Cardiovascular Morbidity and Mortality Among ATTR-CM Patients Treated with Tafamidis in the US

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Conclusions

- **Patients with ATTR-CM continue to experience disease progression, as evidenced by substantial rates of morbidity and mortality, despite treatment with tafamidis**
- **Over a median duration of ~1-year post-tafamidis initiation, approximately 40% of patients treated for ATTR-CM experienced ≥1 cardiovascular event**
- **Approximately 12% of patients died over the same follow-up period after initiating treatment with tafamidis for ATTR-CM**
- **These findings are consistent with previous observations in a large US electronic health records database and highlight a remaining unmet need for effective treatments for ATTR-CM patients**

Background and Rationale

- Approved in 2019, tafamidis was, until recently, the only United States (US) Food & Drug Administration-approved medication for treating patients with transthyretin mediated amyloidosis with cardiomyopathy (ATTR-CM)[1-3]
- Better characterization of real-world treatment outcomes for patients receiving tafamidis may offer valuable insights into the associated treatment burden and highlight the key areas of unmet therapeutic need in ATTR-CM[4]

Objective

The objective of this analysis was to describe the cardiovascular (CV)-related morbidity and mortality observed in a real-world cohort of patients with ATTR-CM after initiating treatment with tafamidis

Methods

- **Data Source**: This retrospective analysis from January 2019 to May 2024 utilized the Komodo Research Dataset, a comprehensive source of adjudicated medical claims from insured individuals in the US
- **Population:** Patients with ATTR-CM, retrospectively selected by International Classification of Diseases, 10th Revision, Clinical Modification (ICD10-CM) codes, were included in the analysis if they received tafamidis and had at least 6 months of continuous enrollment in the health plan prior to tafamidis treatment initiation
- **Subpopulations:** To reflect the heterogeneity of ATTR, patients were divided into 2 cohorts; those with ATTR-CM only and ATTR-CM patients with ICD-10 codes consistent with polyneuropathy (ATTR-CM + PN)
- **Study Design**: In addition to the pre-index period, patients were followed from tafamidis treatment initiation (index date) to the minimum follow-up end date, defined as the end of continuous enrollment in the health plan, death, or study end date, whichever came first

Statistical Analysis

- Baseline patient demographics, clinical characteristics,pre-/post-tafamidis CV event rates, and post-tafamidis mortality rates were analyzed descriptively
- The post-tafamidis initiation period was calculated as the time between the index date and the minimum follow-up end date
- Due to the variable follow-up period of patients post-tafamidis initiation, CV events and mortality were summarized in terms of incidence per 1,000 person-years as well as in terms of the percentages of patients experiencing these events

Results

Baseline Demographics and Clinical Characteristics

- Among the 2,710 tafamidis-treated ATTR-CM patients included in the analysis, mean (SD) age at tafamidis-initiation was 78.1 years (8.5), 79.7% of patients were male, 32.2% had evidence of polyneuropathy, and 83.1% had Medicare coverage **(Table)**
- During the baseline period (the 6 months prior to index), 654 patients (24.1%) experienced ≥1 CV event

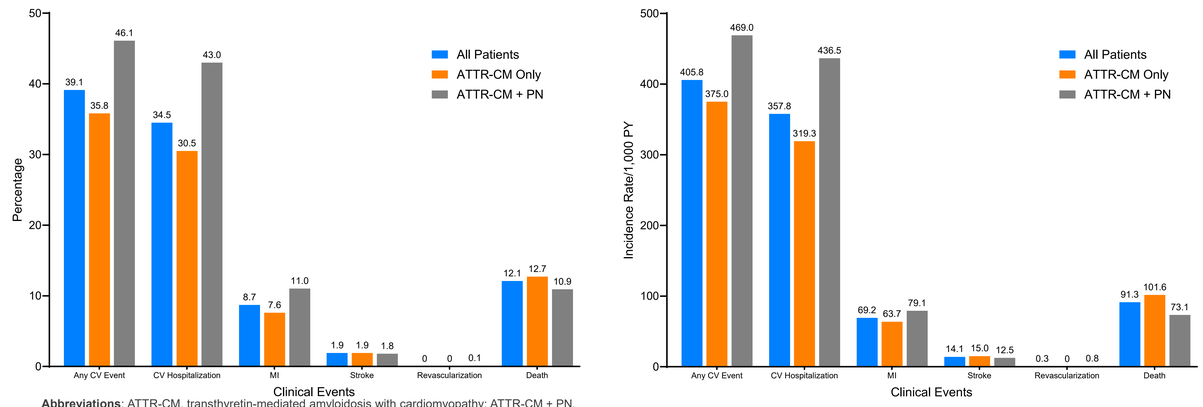
Table. Baseline Demographics and Clinical Characteristics

