means (SEM), LS mean (SEM) differences, 95% CIs, and Month 12 p-value were estimated from the MMRM model. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group). At baseline, the mean (SD) 6-MWT was 360.466 (102.268) in the patisiran group and 374.646 (102.392) in the placebo group. 6-MWT data for 2 patisiran patients were updated for this analysis following database lock, as updated by the investigator. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges–Lehmann; m, meter; M, month; MMRM, mixed effects model repeated measures; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

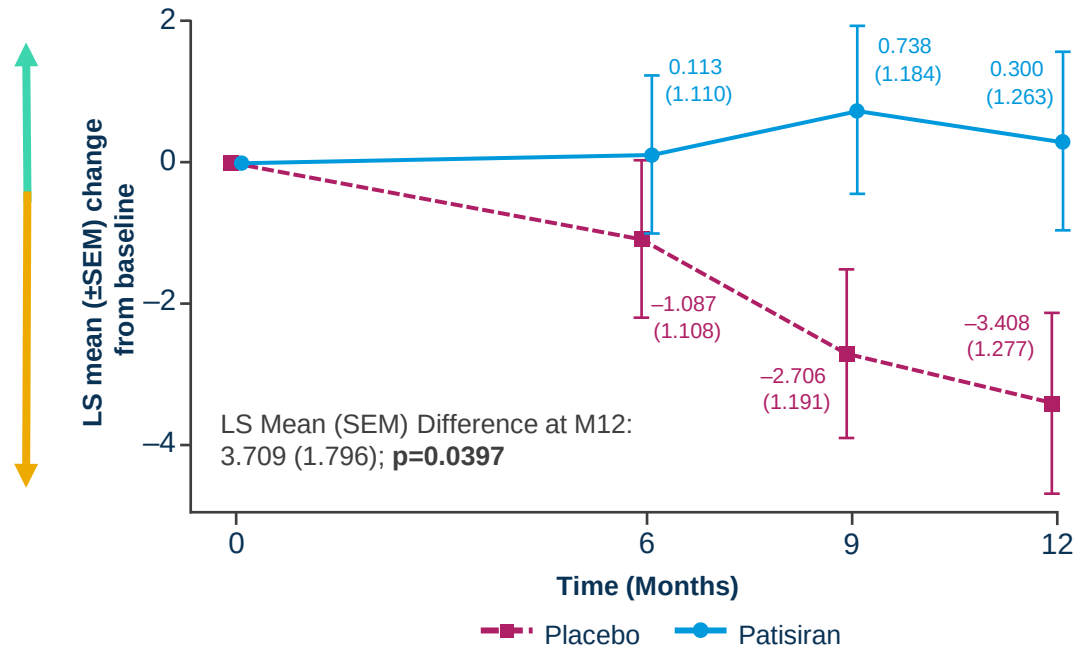
• **References:** 1. Enright et al. *Am J Respir Crit Care Med* 1998;158:1384–7; 2. Troosters et al. *Eur Respir J* 1999;14:270–4; 3. Poh et al. *Respirology* 2006;11:211–6; 4. Camarri et al. *Respir Med* 2006;100:658–65; 5. Jenkins et al. *Physiother Theory Pract* 2009;25:516-22; 6. Casanova et al. *Eur Respir J* 2011;37:150–6; 7. Vaish et al. *Int J Tuberc Lung Dis* 2013;17:698–703.

Results

Secondary Analysis: Health Status/Quality of Life (QOL)

- Patisiran demonstrated significant clinical benefit in health status and QOL (KCCQ-OS) compared with placebo at Month 12 (p=0.0397)[a]

Change from Baseline in KCCQ-OS at Month 12[a]



N evaluable

Placebo	178	170	167	164
Patisiran	181	169	170	170

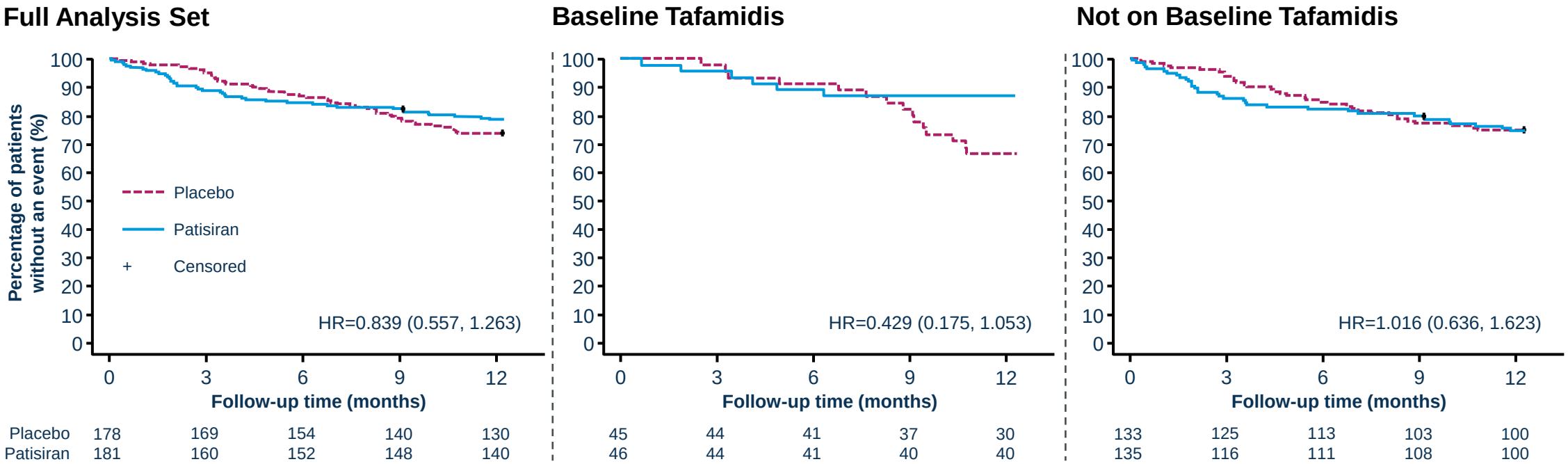
- [a]Analysis based on MMRM method. Missing data not explicitly imputed and assumed to be missing at random. At baseline, the mean (±SD) KCCQ-OS was 69.836 (21.178) in the patisiran group and 70.330 (20.709) in the placebo group.
- **Abbreviations:** KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); LS, least squared; M, month; MMRM, mixed effects model repeated measures; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

Results

Time to First Event over the 12-Month Double-Blind Period

- In the overall population, the HR (95% CI) for time to first event (all-cause hospitalization, urgent HF visit, or a death event) was 0.839 (0.557, 1.263), directionally favoring patisiran over 12 months; subgroup analyses by baseline tafamidis use showed similar trajectories

Kaplan–Meier Plot of Time to First Event over the 12-Month Double-Blind Period



- Heart transplantation and left ventricular assist device placement were handled in the same manner as death. Deaths, hospitalizations, and urgent heart failure visits due to COVID-19 were excluded from analysis. Figures are truncated at Day 372 and do not show 2 events on placebo and 3 events on patisiran that occurred after Day 372. However, these events were counted in the 12-month period per SAP definition and are included in the HR estimate.

