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## Sex differences in wild-type transthyretin amyloidosis: An analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS)

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# Sex Differences in Wild-Type Transthyretin Amyloidosis: An Analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS)

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## ABSTRACT

**Introduction:** Wild-type transthyretin amyloidosis (ATTRwt amyloidosis) is a progressive disease resulting from the accumulation of wild-type transthyretin (TTR) amyloid fibrils, and is diagnosed primarily in males. This analysis examined sex differences in patients with

ATTRwt amyloidosis from the Transthyretin Amyloidosis Outcomes Survey (THAOS).

**Methods:** THAOS is an ongoing, global, longitudinal, observational survey of patients with transthyretin amyloidosis, including both inherited and wild-type disease, and asymptomatic carriers of *TTR* mutations. THAOS data were analyzed to identify potential differences in demographic and clinical characteristics between males and females with ATTRwt amyloidosis (data cutoff: August 1, 2021).

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**Results:** Of 1386 patients with ATTRwt amyloidosis, 84 (6%) were female and 1302 (94%) were male. Females had a higher median age at enrollment (80 vs. 78 years;  $p = 0.002$ ) and symptom onset (75 vs. 73 years;  $p = 0.045$ ) than males. Mean left ventricular (LV) ejection fraction was higher (53% vs. 48%;  $p = 0.001$ ) and mean LV diastolic diameter lower (42 vs. 46 mm;  $p < 0.001$ ) in females versus males, but sex was not identified as a predictor of LV mean wall thickness adjusted for height (beta coefficient  $-0.22$ ;  $p = 0.460$ ) or a predominantly cardiac phenotype (odds ratio 1.60;  $p = 0.191$ ). Modified polyneuropathy disability scores differed between groups ( $p < 0.001$ ), with a larger proportion of scores  $\geq$  IIIa among females (23% vs. 7%).

**Conclusions:** Females with ATTRwt amyloidosis in THAOS tended to present at a later age and showed signs of less severe cardiac impairment and more severe walking impairment.

**Trial Registration:** ClinicalTrials.gov: NCT00628745.

**Keywords:** ATTRwt amyloidosis; Registry; Sex; Transthyretin Amyloidosis Outcomes Survey

### Key Summary Points

#### Why carry out this study?

Wild-type transthyretin amyloidosis (ATTRwt amyloidosis) is a progressive, fatal disease that is primarily characterized by cardiomyopathy and is most often diagnosed in males

This analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) examined sex differences in demographic and clinical characteristics of patients with ATTRwt amyloidosis

### What was learned from the study?

Female patients with ATTRwt amyloidosis in THAOS tended to present at a later age and showed signs of less severe cardiac impairment and more severe neurologic impairment compared with male patients

These findings are suggestive of differences in the clinical presentation of ATTRwt amyloidosis between male and female patients

## INTRODUCTION

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive, life-threatening disease resulting from the deposition of misfolded transthyretin (TTR) protein in the heart, peripheral nerves, and other tissues and organs [1]. The disease can result from pathogenic mutations in the *TTR* gene (ATTRv amyloidosis) or the age-related accumulation of wild-type TTR protein (ATTRwt amyloidosis) [1]. Cardiac involvement is the main clinical manifestation in ATTRwt amyloidosis, which is characterized by heart failure, conduction disorders, and arrhythmias [2, 3]. Symptoms stemming from extracardiac TTR deposits, such as carpal tunnel syndrome, lumbar spinal stenosis, and rupture of the biceps tendon, may also be present [2, 3]. ATTRv amyloidosis has a more heterogeneous clinical presentation and can manifest as polyneuropathy, cardiomyopathy, or a mix of both [4].

