JACC: ADVANCES VOL. 1, NO. 5, 2022

ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Improvements in Efficacy Measures With Tafamidis in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial

Mazen Hanna, MD,[a] Nowell M. Fine, MD,[b] Balarama Gundapaneni, MS,[c] Marla B. Sultan, MD,[d] Ronald M. Witteles, MD[e]

ABSTRACT

BACKGROUND Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal disease. Tafamidis was approved to treat patients with ATTR-CM based on findings from the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial).

OBJECTIVES This post hoc analysis examined the proportion of patients who experienced improved efficacy measures through 30 months of treatment with tafamidis or placebo in ATTR-ACT.

METHODS Patients with ATTR-CM were randomized to tafamidis (80 mg or 20 mg) or placebo. Change from baseline in 6-minute walk test distance, Kansas City Cardiomyopathy Questionnaire Overall Summary score, N-terminal pro-B-type natriuretic peptide concentration, patient global assessment of overall health, and New York Heart Association functional class were assessed at regular time points. The proportion of patients with improvement was summarized for each time point with odds ratio. Missing data were imputed as deterioration.

RESULTS Higher proportions of tafamidis-treated patients (n = 264) than placebo-treated patients (n = 177) showed improvement in all assessments. The odds ratio for improvement favored tafamidis for all measures and at all time points. It was significant ($P < 0.001$) at month 30 for 6-minute walk test distance (4.9; 95% CI: 2.28-10.69), Kansas City Cardiomyopathy Questionnaire Overall Summary score (3.3; 95% CI: 1.85-5.78), N-terminal pro-B-type natriuretic peptide concentration (5.3; 95% CI: 2.66-10.73), and patient global assessment of overall health (2.9; 95% CI: 1.69-4.95).

CONCLUSIONS This analysis found that higher proportions of patients treated with tafamidis experienced improvement from baseline in measures of heart failure, functional capacity, and health-related quality of life than those treated with placebo during ATTR-ACT. These data provide further evidence of the clinical benefits of tafamidis in patients with ATTR-CM. (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy [ATTR-ACT]; NCT01994889) (JACC Adv 2022;1:100148) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Cleveland Clinic, Cleveland, Ohio, USA; [b]University of Calgary, Calgary, Alberta, Canada; [c]Pfizer Inc, Groton, Connecticut, USA; [d]Pfizer Inc, New York, New York, USA; and the [e]Stanford University School of Medicine, Stanford, California, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 14, 2022; revised manuscript received September 16, 2022, accepted October 4, 2022.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2022.100148

ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walk test

ATTR-CM = transthyretin amyloid cardiomyopathy

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

PGA = patient global assessment

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal condition caused by the accumulation of misfolded transthyretin protein (TTR) in the myocardium. The 2 forms of ATTR-CM are hereditary (from gene variants) or wild-type (idiopathic).[1,2] It is most commonly diagnosed in older adults, where the buildup of amyloid over time causes progressive cardiomyopathy and eventually leads to heart failure.[1,2]

The clinical course of ATTR-CM varies based on factors such as genotype and clinical condition at diagnosis, but current untreated median survival expectations are approximately 2 to 5 years from diagnosis.[3,4] During this time, patients with ATTR-CM experience declining health and quality of life.[1,3,4] ATTR-CM is currently considered a rare disease, but the incidence is increasing, largely due to improvements in clinical awareness and diagnosis.[1,5]

Tafamidis is a kinetic stabilizer that inhibits the dissociation of the TTR protein tetramer. It reduces the amount of unstable TTR monomer available to misfold and deposit in various organs as amyloid. The ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) was an international, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of tafamidis in patients with ATTR-CM.[6] The primary outcomes of ATTR-ACT showed that tafamidis significantly reduced mortality (hazard ratio: 0.70; 95% CI: 0.51-0.96) and cardiovascular-related hospitalizations (relative risk ratio: 0.68; 95% CI: 0.56-0.81) compared with placebo over the 30-month study duration.[6] Although both tafamidis- and placebo-treated patients showed progressively declining health, at month 30, patients treated with tafamidis had a better overall 6-minute walk test (6MWT) distance, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, patient global assessment (PGA) of overall health score, and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score than those treated with placebo.[6-8] These findings demonstrated the ability of tafamidis to reduce the progression of ATTR-CM and led to its approval for use in the clinic.[9,10]

In a previously published post hoc outcome from ATTR-ACT, improvements in patient-reported quality of life (as assessed by KCCQ-OS and including no change) and overall health (as assessed by PGA) were observed in a larger proportion of tafamidis-treated patients than in placebo-treated patients.[8] These improvements are notable as ATTR-CM is known to be progressive and fatal. The aim of this post hoc analysis was to characterize the proportions of patients who demonstrate improvement in a range of efficacy measures assessed in the ATTR-ACT.

