Sex Differences at Diagnosis Among Patients With Hereditary or Wild-Type Transthyretin Amyloidosis: Analysis From the ConTTRibute Study

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Conclusions

- Sex-related differences in ATTR vary by subtype:
  - In ATTRv, female patients were younger at symptom onset and diagnosis and were more likely to have a polyneuropathy phenotype than male patients.
  - In ATTRwt, female patients were older at symptom onset and diagnosis and were more likely to have a mixed phenotype than male patients; however, the number of female patients with ATTRwt was limited.
- Indexing echo measures to BSA may improve diagnostic sensitivity in female patients with ATTR:
  - Consistent with previous studies, female patients with ATTR presented with less pronounced ventricular wall thickening than male patients when not indexed to BSA, which may contribute to delayed recognition.
- Larger studies are needed to validate these results and enhance the understanding of sex differences in ATTR, with particular emphasis on improving diagnosis and equitable trial enrollment of female patients, who remain underdiagnosed and underrepresented in clinical research.

Key takeaway

Sex-related differences in baseline characteristics were observed in patients with ATTRv and ATTRwt

After indexing for BSA, sex differences in echo parameters were mitigated

Introduction

Sex Differences in ATTR

- ATTR is a progressive and fatal disease caused by the accumulation of misfolded TTR protein as amyloid deposits in the heart, nerves, and other systems,[1–3] and is classified as ATTRwt (typically presenting as cardiomyopathy) or ATTRv (typically presenting as polyneuropathy, cardiomyopathy, or a mixed phenotype)[2,3]
- Despite growing recognition of sex-related differences in the ATTR phenotype, female patients remain underdiagnosed and underrepresented in pivotal clinical trials (8–11%) and staging systems (9–19%), though recent registries demonstrate improved representation (29–59%)[4]
- Current diagnostic and clinical trial inclusion criteria are mostly derived from male-dominant cohorts (e.g., interventricular septal wall thickness ≥1.2 cm); given that recent data suggests lower diagnostic thresholds may be needed for female patients, this may contribute to delayed recognition and the exclusion of female patients from clinical trials[5–8]
- Understanding sex differences in clinical practice is key to facilitating earlier diagnosis and improving clinical outcomes in ATTR[5]

Objective

- Characterize sex differences at diagnosis and study enrollment in patients with ATTRv or ATTRwt in the ConTTRibute observational study, and evaluate the role of BSA indexing for echo data

Methods

Figure 1. ConTTRibute Study Design and Current Analysis

- ConTTRibute (NCT04561518) is a prospective, global, multicenter, long-term observational study[9]
  - No visits or examinations, laboratory tests, procedures, or treatments are mandated as part of the study
  - Data are collected prospectively after each patient visit as part of routine clinical care
  - Retrospective data for up to 1 year prior to enrollment are also collected, with no requirement for additional historical data
- To account for differences between sexes in body size, echo measurement values were divided by BSA
  - BSA (m^2) was calculated using the weight measurement closest to the echo measurement at diagnosis

ConTTRibute Patient Pool

- Pre-symptomatic carriers of disease-causing TTR variants
- Untreated ATTR patients
- RNAi treated ATTR patients
- Non-RNAi treated ATTR patients

Patient Population (Current Analysis)

- Patients with ATTR (ATTRv or ATTRwt)
- Patients with ATTR who had undergone an echo within ±6 months of diagnosis

Aims (Current Analysis)

- Describe sex- and phenotype-related differences in demographics and disease characteristics in all patients with ATTR, and in patients with available echo data

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Results

Table 1. Demographic and Clinical Characteristics by ATTR Type and Sex Among (A) Patients With a Confirmed ATTR Diagnosis and (B) the Subset of Patients With Available Echo Data [Notable Results Highlighted]

A)

Characteristic	ATTRv Male n=331	ATTRv Female n=222	ATTRv *P*-value	ATTRwt Male n=311	ATTRwt Female n=40	ATTRwt *P*-value
Age, years, mean (SD)						
At symptom onset	**56.6 (14.3)[a]**	**53.6 (14.9)[b]**	**0.0179**	**75.9 (7.8)[c]**	**78.6 (7.9)[d]**	**0.0045**
At diagnosis	58.4 (14.7)	56.6 (14.8)	0.0936	**77.4 (7.2)**	**80.3 (7.7)**	**0.0002**
Clinical phenotype at diagnosis, n (%)						
Polyneuropathy	**180 (54.4)**	**138 (62.2)**	–	10 (3.2)	3 (7.5)	–
Cardiomyopathy	51 (15.4)	25 (11.3)		233 (74.9)	22 (55.0)	
Mixed	98 (29.6)	59 (26.6)		**67 (21.5)**	**15 (37.5)**	
Missing	2 (0.6)	0		1 (0.3)	0	
NYHA class at enrollment[e], n (%)						
I	40 (12.1)	11 (5.0)	–	41 (13.2)	3 (7.5)	–
II	78 (23.6)	40 (18.0)		138 (44.4)	14 (35.0)	
III	24 (7.3)	27 (12.2)		79 (25.4)	14 (35.0)	
IV	1 (0.3)	0		1 (0.3)	1 (2.5)	
Missing	188 (56.8)	144 (64.9)		52 (16.7)	8 (20.0)	
NT-proBNP at enrollment[e], pg/mL, median (IQR)	n=216 235 (80, 1017)	n=127 254 (110, 960)	0.3502	n=187 1797 (788, 3971)	n=22 1180 (523, 3118)	0.0716
Available echo data[f], n (%)	34 (10.3)	22 (9.9)	–	70 (22.5)	9 (22.5)	–

