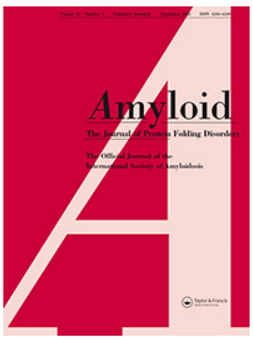

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RESEARCH ARTICLE

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Characteristics of patients with autonomic dysfunction in the Transthyretin Amyloidosis Outcomes Survey (THAOS)

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ABSTRACT

Background: Autonomic dysfunction is common in transthyretin amyloidosis (ATTR amyloidosis), but its frequency, characteristics, and quality-of-life (QoL) impact are not well understood.

Methods: The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal survey of patients with ATTR amyloidosis, including patients with inherited (ATTRv) and wild-type (ATTRwt) disease and asymptomatic patients with *TTR* mutations (ClinicalTrials.gov: NCT00628745). In a descriptive analysis, characteristics and Norfolk QoL-DN total (TQoL) scores at enrolment were compared in patients with vs without autonomic dysfunction (analysis cut-off: 1 August 2020).

Results: Autonomic dysfunction occurred in 1181/2922 (40.4%) symptomatic patients, and more commonly in ATTRv (1107/1181 [93.7%]) than ATTRwt (74/1181 [6.3%]) amyloidosis. Time (mean [SD]) from ATTR amyloidosis symptom onset to first autonomic dysfunction symptom was shorter in ATTRv (3.4 [5.7] years) than ATTRwt disease (9.7 [10.4]). In ATTRv disease, patients with vs without autonomic

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dysfunction had worse QoL (TQoL, 47.3 [33.2] vs 16.1 [18.1]); in ATTRwt disease, those with vs without autonomic dysfunction had similar QoL (23.0 [18.2] vs 19.9 [20.5]).
Conclusions: Autonomic dysfunction was more common and presented earlier in symptomatic ATTRv than ATTRwt amyloidosis and adversely affected QoL in ATTRv disease. These THAOS findings may aid clinicians in diagnosing and treating patients with ATTR amyloidosis.

Trial registration: ClinicalTrials.gov: NCT00628745

Abbreviations: ATTR amyloidosis: transthyretin amyloidosis; ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type amyloidosis; auto dys: autonomic dysfunction; Norfolk QoL-DN: Norfolk Quality of Life Questionnaire-Diabetic Neuropathy; QoL: quality of life; SD: standard deviation; THAOS: Transthyretin Amyloidosis Outcomes Survey; TQoL: total quality of life score; TTR: transthyretin.

Introduction

Transthyretin amyloidosis (ATTR amyloidosis) is a rare, fatal, systemic disease caused by the deposition of amyloid fibrils, composed of misfolded transthyretin monomers, in the extracellular space of various organs and tissues [1,2]. ATTR amyloidosis is more prevalent than previously recognised, but it continues to be a challenging disease to diagnose, with many symptoms mimicking those of other more common disorders [3]. The availability of disease-modifying therapies for ATTR amyloidosis, which may be most effective in early-stage disease, reinforces the need for increased awareness of initial disease symptoms and early diagnosis [4].

The systemic deposition of variant (ATTRv) or wild-type (ATTRwt) amyloidogenic transthyretin (TTR) results in multisystem tissue damage with progressively debilitating symptoms, including symptoms of autonomic nervous system dysfunction [2]. Amyloid fibril deposits and circulating TTR oligomers cause deterioration and loss of unmyelinated and small-diameter myelinated nerve fibres, leading to autonomic dysfunction that affects organ systems such as the cardiovascular, gastrointestinal, and genitourinary systems [2,5]. Cardiovascular autonomic dysfunction in ATTR amyloidosis may result in symptoms such as orthostatic hypotension, syncope, dizziness, and blurred vision upon standing [5], and autonomic denervation of the heart in this disease is linked to cardiac arrhythmias and conduction defects [6]. Manifestations of gastrointestinal autonomic dysfunction in patients with ATTR amyloidosis include early satiety, nausea, vomiting, and severe diarrhoea and/or constipation, which can lead to malnutrition, dehydration, and weight loss, and ultimately to malabsorption and cachexia [7]. Common genitourinary symptoms suggestive of autonomic involvement in ATTR amyloidosis are urinary retention, incontinence, and sexual dysfunction [5].

