Impact of *Tafamidis* on Health-Related Quality of Life in Patients With Transthyretin Amyloid Cardiomyopathy (from the *Tafamidis* in Transthyretin Cardiomyopathy Clinical Trial)

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In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial, tafamidis significantly reduced all-cause mortality and cardiovascular-related hospitalizations in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-CM is associated with a significant burden of disease; further analysis of patient-reported quality of life will provide additional data on the efficacy of tafamidis. In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial, 441 adult patients with ATTR-CM were randomized (2:1:2) to tafamidis 80 mg, tafamidis 20 mg, or placebo for 30 months, with pooled tafamidis (80 mg and 20 mg) compared with placebo. Change in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) domain scores, EQ-5D-3L scores, and patient global assessment, were prespecified exploratory end points. A greater proportion of patients improved KCCQ-OS score at month 30 with tafamidis (41.8%) versus placebo (21.4%). Tafamidis significantly reduced the decline in all 4 KCCQ-OS domains ($p < 0.0001$ for all), and in EQ-5D-3L utility (0.09 [confidence interval 0.05 to 0.12]; $p < 0.0001$) and EQ visual analog scale (9.11 [confidence interval 5.39 to 12.83]; $p < 0.0001$) scores at month 30 versus placebo. A larger proportion of tafamidis-treated patients reported their patient global assessment improved at month 30 (42.3% vs 23.8% with placebo). In conclusion, tafamidis effectively reduced the decline in patient-reported outcomes, providing further insight into its efficacy in health-related quality of life in patients with ATTR-CM. **(Am J Cardiol 2021;141:98−105)**

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the accumulation of transthyretin amyloid fibrils in the myocardium, leading to cardiomyopathy and symptoms of heart failure.[1,2−8] Transthyretin amyloidosis is associated with high levels of impairment in physical health, quality of life (QoL), and productivity, with QoL declining further over time.[9,10,11] In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations in patients with ATTR-CM.[12] Tafamidis also reduced the decline in health status and QoL (as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary [KCCQ-OS] score) and functional capacity.[12] The KCCQ-OS is a composite measure of different domains of a patient's health status and QoL, including the frequency and burden of symptoms, and physical and social limitations associated with disease. We sought to analyse these domains, together with other patient-reported outcomes, to provide new insight into the progression of ATTR-CM and the efficacy of tafamidis on multiple measures of health status.

Methods

The design of this phase 3, multicenter, international, 3-arm, parallel design, placebo-controlled, double-blind, randomized study (ATTR-ACT) has been published previously (NCT01994889).[12,13] Briefly, patients aged ≥18 and ≤90 years with ATTR-CM defined by the presence of either variant *TTR* (ATTRv), or wild-type amyloid deposits (ATTRwt) and a medical history of heart failure were eligible to enroll. Exclusion criteria included: previous treatment with tafamidis, heart failure not due to ATTR-CM, New York Heart Association class IV, diagnosis of light chain amyloidosis, estimated glomerular filtration rate <25 ml/min/m^2, and 6-minute walk test distance <100 meters. Patients with ATTR-CM were randomized in a 2:1:2 ratio to receive tafamidis 80 mg or 20 mg/day or matching placebo for 30 months. All analyses were performed on the

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See page 104 for disclosure information.

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pooled tafamidis treatment group (combined tafamidis 20 mg and 80 mg) compared with the placebo group. Patient data were stratified by *TTR* genotype (ATTRv and ATTRwt) and New York Heart Association baseline severity classification.

The study was approved by the independent review boards or ethics committee at each participating site, and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

The KCCQ is a 23-item, patient-completed questionnaire that assesses patients' ability to perform activities of daily living, frequency and severity of symptoms, the impact of those symptoms, and HRQoL.[14] The questionnaire yields scores for 6 domains: Physical Limitation (comprised of 6 items), Symptom Stability (1 item), Total Symptoms (includes Symptom Frequency [4 items] and Symptom Burden [3 items] sub-scales), Self-efficacy (2 items), QoL (3 items), and Social Limitation (4 items). In addition, the KCCQ generates 2 summary scores: Clinical Summary (the mean of Physical Limitation, Symptom Frequency, and Symptom Burden scores), and Overall Summary (the mean of Physical Limitation, Total Symptoms, QoL, and Social Limitation scores). The Total Symptoms domain can be divided into a Symptom Frequency score (4 items on the questionnaire) and a Symptom Burden score (3 items). All scores are transformed to a 0 to 100 range, with higher scores indicating better health status.

