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Impact of Vutrisiran on Cardiac Biomarkers in Patients With Transthyretin Amyloidosis With Cardiomyopathy From HELIOS-B

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ABSTRACT

BACKGROUND Before the development of disease-modifying therapies for transthyretin amyloidosis cardiomyopathy (ATTR-CM), N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin I/T were recognized as independent prognostic biomarkers of mortality. This study evaluated the prognostic value of these biomarkers in a contemporary patient population and the impact of vutrisiran, an RNA interference therapeutic that rapidly knocks down circulating transthyretin, on biomarker levels.

OBJECTIVES This study sought to evaluate the association between risk of cardiovascular events and all-cause mortality with baseline NT-proBNP and troponin I levels and changes from baseline at month 6 in patients from HELIOS-B and explore how vutrisiran impacts biomarkers over time.

METHODS In HELIOS-B, a double-blind, placebo-controlled study, 655 patients with ATTR-CM were randomized 1:1 to receive vutrisiran or placebo for up to 36 months. The primary endpoint was a composite outcome of all-cause mortality and recurrent cardiovascular events. All-cause mortality through 42 months was a secondary endpoint. NT-proBNP and troponin I were assessed as prespecified exploratory endpoints.

RESULTS Baseline NT-proBNP and troponin I levels were independently associated with risks of the composite outcome and all-cause mortality ($P < 0.0001$ for both biomarkers and endpoints). At month 6, increases in NT-proBNP from baseline were associated with higher risk of the composite outcome and all-cause mortality, and decreases in troponin I were associated with a lower risk of the composite outcome. At month 30, the median changes from baseline of NT-proBNP and troponin I were 753 pg/mL (Q1-Q3: −8 to 2,573 pg/mL) and 9.7 pg/mL (Q1-Q3: −6.3 to 41.2 pg/mL) in the placebo arm and 118 pg/mL (Q1-Q3: −419 to 911 pg/mL) and −5.8 pg/mL (Q1-Q3: −25.0 to 10.0 pg/mL) in the vutrisiran arm. The geometric mean fold-change ratios (vutrisiran/placebo) were 0.68 (95% CI: 0.61-0.76) for NT-proBNP and 0.68 (95% CI: 0.62-0.75) for troponin I ($P < 0.0001$ for both).

CONCLUSIONS Patterns of associations between biomarkers and adverse outcomes support the importance of early treatment initiation and the potential for risk reduction in patients with ATTR-CM. Vutrisiran maintained stable or reduced levels of both biomarkers consistent with the benefit of treatment in reducing the risk of cardiovascular events and all-cause mortality. (HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149) (JACC. 2025;86:459-475) © 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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ABBREVIATIONS AND ACRONYMS

ATTR = transthyretin amyloidosis

ATTR-CM = transthyretin amyloidosis cardiomyopathy

CV = cardiovascular

MMRM = mixed model for repeated measures

NT-proBNP = N-terminal prohormone of B-type natriuretic peptide

TTR = transthyretin

Transthyretin amyloidosis (ATTR) is a progressive and potentially fatal disease caused by the dissociation of the tetrameric transthyretin (TTR) protein into misfolded subunits that accumulate as amyloid fibrils in organs and tissues. The disease can arise either from inherited variants in the *TTR* gene (referred to as hereditary or variant ATTR) that destabilize the TTR protein, or from age-related deposition of wild-type TTR amyloid (wild-type ATTR).[1,2] Amyloid infiltration of the heart causes transthyretin amyloidosis cardiomyopathy (ATTR-CM), which manifests as heart failure, arrhythmia, and/or valvular disease. The natural history is one of unrelenting disease progression leading to frequent hospitalizations and death.[2,3] The median survival from diagnosis is 2 to 6 years without treatment.[2,4]

Early diagnosis, improvements in heart failure management, and disease-modifying therapies have improved prognosis, but morbidity and mortality remain high for patients with ATTR-CM, driving the need for further advances in care.[5] Although there is no accepted definition of optimal response to therapy, key outcomes include survival, hospitalizations, functional capacity, and quality of life.[6] Vutrisiran is a subcutaneously administered RNA interference therapeutic agent that targets both wild-type and variant hepatic *TTR* messenger RNA for degradation. Rapid and durable knockdown of circulating TTR protein in turn reduces the ongoing amyloid deposition that drives disease progression. In the phase 3, randomized, placebo-controlled HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopath; NCT04153149) trial, treatment with vutrisiran in patients with ATTR-CM reduced the risk of death by any cause and cardiovascular (CV) events, with an acceptable safety profile. Vutrisiran also preserved functional capacity, health status and quality of life, and cardiac function.[7,8]

The cardiac biomarkers N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin I/T are commonly measured to assess myocardial stress and myocyte injury in heart failure. Before the current era of early diagnosis and disease-modifying therapies, both biomarkers were shown to be independent predictors of mortality and incorporated into prognostic staging systems for ATTR-CM.[4,5,9-12] More recently, changes in their levels have garnered interest for their potential as prognostic markers of disease progression and adverse clinical outcomes.[5,13-16] The present work evaluates how the risks of the primary endpoint, a composite outcome of all-cause mortality and recurrent CV events, or the secondary endpoint of all-cause mortality alone varied with baseline levels or change from baseline to month 6 of NT-proBNP and troponin I in patients in HELIOS-B. Additionally, it explores how vutrisiran impacts the trajectory of both NT-proBNP and troponin I levels over time.

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METHODS

HELIOS-B STUDY DESIGN. HELIOS-B was a phase 3, randomized, placebo-controlled study of vutrisiran in patients with hereditary or wild-type ATTR-CM. The overall population in the study comprised patients who were not receiving tafamidis at baseline (monotherapy population) or were receiving concomitant tafamidis (baseline tafamidis subgroup). Initiation of on-label tafamidis was permitted in tafamidis-naïve patients after enrollment if considered necessary after at least 12 months. Full details of the study design have been described previously.[7] Briefly, patients were randomized 1:1 to receive 25 mg vutrisiran or placebo, both administered as subcutaneous injections once every 12 weeks for up to 36 months in a double-blind treatment period. This was followed by an ongoing open-label extension period, in which all patients remaining in the study will receive 25 mg vutrisiran every 12 weeks for up to 2 years.

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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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Patients eligible for the study were aged 18 to 85 years; had a documented diagnosis of ATTR-CM (hereditary or wild-type); had a clinical history of heart failure, with at least 1 prior hospitalization for heart failure, or clinical evidence of heart failure; were clinically stable with no CV-related hospitalizations within 6 weeks before randomization; had a screening NT-proBNP level of >300 pg/mL and <8,500 pg/mL (or >600 pg/mL and <8,500 pg/mL in patients with permanent/persistent atrial fibrillation); could complete ≥150 m on the 6-minute walk test; and had a Karnofsky performance status of ≥60%. Key exclusion criteria were known primary amyloidosis or leptomeningeal amyloidosis; NYHA functional class IV heart failure or NYHA functional class III heart failure and National Amyloidosis Centre stage 3 ATTR (defined as NT-proBNP >3,000 pg/mL and estimated glomerular filtration rate <45 mL/min/1.73 m^2)[4]; or a polyneuropathy disability score of IIIa, IIIb, or IV (requiring a cane or stick to walk or confined to a wheelchair or bed).

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.

ENDPOINTS. The primary endpoint was a composite of all-cause mortality (including heart transplantation and left ventricular assist device placement) and recurrent CV events (defined as hospitalizations for CV causes or urgent visits for heart failure) during the double-blind period (up to 36 months). The secondary endpoints included all-cause mortality up to 42 months.[7]

Cardiac biomarkers were measured using validated assays at a central laboratory in blood samples taken from patients at baseline and months 3, 6, 12, 18, 24, and 30. For this analysis, associations between levels of NT-proBNP or troponin I and the primary endpoint and the secondary endpoint were explored. Change in levels of NT-proBNP and troponin I from baseline to month 30 were also assessed, which were the prespecified exploratory endpoints in HELIOS-B.

NT-proBNP and troponin I were evaluated in the overall, monotherapy population, and baseline tafamidis subgroup, and in prespecified subgroups defined by: age at baseline (<75 years; ≥75 years); baseline tafamidis use; ATTR disease type (hereditary; wild-type); NYHA functional class (I/II; III); and baseline NT-proBNP levels (≤2,000 ng/mL; >2,000 ng/mL).

