JACC: HEART FAILURE VOL. 9, NO. 10, 2021

Sex-Related Risk of Cardiac Involvement in Hereditary Transthyretin Amyloidosis

Insights From THAOS

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ABSTRACT

OBJECTIVES Because patients with ATTRv cardiomyopathy are more likely to be male, this analysis aimed to increase information on associations between sex and genotype, phenotype, and degree of myocardial involvement in ATTRv amyloidosis.

BACKGROUND Transthyretin amyloid cardiomyopathy is a progressive, fatal disease that occurs due to accumulation of wild-type or variant (ATTRv) transthyretin amyloid fibrils in the myocardium.

METHODS The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing global longitudinal observational survey of patients with ATTR amyloidosis and asymptomatic carriers with *TTR* mutations. Data from THAOS (data cutoff: January 6, 2020) were analyzed to determine any sex-based differences in genotype, phenotype, and presence of cardiac and neurological symptoms in patients with ATTRv amyloidosis and in patients with ATTRv amyloidosis and cardiomyopathy.

RESULTS There were 2,790 patients with ATTRv amyloidosis enrolled in THAOS, with male patients more likely to have symptoms of cardiac involvement and a cardiac phenotype. Male prevalence was greater in patients with more severe cardiac manifestations of disease, as assessed with N-terminal pro–B-type natriuretic peptide, left-ventricular (LV) ejection fraction, mean LV wall thickness divided by height, and LV mass index divided by height. Sex, age at disease onset, and genotype category were identified by multivariate analyses as risk factors for the development of cardiomyopathy (defined as increased LV septum thickness divided by height).

CONCLUSIONS In this analysis, myocardial involvement was more frequent and pronounced in male patients with ATTRv amyloidosis, suggesting that there may be biological characteristics that inhibit myocardial amyloid infiltration in females or facilitate it in males. (J Am Coll Cardiol HF 2021;9:736–746) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 22, 2021; revised manuscript received May 12, 2021, accepted May 13, 2021.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2021.05.005

Transthyretin amyloidosis (ATTR amyloidosis) is a rare, progressive, life-threatening heterogeneous disease caused by dissociation of the transthyretin (TTR) tetramer into monomers, which misfold, ultimately forming amyloid deposits in peripheral nerves, the heart, and other organs (1). The disease can be caused by pathogenic variations in the *TTR* gene, or by aggregation of nonhereditary wild-type TTR protein. Transthyretin amyloid cardiomyopathy (ATTR-CM) occurs due to accumulation of wild-type (ATTRwt) or variant (ATTRv) TTR amyloid fibrils in the myocardium, leading to cardiomyopathy and symptoms of heart failure (2). Although the true prevalence of ATTR-CM remains unknown, available evidence indicates that, despite being underdiagnosed, ATTRwt is the most common form of disease (3), with incidence of 13% (via scintigraphy) (4) to 17% (at autopsy) (5) in patients with heart failure with preserved ejection fraction and an increased wall thickness.

Sex differences in ATTR amyloidosis have occasionally been reported, with a predominance of male sex in patients with a cardiac phenotype. This is most pronounced in patients with ATTRwt amyloidosis, with more than 80% of patients being male (6–8). There is also evidence of increased male prevalence among patients with ATTRv amyloidosis with mutations associated with cardiomyopathy (Leu111Met, Ile68Leu, Thr60Ala, and Val122Ile) and in patients with ATTRv amyloidosis diagnosed with ATTR-CM, with approximately 70% of patients being male (6,9,10). Although there are few studies investigating the impact of sex on the development of a cardiac phenotype in patients with ATTR amyloidosis, some small studies in patients with ATTRv amyloidosis have suggested that patients with indicators of myocardial involvement are more likely to be male (11,12).

Established in 2007, the Transthyretin Amyloidosis Outcomes Survey (THAOS) is the largest ongoing global disease registry for patients diagnosed with ATTRv amyloidosis and ATTRwt amyloidosis, and asymptomatic carriers of a pathogenic disease-causing *TTR* genetic variant (13). Because THAOS contains baseline and longitudinal data in a diverse global patient population with ATTR amyloidosis, the registry provides the opportunity to investigate the potential of association between sex and cardiac phenotype (13). The objective of the present analysis was to investigate possible associations between sex and the genotype, phenotype, and degree of myocardial involvement in patients with ATTRv amyloidosis enrolled in THAOS.

METHODS

SOURCE DATA. Data from THAOS (data cutoff: January 6, 2020) were analyzed to determine any sex-based differences between patients with ATTRv amyloidosis and patients with ATTRv amyloidosis with cardiomyopathy in terms of genotype, phenotype, and presence of cardiac and neurological symptoms. All study sites received ethical or institutional review board approval before patient enrollment, and each patient provided written informed consent.

STUDY DESIGN AND STATISTICAL METHODS. All patients with ATTRv amyloidosis enrolled in THAOS up to January 6, 2020, were included in the analysis. The design and methodology of THAOS have previously been reported (13). Asymptomatic carriers were those with a pathogenic disease-causing *TTR* genetic variant and no ATTR amyloidosis–related symptoms. Diagnosis of ATTR amyloidosis in this population was made through evidence of a pathogenic disease-causing *TTR* genetic variant and symptoms or signs assessed by the investigator to be definitely related to ATTR amyloidosis.

Phenotype categories, based on clinical presentation at the time of enrollment in THAOS, were: 1) predominantly cardiac; 2) predominantly neurological; or 3) mixed (cardiac and neurological). Phenotype categories were defined as: 1) predominantly cardiac, ie, patients with at least 1 of the following symptoms: heart failure, dyspnea, and/or abnormal electrocardiogram caused by rhythm disturbance; and no more than mild neurological or gastrointestinal symptoms (excluding erectile dysfunction, constipation, and carpal tunnel syndrome); 2) predominantly neurological, ie, patients with walking disability, other neurological symptoms, and/or 1 of the following gastrointestinal symptoms, of any severity: early satiety, nausea, vomiting, unintentional weight loss, diarrhea, or fecal incontinence; and without heart failure, dyspnea, or abnormal electrocardiogram caused by rhythm disturbance (9); and 3) mixed, ie, patients who had at least 1 of the cardiac and 1 of the neurological symptoms as described above.

