Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.

METHODS

In a multicenter, international, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 441 patients with transthyretin amyloid cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. In the primary analysis, we hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations according to the Finkelstein–Schoenfeld method. Key secondary end points were the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), in which higher scores indicate better health status.

RESULTS

In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs. 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test (P<0.001) and a lower rate of decline in KCCQ-OS score (P<0.001). The incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo. (Funded by Pfizer; ATTR-ACT ClinicalTrials.gov number, NCT01994889.)

Transthyretin amyloid cardiomyopathy is a life-threatening disease characterized by the accumulation of amyloid fibrils composed of misfolded transthyretin protein in the heart.[1] Misfolded monomers or oligomers of transthyretin are deposited in the myocardium, leading to cardiomyopathy and symptoms of heart failure, including dyspnea, fatigue, orthostatic hypotension, and syncope.[2] Infiltration of the conduction system can lead to bundle-branch block, atrioventricular block, sinoatrial disease, and atrial fibrillation.

Transthyretin amyloid cardiomyopathy is a late-onset disease; symptoms are predominately manifested in male patients 60 years of age or older.[2] The condition can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene *TTR* (ATTRm) or by the deposition of wild-type transthyretin protein (ATTRwt), previously called senile systemic amyloidosis.[3] There are more than 120 pathogenic mutations in *TTR* that result in a variable phenotypic presentation.[2,3] Although the prevalence of ATTRwt is uncertain, studies that use an approach to diagnosis that is not based on biopsy[4,5] have reported a prevalence of 13% among patients with heart failure with a preserved ejection fraction,[6] 16% among patients undergoing transcatheter aortic-valve replacement for severe aortic stenosis,[7] and 5% among patients with presumed hypertrophic cardiomyopathy.[8] Treatments have been limited to supportive care, with no guideline-recommended treatment. Median survival in untreated patients is reported to be 2.5 years after diagnosis for ATTRm caused by the *TTR* Val122Ile mutation and 3.6 years for ATTRwt.[9,10] Death in most patients is from cardiac causes, including sudden death and heart failure.[9]

Transthyretin is a 127-amino acid, 55-kD protein that is primarily synthesized in the liver and transports thyroxine and retinol-binding protein–retinol (vitamin A) complex.[11,12] Fibrillogenesis occurs when the tetrameric structure of the transthyretin protein dissociates into intermediates, which misassemble into soluble oligomers, protofilaments, and amyloid fibrils.[13] Kelly and colleagues discovered that a polymorphism in *TTR* that encodes the amino-acid substitution Thr119Met stabilized the protein in the context of a destabilizing pathogenic variant (Val30Met), leading to the development of tafamidis,[14,15] a benzoxazole derivative lacking nonsteroidal anti-inflammatory drug activity that binds to the thyroxine-binding sites of transthyretin with high affinity and selectivity and inhibits the dissociation of tetramers into monomers. Tafamidis has been shown to slow the progression of peripheral neurologic impairment in transthyretin amyloid polyneuropathy.[16]

With respect to transthyretin amyloid cardiomyopathy, a phase 2, open-label trial involving 31 patients showed that tafamidis (20 mg daily) stabilized transthyretin and had an acceptable safety profile.[17] A single-center, nonrandomized study showed an association between tafamidis and improved survival.[18] The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT)[19] was designed to determine the efficacy and safety of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy.

METHODS

TRIAL OVERSIGHT

ATTR-ACT was a phase 3, multicenter, international, parallel-design, placebo-controlled, double-blind, randomized trial. Details of the trial have been described previously.[19] The trial was overseen by a steering committee that included investigators and the sponsor. ATTR-ACT was approved by the independent review board 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 trial was designed by the sponsor in collaboration with clinicians with experience in the treatment of transthyretin amyloid cardiomyopathy. Investigators collected and held the data in a blinded fashion until the data were analyzed centrally by the sponsor. An external data and safety monitoring board was responsible for monitoring patient safety and conducted unblinded reviews of cumulative trial data. An independent, end-point adjudication committee, whose members were also unaware of the trial-group assignments, determined whether investigator-reported events met the definition of disease-related efficacy end points with the use of predefined end-point criteria, thereby maintaining the scientific integrity of the trial. The statistical analysis was performed by the sponsor, and data tables were provided to the investiga-

tors. All authors participated in the interpretation of the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The first author wrote the first draft. All authors participated in manuscript development and made the decision to publish the results. Agreements between the sponsor of the trial, Pfizer, and the investigators included data confidentiality.

