Vutrisiran: Left Ventricular Ejection Fraction in HELIOS-B

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SUMMARY

- In the HELIOS-B study, echocardiograms were performed at baseline and at 12, 18, 24, and 30 months.[1]
  - The mean (SD) LVEF at baseline was 55.6% (12.7) and 55.9% (12.4) in the vutrisiran and placebo groups, respectively.[1]
  - In the overall population, the LS mean (±SEM) change from baseline in LVEF at 30 months was -4.1% (±0.6) and -6.2% (±0.7) in the vutrisiran and placebo groups, respectively, resulting in a LSMD of 2.0% (95% CI 0.3, 3.7).[1]
  - A post-hoc analysis was conducted to evaluate the associations between the change from baseline in echocardiographic parameters at 18 months and subsequent clinical outcomes from 18 to 42 months. A decrease in LVEF from baseline to 18 months was associated with an increased risk of subsequent all-cause mortality.[2]
- 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.[3,4]

INDEX

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).[3]

Echocardiograms were performed at baseline and at 12, 18, 24, and 30 months.[1]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 655 patients were enrolled and were randomly assigned to receive vutrisiran (n=326) or placebo (n=329). The median age of study participants was 77 years, 93% were male, 88% had wtATTR, and 78% had NYHA Class II heart failure. The monotherapy population consisted of 395 patients who were not receiving tafamidis at baseline. The demographic and clinical characteristics were similar between the vutrisiran and placebo groups, except that NT-proBNP and troponin I levels were higher in the vutrisiran group than the placebo group in the monotherapy population.[3]

At baseline, concomitant tafamidis use was 40% and 39% in the vutrisiran and placebo groups, respectively. Baseline use of SGLT2 inhibitors was 3% in both treatment groups; and baseline use of diuretics was 80% and 79% in the vutrisiran and placebo groups, respectively.[4]

In the overall population, the mean (SD) LVEF at baseline was 55.6% (12.7) and 55.9% (12.4) in the vutrisiran and placebo groups, respectively. In the monotherapy population, the mean (SD) LVEF at baseline was 54.8% (12.6) and 55.7% (12.1) in the vutrisiran and placebo groups, respectively.[1]

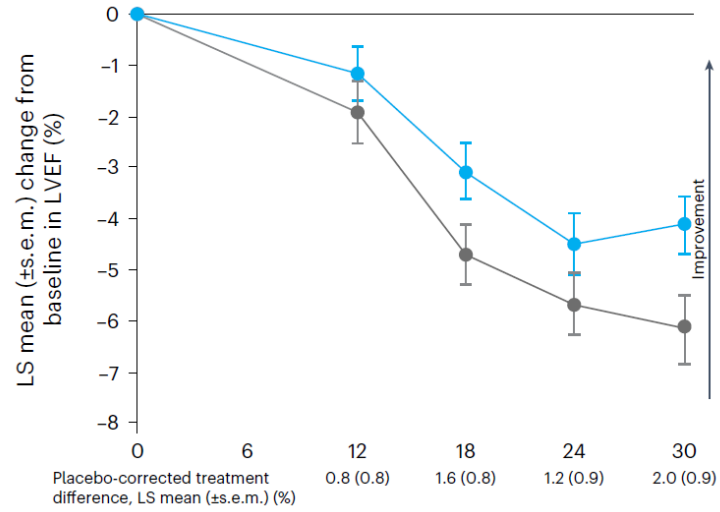
ECHOCARDIOGRAPHIC RESULTS

30-Month Data

The change from baseline in LVEF at 30 months was not a prespecified analysis and is considered an exploratory endpoint. A total of 434 patients in the overall population and 232 patients in the monotherapy population had evaluable data for LVEF at 30 months. Missing data were not imputed.[1]

In the overall population, the LS mean (±SEM) change from baseline in LVEF at 30 months was -4.1% (±0.6) and -6.2% (±0.7) in the vutrisiran and placebo groups, respectively (**Figures 1 and 2**). The LSMD in change from baseline in LVEF between the vutrisiran and placebo groups at 30 months was 2.0% (95% CI 0.3, 3.7).[1]

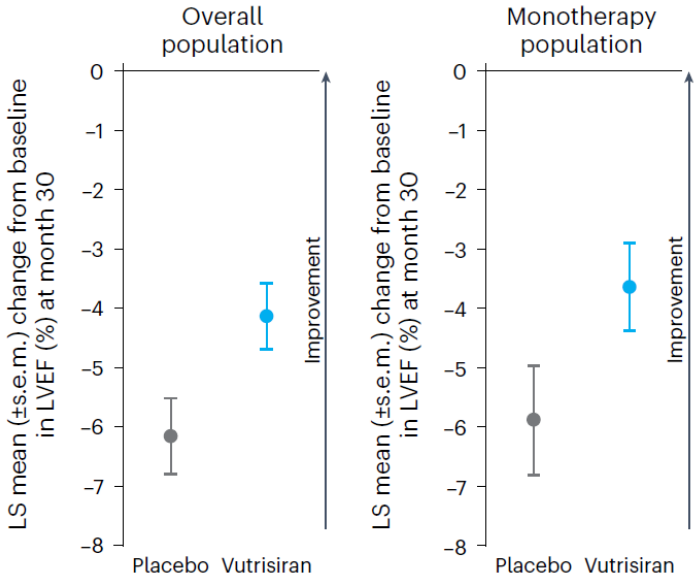
Figure 1. LS Mean Change from Baseline in LVEF Over Time in the Overall Population.[1]



