SERUM TRANSTHYRETIN LEVELS AT DAY 28 ARE ASSOCIATED WITH CARDIOVASCULAR OUTCOMES: INSIGHTS FROM THE ATTRibute-CM STUDY

Nitasha Sarswat,[1] Amrut V. Ambardekar,[2] Richard Wright,[3] Margot K. Davis,[4] Julian D. Gillmore,[5] Justin L. Grodin,[6] Joshua D. Mitchell,[7] Deirdre Mooney,[8] Jose Nativi-Nicolau,[9] Frederick L. Ruberg,[10] Chris Chen,[11] Alan Ji,[11] Jean-François Tamby,[11] Uma Sinha,[11] Jonathan C. Fox,[11] Mathew S. Maurer,[12] and Richard K. Cheng[13]

[1]Division of Cardiovascular Medicine, University of Chicago Medicine, Chicago, IL, USA; [2]Division of Cardiology, Department of Medicine, University of Colorado, Aurora, CO, USA; [3]Pacific Heart Institute and Providence, St. John's Health Center, Santa Monica, CA, USA; [4]Division of Cardiology, University of British Columbia, Vancouver, BC, Canada; [5]National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital, London, UK; [6]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [7]Cardiovascular Division, Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [8]Providence Center for Advanced Heart Disease & Transplant, Spokane, WA, USA; [9]Division of Advanced Heart Failure and Heart Transplantation, Mayo Clinic, Jacksonville, FL, USA; [10]Section of Cardiovascular Medicine, Department of Medicine, Amyloidosis Center, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, Boston, MA, USA; [11]BridgeBio Pharma, Inc., San Francisco, CA, USA; [12]Division of Cardiology, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA; [13]University of Washington, Seattle, WA, USA

Presenter: Nitasha Sarswat

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INTRODUCTION

- Low sTTR levels in patients with ATTR-CM are associated with worse clinical outcomes and increased mortality[1,2]
  - Patients with sTTR levels ≥ 20 mg/dL have a significantly reduced risk of ACM vs those with sTTR levels < 20 mg/dL[2]
  - Regardless of baseline levels, greater increases in sTTR levels are associated with greater improvements in CV outcomes[3]
- Acoramidis, an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, Europe, Japan, and the UK for ATTR-CM[4–8]
- In the phase 3 ATTRibute-CM study,[a] acoramidis led to a rapid (by Day 28) and sustained (through Month 30) increase in sTTR levels and reduced the risk of CV outcomes in participants with ATTR-CM[9,10]

OBJECTIVE:

To assess if the acoramidis-led early increase in sTTR levels to ≥ 20 mg/dL at Day 28 is associated with reduced risks of cardiovascular mortality (CVM) and cardiovascular-related hospitalization (CVH) in patients with ATTR-CM

[a]ClinicalTrials.gov identifier: NCT03860935.

ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular mortality; sTTR, serum transthyretin; TTR, transthyretin.

1. Minervini A, et al. *Eur. J. Intern. Med*. 2025. doi:10.1016/j.ejim.2025.05.015. **2.** Maurer MS, et al. *J Am Coll Cardiol*. 2025;85(20):1911-1923. **3.** Cheng R, et al. *Amyloid*. 2024;31(suppl1):S117. **4.** Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295. **5.** BridgeBio Pharma, Inc. Prescribing information, Attruby (acoramidis). FDA, 2024. Accessed November 04, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf. **6.** BridgeBio Europe B.V. SmPC, Beyonttra (acoramidis). EMA, 2024. Accessed November 04, 2025. https://www.ema.europa.eu/en/documents/product-information/beyonttra-epar-product-information_en.pdf. **7.** Alexion. SmPC, Beyonttra (acoramidis). MHLW Japan, 2025. Accessed November 04, 2025. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/870056_2190048F1029_1_01. **8.** Bayer plc. SmPC, Beyonttra (acoramidis). MHRA UK, 2025. Accessed November 04, 2025. https://mhraproducts4853.blob.core.windows.net/docs/a59718d1af5328302357b1f6a18908322e4eb7f8. **9.** Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142. **10.** Judge DP, et al. *J Am Coll Cardiol.* 2025;85(10):1003-1014.