Symptoms of autonomic dysfunction often present in the early stages of ATTRv amyloidosis, preceding the onset of sensory motor impairment, and have a substantial adverse impact on patients' quality of life (QoL) and survival [8–11]. Autonomic neuropathy is less common in ATTRwt amyloidosis [12,13], but autonomic neurologic involvement manifesting as orthostasis (defined as a reduction in systolic blood pressure of >20 mm Hg after supine-to-standing positional change in patients who are not significantly dehydrated) was recently reported in 12% of patients in a large ATTRwt amyloidosis cohort [14]. Although a well-recognised symptom of ATTR amyloidosis, autonomic dysfunction in this genotypically heterogeneous disease continues to be poorly understood, and further characterisation is needed.

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing, global, longitudinal, observational survey (ClinicalTrials.gov: NCT00628745) of patients with ATTR amyloidosis, including both inherited and wild-type disease, and asymptomatic gene carriers with *TTR* mutations [15]. In this analysis of findings from THAOS, the occurrence of autonomic dysfunction was investigated in patients with ATTR amyloidosis of different genotypes, and the potential relationship between autonomic involvement and patient clinical characteristics and QoL burden was examined.

Methods

The complete methodology of THAOS, including the study design, has been previously described in detail (ClinicalTrials.gov: NCT00628745) [15]. THAOS patients' demographic and clinical characteristics, QoL, *TTR* genotype, and family and medical histories were recorded at enrolment, and clinical functions were regularly assessed at subsequent visits. Additional information relevant to the current analysis is summarised below.

Study population

THAOS patients who had ATTR amyloidosis with at least one symptom rated by investigators as definitely related to ATTRv or ATTRwt amyloidosis at enrolment were included in this analysis (analysis cut-off date, 1 August 2020). Patients were excluded if they had received a liver transplant or participated in a clinical trial of, or received treatment with, a disease-modifying agent for ATTR amyloidosis (i.e. AG10, diflunisal, inotersen, patisiran, or tafamidis) at the time of enrolment. Patients were evaluated as an overall cohort and in the following subgroups based on *TTR* genotype at enrolment: ATTRv amyloidosis (all); Val30Met [p.Val50Met] mutation; non-Val30Met mutations (excluding cardiac mutations and ATTRwt amyloidosis); cardiac

mutations (i.e. Val122lle [p.Val142lle], Thr60Ala [p.Thr80Ala], Leu111Met [p.Leu131Met], and Ile68Leu [p.Ile68Leu]); and ATTRwt amyloidosis (all).

Assessments and analysis

Demographic and clinical characteristics and QoL at enrolment were compared in patients with and without autonomic dysfunction. Patients with autonomic dysfunction were identified as those having orthostatic hypotension or at least one of the following symptoms recorded as definitely related to ATTR amyloidosis: early satiety, nausea, vomiting, constipation, alternating diarrhoea/constipation, diarrhoea, urinary retention, fecal/urinary incontinence, erectile dysfunction, dry eye, dyshidrosis, or dizziness. Orthostatic hypotension was defined as a decrease in systolic blood pressure of at least 20 mm Hg or a decrease in diastolic blood pressure of at least 10 mm Hg within 3 min of standing. Patients who did not satisfy these autonomic symptom criteria but had missing information for at least one symptom were classified as having 'unknown' status.

The frequency of autonomic dysfunction symptoms was analysed in each of the genotype subgroups described above, in addition to early- and late-onset Val30Met subgroups. The early-onset Val30Met subgroup included patients $\leq$50 years of age at symptom onset, and the late-onset Val30Met subgroup included patients >50 years of age at symptom onset.

QoL was assessed using the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) [16,17]. The 35-item, self-administered Norfolk QoL-DN comprises five domains (with higher scores denoting worse QoL): physical functioning/large-fiber neuropathy (score range, −4 to 56); activities of daily living (0–20); symptoms (0–32); small-fiber neuropathy (0–16); and autonomic neuropathy (0–12). The total score (TQoL) ranges from −4 to 136, with a higher score indicating worse QoL impairment.

Ethical statement

All THAOS study sites received ethical or institutional review board approval prior to patient enrolment 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 prior to study participation.

Results

A total of 2922 symptomatic patients with ATTR amyloidosis from 79 study sites across 22 countries were included in this analysis. The proportion of men overall was higher than that of women (73.5% [2147/2922] and 26.5% [775/2922], respectively), and the proportion of patients with ATTRv amyloidosis was higher than that of patients with ATTRwt amyloidosis (66.5% [1943/2922] and 33.5% [979/2922]). The majority of patients were enrolled at centres in Europe/Middle East (55.1% [1611/2922]), with lower proportions born in North America (33.6% [983/2922]), South America (5.9% [173/2922]), and Asia (5.3% [155/2922]).