The EQ-5D-3L questionnaire is a patient-completed health status instrument consisting of 2 parts.[15] In the first, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain, or discomfort, and anxiety or depression), with each dimension having 3 levels of function (1 = no problem, 2 = some problem, and 3 = extreme problem). These scores are used to calculate a single EQ-5D-3L Index Score using country-specific tariffs. United States tariffs were applied for this analysis.[16] In the second, patients rate their current health state on the EQ visual analog scale (EQ VAS), with end points labeled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0).

The patient global assessment (PGA) assesses patients' perception of their heart failure. At each follow-up visit after baseline, patients rated the change in their health status since baseline according to a continuum of 7 categories: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," and "very much worse."

Patients completed all these assessments at the baseline visit and at months 6, 12, 18, 24, and 30 (or at study discontinuation). The assessments were completed in the order of KCCQ, EQ-5D-3L, and EQ VAS, then PGA.

The analyses were carried out on the intent-to-treat population, which included all patients who were enrolled, received at least 1 dose of tafamidis or placebo, and had at least 1 after-baseline efficacy evaluation. The change in KCCQ-OS from baseline to month 30 was a key secondary end point of the study. Changes in other KCCQ summary scores, KCCQ domain scores, EQ-5D-3L Index Score, EQ

Table 1
Demographic and clinical characteristics at baseline

Variable	Pooled tafamidis (N = 264)	Placebo (N = 177)
Age (years)		
Mean (SD)	74.5 (7.2)	74.1 (6.7)
Men	241 (91.3%)	157 (88.7%)
Women	23 (8.7%)	20 (11.3%)
White	211 (79.9%)	146 (82.5%)
Black	37 (14.0%)	26 (14.7%)
Asian	13 (4.9%)	5 (2.8%)
Other	3 (1.1%)	0
Genotype		
ATTRwt	201 (76.1%)	134 (75.7%)
ATTRv	63 (23.9%)	43 (24.3%)
NYHA class		
I	24 (9.1%)	13 (7.3%)
II	162 (61.4%)	101 (57.1%)
III	78 (29.5%)	63 (35.6%)

ATTRv = variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; NYHA = New York Heart Association; SD = standard deviation.

Table 2
Kansas City Cardiomyopathy Questionnaire, EQ-5D, and patient global assessment scores at baseline

Variable	Pooled tafamidis (N = 264)	Placebo (N= 177)
KCCQ domains, mean (SD)		
Quality of Life	62.63 (24.73)	59.98 (24.65)
Social Limitation	63.36 (28.96)	63.10 (28.97)
Physical Limitation	69.07 (22.77)	68.24 (24.18)
Total Symptoms*	73.45 (20.27)	72.11 (20.64)
Symptom Burden	73.58 (20.72)	73.31 (20.82)
Symptom Frequency	73.41 (21.85)	70.90 (22.49)
Self-efficacy	83.10 (20.86)	80.16 (21.42)
Symptom Stability	52.10 (16.18)	49.30 (15.64)
KCCQ summary scores, Mean (SD)		
Clinical Summary†	71.34 (20.04)	70.15 (20.51)
Overall Summary‡	67.28 (21.36)	65.90 (21.74)
EQ-5D, mean (SD)		
EQ-5D-3L Index Score	0.80 (0.16)	0.80 (0.15)
EQ VAS	68.30 (18.57)	66.50 (17.76)
PGA§		
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

EQ VAS = EQ visual analog scale; KCCQ = Kansas City Cardiomyopathy Questionnaire; PGA = patient global assessment; SD = standard deviation.

* Total Symptoms score is the mean of Symptom Frequency and Symptom Burden scores.

† Clinical Summary is the mean of Physical Limitation, Symptom Frequency, and Symptom Burden scores.

