Vutrisiran: Echocardiographic Assessments in HELIOS-B

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SUMMARY

- 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. Echocardiograms were performed at baseline and at 12, 18, 24, and 30 months.[1,2]
- The study met the 10 primary and secondary endpoints in the overall and monotherapy populations. Treatment with vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events in both 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).[1]
- The changes from baseline in measures of cardiac structure, diastolic function, and systolic function were assessed over 30 months in the vutrisiran and placebo groups as exploratory endpoints.[2]
    - Additional post-hoc analyses were conducted at 30 months to assess the change from baseline in measures of right ventricular and left atrial function.[3,4]
- A post-hoc analysis was conducted at 18 months to evaluate the associations between echocardiographic parameters and subsequent clinical outcomes.[5]
- In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment groups. There were no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms in either treatment group.[1,6]

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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 with 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. The primary endpoint

was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline).[1]

Echocardiograms were performed at baseline and at 12, 18, 24, and 30 months by certified sonographers at each site. The changes from baseline in echocardiographic parameters over time were analyzed with MMRM with the corresponding baseline echocardiographic parameter included as a covariate and treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, ATTR disease type, and age group (<75 vs ≥75 years) included as fixed-effect terms in the overall population.[2,5]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Select baseline characteristics of echocardiographic measures in the overall population and the monotherapy population are presented in **Table 1**.[2] The median age of study participants was 77 years, 93% were male, and 88% had wtATTR. The monotherapy population was defined as patients who did not receive tafamidis at baseline and comprised a total of 395 patients (196 patients [60%] in the vutrisiran arm and 199 patients [60%] in the placebo arm).[1]

In the overall population, baseline use of SGLT2 inhibitors was 3% in both treatment arms. Baseline use of diuretics was 80% and 79% in the vutrisiran and placebo arms, respectively.[6]

Table 1. Select Baseline Echocardiographic Parameters in HELIOS-B.[2]

Echocardiographic Parameter	Overall Population			Monotherapy Population		
	n	Placebo (n=328)[a]	Vutrisiran (n=326)	n	Placebo (n=199)	Vutrisiran (n=196)
Mean LV wall thickness (mm)	645	18.2 (2.7)	18.2 (2.6)	388	18.3 (2.9)	18.2 (2.7)
LV mass index (g/m^2)	637	180.8 (46.1)	182.1 (44.2)	382	185.7 (49.5)	186.7 (46.8)
LVEF (%)	627	55.9 (12.4)	55.6 (12.7)	374	55.7 (12.1)	54.8 (12.6)
Absolute GLS (%),	652	14.0 (3.5)	14.0 (3.5)	393	14.3 (3.5)	14.0 (3.4)
Stroke volume (mL)	616	53.8 (19.0)	50.7 (16.3)	373	55.8 (19.6)	51.2 (16.8)
E/A ratio	353	1.9 (1.0)	2.1 (1.1)	202	1.9 (1.0)	2.1 (1.1)
TDI lateral *e'* (mm/s)	627	58.5 (20.5)	61.4 (22.6)	380	58.3 (19.8)	61.2 (22.6)
E/e' lateral	620	15.3 (6.3)	14.8 (6.7)	321	15.3 (5.7)	15.1 (7.1)
RV *S'* (mm/s)	625	93.5 (27.2)	94.0 (26.6)	374	94.8 (28.1)	93.4 (28.1)

Abbreviations: E/A = ratio of early to late diastolic transmitral inflow velocities; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; RV *S'* = right ventricular systolic myocardial velocity; SD = standard deviation; TDI lateral *e'* = lateral peak early diastolic mitral annular tissue velocity.

[a]329 patients were randomized to receive placebo. One patient withdrew from the study and was not dosed.

Data are descriptive and presented as mean (SD).