PATIENTS

Patients between 18 and 90 years of age were eligible to participate in ATTR-ACT if they had transthyretin amyloid cardiomyopathy (ATTRwt or ATTRm) confirmed by the presence of amyloid deposits on analysis of biopsy specimens obtained from cardiac and noncardiac sites (e.g., fat aspirate, gastrointestinal sites, salivary glands, or bone marrow) and, in patients without ATTRm, by the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry. Cardiac involvement was confirmed by means of echocardiography, with an end-diastolic interventricular septal wall thickness exceeding 12 mm; a history of heart failure, with at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) manifested in signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic for improvement; an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level greater than or equal to 600 pg per milliliter; and a 6-minute walk-test distance exceeding 100 m.

Patients were excluded if any one of the following criteria was met: they had, in the opinion of the investigator, heart failure that was not due to transthyretin amyloid cardiomyopathy; New York Heart Association (NYHA) class IV heart failure; the presence of light-chain amyloidosis; a history of liver or heart transplantation; an implanted cardiac device; previous treatment with tafamidis; an estimated glomerular filtration rate lower than 25 ml per minute per 1.73 m² of body-surface area; or liver transaminase levels exceeding two times the upper limit of the normal range. Patients were also excluded if they had severe malnutrition as defined by a modified body-mass index (mBMI) of less than 600, calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters), or were receiving concurrent treatment with nonsteroidal antiinflammatory drugs, tauroursodeoxycholate, doxycycline, calcium-channel blockers, or digitalis.

TRIAL DESIGN

Patients were randomly assigned to receive 80 mg of tafamidis, 20 mg of tafamidis, or matching placebo once daily in ratio of a 2:1:2. Stratification was conducted according to TTR status (variant or wild type) and baseline NYHA class. An interactive Web-response system was used. The trial duration was 30 months, and on completion patients were offered enrollment in an extension study. Patients who had adverse events that may have been associated with treatment and may have affected adherence to the dosing regimen or continued participation in the trial were given the option to receive a reduced dose (patients receiving a dose of 80 mg would instead receive a dose of 40 mg, and all others continued to receive the dose assigned at randomization).

ANALYSIS POPULATIONS

The modified intention-to-treat analysis included all patients who were enrolled, received at least one dose of tafamidis or placebo, with both patient and investigator unaware of group assignment, and underwent at least one postbaseline efficacy evaluation (i.e., postbaseline hospitalization, study visit, or death). The safety analysis set included all enrolled patients who received at least one dose of tafamidis or placebo. Because all patients who were enrolled also fulfilled the three other criteria of the modified intention-to-treat analysis, this analysis was effectively also an intention-to-treat analysis.

OUTCOMES

We hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations over the course of the 30-month trial. This analysis compared the results of a pooled tafamidis (80 mg and 20 mg) treatment group with the placebo group. Key secondary end points were change from baseline to month 30 in both distance walked on the 6-minute walk test,[20] a measure of functional capacity, and the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score,[21] which assesses quality of life. Scores range from 0 to 100, with lower
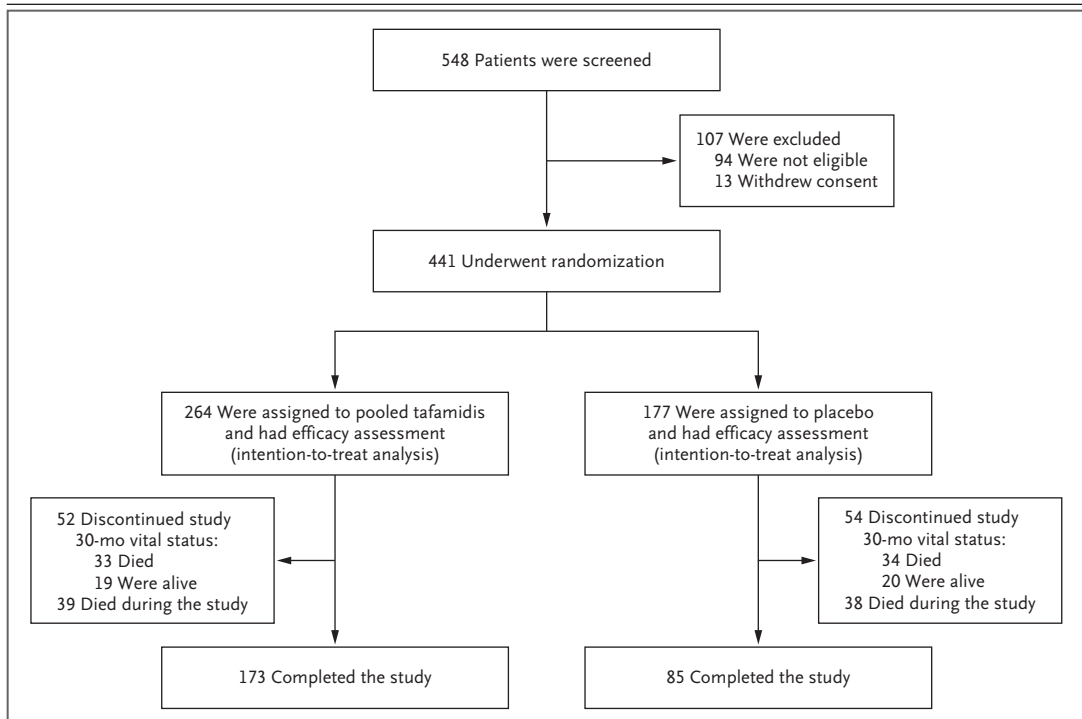
Figure 1. Randomization, Evaluation, and Outcomes.

