JACC: HEART FAILURE VOL. 9, NO. 2, 2021

Efficacy of Tafamidis in Patients With Hereditary and Wild-Type Transthyretin Amyloid Cardiomyopathy

Further Analyses From ATTR-ACT

Claudio Rapezzi, MD,[a,b] Perry Elliott, MD,[c] Thibaud Damy, MD,[d] Jose Nativi-Nicolau, MD,[e] John L. Berk, MD,[f] Eric J. Velazquez, MD,[g] Kurt Boman, MD,[h] Balarama Gundapaneni, MS,[i] Terrell A. Patterson, PhD,[i] Jeffrey H. Schwartz, PhD,[j] Marla B. Sultan, MD, MBA,[j] Mathew S. Maurer, MD[k]

ABSTRACT

OBJECTIVES Tafamidis is an effective treatment for transthyretin amyloid cardiomyopathy (ATTR-CM), this study aimed to determine whether there is a differential effect between variant transthyretin amyloidosis (ATTRv) and wild-type transthyretin (ATTRwt).

BACKGROUND ATTR-CM is a progressive, fatal disorder resulting from mutations in the ATTRv or the deposition of denatured ATTRwt.

METHODS In pre-specified analyses from ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial), baseline characteristics, all-cause mortality, and change from baseline to month 30 in 6-min walk test distance and Kansas City Cardiomyopathy Questionnaire Overall Summary score were compared in patients with ATTRwt and ATTRv.

RESULTS There were 335 patients with ATTRwt (201 tafamidis, 134 placebo) and 106 with ATTRv (63 tafamidis, 43 placebo) enrolled in ATTR-ACT. Patients with ATTRwt (vs. ATTRv) had less advanced disease at baseline and a lower rate of disease progression over the study. The reduction in all-cause mortality with tafamidis compared with placebo was not different between ATTRwt (hazard ratio: 0.706 [95% confidence interval (CI): 0.474 to 1.052]; $p = 0.0875$) and ATTRv (hazard ratio: 0.690 [95% CI: 0.408 to 1.167]; $p = 0.1667$). Tafamidis was associated with a similar reduction (vs. placebo) in the decline in 6-min walk test distance in ATTRwt (mean $\pm$ SE difference from placebo, 77.14 $\pm$ 10.78; $p < 0.0001$) and ATTRv (79.61 $\pm$ 29.83 m; $p = 0.008$); and Kansas City Cardiomyopathy Questionnaire Overall Summary score in ATTRwt (12.72 $\pm$ 2.10; $p < 0.0001$) and ATTRv (18.18 $\pm$ 7.75; $p = 0.019$).

CONCLUSIONS Pre-specified analyses from ATTR-ACT confirm the poor prognosis of untreated ATTRv-related cardiomyopathy compared with ATTRwt, but show the reduction in mortality and functional decline with tafamidis treatment is similar in both disease subtypes. (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy [ATTR-ACT]; NCT01994889) (J Am Coll Cardiol HF 2021;9:115–23) © 2021 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]Cardiovascular Center, University of Ferrara, Ferrara, Italy; [b]Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy; [c]University College London and St. Bartholomew's Hospital, London, United Kingdom; [d]French Referral Center for Cardiac Amyloidosis, Amyloidosis Mondor Network, GRC Amyloid Research Institute and Department of Cardiology, all at APHP, CHU Henri Mondor, and INSERM U955, Clinical Investigation Center 006, and DHU ATVB all at Créteil, France; [e]Department of Medicine, University of Utah Health Care, Salt Lake City, Utah, USA; [f]Boston University School of Medicine, Boston, Massachusetts, USA; [g]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [h]Research Unit, Skellefteå County Hospital, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [i]Pfizer, Groton, Connecticut, USA; [j]Pfizer, New York, New York, USA; and the [k]Columbia University College of Physicians and Surgeons, New York, New York, 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 30, 2020; revised manuscript received September 2, 2020, accepted September 18, 2020.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2020.09.011

ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv = variant transthyretin amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

CI = confidence interval

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary

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

NYHA = New York Heart Association

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM), is an underdiagnosed, fatal disease caused by the misfolding and deposition of transthyretin amyloid fibrils in the heart leading to heart failure (1,2). ATTR-CM can be heritable due to mutations in the transthyretin (TTR) gene (ATTRv), or can occur secondary to deposition of nonmutated (wild-type) transthyretin protein (ATTRwt) (1,2). More than 130 point mutations in the *TTR* gene have been identified, some of which are associated with a predominant cardiac phenotype including Val122Ile (3–5), Thr60Ala (6,7), and Ile68Leu (8).

Tafamidis is a selective transthyretin stabilizer that prevents tetramer dissociation and amyloidogenesis (9). Tafamidis was shown to be an effective treatment for patients with ATTR-CM in the international, double-blind, placebo-controlled, randomized ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) (10,11). ATTR-ACT was the first large clinical trial in ATTR-CM, and included both patients with ATTRwt and patients with ATTRv. Although the clinical presentation of ATTRwt and ATTRv patients with a predominant cardiac phenotype are quite similar, differences in their natural history are reported (7,12–15). For example, ATTRwt is predominantly diagnosed in older Caucasian men, whereas clinical presentation in ATTRv patients occurs with a more even distribution in age, sex, and geography (7). Notably, survival in ATTRv patients with the Val122Ile mutation is worse than in patients with ATTRwt (12,14–16), potentially due to biologic as well as societal differences between these demographically distinct patient populations (13,17). In contrast, Caucasian Ile68Leu patients have an age-adjusted survival similar to patients with ATTRwt (18).

