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 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 hemi-block 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.

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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 1 | Demographic characteristics of patients with ATTRwt amyloidosis according to sex |
|---------|-------------------------------------------------------------------------------------------------------------------------|
|         | Overall (N = 1386) | Male (n = 1302) | Female (n = 84) | p value |
| Age at enrollment (years), n | 1386 | 1302 | 84 | 0.002 |
| Median (10th, 90th percentile) | 78 (69, 87) | 78 (69, 86) | 80 (71, 88) | 0.045 |
| Age at onset of ATTR amyloidosis symptoms (years), n | 1244 | 1172 | 72 | 0.875 |
| Median (10th, 90th percentile) | 73 (60, 83) | 73 (60, 83) | 75 (60, 86) | 0.853 |
| Duration of ATTR amyloidosis symptoms (years), n | 3.0 (0.4, 13.7) | 3.0 (0.4, 13.7) | 2.4 (0.6, 13.2) | 0.853 |
| Time from symptom onset to diagnosis (years), n | 1171 | 1103 | 68 | 0.013 |
| Median (10th, 90th percentile) | 1.7 (0.0, 12.3) | 1.7 (0.0, 12.7) | 1.6 (0.0, 12.3) | 0.013 |
| Follow-up time (years), n | 1386 | 1302 | 84 | 0.013 |
| 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
Table 2  General clinical characteristics of patients with ATTRwt amyloidosis according to sex

|                        | Overall  | Male         | Female       | p value |
|------------------------|----------|--------------|--------------|---------|
|                        | (N = 1386) | (n = 1302)   | (n = 84)     |         |
| 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), n | 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), n | 625 | 585 | 40 |         |
| Mean (SD)              | 6.8 (9.4) | 6.9 (9.3)    | 4.9 (10.7)   | 0.189   |
| BMI, n                 | 1346     | 1262         | 84           |         |
| Mean (SD)              | 29 (29)  | 29 (29)      | 27 (5)       | 0.091   |
| mBMI<sup>c</sup>, n    | 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, n | 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)      |         |
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

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**Table 2 continued**

|                | Overall (N = 1386) | Male (n = 1302) | Female (n = 84) | p 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

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

|                                | Overall (N = 1386) | Male (n = 1302) | Female (n = 84) | p value |
|--------------------------------|--------------------|-----------------|-----------------|---------|
| ATTR-CM (LV septum > 12 mm), n/N (%) | 949/1012 (94)      | 898/956 (94)    | 51/56 (91)      | 0.387   |
| NYHA functional class, n/N (%)    |                    |                 |                 | 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, n (%)            | 198 (14)           | 189 (15)        | 9 (11)          | 0.298   |
| NT-proBNP (pg/mL), n            | 904                | 850             | 54              |         |
| Mean (SD)                       | 4461 (7382)        | 4378 (7249)     | 5781 (9207)     | 0.276   |
| Abnormal ECG, n/N (%)           | 1116/1190 (94)     | 1049/1116 (94)  | 67/74 (91)      | 0.216   |
| Complete AV block or pacemaker, n/N (%) | 441/1057 (42)      | 420/993 (42)    | 21/64 (33)      | 0.136   |
| LAHB, n/N (%)                   | 166/723 (23)       | 151/681 (22)    | 15/42 (36)      | 0.043   |
| LPHB, n/N (%)                   | 17/723 (2)         | 17/681 (3)      | 0/42 (0)        | 0.616   |
| LBBB, n/N (%)                   | 105/724 (15)       | 96/682 (14)     | 9/42 (21)       | 0.189   |
| RBBB, n/N (%)                   | 186/727 (26)       | 174/685 (25)    | 12/42 (29)      | 0.648   |
| Diastolic interventricular septal wall thickness (mm), n | 1012               | 956             | 56              |         |
| Mean (SD)                       | 17 (4)             | 17 (4)          | 17 (3)          | 0.091   |
| Diastolic interventricular septal wall thickness (mm)/height (m), n | 996                | 940             | 56              |         |
| Mean (SD)                       | 10 (2)             | 10 (2)          | 10 (2)          | 0.456   |
| Diastolic posterior wall thickness (mm), n | 1018               | 961             | 57              |         |
| Mean (SD)                       | 15 (3)             | 16 (3)          | 15 (3)          | 0.076   |
| Diastolic posterior wall thickness (mm)/height (m), n | 1002               | 945             | 57              |         |
| Mean (SD)                       | 9 (2)              | 9 (2)           | 9 (2)           | 0.589   |
| LV mean wall thickness (mm), n   | 1035               | 977             | 58              |         |
| Mean (SD)                       | 16 (3)             | 16 (3)          | 16 (3)          | 0.052   |
| LV mean wall thickness (mm)/height (m), n | 1019               | 961             | 58              |         |
| Mean (SD)                       | 10 (2)             | 10 (2)          | 10 (2)          | 0.460   |
| LV mass index (g/m²), n         | 953                | 899             | 54              |         |
| Mean (SD)                       | 166 (50)           | 167 (49)        | 159 (51)        | 0.243   |
| LV diastolic diameter (mm), n   | 1007               | 950             | 57              |         |
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].

**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$^a$  | 632 (46)              | 587 (45)          | 45 (54)            | 0.130     |
| Autonomic neuropathy$^b$   | 735 (53)              | 690 (53)          | 45 (54)            | 0.918     |
| mPND score$^c$             |                       |                   |                   | < 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 $n$ (%)

$^a$Includes neuropathic pain/paresthesia, tingling, numbness, temperature or pain insensitivity, and balance abnormality

$^b$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

$^c$Denominator for mPND score is total of non-missing records

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**Compliance with Ethics Guidelines.** 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.

**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
https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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