The most common reasons that screened patients were not admitted to the trial were as follows: closure of enroll-ment (for patients with wild-type transthyretin protein), N-terminal pro-B-type natriuretic peptide level less than 600 pg per milliliter, clinical instability, and an estimated glomerular filtration rate lower than 25 ml per minute per 1.73 m^2 of body-surface area. Among patients assigned to receive tafamidis who did not complete the trial, 25 were no longer willing to participate, 17 had adverse events, 6 underwent organ transplantation, 2 had implantation of a cardiac mechanical assist device (CMAD), 1 was lost to follow-up, and 1 had a protocol violation. Among patients assigned to receive placebo, 37 were no longer willing to participate, 11 had an adverse event, 5 underwent organ transplantation, and 1 had a protocol violation. Vital status at 30 months was available and confirmed for all pa-tients who underwent randomization. The numbers shown do not depict the death count for the purpose of pri-mary analysis. Some reasons for discontinuation (i.e., heart transplantation and CMAD implantation) were treated as death in the primary analysis. The total number of actual deaths was 144.

scores denoting poorer quality of life. Vital status at month 30 was assessed for all enrolled patients.

STATISTICAL ANALYSIS

A sample size of 400 patients was estimated to give the trial power of at least 90% to detect a 30% reduction in mortality, a reduction in the frequency of cardiovascular-related hospitaliza-tions from 2.5 to 1.5 (over the 30-month dura-tion of the trial), or both given treatment with tafamidis. Our trial population was targeted to comprise at least 30% of patients with ATTRm and at least 30% with ATTRwt. Comparisons were based on the pooled tafamidis treatment groups of 80 mg and 20 mg versus placebo, except for spe-cific dose comparisons. In the primary analysis,

we hierarchically assessed all-cause mortality, fol-lowed by frequency of cardiovascular-related hos-pitalizations with the use of the Finkelstein–Schoenfeld method,[22] which is based on the principle that each patient in the clinical trial is compared with every other patient within each stratum in a pairwise manner. This method gives a higher importance to all-cause mortality. The pairwise comparison proceeds in hierarchi-cal fashion, using all-cause mortality, followed by frequency of cardiovascular-related hospitaliza-tion when patients cannot be differentiated on the basis of mortality. In the analysis of fre-quency of cardiovascular-related hospitalization, when two patients had different follow-up times, the shorter follow-up time was used in compar-

ing the frequency of their cardiovascular-related hospitalizations.

We applied the Finkelstein–Schoenfeld method to the patients stratified according to NYHA class at baseline (class I or II vs. class III) and *TTR* status (variant vs. wild-type), yielding four stratification pools. Heart transplantation, heart and liver transplantation, and implantation of a mechanical cardiac-assist device were treated as death for the purposes of this analysis. Only one patient underwent liver transplantation alone, and this event was not treated as a death. All-cause mortality was analyzed with the use of a Cox proportional-hazards model, with treatment and the stratification factors treated as covariates.