Genotype categories were Val30Met (p.Val50Met) mutation with early-onset disease (onset age <50 years), Val30Met mutation with late-onset disease (aged ≥50 years), non-Val30Met cardiac (*TTR* mutations associated with a predominantly cardiac form of the disease: Val122Ile [p.Val142Ile]

ABBREVIATIONS AND ACRONYMS

ATTR amyloidosis = transthyretin amyloidosis

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv amyloidosis = variant transthyretin amyloidosis

ATTRwt amyloidosis = wild-type transthyretin amyloidosis

LVWT = left ventricular wall thickness

mPND score = modified polyneuropathy disability score

NT-proBNP = N-terminal pro-B-type natriuretic peptide

THAOS = Transthyretin Amyloidosis Outcomes Survey

TTR = transthyretin

[14], Leu111Met [p.Leu131Met] [15], Thr60Ala [p. Thr80Ala] [16], or Ile68Leu [p.Ile88Leu] [17]), and non-Val30Met noncardiac (all other *TTR* mutations).

Baseline clinical and instrumental findings were analyzed according to sex in patients with ATTRv amyloidosis and in the subpopulation of patients with ATTRv amyloidosis and cardiomyopathy (defined as left ventricular wall thickness [LVWT] >12 mm on echocardiography). In patients with ATTRv amyloidosis, the relationship between sex and increasing levels of disease severity (expressed in quartiles) related to both cardiac involvement (mean LVWT in mm divided by height in meters, left ventricular ejection fraction [LVEF], and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) and neurological involvement or global status (modified polyneuropathy disability [mPND] score and Karnofsky score) was investigated.

Male prevalence of each mutation was assessed in the entire cohort in this analysis (all patients with symptoms definitely ATTR amyloidosis related and all asymptomatic carriers with no ATTR amyloidosis-related symptoms). Male prevalence in each of the 3 phenotype categories was assessed for patients with ATTRv amyloidosis. Male prevalence in each of the genotype categories was assessed for asymptomatic carriers, patients with ATTRv amyloidosis, and the subgroup of patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm).

Multivariable analysis of the possible determinants of phenotype (by logistic regression) and mean LVWT (divided by height, to normalize for physiologic sex-related differences; by linear regression) was also conducted to assess the independent contribution of sex in patients with ATTRv amyloidosis.

Simple binary and continuous variables are presented with the use of descriptive statistics. Differences between groups were assessed for statistical significance by analysis of variance to calculate *P* values by comparing means between groups for continuous variables, Pearson's chi-square test to calculate *P* values for variables with counts >5, Kruskal-Wallis test to calculate *P* values by comparing medians between groups for continuous variables, Fisher's exact test to calculate *P* values for nonordinal variables with counts ≤5, and the Cochran-Armitage test for trend for ordinal variables. *P* values for the difference in medians were based on the median 2-sample test. No adjustments to significance levels were made for multiplicity.

RESULTS

PATIENTS WITH ATTRv AMYLOIDOSIS. Demographic and clinical characteristics of the 2,790 patients with ATTRv amyloidosis are presented in Table 1. Mean age at enrollment was higher in men (54.2 years vs 50.4 years; $P < 0.001$), as was age at onset of ATTR amyloidosis symptoms (49.1 years vs 45.0 years; $P < 0.001$). A higher proportion of men had signs and symptoms of cardiac involvement (as assessed by wall thicknesses and LVEF; $P < 0.001$ for all), whereas carpal tunnel syndrome and vitreal and kidney involvement were equally distributed (Table 1).

A predominantly cardiac phenotype was more common among men than women (18.0% vs 13.0%; $P = 0.001$), while a predominantly neurological phenotype was less common (57.4% vs 64.6%; $P < 0.001$) (Figure 1).

Patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm). There were 683 patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm): 493 (72.2%) male and 190 (27.8%) female (Table 2). Mean age at enrollment in THAOS was similar between male and female patients. Echocardiographic parameters were largely similar between the groups. There was a difference in diastolic ventricular septal and posterior wall thickness between men and women (17.6 mm vs 16.4 mm and 15.4 mm vs 14.4 mm, respectively; $P < 0.001$), although this disparity was not seen when these parameters were indexed by height (Table 2).

Neurologic and cardiac disease severity in patients with ATTRv amyloidosis. Male prevalence was significantly greater with more severe cardiac manifestation of disease, where the percentage of male patients increased progressively from the least to most severe disease quartiles as assessed with NT-proBNP, LVEF, mean LVWT divided by height, and LV mass index divided by height (Figure 2). The trend in measures of neurological impairment, Karnofsky score, and mPND score was less apparent.

Multivariate analysis in patients with ATTRv amyloidosis. Multivariate analyses demonstrated that sex, age at onset, and genotype were significant risk factors for increased left ventricular septum thickness divided by height (Table 3). Sex was not confirmed as an independent risk factor for development of a predominantly cardiac or mixed phenotype (Supplemental Table 1).

