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Vutrisiran Improves Survival and Reduces Cardiovascular Events in ATTR Amyloid Cardiomyopathy

HELIOS-B

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ABSTRACT

BACKGROUND Patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) have high mortality and morbidity. Vutrisiran, a subcutaneous RNA interference therapeutic, reduced the composite of all-cause mortality (ACM) and cardiovascular (CV) events (CV hospitalizations and urgent heart failure [HF] visits) in HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy) in patients with ATTR-CM.

OBJECTIVES Here we present data from HELIOS-B evaluating the impact of vutrisiran on ACM and CV mortality with additional patient follow-up through 42 months, and CV events such as CV hospitalizations, HF hospitalizations, and urgent HF visits.

METHODS The HELIOS-B trial randomized 655 patients to vutrisiran 25 mg or placebo once every 3 months for up to 33 to 36 months in the double-blind (DB) period, followed by an open-label extension. Prespecified mortality and CV mortality analyses used data through 39 to 42 months of follow-up (DB period and up to 6 months of the open-label extension). CV hospitalizations and HF events were evaluated over the DB period of 33 to 36 months. Differences between vutrisiran and placebo were evaluated in the overall population, and in those stratified by baseline tafamidis use.

RESULTS In the overall population, vutrisiran reduced the risk of ACM (HR: 0.64; 95% CI: 0.46-0.88) and CV mortality (HR: 0.67; 95% CI: 0.47-0.96) vs placebo. Vutrisiran also reduced the risk of a composite of CV mortality and CV events (HR: 0.72; 95% CI: 0.55-0.94), and lowered rates of CV hospitalizations (rate ratio [RR]: 0.75; 95% CI: 0.62-0.91), urgent HF visits (RR: 0.54; 95% CI: 0.30-0.98), and HF hospitalizations (RR: 0.67; 95% CI: 0.52-0.86) vs placebo. Consistent trends were seen regardless of baseline tafamidis use.

CONCLUSIONS Consistent with the primary trial results, vutrisiran reliably reduced the risk of ACM, CV mortality, CV hospitalizations, HF hospitalizations, and urgent HF visits vs placebo in patients with ATTR-CM. (HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149) (JACC. 2025;85:1959-1970) © 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

ACM = all-cause mortality

ATTR = transthyretin amyloidosis

ATTR-CM = transthyretin amyloidosis with cardiomyopathy

ATTRv = hereditary (variant) transthyretin amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

CV = cardiovascular

DB = double-blind

HF = heart failure

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

OLE = open-label extension

TTR = transthyretin

Transthyretin amyloidosis (ATTR) is a progressive, debilitating, and fatal disease caused by the accumulation of misfolded transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including the heart, nerves, gastrointestinal tract, and musculoskeletal tissues.[1-3] ATTR occurs as a result of inherited *TTR* gene variants (hereditary [variant] transthyretin amyloidosis [ATTRv]) or with aging in the absence of *TTR* gene variants (wild-type transthyretin amyloidosis [ATTRwt]).[1,2,4] Patients with ATTRv often present with a heterogeneous mix of cardiac or neurologic manifestations, whereas patients with ATTRwt have predominantly cardiac manifestations.[5]

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Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) follows a progressive disease course: TTR amyloid accumulates in the myocardium, leading to congestive heart failure (HF), often with conduction disorders, and premature death.[1,6,7] As a result, patients with ATTR-CM have increased symptom severity, declines in functional capacity, worsening quality of life, and reduced life expectancy.[8]

Current treatment options for ATTR-CM include the TTR stabilizers, tafamidis, acoramidis, and the recently approved vutrisiran,[9-11] a subcutaneously administered RNA interference therapeutic that inhibits hepatic synthesis of both wild-type TTR and variant TTR, resulting in rapid knockdown of the amyloidogenic TTR protein.[12-14] Results from the phase 3 HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; NCT04153149) trial demonstrated that vutrisiran reduced the risk of the composite endpoint of all-cause mortality (ACM) and cardiovascular (CV) events vs placebo in patients with ATTR-CM (ATTRwt or ATTRv).[14] Prespecified analyses of ACM used data from the 33- to 36-month double-blind (DB) period and up to 6 additional months of follow-up (through 39-42 months). Here, we report mortality outcomes using a more recent data cut (November 22, 2024, for which 96.3% of patients have data through 42 months) than that used in the previously published primary analysis (May 8, 2024, for which 42.4% of patients had complete data through 42 months), allowing for more events to be included based on an additional 6 months of follow-up of additional patients. We also present data from post hoc analyses of the impact of vutrisiran treatment on CV hospitalizations and HF events over the DB period.

METHODS

STUDY DESIGN. Full details of the HELIOS-B trial design have been reported previously.[14] Briefly, patients age 18 to 85 years, with a diagnosis of ATTR-CM (either ATTRwt or ATTRv) and a clinical history of HF, were randomized 1:1 to receive vutrisiran 25 mg or placebo subcutaneously every 3 months for up to 36 months. Patients were either receiving or not receiving tafamidis at baseline, with no prespecified plan to start the drug during the 12 months following randomization. Those not receiving tafamidis at baseline could initiate it at any time after enrollment if the investigator deemed it necessary. Patients who completed the DB period (33 to 36 months) were eligible to enter the open-label extension (OLE) for up to 24 months to receive vutrisiran 25 mg every 3 months. HELIOS-B 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.

OUTCOMES. HELIOS-B outcomes have been described previously.[14] In the present analyses, we investigated the prespecified outcomes of ACM and CV mortality (including heart transplantation and left ventricular assist device placement), incorporating additional follow-up data based on a more recent data cut than that used for the primary analysis, and conducted additional analyses of CV events, including CV hospitalizations, HF hospitalizations, arrhythmia hospitalizations, urgent HF visits, and the composite of CV mortality and CV events. Analyses were conducted in the overall population, and in patients who were not receiving tafamidis at baseline (monotherapy population). Analyses were also conducted in the subgroup of patients who were receiving tafamidis at baseline (baseline tafamidis subgroup); however, the baseline tafamidis subgroup analyses were not powered to detect differences between treatment groups.