METHODS

ATTR-ACT was approved by the independent review board or ethics committee at each site. It was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All participants gave written informed consent.

TRIAL DESIGN AND PATIENTS. ATTR-ACT (NCT01994889) was an international, multicenter, phase 3, randomized, double-blind, placebo-controlled clinical trial of tafamidis (80 mg and 20 mg). The protocol and primary outcomes of this completed trial have been previously published.[6,11]

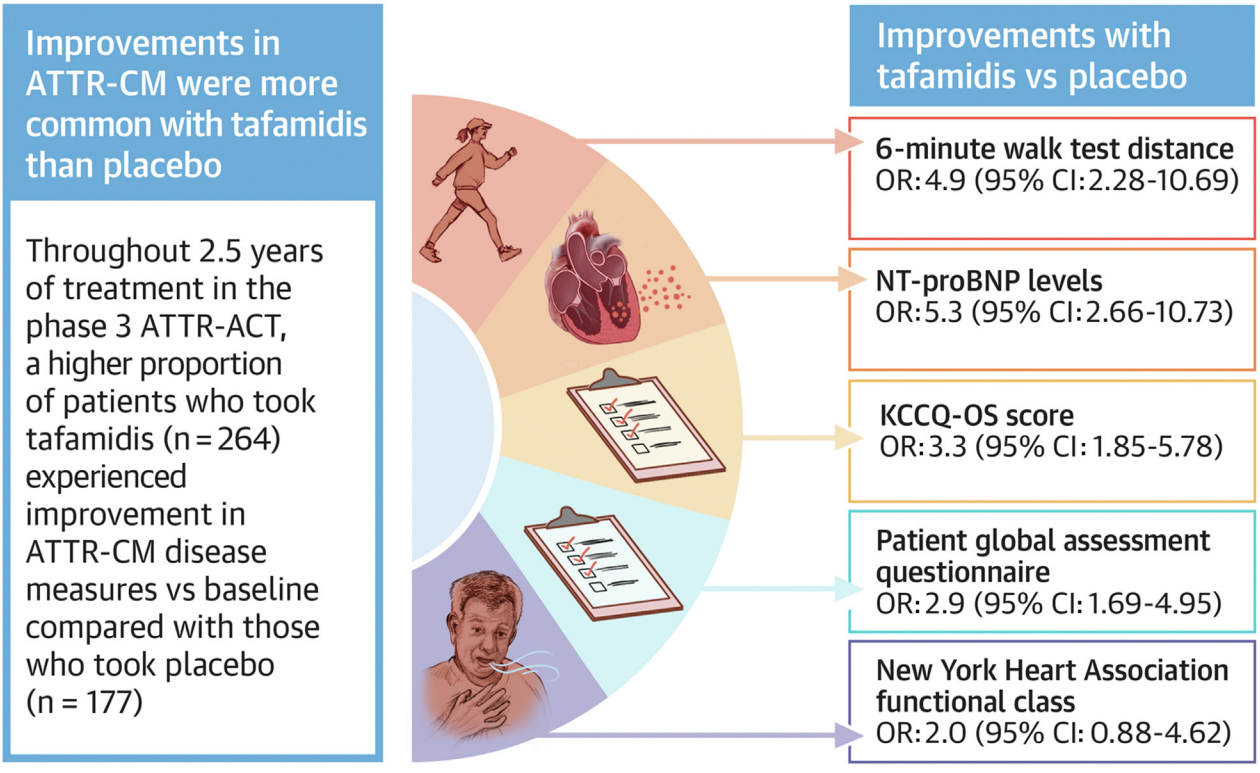
The trial enrolled patients (18-90 years of age) with ATTR-CM, as defined by the presence of either hereditary or wild-type transthyretin amyloidosis and a medical history of heart failure. Patients were required to have a 6MWT distance of >100 m, an NT-proBNP concentration of ≥600 pg/mL, and a New York Heart Association (NYHA) functional classification of class I to III.