We compared the frequency of cardiovascular-related hospitalizations with the use of a Poisson regression model, with treatment, *TTR* status (variant and wild type), NYHA baseline class (NYHA classes I and II combined vs. NYHA class III), treatment-by-*TTR* status interaction, and treatment-by-NYHA baseline class interaction terms as factors, with adjustment for treatment duration. The key secondary end points were assessed with the use of a mixed-effect model, repeated-measure approach and analysis of covariance,[23] with an unstructured covariance matrix. Center and patient-within-center were treated as random effects, and treatment, visit, *TTR* status (ATTRm vs. ATTRwt), and visit-by-treatment interaction were treated as fixed effects, with the baseline value as covariate. A prespecified hierarchical testing order (the 6-minute walk test, followed by the KCCQ-OS) provided multiplicity protection against type 1 error. The remaining secondary and exploratory analyses and end points were not adjusted for multiplicity.

RESULTS

PATIENT CHARACTERISTICS

From December 2013 through August 2015, a total of 548 patients were screened and 441 patients enrolled at 48 sites in 13 countries; 264 patients received tafamidis (80 mg or 20 mg) and 177 patients received placebo (Fig. 1; and Table S1 in the Supplementary Appendix, available at NEJM.org.). Overall, baseline characteristics in the two groups were balanced (Table 1, and Table S2 in the Supplementary Appendix). The median age was 75 years, and patients were predominantly male.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tafamidis (N=264)	Placebo (N=177)
Age — yr		
Mean	74.5±7.2	74.1±6.7
Median (range)	75 (46–88)	74 (51–89)
Sex — no. (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race — no. (%)		
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
TTR genotype — no. (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
Blood pressure — mm Hg		
Supine		
Systolic	115.4±15.4	115.1±15.7
Diastolic	70.4±10.3	70.2±9.5
Standing		
Systolic	115.5±15.5	115.9±15.9
Diastolic	70.6±9.9	71.0±10.3
Heart rate, mean — beats per minute		
Supine	70.7±12.3	69.9±11.7
Standing	72.9±12.9	73.8±12.2
NYHA Class — no. (%)		
Class I	24 (9.1)	13 (7.3)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5)	63 (35.6)
Modified BMI†	1058.8±173.8	1066.4±194.4
NT-proBNP level — pg/ml		
Median	2995.9	3161.0
Interquartile range	1751.5–4861.5	1864.4–4825.0

