

Effects of Vutrisiran on Echocardiographic Cardiac Structure and Function: The HELIOS-B Trial

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Conflicts of interest: None

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Introduction

Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM)

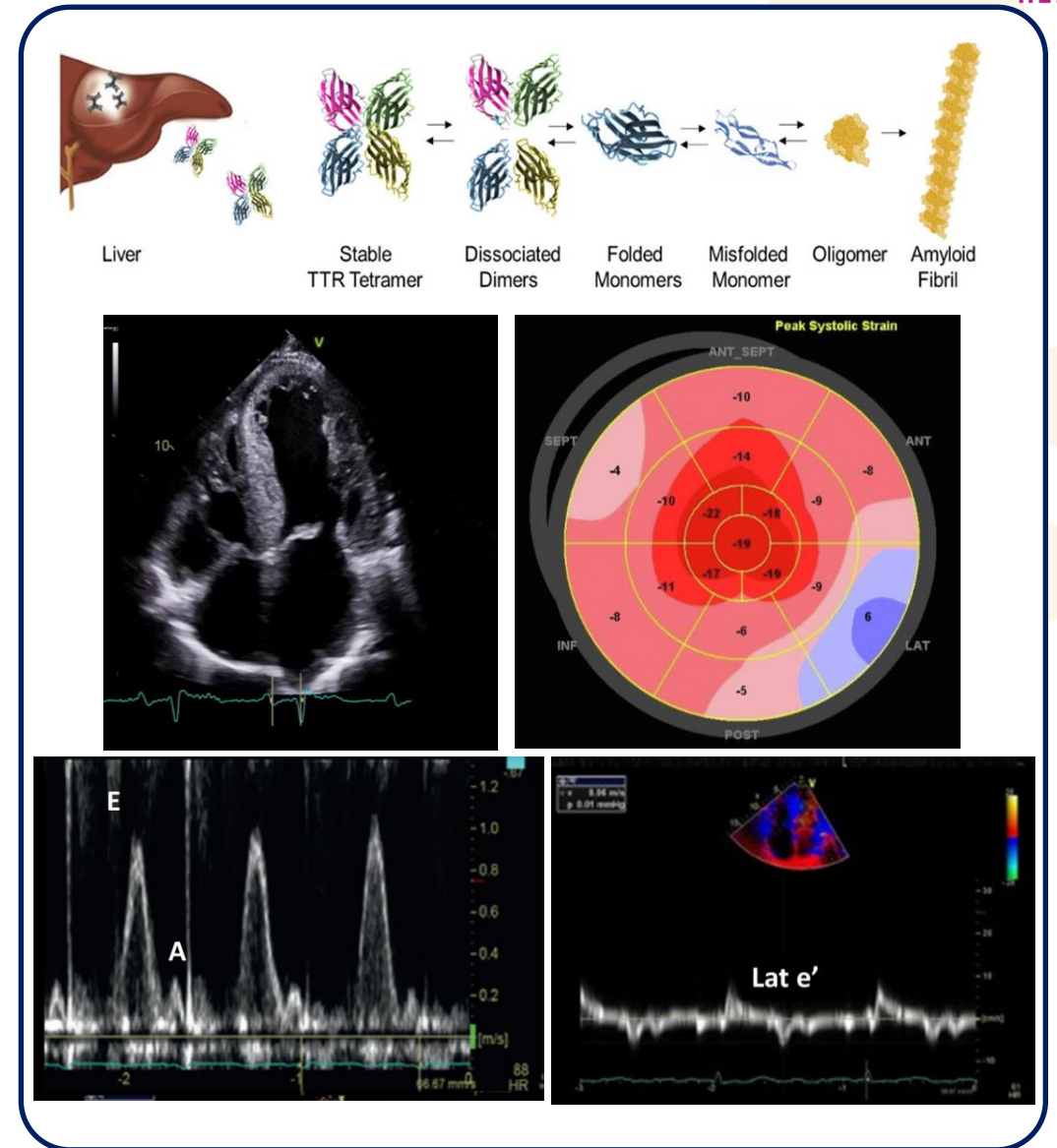
- ATTR-CM is an increasingly diagnosed cause of heart failure associated with high burden of morbidity and mortality¹⁻³
- Contemporary patients have less advanced disease because of earlier diagnosis and improved heart failure management. Many receive tafamidis, SGLT2 inhibitors, and diuretics²
- Extracellular deposition of amyloid fibrils in the heart leads to restrictive physiology, arrhythmias, and conduction disease¹⁻⁴
- Echocardiography is frequently the initial diagnostic modality and is also used to monitor for disease progression, often defined as increases in wall thickness, declines in LVEF or LV peak longitudinal strain, or deterioration in diastolic function^{1,5,6}

HELIOS-B Study

- Evaluated vutrisiran, a SC-administered RNAi therapeutic (quarterly dosing), in patients with ATTR-CM in a Phase 3, randomized, placebo-controlled trial⁷

Objective

- Determine effects of vutrisiran on echocardiographic measures of cardiac structure and function in patients with ATTR-CM



Abbreviations: LV, left ventricular; LVEF LV ejection fraction; SC, subcutaneous; RNAi, RNA interference.

