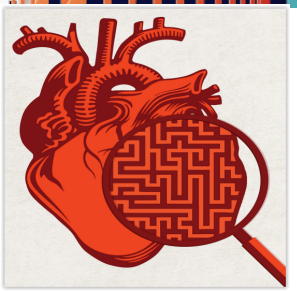
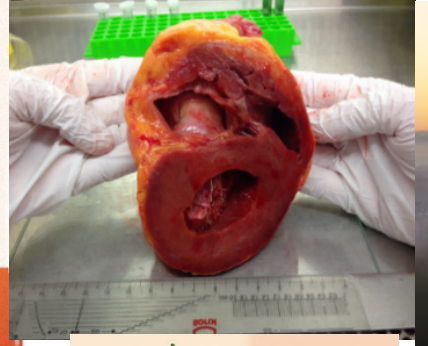
campi modulo

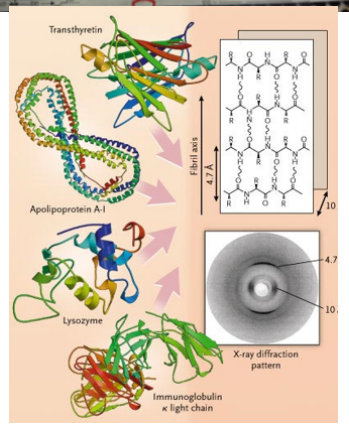
SEDE DEI LAVORI

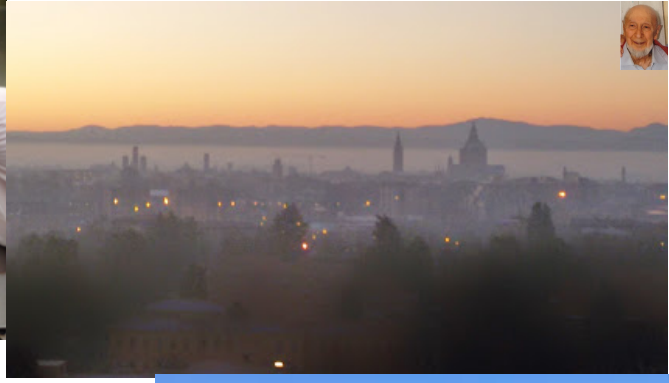
A. Roma Lifestyle Hotel
Via Giorgio Zoega 59, Roma



PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE







La terapia dell'amiloidosi cardiaca ATTR con Tafamidis: dagli studi clinici al *«real word»*

Stefano Perlini
Department of Internal Medicine, Center for Diagnosis and Treatment of Systemic Amyloidosis,
IRCCS Policlinico San Matteo Foundation, University of Pavia, Italy
Roma, 25 giugno 2026

Dislosures: Pfizer, Alnylam, Sanofi, Prothena, Accurate

What factors might guide our clinical decision-making when selecting first-line treatment for our patients?

Survival

Quality of life

Safety profile

Breadth of evidence and clinical experience

Amyloidosis: protein misfolding disease

aggregation of normally soluble proteins into soluble β-sheet fibrils which are deposited in **target tissues** causing **progressive organ dysfunction**

Amyloid precursor

Increased conc.

Increased synthesis
- Monoclonal LC*
- SAA

Reduced clearance
- β2-microglobulin

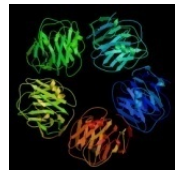
Mutations*
- Transthyretin
- Apolipoprotein AI
- Lysozyme, etc.

Aging
- Transthyretin wt

Interactions with microenvironment of target organs

Proteolysis

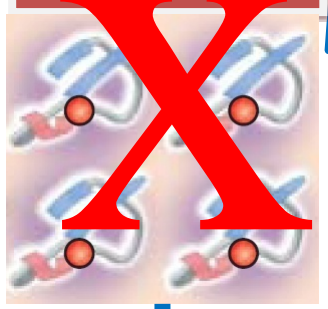
Lysosomal enzymes
Metalloproteases
metal ions,
matrix components



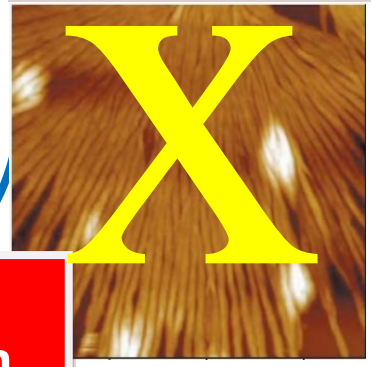
GAGs

SAP

Oligomers



Amyloid fibrils



misfolded

Structural instability

Organ dysfunction

Pavia Amyloidosis Center,, unpublished

TABLE 3 ATTR Specific Disease Modifying Therapies

	Mechanism of Action	Stage of Approval	Route of Administration	Dose	Phase 3 Clinical Trial	Cardiovascular Trial Outcomes	Side Effects
Stabilizers							
Diflunisal	Stabilizes TTR to prevent dissociation	Approved as an NSAID, off-license use for ATTR-CA and ATTR-PN	Oral	250 mg twice daily	NA	Small retrospective studies have demonstrated an	Fluid retention Bleeding
Tafamidis	Stabilizes TTR to prevent dissociation	Approved for ATTR-CA		max 61 mg or Vy mg once daily			
Acoramidis	Stabilizes TTR to prevent dissociation	Due to be reviewed by the FDA					
Silencers							
Patisiran	siRNA targeting TTR mRNA	Approved for ATTR-PN, but not for ATTR-CA	Intravenous infusion	80-min infusion based weight every 3 wks <100 kg = 0.3 mg >100 kg = 30 mg			
Vutrisiran	siRNA targeting TTR mRNA	App... CA		...ion every 3			
Eplontersen	ASO inhibitor of TTR production	Approved for ATTR-PN, but not for ATTR-CA	Subcutaneous injection	45 mg monthly	CARDIO-TTRansform	CARDIO-TTRansform is a phase 3 RCT designed to assess the efficacy of eplontersen in patients with ATTR-CA	Headache Vitamin A deficiency

TABLE 3 Continued

	Mechanism of Action	Stage of Approval	Route of Administration	Dose	Phase 3 Clinical Trial	Cardiovascular Trial Outcomes	Side Effects
Gene Editors							
NTLA-2001	CRISP-Cas9 editing of the TTR gene	Under investigation	Intravenous infusion	0.1 mg/kg or 0.3 mg/kg given once	NA	A small phase 1 trial has demonstrated that NTLA-2001 is safe and results in a sustained TTR knockdown	Headache Vitamin A deficiency
Depleters							
NI006	Recombinant human anti-ATTR monoclonal IgG1 antibody that binds ATTR-amyloid	Under investigation	Intravenous infusion	4 weekly infusions with doses ranging from 0.3-60 mg/kg	NA	A small phase 1 trial has demonstrated that NI006 is safe and at higher doses appeared to reduce NT-proBNP, troponin I, and myocardial extracellular volume. A phase 3 trial will assess efficacy in ATTR-CA.	Arthralgia Thrombocytopenia
PX004	Humanized IgG antibody that binds ATTR-amyloid	Under investigation	Intravenous infusion	4 weekly infusions with doses ranging from 0.1-3.0 mg/kg	NA	A small phase 1 trial has demonstrated that PX004 is safe	Unknown
AT-02	Pan amyloid removal technology using a single-chain fusion protein to stimulate immunological removal of amyloid	Under investigation	Intravenous infusion	Dosing not available	NA	A small phase 1 trial is currently ongoing	Unknown

6MWT = 6-minute walk test; ASO = antisense oligonucleotide; CA = cardiac amyloidosis; FDA = U.S. Food and Drug Administration; IgG = immunoglobulin G; mRNA = messenger RNA; NA = not available; NSAID = nonsteroidal anti-inflammatory drug; PN = polyneuropathy; RCT = Randomized controlled trial; siRNA = small interfering RNA; TTR = Transthyretin; other abbreviations as in Tables 1 and 2.

Continued on the next page

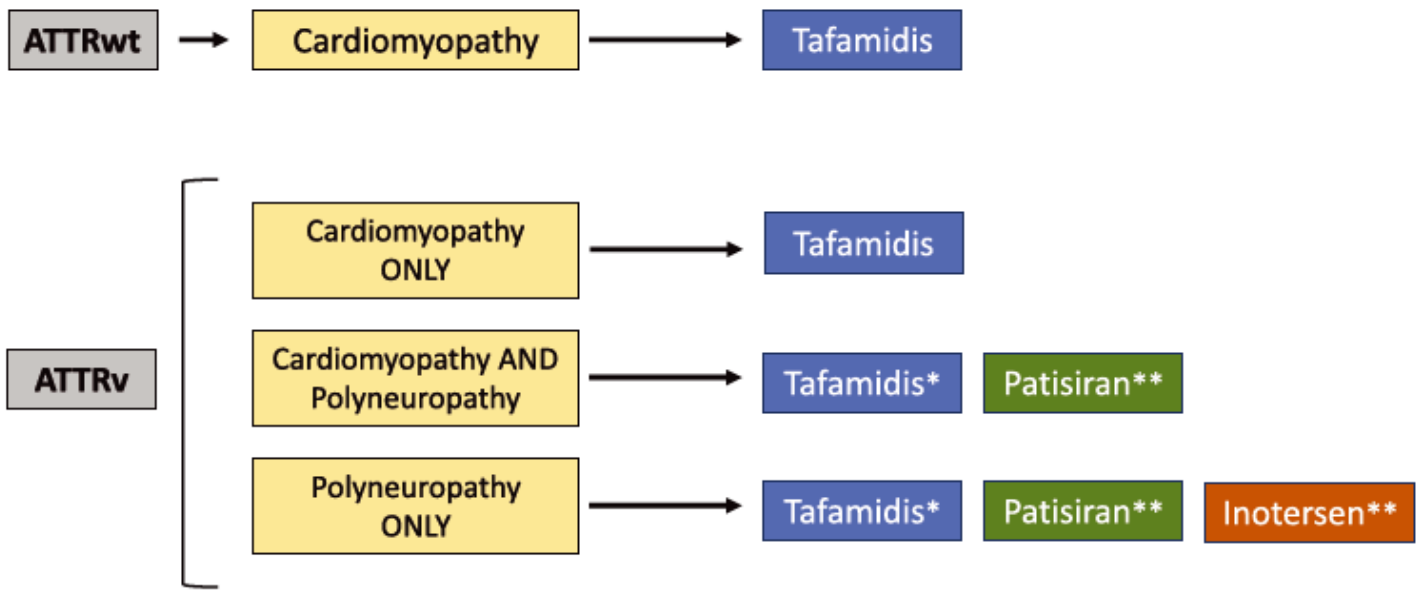
Fontana et al. JACC CV Img 2025, in press

ESC European Society of Cardiology
European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2140

POSITION PAPER

Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Cardiac amyloidosis is "treatable" !



* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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

ATTR-ACT[1]

ATTR-ACT LTE[2]

MDedge LATEST QUIZZES VIDEOS

ATTR-ACT shows treatment breakthrough in amyloid cardiomyopathy

September 4, 2018 | CARDIOLOGY NEWS

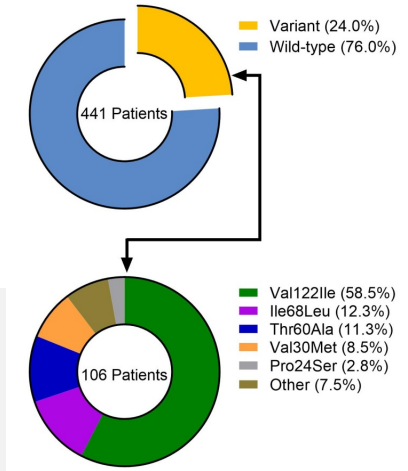
Bruce Jancin

- **NYHA class (I/II and III)**[3]
- **LVEF status**[4]
- **Atrial fibrillation**[5]
- **Octogenarian (aged <80 and ≥80 years)**[6]
- **CKD**[7]

ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CKD: chronic kidney disease; LTE: long-term extension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

1. Maurer MS, et al. *N Engl J Med* 2018;379(11):1007–16; 2. Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193; 3. Elliott P, et al. *Eur J Heart Fail* 2023;25(11):2060–4; 4. Drachman B, et al. *Eur J Heart Fail* 2024;26(9):2038–46; 5. Witteles R, et al. *JACC CardioOncol* 2024;6(4):592–8; 6. Garcia-Pavia P, et al. *JACC Heart Fail* 2024;12(1):150–60; 7. Sperry BW, et al. *JACC CardioOncol* 2024;6(2):300–6.

ATTR-ACT and LTE:* study design[1]



ATTR-ACT

2:1:2 randomization

- Tafamidis meglumine 80 mg oral QD (n=176)
- Tafamidis meglumine 20 mg oral QD (n=88)
- Placebo oral QD plus standard of care[3] (n=177)

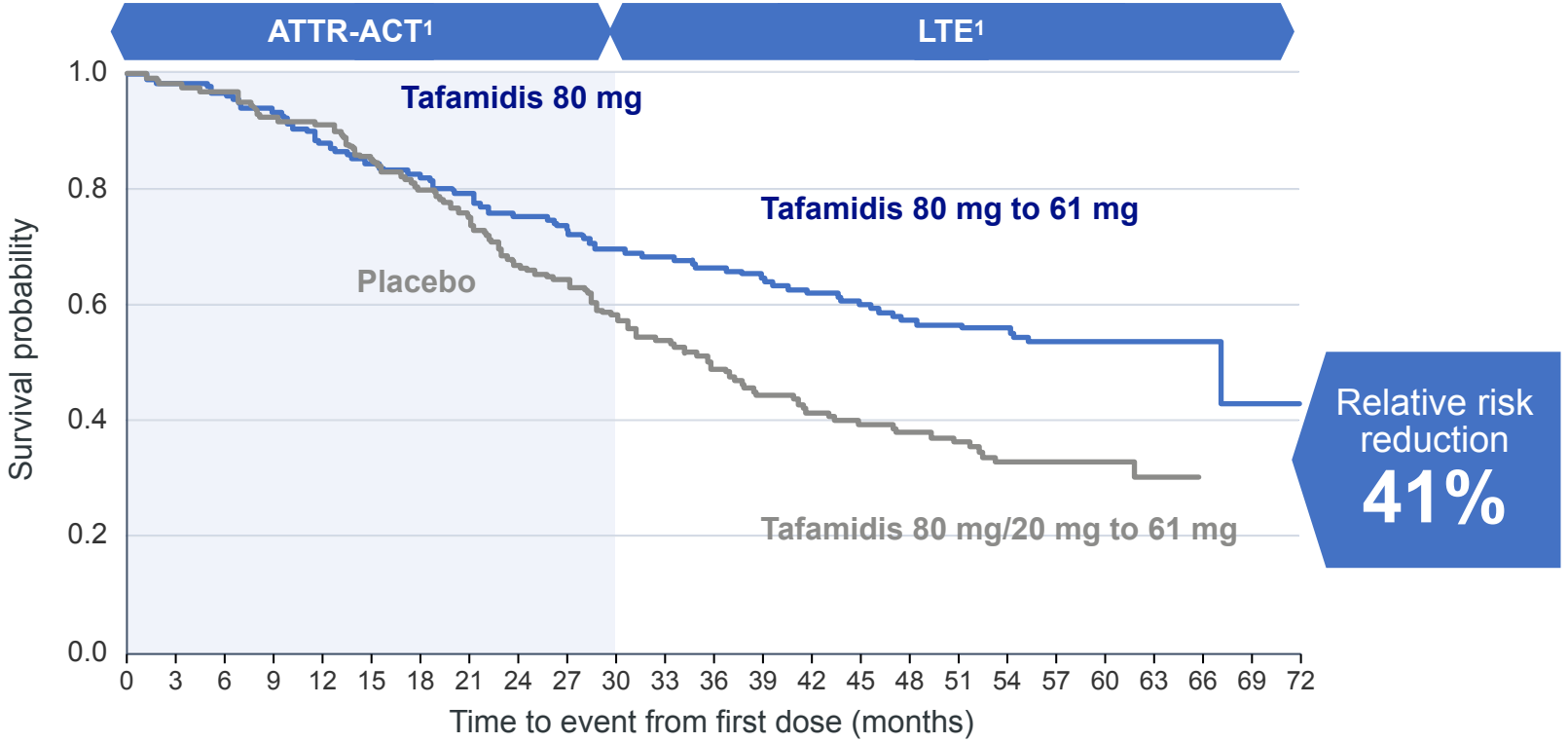
(N=441)

Baseline — **30 months** — **72 months**

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

Tafamidis 61 mg is indicated to treat adult wild-type and hereditary ATTR cardiomyopathy patients.[3] All patients on tafamidis meglumine (20 or 80 mg QD) were analyzed in a combined approach. Tafamidis 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per-mg basis.[2,3]
*Upon completion of ATTR-ACT, patients could enroll in the ongoing LTE study for up to 60 months. Patients receiving tafamidis in ATTR-ACT continued to receive the same dose uninterrupted, while those in the placebo group were randomized 2:1 to tafamidis 80 mg or 20 mg. Patients were treated with tafamidis 80 mg or 20 mg (up to the protocol amendment) for a median of 39 months. Median LTE follow-up was 58.5 months in the continuous tafamidis 80 mg to 61 mg group and 57.1 months in the placebo to tafamidis 80 mg/20 mg to 61 mg group. For both groups, time zero for survival analyses was the time of enrollment in ATTR-ACT;[1,4] †A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[2,3]
ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR cardiomyopathy: transthyretin amyloid cardiomyopathy; LTE: long-term extension; QD, once daily.
1. Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193; 2. Lockwood PA, et al. *Clin Pharmacol Drug Dev* 2020;9(7):849–54; 3. tafamidis (tafamidis), Summary of Product Characteristics, EMA. Available at: https://www.ema.europa.eu/documents/product-informaton/tafamidis-epar-product-information_en.pdf (Accessed April 2025); 4. Maurer MS, et al. *N Engl J Med* 2018;379(11):1007–16.