Patients were randomized (2:1:2) to receive daily oral tafamidis (80 mg or 20 mg) or matching placebo for 30 months. Stratification was based on hereditary or wild-type transthyretin amyloidosis status and NYHA class. During the trial, patients receiving 80 mg of tafamidis who experienced an adverse event that might have been related to the treatment and might affect their ability to continue were allowed to reduce their dose to 40 mg. Data for both doses of tafamidis were pooled for the primary ATTR-ACT outcomes and in this post hoc analysis.

Patients discontinued from the ATTR-ACT for several reasons, including death, being unwilling to continue in the trial, poor tolerability or adverse events, plans to undergo organ transplantation or implantation of a cardiac mechanical assist device, and protocol violations. Vital status was confirmed at month 30 for all patients who received study treatment of any duration.

CLINICAL EVALUATIONS AND STATISTICAL ANALYSES. This post hoc analysis describes patients with

CENTRAL ILLUSTRATION **Improvements in Efficacy Measures Observed With Tafamidis in ATTR-ACT**



Hanna M, et al. JACC Adv. 2022;1(5):100148.

ATTR-ACT = Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM = transthyretin amyloid cardiomyopathy; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

improved efficacy measures compared with baseline in the pooled tafamidis (80 mg and 20 mg) and placebo cohorts at all available time points throughout the ATTR-ACT. Efficacy measures were 6MWT distance, KCCQ-OS score (on a 0-100 scale, where 0 = severe symptoms or limitations and 100 = no symptoms or limitations and excellent quality of life),[12] NT-proBNP concentration, PGA of overall health (categories: "very much improved," "much improved," "minimally improved," "no change from baseline," "minimally worse," "much worse," "very much worse"), and NYHA functional class (I-IV)[13] summarized at all available time points for the pooled tafamidis and placebo cohorts. The 6MWT, KCCQ-OS, PGA, and NYHA assessments were conducted at baseline and every 6 months over the duration of ATTR-ACT. The NT-proBNP concentration was assessed at baseline, month 12, and month 30. Improvement was defined at each assessment as a change from baseline of >0 for 6MWT distance and KCCQ-OS score; <0 for NT-proBNP concentration; a lower NYHA class relative to baseline; or improvement reported in the PGA (Supplemental Table 1).

This post hoc analysis included all patients who received treatment and were evaluated for ≥1 post baseline efficacy evaluation. Outcomes were the proportion of patients with improvement and the OR for improvement (tafamidis vs placebo) with 95% CI and *P* value. Missing data were imputed as not improved, but separate analyses of observed data (without imputation) are provided.

RESULTS

A summary of our findings is presented in the **Central Illustration**. A plain language summary of this study is included in Supplemental Figure 1.

TABLE 1 Efficacy Measures at Baseline

	Pooled Tafamidis (n = 264)	Placebo (n = 177)
6MWT distance, m	350.6 ± 121.30	353.3 ± 125.98
KCCQ-OS score	67.3 ± 21.36	65.9 ± 21.74
NT-proBNP concentration, pg/mL	2,995.9 (1,751.5-4,861.5)	3,161.0 (1,864.4-4,825.0)
PGA of overall health		
Normal, not at all ill	43 (16.3)	21 (11.9)
Borderline ill	52 (19.7)	28 (15.8)
Mildly ill	49 (18.6)	39 (22.0)
Moderately ill	72 (27.3)	55 (31.1)
Markedly ill	35 (13.3)	26 (14.7)
Severely ill	9 (3.4)	3 (1.7)
Among the most extremely ill	1 (0.4)	0
NYHA functional class		
I	24 (9.1)	13 (7.3)
II	162 (61.4)	101 (57.1)
III	78 (29.5)	63 (35.6)

Values are mean ± SD, median (IQR), or n (%).

6MWT = 6-minute walk test; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGA = patient global assessment.