ATTRwt amyloidosis predominantly affects males, accounting for  $> 80\%$  of diagnosed cases [5, 6]. Furthermore, males with ATTRwt amyloidosis reportedly have an earlier age of onset than females [5, 7]. There is also evidence of increased cardiac involvement among male patients with the hereditary form of the disease. Patients with variants primarily associated with a cardiac phenotype and those diagnosed with transthyretin amyloid cardiomyopathy are more likely to be male [8–10]. Based on such findings, it has been suggested that female sex may be a protective factor against the

development of cardiac disease in ATTR amyloidosis [11, 12].

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal, observational survey of patients with ATTR amyloidosis, including both hereditary and wild-type disease, and asymptomatic carriers of *TTR* mutations [13]. A recent THAOS analysis examining sex differences in patients with ATTRv amyloidosis found that male prevalence was greater with more severe cardiac manifestations, as assessed with N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, mean left ventricular (LV) wall thickness adjusted for height, LV mass index adjusted for height, and LV ejection fraction (LVEF). This prior analysis also identified male sex as a risk factor for increased LV wall thickness adjusted for height [12]. The objective of the current analysis was to investigate possible sex differences in demographic and clinical characteristics in patients with ATTRwt amyloidosis from THAOS.

## METHODS

### Study Design and Patient Population

The overall design and methodology of THAOS have been described in detail [13]. All THAOS sites received ethical or institutional review board approval before patient enrollment, and each patient provided written informed consent. The study followed the Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki.

This analysis included all patients with ATTRwt amyloidosis enrolled in THAOS (data cutoff: August 1, 2021). All patients were diagnosed with ATTR amyloidosis by a clinician and met the following THAOS inclusion criteria for ATTRwt amyloidosis. Prior to March 1, 2021, patients must have had genotyped confirmation that they did not possess a known mutation in the *TTR* gene and an echocardiogram with LV mean wall thickness > 12 mm with at least one of the following: recorded TTR amyloid in cardiac or noncardiac biopsy tissue by mass spectrometry or immunohistochemistry or technetium-99m-labeled bone scintigraphy indicating TTR amyloid

in cardiac tissue with no evidence of primary (light chain) amyloidosis. After this date, patients must have had genotyped confirmation that they did not possess a known mutation in the *TTR* gene and one of the following: presence of amyloid in cardiac biopsy tissue confirmed as TTR amyloid by mass spectrometry or immunohistochemistry or an echocardiogram with LV wall thickness > 12 mm and either the presence of amyloid in noncardiac tissue confirmed as TTR amyloid by mass spectrometry or immunohistochemistry or the presence of amyloid in cardiac tissue indirectly confirmed by scintigraphy with a “bone-seeking tracer” with Perugini grade 2.

Demographic and clinical characteristics collected at enrollment were analyzed according to sex.

### Assessments

The Karnofsky performance status score is a measure of patients’ ability to perform normal daily life activities and their need for assistance, and scores range from 10 (moribund; fatal processes progressing rapidly) to 100 (normal; no complaints).

Neurologic measures included the presence of sensory abnormalities and autonomic neuropathy and the modified polyneuropathy disability (mPND) score. The mPND score is a measure of walking disability and ranges from 0 to IV, where 0 indicates no sensory disturbances in the feet and the ability to walk without difficulty; I indicates sensory disturbance in the feet but preserved walking capacity; II indicates some difficulties walking but can walk without aid; IIIa indicates one stick or crutch required for walking; IIIb indicates two sticks or crutches required for walking; and IV indicates patients confined to a wheelchair or bed.

Cardiac characteristics included New York Heart Association (NYHA) functional class, presence of a pacemaker and/or implantable cardioverter defibrillator, electrocardiogram and echocardiogram findings, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration.

Kidney involvement was defined as either a protein/creatinine value > 45 mg/mmol or an albumin/creatinine value > 30 mg/mmol.

Phenotype categories, based on clinical presentation at the time of enrollment in THAOS, were defined as (1) predominantly cardiac: patients with at least one 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 neurologic: patients with neurologic or gastrointestinal symptoms of any severity and without heart failure, dyspnea, or abnormal electrocardiogram caused by rhythm disturbance; and (3) mixed: patients who had at least one of the cardiac and one of the neurologic symptoms described above. At enrollment, all patients with ATTRwt amyloidosis were classified as predominantly cardiac unless they had any definitely ATTR amyloidosis–related neurologic symptom, in which case they were classified as mixed.