Frequency of autonomic dysfunction

Autonomic dysfunction was present in 1181 of 2922 (40.4%) patients in this THAOS analysis (Figure 1). Of these patients, 1107 (93.7%) had ATTRv amyloidosis and 74 (6.3%) had ATTRwt amyloidosis. Among patients with ATTRv disease who were not missing data, autonomic dysfunction was more common in the Val30Met subgroup (735/863 [85.2%]) than in the non-Val30Met (290/365 [79.5%]) or cardiac mutation subgroups (82/103 [79.6%]). In the Val30Met subgroup, autonomic symptoms were more prevalent in patients with early-onset Val30Met ATTR amyloidosis (424/735 [57.7%]) than in those with late-onset Val30Met ATTR amyloidosis (311/735 [42.0%]).

The most common autonomic symptoms (i.e. those occurring in $\geq$20% of patients with autonomic dysfunction overall) occurred more frequently in patients with ATTRv amyloidosis than in those with ATTRwt amyloidosis (Figure 2). The only exception was early satiety, which was more common in the ATTRwt amyloidosis group than in the cardiac mutations group (but not more common than in the early- or late-onset Val30Met or non-Val30Met groups). The two most common autonomic symptoms in patients with early-onset Val30Met ATTRv amyloidosis were erectile dysfunction and early satiety, and in patients with late-onset Val30Met, erectile dysfunction and diarrhoea/constipation. In patients with non-Val30Met, and in patients with cardiac mutations, erectile dysfunction and diarrhoea occurred most frequently. In patients with ATTRwt amyloidosis, the most commonly occurring autonomic symptoms were orthostatic hypotension and erectile dysfunction.

Demographic and clinical characteristics

Across all subgroups, a higher proportion of patients with autonomic dysfunction than without autonomic dysfunction were male (Table 1). The age at enrolment was similar between those with and without autonomic dysfunction across these subgroups. In most genotype subgroups, patients with autonomic dysfunction were younger at ATTR amyloidosis symptom onset than those without. Patients with autonomic dysfunction in the non-Val30Met group were the exception, as they were older at symptom onset than their counterparts without autonomic dysfunction.

With the exception of patients in the non-Val30Met group, patients with autonomic dysfunction had symptoms of ATTR amyloidosis for a longer period than those without it and experienced a longer delay between the time of symptom onset and diagnosis. More than twice as many patients with Val30Met amyloidosis (40.6%) reported that autonomic dysfunction was their first ATTR amyloidosis–related symptom than patients with ATTRwt amyloidosis (11.4%). The proportions of patients in the non-Val30Met and cardiac mutations cohorts (32.6% and 25.2%, respectively) with

