Characteristics of Patients with Late- vs. Early-Onset Val30Met Transthyretin Amyloidosis from the Transthyretin Amyloidosis Outcomes Survey (THAOS)

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ABSTRACT

Introduction: Hereditary transthyretin amyloidosis (ATTRv amyloidosis) is a clinically heterogeneous disease caused by mutations in the transthyretin (TTR) gene. The most common mutation, Val30Met, can manifest as an early- or late-onset disease.

Methods: The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal, observational survey of patients with transthyretin amyloidosis, including both inherited and wild-type disease and asymptomatic patients with TTR mutations. This is a descriptive analysis of symptomatic patients with ATTRv Val30Met amyloidosis with late- (age at least 50 years) vs. early-onset (age less than 50 years) disease in THAOS (data cutoff August 1, 2019).

Results: Of 1389 patients with ATTRv Val30Met amyloidosis, 491 (35.3%) had late-onset disease. Compared with early-onset, patients with late-onset were more likely to be male (66.2% vs. 53.6%) and have a longer mean (standard deviation [SD]) time from onset to diagnosis (3.8 [3.4] vs. 2.7 [4.1] years). Late-onset disease was associated with more severe neurological impairment at enrollment (median [10th, 90th percentile] derived Neuropathy Impairment Score in the Lower Limbs, 25.0 [4.0, 69.3] vs. 8.0 [0, 54.8]; Neurologic Composite Score, 42.0 [2.0, 155.0] vs. 21.0 [0, 102.0]). Cardiac findings were more prominent in late-onset disease. An overall interpretation of electrocardiogram as abnormal was reported in 72.1% of late-onset patients (vs. 44.3% early-onset). A left-ventricular septal thickness of at least 12 mm was reported in 69.7% of late-onset patients (vs. 14.6% early-onset). All differences were statistically significant (p < 0.001).

Conclusion: In THAOS, late-onset ATTRv Val30Met amyloidosis is common, presenting with more severe neurologic and cardiac findings at enrollment. Heterogeneity of disease may make it more difficult to diagnose. Increased recognition of late-onset ATTRv Val30Met amyloidosis could lead to more...
timely diagnosis and improve patient outcomes.

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

**Keywords**: ATTRv amyloidosis; Cardiac; Disease onset; Neurologic

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**Key Summary Points**

**Why carry out this study?**

Hereditary transthyretin (ATTRv) amyloidosis is a clinically heterogeneous disease caused by mutations in the transthyretin (TTR) gene. The most common mutation, Val30Met, can manifest as an early- or late-onset disease.

This analysis from THAOS was carried out to broaden the understanding of the characteristics of patients with late- vs. early-onset ATTRv Val30Met amyloidosis.

**What was learned from the study?**

In THAOS, late-onset ATTRv Val30Met amyloidosis is relatively common, occurring in approximately one-third of participants and presenting with more severe neurologic and cardiac findings at enrollment.

Compared with patients with early-onset ATTRv Val30Met amyloidosis, patients with late-onset disease were more likely to have a longer mean time from symptom onset to diagnosis, and to have experienced misdiagnosis.

Increased recognition of late-onset ATTRv Val30Met amyloidosis could lead to more timely diagnosis and improve patient outcomes.

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**INTRODUCTION**

Hereditary transthyretin amyloidosis (ATTRv amyloidosis) is a progressive, rare, fatal, systemic disorder caused by the deposition of amyloid fibrils composed of misfolded transthyretin (TTR) in peripheral nerves and vital organs. ATTRv amyloidosis is a clinically heterogeneous disease caused by mutations in the TTR gene [1], leading to progressive debilitating sensorimotor polyneuropathy and autonomic dysfunction [2] and, in many cases, cardiac complications [1, 3].

More than 140 ATTRv genotypes have been identified [4, 5]. The most common mutation is Val30Met (p.Val50Met), which may manifest as an early-onset or late-onset disease [1].

