Descriptive Analysis of Unmet Need in a Contemporary Cohort of Tafamidis-Treated Patients with ATTR-CM

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Conclusions

- **Patients treated with tafamidis for ATTR-CM continue to experience cardiac worsening as evidenced by worsening NT-proBNP and eGFR, and substantial rates of new diuretic initiation, CV hospitalizations and death**
- **There remains an unmet need for effective treatments that address disease progression and subsequently reduce excess morbidity and mortality in ATTR-CM**

Background

- ATTR amyloidosis is a multi-systemic, progressive and debilitating disease caused by the deposition of misfolded TTR protein as amyloid in various organs of the body[1]
- In ATTR-CM, TTR-derived amyloid accumulates in the heart, leading to progressive loss of cardiac function and, ultimately, heart failure
- ATTR-CM is associated with substantial chronic morbidity and early mortality
- Tafamidis, a TTR stabilizer, is currently the only approved treatment for ATTR-CM in many geographies including the United States

Objective

- To describe the remaining unmet need with regard to morbidity and mortality in a large population of ATTR-CM patients treated with tafamidis in contemporary real-world practice.

Methods

- This real-world retrospective, observational cohort study utilized secondary, de-identified U.S. patient-level data from Optum's EHR database, from May 1, 2018 to October 31, 2022
- Adult patients meeting criteria for an ATTR-CM diagnosis together with concurrent or subsequent evidence of tafamidis treatment were included in the study. The study periods are described below.
  – Index date: First day on which the patient initiates tafamidis treatment, on or after 1 May 2018
  – Baseline period: 365 days prior to index date - 1 day prior to index date
  – Follow-up period: Index date - censoring at occurrence of clinical events of interest (cardiac worsening unless otherwise noted)

- Parameters evaluated in these patients were as follows
  – Demographic and clinical characteristics over the baseline period (365 days to 1 day prior to index date)
  – Changes in laboratory parameters during post-index follow-up relative to baseline (for each parameter of interest, mean change was calculated as the average [across all patients] of the per-patient mean of all follow-up measurements taken within 365 days post-index minus the patient's baseline measurement)
  – Use of CV therapeutics and diuretics during the post-index follow-up period
  – Incidence rates for CV hospitalizations and all-cause mortality over the post-index follow-up period
  – The percentage of patients experiencing cardiac worsening* and the incidence of cardiac worsening during the follow-up period

Results

Cohort overview

- 4,989 patients met the criteria for ATTR-CM of whom 813 (16.3%) who initiated tafamidis had evidence of tafamidis use in the follow-up period
- Patients more often entered the study cohort in 2019 (34.3%) than in any other year, consistent with timing of FDA approval of tafamidis for treatment of ATTR-CM[2]

Baseline period

- Baseline demographic characteristics of the tafamidis-treated ATTR-CM patient cohort was in-line with those of other real-world studies of ATTR-CM patient cohorts[3,4,5,6]
- Patients were predominantly elderly adults (mean age of 77.8 years); 81.2% were male, 26.2% were African American and approximately two-thirds were Caucasian
- Among patients for whom data on NYHA class was available, more than half were in NYHA class I or II
- Baseline period disease characteristics are summarized in Table 1

Table 1. Clinical and Laboratory Parameters during the Baseline Period

Baseline characteristics	Parameters
Clinical Parameters	
Signs/symptoms; n (%)	
Dyspnea	646 (79.5%)
Syncope	256 (31.5%)
Comorbid conditions; n (%)	
Obesity	148 (18.2%)
Hypertension	636 (78.2%)
New York Heart Association (NYHA) classification; n (%)	
Data available	225 (27.7%)
Class I	18 (8%)
Class II	101 (44.9%)
Class III	91 (40.4%)
Class IV	15 (6.7%)
History of cardiac events during the baseline period; n (%)	
Any cardiac event	382 (47%)
Myocardial infarction	199 (24.5%)
CVD hospitalization	292 (35.9%)
Laboratory Parameters	
NT-proBNP	
Data available; n (%)	302 (37.1%)
Value (pg/mL); Median [IQR]	3,068 [1340, 5443]
eGFR	
Data available; n (%)	685 (84.3%)
Value (mL/min/1.73m²); median [IQR]	64.7 [45.8, 79.4]

Follow-up period (after tafamidis initiation)

- Median (IQR) duration of follow-up was 354 (168 – 577) days
- A total of 153 (18.82%) patients (excluding those who died during the follow-up period) discontinued tafamidis

- 108/461 (23.4%) patients who did not have a history of diuretic use during the baseline period initiated diuretics during the follow-up period (considered as outpatient heart failure worsening**)
- 60 (7.5%) patients initiated treatment with other CV therapeutics during the follow-up period
- Among patients with available data, mean change from baseline through one year of follow-up in key laboratory parameters was as follows:
  – NT-proBNP: Increase of 1,612pg/mL (n=175 with available data); 106/175 (61%) experienced a worsening (any increase) from baseline
  – eGFR: Decrease of 4.5mL/min/1.73m² (n=577 with available data); 357/577 (62%) experienced a worsening (any decrease) from baseline
- Follow-up period clinical event rates are outlined in Table 2

Table 2. Clinical event rates during follow-up period

Outcome	Event N	Cumulative follow-up (person-years)	Rate per 1,000 person years (95% CI)
Cardiac worsening†	428	539.08	793.9 (718.7, 869.2)
Death	58	915.05	63.4 (47.1, 79.7)
CVD-related hospitalization†	294	702.44	418.5 (370.7, 466.4)

†For the purposes of the analysis, patients were censored after first occurrence of the outcome during follow-up

- The mortality rate observed in this cohort was approximately 10x higher than in the U.S general heart failure population aged 65+ years (6.68 per 1,000 person years)[7]

*Defined as the occurrence of any of the following events: MI, DVT, PE, stroke, NYHA Class change to a more severe class from baseline, ACC/AHA Heart Failure Stage change to a more severe stage from baseline, CVD-related hospitalization, aortic valve replacement, aortic stenosis, revascularization, arrhythmia, or progression in ATTR staging relative to baseline
**Not considered in our definition of cardiac worsening

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