References: 1. Porcari et al. *Cardiovasc Res* 2022;118:3517–35; 2. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:512–26; 3. Ruberg et al. *JAMA* 2024;331:778–91; 4. Kittleson et al. *Circulation* 2020;142:e7–e22; 5. Dorbala et al. *J Am Coll Img* 2020;13:1368–83; 6. Cuddy S et al. *Journal of the American Society of Echocardiography*. 2022;35(9):A31-A40 7. Fontana et al. *N Eng J Med* 2024; DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

HELIOS-B Study Design



A phase 3 study to evaluate vutrisiran in patients with ATTR-CM

Patient Population (n=655)

- ATTR: Wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150 m; NT-proBNP limits^b at baseline
- Approximately 40% of patients on tafamidis at baseline

Select Exclusion Criteria:

- NYHA Class IV HF
- PND score ≥III at the screening visit
- Received prior TTR-lowering treatment

➤ All endpoints were prespecified for analysis separately in the **Overall** and **Monotherapy** populations

Primary Endpoint: Composite outcome of all-cause mortality and recurrent CV events during double blind (DB) period (Month 33–36)

Secondary Endpoints: Change from baseline in 6-minute walk test, KCCQ-OS, all-cause mortality through 42 months, NYHA Functional Class

Select Exploratory Endpoints: Change from baseline in mean left ventricular wall thickness and peak longitudinal strain at M30

- Echocardiographic assessments performed at months 12, 18, 24 and 30

Statistical Analysis for Echo Endpoints

- Changes from baseline to month 30 were analyzed with mixed models for repeated measures
- Fixed effect terms were baseline value, treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis and age group

Vutrisiran SC q3M 25 mg

Placebo SC q3M

Screening Period

Variable DB period

OLE

Day -45

Day 1
(Baseline)

M12
Echo

M18
Echo

M24
Echo

M30
Echo

M33

M36

M60

1:1 randomization^a

^aRandomization was stratified according to the use of tafamidis at baseline (yes vs no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years vs all others).

^bNT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). **Abbreviations:** ATTR-CM; transthyretin amyloidosis with cardiomyopathy; FC, functional class; TTR, transthyretin; NYHA, New York Heart Association, 6-MWT, 6-minute walk test, HF, heart failure, PND, polyneuropathy disability score. **Reference:** Clinicaltrials.gov identifier: NCT04153149.