Early-onset disease (at age less than 50 years) has been considered the more common form of disease in endemic regions [1, 6]. However, a distinct late-onset form of disease (at age 50 years or more) is also relatively common in some endemic (e.g., Sweden) and non-endemic regions [2, 6–9]. Data characterizing late-onset disease are limited, though information from patients from Brazil indicates that this form is more difficult to diagnose because of the reduced incidence of family history of disease, which is considered a hallmark of early-onset disease [9]. In patients from Japan, late-onset disease was associated with sensorimotor symptoms beginning in the lower extremities, with disturbance of both superficial and deep sensation and relatively mild autonomic symptoms, while early-onset disease was associated with predominant loss of superficial sensation, severe autonomic dysfunction, and atrioventricular nodal block, which required pacemaker implantation [10]. Amyloid fibrils have been shown to directly damage Schwann cells [11], leading to the predominant loss of small-fiber...
axons commonly seen in early-onset cases, and suggesting that the neuropathy may be impacted by vasculopathy, particularly in late-onset cases [12]. The amyloid fibril type (type A or type B) has been shown to be important for the disease phenotype in transthyretin amyloidosis (ATTR amyloidosis), and type A fibrils are generally associated with a later onset of disease, more pronounced motor neuropathy, and amyloid cardiomyopathy in patients with ATTR Val30Met amyloidosis [13, 14]. Type A fibrils are also more common in wild-type ATTR amyloidosis [15, 16], which presents with cardiomyopathy [17].

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal, observational survey of patients with ATTR amyloidosis, including both inherited and wild-type disease, and asymptomatic carriers with TTR mutations. THAOS was established in 2007 to study differences in disease presentation, diagnosis, and natural history in a large, geographically dispersed, heterogeneous patient population [18]. This is an analysis of the characteristics of patients in THAOS with symptomatic ATTR Val30Met amyloidosis with late-onset (age at least 50 years) compared with early-onset (age less than 50 years) disease.

**METHODS**

**Study Design and Patient Characteristics**

The design of THAOS (NCT00628745) has been published previously [18]. All THAOS study sites received ethical or institutional review board approval prior to patient enrollment and followed the International Council for Harmonisation Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki. Each patient provided written informed consent.

Characteristics of symptomatic patients in THAOS with ATTR Val30Met amyloidosis were assessed, with patients with late-onset disease (aged at least 50 years at symptom onset) compared with patients with early-onset disease (aged less than 50 years at symptom onset) (data cutoff date August 1, 2019).

Patient demographics including sex, geographical location, race/ethnicity, family history, medical history, age at enrollment and symptom onset, family history of ATTR amyloidosis, and time from symptom onset to diagnosis are collected at enrollment in THAOS and were examined in this analysis. Neurologic impairment was measured by a derived Neuropathy Impairment Score in the Lower Limbs (NIS-LL; ranges from 0 to 88) and the Neurologic Composite Score (NCS; ranges from 0 to 294). For both measures, higher scores indicate greater impairment [19]. Walking disability was measured by the modified polyneuropathy disability (mPND) score (ranges from I to IV), where I indicates sensory disturbance in lower limbs but preserved walking capacity; II indicates difficulties in walking but no need of a walking stick; IIIa indicates one stick or one crutch required for walking; IIIb indicates two sticks or two crutches required for walking; and IV indicates patient confined to a wheelchair or bed. Cardiac findings were assessed via electrocardiogram (ECG) and echocardiogram (echo). Overall interpretation of ECG as abnormal was based on investigator judgement.

Quality of life was assessed using the EQ-5D-3L questionnaire, a self-administered health status instrument. Respondents rated their current health state on five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with each dimension having three levels of function (1 = no problem, 2 = some problem, and 3 = extreme problem).

