Vutrisiran: Survival and Mortality

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. All-cause mortality and survival were not evaluated as endpoints in HELIOS-A.[1]
- HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM including both hATTR and wtATTR.[2]
  - Vutrisiran reduced all-cause mortality and recurrent CV events compared with placebo [HR 0.72 (95% CI 0.56, 0.93; P=0.01)] in the overall population and in the monotherapy population [(HR 0.67 (95% CI 0.49, 0.93; P=0.02)].[2]
  - Vutrisiran reduced all-cause mortality through 42 months compared with placebo in the overall population [HR 0.65 (95% CI 0.46, 0.90), P=0.01] and monotherapy population [HR 0.66 (95% CI 0.44, 0.97), P=0.045].[2]
  - In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs were mild or moderate. Cardiac AEs occurred at similar or lower rates with vutrisiran compared to placebo.[3]

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HELIOS-A STUDY

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study (NCT01960348) as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[1]

All-cause mortality and survival were not evaluated as endpoints in HELIOS-A. Death was evaluated as an adverse event and was reported in 2 patients (1.6%) in the vutrisiran arm and 6 patients (7.8%) in the external placebo arm. In the vutrisiran arm, one death was due to COVID-19 pneumonia, and the other death was due to an iliac artery occlusion. Neither death was considered related to vutrisiran therapy.[1,4]

HELIOS-B STUDY

Study Design

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. At the end of the double-blind period (a variable follow-up of 33 or 36 months), patients were eligible to be enrolled in the ongoing OLE period for up to 24 months.[2]

Study Endpoints

The primary endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) during the double-blind exposure period (up to 36 months), which was analyzed using a modified Andersen-Gill model with a robust variance estimator (LWYY model). The primary endpoint was analyzed in both the overall study population and the vutrisiran monotherapy population (patients who were not on tafamidis at baseline). These endpoints were tested in parallel. Heart transplantation or implantation of a left ventricular assist device, or both, were treated as deaths from any cause. Sensitivity analysis was performed using a Mantel-Haenszel-type stratified win ratio method, stratified by baseline NT-proBNP. Prespecified subgroups were stratified according to tafamidis use at baseline, ATTR disease type (wtATTR versus hATTR), NYHA class, and age at baseline.[2,5]

The secondary endpoints were related to functional capacity, patient-reported health status and health-related quality of life, as well as additional assessments of mortality and severity of clinical HF symptoms, including:[2]

- All-cause mortality, including up to 6 months of OLE data (up to Month 42)
- Change from baseline in 6-MWT at Month 30
- Change from baseline in the KCCQ-OS at Month 30
- Change from baseline in NYHA class at Month 30

Baseline Characteristics

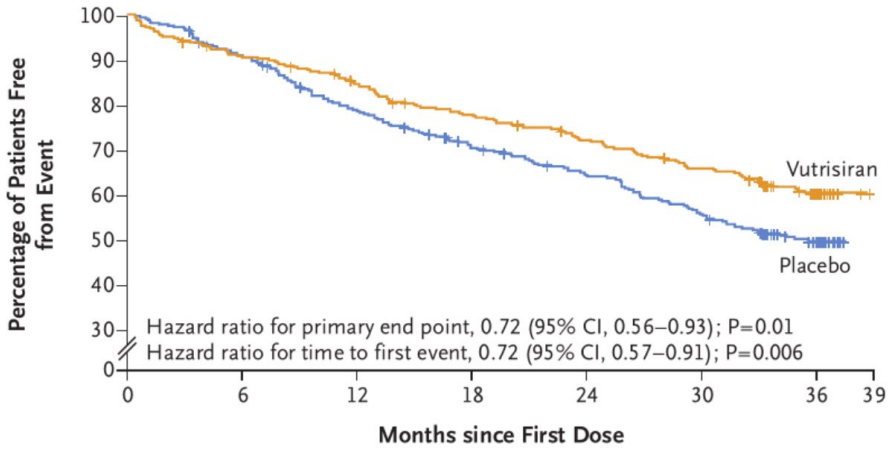
In the overall population, there were 326 patients randomized to receive vutrisiran and 329 patients randomized to receive placebo. Of the patients from the overall population, 60% (196 of 326 patients) in the vutrisiran group and 60% (199 of 329 patients) in the placebo group were not taking tafamidis at baseline (monotherapy population). Patient baseline characteristics and demographics were comparable between groups, except for higher NT-proBNP and troponin I values in the vutrisiran group than the placebo group in the monotherapy population. Baseline demographics and clinical characteristics were not substantially different between the monotherapy population and overall population.[2]

