Therapeutic Options for Patients with TTR cardiomyopathy

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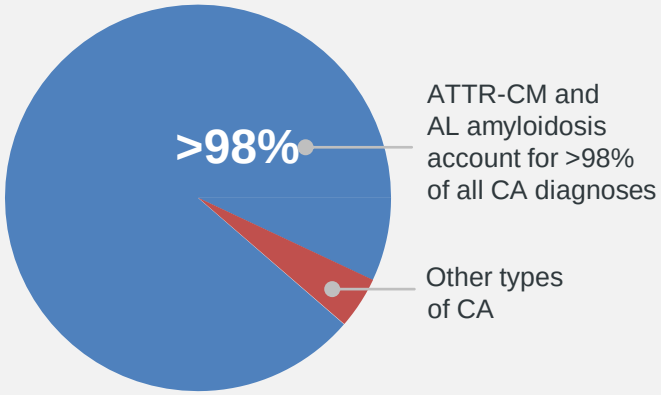
ATTR-CM and AL amyloidosis have similar symptom presentation, which may make diagnosis challenging

- It is important to **clinically differentiate between cardiac manifestations of ATTR and AL amyloidosis**, as they have different clinical courses, and **AL amyloidosis is considered a hematologic emergency** requiring **immediate treatment**[1–3]

Causes of CA[4]



ATTR-CM is underrecognized – patients may present with symptoms similar to other cardiac conditions and may be misdiagnosed due to incomplete testing[5,6]

Symptoms that present in ATTR-CM may also present in AL amyloidosis

Cardiovascular[3,6–8]

- HF without hypertension
- Potential intolerance to standard therapy
- Cardiac arrhythmia[9]
- Aortic stenosis
- Low voltage relative to LV mass
- Echocardiography showing increased LV wall thickness/mass

Ocular[5,11]

- Vitreous opacity
- Glaucoma

Renal[9,12,13]

- Renal impairment
- Nephrotic syndrome*
- Cardiorenal symptoms

Nervous System[5,9–11]

Autonomic

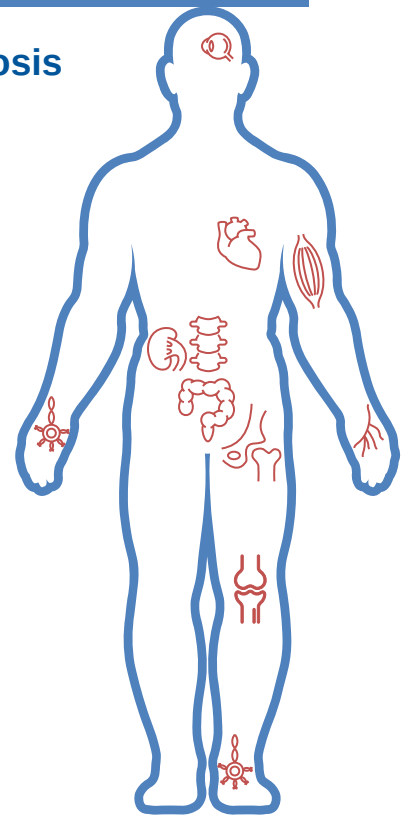
- Automatic neuropathy
- GI complaints
- Unexplained weight loss
- Orthostatic hypotension
- Sexual impotence

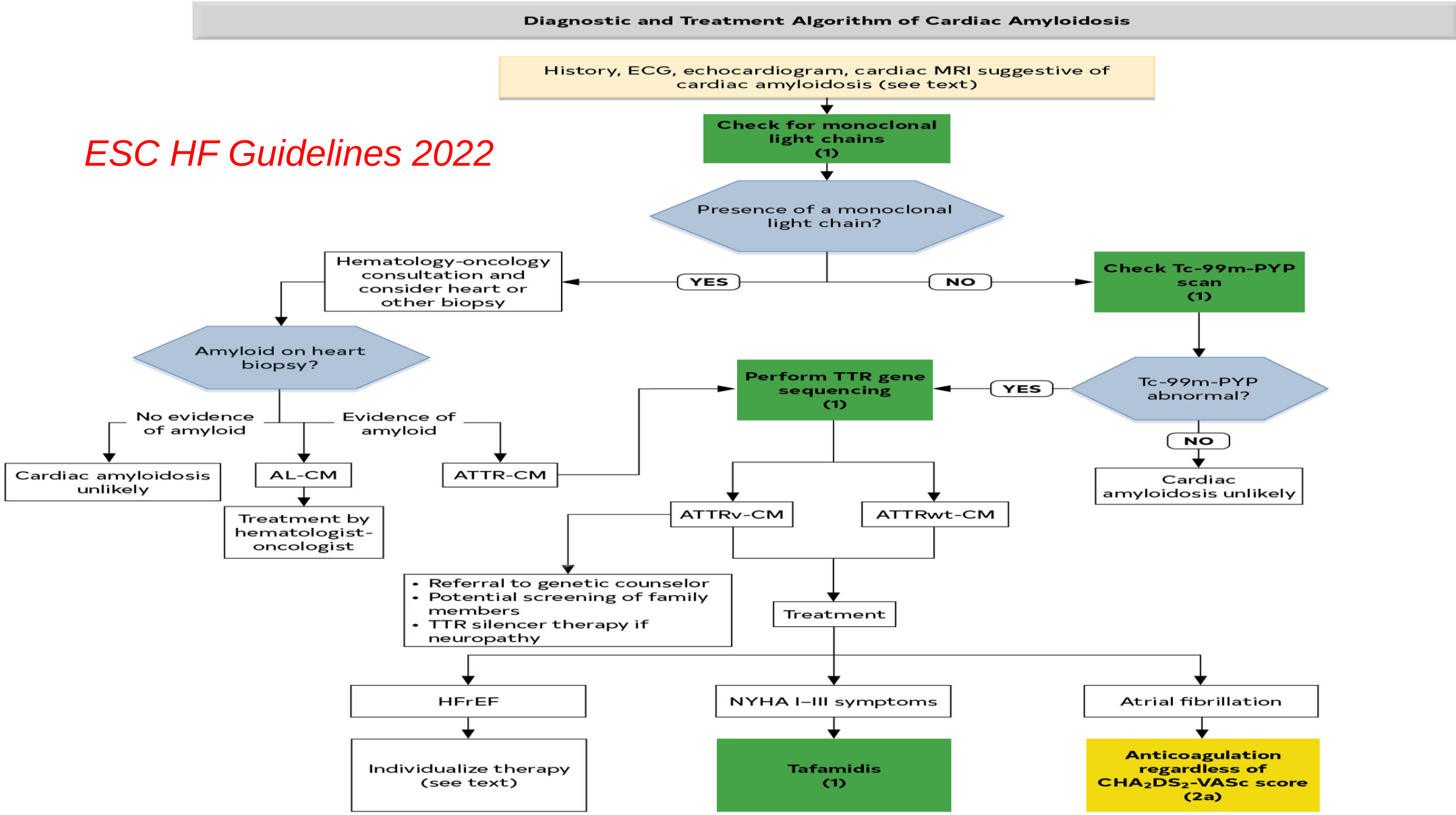
Peripheral

- Peripheral sensory motor dysfunction

Musculoskeletal/orthopedic[14,15]

- Bilateral CTS
- Biceps tendon rupture
- Lumbar spinal stenosis
- Hip/knee arthroplasty



