Cardiac Presentation and Treatment Response by Sex in Patients With Transthyretin Amyloidosis: Pooled Analysis of Vutrisiran and Patisiran Phase 3 Studies

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Study Rationale and Design

Background

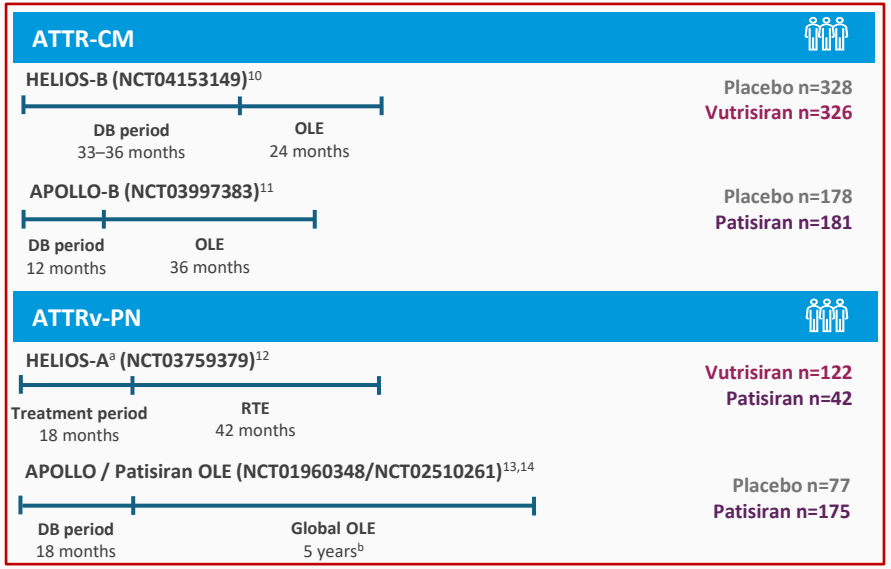
- ATTR, a progressive disease caused by deposition of **misfolded TTR** fibrils in the heart, peripheral nerves and other organs, presents along a continuum of neuropathic and cardiac phenotypes[1–5]
  - Neurologic and cardiac manifestations may coexist to varying degrees at disease onset and subsequent stages of progression[6]
- Sex differences in cardiac remodeling have been described in ATTR, but the extent to which these translate into differences in clinical burden and treatment response is less well characterised, partly due to low female representation in ATTR-CM phase 3 studies[7]
- The **RNAi therapeutics** vutrisiran and patisiran **decrease hepatic TTR synthesis**, reducing formation/deposition of amyloid fibrils[8,9]
  - Both are approved for the treatment of ATTRv-PN; vutrisiran is also approved for ATTR-CM

Objective

- Evaluate the impact of sex on cardiac phenotype, clinical burden, and treatment response across pooled data from phase 3 studies of vutrisiran and patisiran in patients with ATTR-CM and ATTRv-PN

Methods

- Analysis of pooled data from **203 females** and **1199 males** who received vutrisiran, patisiran, or placebo in phase 3 studies[10–14]
  - Endpoints were separately analysed for females and males in individual studies, in pooled ATTR-CM and ATTRv-PN studies, and across all studies



[a]HELIOS-A and APOLLO had similar endpoints and eligibility criteria, so the APOLLO placebo group was used as an external placebo comparator. [b]Included patients from APOLLO and a patisiran phase 2 study (NCT01960348).

Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; ATTRwt, wild-type ATTR; CM, cardiomyopathy; DB, double-blind; OLE, open-label extension; PN, polyneuropathy; RNAi, RNA interference; RTE, randomized treatment extension; TTR, transthyretin.

References: 1. Maurer et al. *Circ Heart Fail* 2019; 12:e006075; 2. Ruberg et al. *JAMA* 2024;331:778–91; 3. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8:3875–84; 4. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 5. Gonzalez-Duarte & Ulloa-Aguirre. *Int J Mol Sci* 2021;22:13158; 6. Gonzalez-Moreno et al. *Cardiol Ther* 2024;13:117–35; 7. Bruno et al. *Heart Fail Rev* 2021;26:35–45; 8. Alnylam Pharmaceuticals. Onpattro. Prescribing information. 2025. Available from: https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf; 9. Alnylam Pharmaceuticals. Amvuttra. Prescribing information. 2025 (accessed 03 August 2026). Available from: https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf; 10. Fontana et al. *N Engl J Med* 2025;392:33–44; 11. Maurer et al. *N Engl J Med* 2023;389:1553–65; 12. Adams et al. *Amyloid* 2023;30:18–26; 13. Adams et al. *N Engl J Med* 2018;379:11–21; 14. Adams et al. *JAMA Neurol* 2025;82:228–36.