Efficacy Results

Primary Endpoint: All-Cause Mortality and Recurrent CV Events

Treatment with vutrisiran reduced the risk of all-cause mortality and recurrent CV events in the overall population [HR 0.72 (95% CI 0.56, 0.93; P=0.01)] and monotherapy population [HR 0.67 (95% CI 0.49, 0.93; P=0.02). Prespecified win ratio sensitivity analyses in both populations were consistent with the results of the primary analysis. The time to first CV event or all-cause mortality in the overall population and monotherapy population are shown in **Figures 1 and 2**, respectively.[2]

Figure 1. Time to All-Cause Mortality or CV Event in the Overall Population.[2]

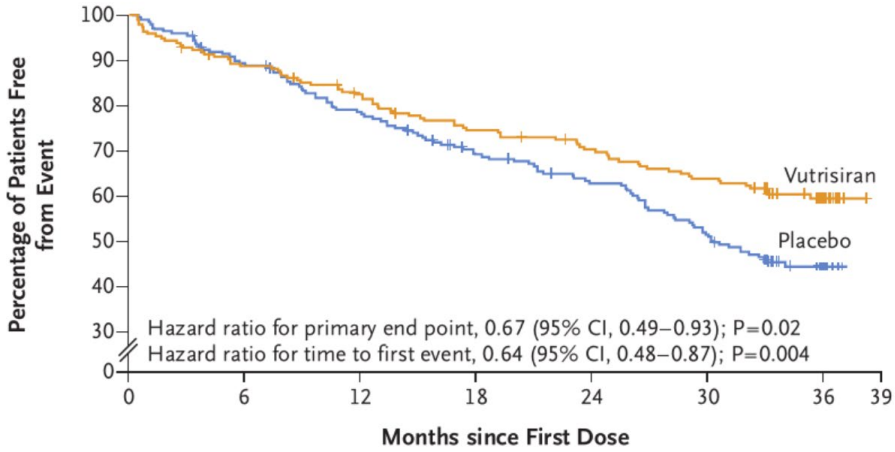


No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125)	0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159)	0 (159)

Abbreviations: CV = cardiovascular; CI = confidence interval.

Figure 2. Time to All-Cause Mortality or CV Event in the Monotherapy Population.[2]



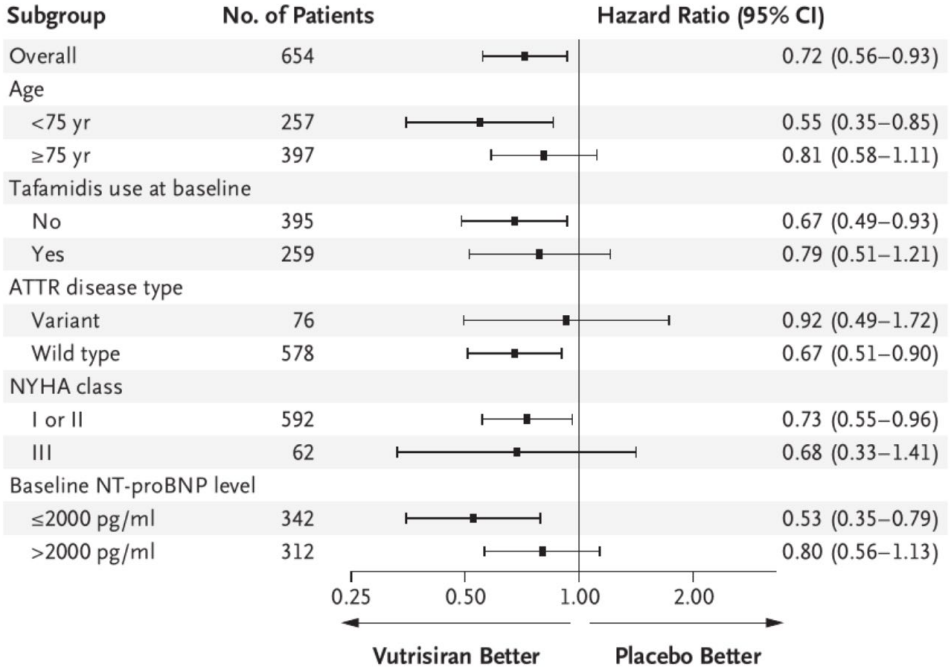
No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	32 (76)	0 (76)
Placebo	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	26 (105)	0 (105)

