THE EFFECT OF VUTRISIRAN ON CARDIOPULMONARY RESPONSE TO EXERCISE IN ATTR-CM

Brinda Thillainathan | National Amyloidosis Centre, Royal Free Hospital, London, UK

#ScientificSessions26

CO-AUTHORS

National Amyloidosis Centre, United Kingdom

Awais Sheikh

Josephine Mansell

Sorayya Kakhi

Lucia Venneri

Daniel Knight

Philip Hawkins

Julian Gillmore

Marianna Fontana

De Gasperi Cardio and Transplant Centre, Italy

Piero Gentile

Cardiology Unit, IRCCS MultiMedica, Italy

Francesco Bandera

Brigham and Women's Hospital, Harvard Medical School, Massachusetts

Scott Solomon

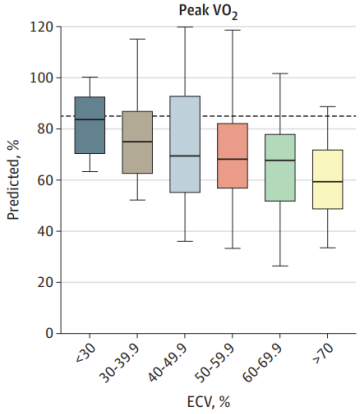
DISCLOSURES

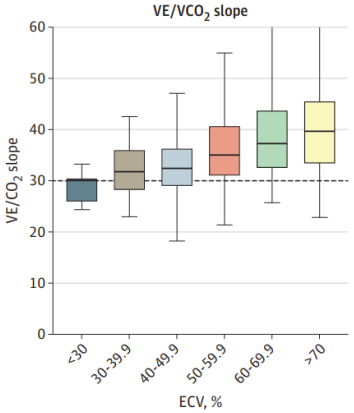
None

BACKGROUND

ATTR cardiomyopathy is characterised by a progressive reduction in exercise tolerance

Combined cardiopulmonary exercise testing and stress echocardiography (CPET imaging) provide insight into mechanisms that contribute to exercise intolerance and impact on prognosis





