# Likelihood of Disease Worsening in Patients Receiving Tafamidis for ATTR Amyloidosis With Cardiomyopathy (ATTR-CM): A Targeted Literature Review

Emre Aldinc[1], Steven Roblin[1], David Danese[1]

1. Alnylam Pharmaceuticals, Inc., Cambridge, MA, USA

ISPOR Acceptance Code

SA30

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## Background

- ATTR amyloidosis is a progressive, debilitating disease caused by deposition of misfolded TTR protein as amyloid in various organs[1]
- In ATTR-CM, TTR-derived amyloid accumulates in the heart, leading to progressive heart failure and conduction disorders
- ATTR-CM is associated with substantial morbidity, including impairment of physical function and quality of life, increased occurrence of CV events, and early mortality
- Tafamidis, a TTR stabilizer, is currently the only approved treatment for ATTR-CM in many geographies, including Europe and the United States

## Objective

- To clarify the existing unmet therapeutic need in ATTR-CM by synthesizing published data on the clinical course of patients treated with tafamidis for ATTR-CM

## Methods

- A targeted literature review was conducted to describe the clinical course of patients receiving tafamidis for the treatment of ATTR-CM, with a focus on patient-level (as opposed to cohort-level) outcomes

## Methods (cont'd)

- The literature review was performed according to a four-step process
  - Step 1: Literature search
    - The PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was queried for publications that 1) contained the term "tafamidis" in any search field and 2) were published between Jan 2018 and Mar 2024
  - Step 2: Abstract screening
    - For all records retrieved from PubMed, abstracts were reviewed to preliminarily assess relevance to the research objective
  - Step 3: Full-text review
    - For all publications identified as possibly relevant via abstract screening, the full text of the publication was comprehensively reviewed to definitively assess its relevance to the research question of interest
  - Step 4: Data extraction
    - For all publications determined to be relevant to the research question of interest based on full-text review, data were extracted regarding 1) the definition of the study cohort reported on in the publication; 2) the duration of follow-up; 3) the outcomes reported; and 4) the percentages of patients in the study cohort who experienced these outcomes during follow-up
- Upon completion of the literature review, the extracted data were summarized descriptively in tabular format

## Results

- The initial PubMed search yielded 391 records for abstract screening; of these, 60 advanced to full-text screening, and 16 advanced to data extraction **(Figure)**
  - In abstract and full-text screening, publications were typically excluded because they were not primary research publications (e.g., editorials), did not report on relevant disease outcomes (e.g., preclinical studies), or reported only cohort-level mean results (vs. patient-level results) for relevant disease outcomes
- Studies included in the review varied widely in terms of sample size, duration of follow-up, and outcomes assessed
  - Among the included studies, cohort sizes ranged from a minimum of 8 to a maximum of 484
  - Reported follow-up duration ranged from 6 to 30 months, although the summary metric for follow-up duration varied across studies, with some reporting mean or median follow-up duration and others reporting a fixed follow-up duration for all patients
  - The outcomes assessed included 1) changes in biomarkers and/or other surrogate endpoints known or thought to predict future morbidity or mortality; 2) the direct occurrence of clinical morbidity (clinical events, hospitalizations); 3) the direct occurrence of mortality; or 4) composites thereof
- Findings from the studies included in the review are presented in **Table 1**, **Table 2**, **Table 3**, and **Table 4**, respectively.

**Figure.** Flow diagram of targeted literature review

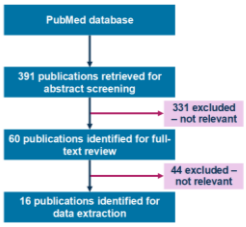


**Table 1**

Summary of patient-level outcomes regarding changes in biomarkers and other intermediate / surrogate endpoints in patients treated with tafamidis for ATTR-CM

