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ORIGINAL RESEARCH

Effect of Tafamidis on Renal Function in Patients With Transthyretin Amyloid Cardiomyopathy in ATTR-ACT

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ABSTRACT

BACKGROUND Chronic kidney disease (CKD) is common among patients with amyloid cardiomyopathy. Tafamidis was approved for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) based on findings from ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy).

OBJECTIVES This post hoc analysis evaluated changes in renal function among patients with ATTR-CM in ATTR-ACT.

METHODS Patients were randomized to receive tafamidis (20 mg and 80 mg pooled) or placebo for 30 months. The change from baseline in the estimated glomerular filtration rate (eGFR) was compared over time. A composite endpoint of all-cause death, dialysis, kidney transplant, or ≥30% decline in eGFR from baseline was analyzed based on the time to first event.

RESULTS The mean baseline eGFR was 57.5 ± 17.3 and 55.6 ± 16.8 mL/min/1.73 m^2 in the tafamidis (n = 264) and placebo (n = 177) groups, respectively. At 30 months, patients treated with tafamidis had a significantly smaller decline in eGFR compared with placebo (least squares mean difference = 3.99 mL/min/1.73 m^2; 95% CI: 1.31-6.68; $P = 0.004$). In patients who completed ATTR-ACT, improvement in CKD staging was more common with tafamidis vs placebo treatment (17.7% vs 7.2%; OR: 2.75; 95% CI: 1.10-6.90; $P = 0.034$). A lower proportion of tafamidis-treated patients reached the composite renal endpoint (crude rates 34.5% vs 44.1%; HR: 0.73, 95% CI: 0.54-0.99; $P = 0.040$).

CONCLUSIONS Renal function deteriorates over time in patients with ATTR-CM, and tafamidis treatment was associated with a reduction in this deterioration, and a higher incidence of improved eGFR and CKD staging over 30 months compared with placebo. (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy [ATTR-ACT] NCT01994889) (J Am Coll Cardiol CardioOnc 2024;6:300-306) © 2024 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/).

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized cause of heart failure/restrictive cardiomyopathy and carries a poor prognosis.[1] Tafamidis is a transthyretin protein stabilizer that was found to reduce all-cause mortality and cardiovascular-related hospitalizations compared with placebo in ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy).[2] This was coupled with changes in 6-minute walk test distance and patient-reported health status (as measured by the Kansas City Cardiomyopathy Questionnaire) significantly favoring treatment with tafamidis.

Renal failure is common in patients with heart failure, and the degree of renal dysfunction predicts excess mortality.[3] Renal dysfunction is also comorbid with amyloidosis, and patients in ATTR-ACT on average had stage 3 chronic kidney disease (CKD). The effect of amyloid-specific treatment on renal function in patients with ATTR-CM is unclear. In this analysis, we investigated the hypothesis that patients treated with tafamidis have significant stabilization or improvement in renal function compared with placebo.

METHODS

ATTR-ACT was a randomized, placebo-controlled, multinational clinical trial of tafamidis vs placebo in patients with ATTR-CM.[2] Briefly, patients with NYHA functional class I, II, or III heart failure and 18 to 90 years of age were eligible for enrollment if their N-terminal pro-B-type natriuretic peptide concentration was ≥600 pg/mL and their 6-minute walk test distance was >100 m. Patients requiring dialysis or those with an estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2 of body surface area (by Modification of Diet in Renal Disease equation) were excluded. Randomization to study drug vs placebo proceeded on a 2:1:2 basis (tafamidis meglumine 80 mg, tafamidis meglumine 20 mg, or placebo). Currently, a free acid formulation of tafamidis is available at 61 mg, which is bioequivalent to the tafamidis meglumine 80-mg dose. The primary outcome was the hierarchical combination of death and frequency of cardiovascular-related hospitalization at 30 months as analyzed using the Finkelstein-Schoenfeld method.[2,4] The study followed the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by the Institutional Review Boards of each institution. All patients provided written informed consent.

In this post hoc analysis, renal function was compared between tafamidis- (pooled 20 mg and 80 mg) and placebo-treated patients. The serum creatinine concentration was measured at baseline and at each follow-up time period. eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation without race.[5] The stage of renal failure was calculated at each time period using standard CKD eGFR cutoff values, with stage 3 being split into stage 3a and 3b. A composite renal endpoint was evaluated, which included all-cause death, dialysis, kidney transplant, or ≥30% decline in eGFR from baseline to 30 months.