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



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*,†

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

Figure adapted from Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193.[1]

Tafamidis 61 mg is indicated to treat adult wild-type and hereditary ATTR cardiomyopathy patients.[2] All patients on tafamidis meglumine (20 or 80 mg QD) were analyzed in a combined approach. Tafamidis 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per-mg basis.[2,3]
*Upon completion of ATTR-ACT, patients could enroll in the ongoing LTE *post hoc* analysis for up to 60 months. In the LTE study, patients treated with tafamidis meglumine 80 mg in ATTR-ACT continued with tafamidis 80 mg, then transitioned to tafamidis free acid 61 mg, and were compared with those treated with placebo in ATTR-ACT, who were randomized to tafamidis meglumine 80 mg or tafamidis meglumine 20 mg (2:1), then transitioned to tafamidis free acid 61 mg. Median LTE follow-up was 58.5 months in the continuous tafamidis meglumine 80 mg to tafamidis free acid 61 mg group and 57.1 months in the placebo to tafamidis meglumine 80 mg/20 mg to tafamidis free acid 61 mg group. For both groups, time zero for survival analyses was the time of enrolment in ATTR-ACT.[1] †The primary efficacy endpoint in the LTE study was all-cause mortality, with heart transplantation and implantation of a cardiac mechanical assist device treated as death. Differential all-cause mortality in the two groups was assessed by a Cox proportional hazards model with treatment, genotype, and NYHA baseline classification in the model.[1]
ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR cardiomyopathy: transthyretin amyloid cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association; QD: once daily.
1. Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193; 2. tafamidis (tafamidis), Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 25, 2025); 3. Lockwood PA, et al. *Clin Pharmacol Drug Dev* 2020;9(7):849–54.

tafamidis® significantly reduced CV-related hospitalizations versus placebo over 30 months[1]

Individual component: CV-related hospitalization frequency over 30 months*,†,1

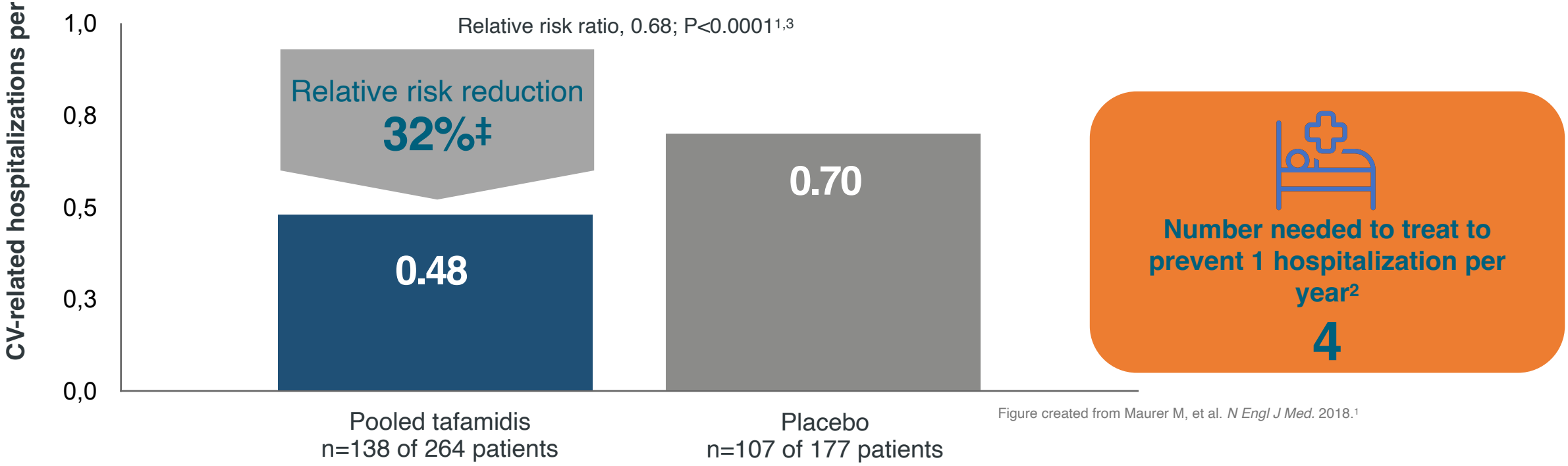


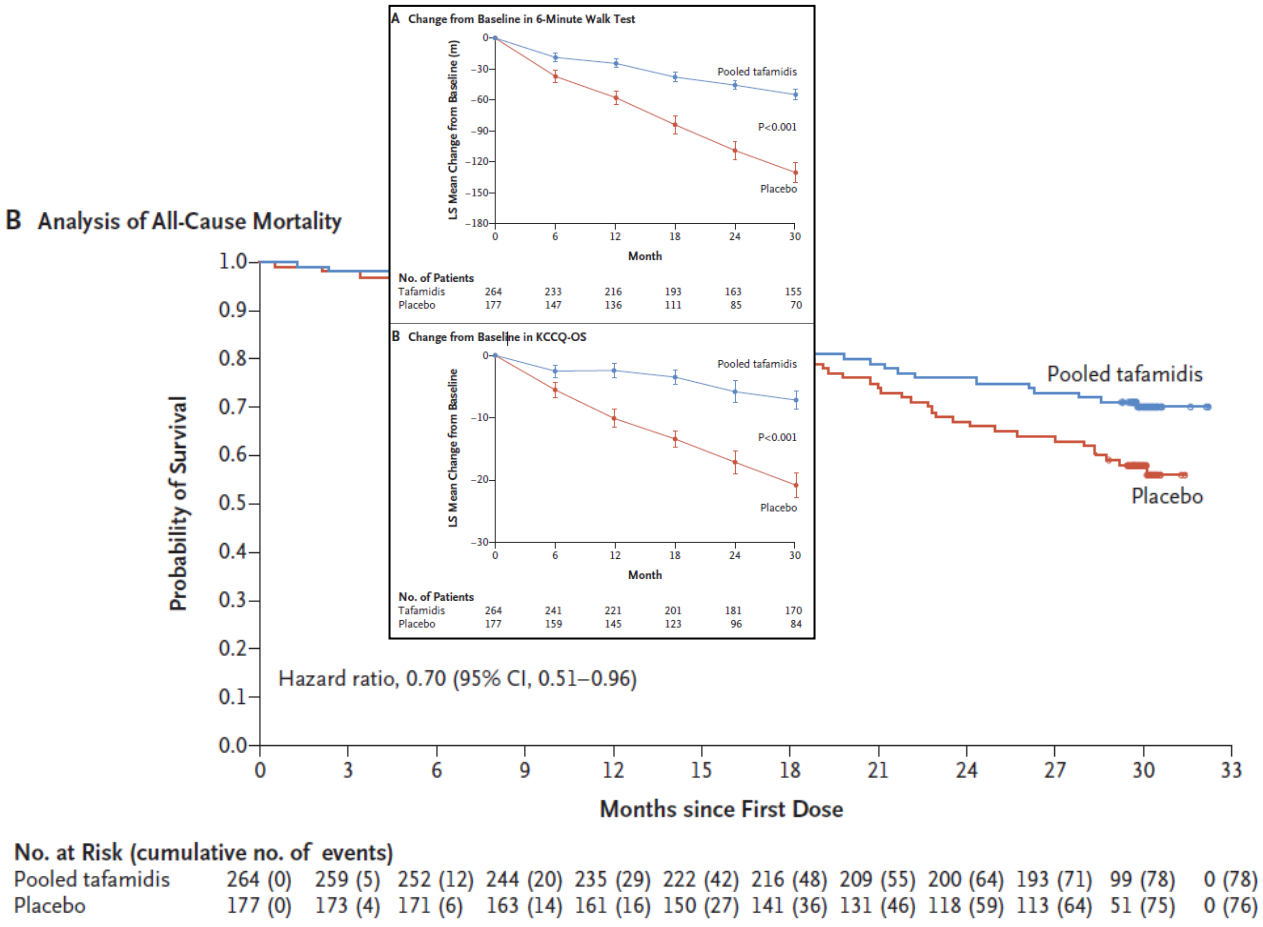
Figure created from Maurer M, et al. *N Engl J Med.* 2018.[1]

*Analysis not adjusted for multiplicity;[1] †The components of the primary analysis, all-cause mortality and CV-related hospitalizations, were evaluated individually.[1] All-cause mortality was analyzed with the use of a Cox proportional hazards model, with treatment and the stratification factors treated as covariates.[1] The CV-related hospitalization analysis was based on a Poisson regression model with treatment, TTR status (hereditary and wild type), NYHA baseline class (NYHA Classes I and II combined versus NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors;[1] ‡Relative risk reduction = (1 - relative risk ratio) * 100; 32% = (1 – 0.68) * 100.[1]

Tafamidis 20 mg is not licensed in ATTR-CM.[3] Tafamidis 20 mg no está indicado en ATTR-CM.[3] tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[3] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[3] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[3,4] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg.[3,4]

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; NYHA, New York Heart Association; TTR, transthyretin.

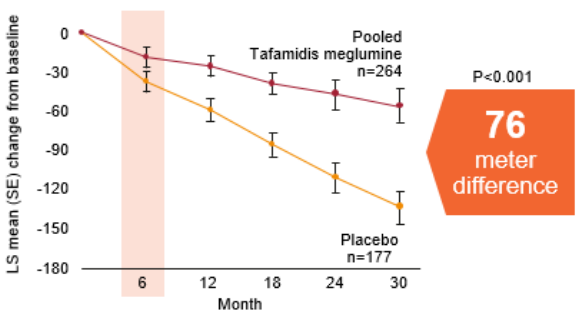
1. Maurer MS, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007–16; 2; 2. Maurer MS, Mann DL. The tafamidis drug development program: a translational triumph. *JACC Basic Transl Sci.* 2018;3(6):871–3; 3. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 4. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;9(7):849–54.



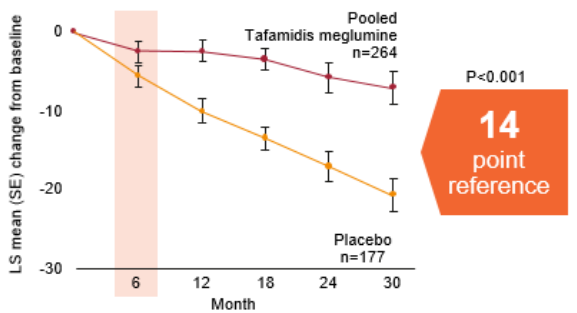
ATTR-ACT: change in functional capacity and quality of life vs placebo

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]



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



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

*The 6-minute walk test (6MWT) evaluated patients' functional capacity by measuring their distance walked in 6 minutes.[1] †The Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score assesses patients' quality of life using the follow domains: total symptoms (symptom frequency, symptom burden), physical limitation, quality of life, and social limitation. Score range from 0 to 100, with higher scores reflecting better health status. Vital status at month 30 was assessed for all enrolled patients.[1,2]

6MWT, 6-minute walk test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squares; SE, standard error.

1. Maurer MS, et al. *N Engl J Med* 2018;379:1007–16; 2. Hanna M, et al. *Am J Cardiol* 2021;141:98–105.

Mean baseline KCCQ-OS

- **67.12** (SD 21.29) for the **continuous tafamidis group***
- **65.90** (SD 21.74) for the **placebo to tafamidis group**

Comparison of treatment groups

- **At both Months 30 and 60**, the **continuous tafamidis group** had a **significantly smaller decline in KCCQ-OS** compared with the placebo to tafamidis group
  - **At Month 30:** LS mean difference in change between groups was 13.38 (95% CI, 9.21–17.54; P<0.0001)
  - **At Month 60:** LS mean difference in change between groups was 18.83 (95% CI, 12.64–25.03; P<0.0001)
- The **continuous tafamidis group** had a **6-point reduction** in LS mean (SE) KCCQ-OS **at Month 30**, with **no further decline over the next 30 months**
- The **placebo to tafamidis group** had a **20-point reduction** in LS mean KCCQ-OS **at Month 30**, but the **decline slowed after initiating tafamidis** during the LTE

LS mean change from baseline in KCCQ-OS

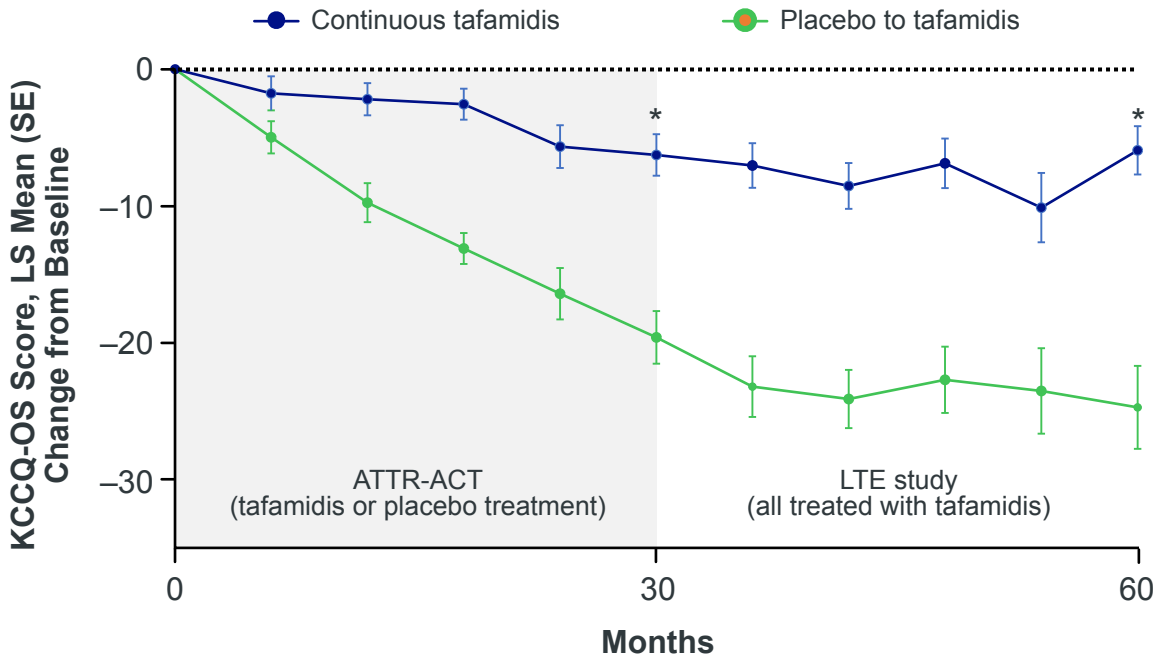


Figure adapted from Grogan M, et al. *Eur J Heart Fail* 2024;26(3):612–5.

*Patients receiving tafamidis 20 mg in ATTR-ACT were excluded from this analysis because this dose is not approved for the treatment of ATTR cardiomyopathy.
ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR cardiomyopathy: transthyretin amyloid cardiomyopathy CI: confidence interval; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary score; LS: least squares; LTE: long-term extension; SD: standard deviation; SE: standard error.
Grogan M, et al. *Eur J Heart Fail* 2024;26(3):612–5.

