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ORIGINAL RESEARCH

Early Increase in Serum Transthyretin by Acoramidis Independently Predicts Improved Survival in TTR Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND Acoramidis is a novel, high-affinity stabilizer that achieves ≥90% transthyretin (TTR) stabilization. The phase 3 study, ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy), met its primary hierarchical efficacy endpoint with mortality, morbidity, and functional components at 30 months. Stabilization of TTR (prealbumin) by acoramidis results in an immediate and sustained rise in serum transthyretin (sTTR) levels, but the association between this pharmacodynamic effect and all-cause mortality (ACM) has not been elucidated.

OBJECTIVES The purpose of this study was to assess the prognostic implication of acoramidis-mediated early change in sTTR and its relationship to ACM.

METHODS We evaluated sTTR levels in 557 participants with ATTR-CM from the ATTRibute-CM study population. For the Kaplan-Meier overall survival assessment, univariate and multivariate modeling were used to evaluate factors associated with ACM. Modeling and simulation analyses described acoramidis population pharmacokinetics.

RESULTS Treatment with acoramidis resulted in a sharp and significant early rise in sTTR levels (mean 9.1 mg/dL) within 28 days which was sustained throughout the 30-month treatment period. Participants with ≥20 mg/dL sTTR at baseline had significantly ($P < 0.0001$) greater overall survival probability than those with <20 mg/dL. An early increase in sTTR levels on day 28 of dosing (early ΔTTR) was associated with reduced ACM in univariate analysis (HR: 0.96 per 1 mg/dL increase in early ΔTTR; 95% CI: 0.93-0.98; $P = 0.002$). In the multivariate analysis, after adjusting for TTR variant status, baseline New York Heart Association functional class, baseline National Amyloidosis Centre stage, and baseline sTTR level, early ΔTTR remained independently associated with reduced ACM ($P < 0.001$). Bootstrap mediation analyses showed that early ΔTTR fully mediates the effect of acoramidis treatment on ACM probability (average causal mediation effect = −0.117; $P = 0.002$; average direct effect = 0.0366; $P = 0.448$). Logistic modeling demonstrated that among participants treated with acoramidis, early ΔTTR was associated with reduced ACM, whereas no such association was observed in participants treated with placebo. For every 5 mg/dL increase in sTTR levels, a logistic model predicted a 31.6% relative reduction in odds of ACM.

CONCLUSIONS Acoramidis-mediated early ΔTTR is independently associated with improved survival after adjusting for known predictors. This provides strong evidence for a direct association between a prompt and sustained increase in sTTR upon initiation of treatment with acoramidis and survival. Early changes in sTTR could be used as a marker of the degree of TTR stabilization. (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy [ATTRibute-CM]; NCT03860935) (JACC. 2025;85:1911-1923) © 2025 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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ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv = transthyretin amyloidosis variant

ATTRwt = transthyretin amyloidosis wild-type

CVH = cardiovascular-related hospitalization

eGFR = estimated glomerular filtration rate

ITT = intent-to-treat

NAC = National Amyloidosis Centre

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

sTTR = serum transthyretin

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, systemic, and ultimately fatal disease.[1,2] Initiating events in the formation of transthyretin (TTR) amyloid include the destabilization and dissociation of the TTR tetramer into its constituent monomers, which are prone to misfolding.[3] Circulating TTR monomers aggregate into oligomeric, amyloid precursors, which subsequently organize into insoluble TTR amyloid fibrils that can be identified histopathologically in a range of organs and tissues, including the heart.[4-6] Progressive amyloid accumulation in the heart manifests as arrhythmia and progressive heart failure.[7-9] Median survival in untreated patients typically ranges between 25 to 41 months, with longer survival in patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt) as compared with variant disease transthyretin amyloid cardiomyopathy (ATTRv).[10-14] TTR stabilizers bind and stabilize the TTR tetramer to prevent its dissociation into amyloidogenic monomers and are an effective therapeutic drug class for the treatment of ATTR-CM.[15] Stabilization of TTR is associated with increases in serum transthyretin (sTTR).[16,17]

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In the phase 3 ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) of tafamidis, the only other TTR stabilizer currently approved by the U.S. Food and Drug Administration, improvements in survival and reductions in cardiovascular-related hospitalization were reported in patients with ATTR-CM.[18] In the pivotal phase 3 ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; NCT03860935) study, stabilization of TTR by acoramidis in participants with ATTR-CM resulted in an early and sustained rise in sTTR, but whether this increase in sTTR with acoramidis is associated with survival independent of other prognostic markers is not known. The underlying therapeutic hypothesis for acoramidis is that as a selective, high-affinity TTR stabilizer designed to bind to sTTR deep within its thyroxine-binding pocket, it achieves near-complete stabilization of the tetrameric form of the protein, thereby resulting in a marked decrease in the formation of amyloidogenic monomers.[15] A significantly better outcome was observed in ATTRibute-CM favoring acoramidis compared with placebo in the hierarchical endpoint that included all-cause mortality (ACM), cardiovascular-related hospitalization (CVH), change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP), and 6-minute walk distance at 30 months with >50% of win ratio ties broken by ACM and CVH.[15] Together, these data suggest that measurement of sTTR levels after the initiation of TTR stabilizing therapy may be an informative biomarker of drug efficacy.

As different therapeutic agents become available, routine evaluation of sTTR as a potential marker of treatment response at an individual level, reflecting degree of stabilization of the TTR protein and therefore reduction in new amyloid production, could guide treatment decisions and optimize patient management. We hypothesized that early increase in sTTR could represent one such biomarker that may be independently associated with ACM and sought to test this among patients with ATTR-CM treated with acoramidis.

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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.