Contemporary Population with Baseline Characteristics Balanced Across Arms



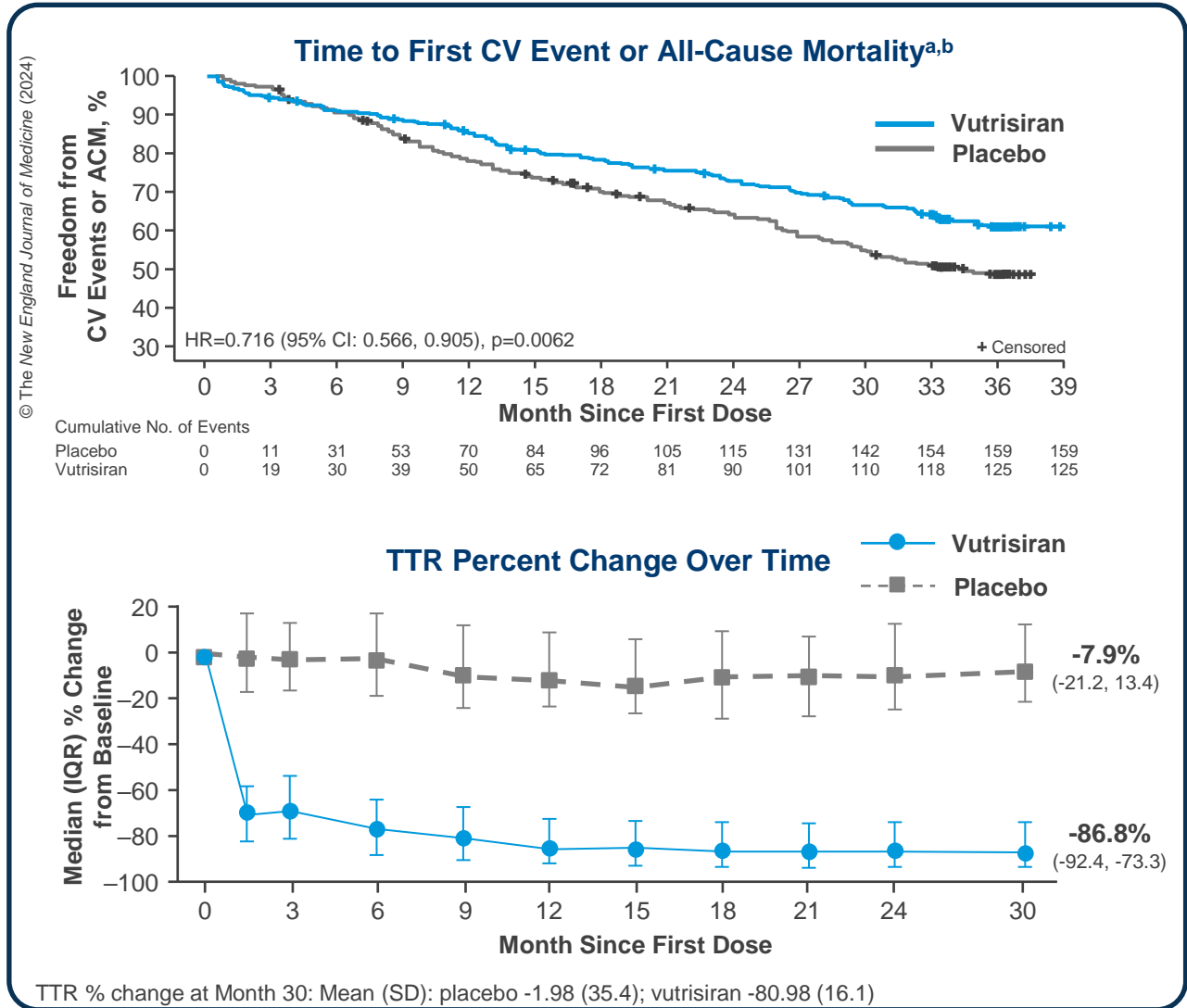
Parameter	Overall Population	
	Placebo (N=328)	Vutrisiran (N=326)
Age (years), median (range)	76 (46, 85)	77 (45, 85)
Male sex, n (%)	306 (93.3)	299 (91.7)
hATTR amyloidosis, n (%)	39 (11.9)	37 (11.3)
NYHA class, n (%)	I	35 (10.7)
	II	258 (78.7)
	III	35 (10.7)
ATTR disease stage, n (%)	1	229 (69.8)
	2	87 (26.5)
	3	12 (3.7)
Baseline 6-MWT, meters, mean (SD)	377 (96)	372 (104)
Baseline KCCQ-OS, points, mean (SD)	72.26 (19.92)	72.96 (19.44)
Baseline NT-proBNP, ng/L, median (IQR)	1801 (1042, 3082)	2021 (1138, 3312)
Baseline Troponin I, ng/L, median (IQR)	65.2 (41.1, 105.5)	71.9 (44.9, 115.9)

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Echo Characteristics	Placebo (N=328)	Vutrisiran (N=326)
LV ejection fraction (%), mean (SD)	55.9 (12.3)	55.6 (12.7)
Peak longitudinal strain (%), mean (SD)	-14.0 (3.5)	-14.0 (3.5)
Stroke volume (mL), mean (SD)	53.8 (19.0)	50.7 (16.3)
Mean LV wall thickness (mm), mean (SD)	18.2 (3.0)	18.2 (3.0)
Relative wall thickness, mean (SD)	0.8 (0.2)	0.8 (0.2)
LV mass index (g/m ²), mean (SD)	180.8 (46.1)	182.1 (44.2)
E/A ratio, mean (SD)	1.9 (1.0)	2.1 (1.1)
Lateral E/e' ratio, mean (SD)	15.3 (6.3)	14.8 (6.7)

- **Tafamidis:** Baseline ~40% in both treatment arms; drop-in during DB ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors:** Baseline ~3% in both treatment arms; drop-in during DB ~35% and ~31% for placebo and vutrisiran, respectively
- **Substantial use of diuretics:** Baseline ~80% in both treatment arms; Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

HELIOS-B Met All 10 Primary and Secondary Endpoints in the Overall and Monotherapy Populations



