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Impact of Heart Failure Severity on Vutrisiran Efficacy in Transthyretin Amyloidosis With Cardiomyopathy

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ABSTRACT

BACKGROUND Vutrisiran reduced the risk of all-cause mortality (ACM) and recurrent cardiovascular (CV) events in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149).

OBJECTIVES This study sought to assess the effect of vutrisiran in HELIOS-B patients with different heart failure severities.

METHODS HELIOS-B randomized patients with ATTR-CM with NYHA functional class I-III (functional class IV or functional class III with National Amyloidosis Centre [NAC] stage 3 were excluded) 1:1 to vutrisiran 25 mg or placebo every 3 months for up to 36 months. This exploratory subgroup analysis assessed the primary composite endpoint of ACM and recurrent CV events, ACM, and additional functional and biomarker endpoints.

RESULTS Of 654 patients, 84 (13%), 508 (78%), and 62 (9%) were in NYHA functional class I, II, and III, respectively. Median baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 1,920 ng/L. Lower risk of ACM and recurrent CV events was observed with vutrisiran vs placebo across baseline severity subgroups: respective HRs were 0.54 (95% CI: 0.27-1.10), 0.77 (95% CI: 0.57-1.03), and 0.68 (95% CI: 0.33-1.41) in NYHA functional classes I, II, and III, respectively; 0.52 (95% CI: 0.30-0.88), 0.61 (95% CI: 0.37-1.00), and 0.93 (95% CI: 0.64-1.35) in NT-proBNP tertiles $<$1,368 ng/L, $\geq$1,368 and $<$2,691 ng/L, and $\geq$2,691 ng/L; 0.49 (95% CI: 0.34-0.72) and 1.08 (95% CI: 0.74-1.56) in NAC stages 1 and 2/3, respectively; and 0.69 (95% CI: 0.45-1.07) and 0.74 (95% CI: 0.53-1.02) in Columbia early and intermediate/late stages, respectively. Similar effects were observed in the monotherapy population (patients not on tafamidis at baseline) and across the additional endpoints evaluated.

CONCLUSIONS Vutrisiran demonstrated evidence of benefit across the range of baseline disease severities in HELIOS-B, with the greatest benefit in earlier, less severe disease. (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy [HELIOS-B]; NCT04153149) (JACC. 2025;85:1927–1939) © 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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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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ABBREVIATIONS AND ACRONYMS

6-MWT = 6-minute walk test

ATTR = transthyretin amyloidosis

ATTR-CM = transthyretin amyloidosis with cardiomyopathy

CV = cardiovascular

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary

LS = least-squares

NAC = National Amyloidosis Centre

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

TTR = transthyretin

Transthyretin amyloidosis (ATTR) is a progressive, debilitating, and potentially fatal disease in the absence of treatment, caused by misfolded transthyretin (TTR) accumulating as amyloid deposits in multiple organs and tissues, including the nerves, heart, gastrointestinal tract, and musculoskeletal tissues.[1-4] When TTR amyloid deposits accumulate in the myocardium, the resulting cardiomyopathy (ATTR with cardiomyopathy [ATTR-CM]) presents as symptoms of progressive heart failure, often with cardiac arrhythmia and conduction system disease.[2,5] These symptoms and the progression of ATTR-CM have a substantial impact on patients' functional status, health status, and quality of life.[6,7]

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Current treatment options for ATTR-CM are limited and only include the TTR stabilizers tafamidis and the recently approved acoramidis.[8-10] Progression of disease in patients receiving TTR stabilizers[11,12] demonstrates an unmet need for more effective treatment options in ATTR-CM. Recent advances in noninvasive imaging technology have increased disease awareness, resulting in patients with ATTR-CM being diagnosed earlier in the course of disease, with these patients showing a less severe clinical phenotype at diagnosis based on cardiac assessments such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and NYHA functional class.[13] It is therefore important to assess the efficacy of treatments for ATTR-CM in patients across the complete spectrum of heart failure severities.

Vutrisiran is a subcutaneously administered RNA interference therapeutic that inhibits hepatic synthesis of both wild-type and variant TTR protein, leading to rapid knockdown.[8,14,15] In the phase III HELIOS-B study (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149), vutrisiran reduced the risk of the primary composite endpoint of all-cause mortality and recurrent cardiovascular (CV) events vs placebo in patients with either wild-type ATTR-CM or hereditary ATTR-CM.[8] Vutrisiran also reduced the risk of all-cause mortality as a standalone secondary endpoint vs placebo, and preserved functional capacity and quality of life. The benefits with vutrisiran vs placebo were observed in both the overall population and in patients not receiving tafamidis at baseline (termed the monotherapy population).

In prespecified subgroup analyses of HELIOS-B, the effect of vutrisiran vs placebo to reduce the risk of the composite of all-cause mortality and recurrent CV events and the standalone endpoint of all-cause mortality was consistent in patients with different disease severities at baseline, as measured by NYHA functional class (I/II vs III) and NT-proBNP (≤2,000 ng/L vs >2,000 ng/L).[8] Here, we present a more comprehensive exploratory subgroup analysis of the effect of vutrisiran vs placebo in patients with different heart failure severities at baseline in HELIOS-B. Analyses of a range of endpoints assessing mortality, recurrent CV events, functional capacity, health status and quality of life, and cardiac biomarkers across baseline disease severities by NYHA functional class, NT-proBNP levels, and other measures of heart failure severity are presented.

METHODS

STUDY DESIGN. Full details of the design of the global, randomized, placebo-controlled, double-blind, multicenter, phase III HELIOS-B study have been reported previously.[8] Briefly, inclusion criteria included an age of 18 to 85 years with a diagnosis of ATTR-CM (either wild-type or hereditary) and NT-proBNP levels of >300 ng/L and <8,500 ng/L. It is important to note that patients with NYHA functional class IV and functional class III with National Amyloidosis Centre (NAC) stage 3 (NT-proBNP level >3,000 ng/L and an estimated glomerular filtration rate <45 mL/min/1.73 m^2 body surface area) were excluded from HELIOS-B. Patients were randomized 1:1 to receive vutrisiran 25 mg or placebo administered subcutaneously every 3 months for up to 36 months, with a variable double-blind treatment duration of 33 to 36 months. Patients were either receiving tafamidis at baseline or were not receiving tafamidis, with no plan to start the drug during the 12 months following randomization. Patients not receiving tafamidis at baseline could begin receiving it any time after enrollment if the investigator deemed it necessary. Patients who completed the double-blind period were eligible to enter the ongoing open-label extension period for up to 24 months to receive vutrisiran 25 mg every 3 months. The study was conducted in accordance with all applicable regulatory requirements, Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. The Institutional Review Board or independent ethics committee at each center approved the study protocol and amendments. All patients provided written informed consent.

