Effects of Vutrisiran on Measures of Cardiac Structure, Function and Amyloid Burden by Cardiovascular Magnetic Resonance from the HELIOS-B Trial

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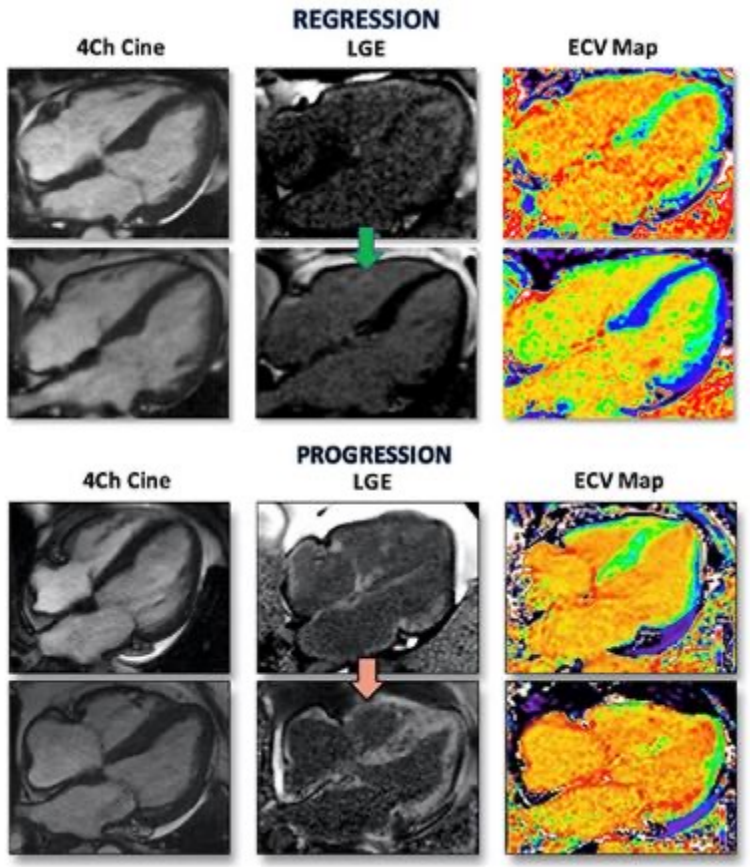
Disclosures

- The HELIOS-B study was funded by Alnylam Pharmaceuticals
- Dr Razvi reports no relevant disclosures

Introduction

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognised cause of heart failure.
- Vutrisiran, an RNAi therapeutic that suppresses hepatic TTR production met its primary and secondary endpoints in the HELIOS-B trial reducing all cause mortality and CV events compared to placebo in patients with ATTR-CM.[1]
- Multiparametric cardiovascular magnetic resonance (CMR) can track cardiac amyloid load with extracellular volume (ECV) mapping.[2]



1: Fontana M, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025 Jan 2;392(1):33-44. doi: 10.1056/NEJMoa2409134

2: Razvi Y, Patel RK, Fontana M and Gillmore JD (2021) Cardiac Amyloidosis: A Review of Current Imaging Techniques. Front. Cardiovasc. Med. 8:751293. doi: 10.3389/fcvm.2021.751293

Objective and design

- **Objective:** To analyze the association between treatment with vutrisiran and changes in cardiac structure, function and amyloid burden assessed by CMR

- **Design**
  - We retrospectively identified UK National Amyloidosis Centre patients participating in HELIOS-B who underwent serial CMR as part of their routine clinical care
  - CMRs were conducted at baseline/pre-dosing and months 12, 24 and 36 post dose

Methodology

- CMR analysis was conducted by two experienced, independent readers, blinded to treatment allocation
- Differences between treatment groups (vutrisiran and placebo) at follow-up were assessed using analysis of covariance with treatment group and baseline CMR values as covariates
- 24- and 36-month data were pooled in a mixed model analysis to assess treatment effect due to reduced patient numbers at follow-up
- Amyloid progression and regression were defined as an absolute change of ≥5% in ECV, as previously published[1]. All changes <5% were considered stable.

1: Patel RK, et al. Transthyretin amyloid cardiomyopathy: natural history and treatment response assessed by cardiovascular magnetic resonance. Eur Heart J. 2025 Jul 11:ehaf412. doi: 10.1093/eurheartj/ehaf412. Epub ahead of print. PMID: 40643267.