SEE PAGE 124

In this analysis, we report pre-specified and post hoc analyses of data from ATTR-ACT, with the aim of comparing the effect of *TTR* stabilization in patients with ATTRwt and ATTRv. Pre-specified analyses included the effect of tafamidis on all-cause mortality, all-cause hospitalizations, functional capacity, and health status and quality of life by genotype. The effect of treatment on N-terminal pro-B-type natriuretic peptide (NT-proBNP) by genotype was also assessed. Finally, we characterized the natural progression of ATTRwt and ATTRv by assessing baseline characteristics and their change over the duration of the study in those treated with placebo.

METHODS

STUDY DESIGN. Data are from ATTR-ACT, a phase III multicenter, international, 3-arm, parallel design, placebo-controlled, double-blind, randomized study, which has been described previously (NCT01994889) (10,11). Briefly, the study enrolled adult patients with: ATTR-CM, due to either ATTRv or ATTRwt; at least 1 prior hospitalization due to heart failure or clinical evidence of heart failure without hospitalization (volume overload or elevated intracardiac pressures) requiring treatment with a diuretic; end-diastolic intraventricular septal wall thickness >12 mm demonstrated by echocardiography; and 6-min walk test (6MWT) distance of >100 m. Patients were excluded if they were in New York Heart Association (NYHA) functional class IV or had prior tafamidis treatment, modified body mass index <600 kg/m^2•g/l (serum concentration of albumin multiplied by body mass index), an estimated glomerular filtration rate <25 ml/min/1.73 m^2, or prior liver or heart transplantation. Patients were randomized to tafamidis 80 or 20 mg once daily or matching placebo in a 2:1:2 ratio for 30 months of treatment. Data from the 2 tafamidis doses were pooled for the primary analysis and for this analysis. The primary outcome of ATTR-ACT was a hierarchical assessment of all-cause mortality followed by frequency of cardiovascular (CV)-related hospitalizations over 30 months. Key secondary outcomes were change from baseline to month 30 in 6MWT distance and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score (ranging from 0 to 100, with lower scores denoting poorer health status and quality of life).

In this analysis, pre-specified sensitivity and exploratory analyses were: all-cause mortality and frequency of all-cause hospitalization (as assessed by the Finkelstein-Schoenfeld method [19]) for tafamidis compared with placebo in all patients; all-cause mortality by genotype (ATTRwt and ATTRv) and by disease severity (as assessed by NYHA functional class); and key secondary endpoints (6MWT and KCCQ-OS) by genotype. Heart (or combined heart and liver) transplantation or implantation of a cardiac mechanical assist device were counted as death equivalents for these analyses. The effect of tafamidis on change from baseline in NT-proBNP was a pre-specified exploratory outcome, and in this analysis was a post hoc assessment stratified by genotype.

ATTR-ACT was approved by the independent review boards or ethics committee at each participating site and was conducted according to the provisions of

TABLE 1 Demographic and Clinical Characteristics at Baseline by Genotype

	ATTRwt			ATTRv			ATTRwt vs. ATTRv p Value*
	Tafamidis (n = 201)	Placebo (n = 134)	All (n = 335)	Tafamidis (n = 63)	Placebo (n = 43)	All (n = 106)	
Age, yrs							<0.0001
Mean ± SD	75.5 ± 6.7	74.9 ± 6.0	75.2 ± 6.4	71.6 ± 8.0	71.4 ± 8.1	71.5 ± 8.0	
Median (range)	75.0 (56-88)	75.0 (57-89)	75.0 (56-89)	74.0 (46-85)	73.0 (51-86)	73.0 (46-86)	
Sex							<0.0001
Male	194 (96.5)	128 (95.5)	322 (96.1)	47 (74.6)	29 (67.4)	76 (71.7)	
Female	7 (3.5)	6 (4.5)	13 (3.9)	16 (25.4)	14 (32.6)	30 (28.3)	
mBMI, kg/m^2†	1,075.3 ± 169.6	1,085.9 ± 180.2	1,079.6 ± 173.7	1,006.0 ± 177.5	1,005.6 ± 225.1	1,005.9 ± 197.2	0.0003
Race							<0.0001
White	183 (91.0)	124 (92.5)	307 (91.6)	28 (44.4)	22 (51.2)	50 (47.2)	
Black	3 (1.5)	5 (3.7)	8 (2.4)	34 (54.0)	21 (48.8)	55 (51.9)	
Asian	12 (6.0)	5 (3.7)	17 (5.1)	1 (1.6)	0 (0.0)	1 (0.9)	
Other	3 (1.5)	0 (0.0)	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	
NYHA functional class							0.0040
I	19 (9.5)	11 (8.2)	30 (9.0)	5 (7.9)	2 (4.7)	7 (6.6)	
II	133 (66.2)	79 (59.0)	212 (63.3)	29 (46.0)	22 (51.2)	51 (48.1)	
III	49 (24.4)	44 (32.8)	93 (27.8)	29 (46.0)	19 (44.2)	48 (45.3)	
6MWT distance, m	367.3 ± 112.2	366.7 ± 126.2	367.1 ± 117.8	297.1 ± 134.0	311.2 ± 117.1	302.8 ± 127.0	<0.0001
KCCQ-OS score	69.5 ± 20.3	65.1 ± 21.3	67.7 ± 20.8	60.2 ± 23.1	68.4 ± 23.1	63.5 ± 23.3	0.0796
NT-proBNP, pg/ml	3,640.0 ± 2,879.5	3,826.3 ± 2,840.2	3,714.5 ± 2,861.0	4,933.6 ± 4,505.9	3,905.4 ± 3,384.2	4,516.5 ± 4,102.1	0.0631