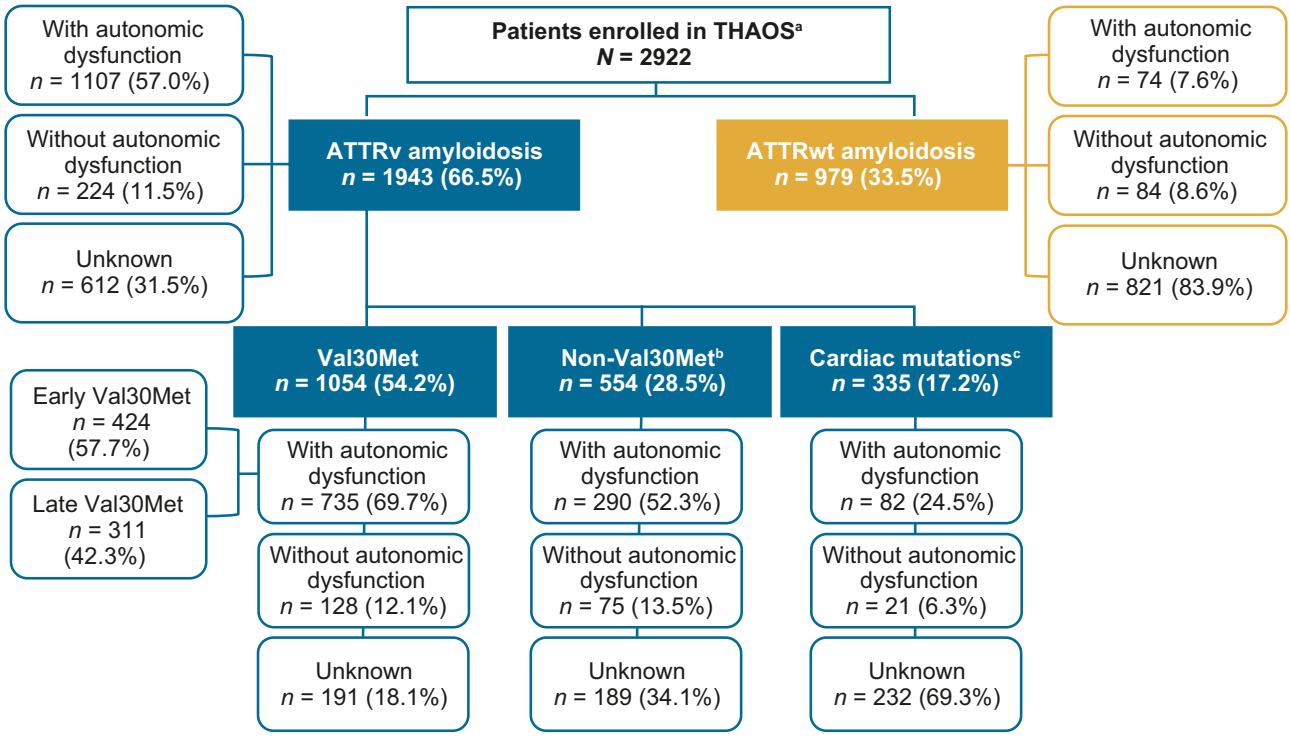

Figure 1. Study population. [a]As of 1 August 2020. [b]Excludes cardiac mutations and wild-type. [c]Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu. ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type transthyretin amyloidosis; THAOS: Transthyretin Amyloidosis Outcomes Survey.

