Real-World Outcomes Among Patients Receiving Tafamidis for Transthyretin Amyloidosis With Cardiomyopathy

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OBJECTIVE

- **To characterise and quantify disease outcomes in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) treated with tafamidis in a real-world setting**

BACKGROUND

- ATTR-CM is a progressive and often life-threatening condition[1,2]
- ATTR-CM manifests from unstable TTR tetramers that dissociate into monomers. The monomers misfold and aggregate into toxic amyloid precursors that deposit as insoluble amyloid fibrils in the heart[3]
- ATTR-CM is broadly categorised into the following 2 forms: variant (ATTRv-CM), resulting from an inherited substitution or deletion mutation in the TTR gene, and wild type (ATTRwt-CM), related to factors such as aging or oxidative stress[4,5]
- Until recently, the TTR stabiliser tafamidis was the only approved therapy for ATTR-CM, indicated for the treatment of cardiomyopathy of ATTRwt-CM and ATTRv-CM in adults to reduce cardiovascular mortality and cardiovascular-related hospitalisation (CVH)[6]
- Real-world disease outcomes in tafamidis-treated patients are not thoroughly characterised[7]

METHODS

- We conducted a retrospective observational study of patients with ATTR-CM in the US using the Komodo Healthcare Map® from 1 January 2016 to 30 June 2024 (**Figure 1**, **Figure 2**)

FIGURE 1. Data Sources and Inclusion/Exclusion Criteria (Study Period: 1 January 2016 to 30 June 2024)

Data source

- Non-interventional, retrospective cohort analysis of tafamidis-treated patients with ATTR-CM in the US from the Komodo Healthcare Map® (**Table 1**)
- The Komodo Healthcare Map is comprised of medical and prescription claims data from a number of sources, including clearing houses and switch outlets; it is characterised by proprietary partnership with >150 key national payers and consortiums, representing over 150 million payer complete lives; this database is representative of the US commercial, Medicare, and Medicaid insured populations

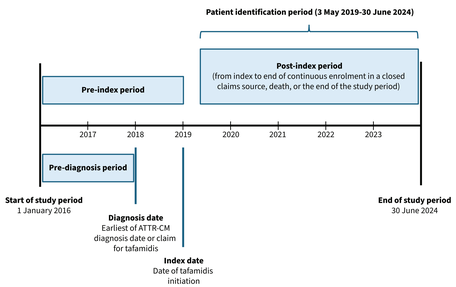
Inclusion criteria

- Two or more claims with an amyloidosis diagnosis code (E85.0, E85.1, E85.2, E85.4, E85.82) occurring on separate days AND ≥2 claims for a cardiac-related ICD-10-CM code OR ≥1 claim for tafamidis based on National Drug Codes
- Were ≥50 years of age on diagnosis date (earlier of ATTR-CM diagnosis or tafamidis claim date)
- Had ≥6 months (182 days) of continuous enrolment before the diagnosis date
- Two or more claims for tafamidis within the patient identification period
- At least 6 months continuous enrolment pre-index date (first tafamidis prescription)
- NT-proBNP or BNP measurement available (90 days pre- or post-index date)

Exclusion criteria

- Two or more claims for multiple myeloma or light chain amyloidosis (E85.81) during the study period
- Received stem cell transplant at any time during the study period