PATIENT CHARACTERISTICS AT BASELINE. ATTR-ACT enrolled 441 patients at 48 international sites between December 2013 and August 2015. Of these, 88 patients received 20 mg of tafamidis, 176 received 80 mg of tafamidis (pooled n = 264), and 177 received placebo.[6]

As previously reported, the median patient age was 75 years (range: 46-88 years) in the tafamidis cohort and 74 years (range: 51-89 years) in the placebo cohort.[6] Most patients were male (91.3% of the tafamidis and 88.7% of the placebo cohort) and White (79.9% and 82.5%, respectively).[6] Approximately one-quarter of patients in each cohort had a variant of the transthyretin genotype (23.9% and 24.3%, respectively).[6]

Baseline measures for 6MWT, KCCQ-OS, NT-proBNP, PGA, and NYHA classification (Table 1) were broadly comparable between the tafamidis and placebo cohorts. The mean 6MWT distance was ~350 m; KCCQ-OS score ~66 (indicating fair to good quality of life)[12]; and NT-proBNP concentration ~3,000 pg/mL. In both cohorts, the most common response on the PGA of overall heath was "moderately ill" (~30% of patients), and the most common NYHA class was II (~60% of patients).

During the 30-month study, 39 patients treated with tafamidis (15%) and 38 patients treated with placebo (21%) discontinued due to death. Another 52 tafamidis-treated patients (20%) and 54 placebo-treated patients (31%) discontinued for other reasons (Table 2). Among these, 33 tafamidis and 34 placebo patients, respectively, had died when the vital status was confirmed at month 30. Overall, 173 tafamidis- and 85 placebo-treated patients completed the study. Data points are missing for some continuing patients, for some outcomes.

PATIENTS ACHIEVING IMPROVEMENT IN EFFICACY MEASURES. Gradually declining proportions of patients with improvement in efficacy measures were observed in both the pooled tafamidis and placebo cohorts over the course of the ATTR-ACT. Despite this, in both imputed and observed data analyses, higher proportions of tafamidis-treated than placebo-treated patients showed improvement in each efficacy measure at all time points assessed (Figure 1, Supplemental Figure 2). The magnitude of difference between the proportions of patients showing improvement with tafamidis and placebo treatment grew over time.

For 6MWT distance, the proportion of tafamidis-treated patients showing improvement from baseline was 19% to 36% at time points over the 30 months, compared with 5% to 27% of placebo-treated patients (Figure 1). At month 30, 19% of tafamidis-treated and 5% of placebo-treated patients had improved 6MWT distance from baseline. KCCQ-OS score was improved from baseline for 26% to 41% of tafamidis-treated and 10% to 40% of placebo-treated patients at time points over the 30 months (Figure 1). At month 30, 26% of tafamidis-treated and 10% of placebo-treated patients had an improved KCCQ-OS score from baseline. NT-proBNP concentration was measured at months 12 and 30 only, where 37% and 24% of tafamidis-treated and 19% and 6% of placebo-treated patients showed improvement from baseline, respectively (Figure 1). In the PGA, 27% to 35% of tafamidis- and

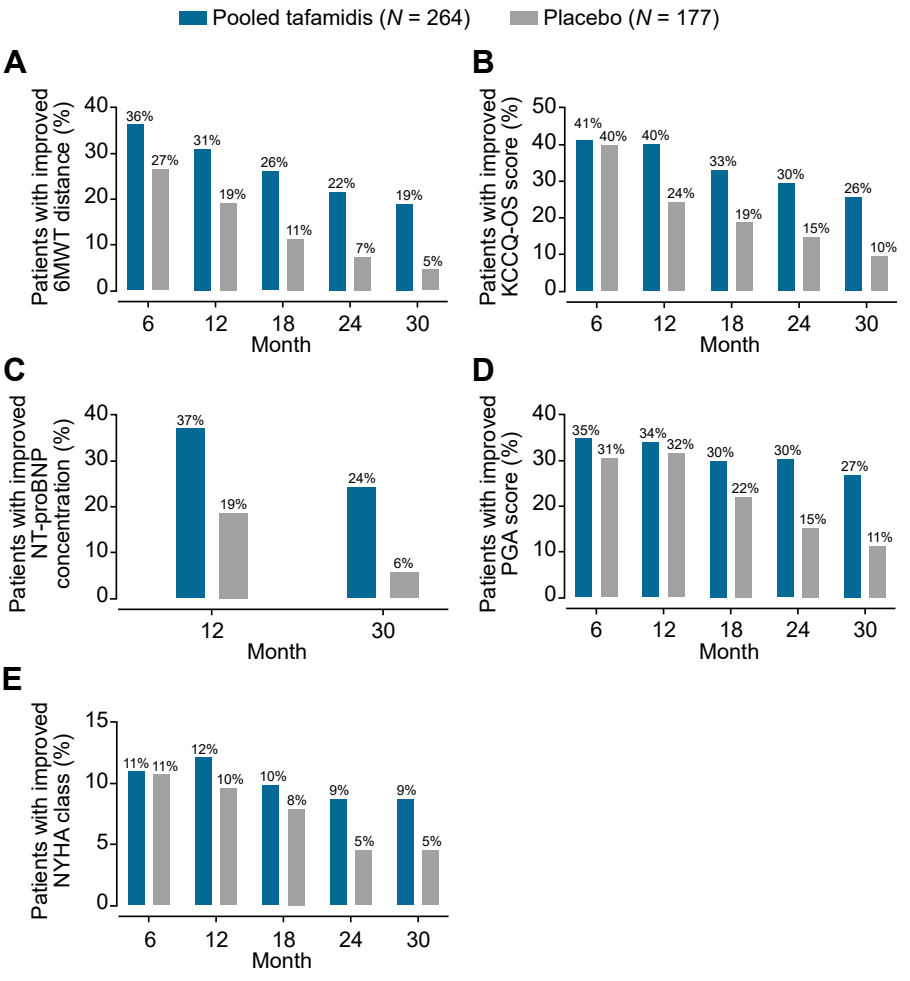
TABLE 2 Patient Discontinuation From ATTR-ACT