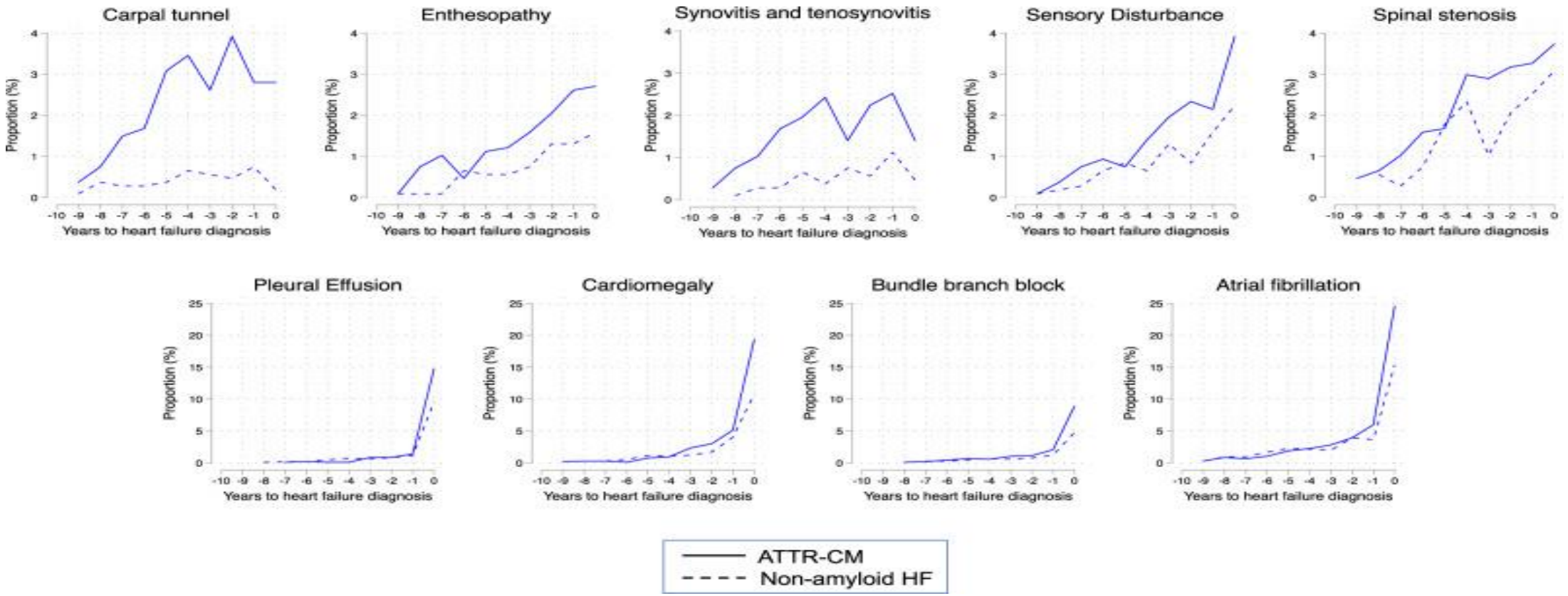

Diagnostic and Treatment Algorithm of Cardiac Amyloidosis
ESC HF Guidelines 2022
History, ECG, echocardiogram, cardiac MRI suggestive of cardiac amyloidosis (see text)
Check for monoclonal light chains (1)
Presence of a monoclonal light chain?
YES
NO
Hematology-oncology consultation and consider heart or other biopsy
Amyloid on heart biopsy?
No evidence of amyloid
Evidence of amyloid
Cardiac amyloidosis unlikely
AL-CM
Treatment by hematologist-oncologist
ATTR-CM
Check Tc-99m-PYP scan (1)
Tc-99m-PYP abnormal?
YES
NO
Cardiac amyloidosis unlikely
Perform TTR gene sequencing (1)
ATTRv-CM
ATTRwt-CM
• Referral to genetic counselor
• Potential screening of family members
• TTR silencer therapy if neuropathy
Treatment
HFrEF
Individualize therapy (see text)
NYHA I–III symptoms
Tafamidis (1)
Atrial fibrillation
Anticoagulation regardless of CHA2DS2-VASc score (2a)

2022 Guideline-Proposed Diagnosis of ATTR Cardiac Amyloidosis

COR	LOE	Recommendations
1	B-NR	1. Patients for whom there is a clinical suspicion for cardiac amyloidosis*[1–5] should have screening for serum and urine monoclonal light chains with serum and urine immunofixation electrophoresis and serum free light chains.[6]
1	B-NR	2. In patients with high clinical suspicion for cardiac amyloidosis, without evidence of serum or urine monoclonal light chains, bone scintigraphy should be performed to confirm the presence of transthyretin cardiac amyloidosis.[7]
1	B-NR	3. In patients for whom a diagnosis of transthyretin cardiac amyloidosis is made, genetic testing with *TTR* gene sequencing is recommended to differentiate hereditary variant from wild-type transthyretin cardiac amyloidosis.[8]

*LV wall thickness ≥14 mm in conjunction with fatigue, dyspnea, or edema, especially in the context of discordance between wall thickness on echocardiogram and QRS voltage on ECG, and in the context of aortic stenosis, HFpEF, carpal tunnel syndrome, spinal stenosis, and autonomic or sensory polyneuropathy.

Artificial intelligence for assessment of wild-type ATTR cardiomyopathy vs. non-amyloid heart failure prior to the diagnosis of heart failure



Nat Commun. 2021; 12: 2725

A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy

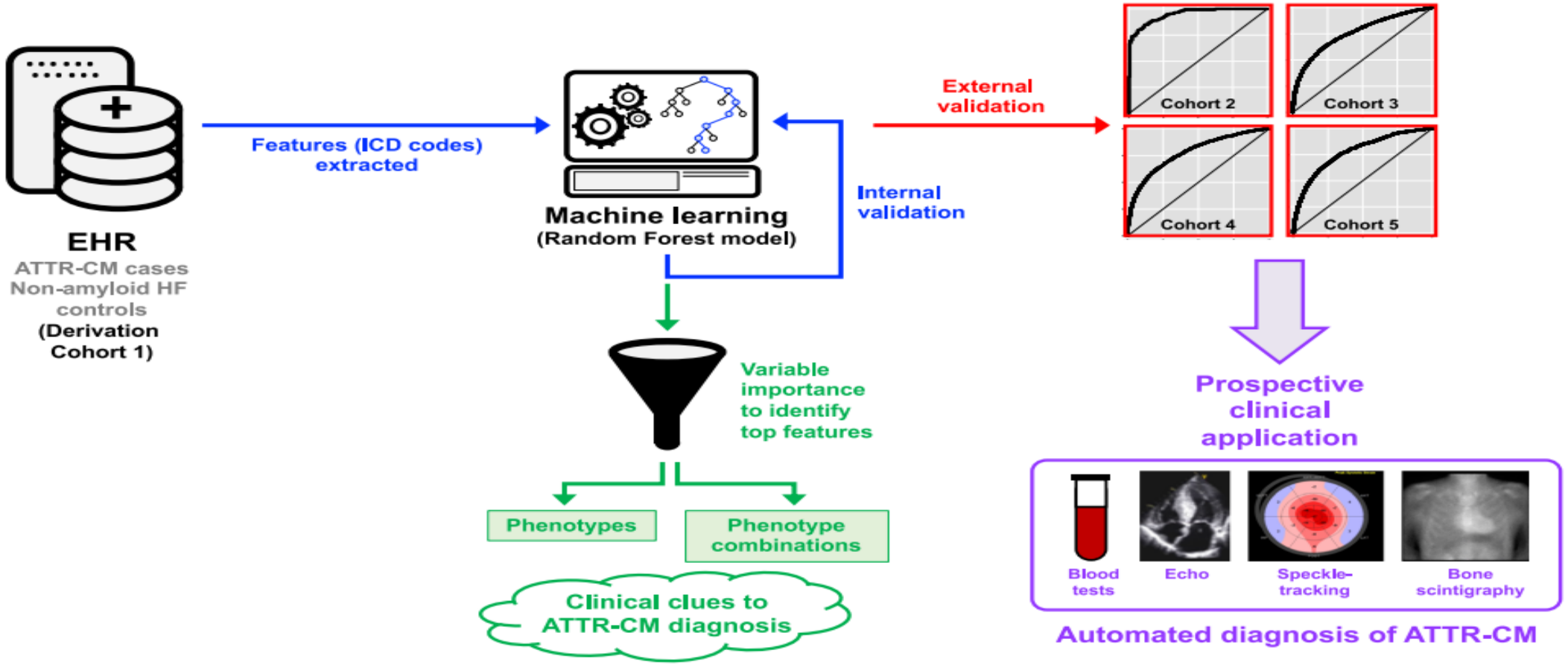
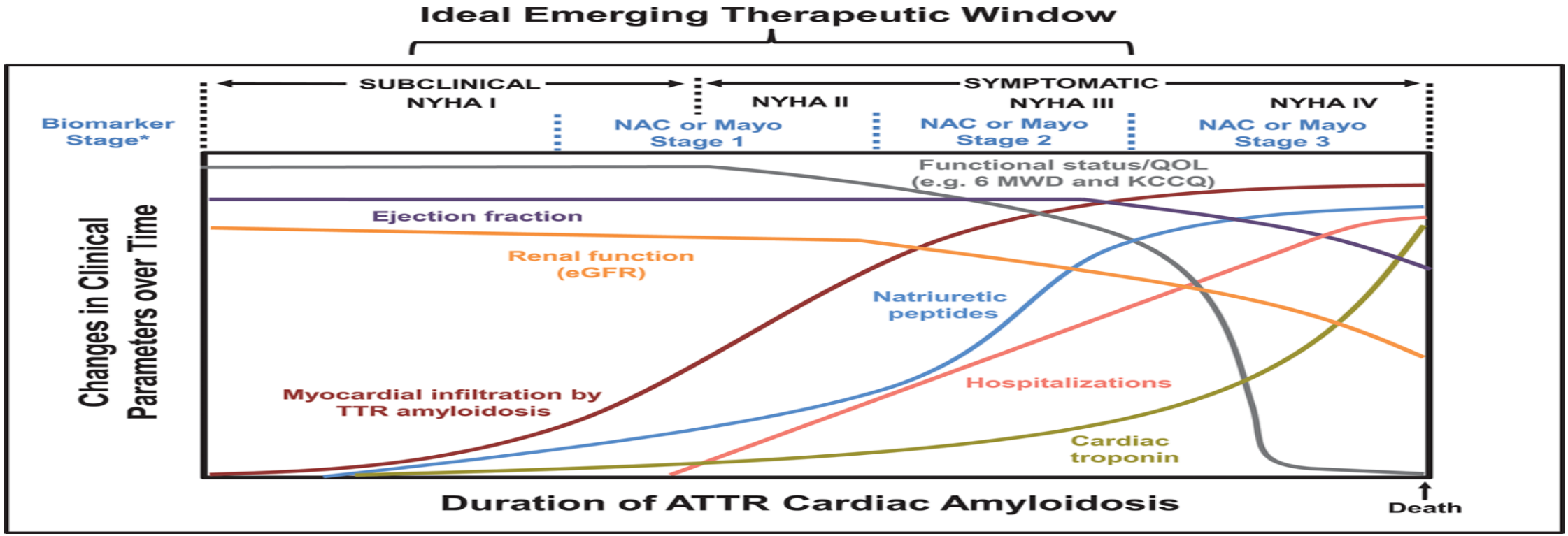