FIGURE 2. Study Schema



- Patients were categorised based on ATTRv-CM or ATTRwt-CM disease and baseline levels of NT-proBNP (measurements taken within 90 days pre- or post-index date) as follows: high (NT-proBNP >3000 pg/mL [or BNP >600 pg/mL if NT-proBNP was not available]) and low (NT-proBNP ≤3000 pg/mL [or BNP ≤600 pg/mL])
- The type of ATTR-CM was determined based on the ATTR-CM diagnosis codes on claims occurring during the identification period
  - To be considered ATTRv-CM, a patient was required to have ≥2 ATTRv-CM codes (on separate days) during the identification period
  - If a patient only had ATTRwt-CM codes and/or <2 ATTRv-CM codes during the identification period, the patient was considered to be ATTRwt-CM
  - If a patient only had 1 tafamidis claim and no relevant ATTR-CM codes during the identification period, then the patient was labeled as 'unknown'
  - If a patient had 1 ATTRv-CM code and no ATTRwt-CM codes (with tafamidis claim), the patient was labeled as 'unknown'
- Outcomes:
  - Baseline demographics and clinical characteristics among patients with ATTR-CM
  - Disease related: described using median time from the index date to first CVH (defined as any inpatient admission with a medical claim for a cardiovascular-related ICD-10-CM diagnosis code in any position) and the occurrence of outpatient worsening heart failure (OWHF) with oral diuretic intensification (defined as an increase in an existing loop diuretic dose or initiation of a newly prescribed loop diuretic)
- Kaplan-Meier estimates assessed time to first CVH, and outcomes were stratified by ATTR-CM type and level of NT-proBNP
- Statistical analyses were descriptive in nature; R statistical software, R version 4.2.1, was used for analytics[8]

CONCLUSIONS

- **CVH: Within the first 6 months of tafamidis treatment, ~1 in 5 patients were hospitalised (overall and in ATTRwt-CM) and ~1 in 3 patients with ATTRv-CM experienced CVH**
- **OWHF: ~1 in 3 tafamidis-treated patients experienced events within the first 12 months**
- **As expected, patients with high NT-proBNP at baseline generally had worse outcomes**
- **As more therapeutic options become available, measuring the clinical effectiveness of therapies for ATTR-CM will be important to help inform treatment decisions**

RESULTS

TABLE 1. Study Attrition

Step	Criteria	n	Percentage of step 1	Percentage of previous step
1	Patients with ≥2 claims with an amyloidosis diagnosis code (E85.0, E85.1, E85.2, E85.4, E85.82) occurring on separate days	128,757	100.0%	
2	Patients with [≥2 claims with an E85 code from code list AND ≥2 claims for a cardiac-related ICD-10-CM code (Appendix A code lists for heart failure and cardiomyopathy)] OR ≥1 claim for tafamidis	75,000	58.2%	58.2%
2a	Patients with ≥2 claims with an amyloidosis diagnosis code (E85.0, E85.1, E85.2, E85.4, E85.82) occurring on separate days AND ≥2 claims for a cardiac-related ICD-10-CM code	70,834	55.0%	94.4%
2b	Patients with ≥1 tafamidis claim	14,742	11.4%	19.7%
3	Patients who were ≥50 years of age on diagnosis date (defined as earlier of ATTR-CM diagnosis date or tafamidis claim date)[a]	72,006	55.9%	96.0%
4	Patients who had ≥6 months of continuous enrolment before the diagnosis date (in both medical and pharmacy)	18,893	14.7%	26.2%
5	Patients without ≥2 claims for multiple myeloma or light chain amyloidosis (E85.81) during the study period	15,142	11.8%	80.1%
6	Patients without evidence of a stem cell transplant during the study period	15,067	11.7%	99.5%
7	Patients who had ≥2 claims for tafamidis within the identification period (first tafamidis date is the index date)	3459	2.7%	23.0%
8	Patients with continuous enrolment ON tafamidis index date and for ≥6 months prior	3239	2.5%	93.6%
9	Patients with NT-proBNP or BNP baseline value available	412	0.3%	12.7%
ATTRv-CM	*Tafamidis-treated patients with ATTRv-CM (≥2 codes for hereditary)*[b]	*56*	*0.0%*	*1.7%*
ATTRwt-CM	*Tafamidis-treated patients with ATTRwt-CM*[b]	*345*	*0.3%*	*10.7%*
Unknown	*Tafamidis-treated patients without an ATTR-CM diagnosis identified*[b]	*11*	*0.0%*	*0.3%*

[a]The database only provides patient year of birth. Therefore, patient age reflects the age the patient will be by the end of the index year. Ages above 89 are masked in the database and recorded as 89. A total of 57 patients had an age recorded as 89.
[b]Type of ATTR-CM was determined based on the ATTR-CM diagnosis codes on claims occurring during the identification period. To be considered ATTRv-CM, a patient was required to have ≥2 ATTRv-CM codes (on separate days) during the identification period. If a patient only had ATTRwt-CM codes and/or <2 ATTRv-CM codes during the identification period, the patient was considered ATTRwt-CM. If a patient only had a tafamidis claim and no relevant ATTR-CM codes during the identification period, then the patient was labeled as 'unknown'. Additionally, if a patient had 1 ATTRv-CM code and 0 ATTRwt-CM codes (with tafamidis claim), the patient was labeled as 'unknown'.