	Pooled Tafamidis (n = 264)	Placebo (n = 177)
Completed study	173 (65.5)	85 (48.0)
Discontinued due to reasons other than death	52 (19.7)	54 (30.5)
Total discontinuations	91 (34.5)	92 (52.0)
Due to		
Death	39 (14.8)	38 (21.5)
Adverse events	17 (6.4)	11 (6.2)
No longer willing to participate	25 (9.5)	37 (20.9)
Protocol violation	1 (0.4)	1 (0.6)
Lost to follow-up	1 (0.4)	0
Other[a]	8 (3.0)	5 (2.8)

Values are n (%). [a]Organ transplantation (6 in the pooled tafamidis cohort and 5 in the placebo cohort) or cardiac mechanical assist device implantation (2 in the pooled tafamidis cohort).

ATTR-ACT = Tafamidis in Transthyretin Cardiomyopathy Clinical Trial.

FIGURE 1 **Patients With Improved Efficacy Measures During ATTR-ACT (Imputed Data)**



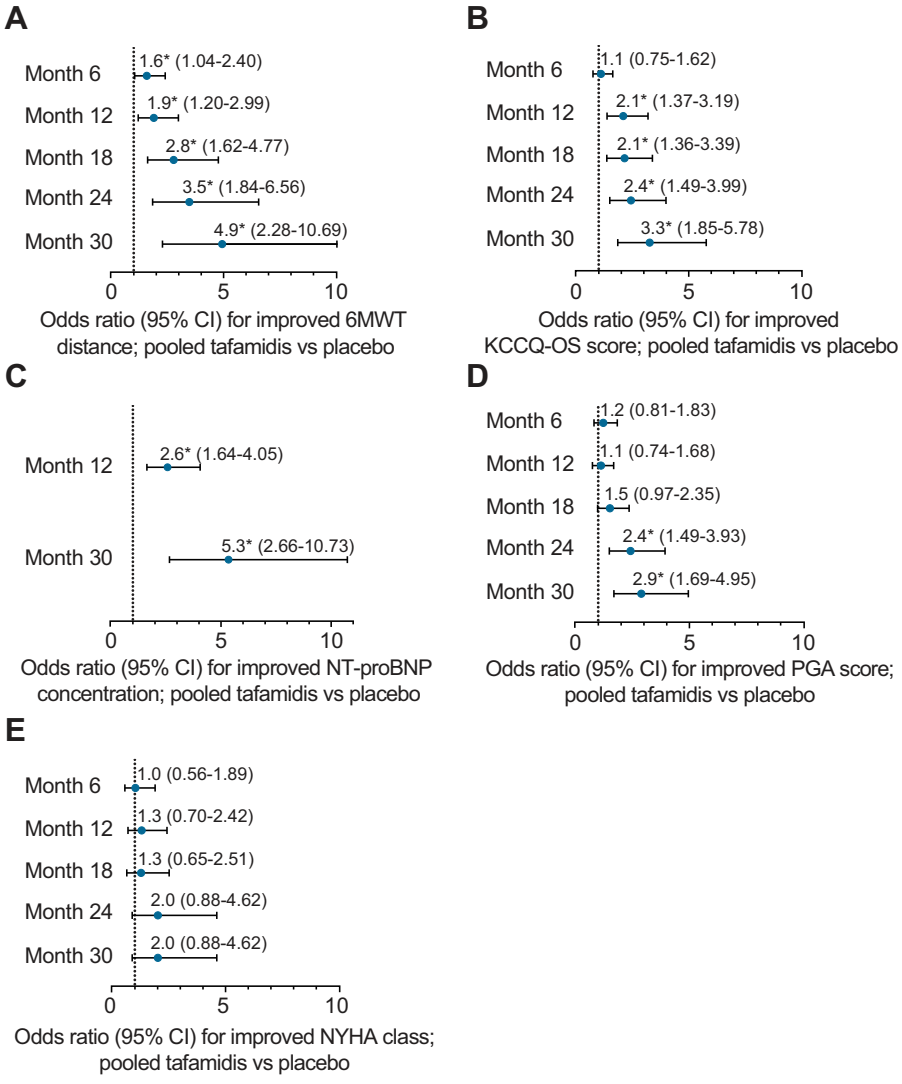
(A) 6MWT distance. **(B)** KCCQ-OS score. **(C)** NT-proBNP concentration. **(D)** PGA of overall health score. **(E)** NYHA functional class. Percentages given above bars are rounded. Improvement is defined as >0 change from baseline to month 30 for 6MWT and KCCQ-OS; <0 for NT-proBNP; "minimally," "much," or "very much improved" for PGA, and a lower class for NYHA. Pooled tafamidis cohort includes patients treated with 80 mg and 20 mg. 6MWT = 6-minute walk test; ATTR-ACT = Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGA = patient global assessment.

11% to 31% of placebo-treated patients reported improvements in overall health from baseline at time points over the 30 months. At month 30, 27% of tafamidis-treated and 11% of placebo-treated patients reported improvement from baseline. NYHA functional class was improved from baseline for 9% to 12% of tafamidis- and 5% to 11% of placebo-treated patients at time points over the 30 months of treatment (**Figure 1**). At month 30, 9% of tafamidis-treated and 5% of placebo-treated patients had an improvement in NYHA class from baseline.