Fig. 4 Development and validation of a machine learning model of medical claims data for the systematic identification of wild-type transthyretin amyloid cardiomyopathy. Nationally representative medical claims data were used to develop a cohort of ATTR-CM and non-amyloid HF controls. ICD

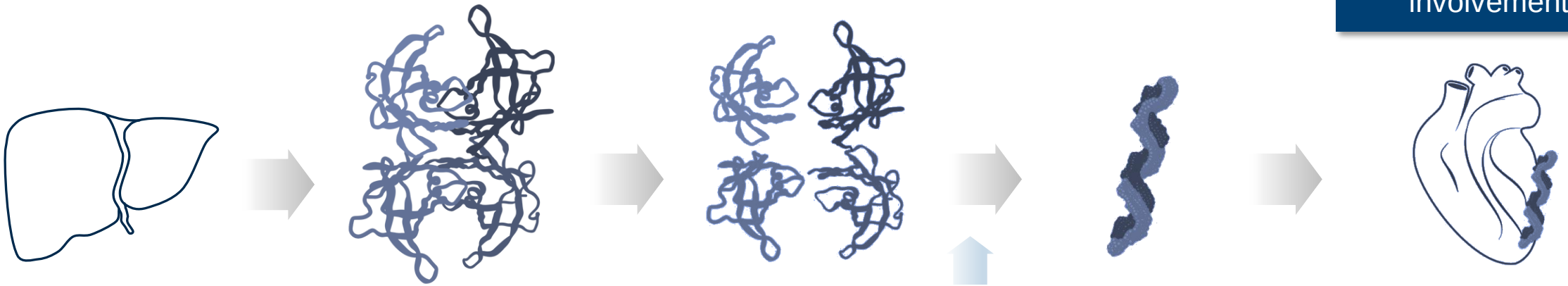
Nat Commun. 2021; 12: 2725.



The Truth Is Unfolding About Transthyretin Cardiac Amyloidosis, Volume: 140, Issue: 1, Pages: 27-30, DOI: (10.1161/CIRCULATIONAHA.119.041015)

Current therapeutic concepts in ATTR-CM[1–3]

Treatment of cardiac involvement



Liver → TTR → TTR dissociation → Amyloid fibril formation → Deposition of fibrils

Suppression of TTR synthesis:
- Liver transplantation
- TTR silencers

TTR stabilizers (tafamidis)

Oligomer disruption

Amyloid fibril degraders

Image reproduced from Ruberg FL, et al. *J Am Coll Cardiol* 2019;73:2872–91.[1]

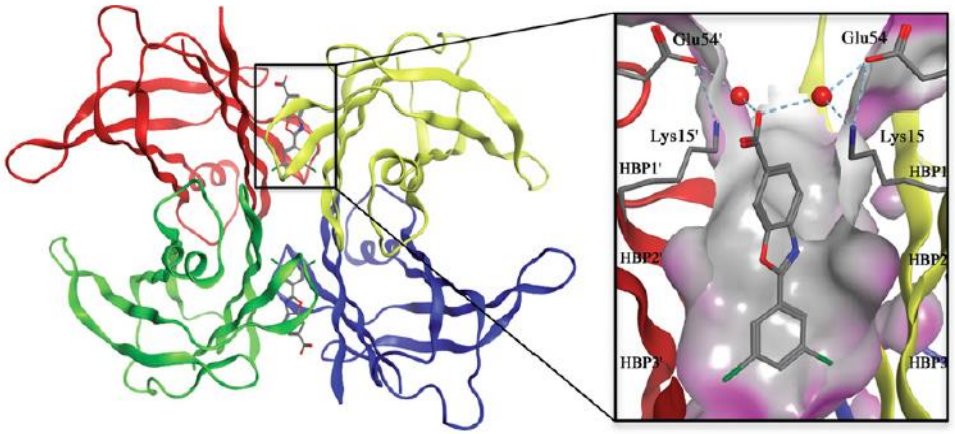
Tafamidis is the only approved treatment that specifically targets TTR destabilization—the cause of disease pathogenesis—and fortifies the TTR tetramer to preserve its natural function; other treatments are investigational only[3–12]

Tafamidis is the only approved treatment that specifically targets TTR destabilization, the cause of disease pathogenesis, to preserve the natural function of the TTR tetramer

Tafamidis binds to TTR at the thyroxine-binding sites, stabilizing the tetramer and inhibiting amyloidosis—allowing TTR to circulate naturally through the bloodstream[1,3–6]

- Tafamidis meglumine (20 mg) was approved for treatment of stage I (ambulatory without assistance) symptomatic
- Tafamidis free acid (61 mg [bioequivalent to 80 mg tafamidis meglumine[7]]) was approved for treatment of

Crystal structure of tafamidis bound to TTR[3]



Left: three-dimensional ribbon diagram depiction of the TTR tetramer with tafamidis bound. The four TTR monomers are individually colored.
Right: magnified image of tafamidis bound in one of the thyroxine (T4) binding sites.
Image reproduced from Bulawa CE, et al. *Proc Natl Acad Sci U S A* 2012;109:9629–34.[3]

Tafamidis is the only approved therapy to date to effectivity treat ATTR-CM in a randomized placebo-controlled trial[2]

Tafamidis: a treatment option for all forms of ATTR amyloidosis

Current therapeutic alternatives distinguish between hATTR and wtATTR amyloidosis and, in the case of hATTR amyloidosis, according to the presence of cardiomyopathy, polyneuropathy, or both.

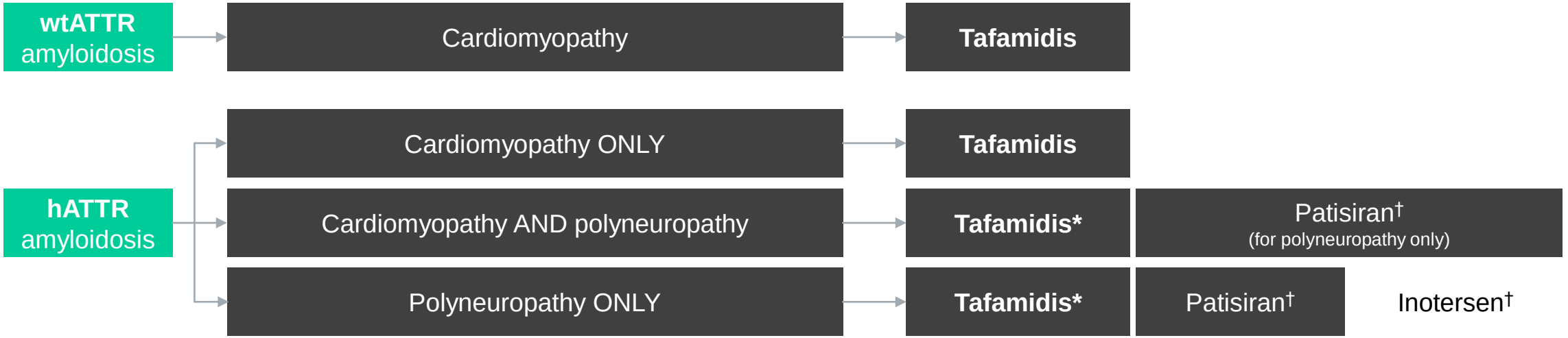
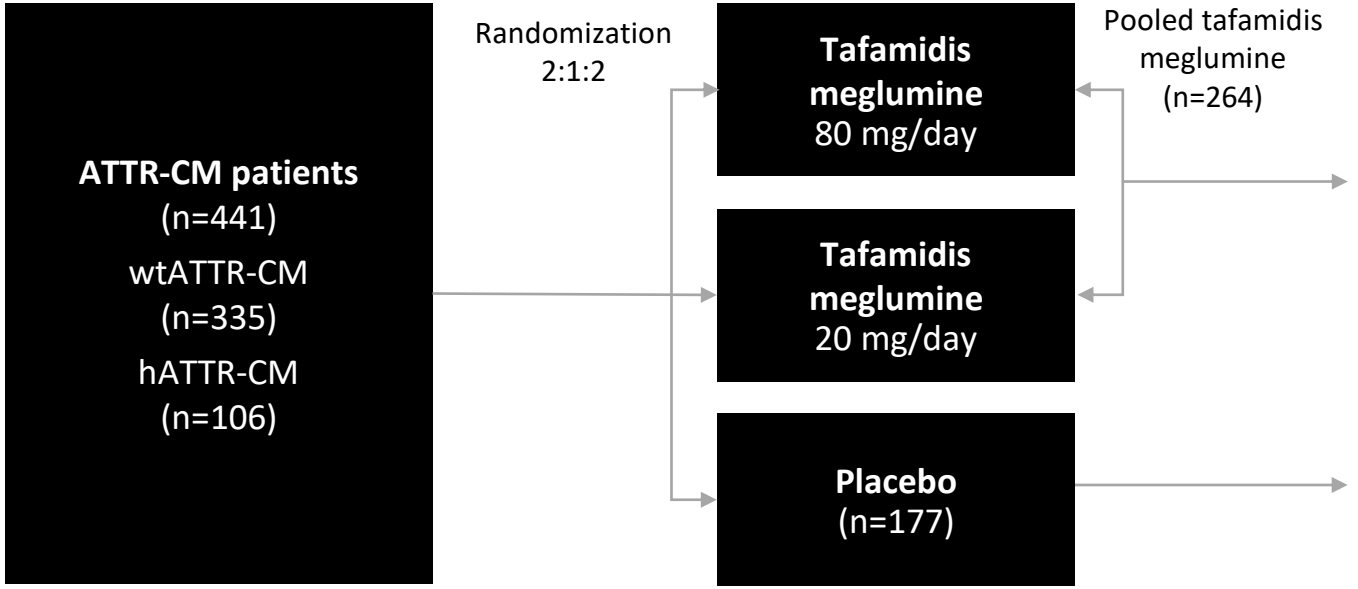


Image adapted from: Garcia-Pavia P, et al. *Eur J Heart Fail* 2021;23(4):512–26.