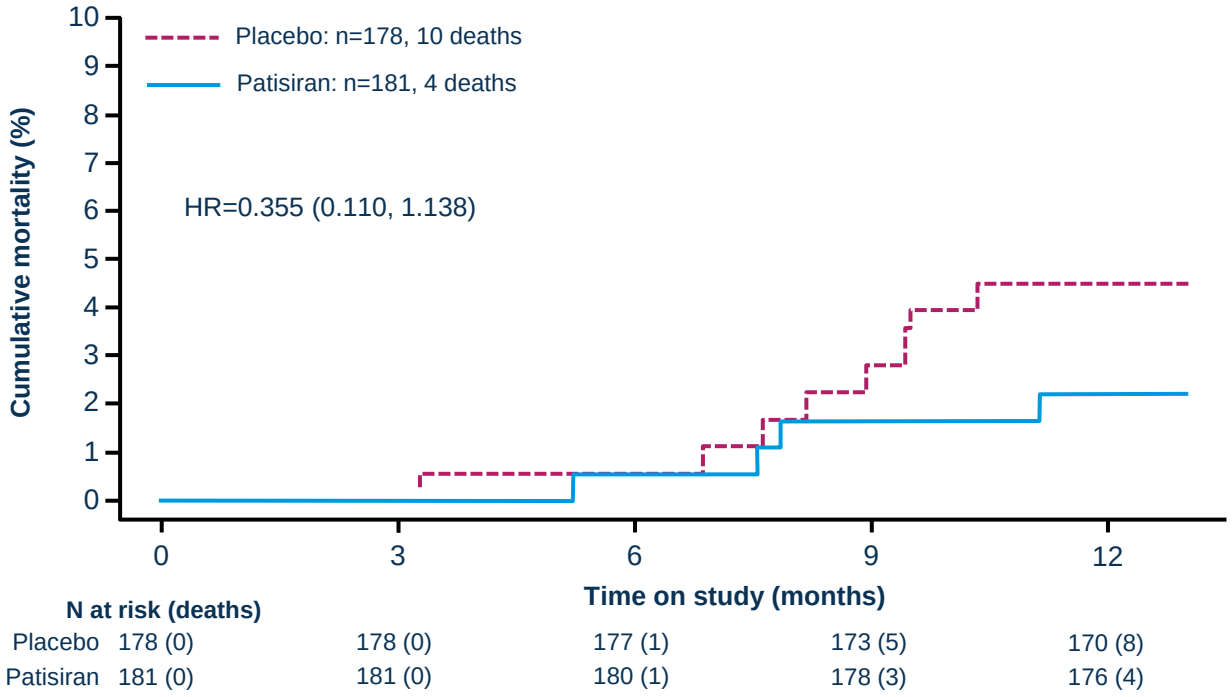
- **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; hATTR, hereditary transthyretin-mediated; HL, Hodges–Lehmann; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire (Overall Summary); NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; ROW, rest of world; wtATTR, wild-type transthyretin-mediated.

Results

All-Cause Mortality over the 12-Month Double-Blind Period

- In the overall population, all-cause deaths[a,b] were observed in 10 (5.6%) placebo vs 4 (2.2%) patisiran patients
  - CV-related deaths: placebo 5 (2.8%); patisiran 2 (1.1%)
    - Heart transplant[a]: placebo 2 (1.1%); patisiran 0 (0.0%)
  - HR estimate (patisiran/placebo): 0.355 (95% CI: 0.110, 1.138)
- For patients on baseline tafamidis, all-cause deaths were observed in 3 (6.7%) placebo vs 1 (2.2%) patisiran patient
  - HR (95% CI): 0.296 (0.031, 2.863)
- For patients not on baseline tafamidis, all-cause deaths were observed in 7 (5.3%) placebo vs 3 (2.2%) patisiran patients
  - HR (95% CI): 0.396 (0.102, 1.538)

All-Cause Mortality over the 12-Month Double-Blind Period[a,b]



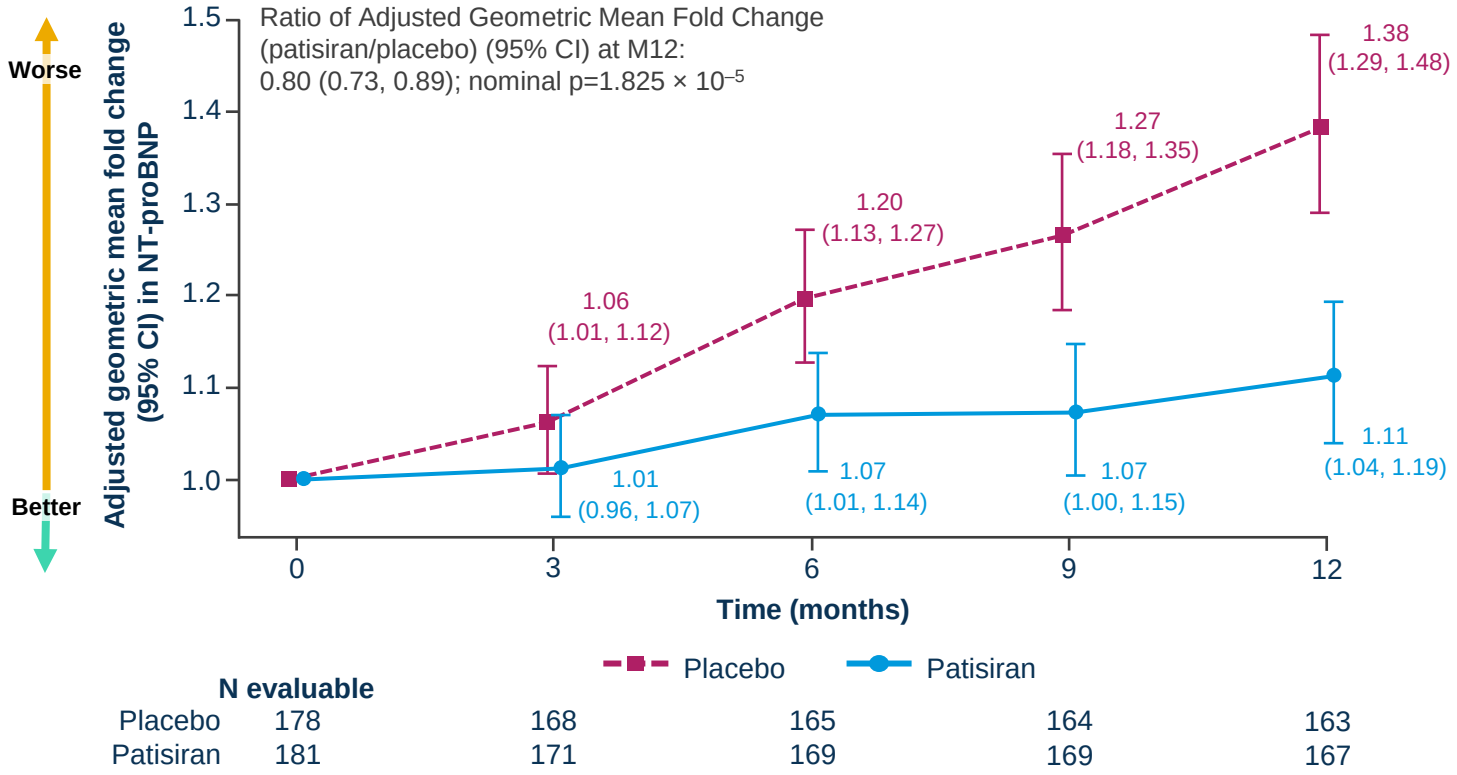
- [a]Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled the same as death in analyses. [b]Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from event rate calculations. Per SAP definition, for patients who discontinued the study, deaths up to Day 417 were counted in the double-blind period. The figure is truncated at Day 372 (end of Month 12 visit window). 2 placebo deaths that occurred after Month 12 and prior to Day 417 are included in the estimate of HR but not shown on the figure.
- **Abbreviations:** CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SAP, statistical analysis plan.