Values are or mean ± SD or n (%), unless otherwise indicated. KCCQ-OS score ranges from 0 to 100, with lower scores denoting poorer health status and quality of life. *The p values are for all patients with ATTRwt compared with all patients with ATTRv, with values from 2-sample Student's *t*-test for continuous variables and Fisher exact test for categorical variables. †The mBMI is calculated as the serum albumin level in g/l multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters).

6MWT = 6-min walk test; ATTRv = variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; mBMI = modified body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

STATISTICAL ANALYSES. The primary efficacy outcome, the hierarchical assessment of all-cause mortality followed by frequency of CV-related hospitalizations, was assessed using the Finkelstein-Schoenfeld method as described previously (11,19). The win ratio (number of pairs of treated-patient "wins" divided by number of pairs of placebo-patient "wins") was used to interpret the Finkelstein-Schoenfeld result. All-cause mortality was assessed by Cox proportional hazards model with baseline NYHA functional classification as a factor. In a post hoc analysis, all-cause mortality by genotype was also assessed by stratified log-rank test (stratified by NYHA functional classification). Genotype was also included as a covariate in a separate Cox proportional hazards model to assess its effect on time to all-cause mortality. Frequency of CV-related hospitalization and all-cause hospitalization was assessed using a Poisson regression model. 6MWT distance, KCCQ-OS score, and NT-proBNP were evaluated using a mixed-model repeated-measures analysis of covariance model with an unstructured covariance matrix; center and patient-within-center as random effects; treatment, visit, *TTR* genotype (ATTRwt and ATTRv), and visit by treatment interaction as fixed effects; and baseline value as covariate.

RESULTS

PATIENT CHARACTERISTICS BY GENOTYPE. There were 335 ATTRwt (201 tafamidis, 134 placebo) and 106 ATTRv (63 tafamidis, 43 placebo) patients enrolled in ATTR-ACT. Patients with ATTRwt were predominantly white men, whereas patients with ATTRv tended to be slightly younger, with a larger proportion of women and a higher proportion of Black patients (Table 1). The majority of patients with ATTRv (57.5%) had the Val122Ile mutation, followed by Ile68Leu and Thr60Ala (Table 2). Patients with ATTRwt had less severe disease at baseline than patients with ATTRv. Specifically, fewer patients with ATTRwt (27.8%) than ATTRv (45.3%) were NYHA

TABLE 2 Patient Genotypes

Genotype	Tafamidis (n = 264)	Placebo (n = 177)	All Patients (N = 441)
ATTRwt	201	134	335
ATTRv	63	43	106
Genotype			
Val122Ile	38 (60.3)	23 (53.5)	61 (57.5)
Ile68Leu	9 (14.3)	4 (9.3)	13 (12.3)
Thr60Ala	6 (9.5)	6 (14.0)	12 (11.3)
Val30Met	3 (4.8)	6 (14.0)	9 (8.5)
Pro24Ser	2 (3.2)	1 (2.3)	3 (2.8)
Val20Ile	1 (1.6)	0 (0.0)	1 (0.9)
Asp18Glu	0 (0.0)	1 (2.3)	1 (0.9)
Glu89Gln	0 (0.0)	1 (2.3)	1 (0.9)
Glu89Lys	1 (1.6)	0 (0.0)	1 (0.9)
Glu54Leu	0 (0.0)	1 (2.3)	1 (0.9)
Phe33Leu	1 (1.6)	0 (0.0)	1 (0.9)
Phe44Tyr	1 (1.6)	0 (0.0)	1 (0.9)
Phe64Leu	1 (1.6)	0 (0.0)	1 (0.9)

Values are n or n (%).
Abbreviations as in Table 1.

functional class III, with the difference in NYHA functional class distribution being significant (p = 0.004). Patients with ATTRwt had a significantly longer mean ± SD 6MWT distance (367.1 ± 117.8 vs. 302.8 ± 127.0; p < 0.0001), whereas the numerically higher KCCQ-OS score was not significant.

SURVIVAL WITH TREATMENT, AND IN UNTREATED PATIENTS, BY GENOTYPE AND NYHA FUNCTIONAL CLASS. In all patients, all-cause mortality and frequency of all-cause hospitalization (assessed by Finkelstein-Schoenfeld method) were lower with tafamidis than placebo (win ratio 1.45 [95% confidence interval (CI): 1.10 to 1.93]; p = 0.0088). A Cox proportional hazards model to test the main effects for time to all-cause mortality in all patients showed genotype to be a statistically significant predictor of survival (Wald Chi-Square value = 9.031; p = 0.0027). All-cause mortality and frequency of CV-related hospitalization (assessed by Finkelstein-Schoenfeld method) was lower with tafamidis, compared with placebo, in patients with ATTRwt (win ratio 1.74 [95% CI: 1.26 to 2.41]; p = 0.0009) and patients with ATTRv (1.30 [95% CI: 0.79 to 2.14]; p = 0.3001).