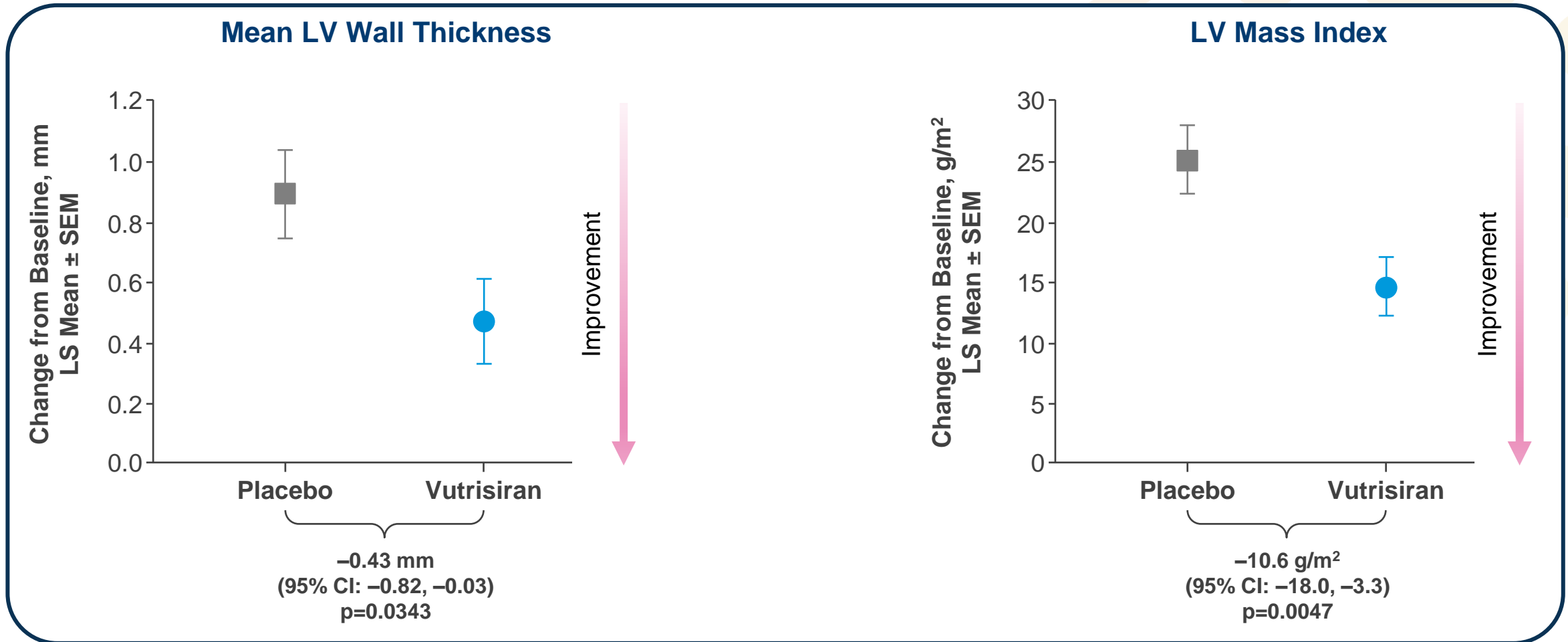
Endpoint	Treatment Effect Estimation	Overall Population (N=654)		Monotherapy Population (N=395)	
		Treatment Effect	p-value	Treatment Effect	p-value
Primary endpoint					
Composite outcome of all-cause mortality and recurrent CV events ^{c,d}	Hazard ratio	0.718	0.0118	0.672	0.0162
Secondary endpoints					
6-MWT change at Month 30 ^e	LS Mean difference	26.46	0.00008	32.09	0.0005
KCCQ-OS change at Month 30 ^e	LS Mean difference	5.80	0.0008	8.69	0.0003
All-cause mortality through Month 42 ^b	Hazard ratio	0.645	0.0098	0.655	0.0454
NYHA class: % stable or improved at Month 30 ^f	Adjusted % difference	8.7%	0.0217	12.5%	0.0121

- **Vutrisiran met all 10 primary and secondary endpoints**
- **Rapid and durable TTR knockdown through Month 30**
- **Knockdown comparable to prior studies with vutrisiran**

^aBased on IPTW-adjusted Kaplan-Meier curves. ^bHR derived from Cox PH model, p-value derived from log-rank test. ^cPrimary analysis based on the modified Andersen-Gill model, also known as LWYY. ^dAssessed at 33-36 months. ^eBased on a MMRM model. ^fBased on CMH method. From N Engl J Med, Fontana et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. DOI: 10.1056/NEJMoa2409134. Epub ahead of print. Copyright © (2024). Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. **Abbreviations:** CV, cardiovascular; 6-MWT, 6-minute walk test; IQR, interquartile range; KCCQ-OS, Kansas City cardiomyopathy questionnaire – Overall Summary; LS, least squares; NYHA, New York Heart Association. **Reference:** Fontana et al. N Eng J Med 2024. DOI: 10.1056/NEJMoa2409134. Epub ahead of print.

