Left Atrial Strain and Clinical Outcomes in Transthyretin Amyloidosis with Cardiomyopathy: Insights from the HELIOS-B Trial on Vutrisiran Efficacy

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Abstract: 4362366

Scientific Sessions

American Heart Association.

November 7-10, 2025
New Orleans, LA

Financial Disclosure

HELIOS-B was sponsored by Alnylam Pharmaceuticals, and the Cardiac Imaging Core Laboratory receives research support from Alnylam Pharmaceuticals.

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Research funding from Pfizer, Speaking fees Pfizer, Advisory board fees Pfizer, Bridge Bio, Novo Nordisk and Bristol Myers Squibb.

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Consultancy for Alnylam, Alexion/Caelum Biosciences, Astrazeneca, Bridgbio/Eidos, Prothena, Attralus, Intellia Therapeutics, Ionis Pharmaceuticals, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Prothena, Pfizer, Novonordisk, Bayer, Mycardium. Research grants from: Alnylam, Bridgbio, Astrazeneca, Pfizer.
Share options in LexeoTherapeutics and shares in Mycardium.

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Grant support from NIH R01HL177670 and AG081582 and research funding from Alnylam, Attralus, BridgeBio, Intellia, and Ionis, and personal fees from Alnylam.

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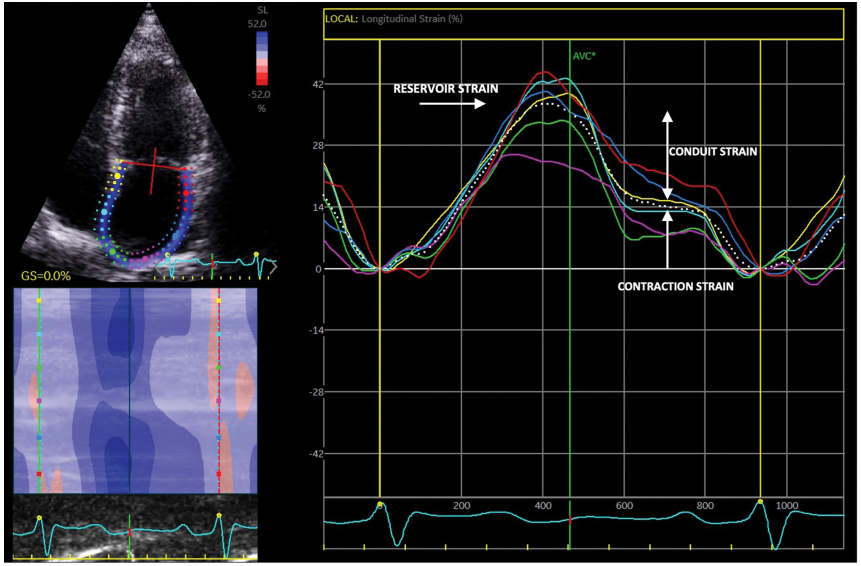
Research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Cytokinetics, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI. Consultancy for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo.

Background

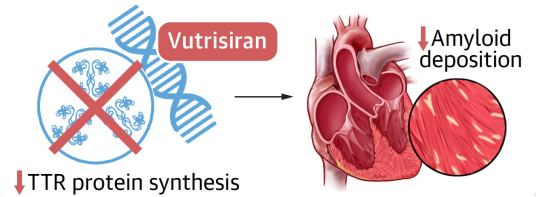
Transthyretin Amyloidosis with Cardiomyopathy (ATTR-CM) and Left Atrial Dysfunction

- ATTR-CM is an increasingly diagnosed cause of heart failure, related to deposition of amyloid fibrils in the heart.
- Infiltration of the left atrium (LA) and LA remodelling in response to elevated filling pressures contribute to LA dysfunction in ATTR-CM.
- LA strain (LAS) measures phasic LA function and has been associated with mortality, incident AF and cardioembolic events across a wide range of disease states.