‡ Overall Summary is the mean of Physical Limitation, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitation scores.

§ Percentage of all patients with a baseline PGA measure.

VAS, and PGA at each time point were prespecified exploratory end points. Continuous variables were analyzed using a mixed model, repeated measures analysis of covariance with an unstructured covariance matrix; center and patient within center as random effects; treatment, visit, *TTR* genotype (ATTRv and ATTRwt), and visit by treatment interaction as fixed effects; and baseline score as covariate.[13] There was no imputation of missing values. Frequency counts were summarized for the PGA categories, with significance at month 30 assessed by 2-sided Mann-Whitney U Test). PGA responses were further categorized as "Improved" (patients who reported they were "very much improved," "much improved," or "minimally improved"), "No change", and "Worsened" (patients who reported they were "very much worse," "much worse," or "minimally worse").

Results

Demographic and clinical characteristics were similar in the tafamidis and placebo groups, with the majority of patients being male, a mean age of 74 years, and >75% ATTRwt (Table 1). Baseline scores were similar between the tafamidis and placebo groups for all KCCQ scores, EQ-5D scores, and PGA health status (Table 2).

As previously reported, tafamidis significantly reduced the decline in KCCQ-OS score, a key secondary end point, with the reduction being evident by month 6 of treatment.[12] Here we report that there was a greater proportion of patients who had an improvement (or no change) in KCCQ-OS score at month 30 with tafamidis (41.8%) compared with placebo (21.4%).

The reduction in decline was significant (p <0.0001) in all 4 of the subdomains of the KCCQ-OS: QoL, Total Symptoms, Social Limitation, and Physical Limitation (Figure 1). Tafamidis also significantly reduced the decline in both Symptom Burden and Symptom Frequency, while the reduction in the decline with tafamidis was not significant for the KCCQ domains of Self-efficacy and Symptom Stability (Figure 2). The decline in KCCQ Clinical Summary score was also significantly reduced with tafamidis (12.41 [confidence interval 8.58 to 16.24]; p <0.0001).