STATISTICAL ANALYSIS. HRs for association of NT-proBNP and troponin I with the primary endpoint were based on the modified Andersen-Gill model with a robust variance estimator. This method is an extension of the Cox proportional hazards model that accounts for patients with multiple events. The HRs for association with the secondary endpoint were based on the Cox proportional hazards model. Data were censored at the end of the double-blind period for the primary endpoint and at month 6 of the open-label extension phase for all-cause mortality secondary endpoint. First, the association of outcomes with $\log_2$-transformed biomarkers at baseline was assessed. These models were stratified by randomized treatment assignment, and, in the overall population, by baseline tafamidis use. Next, the association of outcomes with a spline expansion of biomarkers was assessed. For baseline analysis, a natural cubic spline expansion of the biomarker at baseline was included as the only covariate. For the month 6 analysis, covariates included the biomarker at baseline and a natural cubic spline expansion of change from baseline in biomarker at month 6. The spline expansions had the intercepts suppressed and the number of knots was chosen to minimize Akaike's information criterion. Knots are distributed across the biomarker data distribution following Harrell's recommendation.[17] Patients with missing measurements at the baseline or month 6 visit were excluded from the respective analyses.

The effect of vutrisiran on biomarkers was assessed through a mixed model for repeated measures (MMRM). For patients in the vutrisiran monotherapy group who commenced tafamidis treatment during the study, biomarker data collected after tafamidis initiation were prespecified to be excluded from the analysis to assess the impact of vutrisiran alone. In the MMRM analysis, the outcome variable was change from baseline in log-transformed NT-proBNP or troponin I. Given that NT-proBNP and troponin I are known to be highly skewed, a log transformation was performed. The model included log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. The adjusted geometric mean fold-change ratio and 95% CIs were obtained by exponentially back-transforming the difference in least-squares mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. As a sensitivity analysis, the above MMRM was repeated, including biomarker data collected after tafamidis initiation. For the subgroup analyses, the ratios of

TABLE 1 Baseline Demographics and Clinical Characteristics

	Overall Population		Monotherapy Population		Baseline Tafamidis Subgroup	
	Vutrisiran (N = 326)	Placebo (N = 328)	Vutrisiran (n = 196)	Placebo (n = 199)	Vutrisiran (n = 130)	Placebo (n = 129)
Age at randomization, y	77.0 (45-85)	76.0 (46-85)	77.5 (46-85)	76.0 (53-85)	77.0 (45-85)	75.0 (46-85)
Male	299 (91.7)	306 (93.3)	178 (90.8)	183 (92.0)	121 (93.1)	123 (95.3)
Wild-type ATTR-CM[a]	289 (88.7)	289 (88.1)	173 (88.3)	174 (87.4)	116 (89.2)	115 (89.1)
Time since diagnosis, y	0.9 (0-11.1)	1.0 (0.0-10.8)	0.5 (0.0-8.3)	0.6 (0.0-6.2)	1.3 (0.0-11.1)	1.53 (0.1-10.8)
LVEF, %	55.6 ± 12.7	55.9 ± 12.4	54.8 ±12.6	55.7 ± 12.1	56.9 ± 12.8	56.3 ± 12.8
Global longitudinal strain, %	14.0 ± 3.5	14.0 ± 3.5	14.04 ± 3.4	14.3 ± 3.5	13.9 ± 3.5	13.5 ± 3.4
LV wall thickness, cm	1.82 ± 0.26	1.82 ± 0.27	1.82 ± 0.27	1.83 ± 0.29	1.82 ± 0.26	1.80 ± 0.24
NT-proBNP, pg/mL	2,021 [1,138-3,312]	1,801 [1,042-3,082]	2,402 [1,322-3,868]	1,865 [1,067-3,099]	1,760 [1,085-2,685]	1,746 [968-2,906]
Range	322-8,892	317-7,988	370-8,892	335-7,988	322-7,541	317-6,530
Troponin I, pg/mL	71.9 [44.9-115.9]	65.2 [41.1-105.5]	76.3 [48.4-138.8]	62.2 [39.2-105.6]	64.9 [42.9-93.2]	68.3 [44.8-104.6]
Range	10.0-8712.0	10.0-30827.7	10.0-2304.2	10.0-30827.7	11.2-8712	10.0-631.5

Values are median (minimum-maximum range), n (%), mean ± SD, or median [Q1-Q3], unless otherwise indicated. [a]Patients with hereditary or variant ATTR-CM had 13 *TTR* variants, with the most common being V122I (64%), T60A (11%), and V30M (8%).

ATTR-CM = transthyretin amyloidosis cardiomyopathy; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

adjusted geometric mean fold-change for vutrisiran vs placebo with 95% CI for both biomarkers are presented. These are based on a MMRM using data only from the subgroup, with change from baseline in log-transformed biomarker as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. For the baseline tafamidis subgroup, the model also included type of ATTR and age group but excluded baseline tafamidis use.

Patients were grouped by their baseline level for each biomarker. For NT-proBNP, patient groups were ≤1,000 pg/mL, >1,000 to ≤2,000 pg/mL, >2,000 to ≤3,000 pg/mL, and >3,000 pg/mL. For troponin I, groups were ≤40 pg/mL, >40 to ≤65 pg/mL, >65 to ≤100 pg/mL, and >100 pg/mL. Within each group, cumulative mean events per patient (and 95% CIs) were estimated from the cumulative distribution function and cumulative incidence rates (and 95% CIs) were estimated as the inverse of the Kaplan-Meier estimator.

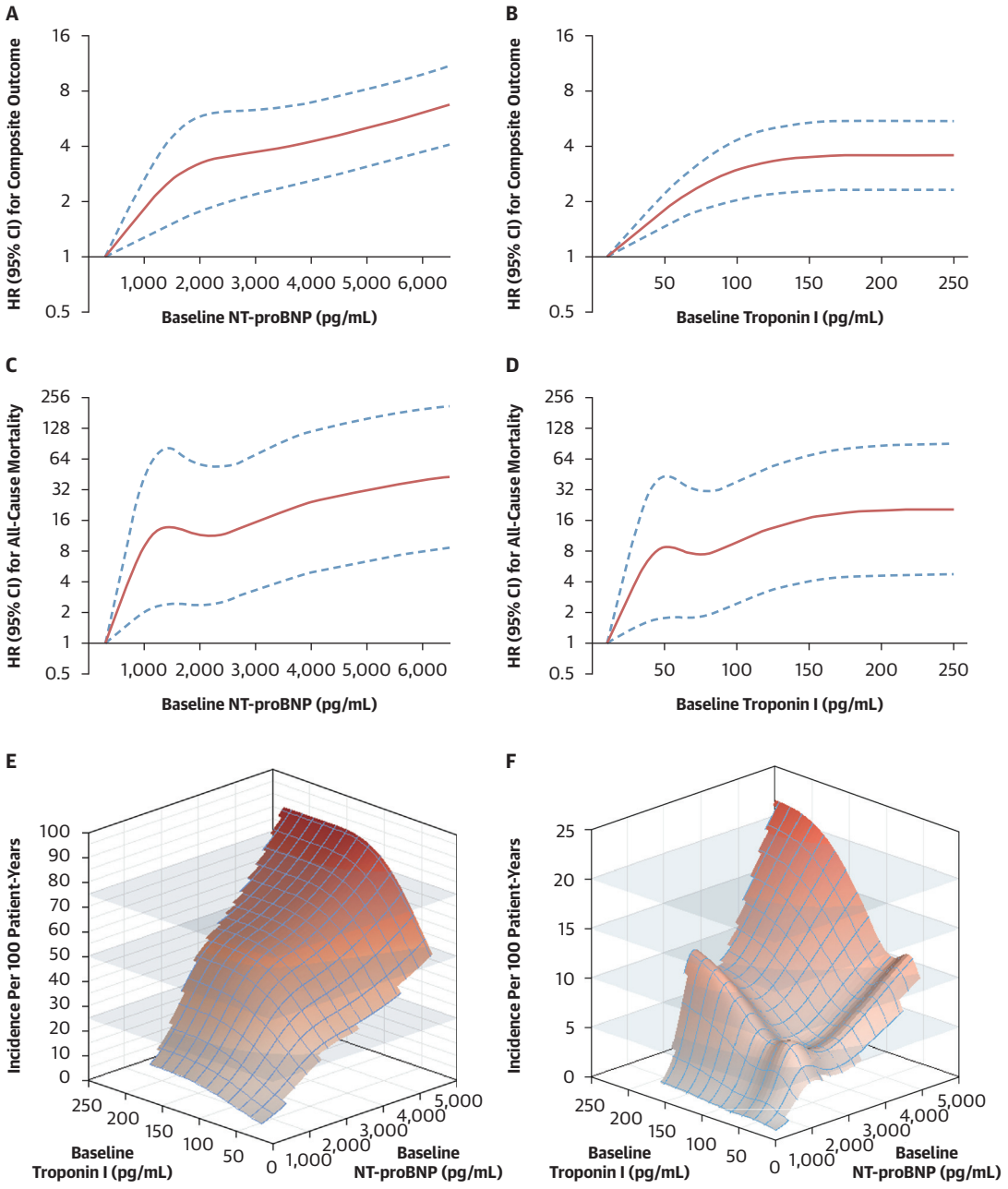
Associations between combinations of baseline biomarkers and change from baseline biomarkers at month 6 with the event rates of the primary outcome and all-cause mortality were analyzed using negative binomial regression and Poisson regression, respectively. The associations were visualized in figures showing the event rates with respect to 2 different covariates. Covariates in the models included natural cubic spline expansions of baseline biomarker or change from baseline in biomarkers at month 6, as indicated by the axes labels. Models used the logarithm of follow-up time as an offset and used the same approach for splines as above. The figures were truncated to the observed data distribution using the following steps. The x-axis variable was truncated at the 90th percentile for baseline variables; for change from baseline variables, the x-axis was truncated at the 5th and 95th percentiles of the data distribution. Quantile regression was used to find the 5th and 95th percentiles of the y-axis variable with respect to a spline expansion of the truncated x-axis variable. Coordinates beyond the estimated 5th and 95th percentiles were then truncated.