Results

Exploratory Analysis: Change from Baseline in NT-proBNP

- Patisiran demonstrated a beneficial effect on NT-proBNP, a biomarker of cardiac stress, compared with placebo at Month 12 (nominal $p=1.825 \times 10^{-5}$)

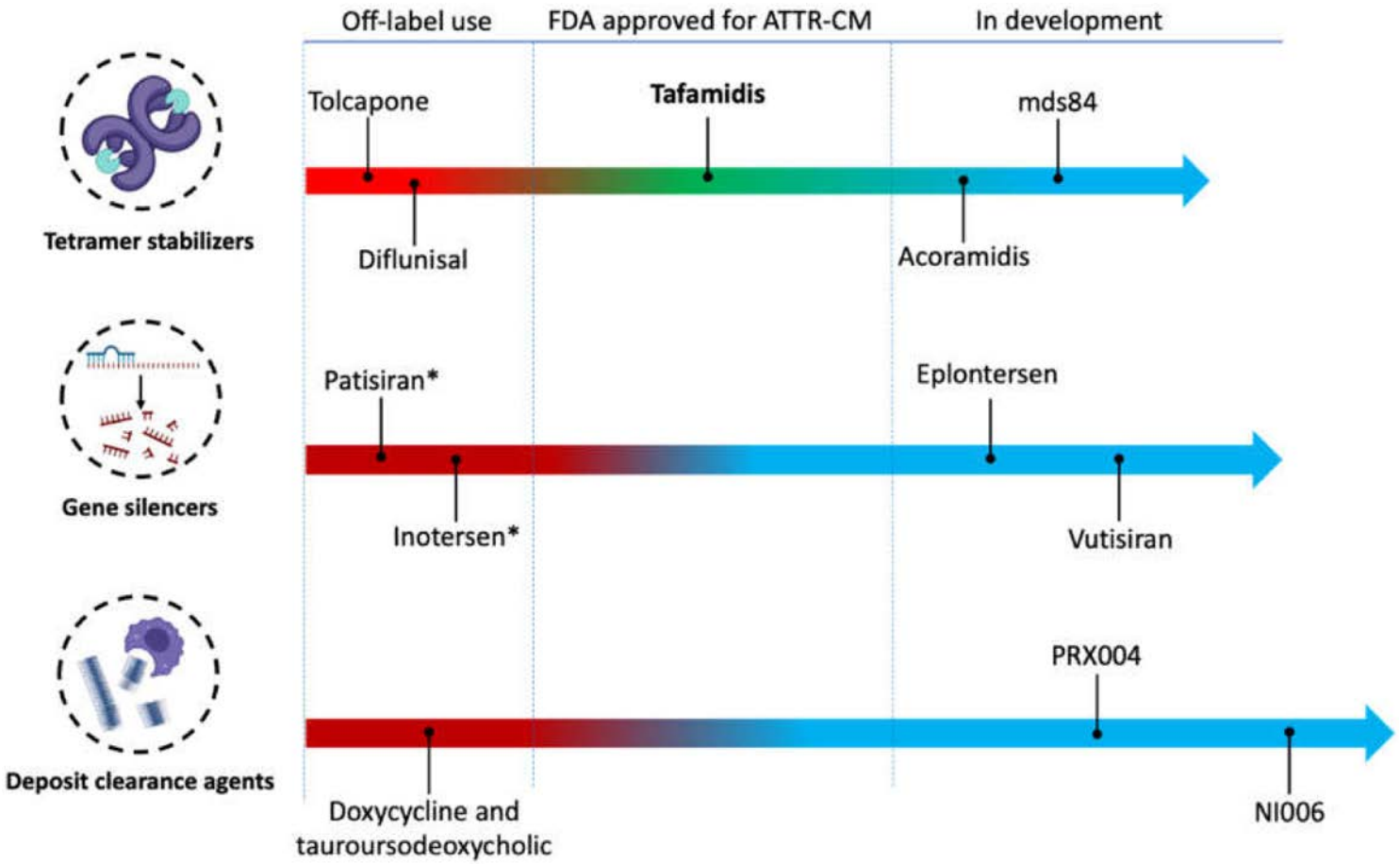
Change from Baseline in NT-proBNP at Month 12[a]



NT-proBNP, ng/L, median (IQR)	Patisiran	Placebo
Baseline	2008 (1135 to 2921)	1813 (952 to 3079)
Month 12	1944 (1158 to 3726)	2299 (1180 to 4364)
Change from baseline to Month 12	131 (–280 to 817)	518 (51 to 1544)

- [a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. Number of evaluable patients at each timepoint are shown.
- **Abbreviations:** CI, confidence interval; IQR, interquartile range; M, month; NT-proBNP, *N*-terminal pro-brain natriuretic peptide.

ATTR-CM pipeline



J. Clin. Med. 2022, 11(8), 2148

Additional stabilizers in clinical trials

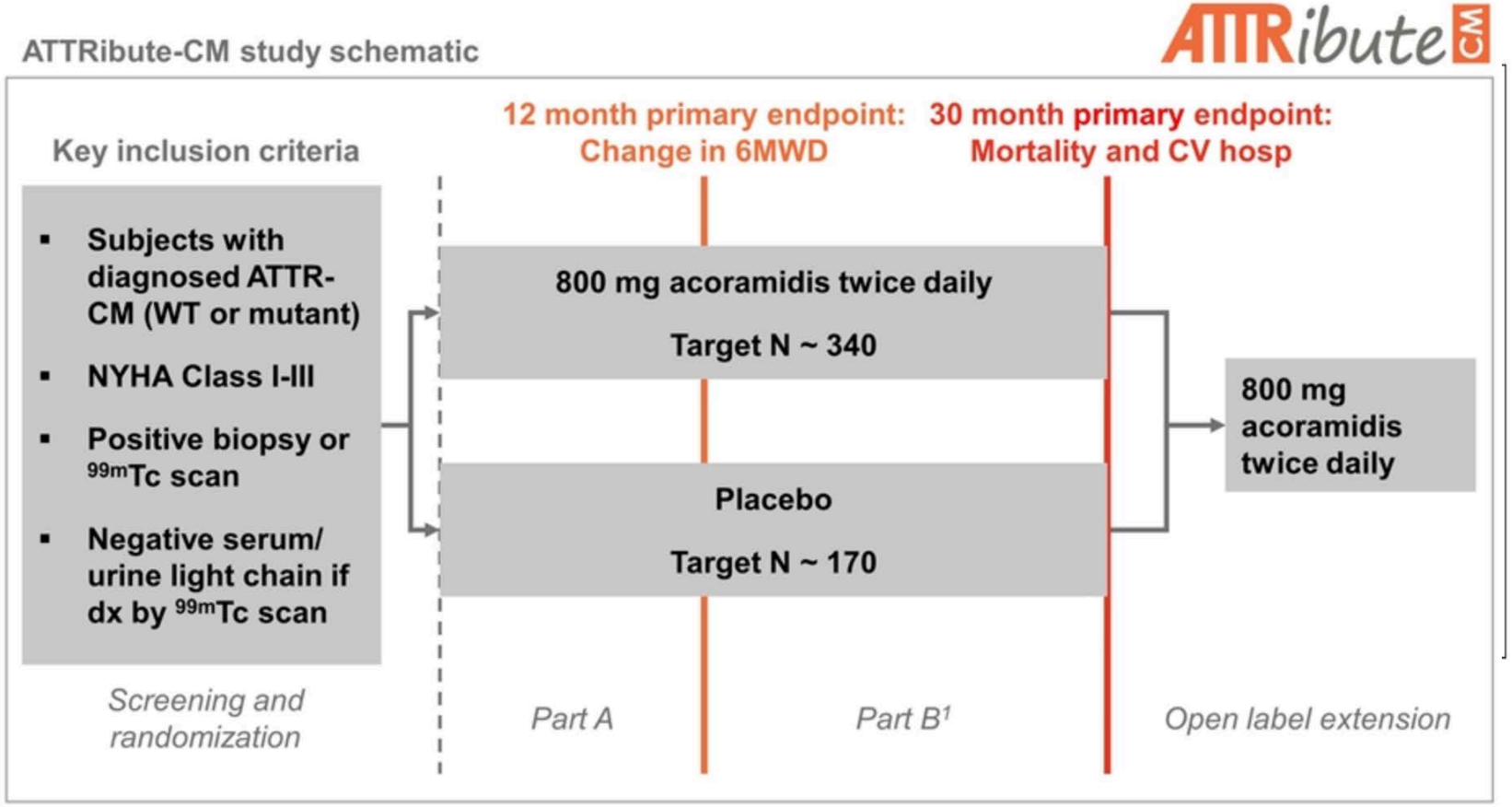
Acoramidis (AG10)