GENOTYPE AND SEX IN THE ENTIRE COHORT. The entire cohort in this analysis consisted of 4,050 patients with a pathogenic disease-causing *TTR* genetic

TABLE 1 Characteristics of Patients With ATTRv Amyloidosis According to Sex

	Overall (N = 2,790)	Male (n = 1,646)	Female (n = 1,144)	*P* Value
Age at enrollment, y	52.6 ± 16.3	54.2 ± 16.5	50.4 ± 15.7	<0.001
Age at onset of ATTR amyloidosis symptoms, y	47.4 ± 16.1	49.1 ± 16.5	45.0 ± 15.3	<0.001
Duration of ATTR amyloidosis symptoms, y	4.0 (1.8-8.3)	3.8 (1.7-7.9)	4.2 (1.9-9.1)	0.074
Abnormal ECG	1,013/1,708 (59.3)	652/1,017 (64.1)	361/691 (52.2)	<0.001
Complete AV block or pacemaker	265/596 (44.5)	182/409 (44.5)	83/187 (44.4)	0.98
LAHB	185/588 (31.5)	117/402 (29.1)	68/186 (36.6)	0.070
LPHB	19/584 (3.3)	17/400 (4.3)	2/184 (1.1)	0.045
LBBB	62/586 (10.6)	47/402 (11.7)	15/184 (8.2)	0.20
RBBB	86/587 (14.7)	61/403 (15.1)	25/184 (13.6)	0.62
Echocardiography measures				
LVEF, %	61.8 ± 12.4	60.7 ± 12.9	63.8 ± 11.3	<0.001
Diastolic interventricular septum wall thickness, mm	14.4 ± 4.7	15.2 ± 4.7	12.8 ± 4.2	<0.001
Diastolic posterior wall thickness, mm	12.9 ± 4.1	13.6 ± 4.1	11.7 ± 3.8	<0.001
Diastolic diameter, mm	44.8 ± 6.4	45.7 ± 6.2	43.0 ± 6.5	<0.001
Kidney involvement[a]	455/780 (58.3)	240/417 (57.6)	215/363 (59.2)	0.64
Neurologic involvement				
Sensory abnormalities	2,268/2,790 (81.3)	1,318/1,646 (80.1)	950/1,144 (83.0)	0.048
Autonomic impairment	1,708/2,790 (61.2)	1,038/1,646 (63.1)	670/1,144 (58.6)	0.017
mPND score				
0	505/2,318 (21.8)	271/1,333 (20.3)	234/985 (23.8)	<0.001
I	1,150/2,318 (49.6)	614/1,333 (46.1)	536/985 (54.4)	
II	365/2,318 (15.7)	253/1,333 (19.0)	112/985 (11.4)	
IIIa	134/2,318 (5.8)	91/1,333 (6.8)	43/985 (4.4)	
IIIb	100/2,318 (4.3)	61/1,333 (4.6)	39/985 (4.0)	
IV	64/2,318 (2.8)	43/1,333 (3.2)	21/985 (2.1)	
Carpal tunnel syndrome	402/2,594 (15.5)	238/1,513 (15.7)	164/1,081 (15.2)	0.70
Vitreal involvement	107/2,756 (3.9)	61/1,621 (3.8)	46/1,135 (4.1)	0.70
NT-proBNP, pg/mL	2,180.8 ± 8,979.6	2,440.1 ± 10,593.8	1,734.0 ± 5,106.5	0.29

Values are mean ± SD, median (interquartile range), or n/N (%). Patients with ATTRv amyloidosis were those with a disease-causing *TTR* genetic variant and symptoms definitely related to ATTR amyloidosis. *P* values were obtained from Student's *t*-test for continuous variables and chi-square test for categorical variables, with *P* values for the difference in median based on the median 2-sample test. [a]Patients with kidney involvement had either a protein/creatinine value >45 mg/mmoL or an albumin/creatinine value >30 mg/mmol.

ATTR amyloidosis = transthyretin amyloidosis; ATTRv amyloidosis = variant transthyretin amyloidosis; AV = atrioventricular; ECG = electrocardiogram; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LPHB = left posterior hemiblock; LVEF = left ventricular ejection fraction; mPND = modified polyneuropathy disability; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RBBB = right bundle branch block.

