Effect of Acoramidis on Temporal Variability of Serum Transthyretin and its Influence on Outcomes:

Insights From the ATTRibute-CM Trial

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Declaration of interest

- Research contracts : SS receives research support from the American Academy of CME, the American Heart Association (#935275), the Foundation for Sarcoidosis Research, the National Heart, Lung, and Blood Institute (K23HL161348 and 1R03HL180898-01) and the Robert A. Winn Foundation Excellence in Clinical Trials
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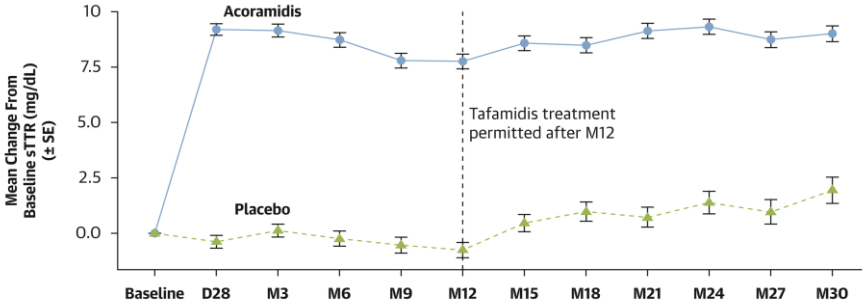
Background

- ATTR-CM is a progressive and potentially fatal disease caused by TTR destabilization[1,2]
- Acoramidis is an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization in vitro[3–5]
- In ATTRibute-CM,[6] acoramidis increased mean sTTR by Day 28 at the trial level, predicting improved survival[7]
- Longitudinal effects on sTTR variability at the individual level remain unknown
  - *Within-participant variability may complement mean achieved sTTR concentrations as a marker of disease severity, risk, and treatment response*
- We hypothesized that lower sTTR variability may reflect more durable pharmacologic stabilization of sTTR



Number of Participants	Baseline	D28	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30
Acoramidis	372	372	335	307	298	309	296	286	276	280	263	287
Placebo	185	185	169	156	155	160	157	148	146	128	118	130

Purpose

- To evaluate biological correlates of TTR variability
- To understand the prognostic importance of intraindividual variation in sTTR beyond mean-achieved sTTR levels
- To examine the effect of acoramidis on sTTR variability

ATTR-CM, transthyretin amyloid cardiomyopathy; D, Day; M, Month; SE, standard error; sTTR, serum transthyretin; TTR, transthyretin.

1. Garcia-Pavia P, et al. *Eur Heart J*. 2021;42:1554-1568. **2.** Ruberg FL, et al. *JAMA*. 2024;331:778-791. **3.** Judge DP, et al. *J Am Coll Cardiol*. 2019;74:285-295.
4. BridgeBio Pharma, Inc. Prescribing Information, Attruby (acoramidis). FDA, 2024. www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf.
5. Ji A, et al. *J Cardiovasc Pharmacol*. 2025;86:204-209. **6.** Gillmore JD, et al. *N Engl J Med*. 2024;390:132-142. **7.** Maurer MS, et al. *J Am Coll Cardiol*. 2025;85:1911-1923.

Methods

- ATTRibute-CM compared acoramidis 800 mg HCl (n = 409) and placebo (n = 202) BID for 30 months (mITT population[a])
  - *Tafamidis usage was allowed after Month 12*

sTTR coefficient of variation (CV*i*)[1] = $\frac{\text{standard deviation of sTTR concentration}}{\text{mean sTTR concentration}}$

A marker of within-participant sTTR variability

Lower sTTR CV*i* → Less sTTR intraindividual variability over time

- In this analysis, participants were included who:
  - *Had ≥2 post-Day 28 sTTR values (between Day 28–Month 12) and were alive at Month 12 (N = 563/611) for landmark analysis*
  - *Had ≥2 post-Day 28 sTTR values between Day 28–Month 30 (N = 596/611) for treatment effect analysis*

[a]The mITT population was the primary analysis population for efficacy endpoints in ATTRibute-CM and included randomized participants who had received ≥ 1 dose of study treatment, had ≥ 1 efficacy evaluation after baseline, and had a baseline eGFR of ≥ 30 mL/min/1.73 m^2.
BID, twice daily; modified intention-to-treat; NT-proBNP, sTTR, serum transthyretin.
1. Gaba P, et al. *J Am Coll Cardiol*. 2025;85:550-553.

