Effect of Vutrisiran According to Baseline Tafamidis Use in Transthyretin Amyloidosis with Cardiomyopathy: Insights from HELIOS-B

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HELIOS·B

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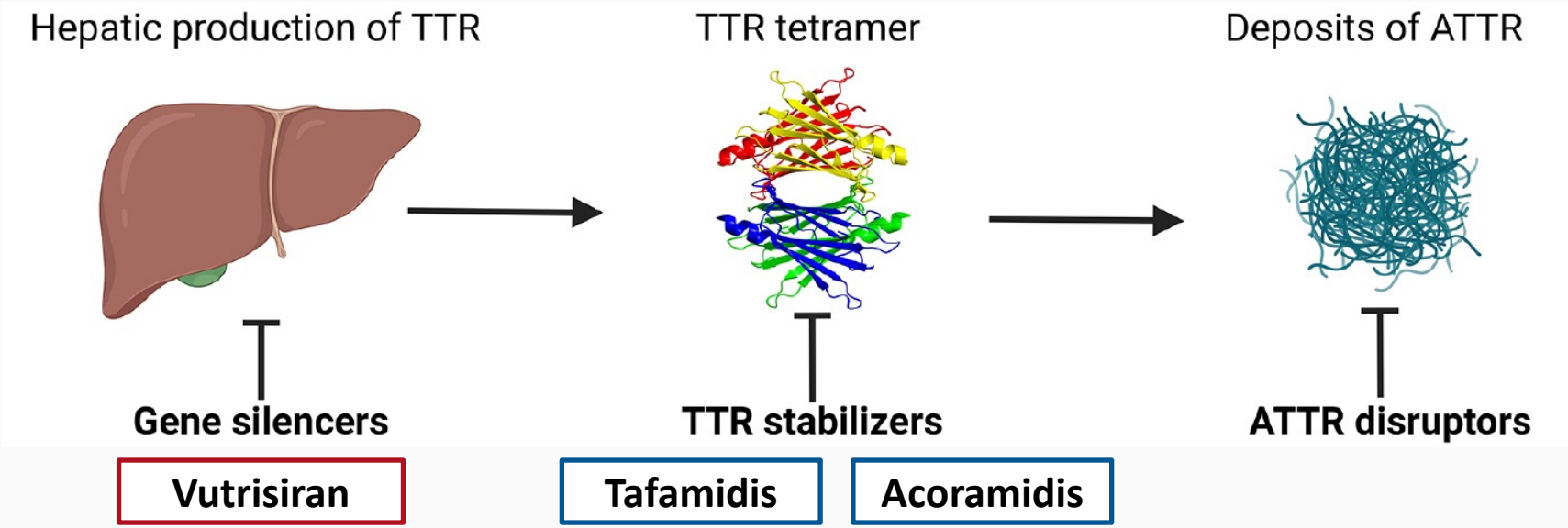
ESC CONGRESS 2026 MUNICH

30 August 2026; Late-Breaking Clinical Science: Cardiac amyloidosis

Disclosure: HELIOS-B was funded by Alnylam Pharmaceuticals. This presenter has no disclosures relevant to this presentation.

Background

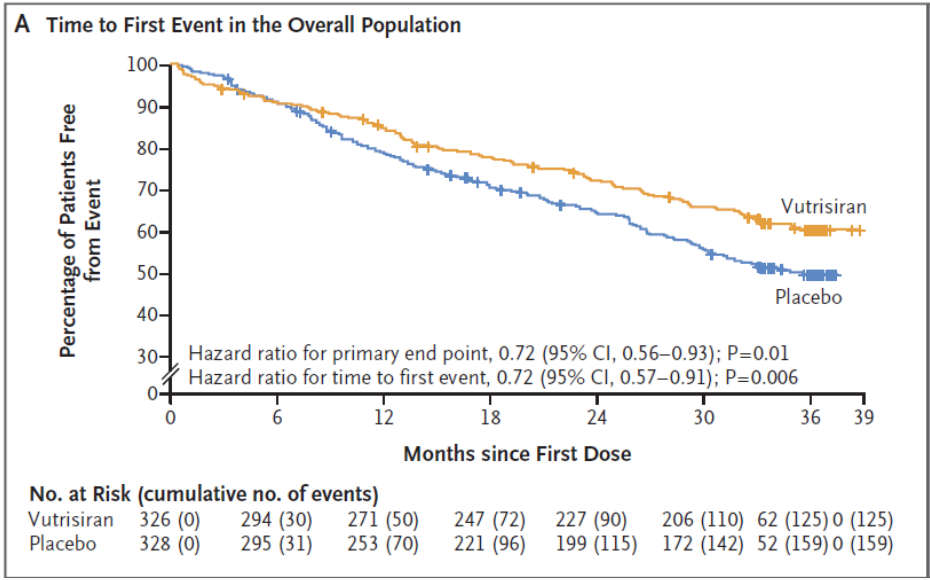
- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and fatal disease caused by deposition of transthyretin amyloid in the myocardium.[1, 2]
- Currently, gene silencers and TTR stabilizers are available as disease-modifying therapies for ATTR-CM.[1-3]