A European Society of Cardiology Working Group position paper states that tafamidis should be generally considered the agent of choice in hereditary and wild-type ATTR-CM patients with reasonable expected survival

ATTR-ACT: study design[1]

- ATTR-ACT was a Phase 3, multicenter, international, double-blind, randomized, placebo-controlled study in 441 patients with wtATTR-CM or hATTR-CM[1]



Stratified by presence or absence of hereditary *TTR* genotype and by baseline severity of disease (NYHA class)

Primary analysis[1]

A hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations[†]

Components of primary analysis for pooled tafamidis meglumine versus placebo:[1]

- All-cause mortality
- Frequency of CV-related hospitalizations

Key secondary endpoints[1,2]

- Change from baseline to Month 30 in:
  - 6MWT[1]
  - KCCQ-OS[2]

30 months

ATTR-ACT: baseline demographic characteristics

In the pooled tafamidis group, the median age of patients at baseline was 75 years

Characteristic	Pooled tafamidis (n=264)	Placebo (n=177)
Age, years		
Mean (SD)	74.5 (7.2)	74.1 (6.7)
Median (minimum, maximum)	75 (46, 88)	74 (51, 89)
Sex, n (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
hATTR amyloidosis, n (%)	**63 (23.9)**	**43 (24.3)**
wtATTR amyloidosis, n (%)	**201 (76.1)**	**134 (75.7)**
Race, n (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0

ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTR amyloidosis, transthyretin amyloidosis; h, hereditary; SD, standard deviation; wt, wild-type.

Maurer MS, et al. *N Engl J Med* 2018;379:1007–16.

ATTR-ACT: baseline clinical characteristics

~1/3 of patients had severe disease (NYHA Class III) at baseline

Characteristic	Pooled tafamidis (n=264)	Placebo (n=177)
mBMI*, mean (SD)	1058.8 (173.8)	1066.4 (194.4)
LV ejection fraction (%), mean (SD)	48.4 (10.3)	48.6 (9.5)
Interventricular wall thickness (mm), mean (SD)	16.7 (3.8)	16.2 (3.5)
LV posterior wall thickness (mm), mean (SD)	17.0 (3.9)	16.7 (4.1)
LA anterior-posterior diameter size (mm), mean (SD)	43.8 (7.0)	43.7 (6.1)
LV stroke volume (ml), mean (SD)	45.8 (16.1)	45.1 (16.9)
Global longitudinal strain (%), mean (SD)	−9.3 (3.5)	−9.4 (3.6)
NYHA class, n (%)		
Class I	**24 (9.1)**	**13 (7.3)**
Class II	**162 (61.4)**	**101 (57.1)**
Class III	**78 (29.5)**	**63 (35.6)**
NT-proBNP (pg/ml), median (Q1, Q3)	2995.9 (1751.5, 4861.5)	3161.0 (1864.4, 4825.0)
Troponin I (ng/ml), median (Q1, Q3)	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)

*mBMI calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (kg/m^2)

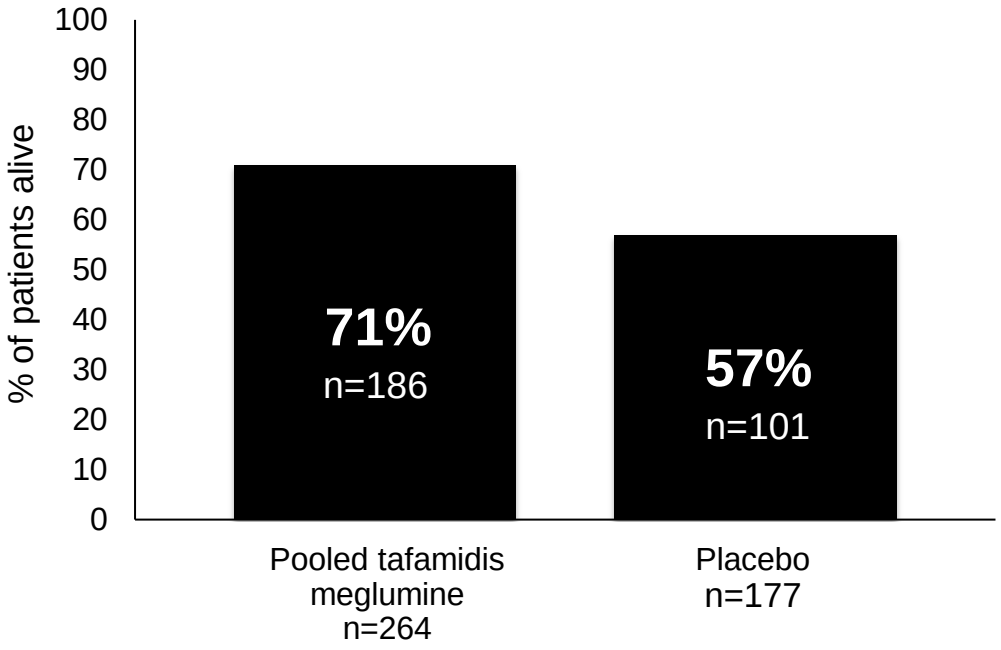
ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; LA, left atrial; LV, left ventricular; mBMI, modififed body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; SD, standard deviation.

Maurer MS, et al. *N Engl J Med* 2018;379:1007–16.

ATTR-ACT: primary analyses[1,2]

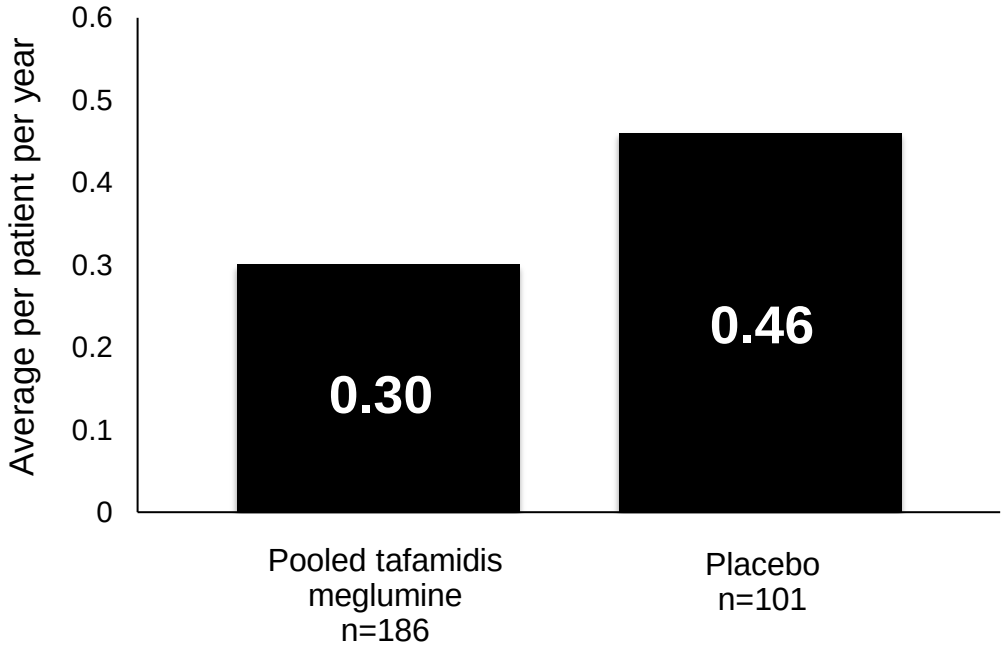
Tafamidis significantly reduced the combination of all-cause mortality and CV-related hospitalizations vs placebo over 30 months (P=0.0006)

Patients alive at Month 30‡



Of the 287 surviving patients at Month 30

Average CV-related hospitalizations per patient per year during 30 months



Primary analysis determined by the Finkelstein–Schoenfeld method, a hierarchical combination of both endpoints, prioritizing all-cause mortality*. The win ratio† was 1.70 (95% CI: 1.26–2.29)

*P=0.0006 versus placebo over 30 months[2,3]; †The win ratio is the number of pairs of treated patient "wins" divided by the number of pairs of placebo patient "wins"; ‡Heart transplantation, combined heart and liver transplantation, and cardiac mechanical assist device implantation are treated as equivalent to death in this analysis.