ATTRibute-CM did not meet its Month 12 primary endpoint

Observed ATTRibute-CM placebo substantially outperformed historical controls

Acoramidis improved NT-proBNP relative to placebo

Acoramidis improved KCCQ-OS relative to placebo



Silencers: Vutrisiran HELIOS-B

HELIOS-B is a global, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vutrisiran in adult patients with ATTR amyloidosis with cardiomyopathy (including both hATTR and wtATTR amyloidosis).[1]

Study Status

- Enrollment is complete with 655 patients.

Study Design

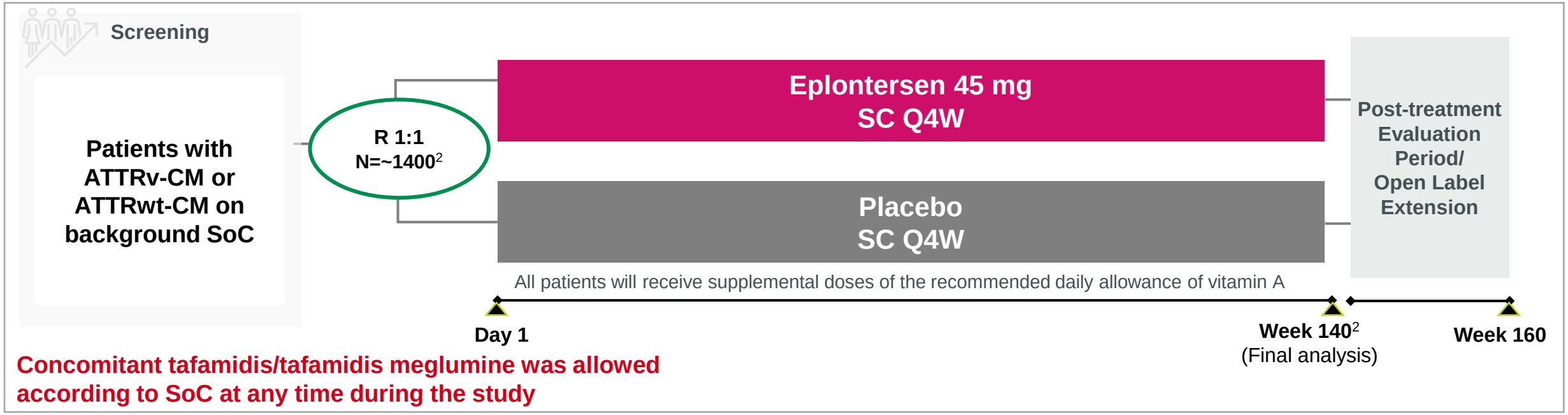
- Patients will be randomized on a 1:1 basis to receive either 25 mg of vutrisiran or placebo administered as a subcutaneous injection once every three months for up to 36 months.

Primary Endpoint

The primary endpoint will evaluate the efficacy of vutrisiran versus placebo on the composite endpoint of all-cause mortality and recurrent cardiovascular (CV) events (CV hospitalizations and urgent heart failure (HF) visits) at 30-36 months.

Silencers: Eplontersen
CARDIO-TTRansform: Study design

Global, randomized, multicenter, double-blind, placebo-controlled trial in patients with ATTRv-CM and ATTRwt-CM[1]



Concomitant tafamidis/tafamidis meglumine was allowed according to SoC at any time during the study

Randomization stratified by:

- **NYHA Classification** (I and II vs. III)
- **ATTR mutation status** (mutated vs. wild- type)
- **6MWT** (≤350 meters vs. >350 meters)
- **Current treatment with tafamidis/tafamidis meglumine** (yes vs. no)

Current Status:[2] Active, recruiting

6MWT = 6-minute walk test; ATTR= amyloid transthyretin; ATTR-CM = amyloid transthyretin amyloidosis with cardiomyopathy; ATTRv-CM = hereditary amyloid transthyretin amyloidosis with cardiomyopathy; ATTRwt-CM = wild-type amyloid transthyretin amyloidosis with cardiomyopathy; NYHA = New York Heart Association; Q4W = every 4 weeks; R = randomization; SC = subcutaneous; SoC = standard of care.

1. Maurer M et al. Poster presented at: CCC (Virtual); October 20-23, 2021; 2. Study NCT04136171. ClinicalTrials.gov website.

Study endpoints

Primary Endpoint

- Composite outcome of CV mortality and recurrent CV clinical events[a] at end of study[1]

Secondary Endpoints

- Change from baseline to Week 121 in:[2]
  - KCCQ score
  - 6MWT
- At end of study, rate of:[1]
  - CV mortality
  - CV clinical events[a]
  - All-cause mortality

Exploratory Endpoints

- Change from baseline in:[3]
  - Cardiac imaging parameters
  - Renal function
  - Biomarkers
  - Patient-reported outcomes questionnaires and disease scores

[a]CV clinical events include: HF-related urgent visits requiring administration of IV diuretics, or hospitalization for myocardial infarction, HF, stroke/transient ischemic attack, or arrhythmias (and/or an arrhythmia requiring medical treatment in outpatient facility or ER).[1]

6MWT = 6-minute walk test; CV = cardiovascular; ER = emergency room; HF = heart failure; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire.

1. In House Data, Ionis Pharmaceuticals, Inc. CSP ION-682884-CS2. September 15, 2022; 2. Study NCT04136171. ClinicalTrials.gov website;
3. Falk RH et al. *Blood.* 2019;134(Suppl 1):5764.

