ORIGINAL ARTICLE

Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

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ABSTRACT

BACKGROUND

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, fatal disease. Vutrisiran, a subcutaneously administered RNA interference therapeutic agent, inhibits the production of hepatic transthyretin.

METHODS

In this double-blind, randomized trial, we assigned patients with ATTR-CM in a 1:1 ratio to receive vutrisiran (25 mg) or placebo every 12 weeks for up to 36 months. The primary end point was a composite of death from any cause and recurrent cardiovascular events. Secondary end points included death from any cause, the change from baseline in the distance covered on the 6-minute walk test, and the change from baseline in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score. The efficacy end points were assessed in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline) and were tested hierarchically.

RESULTS

A total of 655 patients underwent randomization; 326 were assigned to receive vutrisiran and 329 to receive placebo. Vutrisiran treatment led to a lower risk of death from any cause and recurrent cardiovascular events than placebo (hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; P=0.01; hazard ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; P=0.02) and a lower risk of death from any cause through 42 months (hazard ratio in the overall population, 0.65; 95% CI, 0.46 to 0.90; P=0.01). Among the patients in the overall population, 125 in the vutrisiran group and 159 in the placebo group had at least one primary end-point event. In the overall population, treatment with vutrisiran resulted in less of a decline in the distance covered on the 6-minute walk test than placebo (least-squares mean difference, 26.5 m; 95% CI, 13.4 to 39.6; P<0.001) and less of a decline in the KCCQ-OS score (least-squares mean difference, 5.8 points; 95% CI, 2.4 to 9.2; P<0.001). Similar benefits were observed in the monotherapy population. The incidence of adverse events was similar in the two groups (99% in the vutrisiran group and 98% in the placebo group); serious adverse events occurred in 62% of the patients in the vutrisiran group and in 67% of those in the placebo group.

CONCLUSIONS

Among patients with ATTR-CM, treatment with vutrisiran led to a lower risk of death from any cause and cardiovascular events than placebo and preserved functional capacity and quality of life. (Funded by Alnylam Pharmaceuticals; HELIOS-B ClinicalTrials.gov number, NCT04153149.)

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*A complete list of the HELIOS-B trial investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Transthyretin amyloidosis, also called ATTR amyloidosis, is a progressive, systemic, and fatal disease caused by misfolded transthyretin protein that accumulates as amyloid fibrils in multiple organs, commonly leading to cardiomyopathy and polyneuropathy.[1-4] ATTR amyloidosis with cardiomyopathy (ATTR-CM) occurs as a result of inherited *TTR* gene variants (hereditary, or variant, ATTR amyloidosis), often with a mixed phenotype that also includes polyneuropathy, or it occurs with aging in the absence of predisposing *TTR* variants (wild-type ATTR amyloidosis).[2,3,5-8]

In ATTR-CM, extracellular deposition of transthyretin (TTR) amyloid in the heart causes an infiltrative cardiomyopathy, leading to heart failure and arrhythmias.[8,9] Patients with ATTR-CM have progressively debilitating symptoms and high morbidity and mortality, with a median survival of 2 to 6 years after diagnosis.[3,8,10] Current treatment options remain limited. The TTR tetramer stabilizer tafamidis is the only approved agent for the treatment of ATTR-CM. In the ATTR-ACT trial, tafamidis was associated with a reduction in all-cause mortality and cardiovascular-related hospitalizations over 30 months, as compared with placebo; however, mortality remained high and quality of life and functional capacity continued to decline.[11] Similarly, declines in quality of life and functional capacity have been shown in a trial of another TTR tetramer stabilizer.[12]