Categoric variables are presented as a frequency (n) and percentage and were analyzed with the chi-square test or the Fisher exact test when the count was <10. Continuous variables are expressed as mean ± SD or median with 25th to 75th percentiles. The change from baseline in eGFR was analyzed using a mixed-effects model for repeated measures with an unstructured covariance matrix.[2] In this analysis, center and patient within center were included as random effects; treatment, visit, transthyretin genotype, and visit-by-treatment interaction were included as fixed effects; and baseline score was included as a covariate. Because this is a post hoc analysis, no correction was made for multiple comparisons. Results are presented as the least squares mean change from baseline with 95% CI. A change in renal failure stage from baseline to 30 months was considered as progressed, stable, or improved. The OR for improvement with 95% CI was calculated using logistic regression with only treatment in the model. The composite endpoint of all-cause death, dialysis, kidney transplant, or ≥30% decline in eGFR from baseline was analyzed based on the time to first event using the Cox proportional hazards model, with results presented as HR with 95% CI. In this analysis, treatment, transthyretin genotype, and NYHA functional class at baseline were included as covariates. Patients were censored at the time of heart transplantation, left ventricular device implantation, or study discontinuation. Heart transplantation and left ventricular device implantation were not considered competing risks. A Kaplan-Meier plot is used to present the proportion of patients reaching the composite endpoint with censoring. Statistical

ABBREVIATIONS AND ACRONYMS

ATTR-CM = transthyretin amyloid cardiomyopathy

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

MRA = mineralocorticoid receptor antagonists

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analysis was performed using SAS version 9.4 (SAS Institute). A P value < 0.05 was considered statistically significant.

DATA AVAILABILITY. 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 deidentified participant data.

RESULTS

In ATTR-ACT, 264 patients received tafamidis meglumine (20 or 80 mg), and 177 received placebo (Supplemental Figure 1). The baseline demographics, clinical characteristics, and proportion taking relevant concomitant medications were well-balanced between the groups (**Table 1**, Supplemental Tables 1 and 2). The baseline creatinine concentration in the study was 1.4 ± 0.4 mg/dL, and 264 (60%) patients had CKD stage 3 or worse. The baseline mean eGFR was 57.5 ± 17.3 and 55.6 ± 16.8 mL/min/1.73 m^2 in the tafamidis and placebo groups, respectively. Renal function and CKD staging were similar across treatment groups.

After 30 months, patients treated with tafamidis had a significantly smaller decline in eGFR compared with patients treated with placebo (**Central Illustration**). The least squares mean change from baseline in eGFR was significantly better in tafamidis-treated vs placebo-treated patients starting at month 18 and continuing to month 30, with a difference of 3.99 mL/min/1.73 m^2 (95% CI: 1.31-6.68; $P = 0.004$) at month 30.

In patients who completed ATTR-ACT, a greater proportion treated with tafamidis vs placebo had an improvement in eGFR from baseline to 30 months (defined as change >0 mL/min/1.73 m^2) when assessed using continuous eGFR (35.3% vs 22. 9%; OR: 1.84; 95% CI: 1.01-3.35). A sensitivity analysis was performed assuming participants with missing month 30 data did not improve, noting a higher proportion of patients with improved eGFR randomized to tafamidis vs placebo (22.7% vs 10.7%; OR: 2.45; 95% CI: 1.40-4.27).

Additionally, in patients who completed ATTR-ACT, improvement in renal function assessed by CKD staging was more common with tafamidis vs placebo treatment (17.7% vs 7.2%), and worsening of CKD stage was more common with placebo (42.2% vs 34.1%) (**Figure 1A**). There was a 2.75 times greater odds of improved CKD stage with randomization to tafamidis vs placebo (95% CI: 1.10-6.90; $P = 0.034$). At 30 months, patients were more likely to remain in better CKD stages if randomized to tafamidis vs placebo (**Figure 1B**).