30-MONTH ECHOCARDIOGRAPHIC ANALYSES

The changes from baseline in mean LV wall thickness and GLS at 30 months were prespecified as exploratory endpoints in the HELIOS-B study. Changes in other echocardiographic parameters were not prespecified and are considered exploratory. Missing data were not imputed.[2]

The changes from baseline in select echocardiographic parameters at 30 months in the overall and monotherapy populations are summarized in **Tables 2 and 3**, respectively. The changes from baseline in echocardiographic parameters over time in the vutrisiran group compared with the placebo group in the overall population are presented in **Figure 1**.[2]

Table 2. LS Mean Changes from Baseline in Select Echocardiographic Parameters at 30 Months in the Overall Population.[2]

Echocardiographic Parameter	n	Placebo (n=328)	Vutrisiran (n=326)	Placebo-corrected treatment difference (95% CI)
LV structure				
LV wall thickness, mm	455	0.9 (0.1)	0.5 (0.1)	-0.4 (-0.8, 0.0)
LV mass index, g/m^2	434	25.4 (2.8)	14.8 (2.5)	-10.6 (-18.0, -3.3)
LV diastolic function				
TDI lateral *e'*, mm/s	438	-0.2 (1.1)	5.3 (1.1)	5.5 (2.4, 8.5)
Lateral *E/e'*	419	0.7 (0.3)	-1.08 (0.3)	-1.8 (-2.7, -1.0)
LV systolic function				
LVEF, %	434	-6.2 (0.7)	-4.1 (0.6)	2.0 (0.3, 3.7)
Absolute GLS, %	471	-2.2 (0.2)	-1.0 (0.2)	1.2 (0.1, 1.7)
Stroke volume, mL	427	-6.5 (0.8)	-2.4 (0.9)	4.1 (1.7, 6.4)
RV and pulmonary pressure				
RV *S'*, mm/s	408	-9.6 (1.5)	-2.6 (1.5)	7.0 (2.8, 11.2)

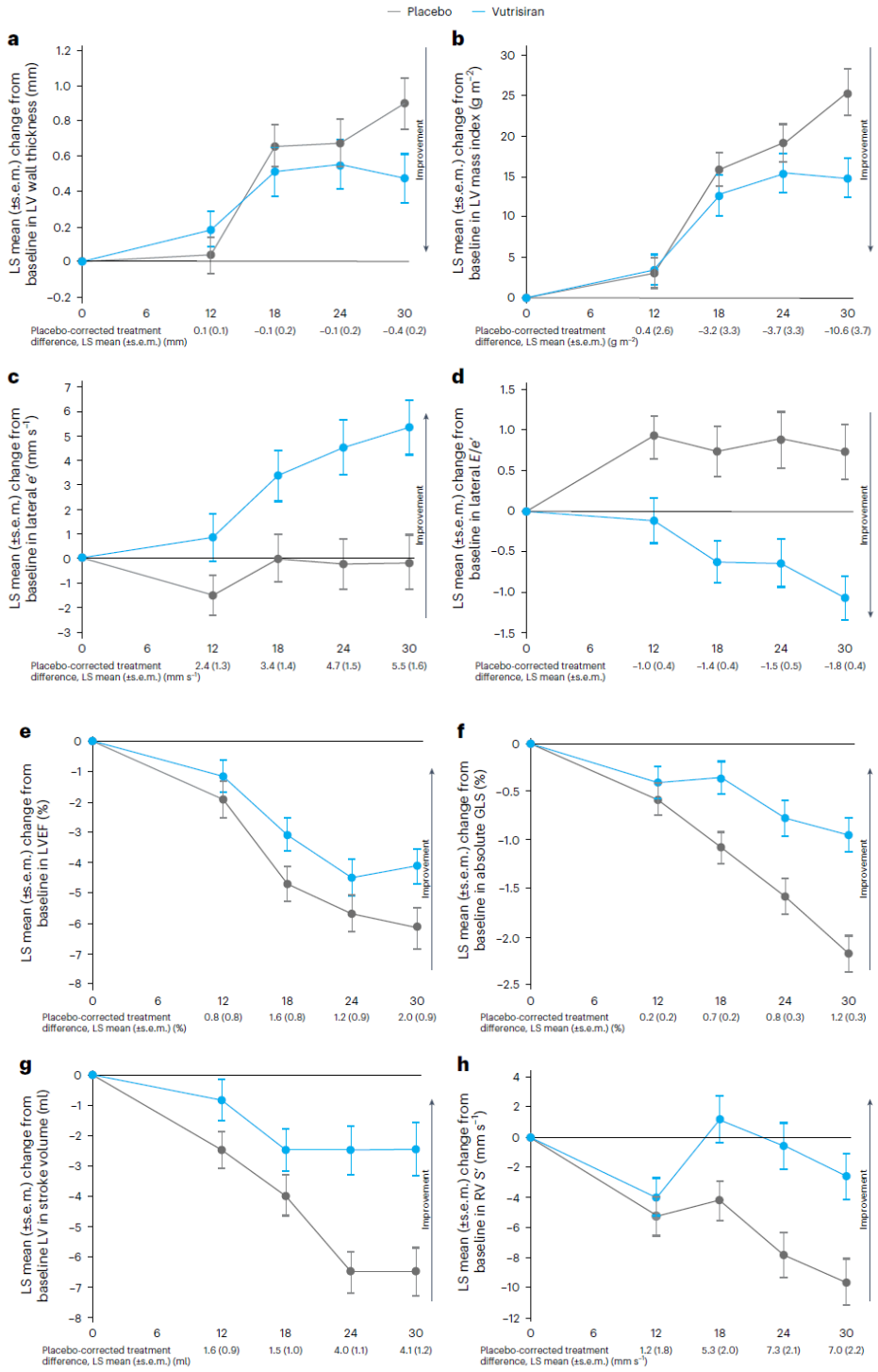
Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; RV *S'* = right ventricular systolic myocardial velocity; SEM = standard error of the mean.
Results are reported as the LS mean difference (SEM) derived from repeated measures models with baseline as a covariate and fixed-effect terms including the treatment group, visit, treatment-by-visit interaction, ATTR disease type, age group, baseline tafamidis use, and treatment-by-baseline tafamidis use interaction.