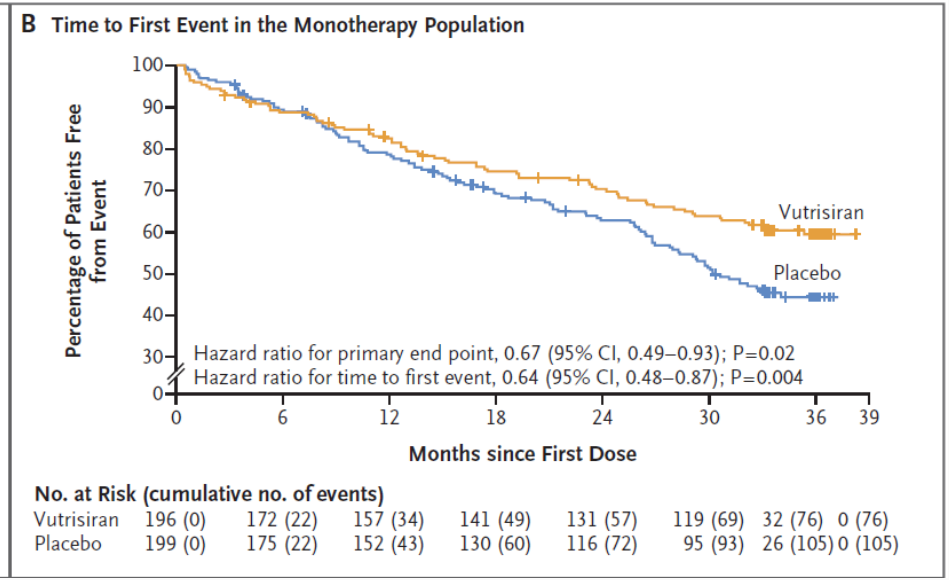


1. *Eur Heart J 2025;46:999–1013*. 2. *J Am Coll Cardiol 2026;87:549-565*. 3. *Curr Heart Fail Rep. 2025;22:16*.

Background

- HELIOS-B randomized patients with ATTR-CM to vutrisiran (silencer) or placebo.
- Baseline tafamidis (stabilizer) was permitted and used for stratification.[1]
- Vutrisiran significantly improved clinical outcomes in the overall population and in the monotherapy population (those without baseline tafamidis use).





1. *HELIOS-B study. Fontana M, et al. N Engl J Med 2025;392:33-44.*

Background

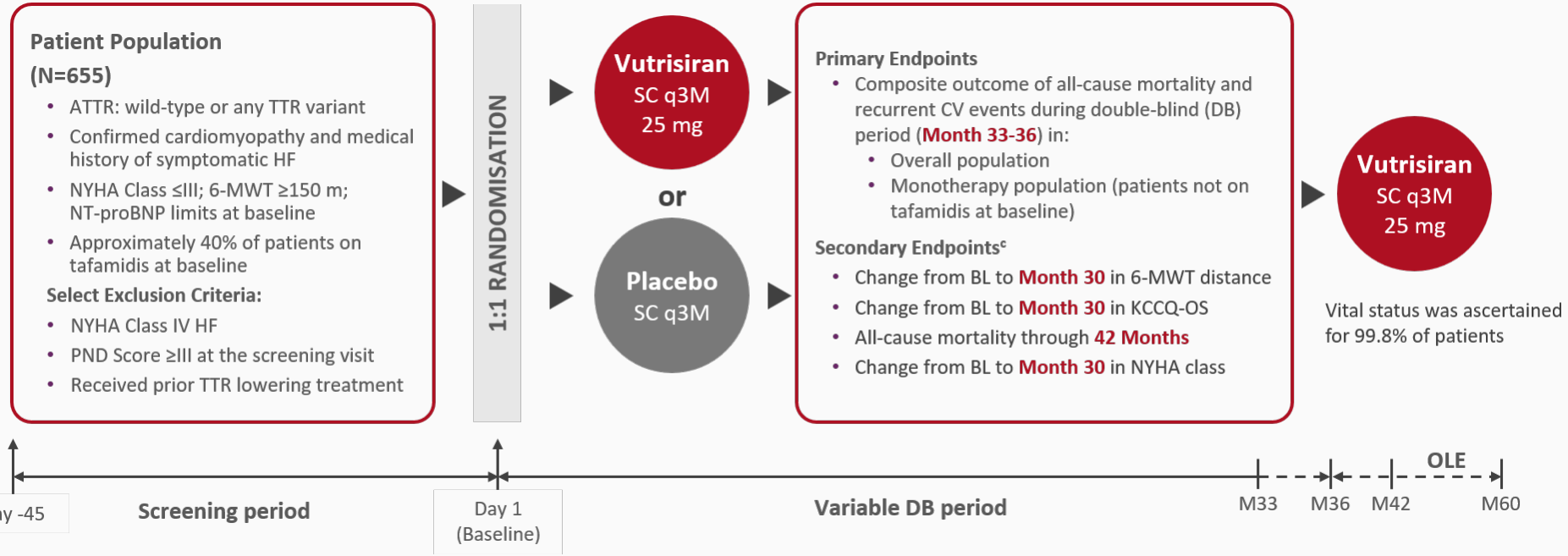
- Tafamidis, a TTR stabilizer, also improves clinical outcomes.[1]
- Although combining TTR silencer and stabilizer is mechanistically appealing, clinical evidence supporting this approach is limited.