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METHODS

STUDY DESIGN. The study design and primary and secondary endpoints results for the ATTRibute-CM study have been previously described by Gillmore et al.[15] Briefly, adults (≥18 to ≤90 years of age) with an established diagnosis of ATTR-CM with either the TTRwt or a confirmed variant TTRv genotype were enrolled in this multicenter, double-blind, placebo-controlled study. Participants were randomized 2:1 to receive acoramidis vs placebo. Participants were permitted to initiate treatment with tafamidis (if available) as a concomitant medication after they completed 12 months of the blinded study treatment. This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All participants provided written informed consent, and the study was approved by an ethics committee at each participating site.

POPULATION SELECTION. The population comprised the 557 participants (among the 632 participants in the intent-to-treat [ITT] population) who had sTTR data available at baseline and day 28, the first time point measured in ATTRibute-CM, and whose TTR variant status (TTRwt or TTRv) was known.

INVESTIGATIONAL MEDICINAL PRODUCT. Acoramidis 712 mg (measured by its active moiety is equivalent to 800 mg acoramidis hydrochloride) or matching placebo (both film-coated tablets) were provided to participants to self-administer orally twice daily for 30 months.

SAMPLE COLLECTION. Blood samples were collected at baseline (predose of investigational product) and 1 hour postdose at day 28 to analyze acoramidis levels (pharmacokinetic analysis) and prealbumin TTR concentrations (pharmacodynamic analysis). Predose blood collection continued every 3 months for a total of 30 months to continue to measure the previously mentioned parameters. Tetrameric TTR stabilization was assessed by sTTR levels using an immunoturbidimetric method (Abbott ARCHITECT system), which measures tetrameric TTR and was interpreted in a blinded centralized manner by central laboratory.

STATISTICAL ANALYSES. Kaplan-Meier overall survival analysis. All analyses were performed using R Statistical Analysis Software (R Core Team 2014). Expected overall survival from baseline to 30 months into the study was estimated by the Kaplan-Meier method. Participants were stratified using a lower limit of 20 mg/dL sTTR (≥20 mg/mL and <20 mg/mL) and the overall survival for the 2 groups compared using a log-rank test.

Waterfall plot analysis. Waterfall plots were generated of early ΔTTR for the overall population with respect to treatment and for the acoramidis-treated population with respect to clinically relevant subgroups, including baseline sTTR levels, age, sex, variant status, NYHA functional class, and National Amyloidosis Centre (NAC) stage.

Population characteristics modeling and exposure-response modeling for the probability of ACM. Continuous variables were presented as mean ± SE or median (Q1-Q3), and categorical variables were summarized as counts and frequency percentages. Two-sided *P* values were used throughout all analyses.

Univariate, Cox proportional hazards models were first developed to identify factors that had statistically significant association with ACM through month 30. Parameters investigated in this model included age, sex, TTR variant status (variant vs wild-type), NYHA functional classification (I, II, III), NAC stage (I, II, III),[11] baseline sTTR levels, and change in TTR at day 28 (early ΔTTR). Subsequently, a full multivariate model included all univariate characteristics that were associated with ACM with $P < 0.05$. As a separate method of evaluating iteratively the statistical significance of each univariate variable, stepwise covariate modeling was also performed to identify significant covariates on top of the selected exposure metric (early ΔTTR) that improved the model fit. Improvement of model fitness was defined by the likelihood ratio test statistic, which follows a chi-square distribution, with $P < 0.01$ for the forward addition and $P < 0.001$ for backward elimination.

Last, the same univariate model described in the previous text was also repeated (alternate model) using the same variables, but replacing NAC stage by its individual components to distinctly visualize their effects as estimated glomerular filtration rate (eGFR) (≥45 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2) and NT-proBNP (<3,000 mg/mL and ≥3,000 mg/mL). Subsequently, an alternate multivariate model included all univariate characteristics that were associated with ACM with $P < 0.05$.

Mediation analyses to investigate mediation by ΔTTR on the effect of acoramidis treatment on probability of ACM through month 30. We used causal mediation analysis to determine the significance of ΔTTR mediating the relationship between acoramidis treatment and the probability of ACM through month 30 as formulated by a logistic regression model.[19] Using the "mediation" package in R, bootstrap simulations were performed with 1,000

TABLE 1 Population Baseline Characteristics

	Placebo (n = 185)	Acoramidis (n = 372)	All (N = 557)
Age, y	78.0 (72.0-82.0)	78.0 (73.0-82.0)	78.0 (73.0-82.0)
Male	162 (87.6)	340 (91.4)	502 (90.1)
Variant status			
Wild-type	168 (90.8)	338 (90.9)	506 (9)
Variant	17 (9.2)	34 (9.1)	51 (9.2)
NYHA functional class			
I	15 (8.1)	47 (12.6)	62 (11.1)
II	142 (76.8)	258 (69.4)	400 (71.7)
III	28 (15.1)	67 (18.0)	96 (17.2)
NAC stage			
I	110 (59.5)	211 (56.7)	321 (57.5)
II	48 (25.9)	110 (29.6)	159 (28.)
III	27 (14.6)	51 (13.7)	78 (14.0)
NT-proBNP, mg/dL	2,327 (1,142-3,595)	2,328 (1,330-3,968)	2,327 (1,285-3,803)
eGFR, mL/min/1.73 m^2	60 (47-74)	61 (48-73)	61 (48-73)
TTR level, mg/dL			
Total	23.4 ± 0.5	23.2 ± 0.3	23.3 ± 0.3
Wild-type	24.1 ± 0.4 168	23.8 ± 0.3 338	23.9 ± 0.3 506
Variant	16.8 ± 1.3 17	17.7 ± 0.9 34	17.4 ± 0.7 51

Values are median (Q1-Q3), n (%), mean ± SE, or n.
eGFR = estimated glomerular filtration rate; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; TTR = transthyretin.

Monte Carlo draws of the data set to compute both the average causal mediation effect of ΔTTR on ACM probability and the average direct effect of acoramidis treatment independent of ΔTTR on ACM probability and their respective levels of statistical significance; 95% CIs were computed using raw percentiles of the bootstrapped statistics.