STATISTICAL ANALYSES. All analyses were conducted using the full analysis set (all randomized patients who received any amount of study drug). Unless specified otherwise, treatment group, ATTR disease type (ATTRv vs ATTRwt), NYHA functional class (I/II vs III), age group (<75 years vs ≥75 years),

and log-transformed baseline N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) were included as covariates.

All-cause and CV mortality include data through 42 months for all patients, regardless of OLE participation (ie, 33-36 months DB period, with up to an additional 6 months of follow-up resulting in 39-42 months total). The ACM endpoint reported in the primary analysis from Fontana et al[14] was conducted after all patients had completed or discontinued the DB period, using a May 8, 2024, data cut. At that time, 42.4% of patients had complete data through 42 months, defined as having data available up to 42 months or up to 6 months after OLE entry, whichever came first. In the present analyses using a November 22, 2024, data cut, 96.3% of patients have complete data through 42 months. Patients who received placebo during the DB period and entered the OLE continued to be analyzed as placebo recipients. ACM and CV mortality analyses were fitted to a Cox proportional hazards model. For the overall population, the model was stratified by baseline tafamidis use. Post hoc event rates were derived from adjusted Kaplan-Meier estimated survival probabilities, with each patient's weight assigned as the inverse of the probability of receiving the treatment, determined from a logistic regression model. The model included vutrisiran treatment as the dependent variable, and independent baseline variables consisted of tafamidis status, age, ATTR disease type, NYHA functional class, log-transformed baseline NT-proBNP and troponin, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire-Overall Summary score, and estimated glomerular filtration rate. HR, CI, and SE are reported consistent with the prior analyses.

Analyses of CV events (CV hospitalizations and urgent HF visits) included data exclusively from the 33- to 36-month DB period (data cutoff: May 8, 2024), which were fitted to a Poisson regression model with logarithm of the follow-up time as an offset. This model was used as the primary method for recurrent CV events in the ATTR-ACT study in the ATTR-CM disease setting to ensure comparability of results. The overall population analysis also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates. Event rates were derived from the same Poisson regression model.

The composite of CV mortality and CV events was analyzed over the DB period using a modified Andersen-Gill model with robust variance estimator. For the overall population, the model was also stratified by baseline tafamidis use. Components of CV events were analyzed equivalently as CV events using a Poisson regression model. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc).

RESULTS

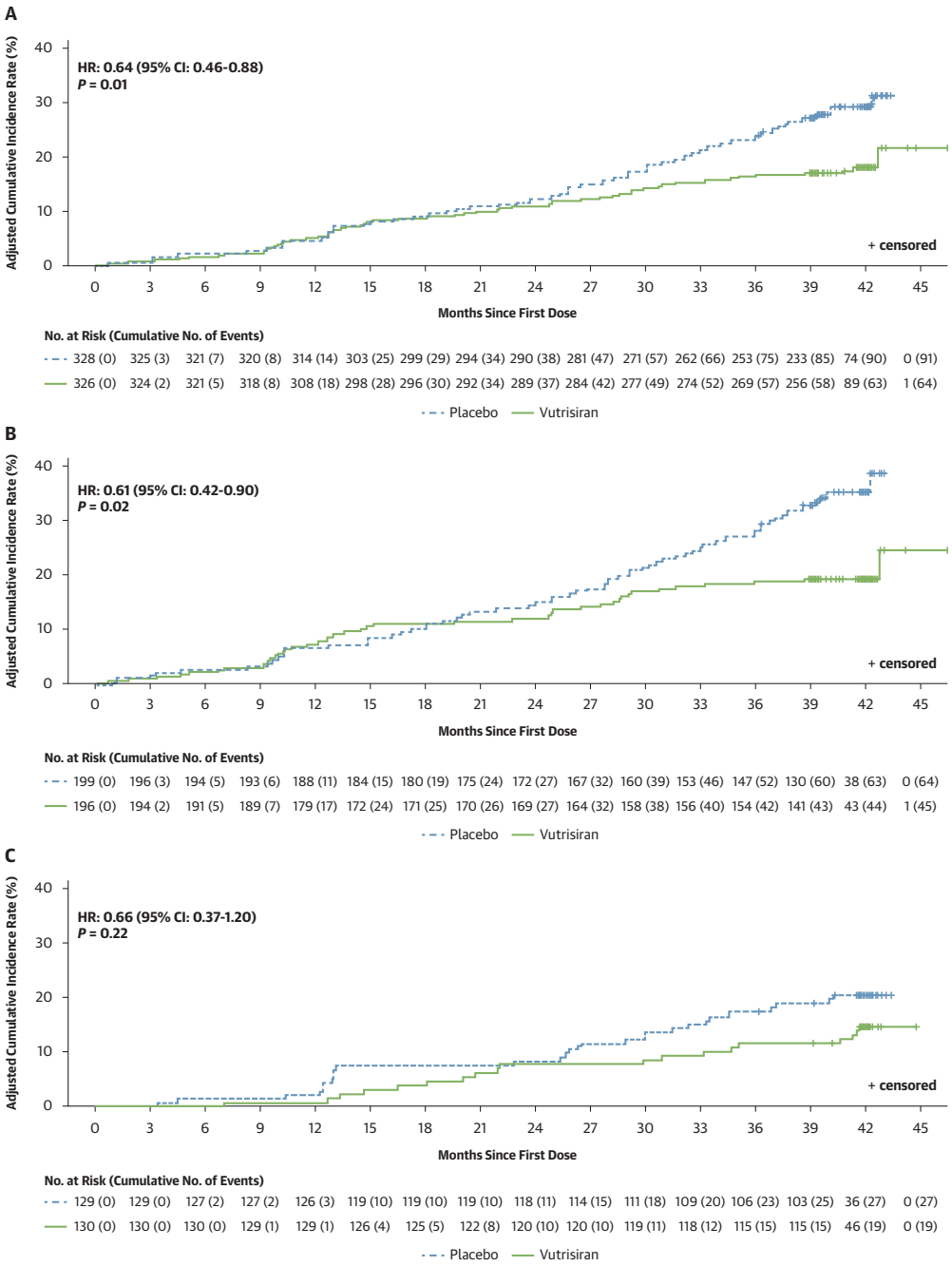
PATIENTS. Of the 655 randomized patients, 326 received vutrisiran, 328 received placebo, and 1 did not receive any study drug (Supplemental Figure 1). Among those who received vutrisiran or placebo, 60.1% and 60.7% of patients, respectively, were not receiving tafamidis at baseline and formed the monotherapy population; 39.9% and 39.3% of patients, respectively, were receiving tafamidis and formed the baseline tafamidis subgroup. Patient characteristics for the baseline tafamidis subgroup are summarized in Supplemental Table 1, alongside the overall and monotherapy populations.[14]