ATTR-ACT: all-cause mortality Cox proportional hazards model

Tafamidis significantly reduced all-cause mortality vs placebo over 30 months

Individual component: all-cause mortality over 30 months[1]

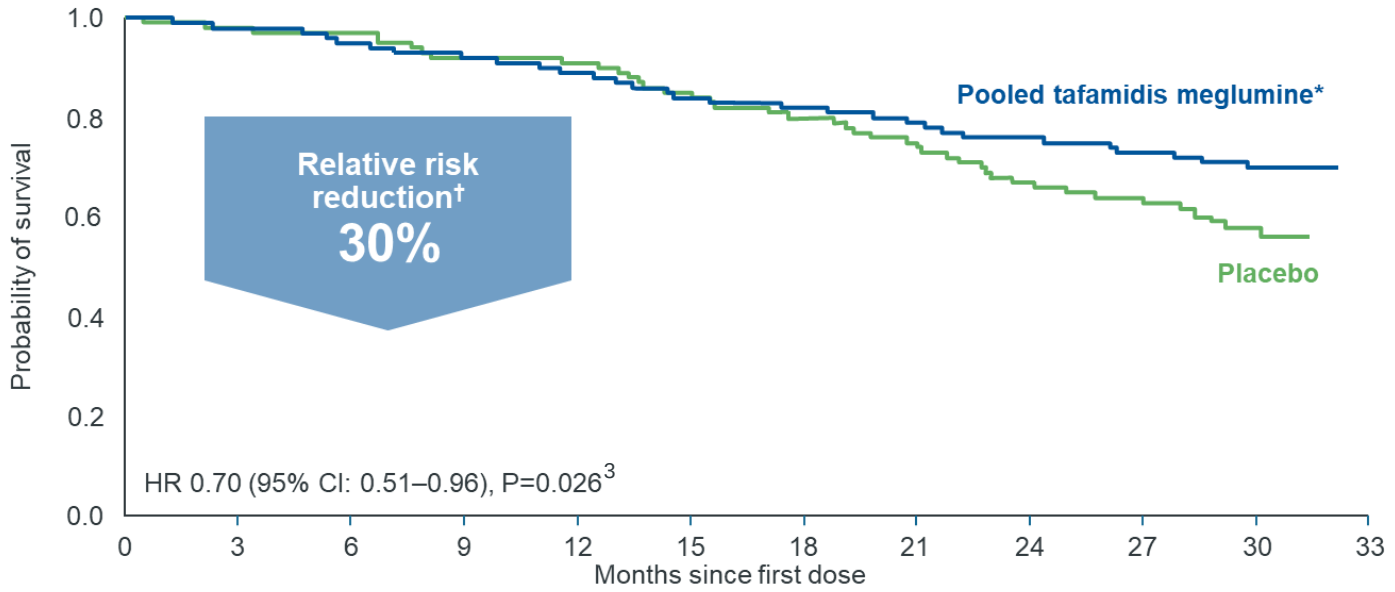


Image reproduced from Maurer MS, et al. *N Engl J Med* 2018;379:1007–16.

Number needed to treat

7.5

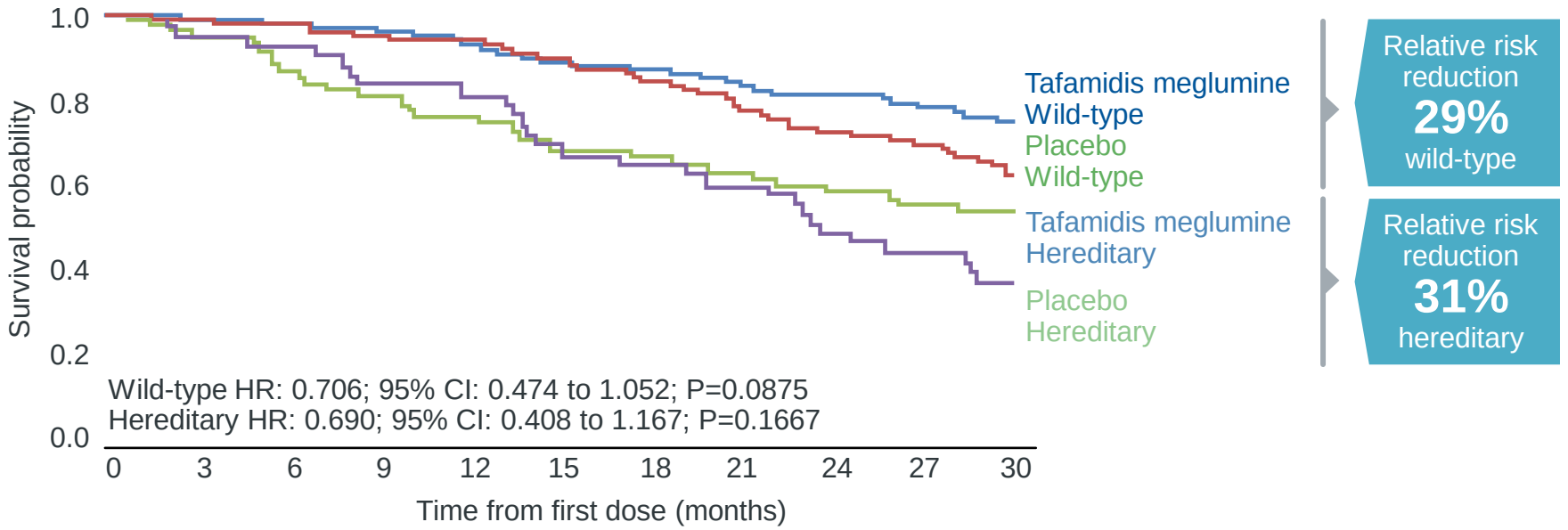
~8 patients would need to be treated to prevent one death within 30 months

No. at risk (cumulative no. of events)[1]

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)

ATTR-ACT: all-cause mortality in patients with wtATTR-CM or hATTR-CM

Similar reductions in wtATTR-CM and hATTR-CM subgroups at 30 months*[1]



Relative risk reduction **29%** wild-type

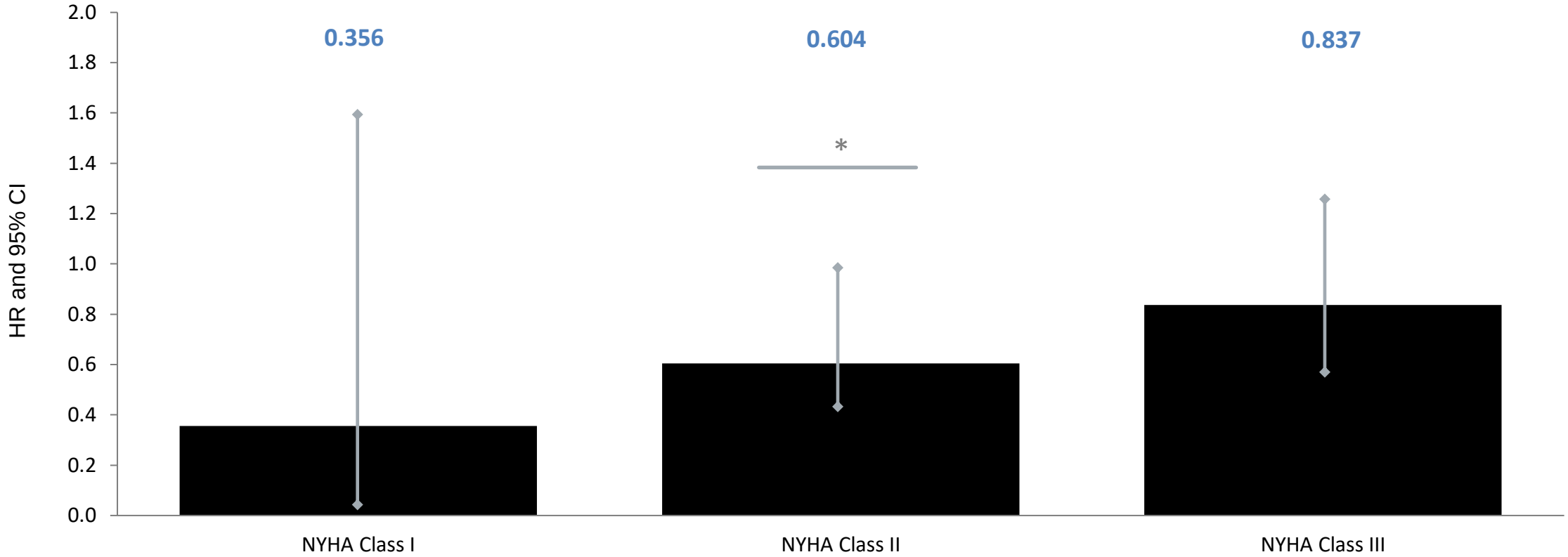
Relative risk reduction **31%** hereditary

Reduced risk of all-cause mortality in both subgroups, despite poorer prognosis in hATTR-CM[1]

Image reproduced from Rapezzi C, et al. *JACC Heart Fail* 2021;9:115–23.