* Plus–minus values are means ±SD. There were 264 patients in the tafamidis group and 177 patients in the placebo group in both the intention-to-treat and safety analyses. Percentages may not total 100 because of rounding. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide, and NYHA New York Heart Association.
† The modified body-mass index (BMI) is calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters).
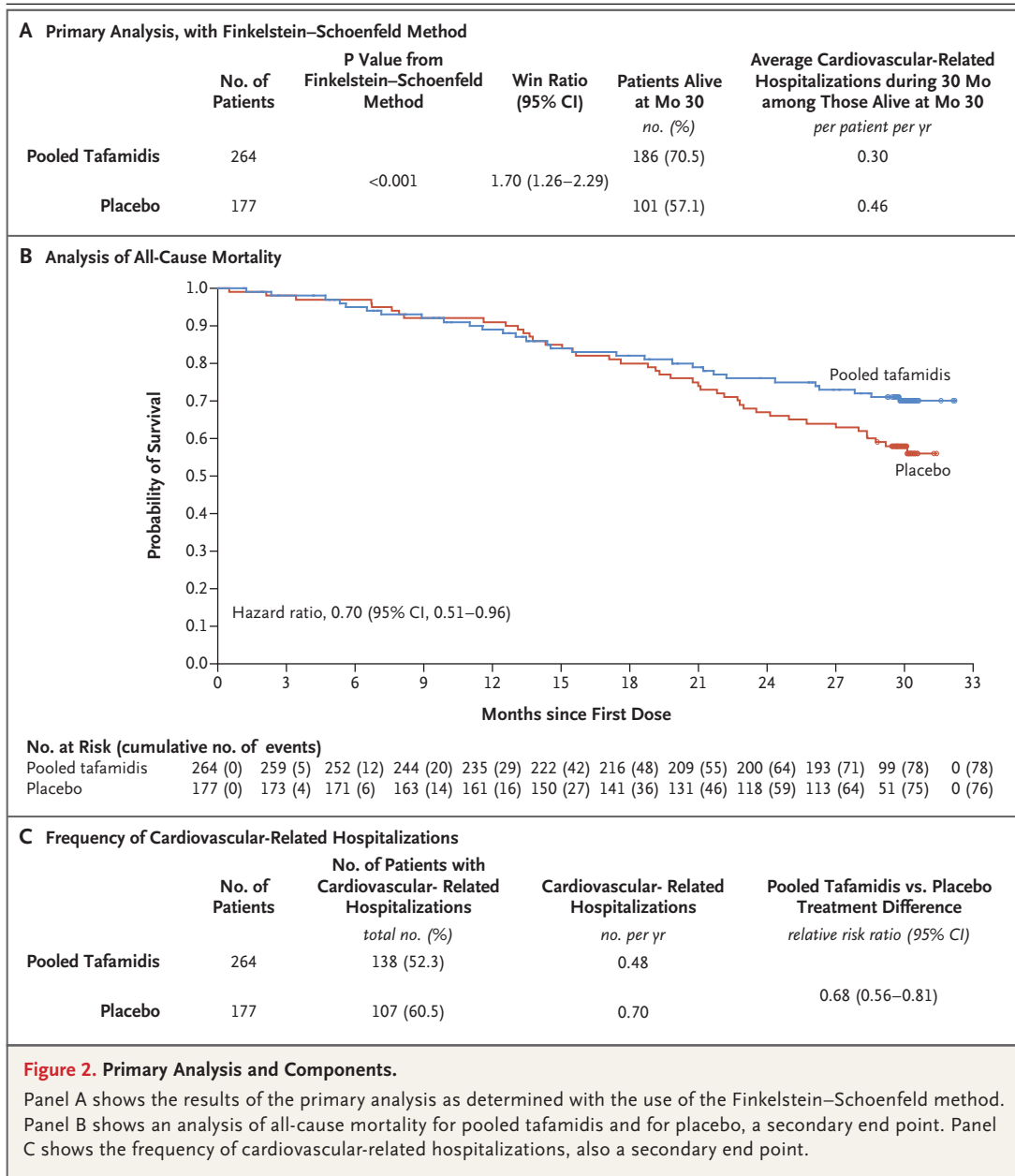
A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264			186 (70.5)	0.30
		<0.001	1.70 (1.26–2.29)		
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality

Hazard ratio, 0.70 (95% CI, 0.51–0.96)

No. at Risk (cumulative no. of events)
Pooled tafamidis 264 (0) 259 (5) 252 (12) 244 (20) 235 (29) 222 (42) 216 (48) 209 (55) 200 (64) 193 (71) 99 (78) 0 (78)
Placebo 177 (0) 173 (4) 171 (6) 163 (14) 161 (16) 150 (27) 141 (36) 131 (46) 118 (59) 113 (64) 51 (75) 0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	
				0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Figure 2. Primary Analysis and Components.
Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.

Among those who underwent randomization, 106 (24%) had ATTRm with Val122Ile, Thr60Ala, and Ile68Leu being the most common mutations. Predefined treatment adherence (taking ≥80% of scheduled doses) was high, at 97.2% for tafamidis and 97.0% for placebo.