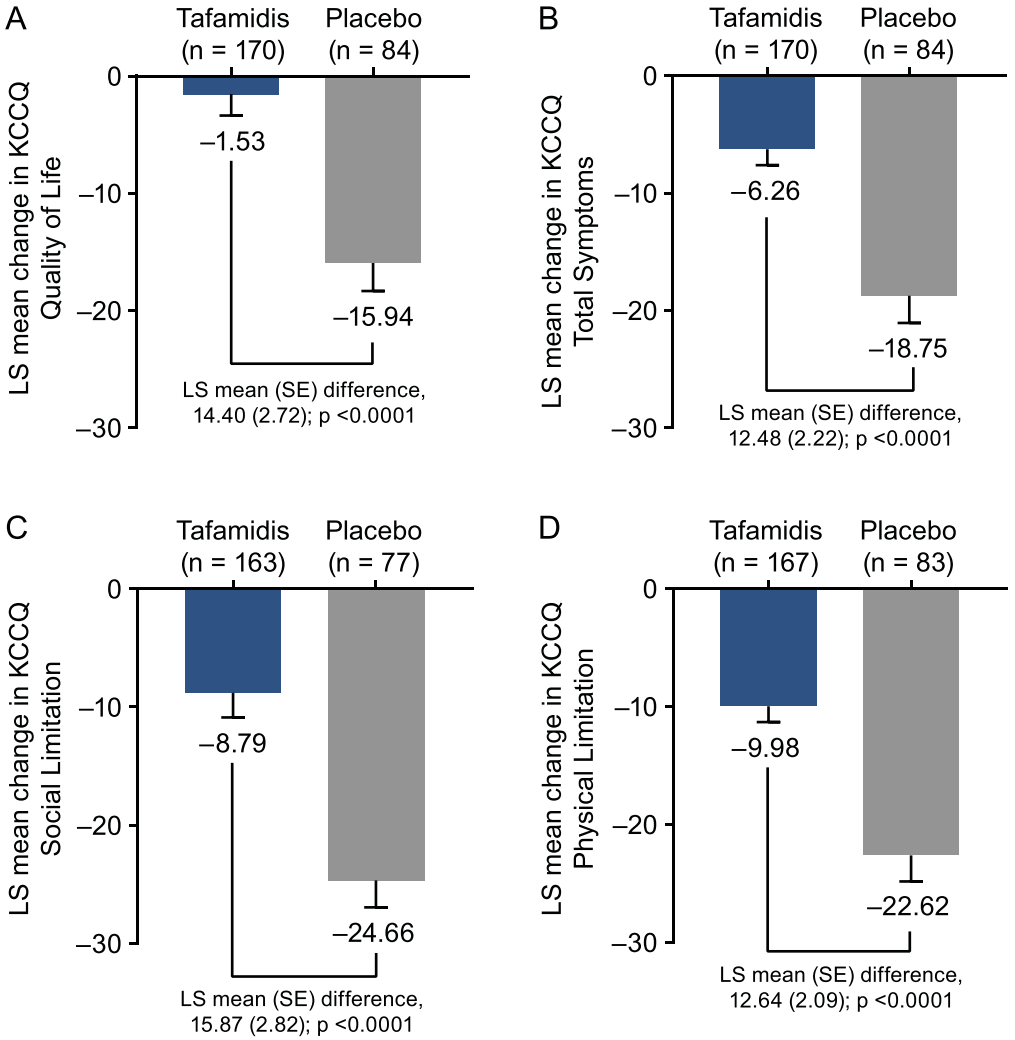

Figure 1. LS mean change (SE) in KCCQ (*A*) Quality of Life; (*B*) Total Symptoms; (*C*) Social Limitation; and (*D*) Physical Limitation scores from baseline to month 30. LS = least-squares; SE = standard error.