Summary statistics for NT-proBNP and troponin I levels at baseline and month 30 are presented as median (Q1-Q3), Because these analyses were conducted post hoc or prespecified as exploratory, all *P* values are nominal.

RESULTS

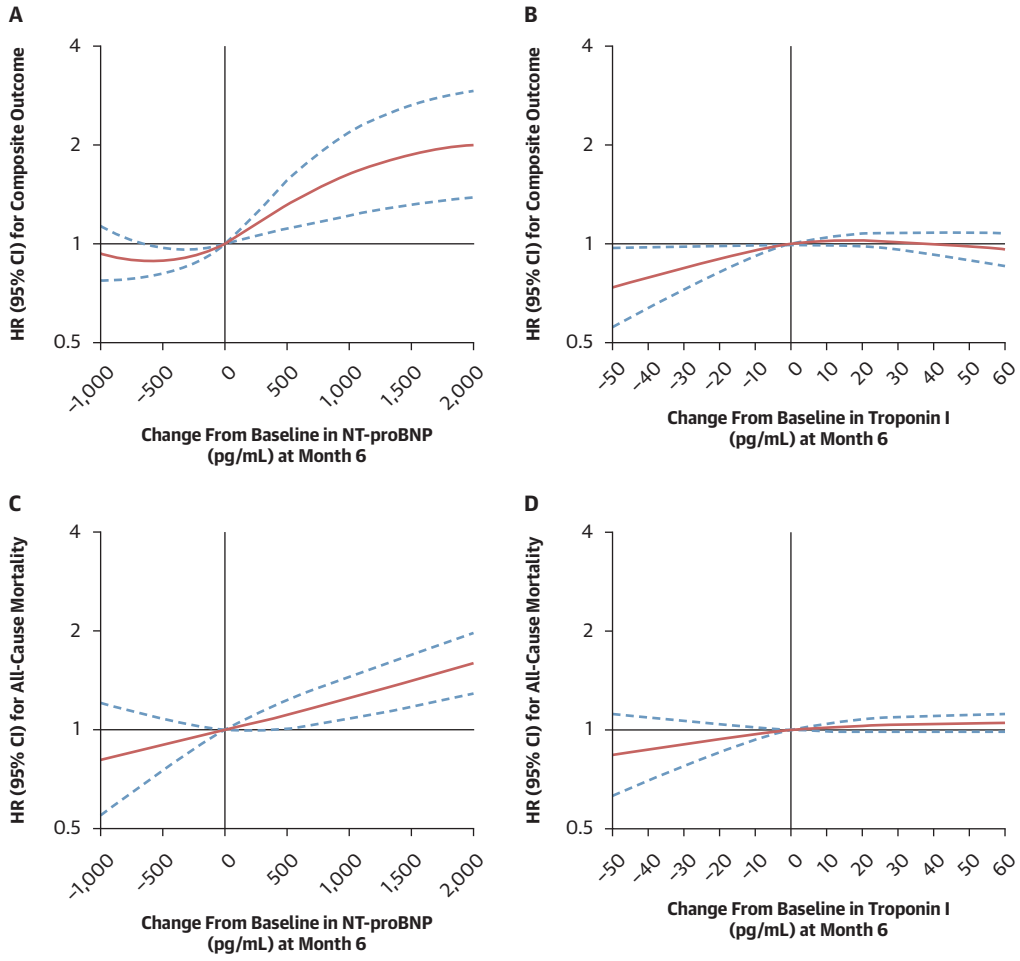
PATIENTS. At baseline, 655 patients were randomized to vutrisiran (n = 326) or placebo (n = 329), and 654 patients received at least 1 dose of either. In the overall population, 60 patients were missing NT-proBNP measurements at month 6 and were excluded from the month 6 landmark analyses (vutrisiran, n = 295; placebo, n = 299). For troponin I, 80 patients were missing month 6 measurements (vutrisiran, n = 284; placebo, n = 290). In the overall population, demographic and clinical characteristics of patients in the 2 treatment groups were similar (Table 1). Of those in the overall population, 395 patients (60.3%) were not taking tafamidis at baseline (monotherapy population). In the monotherapy population, baseline NT-proBNP and troponin I levels were higher in patients randomized to vutrisiran than in those randomized to placebo (Table 1). A total of 85

FIGURE 1 Association Between Biomarker Levels and Risk of the Composite Endpoint and All-Cause Mortality



Association between baseline NT-proBNP or troponin I levels and risk of (A, B) the composite endpoint and (C, D) all-cause mortality in the overall population and the combined impact of baseline levels of both biomarkers on the absolute risk of (E) the composite endpoint and (F) all-cause mortality HRs for the primary endpoint (composite of all-cause mortality [includes heart transplantation and left ventricular assist device placement] and recurrent cardiovascular events) are based on the modified Andersen-Gill model with robust standard error; patients are censored at the end of the double-blind period. HRs for the secondary endpoint of all-cause mortality, which includes heart transplantation and left ventricular assist device placement, are based on the Cox model. HRs are shown relative to a patient with NT-proBNP concentration of 300 pg/mL or troponin I concentration of 10 pg/mL at baseline. The only covariate is a natural cubic spline expansion of NT-proBNP or troponin I concentration at baseline. Event rates of the primary outcome and all-cause mortality were analyzed using negative binomial regression and Poisson regression, respectively, with natural cubic spline expansions of baseline NT-proBNP and troponin I as covariates. NT-proBNP = N-terminal prohormone of B-type natriuretic peptide.

FIGURE 2 **Association Between Change From Baseline to Month 6 in Cardiac Biomarkers and Risk of the Composite Endpoint or All-Cause Mortality**



Association between change from baseline to month 6 in NT-proBNP or troponin I levels and risk of (A, B) the composite endpoint or (C, D) all-cause mortality in the overall population and the relationship between baseline, change from baseline to month 6 and absolute risk with NT-proBNP and troponin I for (E, F) the composite outcome and (G, H) all-cause mortality HRs for the primary endpoint (composite of all-cause mortality [includes heart transplantation and left ventricular assist device placement] and recurrent cardiovascular events) are based on the modified Andersen-Gill model with robust standard error; patients are censored at the end of the double-blind period. HRs for the secondary endpoint of all-cause mortality, which includes heart transplantation and left ventricular assist device placement, are based on the Cox model. HRs are relative to a patient with change from baseline in NT-proBNP or troponin I of 0 pg/mL at month 6. Covariates include log-transformed NT-proBNP or troponin I at baseline and a natural cubic spline expansion of change from baseline in NT-proBNP or troponin I at month 6. Event rates of the primary outcome and all-cause mortality were analyzed using negative binomial regression and Poisson regression, respectively, with natural cubic spline expansions of baseline biomarker and change from baseline in biomarkers at month 6 as covariates. CFB = change from baseline; other abbreviations as in Figure 1.