ATTR-ACT: reductions in risk of death across NYHA classes

Efficacy of tafamidis appeared to be greater in patients with less severe disease at baseline, highlighting the importance of early diagnosis and treatment

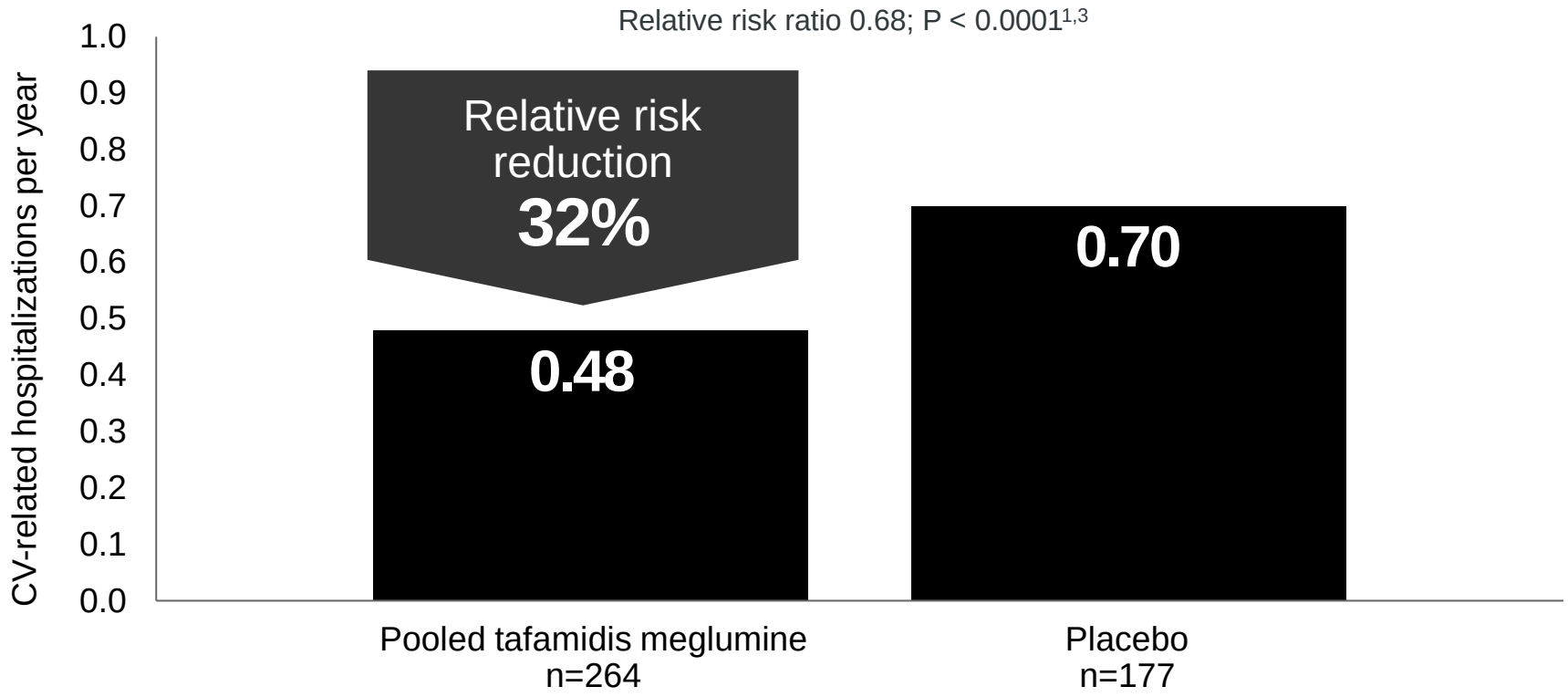


	NYHA Class I	NYHA Class II	NYHA Class III
	n=37	n=263	n=141
Reduction in risk of death	**64.4%**	**39.6%**	**16.3%**

ATTR-ACT: frequency of CV-related hospitalizations

Tafamidis significantly reduced CV-related hospitalizations vs placebo over 30 months[1]

Individual component: CV-related hospitalizations frequency during 30 months[1]*†



Patient-years of treatment needed[2]:

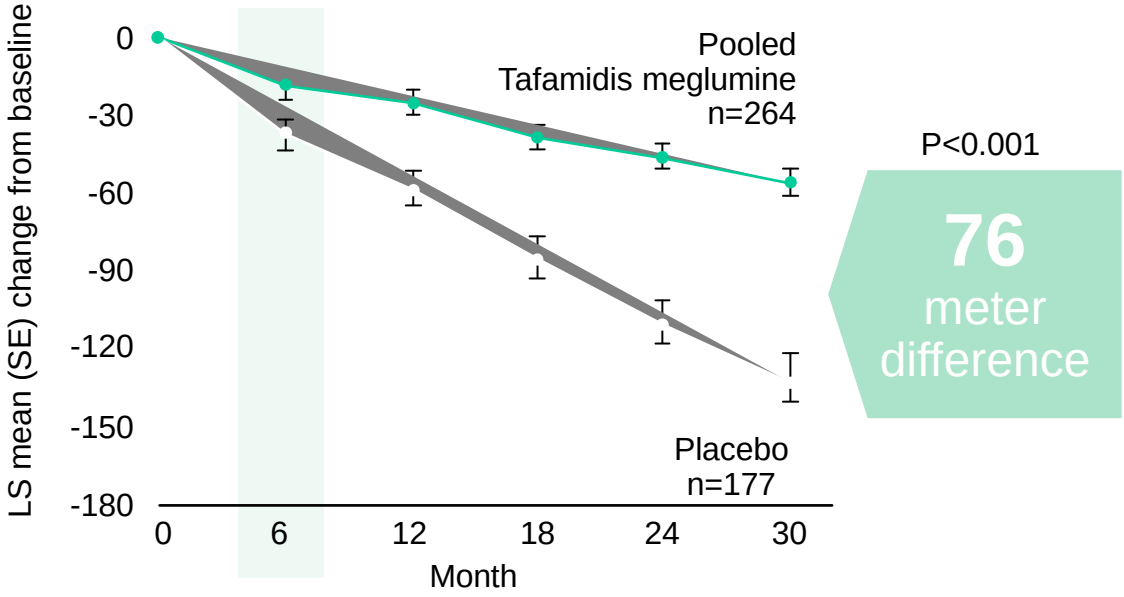
4

~4 patient-years of treatment needed to prevent one CV-related hospitalization

ATTR-ACT: change in functional capacity and quality of life vs placebo

A significant effect favoring tafamidis was first observed at Month 6 and remained consistent through Month 30 on both 6MWT distance and KCCQ-OS score[1]

Functional capacity:
6MWT change from baseline at Month 30*[1]

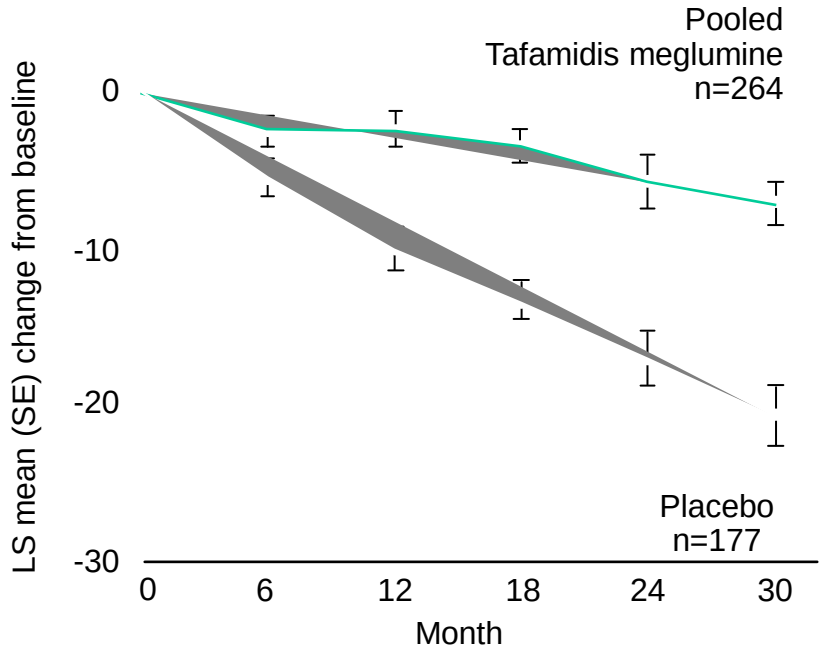


P<0.001

76 meter difference

Image reproduced from Maurer MS, et al. *N Engl J Med* 2018;379:1007–16.

