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ORIGINAL RESEARCH

Survival in a Contemporary, Real-World Cohort of Patients with Mixed-Phenotype Transthyretin Amyloid Cardiomyopathy Treated with Tafamidis: An Analysis from THAOS

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ABSTRACT

Introduction: Tafamidis is approved to treat transthyretin amyloid cardiomyopathy (ATTR-CM). Many patients with ATTR-CM present with a mixed phenotype of both cardiac and neurologic symptoms, but real-world effectiveness studies of tafamidis in this population are lacking. This study assessed survival and other outcomes in a real-world, contemporary cohort of tafamidis-treated and untreated patients with mixed-phenotype ATTR-CM.

Methods: The Transthyretin Amyloidosis Outcomes Survey (THAOS) was a longitudinal, observational, phase 4 study of patients with transthyretin amyloidosis and asymptomatic carriers of pathogenic transthyretin gene variants and was completed in June 2023. This analysis included a contemporary cohort of patients enrolled in THAOS in 2019–2023 who were characterized as having mixed-phenotype ATTR-CM at enrollment. The tafamidis-treated cohort received the approved dose of tafamidis (meglumine 80 mg/free acid 61 mg) throughout the study, and the untreated cohort never received tafamidis.

Results: In tafamidis-treated ($n=116$) and untreated patients ($n=223$), respectively, median age at enrollment was 77.8 and 72.8 years, and 42.2% and 77.6% had variant ATTR-CM.

Prior Presentation: Parts of these data have been presented: J Wixner, E Cariou, A Dispenzieri, M Carlsson, L Amass, FS Angeli, et al. Survival in a Real-World Cohort of Patients With Mixed Phenotype Transthyretin Amyloid Cardiomyopathy Treated With Tafamidis: An Analysis From the Transthyretin Amyloidosis Outcomes Survey. Presented at the Heart Failure 2024 Congress, May 11, 2024, Lisbon, Portugal. J Wixner, E Cariou, A Dispenzieri, M Carlsson, L Amass, FS Angeli, et al. Survival in a Real-World Cohort of Patients With Mixed Phenotype Transthyretin Amyloid Cardiomyopathy Treated With Tafamidis: An Analysis From the Transthyretin Amyloidosis Outcomes Survey. Presented at the XIX International Symposium on Amyloidosis (ISA), May 29, 2024, Rochester, MN, USA.

THAOS investigators are listed in the Acknowledgements section.

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Survival rates at 30 months were 81.5% (95% CI 66.7–90.2) in tafamidis-treated patients and 75.1% (95% CI 66.1–82.0) in untreated patients. Median yearly incidence of cardiovascular-related hospitalizations was 0.89 for tafamidis-treated and 1.70 for untreated patients, and median duration of cardiovascular-related hospitalizations was 7.0 and 11.5 days, respectively. There were 13 (11.2%) and 40 (17.9%) deaths in the respective groups.

Conclusion: Patients with mixed-phenotype ATTR-CM treated with the approved dose of tafamidis had numerically higher survival rates, a numerically lower rate of cardiovascular-related hospitalizations, and fewer deaths than untreated patients. These data parallel recent results for patients with predominantly cardiac ATTR-CM from THAOS and extend results of ATTR-ACT to a contemporary, real-world, mixed-phenotype population.

Trial Registration: ClinicalTrials.gov identifier NCT00628745

Keywords: Mixed phenotype; Tafamidis; Transthyretin amyloid cardiomyopathy; Real-world

Key Summary Points

Why carry out this study?
Tafamidis is approved to treat transthyretin amyloid cardiomyopathy (ATTR-CM)
Many patients with ATTR-CM present with a mixed phenotype of both cardiac and neurologic symptoms, but real-world effectiveness studies of tafamidis in this population are lacking
This study assessed survival and other outcomes in a real-world, contemporary cohort of tafamidis-treated and untreated patients with mixed-phenotype ATTR-CM
What was learned from the study?
Patients with mixed-phenotype ATTR-CM treated with tafamidis in real-world clinical practice had numerically higher survival rates, lower rate of cardiovascular-related hospitalizations, and fewer deaths than untreated patients
These findings are consistent with long-term safety and effectiveness of tafamidis in real-world patients with mixed-phenotype ATTR-CM

INTRODUCTION

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive, degenerative disease caused by the aggregation and accumulation of misfolded transthyretin (TTR) protein, including amyloid fibrils, in the heart, peripheral nerves, and other organs [1–4]. ATTR amyloidosis can result from age-related aggregation of the wild-type TTR protein and/or pathogenic *TTR* variants—variant subunit incorporation into the tetramer leads to destabilization of the TTR protein native state [1–4]. The phenotypic presentation of ATTR amyloidosis can be predominantly cardiac (transthyretin amyloid cardiomyopathy or ATTR-CM), predominantly neurologic (transthyretin amyloid polyneuropathy or ATTR-PN), or a mix of both cardiac and neurologic manifestations [5–7]. Recent

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reports indicate that one-fourth to one-third of patients with ATTR amyloidosis present with a mixed phenotype of both neurologic and cardiac manifestations [5, 7]. Additionally, patients who initially present with a predominantly cardiac or neurologic phenotype may progress to a mixed phenotype over time [5].