IMPACT OF VUTRISIRAN ON ACM, CV MORTALITY, AND A COMPOSITE OF CV MORTALITY AND CV EVENTS. Vutrisiran treatment led to a 36% reduction in risk of ACM through 42 months vs placebo in the overall population (HR: 0.64; 95% CI: 0.46-0.88; $P = 0.01$; event rates at month 42 [SE]: placebo, 28.95 [2.55]; vutrisiran, 18.36 [2.21]) (**Figure 1A**) and a 39% reduction in the monotherapy population (HR: 0.61; 95% CI: 0.42-0.90; $P = 0.02$) (**Figure 1B**). Although not powered for this analysis, the baseline tafamidis subgroup demonstrated a directionally similar trend, though statistically nonsignificant effect (HR: 0.66; 95% CI: 0.37-1.20; $P = 0.22$) (**Figure 1C**). See Supplemental Table 2 for a breakdown of HRs and event rates by mortality type for all study populations and subgroups.

CV mortality risk up to 42 months was reduced by 33% with vutrisiran treatment in the overall population (HR: 0.67; 95% CI: 0.47-0.96; $P = 0.04$; event rates at month 42 [SE]: placebo, 22.70 [2.40]; vutrisiran, 14.96 [2.07]) (**Figure 2A**), and by 36% in the monotherapy population (HR: 0.64; 95% CI: 0.41-0.98; $P = 0.05$) (**Figure 2B**) vs placebo. As with ACM, the risk of CV mortality in the baseline tafamidis subgroup was numerically lower with vutrisiran vs placebo (HR: 0.75; 95% CI: 0.38-1.47; $P = 0.42$) (**Figure 2C**).

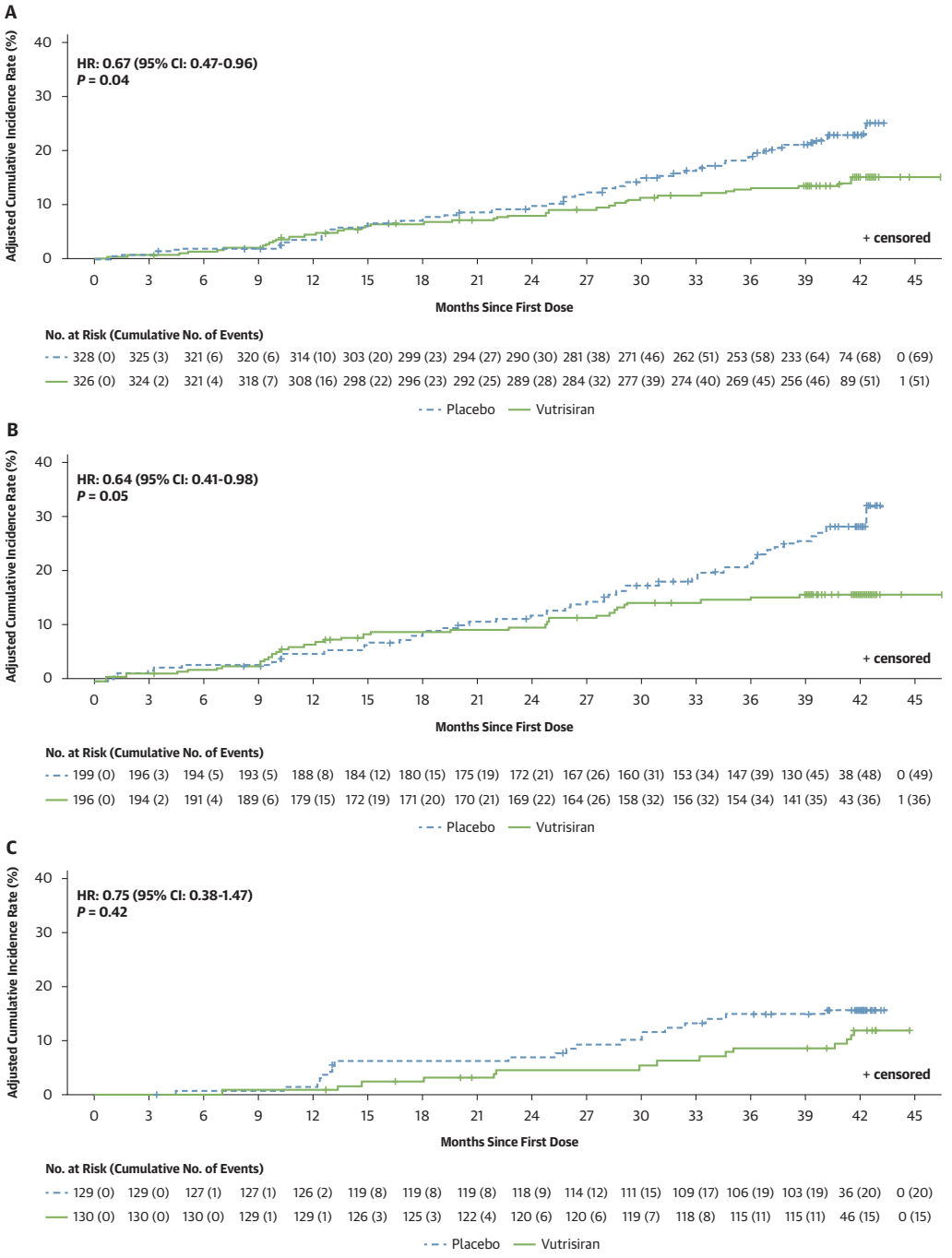
In the composite endpoint of CV mortality and CV events over the DB period of 33 to 36 months, treatment with vutrisiran lowered the risk of an event by 28% in the overall population (HR: 0.72; 95% CI: 0.55-0.94; $P = 0.02$; events per 100 person-years [SE]: placebo, 34.18 [5.96]; vutrisiran, 24.77 [6.77]) (**Figure 3A**), and by 32% in the monotherapy