The reduction in all-cause mortality with tafamidis compared with placebo was the same in patients with ATTRwt (reduction in risk of death, 29.4%; hazard ratio: 0.706 [95% CI: 0.474 to 1.052]; p = 0.0875) and ATTRv (31.0%; 0.690 [95% CI: 0.408 to 1.167]; p = 0.1667) but the separation between tafamidis and placebo was apparent approximately 6 months earlier in patients with ATTRwt compared with ATTRv (Central Illustration). These p values were comparable when assessed by stratified log rank test (p = 0.0832 for ATTRwt and p = 0.1883 for ATTRv). Although the reduction in all-cause mortality with tafamidis was significant in all patients, the reduction was not significant in either genotype subgroup alone.

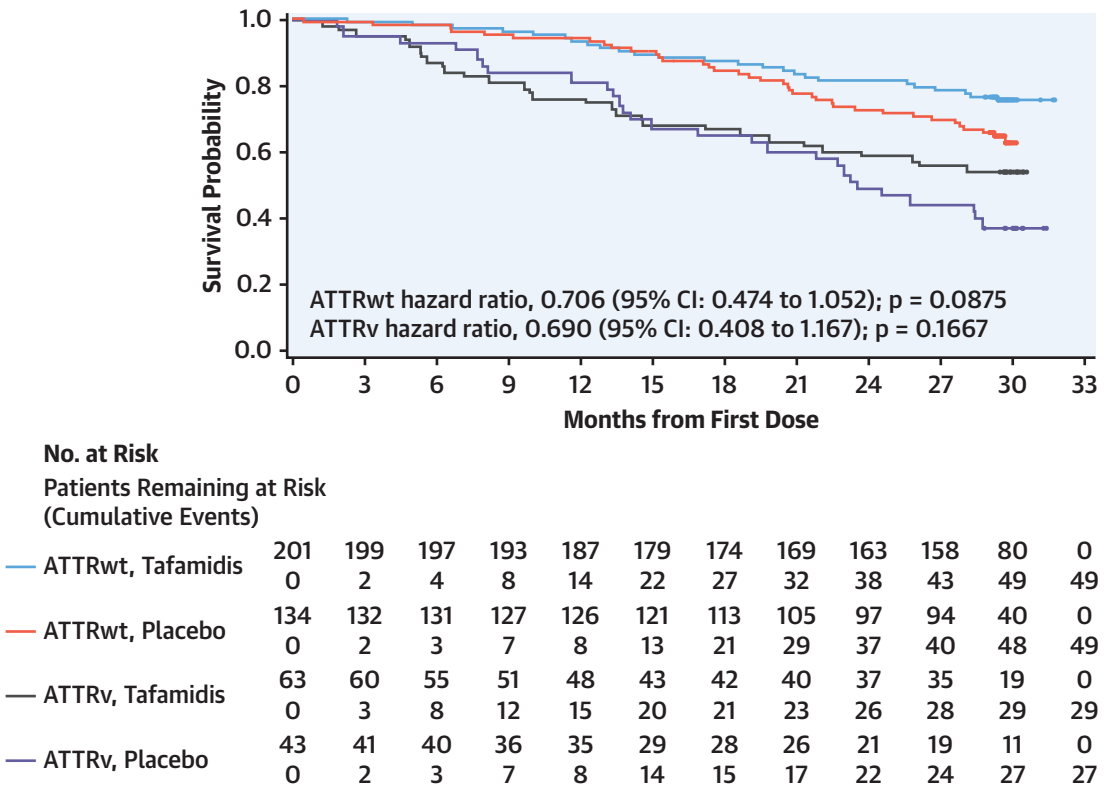
The observed reduction in all-cause mortality with tafamidis in patients with ATTRwt and patients with ATTRv remained evident when only NYHA functional class I and II patients, or only NYHA functional class III patients, were considered, although this was only significant for ATTRwt NYHA functional class I and II patients (Table 3). In patients with ATTRwt and patients with ATTRv combined, the reduction in all-cause mortality with tafamidis compared with placebo was more pronounced in patients with baseline NYHA functional class I (hazard ratio: 0.356 [95% CI: 0.078 to 1.613]; p = 0.1801) and NYHA functional class II (hazard ratio: 0.604 [95% CI: 0.371 to 0.983]; p = 0.0423) than in those with baseline NYHA functional class III (hazard ratio: 0.837 [95% CI: 0.541 to 1.295]; p = 0.4253). The reduction in mortality was only significant in NYHA functional class II patients.

Considering only those patients receiving placebo, there were fewer deaths (or equivalent) in patients with ATTRwt compared with ATTRv over the 30 months of ATTR-ACT (49 [36.6%] vs. 27 [62.8%]) (Central Illustration). This difference was evident both in patients with baseline NYHA functional class I or II (ATTRwt, 25 deaths [27.8%]; ATTRv 12 deaths [50.0%]) and those with baseline NYHA functional class III (ATTRwt, 24 deaths [54.5%]; ATTRv, 15 deaths [78.9%]).