Patel et al. JAMA Cardiol. 2024;9(4):367-376

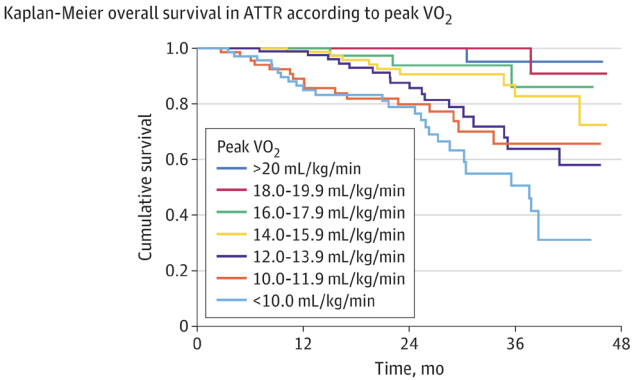
BACKGROUND

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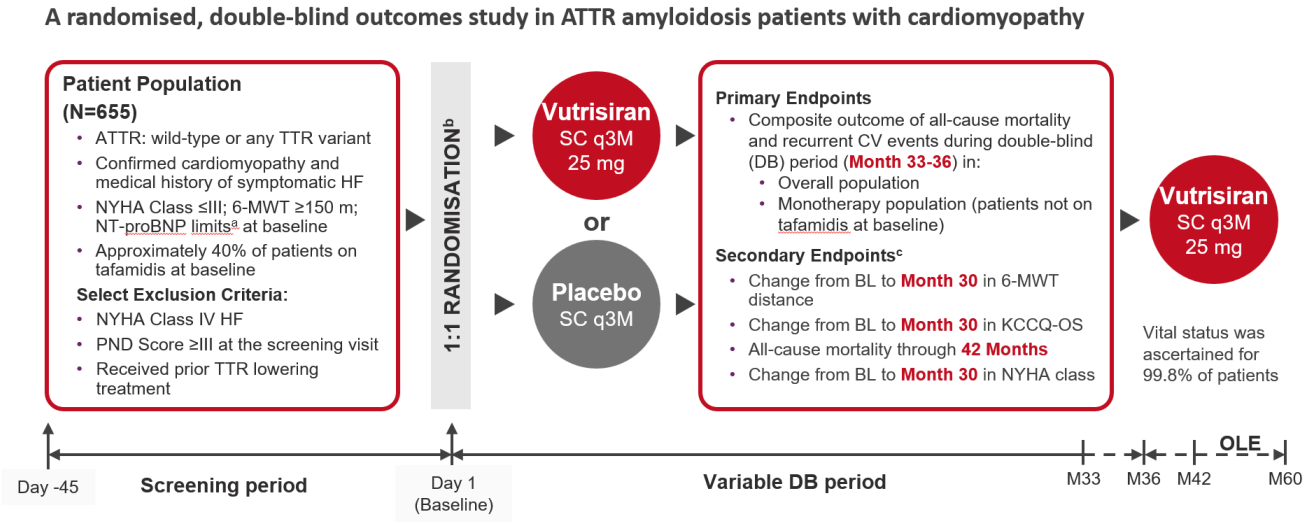
Knowledge of the impact of disease-modifying therapies on cardiopulmonary response to exercise is limited

The aim of this study was to evaluate the effect of vutrisiran on cardiopulmonary response to exercise



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HELIOS-B PHASE 3 TRIAL



Key Significant Findings:

Reduced all-cause mortality and recurrent cardiovascular events compared to placebo

Attenuated decline in distance covered during the 6-minute walk test

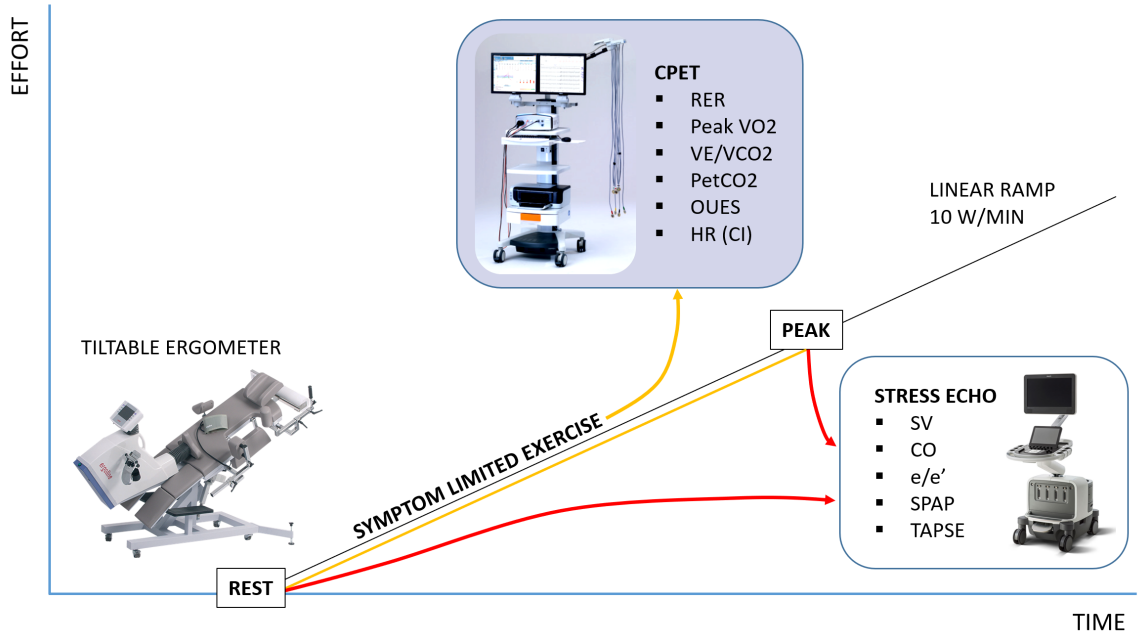
[a]NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation).
[b]Randomisation was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others).
[c]Assessed in the overall population and monotherapy population as separate endpoints.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; BL, baseline; CV, cardiovascular; DB, double-blind; HF, heart failure; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin.
References: Clinicaltrials.gov identifier: NCT04153149