Table 3. LS Mean Changes from Baseline in Select Echocardiographic Parameters at 30 Months in the Monotherapy Population.[2]

Echocardiographic Parameter	n	Placebo (n=199)	Vutrisiran (n=196)	Placebo-corrected treatment difference (95% CI)
LV structure				
LV wall thickness, mm	247	1.1 (0.2)	0.4 (0.2)	-0.8 (-1.4, -0.2)
LV mass index, g/m^2	234	29.8 (4.2)	11.8 (3.7)	-18.0 (-28.9, -7.1)
LV diastolic function				
TDI lateral *e'*, mm/s	244	-4.5 (1.4)	4.3 (1.4)	8.7 (4.8, 12.6)
Lateral *E/e'*	231	1.7 (0.5)	-1.0 (0.4)	-2.7 (-3.9, -1.6)
LV systolic function				
LVEF, %	232	-5.9 (0.9)	-3.6 (0.8)	2.3 (-0.1, 4.6)
Absolute GLS, %	257	-2.4 (0.3)	-1.1 (0.3)	1.3 (0.6, 2.0)
Stroke volume, mL	237	-6.4 (1.2)	-2.2 (1.2)	4.2 (0.9, 7.4)
RV and pulmonary pressure				
RV *S'*, mm/s	226	-13.4 (2.0)	-6.3 (2.0)	7.1 (1.5, 12.7)

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; RV *S'* = right ventricular systolic myocardial velocity; SEM = standard error of the mean.
Results are reported as the LS mean difference (SEM) derived from repeated measures models with baseline as a covariate and fixed-effect terms including the treatment group, visit, treatment-by-visit interaction, ATTR disease type, and age group.