FIGURE 1 Cumulative Rate of All-Cause Mortality by Treatment During the Double-Blind Period and Up to 6 Months of the Open-Label Extension Treatment Period in the Overall Population, Monotherapy Population, and Baseline Tafamidis Subgroup



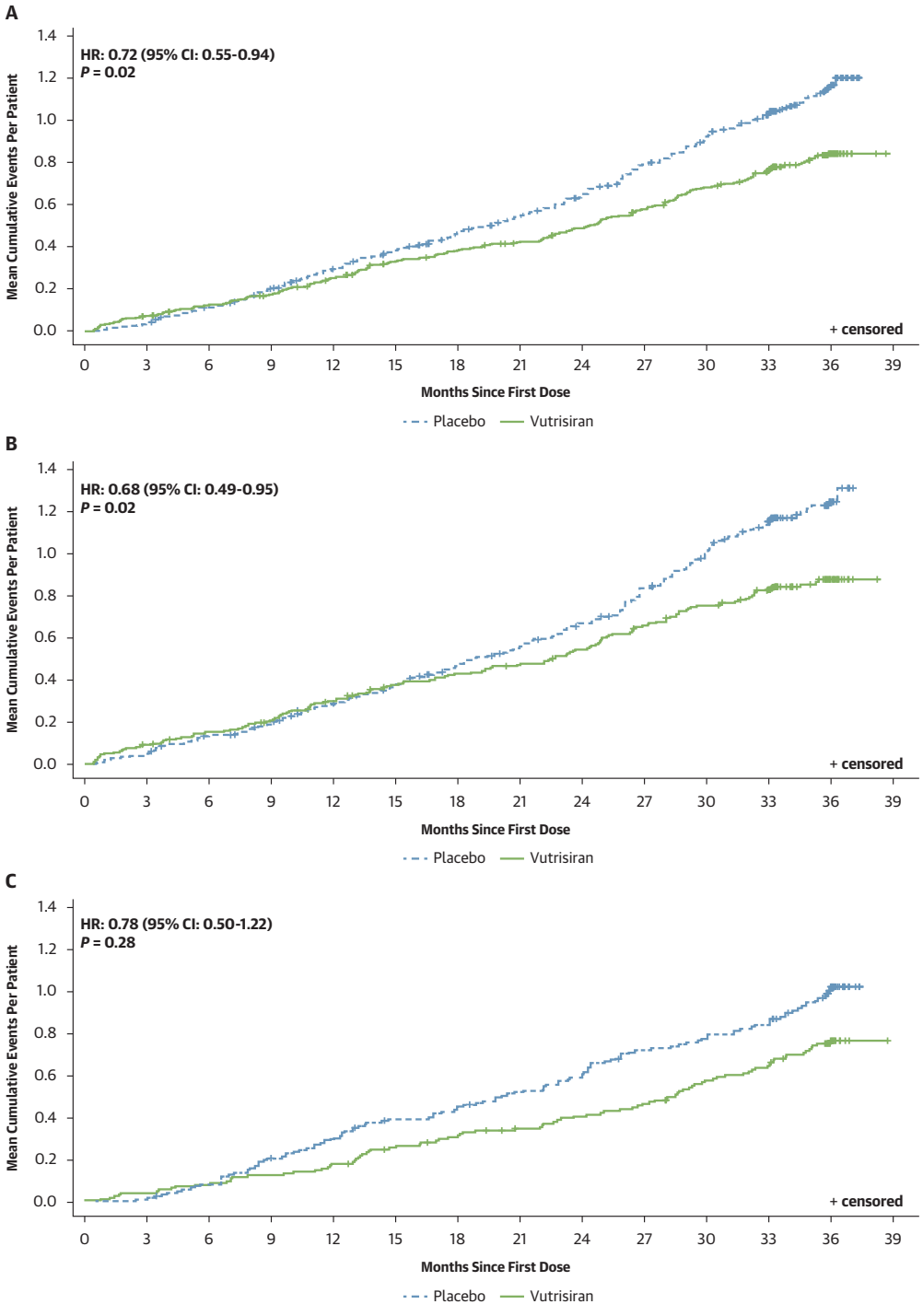
(A) Overall population, (B) monotherapy population, and (C) baseline tafamidis subgroup. All-cause mortality included heart transplantation and left ventricular assist device placement. Deaths after end of study are included in the analysis. The adjusted cumulative incidence rate of all-cause mortality was estimated using the Kaplan-Meier method with inverse probability of treatment weighting applied. Each patient's weight was assigned as the inverse of the probability of receiving the treatment, determined from a logistic regression model. The model included vutrisiran treatment as the dependent variable, and independent baseline variables consisted of baseline tafamidis use, age, transthyretin amyloidosis disease type, NYHA functional class, log-transformed N-terminal prohormone of B-type natriuretic peptide and troponin, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire–Overall Summary, and estimated glomerular filtration rate. Numbers at risk and with events are based on observed data. The HR is derived from a Cox proportional hazards model with treatment group, log-transformed baseline N-terminal prohormone of B-type natriuretic peptide, transthyretin amyloidosis type, NYHA functional class, and age group as covariates. The *P* value is from a log-rank test stratified by baseline N-terminal prohormone of B-type natriuretic peptide and baseline tafamidis use.