**Statistical Analysis**

Data are presented as mean (standard deviation [SD]) and percentages unless stated otherwise. \( p \) values were calculated using Student’s \( t \) test for continuous variables, Fisher’s exact test for dichotomous variables, and chi-squared test for variables with more than two categories. \( p \) values < 0.05 were considered statistically significant, with no adjustment for multiplicity.
RESULTS

Patient Characteristics

Of the 1389 patients with ATTRv Val30Met amyloidosis in THAOS, 491 (35.3%) had late-onset disease, and 898 (64.7%) early-onset disease (Table 1). Countries in which over 50% of enrolled patients with ATTRv Val30Met amyloidosis were late-onset were the USA with 19 of 21 patients (90.5%), Italy with 20 of 24 patients (83.3%), and Sweden with 135 of 185 patients (73.0%). Late-onset disease constituted less than 30% of enrolled patients with ATTRv Val30Met amyloidosis in Argentina with 5 of 28 patients (17.9%), Portugal with 125 of 675 patients (18.5%), and Brazil with 40 of 137 patients (29.2%) (Fig. 1). Patients with late-onset were more likely to be male, with a mean age at enrollment of 68.1 years compared with 40.4 years for early-onset, and a longer time from symptom onset to diagnosis ($p < 0.001$ for all; Table 1). Patients with late-onset were also more likely to have been misdiagnosed than those with early-onset, and a lower percentage had a known family history of disease.

Table 1 Demographic and clinical characteristics of patients with late- and early-onset ATTRv Val30Met amyloidosis at enrollment in THAOS

| Characteristic                              | Late-onset ($n = 491$) | Early-onset ($n = 898$) | $p$ value |
|---------------------------------------------|------------------------|-------------------------|-----------|
| Sex, $n$ (%)                                |                        |                         | $< 0.001$ |
| Male                                        | 325 (66.2)             | 481 (53.6)              |           |
| Female                                      | 166 (33.8)             | 417 (46.4)              |           |
| Country, $n$ (%)                            |                        |                         | $< 0.001$ |
| Race, $n$ (%)a                              |                        |                         |           |
| Caucasian                                   | 292 (59.5)             | 237 (26.4)              |           |
| African descent                             | 2 (0.4)                | 0                       |           |
| American Hispanic                           | 1 (0.2)                | 8 (0.9)                 |           |
| Latino American                             | 3 (0.6)                | 19 (2.1)                |           |
| Asian                                       | 40 (8.1)               | 46 (5.1)                |           |
| Other                                       | 15 (3.1)               | 27 (3.0)                |           |
| Missingb                                    | 138 (28.1)             | 561 (62.5)              |           |
| Total number of biopsies carried out, $n$   | 498                    | 759                     |           |
| Known family history of symptomatic ATTR amyloidosis, $n$ (%) | 289 (58.9) | 862 (96.0) | $< 0.001$ |
| Age at enrollment, mean (SD), years         | 68.1 (7.4)             | 40.4 (9.0)              | $< 0.001$ |
| Age at onset of symptoms, mean (SD), years  | 62.8 (7.7)             | 33.4 (7.2)              | $< 0.001$ |
| Time from symptom onset to diagnosis, mean (SD), years | 3.8 (3.4) | 2.7 (4.1) | $< 0.001$ |
| Misdiagnosis, $n$ (%)                        | 139 (28.3)             | 90 (10.0)               | $< 0.001$ |

ATTRv Val30Met amyloidosis hereditary transthyretin amyloidosis caused by the Val30Met gene mutation, SD standard deviation, THAOS Transthyretin Amyloidosis Outcomes Survey

a "African descent" includes African American and Afro-Caribbean

b Data on race are not collected in all countries

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The most common misdiagnoses in patients with late-onset disease were idiopathic neuropathy (29 of 139 patients with a misdiagnosis [20.9%]), neuropathy (24 patients [17.3%]), lumbar disc disease (16 patients [11.5%]), and chronic inflammatory demyelinating polyneuropathy (13 patients [9.4%]). The most common misdiagnoses in patients with early-onset disease were neuropathy (12 of 90 patients with a misdiagnosis [13.3%]), idiopathic neuropathy (9 patients [10.0%]), and irritable bowel syndrome (8 patients [8.9%]).