Objective

- **We sought to evaluate whether the treatment effects of vutrisiran differed according to background tafamidis use in HELIOS-B.**

1. *ATTR-ACT study. Maurer MS, et al. N Engl J Med 2018;379:1007-1016.*

Study flow chart – HELIOS-B design and tafamidis use –



- Among 654 randomized and treated patients, 259 (40%) were receiving tafamidis at baseline (130 in the vutrisiran arm and 129 in the placebo arm).
- Median duration of tafamidis use before randomization was 11 months (IQR 5–18).

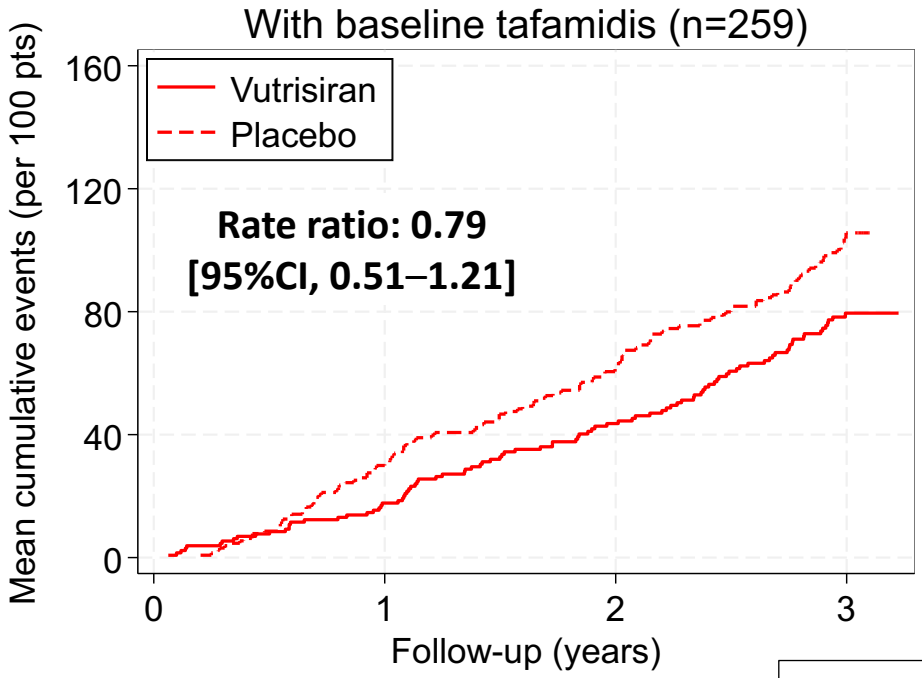
Results – Baseline Characteristics

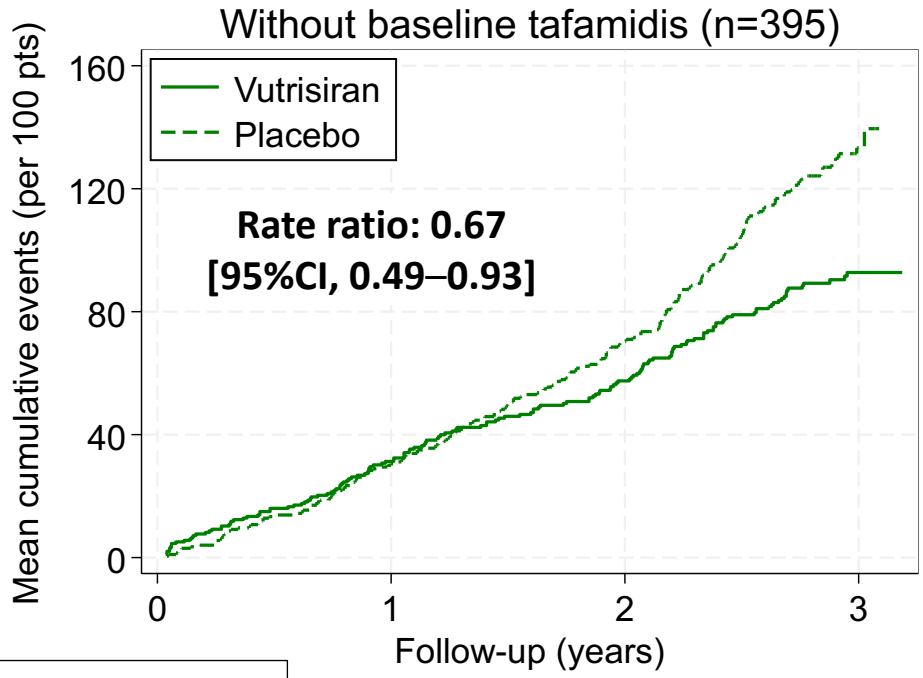
	Baseline tafamidis (n=259)	Without baseline tafamidis (n=395)
Age (years)	74.6 ± 6.9	75.9 ± 6.6
Male sex	94%	91%
Wild-type ATTR	89%	88%
NYHA		
I	22%	7%
II	65%	86%
III	13%	7%
NT-proBNP (pg/mL)	1759 [1068, 2759]	2128 [1135, 3542]
6MWD (meter)	385 ± 99	368 ± 100
KCCQ-OSS (points)	76 ± 18	70 ± 21