METHODS

- The ATTRibute-CM study design has been previously described[1]
  - Participants with ATTR-CM aged 18–90 years were randomized 2:1 to receive acoramidis HCl 800 mg or placebo twice daily for 30 months
- Efficacy analyses were conducted in the mITT population[a]
- sTTR concentrations were assessed using an immunoturbidimetric method[b] in a central laboratory
- The proportions of participants with sTTR levels below the normal range (normal range: 20–40 mg/dL)[2] at baseline and Day 28 were determined
- The relationships between sTTR levels < 20 mg/dL and ≥ 20 mg/dL at Day 28 and the risks of CVM[c] and of first CVH[d] over 30 months were analyzed across pooled acoramidis and placebo treatment groups using a stratified log-rank test

[a]mITT population consisted of all randomized participants who received at least one dose of acoramidis or placebo, had at least one post-baseline efficacy evaluation, and had a baseline eGFR of ≥ 30 mL/min/1.73 m^2. [b]The Abbott ARCHITECT system was used for analysis. [c]CVM included death adjudicated as CV or of undetermined cause by the CEC, cardiac mechanical assist device implantation, or heart transplantation. [d]CVH was defined as a nonelective admission to an acute care setting for CV-related morbidity that resulted in a stay of ≥ 24 hours. CVH included EOCI, which were unplanned medical visits of < 24 hours requiring treatment with an intravenous diuretic for the management of decompensated heart failure.

ATTR-CM, transthyretin amyloid cardiomyopathy; CEC, clinical events committee; CV, cardiovascular; CVM, cardiovascular mortality; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; EOCI, events of clinical interest; mITT, modified intention-to-treat; sTTR, serum transthyretin.

1. Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142. **2.** Maurer MS, et al. *J Am Coll Cardiol.* 2025;85(20):1911-1923.