Baseline Characteristics of Female vs Male Patients With ATTR

Characteristics	ATTR-CM				ATTRv-PN				*P* value[b]
	HELIOS-B		APOLLO-B		HELIOS-A		APOLLO		
	Female n=49	Male n=605	Female n=38	Male n=321	Female n=58	Male n=106	Female n=58	Male n=167	
Age, years, mean (SD)	73.7 (9.5)	75.5 (6.5)	75.9 (7.7)	74.6 (7.1)	57.2 (12.8)	58.2 (12.4)	59.5 (13.5)	60.8 (10.9)	0.5439
Cardiac subpopulation of ATTRv-PN studies,[a] n (%)	N/A	N/A	N/A	N/A	11 (19.0)	42 (39.6)	28 (48.3)	98 (58.7)	**0.0054**
ATTRwt, n (%)	28 (57.1)	550 (90.9)	15 (39.5)	273 (85.0)	N/A	N/A	N/A	N/A	**<0.0001**[c]
NYHA class, n (%) 0 I II III	 0 2 (4.1) 41 (83.7) 6 (12.2)	 0 82 (13.6) 467 (77.2) 56 (9.3)	 0 2 (5.3) 33 (86.8) 3 (7.9)	 0 23 (7.2) 273 (85.0) 25 (7.8)	 36 (62.1) 3 (5.2) 19 (32.8) 0	 54 (50.9) 13 (12.3) 39 (36.8) 0	 0 30 (51.7) 28 (48.3) 0	 0 80 (47.9) 85 (50.9) 0	0.3302
% predicted 6-MWT, m, mean (SD)	83.2 (21.9)	92.2 (22.2)	75.1 (20.2)	90.2 (22.4)	N/A	N/A	N/A	N/A	**<0.0001**
KCCQ-OS score, points, mean (SD)	66.3 (21.6)	73.1 (19.4)	61.2 (25.6)	71.1 (20.1)	N/A	N/A	N/A	N/A	**0.0029**
NT-proBNP, ng/L, median (IQR)	1889.0 (865.0, 3136.0)	1930.0 (1120.0, 3206.0)	1604.5 (684.0, 2637.0)	1964.0 (1056.0, 2982.0)	269.9 (67.8, 831.2)	330.3 (71.9, 1170.5)	531.9 (216.6, 1048.8)	501.9 (182.6, 1501.9)	0.4013
Echocardiography									
LVWT, cm, mean (SD)	1.689 (0.252)	1.828 (0.265)	1.688 (0.230)	1.795 (0.242)	1.259 (0.367)	1.431 (0.396)	1.456 (0.323)	1.611 (0.294)	**<0.0001**
LVWT/height, cm/m, mean (SD)	1.071 (0.164)	1.054 (0.158)	1.066 (0.157)	1.034 (0.142)	0.786 (0.235)	0.823 (0.225)	0.914 (0.200)	0.931 (0.172)	0.6636
LVWT/BSA, cm/m^2, mean (SD)	1.024 (0.166)	0.938 (0.157)	1.019 (0.181)	0.927 (0.144)	0.772 (0.265)	0.766 (0.217)	0.947 (0.248)	0.887 (0.189)	**<0.0001**
GLS, %, mean (SD)	–16.1 (3.3)	–13.8 (3.4)	–12.6 (4.5)	–10.9 (3.0)	–16.6 (3.3)	–15.1 (4.3)	–16.2 (4.0)	–16.0 (3.6)	**<0.0001**
E/e', mean (SD)	19.6 (7.1)	17.8 (6.3)	21.9 (10.5)	18.6 (6.3)	14.5 (8.3)	14.2 (6.9)	16.5 (7.1)	14.8 (6.8)	**0.0156**
LVEF, %, mean (SD)	60.7 (11.5)	55.4 (12.5)	61.4 (13.0)	55.2 (13.0)	63.1 (9.3)	61.8 (9.5)	61.9 (10.9)	62.1 (9.6)	**0.0042**

[a]Patients with baseline LVWT ≥1.3 cm and no medical history of aortic valve disease or hypertension. [b]Overall *P* values for continuous variables, testing for differences in mean values, were obtained from a linear model with stratified intercepts and sex as a common effect, and for categorical variables from a type III test of fixed effects derived from a multinomial model with stratified intercepts and sex as a common effect. [c]As HELIOS-A and APOLLO did not include patients with ATTRwt, these studies were not included in *P* value calculation.

