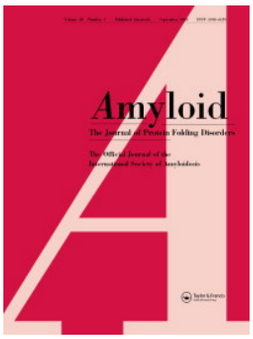

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Patients with transthyretin amyloidosis enrolled in THAOS between 2018 and 2021 continue to experience substantial diagnostic delay

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LETTER TO THE EDITOR

Patients with transthyretin amyloidosis enrolled in THAOS between 2018 and 2021 continue to experience substantial diagnostic delay

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive disease characterised by amyloid fibril deposits in the peripheral nerves, heart and other tissues and organs [1]. ATTR amyloidosis is primarily characterised by polyneuropathy, cardiomyopathy or a mix of both, but other symptoms such as gastrointestinal and kidney impairment or ocular dysfunction may also be present [1]. ATTR amyloidosis has two distinct forms: hereditary (ATTRv amyloidosis) and wild-type (ATTRwt amyloidosis) [1]. ATTR amyloidosis is often misdiagnosed or diagnosed late in the disease course due to low disease awareness, the heterogeneity of the disease, and symptoms that overlap with more common disorders [1,2]. With the recent advent of disease-modifying therapies [3] and less invasive diagnostic techniques for the cardiac form of ATTR amyloidosis [4], the number of ATTR amyloidosis diagnoses is expected to increase and latency to diagnosis to decrease. To explore this hypothesis, we examined temporal trends in the make-up of patients enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS) during four roughly equal time periods (2007–2010, 2011–2014, 2015–2017 and 2018–2021) spanning 15 years.

THAOS is the largest ongoing, global, longitudinal observational study of patients with ATTR amyloidosis, including both ATTRv and ATTRwt amyloidosis, and asymptomatic carriers of pathogenic *TTR* variants. The full study design and eligibility criteria of THAOS (NCT00628745) have been published [5]. All study sites received ethical or institutional review board approval prior to patient enrolment, 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 focussed on symptomatic patients, defined as those with $\geq$1 symptom rated by investigator as definitely related to ATTR amyloidosis at enrolment (data cut-off date: 1 January 2022).

At the data cut-off date, 6042 patients were enrolled in THAOS at 84 study sites in 23 countries. A total of 4206 patients were symptomatic, of whom 548 enrolled in the period 2007–2010, 1273 in 2011–2014, 924 in 2015–2017 and 1461 in 2018–2021 (Table 1). In symptomatic patients with ATTRv amyloidosis, median age at symptom onset and enrolment, respectively, increased from 39.5 and 47.7 years in those enrolled in 2007–2010 to 57.0 and 64.1 years in those enrolled in 2018–2021. Median time from symptom onset to diagnosis also increased, from 1.6 years in those enrolled in 2007–2010 to 2.4 years in those enrolled in 2018–2021. The percentage of males in this group increased from 57.5% in patients enrolled in 2007–2010 to 63.5% in patients enrolled in 2018–2021. Symptomatic patients with ATTRwt amyloidosis were predominantly male (>90% in all time periods), and median age at enrolment (range: 76.1–79.5 years) and symptom onset (range: 71.8–74.5 years) did not vary substantially across the time periods. Median time from symptom onset to diagnosis in this group increased from 1.2 years in patients enrolled in 2007–2010 to 2.3 years in patients enrolled in 2018–2021.

The most striking finding of this THAOS analysis was that time from symptom onset to diagnosis did not decrease as expected, and even increased to >2 years in patients with ATTRv amyloidosis and ATTRwt amyloidosis enrolled in the most recent era. This occurred despite greater disease awareness through the advent of disease-modifying treatments and availability of minimally invasive diagnostic procedures [3,4]. One possible explanation is that these developments are not yet reflected in the THAOS population, and future data will show an eventual decrease in diagnostic delay. Alternatively, ATTR amyloidosis may continue to be misdiagnosed or diagnosed late, highlighting the need for improved education on identifying early symptoms of ATTR amyloidosis. This is especially true for patients with ATTRwt amyloidosis and non-V30M (p.V50M) variants since they are generally older, have more comorbidities, do not live in endemic areas, and seldom have a known family history. Another potential factor for continued late diagnosis is that increased clinical awareness is a dynamic process, and patients with obvious disease with years of progression are often the first to be recognised; as a consequence, these patients receive a late diagnosis when they would otherwise have remained undiagnosed.

A limitation of this analysis is the potential role of selection bias in our results. Specifically, the most severe patients were more likely to be registered in THAOS in the earlier years, as these patients were most readily identified. As clinicians have become more adept at identifying patients, those presenting with less severe and/or atypical symptoms were more likely enrolled in later years. Another limitation is the measure of diagnostic delay may be prone to recall bias since this measure relied on the patient's recall of his or her medical history.

In conclusion, patients with ATTR amyloidosis continue to experience substantial diagnostic delay despite the advent of disease-modifying therapies and minimally invasive diagnostic procedures. THAOS remains a valuable resource for tracking the evolution of ATTR amyloidosis over time.

Table 1. Demographics of symptomatic patients in THAOS, by enrolment time period and genotype.

	ATTRv amyloidosis				ATTRwt amyloidosis			
	2007–2010 $n = 478$	2011–2014 $n = 1043$	2015–2017 $n = 646$	2018–2021 $n = 728$	2007–2010 $n = 70$	2011–2014 $n = 230$	2015–2017 $n = 278$	2018–2021 $n = 732$
Male, *n* (%)	275 (57.5)	601 (57.6)	414 (64.1)	462 (63.5)	69 (98.6)	215 (93.5)	264 (95.0)	684 (93.4)
Age at symptom onset, *n*	476	1040	646	728	70	229	278	732
Median (10th, 90th percentile)	39.5 (26.5, 66.5)	44.0 (27.0, 67.6)	53.2 (29.0, 72.0)	57.0 (33.5, 73.5)	74.0 (59.7, 82.2)	71.8 (60.5, 82.5)	72.0 (60.1, 82.5)	74.5 (59.5, 84.4)
Age at enrolment	478	1043	646	728	70	230	278	732
Median (10th, 90th percentile)	47.7 (30.8, 72.7)	51.1 (31.8, 72.9)	59.3 (37.6, 75.8)	64.1 (40.1, 77.8)	76.9 (67.5, 84.5)	76.1 (67.2, 84.3)	76.8 (67.0, 85.4)	79.5 (69.7, 87.5)
Symptom duration at enrolment	476	1040	646	728	70	229	278	732
Median (10th, 90th percentile)	4.3 (0.9, 12.7)	4.0 (0.8, 14.4)	3.9 (0.7, 16.5)	4.1 (0.8, 14.9)	3.1 (0.5, 12.1)	2.1 (0.3, 10.8)	2.5 (0.4, 14.8)	3.4 (0.4, 14.8)
Time from symptom onset to diagnosis	342	978	608	687	35	215	278	717
Median (10th, 90th percentile)	1.6 (0.1, 7.0)	1.8 (0.0, 9.2)	2.2 (0.0, 10.4)	2.4 (0.0, 11.7)	1.2 (0.2, 9.7)	1.2 (0.0, 10.3)	1.5 (0.0, 13.7)	2.3 (0.0, 13.7)

One patient enrolled in the time period 2018–2021 had missing variant data and was not categorised by genotype.
ATTRv amyloidosis: hereditary transthyretin amyloidosis; ATTRwt amyloidosis: wild-type transthyretin amyloidosis; THAOS: Transthyretin Amyloidosis Outcomes Survey.

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Data availability statement

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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