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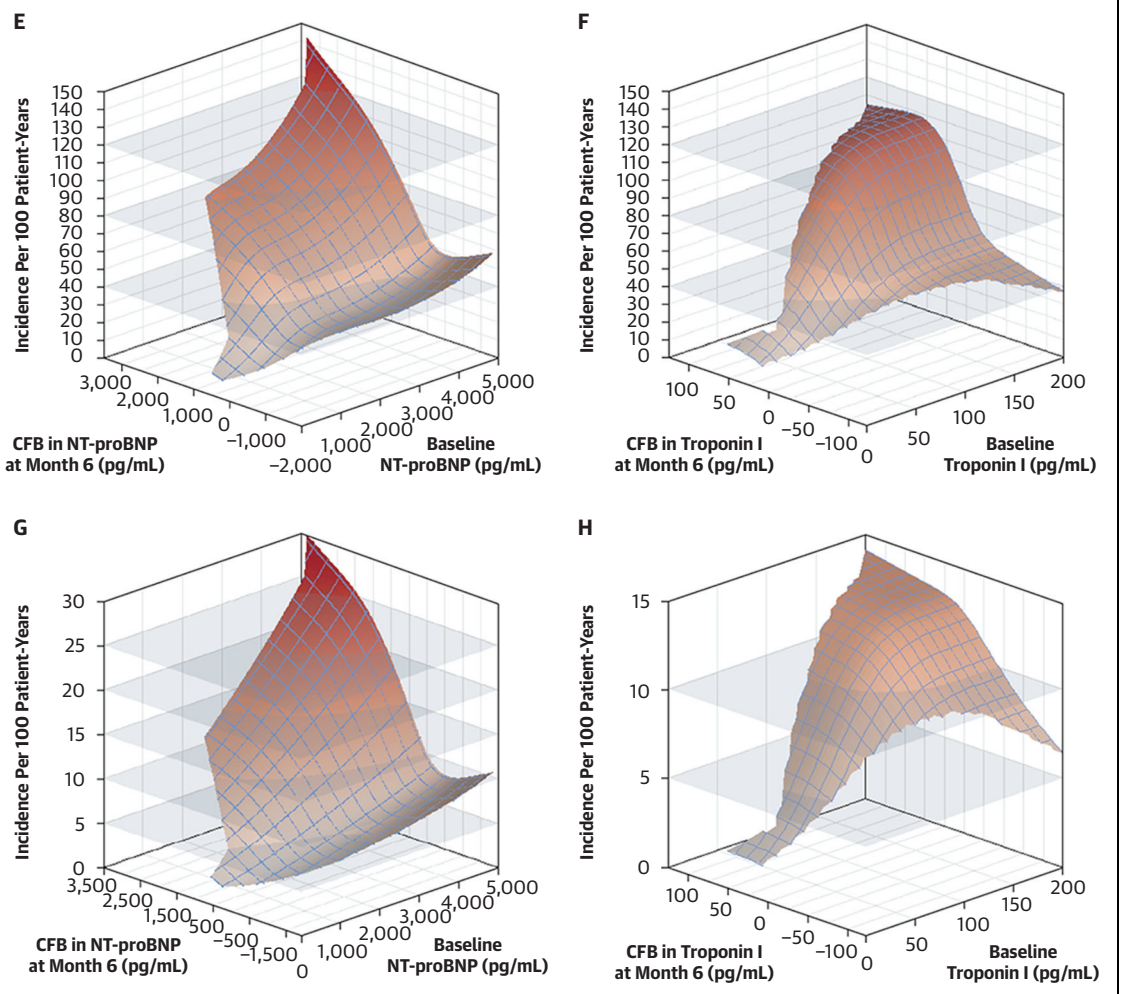
(21.5%) patients in the monotherapy population were prescribed tafamidis during the double-blind period (44 [22.4%] patients in the vutrisiran group and 41 [20.6%] in the placebo group). At baseline, the time from diagnosis was longer in patients in the baseline tafamidis subgroup than for those in the monotherapy population and those who were receiving tafamidis at baseline had lower baseline NT-proBNP levels.

RISKS OF CV EVENTS AND ALL-CAUSE MORTALITY ASSOCIATED WITH CARDIAC BIOMARKERS IN HELIOS-B. Baseline levels of NT-proBNP and troponin I were independently associated with the

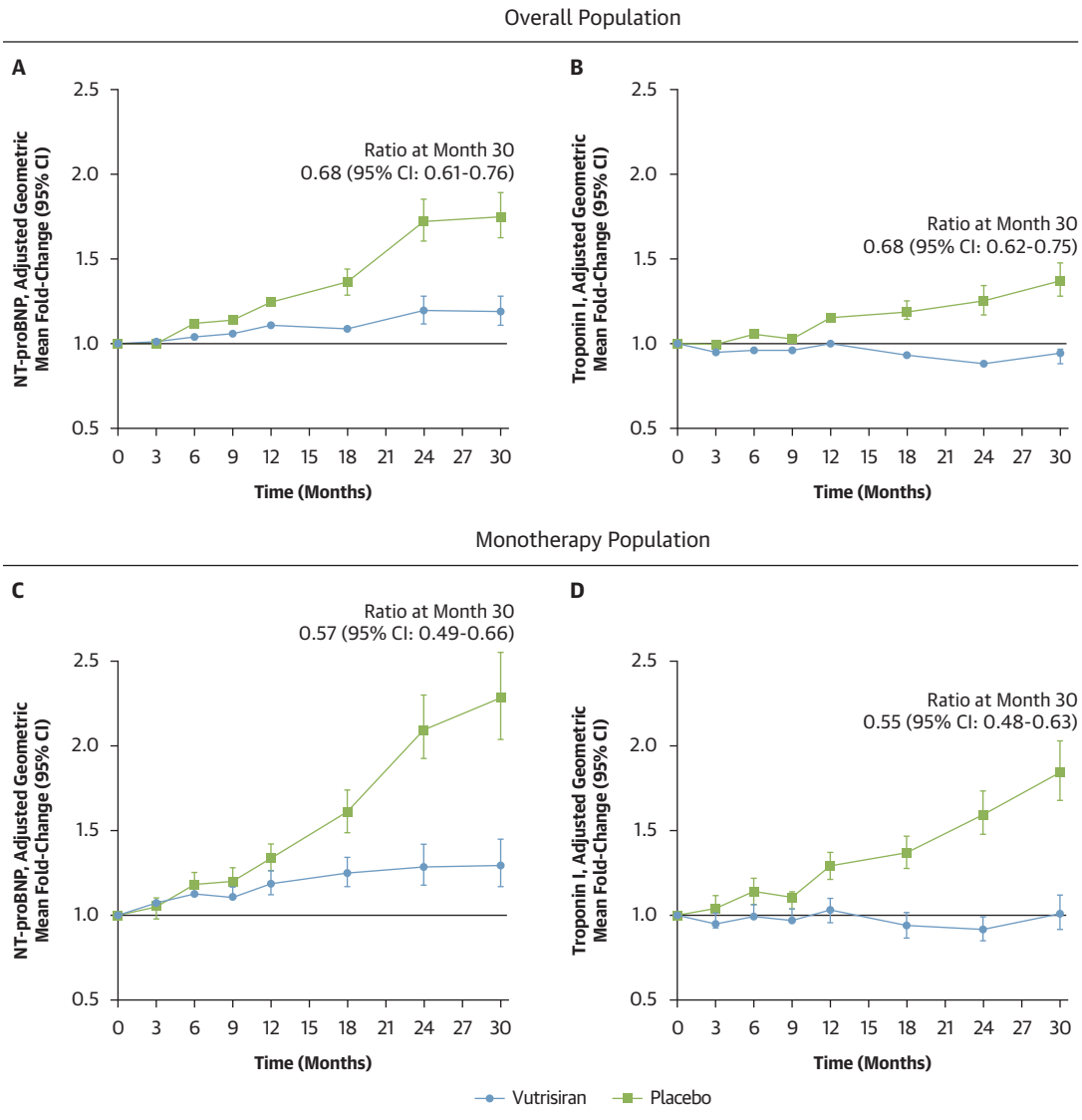
FIGURE 2 Continued



risk of the primary composite outcome of all-cause mortality and recurrent CV events and the secondary outcome of all-cause mortality. In spline analyses, the risk for both the composite outcome and all-cause mortality increased as the baseline level of either biomarker increased (Figures 1A to 1D). For both NT-proBNP and troponin I, there was a greater increase in risk at lower absolute baseline biomarker levels. Relative to a patient with a baseline NT-proBNP of 300 pg/mL or troponin I of 10 pg/mL, there was an approximately 3-fold increase in risk for the composite outcome in patients with an NT-proBNP of 2,000 pg/mL (Figure 1A) or troponin I of 100 pg/mL, respectively (Figure 1B). The rate of increase in risk above an NT-proBNP of 2,000 pg/mL or troponin I of 100 pg/mL was lower compared with levels below these thresholds (Figures 1A and 1B). Similar associations were observed with all-cause mortality for both biomarkers (Figures 1C and 1D). The concentration of each biomarker at baseline was independently associated with the risk of the composite outcome and of all-cause mortality alone ($P < 0.0001$ for both biomarkers and for both multivariate models).