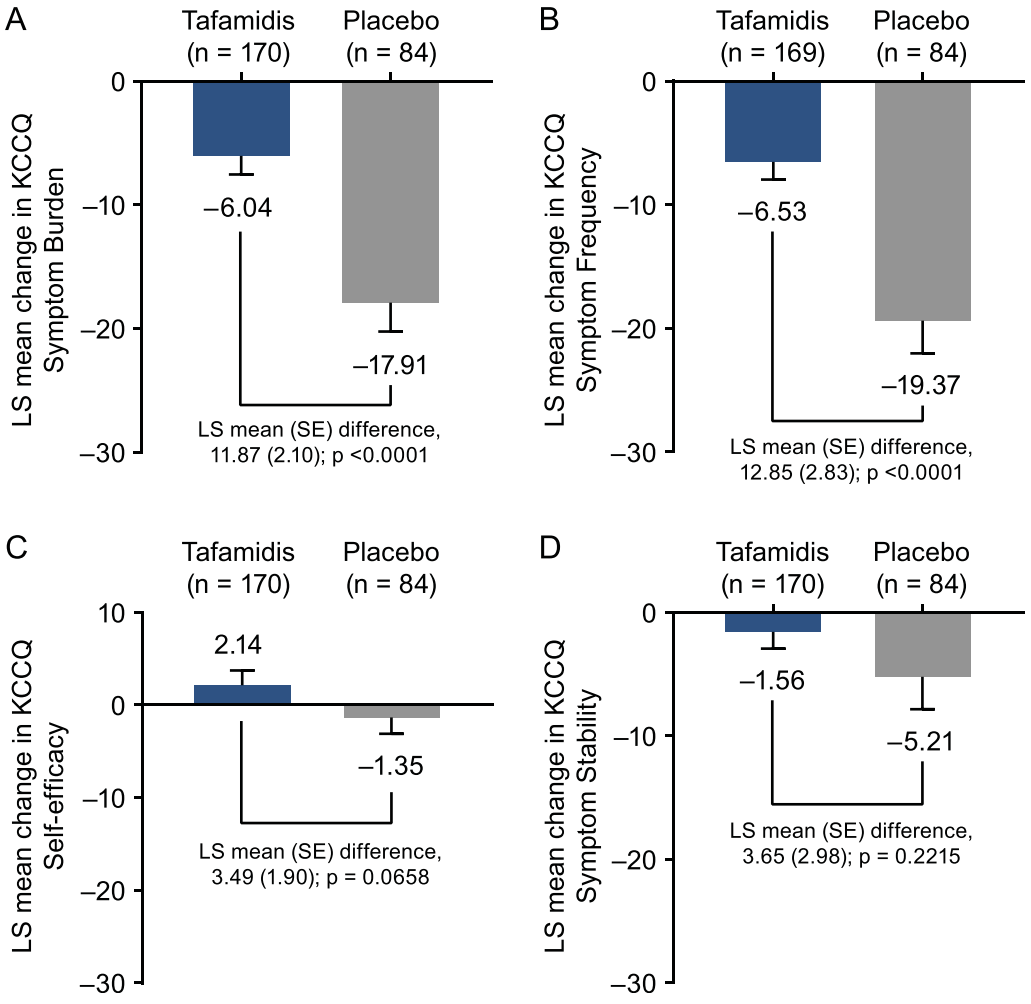

Figure 2. LS mean change (SE) in KCCQ (*A*) Symptom Burden; (*B*) Symptom Frequency; (*C*) Self-efficacy; and (*D*) Symptom Stability scores from baseline to month 30. LS = least squares; SE = standard error.

Tafamidis significantly reduced the decline in EQ-5D-3L Index Score from month 18 (Figure 3), with a least-squares mean difference (95% confidence interval) compared with placebo at month 30 of 0.09 (0.05 to 0.12); p <0.0001. Tafamidis also significantly reduced the decline in EQ VAS from month 12 (Figure 3), with a least-squares mean difference (95% confidence interval) compared with placebo at month 30 of 9.11 (5.39 to 12.83); p <0.0001.

At month 30, a larger proportion of tafamidis-treated patients reported they were "very much improved," "much improved," or "minimally improved" from baseline compared with placebo (42.3% with tafamidis vs 23.8% with placebo) (Figure 4). Placebo-treated patients were more likely to report they were "much worse," "very much worse," or had "no change" compared with tafamidis (26.2% with tafamidis vs 40.5% with placebo).

A larger proportion of patients treated with tafamidis, compared with placebo, were categorized as "improved" at every time point (Figure 5). At each time point, approximately 40% of tafamidis-treated patients reported they were "improved" from baseline. The proportion of patients whose condition worsened tended to increase over the course of the study and was larger in patients treated with placebo than with tafamidis at every time point (Figure 5).

Discussion

In ATTR-ACT, tafamidis was shown to reduce the decline in health status and QoL, as assessed by a key secondary end point of the trial: the change in KCCQ-OS score from baseline to month 30.[12] To further elucidate this outcome, these analyses evaluated changes in the domains that comprise the KCCQ-OS, assessing the impact of tafamidis and providing new data on the progression of disease and the efficacy of tafamidis. Tafamidis similarly reduced the decline in all components of the KCCQ-OS score, demonstrating that treatment with tafamidis had an impact on patients' QoL, the limitations on their social and physical lives, and the frequency and burden of their symptoms. No single domain was responsible for the observed reduction in the decline in the KCCQ-OS score.

In ATTR-ACT, the changes in the other domains of the KCCQ—Self-efficacy and Symptom Stability—were less pronounced overall and the trend toward a reduction in the