Values are %, mean ± SD, or median [IQR]

The Treatment Effects of Vutrisiran for the Primary Outcome were Directionally Consistent across Baseline Tafamidis Strata

Primary outcome (all-cause death and recurrent cardiovascular events)

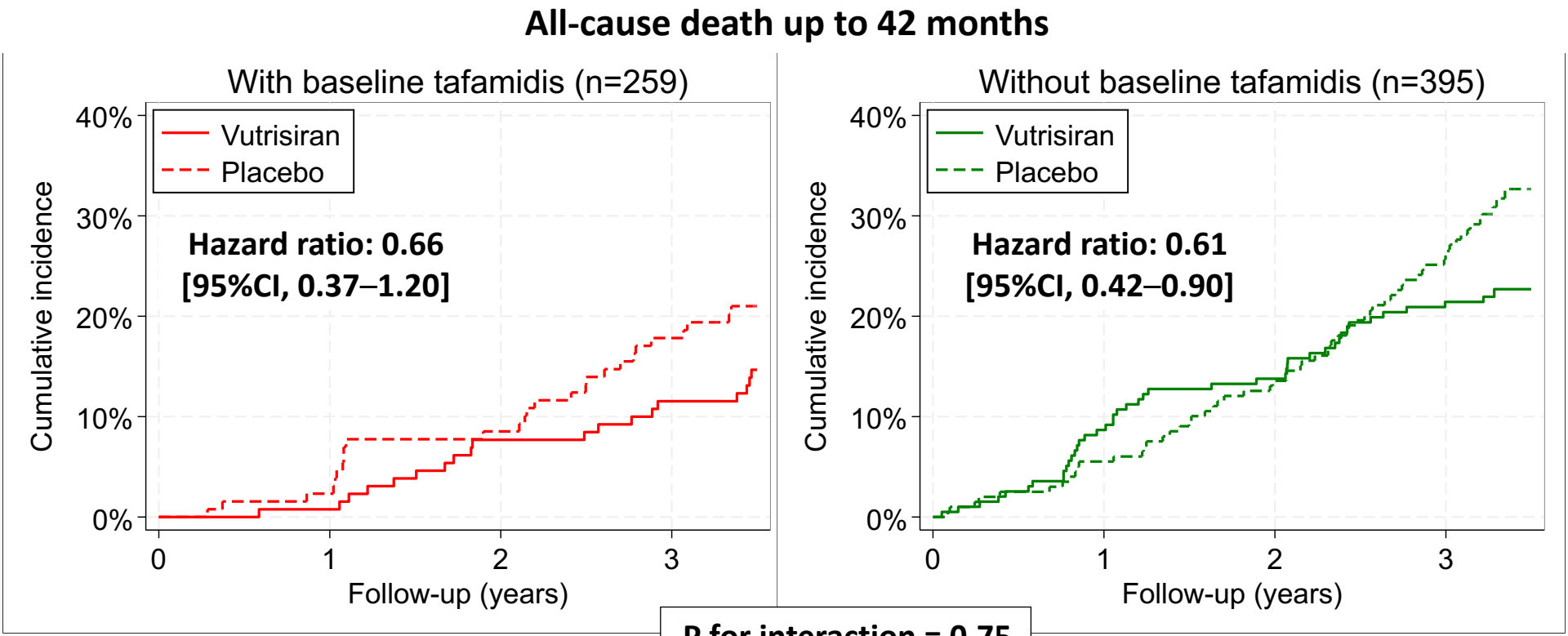




P for interaction = 0.55

*LWYY model adjusted for age, ATTR type, NYHA class, and log-transformed NT-proBNP.