Tafamidis has a similar and comparable safety profile to placebo

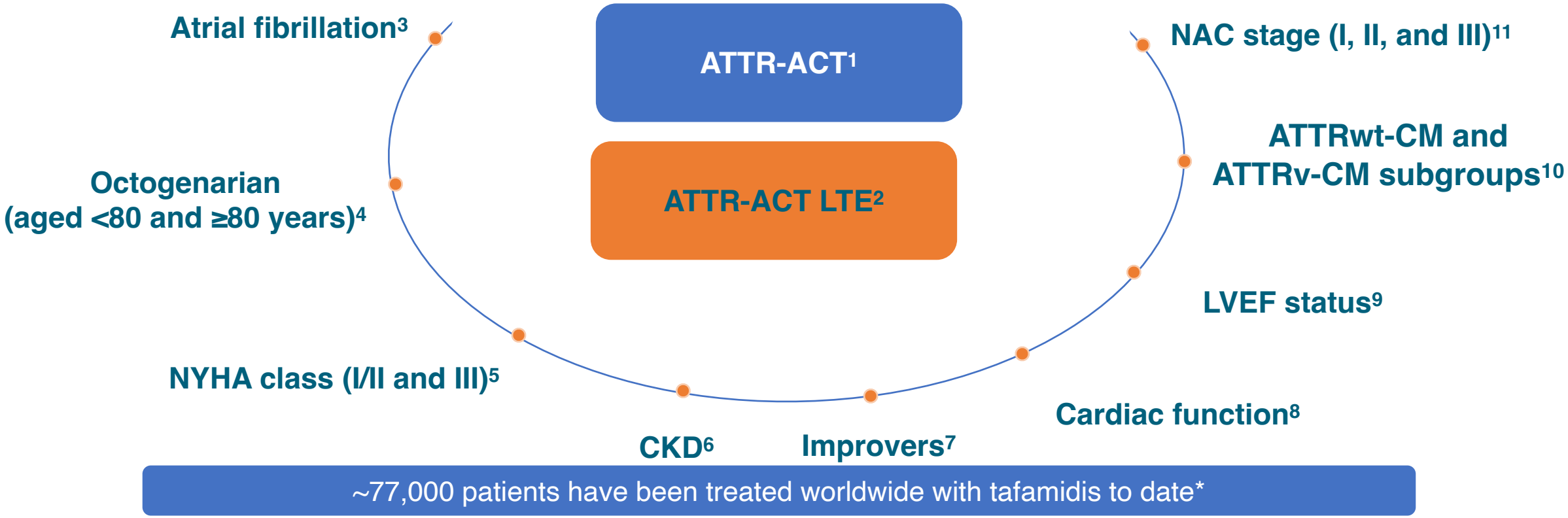
	Tafamidis meglumine 80 mg	Tafamidis meglumine 20 mg*	Placebo (ATTR-ACT only)
ATTR-ACT[1]			
N	176	88	177
Patients with serious TEAEs	75.6%	75.0%	79.1%
Patients with severe TEAEs	62.5%	61.4%	64.4%
ATTR-ACT + LTE[1]			
N	227	115	
Patients with serious TEAEs	69.6%	72.2%	
Patients with severe TEAEs	53.3%	53.0%	

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 group[1,2]

No new safety concerns were identified throughout the LTE, and the **frequency of adverse events remained similar** to that with placebo (median follow-up across both studies: ~58 months)[3]

Tafamidis 61 mg is indicated to treat adult wild-type and hereditary ATTR cardiomyopathy patients.[2]
*Tafamidis meglumine 20 mg is not indicated for use in ATTR-CM.[2] †All patients on tafamidis meglumine (20 or 80 mg QD) were analyzed in a combined approach. Tafamidis 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per-mg basis.[2,4]
ATTR-ACT: Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR cardiomyopathy: transthyretin amyloid cardiomyopathy; LTE: long-term extension; QD: once daily; TEAE: treatment-emergent adverse event.
1. Damy T, et al. *Eur J Heart Fail* 2021;23(2):277–85; 2. tafamidis (tafamidis), Summary of Product Characteristics, EMA. Available at: https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 25, 2025); 3. Elliott P, et al. *Circ Heart Fail* 2022;15(1):e008193; 4. Lockwood PA, et al. *Clin Pharmacol Drug Dev* 2020;9(7):849–54.

Tafamidis has 7+ years of efficacy data, including data across multiple patient populations and parameters[1–11]

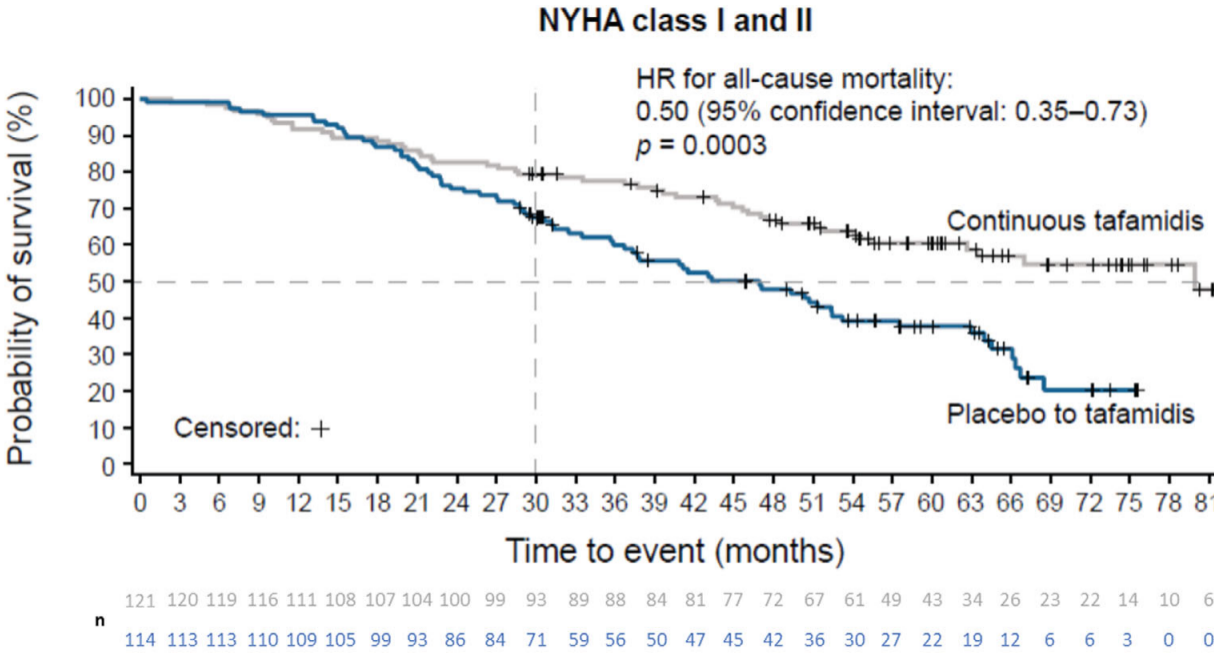


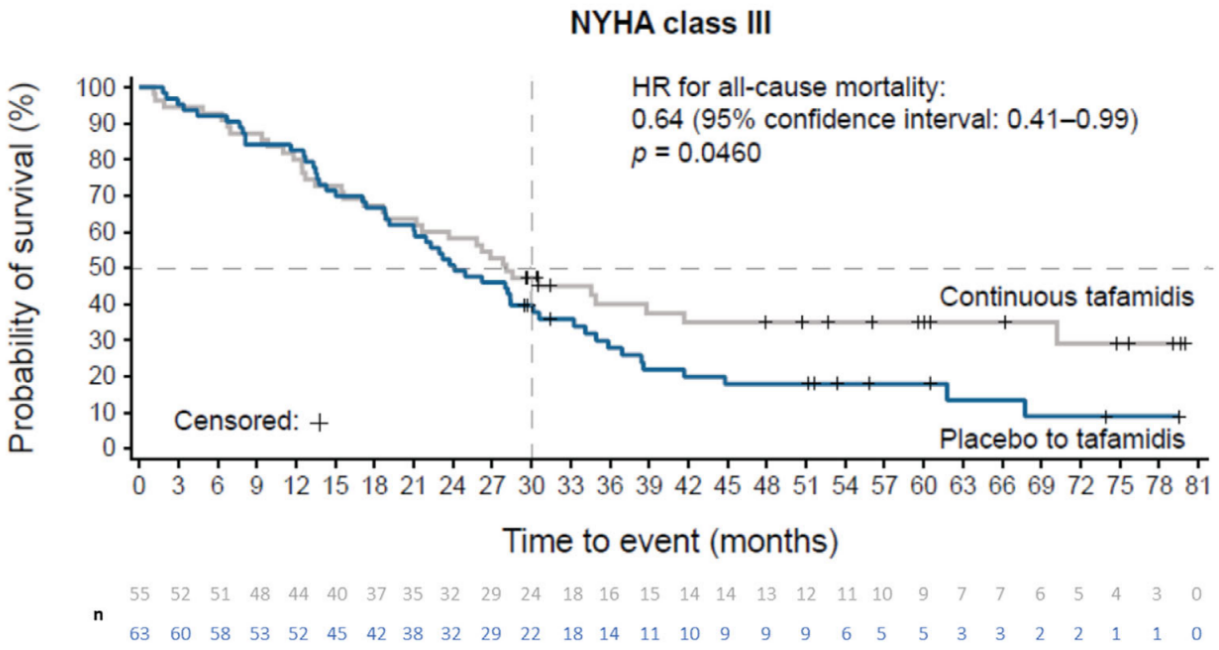
*76,888 from May 2019 to January 2026. Data obtained from multiple sources, such as IQVIA reports, national registry data, distribution reports, and finance data.

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTRv-CM, hereditary transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; LTE, long-term extension; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NYHA, New York Heart Association.

1. Maurer MS, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007–16; 2. Elliott P, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2022;15(1):e008193; 3. Witteles R, et al. Atrial fibrillation as a prognostic factor for all-cause mortality in patients with transthyretin amyloid cardiomyopathy. *JACC CardioOncol*. 2024;6(4):592–8; 4. Garcia-Pavia P, et al. Tafamidis efficacy among octogenarian patients in the Phase 3 ATTR-ACT and ongoing long-term extension study. *JACC Heart Fail*. 2024;12(1):150–60; 5. Elliott P, et al. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. *Eur J Heart Fail*. 2023;25(11):2060–4; 6. Sperry BW, et al. Effect of tafamidis on renal function in patients with transthyretin amyloid cardiomyopathy in ATTR-ACT. *JACC CardioOncol*. 2024;6(2):300–6; 7. Hanna M, et al. Improvements in Efficacy Measures With Tafamidis in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. *JACC Adv*. 2022;1(5):100148; 8. Shah SJ, et al. Effect of tafamidis on cardiac function in patients with transthyretin amyloid cardiomyopathy: a post hoc analysis of the ATTR-ACT randomized clinical trial. *JAMA Cardiol*. 2024;9(1):25–34; 9. Drachman B, et al. Long-term tafamidis efficacy in patients with transthyretin amyloid cardiomyopathy by baseline left ventricular ejection fraction. *Eur J Heart Fail*. 2024;26(9):2038–46; 10. Rapezzi C, et al. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. *JACC Heart Fail*. 2021;9(2):115–23; 11. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail*. 2025;27(12):2998–3009.

ATTR-ACT and LTE: analysis of patients with more severe heart failure





Among patients with **NYHA Class III symptoms at baseline,** those who received **continuous tafamidis treatment** over a median of approx. 5 years had **a lower risk of all-cause mortality than those initially treated with placebo**

Similar findings were observed in patients with **NYHA Class I/II symptoms** at baseline

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; HR, hazard ratio; LTE, long-term extension; NYHA, New York Heart Association.
Elliott P, et al. *Eur J Heart Fail* 2023; doi: 10.1002/ejhf.2974 (Epub ahead of print).

Tafamidis in octogenarians (>80 years)

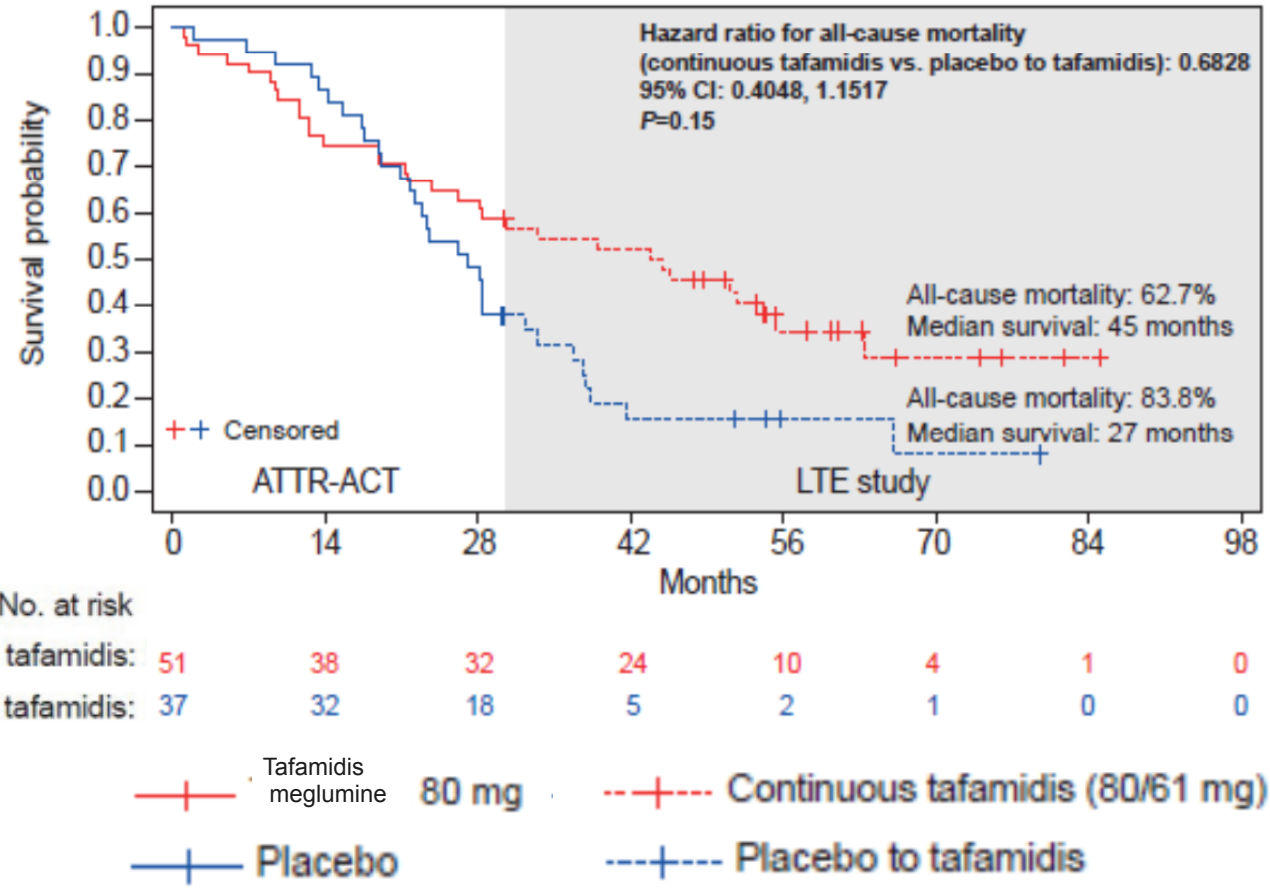
Post hoc analysis of ATTR-ACT and the ongoing LTE study data from patients aged ≥80 years at screening. All patients switched to tafamidis in the LTE

42% of patients were NYHA Class III at baseline

At the end of ATTR-ACT (30 months):

- Significant LS **mean reductions in 6MWT distance (P<0.01) and KCCQ-OS score (P<0.05)** in tafamidis vs placebo groups

The use of continuous tafamidis in octogenarians resulted in longer median survival and lower mortality*, as well as a reduced decline in their perceived health status quality of life



* the HR for all-cause mortality trends in favor of tafamidis (HR:0,68, p=0,1526), but was not statistically significant

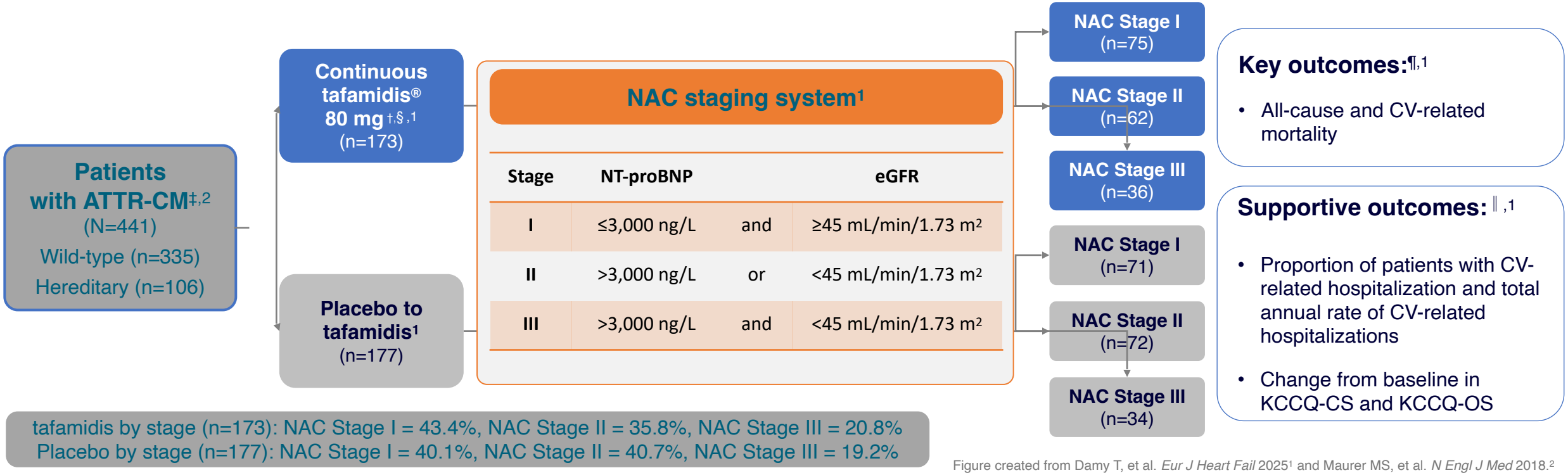
6MWT, 6-minute walk test; ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squares; LTE, long-term extension; NYHA, New York Heart Association.