EFFICACY

In the primary analysis that hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalization, according to analyses performed with the Finkelstein–Schoenfeld method, treatment with tafamidis was superior to placebo over 30 months (P<0.001). The win ratio[24] (number of pairs of treated-patient "wins" divided by number of pairs of placebo-patient "wins") may be helpful in interpreting the Finkelstein–Schoenfeld result. The win ratio is 1.695 (95% confidence interval [CI], 1.255 to 2.289). According to Cox regression analysis, all-cause mortality was lower with tafamidis than with placebo (78 of 264 [29.5%] vs. 76 of 177
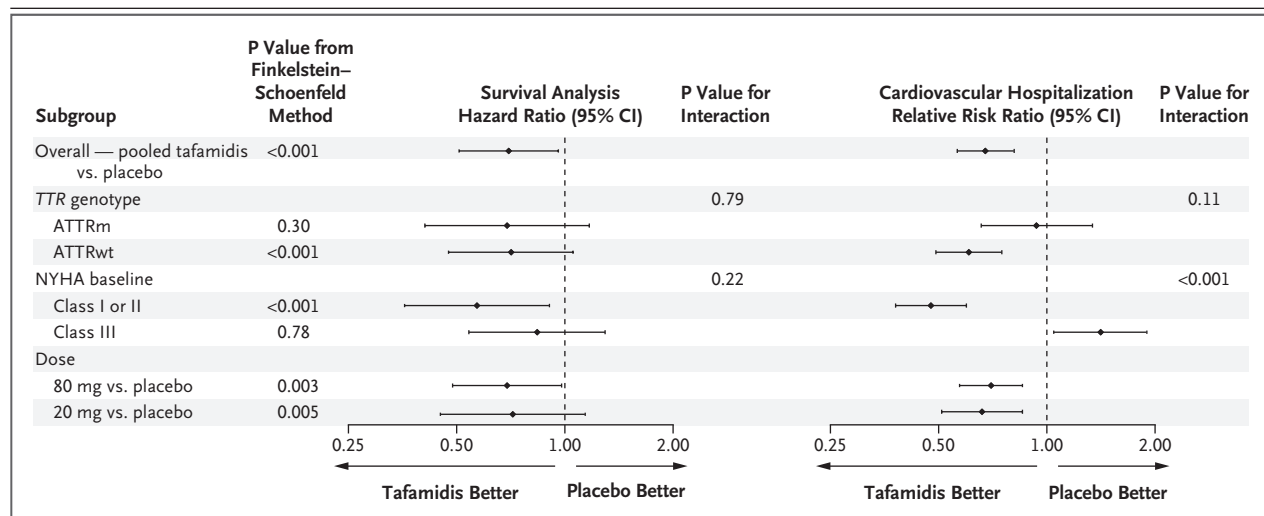
Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.
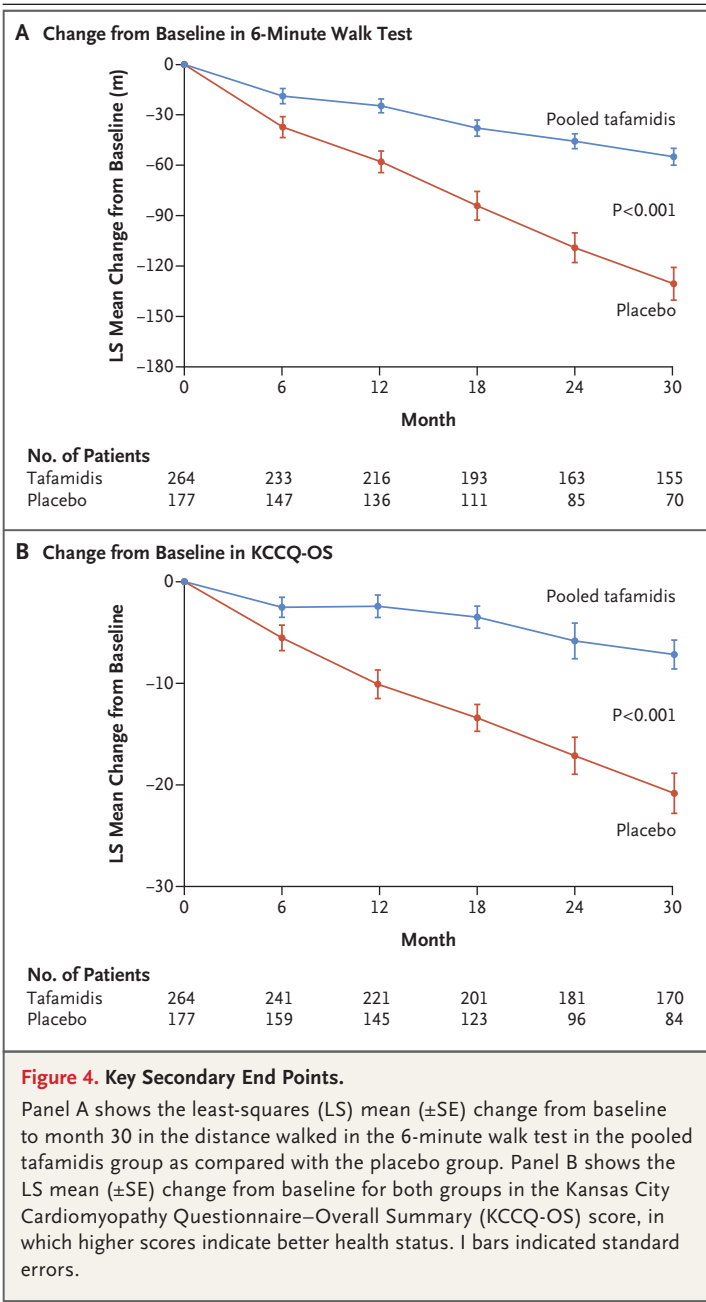
All-cause mortality was evaluated with the use of a Cox proportional-hazards model, with treatment and stratification factors treated as covariates. The survival analysis interaction terms are based on a post hoc analysis. The frequency of cardiovascular-related hospitalizations was assessed with the use of a Poisson regression model. ATTRm denotes disease that results from an inherited autosomal dominant trait that is caused by pathogenic mutations in *TTR,* ATTRwt disease that results from the deposition of wild-type transthyretin protein, and NYHA New York Heart Association.