BASELINE DISEASE SEVERITY GROUP ANALYSES. In this exploratory subgroup analysis, efficacy was assessed in groups based on baseline disease severity, including patients with NYHA functional class I (no symptoms with ordinary physical activity), functional class II (symptoms with ordinary physical activity), or functional class III (symptoms with less than ordinary physical activity) at baseline and with NT-proBNP levels of >300 ng/L to ≤2,000 ng/L (referred to as the ≤2,000 ng/L group) or >2,000 ng/L to <8,500 ng/L (referred to as the >2,000 ng/L group) at baseline. These groups were chosen as prespecified in the statistical analysis plan, apart from NYHA functional classes I and II, which were originally combined. The threshold of 2,000 ng/L for NT-proBNP was chosen for the subgroup analyses, as this represents the approximate median baseline NT-proBNP value in HELIOS-B such that similar numbers of patients are included in each subgroup.[8] Baseline disease severity group analyses were conducted in the overall population and in the monotherapy population.

In addition to the prespecified disease severity measures, treatment effects for the primary composite endpoint and secondary all-cause mortality endpoint were evaluated across subgroups defined by other measures of baseline disease severity, including NAC stage 1 or 2/3; Columbia early stage (score 1-3) or intermediate/late stage (score 4-9)[16,17] (see the Supplemental Methods for stage definitions); and baseline NT-proBNP tertiles (<1,368 ng/L, ≥1,368 and <2,691 ng/L, and ≥2,691 ng/L). Given the small sample sizes in NAC stage 3 and Columbia late stage (score 7-9) at baseline, 2 categories were considered for each measure, namely NAC stage 1 or 2/3, and Columbia early or intermediate/late stage. NT-proBNP tertiles were used to ensure similar numbers of patients in each subgroup. Treatment effects according to these additional baseline disease severity criteria were analyzed in both the overall and monotherapy populations.

OUTCOMES. In the baseline disease severity group analyses, the primary endpoint of the composite of all-cause mortality and recurrent CV events (defined as CV hospitalizations and urgent heart failure visits) was assessed during the double-blind period of up to 36 months. Secondary endpoints analyzed were all-cause mortality, assessed up to 42 months including up to 6 months of the open-label extension period, and change from baseline to Month 30 in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS), and exploratory endpoints analyzed were change from baseline to Month 30 in NT-proBNP and troponin I levels. The 6-MWT and KCCQ-OS were assessed at screening, baseline, then every 6 months to Month 30, and NT-proBNP and troponin I levels were assessed at screening, baseline, every 3 months to Month 12, and then every 6 months to Month 30. Details of the HELIOS-B endpoints have been described previously.[8]

STATISTICAL ANALYSIS. Analysis of data from the double-blind period included data from up to 36 months of follow-up (cutoff May 8, 2024). The composite of all-cause mortality and recurrent CV events by baseline disease severity group was analyzed using a modified Andersen-Gill model with robust variance estimator stratified by baseline tafamidis use (for the overall population only), and adjusted for log-transformed baseline NT-proBNP values, following the prespecified analysis approach for groups.[8] All-cause mortality during the double-blind and 6-month open-label extension period by group was analyzed using a Cox proportional hazards model stratified by baseline tafamidis use (for the overall population only), and adjusted for log-transformed baseline NT-proBNP values, following the prespecified analysis approach for groups.[8] For both of these endpoints, HRs, event counts, and percentages in each treatment arm were presented; heart transplantation (3 patients in the vutrisiran group and 4 patients in the placebo group) and left ventricular assist device placement (0 patients in either group) were treated as deaths in both analyses, per procotol.[8]

Changes from baseline to Month 30 for 6-MWT, KCCQ-OS, NT-proBNP, and troponin I by baseline disease severity group were analyzed using a mixed model for repeated measures, including the baseline value of the endpoint as a continuous covariate and treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use (for the overall population only) as fixed-effect terms. Each model was fit on subgroup data only, as in the prespecified analysis approach. For change from baseline to Month 30 in NT-proBNP and troponin I levels, the endpoint was log-transformed, with baseline log-transformed NT-proBNP or troponin I as the covariate. For the 6-MWT and KCCQ-OS endpoints, adjusted least-squares (LS) mean differences were presented as measures of effect size; for NT-proBNP and troponin I, ratios of adjusted geometric mean fold-changes were presented. Furthermore, median (Q1-Q3) changes from baseline were presented visually for all continuous endpoints to further examine patient response in each treatment arm and contextualize the

TABLE 1 Baseline Demographics and Disease Characteristics in the Overall Population by Baseline Heart Failure Severity

	Baseline NYHA Functional Class					
	I		II		III	
	Vutrisiran (n = 49)	Placebo (n = 35)	Vutrisiran (n = 250)	Placebo (n = 258)	Vutrisiran (n = 27)	Placebo (n = 35)
Age, y	77.0 (72.0-80.0)	76.0 (70.0-80.0)	77.0 (72.0-81.0)	76.0 (72.0-80.0)	77.0 (71.0-81.0)	76.0 (71.0-80.0)
Male	49 (100.0)	33 (94.3)	226 (90.4)	241 (93.4)	24 (88.9)	32 (91.4)
Race						
White	44 (89.8)	31 (88.6)	208 (83.2)	214 (82.9)	25 (92.6)	30 (85.7)
Asian	2 (4.1)	0 (0)	15 (6.0)	18 (7.0)	1 (3.7)	1 (2.9)
Black	3 (6.1)	4 (11.4)	19 (7.6)	18 (7.0)	1 (3.7)	2 (5.7)
Other	0 (0)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	0 (0)
Not reported	0 (0)	0 (0)	6 (2.4)	6 (2.3)	0 (0)	2 (5.7)
Time since diagnosis of ATTR, y	1.1 (0.6-1.7)	1.1 (0.6-2.4)	0.7 (0.2-1.8)	1.0 (0.3-2.1)	0.7 (0.3-2.2)	0.8 (0.5-2.3)
Wild-type ATTR	44 (89.8)	30 (85.7)	220 (88.0)	229 (88.8)	25 (92.6)	30 (85.7)
Tafamidis use at baseline	34 (69.4)	23 (65.7)	78 (31.2)	89 (34.5)	18 (66.7)	17 (48.6)
NAC stage						
1	40 (81.6)	30 (85.7)	154 (61.6)	180 (69.8)	14 (51.9)	19 (54.3)
2	8 (16.3)	4 (11.4)	79 (31.6)	68 (26.4)	13 (48.1)	15 (42.9)
3	1 (2.0)	1 (2.9)	17 (6.8)	10 (3.9)	0 (0)	1 (2.9)
6-MWT, m	422.3 (375.0-485.4)	421.8 (358.9-480.0)	360.0 (298.7-435.3)[a]	383.0 (323.4-450.0)	318.5 (256.0-429.4)	295.0 (244.7-345.0)
KCCQ-OS, points	85.4 ± 12.7	83.7 ± 15.1	72.0 ± 19.2[a]	73.2 ± 19.3[c]	58.8 ± 20.2	54.2 ± 17.0
NT-proBNP, ng/L	1,458 (838-2,703)	1,285 (776-2,045)	2,159 (1,227-3,455)	1,814 (1,080-3,080)	2,468 (1,760-3,796)	2,563 (1,401-3,885)
Troponin I, ng/L	65.0 (38.0-99.3)	68.6 (30.3-130.0)	73.8 (48.4-117.8)	63.6 (40.4-104.8)	48.6 (33.6-140.8)	71.4 (47.7-121.6)
eGFR, mL/min/1.73 m^2	70.8 ± 21.3	70.7 ± 25.1	67.0 ± 21.7	69.5 ± 20.2	60.9 ± 17.2	59.2 ± 16.7
Concomitant SGLT2i use	0 (0)	0 (0)	5 (2.0)	9 (3.5)	2 (7.4)	1 (2.9)
Oral loop diuretic dose, furosemide equivalent dose, mg/d[f]	20.0 (0-40.0)	20.0 (0-60.0)	40.0 (10.0-60.0)	40.0 (10.0-80.0)	40.0 (10.0-120.0)	40.0 (20.0-60.0)

Values are median (Q1-Q3), n (%), or mean ± SD. [a]n = 249. [b]n = 160. [c]n = 257. [d]n = 164. [e]n = 146. [f]Patients who were in the study but did not take any oral loop diuretic agents during a specific period are included in the summary, with daily dose as 0 mg/day.