### Statistical Analysis

Differences in demographic and clinical characteristics between male and female patients were tested for statistical significance using the chi-square test for categorical variables, the *t* test for means (continuous variables), and the Wilcoxon test for medians. The Cochran–Armitage test was used to analyze the trend in male proportion corresponding to mPND scores, Karnofsky Performance Status score, and NYHA functional class (represented as categories); and modified body mass index, mean LV wall thickness/height, LVEF, LV mass index/height, and NT-proBNP (represented as quartiles). Sex was examined as a predictor of LV mean wall thickness/height using linear regression and a predictor of phenotype (cardiac vs. mixed) using logistic regression.

## RESULTS

### Demographic and General Clinical Characteristics

A total of 1386 patients with ATTRwt amyloidosis (female,  $n = 84$  [6%]; male,  $n = 1302$  [94%]) from 52 study sites in 15 countries were

included in the analysis. Median age at enrollment (80 vs. 78 years;  $p = 0.002$ ) and symptom onset (75 vs. 73 years;  $p = 0.045$ ) were higher in female patients than in male patients (Table 1). No significant differences were observed between the sexes in symptom duration or time from symptom onset to diagnosis (Table 1). A predominantly cardiac phenotype was observed in 84% and 89%, and a mixed phenotype in 14% and 10% of female and male patients, respectively. There was no significant difference in the distribution of phenotypes. General clinical characteristics did not differ between the groups except for lumbar spinal stenosis, which occurred at a significantly lower rate in female patients than in male patients (1% vs. 7%;  $p = 0.039$ ) (Table 2).

### Cardiac and Neurologic Characteristics

Female patients had a significantly higher mean LVEF (53% vs. 48%;  $p = 0.001$ ) and lower mean LV diastolic diameter (42 vs. 46 mm;  $p < 0.001$ ) than male patients (Table 3). Additionally, the percentage of patients with left anterior hemiblock was significantly higher in female patients than in male patients (36% vs. 22%;  $p = 0.043$ ) (Table 3). The cumulative incidence curve of transthyretin amyloid cardiomyopathy (ATTR-CM) by sex showed that females tended to develop ATTR-CM at a later age (Fig. 1). Sex was not identified as a significant predictor of LV mean wall thickness/height (beta coefficient  $-0.22$ , standard error 0.30;  $p = 0.460$ ) or presenting with a predominantly cardiac versus mixed phenotype (odds ratio 1.60, confidence interval 0.79–3.22;  $p = 0.191$ ).

In terms of neurologic measures, the distribution of mPND scores differed between groups ( $p < 0.001$ ), with a larger proportion of IIIa or higher scores among female patients (23% vs. 7%) (Table 4). Sensory abnormalities were observed in 54% of female patients and 45% of male patients, but this difference was not statistically significant ( $p = 0.130$ ) (Table 4).

There was no clear trend in male proportion with increasing cardiac or neurologic disease severity.

**Table 1** Demographic characteristics of patients with ATTRwt amyloidosis according to sex

	Overall ( <i>N</i> = 1386)	Male ( <i>n</i> = 1302)	Female ( <i>n</i> = 84)	<i>p</i> value
Age at enrollment (years), <i>n</i>	1386	1302	84	
Median (10th, 90th percentile)	78 (69, 87)	78 (69, 86)	80 (71, 88)	0.002
Age at onset of ATTR amyloidosis symptoms (years), <i>n</i>	1244	1172	72	
Median (10th, 90th percentile)	73 (60, 83)	73 (60, 83)	75 (60, 86)	0.045
Duration of ATTR amyloidosis symptoms (years), <i>n</i>	1244	1172	72	
Median (10th, 90th percentile)	3.0 (0.4, 13.7)	3.0 (0.4, 13.7)	2.4 (0.6, 13.2)	0.875
Time from symptom onset to diagnosis (years), <i>n</i>	1171	1103	68	
Median (10th, 90th percentile)	1.7 (0.0, 12.3)	1.7 (0.0, 12.7)	1.6 (0.0, 12.3)	0.853
Follow-up time (years), <i>n</i>	1386	1302	84	
Median (10th, 90th percentile)	1.6 (0.0, 4.8)	1.6 (0.0, 4.7)	1.0 (0.0, 5.5)	0.013