Vutrisiran

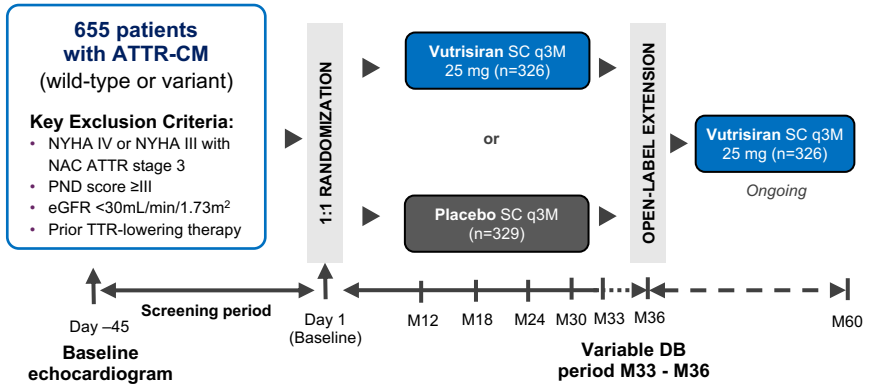
- Vutrisiran, a SC-administered RNAi therapeutic, inhibits hepatic synthesis of transthyretin (TTR).
- We sought to evaluate the association of LAS with clinical outcomes and treatment response to vutrisiran in HELIOS-B.



Bandera F, et al. *JACC Cardiovasc Imaging*. 2022 Jan;15(1):17-29. Adams D, et al. *Amyloid*. 2023 Mar;30(1):1-9. Fontana M, et al. *N Engl J Med*. 2025 Jan;392(1):33-44

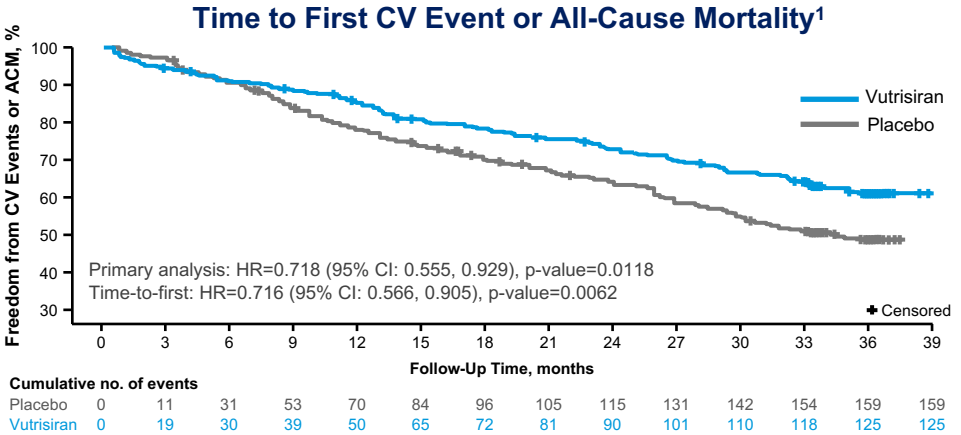
HELIOS-B Study Design and Primary Results

Vutrisiran reduced rates of all-cause mortality and recurrent CV events in HELIOS-B.



Primary endpoint
- Composite of ACM and recurrent CV events up to Month 36

Key secondary endpoint
- ACM up to 42 months



Vutrisiran also had favorable effects on echocardiographic measures of cardiac structure and function.[2]

Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; CI, confidence interval; CM, cardiomyopathy; CV, cardiovascular; DB, double-blind; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; PND, polyneuropathy disability score; SC, subcutaneous.

[1]Fontana M, et al. *N Engl J Med*. 2025 Jan;392(1):33-44; [2]Jering K, et al. *Nat Med*. 2025 Oct;31(10):3560-3568.