BACKGROUND

CPET Imaging at the NAC:

- Semi-recumbent cycle ergometer
- Symptom-limited incremental ramp protocol
- Continuous breath-by-breath gas exchange measurement
- Concurrent stress echo image capture



METHODS

Single-centre post-hoc analysis of patients who participated in the HELIOS-B trial, and underwent CPET imaging as part of routine clinical follow-up at the NAC during the trial period

Inclusion:

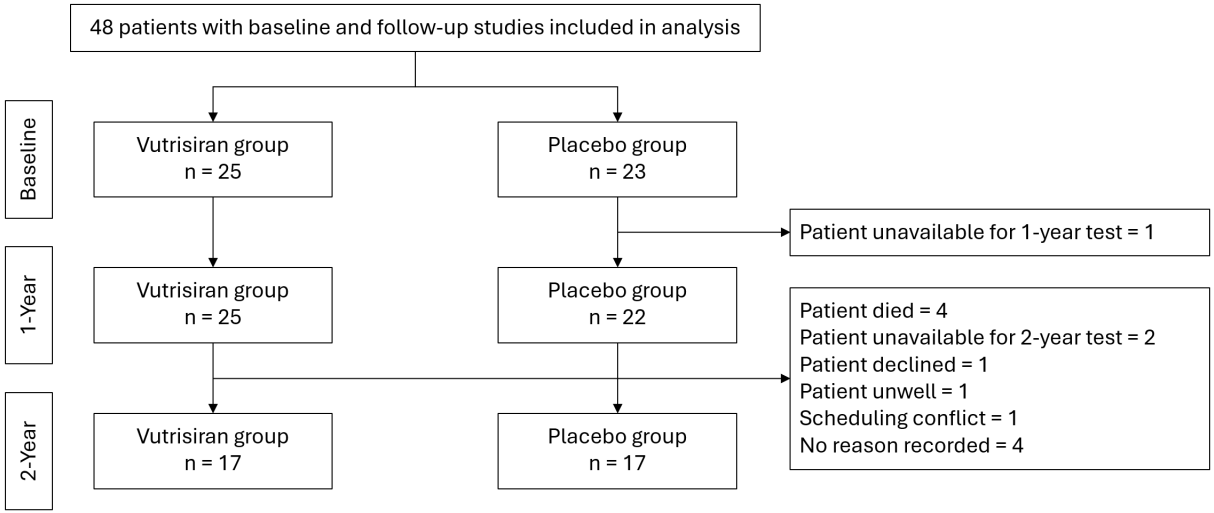
Baseline test performed up to 3 months before or after randomisation

At least one follow-up study at 1- and 2-year timepoints

Statistical approach:

Baseline-adjusted mixed-effects model

RESULTS



No patients were on any other ATTR-CM disease-modifying therapies during the study period