To understand the complex and nonlinear interactions of NT-proBNP and troponin I with the composite outcome and all-cause mortality, the absolute risk was evaluated by event incidence per 100-person years as a function of baseline levels of both biomarkers (Figures 1E and 1F). Among patients with baseline NT-proBNP levels ≤1,000 pg/mL and troponin I levels ≤50 pg/mL, event rates for the composite outcome and all-cause mortality were ≤22 and ≤5 events per 100-person years, respectively. As with the HR plots in Figures 1A to 1D, the rate of increase in event rates was greatest up to NT-proBNP and troponin I levels of ≤2,000 pg/mL

FIGURE 3 Geometric Mean Fold Change Ratio for NT-proBNP and Troponin I Over Time



Geometric mean fold-change ratio for NT-proBNP and troponin I over time in the (A, B) overall, (C, D) monotherapy population, and (E, F) baseline tafamidis subgroup and (G) summary of statistical comparisons between treatment groups. Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the least squares mean of log-transformed NT-proBNP and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. *P* values denote statistical significance in the geometric mean fold-change ratio between vutrisiran and placebo. ATTR = transthyretin amyloidosis; MMRM = mixed models for repeated measures; other abbreviations as in Figure 1.

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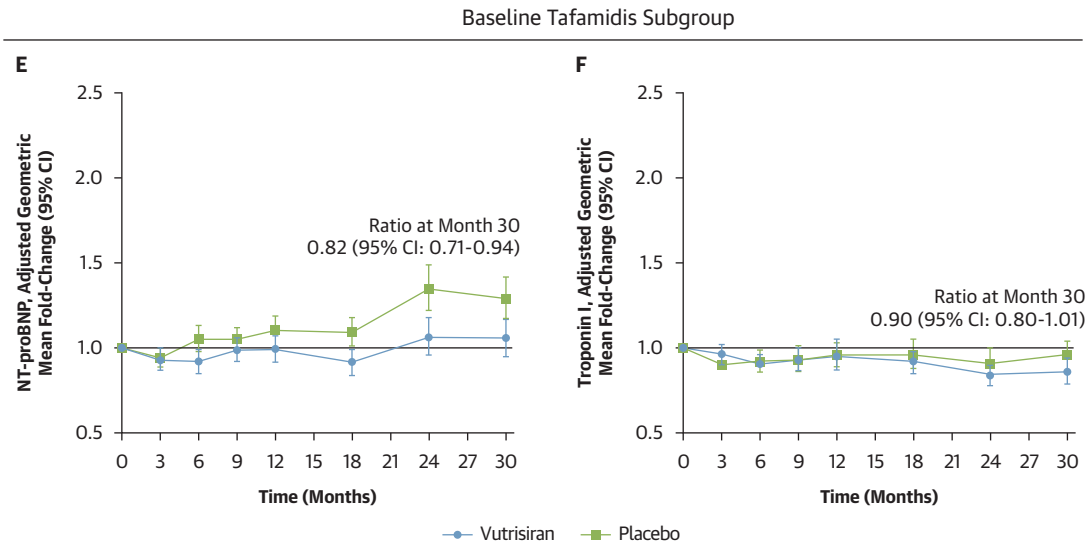
and ≤100 pg/mL. Patients who had baseline NT-proBNP levels >4,000 pg/mL and baseline troponin I levels >100 pg/mL had absolute risks of approximately 66 to 86 composite outcome events and 12 to 22 deaths per 100 person-years.

The cumulative mean events per person for the composite outcome and cumulative incidence rate for all-cause mortality were increased in groups of patients with successively higher baseline biomarker levels. For NT-proBNP, the cumulative mean events

FIGURE 3 Continued



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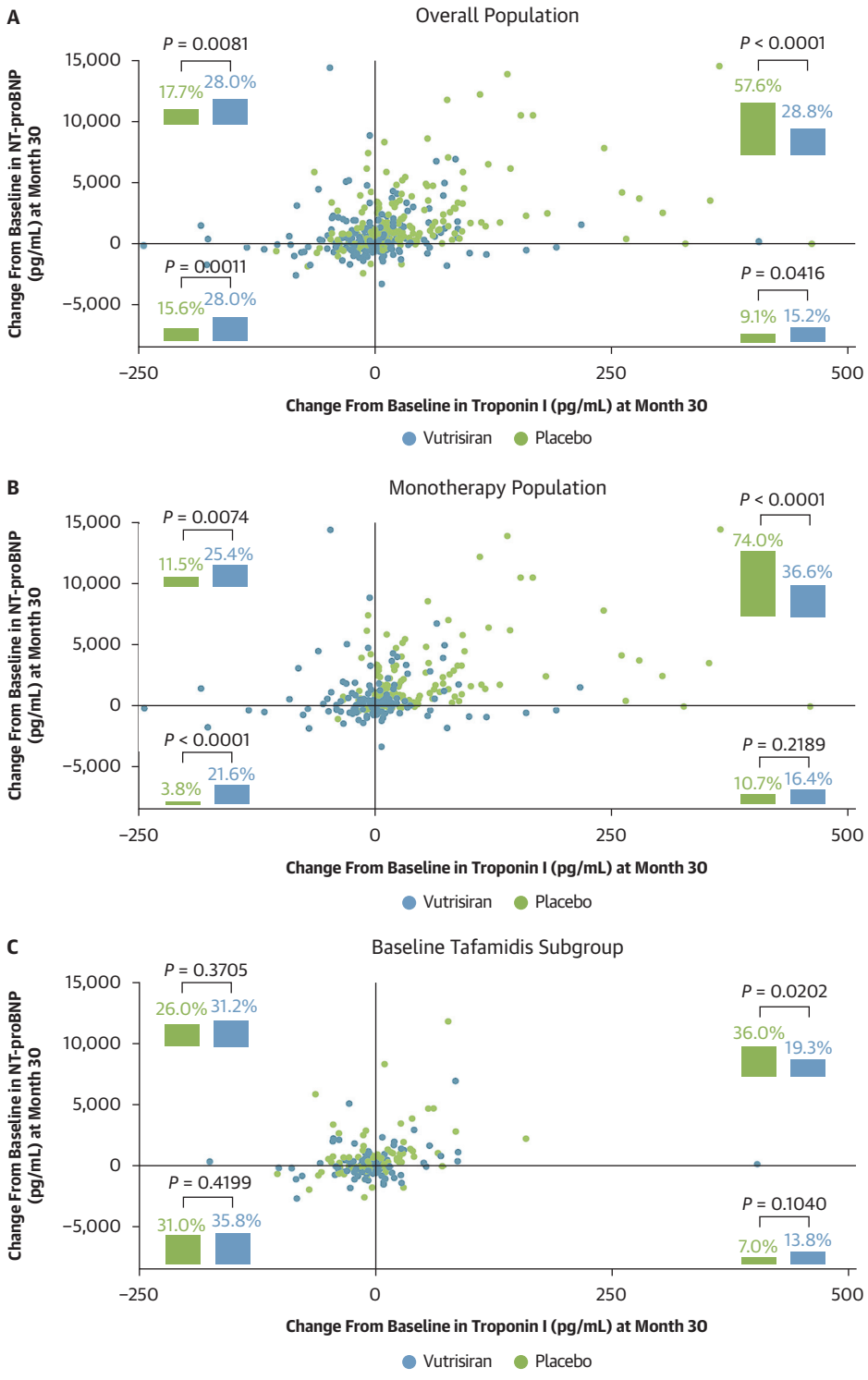
		Time (Months)						
		3	6	9	12	18	24	30
	***P* Value**							
NT-proBNP	Overall Population	0.7177	0.0127	0.0268	0.0012	<0.0001	<0.0001	<0.0001
	Monotherapy Population	0.5875	0.2965	0.0473	0.0120	<0.0001	<0.0001	<0.0001
	Baseline Tafamidis Subgroup	0.8488	0.0083	0.2495	0.0473	0.0022	0.0012	0.0045
	***P* Value**							
Troponin I	Overall Population	0.3425	0.0098	0.0213	0.0002	<0.0001	<0.0001	<0.0001
	Monotherapy Population	0.0492	0.0030	0.0016	<0.0001	<0.0001	<0.0001	<0.0001
	Baseline Tafamidis Subgroup	0.1301	0.7938	0.9295	0.8907	0.4050	0.2027	0.0849

per person for the composite outcome at month 30 increased from 0.351 events (95% CI: 0.24-0.51) in the lowest baseline concentration group (≤1,000 pg/mL) to 1.298 events (95% CI: 1.04-1.62) in the highest group (>3,000 pg/mL) (Supplemental Figure 1A). For troponin I, the cumulative mean events per person for the composite outcome at month 30 increased from 0.390 events (95% CI: 0.27-0.56) in the lowest baseline concentration group (≤40 pg/mL) to 1.264 events (95% CI: 1.01-1.58) in the highest concentration group (>100 pg/mL) (Supplemental Figure 1B). Similar patterns were observed for all-cause mortality (Supplemental Figures 1C and 1D).

