A Final, Consolidated Overview of 16 Years of Data From the Transthyretin Amyloidosis Outcomes Survey

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INTRODUCTION

- Transthyretin amyloidosis (ATTR amyloidosis) is a progressive disease caused by the accumulation of transthyretin (TTR) amyloid fibrils in the heart, peripheral nerves, and other organs.[1,2]
- The Transthyretin Amyloidosis Outcomes Survey (THAOS; NCT00628745) was the largest global, longitudinal, observational study of patients with ATTR amyloidosis, including both hereditary (ATTRv amyloidosis) and wild-type (ATTRwt amyloidosis) disease, and asymptomatic carriers of pathogenic *TTR* variants.[3]
- This analysis provides a final, consolidated overview of 16 years of patient data from THAOS.

METHODS

- Baseline demographic and clinical characteristics for all symptomatic patients and asymptomatic carriers were described overall and by genotype category.
- The symptomatic set included patients with ≥1 symptom definitely related to ATTR amyloidosis; symptoms included motor neuropathy, sensory neuropathy, autonomic neuropathy, gastrointestinal manifestations, cardiac disorder, and other types of symptoms.[4]
- Phenotype definitions have been described.[5]
- The 16-year data period for this analysis was 2007 to 2023 (final dataset date: July 24, 2023).

RESULTS

- 6718 participants (4699 symptomatic patients; 1738 asymptomatic carriers; 281 unclassified) enrolled in THAOS.
  - The unclassified group included 281 patients with wild-type disease who did not meet the definition of the symptomatic set.
- Of 4699 symptomatic patients, 1516 (32%) had ATTRwt amyloidosis and 3183 (68%) had ATTRv amyloidosis.
  - V30M (p.V50M) was the most common *TTR* variant, accounting for 57% (n=1824) of symptomatic patients with ATTRv amyloidosis.
  - Of 1824 with the V30M variant, 1114 (61%) had early onset (age at diagnosis ≤50 years) disease and 710 (39%) had late-onset (age at diagnosis >50 years) disease.
- Patients with ATTRwt amyloidosis had a higher proportion of males (93%) compared with the other genotype groups (range: 52–65%; **Table 1**).
  - Median age at symptom onset and enrollment was higher in patients with ATTRwt amyloidosis than the other genotype groups.
  - Patients with ATTRwt amyloidosis and non-V30M ATTRv amyloidosis had more severe cardiac involvement (as measured by left ventricular septum thickness), whereas those with V30M ATTRv amyloidosis had more severe neurologic impairment (as measured by derived NIS-LL score).
- In this study, ATTRwt was the most common genotype in North America (60%), V30M early onset was most common in South America (51%) and Europe (33%), and non-V30M was most common in Asia (47%; **Figure 1**).
- The most common phenotype was predominantly cardiac in North America (64%) and predominantly neurologic in South America (61%), Europe (48%), and Asia (48%; **Figure 2**).
  - In North America, South America, Europe, and Asia, respectively, 18%, 27%, 27%, and 35% of patients had a mixed phenotype, representing 25% of the overall symptomatic population.

Table 1: Baseline demographic and clinical characteristics of patients with symptomatic ATTR amyloidosis, by genotype

	Overall N=4699	ATTRwt n=1516	ATTRv V30M early onset n=1114	ATTRv V30M late onset n=710	ATTRv Non-V30M n=1359
Male	3326 (71)	1405 (93)	583 (52)	460 (65)	878 (65)
Race/ethnicity					
Caucasian/White	2621 (77)	1225 (94)	278 (69)	404 (83)	714 (59)
African descent	328 (10)	42 (3)	33 (8)	18 (4)	235 (20)
American Hispanic/ Latino American	160 (5)	12 (1)	33 (8)	6 (1)	109 (9)
Asian	259 (8)	19 (1)	56 (14)	53 (11)	131 (11)
Other	22 (1)	6 (<1)	1 (<1)	3 (1)	12 (1)
Age at symptom onset, y	60 (31, 79)	73 (60, 84)	33 (25, 45)	64 (53, 74)	56 (37, 73)
Time from symptom onset to diagnosis, y	2.0 (0.0, 10.9)	2.0 (0.0, 13.3)	1.4 (0.0, 7.0)	2.8 (0.3, 9.2)	2.3 (0.0, 12.8)
Age at enrollment, y	67 (36, 83)	78 (69, 87)	40 (29, 53)	69 (57, 78)	63 (43, 77)
Symptom duration at enrollment, y	3.8 (0.6, 14.5)	3.2 (0.4, 14.0)	4.2 (0.8, 16.7)	4.2 (1.0, 11.3)	3.9 (0.7, 14.4)
Derived NIS-LL score	8.0 (0.0, 50.5)	2.0 (0.0, 14.0)	7.0 (0.0, 50.0)	18.0 (0.0, 65.0)	6.0 (0.0, 46.5)
mBMI	1029.8 (765.7, 1339.4)	1059.8 (822.9, 1340.2)	994.2 (723.9, 1310.9)	1027.7 (761.9, 1341.7)	1015.9 (744.0, 1364.2)
LV septum thickness, mm	16.0 (10.0, 21.0)	17.0 (13.0, 22.0)	10.0 (8.0, 13.0)	14.0 (9.0, 20.0)	16.0 (10.0, 21.0)
LVEF, %	55.0 (34.0, 69.0)	50.0 (31.0, 63.0)	63.0 (51.0, 75.0)	62.0 (50.0, 73.0)	56.0 (31.0, 69.0)
Karnofsky performance score					
10–40	90 (3)	11 (2)	13 (1)	29 (5)	37 (4)
50–70	852 (27)	203 (31)	186 (19)	192 (33)	271 (29)
80–100	2199 (70)	437 (67)	787 (80)	354 (62)	621 (67)