BASELINE CHARACTERISTICS

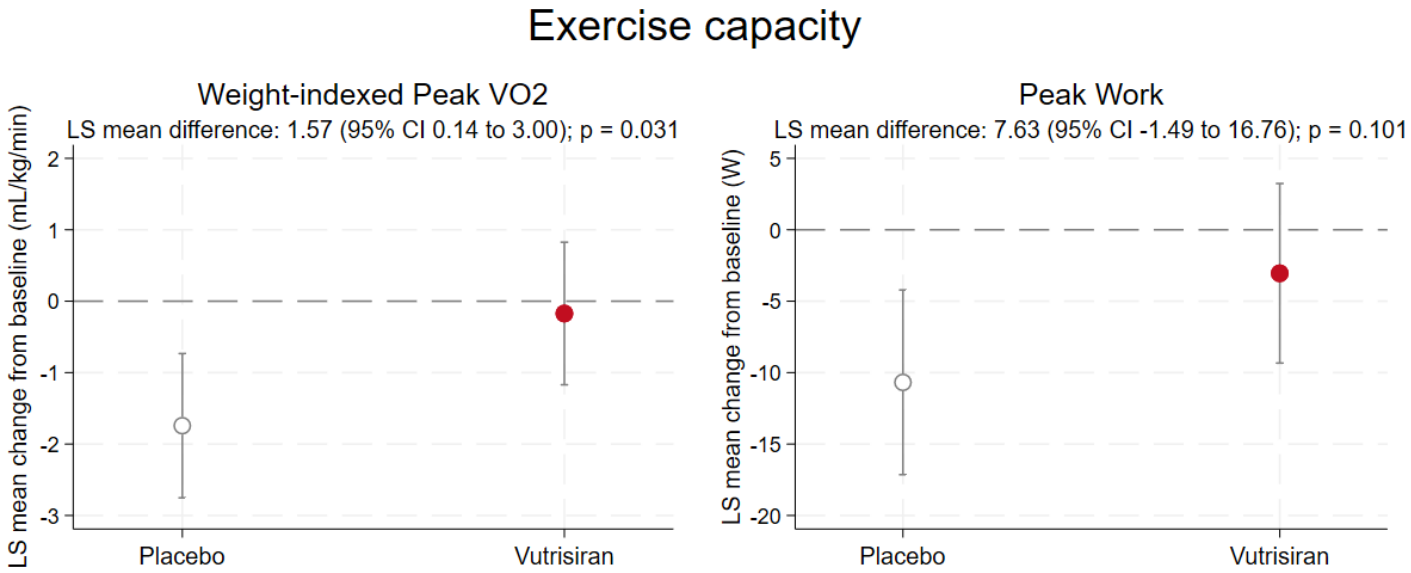
	Vutrisiran (n=25)	Placebo (n=23)	P-value
Median age, years (interquartile range)	78.0 (74.2 – 82.8)	75.6 (70.8 – 78.8)	0.085
Male, n (%)	24 (96.0)	22 (95.7)	0.952
Variant TTR genotype, n (%)	4 (16.0)	5 (21.7)	0.611
New York Heart Association (NYHA) Class, n (%)			
I	3 (12.0)	0 (0.0)	0.229
II	21 (84.0)	22 (95.7)	
III	1 (4.0)	1 (4.3)	
National Amyloidosis Centre (NAC) Stage, n (%)			
I	18 (72.0)	18 (78.3)	
II	4 (16.0)	3 (13.0)	0.786
III	2 (8.0)	2 (8.7)	
IV	1 (4.0)	0 (0.0)	

TREATMENT EFFECTS AT 2 YEARS: CPET

CPET	Baseline mean (SD)	LSMD (95% CI)	P-value
Peak work (W)	73.54 (23.86)	7.63 (-1.49 to 16.76)	0.101
Weight-adjusted peak VO_2 (mL/kg/min)	14.28 (3.80)	1.57 (0.14 to 3.00)	**0.031***
Absolute peak VO_2 (mL/min)	1135.02 (322.99)	150.03 (40.14 to 259.91)	**0.007***
OUES (mL/min per log(L/min))	1419.97 (417.90)	147.96 (-18.96 to 314.88)	0.082
Peak $PETCO_2$ (mmHg)	31.56 (5.27)	5.69 (2.87 to 8.51)	**<0.001***
VE/VCO2 slope	37.34 (7.39)	-6.35 (-10.15 to -2.55)	**0.001***
Peak HR (% of predicted)	80.18 (15.07)	7.54 (1.02 to 14.06)	**0.023***
Chronotropic index	0.62 (0.28)	0.13 (-0.00 to 0.26)	0.050