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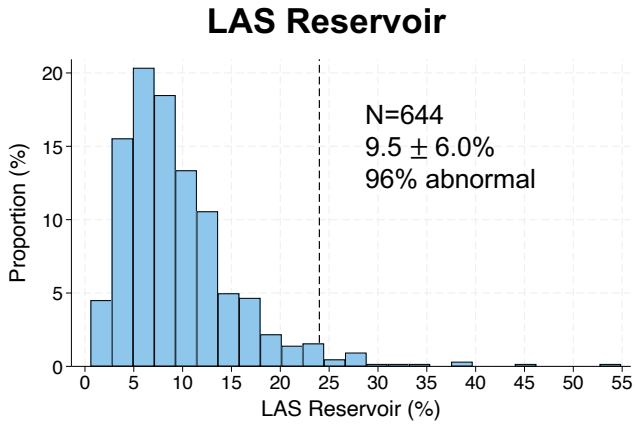
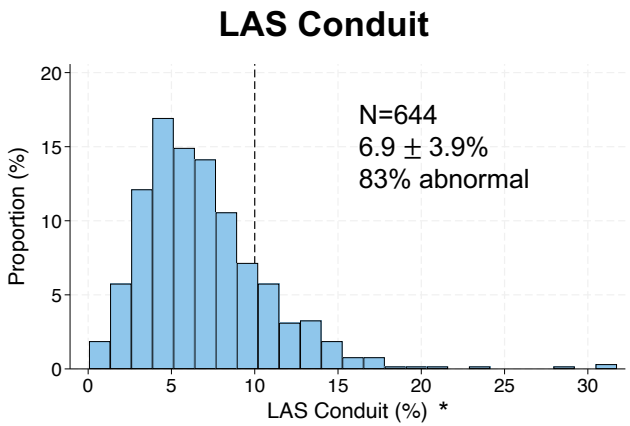
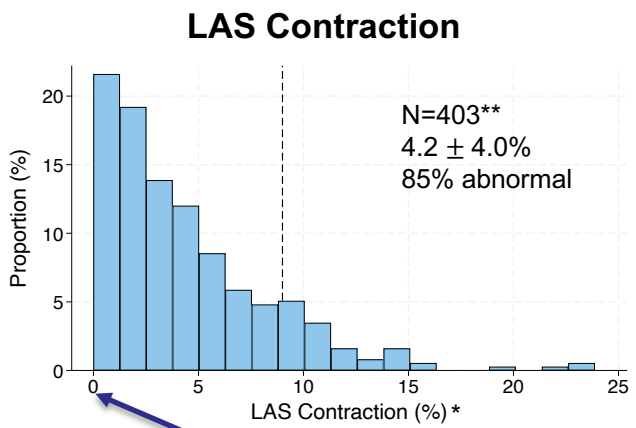
LA Strain in HELIOS-B

LA dysfunction by LA strain is common among patients enrolled in HELIOS-B.







61 patients (9%) with atrial electromechanical dissociation (AEMD)†

Table 1. Upper Limits and Lower Limits of Normal Values for LA Strain

	Men			Women		
	Age 18-40 y	Age 41-65 y	Age >65 y	Age 18-40 y	Age 41-65 y	Age >65 y
LA reservoir strain	25-63	23-61	24-57	29-62	22-56	21-56
LA conduit strain	18-50	12-43	10-36	19-52	12-42	9-36
LA pump strain	2-23	5-28	9-32	2-21	6-28	7-30

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* LAS conduit and contraction are shown as absolute values.
** LAS contraction was only measured in patients without AF/AFl (n=403).
† AEMD defined as LAS contraction of 0%.

