Cardiac Function, Clinical Outcomes and Effect of Vutrisiran in Transthyretin Amyloid Cardiomyopathy - the HELIOS-B Trial

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Background

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by deposition of TTR amyloid fibrils in the heart.
- Vutrisiran, a RNA interference therapeutic agent, rapidly knocks down circulating concentrations of TTR.
- In HELIOS-B, vutrisiran significantly reduced rates of all-cause death and cardiovascular (CV) events among patients with ATTR-CM. Compared with placebo, vutrisiran also had beneficial effects on cardiac structure and function.

Hypotheses

- Echocardiographic measures of systolic and diastolic function are associated with clinical outcomes in ATTR-CM.
- Beneficial changes in cardiac function with vutrisiran are related to clinical outcomes.

Methods

HELIOS-B study

655 patients with ATTR-CM (wild-type or variant)

R → Vutrisiran SC q3m 25 mg (n=326) / Placebo (n=329) → Vutrisiran SC q3m 25 mg (Ongoing)

Screening period: Day–45
Variable DB period: Day 1(Baseline), M12, M18, M24, M30 M33, M36
OLE: M60

↑echocardiogram

Primary outcome: composite of all cause death and recurrent CV events during DB period
Secondary outcome: all-cause death through 42 months

Statistical Analysis:

- Associations of baseline echocardiographic parameters with all-cause death were evaluated using Cox models.
- Changes in echocardiographic parameters from baseline to month 18 were analyzed with mixed models for repeated measures.
- Associations of change in echocardiographic parameters at month 18 with subsequent all-cause death were assessed in landmark analyses.

Results

Table 1. Baseline Clinical and Echocardiographic Characteristics According to Treatment Assignment

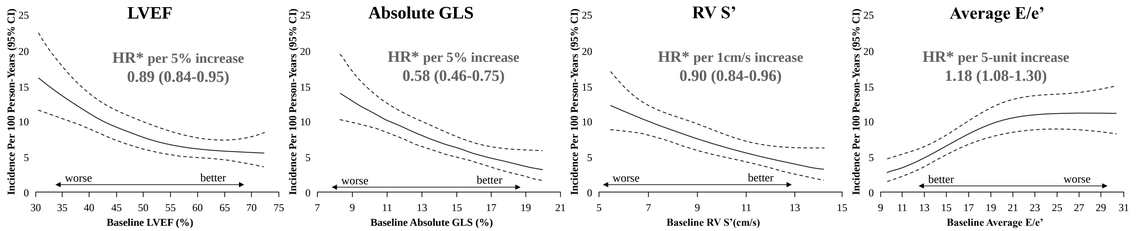
Characteristic	Placebo	Vutrisiran
	n=328	n=326
Median age (range), years	76 (46-85)	77 (45-85)
Male sex	93%	92%
Wild-type ATTR	88%	89%
Tafamidis use at baseline	39%	40%
NAC stage ≥2	30%	36%
Median NT-proBNP (IQR), pg/mL	1801 (1042-3082)	2021 (1138-3312)

Echocardiographic parameter	Placebo	Vutrisiran
	n=328	n=326
Mean LV wall thickness (mm)	18 (3)	18 (3)
LV mass index (g/m²)	181 (46)	182 (44)
LVEF (%)	56 (12)	56 (13)
Absolute GLS (%)	14 (3)	14 (3)
Average E/e'	18 (6)	18 (7)
RV S' (cm/s)	9 (3)	9 (3)

Data presented as means (SD).

