Time From First Recorded Clinical Manifestation to Diagnosis of Transthyretin Amyloid Cardiomyopathy: a Retrospective Cohort Study Using US Claims Data

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OBJECTIVE

- **To assess time from the first recorded clinical manifestation to ATTR-CM diagnosis in the US**

CONCLUSIONS

- **This study demonstrates that the patient journey to an ATTR-CM diagnosis can be prolonged and challenging, which potentially leads to more advanced disease at diagnosis**
- **US patients had a median of 8 clinical manifestations before the diagnosis of ATTR-CM; median time from the first recorded clinical manifestation to ATTR-CM diagnosis was over 5 years, and from first heart failure diagnosis to ATTR-CM diagnosis was over 2 years**
- **Glaucoma and erectile dysfunction were the key manifestations associated with the longest times between clinical manifestation and diagnosis**
- **Patients had many interactions with the healthcare system during the time leading up to diagnosis, with a median of 9 primary care physician visits and 10 specialist visits of interest within the 3 years before ATTR-CM diagnosis; better disease awareness and education related to early clinical manifestations may help improve diagnostic pathways and patient outcomes**

BACKGROUND

- ATTR-CM is a progressive, life-threatening condition caused by destabilisation and dissociation of TTR tetramers into amyloidogenic monomers[1-3]
  - Monomers form amyloid fibrils that deposit in the myocardium, causing restrictive cardiomyopathy and heart failure
- ATTR-CM is broadly categorised into wild type (ATTRwt-CM) and pathogenic variant (ATTRv-CM) forms[1-3]
- Early diagnosis of ATTR-CM is challenging because the associated symptoms and clinical manifestations are non-specific and overlap with other conditions[2]
  - Prior to the approval of therapies to treat ATTR-CM, a previous study demonstrated that mean time from the first clinical manifestation to diagnosis was 6.1 years for ATTRwt-CM and 5.7 years for ATTRv-CM; carpal tunnel syndrome has been reported as one of the first identifiable manifestations[3]
  - Factors associated with diagnostic delay include age <70 years, no family history of amyloidosis, and, in patients with ATTRv-CM, a predominant cardiomyopathy phenotype (as opposed to a mixed phenotype)[3]

METHODS

- This was a retrospective database analysis of patients with ATTR-CM in the US from the Komodo Healthcare Map® (**Figure 1**)

FIGURE 1. Data Source and Inclusion/Exclusion Criteria

Data source	Inclusion criteria
• Retrospective database analysis of patients with ATTR-CM in the US from the Komodo Healthcare Map®; the patient identification period was 1 January 2019 to 30 June 2024 and the study period was 1 January 2016 to 30 June 2024 • The Komodo Healthcare Map is comprised of medical and prescription claims data from a number of sources, including clearing houses and switch outlets; it is characterised by proprietary partnership with >150 key national payers and consortiums, representing over 150 million payer complete lives; this database is representative of the US commercial, Medicare, and Medicaid insured populations	• Two or more claims with an amyloidosis diagnosis code (E85.0, E85.1, E85.2, E85.4, E85.82) occurring on separate days AND ≥2 claims for a cardiac-related ICD-10-CM code; OR ≥1 claim for tafamidis based on National Drug Codes • ≥50 years of age on the index date (earliest date of either ATTR-CM diagnosis or tafamidis claim) • Patients were required to have ≥3 years of continuous enrolment before the index date
	Exclusion criteria
	• More than 1 ICD-10-CM diagnosis code of light chain amyloidosis (E85.81) on different dates during the study period • More than 1 claim (on separate days) for multiple myeloma at any time during the study period • Received haematopoietic stem cell transplant at any time during the study period