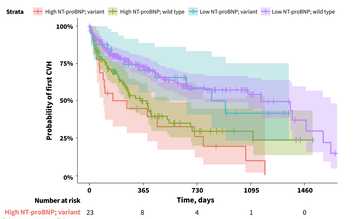
TABLE 2. Baseline Demographics and Clinical Characteristics at the Index Date

Characteristic	Overall[a] (N=412)	ATTRv-CM (n=56)	ATTRwt-CM (n=345)	High NT-proBNP (n=144)	Low NT-proBNP (n=268)
Age, years					
Mean (SD)	77.5 (8.0)	73.1 (8.3)	78.1 (7.8)	79.7 (6.7)	76.3 (8.4)
Median (Q1, Q3)	79.0 (73.0, 84.0)	74.5 (67.5, 79.5)	80.0 (74.0, 84.0)	81.0 (76.0, 85.0)	78.0 (71.0, 83.0)
Min, Max	54.0, 89.0	54.0, 85.0	56.0, 89.0	58.0, 89.0	54.0, 89.0
Age group, years, n (%)					
50-59	12 (2.9)	4 (7.1)	8 (2.3)	2 (1.4)	10 (3.7)
60-69	62 (15.0)	14 (25.0)	48 (13.9)	12 (8.3)	50 (18.7)
70-79	140 (34.0)	24 (42.9)	111 (32.2)	47 (32.6)	93 (34.7)
80+	198 (48.1)	14 (25.0)	178 (51.6)	83 (57.6)	115 (42.9)
Sex, n (%)					
Male	316 (76.7)	38 (67.9)	269 (78.0)	108 (75.0)	208 (77.6)
Female	81 (19.7)	13 (23.2)	67 (19.4)	31 (21.5)	50 (18.7)
Unknown	15 (3.6)	5 (8.9)	9 (2.6)	5 (3.5)	10 (3.7)
Race/Ethnicity, n (%)					
White	257 (62.4)	21 (37.5)	227 (65.8)	81 (56.3)	176 (65.7)
Black or African American	118 (28.6)	31 (55.4)	86 (24.9)	55 (38.2)	63 (23.5)
Asian or Pacific Islander	4 (1.0)	0	4 (1.2)	2 (1.4)	2 (0.8)
Hispanic or Latino	13 (3.2)	2 (3.6)	11 (3.2)	3 (2.1)	10 (3.7)
Other	14 (3.4)	1 (1.8)	12 (3.5)	2 (1.4)	12 (4.5)
Missing/Unknown	6 (1.5)	1 (0.7)	5 (1.5)	1 (0.7)	5 (1.9)
Type of ATTR-CM, n (%)					
Wild type (ATTRwt-CM)	345 (83.7)	N/A	345 (100)	118 (81.9)	227 (84.7)
Variant (ATTRv-CM)	56 (13.6)	56 (100)	N/A	23 (16.0)	33 (12.3)
Unknown	11 (2.7)	N/A	N/A	3 (2.1)	8 (3.0)
NT-proBNP/BNP levels, n (%)					
High (NT-proBNP >3000 pg/mL or BNP >600 pg/mL)	144 (35.0)	23 (41.1)	118 (34.2)	144 (100)	N/A
Low (NT-proBNP ≤3000 pg/mL or BNP ≤600 pg/mL)	268 (65.0)	33 (58.9)	227 (65.8)	N/A	268 (100)

[a]ATTRv-CM and ATTRwt-CM do not add up to the overall population, as some patient's ATTR-CM type is unknown (n=11).