6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; eGFR = estimated glomerular filtration rate; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2i = sodium-glucose co-transporter-2 inhibitor.

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results, especially in the baseline disease severity groups with smaller numbers of patients (ie, the NYHA functional class I and functional class III groups).

Based on the possibility that the effect of disease-modifying treatments can be observed relatively earlier in biomarkers compared with other efficacy parameters,[18] for the NT-proBNP and troponin I analyses, data collected after tafamidis drop-in were excluded from analysis. Adjusted geometric mean fold-change, adjusted geometric mean fold-change ratio, and 95% CI from the mixed model for repeated measures were obtained by exponentially back-transforming LS means, difference in LS means, and the corresponding 95% CI.

As in the primary analysis, per study protocol, 6-MWT assessments that were missing due to death or the patient being unable to walk as a result of ATTR disease progression, heart transplantation, or implantation of a left ventricular assist device were imputed. For KCCQ-OS, the same approach as the 6-MWT was followed, except in this case, values were not imputed when a patient was unable to walk as a result of ATTR disease progression. Furthermore, imputation was conducted separately for each KCCQ domain score (physical function, symptoms, quality of life, and social limitation domains); these scores were then used to compute the overall score. Values were imputed using the mean of 20 random samples with replacement from the worst 10% observed change from baseline of all patients at the same visit in the same treatment group and baseline tafamidis use group, capped by the worst possible change of the patient (0-baseline value).

Given the exploratory nature of these analyses, no adjustments for multiplicity were performed.

TABLE 1 Continued

Baseline NT-proBNP			
≤2,000 ng/L		>2,000 ng/L	
Vutrisiran (n = 161)	Placebo (n = 181)	Vutrisiran (n = 165)	Placebo (n = 147)
76.0 (70.0-79.0)	75.0 (70.0-79.0)	78.0 (74.0-81.0)	77.0 (73.0-80.0)
148 (91.9)	166 (91.7)	151 (91.5)	140 (95.2)
135 (83.9)	142 (78.5)	142 (86.1)	133 (90.5)
10 (6.2)	12 (6.6)	8 (4.8)	7 (4.8)
14 (8.7)	20 (11.0)	9 (5.5)	4 (2.7)
0 (0)	2 (1.1)	2 (1.2)	0 (0)
2 (1.2)	5 (2.8)	4 (2.4)	3 (2.0)
0.8 (0.3-1.7)	1.0 (0.3-1.9)	0.9 (0.3-1.9)	1.1 (0.4-2.6)
140 (87.0)	159 (87.8)	149 (90.3)	130 (88.4)
80 (49.7)	74 (40.9)	50 (30.3)	55 (37.4)
149 (92.5)	172 (95.0)	59 (35.8)	57 (38.8)
12 (7.5)	9 (5.0)	88 (53.3)	78 (53.1)
0 (0)	0 (0)	18 (10.9)	12 (8.2)
406.2 (339.9-472.0)[b]	405.0 (340.7-467.5)	332.1 (264.4-410.5)	360.0 (291.0-411.6)
75.4 ± 19.1	74.4 ± 19.1	70.6 ± 19.6[d]	69.6 ± 20.6[e]
1,126 (807-1,599)	1,110 (776-1,479)	3,294 (2,589-4,579)	3,323 (2,576-4,424)
53.6 (34.5-81.2)	55.1 (33.6-81.0)	89.4 (59.6-143.7)	81.8 (53.0-121.9)
74.4 ± 23.5	73.9 ± 22.1	59.9 ± 16.2	61.9 ± 16.6
3 (1.9)	5 (2.8)	4 (2.4)	5 (3.4)
20.0 (0-40.0)	20.0 (0-40.0)	40.0 (20.0-80.0)	40.0 (20.0-80.0)

Statistical analyses were conducted using the software SAS version 9.4 (SAS Institute Inc).

RESULTS

PATIENT GROUPS BY BASELINE HEART FAILURE SEVERITY. A total of 654 patients with ATTR-CM who received treatment with vutrisiran (n = 326) or placebo (n = 328) were assessed in groups by NYHA functional class I, II, and III and NT-proBNP levels ≤2,000 ng/L and >2,000 ng/L at baseline (Supplemental Figure 1). Although 655 patients were enrolled, 1 patient randomized to placebo did not receive any drug due to withdrawal by their own decision, so this patient was not included in the analysis.

In the vutrisiran and placebo groups, respectively, 196 patients (60.1%) and 199 patients (60.7%) were not receiving tafamidis at baseline (monotherapy population) (Supplemental Figure 1). In the overall population, 84 patients (12.8%) had NYHA functional class I status, whereas 508 (77.7%) were NYHA functional class II, and 62 (9.5%) were NYHA functional class III. Overall, 342 patients (52.3%) had NT-proBNP levels ≤2,000 ng/L, whereas 312 (47.7%) had NT-proBNP levels >2,000 ng/L (Supplemental Figure 1). In both the overall and monotherapy populations, baseline demographic data were generally similar between vutrisiran and placebo arms across the NYHA functional class and NT-proBNP groups, although there were some differences in tafamidis use between the groups in the overall population and more patients had >2,000 ng/L baseline NT-proBNP in the vutrisiran arm in the monotherapy population (**Tables 1 and 2**). As expected, measures of functional capacity, health status, and quality of life (6-MWT and KCCQ-OS) decreased with increasing baseline NYHA functional class and were lower in the baseline NT-proBNP >2,000 ng/L vs the ≤2,000 ng/L group. NT-proBNP levels were generally higher with increasing baseline NYHA functional class, and troponin I levels were higher in the baseline NT-proBNP >2,000 ng/L vs the ≤2,000 ng/L group.