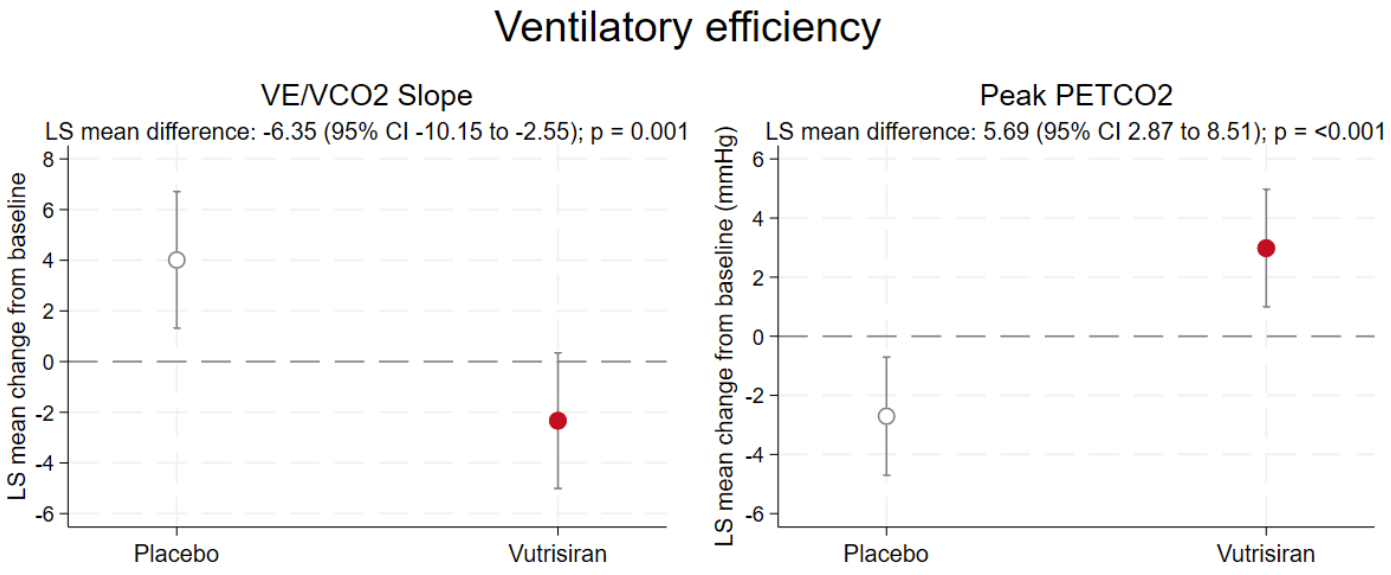
Abbreviations: CI, confidence intervals; HR, heart rate; LSMD, least squares mean difference; OUES, oxygen uptake efficiency slope – the relationship between oxygen uptake and the logarithm of minute ventilation; PETCO2, partial pressure of end-tidal carbon dioxide; SD, standard deviation; VE/VCO2 slope, the slope of the linear relationship between minute ventilation and carbon dioxide production during incremental exercise – a measure of ventilatory efficiency; VO2, oxygen consumption. * indicates statistically significant result