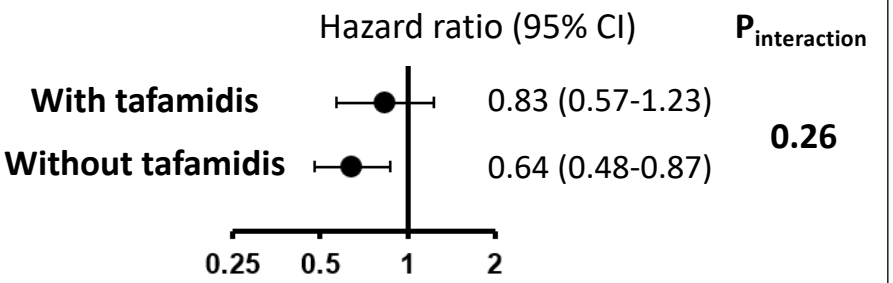
Vutrisiran Showed Directionally Similar Effects on All-Cause Mortality across Baseline Tafamidis Strata



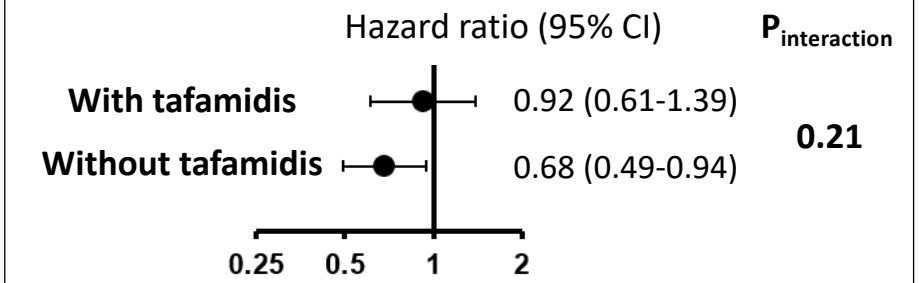
*Cox proportional hazard model adjusted for age, ATTR type, NYHA class, and log-transformed NT-proBNP.

The Patterns of Treatment Effects were Broadly Similar Across Exploratory Clinical Endpoints

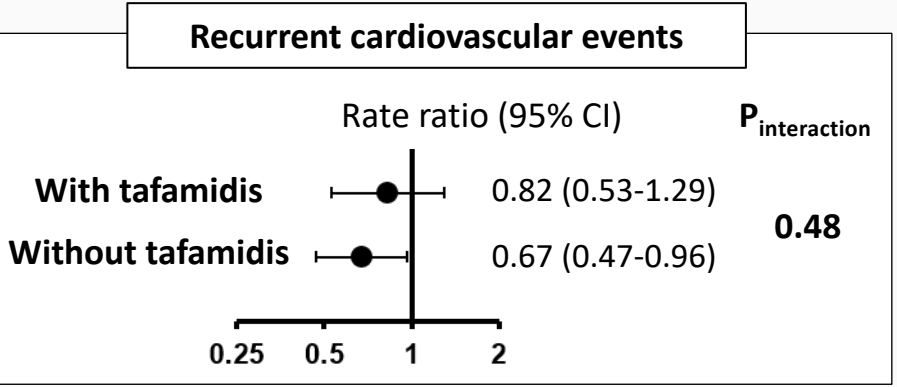
Time to first primary endpoint



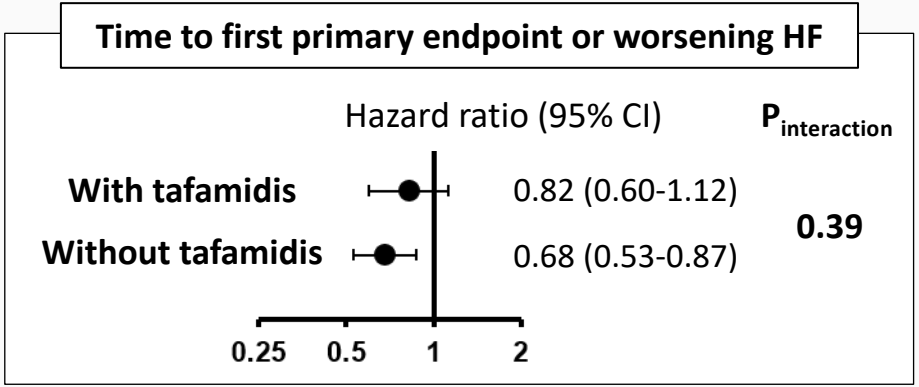
Time to first cardiovascular events



Recurrent cardiovascular events



Time to first primary endpoint or worsening HF



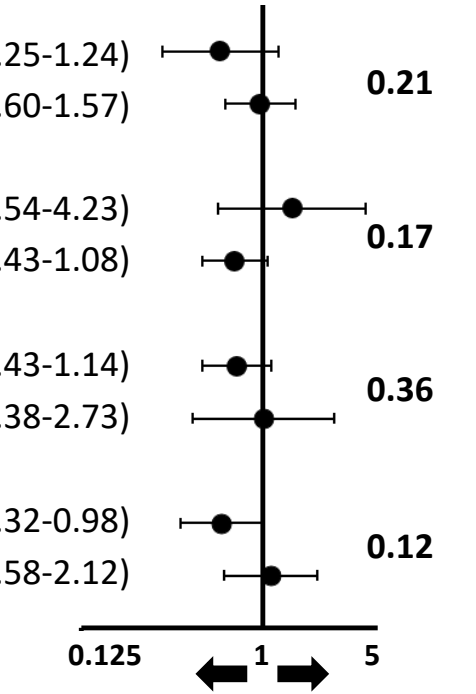
*Cox or LWYY model adjusted for age, ATTR type, NYHA class, and log-transformed NT-proBNP.