- We identified 412 tafamidis-treated patients (**Table 1**) with a mean age of 77.5 years, 76.7% male, 62.4% White, 28.6% Black, 13.6% had ATTRv-CM, and 83.7% had ATTRwt-CM (**Table 2**)
- Among tafamidis-treated patients, 23.1% and 30.1% of patients had a CVH within 6 and 12 months of tafamidis initiation, respectively (**Table 3**)
- Variation in time to first CVH was observed by ATTR-CM type and NT-proBNP (**Figure 3**)
  - Time to first CVH was longer for patients with low versus high NT-proBNP, independent of type of ATTR-CM
    - Median time (95% CI) to first CVH was 1169 days (830-1639) for low NT-proBNP and 347 days (251-467) for high NT-proBNP groups
  - The longest time to first CVH was observed for patients with both ATTRwt-CM and low NT-proBNP; the shortest time to first CVH was observed for patients with both ATTRv-CM and high NT-proBNP
- Overall, 35.9% of patients had OWHF within 12 months of initiating tafamidis (**Table 4**)

FIGURE 3. Time to First CVH



High, NT-proBNP >3000 pg/mL (or BNP >600 pg/mL if NT-proBNP was not available); Low, NT-proBNP ≤3000 pg/mL (or BNP ≤600 pg/mL if NT-proBNP was not available).

TABLE 3. Summary of CVH After Tafamidis Initiation

Parameter	Overall (N=412)	ATTRv-CM (n=56)	ATTRwt-CM (n=345)	High NT-proBNP (n=144)	Low NT-proBNP (n=268)
Any CVH within 6 months, n (%)	95 (23.1)	17 (30.4)	76 (22.0)	46 (31.9)	49 (18.3)
Any CVH within 12 months, n (%)	124 (30.1)	21 (37.5)	101 (29.3)	61 (42.4)	63 (23.5)
Median (95% CI) time to first CVH, days	699 (524-1112)	659 (337-1193)	688 (524-1377)	347 (251-461)	1169 (830-1639)

TABLE 4. Summary of OWHF With Oral Diuretic Intensification After Tafamidis Initiation[a]

Parameter	Overall (N=412)	ATTRv-CM (n=56)	ATTRwt-CM (n=345)	High NT-proBNP (n=144)	Low NT-proBNP (n=268)
Any OWHF event within 6 months, n (%)	117 (28.4)	19 (33.9)	95 (27.5)	54 (37.5)	63 (23.5)
Any OWHF event within 12 months, n (%)	148 (35.9)	24 (42.9)	120 (34.8)	70 (48.6)	78 (29.1)
Median (95% CI) time to OWHF event, days	617 (463-870)	456 (204-N/A)	631 (463-907)	262 (190-447)	827 (631-1089)

[a]For patients with no prior loop diuretic use, an OWHF event was defined as any newly prescribed loop diuretic. For patients who were using loop diuretics in the pre-index period, an OWHF event was defined as any increase in dose. For patients with loop diuretic use during the pre-index period, the dose closest to the index date during the pre-index period was the reference dose and used to define the increase in subsequent dose.

LIMITATIONS

- Patients may have multiple insurers or receive tafamidis through patient assistance programs, resulting in tafamidis-treated patients who may have been misclassified as untreated and therefore not included in this analysis
- Only a small proportion of all tafamidis-treated patients had laboratory data available, thus limiting sample size and generalisability
- An ICD-10-CM coding algorithm was used to classify patients into ATTRwt-CM or ATTRv-CM, which may have resulted in misclassification bias

DATA AVAILABILITY: The data that support the findings of this study were used under license from Komodo Health® and derived from the Komodo Healthcare Map®. Due to data use agreements and its proprietary nature, restrictions apply regarding the availability of the data. Further information is available from the sponsor of the study, BridgeBio Pharma, Inc., San Francisco, CA, USA.

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; BNP, B-type natriuretic peptide; CVH, cardiovascular-related hospitalisation; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; Max, maximum; Min, minimum; N/A, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; OWHF, outpatient worsening heart failure; Q1, first quartile; Q3, third quartile; SD, standard deviation; TTR, transthyretin; US, United States.

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