Vutrisiran is a subcutaneously administered RNA interference therapeutic agent that inhibits hepatic synthesis of both wild-type and variant *TTR* messenger RNA at their source, resulting in rapid knockdown of the pathogenic protein before amyloid-causing monomers can form.[13-15] The stabilization chemistry of vutrisiran includes phosphonothioate linkages at the 5′ end of its small interfering RNA component and a triantennary *N*-acetylgalactosamine ligand that binds to the asialoglycoprotein receptor, which is expressed on the surface of hepatocytes. This and other modifications (increased 2′-*O*-methyl nucleotide content) enhance potency as compared with earlier RNA interference therapeutic agents and allow for administration once every 3 months.[13] Vutrisiran is currently approved for the treatment of hereditary ATTR amyloidosis with polyneuropathy on the basis of results from the phase 3 HELIOS-A trial, which showed significant improvement across multiple disease-relevant outcomes among patients who received vutrisiran, as compared with those in an external placebo group.[14,15] Results from an analysis of exploratory cardiac end points in the HELIOS-A trial indicated a potential benefit of vutrisiran with respect to cardiac manifestations (N-terminal pro–B-type natriuretic peptide [NT-proBNP] level and echocardiographic and technetium-99m scintigraphy measures) in patients with variant ATTR amyloidosis with polyneuropathy; these findings support the hypothesis that a reduction in the level of amyloidogenic TTR protein could have therapeutic benefit in patients with ATTR-CM.[16] We present here the results of the primary analysis of efficacy and safety data from the phase 3 HELIOS-B trial, which assessed vutrisiran in patients with variant or wild-type ATTR-CM.

METHODS

TRIAL OVERSIGHT

The HELIOS-B trial, an international, phase 3, multicenter, double-blind, randomized, placebo-controlled trial, was conducted in accordance with all applicable regulatory requirements, the International Council for Harmonisation 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 trial protocol and amendments (available with the full text of this article at NEJM.org). All the patients provided written informed consent. Alnylam Pharmaceuticals (the sponsor) designed the trial in collaboration with the principal investigators. The trial investigators collected the data, which were analyzed by the sponsor and interpreted jointly by the sponsor and the authors. The authors prepared the first draft of the manuscript with editorial assistance from Adelphi Communications, funded by Alnylam Pharmaceuticals. All the authors participated in the interpretation of the data. The authors who were employed by the sponsor had direct access to the data and vouch for the accuracy and completeness of the data and analyses. All the authors vouch for the fidelity of the trial to the protocol and contributed to the critical revision of the manuscript.

PATIENTS

Key inclusion criteria included an age of 18 to 85 years; a diagnosis of ATTR-CM (either variant or wild-type ATTR amyloidosis), defined as the presence of TTR amyloid deposits in a tissue-biopsy specimen or fulfillment of validated scintigraphy-based diagnostic criteria for ATTR-CM in the absence of monoclonal gammopathy[17,18]; and evidence of cardiac involvement as assessed with transthoracic echocardiography, with an end-diastolic interventricular septal wall thickness exceeding 12 mm. A clinical history of heart failure was required, with at least one previous hospitalization for heart failure or clinical evidence of heart failure, with signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment. At baseline, patients were either receiving tafamidis for ATTR-CM at the dose approved within their country or were not receiving tafamidis, with no active plan to start tafamidis during the first 12 months after randomization. Additional inclusion criteria were an NT-proBNP level of more than 300 pg per milliliter and less than 8500 pg per milliliter (or >600 pg per milliliter and <8500 pg per milliliter for patients with atrial fibrillation) and the ability to cover a distance of at least 150 m on the 6-minute walk test.

Key exclusion criteria were a New York Heart Association (NYHA) class of IV, or a NYHA class of III with a National Amyloidosis Centre ATTR stage of 3 (defined as an NT-proBNP level of >3000 pg per milliliter and an estimated glomerular filtration rate [eGFR] of <45 ml per minute per 1.73 m^2 of body-surface area)[10]; a polyneuropathy disability score of IIIa, IIIb, or IV (indicating that a cane or stick is needed to walk or that the patient is wheelchair-bound); cardiomyopathy that was not associated with ATTR amyloidosis; and an eGFR of less than 30 ml per minute per 1.73 m^2. Full inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

Patients were randomly assigned in a 1:1 ratio to receive vutrisiran (25 mg) or placebo subcutaneously every 12 weeks for up to 36 months. The sequence and chemical modifications of vutrisiran have been described previously.[19] Randomization was stratified according to tafamidis use at baseline (yes vs. no), ATTR amyloidosis disease type (variant vs. wild type), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs. all others). Patients who were not receiving tafamidis at baseline could begin receiving it after enrollment if the investigator considered it to be necessary. All the patients were instructed to take the recommended daily allowance of vitamin A, owing to concerns of potential disruption of vitamin A transport (transthyretin is a vitamin A [retinol] carrier). At the end of the double-blind period (a variable follow-up of 33 to 36 months), patients were eligible to be enrolled in the ongoing open-label extension period for up to 24 months. Additional trial information is provided in the Supplementary Appendix.