TABLE 1 Demographics and Clinical Characteristics of Enrolled Patients at Baseline

	Pooled Tafamidis (n = 264)	Placebo (n = 177)
Age, y[a]		
Mean ± SD	74.5 ± 7.2	74.1 ± 6.7
Sex[a]		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race[a]		
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
Baseline creatinine, mg/dL	1.4 ± 0.4	1.4 ± 0.4
Baseline eGFR,[b] mL/min/1.73 m^2	57.5 ± 17.3	55.6 ± 16.8
CKD stage at baseline		
1: Normal or high	9 (3.4)	7 (4.0)
2: Mild	101 (38.3)	60 (33.9)
3a: Mild to moderate	94 (35.6)	63 (35.6)
3b: Moderate to severe	47 (17.8)	38 (21.5)
4: Severe	13 (4.9)	9 (5.1)
5: Kidney failure	0	0
NAC stage		
I	119 (45.1)	71 (40.1)
II	95 (36.0)	72 (40.7)
III	50 (18.9)	34 (19.2)
Diabetes at baseline[a]	20 (7.6)	13 (7.3)
Hypertension at baseline[a]	145 (54.9)	84 (47.5)

Values are mean ± SD or n (%). [a]Previously published in Maurer et al.[2] [b]Calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine without race equation.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NAC = National Amyloidosis Centre.

The composite endpoint (all-cause death, kidney transplant, dialysis initiation, or ≥30% decline in eGFR from baseline) was reached in a lower proportion of patients in the tafamidis group compared with the placebo group (crude rates 34.5% vs 44.1%; HR: 0.73; 95% CI: 0.54-0.99; $P = 0.040$) (**Table 2**, with Kaplan-Meier plot taking censoring into account in **Figure 2**). This was irrespective of dose and driven by fewer all-cause deaths or declines in eGFR at 30 months because only 3 patients in the study received dialysis or underwent kidney transplantation (**Table 2**).

DISCUSSION

Progressive renal dysfunction is common in patients with ATTR-CM and heart failure and is a harbinger for other adverse outcomes such as hospitalization and

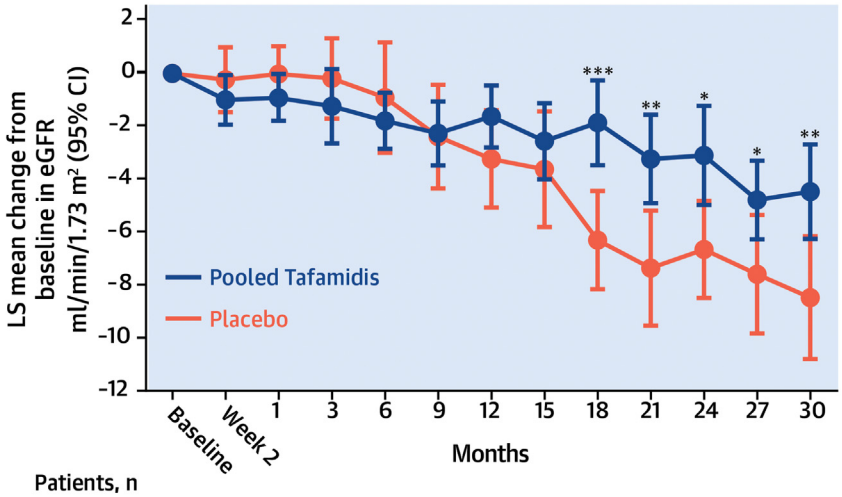
CENTRAL ILLUSTRATION **Change From Baseline in Estimated Glomerular Filtration Rate in Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy**

Post-hoc analysis of change in renal function in ATTR-CM
Phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial
(ATTR-ACT, NCT01994889)

ATTR patients randomized to tafamidis (20 mg and 80 mg pooled) or placebo for 30 months

At 30 months:

- There was a smaller decline in eGFR (P <0.01)
- CKD staging improvement was more common (OR: 2.75, 95% CI: 1.60-6.90)
- A lower proportion reached the composite endpoint of all-cause death, kidney transplant, dialysis initiation, or ≥30% decline in eGFR from baseline (35.1% vs 44.1% P = 0.040)



Patients, n

Tafamidis:	264	253	256	251	239	232	219	205	196	189	180	177	170
Placebo:	177	166	175	170	156	145	142	128	121	106	93	88	83

*P <0.05; **P <0.01; ***P <0.001

While renal function deteriorates over time in patients with ATTR-CM, tafamidis was associated with a reduction in this decline and a greater odds of improvement over 30 months.