QoL:
KCCQ-OS score change from baseline at Month 30†[1]



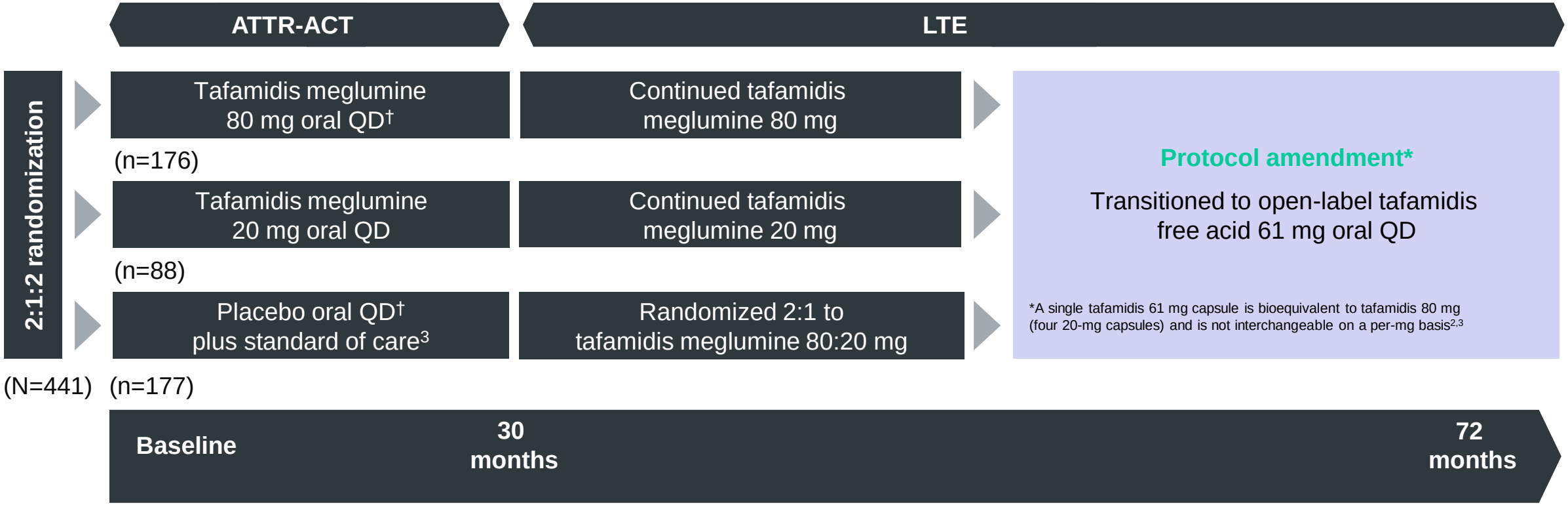
P<0.001

14 point difference

Image reproduced from Maurer MS, et al. *N Engl J Med* 2018;379:1007–16.

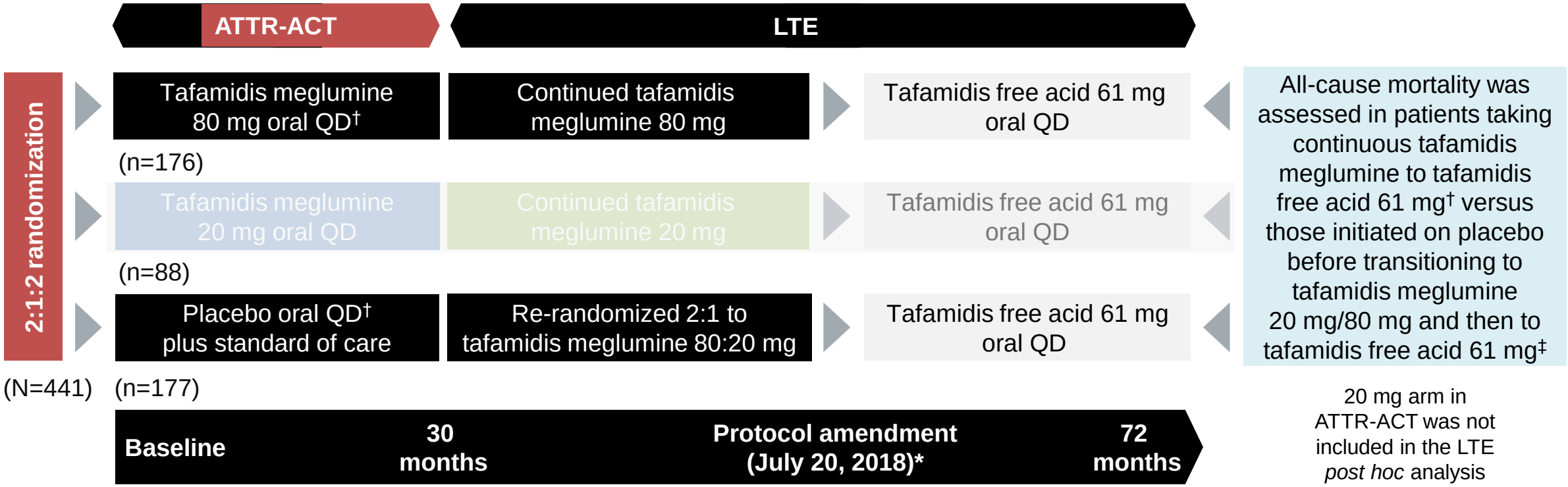
ATTR-ACT and long-term extension[1]

Tafamidis is the only treatment for ATTR-CM with 5 years' clinical data†. Prolonged survival was observed throughout ATTR-ACT and the LTE[1]

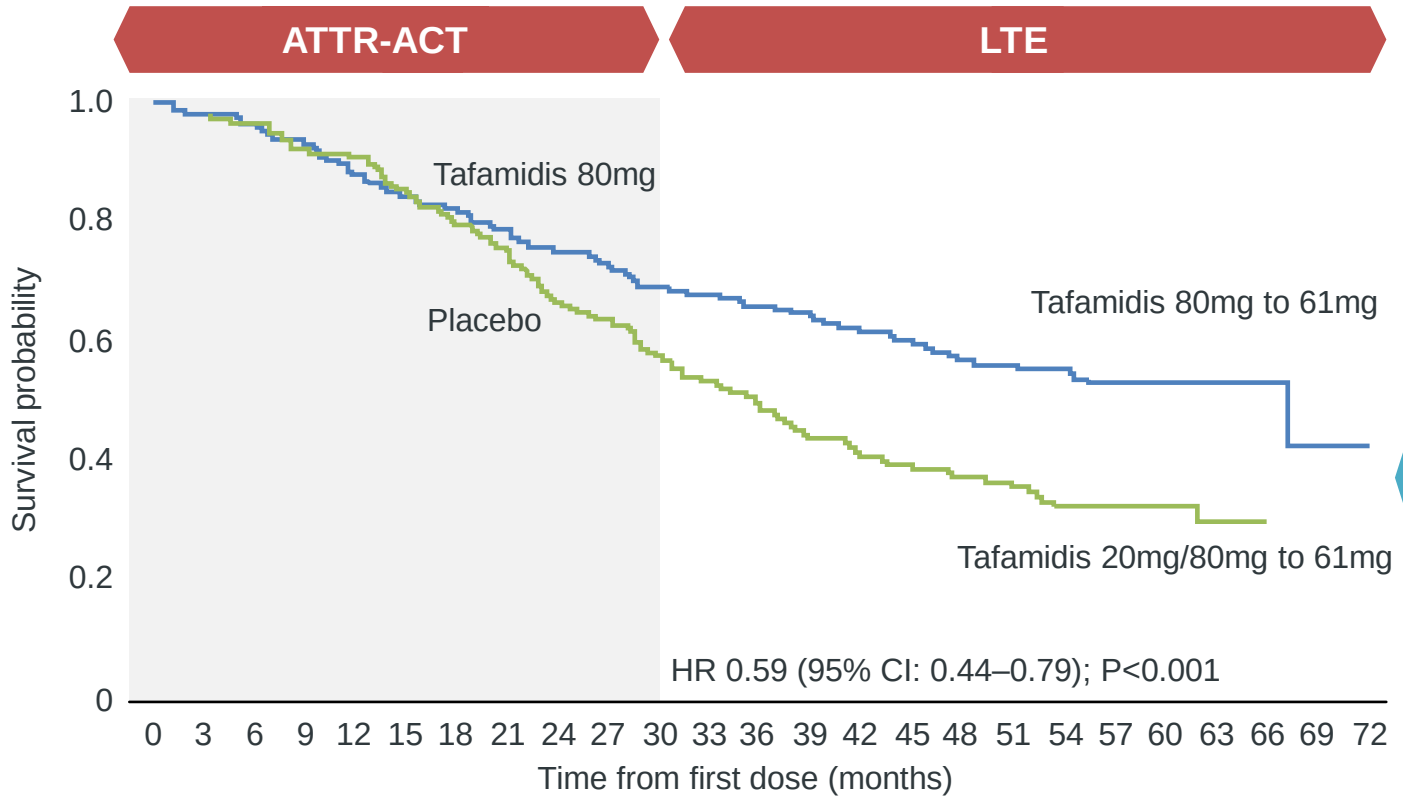


Post hoc analysis of ATTR-ACT and LTE[1]

The tafamidis meglumine 20 mg arm in ATTR-ACT was not included in the LTE *post hoc* analysis[1]



ATTR-ACT and LTE *post hoc* analysis: 5-year all-cause mortality data



relative risk reduction **41%**

Image reproduced from Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193.