[42.9%]; hazard ratio, 0.70; 95% CI, 0.51 to 0.96). According to the Poisson regression analysis, the rate of cardiovascular-related hospitalizations (0.48 vs. 0.70 hospitalizations per year; relative risk ratio, 0.68; 95% CI, 0.56 to 0.81) was lower with tafamidis than with placebo (see Table S3 in the Supplementary Appendix for post hoc negative binomial analysis). Kaplan–Meier survival curves showed that tafamidis resulted in a reduction in all-cause mortality, with the curves diverging after approximately 18 months of treatment (Fig. 2). Across prespecified subgroups, including those based on *TTR* status (ATTRwt vs. ATTRm), NYHA class (I or II vs. III), and tafamidis dose (80 mg vs. 20 mg), the difference in all-cause mortality and frequency of cardiovascular-related hospitalizations favored tafamidis over placebo, except in patients with NYHA class III disease at baseline, among whom the rates of cardiovascular-related hospitalizations were higher among patients receiving tafamidis than among those receiving placebo (Fig. 3). Using a prespecified Poisson-regression analysis, we observed an interaction between treatment and NYHA baseline classification. We did not observe an interaction between treatment and *TTR* status. A prespecified sensitivity analysis of all-cause mortality

that did not treat transplantation involving heart transplantation or implantation of a cardiac mechanical assist device as death yielded a hazard ratio of 0.67 (95% CI, 0.49 to 0.94). An additional post hoc analysis of time to first cardiovascular-related hospitalization is provided (see Fig. S1 in the Supplementary Appendix).

Key secondary end points included the change from baseline to month 30 in the distance walked during the 6-minute walk test and in KCCQ-OS score. Tafamidis reduced the decline in the distance walked during the 6-minute test as compared with placebo (75.68 m [standard error, ±9.24; P<0.001]), with differences first observed at month 6 (Fig. 4A). Tafamidis also reduced the decline in the KCCQ-OS score as compared with placebo (13.65 [standard error, ±2.13; P<0.001]), with differences first observed at month 6 (Fig. 4B).

Exploratory end points included a smaller increase in the NT-proBNP level among patients receiving tafamidis than among those receiving placebo at months 12 and 30 (least-squares mean difference, −735.14 [95% CI, −1249.16 to −221.13] at 12 months and −2180.54 [95% CI, −3326.14 to −1034.95] at 30 months). Directionally positive echocardiographic findings (see Table S4 in the Supplementary Appendix), including a smaller de-

1013

A Change from Baseline in 6-Minute Walk Test

No. of Patients						
Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

B Change from Baseline in KCCQ-OS

No. of Patients						
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Figure 4. Key Secondary End Points.

Panel A shows the least-squares (LS) mean (±SE) change from baseline to month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. Panel B shows the LS mean (±SE) change from baseline for both groups in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score, in which higher scores indicate better health status. I bars indicated standard errors.

crease in left ventricular stroke volume (least-squares mean difference, 6.28), were noted at month 30.

SAFETY AND ADVERSE EFFECTS

The safety profiles of tafamidis and placebo were similar. There was no meaningful difference in the safety of the two doses of tafamidis. Adverse events that emerged during treatment were gen-

erally mild to moderate in severity, and permanent discontinuation of tafamidis or placebo as a result of adverse events was less common in the tafamidis groups than in the placebo group (Table S5 in the Supplementary Appendix). Dose reduction related to adverse events were uncommon (two patients receiving tafamidis [0.8%] and four patients receiving placebo [2.3%]). The results of laboratory analyses related to safety did not differ between the tafamidis and placebo groups. Both diarrhea and urinary tract infections, adverse events previously reported in patients with familial amyloid polyneuropathy,[25] were less common in patients who received tafamidis than in those who received placebo. The most frequent adverse events are summarized in the Supplementary Appendix.