Tafamidis is a potent and selective kinetic stabilizer of TTR that binds to the properly folded TTR tetramer (the native state), thereby stabilizing it and reducing tetramer dissociation—the rate-limiting step in the process of TTR aggregation [8]. Tafamidis was the first disease-modifying, regulatory-agency-approved drug used to treat a degenerative disease by targeting a protein conformation, and was approved in the EU in 2011 for the treatment of ATTR-PN [9]. Tafamidis was subsequently approved for the treatment of ATTR-CM on the basis of results from the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT; NCT01994889) and is currently approved in over 50 countries [10]. In ATTR-ACT, tafamidis compared with placebo was associated with reduced all-cause mortality (hazard ratio 0.70; 95% confidence interval [CI] 0.51–0.96) and a lower rate of cardiovascular (CV)-related hospitalizations per year (relative risk ratio 0.68; 95% CI 0.56–0.81) in patients with wild-type (ATTRwt-CM) or variant (ATTRv-CM) ATTR-CM [10]. In the past decade since enrollment in ATTR-ACT closed, there have been significant advances in the diagnosis and management of patients with ATTR-CM, as well as increased awareness of ATTR-CM among physicians. A recent real-world study demonstrated high survival rates in a contemporary cohort of patients with predominantly cardiac ATTR-CM treated with the approved dose of tafamidis (42-month rate, 86.3% in tafamidis-treated patients vs 67.3% in untreated patients) [11], but real-world effectiveness studies in patients with mixed-phenotype ATTR-CM are lacking. Evaluating the effectiveness of tafamidis in a contemporary cohort of patients with mixed-phenotype ATTR-CM is important given that ATTR-ACT did not collect data on patient phenotype, the mixed-phenotype population appears to be larger than originally thought, and the identification and management of patients with ATTR-CM have evolved over the past decade.

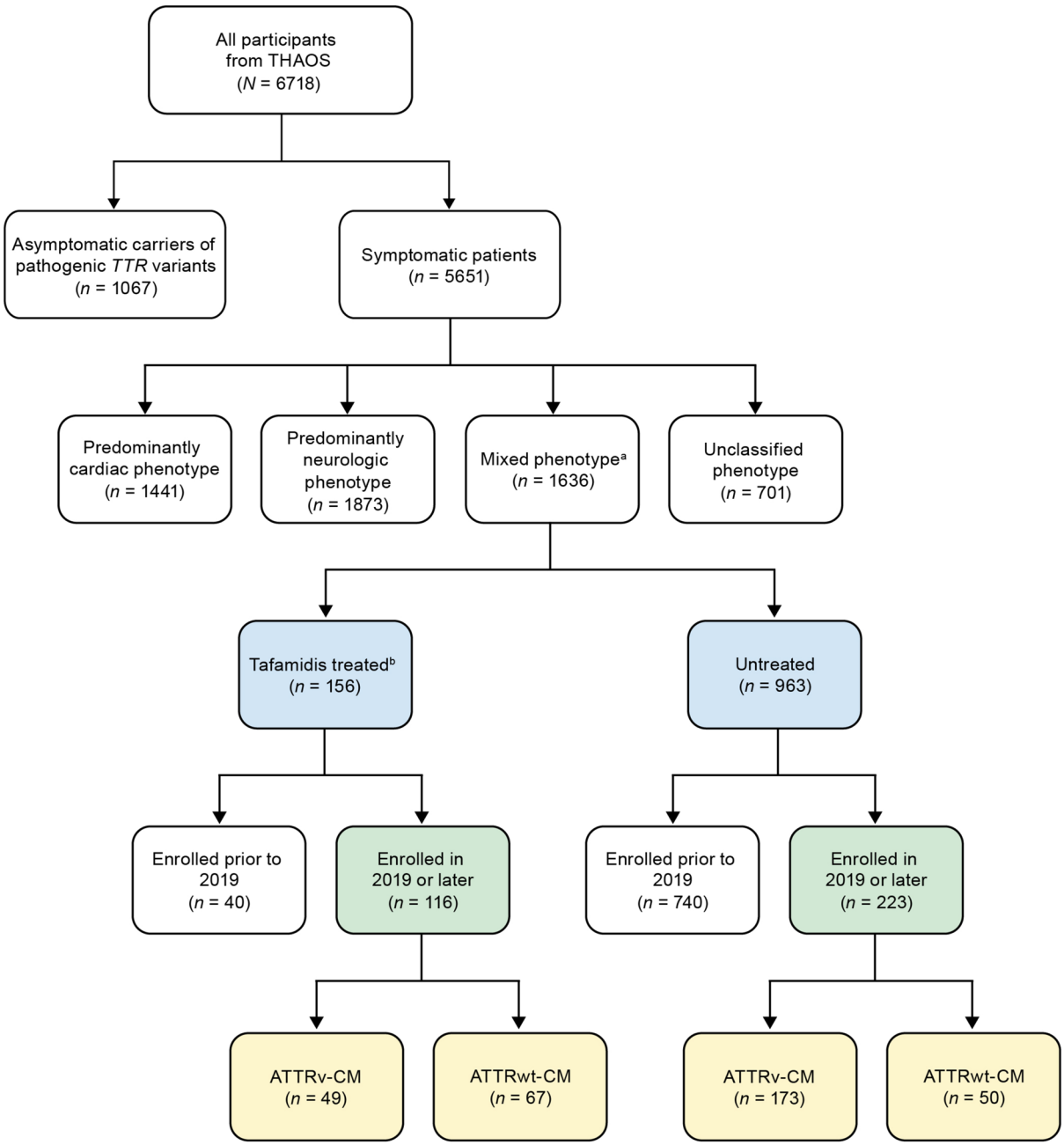
The Transthyretin Amyloidosis Outcomes Survey (THAOS; NCT00628745) was a global, longitudinal, observational, phase 4 study of patients with ATTR amyloidosis (inclusive of ATTR-CM and ATTR-PN) and asymptomatic carriers of pathogenic *TTR* variants. Patients who were receiving tafamidis and tafamidis-naïve patients could enroll in THAOS. THAOS was completed on June 16, 2023, and remains the largest and longest ATTR amyloidosis disease registry to date, enrolling 6718 participants across 33 countries over a 16-year period. This analysis used data from THAOS to evaluate real-world survival in a contemporary cohort (defined as enrolled in THAOS in 2019 or later) of tafamidis-treated and untreated patients with mixed-phenotype ATTR-CM.

METHODS

Study Design and Patients

Full details of study design and eligibility criteria of THAOS have been published [12]. All THAOS sites received ethical or institutional review board approval before patient enrollment (Supplementary Table S1), and all patients provided written informed consent. The study followed the Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki.