Study population

- The study population comprised 43 (mean (SD) age 75.0 (5.67), 41 male, 21 vutrisiran, 22 placebo) UK NAC HELIOS-B participants who underwent baseline CMR
- Baseline parameters comparable between treatment groups
- No patients in either treatment arm received TTR stabilizer therapy during the study period
- Thirty-nine (21 vutrisiran, 18 placebo) completed 1-year CMR
- 26 (14 vutrisiran, 12 placebo) completed 2- year CMR
- 17 (9 vutrisiran, 8 placebo) completed 3-year CMR
- Apart from death which was more common in the placebo group, pattern of attrition was balanced between both treatment arms

Parameter	Placebo (n=22)	Vutrisiran (n=21)	p-value
Demographics & Clinical Biochemistry			
Age (years)	75.81 (±6.17)	74.32 (±5.16)	0.395
Sex (M:F)	21:1	20:1	0.973
NT-proBNP (ng/L)	1915 [940, 2432]	2417 [1210, 3254]	0.25
eGFR (ml/min/1.73m^2)	66.0 [59.0, 83.0]	72.5 [59.0, 82.0]	0.75
Troponin I (ng/L)	51.6 [40.1, 100.3]	77.6 [54.2, 128.7]	0.13
KCCQ Score	72.8 (±22.7)	77.7 (±18.6)	0.44
Wild type: variant TTR genotype	18:4	19:2	0.66
CMR parameters			
LV EDV (ml)	172.83 (±42.29)	164.19 (±35.11)	0.478
LV ESV (ml)	87.77 (±41.11)	86.83 (±36.27)	0.938
LV SV (ml)	85.8 (±24.28)	84.90 (±18.89)	0.472
LVEF (%)	50.62 (±13.32)	51.70 (±11.52)	0.984
LVM (g)	184.76 (±33.08)	188.91 (±38.32)	0.710
RV EDV (ml)	178.30 (±36.72)	183.92 (±52.01)	0.686
RV ESV (ml)	97.18 (±34.03)	99.06 (±43.71)	0.877
RV SV (ml)	81.07 (±20.61)	85/.37 (±19.12)	0.489
RVEF (%)	46.28 (±10.34)	48.36 (±12.05)	0.551
LAA (cm2)	32.60 (±6.21)	32.95 (±7.67)	0.869
RAA (cm2)	31.15 (±7.92)	31.63 (±8.25)	0.851
Native T1 (ms)	1135.91 (±44.69)	1137.29 (±40.38)	0.916
ECV (%)	58.73 (±5.87)	56.05 (±8.71)	0.242

Results

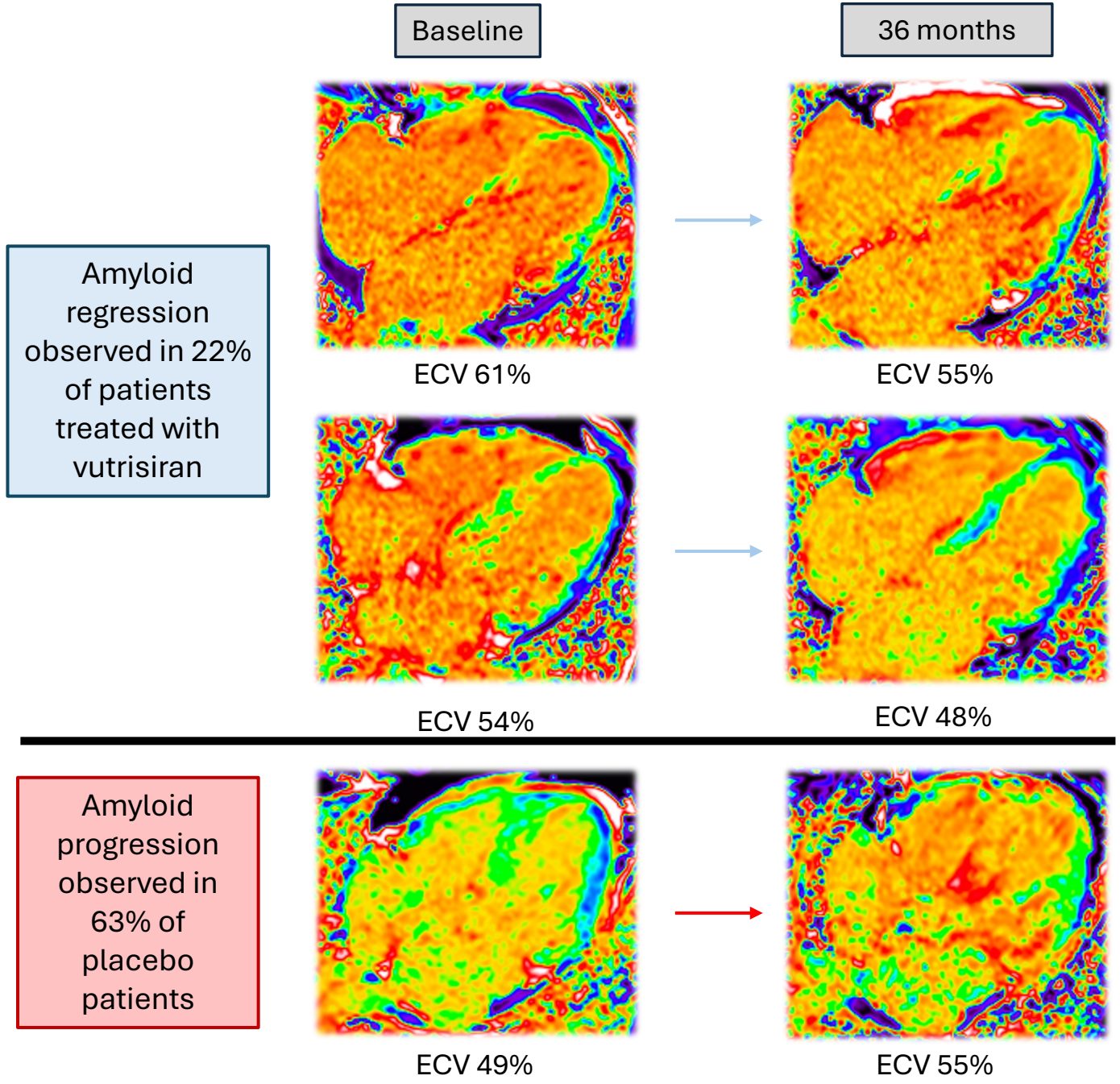
- In the pooled analysis, treatment with vutrisiran was associated with statistically significant and directionally favourable changes in multiple measures of cardiac structure and function compared to placebo