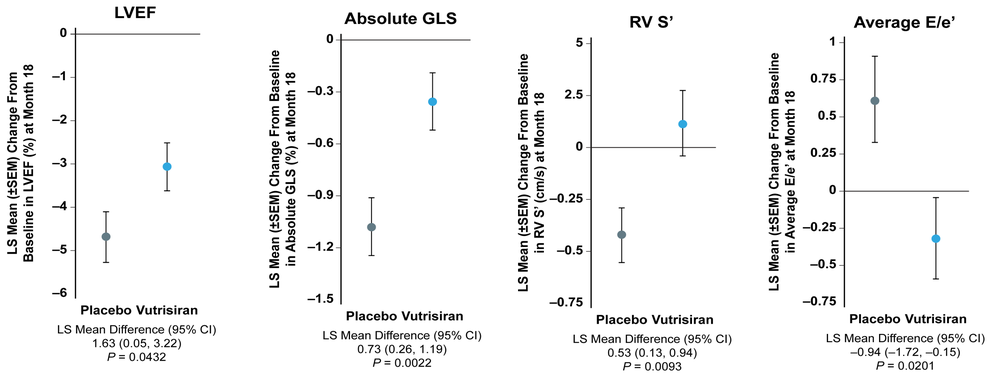
ATTR – transthyretin amyloidosis, NAC – National Amyloidosis Centre, NT-proBNP – *N*-terminal pro-B-type natriuretic peptide, LV - left ventricular, LVEF – left ventricular ejection fraction, E/e' – ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular tissue velocity, GLS – global longitudinal strain, RV – right ventricular, s' –systolic myocardial velocity.

Figure 1. Association of Baseline Echocardiographic Measures of Systolic and Diastolic Function with All-Cause Mortality



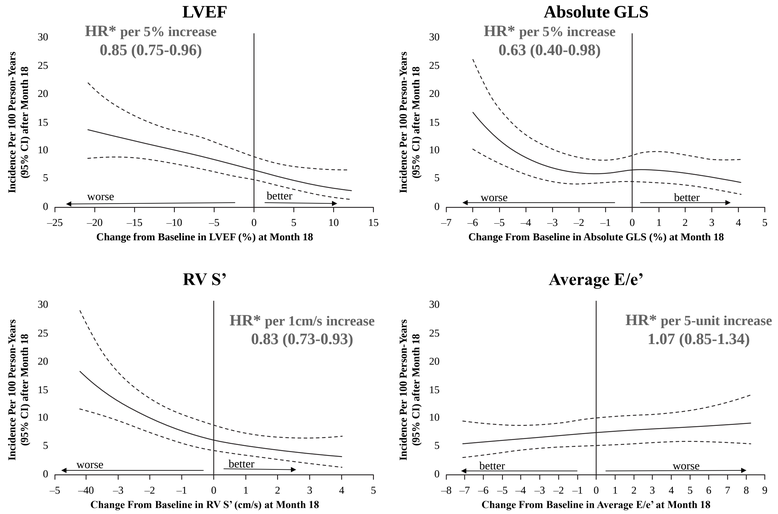
*HR adjusted for age, sex, ATTR disease type (wild-type vs variant), and National Amyloidosis Centre ATTR stage, and stratified by baseline tafamidis use and treatment assignment

Figure 2. Vutrisiran Improved LV Diastolic Function and Attenuated Declines in LV and RV Systolic Function at 18 Months



Models were adjusted for the corresponding baseline echocardiographic parameter, 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).

Figure 3. Association of Changes from Baseline to Month 18 in Echocardiographic Measures of Systolic and Diastolic Function with Subsequent All-Cause Mortality



*HR adjusted for the corresponding baseline echocardiographic parameter, age, sex, ATTR disease type (wild-type vs variant), and National Amyloidosis Centre ATTR stage, and stratified by baseline tafamidis use and treatment assignment

Conclusions

- Baseline measures of LV and RV systolic function and diastolic function provided important prognostic information above and beyond clinical characteristics and the well-validated biomarker-based staging system.
- Vutrisiran improved diastolic function and attenuated declines in LV and RV systolic function at 18 months.
- Worsening LV and RV systolic function over 18 months was associated with a heightened risk of subsequent all-cause mortality.
- The benefits of vutrisiran on cardiac function may, at least in part, mediate the reduced risk of adverse outcomes.

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