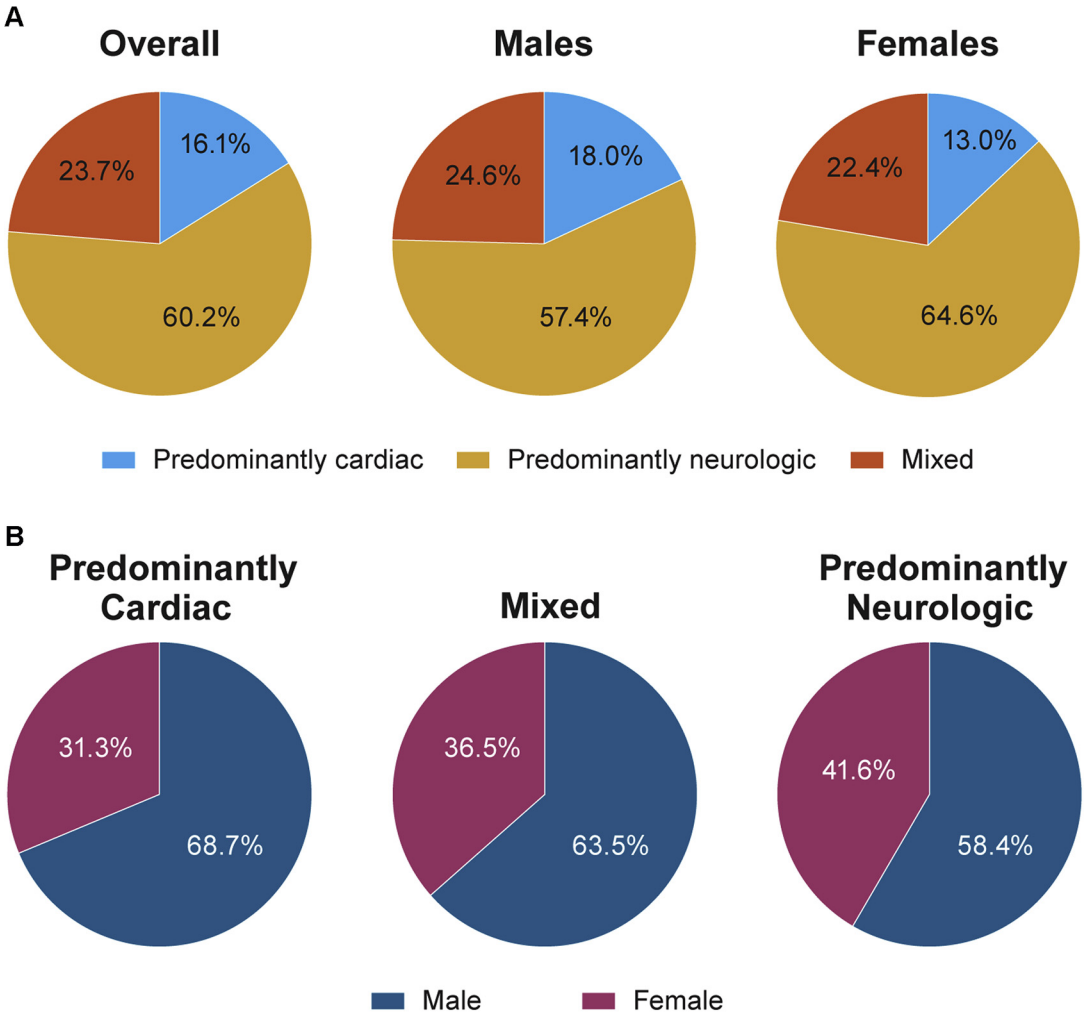
variant, 2,171 (53.6%) of which were male. Of these, 2,790 were patients with ATTRv amyloidosis (1,646 [59.0%] male) and 1,260 were asymptomatic carriers (525 [41.7%] male). Val30Met was the most common mutation in both sexes (with a male:female prevalence ratio of 0.97), although the frequency was lower in men (60.2%) than in women (72.0%) (Table 4). Male prevalence (compared with female) was greater in the non-Val30Met cardiac mutations (Val122Ile, Leu111Met, Thr60Ala, or Ile68Leu) and in the Phe64Leu and Ile107Val mutations (Table 4). Male prevalence in these mutations was typically even greater when only patients with ATTRv amyloidosis were considered, with a male:female prevalence ratio of 6.50 in patients with Ile107Val (p.Ile127Val), 3.42 in Val122Ile, 3.30 in Ile68Leu, 2.29 in Phe64Leu (p.Phe84Leu), 1.80 in Leu111Met, and 1.69 in Thr60Ala (Supplemental Table 2).

Considering the main genotype groups, male prevalence in patients with ATTRv amyloidosis ranged from 50.6% in early-onset Val30Met to 73.2% in non-Val30Met cardiac (Central Illustration). Male prevalence was greater in patients with ATTRv amyloidosis than in asymptomatic carriers in all genotype categories. Male prevalence was also greater in patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm) than in patients with ATTRv amyloidosis in all genotype categories, with the increased male prevalence most pronounced in Val30Met (both early- and late-onset) (Central Illustration).

DISCUSSION

This study represents the largest systematic analysis of the role of sex in ATTRv amyloidosis. Overall, the

FIGURE 1 Association Between Sex and Phenotypes in Patients With ATTRv Amyloidosis



(A) Distribution of phenotype according to sex. **(B)** Distribution of sex according to phenotype. A predominantly cardiac phenotype was more common in men than in women ($P = 0.001$), whereas a predominantly neurologic phenotype was less common in men than in women ($P < 0.001$); similar proportions of men and women had a mixed phenotype ($P = 0.22$). Patients with ATTRv amyloidosis were those with a disease-causing *TTR* genetic variant and symptoms definitely related to ATTR amyloidosis. Patients were grouped into a predominant clinical phenotype based on clinical presentation at enrollment. Predominantly cardiac was defined as at least 1 of the following symptoms: heart failure, dyspnea, or abnormal electrocardiogram caused by rhythm disturbance; and no more than mild neurologic or gastrointestinal symptoms (excluding erectile dysfunction, constipation, and carpal tunnel syndrome). Predominantly neurologic was defined as walking disability, other neurologic symptoms, and/or 1 of the following gastrointestinal symptoms, of any severity: early satiety, nausea, vomiting, unintentional weight loss, diarrhea, or fecal incontinence; and without heart failure, dyspnea, or abnormal electrocardiogram caused by rhythm disturbance (9). Mixed was defined as all remaining patients with at least 1 of the cardiac and 1 of the neurologic symptoms as described above. ATTR amyloidosis = transthyretin amyloidosis; ATTRv amyloidosis = variant transthyretin amyloidosis.

results confirm the hypothesis that some biological characteristic(s) associated with female sex could be protective against myocardial involvement in ATTRv amyloidosis. The higher prevalence of male sex in the predominantly cardiac phenotype and in cardiogenic mutations, along with the association between male sex and severity of morphological and functional cardiac involvement, suggests that male patients are more susceptible to myocardial involvement in ATTRv amyloidosis.

