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

Insights From the ATTRibute-CM Trial

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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

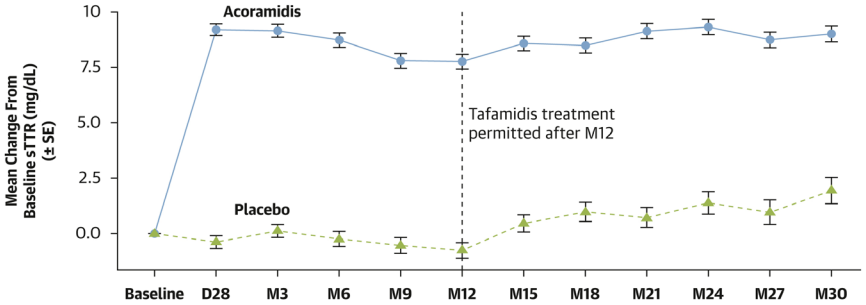

Figure from Maurer MS, et al. *J Am Coll Cardiol*. 2025;85:1911-1923. https://www.jacc.org/doi/10.1016/j.jacc.2025.03.542
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Purpose

- 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*
- 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*

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

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[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 of acoramidis versus placebo on sTTR CV*i* D28–M30 using ANCOVA analysis

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

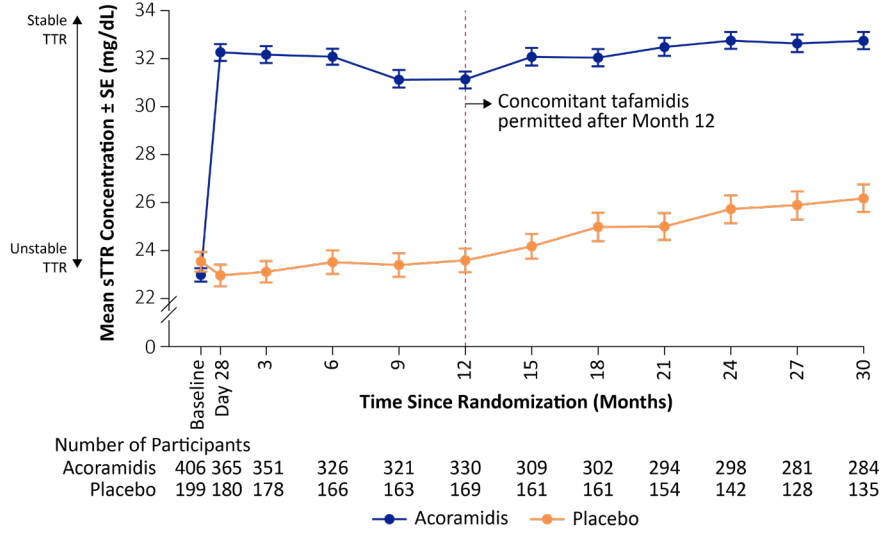
Baseline Characteristic	Low CV*i* (n = 282) ≤ *population median*	High CV*i* (n = 281) *> population median*	*p* Value
Age, years, mean (SD)	76.9 (6.7)	77.1 (6.4)	0.654
Sex, male, n (%)	256 (90.8)	257 (91.5)	0.777
Wild-type ATTR-CM, n (%)	257 (91.1)	254 (90.4)	0.761
NAC stage, n (%)			
I	195 (69.1)	150 (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%*