No Evidence of Heterogeneity across Prespecified Subgroups

Effect on Primary Endpoint*

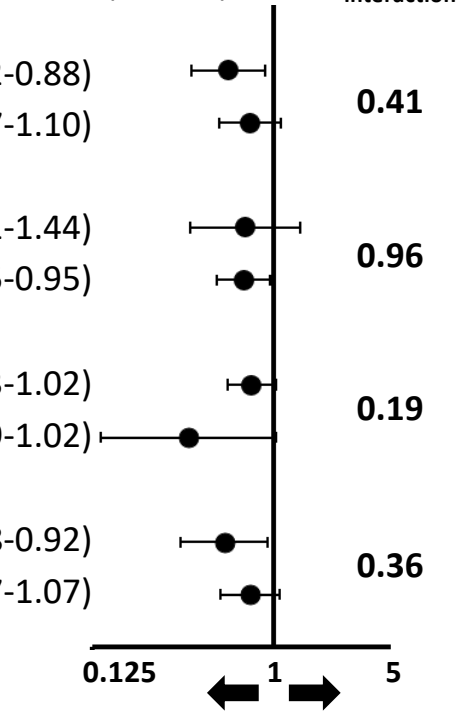
Baseline tafamidis

Subgroup	Rate ratio (95% CI)†	$P_{interaction}$
Age		
<75 years	0.55 (0.25-1.24)	**0.21**
≥75 years	0.97 (0.60-1.57)	
ATTR		
Variant	1.51 (0.54-4.23)	**0.17**
Wild type	0.68 (0.43-1.08)	
NYHA		
I or II	0.70 (0.43-1.14)	**0.36**
III	1.02 (0.38-2.73)	
NT-proBNP		
≤2000	0.56 (0.32-0.98)	**0.12**
>2000	1.11 (0.58-2.12)	



Without tafamidis

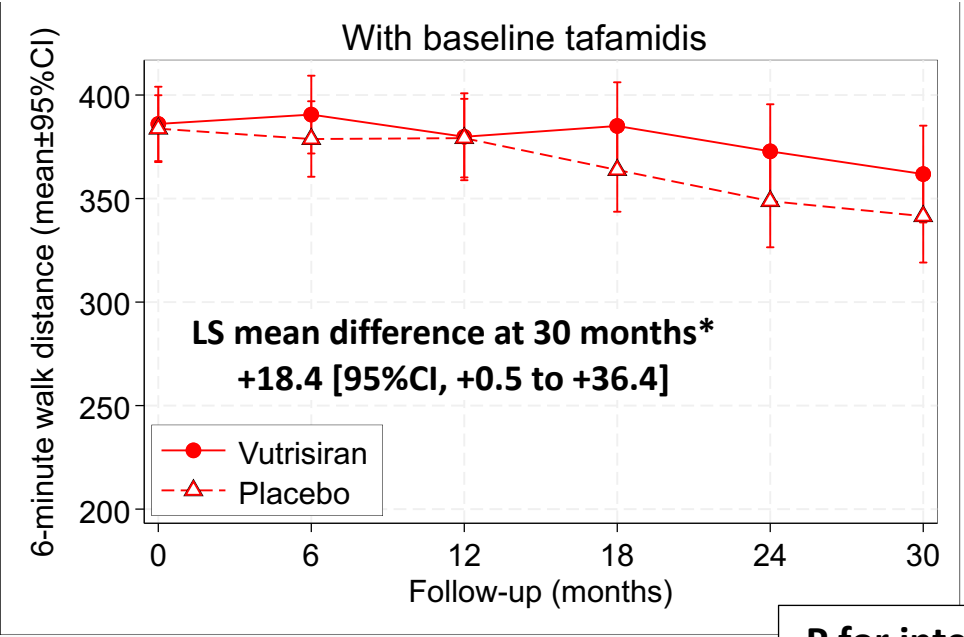
Subgroup	Rate ratio (95% CI)†	$P_{interaction}$
Age		
<75 years	0.53 (0.32-0.88)	**0.41**
≥75 years	0.72 (0.47-1.10)	
ATTR		
Variant	0.67 (0.31-1.44)	**0.96**
Wild type	0.66 (0.45-0.95)	
NYHA		
I or II	0.73 (0.53-1.02)	**0.19**
III	0.31 (0.09-1.02)	
NT-proBNP		
≤2000	0.50 (0.28-0.92)	**0.36**
>2000	0.71 (0.47-1.07)	