This analysis included a contemporary cohort (i.e., enrolled in 2019 or later) of patients with a mixed phenotype at enrollment in THAOS. Phenotypes have been defined [7]. The tafamidis-treated cohort included patients who received only tafamidis meglumine 80 mg or bioequivalent tafamidis free acid 61 mg (the approved dose for ATTR-CM) while in THAOS; patients who received any other dose of tafamidis while in THAOS were excluded. The untreated cohort included patients who had never received tafamidis either before or during THAOS. Patients were not receiving any other investigational treatments for ATTR-CM, and data were



Primary study cohort
Patients with mixed-phenotype ATTR-CM enrolled in THAOS in 2019 or later

Sensitivity analysis cohort
Patients with mixed-phenotype ATTR-CM enrolled in 2019 or later, stratified by TTR genotype

Sensitivity analysis cohort
Patients with mixed-phenotype ATTR-CM enrolled in any year of THAOS

◂**Fig. 1** THAOS participant flowchart. [a]One patient who previously participated in a tafamidis clinical trial but was not treated during THAOS was excluded. [b]Includes patients treated with only tafamidis meglumine 80 mg/free acid 61 mg while in THAOS; patients treated with other tafamidis doses while in THAOS ($n = 516$) were excluded. *ATTRv-CM* variant transthyretin amyloid cardiomyopathy, *ATTRwt-CM* wild-type transthyretin amyloid cardiomyopathy, *THAOS* Transthyretin Amyloidosis Outcomes Survey, *TTR* transthyretin

censored during any time period that a patient participated in another clinical trial.

Outcomes and Analysis

The tafamidis-treated data set included (1) all available data from enrollment to final discontinuation of tafamidis or end of follow-up in THAOS (whichever was earlier) from patients receiving tafamidis at enrollment, or (2) all available data from first tafamidis dose to final discontinuation of tafamidis or end of follow-up in THAOS (whichever was earlier) from patients who initiated tafamidis after enrollment. The untreated data set included all available data (from enrollment to end of follow-up) from mixed-phenotype patients who never received tafamidis before or during THAOS.

Demographic and baseline clinical characteristics are reported as count (percentage) for categorical data and median (10th and 90th percentile) for continuous data. *P* values were calculated to test for group differences in baseline characteristics using the chi-square test for categorical variables or the Wilcoxon test for medians of continuous variables.

Survival was estimated using the Kaplan–Meier method. Kaplan–Meier curves for the tafamidis-treated and untreated sets are presented up to 42 months, and overall survival estimates and two-sided 95% CIs are provided at 30 months. Patients were censored at last follow-up, the study discontinuation date, the treatment discontinuation date (for tafamidis-treated patients), or at enrollment in a clinical trial. Sensitivity analyses were conducted to examine survival (1) by *TTR* genotype (ATTRwt-CM and ATTRv-CM), and (2) in patients with mixed-phenotype ATTR-CM enrolled in any year of THAOS.

Safety data were collected as previously described [11]. All-cause and CV-related hospitalization data are also reported. The incidence rate of hospitalizations per year was defined as a patient's number of hospitalizations divided by their duration on study. A stepwise multivariate Poisson regression model examined nine baseline demographic variables, in addition to treatment group, as potential predictors for all-cause and CV-related hospitalization rates. The additional covariates were sex, race, age, symptom duration, genotype, modified body mass index, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, and estimated glomerular filtration rate (eGFR). A P value < 0.05 was required to enter and stay in the model.

The first patient included in this analysis was enrolled on January 2, 2019, and the final data cutoff date was July 24, 2023.

RESULTS

Patients and Treatment

Of 6718 total participants enrolled in THAOS, 116 tafamidis-treated and 223 untreated patients met inclusion criteria and were included in the primary analysis (Fig. 1). Since this was a real-world analysis, some patients in THAOS received tafamidis at doses not approved for ATTR-CM and were excluded from this analysis (see footnote b of Fig. 1).

Patients included in this analysis were enrolled in 21 countries (Fig. 2). Tafamidis-treated patients were most often enrolled in the USA (39%), France (21%), and Germany (16%), whereas untreated patients were most often enrolled in the USA (23%), Spain (20%), and Italy (12%). In tafamidis-treated and untreated patients, respectively, median age at enrollment was 77.8 and 72.8 years, 78.4% and 67.3% were male, and 21.6% and 32.7% were female (Table 1); 42.2% and 77.6% had ATTRv-CM, and the most common *TTR* variant was V122I (p.V142I) in tafamidis-treated patients (16.4%) and V30M (p. V50M) in