Statistical Analysis

- Baseline predictors of sTTR CV*i* evaluated using Chi-squared test, Welch's t-test, and Wilcoxon rank-sum test
- Chi-squared tests to compare proportions of participants:
  - *Maintaining sTTR levels ≥ thresholds (ranging from 15–40 mg/dL) between D28–M12 in acoramidis and placebo arms*
  - *Above/below sTTR thresholds between D28–M12 and subsequent mortality (M12–M30)*
- KM curves for 4 groups of mean achieved sTTR concentrations (above/below median) and sTTR CV*i* (above/below median), landmarked at 12 months
- Multivariable-adjusted Cox regression landmark analysis at M12 to assess association between both sTTR CV*i* and mean-achieved sTTR levels with fatal outcomes
  - *Adjusted for time-varying tafamidis initiation, 6MWD, age, sex, NYHA class, and BMI, while stratifying by treatment, genotype, eGFR, and NT-proBNP*
  - *Several sensitivity analyses assessing the robustness of CVi calculation and choice of landmark time*
- Treatment effect on sTTR CVi using Wilcoxon rank-sum test and ANCOVA modelling

6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sTTR, serum transthyretin; D, Day; M, Month

1. Gaba P, et al. *J Am Coll Cardiol*. 2025;85:550-553.

High CV*i* Was Associated With Adverse Clinical Features of ATTR-CM

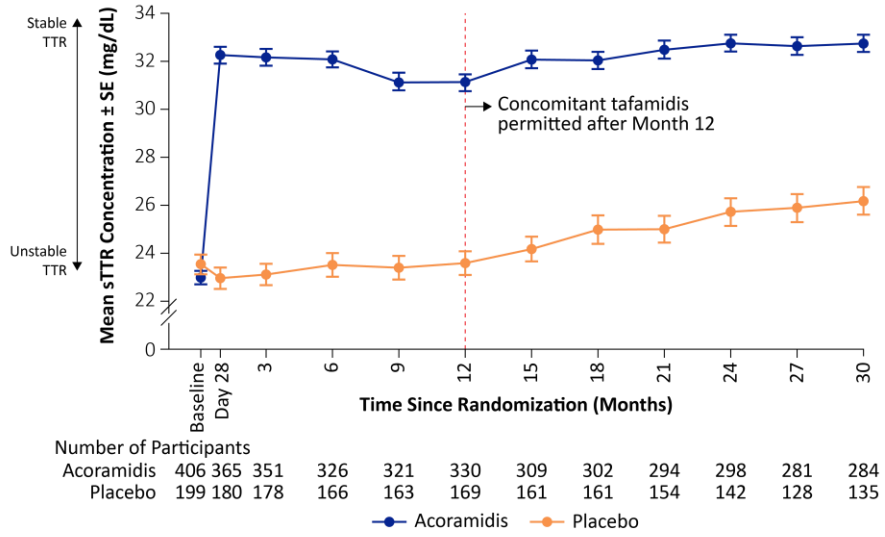
Baseline Characteristic	Low CV*i* (n = 282) ≤ *population median*	High CV*i* (n = 281) > *population median*	*p* Value
Age, years, mean (SD)	76.9 (6.7)	77.1 (6.4)	0.654
Sex, male, n (%)	256 (90.8)	257 (91.5)	0.777
Wild-type ATTR-CM, n (%)	257 (91.1)	254 (90.4)	0.761
NAC stage, n (%)			
I	195 (69.1)	150 (53.4)	
II	68 (24.1)	105 (37.4)	**0.001**
III	19 (6.7)	26 (9.3)	
6MWD, m, mean (SD)	374 (101)	356 (97)	**0.033**
BMI, kg/m^2, mean (SD)	27.1 (3.7)	27.1 (3.7)	0.985
NT-proBNP, pg/mL, median (Q1–Q3)	2030 (1068–3052)	2427 (1308–4115)	**0.001**
eGFR, mL/min/1.73 m^2, mean (SD)	64 (17)	62 (18)	0.101
sTTR, mg/dL, mean (SD)	23.9 (4.9)	22.9 (6.2)	**0.036**
Number of sTTR measurements, median (Q1–Q3)	4 (4–5)	4 (4–5)	0.192

p values for categorical variables are based on the chi-square test; continuous variables are reported as mean (SD) with *p* values based on Welch's t-test, except for NT-proBNP (reported as median [Q1–Q3]), with the *p* value obtained using Wilcoxon rank sum test. Low CV*i* refers to CV*i* of post-D28 sTTR by M12 at or below the overall population median. High CV*i* refers to CV*i* of post-D28 sTTR by M12 above the overall population median. CV*i Population median = 7.94%*