COMPOSITE OF ALL-CAUSE MORTALITY AND RECURRENT CV EVENTS AND ALL-CAUSE MORTALITY BY BASELINE HEART FAILURE SEVERITY. In the overall population, the risk of all-cause mortality and recurrent CV events vs placebo over the double-blind period of up to

TABLE 2 Baseline Demographics and Disease Characteristics in the Monotherapy Population by Baseline Heart Failure Severity

	Baseline NYHA Functional Class						Baseline NT-proBNP			
	I		II		III		≤2,000 ng/L		>2,000 ng/L	
	Vutrisiran (n = 15)	Placebo (n = 12)	Vutrisiran (n = 172)	Placebo (n = 169)	Vutrisiran (n = 9)	Placebo (n = 18)	Vutrisiran (n = 81)	Placebo (n = 107)	Vutrisiran (n = 115)	Placebo (n = 92)
Age, y	79.0 (72.0-83.0)	77.5 (74.5-82.0)	77.0 (73.0-81.0)	76.0 (71.0-80.0)	80.0 (72.0-82.0)	78.0 (72.0-82.0)	76.0 (70.0-81.0)	76.0 (71.0-80.0)	78.0 (74.0-82.0)	76.5 (73.0-80.0)
Male	15 (100.0)	11 (91.7)	155 (90.1)	155 (91.7)	8 (88.9)	17 (94.4)	74 (91.4)	96 (89.7)	104 (90.4)	87 (94.6)
Race										
White	15 (100.0)	11 (91.7)	147 (85.5)	142 (84.0)	7 (77.8)	16 (88.9)	70 (86.4)	86 (80.4)	99 (86.1)	83 (90.2)
Asian	0 (0)	0 (0)	11 (6.4)	14 (8.3)	1 (11.1)	1 (5.6)	6 (7.4)	10 (9.3)	6 (5.2)	5 (5.4)
Black	0 (0)	1 (8.3)	9 (5.2)	10 (5.9)	1 (11.1)	0 (0)	5 (6.2)	9 (8.4)	5 (4.3)	2 (2.2)
Other	0 (0)	0 (0)	2 (1.2)	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (1.9)	2 (1.7)	0 (0)
Not reported	0 (0)	0 (0)	3 (1.7)	1 (0.6)	0 (0)	1 (5.6)	0 (0)	0 (0)	3 (2.6)	2 (2.2)
Time since diagnosis of ATTR, y	0.8 (0.3-1.0)	0.6 (0.2-1.1)	0.5 (0.2-1.5)	0.7 (0.2-1.7)	1.0 (0.3-1.2)	0.7 (0.3-1.7)	0.4 (0.2-1.0)	0.6 (0.2-1.5)	0.7 (0.2-1.8)	0.8 (0.2-1.8)
Wild-type ATTR	14 (93.3)	11 (91.7)	152 (88.4)	147 (87.0)	7 (77.8)	16 (88.9)	70 (86.4)	94 (87.9)	103 (89.6)	80 (87.0)
NAC stage										
1	11 (73.3)	10 (83.3)	97 (56.4)	115 (68.0)	5 (55.6)	13 (72.2)	76 (93.8)	102 (95.3)	37 (32.2)	36 (39.1)
2	3 (20.0)	1 (8.3)	61 (35.5)	49 (29.0)	4 (44.4)	5 (27.8)	5 (6.2)	5 (4.7)	63 (54.8)	50 (54.3)
3	1 (6.7)	1 (8.3)	14 (8.1)	5 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	15 (13.0)	6 (6.5)
6-MWT, m	412.7 (281.0-503.6)	353.4 (305.5-414.8)	353.7 (295.2-435.0)	382.4 (320.0-442.9)	301.2 (240.0-325.0)	315.0 (274.8-351.2)	414.0 (340.3-466.1)	390.7 (332.2-462.1)	321.1 (256.9-404.1)	364.7 (294.4-409.7)
KCCQ-OS, points	81.3 ± 13.4	73.2 ± 20.4	70.3 ± 19.7[a]	71.7 ± 20.5[b]	52.0 ± 27.4	51.7 ± 15.7	72.3 ± 19.6	71.9 ± 20.2	68.9 ± 20.6[c]	67.6 ± 21.4[d]
NT-proBNP, ng/L	1,598 (934-3,390)	1,039 (711-1,658)	2,435 (1,391-3,926)	1,891 (1,091-3,447)	2,679 (1,819-3,585)	2,154 (1,238-2,876)	1,095 (702-1,597)	1,091 (748-1,497)	3,455 (2,691-5,008)	3,448 (2,527-4,685)
Troponin I, ng/L	99.3 (38.0-169.1)	75.4 (51.8-141.6)	75.1 (49.6-127.5)	62.2 (38.3-105.4)	141.9 (48.6-169.5)	57.4 (43.3-98.4)	52.0 (30.3-81.2)	53.4 (31.8-79.7)	99.3 (62.8-158.7)	87.3 (50.5-130.2)
eGFR, mL/min/1.73 m^2	74.3 ± 22.1	65.4 ± 25.8	66.5 ± 23.4	70.9 ± 20.2	67.3 ± 21.1	63.7 ± 19.8	77.2 ± 26.8	75.5 ± 21.8	60.1 ± 17.1	63.4 ± 17.0
Concomitant SGLT2i use	0 (0)	0 (0)	3 (1.7)	5 (3.0)	0 (0)	1 (5.6)	1 (1.2)	2 (1.9)	2 (1.7)	4 (4.3)
Oral loop diuretic dose, furosemide equivalent dose, mg/d[e]	20.0 (8.6-40.0)	40.0 (0-60.0)	40.0 (10.0-70.0)	40.0 (5.7-60.0)	80.0 (20.0-80.0)	40.0 (10.0-40.0)	20.0 (0-40.0)	20.0 (0-40.0)	40.0 (20.0-80.0)	40.0 (20.0-80.0)