Logistic regression model to investigate the association of ACM through month 30 with ΔTTR. A logistic regression model explored the association of ΔTTR and ACM probability in both the full study population and in participants receiving acoramidis only. Among the ATTRibute-CM ITT population,[15] we constructed a multivariate logistic regression model of ACM probability yielded by a stepwise covariate modeling approach. Atop the ΔTTR predictor, NAC stage and baseline sTTR were selected as significant covariates. To assess the goodness of fit for the multivariable ACM model, we compared the uncertainty of model predictions with the variability of the observed ACM data across participants stratified by ΔTTR quartiles (Supplemental Figure 1).

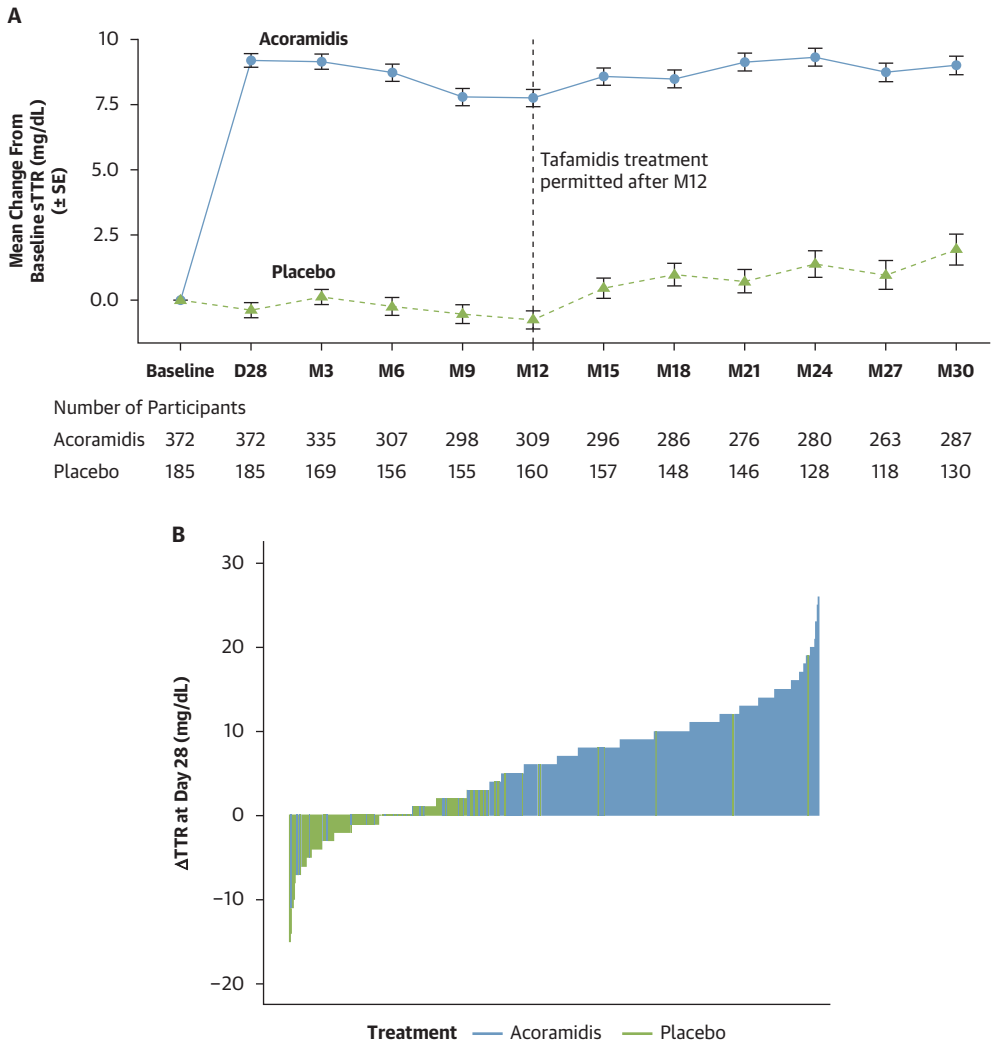
RESULTS

Of the 632 participants randomized in the study (included in the ITT population), 557 participants for whom TTR variant status was known had sTTR level measurements at both baseline and day 28: 372 participants received acoramidis and 185 placebo (Supplemental Figure 2).

Demographics and clinical characteristics at baseline were representative of a cohort of patients with ATTR-CM in the contemporary era (Table 1). Participants enrolled in the study were older adults (median age 78 years [Q1-Q3: 73-82 years]), and 90.7% had TTRwt. Most had symptomatic heart failure (71.7% and 17.2% NYHA functional class II and III, respectively) and broadly distributed NAC stages I, II, and III (57.5%, 28.5%, and 14.0%, respectively). sTTR levels were in the low-normal range at baseline, with a mean of 23.3 ± 0.3 mg/dL (the core laboratory reference range is 20-40 mg/dL). Notably, these demographic and clinical characteristics were well matched between treatment groups.

Within 28 days, treatment with acoramidis resulted in a prompt and significant early rise by a mean 9.1 ± 0.3 mg/dL in sTTR levels (early ΔTTR) and this elevated level was sustained throughout the 30-month treatment period (Figure 1A) (consistent with presentation in Gillmore et al[15]). Among the overall population, waterfall plot analysis demonstrated a clear difference in early ΔTTR between participants treated with acoramidis or placebo, with the vast majority of participants treated with acoramidis experiencing an increase in early ΔTTR and most participants treated with placebo experiencing a decrease or minimal change in early ΔTTR (Figure 1B). Treatment with placebo resulted in a slight decline in early ΔTTR, mean −0.4 ± 0.3 mg/dL. Compared with participants with ATTRwt, those with ATTRv had a lower baseline sTTR level (mean 17.7 ± 0.9 mg/dL for ATTRv vs 23.8 ± 0.3 mg/mL for ATTRwt, respectively), but experienced a greater early ΔTTR after treatment with acoramidis (mean early ΔTTR 12.2 ± 1.3 mg/mL for ATTRv vs 8.8 ± 0.2 mg/dL for ATTRwt). Among participants treated with acoramidis, variant status, and subsequently, lower baseline sTTR levels, were associated with increased early ΔTTR (Supplemental Figures 3A and 3D, respectively). Otherwise, the majority of participants treated with acoramidis demonstrated increased early ΔTTR across other clinical subgroups, including age, sex, NYHA functional class, and NAC stage (Supplemental Figures 3B, 3C, 3E, and 3F, respectively). The association of baseline sTTR levels with probability of ACM through month 30 indicates that participants who had ≥20 mg/dL sTTR at baseline had significantly better survival probability than those who had <20 mg/dL sTTR ($P < 0.0001$) (Figure 2A). Among the acoramidis-treated population, a stepwise