FIGURE 2 **Cumulative Rate of CV Mortality by Treatment During the DB Period and Up to 6 Months of the Open-Label Extension Treatment Period in the Overall Population, Monotherapy Population, and Baseline Tafamidis Subgroup**



(A) Overall population, (B) monotherapy population, and (C) baseline tafamidis subgroup. Cardiovascular mortality included heart transplantation and left ventricular assist device placement. Deaths after end of study are included in the analysis. The adjusted cumulative incidence rate of cardiovascular mortality was estimated using the Kaplan–Meier method with inverse probability of treatment weighting applied. Each patient's weight was assigned as the inverse of the probability of receiving the treatment, determined from a logistic regression model. The model included vutrisiran treatment as the dependent variable, and independent baseline variables consisted of baseline tafamidis use, age, transthyretin amyloidosis disease type, NYHA functional class, log-transformed N-terminal prohormone of B-type natriuretic peptide and troponin, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire–Overall Summary, and estimated glomerular filtration rate. Numbers at risk and with events are based on observed data. The HR is derived from a Cox proportional hazards model with treatment group, log-transformed baseline N-terminal prohormone of B-type natriuretic peptide, transthyretin amyloidosis type, NYHA functional class, and age group as covariates. The *P* value is from a log-rank test stratified by baseline N-terminal prohormone of B-type natriuretic peptide and baseline tafamidis use.

FIGURE 3 **Mean Cumulative Cardiovascular Mortality and Cardiovascular Events per Patient by Treatment During the Double-Blind Period in the Overall Population, Monotherapy Population, and Baseline Tafamidis Subgroup**



(A) Overall population, (B) monotherapy population, and (C) baseline tafamidis subgroup. Based on events as adjudicated by the Clinical Events Committee and determined by investigators. Cardiovascular mortality included heart transplantation and left ventricular assist device placement. Deaths after end of study are included in the analysis. Cardiovascular events were defined as cardiovascular hospitalizations and urgent heart failure visits. The HR was derived using the modified Andersen-Gill model stratified by baseline tafamidis use with treatment group, log-transformed N-terminal prohormone of B-type natriuretic peptide, transthyretin amyloidosis disease type, NYHA functional class, and age group as covariates.

populations (HR: 0.68; 95% CI: 0.49-0.95; $P = 0.02$) (Figure 3B). As with the ACM and CV mortality endpoints, there was a directionally consistent trend in the baseline tafamidis subgroup (HR: 0.78; 95% CI: 0.50-1.22; $P = 0.28$) (Figure 3C).

IMPACT OF VUTRISIRAN ON RECURRENT CV EVENTS. In the overall population, 34.4% of vutrisiran patients had a total of 200 recurrent CV events through 33 to 36 months, while 40.5% of placebo patients had 263 CV events, corresponding to a 27% reduction with vutrisiran (rate ratio [RR]: 0.73; 95% CI: 0.61-0.88; $P < 0.001$) (Figures 4A and 5).

Similarly, vutrisiran reduced the rate of CV events in the monotherapy population by 32% (RR: 0.68; 95% CI: 0.53-0.86; $P < 0.01$) (Figures 4B and 5). Directionally consistent results were observed in the baseline tafamidis subgroup (RR: 0.83; 95% CI: 0.61-1.11; $P = 0.21$) (Figures 4C and 5).

Analyses of CV events in prespecified subgroups in the overall and monotherapy populations were consistent, generally favoring vutrisiran over placebo with no evidence of heterogeneity (Supplemental Figure 2A). In the monotherapy population, patients in subgroups of <75 years of age, ATTRwt, and NT-proBNP ≤2,000 ng/L appeared to derive the greatest benefit, with RRs of 0.51, 0.66, and 0.52, respectively. Notably, a particularly low RR of <0.4 was reported in the small subgroup of monotherapy patients with NYHA functional class III disease at baseline (n = 27) (Supplemental Figure 2B). In the baseline tafamidis subgroup (Supplemental Figure 2C), patients in the subgroups of <75 years of age, ATTRwt, NYHA functional class I/II, and NT-proBNP ≤2,000 appeared to derive the greatest benefits from vutrisiran (Supplemental Figure 2C).

IMPACT OF VUTRISIRAN ON COMPONENTS OF CV EVENTS. Vutrisiran lowered the rate of CV hospitalizations by 25% in the overall population (RR: 0.75; 95% CI: 0.62-0.91; $P < 0.01$) and 34% in the monotherapy population (RR: 0.66; 95% CI: 0.51-0.86; $P < 0.01$) over the DB period of 33 to 36 months (Figure 5). Vutrisiran also numerically reduced the rate of CV hospitalizations compared with placebo in the baseline tafamidis subgroup, but the difference did not reach statistical significance (RR: 0.89; 95% CI: 0.65-1.21; $P = 0.46$) (Figure 5).

Similarly, vutrisiran reduced HF hospitalization rates by 33% in the overall population (RR: 0.67; 95% CI: 0.52-0.86; $P < 0.01$) and 38% in the monotherapy population (RR: 0.62; 95% CI: 0.45-0.86; $P < 0.01$) (Figure 5) with numerically lower hospitalization rates in the baseline tafamidis subgroup (RR: 0.75; 95% CI: 0.49-1.14; $P = 0.18$) (Figure 5).

Vutrisiran reduced urgent HF visits by 46% vs placebo in the overall population (RR: 0.54; 95% CI: 0.30-0.98; $P = 0.04$) (Figure 5). Numerical reductions were observed in the monotherapy population (RR: 0.76; 95% CI: 0.40-1.42; $P = 0.39$) and baseline tafamidis subgroup (RR: 0.38; 95% CI: 0.12-1.19; $P = 0.10$) (Figure 5).

Although arrhythmia hospitalization rates were directionally lower with vutrisiran, the treatment effects vs placebo were not statistically significantly in either the overall population (RR: 0.86; 95% CI: 0.53-1.41; $P = 0.55$), monotherapy population (RR: 0.77; 95% CI: 0.41-1.47; $P = 0.43$), or baseline tafamidis subgroup (RR: 0.96; 95% CI: 0.44-2.07; $P = 0.91$) (Figure 5).