Parameter	Baseline value	Pooled treatment effect from months 24 and 36*	P-value
LVEDV (ml)	168.72(38.82)	-2.66 (-14.11, 8.78)	0.648
LVESV (ml)	**87.32(38.41)**	**-23.30 (-35.55, -11.04)**	**<0.001**
LVSV (ml)	**83.47(21.76)**	**+17.81 (7.34, 28.29)**	**0.001**
LVEF (%)	**50.66(12.34)**	**+11.57 (6.00, 17.15)**	**<0.001**
LV mass (g)	**186.74(35.54)**	**-22.07 (-34.57, -9.57)**	**0.001**
RVEDV (ml)	180.98(44.24)	-15.12 (-31.96, 1.71)	0.078
RVESV (ml)	**98.07(38.46)**	**-26.51 (-41.51, -11.52)**	**0.001**
RVSV (ml)	**83.12(19.79)**	**+12.94 (2.25, 23.62)**	**0.018**
RVEF (%)	**47.27(11.10)**	**+10.51 (5.49, 15.52)**	**<0.001**
LAA (cm2)	32.77(6.89)	-0.30 (-3.37, 2.76)	0.846
RAA (cm2)	31.39(7.99)	+0.75 (-2.52, 4.03)	0.651
Native T1 (ms)	**1136.58(42.14)**	**-18.58 (-35.83, -1.34)**	**0.035**
ECV (%)	**57.42(7.43)**	**-3.42 (-5.98, -0.85)**	**0.009**