Male-to-female prevalence varied considerably according to clinical phenotype and genotype. This ratio was broadly balanced when considering the entire cohort (patients with ATTRv amyloidosis and

TABLE 2 Characteristics of Patients With ATTRv Amyloidosis and Cardiomyopathy (LVWT >12 mm) According to Sex

	Overall (N = 683)	Male (n = 493)	Female (n = 190)	*P* Value
Age at enrollment, y	64.0 ± 11.1	64.0 ± 11.1	63.9 ± 11.2	0.94
Duration of ATTR amyloidosis symptoms, y	4.1 (1.7-8.0)	3.9 (1.6-7.5)	4.6 (2.3-10.0)	0.41
NYHA functional class >II at initial evaluation	185/388 (47.7)	127/272 (46.7)	58/116 (50.0)	0.55
Neurosensorial stage	2.5 ± 1.4	2.4 ± 1.3	2.6 ± 1.4	0.29
Autonomic neuropathy	335/683 (49.0)	246/493 (49.9)	89/190 (46.8)	0.47
E-wave deceleration time, ms	183.2 ± 55.2	184.6 ± 57.9	180.2 ± 48.9	0.53
E-wave:A-wave ratio	1.2 (0.8-2.3)	1.2 (0.8-2.3)	1.4 (0.8-2.2)	0.76
LVEF, %	58.6 ± 13.2	57.9 ± 13.5	60.3 ± 12.2	0.056
Diastolic interventricular septum wall thickness, mm	17.3 ± 3.7	17.6 ± 3.7	16.4 ± 3.6	<0.001
Diastolic interventricular septum wall thickness, mm, ÷ height, m	10.2 ± 2.2	10.1 ± 2.2	10.3 ± 2.3	0.51
Diastolic posterior wall thickness, mm	15.2 ± 3.5	15.4 ± 3.6	14.4 ± 3.1	0.001
Diastolic posterior wall thickness, mm, ÷ height, m	8.9 ± 2.1	8.9 ± 2.1	9.0 ± 2.0	0.35
Mean LVWT, mm	16.2 ± 3.2	16.5 ± 3.3	15.4 ± 2.8	<0.001
Mean LVWT, mm, ÷ height, m	9.5 ± 1.9	9.5 ± 2.0	9.6 ± 1.8	0.39
LV mass index (g/m^2)	167.4 ± 59.3	171.6 ± 62.5	157.1 ± 49.2	0.007
NT-proBNP (pg/mL)	3,250.3 ± 6,264.8	2,927.0 ± 5,510.3	4,152.7 ± 7,971.2	0.11

Values are mean ± SD, median (interquartile range), or n/N (%). Patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm) were those with a disease-causing *TTR* genetic variant, symptoms definitely related to ATTR amyloidosis, and LVWT >12 mm. *P* values were obtained from Student's *t*-test for continuous variables and chi-square test for categoric variables, with *P* values for the difference in medians based on the median 2-sample test.

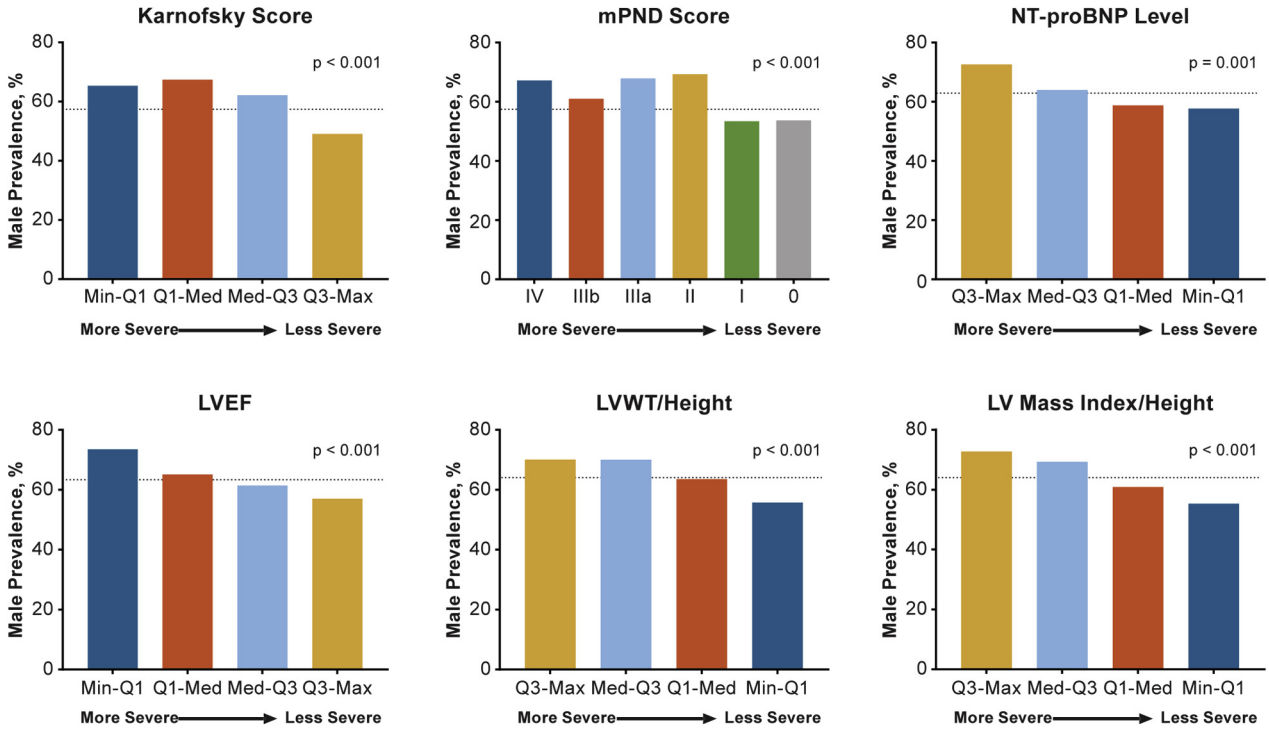
LV = left ventricular; LVWT = left ventricular wall thickness; NYHA = New York Heart Association functional class; other abbreviations as in Table 1.

asymptomatic carriers; 53.6% male vs 46.4% female), yet among patients with ATTRv amyloidosis, the proportion of men was more pronounced (59.0% male vs 41.0% female). The proportion of men was even greater in the mixed (63.5%) and predominantly cardiac phenotypes (68.7%). Most notably, the proportion of men reached 72.2% among patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm). Although this analysis used LVWT >12 mm as the marker of cardiomyopathy, sex-based differences in physiology mean that women may have required a greater degree (or duration) of disease progression to reach LVWT >12 mm than men. This could have contributed to the lower proportion of women among patients with ATTRv amyloidosis and cardiomyopathy in this analysis, but is unlikely to have contributed to the greater proportion of men in the cardiac genotype and phenotype categories.