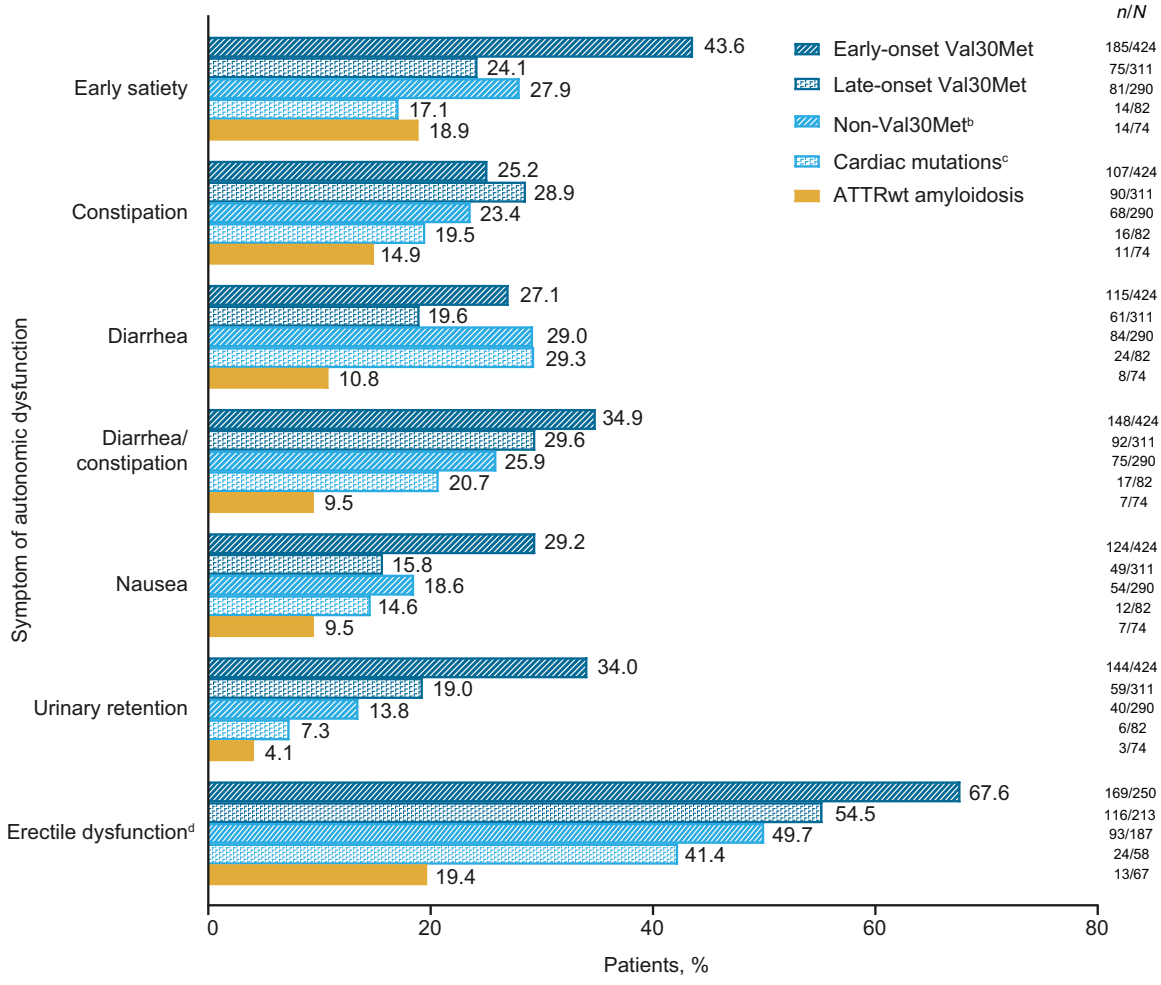

Figure 2. Frequency of common symptoms[a] of autonomic dysfunction. [a]Frequency of ≥20% of patients across all subgroups. [b]Excludes cardiac mutations and wild-type. [c]Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu. [d]Includes only males. ATTRwt amyloidosis: wild-type transthyretin amyloidosis.

autonomic dysfunction as their first ATTR amyloidosis–related symptom were also higher than that of patients in the ATTRwt amyloidosis cohort.

Among the patients whose date of diagnosis was known, 22.8% received their diagnosis on or before the onset of their first autonomic symptom and 77.2% received their diagnosis after the onset of their first autonomic symptom. Analysis by genotype also showed differences in the time from the onset of ATTR amyloidosis symptoms to the onset of the first autonomic symptom (Table 2). The time interval (mean [SD]) between the onset of ATTR amyloidosis and autonomic symptoms was shorter for patients with ATTRv amyloidosis (3.4 years [5.7]) than for patients with ATTRwt amyloidosis (9.7 years [10.4]). Patients with the Val30Met variant had a shorter interval (2.5 years [4.5]) than patients with non-Val30Met (4.8 years [7.3]) or cardiac mutations (5.7 years [7.7]). This interval was also shorter in Val30Met patients with early-onset (2.2 [4.6] years) vs late-onset Val30Met (3.0 [4.2] years) amyloidosis (data not shown). Smaller differences between the genotype subgroups were seen in the time intervals from diagnosis to autonomic dysfunction onset and autonomic dysfunction onset to diagnosis.

Quality of life burden

Among the patients with ATTRv amyloidosis, those with autonomic dysfunction had consistently worse QoL than those without autonomic dysfunction as assessed by the Norfolk QoL-DN TQoL score and each domain score (Figure 3). The greatest difference between patients in the ATTRv amyloidosis group with and without autonomic dysfunction was observed in the physical functioning/large-fiber domain. Smaller differences in TQoL and domain scores were seen in patients with ATTRwt amyloidosis with and without autonomic dysfunction.

Discussion

Autonomic dysfunction was common in symptomatic patients enrolled in THAOS, particularly in patients with ATTRv amyloidosis overall and in those with the Val30Met genotype specifically. Across all genotypes in the analysis, erectile dysfunction occurred most frequently, in nearly two-thirds of symptomatic men, followed by early satiety in approximately one-third of symptomatic patients, and diarrhoea and/or constipation in approximately one-quarter. The frequency of nearly all the most common autonomic dysfunction symptoms was considerably higher in the ATTRv amyloidosis subgroups than in the ATTRwt amyloidosis subgroup. Autonomic dysfunction symptoms presented much sooner after ATTR amyloidosis symptom onset in patients with ATTRv amyloidosis, especially in those with the Val30Met mutation (regardless of early or late onset), than in those with ATTRwt amyloidosis. Importantly, while QoL impairment was associated with autonomic dysfunction in both hereditary and wild-type genotypes, it was at least twice as severe in patients with

Table 1. Patient demographic and disease characteristics in patients with ATTRv and ATTRwt amyloidosis, with and without autonomic dysfunction.