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Estimates for the least squares (LS) mean change from baseline in the estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2) are from a mixed-effects model for repeated measures analysis with an unstructured covariance matrix. Bars denote the 95% CI. Center and patient within center were included as random effects. Treatment, visit, transthyretin genotype, and visit-by-treatment interaction were included as fixed effects and baseline score as a covariate. The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine without race equation. No corrections were made for multiple comparisons. *P < 0.05. **P < 0.01. ***P < 0.001. ATTR-ACT = Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy; ATTR-CM = transthyretin amyloid cardiomyopathy; CKD = chronic kidney disease.

death. In this post hoc analysis of ATTR-ACT, we found that treatment with tafamidis was associated with reduced progression of renal dysfunction in patients with ATTR-CM. Similarly, more patients were alive with stable renal function if randomized to tafamidis vs placebo. These data have important implications for the multisystem benefit of disease-modifying therapy in ATTR-CM.

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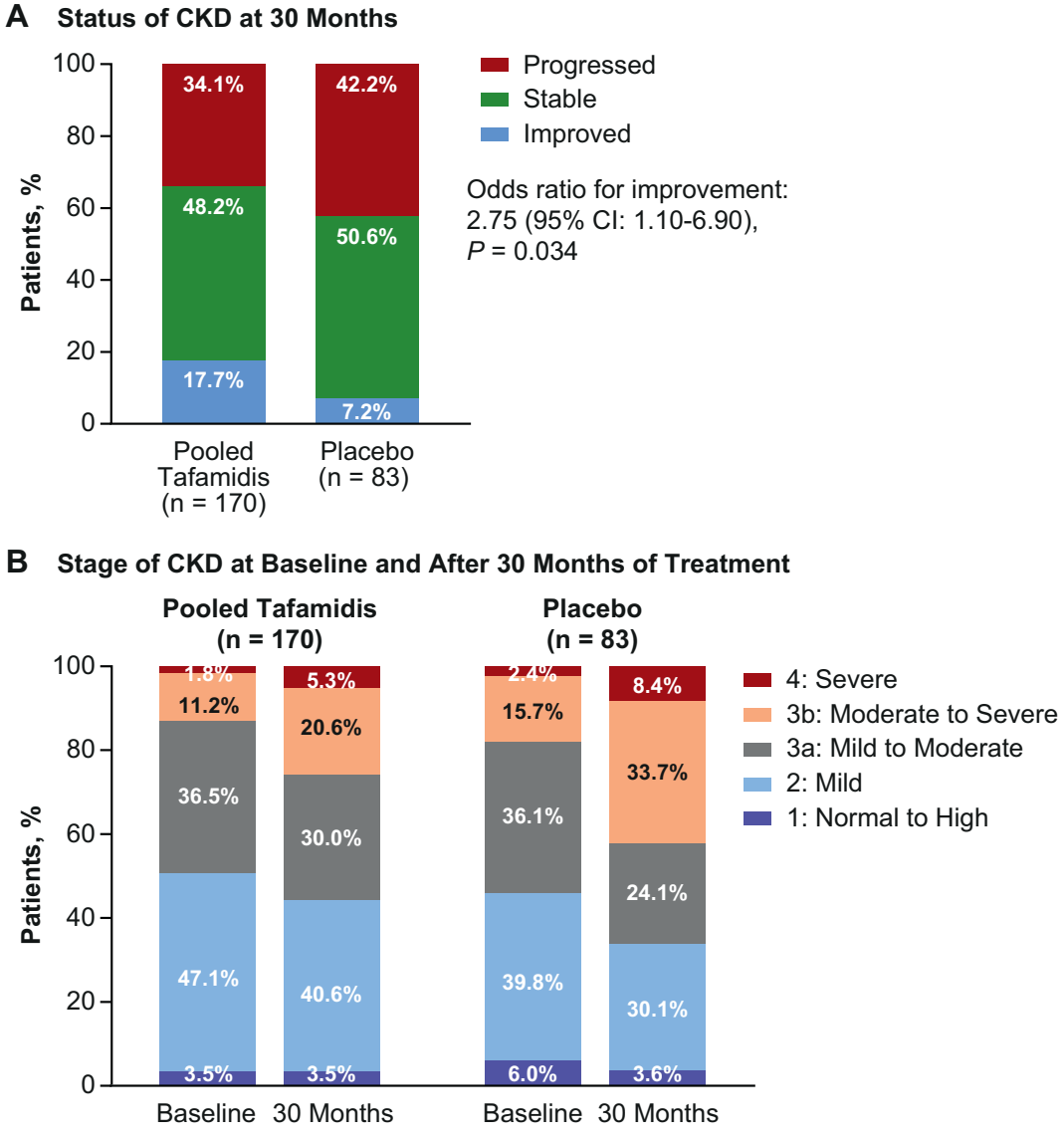
FIGURE 1 Status and Stage of CKD at 30 Months