Among patients with ATTRv amyloidosis in the genotype subgroups, the proportion of men progressively increased, from 50.6% in patients with early-onset Val30Met (the most "neurogenic" mutation) to 61.2% in non-Val30Met noncardiac, to 63.9% in late-onset Val30Met, and to 73.2% among the cardiac mutations (**Central Illustration**). This progressive "rightward shift" seen in patients with ATTRv amyloidosis was less pronounced, and male prevalence was notably lower overall, in asymptomatic carriers, suggesting a lower genetic penetrance in women compared with men. This suggests that the relationship between sex, genetics, and disease expression is not entirely mediated by a higher prevalence of male patients in certain mutations, but also involves genetic factors not limited to *TTR* in addition to nongenetic factors. This apparent age-dependent female protection could be the result of the interaction of epigenetic mechanisms and sex-related hormonal influences rather than innate strictly genetic factors. The potential for a protective role for female sex hormones was supported by one study that showed that female patients with ATTR-CM and the greatest degree of cardiomyopathy were more likely to be postmenopausal (11). Some data from studies in nonhuman animals are also consistent with this hypothesis: stimulation of mice with male sex hormones increases TTR synthesis in the liver and may constitute a risk factor for the development of ATTR amyloidosis (18).

In addition to the higher male prevalence in patients with ATTRv amyloidosis with a cardiac mutation or phenotype, an effect of sex was also detected in the severity of cardiac disease as assessed with LVWT, LV mass index, and LVEF. To correct for the physiologic differences in wall thickness values between men and women, thickness was normalized by height. The percentage of men increased progressively from the first to the fourth quartile of severity as measured by mean LVWT divided by height, LV mass index divided by height, LVEF, and NT-proBNP. A relationship between the quartiles of increasing severity of neurological impairment (Karnofsky score and mPND score) and sex was much less evident.

FIGURE 2 Male Prevalence According to Severity of Disease in Patients With ATTRv Amyloidosis



P values obtained by Cochran-Armitage test for trend. Patients with ATTRv amyloidosis were those with a disease-causing *TTR* genetic variant and symptoms definitely related to ATTR amyloidosis. Horizontal dotted lines show overall male prevalence in each clinical assessment. LV = left ventricular; LVEF = left ventricular ejection fraction; LVWT = left ventricular wall thickness; max = maximum; med = median; min = minimum; mPND = modified polyneuropathy disability; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Q = quartile; other abbreviations as in Figure 1.

Note that Karnofsky score was primarily collected as an imperfect measure of neurological disease progression, but it may also be impaired in patients with cardiac disease. Similarly, LVEF may be an imperfect measure of cardiac disease severity in patients with ATTR-CM because the majority of patients had preserved LVEF, with differences among patients who all have preserved LVEF less likely to be clinically meaningful. However, the lowest quartile in this analysis included patients with reduced and mildly reduced LVEF (range 17.3-54.6%) and this quartile had the most pronounced increase in the proportion of men.

Because sex-related differences in amyloidosis is a relatively little-explored topic, with sex associations reported in either direction, it is difficult to compare the present data with other studies. No major sex imbalance has been described for light-chain amyloidosis, where the male:female ratio ranges from approximately 50:50 to 60:40 (19-23), while atrial amyloidosis secondary to chronic valvular atrial fibrillation (A-type natriuretic peptide derived) preferentially occurs in female patients (24-27). The most striking sex-related association is seen with ATTRwt amyloidosis, with >80% of cases being elderly men (6-8). In ATTRv amyloidosis, a male predisposition for development of amyloid heart disease has been described in late-onset patients with Val30Met in Japan (28) and Sweden (12,29), and for other rarer *TTR* mutations (30). The results of the present study are consistent with a smaller monocentric study in which female prevalence was lower within the highest tercile of echocardiographic indicators of myocardial involvement, and sex was independently associated with LVWT, while female prevalence was similar across the different neurological stages (11). A recent analysis using noninvasive estimates of pressure/volume indices showed similar overall chamber function in men and women with the Val122Ile mutation despite women being, on average, 7 years older at diagnosis, suggesting a less aggressive disease trajectory in women (10). In a cohort of 117 Swedish

patients with Val30Met ATTRv amyloidosis, type A fibrils (consisting of a mixture of truncated and full-length amyloid transthyretin fibrils) were associated with more advanced amyloid heart disease compared with type B fibrils (consisting only of full-length fibrils); however, women with type A fibrils generally developed less cardiac infiltration than men (31).

STUDY LIMITATIONS. Multivariate analysis did not identify sex as an independent risk factor for the development of a predominantly cardiac or mixed (vs neurological) phenotype, despite a predominantly cardiac phenotype being significantly more common in men than in women. This was likely caused by the greater effect of mutation on phenotype obscuring any effect of sex in the multivariate analysis. In the more specific multivariate analysis of risk factors for development of cardiac involvement (increased mean LVWT divided by height), sex was confirmed as an independent determinant of the severity of cardiac involvement.