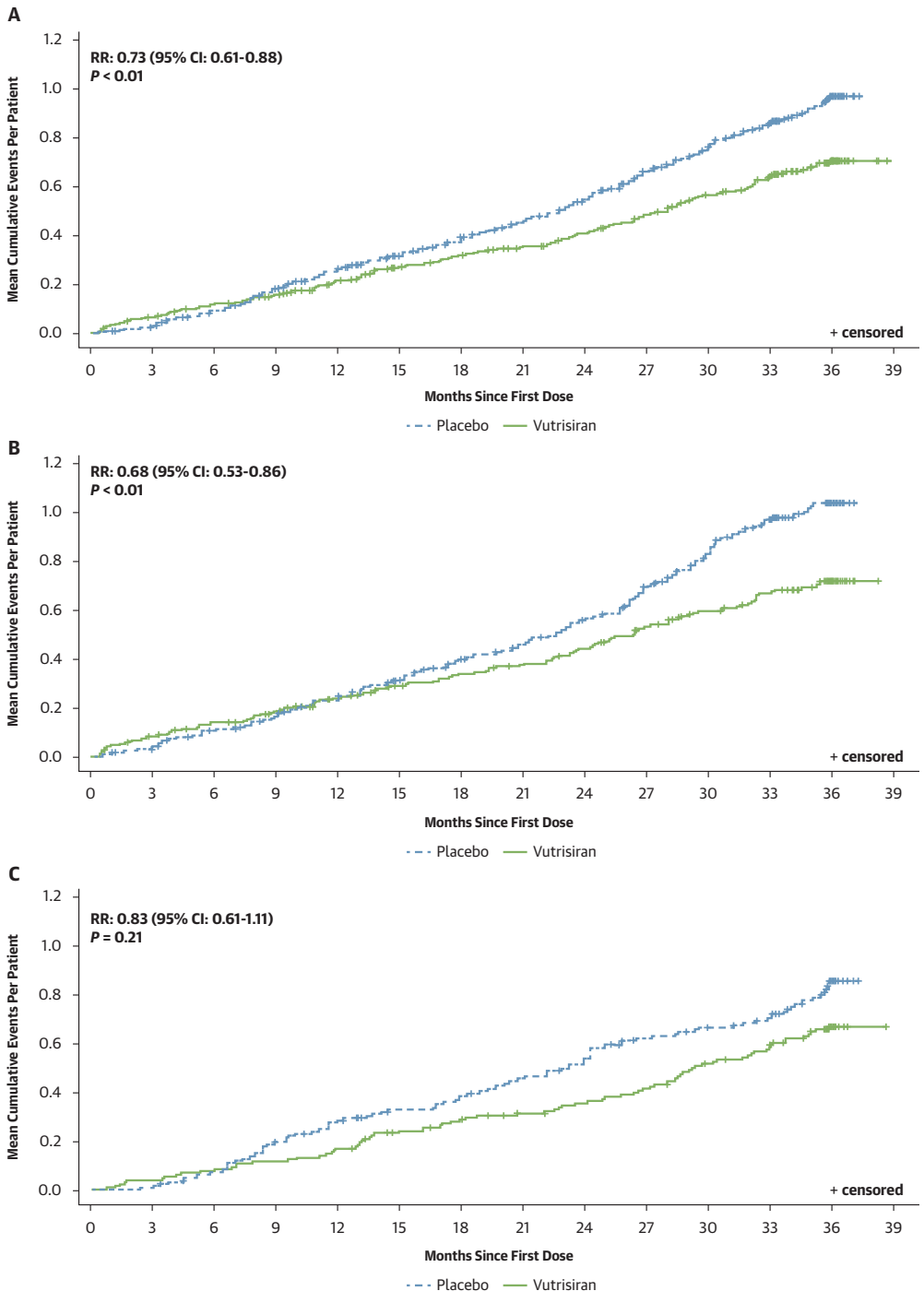
DISCUSSION

These results extend the positive findings from the HELIOS-B primary analysis[14] and provide further information regarding the impact of vutrisiran on mortality and the spectrum of CV morbidity in patients with ATTR-CM. We show that vutrisiran reduced the risk of ACM, CV mortality, CV hospitalizations, HF hospitalizations, and urgent HF visits compared with placebo in the overall population, with similar and consistent benefits in the monotherapy population.

There are 2 main takeaways from these analyses. First, the current mortality analyses, based on a later data cutoff date, were consistent with the findings from the primary analysis of HELIOS-B.[14] With additional follow-up, vutrisiran reduced the risk of the trial's prespecified secondary endpoint of ACM through 42 months by 36% and 39% in the overall and monotherapy populations, respectively, compared with 35% and 34%, respectively, in the primary analysis by Fontana et al.[14]

Based on prior studies that demonstrate a delayed benefit on mortality of ≥18 months,[14-16] a survival benefit within the first 6 months of active vutrisiran treatment in the HELIOS-B OLE period (ie, through Month 42) was not expected among patients who had received placebo in the DB period. Indeed, the results of HELIOS-B are consistent with this expectation, with the favorable impact of vutrisiran on mortality appearing to increase over time.[14] This finding is relevant, given the treatment arm of HELIOS-B already approximates age-adjusted mortality rates. The comparable timing of the onset of mortality benefit in the ATTR-ACT trial[16] and the contemporary population of HELIOS-B is striking, given that today's patients are likely to be younger, to begin treatment earlier in their disease course, and therefore, to be generally healthier.[17,18]

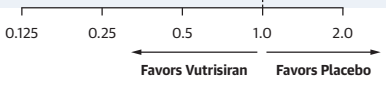
FIGURE 4 **Mean Cumulative Cardiovascular Events per Patient by Treatment During the Double-Blind Period in the Overall Population, Monotherapy Population, and Baseline Tafamidis Subgroup**



(A) Overall population, (B) monotherapy population, and (C) baseline tafamidis subgroup. Based on events as adjudicated by the Clinical Events Committee and determined by investigators. cardiovascular events defined as cardiovascular hospitalizations and urgent heart failure visits. The RR and *P* value are derived from a Poisson regression model with randomized treatment, log-transformed N-terminal prohormone of B-type natriuretic peptide, transthyretin amyloidosis disease type, NYHA functional class, age group, baseline tafamidis use, and treatment-by-baseline tafamidis use interaction as covariates and the logarithm of the follow-up time as an offset variable.