HOSPITALIZATIONS WITH TREATMENT, AND IN UNTREATED PATIENTS, BY GENOTYPE. The reduction in the frequency of CV-related hospitalizations with tafamidis (compared with placebo) was more pronounced in patients with ATTRwt (relative risk ratio: 0.607 [95% CI: 0.492 to 0.750]; p < 0.0001) than in patients with ATTRv (relative risk ratio: 0.938 [95% CI: 0.656 to 1.342]; p = 0.7256) (11).

For only those patients receiving placebo, the frequency of CV-related hospitalizations per year (95% CI) was greater in patients with ATTRv (0.812 [95% CI: 0.623 to 1.074]) than in patients with ATTRwt (0.671 [95% CI: 0.579 to 0.778]).

CENTRAL ILLUSTRATION **All-Cause Mortality With Tafamidis and Placebo in Patients With Wild-Type and With Variant Transthyretin Amyloidosis**



Rapezzi, C. et al. J Am Coll Cardiol HF. 2021;9(2):115–23.

Patients who discontinued due to heart or combined heart and liver transplantation, or due to implantation of a cardiac mechanical assist device, were counted as death for this analysis. CI = confidence interval.

FUNCTIONAL OUTCOMES WITH TREATMENT, AND IN UNTREATED PATIENTS, BY GENOTYPE. Tafamidis reduced the decline in 6MWT distance from baseline to month 30 in ATTRwt (least-squares mean difference from placebo: 77.14 m [95% CI: 55.98 to 98.29 m]; $p < 0.0001$) and ATTRv (79.61 m [95% CI: 21.08 to 138.13 m]; $p = 0.0077$), and the decline in KCCQ-OS score in ATTRwt (12.72 [95% CI: 8.60 to 16.85]; $p < 0.0001$) and ATTRv (18.18 [95% CI: 2.97 to 33.38]; $p = 0.0192$). The difference between tafamidis and placebo was evident within the first 12 months of treatment for both 6MWT distance (Figure 1) and KCCQ-OS score (Figure 2). Tafamidis also reduced the increase in mean levels of NT-proBNP from baseline, compared with placebo, in patients with ATTRwt and patients with ATTRv (Figure 3).

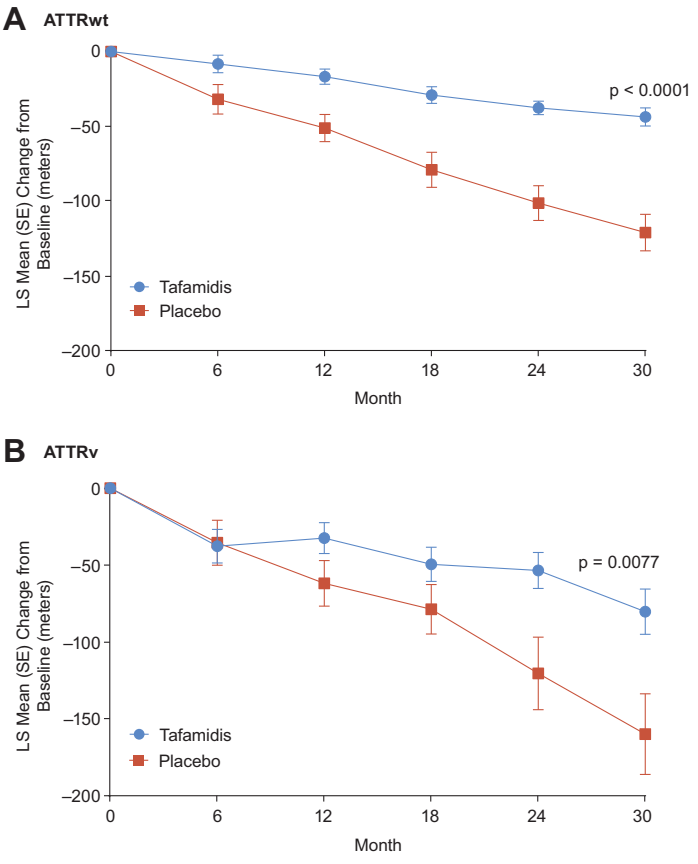
In only those patients receiving placebo, the change in 6MWT distance from baseline to month 30

TABLE 3 **Relative Risk Reduction (95% CI) in All-Cause Mortality at Month 30 With Tafamidis by NYHA Functional Class in ATTRwt and ATTRv**

	ATTRwt	ATTRv
All patients		
n	335	106
HR (95% CI)	0.706 (0.474–1.052)	0.690 (0.408–1.167)
Reduction in risk of death, %	29.4	31.0
NYHA functional class I/II		
n	242	58
HR (95% CI)	0.566 (0.325–0.986)*	0.584 (0.252–1.354)
Reduction in risk of death, %	43.4	41.6
NYHA functional class III		
n	93	48
HR (95% CI)	0.884 (0.501–1.558)	0.795 (0.403–1.567)
Reduction in risk of death, %	11.6	20.5

*p = 0.0445.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 1 LS Mean Change in 6MWT Over 30 Months' Treatment With Tafamidis and Placebo in Patients With ATTRwt and With ATTRv



(A) Numbers of ATTRwt patients at each time point for tafamidis and placebo, respectively, were: baseline, 201 and 134; month 6, 186 and 118; month 12, 175 and 110; month 18, 159 and 93; month 24, 137 and 73; and month 30, 131 and 62. **(B)** Numbers of ATTRv patients at each time point for tafamidis and placebo, respectively, were: baseline, 63 and 43; month 6, 47 and 29; month 12, 41 and 26; month 18, 34 and 18; month 24, 26 and 18; and month 30, 24 and 8. 6MWT = 6-min walk test; ATTRv = variant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; LS = least-squares.

was lower in patients with ATTRwt (least-squares mean ± SE: −120.8 ± 12.2) than ATTRv (−159.9 ± 26.2), as was that in KCCQ-OS score (ATTRwt, −18.3 ± 2.0; ATTRv, −27.4 ± 6.2).