TABLE 3 Multivariate Linear Regression Analysis to Model Mean LVWT (mm) Divided by Height (m) in Patients With ATTRv Amyloidosis

	Comparison	Estimate	SE	*P* Value
Sex	Male[a] vs female	0.4383	0.1457	0.0027
Onset	Late[a] vs early	1.5897	0.1490	<0.0001
Genotype	Non-Val30Met cardiac[a] vs Val30Met	1.8068	0.1980	<0.0001
	Non-Val30Met noncardiac[a] vs Val30Met	1.6269	0.1547	<0.0001

An estimate >0 favors the first comparator listed. Increased mean LVWT divided by height was significantly associated with: male (vs female) sex; late-onset (vs early-onset) disease; non-Val30Met cardiac (vs Val30Met) genotype; and non-Val30Met noncardiac (vs Val30Met) genotype. Patients with ATTRv amyloidosis were those with a disease-causing *TTR* genetic variant and symptoms definitely related to ATTR amyloidosis. Non-Val30Met cardiac defined as Val122Ile, Leu111Met, Thr60Ala, or Ile68Leu. [a]Significant comparator.

Abbreviations as in Tables 1 and 2.

CONCLUSIONS

This large analysis in THAOS suggests that myocardial involvement appears to be more frequent and pronounced in male patients with ATTRv amyloidosis. Although male sex is more represented in cardiogenic mutations, part of its association with increasing LV thickness is independent from genotype and age, supporting the hypothesis that some biological characteristics may prevent myocardial amyloid infiltration in women (or facilitate it in men). Physiological differences between sexes may have resulted in an underestimate of the proportion of women with cardiomyopathy (as defined as LVWT >12 mm), although in subsequent analyses these differences were normalized by height. These data complement the well-established greater male prevalence in patients with ATTRwt amyloidosis, in which all patients have cardiomyopathy (6,8). The observations and hypotheses reported here must be interpreted in the context of the well-known complexity of the determinants of phenotypic heterogeneity of ATTRv amyloidosis, including not only sex and age, but also sex of the transmitting parent, geographic area and type of aggregation (endemic or nonendemic), and fibril composition (1). Future studies might investigate potential prognostic factors and examine the underlying biology of a potential protective mechanism conferred by female sex.

ACKNOWLEDGMENTS The authors thank all THAOS patients and investigators for their important contributions to this study. They also thank Rajiv Mundayat, Jan Kiszko and Denise Rill for their contributions to earlier versions of this work. Additional THAOS investigators contributing to this analysis: Johan van Cleemput, Afdeling Klinische Cardiologie, O&N I, Leuven, Belgium; Marcia Waddington-Cruz, Hospital Universitario Clementino Fraga Filho, Rio

TABLE 4 Frequency of Different Genotypes by Sex in the Entire Cohort

Mutation	Overall (N = 4,050)	Male (n = 2,171)	Female (n = 1,879)	Male:Female Prevalence Ratio
Val30Met	2,659 (65.7)	1,307 (60.2)	1,352 (72.0)	0.97
Val122Ile[a]	305 (7.5)	226 (10.4)	79 (4.2)	2.86
Thr60Ala[a]	121 (3.0)	70 (3.2)	51 (2.7)	1.37
Glu89Gln	111 (2.7)	53 (2.4)	58 (3.1)	0.91
Ser50Arg	93 (2.3)	48 (2.2)	45 (2.4)	1.07
Ile68Leu[a]	69 (1.7)	46 (2.1)	23 (1.2)	2.00
Phe64Leu	68 (1.7)	48 (2.2)	20 (1.1)	2.40
Gly6Ser/Val30Met	54 (1.3)	27 (1.2)	27 (1.4)	1.00
Ser77Tyr	51 (1.3)	34 (1.6)	17 (0.9)	2.00
Ile107Val	36 (0.9)	30 (1.4)	6 (0.3)	5.00
Asp38Ala	31 (0.8)	18 (0.8)	13 (0.7)	1.38
Gly47Ala	29 (0.7)	14 (0.6)	15 (0.8)	0.93
Glu89Lys	26 (0.6)	16 (0.7)	10 (0.5)	1.60
Val20Ile	23 (0.6)	16 (0.7)	7 (0.4)	2.29
Leu111Met[a]	21 (0.5)	12 (0.6)	9 (0.5)	1.33
Val28Met	19 (0.5)	10 (0.5)	9 (0.5)	1.11
DelVal122	17 (0.4)	5 (0.2)	12 (0.6)	0.42
Thr49Ala	16 (0.4)	9 (0.4)	7 (0.4)	1.29
His88Arg	13 (0.3)	8 (0.4)	5 (0.3)	1.60
Val122Ala	13 (0.3)	8 (0.4)	5 (0.3)	1.60
Ser52Pro	12 (0.3)	7 (0.3)	5 (0.3)	1.40
Ser77Phe	12 (0.3)	6 (0.3)	6 (0.3)	1.00
Thr59Lys	10 (0.2)	7 (0.3)	3 (0.2)	2.33

Values are n (%), unless otherwise indicated. Mutations in the entire cohort in this analysis (all patients with ATTRv amyloidosis and symptoms definitely ATTR amyloidosis related and all asymptomatic carriers with no ATTR amyloidosis-related symptoms). Only mutations with ≥10 patients are shown. Male:female prevalence ratio calculated as proportion of men with mutation divided by proportion of women with mutation. $P < 0.001$ for overall chi-square test for association between sex and genotype (including all patients). [a]Cardiac mutations (associated with cardiomyopathy).

Abbreviations as in Table 1.

