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CARDIOVASCULAR SYMPTOM BURDEN PRIOR TO DIAGNOSIS OF TRANSTHYRETIN AMYLOIDOSIS AMONG MEDICARE BENEFICIARIES*

Duncan Brown, PhD[1]; Montserrat Vera Llonch, MD, MPH, MSc[1]; Jose Tomas Ortiz Perez, PhD[2]; Sheila R. Reddy, PhD, RPh[3]; Eunice Chang, PhD[3]; Marian H Tarbox, MPP[3]; Jose Nativi-Nicolau, MD[4]; Nowell M. Fine, MD, SM[5]

Institutions: [1] Akcea Therapeutics, Boston, MA. [2] Amyloidosis and Myeloma Unit, Hospital Clínic Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Universitat de Barcelona. [3] Partnership for Health Analytic Research, LLC, Beverly Hills, CA. [4] School of Medicine, University of Utah, Salt Lake City, UT. [5] University of Calgary, Calgary AB.

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BACKGROUND

- Transthyretin amyloidosis (ATTR) is often associated with cardiovascular (CV) involvement, with CV symptoms occurring sometimes years before diagnosis[1,2]
  - CV symptoms are often misdiagnosed as cardiac conditions that are common in the general population, especially in older patients[3-5]
- Identifying the CV symptoms commonly associated with ATTR could increase earlier diagnosis and intervention, which are essential for prognosis as treatment is most effective when started at early stages of the disease[1]
- The study's aim was to examine CV symptom manifestation and healthcare use leading up to an ATTR diagnosis among Medicare beneficiaries in the US

METHODS

Study Design and Data Source

Retrospective analysis using claims data from the 100% Medicare Research Identifiable Files from 1/1/2011-12/31/2018

Patient Identification

Inclusion criteria

- Patients ≥68 years newly diagnosed with ATTR identified using a claims-based algorithm as follows:
  - Diagnosis required ≥1 inpatient or ≥2 outpatient claims with ATTR ICD-10-CM code (E85.1, E85.2, E85.82) between 2016-2018 (ID period) or other amyloidosis form during ID period plus the following between 2011-2018:
    - ≥1 claim for congestive heart failure (CHF), cardiomyopathy or neuropathy; and no chemotherapy, stem cell transplant, or light-chain amyloidosis claims
  - Study index date was date of first amyloidosis claim in ID period
  - Patients had continuous enrollment in fee-for-service Medicare (Part A/Part B) and in Medicare Part D for 3 years pre-index (look-back period)

Exclusion criteria

- Evidence of amyloidosis during look-back period (ICD-9 or ICD-10 codes) or evidence of dementia at any time in the study period

Disease-free Control Group

- To serve as a reference group, an ATTR-free cohort was created from a 5% random sample of Medicare enrollees who, during the study period, had no diagnosis of amyloidosis
  - ATTR-free patients were matched 1:1 to patients with ATTR based on age, gender, region
- ATTR-free patients were assigned the same index date and had the same enrollment requirements as the matched ATTR patients

Study Measures

- Demographics and Charlson comorbidity index (CCI) measured 1-year pre-index
- Occurrence (first and any observed) of selected CV conditions and of healthcare utilization (all-cause and CV-related hospitalization and emergency department/ED visits) measured during the 3-year look-back period
  - Selected CV conditions of interest: aortic stenosis, CHF, restrictive cardiomyopathy, atrial fibrillation/flutter, hypertrophic cardiomyopathy, ventricular hypertrophy, atrioventricular (AV) block/bradycardia, dyspnea, edema, hypotension, chest pain, coronary artery disease, myocardial infarction
  - CV-related utilization defined by an inpatient or ED visit claim with a primary diagnosis code for a CV condition (CV condition broadly defined to include syncope, stroke, and hemorrhages in addition to the above selection of CV conditions)

RESULTS†

Table 1. Baseline Demographics and Comorbidities During 1-year Pre-index Period

	ATTR N=552	Matched DF Controls[a] N=552	*P* Value
Age, year, mean (SD)	**78.3 (6.3)**	**78.3 (6.3)**	**n/a[b]**
68-69, n (%)	29 (5.3)	29 (5.3)	n/a[b]
70-74	149 (27.0)	149 (27.0)	
75-84	281 (50.9)	281 (50.9)	
85+	93 (16.8)	93 (16.8)	
Female, n (%)	**196 (35.5)**	**196 (35.5)**	**n/a[b]**
Race, n (%)			**<0.001**
White	463 (83.9)	505 (91.5)	
Black	67 (12.1)	30 (5.4)	
Other/Unknown	22 (4.0)	17 (3.1)	
Region			**n/a[b]**
Midwest	149 (27.0)	149 (27.0)	
Northeast	163 (29.5)	163 (29.5)	
South	146 (26.4)	146 (26.4)	
West	94 (17.0)	94 (17.0)	
Charlson comorbidity index, mean (SD)	**3.1 (2.5)**	**2.0 (2.4)**	**<0.001**
Number of chronic conditions, mean (SD)	**5.4 (2.0)**	**4.3 (2.0)**	**<0.001**

ATTR: transthyretin-mediated amyloidosis; SD: standard deviation.
[a] Matched with age, gender, region.
[b] Matched exactly.