Abbreviations: CV = cardiovascular; CI = confidence interval.

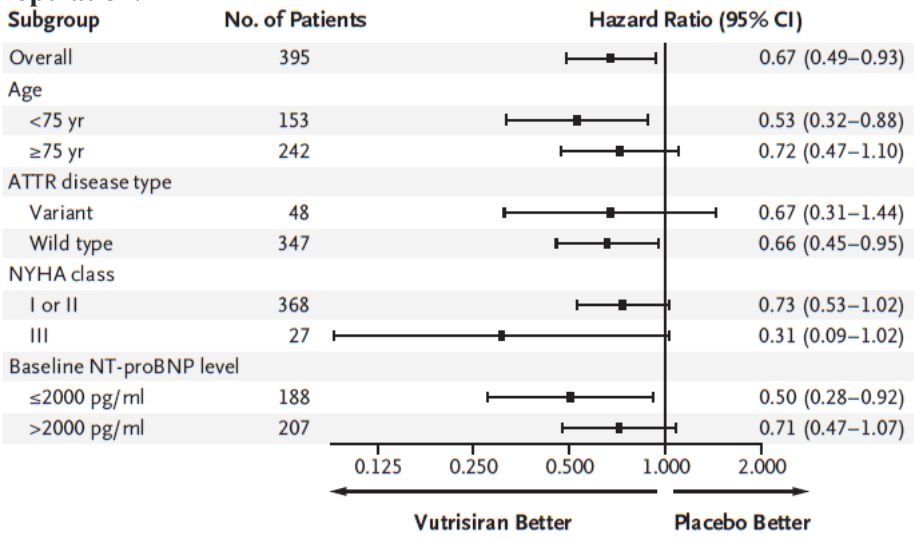
Similar effects were observed on all-cause mortality and recurrent CV events across all prespecified subgroups shown in **Figures 3** and **4**.[2]

Figure 3. All-Cause Mortality and CV Events in Prespecified Subgroups in the Overall Population.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Figure 4. All-Cause Mortality and CV Events in Prespecified Subgroups in the Monotherapy Population.[2]

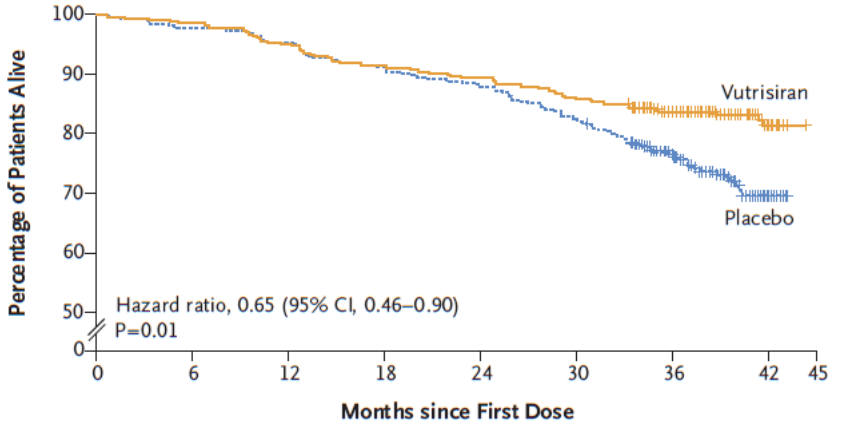


Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Secondary Endpoints: All-Cause Mortality