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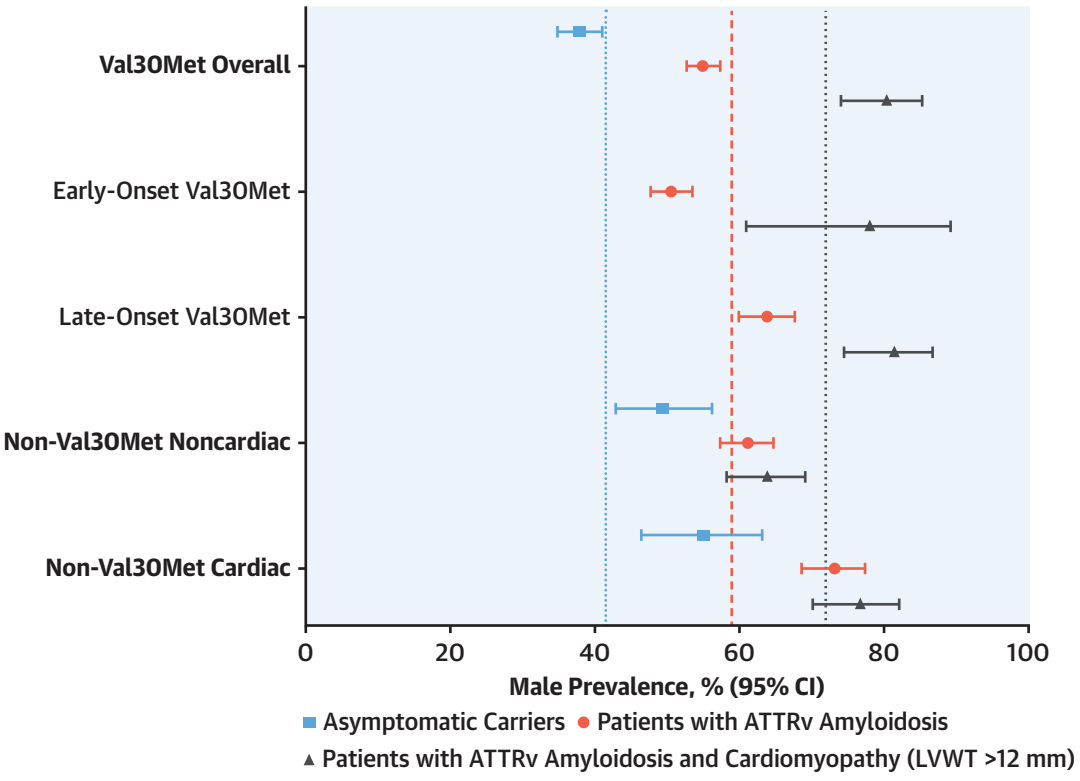
CENTRAL ILLUSTRATION **Proportion of Male Patients Among Asymptomatic Carriers, Patients With ATTRv Amyloidosis, and Patients With ATTRv Amyloidosis and Cardiomyopathy (LVWT >12 mm) According to Main Genotype Groups**



Caponetti, A.G. et al. J Am Coll Cardiol HF. 2021;9(10):736–746.

There was a progressive "rightward shift," with greater proportions of men in those genotype groups more associated with cardiac disease. The proportion of men in the entire cohort was 53.6%: 42.7% in asymptomatic carriers, as shown by the **dotted blue line**; 59.0% in patients with ATTRv amyloidosis, as shown by the **dashed red line**; and 72.2% in patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm), as shown by the **dashed gray line**). Asymptomatic carriers were those with a disease-causing *TTR* genetic variant and no ATTR amyloidosis-related symptoms (and therefore not present in the early- and late-onset Val30Met groups). Patients with ATTRv amyloidosis were those with a disease-causing *TTR* genetic variant and symptoms definitely related to ATTR amyloidosis. Patients with ATTRv amyloidosis and cardiomyopathy (LVWT >12 mm) were those with a disease-causing *TTR* genetic variant, symptoms definitely related to ATTR amyloidosis, and LVWT >12 mm. Non-Val30Met cardiac was defined as Val122Ile, Leu111Met, Thr60Ala, or Ile68Leu. ATTR amyloidosis = transthyretin amyloidosis; ATTRv amyloidosis = variant transthyretin amyloidosis; LVWT = left-ventricular wall thickness.

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FUNDING SUPPORT AND AUTHOR DISCLOSURES

The THAOS registry and this analysis were sponsored by Pfizer. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions and funded by Pfizer. Dr Rapezzi has received research grants from Pfizer and consultancy fees from Pfizer; Alnylam, and Prothena. Dr Milandri has received consultancy fees from Alnylam. Dr. Dispenzieri has received research grants from Celgene, Millennium, Pfizer, Janssen, and Alnylam; funding from Pfizer for meeting expenses (travel); and attended advisory boards for Akcea and Intellia. Dr Kristen has received research support from and advisory board attendance for Pfizer. Dr Wixner has received consulting fees, travel support for lectures, and advisory boards from Pfizer, Akcea, and Alnylam. Dr Maurer has received grants and/or personal fees from Akcea, Alnylam, Eidos, GlaxoSmithKline, Ionis, Pfizer, and Prothena. Dr Garcia-Pavia has received speaker and/or consulting fees from Pfizer, Eidos, Alnylam, Prothena, Neurimmune, and Akcea; and research funding from Alnylam and Pfizer. Dr Tournev has received sponsorship from Pfizer for participation in advisory boards, congresses, and conferences. Dr Planté-Bordeneuve is serving as a medical advisor for Pfizer, Alnylam, Eidos, and Ionis. Drs Chapman and Amass are full-time employees of Pfizer and hold stock and/or stock options with Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Although patients with ATTRv cardiomyopathy are more likely to be male, little is known of the role of sex in the development of cardiac manifestations in patients with ATTRv amyloidosis. This analysis supports the hypothesis that there are biological characteristics that either inhibit myocardial amyloid infiltration in women or facilitate it in men, making male patients more susceptible to myocardial involvement in ATTRv amyloidosis.

TRANSLATIONAL OUTLOOK: Future studies could investigate potential prognostic factors and examine the underlying biology of a potential protective mechanism conferred by female sex.

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KEY WORDS ATTRv amyloidosis, myocardial involvement, registry, sex

APPENDIX For supplemental tables, please see the online version of this paper.