Eplontersen demonstrated clinically and statistically significant benefits in a contemporary population of patients with hereditary ATTR-PN

neuro TTRansform

Phase III, multicenter, open-label[1,2]

- Stage 1 or 2 ATTRv-PN[a]
- Documented TTR sequence variant
- Signs and symptoms of PN

Randomized 6:1

N=168

NEURO-TTR external placebo control[3]

Eplontersen 45 mg SC Q4W

Inotersen 300 mg SC QW → Eplontersen 45 mg SC Q4W

Open-label Extension With **Eplontersen** (up to 3 years)

OR 20-week post-treatment evaluation period

Key exclusion criteria: Current or previous treatment with ASOs, siRNAs, tafamidis, diflunisal, or doxycycline ± TUDCA; NYHA ≥III

Study Timeline (weeks): 0 — 35 Interim analysis — 66 Final analysis[b] — 85 EOT analysis — 105

Baseline characteristics[4]

Representative of a global contemporary ATTRv-PN population

- **53 years** Mean age
- **79.2%** Coutinho stage 1 (mild)
- **60.1%** V30M TTR variant
- **68.5%** Previous use of a stabilizer[c]
- **27.4%** ATTRv-CM

Eplontersen sustained benefit through Week 66 vs. placebo[5]

Co-primary endpoints[2]

Significant and sustained reduction in serum TTR levels

-81.7% reduction from baseline with eplontersen at Week 65[d]

Significant benefit in neuropathy impairment score

-24.8 point difference in mNIS +7 composite score vs. placebo at Week 66[e] (p<0.0001)

Significant benefit in QoL score

-19.7 point difference in Norfolk QoL-DN total score vs. placebo at Week 66[e] (p<0.0001)

Statistically significant benefit in all secondary endpoints[2]

vs. placebo at final analysis (p<0.0001 for NSC, SF-36 PCS, mBMI; p<0.05 for PND)

- NSC
- SF-36 PCS
- PND
- mBMI

Safety profile[2]

TEAEs comparable with eplontersen vs. placebo

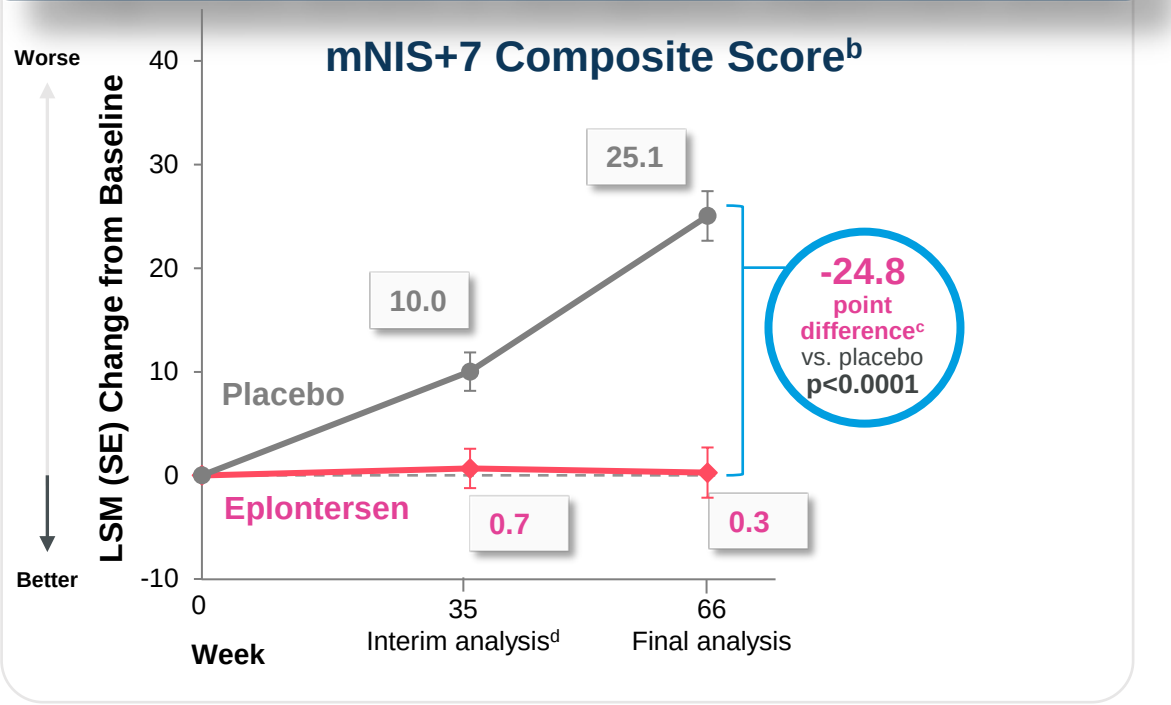
Incidence, n (%)	Placebo (n=60)	Eplontersen (n=144)
Any TEAE	60 (100)	140 (97.2)
Related to study drug	23 (38.3)	53 (36.8)
Leading to study drug discontinuation	2 (3.3)	5 (3.5)
TEAE of special interest	12 (20.0)	41 (2.5)
Ocular AEs potentially related to vitamin A deficiency[f]	9 (15.0)	39 (27.1)
Thrombocytopenia[g]	1 (1.7)	3 (2.1)
Glomerulonephritis[h]	2 (3.3)	0
Other TEAE of interest	47 (78.3)	87 (60.4)
Any Serious TEAE	12 (20.0)	21 (14.6)
Related to study drug	1 (1.7)	0
Fatal TEAE[i]	0	2 (1.4)
Related to study drug	0	0

[a]Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance);[1] [b]Final analysis endpoints were performed at Week 65 or Week 66 to reduce patient burden in data collection;[2] [c]Tafamidis or diflunisal;[2] [d]LSM change from baseline;[2] [e]LSM difference in change from baseline between groups;[2] [f]Vitamin A levels were blinded in the placebo group but not in the eplontersen group; [g]All events were mild, grade 1, and not associated with bleeding adverse events, did not lead to study drug discontinuation, and resolved without sequelae; [h]There were two cases of potential glomerulonephritis identified (1 glomerulonephritis chronic, 1 nephrotic syndrome); [i]One patient with intracerebral hemorrhage in setting of normal platelet counts; one patient with arrhythmia in setting of known ATTR-CM. Neither were assessed as related to study drug.[2]