García-Pavía P, et al. *J Am Coll Cardiol* 2023;81(Suppl 8):337 (poster 1065-05)

dose i.e. Tafamidis meglumine 80 mg, Tafamidis 61 mg..

Post-hoc analysis

Post hoc analysis by baseline NAC stage in ATTR-ACT[1]



Key outcomes:¶,1

- All-cause and CV-related mortality

Supportive outcomes: ‖,1

- Proportion of patients with CV-related hospitalization and total annual rate of CV-related hospitalizations
- Change from baseline in KCCQ-CS and KCCQ-OS

tafamidis by stage (n=173): NAC Stage I = 43.4%, NAC Stage II = 35.8%, NAC Stage III = 20.8%
Placebo by stage (n=177): NAC Stage I = 40.1%, NAC Stage II = 40.7%, NAC Stage III = 19.2%

Figure created from Damy T, et al. *Eur J Heart Fail* 2025[1] and Maurer MS, et al. *N Engl J Med* 2018.[2]

*Heart transplantation and cardiac mechanical assist device implantation were treated as death in the mortality assessments;[1] †Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT were not included in the main analysis;[1] ‡Patients classified as NYHA Stage IV were excluded;[2] §Of the 176 patients randomized to tafamidis meglumine 80 mg, 3 did not have both a baseline eGFR and NT-proBNP concentration to allow NAC staging;[1] ¶All-cause and CV-related mortality were assessed by Cox proportional models adjusted for baseline *TTR* genotype and visualized using Kaplan–Meier curves;[1] ‖ Change from baseline in KCCQ-OS and KCCQ-CS was reported to reflect LSM change from baseline, and rate of CV-related hospitalizations was evaluated using both the proportion of patients with at least one CV-related hospitalization and the total annualized rate of CV-related hospitalizations.[1]

Tafamidis 20 mg is not licensed in ATTR-CM.[3] Tafamidis 20 mg no está indicado en ATTR-CM.[4] tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[3] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[3] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[3,4] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg.[3,4]

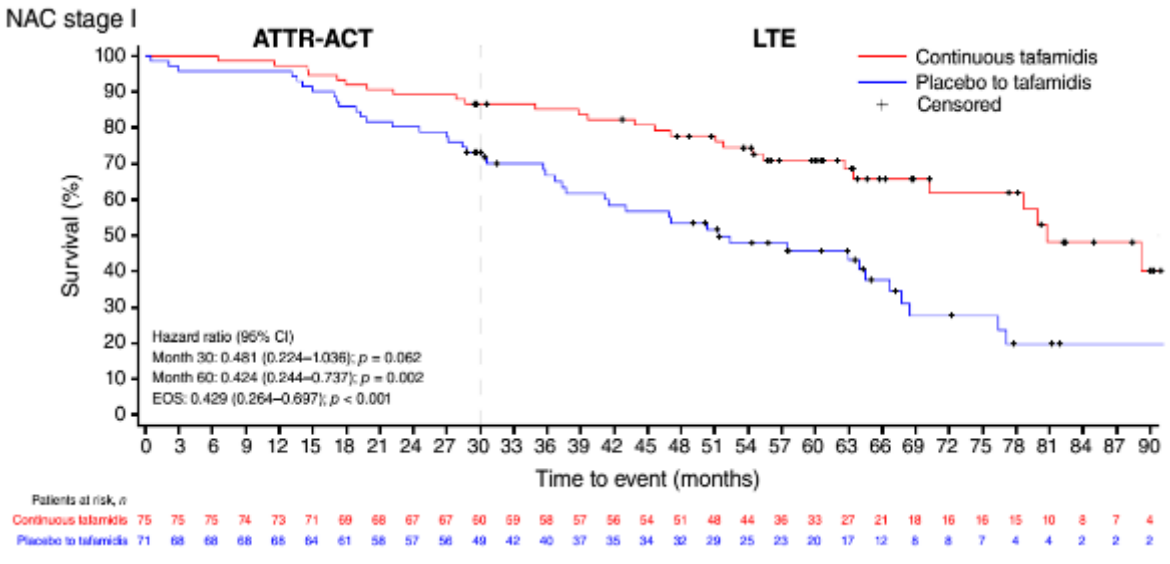
ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire Clinical Summary score; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary score; LSM, least-squares mean; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

1. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail*. 2025;27(12):2998–3009; 2. Maurer MS, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007–16; 3. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 4. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev*. 2020;9(7):849–54.

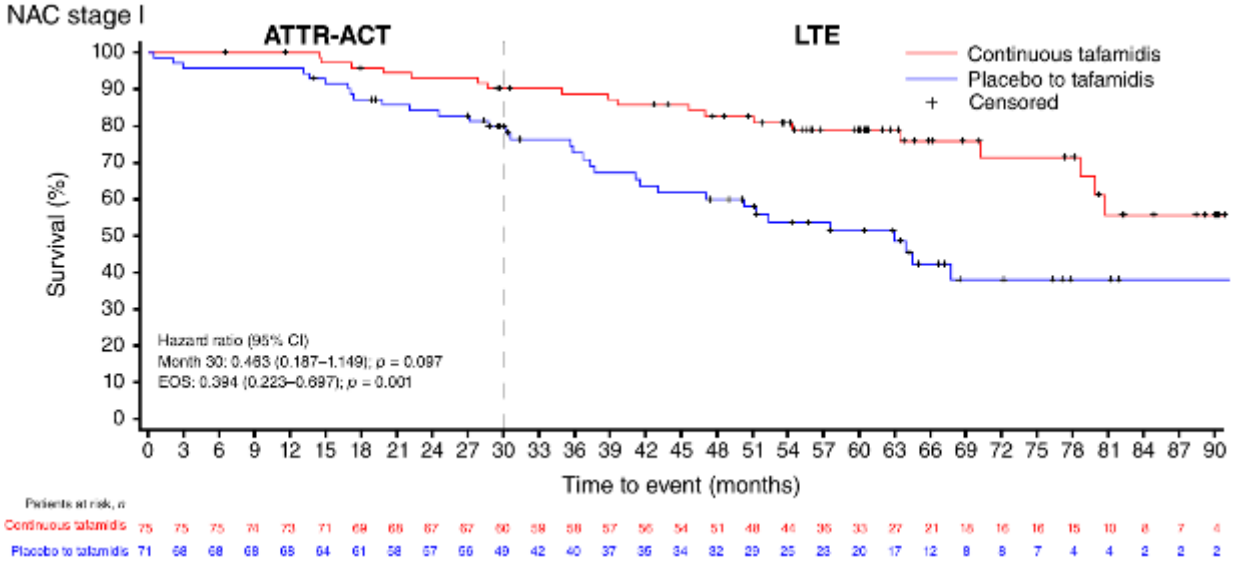
Post-hoc analysis

Continuous tafamidis® treatment demonstrated widespread survival benefits in patients in NAC Stages I and II, supported by 7+ years of pivotal and LTE data

All-cause mortality in patients with NAC Stage I receiving continuous tafamidis or placebo[1]



CV-related mortality in patients in NAC Stage I receiving continuous tafamidis or placebo[1]



Figures extracted from Damy T, et al. *Eur J Heart Fail.* 2025.[1]

Reduction in risk of all-cause mortality by NAC stage[1]

- **NAC I**: **57%** lower chance of mortality (P<0.001)
- **NAC II**: **49%** lower chance of mortality (P=0.003)

Reduction in CV-related mortality risk by NAC stage[1]

- **NAC I**: **61%** lower chance of mortality (P=0.001)
- **NAC II**: **49%** lower chance of mortality (P=0.009)

Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT were not included in the main analysis.[1]
Tafamidis 20 mg is not licensed in ATTR-CM.[2] Tafamidis 20 mg no está indicado en ATTR-CM.[2] tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[2] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[2] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[2,3] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg.[2,3]
ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CV, cardiovascular; LTE, long-term extension; NAC, National Amyloidosis Centre.
1. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail.* 2025;27(12):2998–3009; 2. Pfizer Inc. tafamidis (tafamidis meglumine) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 3. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;9(7):849–54.

Post-hoc analysis

In NAC Stage I–II patients, continuous tafamidis® treatment over >7 years significantly reduced CV-related hospitalizations* vs those initially on placebo[1]

NAC I

39.2% lower risk of CV-related hospitalizations (P=0.007)

NAC II

51.1% lower risk of CV-related hospitalizations (P=0.008)

NAC III

43.7% lower risk of CV-related hospitalizations (P=0.288)

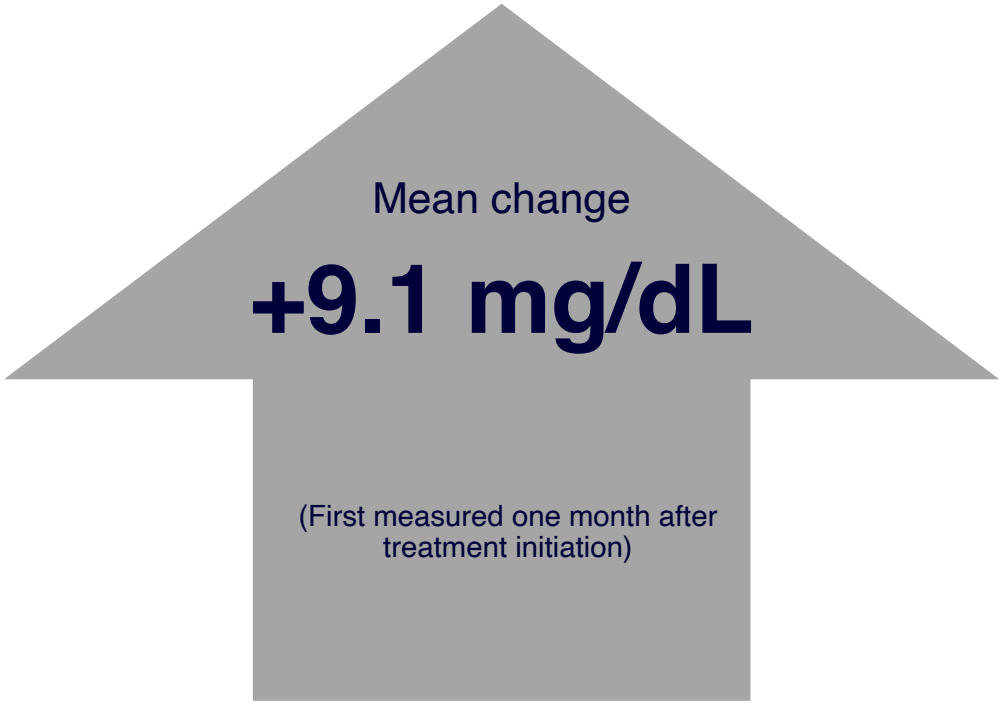
- A favorable numerical trend was seen in patients in NAC Stage III receiving continuous tafamidis vs the placebo to tafamidis group

These findings highlight the importance of early diagnosis and treatment initiation

*In ATTR-ACT, CV-related hospitalization was defined as the number of times a patient was hospitalized (i.e., admitted to a hospital) for CV-related morbidity.
Risk percentages calculated from risk ratios (NAC I: 1-0.608 = 0.392 = 39.2%; NAC II: 1-0.489 = 0.511 = 51.1%; NAC III: 1-0.563 = 0.437 = 43.7%)
Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT were not included in the main analysis.
Tafamidis 20 mg is not licensed in ATTR-CM.[2] Tafamidis 20 mg no está indicado en ATTR-CM.[2] tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[2] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[2] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis[2,3] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg[2,3]
ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; NAC, National Amyloidosis Centre.
1. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail* 2025;27(12):2998–3009; 2. Pfizer Inc. tafamidis (tafamidis meglumine) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed February 2026); 3. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;9(7):849–54.

Stabilization of TTR is associated with increases in serum TTR

Data from the ATTRibute-CM trial found elevated serum TTR levels following treatment with acoramidis

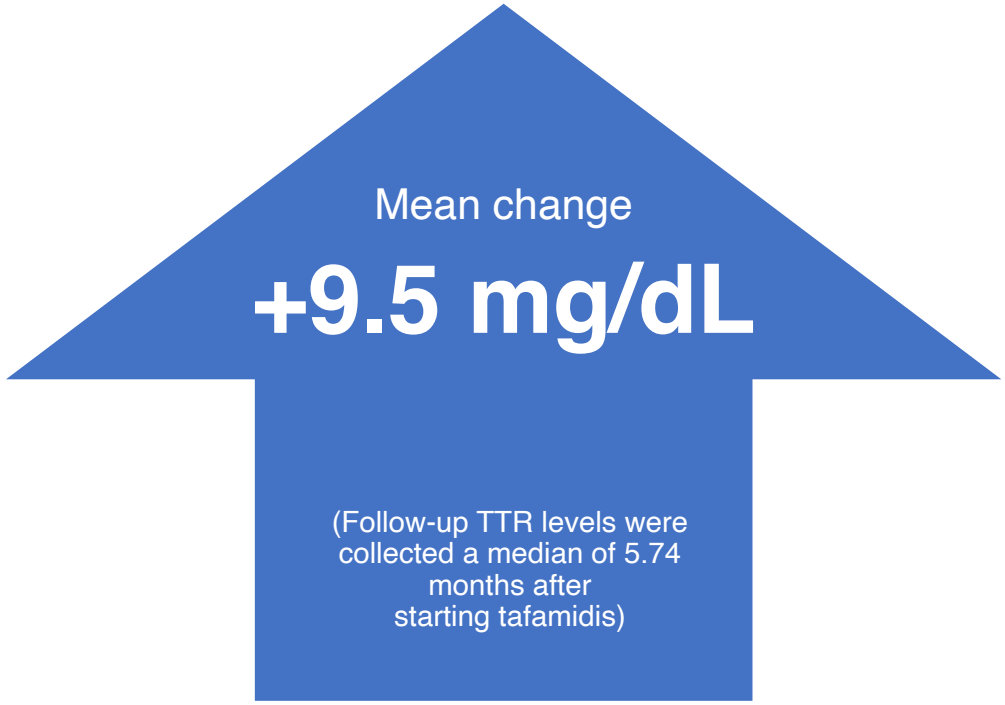


TTR, transthyretin.

Maurer MS, et al. Early Increase in Serum Transthyretin by Acoramidis Independently Predicts Improved Survival in TTR Amyloid Cardiomyopathy. *J Am Coll Cardiol.* 2025;85 (20):1911–1923.

The increase in serum TTR and correlation with survival outcomes represents a class effect for TTR kinetic stabilizers[1]

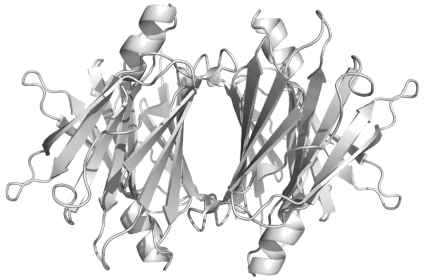
In a retrospective cohort of 185 **tafamidis-treated** patients, **serum TTR rose significantly**

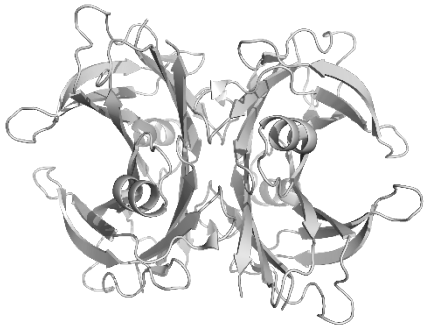


tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients. Tafamidis 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per-mg basis[2,3]

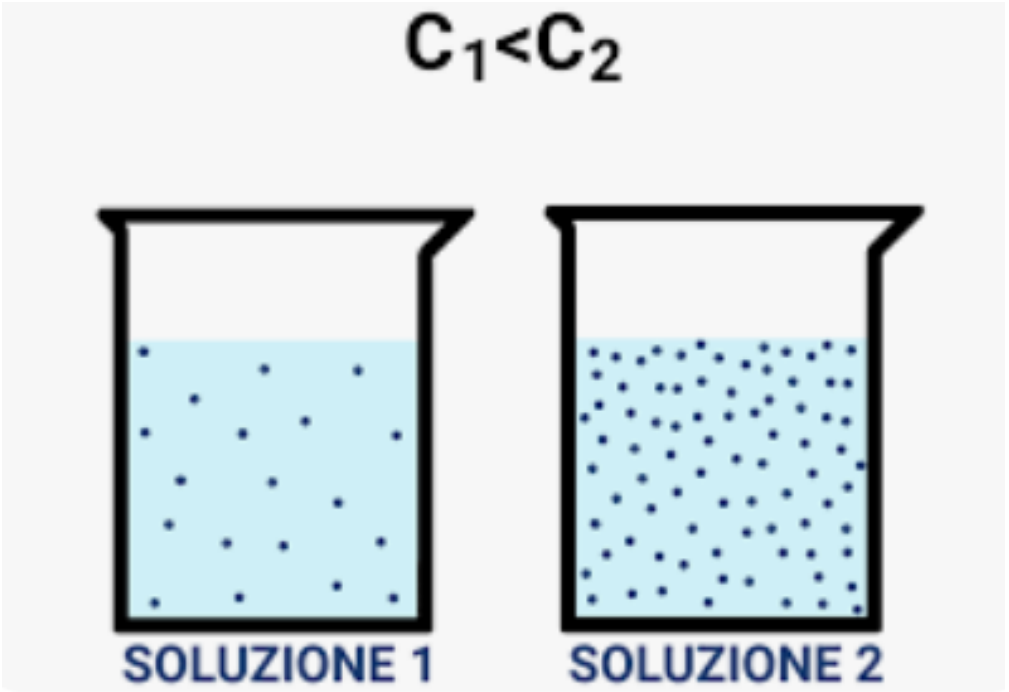
ATTR-CM, transthyretin amyloid cardiomyopathy; TTR, transthyretin.