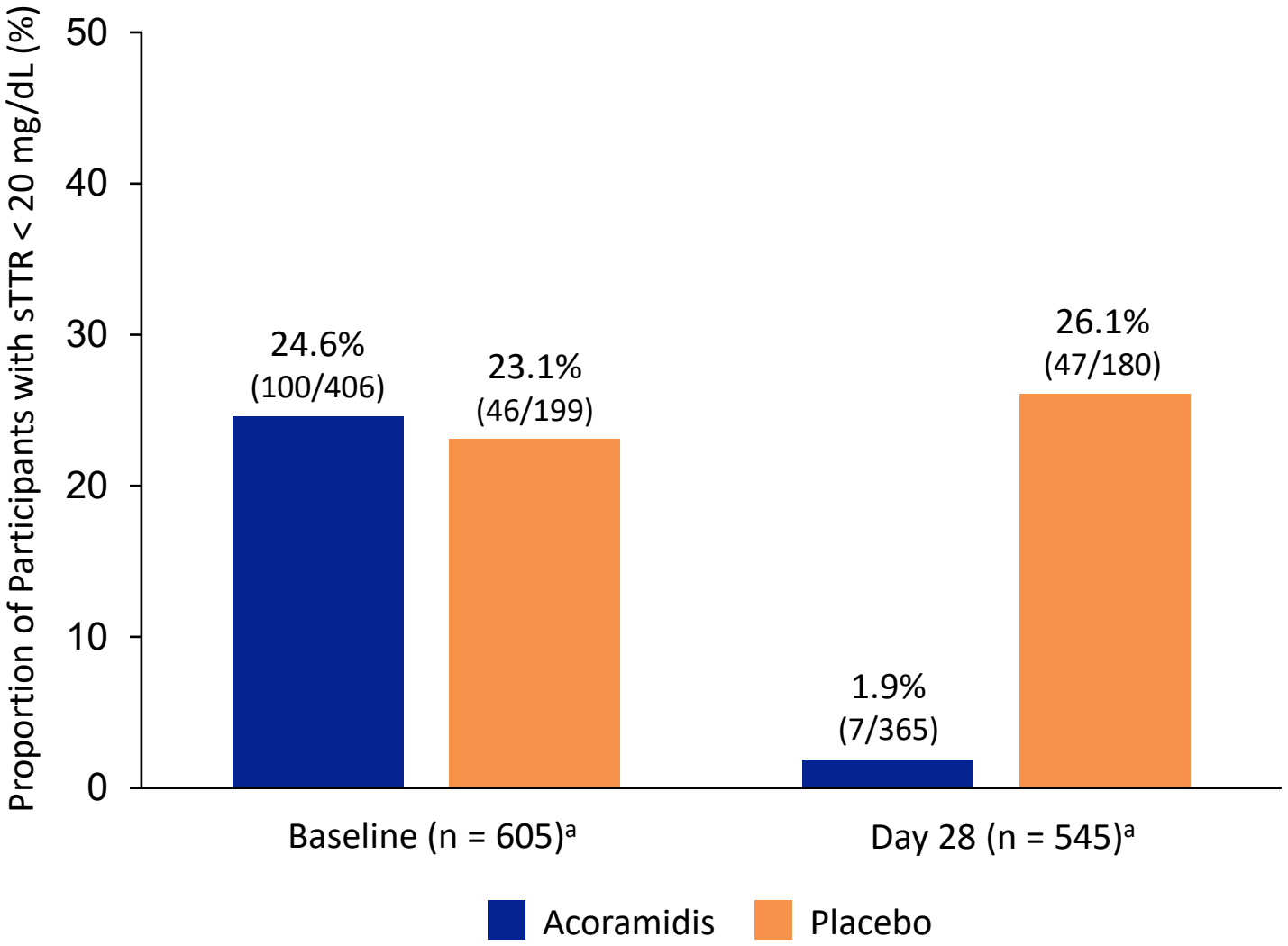
BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS WERE COMPARABLE BETWEEN TREATMENT GROUPS[1]

Baseline Demographic/Characteristic		Acoramidis (n = 409)	Placebo (n = 202)	Overall (N = 611)
Age, years	Mean (SD)	77.3 (6.5)	77.0 (6.7)	77.2 (6.6)
Sex, male	n (%)	374 (91.4)	181 (89.6)	555 (90.8)
Wild-type ATTR-CM[a]	n (%)	370 (90.5)	182 (90.1)	552 (90.3)
NYHA functional class	n (%)			
I		51 (12.5)	17 (8.4)	68 (11.1)
II		288 (70.4)	156 (77.2)	444 (72.7)
III		70 (17.1)	29 (14.4)	99 (16.2)
sTTR level, mg/dL	n	406	199	605
	Mean (SD)	23.0 (5.6)	23.6 (6.1)	23.2 (5.8)
< 20 mg/dL	n (%)	100 (24.6)	46 (23.1)	146 (24.1)
≥ 20 mg/dL	n (%)	306 (75.4)	153 (76.9)	459 (75.9)

[a]TTR genotype was reported in the interactive voice/web response system at randomization.
ATTR-CM, transthyretin amyloid cardiomyopathy; NYHA, New York Heart Association; SD, standard deviation; sTTR, serum transthyretin.
1. Judge DP, et al. *J Am Coll Cardiol.* 2025;85(10):1003-1014.