*The treatment effect values reported are the least square mean differences

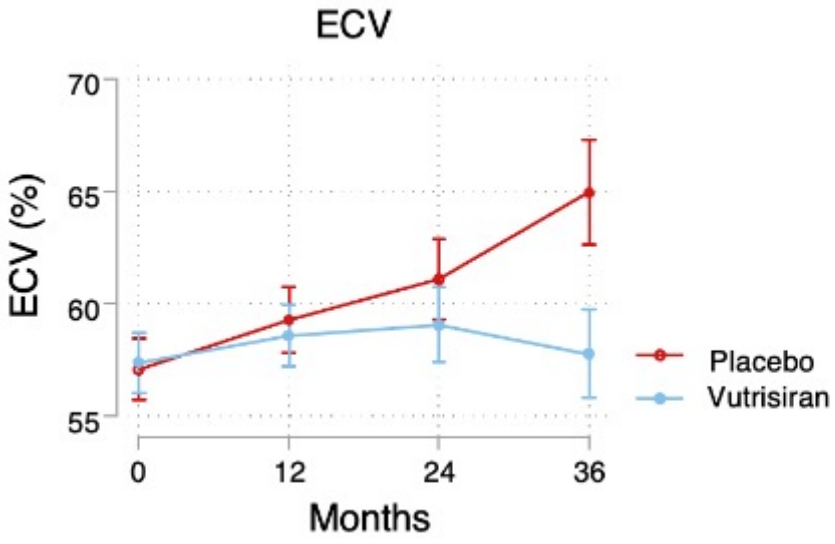
Results – ECV

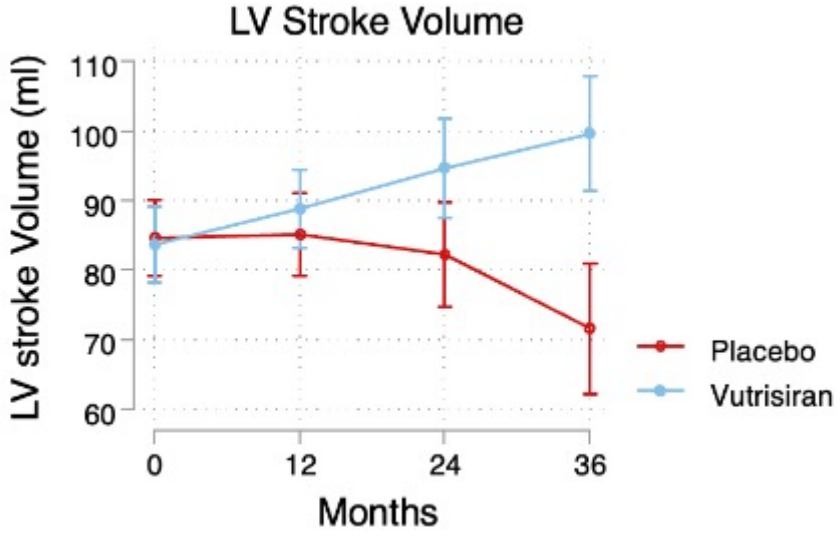
- At year 3, amyloid regression was observed in 2/9 (22%) of vutrisiran patients whereas no placebo patients regressed
- Conversely, 5/8 (63%) of patients receiving placebo progressed vs 1/9 (11%) of patients who received vutrisiran
- At 36 months, patients receiving vutrisiran exhibited an absolute mean (SD) reduction in ECV of -0.10% (±4.72) vs an increase of +7.86% (±5.67) in the placebo group (p=0.006)

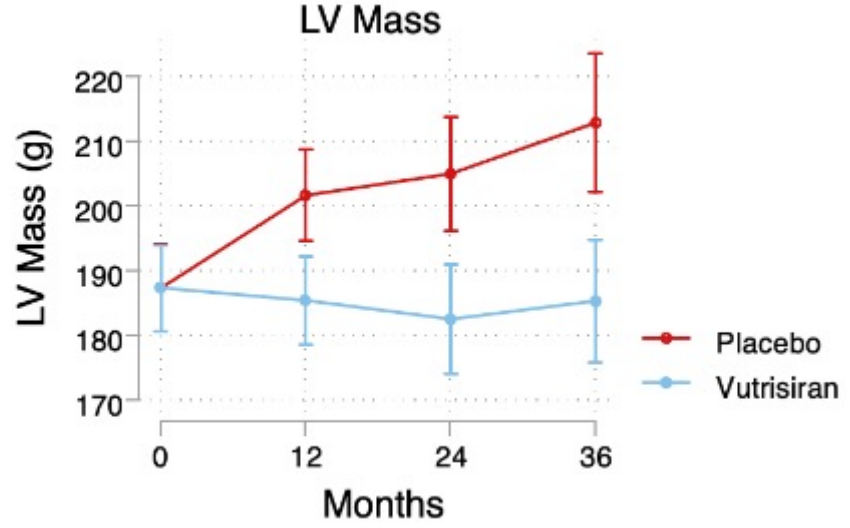


Discussion

- In this study, treatment with vutrisiran was associated with changes consistent with favourable effects on cardiac structure, function, and amyloid burden compared with placebo.
- Over 3 years, patients receiving vutrisiran demonstrated statistically significant increases in biventricular ejection fraction and stroke volumes, alongside reductions in left ventricular mass and extracellular volume







Conclusions

- These findings support the hypothesis that effective suppression of TTR production can shift the balance between amyloidogenesis and clearance, permitting amyloid regression and cardiac remodelling
- Overall, these data complement the findings of the main HELIOS-B study and inform disease modification with siRNA therapy in ATTR-CM
- Results should be interpreted with caution in the context of limitations including the small sample size and attrition over follow up

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