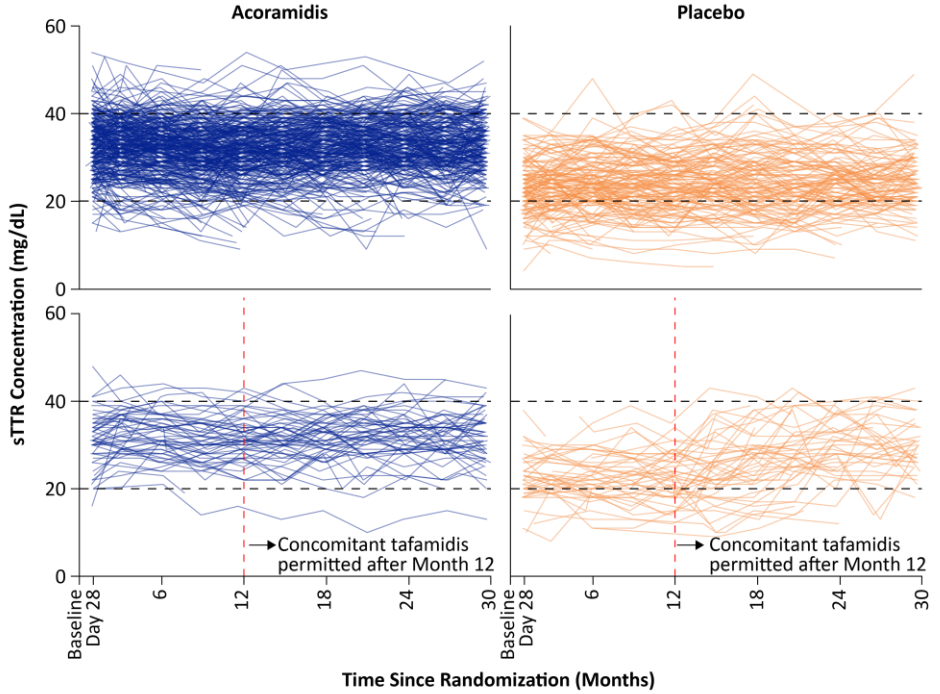
6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; BMI, body mass index; CV*i*, intraindividual coefficient of variation; D, Day; eGFR, estimated glomerular filtration rate; M, Month; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; SD, standard deviation; sTTR, serum transthyretin.

Participant-Level Variation in sTTR Concentration During the ATTRibute-CM Trial[a]

Mean sTTR Concentrations Through Month 30 by Treatment Group in ATTRibute-CM



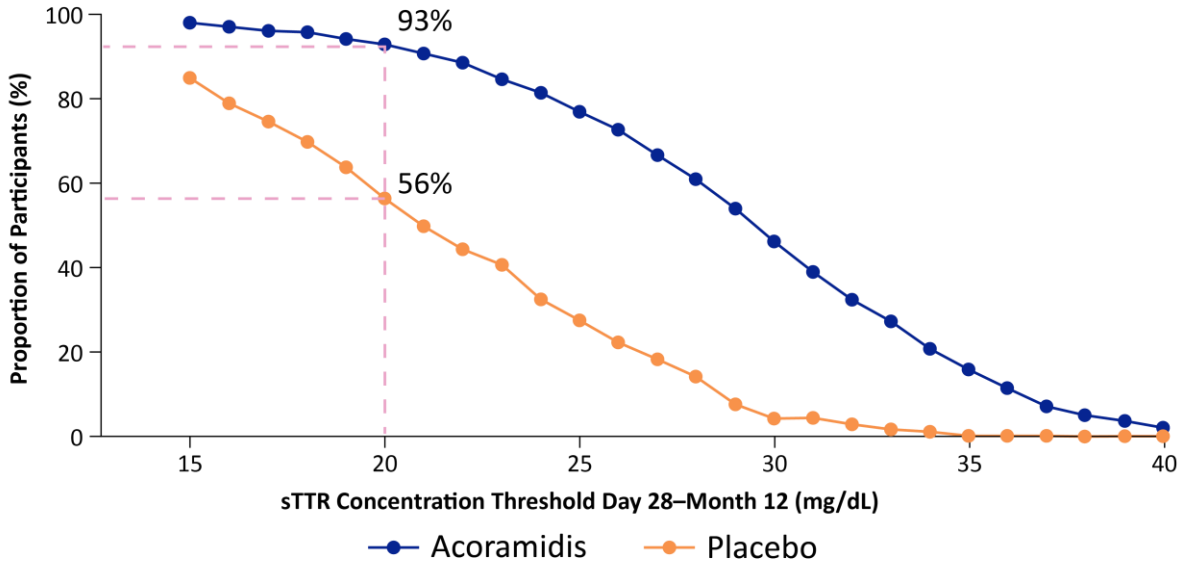
Individual sTTR Concentrations by Treatment Arm and Tafamidis Initiation