Vutrisiran Significantly Attenuated Increases in LV Wall Thickness and LV Mass Index at Month 30 vs Placebo

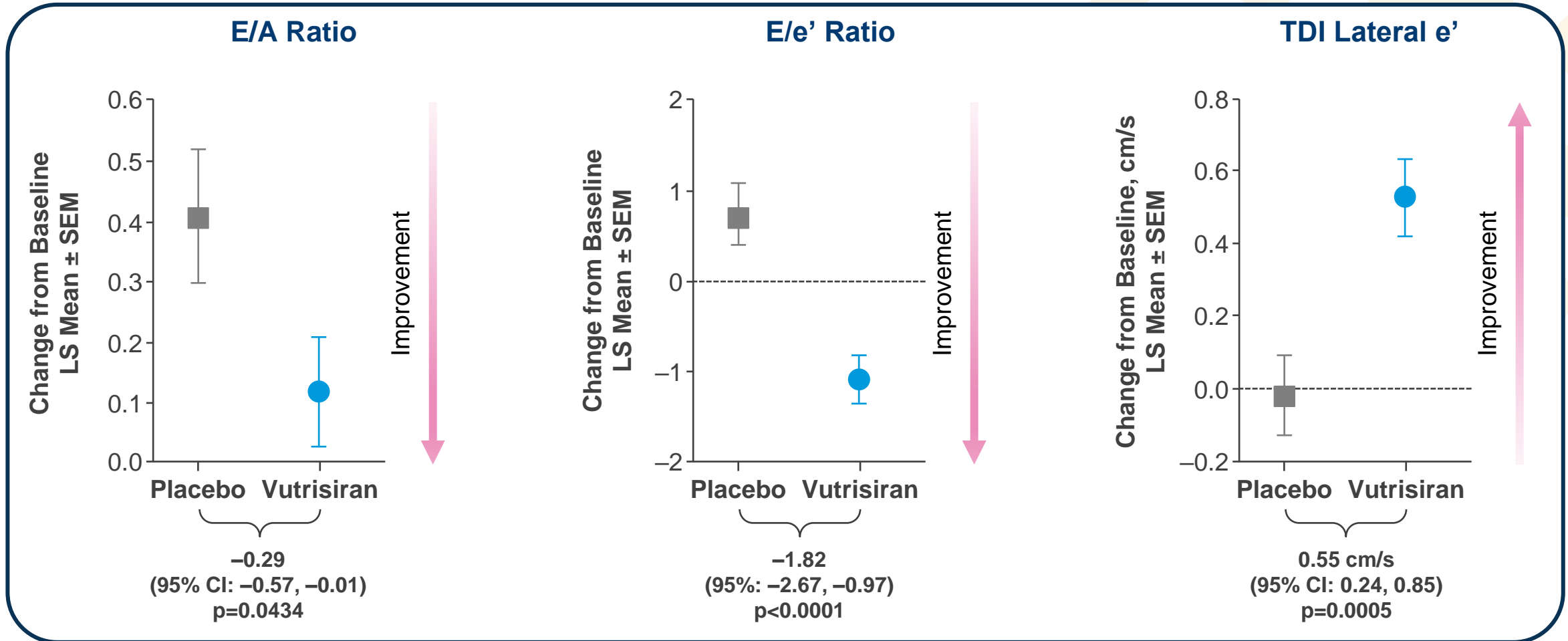
Overall Population



Vutrisiran Significantly Improved LV Diastolic Function at Month 30 vs Placebo



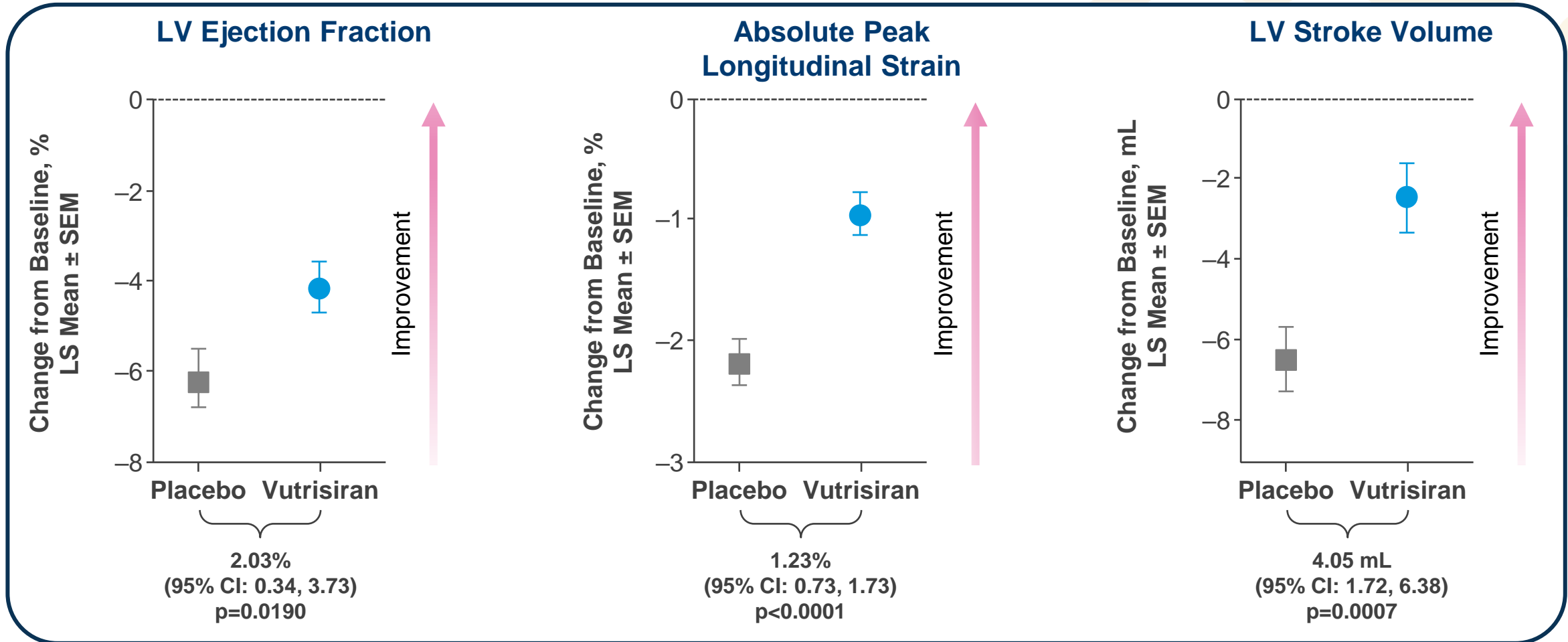
Overall Population



Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** CI, confidence interval; E/A, ratio of early to late diastolic transmitral inflow velocities; E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; SEM, standard error of the mean; TDI lateral e', lateral peak early diastolic mitral annular tissue velocity.

Vutrisiran Significantly Attenuated Decline in LV Systolic Function at Month 30 vs Placebo