AT DAY 28, FEWER THAN 2% OF PARTICIPANTS WHO RECEIVED ACORAMIDIS HAD sTTR LEVELS < 20 mg/dL

sTTR Level, mg/dL		Acoramidis (n = 409)	Placebo (n = 202)
Baseline	n	406	199
	Mean (SD)	23.0 (5.6)	23.6 (6.1)
Day 28	n	365	180
	Mean (SD)	32.2 (6.5)	23.0 (6.1)

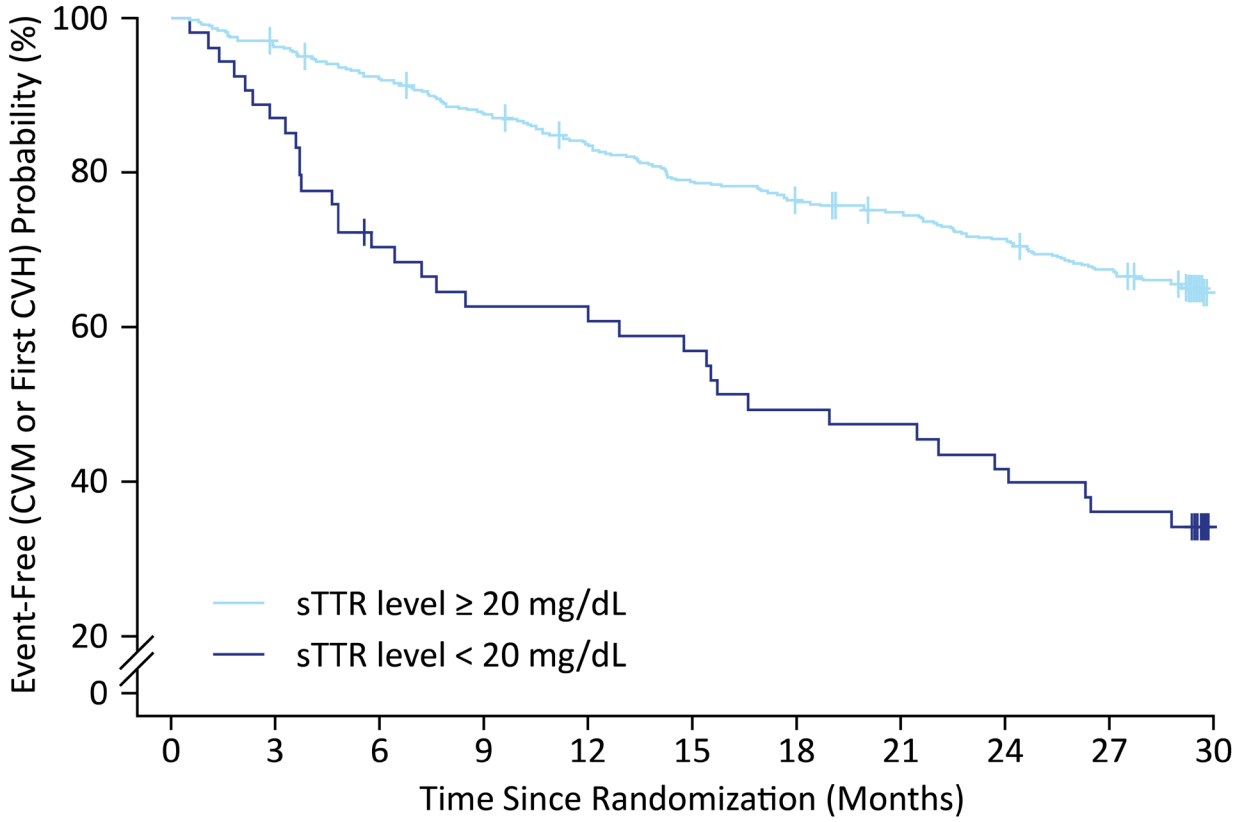


Data are for the mITT population in the ATTRibute-CM study, defined as all randomized participants who received at least one dose of acoramidis or placebo, had at least one post-baseline efficacy evaluation, and had a baseline eGFR of ≥ 30 mL/min/1.73 m^2.

[a]Number of participants with available sTTR values.

eGFR, estimated glomerular filtration rate; mITT, modified intention-to-treat; SD, standard deviation; sTTR, serum transthyretin.