[a]Mean observed sTTR concentrations through Month 30 by treatment group in ATTRibute-CM.
M, Month; SE, standard error; sTTR, serum transthyretin; TTR, transthyretin.

Acoramidis Maintained sTTR Levels at or Above Clinically Relevant Thresholds

Proportion of Participants Whose sTTR Stayed Equal to or Above Given Thresholds (D28–M12) for Acoramidis Versus Placebo

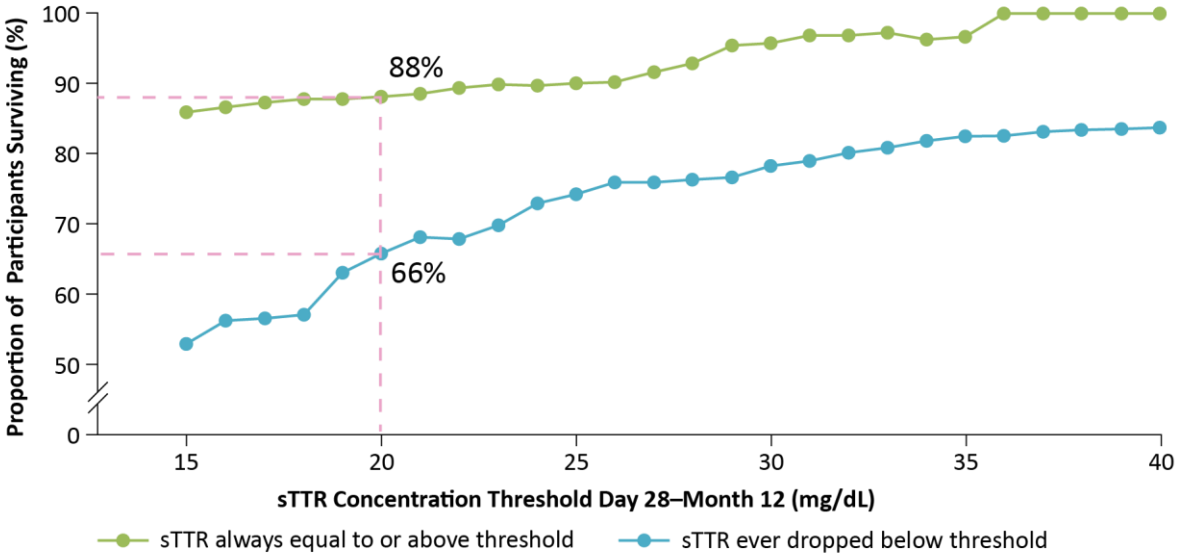


sTTR Threshold mg/dL	Acoramidis n = 378 n (%)	Placebo n = 185 n (%)	*p* Value
17	363 (96)	138 (75)	< 0.001
18	362 (96)	129 (70)	< 0.001
20	**351 (93)**	**104 (56)**	**< 0.001**
23	320 (85)	75 (41)	< 0.001
25	291 (77)	51 (28)	< 0.001
28	230 (61)	26 (14)	< 0.001

D, Day; M, Month; sTTR, serum transthyretin.