Figure 1. Change from Baseline in Echocardiographic Parameters Over Time in the Overall Population.[2]



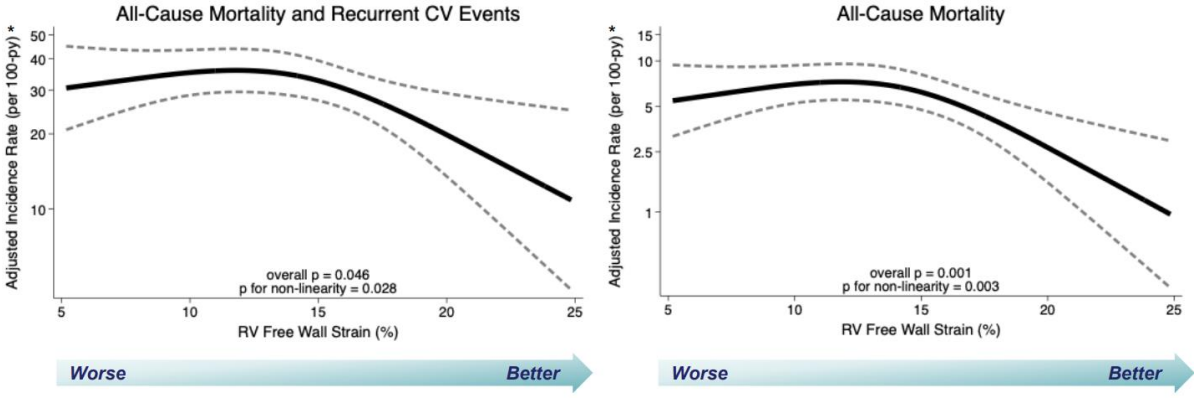
Abbreviations: E/e' = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; RV S' = right ventricular systolic myocardial velocity; SEM = standard error of the mean.
Error bars represent the SEM.
From Jering et al.[2]

Additional post-hoc analyses of the HELIOS-B study were conducted to assess the changes from baseline in measures of right ventricular and left atrial function with vutrisiran treatment.[3,4]

Right Ventricular Free Wall Strain

Among 548 patients who had available baseline RVFWS, the absolute mean RVFWS was 14.4 ± 5.1%. RV dysfunction, defined as RVFWS <20%, was present in 85% of patients. Lower RVFWS at baseline was non-linearly associated with an increased risk of all-cause mortality and recurrent CV events, independent of age, sex, ATTR disease type, NAC disease stage, atrial fibrillation/flutter, baseline tafamidis use, and LV GLS (**Figure 2**).[3]

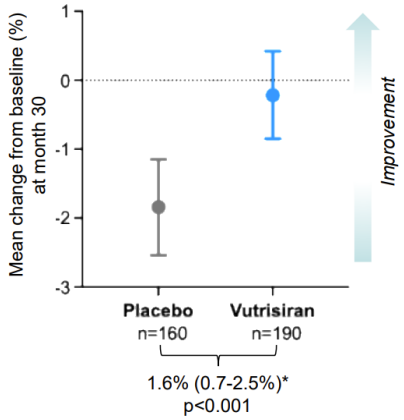
Figure 2. Association of Baseline RVFWS with Subsequent Clinical Outcomes.[3]



Abbreviations: ATTR = transthyretin amyloidosis; GLS = global longitudinal strain; LV = left ventricular; NAC = National Amyloidosis Centre; RV = right ventricular; RVFWS = right ventricular free wall strain.
*Adjusted for age, sex, ATTR genotype (wild-type vs. variant), NAC disease stage, atrial fibrillation/flutter, baseline tafamidis use, and LV GLS. RVFWS is shown as absolute value.
From Manafi et al.[3]

At 30 months, the between-group difference in mean change from baseline in RVFWS between the vutrisiran and placebo groups was 1.6% (95% CI 0.7, 2.5) (**Figure 3**).[3]

Figure 3. Mean Change from Baseline in RVFWS at 30 Months.[3]