Rising cardiac biomarker levels are a sign of disease progression but the prognostic value of changes over relatively short time periods is less clear. In the present analysis, increases in NT-proBNP from baseline to month 6 were associated with an increase in risk for the composite outcome and for all-cause mortality relative to a patient with no change in NT-proBNP; decreases from baseline to month 6 in NT-proBNP were associated with a trend toward lower risk (**Figures 2A and 2B**). For troponin I, increases from baseline to month 6 were associated with relatively stable risk for the composite outcome and all-cause mortality relative to a patient with no change from baseline (**Figures 2C and 2D**). Of note, decreases in troponin I from baseline to month 6 were associated with a reduction in risk for the composite outcome and all-cause mortality relative to a patient with no change (**Figures 2C and 2D**).

How event rates for the composite outcome or all-cause mortality vary by baseline biomarker levels (a marker for disease status), and the change in levels from baseline to month 6 (a marker for disease progression) illustrate how the relative impacts of disease

FIGURE 4 Scatterplots of Month 30 Change From Baseline in NT-proBNP and Troponin I



Scatterplots of month 30 change from baseline in NT-proBNP and troponin I in the (A) overall population, (B) monotherapy population, and (C) baseline tafamidis subgroup. The axes are truncated to exclude the top and bottom 2.5% of patients (ie, patients with a change from baseline in troponin I at month 30 >500 or <−250 or patients with a change from baseline in NT-proBNP at month 30 >15,000 or <−5,000). Bar graphs show the proportion of vutrisiran (blue) and placebo (green) patients in each quadrant. *P* values are from a chi square test. Abbreviations as in Figure 1.

status and the rate of disease progression are intertwined, complex, and nonlinear (Figures 2E to 2H). Figure 2E illustrates, for example, that for 2 patients with NT-proBNP levels at baseline of 1,000 and 1,500 pg/mL, and then 1,500 pg/mL for both at month 6, the event rates for the composite outcome for both patients are similar at 30 per 100-person years. Conversely, for 2 patients with levels of 1,500 pg/mL and 2,000 pg/mL, at baseline and 2,000 pg/mL at month 6, the event rates are 40 and 34 per 100-person years, respectively. The difference reflects the greater impact of disease progression in the first patient, despite both patients having the same disease status as marked by NT-proBNP at month 6. In another example, 2 patients who have troponin I levels of 150 pg/mL and 130 pg/mL, at baseline and then 130 pg/mL at month 6 have event rates for the composite outcome of 54 and 68 per 100-person years, respectively; the difference reflects an absolute risk reduction for the first patient with the decrease in troponin I (Figure 2F). Similar patterns between baseline levels of NT-proBNP or troponin I, month 6 change, and all-cause mortality were also observed (Figures 2G and 2H).

LONGITUDINAL IMPACT OF VUTRISIRAN ON CARDIAC BIOMARKERS. The impact of vutrisiran treatment on NT-proBNP and troponin I levels compared with placebo manifested soon after treatment initiation and increased over time. In the overall population, the ratio in geometric mean fold-changes from baseline (95% CI) at month 6 between those who received vutrisiran and those who received placebo were statistically significant for NT-proBNP (ratio: 0.92; 95% CI: 0.87-0.98; $P = 0.0127$) (Figure 3A) and for troponin I (ratio: 0.91; 95% CI: 0.86-0.98; $P = 0.0098$) (Figure 3B). The ratio between treatment arms decreased through month 30, at which point vutrisiran reduced the geometric mean-fold change from baseline by 32% in both NT-proBNP (ratio: 0.68; 95% CI: 0.61-0.76; $P < 0.0001$) and troponin I (ratio: 0.68; 95% CI: 0.62-0.75; $P < 0.0001$) (Figures 3A and 3B). A sensitivity analysis that included data after tafamidis treatment initiation during the double-blind period yielded similar results (NT-proBNP ratio: 0.68; 95% CI: 0.62-0.75; troponin I ratio: 0.70; 95% CI: 0.64-0.76). The monotherapy population showed greater reductions than the overall population, with 43% and 45% relative reductions in NT-proBNP and troponin I, respectively, with vutrisiran compared with placebo (Figures 3C and 3D). In the baseline tafamidis subgroup, the difference was attenuated compared with the overall group with 18% and 10% relative reductions in NT-proBNP and troponin I, respectively, at month 30 (Figures 3E and 3F).

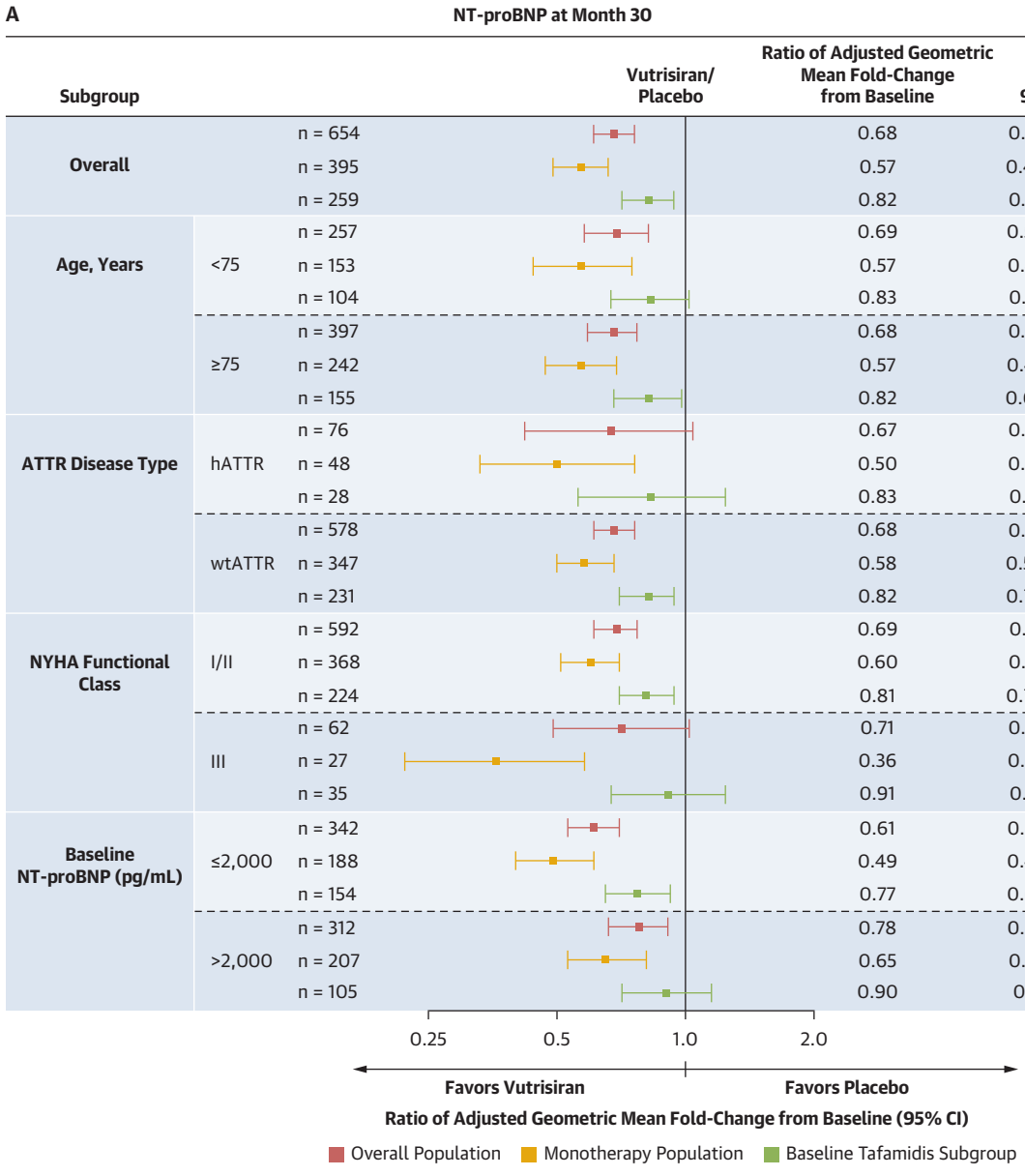
In both the overall and monotherapy populations, patients treated with vutrisiran maintained relatively stable absolute levels of NT-proBNP and reduced levels of troponin I from baseline to month 30. In contrast, in patients who received placebo, absolute levels of NT-proBNP and troponin I increased from baseline to month 30 (Supplemental Figure 2). In the overall population, the median change from baseline in the vutrisiran arm for NT-proBNP at month 30 was 118 pg/mL (Q1-Q3: −419 to 911 pg/mL) and for troponin I was −5.8 pg/mL (Q1-Q3: −25.0 to 10.0 pg/mL). In contrast, the median change from baseline in the placebo arm was 753 pg/mL (Q1-Q3: −8 to 2,573 pg/mL) and 9.7 pg/mL (Q1-Q3: −6.3 to 41.2 pg/mL) for the respective biomarkers (Supplemental Figure 2). In the baseline tafamidis subgroup, the differences in the median changes from baseline between the vutrisiran and placebo arms were attenuated (Supplemental Figure 2). The percentage of patients who showed increases in both NT-proBNP and troponin I from baseline to month 30 was approximately halved by vutrisiran with 57.6%, 74.0%, and 16.4% of the placebo group showing increases in both biomarkers in the overall population ($P < 0.0001$), monotherapy population ($P < 0.0001$), and baseline tafamidis subgroup ($P = 0.0202$) (Figure 4). Likewise, vutrisiran treatment was associated with a greater likelihood of reductions from baseline in 1 or both biomarkers. In the overall population, 28.0% of vutrisiran-treated patients had reductions in both NT-proBNP and troponin I compared with 15.6% with placebo ($P = 0.0011$) (Figure 4A). The difference was greater in the monotherapy population, where 21.6% and 3.8% of vutrisiran and placebo-treated patients had decreases in both biomarkers ($P < 0.0001$) (Figure 4B).