Maintaining sTTR Levels Was Associated With an Increased Probability of Survival Across Treatment Groups

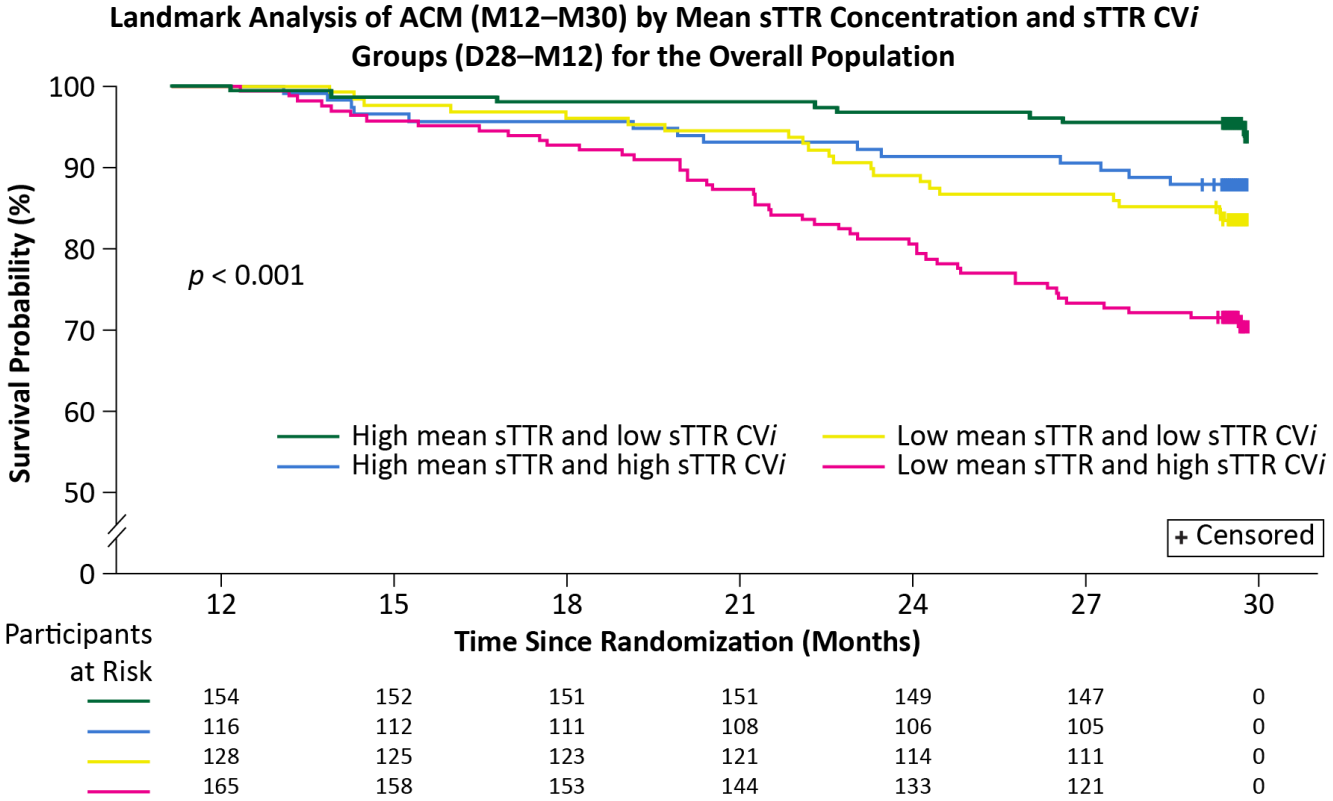
Proportion of Participants Surviving (M12–M30), as a Function of Whether sTTR Concentrations Always Stayed Equal to or Above Versus Ever Dropped Below Given Thresholds (D28–M12)[a]



sTTR Threshold mg/dL	Ever Dropped Below n/N (%)	Equal to or Above n/N (%)	*p* Value
17	35/62 (56)	437/501 (87)	< 0.001
18	41/72 (57)	431/491 (88)	< 0.001
20	**71/108 (66)**	**401/455 (88)**	**< 0.001**
23	117/168 (70)	355/395 (90)	< 0.001
25	164/221 (74)	308/342 (90)	< 0.001
28	234/307 (76)	238/256 (93)	< 0.001