FIGURE 5 Effect of Vutrisiran vs Placebo on CV Outcomes in the Overall Population, Monotherapy Population, and Baseline Tafamidis Subgroup During the Double-Blind Period

	Patients With ≥1 Event, n (%)		Total n Events		Adjusted Events per 100 Person-Years (SE)		RR (95% CI)	*P* Value
	Vutrisiran	Placebo	Vutrisiran	Placebo	Vutrisiran	Placebo		
CV Events								
Overall Population	112 (34.4)	133 (40.5)	200	263	21.09 (7.35)	28.76 (6.49)	0.73 (0.61-0.88)	<0.01
Monotherapy Population	66 (33.7)	87 (43.7)	119	165	20.67 (9.75)	30.58 (8.28)	0.68 (0.53-0.86)	<0.01
Baseline Tafamidis Subgroup	46 (35.4)	46 (35.7)	98	81	21.09 (11.27)	25.54 (10.64)	0.83 (0.61-1.11)	0.21
CV Hospitalizations								
Overall Population	105 (32.2)	120 (36.6)	174	224	18.76 (7.81)	25.05 (6.95)	0.75 (0.62-0.91)	<0.01
Monotherapy Population	61 (31.1)	79 (39.7)	97	139	33.95 (13.59)	51.16 (11.75)	0.66 (0.51-0.86)	<0.01
Baseline Tafamidis Subgroup	44 (33.8)	41 (31.8)	77	85	27.89 (15.43)	31.32 (14.67)	0.89 (0.65-1.21)	0.46
HF Hospitalizations								
Overall Population	64 (19.6)	82 (25.0)	98	143	9.41 (10.84)	14.11 (9.33)	0.67 (0.52-0.86)	<0.01
Monotherapy Population	41 (20.9)	51 (25.6)	60	91	20.77 (17.31)	33.45 (14.58)	0.62 (0.45-0.86)	<0.01
Baseline Tafamidis Subgroup	23 (17.7)	31 (24.0)	38	52	13.77 (20.99)	18.36 (18.97)	0.75 (0.49-1.14)	0.18
Urgent HF Visits								
Overall Population	17 (5.2)	22 (6.7)	22	34	2.01 (25.17)	3.70 (18.16)	0.54 (0.30-0.98)	0.04
Monotherapy Population	13 (6.6)	14 (7.0)	18	21	2.46 (47.90)	3.25 (45.31)	0.76 (0.40-1.42)	0.39
Baseline Tafamidis Subgroup	4 (3.1)	8 (6.2)	4	13	1.40 (60.52)	3.71 (42.58)	0.38 (0.12-1.19)	0.10
Arrhythmia Hospitalizations								
Overall Population	27 (8.3)	31 (9.5)	30	34	3.42 (18.46)	3.98 (17.35)	0.86 (0.53-1.41)	0.55
Monotherapy Population	17 (8.7)	20 (10.1)	17	21	3.80 (43.37)	4.91 (40.87)	0.77 (0.41-1.47)	0.43
Baseline Tafamidis Subgroup	10 (7.7)	11 (8.5)	13	13	4.52 (38.97)	4.72 (39.16)	0.96 (0.44-2.07)	0.91



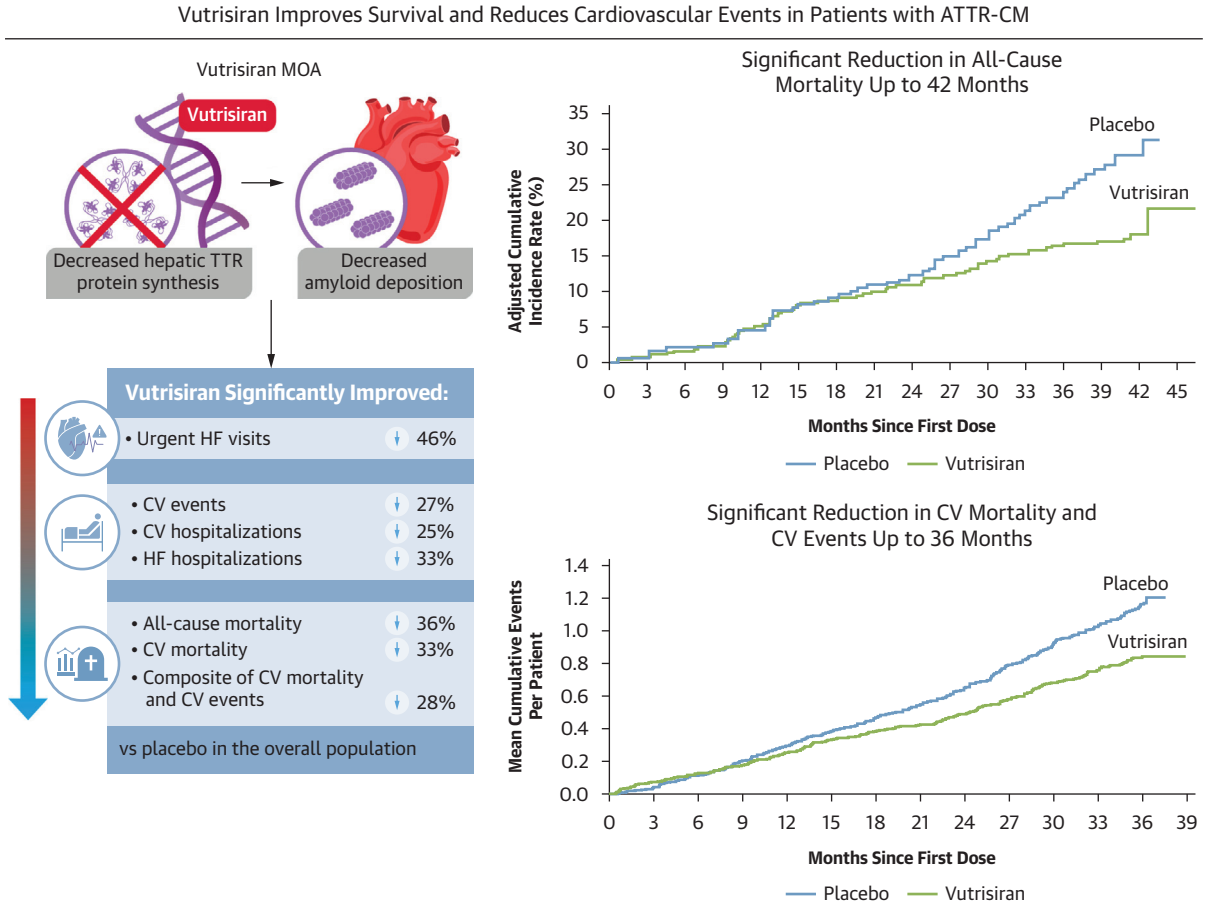
Cardiovascular (CV) events were defined as CV hospitalizations and urgent heart failure (HF) visits. CV outcomes were analyzed using Poisson regression with randomized treatment, transthyretin amyloidosis disease type, NYHA functional class, age group, and baseline N-terminal prohormone of B-type natriuretic peptide as covariates, adjusting for the event follow-up time. The overall population analysis also included baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates. Principal investigator-reported causes for arrhythmia hospitalizations included: atrial fibrillation (n = 13), complete atrioventricular block (n = 9), ventricular tachycardia (n = 9), bradycardia (n = 6), syncope (n = 5), atrial flutter (n = 3), arrhythmia (n = 2), atrial tachycardia (n = 2), atrioventricular block (n = 2), cardiac failure (n = 2), acute kidney injury, acute myocardial infarction, acute respiratory failure, cardiac arrest, chest pain, hypoxic-ischemic encephalopathy, pleural effusion, sinus node dysfunction, supraventricular tachycardia, tachycardia, and ventricular tachyarrhythmia (all n = 1). All 6 bradycardia hospitalizations were adjudicated as arrhythmia hospitalizations: 1 resulted in implantation of a cardiac resynchronization therapy defibrillator, 2 resulted in a pacemaker placement, 1 resulted in a pacemaker/implantable cardioverter-defibrillator system fitted, 1 resulted in a placement of a cardiac resynchronization therapy pacemaker, and the last 1 included no placements.