| Authors | Patient Population | *N* | Follow-up Duration | Outcome | % of Patients With Outcome |
|---|---|---|---|---|---|
| Badr Eslam et al.[2] | Patients receiving tafamidis at a single Austrian center | 54 | Mean (SD): 9.5 (5.1) mos | Decline in peak $VO_2$ from baseline | 46.3% |
| Nakaya et al.[3] | Patients receiving tafamidis at a single Japanese center | 8 | 12 mos | At least 1-unit worsening in Clinical Frailty Score from baseline | 87.5% |
| Nakamura et al.[4] | Patients receiving tafamidis at a single Japanese center | 18 | Median (IQR): 14 (6.3 – 22) mos | Increase in troponin levels from baseline (as measured at 1-12 mos from baseline) | 27.8% |
| Oghina et al.[5] | Patients receiving tafamidis at a single French center | 248 | Median (IQR): 17.5 (10.9 – 18.2) mos | NT-proBNP >3000 ng/L (or died) at 6, 12, and 18 mos, respectively | 37.7%/45.1%/44.8% (vs. 32.3% at baseline) |
| | | | | hs-cTnT >50 ng/L (or died) at 6, 12, and 18 mos, respectively | 55.9%/67.3%/57.5% (vs. 53.8% at baseline) |
| Hanna et al.[6] | Patients randomized to tafamidis in a phase 3 clinical trial | 264 | 30 mos | Decrease (any amount) in 6-MWT distance | ~68% |
| | | | | Increase (any amount) in NT-proBNP level | ~62% |

**Table 2**

Summary of findings regarding percentage of patients experiencing clinical morbidity among those treated with tafamidis for ATTR-CM

| Authors | Patient Population | *N* | Follow-up Duration | Outcome | % of Patients With Outcome |
|---|---|---|---|---|---|
| Chamling et al.[7] | Patients receiving tafamidis at a single German center | 20 | 12 ± 3 mos | NYHA class worsening by ≥1 class from baseline | 10% |
| Dalia et al.[8] | Patients receiving tafamidis at a single US center | 33 | 1 yr | Any HF hospitalization | 30.3% |
| Ghoneem et al.[9] | US patients receiving tafamidis | 421 | 12 mos | Any hospitalization | 27.8% |
| Kim et al.[10] | Patients receiving tafamidis at a single US center | 79 | Median (range): 1.3 (0.7 – 2.2) yrs | Any HF hospitalization | 27.8% |
| Ochi et al.[11] | Patients receiving tafamidis at a single Japanese center | 38 | Median (IQR): 16.4 (9.6 – 23.2) mos | Any CV hospitalization | 18.4% |
| Takashio et al.[12] | Patients receiving tafamidis at a single Japanese center | 125 | Median (IQR): 21 (10 – 31) mos | Any HF hospitalization | 17% |

**Table 3**

Summary of findings regarding percentage of patients dying among those treated with tafamidis for ATTR-CM

| Authors | Patient Population | *N* | Follow-up Duration | Outcome | % of Patients With Outcome |
|---|---|---|---|---|---|
| Bampatsias et al.[13] | Patients receiving tafamidis at a single Greek center | 65 | Median: 36 mos | Death by 1 year / 2 years | 13% / 17% |
| Dalia et al.[8] | Patients receiving tafamidis at a single US center | 33 | 1 yr | Death | 24.2% |
| Ghoneem et al.[9] | US patients receiving tafamidis | 421 | 12 mos | Death | 10.7% |
| Kim et al.[10] | Patients receiving tafamidis at a single US center | 79 | Median (range): 1.3 (0.7 – 2.2) yrs | Death | 11.4% |
| Ochi et al.[11] | Patients receiving tafamidis at a single Japanese center | 38 | Median (IQR): 16.4 (9.6 – 23.2) mos | Death | 7.9% |
| Oghina et al.[5] | Patients receiving tafamidis at a single French center | 248 | Median (IQR): 17.5 (10.9 – 18.2) mos | Death | 10.9% |
| Sarkar et al.[14] | Patients receiving tafamidis at 1 of 2 US centers | 484 | Median (IQR): 18.5 (10.6 – 29.8) mos | Death by 1 year / 2 years | 5.3% - 6.8% / 14.0% - 15.2% |
| Takashio et al.[12] | Patients receiving tafamidis at a single Japanese center | 125 | Median (IQR): 21 (10 – 31) mos | Death | 8% |