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; ATTRwt, wild-type ATTR; BSA, body surface area; E/e', early mitral inflow velocity/mitral annular early diastolic velocity; GLS, global longitudinal strain; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; N/A, not applicable; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; vs, versus.

Statistically Significant Differences Were Observed Between Sexes at Baseline

- Females exhibited:
  - **Worse % predicted 6-MWT distance**, showing **worse functional capacity** vs males (*P*<0.0001)
  - **Lower KCCQ-OS score**, indicating **worse health status** and **QoL** vs males (*P*=0.0029)
  - **Higher E/e' ratio**, indicating **worse diastolic function** (*P*=0.0156)
  - **Higher LVEF** (*P*=0.0042) and **more favourable GLS** (*P*<0.0001), indicating **better systolic function**
  - **Lower unindexed LVWT** vs males; **however**, LVWT indexed to height was similar between males and females, and **LVWT indexed to BSA** was **modestly, but significantly higher in females** (*P*<0.0001)

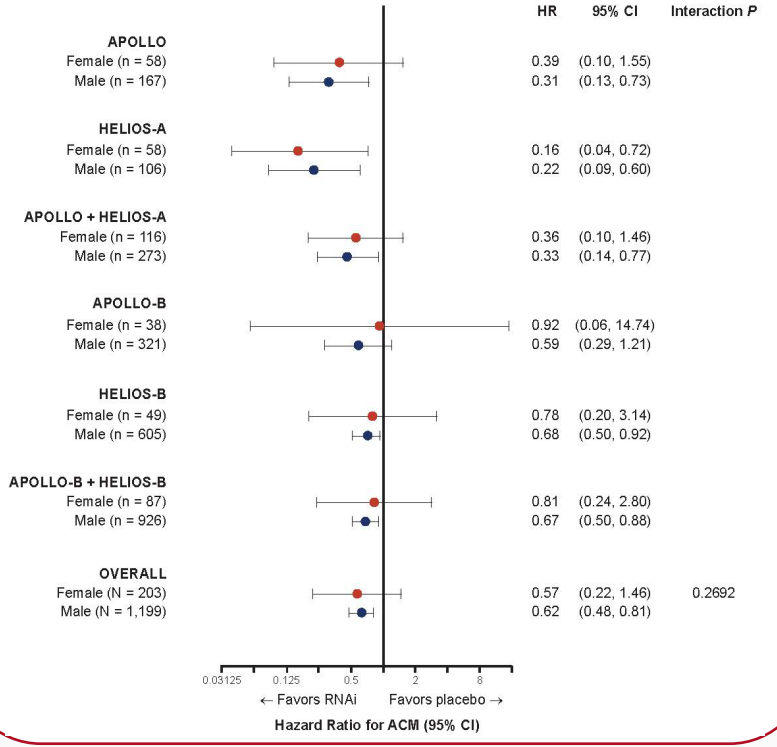
- In addition:
  - Mean age and racial distribution was similar between sexes, but patients were generally younger in the ATTRv-PN studies vs the ATTR-CM studies
  - Females were more likely to have ATTRv than males in the ATTR-CM studies (*P*<0.0001)
  - There was no significant sex-based difference in neuropathy impairment at baseline in the ATTRv-PN studies

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; BSA, body surface area; E/e', early mitral inflow velocity/mitral annular early diastolic velocity; GLS, global longitudinal strain; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; QoL, quality of life; vs, versus.