- Outcomes included:
  - Baseline demographics and clinical characteristics among patients with ATTR-CM
  - Clinical manifestations recorded before diagnosis of ATTR-CM
    - Clinical manifestations of interest were based on previous studies and the 2023 ACC Expert Consensus and further categorised as cardiovascular, musculoskeletal, neurological, ocular, or renal[4-8]
  - Time from the individual clinical manifestation to first diagnosis of ATTR-CM
  - Number of visits to primary care providers, specialists of interest, or all specialists was calculated during the 6 months and 3 years before the index date; the most common providers for outpatient visits was determined
- Demographics and outcomes were stratified by the type of ATTR-CM
  - The type of ATTR-CM was determined based on the ATTR-CM diagnosis codes on claims occurring during the identification period
    - To be considered ATTRv-CM, a patient was required to have ≥2 ATTRv-CM codes (E85.0, E85.1, E85.2; on separate days) during the identification period
    - If a patient had ≥1 ATTRwt-CM codes (E85.4, E85.82) and <2 ATTRv-CM codes during the identification period, the patient was considered to be ATTRwt-CM
    - If a patient had 1 ATTRv-CM code and no ATTRwt-CM codes (with tafamidis claim), the patient was labeled as 'unknown'
    - If a patient only had a tafamidis claim and no relevant ATTR-CM codes during the identification period, then the patient was labeled as 'unknown'
- Statistical analyses were descriptive in nature; R statistical software, R version 4.2.1, was used for analytics[9]

RESULTS

- A total of 7509 patients were included in the analysis (**Table 1**)
  - The median baseline period for the overall population was 58.7 months (IQR, 46.0-74.3)
  - The diagnosis of ATTRwt-CM was the most common (n=6761 [90.0%]), followed by ATTRv-CM (n=603 [8.0%]) and ATTR-CM of unknown type (n=145 [1.9%])
- Overall, the mean age was 75.9 years (SD, 9.6), 63.2% were male, 54.5% were White, and 28.6% were Black or African American
  - Patients with ATTRv-CM were generally younger at diagnosis (mean, 70.4 years [SD, 10.2]) compared with patients with ATTRwt-CM (mean, 76.3 years [SD, 9.5])
  - A total of 27.4% of patients with ATTRwt-CM and 43.4% of patients with ATTRv-CM were Black or African American
- The majority of patients (75.7%) were enrolled in Medicare

TABLE 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Overall[a] (N=7509)	ATTRwt-CM (n=6761)	ATTRv-CM (n=603)
Age, years			
Mean (SD)	75.9 (9.6)	76.3 (9.5)	70.4 (10.2)
Median (IQR)	78.0 (70.0, 84.0)	79.0 (71.0, 84.0)	71.0 (62.0, 79.0)
Sex, n (%)			
Male	4742 (63.2)	4286 (63.4)	356 (59.0)
Female	2546 (33.9)	2278 (33.7)	228 (37.8)
Unknown	221 (2.9)	197 (2.9)	19 (3.2)
Race/Ethnicity, n (%)			
White	4095 (54.5)	3798 (56.2)	205 (34.0)
Black or African American	2146 (28.6)	1850 (27.4)	262 (43.4)
Hispanic or Latino	622 (8.3)	547 (8.1)	69 (11.4)
Asian or Pacific Islander	194 (2.6)	183 (2.7)	8 (1.3)
Other	137 (1.8)	119 (1.8)	16 (2.7)
Missing/Unknown	315 (4.2)	264 (3.9)	43 (7.1)
Region, n (%)			
Northeast	3187 (42.4)	2890 (42.7)	239 (39.6)
Midwest	1756 (23.4)	1609 (23.8)	118 (19.6)
South	1570 (20.9)	1363 (20.2)	165 (27.4)
West	958 (12.8)	868 (12.8)	76 (12.6)
Missing/Unknown	38 (0.5)	31 (0.5)	5 (0.8)
Insurance type, n (%)[b]			
Medicare	5686 (75.7)	5201 (76.9)	361 (59.9)
Commercial	1017 (13.5)	863 (12.8)	142 (23.5)
Medicaid	431 (5.7)	357 (5.3)	71 (11.8)
Mixed/Partial	361 (4.8)	329 (4.9)	27 (4.5)
Missing/Unknown	14 (0.2)	11 (0.2)	2 (0.3)