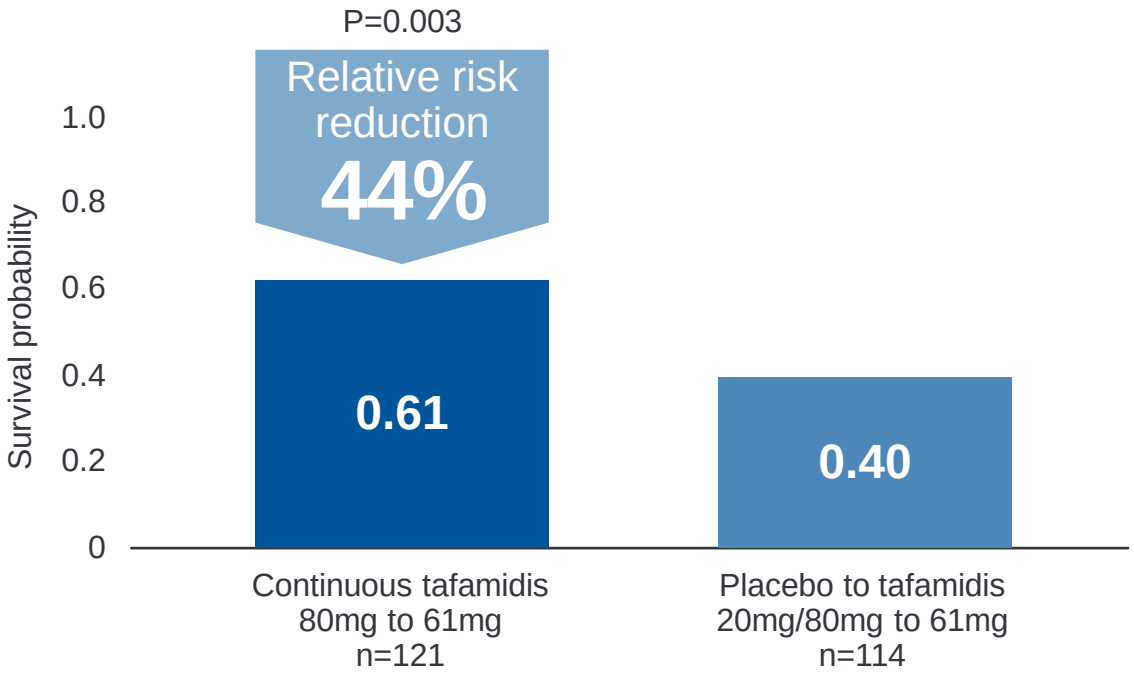
Patients taking continuous tafamidis meglumine 80 mg to tafamidis free acid 61 mg* showed a clinically significant improvement in survival at 5 years versus those first treated with placebo†‡

53% preliminary 5-year survival rate with tafamidis versus 32% in patients who first received placebo (P<0.001)

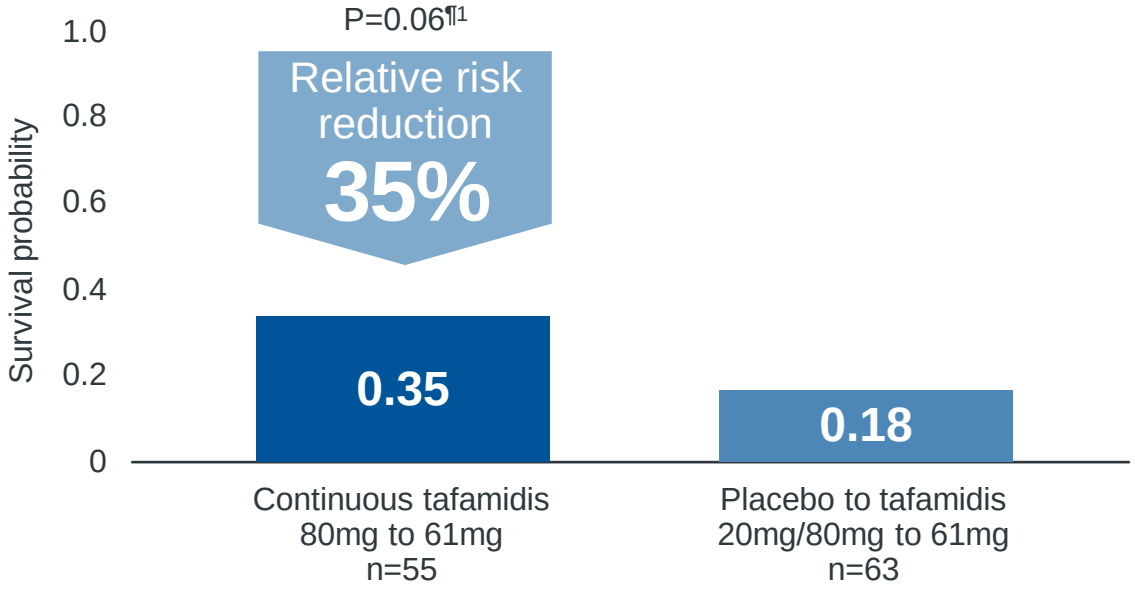
ATTR-ACT and LTE *post hoc* analysis: reduction in risk of mortality†[1]

Continuous tafamidis* treatment showed greater survival in patients with ATTR-CM with baseline NYHA Classes I, II or III vs those first treated with placebo

All-cause mortality in patients with ATTR-CM with baseline NYHA Class I/II at 60 months‡



All-cause mortality in patients with ATTR-CM with baseline NYHA Class III at 60 months§



Tafamidis has a similar and comparable safety profile to placebo

In the ATTR-ACT study, the frequency of adverse events in patients treated with tafamidis meglumine 80 mg* was generally similar and comparable to that of the placebo[1,2]

	Tafamidis meglumine 80 mg	Tafamidis meglumine 20 mg	Placebo (ATTR-ACT only)
N	176	88	177
Patients with serious TEAEs	75.6%	75.0%	79.1%
Patients with severe TEAEs	62.5%	61.4%	64.4%
N	227	115	
Patients with serious TEAEs	69.6%	72.2%	
Patients with severe TEAEs	53.3%	53.0%	

In patients treated continuously with tafamidis meglumine 80 mg to tafamidis free acid 61 mg, no new safety concerns were identified throughout the ATTR-ACT LTE study, and frequency of adverse events remained similar to that with placebo (median follow-up across both studies: ~58 months)[4]

APOLLO-B >

A Study to Evaluate Patisiran in Participants with Transthyretin Amyloidosis with Cardiomyopathy

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Evaluating efficacy and safety of patisiran (Onpattro, Alnylam) in adults with transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy.

Cardiology today

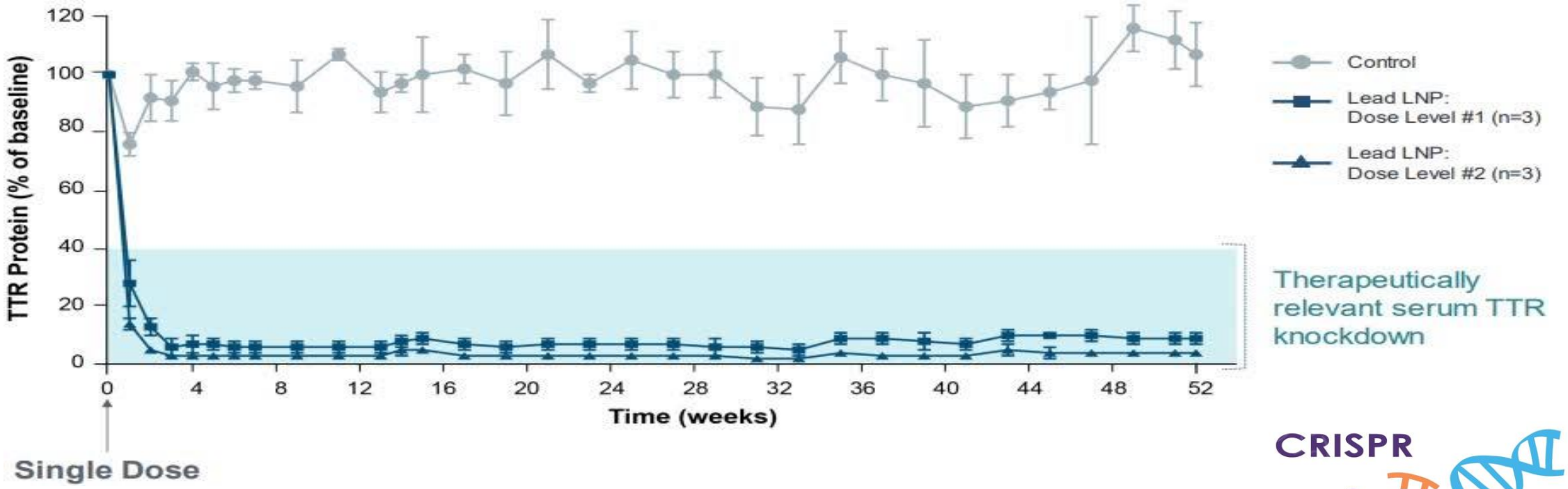
DESIGN: randomized, parallel

PATIENTS: 360

RESULTS: At 12 months, serum transthyretin was reduced by 86.8% (standard deviation, 13.6) in the patisiran group but did not change in the placebo group. Change from baseline to 12 months in 6-minute walk test was −21.35 m in the placebo group and −8.15 m in the patisiran group (P = .0162).

Maurer MS, et al. APOLLO-B. Presented at: International Symposium on Amyloidosis; Sept. 4-8, 2022; Heidelberg, Germany.

Gene Editing by CRISPR/CAS in Patients with ATTR Amyloidosis



NEJM 2021

CRISPR

Clustered
Regularly
Interspaced
Short
Palindromic
Repeats

RICHMOND Pharmacology

Conclusions and perspectives

- Tafamidis has proven safety and efficacy in patients with hereditary and wtATTR. *Not a Class effect*
- Caution should be taken in patients with NYHA III and preferably avoided if clinically unstable.
- Current upcoming studies will test the role of TTR silencers with initial results pointing to mild effects.
- The role of combo with other HF medications remains controversial.
- No drug yet addresses the preexisting plaques