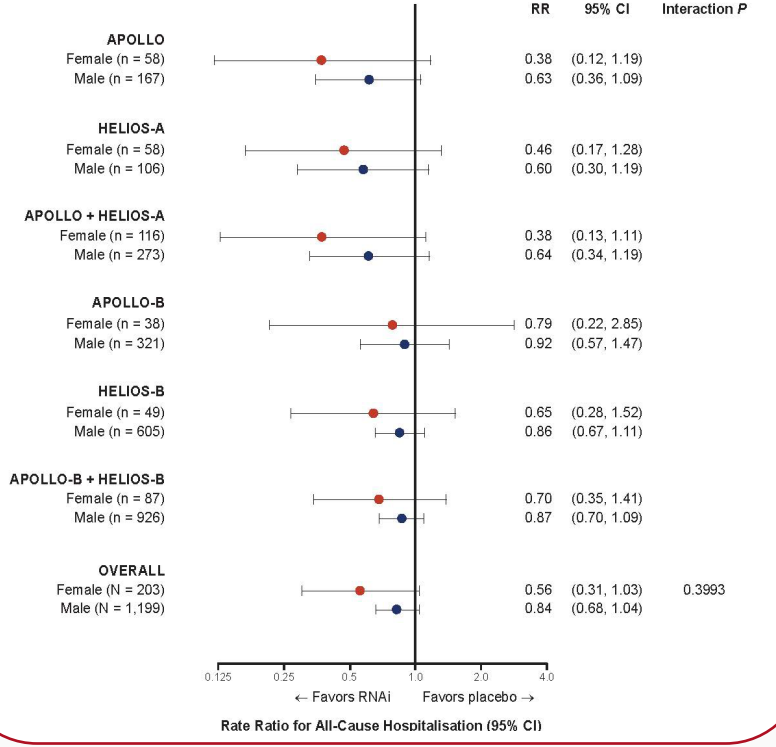
RNAi Therapeutics Reduced the Risk of All-Cause Mortality and All-Cause Hospitalisation vs Placebo in Females and Males with ATTR

Results were consistent across individual studies and pooled analyses, without significant treatment-by-sex interaction

All-Cause Mortality[a]