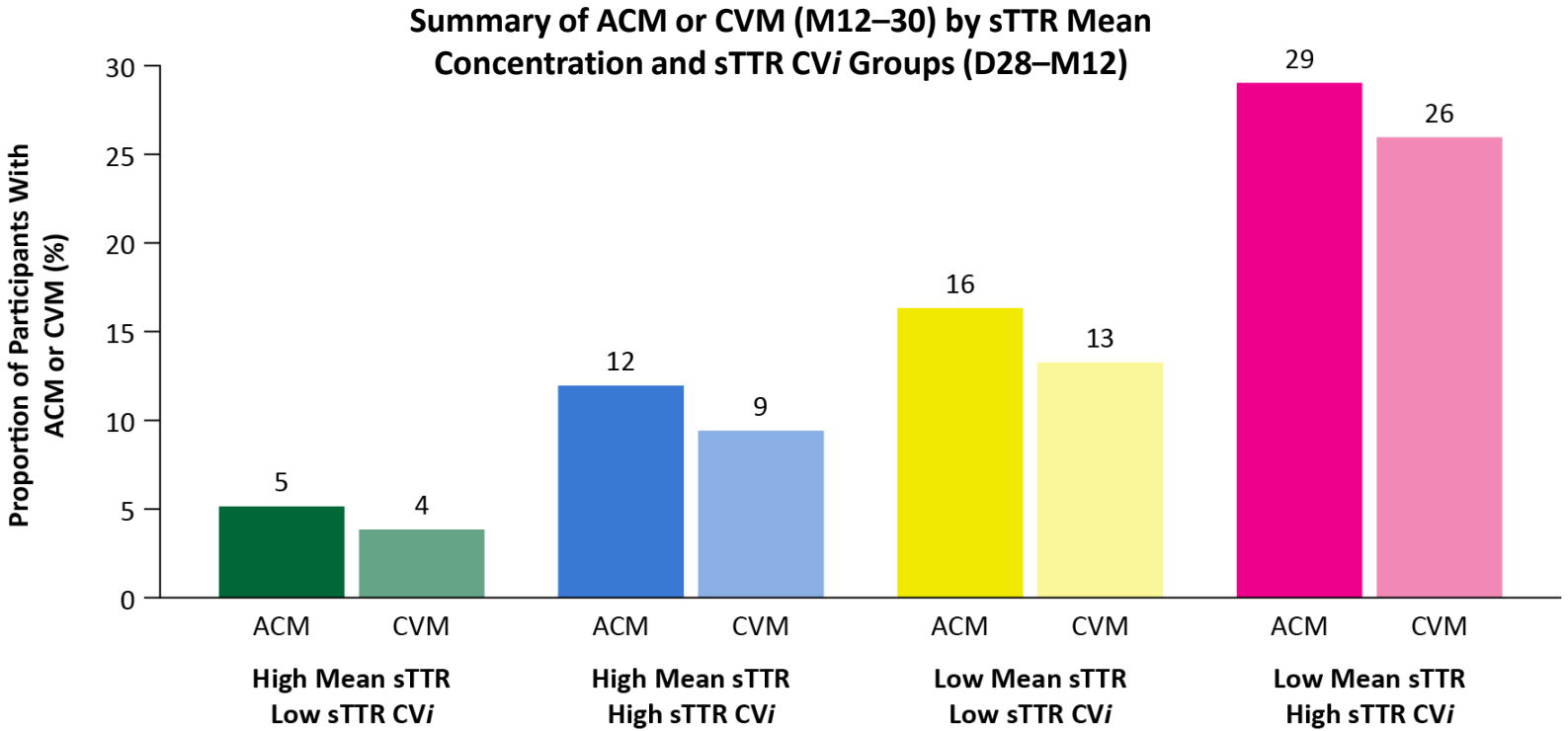
[a]Participants surviving were also free of heart transplantation and implantation of a cardiac mechanical assist device.
D, Day; M, Month; sTTR, serum transthyretin.

Higher Mean-Achieved sTTR and Lower CV*i* Were Associated With Lower ACM



Data are for the overall modified intention-to-treat population. Participants were divided into those above (high) vs at/below (low) population median values of sTTR mean and CV*i* between D28–M12.
ACM, all-cause mortality; CV*i*, intraindividual coefficient of variation; D, Day; M, Month; sTTR, serum transthyretin.

Higher Mean-Achieved sTTR and Lower CV*i* Were Associated With Lower ACM and Lower CVM



ACM, all-cause mortality; CV*i*, intraindividual coefficient of variation; CVM, cardiovascular-related mortality; D, Day; M, Month; sTTR, serum transthyretin.