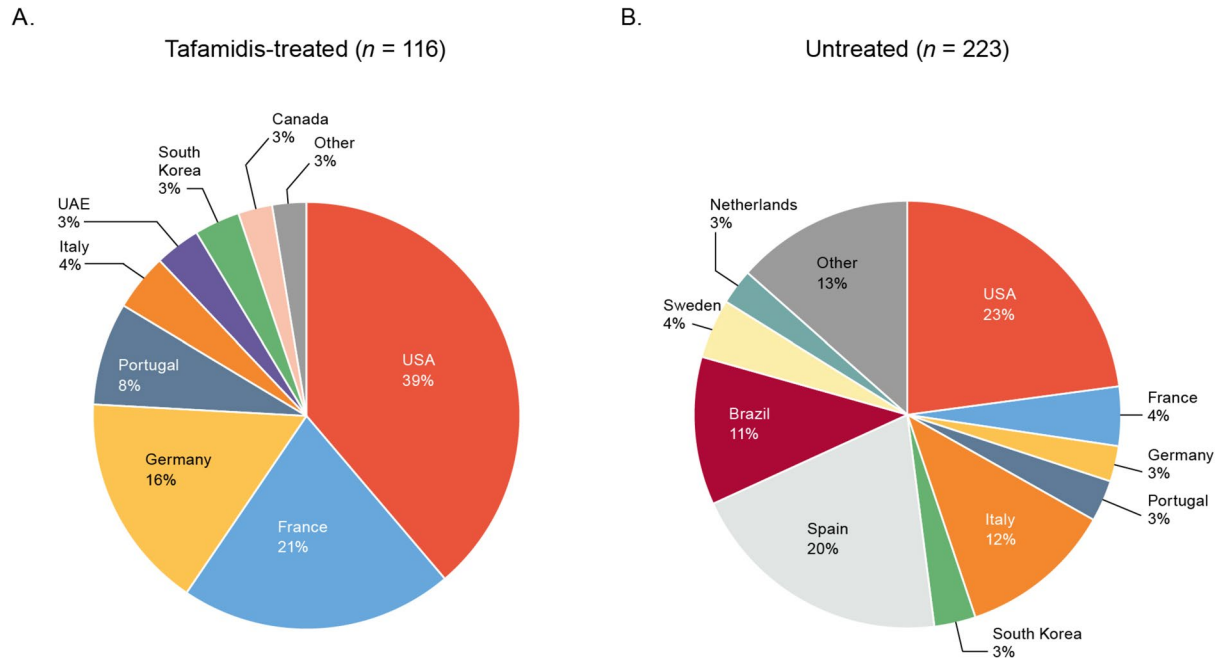


Fig. 2 Country of enrollment for patients with mixed-phenotype ATTR-CM: **a** tafamidis-treated. b untreated. Other includes countries with ≤ 2% of enrolled patients in each group. *ATTR-CM* transthyretin amyloid cardiomyopathy

untreated patients (29.6%). A total of 89 (76.7%) tafamidis-treated and 167 (74.9%) untreated patients had heart failure, of whom 58 (65.2%) and 113 (67.7%) were in NYHA class I/II, and 29 (32.6%) and 52 (31.1%) were in NYHA class III/IV. In patients with available data, median LV septal thickness was 16.0 mm in tafamidis-treated patients ($n = 82$) and 16.7 mm in untreated patients ($n = 124$); median LV ejection fraction was 52.0% in tafamidis-treated patients ($n = 84$) and 54.0% in untreated patients ($n = 120$); and median NT-proBNP concentration was 2308 pg/mL in tafamidis-treated patients ($n = 46$) and 2004 pg/mL in untreated patients ($n = 122$). Median eGFR was 52.9 mL/min/1.73 m^2 in tafamidis-treated patients ($n = 110$) and 63.2 mL/min/1.73 m^2 in untreated patients ($n = 176$). Median follow-up time was 0.9 years in tafamidis-treated patients and 1.2 years in untreated patients. Study discontinuations in tafamidis-treated and untreated patients, respectively, were most often due to site closure (24.1% and 25.6%) and patient death (11.2% and 17.9%) (Table 2).

Median (10th, 90th percentile) tafamidis treatment duration in tafamidis-treated patients was 0.8 (0.1, 2.2) years. In tafamidis-treated patients, 70 (60.3%) received concomitant medication for CV disease prior to tafamidis, and 28 (24.1%) received concomitant medication for CV disease on or after the first dose of tafamidis (Table 3). In untreated patients, 77 (34.5%) received concomitant medication for CV disease prior to or after enrollment in THAOS (Table 3).

Survival

Survival rates in tafamidis-treated and untreated patients, respectively, were 81.5% (95% CI 66.7–90.2) and 75.1% (95% CI 66.1–82.0) at 30 months (Fig. 3). In patients with ATTRv-CM, survival rates at 30 months were 79.2% (95% CI 59.0–90.2) for tafamidis-treated patients ($n = 49$) and 83.7% (95% CI 74.5–89.8) for untreated patients ($n = 173$) (Fig. 4a). In patients with ATTRwt-CM, survival rates at 30 months were 83.6% (95% CI

Table 1 Demographic and baseline clinical characteristics of patients with mixed-phenotype ATTR-CM enrolled in THAOS in 2019 or later

	Tafamidis-treated (*n* = 116)	Untreated (*n* = 223)	*P* value
Sex, *n* (%)			0.0312
Female	25 (21.6)	73 (32.7)	
Male	91 (78.4)	150 (67.3)	
Race/ethnicity[a], *n* (%)			0.0296
Afro-Caribbean	0	3 (1.3)	
American Hispanic	1 (0.9)	0	
Asian	5 (4.3)	20 (9.0)	
Black or African American	19 (16.4)	26 (11.7)	
Latino American	2 (1.7)	7 (3.1)	
White	54 (46.6)	129 (57.8)	
Other	0	13 (5.8)	
Age at symptom onset (years)	*n* = 98	*n* = 210	0.0277
Median (10th, 90th percentile)	68.2 (51.0, 83.5)	63.5 (46.8, 79.9)	
Time from symptom onset to diagnosis (years)	*n* = 98	*n* = 197	0.1042
Median (10th, 90th percentile)	4.5 (0.2, 18.5)	3.2 (0.0, 12.1)	
Age at enrollment (years), median (10th, 90th percentile)	77.8 (66.0, 88.5)	72.8 (53.6, 85.3)	< 0.0001
Symptom duration at enrollment (years)	*n* = 98	*n* = 210	0.2781
Median (10th, 90th percentile)	6.7 (0.9, 19.4)	4.7 (1.0, 18.5)	
Follow-up time[b] (years), median (10th, 90th percentile)	0.9 (0.2, 2.7)	1.2 (0.3, 3.3)	0.0182
TTR genotype, *n* (%)			< 0.0001
Variant	49 (42.2)	173 (77.6)	
Wild-type	67 (57.8)	50 (22.4)	
Most frequent (≥ 10%) *TTR* variants[c], *n* (%)			< 0.0001
V30M (p.V50M)[d]	8 (6.9)	66 (29.6)	
V122I (p.V142I)	19 (16.4)	41 (18.4)	
Heart failure, *n* (%)	89 (76.7)	167 (74.9)	0.7091
NYHA class[e], *n* (%)			0.8770
I	8 (9.0)	15 (9.0)	
II	50 (56.2)	98 (58.7)	
III	28 (31.5)	48 (28.7)	
IV	1 (1.1)	4 (2.4)	
NT-proBNP (pg/mL)	*n* = 46	*n* = 122	0.3796
Median (10th, 90th percentile)	2308 (430, 9325)	2004 (192, 8307)	
LV septum thickness (mm)	*n* = 82	*n* = 124	0.4750