ATTR amyloidosis transthyretin amyloidosis; ATTRwt amyloidosis wild-type transthyretin amyloidosis; SD standard deviation

## DISCUSSION

In this THAOS analysis of over 1300 patients with ATTRwt amyloidosis, over 90% were male, highlighting the male predominance among patients diagnosed with this form of the disease. Consistent with prior reports [7, 8, 14–16], female patients were older than male patients and had a greater LVEF and lower LV diastolic diameter, which may have contributed to the LVEF differences. Previous studies have also reported a lower interventricular septal thickness and posterior wall thickness [7, 17] but a higher interventricular septal thickness when normalized to body surface area [16] among female patients with ATTRwt amyloidosis. Group differences in these measures did not reach statistical significance in the current analysis. Overall, the findings of the current analysis suggest that female patients present later and with a lower degree of cardiac remodeling than male patients.

Given the low frequency of females diagnosed with ATTRwt amyloidosis, a protective factor may prevent or slow the development of the disease in female patients [5]. For example,

estrogen has been shown to have cardioprotective effects [18] and could be a factor in the imbalance of ATTRwt amyloidosis between men and women. Evidence to support this claim includes a prior study showing that female patients with ATTRv amyloidosis and advanced cardiomyopathy were more likely to be postmenopausal [11]. Furthermore, the proportion of females with ATTRwt amyloidosis is higher in patients older versus younger than 80 years, suggesting that the frequency of ATTRwt amyloidosis increases in females with increasing age [5].

Alternatively, female patients with ATTRwt amyloidosis might be underdiagnosed. In a retrospective study of patients with ATTRwt amyloidosis, those diagnosed postmortem were more likely to be female than those diagnosed antemortem (31% vs. 9%) [19]. Additionally, an autopsy study of patients with an antemortem diagnosis of heart failure with preserved ejection fraction without clinically apparent amyloid reported a similar rate of LV wild-type amyloid deposits among men (19%) and women (15%) postmortem [20]. Clinical suspicion of ATTRwt amyloidosis may be low for

**Table 2** General clinical characteristics of patients with ATTRwt amyloidosis according to sex

	<b>Overall (N = 1386)</b>	<b>Male (n = 1302)</b>	<b>Female (n = 84)</b>	<b>p value</b>
Kidney involvement	17 (1)	15 (1)	2 (2)	0.321
Carpal tunnel syndrome	766 (55)	721 (55)	45 (54)	0.747
Time from carpal tunnel onset to cardiomyopathy onset <sup>a</sup> (years), <i>n</i>	670	630	40	
Mean (SD)	6.9 (9.6)	7.1 (9.5)	4.9 (10.7)	0.165
Time from carpal tunnel onset to ATTR-CM diagnosis <sup>b</sup> (years), <i>n</i>	625	585	40	
Mean (SD)	6.8 (9.4)	6.9 (9.3)	4.9 (10.7)	0.189
BMI, <i>n</i>	1346	1262	84	
Mean (SD)	29 (29)	29 (29)	27 (5)	0.091
mBMI <sup>c</sup> , <i>n</i>	832	777	55	
Mean (SD)	1075 (204)	1074 (203)	1090 (221)	0.575
Diabetes mellitus	197 (14)	180 (14)	17 (20)	0.103
Inflammatory arthritis	86 (6)	83 (6)	3 (4)	0.302
Osteoarthritis	261 (19)	244 (19)	17 (20)	0.734
Cerebrovascular accident/stroke	138 (10)	127 (10)	11 (13)	0.322
Biceps tendon rupture <sup>d</sup>	14 (1)	13 (1)	1 (1)	0.585
Achilles tendon rupture <sup>d</sup>	1 (< 1)	1 (< 1)	0	1.000
Joint replacement <sup>d</sup>	32 (2)	31 (2)	1 (1)	0.722
Arthroplasty <sup>d</sup>	5 (< 1)	5 (< 1)	0	1.000
Rotator cuff repair <sup>d</sup>	21 (2)	20 (2)	1 (1)	1.000
Lumbar spinal stenosis <sup>d</sup>	90 (7)	89 (7)	1 (1)	0.039
Trigger finger <sup>d</sup>	18 (1)	18 (1)	0	0.621
Karnofsky Performance Status score, <i>n</i>	605	557	48	0.094
10–30	2 (< 1)	2 (< 1)	0	
40–60	97 (16)	82 (15)	15 (31)	
70–90	462 (76)	430 (77)	32 (67)	