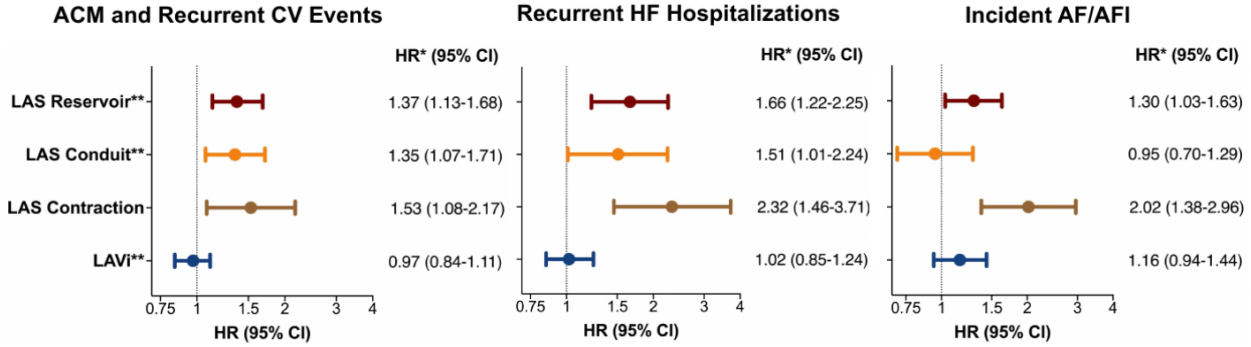


Abbreviations: ATTR = transthyretin amyloidosis; RVFWS = right ventricular free wall strain.
*Derived in the overall population using linear regression adjusted for baseline value, age, ATTR genotype (wild-type vs. variant), baseline tafamidis use, and treatment assignment.
From Manafi et al.[3]

Left Atrial Strain

Among 644 patients with available baseline LAS, lower LAS at baseline was associated with an increased risk of all-cause mortality and recurrent CV events, independent of LV systolic function and E/e' (**Figure 4**).[4]

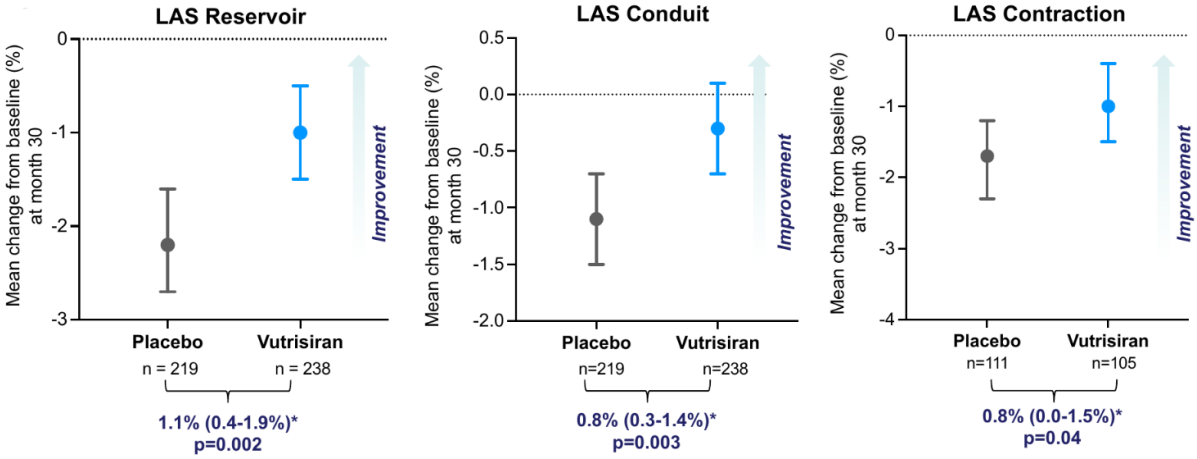
Figure 4. Association of Baseline LAS with Subsequent Clinical Outcomes.[4]



Abbreviations: ACM = all-cause mortality; AF = atrial fibrillation; AFl = atrial flutter; CI = confidence interval; CV = cardiovascular; E/e' = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; HF = heart failure; HR = hazard ratio; LAS = left atrial strain; LAVi = left atrial volume index; LV = left ventricular; NAC = National Amyloidosis Centre.
*HR scaled to 5% increase in LAS and 10 mL/m^2 increase in Lavi. Adjusted for age, sex, ATTR genotype (wild-type vs. variant), NAC stage, treatment assignment, baseline tafamidis use, LV GLS, E/e', and LAVi.
From Jering et al.[4]