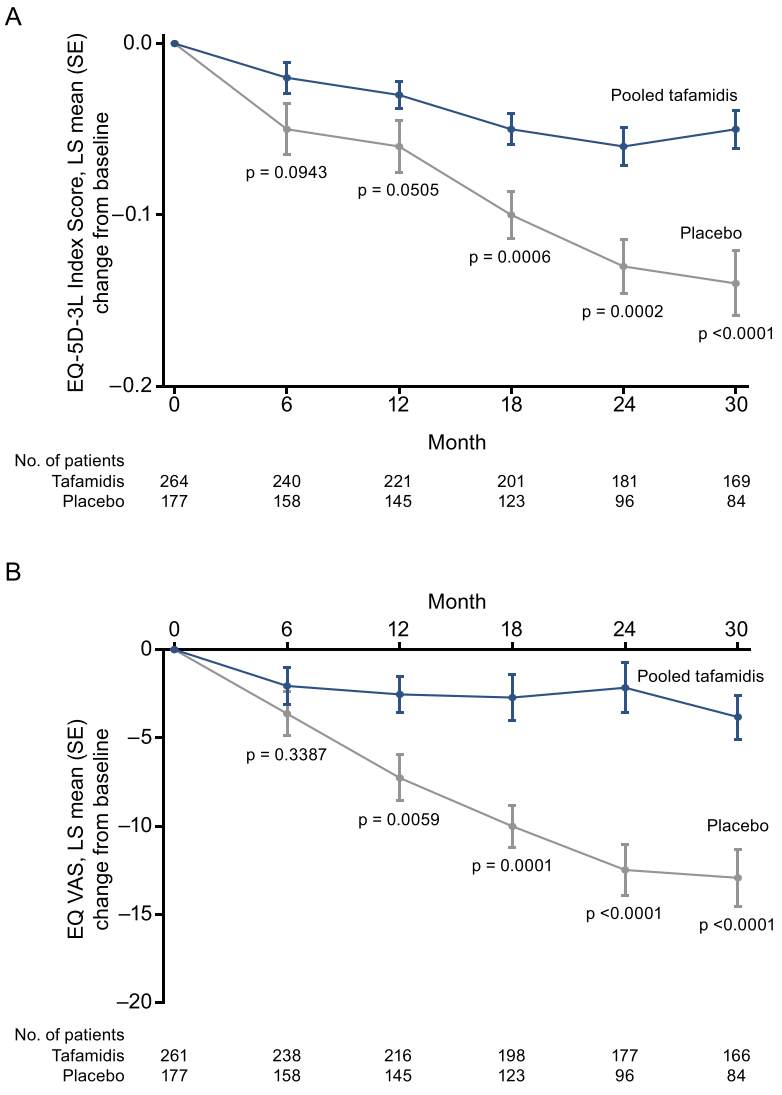

Figure 3. LS mean change (SE) in (*A*) EQ-5D-3L Index Score and (*B*) EQ VAS from baseline. LS = least squares; SE = standard error.

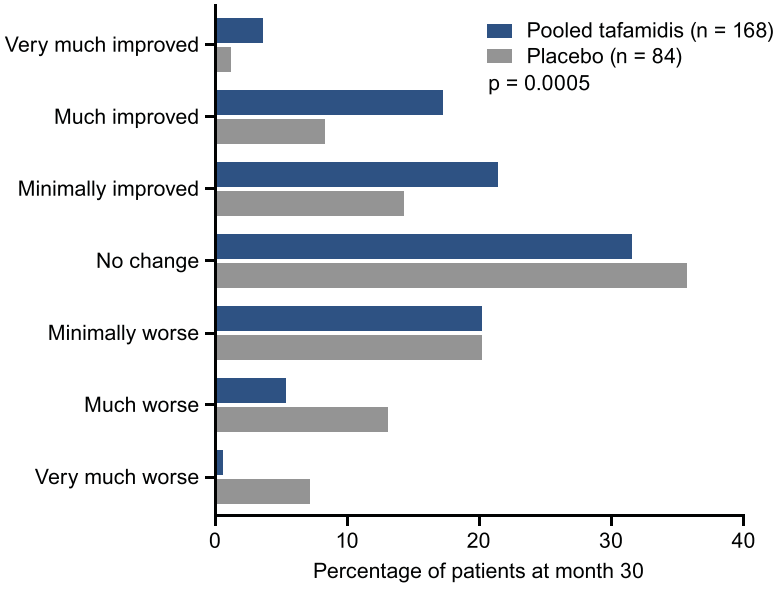

Figure 4. Patient impression of change from baseline at month 30 on PGA. $p = 0.0005$ for pooled tafamidis versus placebo (assessed by 2-sided Mann-Whitney U Test).