FIGURE 1 **Change From Baseline in sTTR Levels Through Month 30 and Waterfall Plot of Early ΔTTR From Baseline at Day 28 by Treatment in the Overall Population**



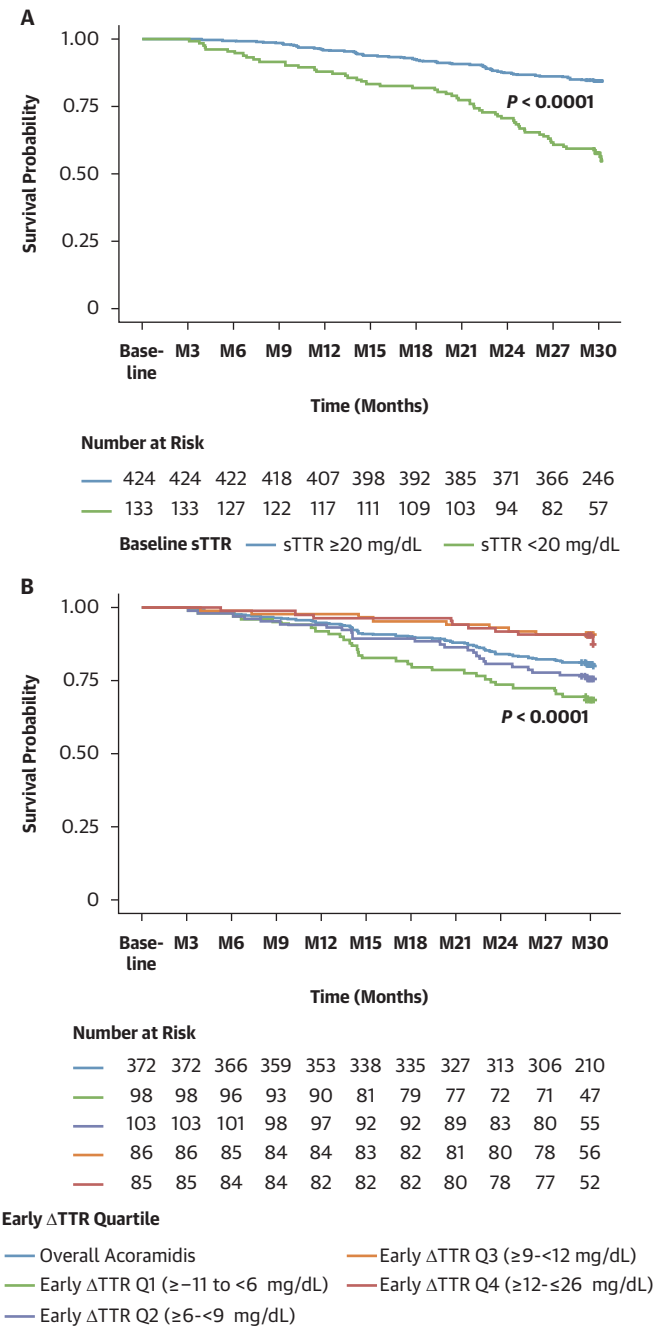
(A) Observed measurements for intent-to-treat population without imputation for participants with baseline and D28 serum transthyretin (sTTR) levels available. No adjustment was made for early discontinuation for any reason, including death. Circles represent acoramidis, triangles represent placebo. (B) Waterfall plot demonstrating early ΔTTR among participants treated with acoramidis (blue) and placebo (green).

increase in survival was observed with increasing early ΔTTR quartile ($P < 0.0001$), consistent with the overall treated population result demonstrating improved outcomes over placebo (Figure 2B).

In univariate Cox regression modeling, variant status, baseline NYHA functional class II and III, and baseline NAC stages II and III, were significantly associated with worse ACM, similar to what has been observed in prior observational studies (Figure 3A).[20,21] Consistent with the probability of overall survival, higher baseline sTTR (per 1 mg/dL increase) and higher early ΔTTR (per 1 mg/dL increase) were significantly associated with improved ACM (HR: 0.91 and HR: 0.96, respectively).

In a full multivariate model that included all univariate parameters found to be significantly associated with ACM ($P < 0.05$), higher early ΔTTR (per 1 mg/dL increase) continued to be significantly associated with improved ACM after adjusting for variant status, baseline NYHA functional class, NAC stage,

FIGURE 2 Survival by Baseline sTTR Level Through Month 30 in the Overall Population and Survival by Early ΔTTR Quartiles Through Month 30 in the Acoramidis-Treated Population



(A) Data represent modified intent-to-treat population from ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy) who had serum transthyretin (sTTR) levels available at the corresponding time points. All-cause mortality includes heart transplant, cardiac mechanical assist device, and all-cause death. Solid lines represent median survival probability. (B) Data demonstrate survival by early ΔTTR quartiles through month 30 in the acoramidis-treated population.

and baseline sTTR levels (**Figure 3B**) (HR: 0.91 and HR: 0.94, respectively). In stepwise covariate modeling, NAC stage, higher baseline sTTR level (per 1 mg/dL increase), and early ΔTTR (per 1 mg/dL increase) also remained significantly associated with ACM (**Figure 3C**). Thus, the risk of mortality was dependent not only on baseline sTTR and NAC stage at the start of treatment with acoramidis, but also on the magnitude of early ΔTTR increase.