The proportion of patients with improved measures was marginally lower at each time point in the imputation analysis (**Figure 1**) as compared with observed data (Supplemental Figure 2), but the general trends over time were indistinguishable.

The ORs of experiencing improvement in efficacy measures with tafamidis vs placebo treatment are shown in **Figure 2** and Supplemental Figure 3.

FIGURE 2 Odds Ratio for Improvement in Efficacy Measures During ATTR-ACT (Imputed Data)



(A) 6MWT distance. **(B)** KCCQ-OS score. **(C)** NT-proBNP concentration. **(D)** PGA of overall health score. **(E)** NYHA functional class. *$P < 0.05$. Improvement defined as >0 change from baseline to month 30 for 6MWT and KCCQ-OS; <0 for NT-proBNP; "minimally," "much," or "very much improved" for PGA, and a lower class for NYHA. Pooled tafamidis cohort includes patients treated with 80 mg and 20 mg. Abbreviations as in Figure 1.

In both the imputation analysis and observed data, there were trends for increasing ORs (favoring tafamidis) as the study progressed. In the analysis with imputation, the odds of improved 6MWT distance with tafamidis treatment vs placebo was 4.9 by month 30 (95% CI: 2.28-10.69; $P < 0.0001$) and significant at all prior time points ($P < 0.05$) (Figure 2). The OR for improvement in the KCCQ-OS score was 3.3 by month 30 (95% CI: 1.85-5.78; $P < 0.0001$) and significant at all prior time points except for month 6 ($P < 0.01$) (Figure 2). The OR for improvement in the NT-proBNP concentration was 5.3 at month 30 (95% CI: 2.66-10.73; $P < 0.0001$) and 2.6 at month 12 (95% CI: 1.64-4.05; $P < 0.0001$) (Figure 2). The OR

for improvement in PGA of overall health was 2.9 at month 30 (95% CI: 1.69-4.95; $P < 0.0001$) and was also significant at month 24 ($P < 0.001$). The OR for improvement in NYHA class was 2.0 at month 30 (95% CI: 0.88-4.62; $P = 0.09$) (**Figure 2**).