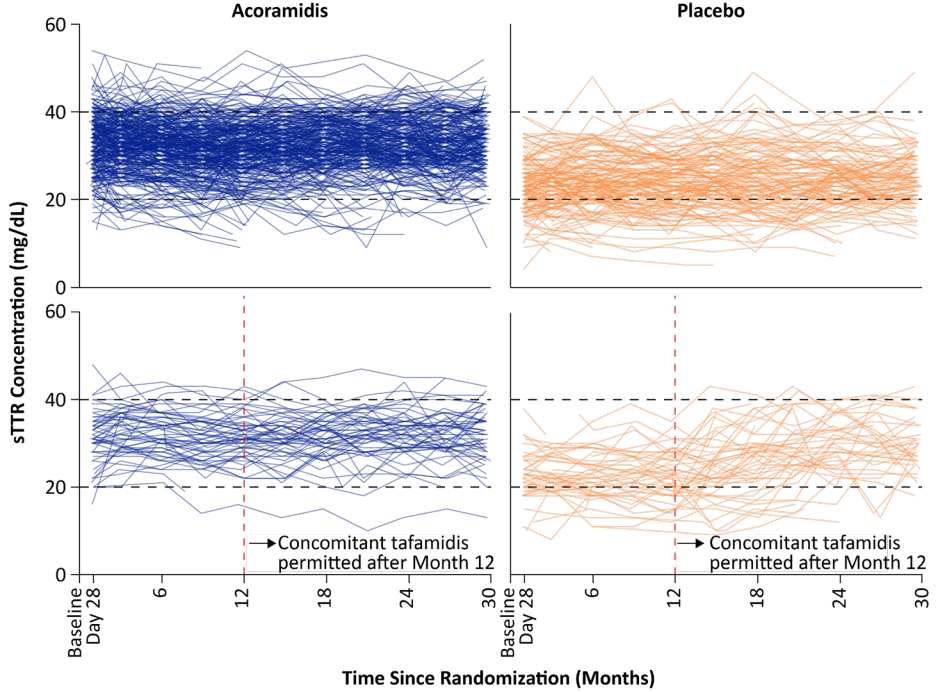
6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; BMI, body mass index; CV*i*, intraindividual coefficient of variation; D, Day; eGFR, estimated glomerular filtration rate; M, Month; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, 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



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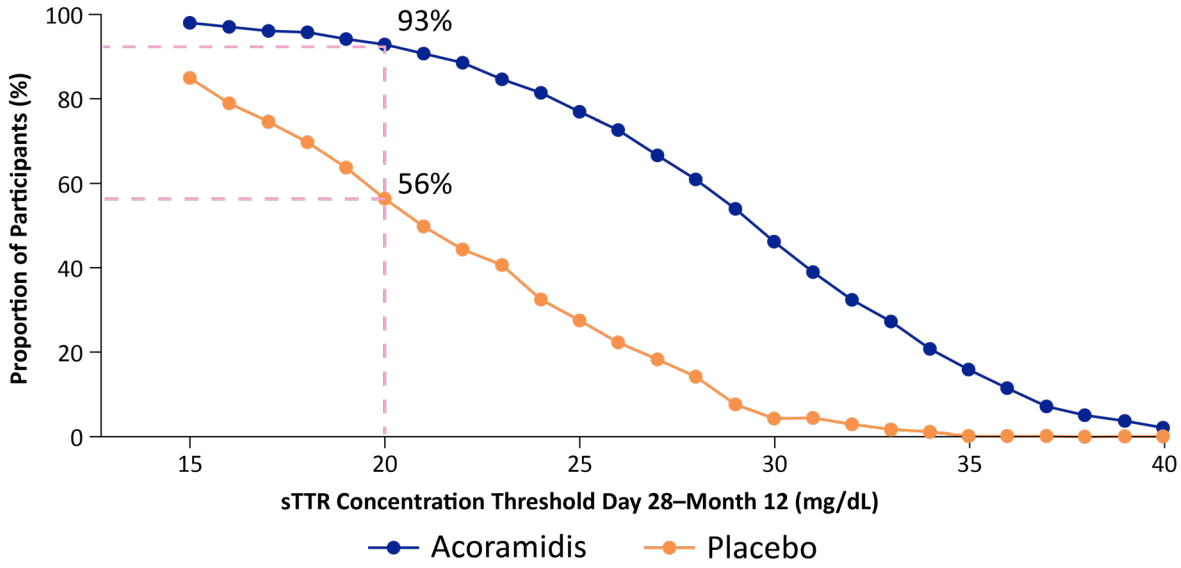
[a]Mean observed sTTR concentrations through Month 30 by treatment group in ATTRibute-CM.
M, Month; SE, standard error; sTTR, serum transthyretin; TTR, transthyretin.