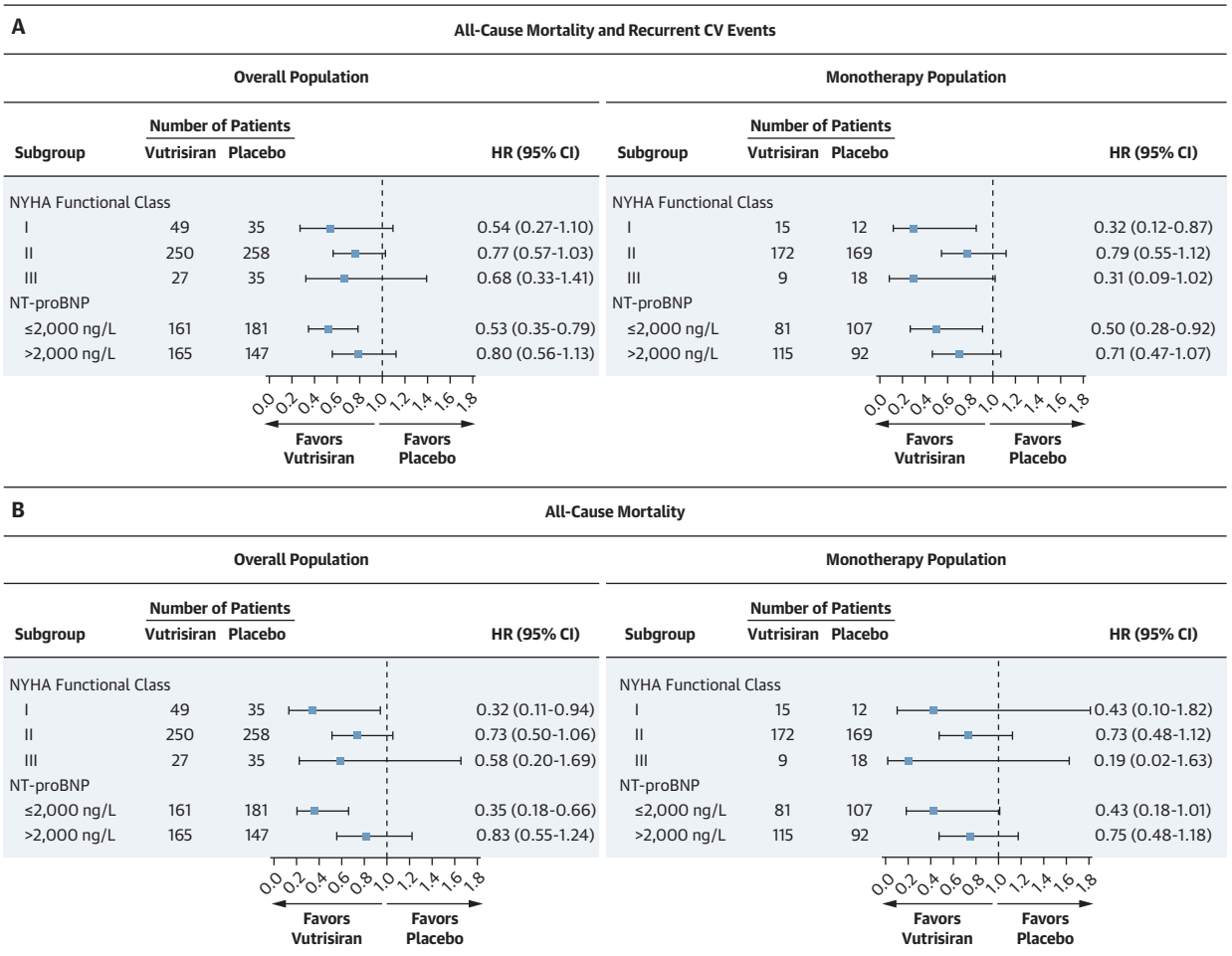
Values are median (Q1-Q3), n (%), or mean ± SD. [a]n = 171. [b]n = 168. [c]n = 114. [d]n = 91. [e]Patients who were in the study but did not take any oral loop diuretic agents during a specific period are included in the summary, with daily dose as 0 mg/day.

Abbreviations as in Table 1.

36 months was lower in vutrisiran-treated compared with placebo-treated patients regardless of baseline heart failure severity; HRs were 0.54 (95% CI: 0.27-1.10), 0.77 (95% CI: 0.57-1.03), and 0.68 (95% CI: 0.33-1.41) in the baseline NYHA functional class I, II, and III groups, respectively, and 0.53 (95% CI: 0.35-0.79) and 0.80 (95% CI: 0.56-1.13) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1A**, Supplemental Table 1). Similarly, in the monotherapy population, risk was lower in vutrisiran-treated compared with placebo-treated patients across all groups, with HRs of 0.32 (95% CI: 0.12-0.87), 0.79 (95% CI: 0.55-1.12), and 0.31 (95% CI: 0.09-1.02) in the baseline NYHA functional class I, II, and III groups, respectively, and 0.50 (95% CI: 0.28-0.92) and 0.71 (95% CI: 0.47-1.07) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1A**, Supplemental Table 2).

Similarly, the risk of all-cause mortality was lower for vutrisiran-treated vs placebo-treated patients up to 42 months across baseline disease severity groups in the overall and monotherapy populations. In the overall population, HRs for vutrisiran vs placebo for all-cause mortality were 0.32 (95% CI: 0.11-0.94), 0.73 (95% CI: 0.50-1.06), and 0.58 (95% CI: 0.20-1.69) in the baseline NYHA functional class I, II, and III groups, respectively, and 0.35 (95% CI: 0.18-0.66) and 0.83 (95% CI: 0.55-1.24) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1B**, Supplemental Table 1). In the monotherapy population, HRs were 0.43 (95% CI: 0.10-1.82), 0.73 (95% CI: 0.48-1.12), and 0.19 (95% CI:

FIGURE 1 Outcomes Endpoints by Baseline Heart Failure Severity



Analyses in the overall and monotherapy populations for the effect of vutrisiran vs placebo on (A) the composite of all-cause mortality and recurrent cardiovascular (CV) events and (B) all-cause mortality by baseline NYHA functional class and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤2,000 ng/L and >2,000 ng/L. The primary composite endpoint of all-cause mortality and recurrent CV events was analyzed using a modified Andersen-Gill model with robust variance estimator stratified by baseline tafamidis use (overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups. The secondary endpoint, all-cause mortality, was analyzed using a Cox proportional hazards model stratified by baseline tafamidis use (for the overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups. All-cause mortality in both endpoints included heart transplantation and left ventricular assist device placement.

0.02-1.63) in the baseline NYHA functional class I, II, and III groups, respectively, and 0.43 (95% CI: 0.18-1.01) and 0.75 (95% CI: 0.48-1.18) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 1B**, Supplemental Table 2).

In further analyses based on additional measures of baseline heart failure severity including Columbia stage, NAC stage, and NT-proBNP tertile at baseline, reductions vs placebo with vutrisiran were observed in the risk of the composite endpoint of all-cause mortality and recurrent CV events, and in the standalone secondary endpoint of all-cause mortality, with greatest benefit seen in patients with earlier, less severe disease: HRs for vutrisiran vs placebo for all-cause mortality and recurrent CV events 0.49 (95% CI: 0.34-0.72) in patients with baseline NAC stage 1, and 0.52 (95% CI: 0.30-0.88) in patients with baseline NT-proBNP <1,368 ng/L (**Table 3**).

FUNCTIONAL ASSESSMENTS BY BASELINE HEART FAILURE SEVERITY. In the overall population, across baseline NYHA functional class and NT-proBNP groups (≤2,000 ng/L and >2,000 ng/L), changes from baseline to Month 30 for 6-MWT distance

TABLE 3 All-Cause Mortality and Recurrent CV Events by Baseline Heart Failure Severity

	Baseline Columbia Stage		Baseline NAC Stage		Baseline NT-proBNP		
	Early	Intermediate/Late	1	2/3	<1,368 ng/L	≥1,368 and <2,691 ng/L	≥2,691 ng/L
Overall population	312	342	437	217	217	218	219
All-cause mortality and recurrent CV event[a]	0.69 (0.45-1.07)	0.74 (0.53-1.02)	0.49 (0.34-0.72)	1.08 (0.74-1.56)	0.52 (0.30-0.88)	0.61 (0.37-1.00)	0.93 (0.64-1.35)
All-cause mortality[b]	0.58 (0.30-1.12)	0.70 (0.48-1.03)	0.42 (0.25-0.69)	0.91 (0.58-1.43)	0.38 (0.15-0.95)	0.48 (0.26-0.91)	0.85 (0.54-1.33)
Monotherapy population	179	216	251	144	120	128	147
All-cause mortality and recurrent CV event[a]	0.69 (0.37-1.28)	0.66 (0.45-0.97)	0.48 (0.29-0.82)	0.90 (0.58-1.38)	0.56 (0.25-1.26)	0.56 (0.29-1.08)	0.82 (0.54-1.22)
All-cause mortality[b]	0.60 (0.27-1.36)	0.69 (0.44-1.09)	0.44 (0.22-0.86)	0.83 (0.50-1.37)	0.39 (0.11-1.39)	0.57 (0.25-1.28)	0.77 (0.46-1.27)

Values are n or HR (95% CI). The primary composite endpoint of all-cause mortality and recurrent cardiovascular (CV) events was analyzed using a modified Andersen-Gill model with robust variance estimator stratified by baseline tafamidis use (overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups. The secondary endpoint, all-cause mortality, was analyzed using a Cox proportional hazards model stratified by baseline tafamidis use (for the overall population only) and adjusted for baseline log-transformed NT-proBNP, following the prespecified analysis approach for groups. [a]During the double-blind period. [b]During the double-blind period and up to 6 months of the open-label extension.