Abbreviations: LS = least squares; LVEF = left ventricular ejection fraction; SEM = standard error of the mean.
Blue denotes vutrisiran group; gray denotes placebo group. Error bars represent the SEM.
A total of 434 patients in the overall population had evaluable data for LVEF at 30 months. Missing data were not imputed.
From Jering et al.[1]

In the monotherapy population, the LS mean (±SEM) change from baseline in LVEF at 30 months was -3.6% (±0.8) and -5.9% (±0.9) in the vutrisiran and placebo groups, respectively (**Figure 2**). The LSMD in change from baseline in LVEF between the vutrisiran and placebo groups at 30 months was 2.3% (95% CI -0.1, 4.6).[1]

Figure 2. LS Mean Change from Baseline in LVEF at 30 Months.[1]



Abbreviations: LS = least squares; LVEF = left ventricular ejection fraction; SEM = standard error of the mean.
A total of 434 patients in the overall population and 232 patients in the monotherapy population had evaluable data for LVEF at 30 months. Missing data were not imputed.
From Jering et al.[1]

18-Month Analysis

A post-hoc analysis was conducted to evaluate the associations between baseline echocardiographic parameters, including LVEF, and the change from baseline in echocardiographic parameters to 18 months with subsequent clinical outcomes.[2]

Baseline LVEF was independently associated with the primary composite outcome and all-cause mortality (**Table 1**).[2]

Table 1. Association of Baseline LVEF with Clinical Outcomes.[2]

	Primary Outcome				All-Cause Mortality			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	0.89	0.85, 0.93	0.90	0.86, 0.95	0.87	0.81, 0.92	0.89	0.84, 0.95

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre.
Evaluable data from 627 patients.
[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.

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 (n=253) and -4.7% (0.6) in the placebo group (n=250), resulting in a LSMD of 1.6 (95% CI 0.1, 3.2).[5]

The associations of the change from baseline in LVEF to 18 months with subsequent clinical outcomes are presented in **Table 2**. A decrease in LVEF from baseline was associated with an increased risk of the primary outcome and all-cause mortality.[2]

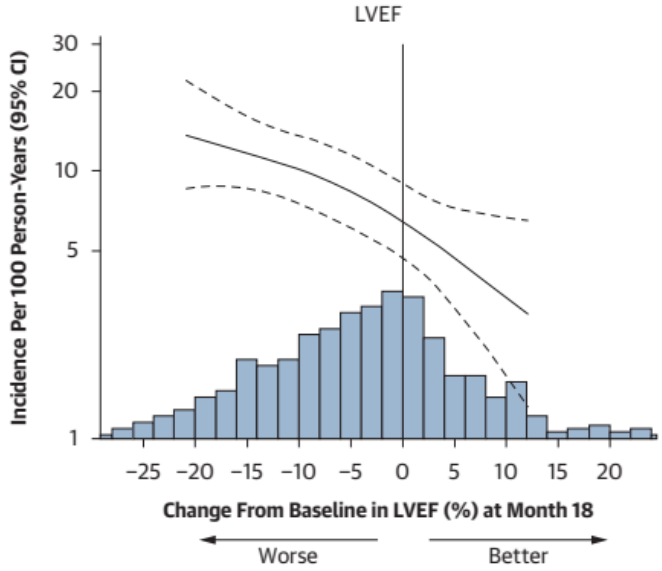
Table 2. Association of Changes in LVEF from Baseline to 18 Months with Subsequent Clinical Outcomes.[2]

	Primary Composite Outcome				All-Cause Mortality			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
LVEF (per 5% increase)	0.84	0.78, 0.91	0.88	0.81, 0.95	0.81	0.72, 0.92	0.85	0.75, 0.96

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval HR = hazard ratio; LVEF = left ventricular ejection fraction; NAC = National Amyloidosis Centre.
Evaluable data from 503 patients.
[a]Model 1 is adjusted for the corresponding baseline echocardiographic parameter.
[b]Model 2 is 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.

The association of change from baseline in LVEF at 18 months with subsequent all-cause mortality is shown in **Figure 3**.[2]

Figure 3. Association of Change from Baseline in LVEF at 18 Months with All-Cause Mortality.[2]



Abbreviations: CI = confidence interval; LVEF = left ventricular ejection fraction.
Analysis shows the continuous association of baseline to month 18 changes in LVEF with the incidence of all-cause mortality occurring after 18 months. Models are adjusted for the corresponding baseline echocardiographic parameter. P for nonlinearity > 0.15. The histogram illustrates the distribution of change from baseline at 18 months.
From Jering et al.[2]

SAFETY RESULTS

In the overall population, the incidence of AEs and cardiac AEs were similar between the treatment arms. A summary of the safety results during the double-blind period are presented in **Table 1**.[3,4]

Table 1. HELIOS-B Safety Summary.[4]

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]SAEs 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 arm.[3]

ABBREVIATIONS

AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; HR = hazard ratio; LS = least squares; LSMD = least squares mean difference; LVEF = left ventricular ejection fraction; MMRM = mixed models for repeated measures; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SGLT2 = sodium-glucose cotransporter-2; wtATTR = wild-type transthyretin amyloidosis.

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2. Jering KS, Fontana M, Skali H, et al. Effects of vutrisiran on cardiac function and outcomes in patients with transthyretin amyloidosis with cardiomyopathy. *J Am Coll Cardiol*. 2025;86(6):444-455. doi:10.1016/j.jacc.2025.06.022
3. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134
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