	All patients N = 2,710	ATTR-CM Only N = 1,838	ATTR-CM + PN N = 872
Age, years, mean (SD)	78.1 (8.5)	78.3 (8.4)	77.6 (8.7)
Age category, years, No. (%)			
18-64	228 (8.4)	149 (8.1)	79 (9.1)
65-74	534 (19.7)	357 (19.4)	177 (20.3)
75-84	1,203 (44.4)	803 (43.7)	400 (45.9)
85-99	745 (27.5)	529 (28.8)	216 (24.8)
Gender, No. (%)			
Female	547 (20.2)	358 (19.5)	189 (21.7)
Male	2,159 (79.7)	1,476 (80.3)	683 (78.3)
Unknown	4 (0.2)	4 (0.2)	0 (0.0)
Year of tafamidis treatment initiation, No. (%)			
2018	1 (0.0)	0 (0.0)	1 (0.1)
2019	338 (12.5)	207 (11.3)	131 (15.0)
2020	340 (12.6)	218 (11.9)	122 (14.0)
2021	391 (14.4)	262 (14.3)	129 (14.8)
2022	541 (20.0)	353 (19.2)	188 (21.6)
2023	821 (30.3)	594 (32.3)	227 (26.0)
2024	278 (10.3)	204 (11.1)	74 (8.5)
Insurance, No. (%)			
Commercial	398 (14.7)	274 (14.9)	124 (14.2)
Medicaid	53 (2.0)	34 (1.9)	19 (2.2)
Medicare	2,253 (83.1)	1,527 (83.1)	726 (83.3)
Missing	6 (0.2)	3 (0.2)	3 (0.3)
Geographic Region			
Northeast	1,177 (43.4)	835 (45.4)	342 (39.2)
Midwest	645 (23.8)	432 (23.5)	213 (24.4)
West	288 (10.6)	179 (9.7)	109 (12.5)
South	598 (22.1)	391 (21.3)	207 (23.7)
Missing	2 (0.1)	1 (0.1)	1 (0.1)
CCI, mean (SD)	4.7 (2.6)	4.6 (2.5)	4.9 (2.8)

Abbreviations: ATTR-CM, transthyretin mediated amyloidosis with cardiomyopathy; ATTR-CM + PN, ATTR-CM with polyneuropathy; CCI, Charlson Comorbidity Index; SD, standard deviation.

- The median duration (range) of follow-up post-tafamidis initiation for all patients was 348 days (0–1,790),† and the mean duration was 485.3 days
- Accounting for treatment discontinuation and censoring, the median (range) duration of tafamidis treatment for all patients was 188 days (0–1,766)

Figure 1. Percentage of ATTR-CM Patients with Clinical Events (left) and the Incidence of Clinical Events per 1,000 Person-Years (right) Post-Tafamidis Initiation

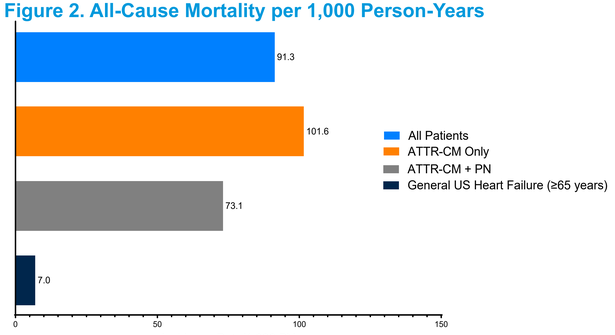


Abbreviations: ATTR-CM, transthyretin-mediated amyloidosis with cardiomyopathy; ATTR-CM + PN, ATTR-CM with polyneuropathy; CV, cardiovascular; MI, myocardial infarction; PY, person-years.

Cardiovascular Events and Mortality

- Post-tafamidis initiation, 1,060 ATTR-CM patients (39.1%) experienced ≥1 CV event **(Figure)**
  - 936 patients (34.5%) had CV-related hospitalizations
  - 235 patients (8.7%) had myocardial infarction
  - 50 patients (1.9%) had stroke
- A total of 329 ATTR-CM patients (12.1%) died post-tafamidis initiation
- The incidence rates of CV events and mortality post-tafamidis initiation were 405.8 and 91.3 per 1,000 person-years, respectively

Figure 2. All-Cause Mortality per 1,000 Person-Years



Discussion

- This retrospective real-world analysis evaluated the CV-related morbidity and all-cause mortality that occurred post-tafamidis initiation in patients with ATTR-CM
  - Observed mortality post-tafamidis initiation was approximately 10x higher than that reported in the US general heart failure population aged ≥65 years (6.98 per 1,000 person-years; **Figure 2**) and ATTR-CM patients continued to experience substantial CV-related morbidity[5]
- Thus, there remains an unmet need for effective treatments that reduce the burden of ATTR-CM

Strengths and Limitations

- Strengths
  - To our knowledge, this is the largest study in a geographically diverse population representing all payor types to evaluate morbidity and mortality rates in ATTR-CM patients receiving tafamidis in real-world settings
- Limitations
  - Coding errors and misdiagnoses could have led to inaccurate reporting of events in the study data set, which may impact the reported rates of these events
  - Generalizability of the findings of this analysis to patient populations outside the Komodo Research Dataset, such as uninsured patients or those outside of the US, is unclear[6]

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References: 1. Porcari et al. Eur J Intern Med 2024;123:29-36 **2**. Chung et al. Sci Rep 2024;14:16261; **3.** FDA approves new treatments for heart disease caused by a serious rare disease, transthyretin mediated amyloidosis. Accessed January 16, 2025, https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatments-heart-disease-caused-serious-rare-disease-transthyretin-mediated; **4.** Ruberg et al. J Am Coll Cardiol 2019;73:2872-91; **5**. Centers for Disease Control and Prevention – Interactive Atlas of Heart Disease and Stroke. Accessed April 23, 2025, https://nccd.cdc.gov/dhdspatlas/reports.aspx; **6.** Komodo Healthcare Mao. Accessed April 23, 2025, https://www.komodohealth.com/solutions/healthcare-map/.

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Abbreviations: ATTR, transthyretin-mediated amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTR-CM + PN, ATTR-CM with polyneuropathy; CCI, Charlson Comorbidity Index; CV, cardiovascular; ICD10-CM, International Classification of Diseases, Tenth Revision-Cinical Modification; PN, polyneuropathy; SD, standard deviation; TTR, transthyretin; US, United States

Footnotes: †, Three patients (2 ATTR-CM and 1 ATTR-CM + PN) initiated tafamidis treatment on the final day of their enrollment, giving a minimum follow-up period of 0 days.