[a]The sum of the ATTRwt-CM and ATTRv-CM populations does not equal that of the overall population because ATTR-CM type was unknown in 145 patients.
[b]Patients in the Commercial, Medicaid, and Medicare categories had the respective insurance type for both medical and prescription coverage at index. Patients in the Mixed/Partial category had different types of medical and prescription insurance at index, had medical insurance but unknown prescription insurance at index, or had prescription insurance and unknown medical insurance at index. Patients in the Missing/Unknown category had no available information on medical or prescription insurance at index.

- Of the 28 clinical manifestations of interest, patients had a median of 8.0 manifestations (IQR, 6.0-11.0) before the diagnosis of ATTR-CM, and the median time from the first recorded clinical manifestation to diagnosis was 61.6 months (IQR, 45.1-76.7) (**Table 2**)
  - The time from the first recorded clinical manifestation to diagnosis was shorter for patients with ATTRv-CM compared with ATTRwt-CM (median, 51.6 months [IQR, 38.8-70.1] vs 61.9 months [IQR, 45.8-76.8], respectively)

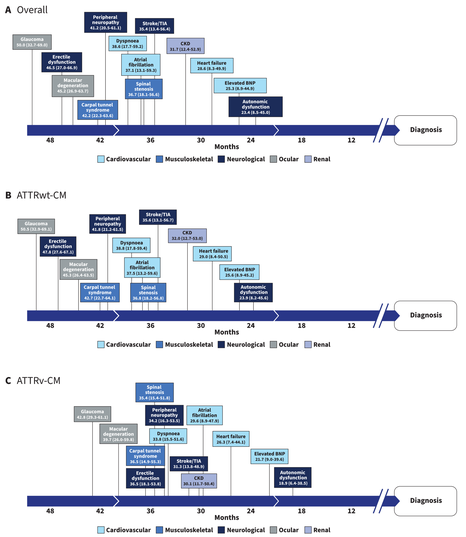
TABLE 2. Time to Diagnosis of ATTR-CM and the First Recorded Clinical Manifestation