Table 1 continued

	Tafamidis-treated (*n* = 116)	Untreated (*n* = 223)	*P* value
Median (10th, 90th percentile)	16.0 (13.0, 21.7)	16.7 (12.8, 23.0)	
LV ejection fraction (%)	*n* = 84	*n* = 120	0.1291
Median (10th, 90th percentile)	52.0 (28.0, 63.0)	54.0 (35.5, 66.0)	
mBMI	*n* = 86	*n* = 141	0.0655
Median (10th, 90th percentile)	1078 (883.6, 1382.0)	1027 (792.8, 1375.2)	
Past or current clinical trial participation, *n* (%)			0.1083
Yes	6 (5.2)	23 (10.3)	
Tafamidis trial	0	0	
Non-tafamidis trial	6 (5.2)	23 (10.3)	
No	110 (94.8)	200 (89.7)	
Diagnostic method[f], *n* (%)			0.5434
Clinical symptoms	114 (98.3)	203 (91.0)	
Amyloid confirmed on tissue biopsy	39 (33.6)	69 (30.9)	
TTR confirmed as precursor protein on tissue biopsy	33 (28.4)	39 (17.5)	
Scintigraphy	81 (69.8)	123 (55.2)	
Other	28 (24.1)	40 (17.9)	
eGFR (mL/min/1.73 m^2)	*n* = 110	*n* = 176	0.0007
Median (10th, 90th percentile)	52.9 (23.7, 87.4)	63.2 (28.9, 117.4)	
NAC stage, *n* (%)	*n* = 46	*n* = 107	0.3615
I	18 (39.1)	55 (51.4)	
II	17 (37.0)	32 (29.9)	
III	11 (23.9)	20 (18.7)	

The number of patients with recorded data shown for variables with missing data. Baseline refers to enrollment or tafamidis treatment initiation (whichever was later) for tafamidis-treated patients, and enrollment for untreated patients

eGFR estimated glomerular filtration rate, *LV* left ventricular, *mBMI* modified body mass index, *NAC* National Amyloidosis Centre, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *THAOS* Transthyretin Amyloidosis Outcomes Survey, *TTR* transthyretin

[a]Race was not collected in France or Portugal

[b]Follow-up time is based on consent date to last available follow-up date

[c]One untreated patient had both the V30M and V122I variant and was counted in both groups

[d]Includes patients with G6S (p.G26S) in addition to V30M

[e]Denominator is number of patients with heart failure; 2 patients in each cohort had missing data

[f]Patients could be diagnosed on the basis of > 1 diagnostic method

54.3–94.8) for tafamidis-treated patients (*n* = 67) and 49.4% (95% CI 29.7–66.4) for untreated patients (*n* = 50) (Fig. 4b). In tafamidis-treated (*n* = 156) and untreated (*n* = 963) patients, respectively, enrolled in any year of THAOS (Supplementary Table S2), survival rates were 81.7% (95% CI 71.1–88.7) and 72.4% (95% CI 69.2–75.4) at 30 months (Fig. 5).

Table 2 Patient disposition

	Tafamidis-treated (*n* = 116)	Untreated (*n* = 223)
Discontinuations, *n* (%)	116 (100.0)	222 (99.6)
Site closure	28 (24.1)	57 (25.6)
Death	13 (11.2)	40 (17.9)
Patient moved out of the area and did not transfer to another THAOS site	11 (9.5)	2 (0.9)
Lost to follow-up	2 (1.7)	17 (7.6)
Patient did not meet inclusion criteria	4 (3.4)	1 (0.4)
Patient discontinued by principal investigator	1 (0.9)	1 (0.4)
Participation in an interventional clinical trial	0	6 (2.7)
Other	56 (48.3)	98 (43.9)
Missing	1 (0.9)	0

THAOS Transthyretin Amyloidosis Outcomes Survey

Safety

All causality, treatment-emergent adverse events (AEs) occurred in 40 (34.5%) patients (Table 4). No patient had a dose reduction due to AEs and 5 (4.3%) had tafamidis withdrawn (temporarily or permanently) due to AEs.

The median incidence rate of CV-related hospitalizations per year was 0.89 for tafamidis-treated patients and 1.70 for untreated patients, and the median duration of CV-related hospitalizations was 7.0 and 11.5 days, respectively. Regression analysis identified eGFR as the only factor significantly associated with a higher rate of CV-related hospitalizations. The eGFR-adjusted risk ratio (tafamidis-treated vs untreated) was 0.80 (95% CI 0.40–1.58).

The median incidence rate of all-cause hospitalizations per year was 1.13 for tafamidis-treated patients and 0.96 for untreated patients, and the median duration of all-cause hospitalizations was 7.0 and 4.0 days. Younger age was the only factor significantly associated with a higher rate of all-cause hospitalizations. The age-adjusted risk ratio (tafamidis-treated vs untreated) for all-cause hospitalizations per year was 0.99 (95% CI 0.64–1.55).

In the survival analysis, there were 13 (11.2%) and 40 (17.9%) deaths in tafamidis-treated and untreated patients, respectively.

DISCUSSION

In this real-world, observational study of a contemporary cohort of patients with mixed-phenotype ATTR-CM, patients who received the approved dose of tafamidis in clinical practice had a 30-month survival rate of 81.5%, whereas patients who never received tafamidis had a 30-month survival rate of 75.1%. These findings are directionally consistent with the 30-month survival rates reported in ATTR-ACT (treated vs placebo group, 70.5% vs 57.1%) [10]. However, the survival rates observed in the current study were higher than in ATTR-ACT, suggesting that patients with ATTR-CM are living longer in this contemporary era (2019–2023) than in the time period of ATTR-ACT (2013–2018). Improved survival in patients with ATTR-CM over time is consistent with other recent reports and is likely the result of advances in disease identification and diagnosis and the availability of new medications for managing heart failure [11, 13–15].