**Table 2** continued

	Overall ( <i>N</i> = 1386)	Male ( <i>n</i> = 1302)	Female ( <i>n</i> = 84)	<i>p</i> value
100	44 (7)	43 (8)	1 (2)	

Values are *n* (%) unless otherwise indicated

*ATTR amyloidosis* transthyretin amyloidosis; *ATTR-CM* transthyretin amyloid cardiomyopathy; *ATTRwt amyloidosis* wild-type transthyretin amyloidosis; *BMI* body mass index; *mBMI* modified body mass index; *SD* standard deviation

<sup>a</sup>Cardiomyopathy onset is defined as the date of the first definitely ATTR amyloidosis–related cardiac symptom(s)

<sup>b</sup>ATTR-CM diagnosis date is defined as the date of the first definitely ATTR amyloidosis–related cardiac symptom(s) for all patients with predominantly cardiac or mixed phenotypes

<sup>c</sup>Calculated by multiplying BMI by serum albumin level to compensate for fluid accumulation

<sup>d</sup>Results from search of free text fields in Medical History–Musculoskeletal–Other and General Assessment–Musculoskeletal–Other

females, since the disease is thought to primarily affect elderly men. Female patients may also demonstrate fewer or less severe cardiac manifestations or have different symptoms that are not captured using commonly accepted screening criteria [8]. Results of the current analysis indicate that female patients may have greater neurologic impairment than male patients. Female patients were more likely to display impairments in walking, as measured by the mPND, and showed a trend toward lower Karnofsky Performance Status scores and more sensory abnormalities and mixed phenotypes, although group differences in these measures did not reach statistical significance. The incidence of autonomic neuropathy did not differ between the sexes, but it is important to note that this symptom category included erectile dysfunction, which has no equivalent in female patients and therefore complicates this comparison.

Although there were signs of differences in cardiac characteristics between male and female patients with ATTRwt amyloidosis, sex was not found to be a significant predictor of the degree of cardiac involvement, as measured by LV mean wall thickness/height, or a predominantly cardiac versus mixed phenotype in this analysis.

These findings are in contrast with a recent study of patients with ATTRv amyloidosis in THAOS [12], wherein male sex was identified as a risk factor for cardiomyopathy.