END POINTS

All the end points were assessed separately in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline), resulting in 10 prespecified end points for analysis (2 primary and 8 secondary). The primary end point was a composite of death from any cause and recurrent cardiovascular events (defined as hospitalizations for cardiovascular causes or urgent visits for heart failure) during the double-blind period (up to 36 months). Death from any cause through 42 months was included as a separate secondary end point; this time point was selected to allow more events to be included in the analysis and to improve the precision of the estimate of treatment effect on mortality. Because previous studies involving patients with ATTR-CM suggested that there would be a delayed effect on mortality,[11,12,20] a mortality benefit within the first 6 months was not expected among patients who had been assigned to receive placebo and switched to vutrisiran in the open-label extension period.

Other secondary end points were the change from baseline at 30 months in functional capacity, as assessed with the 6-minute walk test; patient-reported health status and health-related quality of life, as assessed with the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) (scores range from 0 to 100, with higher scores indicating better quality of life[21]); and severity of clinical heart failure symptoms,

as determined by NYHA class. Multiple studies in diverse causes of heart failure have established that a change of 5 points in the KCCQ-OS score is clinically significant.[22] The time to a first cardiovascular event or death from any cause was assessed as an exploratory end point. Safety was monitored throughout the trial by an independent data monitoring committee. Safety assessments included adverse events, clinical laboratory measures, and vital signs. Additional details regarding end-point assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 654 patients (with 60% of the patients representing the monotherapy population) would give the trial approximately 80% power to detect a between-group difference in the composite event rate of death from any cause and recurrent cardiovascular events in both the overall and monotherapy populations. Assumptions for the sample-size calculations are provided in the Supplementary Appendix.

The primary end points were analyzed with the use of a modified Andersen–Gill model with a robust variance estimator (Lin–Wei–Yang–Ying [LWYY] model),[23] with treatment group, ATTR amyloidosis disease type (variant vs. wild type), NYHA class (I or II vs. III), age group (<75 vs. ≥75 years), and log-transformed baseline NT-proBNP level included as covariates; the model was also stratified according to tafamidis use at baseline (yes vs. no) for the analysis of the primary end point in the overall population. Heart transplantation or implantation of a left ventricular assist device, or both, were treated as deaths in the analyses that included death from any cause. Sensitivity analyses of the primary end point and the secondary end point of death from any cause were also performed, as described in the Supplementary Appendix.

The overall type I error rate for the primary and secondary end points was controlled at a two-sided 0.05 significance level with the use of a truncated Hochberg-based gatekeeping procedure.[24,25] The efficacy end points were assessed in the overall population and in the monotherapy population, resulting in 10 prespecified end points (2 primary, 8 secondary) that were tested hierarchically. No adjustment for multiplicity was made for the exploratory end points. Additional details regarding the statistical methods are described in the statistical analysis plan, available with the protocol.

RESULTS

PATIENTS

From December 2019 through August 2021, a total of 655 patients were enrolled at 87 sites in 26 countries and were randomly assigned to receive vutrisiran (326 patients) or placebo (329 patients) (Fig. S1 in the Supplementary Appendix). A total of 196 of the 326 patients (60%) in the vutrisiran group and 199 of the 329 patients (60%) in the placebo group were not taking tafamidis at baseline; these patients made up the monotherapy population. Among the patients in the monotherapy population, 44 of 196 (22%) in the vutrisiran group and 41 of 199 (21%) in the placebo group initiated tafamidis after randomization.