SUBGROUP ANALYSES. In both the overall and the monotherapy populations, the beneficial effects of vutrisiran vs placebo on NT-proBNP and troponin I levels were consistent across all prespecified subgroups at month 30. The geometric mean fold-change ratios favored vutrisiran over placebo across all subgroups. In the baseline tafamidis group, the difference between the vutrisiran group and the placebo group was attenuated across most subgroups for both biomarkers (Figure 5).

DISCUSSION

Although the associations between NT-proBNP or troponin I and the risk of adverse outcomes for

FIGURE 5 Ratio of Adjusted Mean Fold-Change in Biomarker Levels From Baseline for Vutrisiran vs Placebo

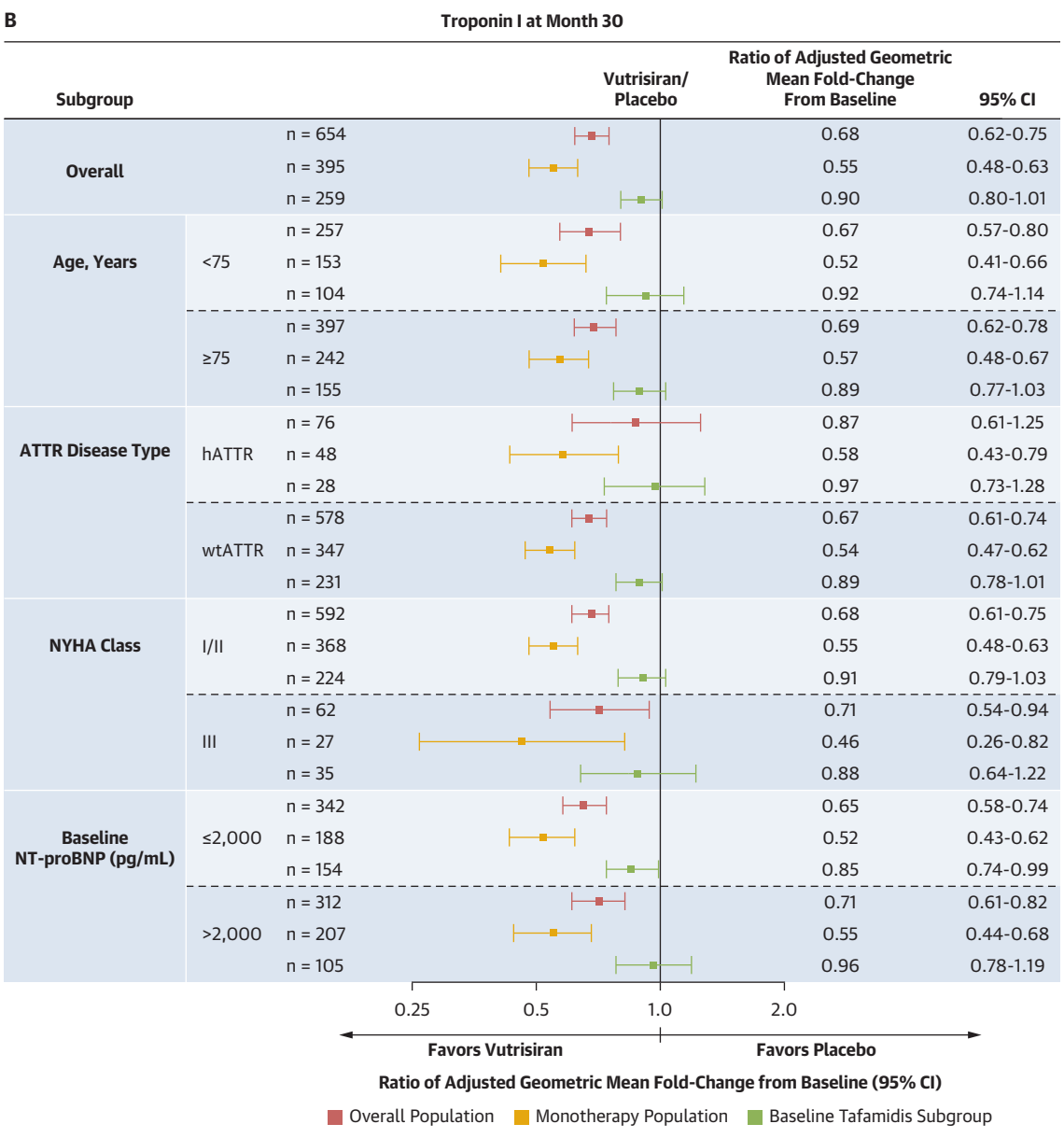


(A) NT-proBNP and (B) troponin I fold-change ratio at month 30 in prespecified subgroups. For all subgroups, results are based on subgroup data only from MMRM with change from baseline in log-transformed biomarker as the outcome, log-transformed baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, and baseline tafamidis use. For baseline tafamidis subgroup, the model also includes type of ATTR and age group but excludes baseline tafamidis use term. For patients in the vutrisiran monotherapy group with tafamidis drop-in during the study, data collected after tafamidis drop-in are excluded from analysis. hATTR = hereditary transthyretin amyloidosis; wtATTR = wild-type transthyretin amyloidosis; other abbreviations as in Figures 1 and 3.

Continued on the next page

patients with ATTR-CM have long been recognized, the present study offers novel insights into the complex and dynamic relationships between cardiac biomarkers and risk as well as the impact of vutrisiran treatment on the biomarkers in a contemporary patient population. First, these analyses demonstrate how the risk of adverse outcomes varies in a nonlinear manner with changes in baseline biomarker

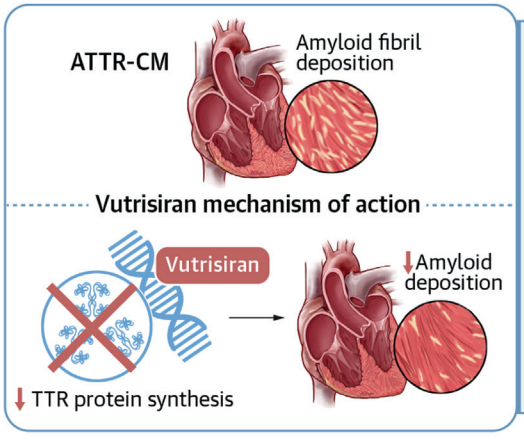
FIGURE 5 Continued

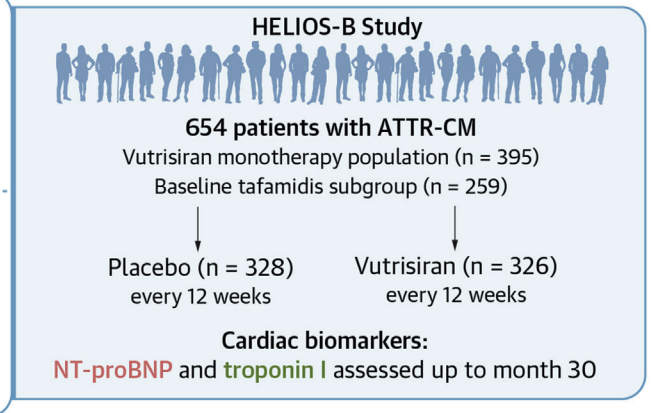


levels and how measuring biomarkers at 6-month intervals may detect meaningful shifts in disease trajectory. These observations support the potential benefits of early initiation of disease-modifying treatment and regular monitoring. Second, while the natural history of ATTR-CM has been characterized by unrelenting disease progression with steadily increasing cardiac biomarkers, the results suggest that reductions in their levels from baseline may be associated with a reduction in the absolute risk of adverse outcomes. Third, these data demonstrate that rapid TTR knockdown by vutrisiran produces early reductions in cardiac biomarkers compared with placebo. The impact of vutrisiran on biomarkers grows over time but the treatment effect is attenuated in patients receiving tafamidis (**Central Illustration**).

