Transthyretin Amyloid Cardiomyopathy Among Patients With Hypertrophic Cardiomyopathy: Clinical, Cardiac Imaging, and Electrocardiographic Findings From the TTRACK Study

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INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a clinically heterogeneous, progressive, fatal disease caused by the misfolding of TTR protein forming amyloid fibrils that accumulate in the heart and other tissues and organs.[1,2]
- Recognition and diagnosis of ATTR-CM in early stage disease is essential to allow prompt initiation of disease-modifying treatment and improve clinical outcomes.[2]
- Accurate noninvasive ATTR-CM diagnosis can now be achieved using nuclear imaging techniques and monoclonal protein testing in appropriate clinical scenarios, potentially facilitating early diagnosis with low risk.[2,3]
- Despite advances in diagnostic techniques, delayed and missed diagnosis of ATTR-CM are common.[4] Challenges in diagnosing ATTR-CM are due in part to overlapping signs/symptoms with other more common conditions.
- Increased left ventricular (LV) wall thickness, a common finding in ATTR-CM, may be mistaken for hypertrophic cardiomyopathy (HCM) in some patients with undiagnosed cardiac amyloid disease.[2] As a result, greater awareness is needed of the broad spectrum of manifestations that characterize ATTR-CM.
- In this analysis of the TTRACK study, we investigated ATTR-CM–related features that may heighten suspicion of amyloid disease and signal the need for additional screening in older patients with HCM defined based on the 2014 European Society of Cardiology (ESC) guidelines.[5]

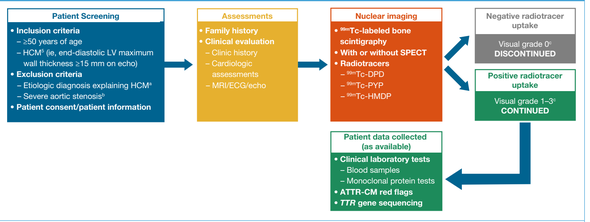
PURPOSE

- To explore clinical, echocardiogram (echo), magnetic resonance imaging (MRI), and electrocardiogram (ECG) findings of older patients with HCM[5] screened for ATTR-CM in the TTRACK study.

METHODS

- Study design: TTRACK was a multicenter, noninterventional, cross-sectional, epidemiologic study (NCT03842163) (**Figure 1**).

Figure 1: TTRACK study flow



[a] Genetic hypertropic cardiomyopathy, Fabry disease, sarcoidosis, any type of amyloidosis.
[b] Aortic valve area <1.0 cm².
[c] Visual grade 0 / 1 / 2 / 3 = absent / low / moderate / high radiotracer uptake.[6]
99mTc=99mtechnetium; 99mTc-HMDP=99mTc-hydroxymethylene diphosphonate; 99mTc-DPD=99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid; 99mTc-PYP=99mTc-pyrophosphate; ATTR-CM=transthyretin amyloid cardiomyopathy; ECG=electrocardiogram; echo=echocardiogram; HCM=hypertrophic cardiomyopathy; LV=left ventricular; SPECT=single-photon emission computed tomography; *TTR*=transthyretin

- Study sites: 20 centers in 11 countries (Australia, Austria, France, Italy, Portugal, Romania, Slovakia, Slovenia, South Korea, Spain, and the UK).
- Final analysis dates: July 2018 and October 2022.
- Main eligibility criteria: Patients ≥50 years of age with HCM based on the 2014 ESC guidelines (end-diastolic LV maximum wall thickness ≥15 mm on echo).[5] Patients with an etiologic diagnosis for HCM were excluded.
- Nuclear image review and grading:
  - A nuclear medicine expert at each center and a centralized independent expert reviewer graded cardiac uptake of radiotracers on each image.
  - A second central reader reviewed images with discrepant grades on the initial reading. The final grade was decided by a consensus of 2 of 3 readers.
  - Nuclear image grading was based on cardiac vs bone radiotracer uptake following the Perugini system (**Table 1**).[6]
  - Grade 2 or 3 (moderate or high) cardiac uptake was categorized as cardiac amyloidosis (CA); grade 2 or 3 and no monoclonal protein abnormalities was categorized as ATTR-CM.[2]
- Analyses: Descriptive statistics were used to analyse all data.