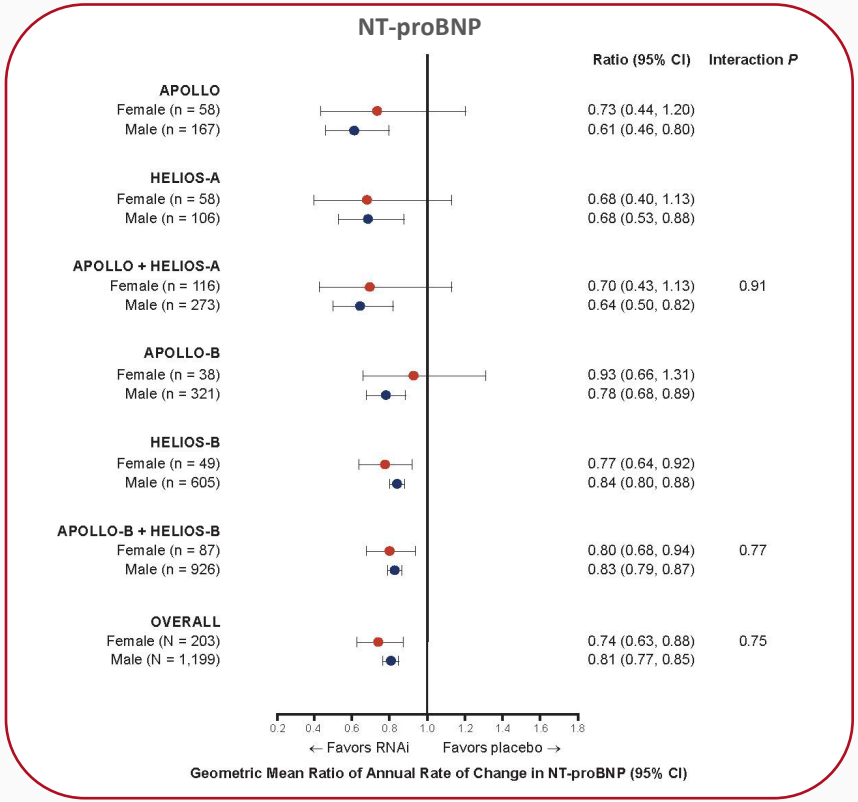
All-Cause Hospitalisation

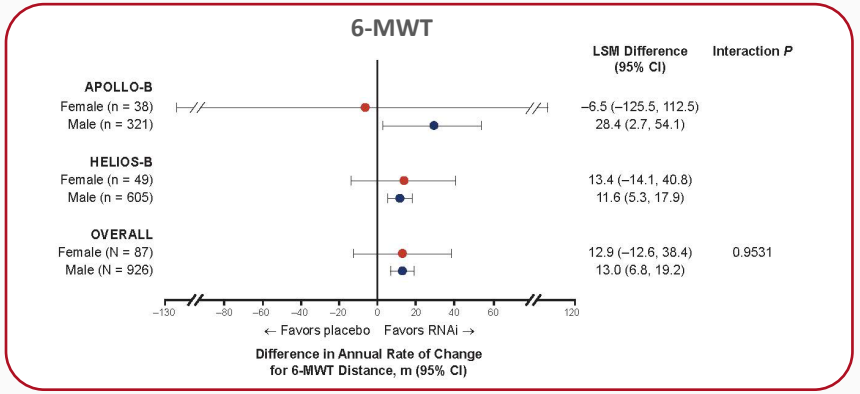


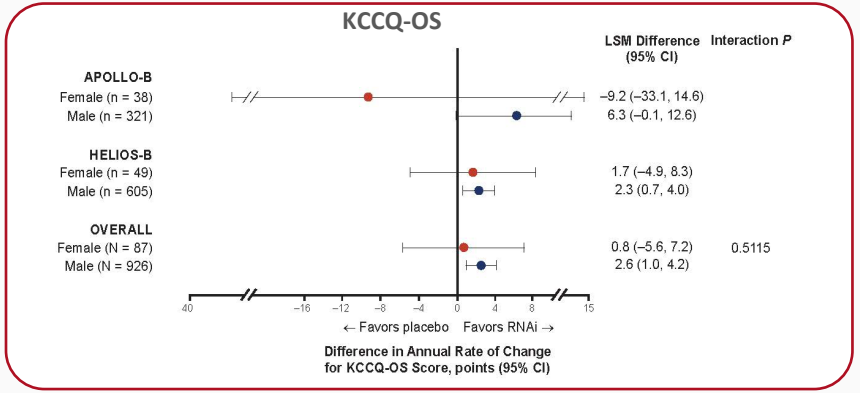
[a]Includes heart transplantation and left ventricular assist device placement.
For the pooled overall and ATTR-CM (APOLLO-B and HELIOS-B) analyses, a CPH model stratified by study was used to estimate the pooled HR and corresponding 95% CI, with treatment group as a covariate. For the pooled ATTRv-PN (APOLLO and HELIOS-A) analyses, an unstratified CPH model was used to estimate the pooled HR and 95% CI, with treatment group as a covariate.
Abbreviations: ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; CI, confidence interval; CPH, Cox proportional hazards; HR, hazard ratio; RNAi, RNA interference; RR, rate ratio; vs, versus.

Consistent Benefits with RNAi Therapeutics vs Placebo in NT-proBNP, Functional Capacity, Health Status and Quality of Life in Females and Males with ATTR

Results were consistent across individual studies and pooled analyses, without significant treatment-by-sex interaction





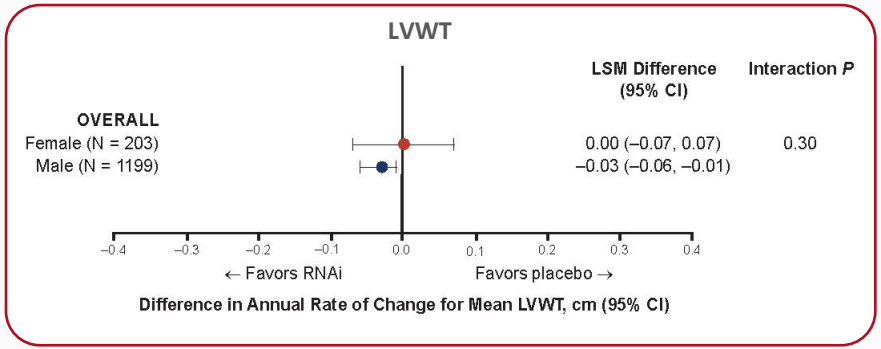


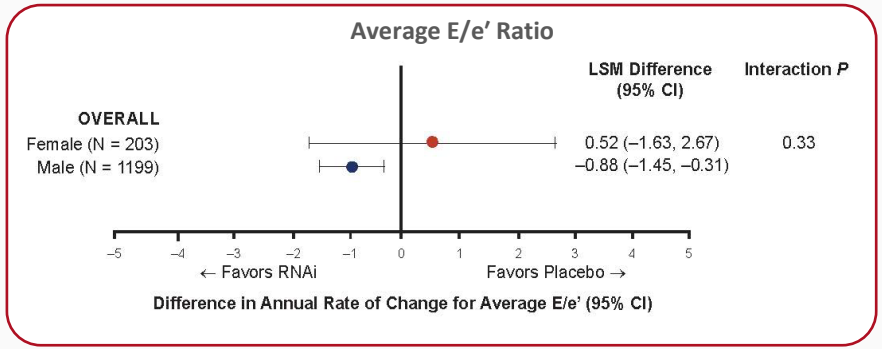
The effect of treatment on the annual rate of change in NT-proBNP was estimated with a longitudinal mixed-effects model that included fixed effects for log-transformed baseline value, visit, treatment group, and the interaction between treatment and visit. The effect of treatment on the annual rate of change in 6-MWT distance and KCCQ-OS score was evaluated using double-blind period data from APOLLO-B and HELIOS-B; within-study treatment effect was estimated using a mixed model with random coefficients; overall treatment effect was modeled using a slope-based meta-analysis.