Nagueh SF, et al. *JACC Cardiovasc Imaging*. 2023 May;16(5):691-707

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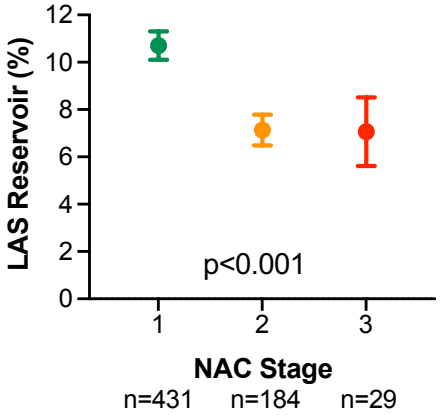
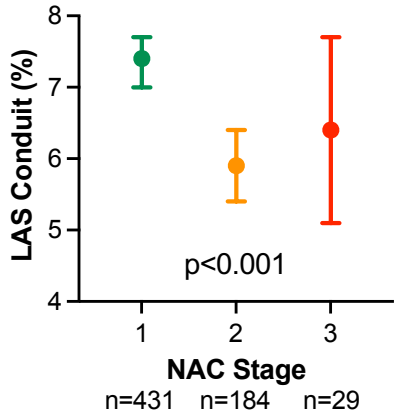
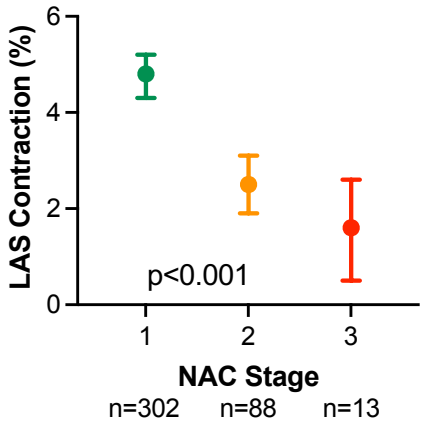
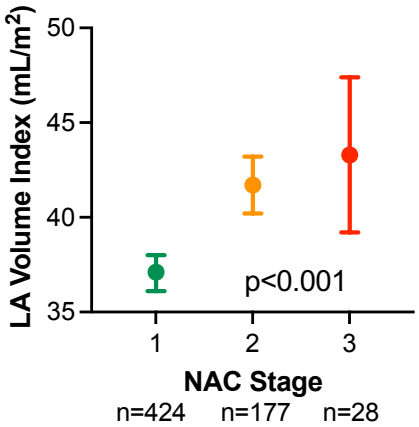
LA Strain Correlates with ATTR-CM Disease Severity

LA strain worsens and LA volume index increases with worse National Amyloidosis Centre disease stage.









Values represent mean (95% CI).

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Baseline Characteristics According to LAS Reservoir

Worse LAS reservoir → *Better LAS reservoir*

LAS Reservoir	Quartile 1 <5.5% (n=161)	Quartile 2 5.5 - 8.2% (n=161)	Quartile 3 8.2-12.0% (n=161)	Quartile 4 >12.0% (n=161)	p-value
Age (years)	76 ± 6	75 ± 7	76 ± 6	75 ± 8	0.51
Male sex	95%	98%	90%	87%	<0.001
ATTRwt	92%	88%	89%	84%	0.04
AF/AFl	84%	70%	65%	39%	<0.001
Pacemaker	21%	19%	17%	10%	0.01
NT-proBNP (ng/L)	2903 [1906, 4470]	2231 [1494, 3567]	1852 [1096, 2838]	1029 [646, 1757]	<0.001
Echocardiographic Characteristics					
LV mass index (g/m^2)	192 ± 49	188 ± 43	181 ± 43	164 ± 42	<0.001
LVEF (%)	50 ± 14	55 ± 12	58 ± 11	60 ± 11	<0.001
Absolute GLS (%)	12 ± 3	14 ± 4	14 ± 3	16 ± 3	<0.001
Lateral e' (cm/s)	5 ± 2	6 ± 2	6 ± 2	7 ± 2	<0.001
E/e'	20 ± 6	19 ± 7	18 ± 6	15 ± 5	<0.001
A wave (cm/s)	38 ± 20	38 ± 21	45 ± 20	57 ± 22	<0.001
LA volume index (mL/m^2)	41 ± 10	40 ± 10	39 ± 10	35 ± 10	<0.001

Abbreviations: AF/AFl, atrial fibrillation/flutter; ATTR, transthyretin amyloidosis; A wave, late mitral inflow velocity; E wave, early mitral inflow velocity; e', early diastolic mitral annular tissue velocity; GLS, global longitudinal strain; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; wt, wild-type.