Symptom Profile

Medical History

Nearly all patients in both groups had a medical history of neurologic disorders (Table 2). However, there were differences in the incidence of types of neurologic disorder (Table 3). Symptoms of motor neuropathy were more common (62.1% of patients with late-onset vs. 43.3% with early-onset disease; \( p < 0.001 \)), and symptoms of autonomic neuropathy less common (73.1% late-onset vs. 86.0% early-onset; \( p < 0.001 \)) in patients with late-onset disease. There was also a greater incidence of a history of cardiovascular disorders, and a lower incidence of genitourinary/renal/reproductive disorders and gastrointestinal disorders in patients with late-onset disease (\( p < 0.01 \) for all; Table 2).

Neurologic Impairment

Median (10th, 90th percentile) derived NIS-LL was higher in patients with late- vs. early-onset disease (25.0 [4.0, 69.3] compared with 8.0 [0, 54.8], respectively; \( p < 0.001 \); Table 4). Median (10th, 90th percentile) NCS was also higher in patients with late- vs. early-onset disease (42.0 [2.0, 155.0] compared with 21.0 [0, 102.0], respectively; Table 4), as was each component.
of the NCS (p < 0.001 for all; Table 4). Patients with late-onset disease were also more likely to experience more severe walking disability, as assessed by mPND score (p < 0.001; Table 5).

Cardiac Findings
Cardiac findings were also more prominent in patients with late-onset disease. A greater proportion of late-onset had an overall interpretation of ECG as abnormal (72.1% vs. 44.3% early-onset) and left-ventricular septal thickness of at least 12 mm (69.7% vs. 14.6%). Patients with late-onset disease also had a greater mean left-ventricular septal thickness (p < 0.001 for all; Fig. 2). There were also differences in other ECG and echo measures (Table 6).

Quality of Life
There was no difference between mean (SD) EQ-5D-3L scores in patients with late- and early-onset disease when grouped by age at enrollment into 50–64 years (0.7 [0.3] late-onset vs. 0.6 [0.2] early-onset) and at least 65 years (0.6 [0.2] vs. 0.7 [0.2]).

DISCUSSION
This analysis from THAOS broadens the understanding of the characteristics of patients with late-onset ATTRv Val30Met amyloidosis across many countries. The presentation of late-onset disease is relatively common, occurring in around one-third of patients in THAOS overall. Most of the patients in this analysis were from

### Table 2 Medical history at enrollment of patients with late- and early-onset ATTRv Val30Met amyloidosis

| Symptom category, n/N (%) | Late-onset (n = 491) | Early-onset (n = 898) | p value |
|---------------------------|----------------------|-----------------------|---------|
| Neurologic                | 465/490 (94.9)       | 855/898 (95.2)        | 0.80    |
| Eye<sup>a</sup>           | 115/486 (23.7)       | 208/895 (23.2)        | 0.89    |
| Cardiovascular<sup>b</sup> | 293/488 (60.0)       | 434/897 (48.4)        | < 0.001 |
| Genitourinary/renal/reproductive<sup>c</sup> | 131/485 (27.0) | 414/896 (46.2) | < 0.001 |
| Gastrointestinal<sup>d</sup> | 290/488 (59.4)       | 722/898 (80.4)        | < 0.001 |
| Endocrine/metabolic<sup>e</sup> | 18/487 (3.7)        | 12/897 (1.3)          | 0.006   |
| Musculoskeletal<sup>f</sup> | 20/488 (4.1)        | 32/895 (3.6)          | 0.66    |
| Respiratory<sup>g</sup>   | 2/488 (0.4)          | 4/894 (0.4)           | > 0.99  |
| Psychiatric<sup>h</sup>   | 20/488 (4.1)         | 58/898 (6.5)          | 0.087   |