TREATMENT EFFECTS AT 2 YEARS: CPET



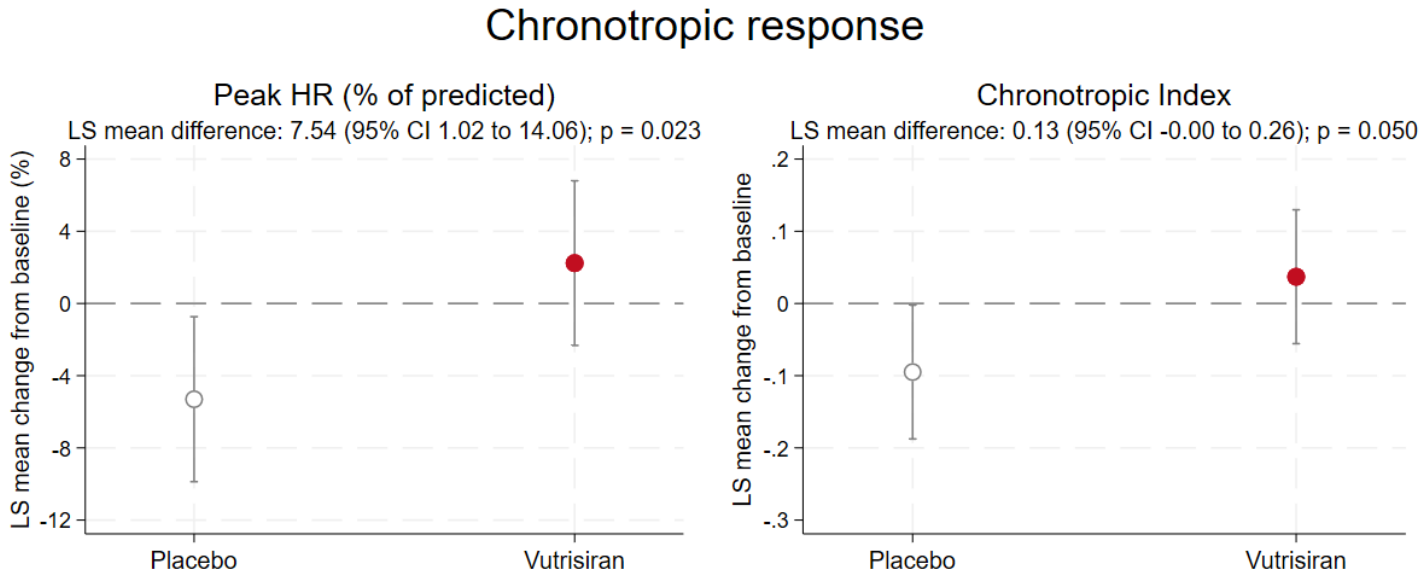
Error bars indicate 95% confidence intervals

TREATMENT EFFECTS AT 2 YEARS: CPET



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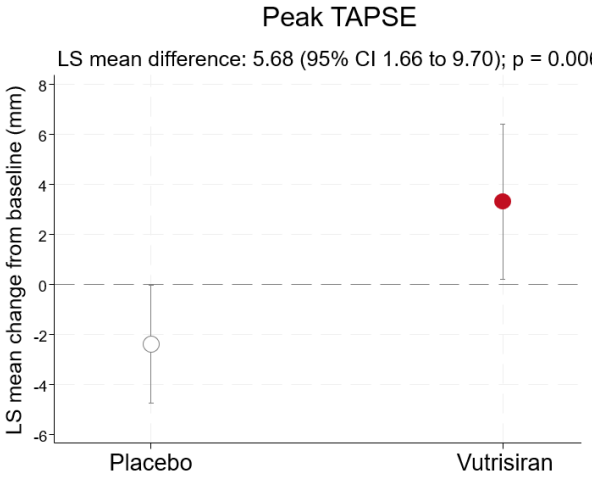
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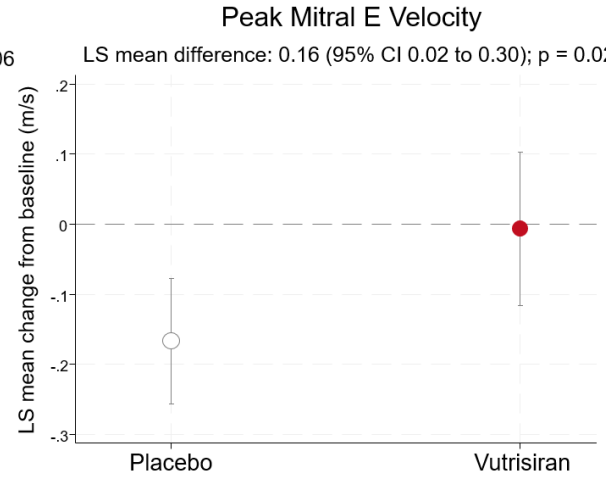
TREATMENT EFFECTS AT 2 YEARS: STRESS ECHO