The present analysis builds on the primary analysis from Fontana et al[14] with the incorporation of additional patient follow-up through 42 months. Although both this analysis and Fontana et al[14] incorporated up to 6 months of follow-up beyond the DB period (regardless of whether the patient enrolled in the OLE), 42.4% of patients from the primary data cut had follow-up through 42 months vs 96.3% in the present analyses, thereby underestimating this specific treatment effect. Importantly, for both analyses, vital status was ascertained for >99% of all randomized patients at the data cutoff.

Second, we demonstrate the robust and consistent effect of vutrisiran across a spectrum of CV and HF outcomes, with a notably large impact on urgent HF visits. These effects were consistent in patients receiving vutrisiran monotherapy and across a wide range of subgroups. The reductions in HF events seen with an upstream targeted gene silencer, such as vutrisiran, compared with drugs such as sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, or mineralocorticoid receptor antagonists that work on the final common downstream pathway, lend credence to the merits of precision therapy in HF with preserved ejection fraction.[19-23]

The therapeutic effect of vutrisiran on ACM, CV mortality, CV hospitalizations, and HF events may be explained by its mechanism of action. Vutrisiran targets the liver, where it inhibits hepatic synthesis of both wild-type and variant TTR mRNA through RNA

CENTRAL ILLUSTRATION **Vutrisiran Reduces the Risk of Mortality and Cardiovascular Events Among Patients With Transthyretin Amyloidosis With Cardiomyopathy**



Witteles RM, et al. JACC. 2025;85(20):1959–1970.

ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; HF = heart failure; MOA = mechanism of action; TTR = transthyretin.

interference, resulting in rapid knockdown of the amyloidogenic protein before further accumulation of amyloid deposits in the heart.[11] The primary HELIOS-B analysis and findings, alongside the results reported here, indicate that rapid knockdown of amyloidogenic TTR protein with vutrisiran reduced subsequent CV and HF morbidity, and overall mortality, in patients with ATTR-CM.

Previously reported study results also suggest that these effects were associated with preservation of functional capacity and quality of life.[14] Overall, our findings provide further evidence that vutrisiran offers an effective treatment option that potentially extends and improves patients' lives by lowering both the rate of CV events and the risk of all-cause and CV mortality. The ongoing HELIOS-B open-label follow-up of up to an additional 2 years will shed further light on the longer-term benefit of early, deep, and sustained TTR knockdown with vutrisiran.

Finally, we demonstrate interesting trends for numeric reductions in patients receiving tafamidis at baseline in the risk of CV mortality and rates of CV events, CV hospitalizations, HF hospitalizations, and urgent HF visits. Most notably, within the baseline tafamidis subgroup, there appeared to be an incremental benefit of combination vutrisiran and tafamidis (vs tafamidis alone) in patients <75 years of age or with less severe HF, underscoring the need for

early intervention. Importantly, the baseline tafamidis subgroup and these post hoc subgroup analyses were not powered for statistical analysis, and therefore, these data should be interpreted with caution. However, they raise the possibility that combination therapy may be more effective than monotherapy at reducing amyloid accumulation in the heart. Further assessment of combination regimens in large, prospectively designed, studies are warranted to shed light on potential synergies.

STUDY LIMITATIONS. The results of our analyses need to be interpreted within the limitations of the overall HELIOS-B trial. The HELIOS-B study population was at lower risk for CV events than prior studies because of the study inclusion criteria and improvements in the diagnosis and management of ATTR-CM.[17,18,24] This is especially relevant given the significant impact of sodium-glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists on HF hospitalization and urgent HF visits.[21,22,25] For context, the use of sodium-glucose cotransporter 2 inhibitors was >10-fold higher in HELIOS-B compared with a contemporaneous stabilizer trial. Although the subgroup analyses demonstrate some interesting observations, these were performed post hoc, study randomization was not stratified by all subgroup parameters, and some groups consisted of small patient numbers. Finally, because the HELIOS-B study was not designed to evaluate the efficacy of combination therapy, it cannot definitively answer the question of whether vutrisiran in combination with tafamidis is superior to tafamidis alone, caused by the limited number of patients in the respective study groups.

CONCLUSIONS

In these prespecified and post hoc analyses of data from the phase III HELIOS-B trial in patients with ATTR-CM, treatment with vutrisiran consistently reduced risk of all-cause and CV mortality, and rates of CV and HF hospitalizations and urgent HF visits, compared with placebo (**Central Illustration**). These findings are consistent with the primary results of the HELIOS-B trial and provide further evidence of the beneficial effects of vutrisiran in this patient population.

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