<sup>a</sup> Includes dry eye, glaucoma, visual impairment, vitrectomy, other eye disease
<sup>b</sup> Includes arterial hypertension, coronary artery disease, dizziness, dyspnea, heart failure, palpitations, rhythm disturbance, syncope, other cardiovascular disease
<sup>c</sup> Includes dialysis, genitourinary/renal/reproductive malignancy, kidney stones, recurrent urinary tract infections, renal impairment, urinary incontinence, urinary retention, urinary tract infection, other genitourinary/reproductive disease
<sup>d</sup> Includes constipation, diarrhea, diarrhea/constipation, early satiety, fecal incontinence, hepatic impairment, hepatitis, hepatotoxicity, inflammatory bowel disease, nausea, peptic ulcer disease, unintentional weight loss, upper abdominal pain, vomiting, other gastrointestinal disease
<sup>e</sup> Includes adrenal insufficiency, diabetes mellitus, hyperlipidemia, thyroid dysfunction, other endocrine/metabolic disease
<sup>f</sup> Includes fractures, inflammatory arthritis, osteoarthritis, osteoporosis, other musculoskeletal disease
<sup>g</sup> Includes pneumonia, respiratory malignancy, other respiratory disease
<sup>h</sup> Includes anxiety, depression, schizophrenia, other psychiatric diagnosis

ATTRv Val30Met amyloidosis hereditary transthyretin amyloidosis caused by the Val30Met gene mutation

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### Table 3: Most common neurologic symptoms at enrollment of patients with late- and early-onset ATTRv Val30Met amyloidosis

| Neurologic symptoms                      | Late-onset (n = 491) | Early-onset (n = 898) | p value |
|-----------------------------------------|----------------------|-----------------------|---------|
| Balance abnormality                     | 226/485 (46.6)       | 194/894 (21.7)        | < 0.001 |
| Carpal tunnel syndrome                  | 62/456 (13.6)        | 25/816 (3.1)          | < 0.001 |
| Dyshidrosis                             | 47/480 (9.8)         | 116/892 (13.0)        | 0.081   |
| Erectile dysfunction                     | 151/305 (49.5)       | 307/518 (59.3)        | 0.007   |
| Muscle weakness                         | 266/487 (54.6)       | 291/896 (32.5)        | < 0.001 |
| Neuropathic pain/paresthesia            | 390/489 (79.8)       | 704/897 (78.5)        | 0.63    |
| Numbness                                | 372/483 (77.0)       | 510/890 (57.3)        | < 0.001 |
| Temperature or pain insensitivity       | 333/483 (68.9)       | 602/895 (67.3)        | 0.55    |
| Tingling                                | 316/483 (65.4)       | 402/886 (45.4)        | < 0.001 |
| Walking disability                      | 151/247 (61.1)       | 262/659 (39.8)        | < 0.001 |

Symptoms with incidence < 5% in both groups were cerebrovascular accident/stroke, chronic demyelinating inflammatory polyneuropathy, cognitive decline, neurologic malignancy, neuropathic arthropathy, seizures, and other neurologic diagnosis. **ATTRv Val30Met amyloidosis** hereditary transthyretin amyloidosis caused by the Val30Met gene mutation.

* Neurologic symptoms with incidence ≥ 5% in either group.

### Table 4: Neurologic impairment at enrollment in patients with late- and early-onset ATTRv Val30Met amyloidosis

| Neurologic measure          | Late-onset (n = 491) | Early-onset (n = 898) | p value |
|-----------------------------|----------------------|-----------------------|---------|
| Derived NIS-LL, n           | 214                  | 645                   | < 0.001 |
| Median (10th, 90th percentile) | 25.0 (4.0, 69.3)    | 8.0 (0, 54.8)         |         |
| NCS, n                      | 172                  | 561                   | < 0.001 |
| Median (10th, 90th percentile) | 42.0 (2.0, 155.0)   | 21.0 (0, 102.0)       |         |
| NCS Reflex score, n         | 376                  | 832                   | < 0.001 |
| Median (10th, 90th percentile) | 2.0 (0, 10.0)       | 0 (0, 5.0)            |         |
| NCS Motor score, n          | 307                  | 790                   | < 0.001 |
| Median (10th, 90th percentile) | 3.0 (0, 54.0)       | 0 (0, 40)             |         |
| NCS Sensory score, n        | 191                  | 583                   | < 0.001 |
| Median (10th, 90th percentile) | 31.0 (0, 91.0)     | 20 (0, 67.0)          |         |