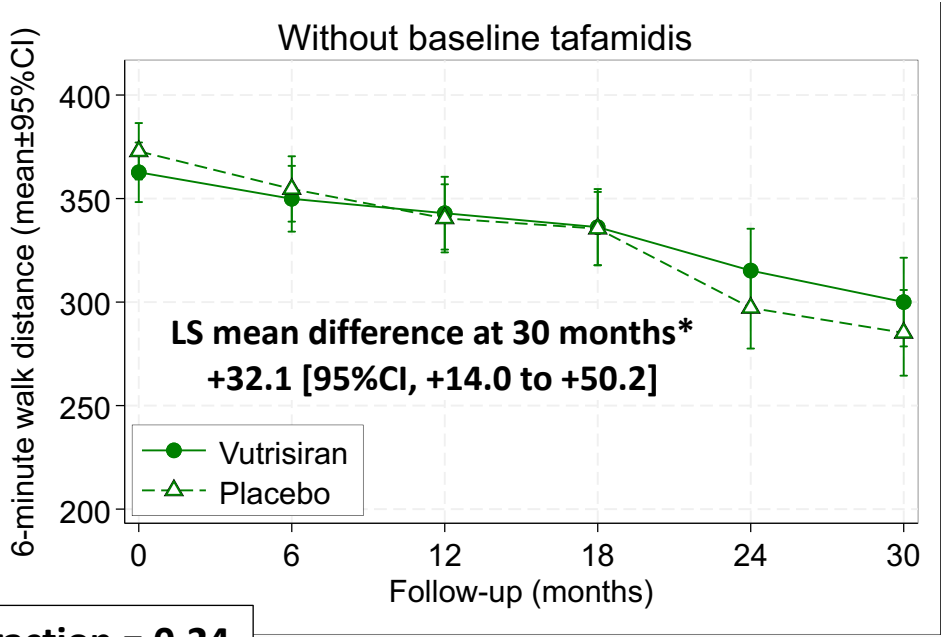


*Primary endpoint: All-cause death and recurrent CV events. †LWYY model adjusted for log-transformed NT-proBNP.

Vutrisiran Preserved 6-minute Walk Distance both in Baseline Tafamidis and Monotherapy Population