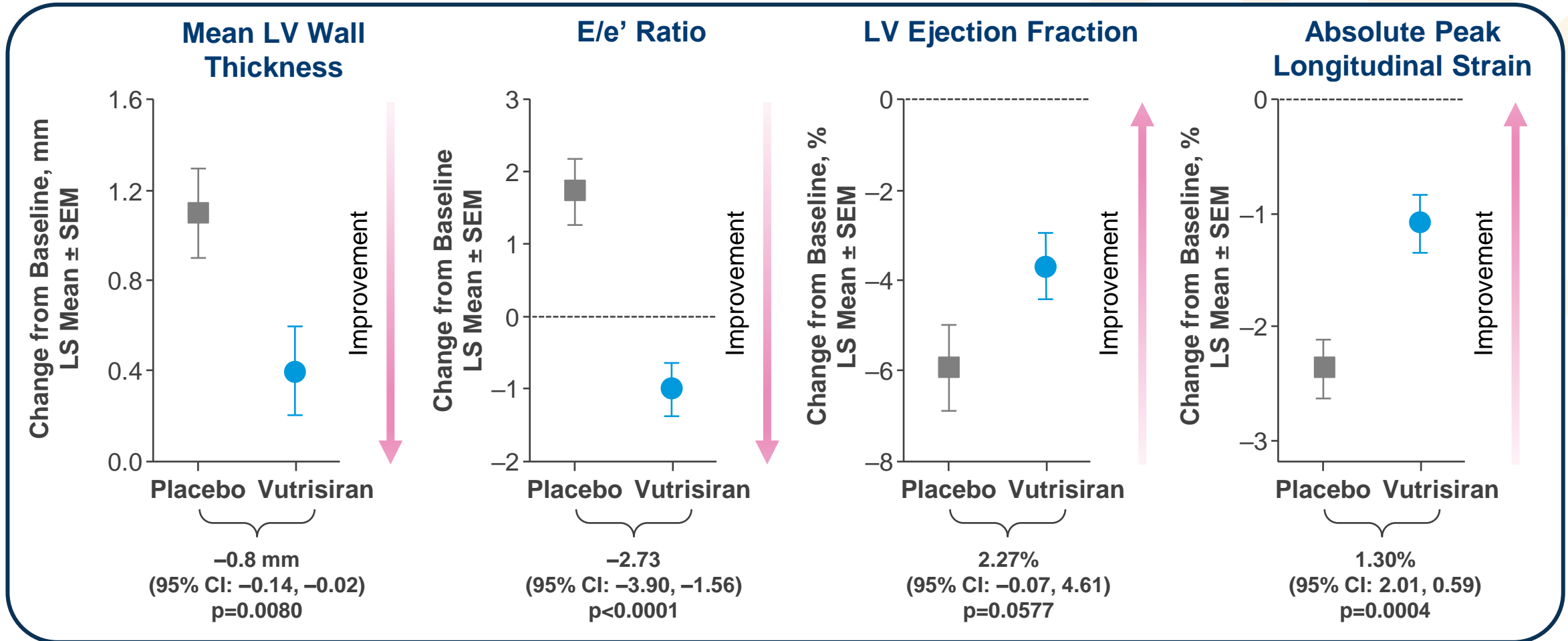
Overall Population



The Benefits of Vutrisiran on Cardiac Structure and Function were Similar or Larger in the Monotherapy Population



Monotherapy Population

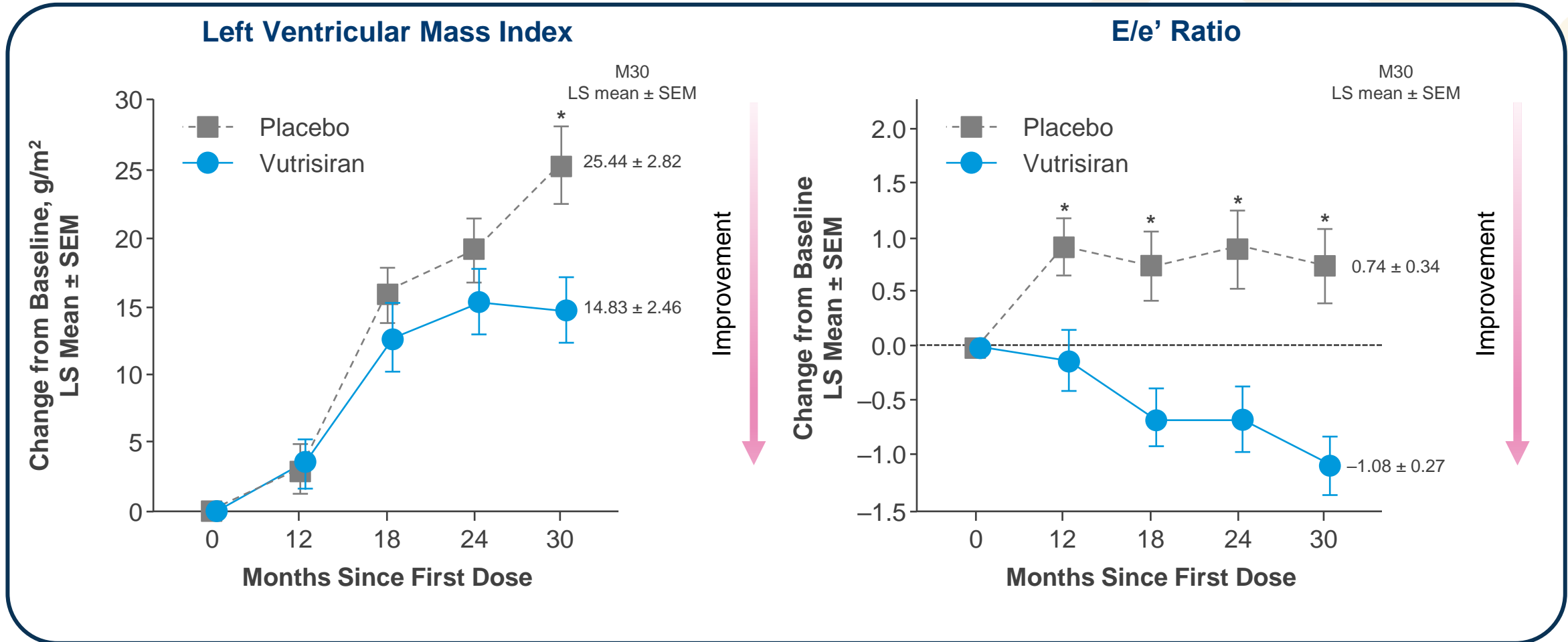


Results are from MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.