Baseline Demographics and Comorbidity During 1-year Pre-Index Period (Table 1)

- Among the 552 matched ATTR-control pairs identified, mean (SD) age was 78.3 (6.3) and 64.5% were male
- Mean (SD) CCI was higher among ATTR patients vs. controls: 3.1 (2.5) vs. 2.0 (2.4)

Selected CV Conditions and Healthcare Utilization During 3-Year Look-Back Period

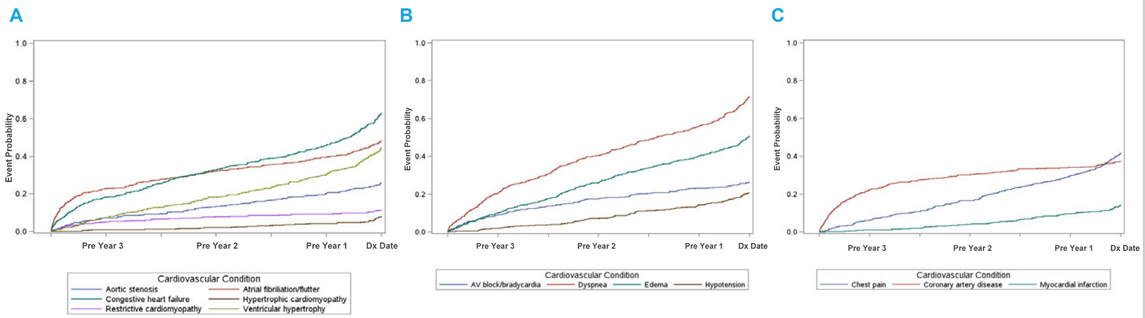
- All of the selected CV conditions were more common among ATTR patients vs. controls during the look-back period compared to controls **(Table 2)**
  - Dyspnea (71.7% vs. 37.7%), CHF (63.0% vs. 21.9%), edema (50.5% vs. 21.9%), atrial fibrillation/flutter (48.4% vs. 23.2%), ventricular hypertrophy (44.9% vs. 14.7%) were the most frequent
  - All observed differences were statistically significant (p<0.05)
  - For patients with ATTR, manifestation of the selected CV conditions was common more than 2 years prior to diagnosis of ATTR (**Figure 1A, 1B, 1C**)
    - Initial CV manifestation before ATTR diagnosis occurred earliest for coronary artery disease (943.9 days; interquartile mean) and atrial fibrillation/flutter (809.2 days) (results not shown)
- Hospitalization (54.0% vs. 35.5%), ED visits (56.0% vs. 43.5%) and cardiac imaging (81.7% vs. 48.2%) were also more frequent among ATTR patients vs. controls
  - CV-related hospitalization (29.7% vs. 11.4%) and CV-related ED visits (22.8% vs. 13.0%) were also more frequent among ATTR patients (results not displayed)

Table 2. Evidence of Cardiovascular Conditions Within 3 Years Prior to ATTR Diagnosis or Index Date