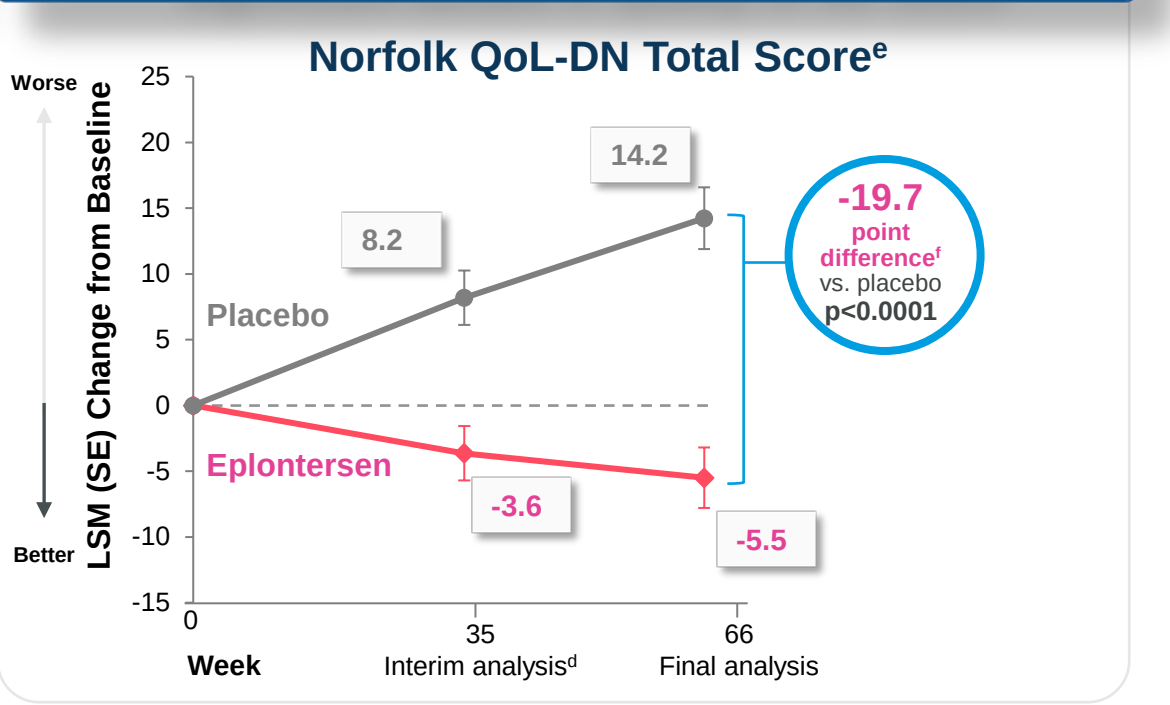
Abbreviations and references in slide notes.

Progression of neuropathy impairment[a] and Norfolk quality of life score

Significant benefit in neuropathic impairment score[1]



Significant benefit in quality of life score[1]



- **Consistent effect with eplontersen across prespecified subgroups, as well as for mNIS+7 components and Norfolk QoL-DN domains[1]**

[a]As reflected by mNIS+7; [b]mNIS+7 (co-primary endpoint at Week 35 and 66) scores can range from −22.3 to 346.3, with higher scores indicative of greater neuropathic impairment; a decrease in score indicates improvement;[1,2] [c]LSM difference in change from baseline (95%CI -31.0 to -18.6) between groups;[1] [d]Eplontersen resulted in a statistically significant change from baseline vs. placebo at Week 35 interim analysis (p<0.0001);[2] [e]Norfolk QoL-DN (key secondary endpoint at Week 35 and co-primary endpoint at Week 66) scores can range from −4 to 136, with higher scores indicative of worse quality of life; a decrease in score indicates improvement;[1,2] [f]LSM difference from baseline (95%CI -25.6 to -13.8) between groups.[1]

LSM = least squares mean; mNIS+7 = modified neuropathy impairment score + 7; Norfolk QoL-DN = Norfolk Quality of Life Questionnaire-Diabetic Neuropathy.

1. Khella S et al. Poster presented at: AAN 2023 Annual Meeting; April 22-27, 2023; Boston, MA, and Virtual. Poster 008; 2. Coelho T et al. Poster presented at: AANEM Annual Meeting; September 21-24, 2022; Nashville, TN, and Virtual. Poster 130.

Study Designs of Key Phase III Trials Assessing the Efficacy and Safety of TTR Silencers and Stabilizers in Patients With ATTR-CM

	CARDIO-TTRansform[1-4]	HELIOS-B[5-7]	APOLLO-B[8,9]	ATTRibute-CM[10-12]	ATTR-ACT[13,14]
MOA[a]	TTR Silencer	TTR Silencer	TTR Silencer	TTR Stabilizer	TTR Stabilizer
Sample size	~1400	655	360	632	441
Interventions (randomization)	Eplontersen 45 mg or PBO (1:1) (SC every 4 weeks)	Vutrisiran 25 mg or PBO (1:1) (SC every 3 months)	Patisiran 0.3 mg/kg or PBO (1:1) (IV every 3 weeks)	Acoramidis 800 mg or PBO (2:1) (oral twice daily)	Tafamidis 20/80 mg or PBO (2:1:2) (oral once daily)
Key inclusion criteria: general	• Age: 18-90 years • ATTRwt-CM or ATTRv-CM	• Age: 18-85 years • ATTRwt-CM or ATTRv-CM	• Age: 18-85 years • ATTRwt-CM or ATTRv-CM	• Age: 18-90 years • ATTRwt-CM or ATTRv-CM	• Age: 18-90 years • ATTRwt-CM or ATTRv-CM
Key inclusion criteria: cardiac function	• History of HF[c] • NT-proBNP ≥600 pg/mL[d] • NYHA Class I-III • 6MWT ≥100 meters • Amyloid deposits in cardiac or non-cardiac tissue[e] • End-diastolic interventricular septum thickness >12 mm	• History of HF[c] • NT-proBNP >600 pg/mL and <8500 pg/mL • NYHA Class I-III[f] • 6MWT ≥150 meters	• History of HF[c] • NT-proBNP >300 pg/mL and <8500 pg/mL[g] • NYHA Class I-III[f] • 6MWT ≥150 meters	• History of HF[c] • NT-proBNP ≥300 pg/mL and <8500 pg/mL • NYHA Class I-III • 6MWT ≥150 meters[h] • LV wall thickness ≥12 mm	• History of HF[c] • NT-proBNP ≥600 pg/mL • NYHA Class I-III • 6MWT >100 meters • Cardiac involvement confirmed by ECHO and end-diastolic interventricular septum thickness >12 mm
Key exclusion criteria	• eGFR[i] <30 mL/min/1.73 m^2 • Current/previous treatment with oligonucleotide or RNA therapeutics, including siRNA • Platelet count <125 x 10^9/L • UPCR ≥750 mg/g • Prior liver or heart transplant or anticipated liver transplant within 1 year after randomization	• eGFR <30 mL/min/1.73 m^2 • Prior treatment to lower TTR • PND score ≥IIIa • Prior or anticipated liver, heart, or other organ transplant within 1 year after randomization	• eGFR <30 mL/min/1.73 m^2 • Prior treatment to lower TTR • Prior or anticipated liver, heart, or other organ transplant	• eGFR[i] <15 mL/min/1.73 m^2 • Current treatment with agents for ATTR-CM • Anticipated heart transplant within 1 year of screening	• eGFR <25 mL/min/1.73 m^2 • mBMI[j] <600 kg/m^2 x g/L • Prior use of tafamidis • Prior liver or heart transplant

Note: It is inappropriate to make direct comparisons as the study design, demographics, and other criteria may be different as these trials were not head-to-head.

[a]Relates to the MOA of the assessed intervention; [c]Determined by prespecified criteria which may differ across the trials; [d]NT-proBNP ≥1200 pg/mL in the presence of atrial fibrillation; [e]Confirmed by either Congo Red (or equivalent) staining or technetium scintigraphy. Positive scintigraphy confirmed by Grade 2 or 3 cardiac uptake in the absence of abnormal light chains ratio; [f]Patients are excluded if they have NYHA Class III and are considered as high risk; [g]NT-proBNP >600 pg/mL and <8500 pg/mL in the presence of atrial fibrillation; [h]Completed 2 tests that are within 15% of total distance walked prior to randomization; [i]Calculation based on CKD-EPI formula in CARDIO-TTRansform and MDRD formula in ATTRibute-CM; [j]Calculated using body mass index in kg/m^2 x serum albumin (g/L).