DISCUSSION

ATTR-ACT represents one of the largest collections of follow-up data in both wild-type and hereditary ATTR-CM patients. Importantly, the size of ATTR-ACT permitted the comparison of patient characteristics and disease progression by genotype. In pre-specified analyses of ATTR-ACT, we confirm the poor prognosis of untreated patients with ATTRv-related cardiomyopathy compared with that of patients with ATTRwt, but show that the reduction in mortality and functional decline with tafamidis treatment, as measured by 6MWT and KCCQ-OS, is similar in both disease subtypes.

PROGNOSIS IN ATTRwt AND ATTRv. Prior smaller studies have suggested that patients with the Val122Ile mutation may present with more severe disease and have worse outcomes than patients with ATTRwt (12-15,17). Consistent with these prior studies, in ATTR-ACT almost one-half of patients with ATTRv (the majority of whom were Val122Ile) were NYHA functional class III, compared with approximately one-quarter of patients with ATTRwt. Patients with ATTRv also had worse 6MWT distance and KCCQ-OS scores, and more signs of advanced disease by echocardiography. Furthermore, in patients treated with placebo, there was greater progression of disease over the course of the study, as assessed by mortality, functional capacity, and health status and quality of life in patients with ATTRv.

The greater clinical severity of patients with ATTRv at presentation could have contributed to their worse outcomes. In turn, the more advanced disease in patients with ATTRv at presentation (despite a median age 4 years younger) may be due to either nature (e.g., the presence of a mutation) or nurture (e.g., disparities related to access to care or duration of disease). Emerging data favors a biologic explanation for adverse outcomes in the presence of a mutation; in areas where there is universal access to health care, patients with Val122Ile have worse survival outcomes than patients with ATTRwt (16). Additionally, small studies comparing outcomes among patients with Val122Ile stratified by race do not suggest that outcomes differ between Afro-Caribbeans and Caucasians (20).

IMPACT OF TREATMENT WITH TAFAMIDIS. The primary and key secondary endpoints in ATTR-ACT assessed survival, functional capacity, and health status and quality of life in all patients with ATTR-CM, demonstrating significant and clinically meaningful benefits with tafamidis (11). Tafamidis reduced all-cause mortality and rates of CV-related hospitalizations compared with placebo ($p = 0.0006$), with a notable 30% reduction in the risk of all-cause mortality ($p = 0.0259$) and a 32% reduction in the rate of CV-related hospitalizations ($p < 0.0001$) (11,21). It is notable that despite differences in disease severity and progression between patients with ATTRwt and patients with ATTRv, tafamidis still effectively

reduced mortality and the decline in functional capacity, and health status and quality of life in both genotypes.

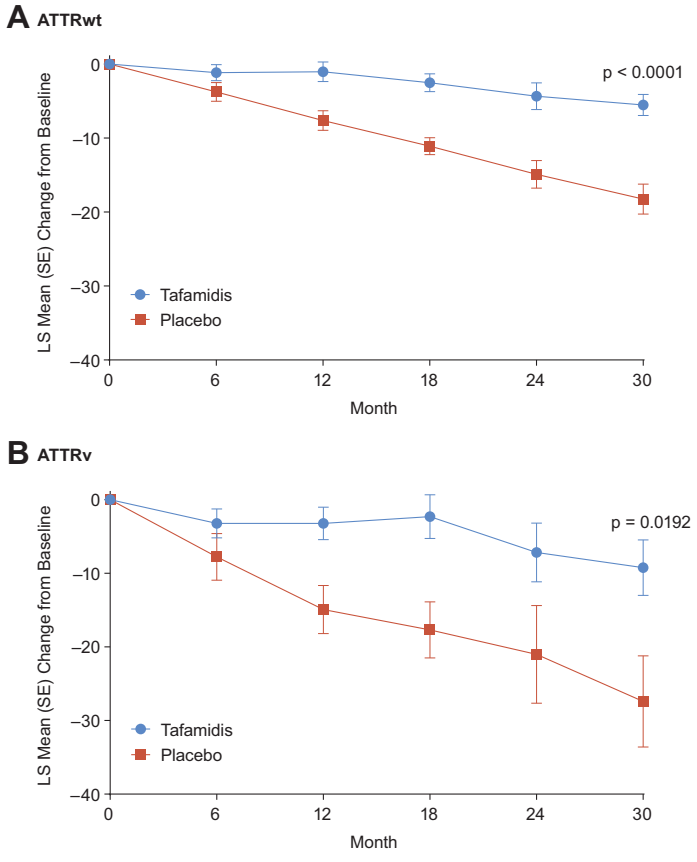
The significant reductions in the decline in functional capacity and health status and quality of life with tafamidis compared with placebo were similar for both patients with ATTRwt and patients with ATTRv. Estimates of the minimum clinically important difference in 6MWT distance in patients with cardiac disease range from 14 to 33 m (22–24), highlighting the clinical importance of the reduction in the decline with tafamidis in ATTR-ACT of approximately 80 m. Similarly, the reduction in the decline in KCCQ-OS of approximately 13 to 18 points with tafamidis was notably higher than the 5-point change considered clinically meaningful (25). Although mean levels of NT-proBNP increased over the study in all groups of patients, this increase over time was reduced with tafamidis compared with placebo. Higher levels of NT-proBNP have previously been shown to be associated with increased mortality in patients with ATTR-CM (26,27).