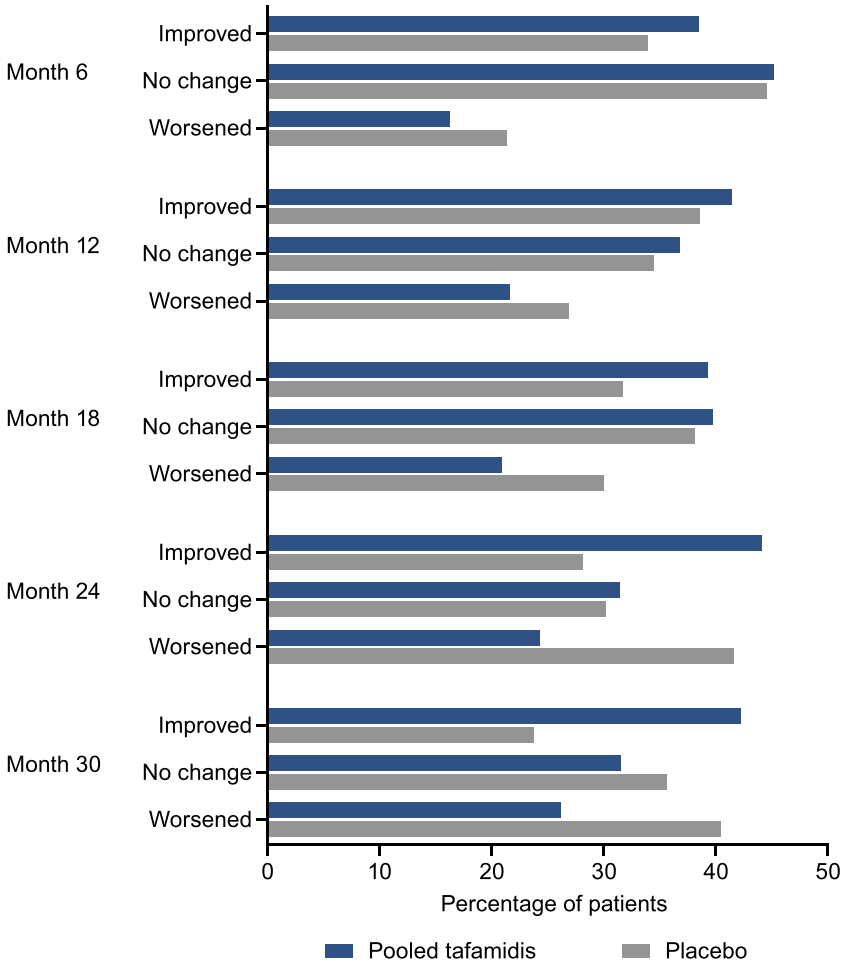

Figure 5. Patient impression of change from baseline at each clinic visit on PGA. "Improved" shows the percentage of all patients who reported they were "very much improved," "much improved," or "minimally improved." "Worsened" shows the percentage of all patients who reported they were "very much worse," "much worse," or "minimally worse."

decline with tafamidis was not significant. The comparatively higher scores (ie, better health status) for Self-efficacy and lower scores for Symptom Stability at baseline in this trial were consistent with previous surveys of patients with transthyretin amyloidosis.[9,11] Self-efficacy is a measure of the patient's knowledge of, and confidence in, their medical care, including what they should do if their heart failure gets worse.[14] The relatively smaller changes in these measures may reflect the fact that patients in ATTR-ACT had been living with ATTR-CM for some time, in addition to being enrolled in a clinical trial, and thus had a great deal of support and were generally aware of how to manage their disease.

The overall poor HRQoL observed in patients in ATTR-ACT is consistent with previous studies, including a recent large, prospective, observational study of 1,034 patients with ATTR-CM who attended the National Amyloidosis Centre (United Kingdom) between 2000 and 2017.[11] At baseline, patients in ATTR-ACT, compared with the observational study, were slightly younger, with a lower proportion of patients with ATTRv (24% vs 31%); however, cardiac biomarkers and functional capacity were similar between the 2 studies.[11,12] KCCQ domain scores at baseline were also similar for several scores (QoL, Symptom Burden, Symptom Frequency, and Symptom Stability) but somewhat better for others (Social Limitation, Physical Limitation, and Self-efficacy). The "better" Self-efficacy scores in ATTR-ACT were most likely due to patients being in a clinical trial, as previously mentioned. The "better" Social Limitation and Physical Limitation scores in ATTR-ACT may be due to patients in the observational study being older with more advanced disease. In placebo-treated patients in ATTR-ACT, the greatest declines over the course of the study were in the Social Limitation and Physical Limitation domains; although all KCCQ domain scores and the KCCQ-OS score declined markedly over time in both placebo-treated patients in ATTR-ACT and all patients in the observational study.[11,12]