1. Ansari B, et al. Increase in serum transthyretin after tafamidis is associated with improved survival in transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2026; Epub ahead of print; 2. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 3. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4× 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev*. 2020;9(7):849–54.





Concentration ….



… or stabilization?

At the approved dose, tafamidis achieved ≥96% stabilization *in vitro*[1]*

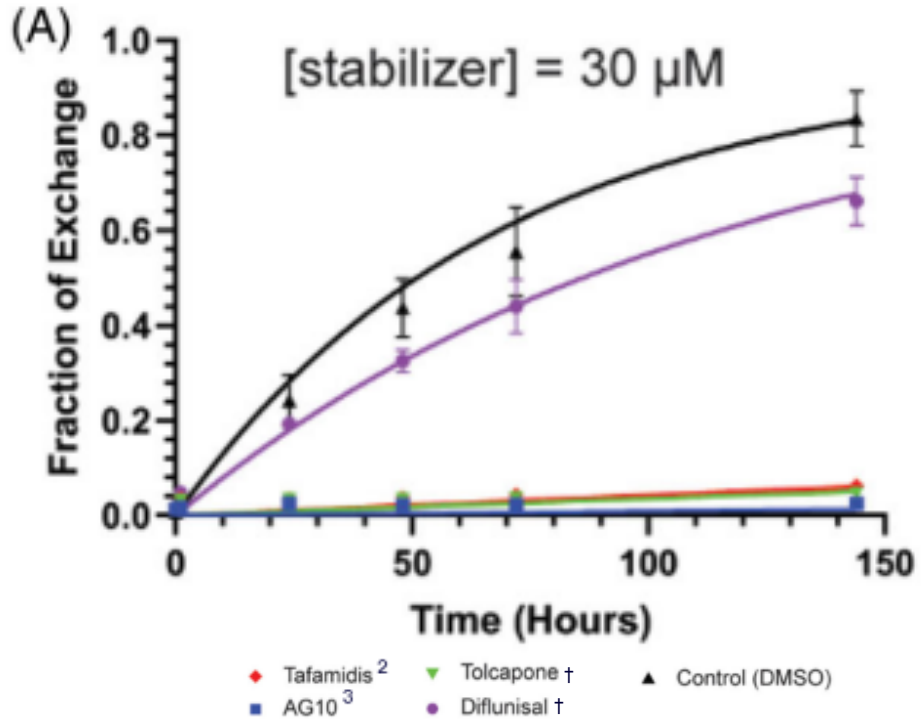


Figure extracted from Nelson, L, et al. *Amyloid*. 2021;28(1):24–9.[1]

≥96%
REDUCTION IN TTR DISSOCIATION

At relevant concentrations, multiple molecules, including tafamidis and acoramidis can **reduce the rate of dissociation by ≥96%**

Relevant range: 10–30 μM at tafamidis dose of 80 mg/61 mg* and acoramidis dose of 1600 mg[1]
TTR subunit exchange kinetics in the presence of kinetic stabilizers at varying concentrations, experiments 1 and 2 combined. Time courses of subunit exchange between endogenous plasma TTR tetramers (~3 μM) and added dual-flag-tagged TTRwt (1 μM) in the presence of kinetic stabilizers at the indicated concentrations. Data from experiments 1 and 2 were combined and fit globally. (A) Subunit exchange time courses in the presence of kinetic stabilizers at a concentration of 30 μM. (B) As in panel A, but at a stabilizer concentration = 20 μM. (C) As in panel A, but at a stabilizer concentration = 10 μM. (D) As in panel A, but at a stabilizer concentration = 5 μM. (E) As in panel A, but at a stabilizer concentration = 1 μM. The same DMSO control time course is shown in each plot. Data points represent the mean and error bars the standard deviation of the combined data set from experiments 1 and 2. The curves in each plot represent the best fits to the combined data based on the model described in the text.

The degree of stabilization does not reflect treatment efficacy.
*tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients. Tafamidis 61 mg corresponds to 80 mg tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per-mg basis.[2,4] †This drug is not marketed in Spain. / Este medicamento no se encuentra comercializado en España.
ATTR-CM, transthyretin amyloid cardiomyopathy; DMSO, dimethyl sulfoxide; TTR, transthyretin.
1. Nelson L, et al. Blinded potency comparison of transthyretin kinetic stabilisers by subunit exchange in human plasma. *Amyloid*. 2021;28(1):24–9; 2. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 3. Beyonttra (acoramidis), Rottendorf Pharma GmbH. Summary of product characteristics, November 2025. https://www.ema.europa.eu/en/documents/product-information/beyonttra-epar-product-information_en.pdf (Accessed April 2026); 4. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4× 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev*. 2020;9(7):849–54.

In ATTR-ACT, tafamidis achieved a rapid increase in TTR concentration as early as Month 1[1,2]

TTR levels increased rapidly within the first month, and were sustained over 30 months

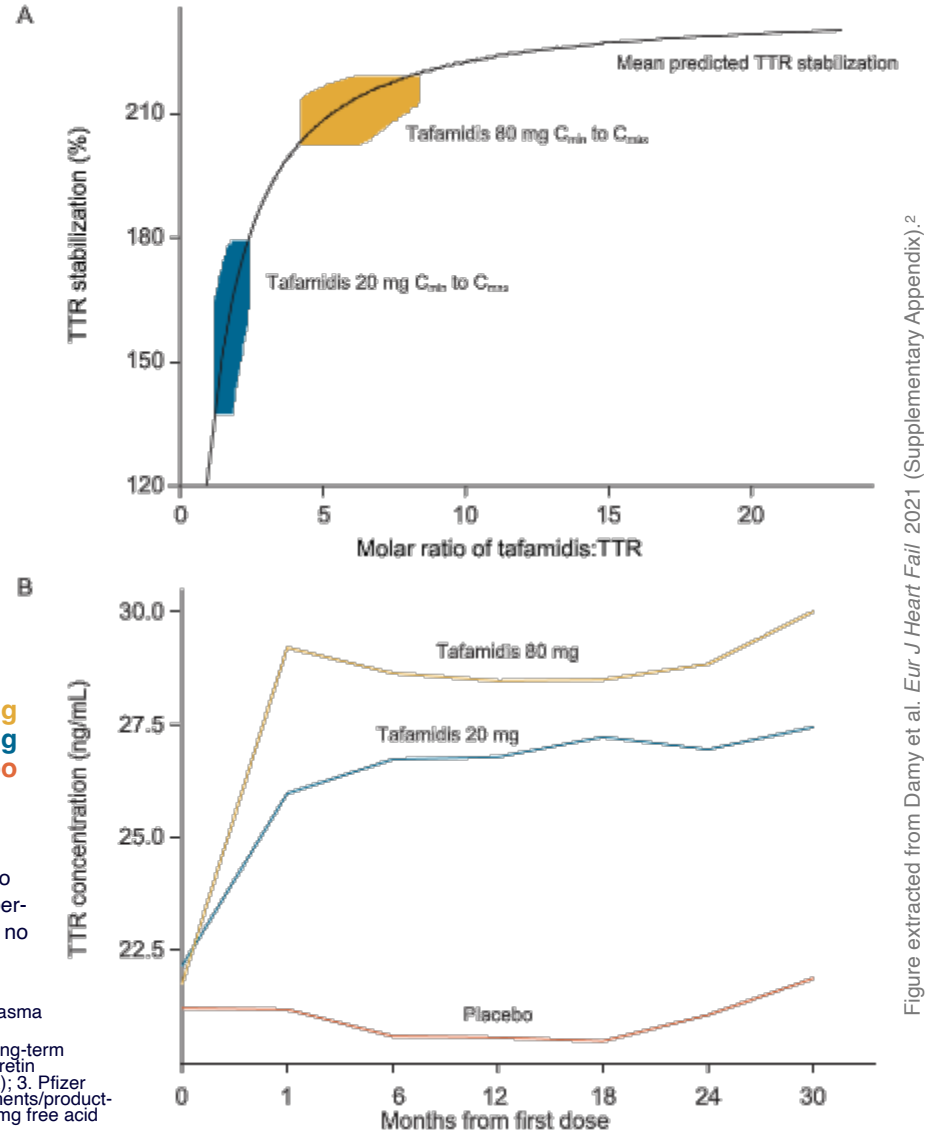


Figure extracted from Damy et al. *Eur J Heart Fail* 2021 (Supplementary Appendix).[2]

(A) TTR tetramer stabilization with tafamidis 80 mg and tafamidis 20 mg in ATTR-ACT. *(B)* Mean TTR concentration with tafamidis 80 mg, tafamidis 20 mg, and placebo in ATTR-ACT. The black line represents the mean percentage TTR stabilization in patients with ATTR-CM. The orange-shaded region demonstrates the percentage stabilization expected over the geometric mean steady-state C_{min} to C_{max} following daily administration of tafamidis 80 mg. This approaches the plateau considered to be the target for stabilization. The blue-shaded region demonstrates the tafamidis 20 mg steady-state exposures and is well below the stabilization plateau.

Tafamidis 80 mg
Tafamidis 20 mg
Placebo

Tafamidis 20 mg is not licensed in ATTR-CM.[3] Tafamidis 20 mg no está indicado en ATTR-CM.[3] tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[3] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[3] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[3,4] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg.[3,4]

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; TTR, transthyretin.

1. Damy T, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail.* 2021;23(2):277–85; 2. Damy T, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail.* 2021;23(2):277–85 (Supplementary Appendix); 3. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 4. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;9(7):849–54.

ESC European Society of Cardiology

European Journal of Heart Failure (2025) **27**, 623–627
doi:10.1002/ejhf.3614

VIEWPOINT

Silencers versus stabilizers in amyloid cardiomyopathy. Are we asking the wrong questions?

Rodney H. Falk[1]*, Sarah A.M. Cuddy[1], and Osnat Itzhaki Ben Zadok[1,2]

[1]Brigham and Women's Hospital Amyloidosis Program and Section of Cardiology, Brigham and Women's Hospital, Boston, MA, USA; and [2]School of Medicine, Tel Aviv University, Tel Aviv, Israel

Table 1 Summary data from published transthyretin amyloid cardiomyopathy randomized controlled trials

	ATTR-ACT[2]	ATTRibute-CM[3]	HELIOS-B[7]
Study drug	Tafamidis	Acoramidis	Vutrisiran
Mechanism of action	TTR protein-stabilizer	TTR protein-stabilizer	TTR gene-silencer
Administration mode, dosage	Oral, 20 mg or 80 mg once daily	Oral, 800 mg twice daily	SC, 25 mg every 3 months
Enrolment period	12/2013–8/2015	4/2019–10/2020	12/2019–8/2021
Total number of patients	441	632	655
Treatment, *n* (%)	264 (60)	421 (67)	326 (50)
Placebo, *n* (%)	177 (40)	211 (33)	329 (50)
Patient characteristics			
Age at enrolment (years)	75	77	77
Female sex, *n* (%)	23 (9)	62 (10)	50 (9)
TTR variant, *n* (%)	106 (24)	61 (10)	77 (12)
NYHA functional class, *n* (%)			
I	24 (8)	68 (11)	84 (13)
II	263 (60)	455 (72)	508 (78)
III	141 (32)	109 (17)	62 (9)
NT-proBNP (pg/ml), median	~3000	2326	~1900
Background tafamidis, *n* (%)	NA	153 (24) The median time to initiation of tafamidis was 17 months (not permitted during the initial 12 months of the trial)	259 (40) The median time of use of tafamidis before study initiation was ~10 months (tafamidis was permitted following enrolment)[a]
All-cause mortality			
Primary study			
Treatment	29% at 30 months	19% at 30 months	16% at 36 months
Placebo	43% at 30 months	26% at 30 months	21% at 36 months
Extended follow-up including open-label extended			
Total number of patients	OLE[9], 353	OLE[10], 389	
Treatment	45% at 58 months	23% at 42 months	18% at 42 months
Placebo	63% at 58 months	35% at 42 months	26% at 42 months
Composite endpoint RRR (mortality and HF hospitalizations)	0.7	0.77	HR 0.72 at up to 36 months (HR 0.67 in monotherapy group up to 36 months)
RRR in mortality at 30 months	0.7	0.77	HR 0.86 (HR 0.69 up to 36 months)
RRR in hospitalization/CV events	Annual 0.68	0.496	HR 0.73 up to 36 months (HR 0.68 in vutrisiran monotherapy group)

CV, cardiovascular; HF, heart failure; HR, hazard ratio; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; RRR, relative risk reduction; SC, subcutaneous; TTR, transthyretin.

[a]In HELIOS-B, 40% of subjects entered the trial taking tafamidis. The primary endpoint was up to 36 months as the trial was lengthened slightly after some patients had completed original trial duration. In this trial, recurrent CV events was used rather than CV hospitalizations, and was defined as hospitalization for HF or urgent visits for HF

	Tafamidis (Pfizer Inc.)	Acoramidis[2] (Beyonttra®, BridgeBio/Bayer AG)	Vutrisiran ▼[3] (Amvuttra®, Alnylam Pharmaceuticals)
Mechanism of action	TTR stabilizer	TTR stabilizer	siRNA *TTR* gene silencer
Approved dose	One capsule of tafamidis 61 mg orally once daily	Two 356-mg tablets orally twice daily	25 mg subcutaneously every 3 months **Vitamin A supplementation at ~≤2,500–3,000 IU/day is advised**

▼ This drug is subject to additional follow-up. It is a priority to report suspected adverse reactions associated with this medicinal product.

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[1] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[1] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[1,4] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg[1,4]

ATTR-CM, transthyretin amyloid cardiomyopathy; IU, international units; siRNA, small interfering RNA; TTR, transthyretin.

1. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 2. Bayer AG. Beyonttra (acoramidis) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/beyonttra-epar-product-information_en.pdf (Accessed April 2026); 3. Alnylam. Amvuttra (vutrisiran) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/amvuttra-epar-product-information_en.pdf (Accessed April 2026); 4. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev.* 2020;9(7):849–54.

Patient preference for frequency and mode of administration is an important factor for treatment selection

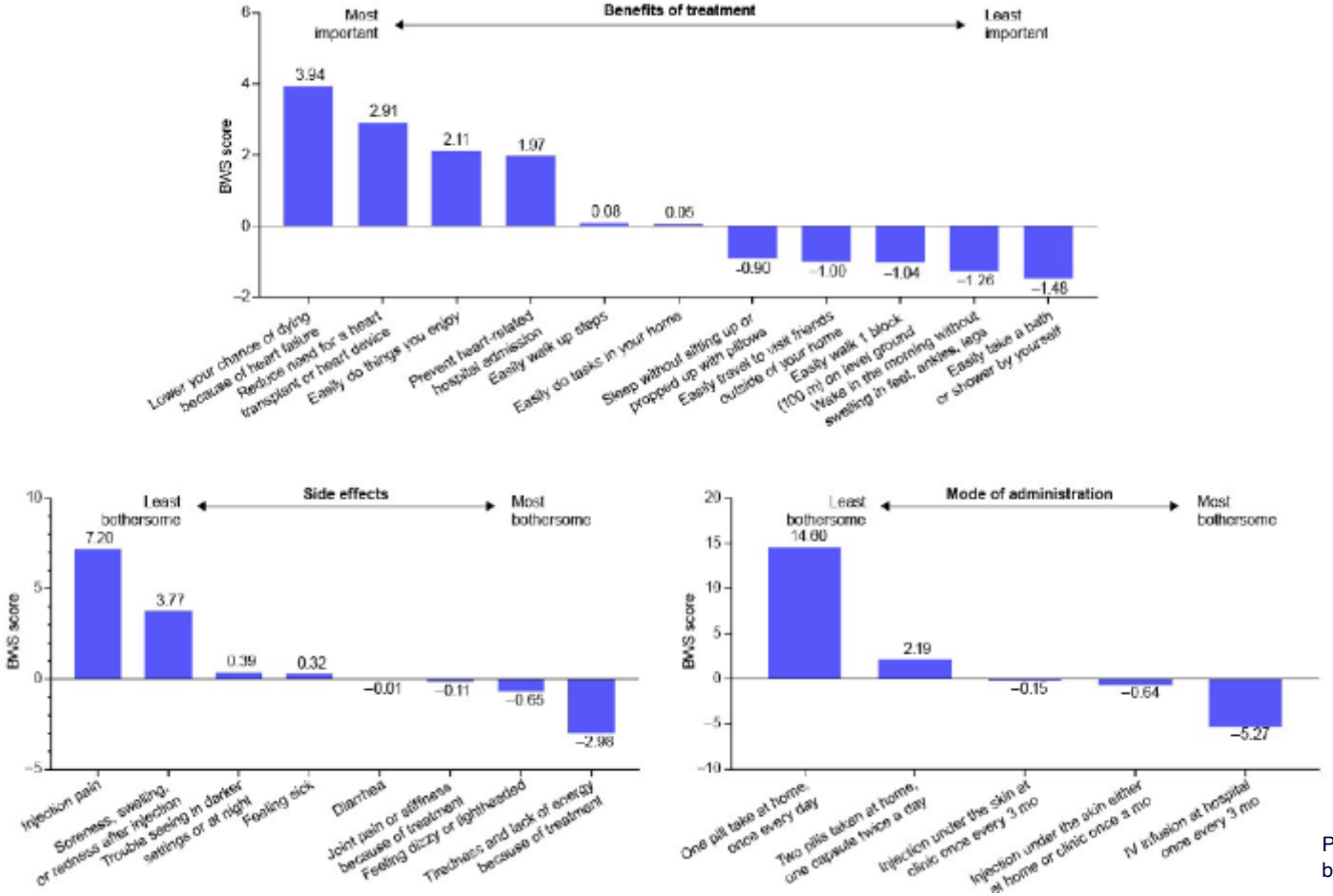


Figure extracted from Carr AM, et al. 2025

Patient-reported value of hypothetical treatment benefits, side-effects and modes of administration

BWS, best–worst scaling; IV, intravenous.