### Study Strengths and Limitations

Strengths of this analysis include the large size of the study population (> 1300 patients with ATTRwt amyloidosis) and the geographic diversity of the population. However, the relatively low proportion of females may have limited the ability to discern patient differences based on sex, particularly on measures for which data were not available for all patients. In addition, the incidence of orthopedic manifestations was low compared with other studies [3, 21], which may be the result of under-reporting due to inconsistent assessment across study sites. THAOS includes detailed data on cardiac manifestations in ATTRwt amyloidosis, but fewer details are available for neuropathy and musculoskeletal symptoms. In particular, mPND scores were not available for many patients with ATTRwt amyloidosis, and carpal tunnel syndrome is the only musculoskeletal manifestation systematically collected in

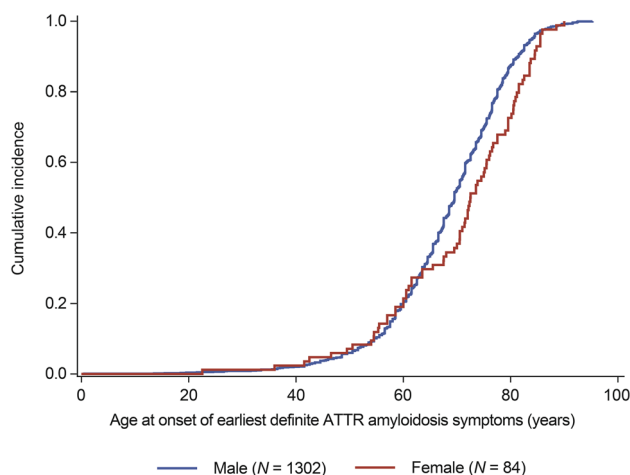
**Table 3** Cardiac characteristics of patients with ATTRwt amyloidosis according to sex

	<b>Overall (<i>N</i> = 1386)</b>	<b>Male (<i>n</i> = 1302)</b>	<b>Female (<i>n</i> = 84)</b>	<b><i>p</i> value</b>
ATTR-CM (LV septum > 12 mm), <i>n/N</i> (%)	949/1012 (94)	898/956 (94)	51/56 (91)	0.387
NYHA functional class, <i>n/N</i> (%)				0.907
I	125/1183 (11)	118/1110 (11)	7/73 (10)	
II	703/1183 (59)	658/1110 (59)	45/73 (62)	
III	325/1183 (28)	305/1110 (28)	20/73 (27)	
IV	30/1183 (3)	29/1110 (3)	1/73 (1)	
Pacemaker/ICD, <i>n</i> (%)	198 (14)	189 (15)	9 (11)	0.298
NT-proBNP (pg/mL), <i>n</i>	904	850	54	
Mean (SD)	4461 (7382)	4378 (7249)	5781 (9207)	0.276
Abnormal ECG, <i>n/N</i> (%)	1116/1190 (94)	1049/1116 (94)	67/74 (91)	0.216
Complete AV block or pacemaker, <i>n/N</i> (%)	441/1057 (42)	420/993 (42)	21/64 (33)	0.136
LAHB, <i>n/N</i> (%)	166/723 (23)	151/681 (22)	15/42 (36)	0.043
LPHB, <i>n/N</i> (%)	17/723 (2)	17/681 (3)	0/42 (0)	0.616
LBBB, <i>n/N</i> (%)	105/724 (15)	96/682 (14)	9/42 (21)	0.189
RBBB, <i>n/N</i> (%)	186/727 (26)	174/685 (25)	12/42 (29)	0.648
Diastolic interventricular septal wall thickness (mm), <i>n</i>	1012	956	56	
Mean (SD)	17 (4)	17 (4)	17 (3)	0.091
Diastolic interventricular septal wall thickness (mm)/ height (m), <i>n</i>	996	940	56	
Mean (SD)	10 (2)	10 (2)	10 (2)	0.456
Diastolic posterior wall thickness (mm), <i>n</i>	1018	961	57	
Mean (SD)	15 (3)	16 (3)	15 (3)	0.076
Diastolic posterior wall thickness (mm)/height (m), <i>n</i>	1002	945	57	
Mean (SD)	9 (2)	9 (2)	9 (2)	0.589
LV mean wall thickness (mm), <i>n</i>	1035	977	58	
Mean (SD)	16 (3)	16 (3)	16 (3)	0.052
LV mean wall thickness (mm)/height (m), <i>n</i>	1019	961	58	
Mean (SD)	10 (2)	10 (2)	10 (2)	0.460
LV mass index (g/m <sup>2</sup> ), <i>n</i>	953	899	54	
Mean (SD)	166 (50)	167 (49)	159 (51)	0.243
LV diastolic diameter (mm), <i>n</i>	1007	950	57	