The demographic and clinical characteristics of the patients at baseline were similar in the two groups, except that among the patients in the monotherapy population, the NT-proBNP and troponin I levels were higher in the vutrisiran group than in the placebo group (Table 1 and Table S1). Baseline data were generally representative of the global population of patients with ATTR-CM (Table 1 and Table S2). In the overall population, the median age was 77 years, and the majority of the patients were men (93%), had wild-type ATTR amyloidosis (88%), and had NYHA class II heart failure (78%). Among the 76 patients with variant ATTR amyloidosis, there were 13 different pathogenic *TTR* variants; 49 patients (64%) had the V122I variant, which was the most common (Table S3). The demographic and clinical characteristics of the patients in the monotherapy population at baseline did not differ substantially from those in the overall population (Table 1). Details regarding receipt of tafamidis, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and oral diuretic agents after randomization are provided in Table S4.

PRIMARY END POINT

In both populations, treatment with vutrisiran led to a lower risk of death from any cause and recurrent cardiovascular events than placebo (hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; P=0.01; hazard

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Overall Population		Monotherapy Population	
	Vutrisiran (N=326)	Placebo (N=328)	Vutrisiran (N=196)	Placebo (N=199)
Median age at randomization (range) — yr	77.0 (45–85)	76.0 (46–85)	77.5 (46–85)	76.0 (53–85)
Male sex — no. (%)	299 (92)	306 (93)	178 (91)	183 (92)
Race — no. (%)†				
White	277 (85)	275 (84)	169 (86)	169 (85)
Asian	18 (6)	19 (6)	12 (6)	15 (8)
Black	23 (7)	24 (7)	10 (5)	11 (6)
Other or not reported	8 (2)	10 (3)	5 (3)	4 (2)
Wild-type ATTR — no. (%)	289 (89)	289 (88)	173 (88)	174 (87)
Median time since diagnosis of ATTR (range) — yr	0.86 (0–11.1)	1.03 (0–10.8)	0.50 (0–8.3)	0.63 (0–6.2)
Tafamidis use at baseline — no. (%)	130 (40)	129 (39)	—	—
Median duration of tafamidis use before start of trial (range) — mo	9.2 (1.1–65.3)	11.3 (1.1–65.5)	—	—
NYHA class — no. (%)				
I	49 (15)	35 (11)	15 (8)	12 (6)
II	250 (77)	258 (79)	172 (88)	169 (85)
III	27 (8)	35 (11)	9 (5)	18 (9)
NAC stage — no. (%)‡				
1	208 (64)	229 (70)	113 (58)	138 (69)
2	100 (31)	87 (27)	68 (35)	55 (28)
3	18 (6)	12 (4)	15 (8)	6 (3)
Laboratory values				
Median NT-proBNP level (IQR) — pg/ml	2021 (1138–3312)	1801 (1042–3082)	2402 (1322–3868)	1865 (1067–3099)
Median high-sensitivity troponin I level (IQR) — 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)

* Additional baseline characteristics are provided in Table S1 in the Supplementary Appendix. The monotherapy population was defined as the patients who were not receiving tafamidis at baseline. Percentages may not total 100 because of rounding. ATTR denotes transthyretin amyloidosis, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patients.
‡ National Amyloidosis Centre (NAC) stages are determined on the basis of the levels of the serum biomarkers NT-proBNP and estimated glomerular filtration rate. Additional details are provided in the Supplementary Appendix.

ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; P=0.02) (Table 2). This benefit was broadly consistent across both components of the primary end point. Among the patients in the overall population, 125 (38%) in the vutrisiran group and 159 (48%) in the placebo group had at least one primary end-point event. Among the patients in the monotherapy population, 76 (39%) in the vutrisiran group and 105 (53%) in the placebo group had at least one primary end-point event. The results of prespecified win ratio sensitivity analyses in both populations were consistent with those of the primary analyses (see the Supplementary Appendix). Kaplan–Meier plots illustrating the time to a first cardiovascular event or death from any cause showed that the curves for vutrisiran and placebo diverged after approximately 6 months (Fig. 1A and 1B), although a formal test showed no violation of the proportional-hazards assumption (see the Supplementary Appendix). Similar effects were observed with respect to death from any cause and recurrent