DISCUSSION

This post hoc analysis of data from ATTR-ACT shows that a proportion of patients with ATTR-CM demonstrate improvements in heart failure, physical function, and quality of life measures at time points over 30 months of treatment with tafamidis or placebo. Although both cohorts showed a mean decline in health over the study duration, at all time points assessed, the proportion of patients with improvements from baseline was higher with tafamidis treatment than with placebo treatment. Furthermore, the OR for improvement favored tafamidis in all assessments. Our findings extend the understanding of the clinical expectation of tafamidis treatment and have important clinical implications for patients with ATTR-CM.

ATTR-ACT was a pivotal phase 3 trial that led to the approval of tafamidis for use in the treatment of patients with ATTR-CM.[6] The published primary outcomes showed mortality and cardiovascular-related hospitalizations to be significantly reduced in tafamidis-treated patients compared with those in placebo-treated patients at 30 months.[6] Recently published observations additionally showed that improvement in KCCQ-OS score and PGA of overall health at month 30 was reported in a larger proportion of tafamidis-treated patients than in placebo-treated patients.[8] The current post hoc analysis looked at improvement in a range of efficacy assessments over the course of the ATTR-ACT. To allow for potential bias in the observed data, we employed imputation to account for patients who discontinued or had missing data, assuming their condition to have deteriorated. Comparable trends were also seen with the observed data.

Our findings confirm that improvement in quality of life (as assessed by KCCQ-OS score and PGA of overall health) is more likely with tafamidis than with placebo treatment through 30 months of treatment. Similar conclusions can also be extended to measures of heart failure (NT-proBNP concentration) and physical function (6MWT distance and NYHA class). We note that improvement from baseline requires varying degrees of change for each efficacy measure. Moreover, no single measure of heart failure symptoms is able to fully characterize a patient's condition.[14] For these reasons, it is perhaps more valuable to consider the trends across measures rather than the absolute proportions of patients showing improvement, or ORs. Across all efficacy measures, our results showed tafamidis treatment to be associated with a higher likelihood of improvement. The difference between tafamidis treatment and placebo treatment grew over the duration of the ATTR-ACT.

Although improvements in the symptoms of heart failure and health are desirable in the short term, they also have prognostic implications. Passantino et al (2006)[15] showed that a short-term improvement in 6MWT distance following treatment adjustment is a significant predictor of survival in patients with chronic heart failure for the following 3 years. Consistent with some previous studies, the authors also found lower NYHA class to be an independent predictor of survival.[15,16] Greene et al[17] have recently shown that a 5-point improvement in KCCQ-OS score has a higher prognostic sensitivity to predict reduced mortality and heart failure-related hospitalizations in the following 12 months than a 1-level change in NYHA class. Although improvements in the NT-proBNP concentration and PGA of overall health have also been shown to indicate longer-term prognosis in patients with heart failure,[18-21] none of the individual measures has a universally accepted prognostic role, and further studies of the factors specific to patients with ATTR-CM are warranted.[17,22]

STUDY LIMITATIONS. There are limitations to our post hoc analysis. First, the number of patients treated in the ATTR-ACT provided a set sample size that limited the power of our subanalyses. Second, this was further affected by the 35% of pooled tafamidis- and 52% of placebo-treated patients who discontinued the study. Although the outcome for a proportion of these patients is known to be death, data for the remaining discontinuing patients and any missing data from continuing patients were imputed as a deterioration. Third, the duration of ATTR-ACT was 30 months, and we were unable to extrapolate findings over a longer term.

CONCLUSIONS

Although ATTR-CM is a progressive disease, this analysis demonstrates that a consistently higher proportion of tafamidis-treated patients in the ATTR-ACT experienced improvement from baseline in measures of heart failure, functional capacity, and health-related quality of life than placebo patients.

These data provide further evidence of the clinical benefits with tafamidis in patients with ATTR-CM.