DISCUSSION

ATTR-ACT showed that tafamidis is superior to placebo in reducing the combination of all-cause mortality and cardiovascular-related hospitalizations. The evidence also supports the assertion that the risk of each component, when analyzed independently of the other, is reduced. Tafamidis was also associated with a significant reduction in the decline in functional capacity (as measured by the 6-minute walk test) and the decline in quality of life (as measured by the KCCQ-OS) at month 30, with differences first observed at 6 months. In contrast, the effect on overall survival emerged after approximately 18 months. This dissociation between the effect on symptoms and survival has also been observed with other therapies for systolic heart failure in which ventricular remodeling takes months to achieve.[26-28]

We observed a consistent benefit from tafamidis related to mortality across all subgroups. We also observed fewer cardiovascular-related hospitalizations among those who received tafamidis across all subgroups, with the exception of those with NYHA class III. We speculate that the higher hospitalization rate observed in this group is attributable to longer survival during a more severe period of disease, underscoring the importance of early diagnosis and treatment of this fatal, progressive disease, which can be difficult to diagnose.[29] Given the progressive nature of the disease and the mechanism through which tafamidis reduces amyloidogenesis — by specifically

stabilizing transthyretin tetramers — the drug is expected to have greater benefit when administered early in the disease course.[30]

When the trial was designed, tissue biopsy was required for diagnosis, but an approach without biopsy — in which technetium-labeled bone scintigraphy tracing is used instead — has been validated as a method for the identification of patients. This approach is highly sensitive and specific for the diagnosis of transthyretin amyloid cardiomyopathy[4,5,31] and can detect amyloid deposits before an increase in left ventricular wall thickness or the clinical syndrome of heart failure and a rise in cardiac biomarkers has occurred.[32,33] This method can even predict prognosis.[5,34] Early identification and treatment are now more likely given the availability of effective diagnostic tools and therapy.

Similarly, innovative methods are being developed and used for research in rare disease. In studies of rare disease such as transthyretin amyloid cardiomyopathy, small patient populations often limit recruitment and hinder the conduct of randomized trials. The Finkelstein–Schoenfeld method, used in this trial, is a validated technique that increases the sensitivity and power of the analysis of smaller cohorts and prioritizes the importance of mortality while also addressing morbidity.

The overall incidence and type of adverse events were similar in the tafamidis and placebo groups. Discontinuation of the trial drug owing to adverse events that occurred during treatment was less common in patients who received tafamidis than in those who received placebo, and dose reductions were uncommon and occurred more often in the placebo group.

In conclusion, in patients with heart failure due to transthyretin amyloid cardiomyopathy, treatment with tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations as compared with placebo. Tafamidis treatment also significantly reduced the decline in functional capacity and quality of life. These findings indicate that tafamidis is an effective therapy for patients with transthyretin amyloid cardiomyopathy.

APPENDIX

From the Columbia University Vagelos College of Physicians and Surgeons (M.S.M.) and Pfizer (J.H.S., A.I.B., P.H., J.S., M.B.S.), New York; Syneos Health, Raleigh, NC (B.G.); University College London and St. Bartholomew's Hospital, London (P.M.E.); the Amyloidosis Center, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, and the University of Pavia, Pavia (G.M.), and the Department of Experimental, Diagnostic, and Specialty Medicine, University of Bologna, Bologna (C.R.) — both in Italy; the Amyloidosis Center (CEPARM), Federal University of Rio de Janeiro, Rio de Janeiro (M.W-C.); the Amyloidosis Center, Medical University of Heidelberg, Heidelberg, Germany (A.V.K.); the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (M.G.); Stanford University School of Medicine, Stanford, CA (R.W.); the French Referral Center for Cardiac Amyloidosis, Amyloidosis Mondor Network, GRC Amyloid Research Institute and Department of Cardiology, Assistance Publique–Hôpitaux de Paris, CHU Henri Mondor, and INSERM Unité 955, Clinical Investigation Center 006, and DHU ATVB, Creteil, France (T.D.); Penn Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia (B.M.D.); the Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago (S.J.S.); Cleveland Clinic, Cleveland (M.H.); the Medical University of South Carolina, Charleston (D.P.J.); and Pfizer, Groton, CT (T.A.P., S.R., M.S.).

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1015

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