The NIS-LL ranges from 0 to 88. The NCS ranges from 0 to 294. The components of the NCS are the reflex (range, 0–10), motor (range, 0–160), and sensory (range, 0–124) scores. Higher scores indicate greater impairment. **ATTRv Val30Met amyloidosis** hereditary transthyretin amyloidosis caused by the Val30Met gene mutation, NIS-LL Neuropathy Impairment Score in the Lower Limbs, NCS Neurologic Composite Score.
Table 5  Walking disability at enrollment in patients with late- and early-onset ATTRv Val30Met amyloidosis

| mPND score, n (%)          | Late-onset (n = 491) | Early-onset (n = 898) | p value |
|----------------------------|----------------------|-----------------------|---------|
| Missing                    | 80 (16.3)            | 61 (6.8)              | < 0.001 |
| Symptomatic, but no lower limb sensory/motor deficits | 14 (2.9) | 64 (7.1) |         |
| I or II                    | 289 (58.9)           | 694 (77.3)            |         |
| IIIa or IIIb               | 81 (16.5)            | 64 (7.1)              |         |
| IV                         | 27 (5.5)             | 15 (1.7)              |         |

mPND score: I indicates sensory disturbance in lower limbs but preserved walking capacity; II indicates difficulties in walking but no need of a walking stick; IIIa indicates one stick or one crutch required for walking; IIIb indicates two sticks or two crutches required for walking; IV indicates patient confined to a wheelchair or bed

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Fig. 2  Electrocardiographic (ECG) (a) and echocardiographic (b, c) findings at enrollment in patients with late- and early-onset ATTRv Val30Met amyloidosis. LV left ventricular

Sweden and Portugal, reflecting the endemic loci of ATTRv Val30Met amyloidosis in those countries. Although early-onset is the most common form of the disease in the majority of countries, late-onset was more common in
Sweden, Italy, and the USA. In Spain and Japan, late-onset was as common as early-onset.

Patients with late-onset disease tended to have more severe neurologic and cardiac findings compared with patients with early-onset disease. Previous investigations from Japan and Brazil have also suggested that patients with late-onset ATTRv Val30Met amyloidosis experience a more severe and faster-progressing disease in comparison with early-onset [9, 20, 21]. In Japan and Brazil, patients with late-onset disease experience faster-progressing neuropathy, as measured by imbalance, deep sensory loss, NCS, and shorter times to requirement of a walking aid, as assessed by PND [9, 20, 21]. Results from a cohort of patients in THAOS from Brazil indicated that muscle weakness and balance abnormality were reported at enrollment by more patients with late-onset disease compared with early-onset disease, with similar percentages of patients reporting temperature or pain insensitivity [9]. These results are in line with the present analysis, which benefits from an additional 3 years of data and the inclusion of the global THAOS population. Differences in amyloid composition and deposition have been seen in patients with late-onset vs. those with early-onset disease [22, 23], which may point to