ACKNOWLEDGMENT Medical writing support was provided by Jennifer Bodkin of Engage Scientific Solutions and was funded by Pfizer.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was sponsored by Pfizer. Dr Hanna has received honoraria for advisory board participation from Pfizer, Alnylam, Akcea, and Eidos and served as a speaker for a scientific meeting session funded by Alnylam. Dr Fine has received consultancy fees from Pfizer, Alnylam, and Akcea and research support from Pfizer, Alnylam, and Akcea. B. Gundapaneni and Dr Sultan are full-time employees of Pfizer and hold stock/stock options. Dr Witteles has received honoraria for advisory board participation from Pfizer, Alnylam, Ionis, Janssen, Intelia, and Eidos and funding for clinical trials from Pfizer, Alnylam, Janssen, and Eidos.

ADDRESS FOR CORRESPONDENCE: Dr Mazen Hanna, Amyloidosis Center, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA. E-mail: HANNAM@ccf.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: We found that, compared with placebo, a higher proportion of patients treated with tafamidis had improved efficacy measures through 30 months of treatment in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. As several of these measures are also suggested to have prognostic value, our findings add to the existing evidence showing tafamidis treatment to be associated with a slowing of transthyretin amyloid cardiomyopathy progression and an extended survival time. These data further establish the clinical benefits of tafamidis.

TRANSLATIONAL OUTLOOK: Further research on the long-term effects of tafamidis treatment in the real world will allow better understanding of the treatment benefit.

REFERENCES

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872-2891.

2. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012;126:1286-1300.

3. Nativi-Nicolau J, Judge DP, Hoffman JE, et al. Natural history and progression of transthyretin amyloid cardiomyopathy: insights from ATTR-ACT. *ESC Heart Fail*. 2021;8:3875-3884.

4. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140:16-26.

5. Burton A, Castaño A, Bruno M, et al. Drug discovery and development in rare diseases: taking a closer look at the tafamidis story. *Drug Des Devel Ther*. 2021;15:1225-1243.

6. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007-1016.

7. Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail*. 2021;23:277-285.

8. Hanna M, Damy T, Grogan M, et al. Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Am J Cardiol*. 2021;141:98-105.

9. Pfizer Laboratories Division, Pfizer Inc. VYNDAQEL and VYNDAMAX highlights of prescribing information. Accessed September 2, 2021. http://labeling.pfizer.com/ShowLabeling.aspx?id=11685

10. European Medicines Agency. Vyndaqel (tafamidis) summary of product characteristics. Accessed September 2, 2021. https://www.ema.europa.eu/documents/product-information/vyndaqel-epar-product-information_en.pdf

11. Maurer MS, Elliott P, Merlini G, et al. Design and rationale of the phase 3 ATTR-ACT clinical trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Circ Heart Fail*. 2017;10:e003815.

12. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas city cardiomyopathy questionnaire in clinical trials and clinical care: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:2379-2390.

13. The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Little, Brown & Co; 1994:253.

14. Caraballo C, Desai NR, Mulder H, et al. Clinical implications of the New York Heart Association classification. *J Am Heart Assoc*. 2019;8:e014240.

15. Passantino A, Lagioia R, Mastropasqua F, Scrutinio D. Short-term change in distance walked in 6 min is an indicator of outcome in patients with chronic heart failure in clinical practice. *J Am Coll Cardiol*. 2006;48:99-105.

16. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. *Eur Heart J*. 2002;23:1861-1866.

17. Greene SJ, Butler J, Spertus JA, et al. Comparison of New York Heart Association class and patient-reported outcomes for heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6:522-531.

18. Hartmann F, Packer M, Coats AJS, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure. *Circulation*. 2004;110:1780-1786.

19. Salah K, Stienen S, Pinto YM, et al. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart*. 2019;105:1182-1189.

20. Eriksson B, Wändell P, Dahlström U, et al. Limited value of NT-proBNP as a prognostic marker of all-cause mortality in patients with heart failure with preserved and mid-range ejection fraction in primary care: a report from the Swedish Heart Failure Register. *Scand J Prim Health Care*. 2019;37:434-443.

21. Tate CW 3rd, Robertson AD, Zolty R, et al. Quality of life and prognosis in heart failure: results of the Beta-Blocker Evaluation of Survival Trial (BEST). *J Card Fail*. 2007;13:732-737.

22. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. *Eur Heart J*. 2005;26:778-793.

KEY WORDS amyloidosis, heart failure, treatment

APPENDIX For a supplemental table and figures, please see the online version of this paper.