The mean change from baseline in LAS at 30 months in the vutrisiran and placebo groups are presented in **Figure 5**.[4]

Figure 5. Mean Change from Baseline in LAS at 30 Months.[4]



Abbreviations: ATTR = transthyretin amyloidosis; LAS = left atrial strain.
*Derived in the overall population using linear regression adjusted for baseline value, age, ATTR genotype (wild-type vs. variant), baseline tafamidis use, and treatment assignment.
From Jering et al.[4]

18-MONTH ECHOCARDIOGRAPHIC ANALYSES

A post-hoc analysis of the HELIOS-B study was conducted to evaluate the associations between baseline echocardiographic parameters with clinical outcomes and to assess how changes in echocardiographic parameters at 18 months related to subsequent clinical outcomes.[5]

Association of Baseline Echocardiographic Parameters with Clinical Outcomes

Over a median follow-up period of 35.7 months, 125 patients in the vutrisiran group and 159 patients in the placebo group experienced the primary composite outcome of all-cause mortality and recurrent CV events. Sixty patients (18%) in the vutrisiran group and 85 patients (26%) in the placebo group died during the double-blind and 6-month OLE period.[5]

The association of select baseline echocardiographic parameters with the primary composite outcome and with the secondary outcome of all-cause mortality are presented in **Tables 4 and 5**, respectively.[5]

Table 4. Association of Select Baseline Echocardiographic Parameters with the Primary Composite Outcome.[5]

Echocardiographic Parameter		Unadjusted		Adjusted[a]	
	n	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	627	0.89	0.85, 0.93	0.90	0.86, 0.95
Absolute GLS (per 1% increase)	652	0.91	0.87, 0.95	0.92	0.89, 0.96
RV *S'*	625	0.92	0.88, 0.97	0.94	0.90, 0.98
Lateral *E/e'* (per 1-U increase)	620	1.03	1.01, 1.05	1.02	1.00, 1.04

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre; RV *S'* = tricuspid annular systolic myocardial velocity.

[a]Models are adjusted for age, sex, ATTR disease type (wild-type vs variant), and NAC ATTR stage, and are stratified by baseline tafamidis use and treatment assignment.

Table 5. Association of Select Baseline Echocardiographic Parameters with All-Cause Mortality.[5]

Echocardiographic Parameter		Unadjusted		Adjusted[a]	
	n	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	627	0.87	0.81, 0.92	0.89	0.84, 0.95
Absolute GLS (per 1% increase)	652	0.88	0.84, 0.93	0.90	0.85, 0.94
RV *S'*	625	0.86	0.81, 0.92	0.90	0.84, 0.96
Lateral *E/e'* (per 1-U increase)	620	1.03	1.01, 1.06	1.02	1.00, 1.05

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre; RV *S'* = tricuspid annular systolic myocardial velocity.

[a]Models are adjusted for age, sex, ATTR disease type (wild-type vs variant), and NAC ATTR stage, and are stratified by baseline tafamidis use and treatment assignment.

Change from Baseline in Echocardiographic Parameters at 18 Months

In the overall population, the LS mean (±SEM) change from baseline in LVEF at 18 months was -3.1% (0.6) in the vutrisiran group and -4.7% (0.6) in the placebo group, resulting in a LS mean difference (95% CI) of 1.6% (0.1, 3.2).[7]

The LS mean (±SEM) change from baseline in absolute GLS at 18 months was -0.4% (0.2) in the vutrisiran group and -1.1% (0.2) in the placebo group, resulting in a LS mean difference (95% CI) of 0.7% (0.3, 1.2).[7]

The LS mean (±SEM) change from baseline in RV *S'* at 18 months was 0.1 cm/s (0.2) in the vutrisiran group and -0.4 cm/s (0.1) in the placebo group, resulting in a LS mean difference (95% CI) of 0.5 cm/s (0.1, 0.9).[7]