In an alternate univariate and multivariate model, even when considering baseline eGFR as a dichotomous variable ≥45 mL/min/1.73 m^2, in addition to variant status, NYHA functional class, NT-proBNP, baseline TTR, and early ΔTTR remained significantly associated with a reduction in ACM (Supplemental Figures 4A and 4B).

When pooling clinical parameters known to be associated with ACM (including age, variant status, baseline NYHA functional class, and baseline NAC stage) and diuretic use, the addition of early ΔTTR added significant value in evaluating ACM, with a likelihood ratio test for model improvement of $P = 0.0205$ (Supplemental Figure 5).

Causal mediation analysis showed evidence of full mediation of acoramidis treatment on ACM probability through month 30 by ΔTTR. Potential confounders accounted for include baseline TTR, NAC stage, NYHA functional class, concomitant loop diuretic use, age at baseline, and genetic variant status. The bootstrap approach yielded an average causal mediation effect of −0.117 (95% CI: −0.204 to −0.05) with $P = 0.002$, while the average direct effect for acoramidis treatment was calculated to be 0.0366 (95% CI: −0.0586 to 0.14) with $P = 0.448$. Taken together, these results suggest that the total effect of acoramidis treatment on ACM probability through month 30 is primarily the result of acoramidis treatment inducing early increases in sTTR levels.

Logistic modeling of ACM as a function of early ΔTTR in the overall ATTRibute-CM population (both acoramidis- and placebo-treated participants) showed an inverse relationship between the magnitude of the early ΔTTR increase and ACM; higher early ΔTTR increase was associated with lower probability of ACM (**Figure 4A**). Among the participants treated with acoramidis only, the model depicted that increasing sTTR levels early (as a result of exposure to acoramidis) had an even greater effect on decreasing the probability of ACM (**Figure 4B**). The variance in the 0-mg/dL to 10-mg/dL range in early ΔTTR was appreciably wider in patients treated with acoramidis only as compared with the overall population because very few participants treated with acoramidis

experienced a decline from baseline at day 28 in sTTR levels. Among participants who received placebo, no significant correlation was observed between ΔTTR and ACM through month 30 (**Figure 4C**).

As a further test of the validity and reliability of the model, we compared the final model with covariates of day 28 sTTR, baseline sTTR, and NAC stage with respect to the goodness of fit between the model predicted simulated probability of ACM and the actual observed proportion of ACM by quartile of change from baseline in sTTR at day 28. The simulated predictions from model uncertainty (boxes) and the observed probabilities of death with 95% CI (error bars) showed considerable overlap across all 4 quartiles suggesting a very good model fit (Supplemental Figure 1).

DISCUSSION

Using the data from the ATTRibute-CM study, we show here that increased baseline TTR was associated with improved survival and that early ΔTTR remained independently associated with decreased mortality (after adjusting for known predictors). For every 5 mg/dL increase in sTTR levels, a 31.6% relative reduction in the odds of death through month 30 was predicted by the logistic model and a 26.6% relative reduction in the risk of death was predicted by the Cox proportional hazards model (**Central Illustration**). These results confirm earlier findings that showed circulating TTR values lower than the normal limit was associated with shorter median overall survival (2.8 years for those with TTR <18 mg/dL vs 4.1 years for those with TTR ≥18 mg/dL [HR: 2.3 (95% CI: 1.2-4.3); $P = 0.03$]).[22]

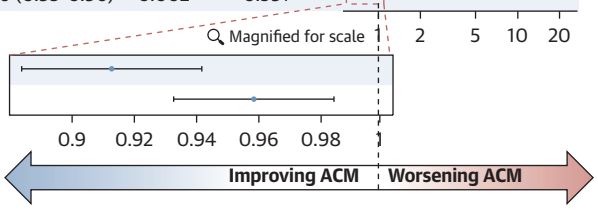
Enhanced stability of the TTR tetramer by acoramidis slows or halts the generation of toxic oligomeric TTR aggregates, thereby slowing their systemic pathologic deposition as amyloid in different organs and tissues. Stabilization of TTR has been assessed by several ex vivo and in vitro assays (eg, fluorescence probe exclusion, Western Blot, and sTTR levels).[23-26] The acoramidis-dependent stabilization, as reflected in an early increase in sTTR, results from a leftward shift in the amyloidogenic cascade towards intact tetrameric TTR, thereby increasing measured sTTR levels, which can be interpreted as a biological surrogate for TTR stabilization in vivo.[23-26] In the current analysis, changes in early sTTR levels with acoramidis were utilized as the in vivo correlate of TTR stability. This is the first study to demonstrate the exposure-response between acoramidis treatment and sTTR, with early ΔTTR after dosing being a strong independent predictor of survival in patients with ATTR-CM treated with acoramidis. In the ATTRibute-CM study, treatment with acoramidis, a near-complete (≥90%) TTR stabilizer, resulted in an early increase in sTTR by a mean 9.1 ± 0.3 mg/dL and by a median 9 mg/dL (Q1-Q3: 6-12 mg/dL) representing a 44% and 40% increase from baseline, respectively, that was sustained for the duration of the study. Hierarchical outcomes assessments showed that acoramidis treatment resulting in a sTTR increase was associated with improved clinical outcomes, including a 42% reduction in ACM and recurrent CVH, a treatment effect that was evident as early as 3 months into the study, a 50% reduction in the annual frequency of CVH, as well as important beneficial effects on NT-proBNP, 6-minute walk distance, and ACM.[15,27] The results from this analysis demonstrate that the early, substantial, and sustained increase in sTTR achieved by near-complete TTR stabilization can directly (or jointly with other clinical assessments) predict a treatment-related improvement in overall survival.