NT-proBNP and troponin I/T are independent prognostic indicators and have previously been used to categorize risk relative to threshold levels, eg, NT-proBNP >3,000 or >3,000 pg/mL.[4] The present results characterize risk along a continuous range of

CENTRAL ILLUSTRATION **Impact of Vutrisiran on Cardiac Biomarkers in HELIOS-B**

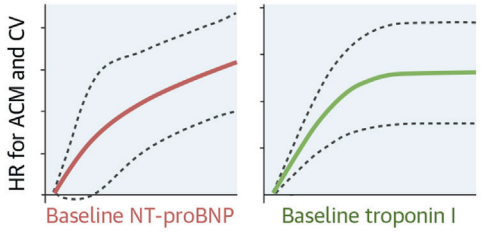




Cardiac biomarker associations at baseline

Higher biomarker levels at baseline were associated with:

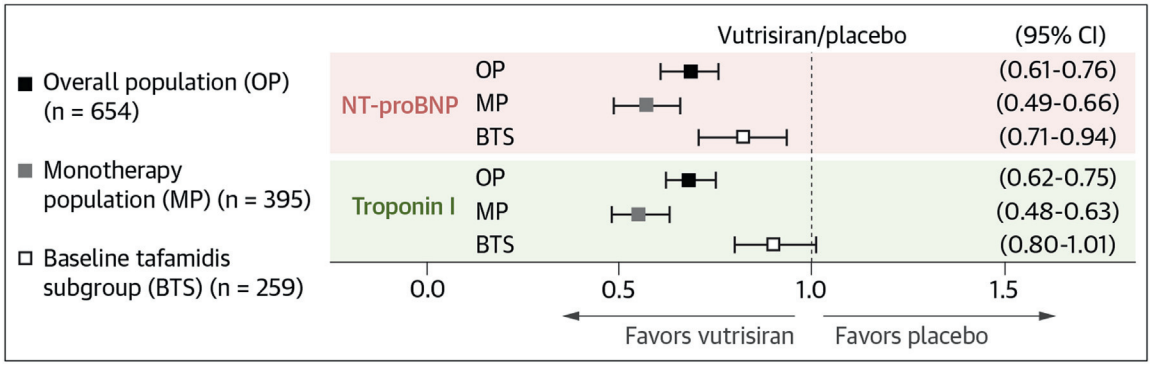
- ↑ risk of all-cause mortality (ACM) and CV events
- ↑ risk of ACM alone
- ↑ incidence of ACM and CV events



Treatment effect on cardiac biomarkers to month 30

In the overall population:

- Vutrisiran treatment maintained relatively stable levels of NT-proBNP compared to placebo
- More than half of patients showed a decline from baseline in troponin I



- Associations between biomarkers and adverse outcomes supports importance of early treatment and potential for risk reductions.
- Vutrisiran maintained stable or improved biomarker levels, consistent with the treatment benefit of reducing the risk of CV events and ACM.

Maurer MS, et al. JACC. 2025;86(6):459–475.

biomarker levels at baseline and of changes from baseline to month 6. Notably, the risk of adverse outcomes increases more rapidly at early disease stages when NT-proBNP and troponin I are <2,000 pg/mL and <100 pg/mL, respectively. Nevertheless, risk continues to increase past these levels, albeit at a lower rate, which reflects the high morbidity and mortality associated with more advanced disease. The patterns reinforce the importance of early diagnosis and treatment initiation to mitigate potentially irreversible disease progression.

The analyses of changes from baseline to month 6 of cardiac biomarker levels suggest that worsening risk can be detected over relatively short timeframes and that absolute risk can decrease in some patients. As with risk stratification at baseline, biomarker-based criteria for disease progression have typically used high thresholds based on historical experience in patients with more advanced disease.[18] More modest changes, however, can signal a clinically relevant increased risk. For example, patients with a 500 pg/mL increase from baseline in NT-proBNP at month 6 had a 32% and 39% greater risk of the composite outcome and all-cause mortality, respectively, relative to a patient with no change from baseline in NT-proBNP at month 6. Interestingly, decreases from baseline in troponin I at month 6 may signal a decreasing risk of CV events and all-cause mortality. The observation is notable because inexorable disease progression has been a hallmark of ATTR-CM. An appreciation of the complex and dynamic relationships between cardiac biomarkers and risk may help to inform the management of ATTR-CM, especially as patients are diagnosed earlier and treated with therapies that have different mechanisms of action.[7,19-21] Although it is beyond the scope of this analysis to define actionable thresholds or patterns of biomarker change, these data suggest that the increase in risk is greater at lower absolute biomarker levels and that the risk attributable to increasing biomarkers may be underestimated at earlier stages of disease.[5] The results also make clear that risk is a complex function of both disease status, as reflected by cardiac biomarker levels at a time point, and the rate of disease progression, as assessed by the change in biomarker levels over time.

In HELIOS-B, vutrisiran suppressed the steady increase in NT-proBNP and troponin I that occurred in placebo-treated patients, keeping absolute levels of NT-proBNP relatively stable and lowering troponin I from baseline over the 30-month study period. The largest differences vs placebo were in the monotherapy population, and the differences were consistent across prespecified subgroups. Baseline use of tafamidis reduced the differences between the vutrisiran and placebo groups with both biomarkers. Administered every 3 months, vutrisiran suppressed circulating levels of TTR within weeks of the first dose with the maximum effect observed after ~12 months.[7] Effects on myocardial stress and myocyte injury were detectable soon afterward, as shown by the impact of vutrisiran vs placebo on NT-proBNP and troponin I at 6 months. Compared with placebo, vutrisiran treatment resulted in a greater percentage of patients showing improvements from baseline in NT-proBNP, troponin I, or both through month 30. In combination with echocardiographic observations demonstrating improvements from baseline in diastolic function at month 30,[22] the biomarker improvements from baseline suggest that vutrisiran can not only reduce the risk of adverse outcomes compared with placebo but also the absolute risk from baseline in some patients across a range of biomarker levels.[23,24] Indeed, in HELIOS-B, vutrisiran produced consistent reductions in risk of both the composite outcome and all-cause mortality in patients with baseline NT-proBNP ≤2,000 pg/mL or >2,000 pg/mL.[7] Furthermore, the impact of vutrisiran on biomarkers was consistent across prespecified subgroups, in parallel with the consistent benefits across the same subgroups on all-cause mortality, recurrent CV events, and outpatient worsening heart failure compared with placebo.[7,25] These results, in combination with the early impact of vutrisiran on cardiac function,[8] can help to explain the clinical benefits of suppressing TTR production via RNA interference.

STUDY LIMITATIONS. The precision of estimates of risks associated with biomarker levels at baseline and their change from baseline is limited by the number of events, duration of the study, and small number of patients at the extremes of biomarker distributions. Analyses of the impact of vutrisiran on biomarkers did not adjust for multiplicity. NT-proBNP is sensitive to intravascular volume status. Estimates of risk associated with NT-proBNP and the impact of vutrisiran on the biomarker were not adjusted for diuretic dosage or sodium-glucose cotransporter protein 2 inhibitor use, although vutrisiran has been shown to reduce the risk of worsening heart failure that requires oral loop diuretic intensification, and sodium-glucose cotransporter protein 2 inhibitor use was equal in the 2 treatment arms.[7,25] Although the treatment effects on biomarkers are shown for the monotherapy population and baseline tafamidis subgroup, we note that patients were not randomized for tafamidis treatment. Therefore, comparisons between the 2 groups may be partly confounded by clinical differences, such as lower baseline

NT-proBNP levels and longer time since diagnosis in the baseline tafamidis subgroup.

CONCLUSIONS

The analyses of a contemporary population of patients with ATTR-CM from the randomized, placebo-controlled HELIOS-B study of vutrisiran illustrate how risk increases with increasing levels of NT-proBNP and troponin I at baseline, how risk varies with changes from baseline at month 6, and how vutrisiran positively impacts levels of each cardiac biomarker compared with placebo. The relationships between NT-proBNP and troponin I and adverse outcomes in patients with ATTR-CM are complex and nonlinear and also suggest the potential for absolute risk reduction from baseline. Treatment with vutrisiran maintained stable or improved levels of NT-proBNP and troponin I, which supports the clinical benefits observed in HELIOS-B and the link between stabilization of cardiac biomarkers and improved outcomes for patients with ATTR-CM.

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KEY WORDS amyloidosis, cardiac biomarkers, N-terminal prohormone of B-type natriuretic peptide, transthyretin amyloidosis cardiomyopathy, troponin I

APPENDIX For supplemental figures, please see the online version of this paper.