Table 3 Concomitant medications for cardiovascular disease

Patients, *n* (%)	Tafamidis-treated (*n* = 116)		Untreated (*n* = 223)
	Prior to tafamidis	On or after first dose of tafamidis	Prior to or after enrollment in THAOS
Any cardiovascular concomitant medication	70 (60.3)	28 (24.1)	77 (34.5)
Diuretics	51 (44.0)	11 (9.5)	63 (28.3)
Anticoagulants and antiplatelets	39 (33.6)	5 (4.3)	43 (19.3)
Statins	33 (28.4)	1 (0.9)	23 (10.3)
Beta blockers	32 (27.6)	5 (4.3)	39 (17.5)
Angiotensin II receptor antagonists	16 (13.8)	0	18 (8.1)
Antiarrhythmics	11 (9.5)	2 (1.7)	12 (5.4)
ACE inhibitors	8 (6.9)	0	11 (4.9)
Antihypertensives (other)	4 (3.4)	2 (1.7)	3 (1.3)
Hypolipidemic (other)	4 (3.4)	0	3 (1.3)
Calcium-channel blockers	3 (2.6)	0	6 (2.7)
Nitrates and anti-angina drugs	2 (1.7)	3 (2.6)	1 (0.4)
Alpha blockers	2 (1.7)	0	6 (2.7)
Cardiac glycosides	2 (1.7)	0	1 (0.4)
Other	25 (21.6)	14 (12.1)	10 (4.5)

ACE angiotensin-converting enzyme

Patients with mixed-phenotype ATTR-CM in this analysis had similar survival rates as a comparable cohort of THAOS patients with predominantly cardiac ATTR-CM (30-month rates: tafamidis-treated, 86.3%; untreated, 77.2%) [11]. This finding is notable because ATTR-ACT did not collect data on phenotype, raising questions about the effectiveness of tafamidis in improving survival in patients presenting with both cardiac and neurologic symptoms. Although the current data are limited by the observational nature of the study and small number of patients with adequate follow-up, tafamidis-treated patients with mixed-phenotype ATTR-CM showed numerically higher survival rates than untreated patients. Combined with the fact that the survival rates observed here were comparable to patients with only cardiac symptoms, these findings suggest that tafamidis may be effective in improving survival in a mixed-phenotype population. The potential benefit of tafamidis in delaying neurologic progression in patients with a mixed phenotype was observed in a recent single-center, real-world, exploratory study in patients with mixed-phenotype ATTRv-CM treated with tafamidis meglumine 80 mg/free acid 61 mg, which showed stabilization or improvement on various measures of neurologic disease progression after a mean treatment duration of 20.8 months [16].

Nevertheless, it is important to consider that this was a descriptive, observational study. Therefore, patients in the tafamidis-treated and untreated cohorts were not matched on baseline characteristics, and between-group differences also may have contributed to differences

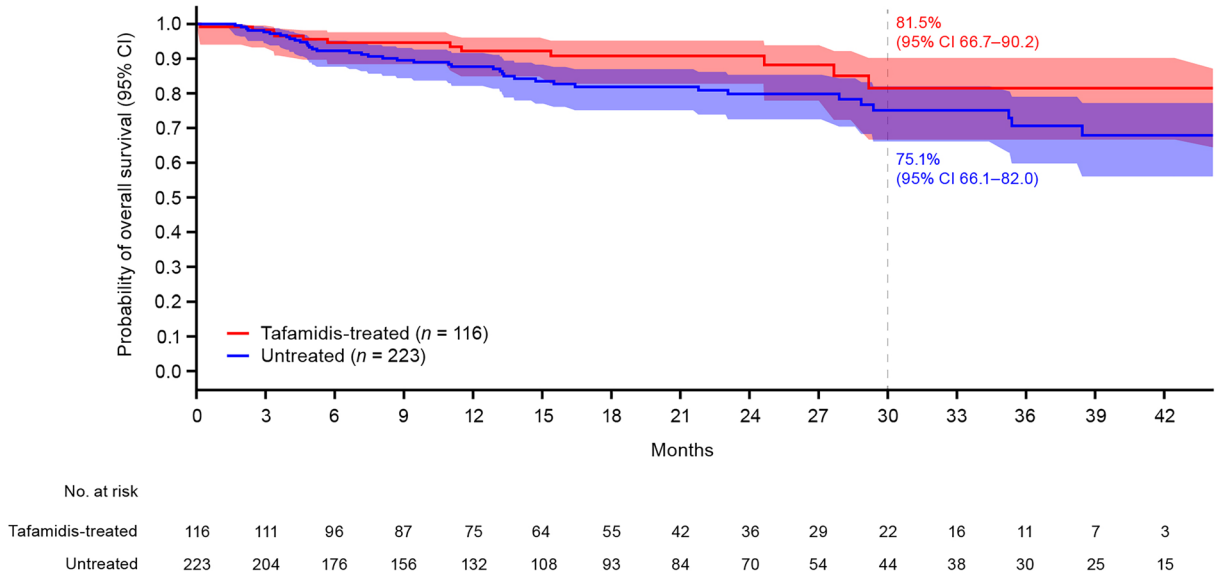


Fig. 3 Kaplan–Meier plot of overall survival in tafamidis-treated and untreated patients with mixed-phenotype ATTR-CM in enrolled in THAOS in 2019 or later. *ATTR-CM* transthyretin amyloid cardiomyopathy, *CI* confidence interval, *OS* overall survival, *THAOS* Transthyretin Amyloidosis Outcomes Survey

in survival. Most notable was the imbalance of patients with ATTRv-CM and ATTRwt-CM between cohorts. The majority of untreated patients had ATTRv-CM, whereas the tafamidis-treated cohort had a more equal distribution of ATTRv-CM and ATTRwt-CM. This discrepancy likely reflects that a larger proportion of tafamidis-treated patients were from the USA, where wild-type disease is more prevalent and tafamidis had earlier regulatory approval than other regions of the world [17]. Differences in the underlying pathophysiology and neurologic manifestations between patients with ATTRwt-CM and those with ATTRv-CM could have contributed to the overall differences [18–21]. Genotype subgroup analyses showed a larger numerical difference in 30-month survival rates in patients with ATTRwt-CM (83.6% in tafamidis-treated patients vs 49.4% in untreated patients) than those with ATTRv-CM (79.2% in treated patients vs 83.7% in untreated patients), which might suggest a greater therapeutic benefit of tafamidis in wild-type patients. However, the genotype subgroup analysis was further complicated by differences in the variants represented in each cohort; V122I was the most prominent *TTR* variant in the tafamidis-treated cohort and is associated with poorer outcomes than the V30M variant, the most prominent variant in the untreated cohort [22, 23]. In addition, the genotype subgroups had very small sample sizes, thereby precluding any definitive conclusions.