Table 2. Primary and Secondary End Points.*

End Point	Overall Population			Monotherapy Population		
	Vutrisiran (N=326)	Placebo (N=328)	Measure of Effect	Vutrisiran (N=196)	Placebo (N=199)	Measure of Effect
Primary end point						
Death from any cause and recurrent cardiovascular events			Hazard ratio, 0.72 (95% CI, 0.56 to 0.93) P=0.01			Hazard ratio, 0.67 (95% CI, 0.49 to 0.93) P=0.02
Death from any cause			Hazard ratio, 0.69 (95% CI, 0.49 to 0.98) P=0.04			Hazard ratio, 0.71 (95% CI, 0.47 to 1.06) P=0.12
Recurrent cardiovascular events			Relative rate ratio, 0.73 (95% CI, 0.61 to 0.88) P=0.001			Relative rate ratio, 0.68 (95% CI, 0.53 to 0.86) P=0.001
Patients with at least one event — no. (%)	125 (38)	159 (48)		76 (39)	105 (53)	
Death from any cause†	51 (16)	69 (21)		36 (18)	46 (23)	
Recurrent cardiovascular events	112 (34)	133 (41)		66 (34)	87 (44)	
Secondary end points						
Death from any cause through 42 mo			Hazard ratio, 0.65 (95% CI, 0.46 to 0.90) P=0.01			Hazard ratio, 0.66 (95% CI, 0.44 to 0.97) P=0.045
Patients who died — no. (%)	60 (18)	85 (26)		43 (22)	58 (29)	
Least-squares mean change from baseline at 30 mo in distance covered on the 6-min walk test — m‡	−45.4 (95% CI, −54.5 to −36.3)	−71.9 (95% CI, −81.3 to −62.4)	Difference, 26.5 (95% CI, 13.4 to 39.6) P<0.001§	−59.7 (95% CI, −72.7 to −46.7)	−91.8 (95% CI, −104.4 to −79.2)	Difference, 32.1 (95% CI, 14.0 to 50.2) P<0.001§
Least-squares mean change from baseline in KCCQ-OS score at 30 mo — points¶	−9.7 (95% CI, −12.0 to −7.4)	−15.5 (95% CI, −18.0 to −13.0)	Difference, 5.8 (95% CI, 2.4 to 9.2) P<0.001§	−10.8 (95% CI, −14.1 to −7.5)	−19.5 (95% CI, −22.9 to −16.1)	Difference, 8.7 (95% CI, 4.0 to 13.4) P<0.001§
Improved or stable NYHA class at 30 mo — %	68	61	Difference, 8.7 (95% CI, 1.3 to 16.1) P=0.02‖	66	56	Difference, 12.5 (95% CI, 2.7 to 22.2) P=0.01‖

* For the analyses that included death from any cause, heart transplantation and implantation of a left ventricular assist device were treated as deaths. The hazard ratio for the primary end point was calculated with the use of the LWYY model. Hazard ratios for death from any cause were calculated with the use of the Cox proportional-hazards model. The relative rate ratios for recurrent cardiovascular events were generated with the use of a Poisson regression model.

† Three patients in the vutrisiran group and four in the placebo group had a heart transplantation. No patients had implantation of a left ventricular assist device.

‡ For the 6-minute walk test, a farther distance walked indicates better function. Assessments that were missing because of death, 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 from resampling of the worst 10% of observed changes.

§ The difference is the least-squares mean difference.

¶ Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) scores range from 0 to 100, with higher scores indicating better quality of life. For assessments that were missing because of death, heart transplantation, or implantation of a left ventricular assist device, data were imputed from resampling of the worst 10% of observed changes.

‖ The difference is the adjusted difference in percentage points.

cardiovascular events across all prespecified subgroups (Fig. 1C and 1D).