Both Higher Mean-Achieved sTTR and Lower CV*i* Were Independently Associated With Lower ACM Even After Adjusting for Other Variables[a]

Model	sTTR Mean (High vs Low)		sTTR CV*i* (Low vs High)	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Baseline sTTR + sTTR mean	0.42 (0.23, 0.77)	0.005	-	-
Baseline sTTR + sTTR CV*i*	-	-	0.59 (0.37, 0.94)	0.025
Baseline sTTR + sTTR mean + sTTR CV*i*	0.43 (0.23, 0.78)	0.006	0.61 (0.38, 0.96)	0.033
Full model*	**0.46 (0.24, 0.85)**	**0.014**	**0.56 (0.35, 0.89)**	**0.014**

*Full model additionally adjusted for time-varying tafamidis initiation, 6MWD, age, sex, NYHA class, and BMI; and stratified by treatment, genotype, baseline NT-proBNP levels, and baseline eGFR

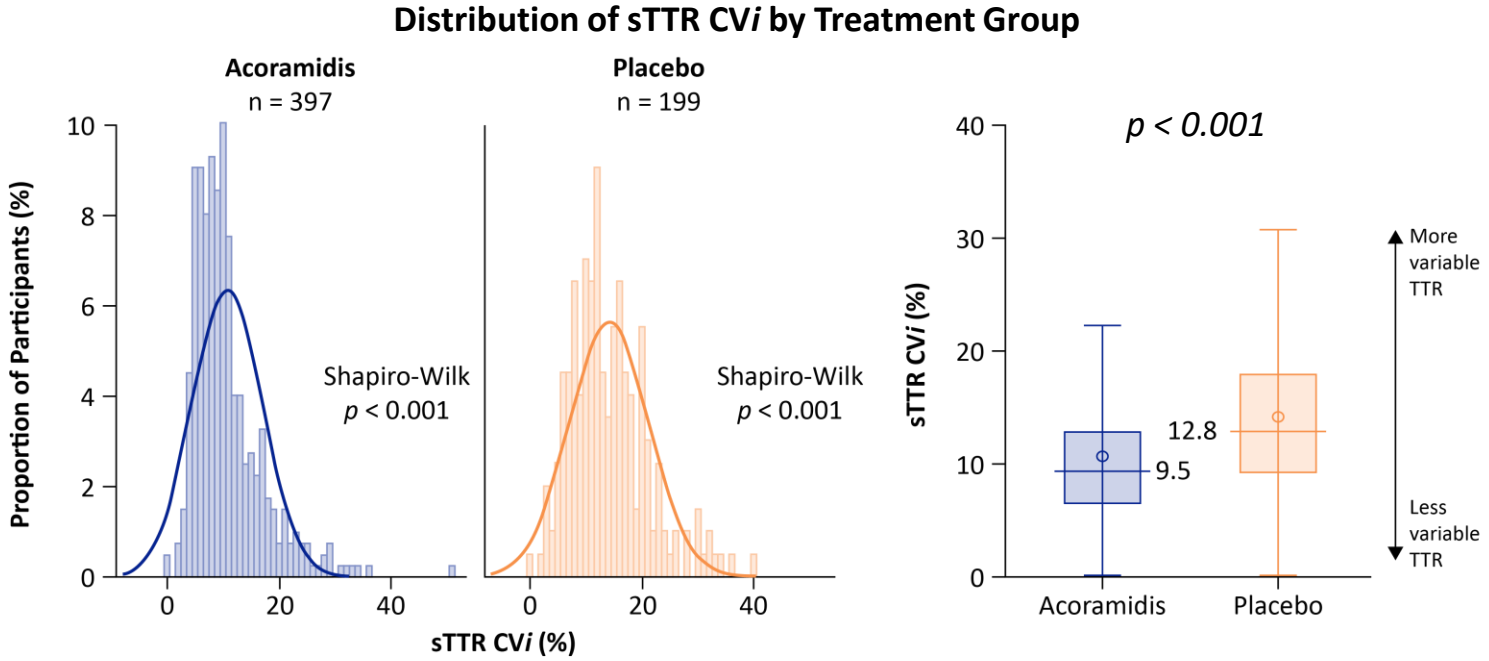
Sensitivity analyses showed consistent results after accounting for the following:

- *Excluding participants with only 2 sTTR measurements*
- *Adjusting for number of sTTR measurements in the full model*
- *Adjusting for the change from baseline in sTTR at Day 28 in the full model*
- *Shifting the landmark time from Month 12 to Month 6 in the full model*

[a]Sequential landmark analyses with multivariable-adjusted Cox proportional hazards models. For sTTR mean concentration (D28–M12) and sTTR CV*i* (D28–M12), high vs low was defined as > vs ≤ the median, respectively. The Cox proportional hazards model was stratified by treatment group and the 3 randomization stratification factors (genotype, baseline NT-proBNP levels, and baseline eGFR). Tafamidis initiation status was set as a time-varying covariate.