Characteristic	ATTRv amyloidosis								ATTRwt amyloidosis	
	All ($n = 1331$)		Val30Met ($n = 863$)		Non-Val30Met[a] ($n = 365$)		Cardiac mutations[b] ($n = 103$)		($n = 158$)	
	With auto dys ($n = 1107$)	Without auto dys ($n = 224$)	With auto dys ($n = 735$)	Without auto dys ($n = 128$)	With auto dys ($n = 290$)	Without auto dys ($n = 75$)	With auto dys ($n = 82$)	Without auto dys ($n = 21$)	With auto dys ($n = 74$)	Without auto dys ($n = 84$)
Male, *n* (%)	708 (64.0)	117 (52.2)	463 (63.0)	66 (51.6)	187 (64.5)	37 (49.3)	58 (70.7)	14 (66.7)	67 (90.5)	74 (88.1)
Age at enrolment, years	54.6 (15.8)	54.0 (15.8)	52.1 (16.9)	50.9 (16.4)	57.2 (11.6)	54.1 (12.5)	67.7 (8.8)	72.0 (8.7)	77.6 (8.2)	77.6 (7.6)
Age at onset of ATTR amyloidosis symptoms, years	47.9 (15.1)	48.7 (15.4)	46.2 (15.9)	47.0 (15.7)	49.3 (12.1)	46.5 (12.8)	58.0 (12.9)	66.9 (9.3)	65.9 (12.5)	67.7 (11.9)
Age at onset of autonomic dysfunction,[c] years	51.0 (15.8)	52.5 (14.1)	48.6 (16.6)	50.4 (14.7)	53.7 (12.0)	55.3 (10.9)	63.6 (11.2)	72.7 (7.6)	75.3 (9.1)	69.4 (8.0)
Duration of ATTR amyloidosis symptoms, years	6.7 (6.7)	5.4 (7.0)	5.8 (5.5)	3.9 (5.4)	8.0 (7.8)	8.1 (9.2)	8.1 (10.0)	5.1 (3.7)	11.7 (11.0)	9.9 (9.1)
Time from symptom onset to diagnosis, years	5.2 (6.5)	4.7 (7.4)	4.2 (4.9)	3.3 (5.6)	6.5 (7.9)	7.1 (9.7)	8.9 (10.5)	3.8 (4.5)	10.6 (10.9)	8.7 (9.0)

All data are mean (SD) unless otherwise indicated.
ATTR amyloidosis: transthyretin amyloidosis; ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type transthyretin amyloidosis; auto dys: autonomic dysfunction; SD: standard deviation.
[a]Excluding cardiac mutations and wild-type.
[b]Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu.
[c]For patients who were classified as not having autonomic dysfunction at enrolment, age at onset of autonomic dysfunction is the age at which their first autonomic dysfunction symptom was reported.

Table 2. Time intervals between symptom onset, autonomic dysfunction onset, and diagnosis in patients with ATTR amyloidosis by genotype.

	Time, years				
	ATTRv amyloidosis				
Time interval	All ($n = 1331$)	Val30Met ($n = 863$)	Non-Val30Met[a] ($n = 365$)	Cardiac mutations[b] ($n = 103$)	ATTRwt amyloidosis ($n = 158$)
ATTR amyloidosis symptom onset to first autonomic dysfunction symptom[c]	3.4 (5.7)	2.5 (4.5)	4.8 (7.3)	5.7 (7.7)	9.7 (10.4)
Diagnosis to first autonomic dysfunction symptom[d]	1.8 (3.1)	1.7 (2.9)	2.3 (3.8)	1.0 (1.3)	1.1 (1.3)
First autonomic dysfunction symptom to diagnosis[e]	2.8 (3.7)	2.5 (2.7)	3.1 (4.2)	3.8 (7.9)	2.9 (3.5)

All data are mean (SD).
ATTR amyloidosis: transthyretin amyloidosis; ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type transthyretin amyloidosis; SD: standard deviation.
[a]Excludes cardiac mutations and wild-type.
[b]Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu.
[c]In patients whose date of symptom onset is reported on or before the date of first autonomic dysfunction.
[d]In patients whose date of diagnosis is reported on or before the date of first autonomic dysfunction.
[e]In patients whose date of diagnosis is reported after the date of first autonomic dysfunction.

ATTRv amyloidosis than in patients with ATTRwt amyloidosis. Minimal difference was seen in Norfolk QoL-DN TQoL score between patients with ATTRwt amyloidosis with and without autonomic dysfunction. In this regard, it should be noted that the Norfolk QoL-DN TQoL score is designed to assess the impact of the neurological impairments related to neuropathy on quality of life. Therefore, it is not unexpected that patients with ATTRv amyloidosis, who frequently present with a neuropathic or a mixed neuropathic/cardiac phenotype, report higher Norfolk QoL-DN TQoL scores than patients with ATTRwt amyloidosis, who present with a cardiac phenotype. In addition, the Norfolk QoL-DN TQoL score is based on several items that assess neuropathic deficits related to abnormalities in large nerve fibres, which mediate touch and proprioception, as well as motor functions, and contains fewer items related to the symptoms of autonomic dysfunction, helping to explain the small difference observed between ATTRwt amyloidosis with and without autonomic dysfunction.