SECONDARY END POINTS

Treatment with vutrisiran resulted in a lower risk of death from any cause through 42 months than placebo (hazard ratio in the overall population, 0.65; 95% CI, 0.46 to 0.90; P=0.01; hazard ratio in the monotherapy population, 0.66; 95% CI, 0.44 to 0.97; P=0.045) (Fig. 2A and 2B). Among the patients in the overall population, through 42 months of follow-up, 60 patients (18%) in the vutrisiran group and 85 (26%) in the placebo group had died from any cause. In both populations, similar effects were observed with respect to death from any cause across all prespecified subgroups (Fig. 2C and 2D). A sensitivity analysis that used a weighted log-rank test, the Fleming–Harrington (1,1) test, showed similar results (see the Supplementary Appendix).

In the overall population, at 30 months, the least-squares mean change from baseline in the distance covered on the 6-minute walk test was −45.4 m in the vutrisiran group and −71.9 m in the placebo group (least-squares mean difference, 26.5 m; 95% CI, 13.4 to 39.6; P<0.001) (Table 2). In the overall population, at 30 months, the least-squares mean change from baseline in the KCCQ-OS score was −9.7 points in the vutrisiran group and −15.5 points in the placebo group (least-squares mean difference, 5.8 points; 95% CI, 2.4 to 9.2; P<0.001) (Table 2). At 30 months, in the overall population, 68% of the patients in the vutrisiran group and 61% in the placebo group had improvement or no change in NYHA class (least-squares mean difference, 8.7 percentage points; 95% CI, 1.3 to 16.1; P=0.02). Similar benefits were observed in the monotherapy population for all secondary end points (Table 2). Additional data regarding results for the distance covered on the 6-minute walk test and the KCCQ-OS score, including the median scores over time, are available in Figure S6.

EXPLORATORY END POINTS AND PHARMACODYNAMICS

The results of the analyses of the exploratory end points of NT-proBNP level, troponin I level, peak longitudinal strain, and quality of life as assessed with the EuroQol 5-Dimension 5-Level questionnaire are provided in Table S5. A rapid and sustained reduction in serum TTR levels was observed with vutrisiran. The mean trough percent reduction was 81.0% (95% CI, 79.0 to 83.0) at 30 months in the overall population (Fig. S7).

SAFETY

In the overall population, the incidence of adverse events was similar in the two groups; 322 patients (99%) in the vutrisiran group and 323 patients (98%) in the placebo group had at least one adverse event. Serious adverse events occurred in 201 patients (62%) in the vutrisiran group and in 220 patients (67%) in the placebo group. Adverse events leading to discontinuation of vutrisiran or placebo occurred in 10 patients (3%) and 13 patients (4%), respectively. Information about the most common adverse events, severe adverse events, cardiac adverse events, and adverse events leading to death is provided in Table S6. No clinically relevant changes in laboratory measures (including hematologic measures, blood-chemistry values, liver-function tests, and renal-function tests), vital signs, or electrocardiograms were observed in either group.

DISCUSSION

In this randomized, placebo-controlled trial involving patients with ATTR-CM, treatment with vutrisiran resulted in a lower risk of death from any cause and recurrent cardiovascular events than placebo in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline). Similar effects were seen in all prespecified subgroups. Preservation of functional capacity and quality of life were better with vutrisiran than with placebo, and vutrisiran prevented the worsening of heart failure symptoms. Although the least-squares mean distance covered on the 6-minute walk test and the KCCQ-OS score declined in both groups, the median changes reflecting the observed trajectory for surviving patients showed relative stability in the vutrisiran group. These benefits were observed in both the overall population and the monotherapy population and are particularly meaningful for patients whose quality of life and functional capacity are impaired by this disease. These data suggest that reducing levels of the circulating amyloidogenic TTR protein with vutrisiran in patients with ATTR-CM leads to a reduction in the risk of death from any cause and cardiovascular events.

Figure 1 (facing page). Death from Any Cause and Recurrent Cardiovascular Events.