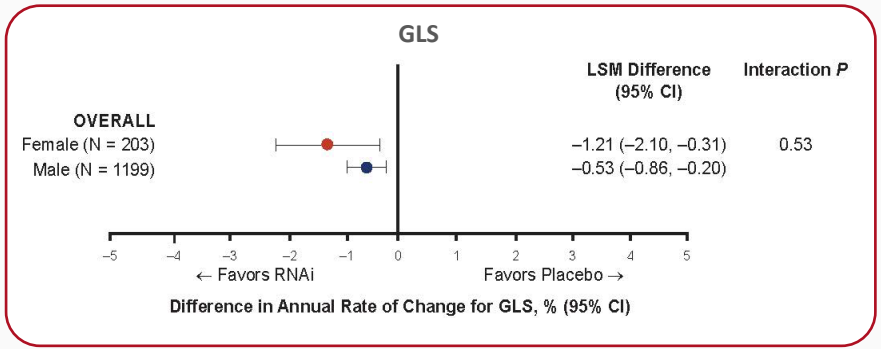
Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LSM, least squares mean; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; RNAi, RNA interference; vs, versus.

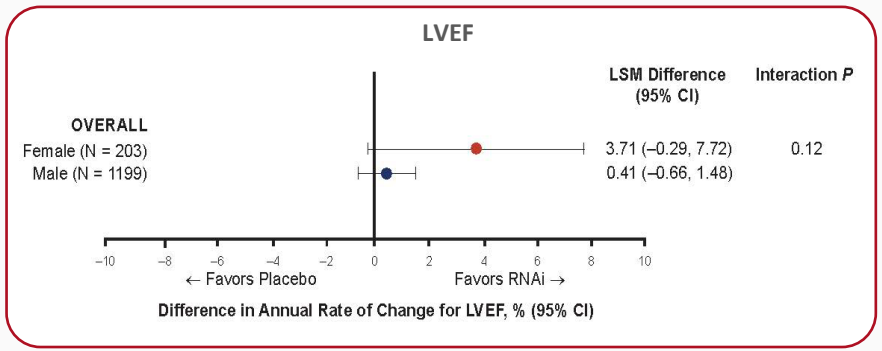
Impact of RNAi Therapeutics on Cardiac Structure and Function was Consistent Between Females and Males With ATTR

Non-significant interaction *P* values for all measures show lack of notable treatment-by-sex interaction









The treatment effect on the annual rate of change in echocardiographic parameters was estimated with a longitudinal mixed-effects model. The model included fixed effects for log-transformed baseline value, visit, treatment group, and the interaction between treatment and visit. The heterogeneity of treatment effect between sexes was assessed by a treatment-by-sex interaction; within-sex treatment estimates are derived from a separate model that estimates a subgroup-specific estimate alone.

Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; E/e', early mitral inflow velocity/mitral annular early diastolic velocity; GLS, global longitudinal strain; LS mean, least squares mean; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; LSM, least squares mean; RNAi, RNA interference.

Conclusions

- The results of this pooled analysis of phase 3 clinical studies support the presence of **sex-specific differences across the ATTR disease continuum** of cardiomyopathy and polyneuropathy phenotypes
- Across the ATTR spectrum, females exhibited a distinct baseline phenotype vs males, characterized by:
  - Less overt structural cardiac remodeling and better-preserved systolic function
  - Greater impairment of diastolic function, functional capacity, health status and quality of life
- This apparent **dissociation between structural remodeling and clinical burden** suggests that conventional measures of cardiac involvement may incompletely capture disease burden in females
- The findings suggest that the main sex-related differences relate to cardiac rather than neuropathic presentations of ATTR
- Importantly, **treatment effects of RNAi therapeutics were consistent between females and males** across both ATTR-CM and ATTRv-PN, despite baseline phenotypic differences
- There remains a need for greater recognition of sex-specific disease presentation to improve awareness and earlier recognition of ATTR-CM in female patients

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Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ATTRv-PN, hereditary (variant) ATTR with polyneuropathy; ATTRwt, wild-type ATTR; RNAi, RNA interference.