**Table 3** continued

	Overall ( <i>N</i> = 1386)	Male ( <i>n</i> = 1302)	Female ( <i>n</i> = 84)	<i>p</i> value
Mean (SD)	45 (7)	46 (7)	42 (7)	< 0.001
LV ejection fraction (%), <i>n</i>	1030	974	56	
Mean (SD)	48 (12)	48 (12)	53 (13)	0.001
E wave deceleration time (ms), <i>n</i>	502	477	25	
Mean (SD)	186 (56)	186 (56)	191 (58)	0.656
E wave/A wave ratio, <i>n</i>	300	284	16	
Median (Q1, Q3)	2 (1, 3)	2 (1, 3)	2 (1, 2)	0.334

*ATTR-CM* transthyretin amyloid cardiomyopathy; *ATTRwt amyloidosis* wild-type transthyretin amyloidosis; *AV* atrioventricular; *ECG* electrocardiogram; *ICD* implantable cardioverter defibrillator; *LAHB* left anterior hemiblock; *LBBB* left bundle branch block; *LPHB* left posterior hemiblock; *LV* left ventricular; *NT-proBNP* N-terminal pro-B-type natriuretic peptide; *NYHA* New York Heart Association; *Q* quartile; *RBBB* right bundle branch block; *SD* standard deviation



**Fig. 1** Cumulative incidence of ATTR-CM according to sex. The cumulative incidence curve showed that female patients tended to develop ATTR-CM at a later age.

THAOS. Examination of additional echocardiographic variables to those reported here, particularly those measuring systolic dysfunction, may reveal further sex differences and should be included in future studies. Lastly, it is possible that the inclusion criterion of LV wall thickness > 12 mm may have resulted in some female patients not being captured due to milder hypertrophy and/or a generally smaller cardiac anatomy [8].

*ATTR amyloidosis* transthyretin amyloidosis; *ATTR-CM* transthyretin amyloid cardiomyopathy

### CONCLUSIONS

In this THAOS analysis, female patients with *ATTRwt* amyloidosis tended to present at a later age and showed signs of less severe cardiac impairment and more severe neurologic impairment. These findings are suggestive of differences in the presentation of *ATTRwt* amyloidosis between male and female patients.

**Table 4** Neurologic characteristics of patients with ATTRwt amyloidosis according to sex

	Overall (N = 1386)	Male (n = 1302)	Female (n = 84)	p value
Sensory abnormalities <sup>a</sup>	632 (46)	587 (45)	45 (54)	0.130
Autonomic neuropathy <sup>b</sup>	735 (53)	690 (53)	45 (54)	0.918
mPND score <sup>c</sup>				< 0.001
0	351 (61)	336 (62)	15 (43)	
I	140 (24)	130 (24)	10 (29)	
II	42 (7)	40 (7)	2 (6)	
IIIa	30 (5)	28 (5)	2 (6)	
IIIb	10 (2)	4 (1)	6 (17)	
IV	4 (1)	4 (1)	0	

*ATTRwt amyloidosis* wild-type transthyretin amyloidosis; *mPND* modified polyneuropathy disability

Values are n (%)

<sup>a</sup>Includes neuropathic pain/paresthesia, tingling, numbness, temperature or pain insensitivity, and balance abnormality

<sup>b</sup>Includes dizziness, palpitations, dry eye, constipation, diarrhea, diarrhea/constipation, early satiety, fecal incontinence, nausea, vomiting, recurrent urinary tract infections, urinary incontinence, urinary retention, dyshidrosis, and erectile dysfunction

<sup>c</sup>Denominator for mPND score is total of non-missing records

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**Data Availability .** Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See

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