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

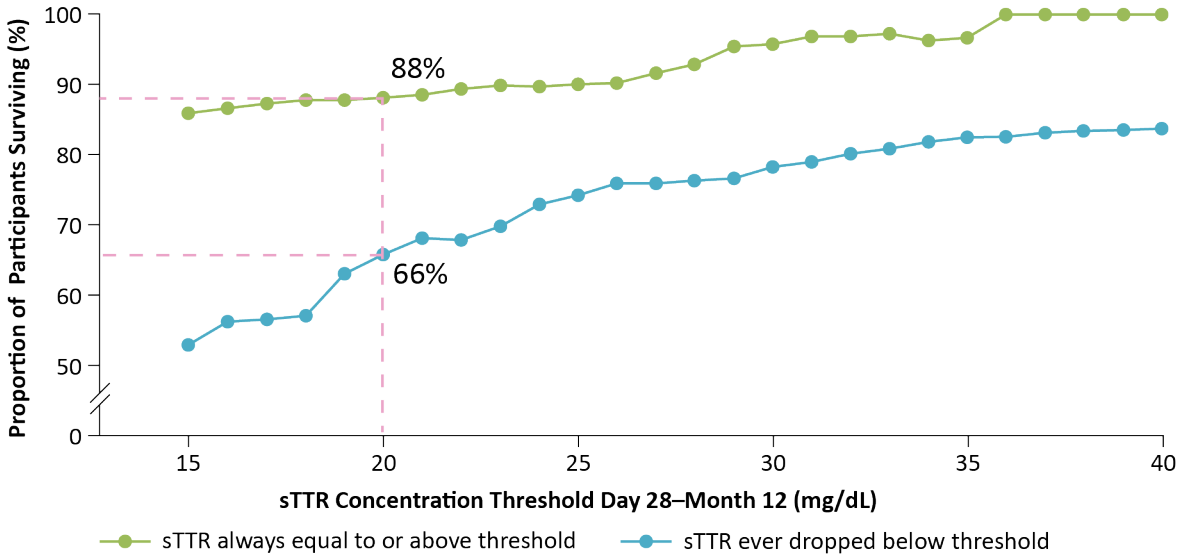


sTTR Threshold mg/dL	Acoramidis n = 378 n (%)	Placebo n = 185 n (%)	*p* Value
17	363 (96)	138 (75)	< 0.001
18	362 (96)	129 (70)	< 0.001
20	**351 (93)**	**104 (56)**	**< 0.001**
23	320 (85)	75 (41)	< 0.001
25	291 (77)	51 (28)	< 0.001
28	230 (61)	26 (14)	< 0.001

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

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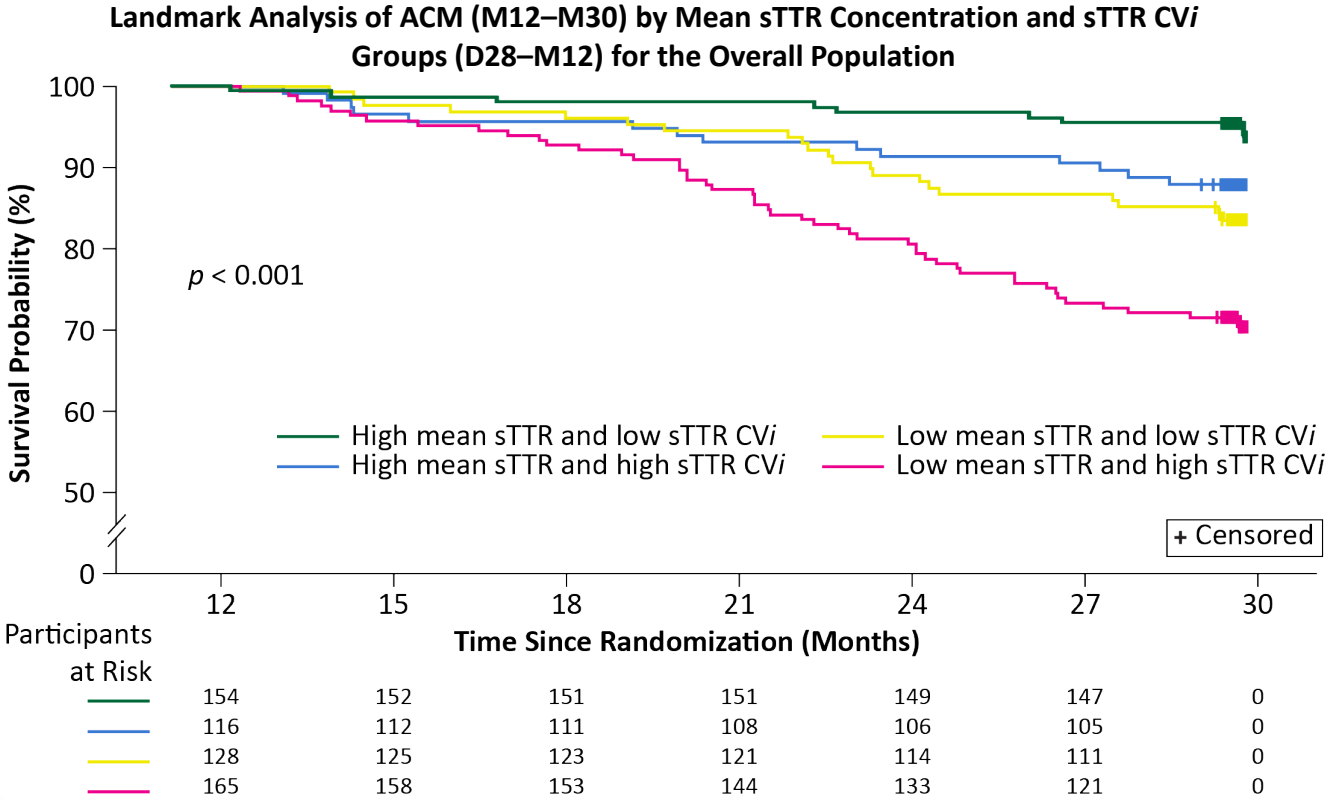
[a]Participants surviving were also free of heart transplantation and implantation of a cardiac mechanical assist device.
D, Day; M, Month; sTTR, serum transthyretin.