Data are n (%) or median (10th, 90th percentile).
For variables with missing data, number of patients available in the respective columns (n): race/ethnicity (3390, 1304, 401, 484, 1201); age at symptom onset (4693, 1515, 1114, 710, 1354); time from symptom onset to diagnosis (4320, 1448, 1019, 636, 1217); symptom duration at enrollment (4693, 1515, 1114, 710, 1354); derived NIS-LL score (1843, 173, 810, 342, 518); mBMI (3099, 974, 865, 506, 754); LV septum thickness (2531, 1179, 248, 291, 813); LVEF (2402, 1184, 203, 209, 806); Karnofsky performance score (3141, 651, 986, 575, 929).
ATTR amyloidosis=transthyretin amyloidosis; ATTRv=hereditary transthyretin amyloidosis; ATTRwt=wild-type transthyretin amyloidosis; LV=left ventricular; LVEF=left ventricular ejection fraction; mBMI=modified body mass index; NIS-LL=Neuropathy Impairment Score in the Lower Limbs

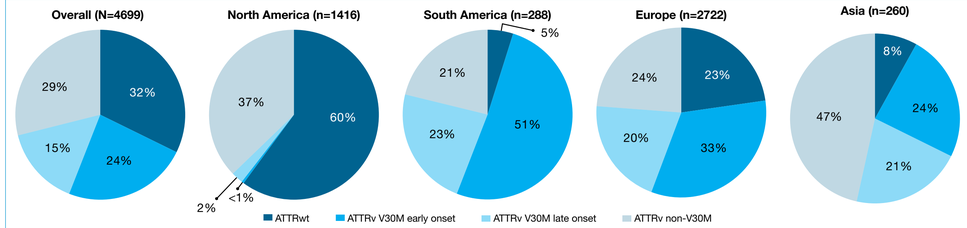
- Of the 1738 asymptomatic carriers, 42% were male and V30M was the most prevalent *TTR* variant (74%; **Table 2**).
  - Median age at enrollment was higher in those with non-V30M variants than the V30M variant (**Table 2**).

Table 2: Baseline demographics of asymptomatic carriers of pathogenic *TTR* variants, by genotype

	Overall n=1738	V30M n=1286	Non-V30M n=452
Male	730 (42)	500 (39)	230 (51)
Race/ethnicity[a]			
Caucasian/White	691 (80)	420 (88)	271 (70)
African descent	88 (10)	30 (6)	58 (15)
American Hispanic/Latino American	48 (6)	16 (3)	32 (8)
Asian	36 (4)	9 (2)	27 (7)
Other	4 (<1)	3 (1)	1 (<1)
Age at enrollment, y	39 (23, 65)	37 (22, 62)	47 (30, 72)

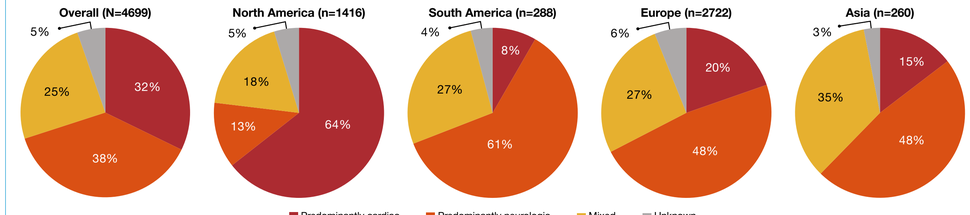
Data are n (%) or median (10th, 90th percentile).
[a] Race/ethnicity (n) available in 867, 478, and 389 patients in the respective columns.
TTR=transthyretin gene

Figure 1: Genotype distribution of symptomatic patients, by region



ATTRv=hereditary transthyretin amyloidosis; ATTRwt=wild-type transthyretin amyloidosis

Figure 2: Phenotype distribution of symptomatic patients, by region



CONCLUSIONS

- This descriptive analysis of more than 6000 patients from THAOS is the largest overview of ATTR amyloidosis to date.
- Results revealed regional differences in the distribution of genotypes and phenotypes.
- The increasing proportion of patients with a mixed phenotype worldwide reinforces the need for multidisciplinary management of ATTR amyloidosis.
- As with any disease registry, underreporting of disease characteristics and under-ascertainment of patients are potential limitations that also apply to this analysis of ATTR amyloidosis in THAOS.

REFERENCES

1. Ando Y, et al. Orphanet J Rare Dis 2013;8:31. **2.** Maurer MS, et al. J Am Coll Cardiol 2016;68:161-72. **3.** Planté-Bordeneuve V, et al. Curr Med Res Opin 2013;29:77-84. **4.** Gonzalez-Moreno J, et al. Cardiol Ther 2024;13:117-35. **5.** Gentile L, et al. Orphanet J Rare Dis 2023;10:350.

DISCLOSURES

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