International patient advisory board study, using an online survey with experimentally designed object-case BWS exercises to assess preferences for ATTR-CM treatment benefits, side effects, and administration.

Carr AM, et al. Which treatment attributes do patients with transthyretin amyloid cardiomyopathy value most? Abstract. In: Heart Failure Congress; 17–20 May 2025; Belgrade, Serbia.

Patient preference for frequency and mode of administration is an important factor for treatment selection

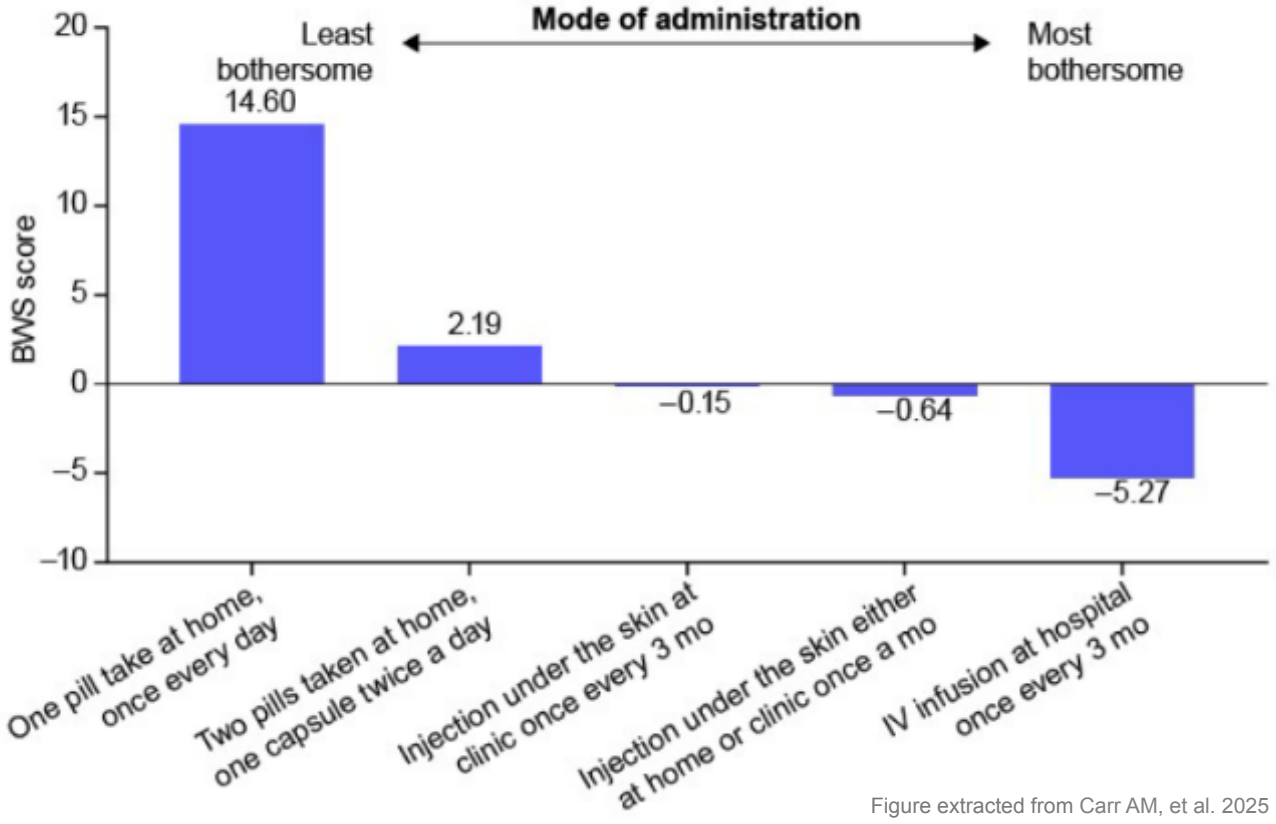


Figure extracted from Carr AM, et al. 2025

When asked in a survey, a once-daily oral pill was the preferred mode of administration by patients

BWS, best–worst scaling; IV, intravenous.

International patient advisory board study, using an online survey with experimentally designed object-case BWS exercises to assess preferences for ATTR-CM treatment benefits, side effects, and administration.

Carr AM, et al. Which treatment attributes do patients with transthyretin amyloid cardiomyopathy value most? Abstract. In: Heart Failure Congress; 17–20 May 2025; Belgrade, Serbia.

Yes, but….
What about real world?

The NEW ENGLAND JOURNAL of MEDICINE

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Tafamic

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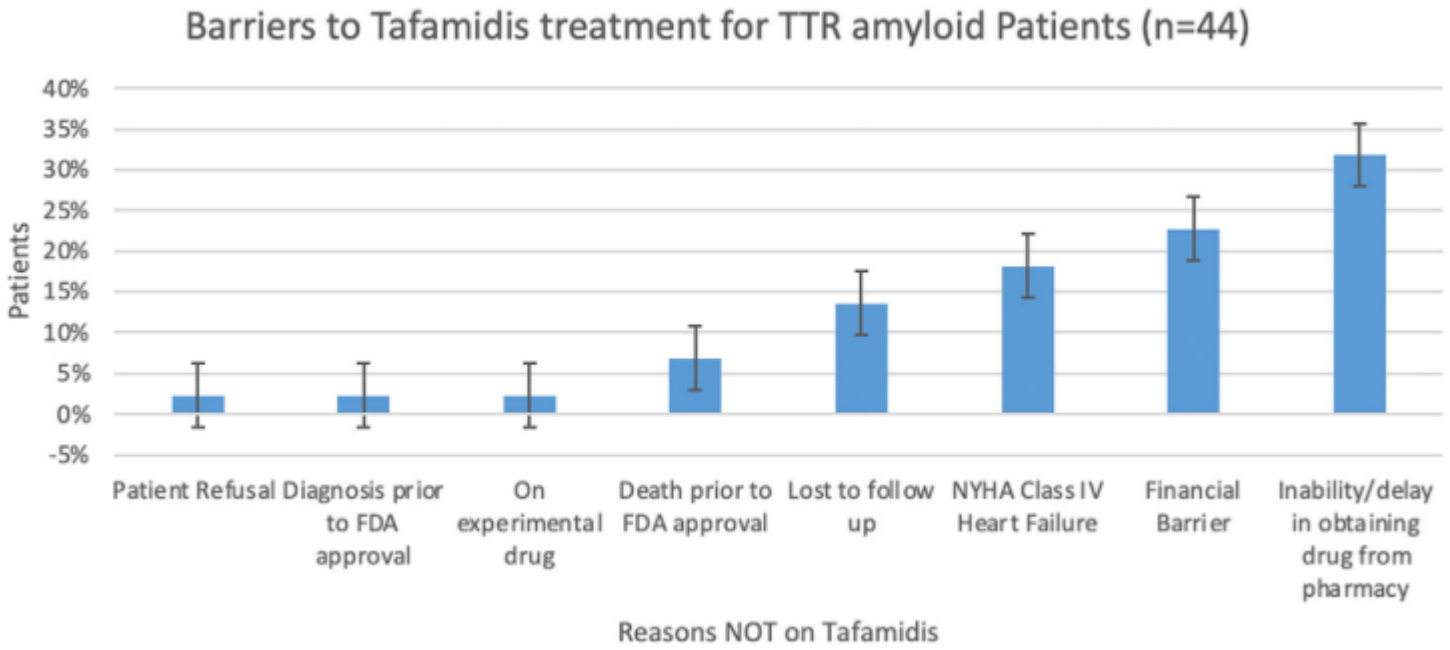
Real-world versus trial patients with transthyretin amyloid cardiomyopathy

Marco Canepa[1,2,*], Giacomo Tini[1,2], Beatrice Musumeci[3], Francesco Cappelli[4], Agnese Milandri[5], Roberta Mussinelli[6], Camillo Autore[3], Federico Perfetto[4], Claudio Rapezzi[5], and Stefano Perlini[6]

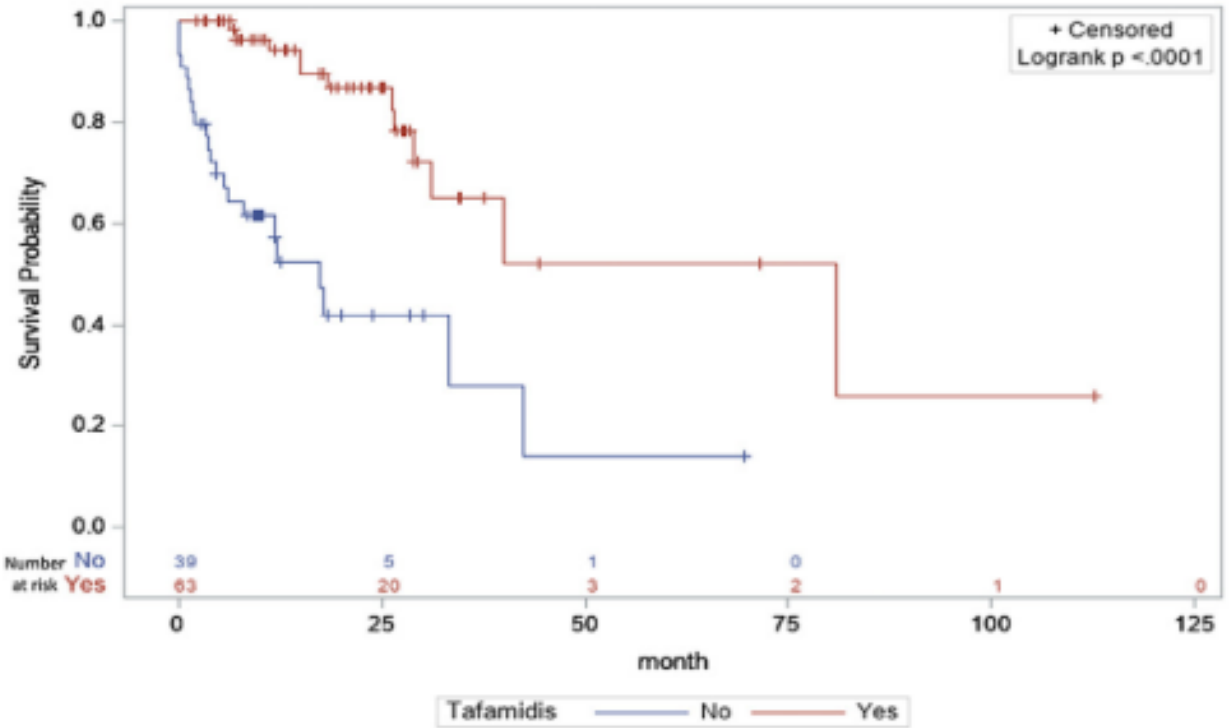
In conclusion, our findings that RW ATTR-AC patients closely resemble those enrolled in ATTR-ACT have relevant implications, considering that ATTR-AC is still considered a rare condition, and specific treatments will likely become initially available for a small proportion of the affected patients, primarily because of the relevant costs.

Table 1 Characteristics of transthyretin amyloid cardiomyopathy trial patients at enrolment versus real-world patients at diagnosis

	ATTR-ACT trial	Real-world	*P*-value
Total population	264 (tafamidis pooled)	507 (Italian cohort)	
Age (years)	74.5 ± 7.2	74.5 ± 8.7	0.988
Male sex	241 (91.3)	429 (84.6)	<0.0001
Caucasian	211 (79.9)	507 (100)	<0.0001
Co-morbidities			
Hypertension	145 (54.9)	301 (59.4)	0.021
Diabetes	20 (7.6)	67 (13.2)	<0.0001
TTR genotype			
ATTRv	63 (23.9)	120 (23.7)	0.458
ATTRwt	201 (76.6)	368 (72.6)	0.070
Genetics not performed	0 (0)	19 (3.7)	
Blood pressure (supine) (mmHg)			
SPB	115.4 ± 15.4	130.3 ± 18.7	<0.0001
DPB	70.4 ± 10.3	76.9 ± 10.1	<0.0001
Heart rate (supine) (b.p.m.)	70.7 ± 12.3	73.1 ± 12.7	<0.0001
NYHA class			
I	24 (9.1)	106 (20.9)	<0.0001
II	162 (61.4)	287 (56.6)	0.026
III	78 (29.5)	112 (22.1)	<0.001
IV	0 (0)	2 (0.4)	
NT-proBNP (pg/mL)	2995.9 [1751.5–4861.5]	2547 [1333–4578] (n = 398)[a]	<0.001
BNP (pg/mL) [if NT-proBNP not available]		285 [150–629] (n = 71)[a]	
Creatinine clearance (mL/min)	58.8 ± 17.9	66.5 ± 25.5 (n = 475)[a]	<0.0001
Troponin I (ng/mL)	0.14 [0.09–0.20]	0.02 [0.01–0.07] (n = 294)[a]	<0.0001
Troponin T (ng/L) [if troponin I not available]		54.5 (42.0–88.0) (n = 78)[a]	
Echocardiography			
LA diameter (mm)	43.8 ± 7	46.6 ± 6.5	<0.0001
IVS thickness (mm)	16.7 ± 3.8	16.9 ± 3.0	0.134
LVEF (%)	48.4 ± 10.3	53.4 ± 10.7	<0.0001
Medications			
Diuretics	175 (66.3)	391 (77.1)	<0.0001
Beta-blockers	76 (28.8)	233 (46.0)	<0.0001
ACEi/ARBs	69 (26.1)	251 (49.5)	<0.0001
Antithrombotics	105 (39.8)	199 (39.3)	0.818

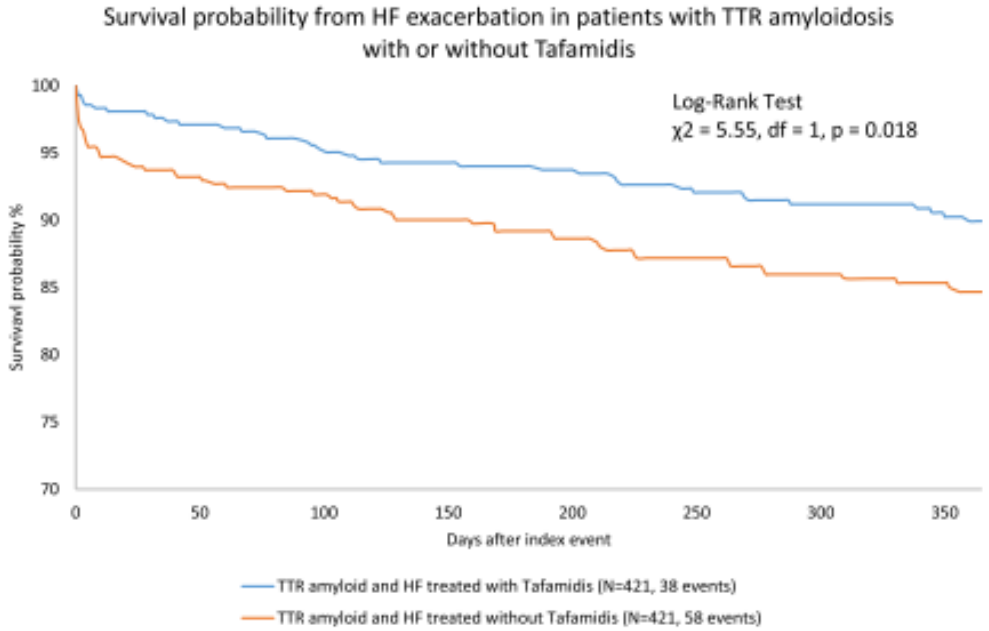


N=107 (63 on treatment)