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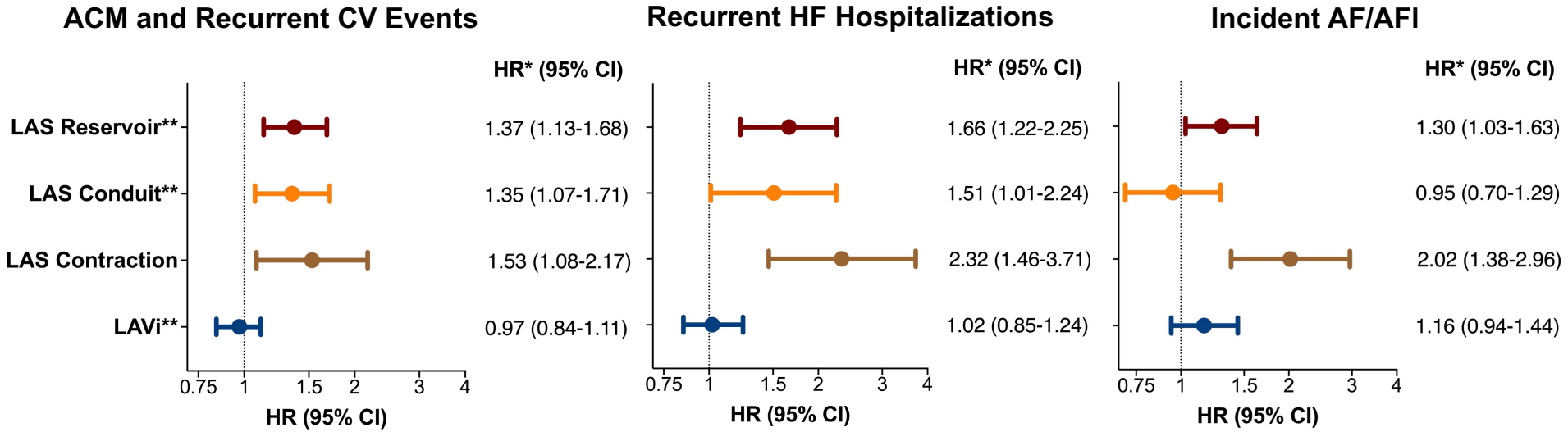
Association of LA Strain and Clinical Outcomes

LA strain, but not LAVi, is associated with all-cause mortality and recurrent CV events and HF hospitalizations independent of LV systolic function and E/e'.



*HR scaled to 5% decrease in LAS and 10mL/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 LA volume index.

**Additionally adjusted for AF/AFI.

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Abbreviations: ACM, all-cause mortality; AF, atrial fibrillation; AFI, atrial flutter; ATTR, transthyretin amyloidosis; CV, cardiovascular; E wave, early mitral inflow velocity; e', early diastolic mitral annular tissue velocity; GLS, global longitudinal strain; HF, heart failure; HR, hazard ratio; LAS, LA strain; LAVi, LA volume index; LV, left ventricular; NAC, National Amyloidosis Centre.