Characteristic	Overall[a] (N=7509)	ATTRwt-CM (n=6761)	ATTRv-CM (n=603)
Number of clinical manifestations before diagnosis			
Mean (SD)	8.4 (3.4)	8.5 (3.4)	7.8 (3.5)
Median (IQR)	8.0 (6.0, 11.0)	8.0 (6.0, 11.0)	8.0 (5.0, 10.0)
Time from the first recorded clinical manifestation to ATTR-CM diagnosis, months			
Mean (SD)	60.0 (21.6)	60.4 (21.3)	52.8 (21.3)
Median (IQR)	61.6 (45.1, 76.7)	61.9 (45.8, 76.8)	51.6 (38.8, 70.1)
Type of ATTR-CM clinical manifestation, n (%)			
Cardiovascular	7327 (98.4)	6604 (98.5)	583 (97.5)
Atrial fibrillation	3933 (52.8)	3623 (54.0)	230 (38.5)
Dyspnoea	5999 (80.6)	5426 (80.9)	464 (77.6)
Oedema	4297 (57.7)	3890 (58.0)	331 (55.4)
EKG branch block/atrioventricular block	3362 (45.2)	3069 (45.8)	226 (37.8)
EKG low voltage	4376 (58.8)	3960 (59.1)	334 (55.9)
Elevated BNP (or NT-proBNP)	2987 (40.1)	2696 (40.2)	240 (40.1)
Fatigue	3701 (49.7)	3359 (50.1)	277 (46.3)
Heart failure	5572 (74.8)	5051 (75.3)	417 (69.7)
Left ventricular hypertrophy	4240 (57.0)	3867 (57.7)	295 (49.3)
Pacemaker	1200 (16.1)	1098 (16.4)	76 (12.7)
Musculoskeletal	3299 (44.3)	2931 (43.7)	302 (50.5)
Carpal tunnel syndrome (bilateral or unilateral)	1753 (23.5)	1518 (22.6)	197 (32.9)
Hip replacement	102 (1.4)	95 (1.4)	4 (0.7)
Knee replacement	120 (1.6)	111 (1.7)	6 (1.0)
Spinal stenosis	2212 (29.7)	1988 (29.6)	180 (30.1)
Spontaneous biceps tendon rupture	29 (0.4)	28 (0.4)	1 (0.2)
Neurological	5349 (71.8)	4815 (71.8)	432 (72.2)
Autonomic dysfunction	922 (12.4)	830 (12.4)	78 (13.0)
Chronic constipation	137 (1.8)	123 (1.8)	12 (2.0)
Chronic diarrhoea	71 (1.0)	65 (1.0)	6 (1.0)
Orthostatic hypotension	745 (10.0)	670 (10.0)	63 (10.5)
Erectile dysfunction	1327 (17.8)	1194 (17.8)	99 (16.6)
Gastroparesis	127 (1.7)	115 (1.7)	12 (2.0)
Peripheral neuropathy	2572 (34.5)	2270 (33.9)	268 (44.8)
Stroke/TIA	2782 (37.4)	2566 (38.3)	172 (28.8)
Urinary incontinence	1552 (20.8)	1415 (21.1)	107 (17.9)
Ocular	3764 (50.6)	3412 (50.9)	265 (44.3)
Glaucoma	2304 (30.9)	2072 (30.9)	184 (30.8)
Macular degeneration	1946 (26.1)	1798 (26.8)	102 (17.1)
Optic neuropathy	77 (1.0)	70 (1.0)	7 (1.2)
Vitreous opacity	763 (10.2)	684 (10.2)	61 (10.2)
Renal	3602 (48.4)	3287 (49.0)	244 (40.8)
CKD	3602 (48.4)	3287 (49.0)	244 (40.8)

[a]The sum of the ATTRwt-CM and ATTRv-CM populations does not equal that of the overall population because ATTR-CM type was unknown in 145 patients.

- There were no readily apparent trends observed in the rate or number of clinical manifestations recorded before diagnosis or the time from the first recorded manifestation to diagnosis across subgroups of sex, race/ethnicity, and region
- In the overall population, chronic constipation (a subset of autonomic dysfunction; median, 21.4 months [IQR, 8.2-41.0]) and glaucoma (median, 50.0 months [IQR, 32.7-69.0]) were associated with the shortest and longest times between the recorded clinical manifestation and ATTR-CM diagnosis, respectively (**Figure 2**)
  - Heart failure was associated with a median time of 28.6 months (IQR, 8.3-49.9) from clinical manifestation to diagnosis
  - In patients with ATTRwt-CM, chronic constipation (median, 21.8 months [IQR, 8.7-41.9]) and glaucoma (median, 50.5 months [IQR, 32.9-69.1]) were associated with the shortest and longest times between the recorded clinical manifestation and diagnosis, respectively
  - In patients with ATTRv-CM, chronic constipation (median, 12.5 months [IQR, 4.4-31.3]) and vitreous opacity (median, 47.2 months [IQR, 24.2-61.8]) were associated with the shortest and longest times between the recorded clinical manifestation and diagnosis, respectively

FIGURE 2. Median (IQR) Time From Key Clinical Manifestations to ATTR-CM Diagnosis. (A) Overall, (B) ATTRwt-CM, and (C) ATTRv-CM



- The number of primary care and specialist visits occurring 6 months or 3 years before ATTR-CM diagnosis is summarised in **Table 3**
  - Patients had a median of 9.0 (IQR, 3.0-17.0) primary care physician visits and 10.0 (IQR, 3.0-20.0) specialist visits of interest within 3 years before ATTR-CM diagnosis