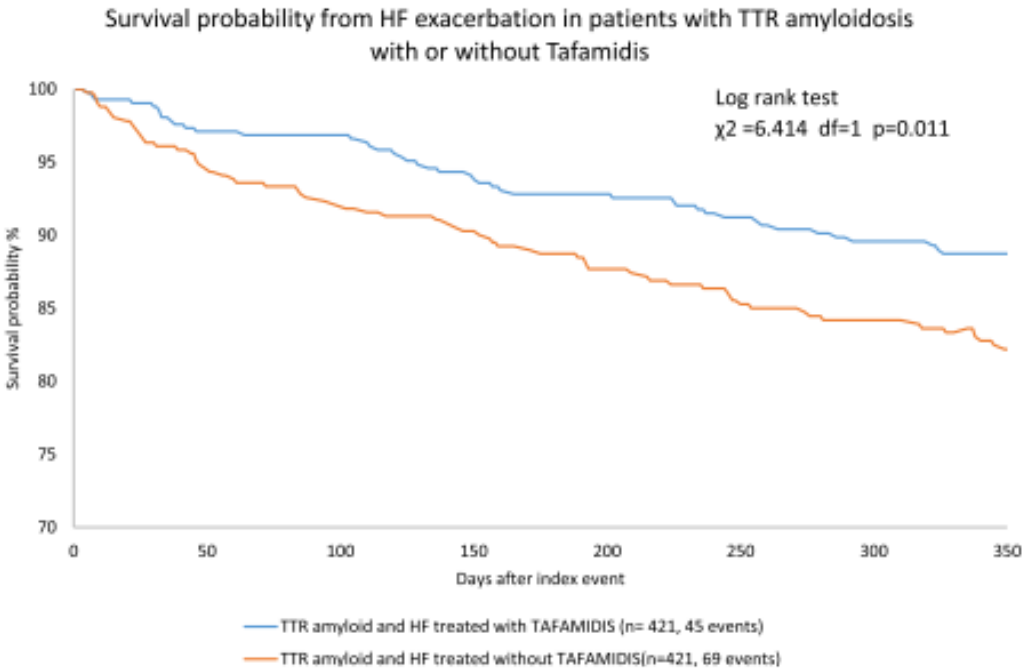


Hussaim, K. et al. Curr Probl Cardiol 2022; 47: 101358

A)



B)



N=1362 (553 on treatment; PSM: 421)

Propensity score matching

After PSM, 421 patients were in each group (tafamidis vs nontafamidis). During the 12-month follow-up period, patients treated with tafamidis experienced significantly less HFE and all-cause mortality. A higher probability of event-free survival for HFE and all-cause mortality was noted with tafamidis.

Ghoneem, A. et al. Curr Probl Cardiol 2023; 48: 101667

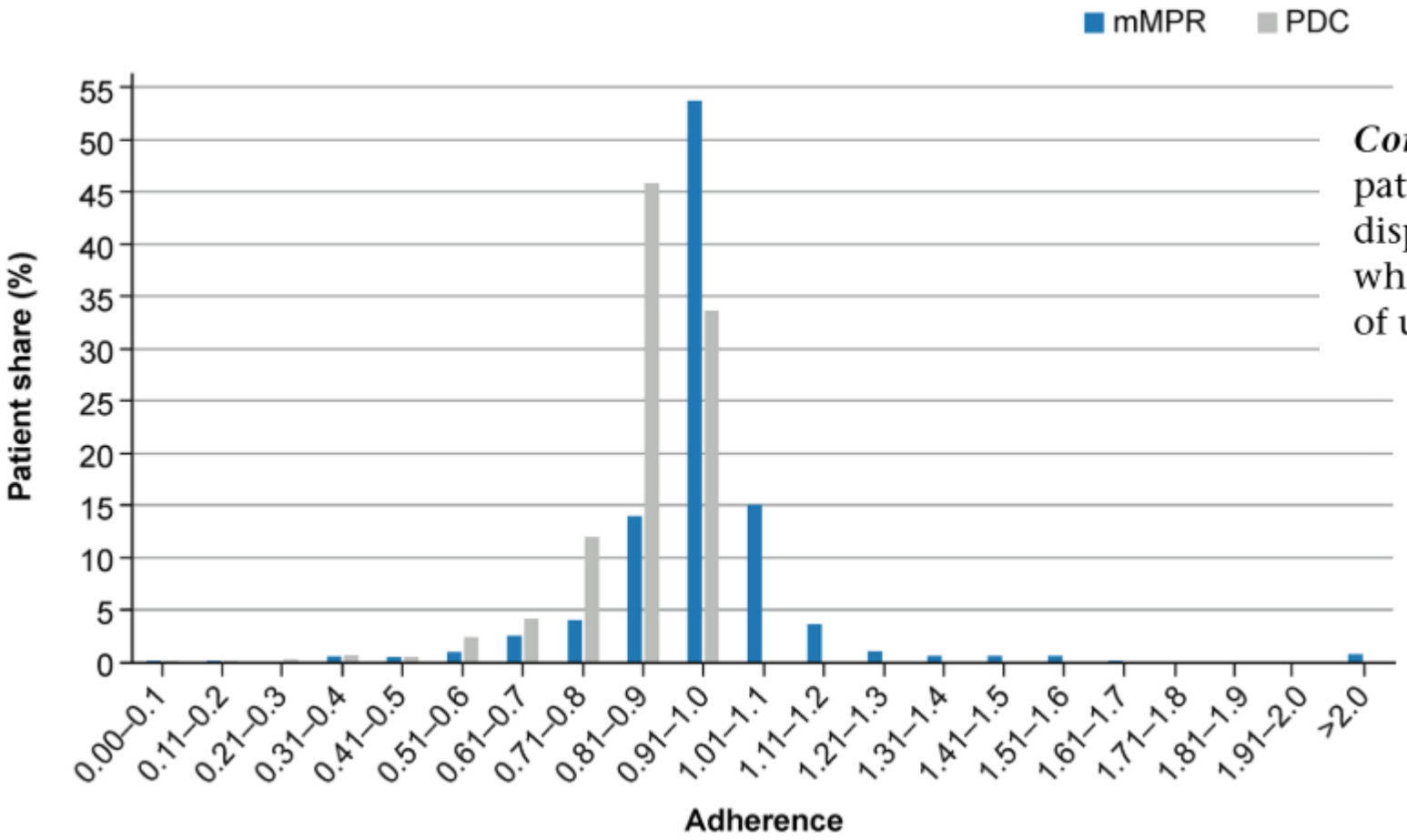
N=210 (all on treatment)

Adherence / Persistence

Conclusions This study found high adherence rates to tafamidis in this real-world Japanese patient population. Adherence rates in this study were similar to those reported by the tafamidis clinical trial and a previously published US commercial claims adherence analysis. Further studies should be conducted to assess the impact of real-world adherence on real-world outcomes.

Kato, T. et al. ESC Heart Failure 2024; 11: 2881

Adherence / Persistence



N=1565 (all on treatment)

Conclusions: In the IQVIA™ LRx database, patients prescribed tafamidis 61 mg in Germany displayed high adherence and persistency rates, which suggest good drug tolerability and ease of use.

Attal, S. et al. Cardiol Therapy 2024; 13: 369

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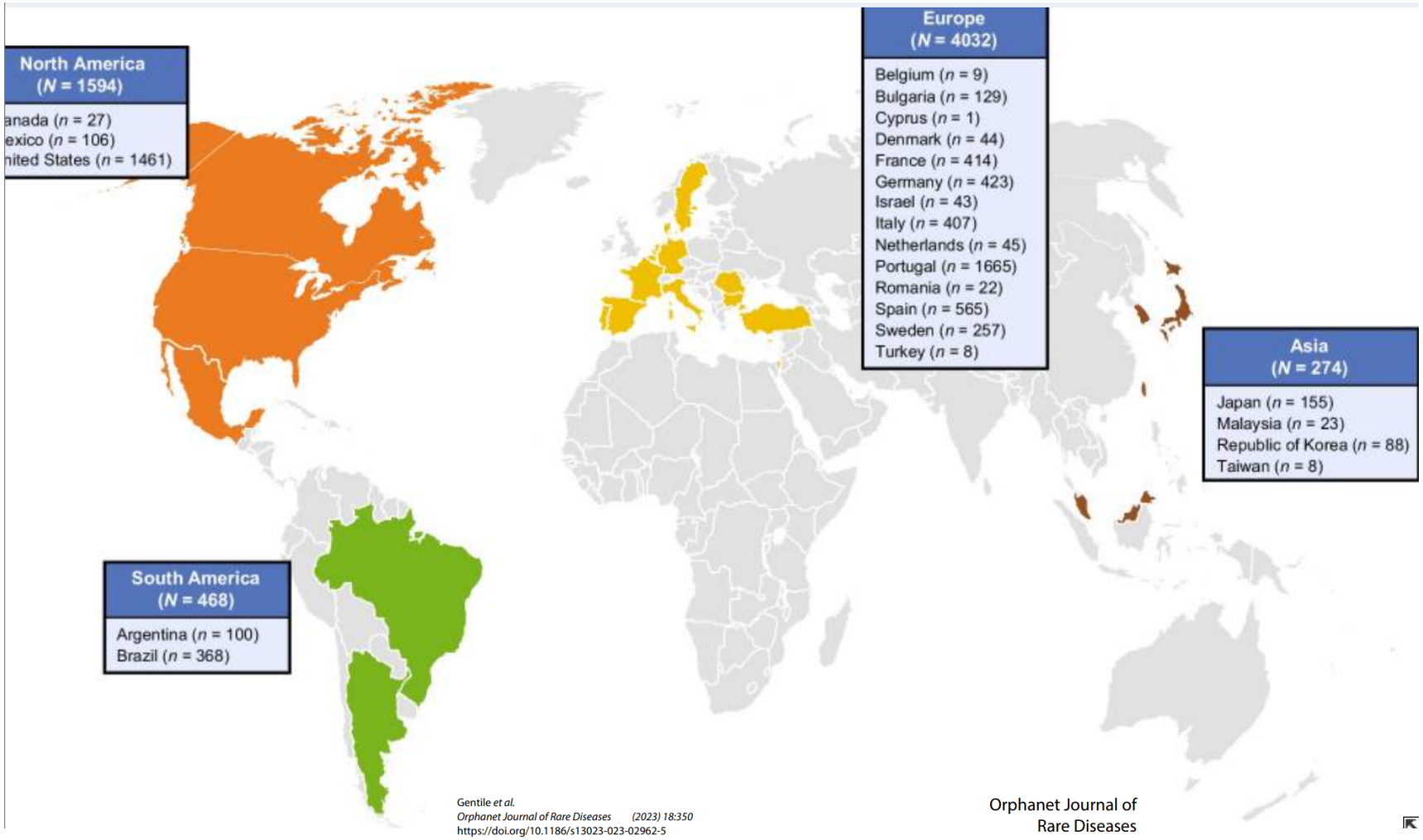
Journal of Cardiac Failure 00 (2024) 1–9

JCF
Journal of Cardiac Failure

Survival in a Real-World Cohort of Patients With Transthyretin Amyloid Cardiomyopathy Treated With Tafamidis: An Analysis From the Transthyretin Amyloidosis Outcomes Survey (THAOS)

PABLO GARCIA-PAVIA, MD, PhD[1,2,3] ARNT V. KRISTEN, MD[4] BRIAN DRACHMAN, MD[5] MARTIN CARLSSON, MS[6] LESLIE AMASS, PhD[6] FRANCA STEDILE ANGELI, MD, PhD[6] and MATHEW S. MAURER, MD[7], on behalf of the THAOS investigators[a]

Madrid, and Pozuelo de Alarcon, Spain; Heidelberg, Germany; and Philadelphia, and New York, USA



Gentile *et al.*
Orphanet Journal of Rare Diseases (2023) 18:350
https://doi.org/10.1186/s13023-023-02962-5

Orphanet Journal of
Rare Diseases

RESEARCH Open Access

A 15-year consolidated overview of data in over 6000 patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS)

Luca Gentile[1*], Teresa Coelho[2], Angela Dispenzieri[3], Isabel Conceição[4], Márcia Waddington-Cruz[5], Arnt Kristen[6], Jonas Wixner[7], Igor Diemberger[8,9], Juan Gonzalez-Moreno[10], Eve Cariou[11], Mathew S. Maurer[12], Violaine Planté-Bordeneuve[13], Pablo Garcia-Pavia[14,15], Ivailo Tournev[16,17], Jose Gonzalez-Costello[18], Alejandra Gonzalez Duarte[19,20], Martha Grogan[21], Anna Mazzeo[1], Doug Chapman[22], Pritam Gupta[23], Oliver Glass[22] and Leslie Amass[22] on behalf of the THAOS investigators

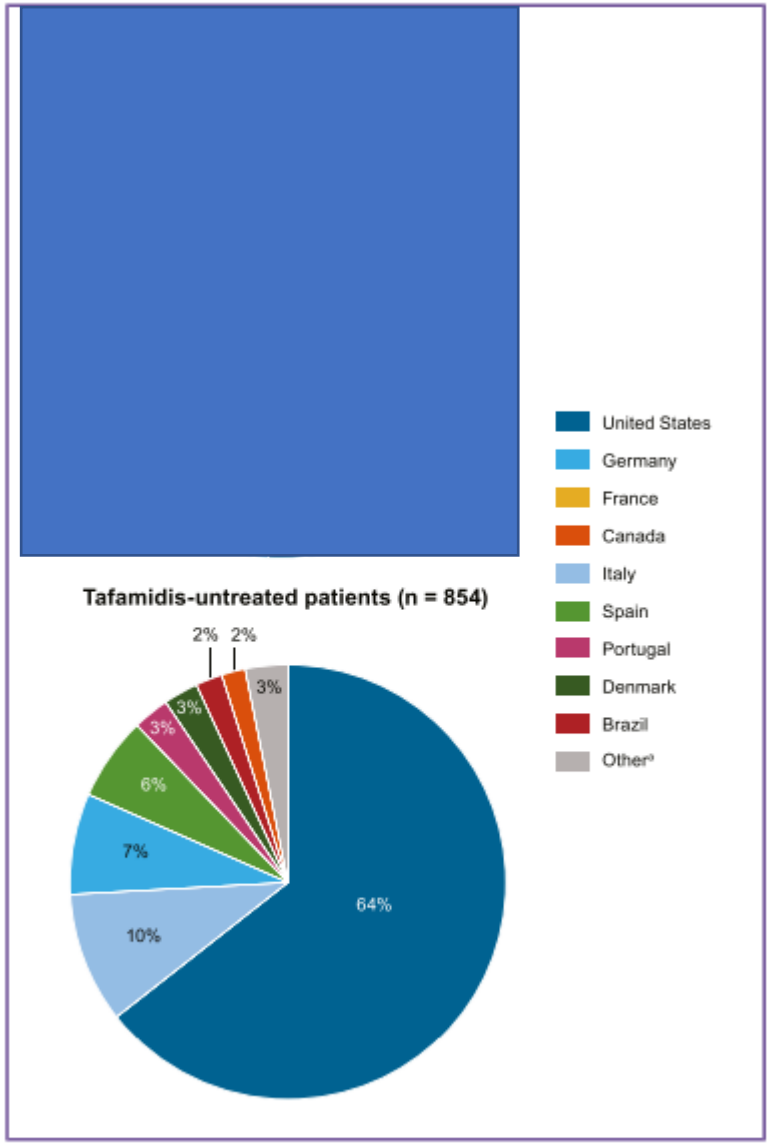
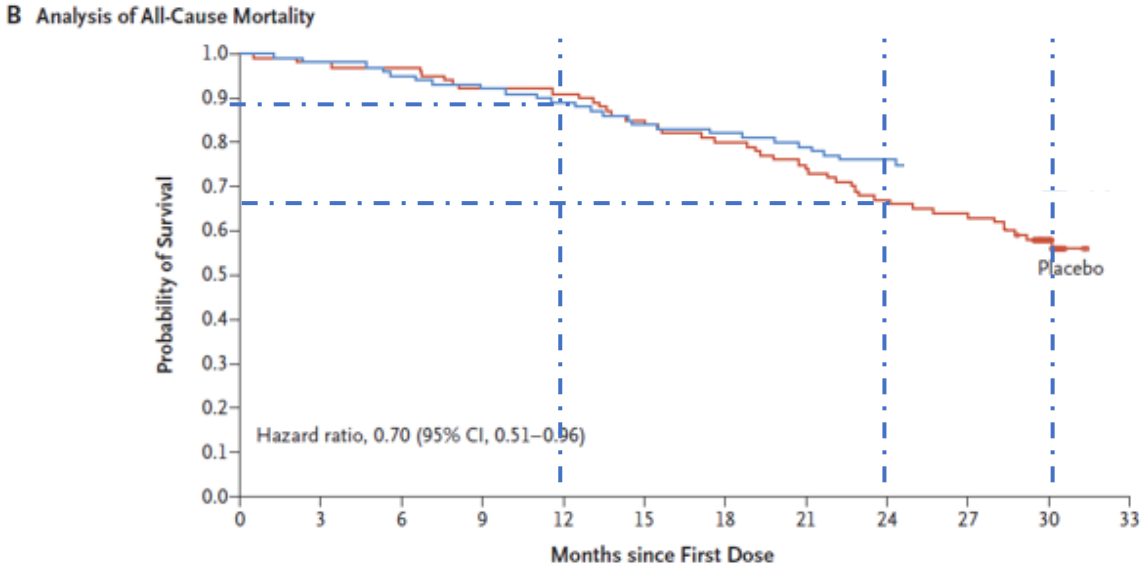