Vutrisiran reduced all-cause mortality through up to 42 months of follow-up vs. placebo in the overall population [HR 0.65 (95% CI 0.46, 0.90; P=0.01; **Figure 5**], and monotherapy population [HR 0.66 (95% CI 0.44, 0.97; P=0.045; **Figure 6**].[2]

Figure 5. Death from Any Cause in the Overall Population.[2]

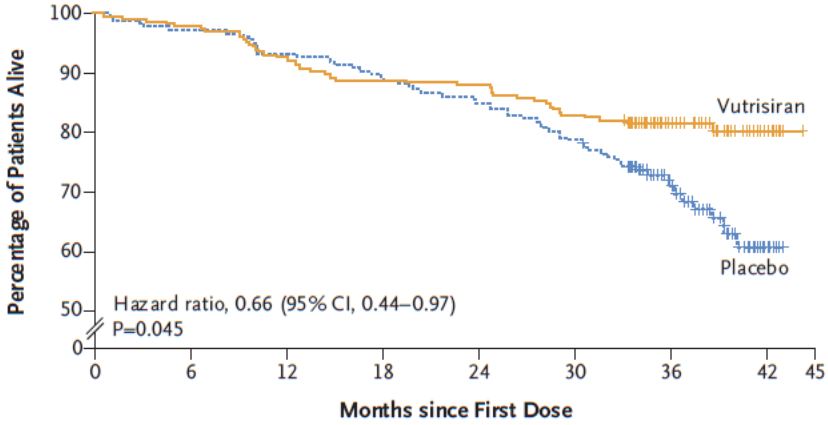


No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	321 (5)	308 (18)	296 (30)	289 (37)	277 (49)	198 (56)	33 (60) 0 (60)
Placebo	328 (0)	321 (7)	314 (14)	299 (29)	290 (38)	271 (57)	180 (74)	24 (85) 0 (85)

Abbreviations: CI = confidence interval

Figure 6. Death from Any Cause in the Monotherapy Population.[2]



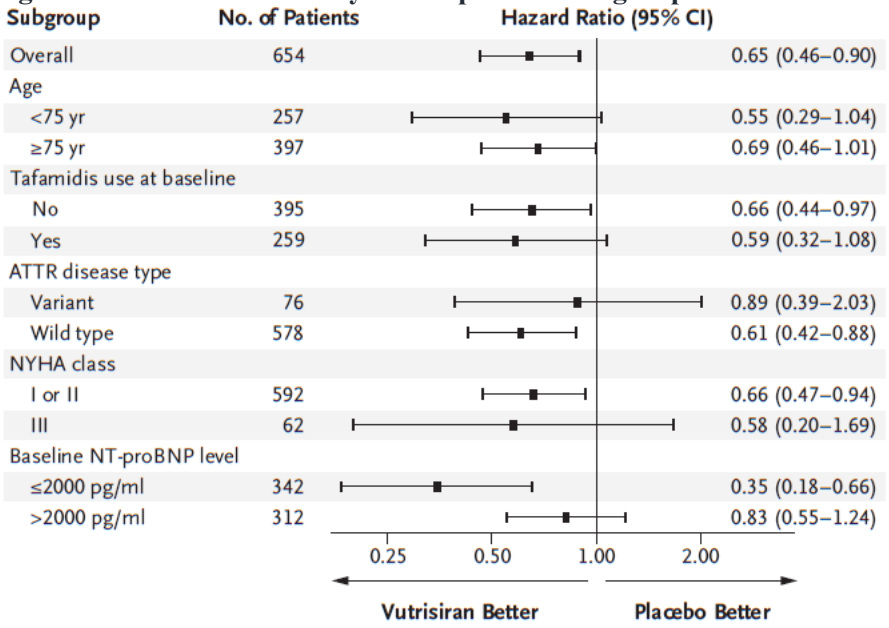
No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	191 (5)	179 (17)	171 (25)	169 (27)	158 (38)	86 (41)	17 (43) 0 (43)
Placebo	199 (0)	194 (5)	188 (11)	180 (19)	172 (27)	160 (39)	79 (51)	16 (58) 0 (58)