These findings from THAOS confirm previous reports that autonomic dysfunction is a prevalent manifestation of ATTRv amyloidosis that frequently presents early in the course of the disease and has a substantial adverse impact on patients' QoL burden [8–12,17,18]. However, this THAOS analysis provides a detailed description of the frequency, onset, characteristics, and QoL burden of autonomic manifestations of ATTR amyloidosis by genotype, including ATTRv disease, with and without Val30Met mutation (and the latter, with and without cardiac mutations), and ATTRwt disease, which, to the authors' knowledge, has not been reported previously.

Although the current THAOS analysis provides a greater depth and breadth of information on autonomic dysfunction in ATTR amyloidosis, the diverse cardiovascular, gastrointestinal, urinary, and sexual autonomic dysfunction symptoms present in patients with ATTRv amyloidosis overall have been well documented previously [9,10,18,19]. In this THAOS population, erectile dysfunction, early satiety, diarrhoea and/or constipation, nausea, and urinary retention were the most common symptoms of autonomic dysfunction across genotypes. While these symptoms can occur at any age, several (e.g. erectile dysfunction, early satiety, constipation, and urinary retention) are more common in older adults in the general population. In an older patient population, such as that included in this THAOS analysis, a greater frequency of these autonomic abnormalities may therefore be expected. However, in this analysis, patients with autonomic dysfunction were defined as those with autonomic dysfunction symptoms that investigators considered definitely related to ATTR amyloidosis. In addition, the mean age of patients with ATTRv amyloidosis in this analysis (who comprised the vast majority of the THAOS population analysed) was approximately 54 years.

Although the finding that symptoms of autonomic dysfunction have a major impact on QoL in patients with ATTRv amyloidosis was not unexpected, the observation that the impact in ATTRv amyloidosis was greatest on the physical functioning/large-fiber domain score (not the autonomic domain score) was surprising, given that autonomic dysfunction is generally considered a manifestation of small-fiber neuropathy [20]. This finding may be explained by the longer average duration of disease observed in patients with autonomic involvement in the ATTRv amyloidosis subgroup (6.7 vs 5.4 years in patients without autonomic involvement), as more advanced disease is associated with more large-fiber involvement [5].

The current analysis has several strengths, including a large and geographically diverse study sample of nearly 3000 symptomatic patients with ATTR amyloidosis from over 20 countries worldwide. The classification rule for the absence of autonomic dysfunction was stringent and conservative, requiring that patients have no missing data for any criteria. If no defining criteria were present and any defining criteria were missing, then autonomic function status was set to missing. This approach avoids potential misclassification by not assuming that a missing symptom must have been negative.

Limitations of this analysis include the large amount of missing data on autonomic dysfunction excluded from analysis due to the strict criteria used to define autonomic dysfunction. In addition, the older age of patients with