A 5-point difference in KCCQ is considered clinically meaningful in patients with heart failure.[17–20] Previous studies have suggested that a 5-point change corresponds to changes in measures of functional capacity, such as a 112-m change in 6-minute walk test distance,[18] and a 10% change in the risk of death or rehospitalization.[20] Overall, a lower KCCQ-OS score has been shown to be an independent predictor of poor prognosis.[21] In this context, the reduction in the decline in KCCQ domain scores with tafamidis (compared with placebo) in ATTR-ACT, which ranged from

12 to 16 points, represents a large, clinically meaningful change in patients' outcomes. Similarly, the 9-point difference in EQ VAS between tafamidis and placebo at month 30 is notably greater than the 3-point difference considered clinically meaningful in patients with heart failure.[19]

A particularly striking aspect of these data was the observation that a large proportion of patients reported that their QoL (as assessed by the KCCQ-OS and the global PGA) had improved with tafamidis treatment. This improvement was observed despite the fact that ATTR-CM is associated with a poor and declining QoL and severe disease burden.[9,11,22] In the context of a degenerative disease like ATTR-CM, no change (ie, no decline) in symptoms would represent a meaningful benefit to patients. Over 40% of patients treated with tafamidis reported an improvement (or no change) in KCCQ-OS at month 30. Similarly, >40% of patients reported their PGA was "improved" at every time point of the trial.

Although this analysis was limited to prespecified end points from ATTR-ACT and does not assess the clinical characteristics associated with improvements in HRQoL, further studies could validate a clinically meaningful change in QoL in patients with ATTR-CM. Comparisons with objective measures of disease would provide further insight into the characteristics of those patients whose HRQoL improved with tafamidis treatment and confirm any correlation with improvements in objective assessments such as functional capacity.

Overall, these data illustrate the value of patient-reported outcomes in providing a broader picture of patient health and outcomes. Examining the individual KCCQ domains, as opposed to simply the Overall Summary score, allows the translation of clinical trial results into what the patient is experiencing. This can facilitate discussions between the patient and physician on what can be expected from the disease and the impact of treatment. These findings provide further insight into the favorable effect of tafamidis treatment in patients with ATTR-CM.

Author Contributions

Mazen Hanna: Conceptualization, Methodology, Writing - Original Draft, Investigation, Visualization. Thibaud Damy: Conceptualization, Methodology, Writing - Review & Editing, Investigation. Martha Grogan: Conceptualization, Methodology, Writing - Review & Editing, Investigation. Michelle Stewart: Conceptualization, Methodology, Writing - Original Draft, Visualization. Balarama Gundapaneni: Conceptualization, Methodology, Formal analysis Writing - Review & Editing. Terrell A. Patterson: Conceptualization, Methodology, Writing - Review & Editing. Jeffrey H. Schwartz: Conceptualization, Methodology, Formal analysis Writing - Review & Editing. Marla B. Sultan: Conceptualization, Methodology, Writing - Review & Editing. Mathew S. Maurer: Conceptualization, Methodology, Writing - Original Draft, Investigation.

Data sharing

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Disclosures

M. 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. T. Damy has served on a scientific advisory board for Pfizer; received funding from Pfizer for scientific meeting expenses; and his institution has received grant support from Pfizer. M. Grogan has received research grants from Alnylam, Eidos, Pfizer, and Prothena. M. Stewart, T.A. Patterson, M.B. Sultan, and B. Gundapaneni are full-time employees of Pfizer and hold stock and stock options with Pfizer. At the time of this analysis, J.H. Schwartz was an employee of Pfizer; he holds stock and stock options with Pfizer and is now retired. M.S. Maurer's institution received funding for clinical trials for Pfizer, Prothena, Eidos, and Alnylam; and he has received consulting income from Pfizer, GlaxoSmithKline, Eidos, Prothena, Akcea, and Alnylam. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions, and was funded by Pfizer.

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