(A) The status of chronic kidney disease (CKD) in patients who completed 30 months of treatment in Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT). (B) The stage of CKD at baseline and after 30 months of treatment in ATTR-ACT.

Renal dysfunction is common in patients with cardiac amyloidosis. Baseline creatinine concentration was 1.4 mg/dL with eGFR of 56 mL/min/1.73 m^2 in this study, and 60% of patients had CKD stage 3 or worse. The staging system for transthyretin amyloid cardiac amyloidosis from the United Kingdom incorporates eGFR into disease stage, and the baseline eGFR was 61 mL/min/1.73 m^2 in that cohort of 869 patients.[6] In light chain amyloidosis, an elevated serum creatinine concentration is associated with more severe disease, although measures of renal function are not included in either the Mayo or Boston University staging systems.[7,8]

It is thought that cardiorenal syndrome is the most common pathophysiologic mechanism of progressive renal dysfunction in cardiac amyloidosis. The reduction in cardiac output and renal blood flow seen in severe amyloid cardiomyopathy coupled with venous

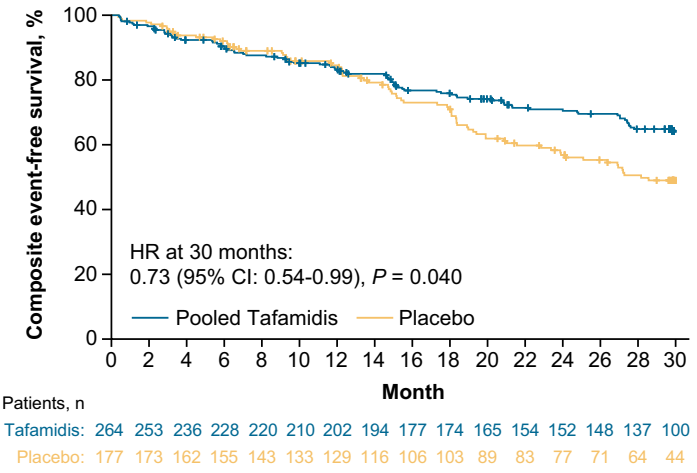
TABLE 2 Composite Outcome

	Pooled Tafamidis[a] (n = 264)	Placebo (n = 177)
Patients who reached the composite endpoint	91 (34.5)	78 (44.1)
≥30% decline in eGFR from baseline to 30 months	60 (22.7)	51 (28.8)
All-cause death	29 (11.0)	26 (14.7)
Dialysis	1 (0.4)	1 (0.6)
Kidney transplant	1 (0.4)	0 (0)

Values are n (%). These numbers and crude percentages reflect an analysis of first events that contribute to the composite endpoint at month 30. Six patients in the pooled tafamidis group and 1 in the placebo group were censored during follow-up because of receipt of a heart transplantation or left ventricular device implantation without meeting the composite endpoint. [a]HR for reaching the composite endpoint in patients taking tafamidis meglumine 20 mg vs 80 mg was 0.77 (95% CI: 0.48-1.21).

eGFR = estimated glomerular filtration rate.