Trajectory of 6-minute walk distance



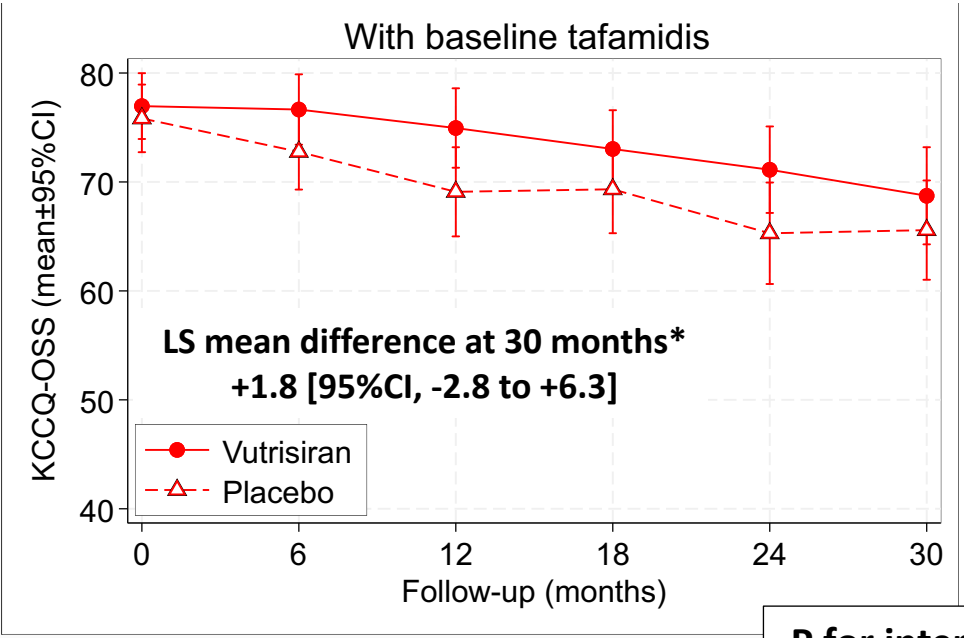


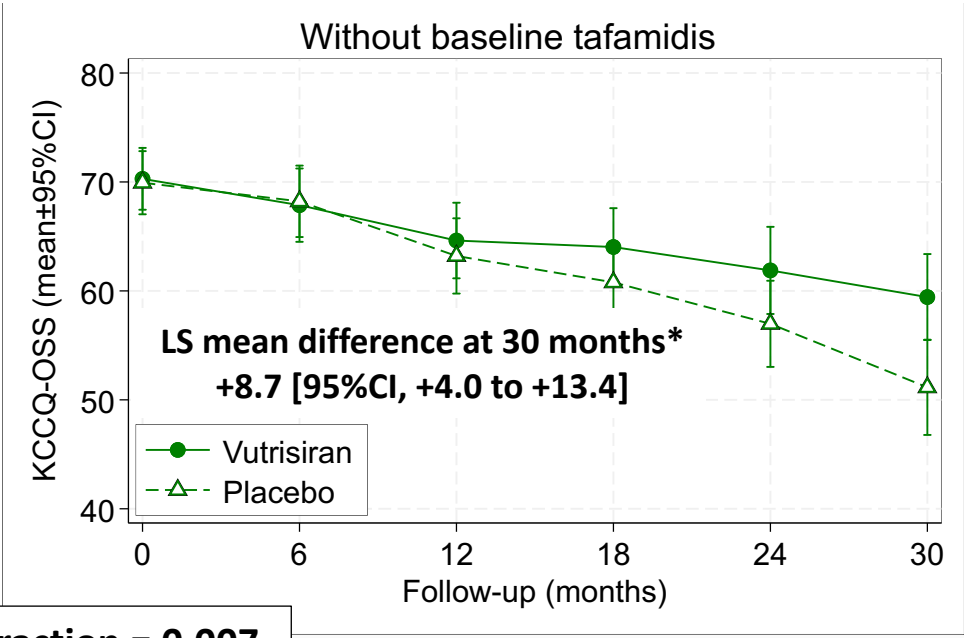
P for interaction = 0.24

*Mixed-effects model adjusted for baseline value, treatment, visit, treatment-by-visit interaction, age, and ATTR type.

Improvement in the KCCQ-Overall Summary Score appeared Attenuated among Patients receiving Tafamidis at Baseline

Trajectory of KCCQ-Overall Summary Score





P for interaction = 0.007

*Mixed-effects model adjusted for baseline value, treatment, visit, treatment-by-visit interaction, age, and ATTR type.

Safety Outcomes were Similar Between Vutrisiran and Placebo Irrespective of Baseline Tafamidis use

	Baseline tafamidis		Without tafamidis	
Adverse event (AEs)	Combination of vutrisiran and tafamidis (n=130)	Tafamidis alone (n=129)	Vutrisiran (n=196)	Placebo (n=199)
Any AEs	100%	100%	98%	98%
Any serious AEs	69%	66%	57%	68%
AEs leading to treatment discontinuation	3%	2%	3%	5%
Cardiac AEs	72%	72%	68%	75%
Cardiac serious AEs	43%	36%	31%	39%

Summary

- **In this prespecified subgroup analysis, there was no statistically significant heterogeneity in the treatment effect of vutrisiran on the primary outcome according to baseline tafamidis use.**

- **Treatment effects were directionally consistent across all clinical endpoints examined.**

- **The magnitude of the treatment effect in patients receiving baseline tafamidis was lower than in those without tafamidis at baseline.**

- **As the findings in the baseline tafamidis subgroup did not reach statistical significance and this subgroup lacked statistical power, they warrant confirmation in larger studies.**

Simultaneously published in *JACC*

JACC VOL. ■, NO. ■, 2026

ORIGINAL RESEARCH

Effect of Vutrisiran According to Baseline Tafamidis Use in Transthyretin Amyloidosis With Cardiomyopathy

Insights From HELIOS-B

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ABSTRACT

BACKGROUND Vutrisiran, an RNA interference therapeutic that suppresses hepatic transthyretin production, improved survival and cardiovascular outcomes in transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy). Tafamidis, a transthyretin stabilizer, also improves clinical outcomes. Although combining these therapies is mechanistically appealing, clinical evidence supporting this approach is limited.

OBJECTIVES We sought to evaluate whether the treatment effects of vutrisiran differed according to baseline tafamidis use in HELIOS-B.

METHODS In HELIOS-B, patients with ATTR-CM were randomized to vutrisiran 25 mg or placebo every 3 months for up to 36 months, with tafamidis use permitted and stratified. We assessed treatment effects according to baseline tafamidis use for the primary outcome of all-cause mortality and recurrent cardiovascular events and secondary endpoints, including individual components of the primary outcome, composite of all-cause mortality, cardiovascular events and outpatient worsening heart failure events, functional capacity (6-minute walk distance), and health status (Kansas City Cardiomyopathy Questionnaire–overall summary score [KCCQ-OSS]).

RESULTS Among 654 participants, 259 (40%) were receiving tafamidis at baseline. Patients on tafamidis were slightly younger and had higher baseline 6-minute walk distance and higher KCCQ-OSS, while baseline characteristics were generally balanced between randomized groups. The treatment effect estimates of vutrisiran compared with placebo for the primary outcome were directionally consistent across baseline tafamidis strata (rate ratio: 0.79 [95% CI: 0.51-1.21] with tafamidis *vs* 0.67 [95% CI: 0.49-0.93] without), with no statistically significant interaction ($P_{interaction}$ = 0.55). Similar patterns were observed for all-cause mortality, cardiovascular events, and outpatient worsening heart failure (all $P_{interaction}$ > 0.20), although the magnitudes of the estimated effects were numerically smaller among patients receiving tafamidis at baseline. Vutrisiran preserved 6-minute walk distance in both baseline tafamidis strata ($P_{interaction}$ = 0.24), whereas improvement in KCCQ-OSS appeared attenuated among patients receiving tafamidis at baseline.

CONCLUSIONS Treatment effect estimates for vutrisiran on clinical outcomes were consistent across baseline tafamidis strata, with no statistically significant interaction according to baseline tafamidis use, with reduced effect size noted in those receiving baseline stabilizers in comparison to monotherapy. These data underscore the need for future prospective studies examining combination therapy in this population. (HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149) (JACC. 2026;■:■–■) © 2026 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/).

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2026.07.022