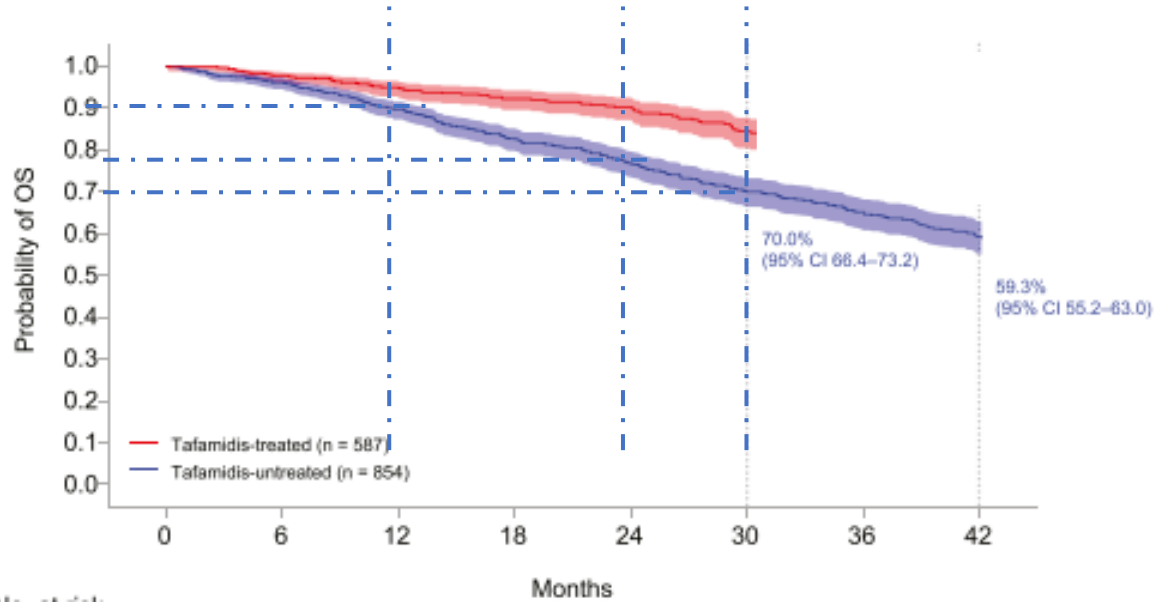
Fig. 1. Country of enrollment for tafamidis-treated and tafamidis-untreated patients. [a]Includes countries with fewer than 10 enrolled patients.

Garcia- Pavia et al. J Cardiac Failure Jun 21:S1071-9164(24)00222-7

Update in the prognosis of untreated ATTR-CM *(placebo)*

	ATTR-ACT trial (NEJM 2018)	Garcia- Pavia et al. (J Cardiac Failure 2024)
1 year		
2 year		
30 months	57%	
42 months		





Update in the prognosis of treated ATTR-CM (tafamidis)

	ATTR-ACT trial (NEJM 2018) - Placebo	Tafamidis	Garcia- Pavia et al. J Cardiac Failure 2024 (in press) - Placebo	Tafamidis
			90%	93%
			76%	89%
			*70% (*72%)*	84% (*87%)
			*59% (*67%)*	77% (*83%)

*(*patients enrolled after 2019)*

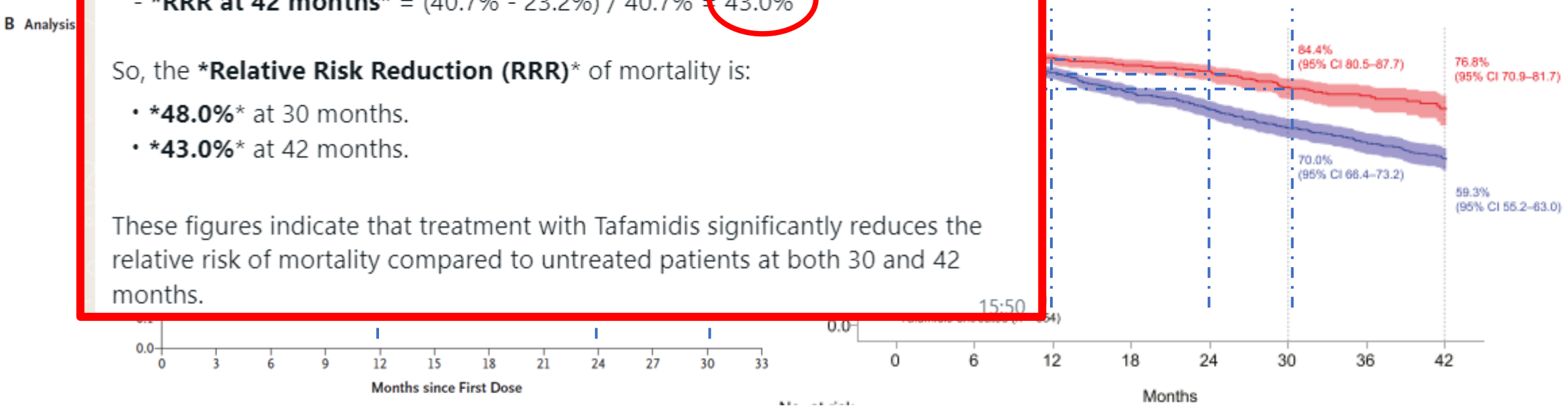
1. ***Relative Risk Reduction (RRR) at 30 months***:
   - ***Mortality in untreated patients*** at 30 months = 1 - 70.0% = 30.0%
   - ***Mortality in treated patients*** at 30 months = 1 - 84.4% = 15.6%
   - ***RRR at 30 months*** = (30.0% - 15.6%) / 30.0% = 48.0%

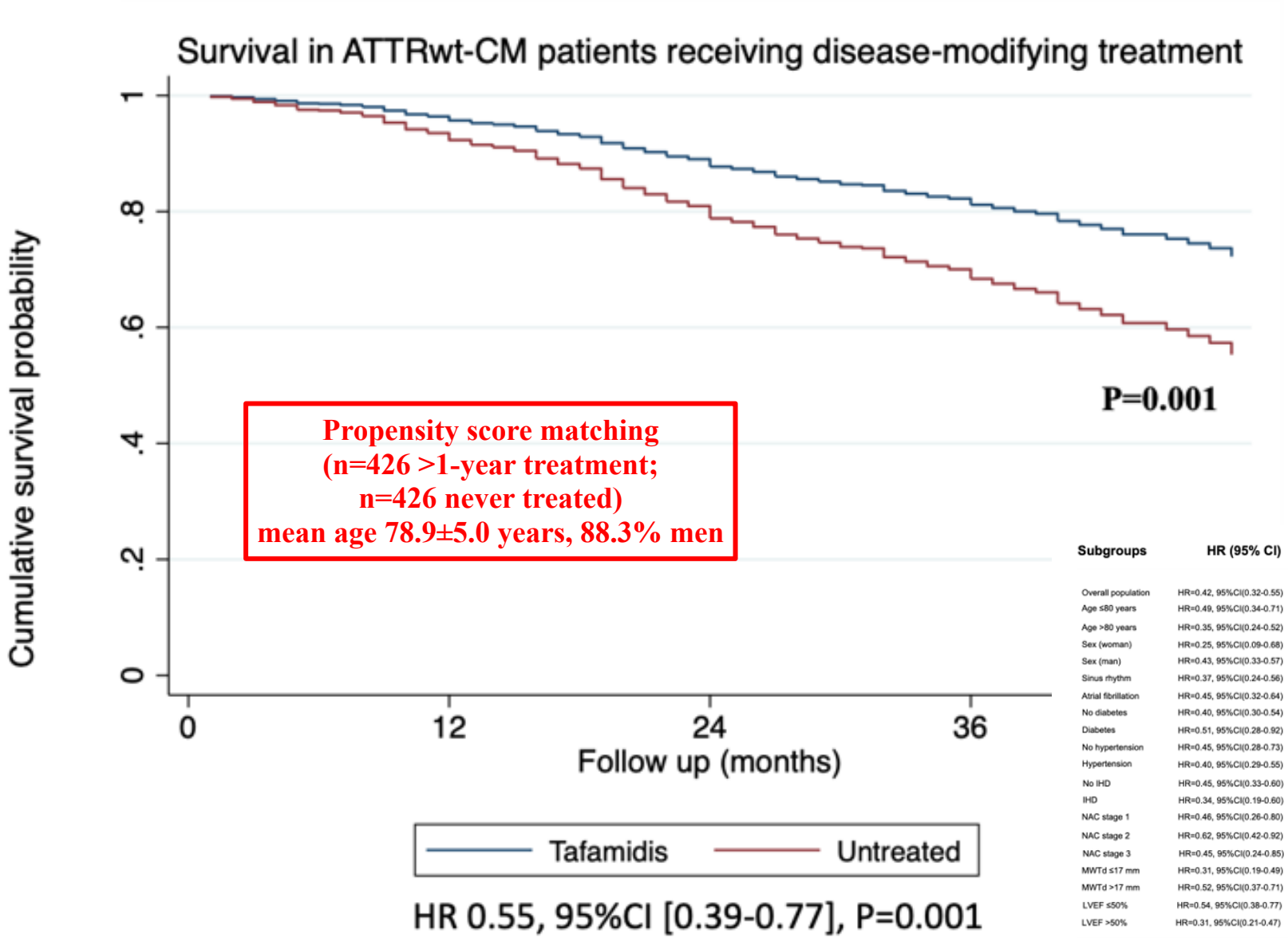
2. ***Relative Risk Reduction (RRR) at 42 months***:
   - ***Mortality in untreated patients*** at 42 months = 1 - 59.3% = 40.7%
   - ***Mortality in treated patients*** at 42 months = 1 - 76.8% = 23.2%
   - ***RRR at 42 months*** = (40.7% - 23.2%) / 40.7% = 43.0%

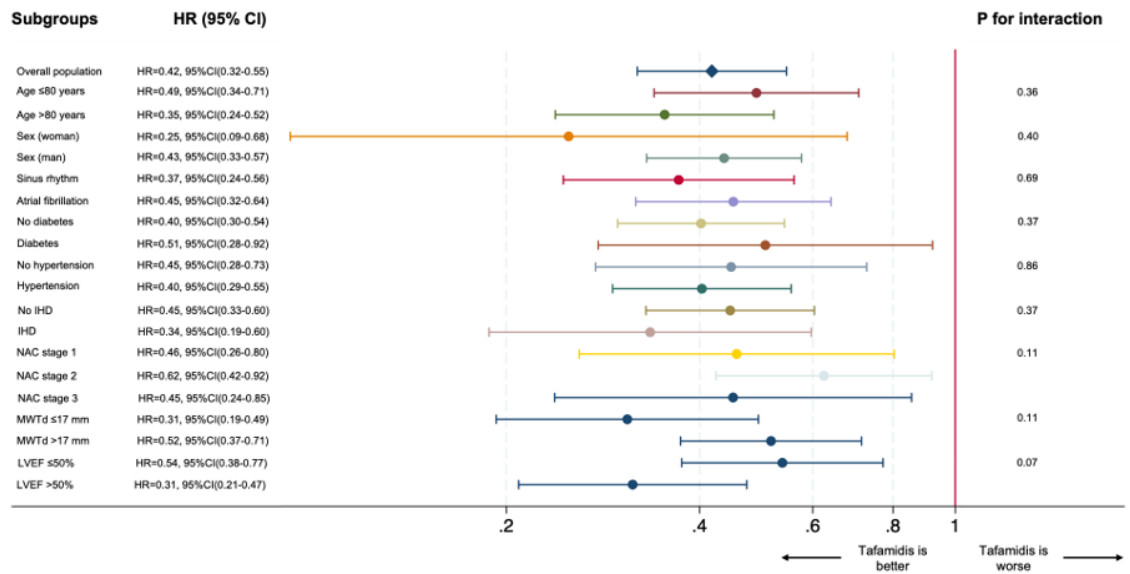
So, the ***Relative Risk Reduction (RRR)*** of mortality is:

- ***48.0%*** at 30 months.
- ***43.0%*** at 42 months.

These figures indicate that treatment with Tafamidis significantly reduces the relative risk of mortality compared to untreated patients at both 30 and 42 months.







Porcari A et al. 2025

Yes, but….
What about real world?

Use of tafamidis in ATTR-CM is supported by 7+ years of clinical data that demonstrate meaningful impact on long-term outcomes

Survival

Robust data from ATTR-ACT, its LTE, and *post hoc* analyses demonstrate that the use of tafamidis **increased survival rates** across various patient populations versus placebo[1–3]

Quality of life

tafamidis demonstrates **long-term benefits** in **health-related quality of life** versus placebo, with impact first observed from **6 months**[4–6]

Dosing and safety profile

tafamidis is the only oral once-daily ATTR-CM treatment, and has a safety profile similar to placebo[1,4,7]

In ATTR-ACT, the following adverse events were reported more often in patients treated with tafamidis (tafamidis meglumine 80 mg) compared with placebo[8]:

- Flatulence (8 patients [4.5%] versus 3 patients [1.7%])
- Liver function test increased (6 patients [3.4%] versus 2 patients [1.1%])

No new safety signals were identified in the LTE[2]

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; LTE, long-term extension.

tafamidis (tafamidis 61 mg) is indicated to treat adult wild-type and hereditary ATTR-CM patients.[8] tafamidis (tafamidis 61 mg) está indicado para el tratamiento de pacientes adultos con ATTR-CM de tipo silvestre y hereditario.[8] A single tafamidis 61 mg capsule is bioequivalent to tafamidis 80 mg (four 20-mg capsules) and is not interchangeable on a per-mg basis.[8,9] Una sola cápsula de ácido libre de tafamidis de 61 mg es bioequivalente a tafamidis meglumina de 80 mg (cuatro cápsulas de 20 mg) y no es intercambiable por mg.[8,9]

1. Elliott P, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2022;15(1):e008193; 2. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail*. 2025;27(12):2998–3009; 3. Sperry BW, et al. Effect of tafamidis on renal function in patients with transthyretin amyloid cardiomyopathy in ATTR-ACT. *JACC CardioOncol*. 2024;6(2):300–6; 4. Maurer MS, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007–16; 5. Grogan M, et al. Effect of long-term tafamidis treatment on health-related quality of life in patients with transthyretin amyloid cardiomyopathy. *Eur J Heart Fail*. 2024;26(3):612–5; 6. Garcia-Pavia P, et al. Tafamidis efficacy among octogenarian patients in the Phase 3 ATTR-ACT and ongoing long-term extension study. *JACC Heart Fail*. 2024;12(1):150–60; 7. Damy T, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail*. 2021;23(2):277–85; 8. Pfizer Inc. tafamidis 20 mg (tafamidis meglumine) and 61 mg (tafamidis) summary of product characteristics. https://www.ema.europa.eu/documents/product-information/tafamidis-epar-product-information_en.pdf (Accessed April 2026); 9. Lockwood PA, et al. The bioequivalence of tafamidis 61-mg free acid capsules and tafamidis meglumine 4 × 20-mg capsules in healthy volunteers. *Clin Pharmacol Drug Dev*. 2020;9(7):849–54.

From every angle: ATTR-CM management beyond initiation of TTR disease-modifying therapy

The *JACC:HF* Position Statement notes[2]:

- Progression according to these criteria should not prompt a change in disease-modifying treatment as this would not necessarily address factors driving progression (e.g., worsening HF)
- There is currently no evidence that switching or combining ATTR-CM therapies improved clinical outcomes

ATTR-CM, transthyretin amyloid cardiomyopathy; TTR transthyretin.

1. Elliott P, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail* 2022;15(1):e008193; 2. García-Pavía, P, et al. Monitoring disease progression in patients with transthyretin amyloid cardiomyopathy. *JACC Heart Fail* 2026;14(1):102766; 3. Garcia-Pavia P, et al. Non-amyloid specific treatment for transthyretin cardiac amyloidosis: a clinical consensus statement of the ESC Heart Failure Association. *Eur Heart J* 2026;47(1):22–36; 4. Damy T, et al. Long-term efficacy of tafamidis in patients with transthyretin amyloid cardiomyopathy by National Amyloidosis Centre stage. *Eur J Heart Fail* 2025;27(12):2998–3009.

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