The therapeutic landscape of TTR-modifying therapies within several drug classes is rapidly evolving, and includes TTR stabilizers, TTR protein synthesis suppressors, and TTR amyloid depleters. As a result, there remains an unmet clinical need to identify class-specific markers of treatment response. TTR protein stabilizers for the treatment of ATTR-CM work mechanistically by stabilization of the native, circulating tetramer, thereby slowing its dissociation into monomers that can generate toxic, oligomeric TTR amyloid precursors (prefibrillar species). Greater TTR stabilization manifests in vivo as increased sTTR levels, and although stabilizers as a class are associated with increases in sTTR levels, the increase is variable and tightly linked to the degree of stabilization between the currently available agents. For example, although the other widely approved TTR stabilizer tafamidis has also been shown to lead to an increase in sTTR levels, this increase did not show a corresponding sTTR-mediated benefit in either NT-proBNP levels or outcomes as measured by major adverse cardiac events, as reported in data from small cohorts.[16,17] In the present study, the exposure-response relationship between treatment with acoramidis and early ΔTTR was shown to be an important independent predictor of survival in ATTR-CM. However, these are population-level data and there are limitations to applying these to individual-level patients. The early and sustained increase in TTR levels observed in this study may represent a novel ATTR-CM disease-specific prognostic biomarker unique to the stabilizer class that could further inform optimal patient management. Routine clinical measurement of sTTR levels may be useful to inform

FIGURE 3 Forest Plots for ACM Through Month 30 Using Univariate, Multivariate, and Stepwise Covariate Modeling

A

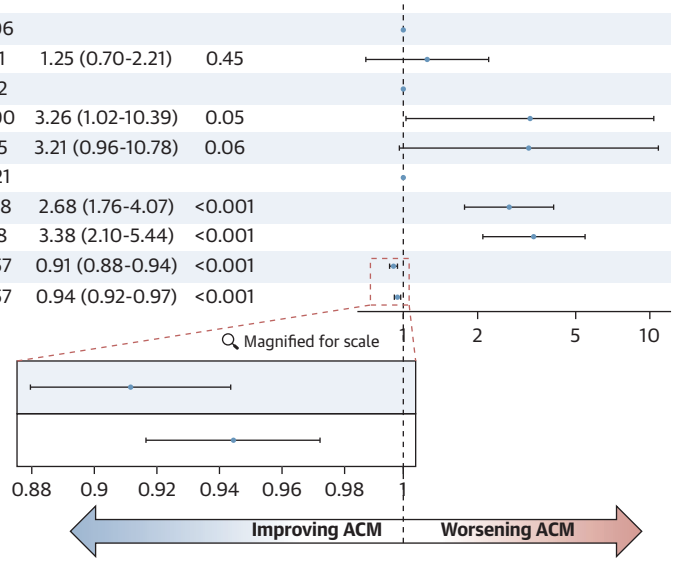
Variable		N	HR (95% CI)	*P* Value	C-Statistic
Age (Per 1 y)		557	1.03 (1.00-1.06)	0.072	0.548
Sex	Male	502			
	Female	55	1.13 (0.61-2.09)	0.708	0.504
Variant	Wild-type	506			
	Variant	51	1.74 (1.04-2.90)	0.035	0.524
NYHA Functional Class	I	62			
	II	400	5.27 (1.67-16.63)	0.005	
	III	95	6.95 (2.11-22.90)	0.001	0.570
NAC Stage	I	321			
	II	158	2.92 (1.93-4.41)	<0.001	
	III	78	3.90 (2.45-6.20)	<0.001	0.652
Increasing Baseline TTR (Per 1 mg/dL)		557	0.91 (0.88-0.94)	<0.001	0.652
Early ΔTTR (Per 1 mg/dL)		557	0.96 (0.93-0.96)	0.002	0.591



Univariate Cox Regression Modeling for ACM through Month 30. Values are HR (95% CI).

B

Variable		N	HR (95% CI)	*P* Value
Variant	Wild-type	506		
	Variant	51	1.25 (0.70-2.21)	0.45
NYHA Functional Class	I*	62		
	II	400	3.26 (1.02-10.39)	0.05
	III	95	3.21 (0.96-10.78)	0.06
NAC Stage	I*	321		
	II	158	2.68 (1.76-4.07)	<0.001
	III	78	3.38 (2.10-5.44)	<0.001
Increasing Baseline TTR (Per 1 mg/dL)		557	0.91 (0.88-0.94)	<0.001
Early ΔTTR (Per 1 mg/dL)		557	0.94 (0.92-0.97)	<0.001
C-Statistic = 0.737				



(A) Univariate, (B) multivariate, and (C) stepwise covariate modeling. Plotted values are HR (95% CI). The "final" model using stepwise covariate modeling for all-cause mortality (ACM) through month 30 considered all noncollinear predictors with $P < 0.01$ in forward selection and $P < 0.001$ in backwards elimination. early ΔTTR = early change from baseline in serum transthyretin at day 28; NAC = National Amyloidosis Centre; TTR = transthyretin.

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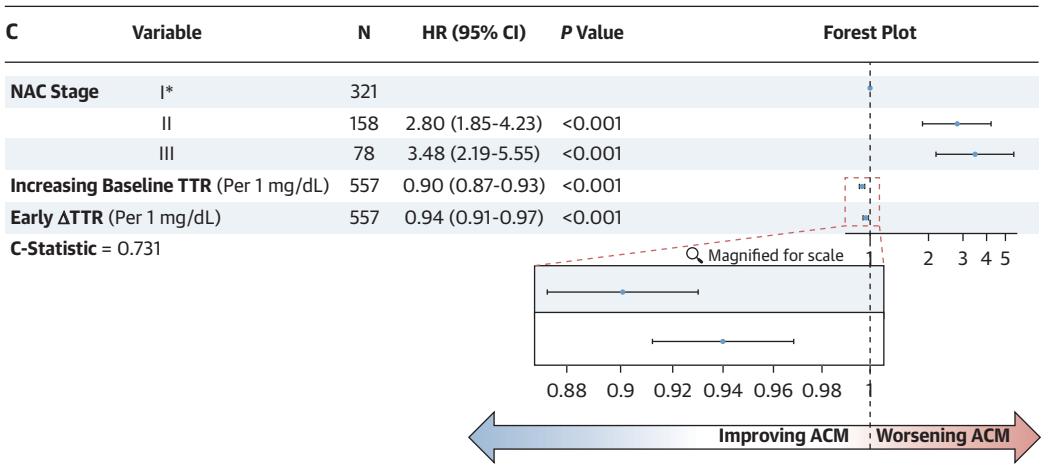
FIGURE 3 Continued