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



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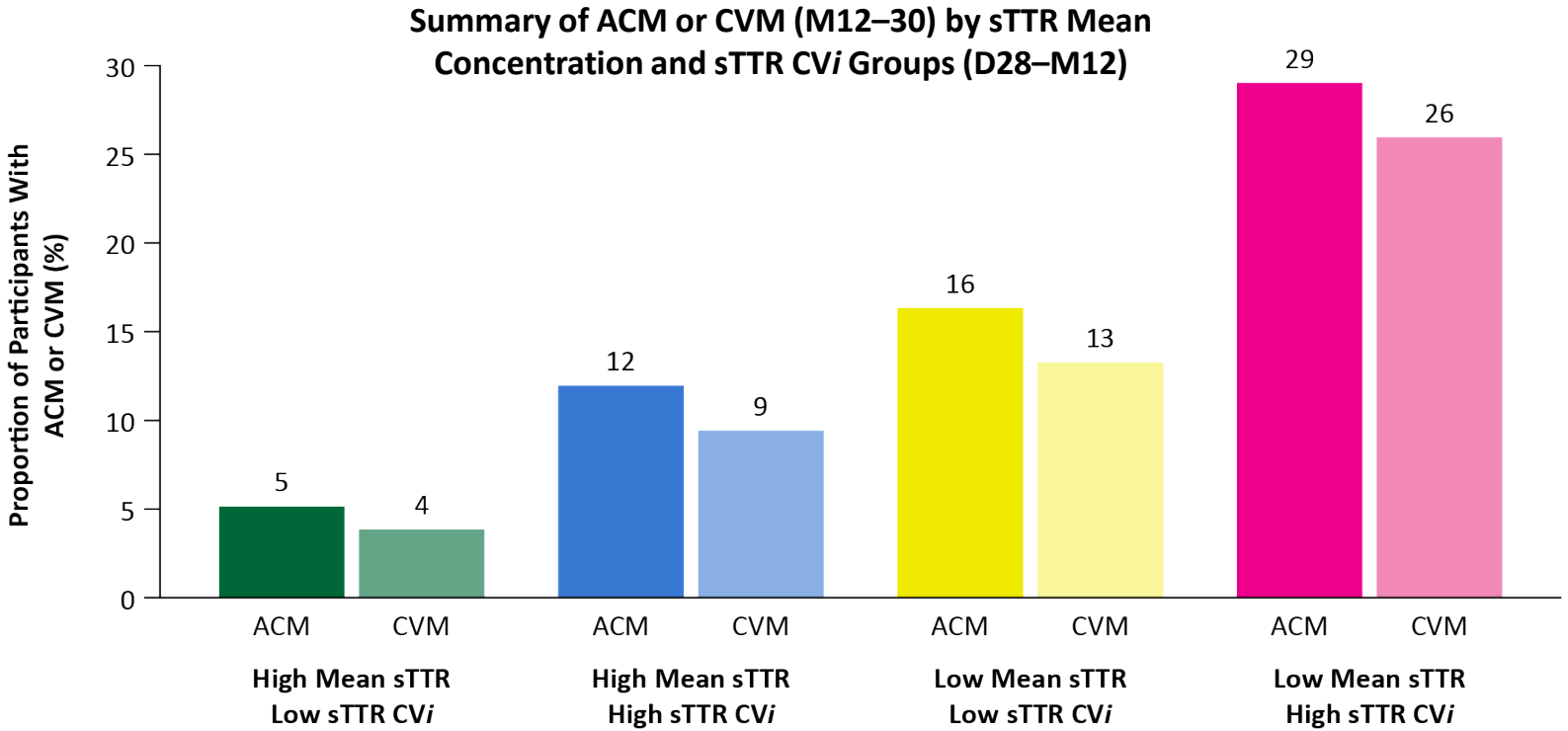
Data are for the overall modified intention-to-treat population. Participants were divided into those above (high) vs at/below (low) population median values of sTTR mean and CV*i* between D28–M12.
ACM, all-cause mortality; CV*i*, intraindividual coefficient of variation; D, Day; M, Month; sTTR, serum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

