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

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INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the accumulation of misfolded transthyretin (TTR) amyloid fibrils in the extracellular matrix of the heart, leading to progressive heart failure, arrhythmias, and conduction system disease.[1]
- Tafamidis, a selective TTR stabilizer, is the first disease-modifying therapy for the treatment of patients with ATTR-CM and has regulatory approval in over 50 countries worldwide.
  - The approval was based on positive findings from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), a phase 3 study (NCT01994889) conducted from 2013 to 2018 that investigated the efficacy and safety of tafamidis in patients with wild-type (ATTRwt-CM) or hereditary (ATTRv-CM) ATTR-CM.[2]
- The Transthyretin Amyloidosis Outcomes Survey (THAOS) was the largest global, longitudinal, observational study (NCT00628745) of patients with ATTR amyloidosis, including ATTR-CM and transthyretin amyloid polyneuropathy, and asymptomatic carriers of pathogenic *TTR* variants.[3]
- This analysis from THAOS examines real-world survival in a tafamidis-treated and -untreated ATTR-CM population.

METHODS

- Patients from THAOS with a predominantly cardiac phenotype who received any dose of tafamidis at any time during THAOS (tafamidis-treated) or never received tafamidis during THAOS (tafamidis-untreated) were included.
- Survival was analyzed in tafamidis-treated and -untreated patients using the Kaplan–Meier method; sensitivity analyses examined survival in patients with a wild-type or variant *TTR* genotype and in patients enrolled in THAOS before and after 2019.
- Safety data were collected prospectively from tafamidis initiation or enrollment (whichever was later) to the end of the observation period of the study, which must have included ≥28 days after the last administration of tafamidis.
- Results are based on the completed THAOS dataset (data cutoff date: July 24, 2023).

RESULTS

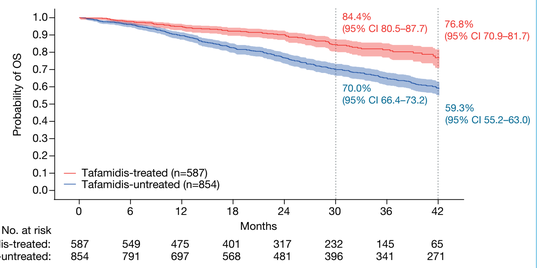
- Of 6718 patients enrolled in THAOS, 1441 patients (tafamidis-treated, n=587; tafamidis-untreated, n=854) from 18 countries had a predominantly cardiac phenotype and were included in this analysis.
- In tafamidis-treated and -untreated patients, respectively, 8.2% and 16.2% had a variant *TTR* genotype; the most common *TTR* variant was V122I (p.V142I), which was identified in 3.6% and 8.1% of patients (**Table 1**).
  - In the respective groups, 21.1% and 26.9% were in New York Heart Association functional class III (**Table 1**).
- In the tafamidis-treated group, 77.5% of patients received tafamidis meglumine 80 mg/free acid 61 mg throughout the study; 8.9% received tafamidis meglumine 20 mg throughout the study; 12.4% initially received tafamidis meglumine 20 mg then switched to tafamidis meglumine 80 mg/free acid 61 mg; and 1.2% received a different dose.
  - Median (10th, 90th percentile) treatment duration was 2.0 (0.6, 3.5) years.
- Median follow-up was 2.2 years for tafamidis-treated patients and 2.3 years for tafamidis-untreated patients (**Table 1**).
- Survival rates at 30 and 42 months, respectively, were 84.4% and 76.8% in tafamidis-treated patients, and 70.0% and 59.3% in tafamidis-untreated patients (**Figure 1**).
  - Survival rates did not differ numerically between patients with ATTRwt-CM and ATTRv-CM among tafamidis-treated (**Figure 2A**) and tafamidis-untreated (**Figure 2B**) patients, although the number of patients with ATTRv-CM was small, especially past Month 12.
  - In patients enrolled in THAOS in 2019 or later, survival rates at 30 and 42 months, respectively, were 87.3% and 82.8% in tafamidis-treated patients, and 77.2% and 67.3% in tafamidis-untreated patients; in those enrolled before 2019, corresponding rates were 77.7% and 66.0% in tafamidis-treated patients, and 68.7% and 58.0% in tafamidis-untreated patients (**Figure 3**).
- All-causality, treatment-emergent adverse events (AEs) occurred in 161 (27.4%) tafamidis-treated patients.
  - No tafamidis-treated patient had a dose reduction due to AEs and 16 (2.7%) had the study drug withdrawn (temporarily, permanently, or delayed) due to AEs.

Table 1: Baseline demographic and clinical characteristics in patients with predominantly cardiac ATTR-CM

	Tafamidis-treated n=587	Tafamidis-untreated n=854	P value
Sex			0.25
Male	539 (91.8)	769 (90.0)	
Female	48 (8.2)	85 (10.0)	
Age at symptom onset, y	72.5 (59.5, 82.5)	72.5 (57.5, 82.5)	0.86
Time from symptom onset to diagnosis, y	1.6 (0.0, 13.0)	1.4 (0.0, 10.7)	0.45
Age at enrollment, y	77.7 (68.0, 85.9)	76.4 (65.2, 85.7)	0.02
Symptom duration at enrollment, y	3.0 (0.4, 13.7)	2.7 (0.3, 11.9)	0.30
Follow-up time, y	2.2 (0.5, 5.3)	2.3 (0.6, 5.7)	0.07
TTR genotype			<0.001
Variant	48 (8.2)	138 (16.2)	
Wild-type	539 (91.8)	716 (83.8)	
Most frequent *TTR* variants[a]			0.01
V122I (p.V142I)	21 (3.6)	69 (8.1)	
V30M (p.V50M)[b]	3 (0.5)	18 (2.1)	
I68L (p.I88L)	5 (0.9)	10 (1.2)	
NYHA functional class			<0.001
I	76 (15.7)	80 (10.4)	
II	305 (63.0)	456 (59.3)	
III	102 (21.1)	207 (26.9)	
IV	1 (0.2)	26 (3.4)	