Abbreviations as in Table 1.

demonstrated lower decline with vutrisiran vs placebo. LS mean treatment differences were 34.8 m (95% CI: −1.6 to 71.2), 22.6 m (95% CI: 7.5-37.6), and 28.4 m (95% CI: −12.1 to 68.9) in the baseline NYHA functional class I, II, and III groups, respectively, and 35.2 m (95% CI: 17.6-52.8) and 21.7 m (95% CI: 2.8-40.6) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 2A**, Supplemental Table 1, Supplemental Figure 2A). Similar results for 6-MWT were also observed in the monotherapy population, with LS mean differences between vutrisiran and placebo of 62.9 m (95% CI: −31.3 to 157.2 m), 29.0 m (95% CI: 9.5-48.5 m), and 72.2 m (95% CI: 2.7-141.7 m) in the baseline NYHA functional class I, II, and III groups, respectively, and 44.0 m (95% CI: 17.5-70.6 m) and 32.1 m (95% CI: 8.6-55.5 m) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 2A**, Supplemental Table 2, Supplemental Figure 2A).

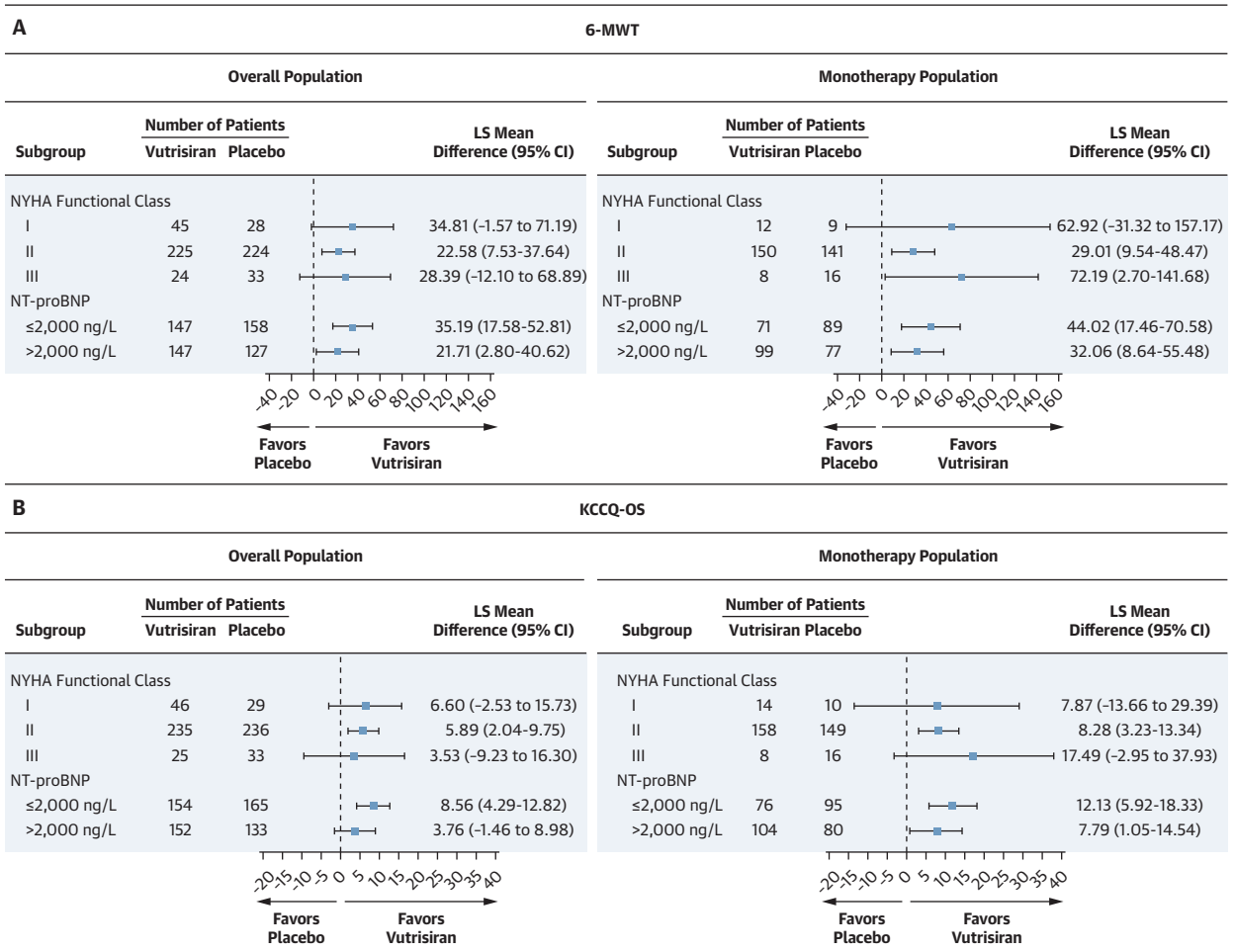
Similarly, change from baseline to Month 30 for KCCQ-OS score demonstrated lower decline with vutrisiran vs placebo regardless of baseline heart failure severity. In the overall population, LS mean differences between vutrisiran and placebo were 6.6 (95% CI: −2.5 to 15.7), 5.9 (95% CI: 2.0-9.8), and 3.5 (95% CI: −9.2 to 16.3) in the baseline NYHA functional class I, II, and III groups, respectively, and 8.6 (95% CI: 4.3-12.8) and 3.8 (95% CI: −1.5 to 9.0) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 2B**, Supplemental Table 1, Supplemental Figure 2B). In the monotherapy population, LS mean differences between vutrisiran and placebo were 7.9 (95% CI: −13.7 to 29.4), 8.3 (95% CI: 3.2-13.3), and 17.5 (95% CI: −3.0 to 37.9) in the baseline NYHA functional class I, II, and III groups, respectively, and 12.1 (95% CI: 5.9-18.3) and 7.8 (95% CI: 1.1-14.5) in the baseline NT-proBNP ≤2,000 ng/L and >2,000 ng/L groups, respectively (**Figure 2B**, Supplemental Table 2, Supplemental Figure 2B).