TABLE 3. Physician Visits Before ATTR-CM Diagnosis

Characteristic	6 months before diagnosis (N=7509)	3 years before diagnosis (N=7509)
Number of primary care physician visits[a] before diagnosis		
Mean (SD)	2.4 (3.0)	12.0 (12.2)
Median (IQR)	1.0 (0.0, 3.0)	9.0 (3.0, 17.0)
Number of specialist visits[a] of interest[b] before diagnosis		
Mean (SD)	3.2 (3.6)	13.8 (14.1)
Median (IQR)	2.0 (0.0, 5.0)	10.0 (3.0, 20.0)
Number of all specialist[c] visits[a] before diagnosis		
Mean (SD)	6.4 (6.1)	29.6 (25.6)
Median (IQR)	5.0 (2.0, 9.0)	24.0 (11.0, 41.0)
Most common physician types, n (%)		
Primary care physician	4992 (66.5)	6459 (86.0)
Cardiologist	4460 (59.4)	5837 (77.7)
Ophthalmologist	1598 (21.3)	3474 (46.3)
Nephrologist	804 (10.7)	1213 (16.2)
Dermatologist	792 (10.5)	1952 (26.0)
Gastroenterologist	643 (8.6)	2075 (27.6)
Heamatologist-oncologist	526 (7.0)	973 (13.0)
Haematologist	101 (1.3)	202 (2.7)
Hepatologist	12 (0.2)	34 (0.5)
Other specialists	5616 (74.8)	6977 (92.9)

[a]Number of visits was defined as the total number of visits on separate days. Patients could have seen >1 specialist on the same day.
[b]Specialists of interest included cardiologist, dermatologist, gastroenterologist, haematologist, haematologist-oncologist, hepatologist, nephrologist, and ophthalmologist.
[c]All specialists include specialists of interest and any other specialists.

LIMITATIONS

- Time to diagnosis may be underestimated, as the first symptom captured in the database may not have been the first symptom ever experienced by the patient; however, 3 years of continuous enrolment before the index date was required to allow for sufficient follow-up
- Cases of ATTR-CM were not adjudicated individually from the primary data source; however, specificity should be high because ≥2 ICD-10-CM amyloidosis codes and ≥2 ICD-10-CM cardiac codes, or tafamidis prescription, were required
- An ICD-10-CM coding algorithm was used to classify patients into ATTRwt-CM or ATTRv-CM, which may have resulted in misclassification bias
- Patient location was determined by the provider or pharmacy zip code, which may not always accurately reflect the zip code of the patient
- The database provided patient year of birth; therefore, patient age reflects the age the patient will be by the end of the index year. Ages above 89 years (n=59) were masked in the database and recorded as 89 years; as a result, mean ages may be slightly underestimated

DATA AVAILABILITY: The data that support the findings of this study were used under license from Komodo Health® and derived from the Komodo Healthcare Map®. Due to data use agreements and its proprietary nature, restrictions apply regarding the availability of the data. Further information is available from the sponsor of the study, BridgeBio Pharma, Inc., San Francisco, CA, USA.

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ABBREVIATIONS: ACC, American College of Cardiology; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild type transthyretin amyloid cardiomyopathy; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; EKG, electrocardiogram; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation; TIA, transient ischaemic attack; TTR, transthyretin; US, United States.

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DISCLOSURES: JDM: Researcher for Abbott Laboratories and Myocardial Solutions; consultant, advisor and speaker for Alnylam, BridgeBio Pharma, Inc., Jazz Pharmaceuticals, Pfizer, and Race Oncology; **MU** and **LH:** Employees and stockholders of BridgeBio Pharma, Inc. MU is a stockholder of Pfizer; **HDD, MK,** and **EN:** Contractors for BridgeBio Pharma, Inc.; **KMA:** Consultant, advisor and speaker for Arbor Biotechnologies, Attralus, Intellia Therapeutics, and Prothena Biosciences; **RC:** No relevant financial relationships to disclose.

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