No new safety signals were detected for tafamidis in this analysis. No patients had a dose reduction due to AEs in this cohort and treatment withdrawals (temporary or permanent) were observed in fewer than 5% of patients. Tafamidis-treated patients had a lower yearly incidence and shorter duration of CV-related hospitalizations than untreated patients. Conversely, tafamidis-treated patients had a higher yearly incidence of all-causality hospitalizations. The regression analysis indicated that younger age was associated with a higher rate where the age-adjusted estimated risk ratio (tafamidis-treated vs untreated) was 0.99 (95% CI 0.64–1.55). In the survival analysis, 11.2% of tafamidis-treated and 17.9% of untreated patients died. These data continue to support the long-term safety and tolerability of tafamidis in a real-world setting.

Strengths of this analysis include the inclusion of patients with mixed-phenotype ATTR-CM from 21 countries and the inclusion of a

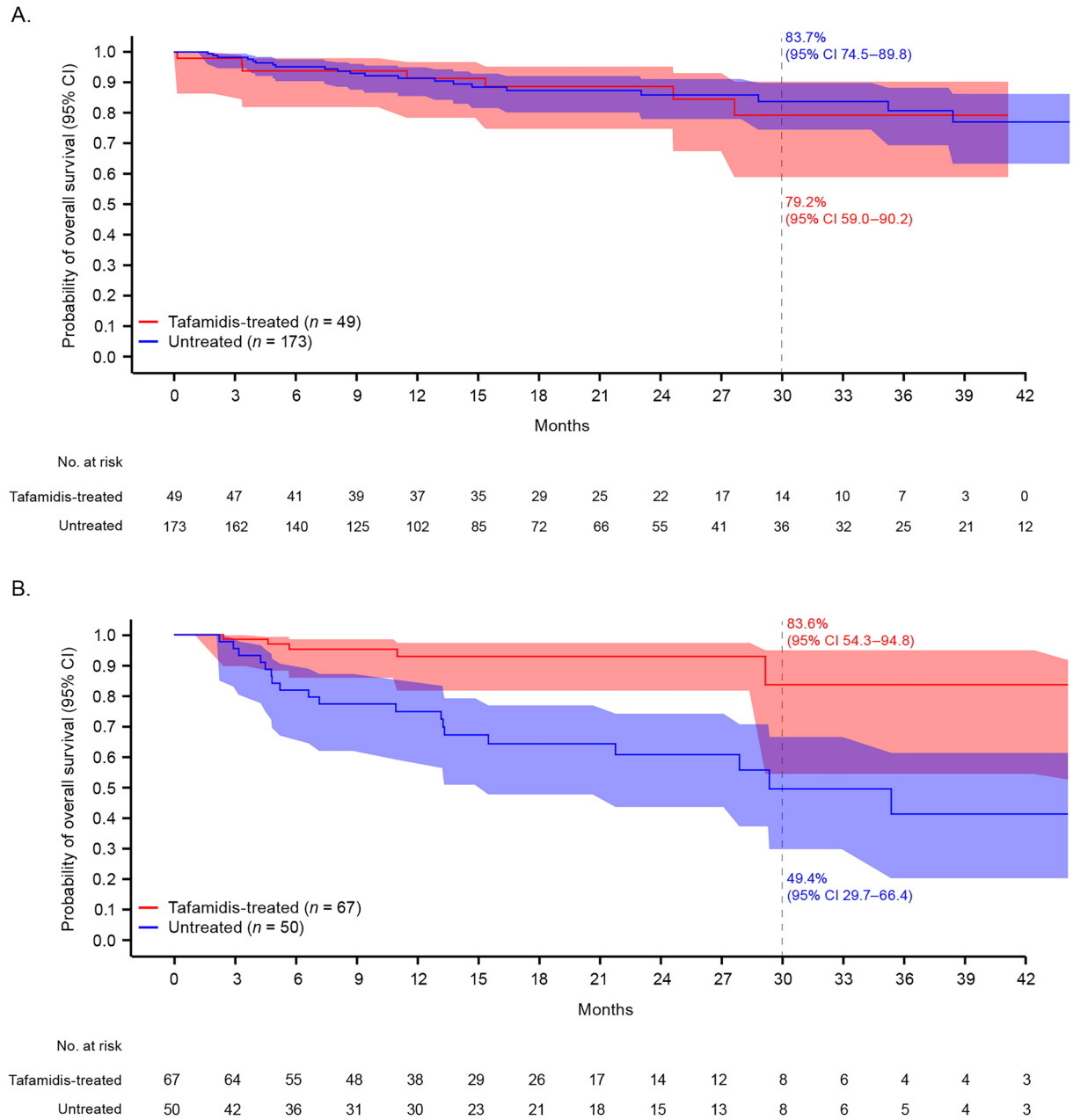


Fig. 4 Kaplan–Meier plot of overall survival by *TTR* genotype in patients with mixed-phenotype ATTR-CM: **a** ATTRv-CM. **b** ATTRwt-CM. *ATTRv-CM* variant transthyretin amyloid cardiomyopathy, *ATTRwt-CM* wild-type transthyretin amyloid cardiomyopathy, *CI* confidence interval, *OS* overall survival, *TTR* transthyretin

contemporary cohort of patients treated in real-world clinical practice representative of patients treated worldwide today. A limitation of this analysis was that the median follow-up time was approximately 1 year in both cohorts, thus limiting the reliability of the survival analyses in later months due to the small number of patients with adequate follow-up. Further studies are needed to confirm these findings in a larger sample. In addition, and as described above, differences in baseline characteristics of the tafamidis-treated and untreated