Abbreviations: CI = confidence interval

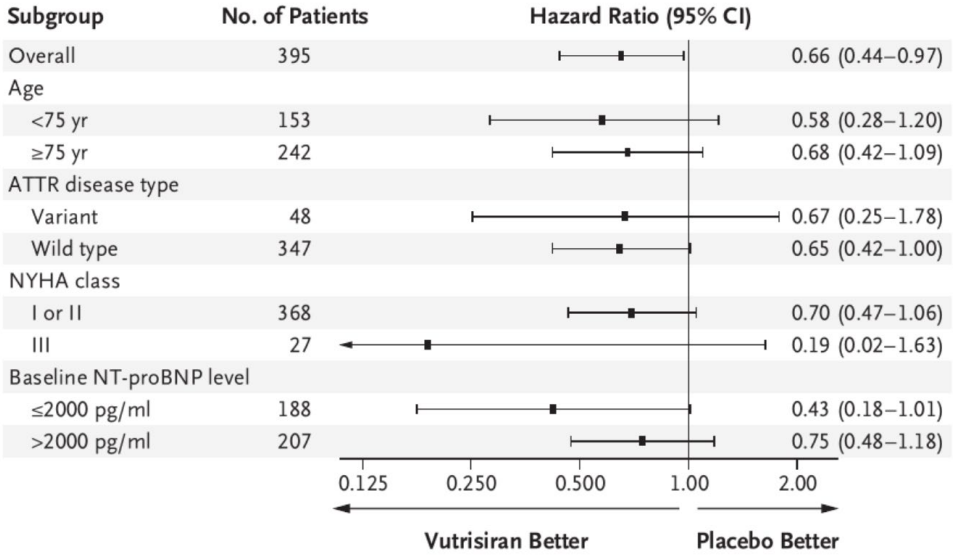
In both populations, similar effects were observed on all-cause mortality across all prespecified subgroups shown in **Figures 7** and **8**. Sensitivity analyses of the secondary endpoint were consistent with the secondary endpoint analysis.[2]

Figure 7. All-Cause Mortality in Prespecified Subgroups in the Overall Population.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Figure 8. All-Cause Mortality in Prespecified Subgroups in the Monotherapy Population.[2]



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

Safety Results

In the overall population, the proportion of patients with at least one AE was similar between treatment arms, and the majority of AEs were mild or moderate.[3] A summary of the safety results during the double-blind period are presented in **Table 1**.[5] Cardiac AEs occurred at similar or lower rates with vutrisiran than placebo. There were no clinically relevant changes in laboratory measures (including hematologic measures, blood chemistry measures, liver function tests, and renal function tests), vital signs, or electrocardiograms in either treatment arm.[2]

Table 1. Safety Summary.[5]

Event, n (%)	Overall Population	
	Vutrisiran (N=326)	Placebo (N=328)
At least 1 AE	322 (99)	323 (98)
Any SAE[a]	201 (62)	220 (67)
Any severe AE[b]	158 (48)	194 (59)
Any AE leading to treatment discontinuation	10 (3)	13 (4)
Any AE leading to death[c]	49 (15)	63 (19)

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a]Serious AEs were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.
[b]Severe AEs were defined as AEs for which more than minimal, local, or noninvasive intervention was received; which had a severe effect on limiting self-care activities of daily living; or which had the potential for life-threatening consequences or death.
[c]Deaths that occurred after the end of study visit or after the data cut-off date were not included.

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HF = heart failure; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire-Overall Summary; IV = intravenous; LWYY = Lin-Wei-Yang-Ying; mNIS+7 = modified Neuropathy Impairment Score +7; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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