1. In House Data, Ionis Pharmaceuticals, Inc. CSP ION-682884-CS2. September 15, 2022; 2. Study NCT04136171. ClinicalTrials.gov website; 3. Maurer M et al. Poster presented at: CCC (Virtual); October 20-23, 2021; 4. Falk RH et al. *Blood*. 2019;134(suppl 1):5764; 5. Study NCT04153149. ClinicalTrials.gov website; 6. Shilling R et al. *J Am Coll Cardiol*. 2020;75(11)(suppl 1):3579; 7. EudraCT Number 2019-003153-28. ClinicalTrialsRegister.eu website; 8. Study NCT03997383. ClinicalTrials.gov website; 9. Maurer MS et al. Presented at: XVIII ISA meeting; September 4-8, 2022; Heidelberg, Germany;
10. Gillmore JD et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA; 11. BridgeBio Pharma, Inc. press release. Published December 27, 2021; 12. Study NCT03860935. ClinicalTrials.gov website; 13. Study NCT01994889. ClinicalTrials.gov website; 14. Maurer MS et al. *N Engl J Med*. 2018;379(11):1007-1016.

Study Designs of Key Phase III Trials Assessing the Efficacy and Safety of TTR Silencers and Stabilizers in Patients With ATTR-CM

	CARDIO-TTRansform[1-4]	HELIOS-B[5-7]	APOLLO-B[8,9]	ATTRibute-CM[10-12]	ATTR-ACT[13,14]
Primary Endpoint	• Composite of CV mortality and recurrence of CV clinical events[a] at end of study	• Composite of all-cause mortality and recurrent CV events[b] at 30-36 months	• Change from BL to Month 12 in 6MWT	• Change from BL to Month 12 in 6MWT (Part A) • Hierarchical combination of all-cause mortality, frequency of CV-related hospitalization over 30 months, and change from BL to Month 30 in 6MWT (Part B)	• Hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations over 30 months
Secondary Endpoints	• Change from BL to Week 121 in 6MWT, and KCCQ score • At study end, rate of CV mortality, CV clinical events[a], and all-cause mortality	• Change from BL to Month 30 in 6MWT, KCCQ-OS score, cardiac structure and function[c], and NT-proBNP • Safety events to Month 30-36 including all-cause mortality, recurrent CV events,[b] and a composite of all-cause mortality, recurrent all-cause hospitalizations, and urgent HF visits	• Change from BL to Month 12 in KCCQ-OS • Composite of all-cause mortality, frequency of CV events over 12 months,[b] and change from BL to Month 12 in 6MWT • Composite of all-cause mortality, all-cause hospitalizations, and HF-related urgent visits over 12 months	• Change from BL to Month 12 in KCCQ-OS • Change from BL to Month 30 in • 6MWT and KCCQ-OS • Treatment-emergent AEs and SAEs over 12 months and 30 months • PD assessments of TTR stabilization by acoramidis at Day 28 and Month 30[d] • All-cause mortality, CV-related hospitalization, and CV-related mortality over 30 months	• All-cause mortality, CV-related hospitalizations, and number of patients with CV mortality over 30 months • Change from BL to Month 30 in 6MWT, and KCCQ-OS • Percentage of patients with stabilized TTR at Month 1
Estimated study completion	**November 2025**	**December 2026**	**Double-blind phase: Completed; Open-label extension phase: June 2025**	**Part A at 12 months: Completed; Part B at 30 months: May 2023**	**Completed**

Note: It is inappropriate to make direct comparisons as the study design, demographics, and other criteria may be different as these trials were not head-to-head.

[a]HF-related urgent visits requiring administration of IV diuretics, or hospitalization for MI, HF, stroke/transient ischemic attack, or arrhythmias (and/or an arrythmia requiring medical treatment in outpatient facility of ER); [b]CV hospitalizations and urgent HF visits; [c]Includes LV wall thickness and global longitudinal strain; [d]Schedule dependent on type of assessment.

1. In House Data, Ionis Pharmaceuticals, Inc. CSP ION-682884-CS2. September 15, 2022; 2. Study NCT04136171. ClinicalTrials.gov website; 3. Maurer M et al. Poster presented at: CCC (Virtual); October 20-23, 2021; 4. Falk RH et al. *Blood*. 2019;134(suppl 1):5764; 5. Study NCT04153149. ClinicalTrials.gov website; 6. Shilling R et al. *J Am Coll Cardiol*. 2020;75(11)(suppl 1):3579; 7. EudraCT Number 2019-003153-28. ClinicalTrialsRegister.eu website; 8. Study NCT03997383. ClinicalTrials.gov website; 9. Maurer MS et al. Presented at: XVIII ISA meeting; September 4-8, 2022; Heidelberg, Germany; 10. Gillmore JD et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA; 11. BridgeBio Pharma, Inc. press release. Published December 27, 2021; 12. Study NCT03860935. ClinicalTrials.gov website; 13. Study NCT01994889. ClinicalTrials.gov website;
14. Maurer MS et al. *N Engl J Med*. 2018; 379(11):1007-1016.

Silencers: CRISPR-Cas9 Gene Editing in ATTR

RESEARCH SUMMARY

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Gillmore JD et al. DOI: 10.1056/NEJMoa2107454

CLINICAL PROBLEM

In transthyretin amyloidosis, misfolded transthyretin (TTR) protein accumulates, primarily in the nerves and heart, and is ultimately fatal. Current therapies reduce amyloid formation through repeated infusions that can have serious adverse effects or require infusion premedications. These treatments slow but do not stop disease progression.

CLINICAL TRIAL

Study Design: An open-label, phase 1 clinical study evaluated the safety and pharmacodynamic effects of NTLA-2001, a CRISPR-Cas9–based in vivo gene-editing therapy targeting *TTR* in human hepatocytes, in adults with hereditary transthyretin amyloidosis and polyneuropathy with or without cardiomyopathy.

Intervention: 6 patients received a single intravenous infusion of NTLA-2001 at a dose of either 0.1 or 0.3 mg per kilogram of body weight.

RESULTS

Efficacy: At 28 days after infusion, TTR levels were reduced from baseline with both doses; the reduction was greater with the larger dose.

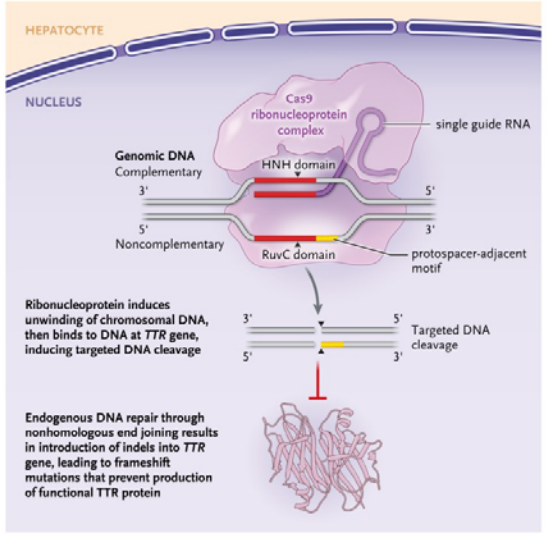
Safety: Adverse effects occurred in 3 patients and were mild.