PARTICIPANTS WITH sTTR LEVELS ≥ 20 mg/dL AT DAY 28 HAD A LOWER RISK OF CVM OR FIRST CVH BY MONTH 30 VS THOSE WITH sTTR LEVELS < 20 mg/dL



No. of participants at risk (cumulative events)

sTTR < 20 mg/dL	54 (0)	47 (7)	37 (16)	33 (20)	33 (20)	30 (23)	26 (27)	25 (28)	22 (31)	19 (34)	0 (35)
sTTR ≥ 20 mg/dL	491 (0)	472 (18)	451 (38)	428 (60)	406 (80)	383 (103)	370 (115)	360 (122)	343 (139)	323 (158)	0 (171)

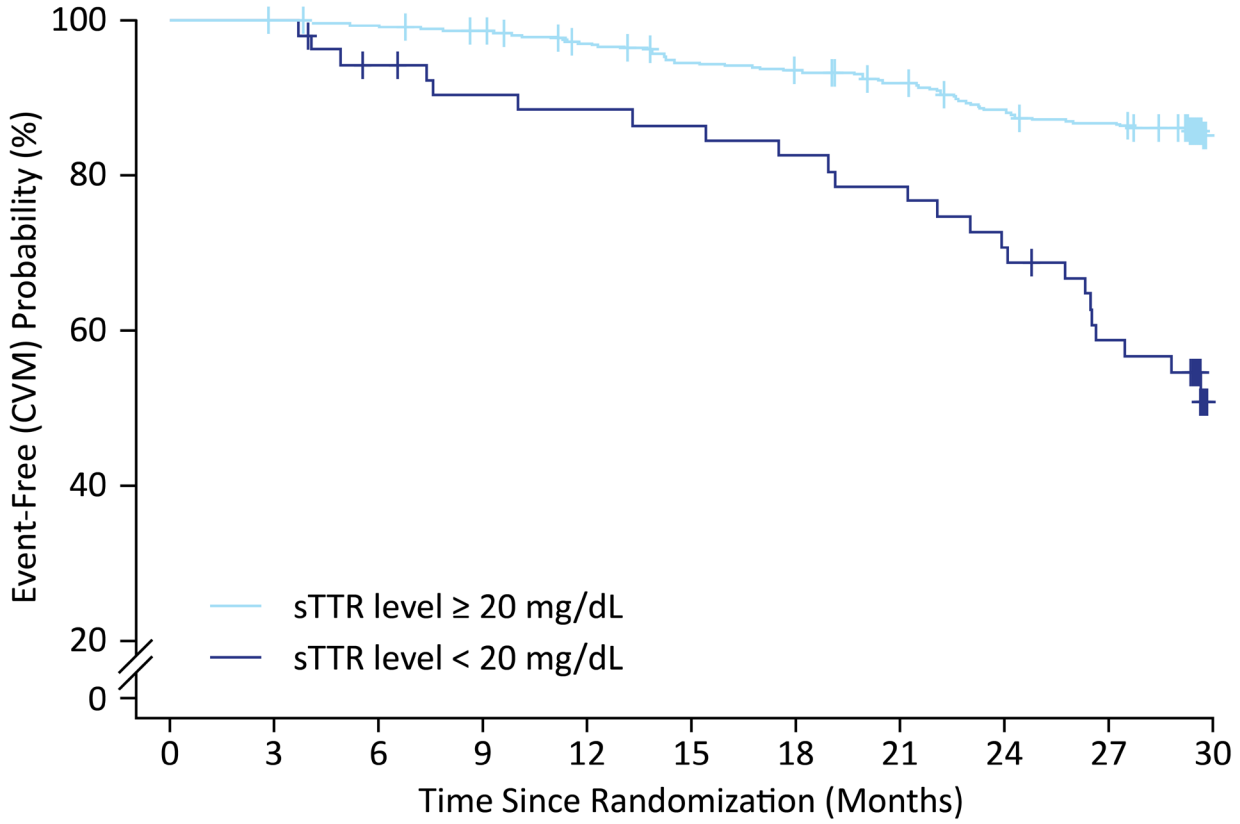
	sTTR Level < 20 mg/dL (n = 54)	sTTR Level ≥ 20 mg/dL (n = 491)
Percentage of participants free from CVM or first CVH at Month 30 (95% CI)	34.2 (21.9, 46.9)	64.4 (59.9, 68.6)
***p* value[a]**	< 0.0001	