The LS mean (±SEM) change from baseline in lateral *E/e'* at 18 months was -0.6 (0.3) in the vutrisiran group and 0.7 (0.3) in the placebo group, resulting in a LS mean difference (95% CI) of -1.4 (-2.2, -0.6).[7]

Association of Change from Baseline to 18 Months in Echocardiographic Parameters and Subsequent Clinical Outcomes

The associations of the changes in echocardiographic parameters from baseline to 18 months were assessed in landmark analyses using modified Andersen-Gill and Cox proportional hazards regression models, respectively.[5]

The association of changes in select echocardiographic parameters from baseline to 18 months with the subsequent primary composite outcome is presented in **Table 6**.[5]

Table 6. Association of Changes in Select Echocardiographic Parameters from Baseline to 18 Months with the Subsequent Primary Composite Outcome.[5]

Echocardiographic Parameter		Model 1[a]		Model 2[b]	
	n	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	503	0.84	0.78, 0.91	0.88	0.81, 0.95
Absolute GLS (per 1% increase)	547	0.91	0.85, 0.97	0.93	0.88, 1.00
RV *S'*	490	0.80	0.73, 0.88	0.82	0.75, 0.90
Lateral *E/e'* (per 1-U increase)	489	1.01	0.97, 1.04	0.99	0.96, 1.02

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; E/e' = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre; RV *S'* = tricuspid annular systolic myocardial velocity.

[a]Model 1 is adjusted for the corresponding baseline echocardiographic parameter.

[b]Model 2 is adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR disease type (wild-type vs variant), and NAC ATTR stage, and is stratified by baseline tafamidis use and treatment assignment.

The association of changes in select echocardiographic parameters from baseline to 18 months with subsequent all-cause mortality are presented in **Table 7** and **Figure 6**. A 1% point worsening in absolute GLS, a 5% decline in LVEF, and a 1 cm/s decline in RV *S'* were associated with a 9%, 15%, and 18% increased risk of subsequent all-cause mortality, respectively, independent of age, sex, ATTR disease type, NAC disease stage, baseline tafamidis use, and treatment assignment.[5]

Table 7. Association of Changes in Select Echocardiographic Parameters from Baseline to 18 Months with Subsequent All-Cause Mortality.[5]

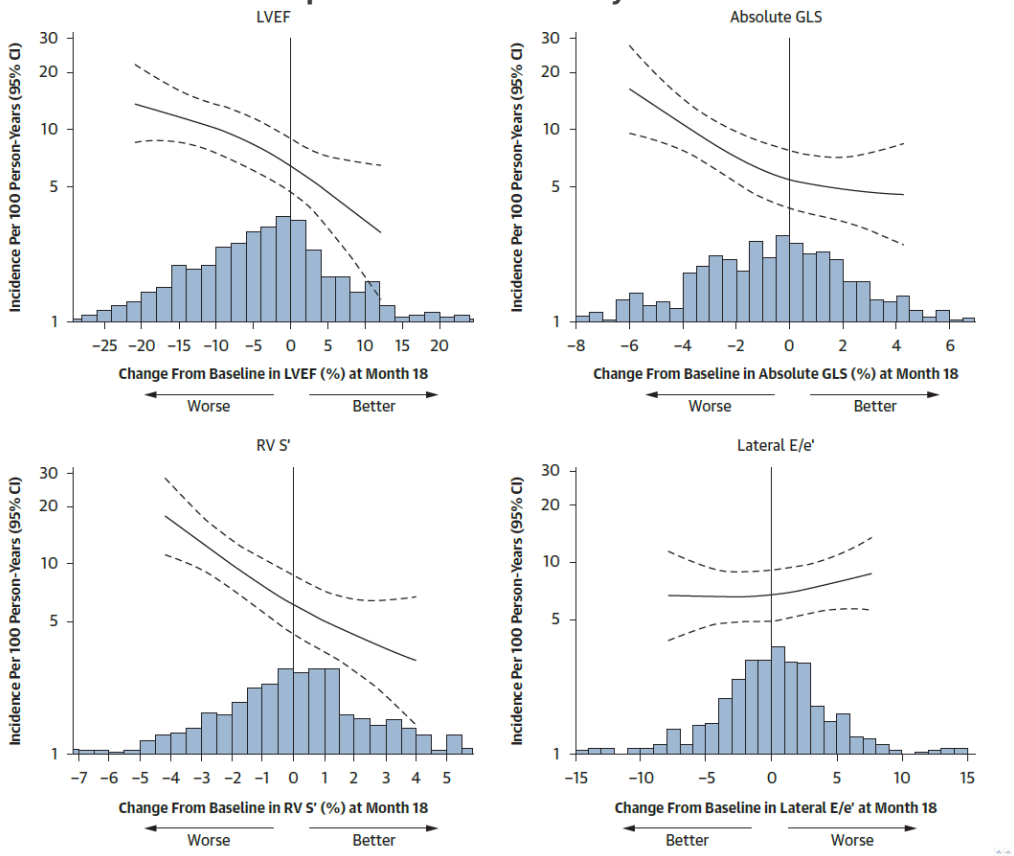
Echocardiographic Parameter		Model 1[a]		Model 2[b]	
	n	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	503	0.81	0.72, 0.92	0.85	0.75, 0.96
Absolute GLS (per 1% increase)	547	0.88	0.81, 0.97	0.91	0.83, 1.00
RV *S'*	490	0.80	0.71, 0.90	0.83	0.73, 0.93
Lateral *E/e'* (per 1-U increase)	489	1.02	0.98, 1.07	1.00	0.96, 1.05