Table 1: Visual grading system for cardiac uptake of bisphosphonate radiotracers and classification of findings

Level of cardiac uptake	Visual grade	Classification	
		CA	ATTR-CM
No cardiac uptake	0	No	No
Low (cardiac uptake less than bone)	1	Undetermined	Undetermined
Moderate (cardiac uptake equal to bone)	2	Yes	Yes/Possible[a]
High (cardiac uptake greater than bone)	3	Yes	Yes/Possible[a]

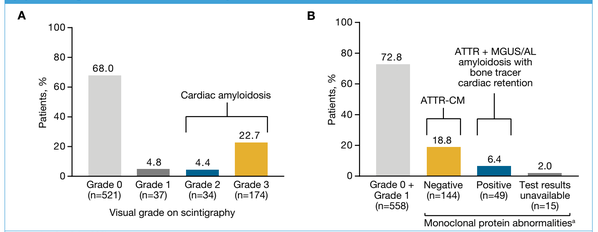
[a] In the absence of monoclonal gammopathy.
ATTR-CM=transthyretin amyloid cardiomyopathy; CA=cardiac amyloidosis

RESULTS

Patient Disposition

- Among eligible patients, 208/766 (27.2%) had CA (**Figure 2A**).
- Among eligible patients, 144/766 (18.8%) had confirmed ATTR-CM (**Figure 2B**).

Figure 2: Patient disposition by (A) visual grade on scintigraphy and (B) visual grade and monoclonal protein test results (n=766)

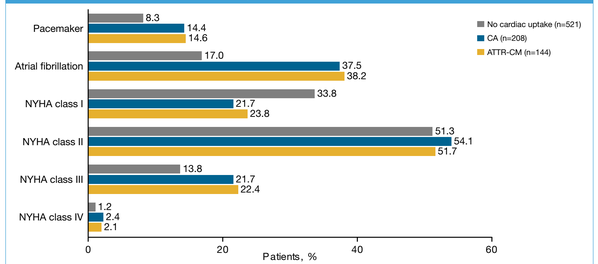


[a] In grades 2 + 3 (n=208).
ATTR-CM=transthyretin amyloid cardiomyopathy; MGUS/AL=monoclonal gammopathy/light chain

Cardiologic Assessment

- Higher proportions of patients with ATTR-CM had pacemakers and atrial fibrillation vs patients with no cardiac uptake on imaging (**Figure 3**).
- Numerical differences in New York Heart Association (NYHA) classification were also observed in patients with ATTR-CM vs patients with no cardiac uptake.
  - Lower proportions of patients with ATTR-CM were asymptomatic (NYHA class I) vs those with no cardiac uptake (23.8% vs 33.8%).
  - Similar proportions in both groups had mild heart failure symptoms (NYHA class II) (51.7% vs 51.3%).
  - Higher proportions of patients with ATTR-CM had more severe heart failure symptoms (NYHA class III/IV) vs patients with no cardiac uptake (24.5% vs 15.0%).

Figure 3: Cardiac characteristics of patients with HCM[5] screened for CA/ATTR-CM



ATTR-CM=transthyretin amyloid cardiomyopathy; CA=cardiac amyloidosis; NYHA=New York Heart Association

Cardiac Imaging and ECG Findings

- Marked numerical differences were observed in some echo findings of patients with no cardiac uptake vs those with CA and ATTR-CM (**Table 2**), including:
  - Mean LV mass index (155.6 vs 177.0 and 179.0 g/m²).
  - % Patients with preserved apical strain (57.9% vs 69.8% and 73.4%).
  - % Patients with a concentric hypertrophic pattern (38.8% vs 77.9% and 77.5%).
  - On echo, LV outflow tract (LVOT) obstruction was most common in patients with no cardiac uptake (18.4%), but it was found in ~13% of patients with ATTR-CM.
- On MRI, a substantially lower proportion of patients with no cardiac uptake (54.7%) had late gadolinium enhancement than those with ATTR-CM (85.0%) (**Table 2**).
- Notable numerical differences were seen between patients with no cardiac uptake vs those with ATTR-CM in 2 parameters on ECG (**Table 3**):
  - PR interval (179.4 vs 197.7 ms).
  - % Patients with poor precordial R wave progression (21.9% vs 48.8%).