The primary end point was a composite of death from any cause and recurrent cardiovascular events (defined as hospitalizations for cardiovascular causes or urgent visits for heart failure). Panels A and B show the time to a first event (death from any cause or recurrent cardiovascular event) in the overall population and the monotherapy population, respectively. The monotherapy population was defined as the patients who were not receiving tafamidis at baseline. The Kaplan–Meier curves were adjusted according to disease severity characteristics at baseline with the use of the inverse probability of treatment weighting method. The unadjusted Kaplan–Meier curves are shown in Figures S2 and S3. Tick marks indicate censored data. Panels C and D show the subgroup analyses of death from any cause and recurrent cardiovascular events in the overall population and the monotherapy population, respectively. ATTR denotes transthyretin amyloidosis, NYHA New York Heart Association, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

In a previous trial (HELIOS-A) of vutrisiran that involved patients with variant ATTR amyloidosis with polyneuropathy, treatment with vutrisiran improved the change from baseline in the modified Neuropathy Impairment Score+7 at 9 months; and the outcomes with respect to all secondary efficacy end points that assessed multiple disease-relevant variables were better among the patients who received vutrisiran than among those in an external placebo group.[14] The results of the HELIOS-B trial extend the favorable effects of TTR lowering by RNA interference, initially seen in patients with polyneuropathy due to variant ATTR amyloidosis, to patients with cardiomyopathy due to either wild-type or variant ATTR amyloidosis.

The HELIOS-B trial was designed to include a patient group that is representative of contemporary ATTR-CM populations. Over the past decade, advances in noninvasive imaging techniques have led to a higher proportion of patients receiving a diagnosis earlier in their disease process, with a less severe clinical phenotype and better prognosis.[26] Evidence for this evolution in the population of patients with ATTR-CM can be seen by comparing the baseline characteristics in phase 3 clinical trials over time. For example, patients in the HELIOS-B trial generally had less disease severity at baseline (according to the distance covered on the 6-minute walk test, KCCQ-OS score, NT-proBNP level, troponin I level, and NHYA class) than those enrolled in the ATTR-ACT trial.[25] Despite a healthier patient population at the outset and substantial concurrent tafamidis and SGLT2 inhibitor use (40% of the patients were taking tafamidis at baseline, 22% of the patients in the monotherapy population started tafamidis during the trial, and 33% of the patients in the overall population started therapy with an SGLT2 inhibitor during the trial), vutrisiran, as compared with placebo, was associated with a hazard ratio of 0.65 for death from any cause through 42 months in the overall population. These data also suggest that vutrisiran may provide benefit to patients in relatively early stages of disease, when functional capacity and quality of life may be more effectively preserved.

In the HELIOS-B trial, the incidence of adverse events among patients in the vutrisiran group was similar to or lower than that among the patients in the placebo group, a finding that is consistent with the incidence of adverse events in the HELIOS-A trial.[14] No new safety signs were identified.

Several limitations should be considered when interpreting the trial results. Tafamidis was an allowed background therapy at baseline to which patients were not randomly assigned; therefore, this trial does not allow for a randomized comparison of vutrisiran alone with tafamidis alone. In addition, although 40% of the patients were taking tafamidis at baseline, the trial was not powered to show statistical significance within this subgroup. The main limitation of the primary analysis method (LWYY model) is that it treats recurrent cardiovascular events and death equally. However, additional analyses — including analyses of the individual components of the primary end point, win ratio analyses, and time-to-first-event analyses — all yielded consistent results. The majority of the patients were men and were White, but this was expected, given the reported demographic characteristics of ATTR-CM patient populations. The trial also included a low proportion of patients with variant ATTR amyloidosis, a result that most likely reflects the global preponderance of wild-type ATTR-CM relative to variant ATTR-CM.

In patients with ATTR-CM, treatment with vutrisiran resulted in a lower risk of death from any cause and recurrent cardiovascular events than placebo. Vutrisiran also preserved functional capacity and quality of life and prevented worsening