**Table 4**

Summary of findings regarding percentage of patients experiencing composite outcomes among those treated with tafamidis for ATTR-CM

| Authors | Patient Population | *N* | Follow-up Duration | Outcome | % of Patients With Outcome |
|---|---|---|---|---|---|
| aus dem Siepen et al.[15] | Patients receiving tafamidis at a single German center | 293 | 1 year | Worsening of ≥1 clinical/functional endpoint AND ≥1 lab marker AND ≥1 imaging/EKG parameter, per Garcia-Pavia criteria[16] | 9%<br>38% and 33% with worsening in 1 and 2 domains, respectively |
| Ben Zadok et al.[17] | Patients receiving tafamidis at a single Israeli center | 14 | 18 mos | Worsening of ≥1 clinical/functional endpoint AND ≥1 lab marker AND ≥1 imaging/EKG parameter, per Garcia-Pavia criteria[16] | 7.1%<br>14.3% and 0% with worsening in 1 and 2 domains, respectively |
| Kim et al.[10] | Patients receiving tafamidis at a single US center | 79 | Median (range): 1.3 (0.7 – 2.2) yrs | Death, HF hospitalization, MI, or stroke | 30.4% |
| Ney et al.[18] | Patients receiving tafamidis at a single German center | 62 | 6 mos | Worsening of ≥1 clinical/functional endpoint AND ≥1 lab marker AND ≥1 imaging/EKG parameter, per Garcia-Pavia criteria[16] | 0%<br>35.5% and 29.0% with worsening in 1 and 2 domains, respectively |

## Conclusions

- **While tafamidis has been shown in clinical trials to provide benefits for patients with ATTR-CM, there is a continuing unmet need for additional therapeutic options, as a review of published literature shows that some patients treated with tafamidis continue to experience worsening from pre-treatment baseline in biomarkers and intermediate/surrogate endpoints, clinical morbidity, and death.**
- Limitations of this review include small cohort sizes in some included studies, potentially leading to imprecise estimation of the percentage of patients experiencing a given outcome, as well the possibility of missing results due to publication bias and due to the exclusion of non-English-language publications

•Disclosures: EA, SR, and DD are employees of Alnylam Pharmaceuticals Inc. and own equity in Alnylam Pharmaceuticals Inc.
•Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTR-CM, ATTR amyloidosis with cardiomyopathy; CV, cardiovascular; EKG, electrocardiogram; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PGA, patient global assessment; SD, standard deviation; $VO_2$, oxygen consumption
•References: 1. Benson MD, Kincaid JC. *Muscle Nerve*. 2007;36(4):411-423. 2. • Badr Eslam R, et al. *Circ Heart Fail*. 2022;15:e008381. 3. Nakaya Y, et al. *Int Heart J*. 2023;64(4):647-653. 4. Nakamura M, et al. *J Clin Med*. 2023;12(14):4631. 5. Oghina S, et al. *J Clin Med*. 2021;10(21):4868. 6. Hanna M, et al. *JACC Adv*. 2022;1(5):100148. 7. Chamling B, et al. *Clin Res Cardiol*. 2023;112:353-362. 8. Dalia T, et al. *J Card Fail*. 2021;27(11):1285-1289. 9. Ghoneem A, et al. *Curr Probl Cardiol*. 2023;48(6):101667. 10. Kim M, et al. *J Am Heart Assoc*. 2023;12(15):e029705. 11. Ochi Y, et al. *Circ J*. 2022;86(7):1121-1128. 12. Takashio S, et al. *ESC Heart Fail*. 2023;10(4):2319-2329. 13. Bampatsias D, et al. *Hellenic J Cardiol*. 2023:S1109-9666(23)00190-2. 14. Sarkar A, et al. *Am J Cardiol*. 2024 Mar 1;214:144-148. 15. aus dem Siepen F, et al. *Amyloid*. 2024 Jul 17:1-6. 16. Garcia-Pavia P, et al. Eur J Heart Fail. 2021 Jun;23(6):895-905. 17. Ben Zadok O, et al. *Acta Cardiol*. 2023;78(4):417-422. 18. Ney S, et al. *J Clin Med*. 2024;13(1):284.