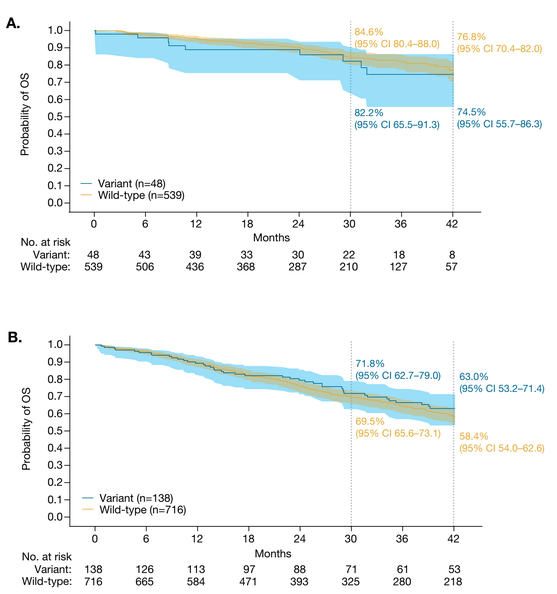
Data are n (%) or median (10th, 90th percentile).
In tafamidis-treated vs -untreated patients, age of symptom onset and symptom duration at enrollment available in 500 vs 783 patients; time from symptom onset to diagnosis available in 495 vs 726 patients; NYHA functional class available in 484 vs 769 patients.
[a] Variants identified in ≥10 patients in either group shown.
[b] With or without G6S (p.G26S).
ATTR-CM=transthyretin amyloid cardiomyopathy; NYHA=New York Heart Association; *TTR*=transthyretin

Figure 1: Kaplan–Meier plot of overall survival in patients with predominantly cardiac ATTR-CM



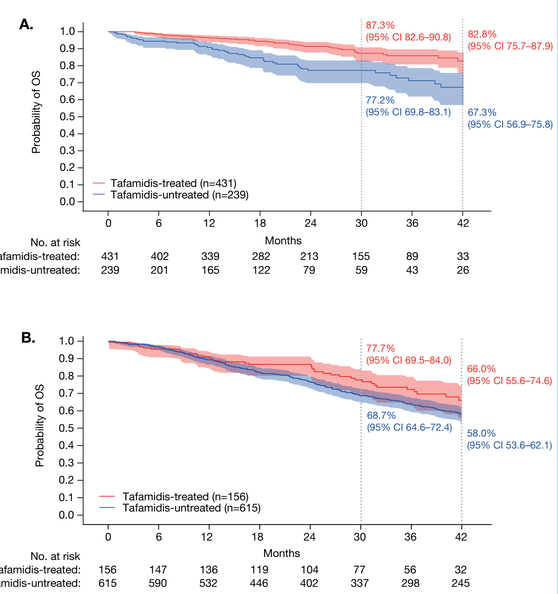
ATTR-CM=transthyretin amyloid cardiomyopathy; OS=overall survival

Figure 2: Kaplan–Meier plot of overall survival in patients with predominantly cardiac ATTR-CM according to *TTR* genotype: (A) tafamidis-treated and (B) tafamidis-untreated



ATTR-CM=transthyretin amyloid cardiomyopathy; OS=overall survival; *TTR*=transthyretin

Figure 3: Kaplan–Meier plot of overall survival in patients with predominantly cardiac ATTR-CM enrolled in THAOS (A) in 2019 or later, or (B) earlier than 2019



ATTR-CM=transthyretin amyloid cardiomyopathy; OS=overall survival; THAOS=Transthyretin Amyloidosis Outcomes Survey

CONCLUSIONS

- In this THAOS analysis, a real-world population of patients with ATTR-CM receiving tafamidis in clinical practice had better survival relative to a group of untreated patients.
- Survival rates in this treated population from THAOS were greater than those previously observed in ATTR-ACT[2] and were consistent with a more recent report,[4] suggesting early diagnosis and treatment with tafamidis improved life expectancy in ATTR-CM.
- These results provide further evidence supporting the safety and effectiveness of tafamidis.

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3. Planté-Bordeneuve V, et al. Curr Med Res Opin 2013;29:77-84. **4.** Ioannou A, et al. Circulation 2022;146:1657-70.

DISCLOSURES

PG-P: Speaker in scientific meetings for Alnylam, BridgeBio, Ionis, Intellia, AstraZeneca, Novo Nordisk, and Pfizer; funding from Alnylam and Pfizer for scientific meeting expenses; consultancy fees from Alnylam, Attralus, BridgeBio, Neuroimmune, AstraZeneca, Novo Nordisk, Alexion, Intellia, and Pfizer; and his institution received research grants/educational support from Alnylam, BridgeBio, AstraZeneca, Novo Nordisk, Intellia, and Pfizer. **AVK:** Research support from and attended advisory boards for Pfizer, Neurimmune, Alnylam, Intellia, Ionis, Akcea, Novo Nordisk, AstraZeneca, and Alexion. **BD:** Consultancy fees from Alnylam and Eidos. **MC, LA, and FSA:** Full-time employees of Pfizer and hold stock and/or stock options in Pfizer. **MSM:** Grant support from NIH R01HL139671 and grants from Pfizer during the conduct of the study; grants and personal fees from Alnylam, Pfizer, BridgeBio, Prothena, and Ionis; and personal fees from AstraZeneca, Ionis, Intellia, and Novo Nordisk.

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