CARDIAC BIOMARKERS BY BASELINE HEART FAILURE SEVERITY. Similar trends as observed for 6-MWT and KCCQ-OS were also observed for the cardiac biomarkers in the overall and monotherapy populations. The geometric mean fold-changes from baseline to Month 30 in NT-proBNP and troponin I levels were lower for vutrisiran-treated compared with placebo-treated patients across baseline NYHA functional classes and NT-proBNP groups (**Figure 3**, Supplemental Tables 1 and 2, Supplemental Figure 3A). Additionally, troponin I levels were stable vs baseline throughout 30 months in patients who received vutrisiran across baseline disease severity groups (Supplemental Figure 3B).

DISCUSSION

This exploratory subgroup analysis of the HELIOS-B study provided evidence for the benefits of vutrisiran vs placebo in measures of mortality, recurrent CV events, functional capacity, health status and quality of life, and cardiac biomarkers across a range of baseline heart failure severity groups defined primarily by NYHA functional class or NT-proBNP levels (**Central Illustration**). NYHA functional class is an independent predictor of all-cause mortality and the composite endpoint of all-cause mortality or cardiac transplantation in ATTR-CM,[16] and NT-proBNP has also been shown to be prognostic of survival in ATTR-CM.[19,20] In addition, higher levels of

FIGURE 2 Functional Assessments, 6-MWT and KCCQ-OS, by Baseline Heart Failure Severity



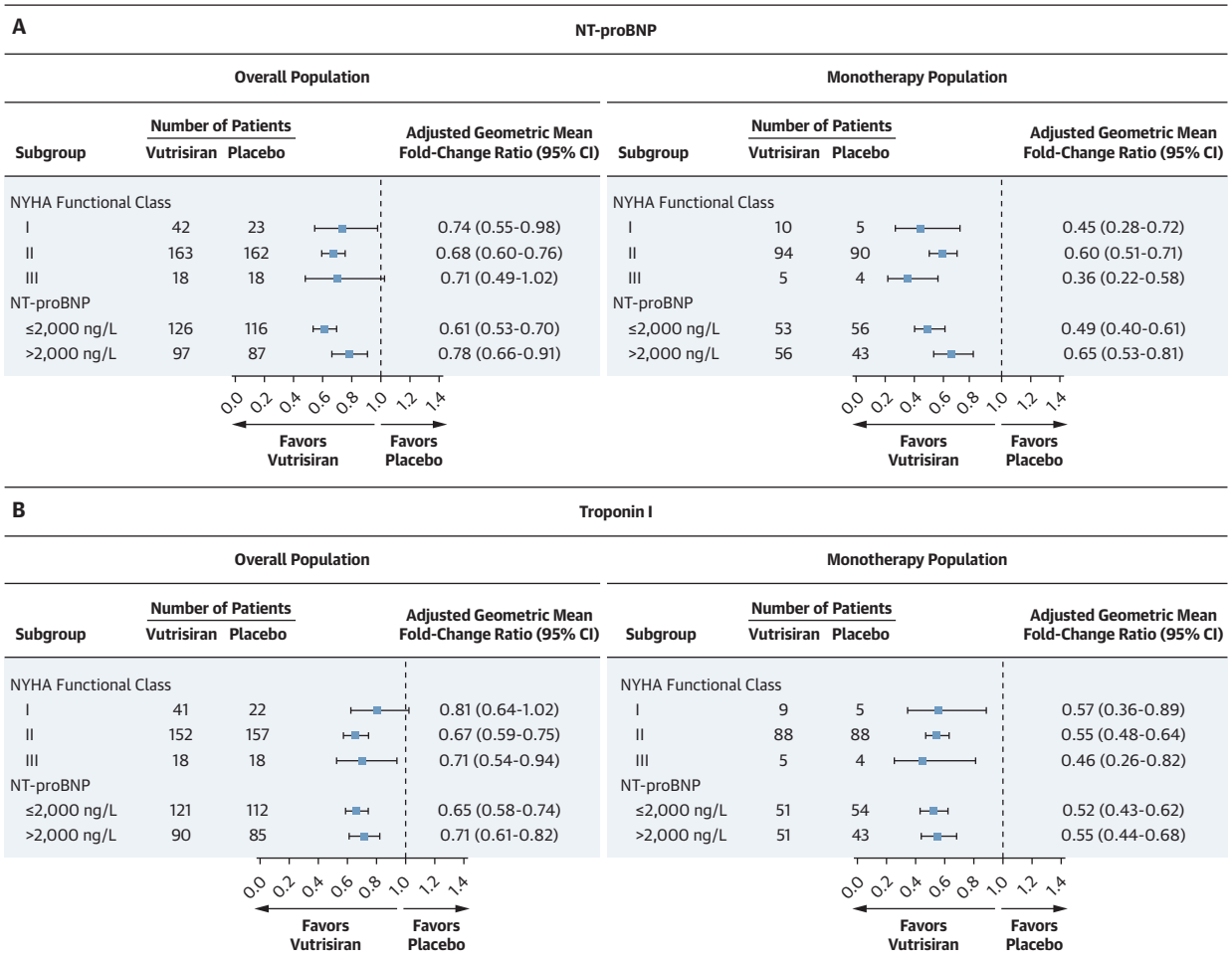
Analyses in the overall and monotherapy populations for the effect of vutrisiran vs placebo on the change from baseline at Month 30 for (A) 6-minute walk test (6-MWT) and (B) Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) by baseline NYHA functional class and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤2,000 ng/L and >2,000 ng/L. Changes from baseline to Month 30 for 6-MWT and KCCQ-OS were analyzed using a mixed model for repeated measures including baseline endpoint as a continuous covariate and treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use (overall population only) as fixed-effect terms. LS = least-squares.

NT-proBNP at ATTR-CM diagnosis have been shown to predict worse response to treatment, reinforcing the benefit of early therapeutic intervention.[21]

In the overall and monotherapy populations enrolled in HELIOS-B, the observed risk of the composite endpoint of all-cause mortality and recurrent CV events, as well as the standalone all-cause mortality endpoint, was lower with vutrisiran compared with placebo across subgroups of heart failure severity defined by NYHA functional class or the prespecified NT-proBNP thresholds of ≤2,000 ng/L or >2,000 ng/L. Additional analyses that considered baseline heart failure severity defined by other clinical staging systems, including NAC stage and Columbia stage, as well as baseline NT-proBNP tertiles, yielded generally consistent results overall, with the greatest treatment effect observed in patients with less severe disease.