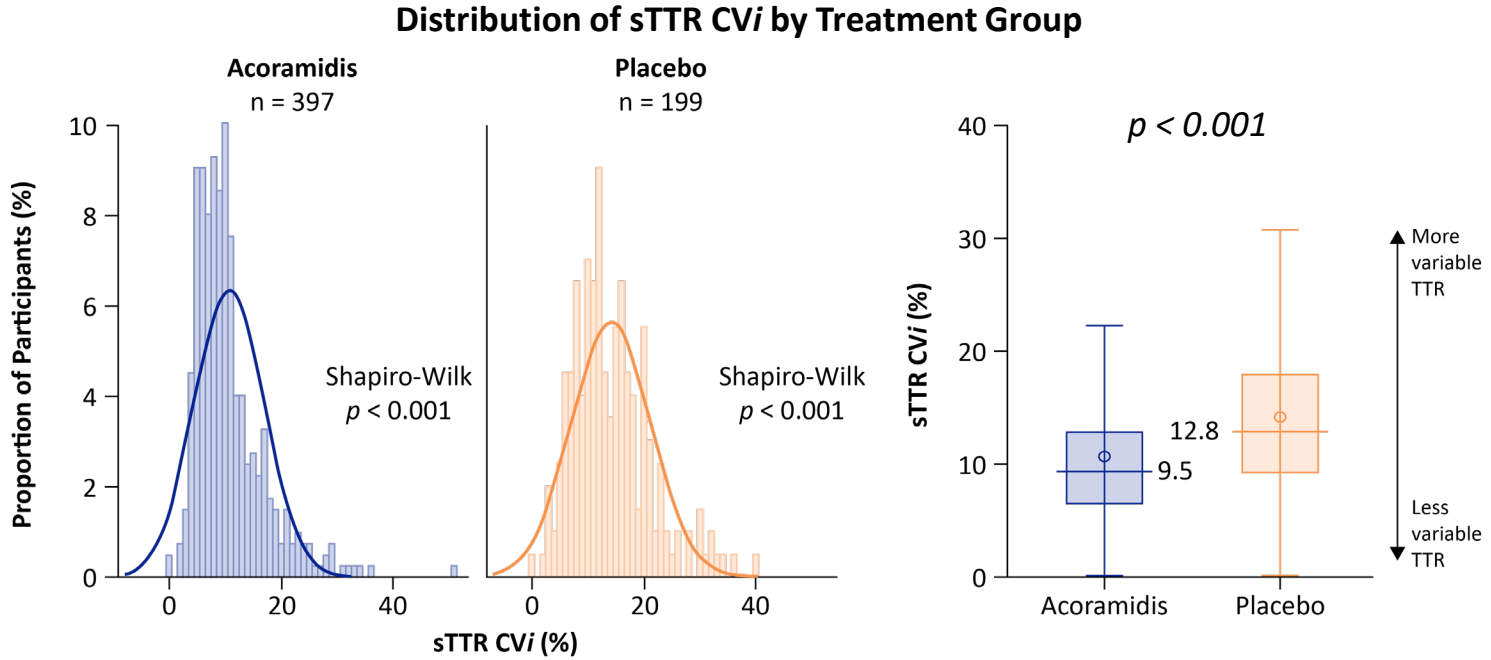
Sensitivity analyses showed consistent results after accounting for the following:

- *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.

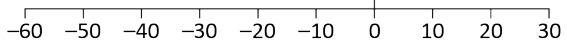
Acoramidis Reduced sTTR Variability Compared With Placebo From Day 28 Through Month 30



- 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 (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 m^2)				
< 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	



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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 change in sTTR*
- 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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