Abbreviations: CI, confidence interval; E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; NS, non-significant; SEM, standard error of the mean.

Significant Between-Group Differences in LV Diastolic Function Emerged as Early as 12 Months

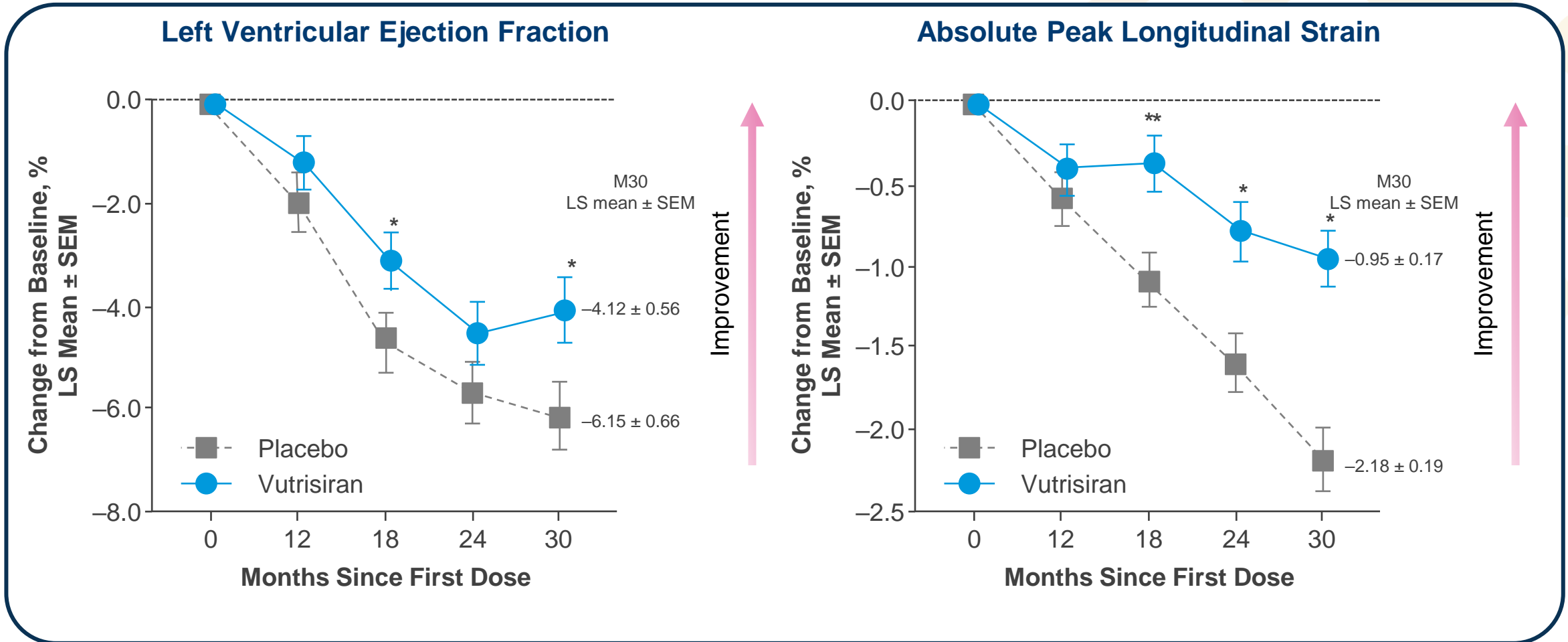
Overall Population



*p<0.05. Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; LV, left ventricular; SEM, standard error of the mean.

Significant Between-Group Differences in LV Systolic Function Emerged as Early as 18 Months

Overall Population



*p<0.05. Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. **Abbreviations:** LS, least squares; LV, left ventricular; SEM, standard error of the mean.

Summary



HELIOS-B



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- In this contemporary population, compared with placebo, vutrisiran had beneficial impact across all measures of cardiac structure, systolic, and diastolic function, providing further evidence of the disease-modifying effect of vutrisiran treatment.
- These echocardiographic findings were consistent with the benefit observed with vutrisiran on clinical outcomes, biomarkers, and health status.
- The magnitude of the treatment effects with vutrisiran compared to placebo were similar or greater in the monotherapy population.
- Significant improvement in diastolic function with vutrisiran was observed early, followed by significant favorable effects on cardiac structure and systolic function.
- If approved, vutrisiran has the potential to become a standard of care for newly diagnosed patients with ATTR-CM and those progressing on stabilizing therapies.

We thank the patients, their families, investigators, staff, and collaborators for their participation in HELIOS-B