Compared with placebo, vutrisiran also demonstrated evidence of a beneficial effect on functional status (6-MWT) and health status and quality of life (KCCQ-OS) as well as cardiac biomarkers NT-proBNP and troponin I across subgroups of heart failure severity. For levels of troponin I, in both the overall and monotherapy populations, vutrisiran-treated patients also demonstrated stabilization over

FIGURE 3 Cardiac Biomarkers, NT-proBNP and Troponin I, by Baseline Heart Failure Severity

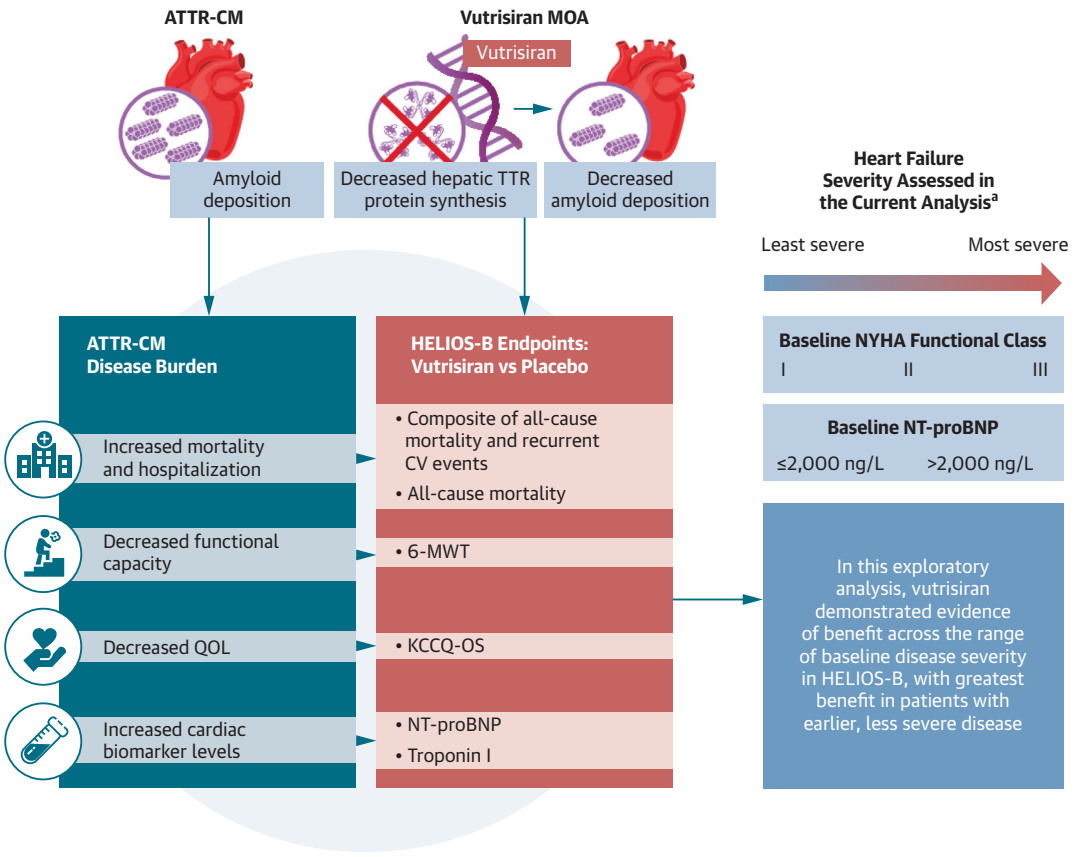


Analyses in the overall and monotherapy populations for the effect of vutrisiran vs placebo on change from baseline at Month 30 for (A) NT-proBNP levels and (B) troponin I levels by baseline NYHA functional class and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤2,000 ng/L and >2,000 ng/L. Changes from baseline to Month 30 for NT-proBNP and troponin I were analyzed using a mixed model for repeated measures including baseline log-transformed endpoint as a continuous covariate and treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use (overall population only) as fixed-effect terms.

30 months of follow-up in all baseline disease severities, compared with the expected steady worsening observed in the placebo arm.

The evidence of a beneficial effect of vutrisiran vs placebo that was observed across the range of baseline heart failure severities in patients with ATTR-CM enrolled in HELIOS-B suggests that use of this disease-modifying treatment may be considered in patients with either milder or more advanced disease. The analyses demonstrating that the greatest treatment effect was observed in patients with early, less severe disease supports early diagnosis and the initiation of effective treatment as soon as possible following diagnosis in order to derive the highest level of benefit. This is in line with consensus statements highlighting the importance of early diagnosis, monitoring response to treatment, and treatment with disease-modifying therapies to reduce further amyloid deposition and prevent disease progression and worsening symptoms.[5,22] Similar analyses have been performed with other ATTR-CM treatments. In the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) trial, rates of CV hospitalizations were higher with tafamidis vs placebo in patients with baseline NYHA functional class III.[11] However, direct comparisons

CENTRAL ILLUSTRATION **Impact of Heart Failure Severity on Vutrisiran Efficacy**



Maurer MS, et al. JACC. 2025;85(20):1927–1939.

[a]Patients with NYHA functional class IV and functional class III with National Amyloidosis Centre (NAC) stage 3 (N-terminal pro-B-type natriuretic peptide [NT-proBNP] level >3,000 ng/L and estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2 body surface area) were excluded from the HELIOS-B study (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy). In exploratory subgroup analyses of HELIOS-B, the efficacy of vutrisiran vs placebo was assessed in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) primarily by baseline NYHA functional class and baseline NT-proBNP levels. Across baseline disease severities, reduced risk of the composite of all-cause mortality and recurrent cardiovascular (CV) events as well as all-cause mortality alone, and improved measures of functional capacity, health status and quality of life (QOL), and cardiac biomarkers, were observed in vutrisiran-treated patients compared with placebo. These data show evidence of benefit of vutrisiran vs placebo across the range of baseline disease severities in patients enrolled in HELIOS-B, with the greatest benefit observed in patients with earlier, less severe disease.
6-MWT = 6-minute walk test; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; MOA = mechanism of action; TTR = transthyretin

should not be made between these data and the HELIOS-B subgroup data due to differences in study designs.

STUDY LIMITATIONS. When interpreting these results, certain limitations should be considered. Patients with NYHA functional class IV and those with NYHA functional class III and NAC stage 3 (NT-proBNP level >3,000 ng/L and an estimated glomerular filtration rate <45 mL/min/1.73 m^2 body surface area) were excluded from HELIOS-B; thus, the conclusions drawn from the data cannot be extended to these patients. Some baseline disease severity groups had a small number of patients, particularly NYHA functional class I (12.8%) and III (9.5%), resulting in an uneven distribution of groups in analyses stratified for NYHA functional class, with a high percentage (77.7%) of patients in NYHA functional class II. Furthermore, for event-based endpoints in smaller subgroups, uncertainty in the presented HRs may be

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larger than what is quantified by the CIs. The descriptive nature of these analyses should therefore be kept in mind when interpreting these results. These analyses were exploratory in nature, so there were no statistical comparisons between subgroups and randomization in the study was not stratified by these subgroups.

CONCLUSIONS

Collectively, this exploratory subgroup analysis of the HELIOS-B study provides evidence that vutrisiran had a beneficial impact on all-cause mortality and recurrent CV events, and multiple measures of ATTR-CM disease progression, in patients across a range of baseline heart failure severity. Benefit was greatest in patients with earlier, less severe disease, highlighting the need for timely diagnosis and starting effective therapy as soon as possible.

DATA SHARING STATEMENT. Access to anonymized individual participant data that support these results is made available 12 months after trial completion and not less than 12 months after the product and indication have been approved in the United States and/or the Economic Union. Data will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website: www.vivli.org.

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APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this paper.