CVM included death adjudicated as CV or of undetermined cause by the CEC, cardiac mechanical assist device implantation, or heart transplantation. CVH was defined as a nonelective admission to an acute care setting for CV-related morbidity that resulted in a stay of ≥ 24 hours. CVH included EOCI, which were unplanned medical visits of < 24 hours requiring treatment with an intravenous diuretic for the management of decompensated heart failure.

[a]*p* values were based on a log-rank test that was stratified by randomization factors of genotype, NT-proBNP level, and eGFR at randomization.

CEC, clinical events committee; CI, confidence interval; CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular mortality; eGFR, estimated glomerular filtration rate; EOCI, events of clinical interest; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTTR, serum transthyretin.

PARTICIPANTS WITH sTTR LEVELS ≥ 20 mg/dL AT DAY 28 HAD A LOWER RISK OF CVM BY MONTH 30 VS THOSE WITH sTTR LEVELS < 20 mg/dL



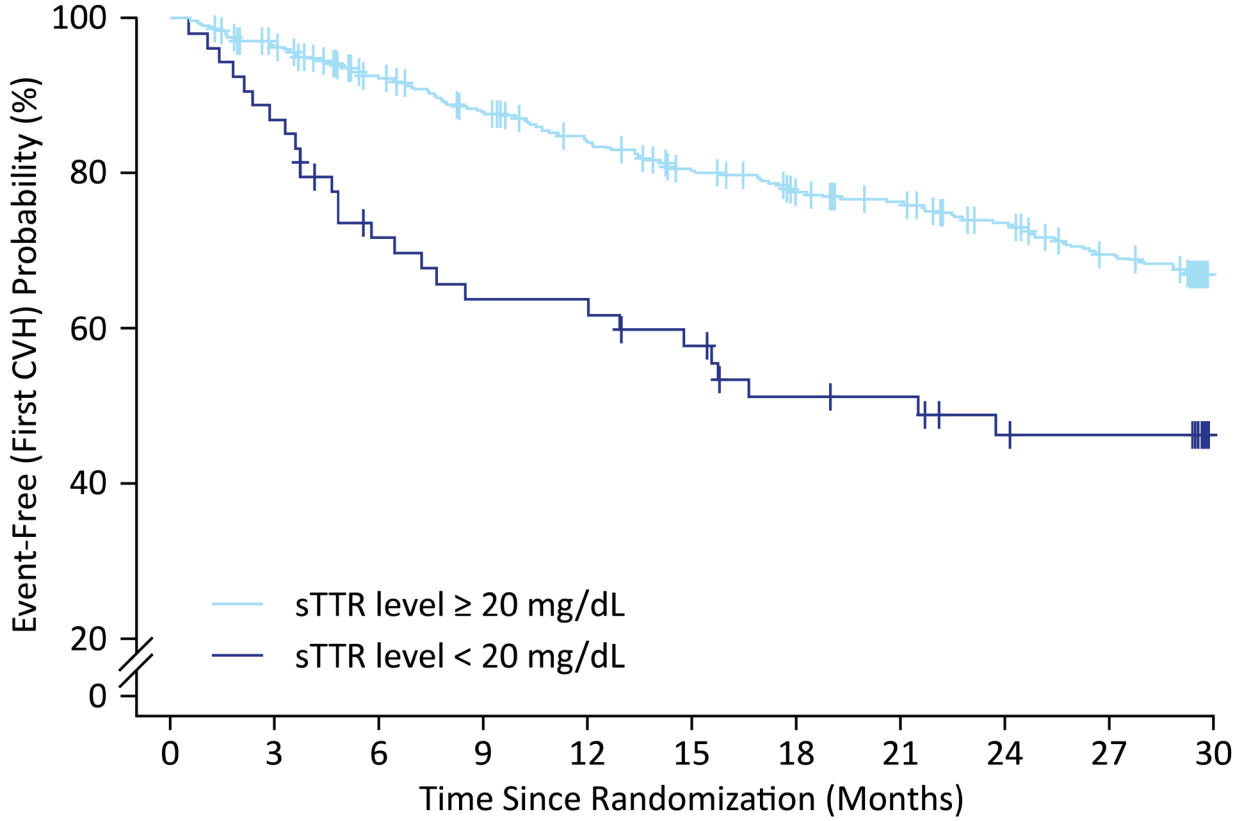
No. of participants at risk (cumulative events)