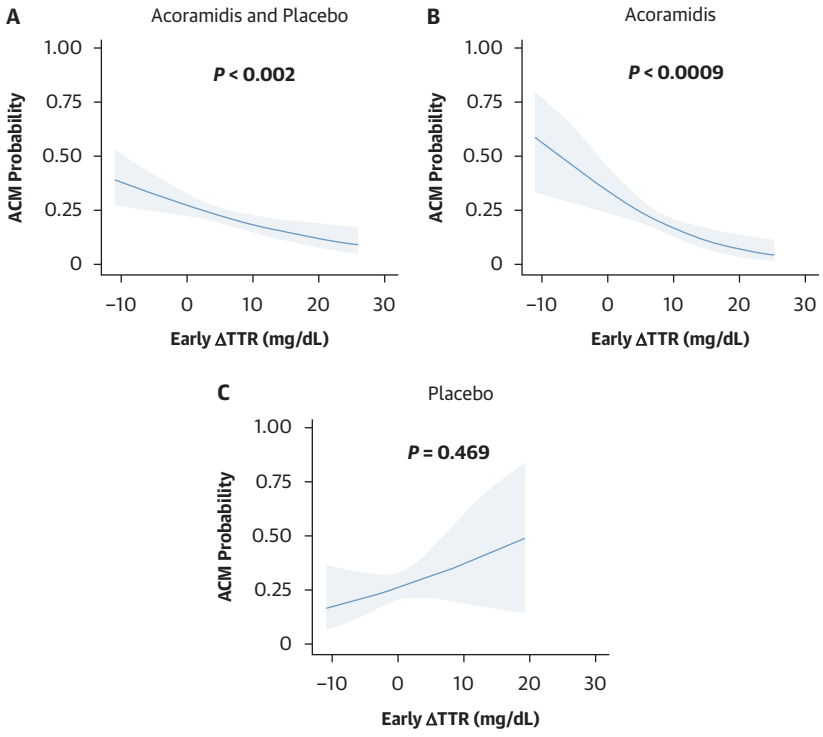
clinical practice in this therapeutic context. By contrast, suppressors of TTR protein synthesis work mechanistically by reducing circulating *native* tetrameric TTR, thereby reducing the potential of *unstable* TTR to dissociate and generate circulating toxic oligomeric TTR amyloid precursors. Knockdown of TTR protein synthesis results in a decrease in sTTR levels, which converge on the common pathway that generates decreased TTR oligomeric amyloid precursors. Although this may be an effective alternate mechanism of treatment, the long-term safety of different modes of suppressing TTR synthesis or the adverse physiological consequences of chronic suppression of tetrameric TTR remains unknown.

In the absence of a reliable clinical assay for circulating oligomeric TTR amyloid precursors, nonspecific indicators of disease progression and treatment response have been developed as follows: changes in NT-proBNP coupled with information on changes in the choice or dosage of oral loop diuretics, changes in troponin T and eGFR, changes in functional capacity as measured by the 6-minute walk test, and quality of life as measured by the Kansas City Cardiomyopathy Questionnaire.[13,28] Although these are simple and widely available parameters to assess, a notable limitation is the nonspecific nature of these different blood biomarkers and other assessments that share the final common pathway of several mechanisms, including worsening in fluid status, renal impairment, neurohormonal activations, and comorbidities. None of these biomarkers and functional tests track the specific pathways of new amyloid production, which is modifiable with treatment.

As the ATTR-CM pharmacopoeia continues to expand, it is increasingly important that the rationale and interventional strategy behind novel therapies be fully communicated so that clinicians can make informed decisions regarding which therapy to choose for their individual patients. To that end, the development of acoramidis has followed a logical path from rational drug design through phase 1 and 2 studies to establish the right dose and generate enough safety data to inform a favorable benefit-risk relationship. Based on human genetic data already available, acoramidis was designed to mimic the disease-protective T119M variant in its TTR binding characteristics resulting in near-complete stabilization across the dosing interval. The importance of this mechanistic feature is highlighted by the established observation that in ATTRv, the more destabilizing a pathological TTR variant, the more severe the clinical phenotype as compared with ATTRwt. Large epidemiologic data sets from Denmark have demonstrated that plasma TTR tetramer destabilization among the most destabilizing ATTRv was associated with worsened ACM and CV mortality.[29] However, despite a worse phenotype and lower sTTR levels in ATTRv, univariate and multivariate analyses show that ΔTTR remains an important predictor of improved outcomes and response to therapy.