IMPLICATIONS FOR CLINICAL PRACTICE. In ATTR-ACT, there were relatively few patients who were NYHA functional class I at baseline. In addition, a smaller proportion of patients with ATTRv (6.6%) than patients with ATTRwt (9.0%) were NYHA functional class I at baseline. This suggests that a more widespread application of genetic testing could help to identify currently under-recognized individuals earlier in the course of their disease (17,28).

The efficacy of tafamidis appeared to be greater in patients with less severe disease at baseline (as assessed by NYHA functional class), which highlights the importance of early diagnosis and treatment (29). However, there remained a nonsignificant reduction in the risk of death in patients with more severe disease (NYHA functional class III) and further studies may reveal more details on the efficacy of tafamidis in patients with ATTR-CM with more severe disease. In patients with transthyretin amyloid polyneuropathy, tafamidis has been shown to delay disease progression similarly across patients with a range of baseline disease severities (30).

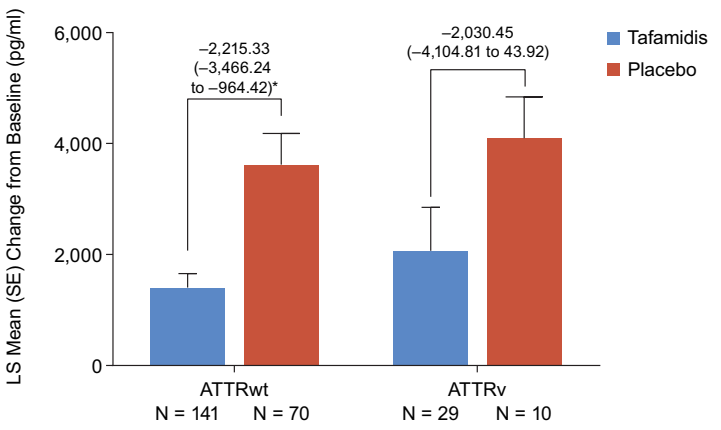
STUDY LIMITATIONS. Clinical trials in rare and underdiagnosed diseases such as ATTR-CM face a number of challenges arising from small patient populations. Subgroup analyses of smaller numbers of patients are even more challenging and can result in greater variability in outcomes and limited power to detect differences. Although these analyses by genotype were pre-specified outcomes of ATTR-ACT, the smaller size of the subgroups may limit generalizability. Further post hoc subgroup analyses, which can only be considered hypothesis generating, are limited by the small numbers of patients. In particular, the smaller number of patients with ATTRv in ATTR-ACT limit further analysis of the efficacy of tafamidis in patients with ATTRv with specific mutations.

FIGURE 2 LS Mean Change in KCCQ-OS Score Over 30 Months' Treatment With Tafamidis and Placebo in Patients With ATTRwt and With ATTRv



(A) Numbers of ATTRwt patients at each time point for tafamidis and placebo, respectively, were: baseline, 201 and 134; month 6, 189 and 123; month 12, 178 and 114; month 18, 165 and 100; month 24, 150 and 82; and month 30, 140 and 74. **(B)** Numbers of ATTRv patients at each time point for tafamidis and placebo, respectively, were: baseline, 63 and 43; month 6, 52 and 36; month 12, 43 and 31; month 18, 36 and 23; month 24, 31 and 14; and month 30, 30 and 10. KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; other abbreviations as in Figure 1.

FIGURE 3 LS Mean Change in NT-proBNP From Baseline to Month 30 With Tafamidis and Placebo in Patients With ATTRwt and With ATTRv



LS mean difference (95% CI) with tafamidis from placebo shown **above the columns**. *$p < 0.05$ for tafamidis compared with placebo. CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 1.

CONCLUSIONS

These pre-specified analyses from ATTR-ACT confirm the poorer prognosis of patients with ATTRv compared with patients with ATTRwt. Notably, treatment with tafamidis similarly reduced mortality and functional decline, as measured by 6MWT and KCCQ-OS, in both disease subtypes. These data strengthen the evidence that tafamidis is an effective therapy for all patients with ATTR-CM, regardless of genotype.