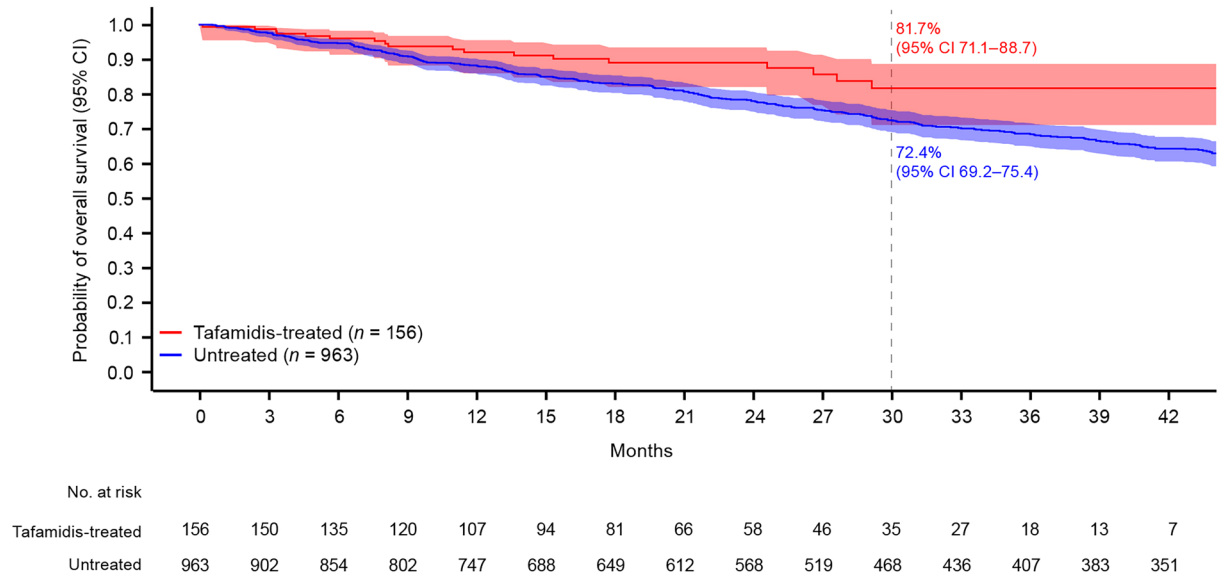


Fig. 5 Kaplan–Meier plot of overall survival in tafamidis-treated and untreated patients with mixed-phenotype ATTR-CM enrolled in any year of THAOS. *ATTR-CM* transthyretin amyloid cardiomyopathy, *CI* confidence interval, *THAOS* Transthyretin Amyloidosis Outcomes Survey

Table 4 Summary of all causality, treatment-emergent adverse events in tafamidis-treated patients

	Tafamidis-treated (*n* = 116)
Number of AEs, *n*	149
Patients with AEs, *n* (%)	40 (34.5)
Patients with serious AEs, *n* (%)	33 (28.4)
Patients with severe AEs, *n* (%)	29 (25.0)
Patients for whom treatment was withdrawn due to AEs[a], *n* (%)	5 (4.3)
Patients with dose reductions due to AEs, *n* (%)	0

AE adverse event

[a]Treatment temporarily or permanently withdrawn or delayed, but patient continued in the study

cohorts complicated the comparison between groups, especially regarding genotypic differences. Patients in the tafamidis-treated cohort also had a lower eGFR at baseline, which may reflect the older age of these patients. These baseline differences could have contributed to differences in survival outcomes. Propensity-matched analyses were not possible given the amount of incomplete data, which is common in registry studies, and formal statistical comparisons were not made between groups in the survival analysis. Additionally, data on changes in neurologic measures were insufficient to assess the impact of the approved dose of tafamidis on neurologic disease progression, and further research is needed in this area. Selection and/or ascertainment bias may have been introduced as a result of the observational nature of this study, and because physicians were responsible for submitting patients to the

registry and could have potentially favored inclusion of certain patients over others based on disease severity, phenotype, treatment history, or other factors. These potential biases may limit the generalizability of the findings to a broader population. Lastly, the use of SPECT (single-photon emission computed tomography imaging) in patients diagnosed by scintigraphy was not recorded in THAOS, raising the possibility of misdiagnosis in some patients.

CONCLUSION

This THAOS analysis of a contemporary, real-world population of patients with mixed-phenotype ATTR-CM showed numerically higher survival rates, lower yearly incidence of CV-related hospitalizations, shorter duration of CV-related hospital stays, and fewer deaths in patients receiving the approved dose of tafamidis compared with untreated patients. These results are directionally aligned with results of ATTR-ACT and parallel previous findings from a real-world cohort of patients with predominantly cardiac ATTR-CM.

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Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/data-and-results for more information.

Declarations

Conflict of Interest. Jonas Wixner reports consulting fees and travel support for lectures and advisory boards from Alnylam and Pfizer and consulting fees from Akcea, AstraZeneca, Bayer and Intellia. Angela Dispenzieri reports research grants from Alnylam, Celgene, Janssen, Millennium, and Pfizer; funding for meeting expenses (travel) from Pfizer; and attending advisory boards for Akcea and Intellia. Leslie Amass, Martin Carlsson, and Steve Riley are employees of Pfizer. Evan Powers receives royalty payments from tafamidis sales. Jeffery W Kelly receives royalty payments from tafamidis sales and reports consulting fees and travel support for lectures from Pfizer and attending advistory boards for Pfizer.

Ethical Approval. All THAOS sites received ethical or institutional review board approval before patient enrollment, and all patients provided written informed consent. The ethics committee that approved the study at the lead author's institution was Regionala etikprövningsnämnden i Umeå. All other committees are listed in Supplementary Table S1. The study followed the Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki.

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