The relationship between more effective reduction in the generation of toxic TTR oligomers, whether by stabilization or suppression of tetrameric TTR, has

FIGURE 4 Probability of ACM as a Function of Early ΔTTR Through Month 30 for Acoramidis and Placebo, Acoramidis Only, and Placebo Only



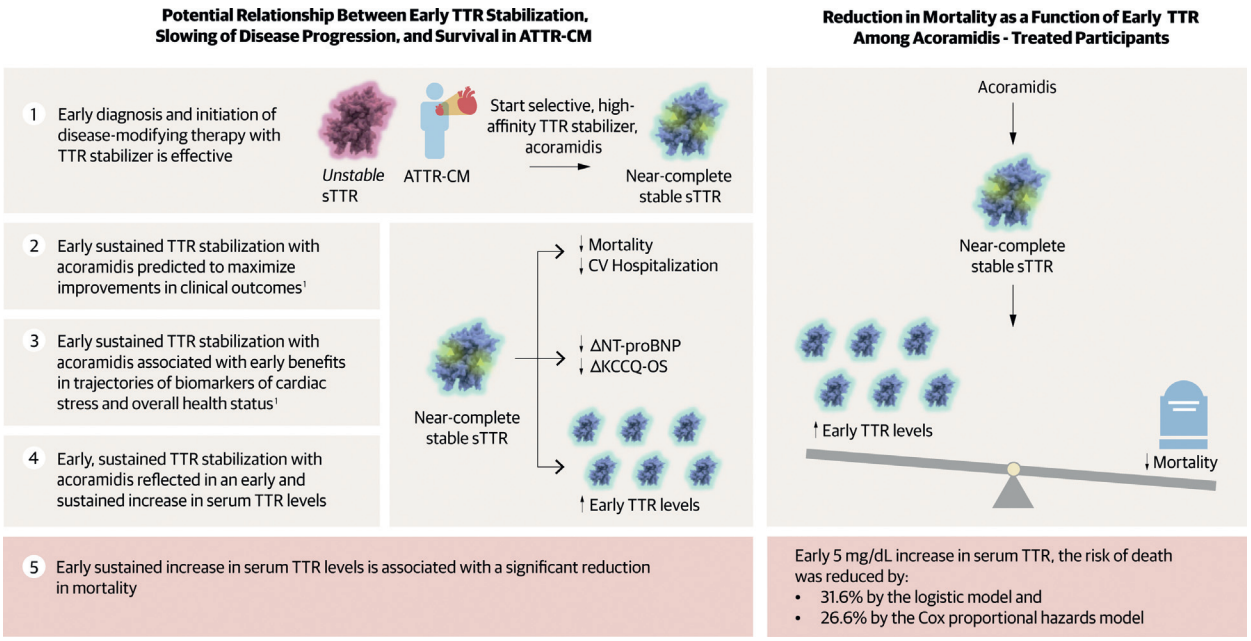
Logistic model of ACM probability based on early ΔTTR among (A) acoramidis and placebo, (B) acoramidis only, and (C) placebo-only–treated participants. Black line represents model prediction, gray regions represent 95% CI, and width of gray band corresponds with the goodness of fit at that specific serum TTR level. *P* value describes the univariate association between ACM and early ΔTTR. Abbreviations as in Figure 3.

been demonstrated in studies of patients with ATTR-CM and ATTR polyneuropathy. This is also reflected in greater proportional treatment effects in ATTRv-CM vs ATTRwt-CM in ATTRibute-CM. That a greater degree of stabilization leads to greater clinical benefits was also apparent in the data from the tafamidis program. In the ATTR-ACT study, higher levels of sTTR were observed with the 80-mg dose of tafamidis, which also demonstrated improved outcomes as compared with the 20-mg dose.[18,30] Although a deeper understanding of the role of TTR in human biology continues to be sought, the fact remains that TTR is an abundant plasma protein carrier of thyroxine and retinol. TTR has a relatively short circulating half-life requiring a considerable expenditure of metabolic energy and is evolutionarily conserved throughout vertebrate evolution.

We have previously reported the results of the ATTRibute-CM study that documented the efficacy and safety of acoramidis as assessed by the hierarchical analysis of ACM, CVH, NT-proBNP, and 6-minute walk distance. In this report, we take an important next step that completes a chain of evidence linking rational, genetic, and structural biology-based drug design to near-complete TTR stabilization, through to in vivo evidence of drug effect on sTTR and efficacy on clinical endpoints, and now a direct, quantitative relationship between increases in sTTR and their ability to predict survival across the ATTRibute-CM study population.

STUDY LIMITATIONS. A potential source of bias in this analysis is that it reflects the ATTRibute-CM phase 3 clinical study population and may not be fully representative of the general population. It also only included participants (a majority but not all) for whom sTTR levels were available at both baseline and day 28. In addition, this study reports the effect on ACM by early ΔTTR as a result of treatment with acoramidis and this effect may not be generalizable to other TTR stabilizers. It should be emphasized that sTTR levels are challenging to interpret in the

CENTRAL ILLUSTRATION **Predicted Relationship Between Early Stabilization of Serum Transthyretin by Acoramidis and Survival in Participants With Transthyretin Amyloid Cardiomyopathy Through Month 30**



Maurer MS, et al. JACC. 2025;85(20):1911–1923.

Data on outcomes, biomarkers, and quality of life were reported in the original trial.[15] ACM = all-cause mortality; ATTR-CM = transthyretin amyloid cardiomyopathy; CVH = cardiovascular-related hospitalization; early ΔTTR = change from baseline in serum transthyretin levels at day 28; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sTTR = serum transthyretin; TTR = transthyretin.

presence of combination stabilizer/TTR knockdown therapy; no TTR knockdown agents were permitted as concomitant medications in the ATTRibute-CM study. Altogether, despite these limitations, modeling was repeated with a variety of covariates using different statistical methods to ensure reproducibility of the findings reported.

CONCLUSIONS

In the landmark phase 3 ATTRibute-CM study, early and sustained increase in TTR levels as a result of treatment with acoramidis in the ATTRibute-CM study independently predicted improved survival. These results demonstrated that for every 5-mg/dL increase in sTTR level, the Cox proportional hazards model predicted a relative risk reduction of mortality of 26.6% and the logistic model predicted a relative reduction of 31.6% in odds of death through month 30. This is the first study to show an association between an increase in sTTR and survival with a TTR stabilizer drug. Early and sustained increase in TTR levels may represent a novel ATTR-CM disease-specific prognostic biomarker that could further inform optimal patient management.

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KEY WORDS acoramidis, all-cause mortality, ATTR-CM, serum TTR, transthyretin, TTR stabilization

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