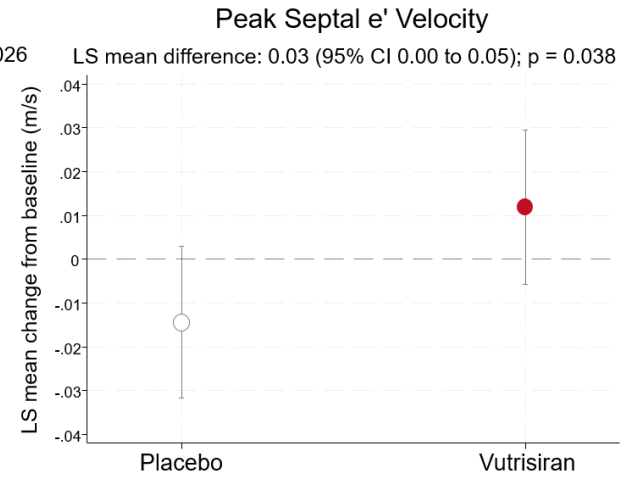
Stress Echocardiography	Baseline mean (SD)	LSMD (95% CI)	P-value
Peak stroke volume (mL)	59.23 (15.29)	3.43 (-7.68 to 14.55)	0.545
Peak cardiac output (L/min)	6.53 (2.12)	0.56 (-1.23 to 2.35)	0.540
Peak TAPSE (mm)	15.76 (4.78)	5.68 (1.66 to 9.70)	**0.006***
Peak sPAP (mmHg)	52.24 (16.94)	1.97 (-7.03 to 10.98)	0.667
Peak TAPSE/sPAP (mm/mmHg)	0.31 (0.11)	0.03 (-0.06 to 0.11)	0.572
Peak mitral E (m/s)	1.04 (0.21)	0.16 (0.02 to 0.30)	**0.026***
Peak septal e' (m/s)	0.07 (0.03)	0.03 (0.00 to 0.05)	**0.038***
Peak septal E/e'	16.54 (6.55)	-1.42 (-9.23 to 6.40)	0.722

Abbreviations: CI, confidence intervals; LSMD, least squares mean difference; SD, standard deviation; sPAP, systolic pulmonary artery pressure, TAPSE, tricuspid annular plane systolic excursion, TAPSE/sPAP – a measure of right ventricular-pulmonary artery coupling. W * indicates statistically significant result

TREATMENT EFFECTS AT 2 YEARS: STRESS ECHO







Error bars indicate 95% confidence intervals

SUMMARY OF FINDINGS

Compared to placebo, vutrisiran:

On CPET:

- Preserves peak oxygen consumption
- Preserves chronotropic response to exercise
- Improves ventilatory efficiency

On stress echo:

- Contributes to favourable changes in right ventricular systolic reserve and left ventricular diastolic reserve

LIMITATIONS

Single-centre post-hoc subgroup analysis

Modest sample size

Possible selection bias

No direct measurement of pulmonary diffusion, physiological dead space, peripheral oxygen extraction, or pulmonary amyloid burden

CONCLUSION

1. **Vutrisiran confers a treatment effect across several components of cardiopulmonary response to exercise:**

    - Preservation of exercise capacity and chronotropic response
    - Improvement in ventilatory efficiency
    - Favourable changes in right ventricular systolic reserve and left ventricular diastolic reserve

2. **CPET imaging is a valuable tool in analysing response to disease-modifying therapy in ATTR-CM**

THANK YOU

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