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre; RV *S'* = tricuspid annular systolic myocardial velocity.

[a]Model 1 is adjusted for the corresponding baseline echocardiographic parameter.

[b]Model 2 is adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR disease type (wild-type vs variant), and NAC ATTR stage, and is stratified by baseline tafamidis use and treatment assignment.

Figure 6. Association of Changes from Baseline to Month 18 in Select Echocardiographic Parameters with Subsequent All-Cause Mortality.[5]



Abbreviations: CI = confidence interval; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; RV *S'* = right ventricular systolic myocardial velocity.
Models are adjusted for the corresponding baseline echocardiographic parameter. *P* for nonlinearity >0.15 for all. The histograms illustrate the distribution of change from baseline at 18 months.
From Jering et al.[5]

SAFETY RESULTS

In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment groups. A summary of the safety results during the double-blind period are presented in **Table 8**.[1,6]

Table 8. HELIOS-B Safety Summary.[6]

Event, n (%)	Overall Population	
	Vutrisiran (n=326)	Placebo (n=328)[a]
At least 1 AE	322 (99)	323 (98)
Any SAE[b]	201 (62)	220 (67)
Any severe AE[c]	158 (48)	194 (59)
Cardiac AEs	227 (70)	242 (74)
Cardiac SAEs	116 (36)	124 (38)
Any AE leading to treatment discontinuation	10 (3)	13 (4)
Any AE leading to death[d]	49 (15)	63 (19)

Abbreviations: AE = adverse event; SAE = serious adverse event.

[a]Of the 329 patients randomized to receive placebo, 1 patient withdrew from the study and was not dosed.

[b]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.

[c]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.

[d]Deaths that occurred after the end of study visit or after the data cut-off date were not included.

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 group.[1]

ABBREVIATIONS

ACM = all-cause mortality; AE = adverse event; AF = atrial fibrillation; AFl = atrial flutter; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; E/A = ratio of early to late diastolic transmitral inflow velocities; *E/e'* = ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity; GLS = global longitudinal strain; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; LAS = left atrial strain; LAVi = left atrial volume index; LS = least squares; LV = left ventricular; LVEF = left ventricular ejection fraction; MMRM = mixed models for repeated measures; NAC = National Amyloidosis Centre; RV = right ventricular; RV *S'* = right ventricular systolic myocardial velocity; RVFWS = right ventricular free wall strain; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; TDI lateral *e'* = lateral peak early diastolic mitral annular tissue velocity; wtATTR = wild-type transthyretin amyloidosis.

Updated 21 January 2026

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