ACKNOWLEDGMENT Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions (funded by Pfizer).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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. This study was sponsored by Pfizer. Dr. Rapezzi has received unrestricted research grants and fees for advisory board meetings from Pfizer. Dr. Elliott has received consultancy fees from Pfizer and Alnylam. Dr. Damy has served on a scientific advisory board for Pfizer; has received funding from Pfizer for scientific meeting expenses; and his institution has received grant support from Pfizer. Dr. Nativi-Nicolau's institution has received funding for clinical trials from Pfizer, Akcea, and Eidos; and has received educational grants from Pfizer. Dr. Nativi-Nicolau has been a consultant for Pfizer, Eidos, Akcea, and Alnylam. Dr. Berk has received consultancy fees from Alnylam Pharmaceutical, Akcea Therapeutics, Intellia Therapeutics, and Corino Therapeutics. Dr. Boman has served on scientific advisory boards for Pfizer; and has received funding for scientific meetings. Mr. Gundapaneni, Drs. Patterson and Sultan are employees of and hold stock options with Pfizer. At the time of this analysis, Dr. Schwartz was an employee of Pfizer; holds stock and stock options with Pfizer, and is now retired. Dr. Maurer has received grant support from the National Institutes of Health (HL HL139671-01, AG R21AG058348, and AG K24AG036778); his institution has received funding for clinical trials from Pfizer, Prothena, Eidos, and Alnylam; and he has received consulting income from Pfizer, GlaxoSmithKline, Eidos, Prothena, Akcea, and Alnylam. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof. Claudio Rapezzi, Cattedra di Cardiologia, Azienda Ospedaliero-Universitaria di Ferrara, Ospedale di Cona, Via Aldo Moro 8, 44124 Cona (Ferrara), Italy. E-mail: claudio.rapezzi@unife.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In ATTR-ACT, tafamidis was shown to improve survival and reduce the decline in measures of functional capacity and health status and quality of life in patients with ATTR-CM. Data from ATTR-ACT confirm the poor prognosis of untreated ATTRv compared with ATTRwt. However, these pre-specified analyses show that the observed reduction in mortality and functional decline with tafamidis treatment is similar in both patients with ATTRwt and with ATTRv.

TRANSLATIONAL OUTLOOK: Clinical trials in patients with ATTR-CM present unique challenges associated with the limited numbers of patients. The efficacy of tafamidis in patients with less severe disease highlights the importance of early diagnosis and treatment. Further studies may provide additional insight into the impact of treatment in patients with more severe disease.

REFERENCES

1. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7:398–408.

2. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012;126:1286–300.

3. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. Amyloid 2015;22:171–4.

4. Jacobson DR, Alexander AA, Tagoe C, et al. The prevalence and distribution of the amyloidogenic transthyretin (TTR) V122I allele in Africa. Mol Genet Genomic Med 2016;4:548–56.

5. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med 2015;372:21–9.

6. Reilly MM, Staunton H, Harding AE. Familial amyloid polyneuropathy (TTR ala 60) in north west Ireland: a clinical, genetic, and epidemiological study. J Neurol Neurosurg Psychiatry 1995;59:45–9.

7. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol 2016;68:161–72.

8. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. Eur Heart J 2013;34:520–8.

9. Waddington Cruz M, Benson MD. A review of tafamidis for the treatment of transthyretin-related amyloidosis. Neurol Ther 2015;4:61–79.

10. 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.

11. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.

12. Givens RC, Russo C, Green P, Maurer MS. Comparison of cardiac amyloidosis due to wild-type and V122I transthyretin in older adults referred to an academic medical center. Aging Health 2013;9:229–35.

13. Maurer MS, Mundayat R, Rapezzi C. Reply: Val122Ile mt-ATTR has a worse survival than wt-ATTR cardiac amyloidosis. J Am Coll Cardiol 2017;69:758–9.

14. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J 2012;164:222–8.e1.

15. Singh A, Geller HI, Falk RH. Val122Ile mt-ATTR has a worse survival than wt-ATTR cardiac amyloidosis. J Am Coll Cardiol 2017;69:757–8.

16. 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.

17. Shah KB, Mankad AK, Castano A, et al. Transthyretin cardiac amyloidosis in black Americans. Circ Heart Fail 2016;9:e002558.

18. Gagliardi C, Perfetto F, Lorenzini M, et al. Phenotypic profile of Ile68Leu transthyretin amyloidosis: an underdiagnosed cause of heart failure. Eur J Heart Fail 2018;20:1417–25.

19. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med 1999;18:1341–54.

20. Cappelli F, Frusconi S, Bergesio F, et al. The Val142Ile transthyretin cardiac amyloidosis: not only an Afro-American pathogenic variant? A single-centre Italian experience. J Cardiovasc Med (Hagerstown) 2016;17:122–5.

21. Pfizer. VYNDAQEL® and VYNDAMAX™ highlights of prescribing information. Available at: https://www.fda.gov/media/126283/download. Accessed September 19, 2019.

22. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD 2005;2:125–9.

23. Gremeaux V, Troisgros O, Benaim S, et al. Determining the minimal clinically important difference for the six-minute walk test and the 200-meter fast-walk test during cardiac rehabilitation program in coronary artery disease patients after acute coronary syndrome. Arch Phys Med Rehabil 2011;92:611–9.

24. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2012;186:428–33.

25. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707–15.

26. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2018;39:2799–806.

27. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014–20.

28. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. JAMA 2019;322:2191–202.

29. Sultan MB, Gundapaneni B, Schumacher J, Schwartz JH. Treatment with tafamidis slows disease progression in early-stage transthyretin cardiomyopathy. Clin Med Insights Cardiol 2017;11:1179546817730322.

30. Gundapaneni BK, Sultan MB, Keohane DJ, Schwartz JH. Tafamidis delays neurological progression comparably across Val30Met and non-Val30Met genotypes in transthyretin familial amyloid polyneuropathy. Eur J Neurol 2018;25:464–8.

KEY WORDS clinical trial, hereditary, tafamidis, transthyretin amyloid cardiomyopathy, wild-type