sTTR < 20 mg/dL	54 (0)	54 (0)	49 (3)	46 (5)	45 (6)	44 (7)	42 (9)	40 (11)	36 (15)	29 (21)	0 (24)
sTTR ≥ 20 mg/dL	491 (0)	490 (0)	487 (2)	481 (6)	468 (14)	454 (26)	448 (31)	438 (38)	419 (55)	410 (63)	0 (69)

	sTTR Level < 20 mg/dL (n = 54)	sTTR Level ≥ 20 mg/dL (n = 491)
Percentage of participants free from CVM at Month 30 (95% CI)	50.7 (35.3, 64.3)	85.3 (81.6, 88.2)
***p* value[a]**	< 0.0001	

CVM included death adjudicated as CV or of undetermined cause by the CEC, cardiac mechanical assist device implantation, or heart transplantation.
[a]*p* values were based on a log-rank test that was stratified by randomization factors of genotype, NT-proBNP level, and eGFR at randomization.
CEC, clinical events committee; CI, confidence interval; CV, cardiovascular; CVM, cardiovascular mortality; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type-natriuretic peptide; sTTR, serum transthyretin.

PARTICIPANTS WITH sTTR LEVELS ≥ 20 mg/dL AT DAY 28 HAD A LOWER RISK OF FIRST CVH BY MONTH 30 VS THOSE WITH sTTR LEVELS < 20 mg/dL



No. of participants at risk (cumulative events)

sTTR < 20 mg/dL	54 (0)	47 (7)	36 (15)	32 (19)	32 (19)	28 (22)	23 (25)	22 (25)	18 (27)	17 (27)	0 (27)
sTTR ≥ 20 mg/dL	491 (0)	466 (18)	432 (36)	406 (57)	380 (75)	357 (91)	338 (103)	327 (109)	309 (120)	286 (137)	0 (148)

	sTTR Level < 20 mg/dL (n = 54)	sTTR Level ≥ 20 mg/dL (n = 491)
Percentage of participants free from first CVH at Month 30 (95% CI)	46.3 (31.9, 59.6)	67.0 (62.4, 71.1)
***p* value[a]**	0.0011	

CVH was defined as a nonelective admission to an acute care setting for CV-related morbidity that resulted in a stay of ≥ 24 hours. CVH included EOCI, which were unplanned medical visits of < 24 hours requiring treatment with an intravenous diuretic for the management of decompensated heart failure.

[a]*p* values were based on a log-rank test that was stratified by randomization factors of genotype, NT-proBNP level, and eGFR at randomization.

CI, confidence interval; CV, cardiovascular; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; EOCI, events of clinical interest; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTTR, serum transthyretin.

CONCLUSIONS

- Regardless of treatment, sTTR levels at Day 28 of ≥ 20 mg/dL were associated with a lower risk of CV outcomes through Month 30 vs sTTR levels below the normal range (< 20 mg/dL) in the pooled analyses
- These results demonstrate that higher sTTR levels shortly after treatment initiation have potential clinical benefits, including lower risks of CVM and CVH over 30 months

CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular mortality; sTTR, serum transthyretin.