Table 6 Electrocardiogram and echocardiogram measures at enrollment in patients with late- and early-onset ATTRv Val30Met amyloidosis

| ECG/echo measure                        | Late-onset  | Early-onset | p value |
|-----------------------------------------|-------------|-------------|---------|
|                                         | (n = 491)   | (n = 898)   |         |
| Rhythm abnormalities, n/N (%)           | 51/179 (28.5) | 31/200 (15.5) | 0.003   |
| Atrial fibrillation, n/N (%)            | 18/53 (34.0) | 4/30 (13.3)  | 0.068   |
| Atrial flutter, n/N (%)                 | 4/53 (7.5)  | 2/30 (6.7)   | > 0.99  |
| PR interval, median (10th, 90th percentile) | 180.0 (122.0, 234.0) | 169.0 (133.0, 227.0) | 0.64    |
| QRS interval, mean (SD)                 | 106.4 (27.5) | 98.9 (19.3)  | < 0.001 |
| Conduction abnormalities, n/N (%)       | 113/154 (73.4) | 138/185 (74.6) | 0.80    |
| First-degree AV block, n/N (%)          | 54/108 (50.0) | 83/134 (61.9) | 0.069   |
| LBBB, n/N (%)                           | 14/102 (13.7) | 10/134 (7.5)  | 0.13    |
| RBBB, n/N (%)                           | 15/103 (14.6) | 8/133 (6.0)   | 0.044   |
| Morphology abnormalities, n/N (%)       | 18/141 (12.8) | 28/183 (15.3) | 0.63    |
| Low voltage, n/N (%)                    | 19/169 (11.2) | 25/396 (6.3)  | 0.058   |
| Pathologic Q waves, n/N (%)             | 39/142 (27.5) | 13/181 (7.2)  | < 0.001 |
| ST segment – T wave abnormalities, n/N (%) | 42/141 (29.8) | 48/183 (26.2) | 0.53    |
| IV septal thickness, mm, mean (SD)      | 15.0 (4.3)  | 10.3 (2.4)   | < 0.001 |
| PW thickness, mm, mean (SD)             | 12.3 (3.7)  | 9.5 (2.1)    | < 0.001 |
| Left atrial size, mm, mean (SD)         | 41.1 (7.9)  | 34.2 (5.6)   | < 0.001 |
| LVIDd, mm, mean (SD)                    | 46.1 (6.4)  | 45.0 (5.6)   | 0.072   |
| Ejection fraction, %, mean (SD)         | 60.2 (10.3) | 61.9 (10.5)  | 0.18    |

ATTRv Val30Met amyloidosis hereditary transthyretin amyloidosis caused by the Val30Met gene mutation, AV atrioventricular, ECG electrocardiogram, echo echocardiogram, IV interventricular, LBBB left bundle branch block, LVIDd left-ventricular internal dimension in diastole, PW posterior wall, RBBB right bundle branch block, SD standard deviation
an explanation for the distinct patterns of clinical presentation reported in this study and previously [9, 20, 21]. Studies in patients from Sweden and Japan indicate that type B fibrils (full-length, arranged in parallel) are mainly found in early-onset cases, while type A fibrils (a mixture of full-length and fragments of TTR arranged haphazardly, resembling wild-type fibrils) are more commonly associated with late-onset ATTRv Val30Met amyloidosis, non-Val30Met mutations, and in patients with wild-type ATTR amyloidosis [13, 15, 16, 23, 24]. Type A fibrils have been associated with more pronounced motor neuropathy [13, 14, 23]. Late-onset disease has been associated with a greater effect on larger myelinated fibers than early-onset disease, which is predominantly associated with small-fiber loss [7]. In late-onset disease, type A fibrils may affect the larger motor nerves, resulting in the more severe walking disability observed in the present study and as previously reported [21]. There have also been differences reported in the site of deposition, with greater amyloid deposition in the dorsal root ganglia than in the sympathetic ganglia in late-onset disease, and vice versa in early-onset disease [22]. Another factor potentially contributing to the more severe neuropathy seen in late-onset disease could be the longer delays in diagnosis that were seen more frequently in these patients [9, 25]. As a rare disease, physicians may not recognize the symptoms associated with ATTRv amyloidosis. Accurate diagnosis, particularly of late-onset disease, can be confounded by the perception that ATTRv amyloidosis affects only younger people who have relatives diagnosed with ATTRv amyloidosis [14]. There may also be a relationship between baseline disease severity and natural disease progression, with one clinical trial showing that higher baseline disease severity was associated with a faster rate of neurological progression in the following 12 months [26]. Given its progressive, irreversible, degenerative nature, early diagnosis and treatment of ATTRv amyloidosis has the potential to improve patient outcomes [14, 27].