B)

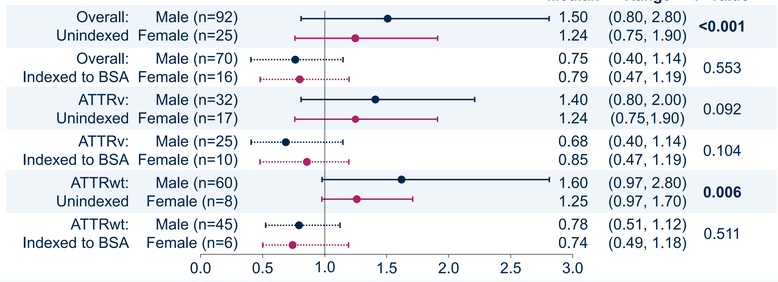
Characteristic	ATTRv Male n=34	ATTRv Female n=22	ATTRwt Male n=70	ATTRwt Female n=9
Age, years, mean (SD)				
At symptom onset	**65.0 (10.1)**	**61.1 (13.8)**	**79.3 (6.6)[g]**	**82.1 (8.4)**
At diagnosis	**66.8 (9.8)**	**63.0 (13.5)**	**80.3 (6.4)**	**82.6 (8.2)**
Clinical phenotype at diagnosis, n (%)				
Polyneuropathy	**9 (26.5)**	**12 (54.5)**	0	0
Cardiomyopathy	10 (29.4)	3 (13.6)	52 (74.3)	6 (66.7)
Mixed	14 (41.2)	7 (31.8)	**18 (25.7)**	**3 (33.3)**
Missing	1 (2.9)	0	0	0
NYHA class at enrollment[e], n (%)				
I	0	2 (9.1)	5 (7.1)	0
II	20 (58.8)	3 (13.6)	31 (44.3)	3 (33.3)
III	3 (8.8)	4 (18.2)	25 (35.7)	4 (44.4)
IV	1 (2.9)	0	0	1 (11.1)
Missing	10 (29.4)	13 (59.1)	9 (12.9)	1 (11.1)
NT-proBNP at enrollment[e], pg/mL, median (IQR)	n=23 **772** **(124, 2257)**	n=14 **362** **(205, 481)**	n=44 1983 (784, 4449)	n=3 1744 (446, 7972)
BSA, m^2	n=27	n=14	n=53	n=7
Mean (SD)	2.0 (0.2)	1.7 (0.3)	2.0 (0.2)	1.8 (0.3)
Median (range)	2.0 (1.7, 2.4)	1.6 (1.3, 2.1)	2.0 (1.6, 2.3)	1.7 (1.4, 2.1)

[a]n=328; [b]n=219; [c]n=297; [d]n=38; [e]Within enrollment window (±6 months from enrollment date); [f]Within diagnosis window (±6 months from diagnosis date; echo data collected >1 year prior to enrollment were not required by the study protocol and may have been unavailable for some patients); [g]n=69. –, *P* value not calculated.

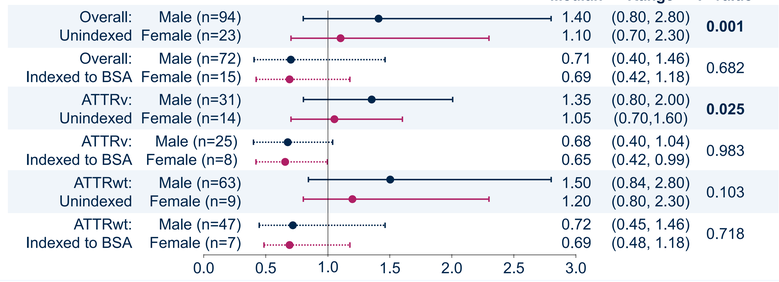
Figure 2. Echo Parameters by ATTR Type and Sex: Unindexed and BSA-Indexed Values

- Across ATTR populations, unindexed interventricular septal and LV posterior wall thickness measurements were generally higher in male patients than in female patients, with statistical significance in the overall population; however, **these differences were no longer statistically significant after BSA indexing**
- To note, pooling patients across ATTR diagnosis types and clinical phenotypes may confound sex-based comparisons of echocardiographic measures, particularly given small sample sizes in some subgroups

Interventricular Septal Wall Thickness (cm; cm/m^2 for Indexed to BSA)



LV Posterior Wall Thickness (cm; cm/m^2 for Indexed to BSA)



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Abbreviations: ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BSA, body surface area; echo, echocardiogram; IQR, interquartile range; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RNAi, RNA interference; SD, standard deviation; TTR, transthyretin.