FIGURE 2 Composite Endpoint



A Kaplan-Meier curve showing the time from baseline to event for the composite endpoint of all-cause death, kidney transplant, dialysis initiation, or ≥30% decline in estimated glomerular filtration rate. Patients treated with tafamidis were less likely to reach this endpoint at 30 months compared with those treated with placebo (crude rates 34.5% vs 44.1%; HR: 0.73; 95% CI: 0.54-0.99; $P = 0.040$). + = censored.

congestion sets the stage for abnormalities in renal function. Amyloid cardiomyopathy leads to biventricular dysfunction, and increases in right atrial pressure are most correlated with CKD severity.[9] Amyloidosis may also lead to ascites and elevated intra-abdominal pressure, contributing to renal compression and decreased perfusion.[10] However, direct deposition of amyloid fibrils in the renal parenchyma may also be a factor in some cases and subtypes.[11] In light chain cardiac amyloidosis, renal dysfunction may stem from direct light chain deposition in the vascular, tubulointerstitial, and/or glomerular structures in the kidneys,[12] and proteinuria may result from glomerular deposition. In ATTR-CM, direct deposition of the transthyretin protein is relatively uncommon, although it has been noted in pathologic samples from patients, particularly in those with hereditary disease.[13,14] It is possible that imaging studies using amyloid-specific nuclear radiotracers will help clarify the prevalence of direct amyloid deposition in the kidneys. We postulate that the stabilization of renal dysfunction seen with tafamidis vs placebo is most likely related to a slower progression of the cardiorenal syndrome.

Other medications for heart failure with preserved ejection fraction have been used in patients with cardiac amyloidosis, including mineralocorticoid receptor antagonists (MRAs) and sodium glucose cotransporter 2 inhibitors. Steroidal MRAs reduce heart failure hospitalizations and mortality, although the effect size is reduced in patients with eGFR ≤30 mL/min/1.73 m^2.[15] Although these medications show a higher incidence of worsening renal function compared with placebo, the rates of progression of CKD to end-stage renal disease are reduced.[16] A nonsteroidal MRA has also been shown to reduce the risk of CKD progression and cardiovascular events compared with placebo.[17] Similarly, sodium glucose co-transporter 2 inhibitors have been shown to reduce cardiovascular events across the spectrum of ejection fractions and can also reduce renal adverse events.[18,19] Finally, other disease-modifying therapies for ATTR-CM are in various stages of development and investigation, including other transthyretin protein stabilizers, gene silencers, gene knockout, and amyloid fibril destabilizers. Future research is needed on these new compounds with respect to cardiovascular and renal outcomes.

STUDY LIMITATIONS. This study should be interpreted in the context of the following limitations. Because this was a post hoc analysis, changes in kidney function, and therefore CKD staging in patients, could not be confirmed as transient or long-term. Furthermore, altered cardiac function and blood volume with diuresis can affect kidney function, and this was not systematically assessed. Furthermore, other measures of renal function were not collected in ATTR-ACT, including cystatin C and analyses of urine protein or albumin. Finally, eGFR and CKD staging were not assessed for all patients or

at all visits, and besides those who discontinued or died, there were 5 patients who completed ATTR-ACT with no renal data at the month 30 time point.

CONCLUSIONS

In ATTR-ACT, tafamidis treatment was associated with a reduced decline in renal function and a higher incidence of improvement in eGFR and CKD staging compared with placebo over 30 months. Future studies are needed to determine the effects of other heart failure and transthyretin amyloidosis treatments on renal function in patients with ATTR-CM.

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This study was sponsored by Pfizer. Dr Sperry is a consultant for Alnylam and BridgeBio; and is a speaker for Pfizer. Dr Sultan is an employee of Pfizer; and holds stock/stock options in Pfizer. Dr Gundapaneni is an employee of Pfizer; and holds stock/stock options in Pfizer. Dr Tai is an employee of Pfizer; and holds stock/stock options in Pfizer. Dr Witteles is a consultant for Pfizer, Alnylam, Ionis, BridgeBio, NovoNordisk, Janssen, Alexion, AstraZeneca, and Intellia.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Chronic kidney disease is common among patients with amyloid cardiomyopathy, and renal function generally deteriorates over time. Tafamidis treatment mitigates the decline in renal function in patients with ATTR-CM.

TRANSLATIONAL OUTLOOK IMPLICATIONS: Although the mechanism of renal dysfunction in ATTR-CM is thought to be cardiorenal syndrome, additional studies are needed to understand the role of direct amyloid deposition in the kidneys.

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KEY WORDS dialysis, glomerular filtration rate, heart failure, kidney, renal failure, transthyretin

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