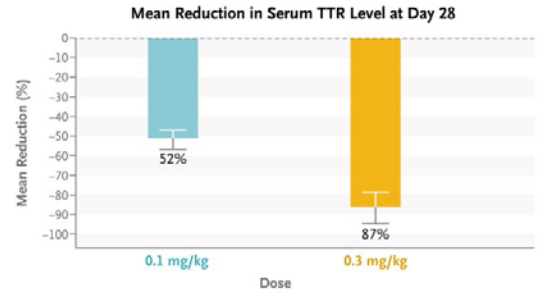
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- The duration of TTR reduction after a single infusion of NTLA-2001 at the doses used in this study and at higher doses
- Clinical outcomes in these 6 patients and in larger trials
- Whether other adverse effects, including off-target gene editing, occur in the longer term

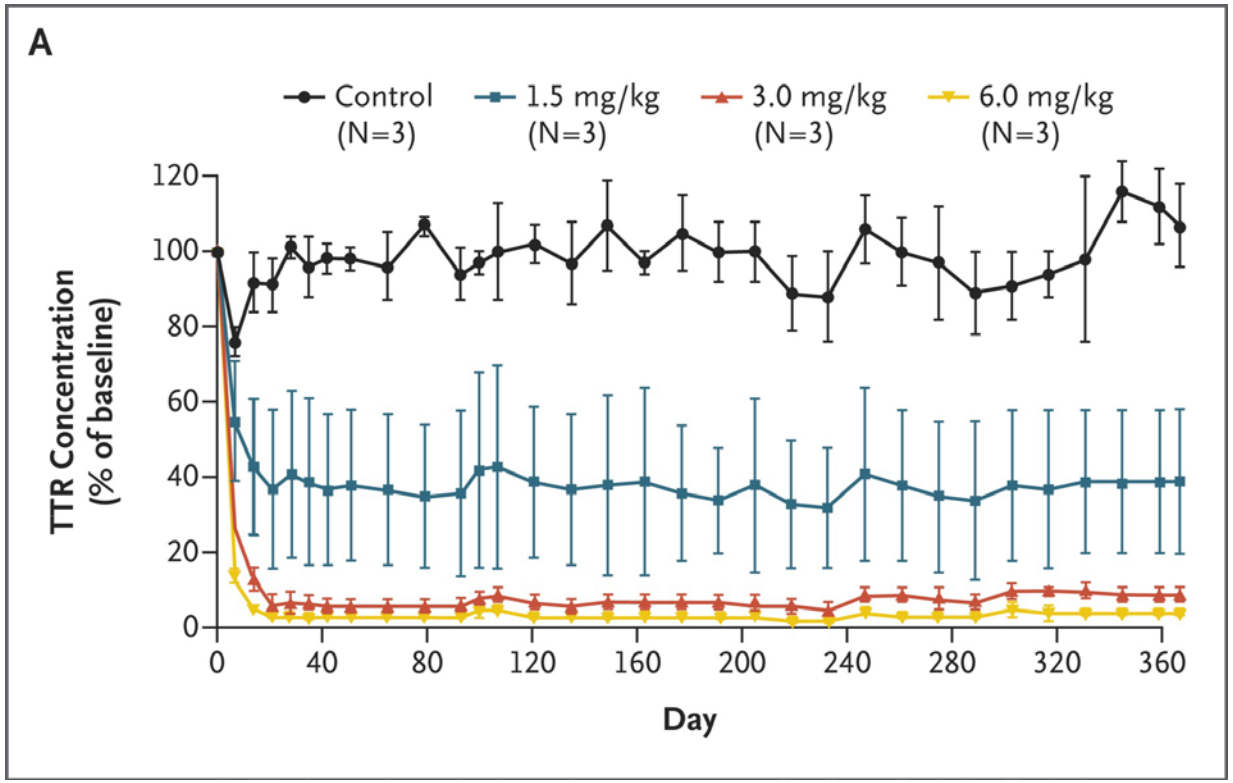
Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

This trial involving a small number of patients with hereditary transthyretin amyloidosis provides proof-of-concept evidence that CRISPR-Cas9–based gene editing with NTLA-2001 greatly reduces TTR levels after a single infusion, with only mild adverse events.



Depleters: Anti-TTR mAbs PRX004 & NI006

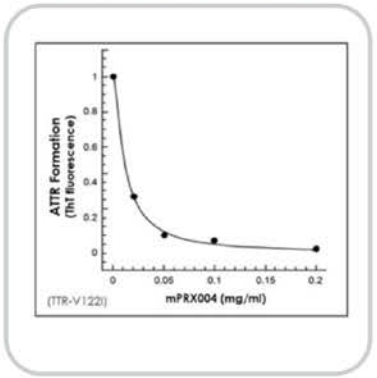
PRX004: Designed to Deplete Amyloid

Summary of preclinical effects of mPRX004

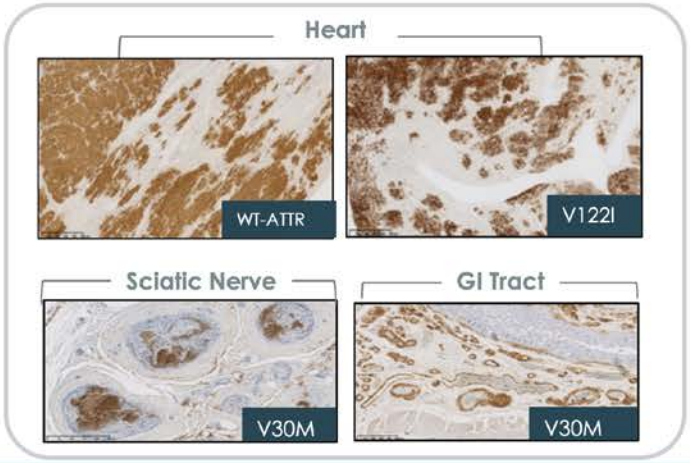
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ Inhibits fibril formation
- ✓ Specifically binds to pathogenic TTR
- ✓ Reacts to amyloid deposits in multiple organs in both wtATTR and hATTR patients
- ✓ Promotes in vivo ATTR amyloid clearance

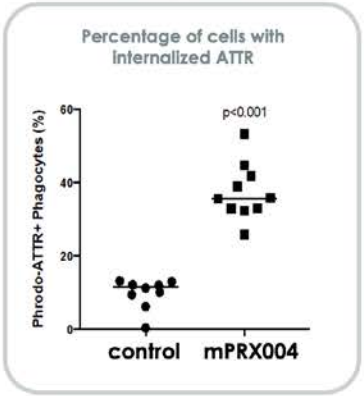
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid



[1]Higaki JN et al. *Amyloid*, 2016; Preclinical studies of mPRX004, the murine form of PRX004

Source: www.ir.prothena.com

Summary

- The diagnosis of ATTR-CM can be made efficiently using an established diagnostic algorithm
- Genetic testing is recommended in all cases of ATTR, as clinical variables are not reliable in discriminating wtATTR from hATTR
- The development of screening algorithms and ML-based techniques will enable earlier diagnosis and more effective therapy
- Many exciting new drugs in the stabilizer, silencer, and depleter classes are in various stages of development and will hopefully allow further personalization of therapeutic decision making in patients with wtATTR and hATTR

Canadian Cardiovascular Society

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Thank you

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