6MWD, 6-minute walk distance; ACM, all-cause-mortality; BMI, body mass index; CI, confidence interval; CV*i*, intraindividual coefficient of variation; D, Day; eGFR, estimated glomerular filtration rate; HR, hazard ratio; M, Month; N/A, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sTTR, serum transthyretin.

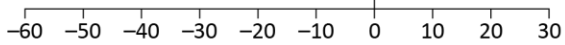
Acoramidis Reduced sTTR Variability Compared With Placebo From Day 28 Through Month 30



- Results were consistent from Day 28 through Month 12 (before tafamidis initiation allowed)
- Reducing sTTR variability accounted for 20% of the acoramidis effect on ACM

Acoramidis Decreased sTTR Variability (CV*i*) Compared With Placebo Consistently Across all Pre-Specified Trial Subgroups

Subgroup	No. (%) of Participants	% Difference in CV	% Difference in CV (95% CI)	*p* Value	Interaction *p* Value
Overall	596 (100.0)		−25.6 (−32.2, −18.4)	< 0.001	
Age (Years)					
< 78	296 (49.7)		−29.3 (−38.0, −19.3)	< 0.001	0.293
≥ 78	300 (50.3)		−21.8 (−31.5, −10.9)	< 0.001	
Sex					
Male	543 (91.1)		−25.2 (−32.2, −17.5)	< 0.001	0.748
Female	53 (8.9)		−29.0 (−47.3, −4.1)	0.025	
Race					
White	524 (87.9)		−23.8 (−31.0, −15.9)	< 0.001	0.163
Non-White	72 (12.1)		−37.9 (−52.6, −18.6)	< 0.001	
Genotype					
Variant	59 (9.9)		−34.4 (−51.1, −11.9)	0.005	0.376
Wild-Type	537 (90.1)		−24.5 (−31.6, −16.7)	< 0.001	
NT-proBNP (pg/mL)					
≤ 3000	398 (66.8)		−25.9 (−33.8, −16.9)	< 0.001	0.903
> 3000	198 (33.2)		−24.9 (−36.1, −11.8)	< 0.001	
eGFR (mL/min/1.73 m²)					
< 45	89 (14.9)		−29.7 (−45.1, −9.9)	0.005	0.644
≥ 45	507 (85.1)		−25.1 (−32.2, −17.2)	< 0.001	
NAC Stage					
I	359 (60.2)		−25.4 (−33.7, −16.0)	< 0.001	0.987
II	187 (31.4)		−25.7 (−37.0, −12.4)	< 0.001	
III	50 (8.4)		−27.5 (−48.0, 0.9)	0.057	
NYHA Class					
I	67 (11.2)		−32.1 (−49.6, −8.4)	0.011	0.106
II	434 (72.8)		−28.2 (−35.5, −20.1)	< 0.001	
III	95 (15.9)		−5.6 (−25.9, 20.4)	0.644	



Percentage reduction in CV*i* (95% CI) for acoramidis vs placebo is shown for the overall population and by subgroups of age, sex, race, genotype, NT-proBNP, eGFR, NAC stage, and NYHA class.
CI, confidence interval; CV*i*, intraindividual coefficient of variation; eGFR, estimated glomerular filtration rate; NAC, National Amyloidosis Centre; no., number; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sTTR, serum transthyretin.

Conclusions

- Higher intraindividual sTTR variability (CV*i*) was associated with higher-risk clinical features
- Maintaining sTTR levels above physiologic thresholds was associated with reduced ACM risk
- Having both low sTTR variability (CV*i*) *and* high sTTR levels was independently associated with the lowest risk for fatal events
  - *Results consistent after comprehensive multivariable adjustment including baseline sTTR levels and mean-achieved sTTR levels*
- Acoramidis significantly decreased sTTR variability compared with placebo
  - *Consistency observed across all pre-specified trial subgroups*
- Limitations: Landmark analysis required survival to Month 12; residual confounding

- **These results support sTTR variability (CV*i*) as a novel biomarker of ATTR-CM severity, risk, and treatment response**
- **Acoramidis not only rapidly increases sTTR, but also stabilizes sTTR levels over time**

ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; sTTR, serum transthyretin; TTR, transthyretin.

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