Reports from Brazil and Sweden indicate that cardiac findings such as ECG abnormalities [9], interventricular hypertrophy [9, 28], and cardiomyopathy [28] occur more frequently in patients with late-onset disease. Late-onset patients also have a shorter survival time [20, 21], with cardiomyopathy observed as a major cause of death [21]. In this analysis, the cardiac findings of rhythm abnormalities, pathologic Q waves, and increased QRS interval and wall thicknesses were significantly more common in patients with late-onset disease. Substantial cardiomyopathy at presentation and increased interventricular septal thickness have been associated with patients with type A fibrils [23]. One study reported that more amyloid was observed in the heart and pituitary gland in patients with late-onset ATTRv Val30Met amyloidosis (compared with early-onset disease), with the main recorded cause of death being heart failure due to cardiac amyloidosis [22]. In one small group of patients with late-onset ATTRv Val30Met amyloidosis over half of the cardiac amyloid deposits were shown to be composed of wild-type TTR [24]. This suggests that it may be a combination of both increased type A fibrils and aging that contributes to the increased cardiac findings seen in patients with late-onset ATTRv Val30Met amyloidosis. Delays in diagnosis could also have contributed to the more severe cardiac findings in patients with late-onset disease. However, cardiac disease is generally less pronounced in patients with early-onset disease, although arrhythmias are quite common in these patients, and increased levels of amyloid deposition in the myocardium is associated with cardiomyopathy in patients with late-onset disease [22].

While a greater proportion of patients with late-onset disease had cardiac findings, the greater age of these patients does mean that they may have been more likely to have developed underlying cardiovascular disease unrelated to ATTRv amyloidosis. Further, data were more limited for many of the cardiac assessments. This may have been a reflection of the different specialties of enrolling centers, with many focusing on neurological assessments and performing fewer routine cardiac assessments. This could have led to a bias in which the likelihood of cardiac abnormalities being detected was reduced. These limitations are offset by the ability to assess large numbers of patients with a
rare disease from a global population, providing data on a broad range of patients.

While the reasons for the different age of onset in patients with ATTRv Val30Met amyloidosis are still not fully elucidated, reports have identified several different genetic factors that may influence age of disease onset, including sex [29], C1Q polymorphisms [30, 31], single nucleotide haplotype polymorphisms in the TTR gene [32, 33], mitochondrial haplogroup polymorphisms [34], RBP4 and AR gene variation [35], and mitochondrial DNA copy number [36]. It may be that environmental factors are also involved.

CONCLUSIONS

As a result of heterogeneity of disease and lack of awareness, late-onset ATTRv Val30Met amyloidosis may be more difficult to diagnose than early-onset disease. This analysis of patients with late-onset ATTRv Val30Met amyloidosis in THAOS further characterizes this patient group, providing valuable information that further defines the nature and severity of the neurological and cardiac disease findings in these patients. Results from this analysis indicate that patients with late-onset ATTRv Val30Met amyloidosis are more likely to be male, have a history of cardiovascular disease, overall interpretation of ECG as abnormal, and left-ventricular thickness of at least 12 mm as well as greater mean ventricular septal thickness. Neurologically, they are more likely to have higher median derived NIS-LL and NCS, and more severe walking disability. Increased recognition of late-onset ATTRv Val30Met amyloidosis could lead to earlier diagnosis and improve patient outcomes [14, 27].

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**Data Availability.** Pfizer provides secure access to anonymized patient-level data to qualified researchers in response to scientifically valid research proposals. Further details can be found at https://www.pfizer.com/science/clinical-trials/trial-data-and-results.

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