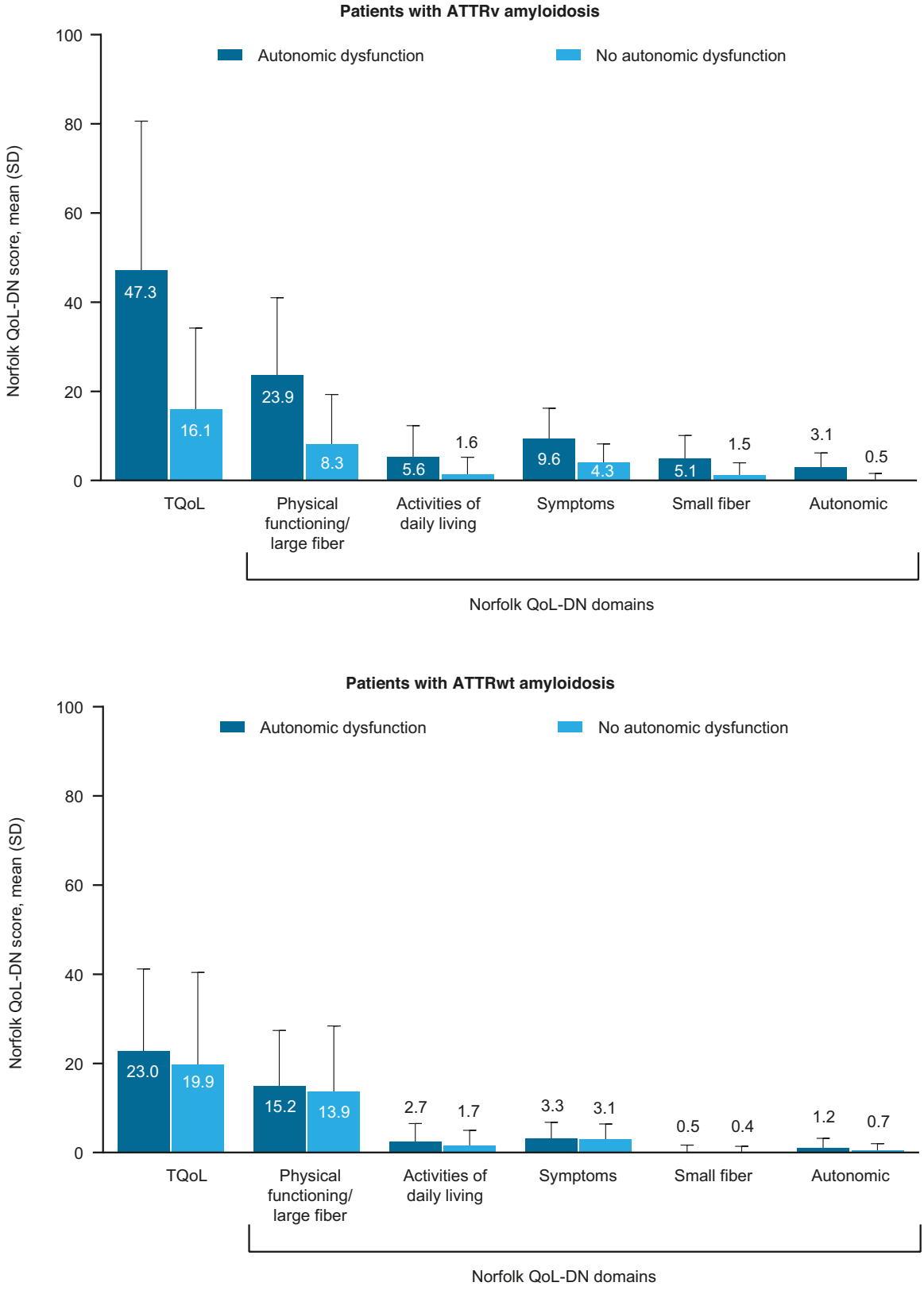

Figure 3. Quality of life[a] in patients with ATTRv and ATTRwt amyloidosis, with and without autonomic dysfunction. [a]Assessed using the Norfolk QoL-DN total and domain scores; higher scores denote poorer quality of life. ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type transthyretin amyloidosis; Norfolk QoL-DN: Norfolk Quality of Life Questionnaire-Diabetic Neuropathy; SD: standard deviation; TQoL: Norfolk QoL-DN total quality of life score.

ATTRwt amyloidosis in the current analysis may be considered a limitation, as the autonomic dysfunction symptoms observed in these patients could have been attributable to ageing rather than ATTR amyloidosis. For instance, the prevalence of erectile dysfunction of moderate degree increases with age, from 17% of men in their forties to 34%

in their seventies. Furthermore, some disorders highly prevalent in people of advanced age, like diabetes, arterial hypertension, and heart disease, also increase the risk of suffering erectile dysfunction [21]. The prevalence of chronic idiopathic constipation in the general population is 14%, being more common in women, older age, and individuals with low socioeconomic status [22]. Finally, lower urinary tract symptoms, such as urinary incontinency, urinary urgency and retention, are reported by up to 35% of older individuals living in the community and up to 50% of institutionalised individuals, increasing the difficulty of attributing these symptoms to a single cause [23].

However, as noted previously, only autonomic dysfunction symptoms defined by the investigator as definitely related to ATTR amyloidosis were included in the analysis. The higher prevalence of autonomic dysfunction in men is likely due in part to the inclusion of 'erectile dysfunction' as a defining symptom of the condition; sexual dysfunction in women was not evaluated (as it is more difficult to assess), introducing potential bias in the analysis. The symptoms used to define autonomic dysfunction in this cohort, such as erectile dysfunction, may have been caused by factors unrelated to dysautonomia in some patients. Moreover, some of the defining symptoms are difficult to classify; for example, gastrointestinal symptoms may have been related specifically to gastrointestinal amyloidosis rather than damage to autonomic nerves.

In conclusion, THAOS offers a valuable data source and important insights regarding the natural history of ATTR amyloidosis, with the current analysis showing that autonomic dysfunction is a common and debilitating manifestation of the disease. Autonomic dysfunction often occurred early in the disease course and substantially increased the burden of the disease on patients. Improved recognition and understanding of the clinical characteristics of autonomic dysfunction in ATTR amyloidosis may help facilitate more timely diagnosis and optimal disease management.

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Data availability statement

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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