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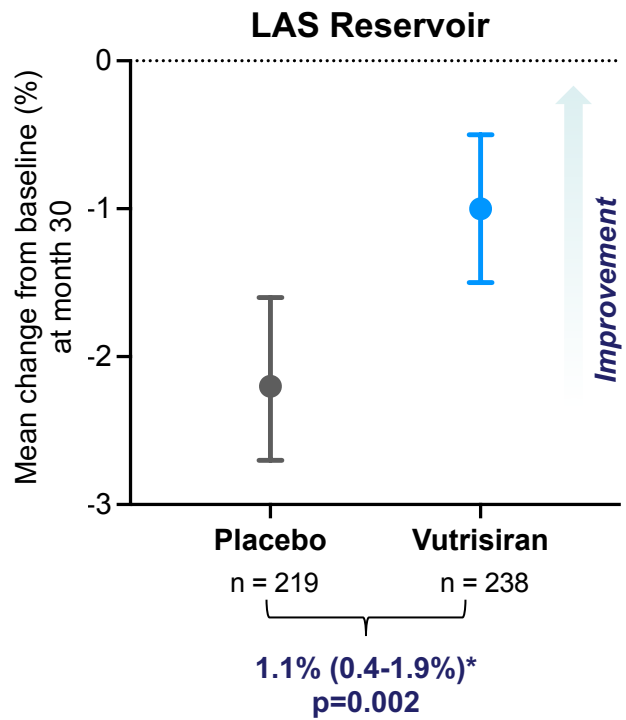
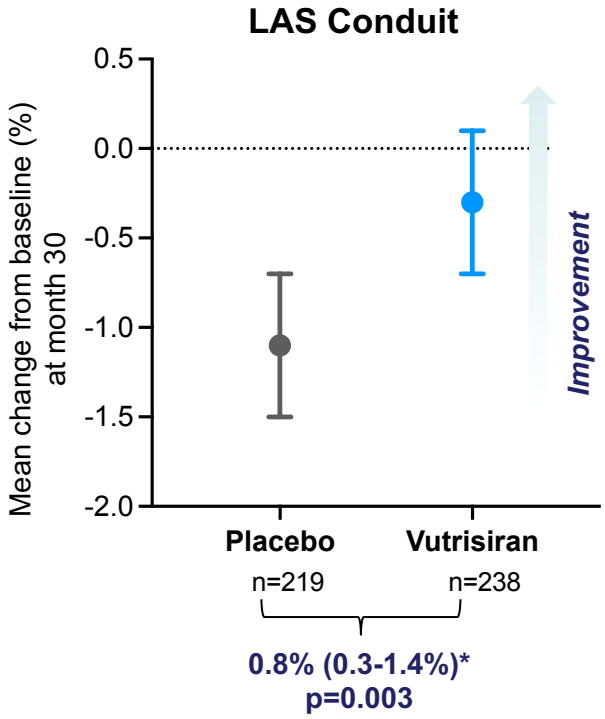
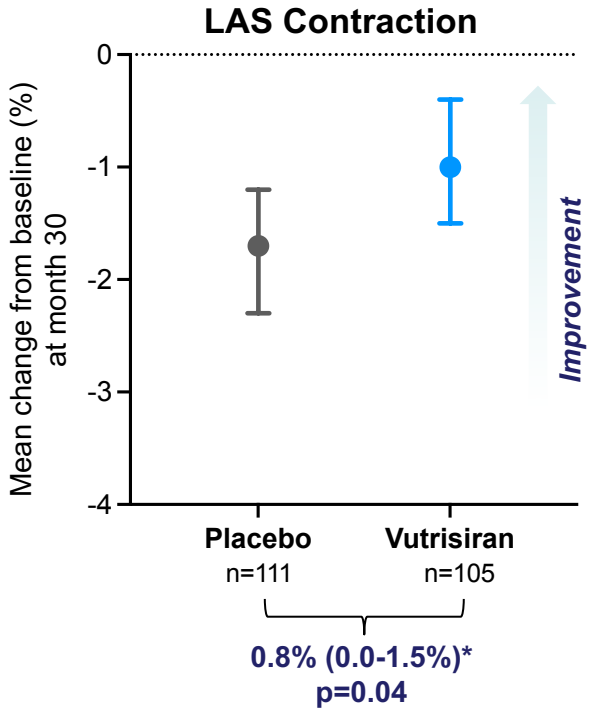
Treatment Effect of Vutrisiran on LA Strain

Vutrisiran attenuates worsening of LA strain at month 30 compared with placebo.







The treatment effect of vutrisiran on the primary outcome is not modified by LA strain (p-interaction >0.46).

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*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.

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Conclusions

- LA function is markedly impaired among patients with ATTR-CM enrolled in HELIOS-B and correlates with disease severity.
- LA strain, but not LA volume index, is independently associated with ACM and recurrent CV events and HF hospitalizations. LAS reservoir and contraction are independently associated with incident AF.
- Consistent with its beneficial effects on other measures of cardiac structure and function, vutrisiran attenuates worsening of LA strain at 30 months compared with placebo.
- These findings support the central role of LA function in the pathophysiology of ATTR-CM.

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

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