Table 2: Cardiac imaging results in patients with HCM[5] screened for CA/ATTR-CM

Parameter	No cardiac uptake (grade 0) n=521	Moderate or high cardiac uptake (grade 2 or 3)	
		CA n=208	ATTR-CM n=144
Echo			
LV ejection fraction, %	61.4 (10.2)	55.2 (11.2)	55.7 (11.2)
LV end-diastolic diameter, mm	44.3 (8.2)	43.2 (7.9)	43.2 (7.5)
Maximal wall thickness, mm	17.6 (2.8)	17.5 (2.4)	17.9 (2.6)
LV mass index, g/m²	155.6 (56.9)	177.0 (53.2)	179.0 (53.1)
Aortic valvular stenosis area, cm²	2.2 (0.9)	2.2 (0.7)	2.3 (0.7)
LVOT obstruction, n (%)	95 (18.4)	22 (10.7)	18 (12.6)
Preserved apical strain, n (%)	84 (57.9)	60 (69.8)	47 (73.4)
Hypertrophic pattern, n (%)			
Apical	33 (6.4)	4 (2.0)	1 (0.7)
Concentric	200 (38.8)	159 (77.9)	110 (77.5)
Asymmetric	274 (53.1)	37 (18.1)	29 (20.4)
Pericardial effusion, n (%)	58 (11.2)	33 (16.0)	21 (14.7)
MRI			
Late gadolinium enhancement, n (%)	81 (54.7)	50 (87.7)	34 (85.0)

Values are mean (SD) unless otherwise specified.
ATTR-CM=transthyretin amyloid cardiomyopathy; CA=cardiac amyloidosis; ECG=electrocardiogram; echo=echocardiogram; HCM=hypertrophic cardiomyopathy; LV=left ventricular; LVOT=left ventricular outflow tract

Table 3: ECG results in patients with HCM[5] screened for CA/ATTR-CM

Parameter	No cardiac uptake (grade 0) n=497	Moderate or high cardiac uptake (grade 2 or 3)	
		CA n=190	ATTR-CM n=133
PR interval, ms	179.4 (33.4)	201.7 (44.9)	197.7 (40.2)
QRS interval	105.8 (23.7)	106.9 (25.3)	105.4 (26.0)
Sokolow index	24.7 (11.1)	18.7 (8.6)	19.5 (8.6)
Poor precordial R wave progression, n (%)	103 (21.9)	83 (46.4)	62 (48.8)
Left bundle branch block, n (%)	37 (7.8)	23 (12.7)	19 (14.8)
Right bundle branch block, n (%)	65 (13.7)	32 (17.7)	19 (14.8)
Intraventricular conduct delay, n (%)	44 (9.3)	32 (17.7)	19 (14.8)

Values are mean (SD) unless otherwise specified.
ATTR-CM=transthyretin amyloid cardiomyopathy; CA=cardiac amyloidosis; ECG=electrocardiogram; HCM=hypertrophic cardiomyopathy

CONCLUSIONS

- In the TTRACK study, ~19% of patients aged ≥50 years with a clinical diagnosis of HCM (based on 2014 ESC guidelines[5]) had findings indicative of ATTR-CM.
- Although some noteworthy differences in clinical, cardiac imaging, and ECG findings were reported between patients with HCM with and without ATTR-CM, none appeared to be definitive.
- These findings suggest diagnostic evaluation of older patients with HCM should not be limited by the assumption that HCM alone is responsible for their presentation. Broader screening for amyloid disease with scintigraphy is warranted in this population.

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DISCLOSURES

PGP: Alexion, Alnylam, AstraZeneca, ATTRalus, Bridgebio, General Electric, Intellia, Ionis, Neurimmune, Novo Nordisk, and Pfizer. **TD:** Alnylam, GlaxoSmithKline, Pfizer, and Prothena. **RBV:** Consultancy fees from Alnylam, Amicus, Bristol Myers Squibb, Chiesi, Cytokinetics, Pfizer, and Sanofi. **NP:** Alnylam and Pfizer. **FC:** Akcea, Alnylam, Novo Nordisk, and Pfizer. **CM, CB, DK,** and **PM:** Employees of Pfizer and hold stock/stock options.

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