	ATTR N=552	Matched DF Controls[a] N=552	*P* Value	ATTR N=552	Matched DF Controls[a] N=552	*P* Value	ATTR N=552	Matched DF Controls[a] N=552	*P* Value	ATTR N=552	Matched DF Controls[a] N=552	*P* Value
	Aortic Stenosis			**Congestive Heart Failure**			**Restrictive Cardiomyopathy**			**Atrial Fibrillation/Flutter**		
N (%)	**143 (25.9)**	**87 (15.8)**	**<0.001**	**348 (63.0)**	**121 (21.9)**	**<0.001**	**63 (11.4)**	**18 (3.3)**	**<0.001**	**267 (48.4)**	**128 (23.2)**	**<0.001**
First evidence occurred			<0.001			<0.001			<0.001			<0.001
No evidence	409 (74.1)	465 (84.2)		204 (37.0)	431 (78.1)		489 (88.6)	534 (96.7)		285 (51.6)	424 (76.8)	
Pre Y1	50 (9.1)	21 (3.8)		133 (24.1)	25 (4.5)		15 (2.7)	--[b]		70 (12.7)	18 (3.3)	
Pre Y2	40 (7.2)	23 (4.2)		73 (13.2)	31 (5.6)		11 (2.0)	--[b]		43 (7.8)	20 (3.6)	
Pre Y3	53 (9.6)	43 (7.8)		142 (25.7)	65 (11.8)		37 (6.7)	15 (2.7)		154 (27.9)	90 (16.3)	
	Hypertrophic Cardiomyopathy			**Ventricular Hypertrophy**			**AV Block/Bradycardia**			**Dyspnea**		
N (%)	**44 (8.0)**	**--[b]**	**<0.001**	**248 (44.9)**	**81 (14.7)**	**<0.001**	**146 (26.4)**	**97 (17.6)**	**<0.001**	**396 (71.7)**	**208 (37.7)**	**<0.001**
First evidence occurred			<0.001			<0.001			0.002			<0.001
No evidence	508 (92.0)	546 (98.9)		304 (55.1)	471 (85.3)		406 (73.6)	455 (82.4)		156 (28.3)	344 (62.3)	
Pre Y1	26 (4.7)	--[b]		118 (21.4)	27 (4.9)		33 (6.0)	14 (2.5)		126 (22.8)	58 (10.5)	
Pre Y2	11 (2.0)	--[b]		58 (10.5)	26 (4.7)		36 (6.5)	29 (5.3)		100 (18.1)	66 (12.0)	
Pre Y3	--[b]	--[b]		72 (13.0)	28 (5.1)		77 (13.9)	54 (9.8)		170 (30.8)	84 (15.2)	
	Edema			**Hypotension**			**Chest Pain**			**Coronary Artery Disease**		
N (%)	**279 (50.5)**	**121 (21.9)**	**<0.001**	**114 (20.7)**	**62 (11.2)**	**<0.001**	**231 (41.8)**	**142 (25.7)**	**<0.001**	**207 (37.5)**	**163 (29.5)**	**0.005**
First evidence occurred			<0.001			<0.001			<0.001			0.015
No evidence	273 (49.5)	431 (78.1)		438 (79.3)	490 (88.8)		321 (58.2)	410 (74.3)		345 (62.5)	389 (70.5)	
Pre Y1	91 (16.5)	32 (5.8)		51 (9.2)	25 (4.5)		100 (18.1)	52 (9.4)		22 (4.0)	11 (2.0)	
Pre Y2	90 (16.3)	36 (6.5)		41 (7.4)	22 (4.0)		71 (12.9)	49 (8.9)		33 (6.0)	21 (3.8)	
Pre Y3	98 (17.8)	53 (9.6)		22 (4.0)	15 (2.7)		60 (10.9)	41 (7.4)		152 (27.5)	131 (23.7)	
	Myocardial Infarction											
N (%)	**80 (14.5)**	**34 (6.2)**	**<0.001**									
First evidence occurred			<0.001									
No evidence	472 (85.5)	518 (93.8)										
Pre Y1	43 (7.8)	14 (2.5)										
Pre Y2	26 (4.7)	11 (2.0)										
Pre Y3	11 (2.0)	--[b]										

ATTR: transthyretin-mediated amyloidosis; AV: atrioventricular; DF: disease-free; Y: year.
[a] Matched with age, gender, region.
[b] Reported per Centers for Medicare and Medicaid Services (CMS) cell size suppression policy (frequency <11).

Figure 1. First Observed Evidence of Cardiovascular Conditions Within 3 Years Prior to ATTR Diagnosis



ATTR: transthyretin-mediated amyloidosis; Dx: diagnosis.

† Results may have changed from those reported in abstract due to changes in measure definitions.

LIMITATIONS

- Our approach to identifying patients with ATTR has not been validated using medical records
- The 3-year look-back period limited our ability to examine earlier manifestations of disease; however, this length was chosen in order to ensure an adequate sample size
- The study sample had a low representation of patients with the wild-type amyloidosis (ATTRwt) code, as would be expected given recent availability of this code for administrative coding in claims with respect to study period

CONCLUSIONS

- Medicare beneficiaries with ATTR have considerable CV disease burden in the 3 years prior to diagnosis
- Increased awareness of characteristic CV symptoms may lead to earlier diagnosis and prompt intervention

DISCLOSURES

- SRR, EC, and MHT are employees of Partnership for Health Analytic Research, LLC, which was paid by Akcea to perform this research.
- JP: Advisory board fees: Akcea
- JN: Financial: Pfizer, Akcea and Eidos; Grants: Pfizer. Consultant: Pfizer, Eidos, Akcea, and Alnylam
- NF: Consulting/Speakers: honoraria-Akcea, Alnylam, Pfizer; Research support/clinical trial participation: Akcea, Alnylam, Pfizer, Eidos

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dbrown@akceatx.com

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