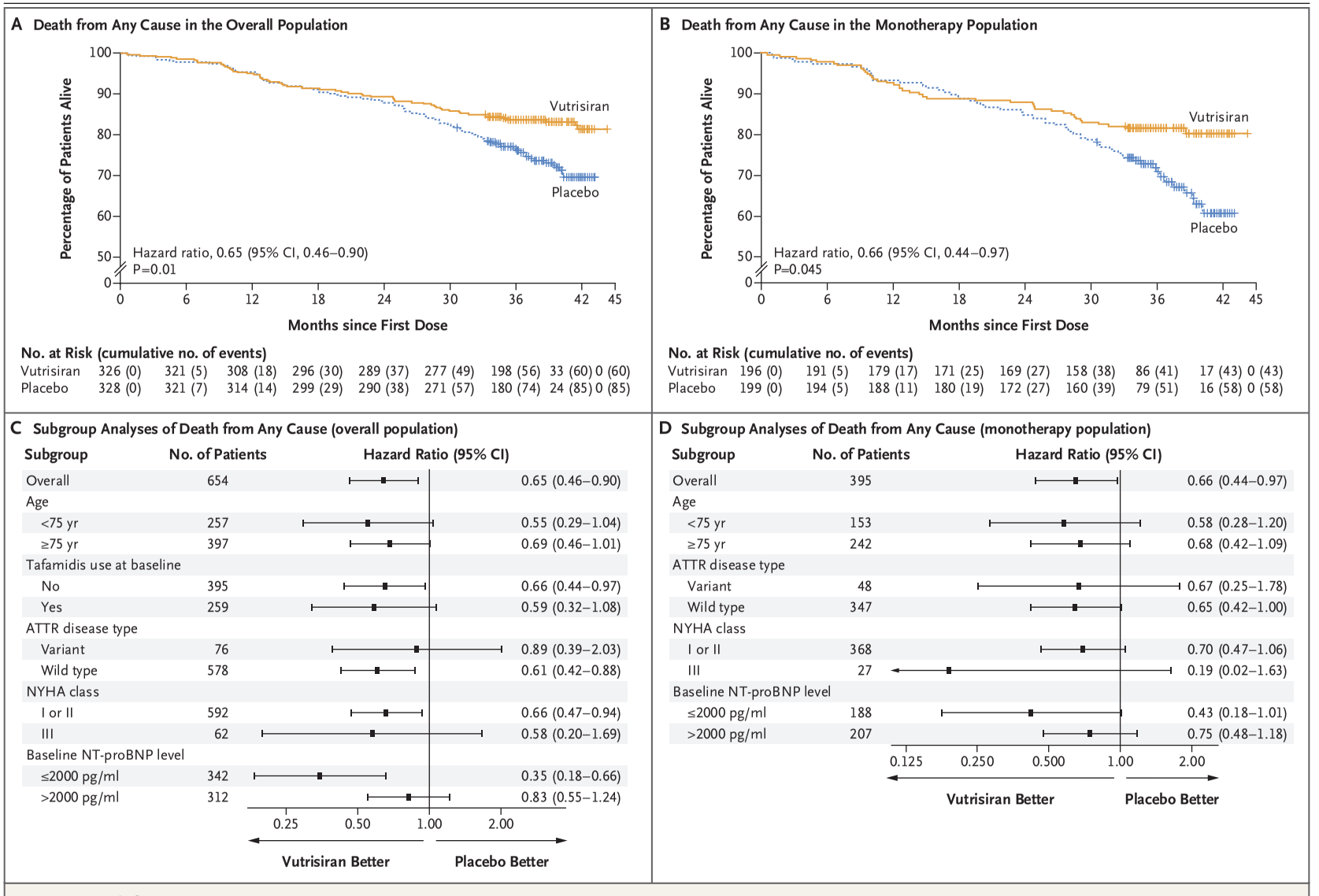

Figure 2. Death from Any Cause.

Panels A and B show death from any cause through 42 months in the overall population and the monotherapy population, respectively. The Kaplan–Meier curves were adjusted according to disease severity characteristics at baseline with the use of the inverse probability of treatment weighting method. The unadjusted Kaplan–Meier curves are shown in Figures S4 and S5. Tick marks indicate censored data. Panels C and D show subgroup analyses of death from any cause through 42 months in the overall population and the monotherapy population, respectively.

of heart failure symptoms. These effects were consistent across all prespecified subgroups, including patients who were receiving background tafamidis. Collectively, these data suggest that rapid knockdown of TTR by vutrisiran reduces morbidity and mortality among patients with ATTR-CM.

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APPENDIX

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