Clinical Red Flags Associated With Transthyretin Amyloid Cardiomyopathy in Patients With Unexplained Hypertrophic Cardiomyopathy: Results of the TTRACK study

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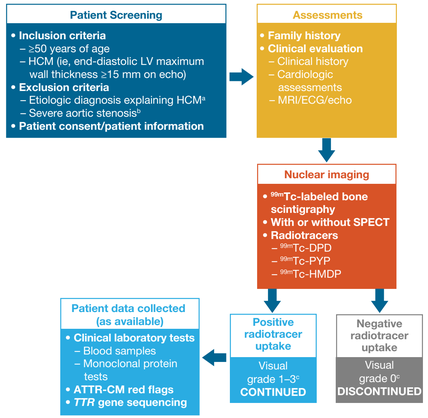
BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal, progressive disease that:
  - has a broad clinical spectrum *and*
  - mimics common cardiac conditions, eg, hypertrophic cardiomyopathy (HCM).[1,2]
- If ATTR-CM remains untreated, median survival after diagnosis is:
  - ~2.6 years in variant disease[3] *and*
  - ~3.6 years in wild-type disease.[4]
- Delayed diagnosis is common in ATTR-CM and can adversely affect cardiac function and quality of life.[5,6]
  - ~40% of patients with the disease have ≥4-year delay after cardiac symptoms present.[3]
  - Many patients visit between 3 and 5 clinicians before they receive an accurate diagnosis.[7]
- Overall ATTR-CM awareness has increased, along with the use of cardiac scintigraphy and monoclonal protein tests for non-invasive diagnosis; however, better recognition of ATTR-CM clinical clues ("red flags") is needed to help identify patients who may benefit from further diagnostic testing.[5]
- Early diagnosis and timely disease-modifying treatment may help improve clinical outcomes.[8]
- The TTRACK study (NCT03842163) was conducted to improve our knowledge of ATTR-CM in older patients with unexplained HCM.
  - In the current analysis, we examined the association between diagnostic red flags and ATTR-CM in the TTRACK population.

METHODS

- Study design: Noninterventional, cross-sectional, epidemiologic study in older patients with unexplained HCM based on 2014 ESC guidelines[9] (**Figure 1**).
- Study sites: 20 centers in 11 countries (Australia, Austria, France, Italy, Portugal, Romania, Slovakia, Slovenia, South Korea, Spain, and UK).
- Final analysis date range: July 2018–October 2022.
- Scintigraphy assessment: Cardiac uptake of bisphosphonate radiotracers (**Table 1**; **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.
^{99m}Tc-DPD / HMDP / PYP=technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid / hydroxymethylene diphosphonate / pyrophosphate; ATTR-CM=transthyretin amyloid cardiomyopathy; ECG=electrocardiogram; echo=echocardiogram; HCM=hypertrophic cardiomyopathy; LV=left ventricular; SPECT=single photon emission computed tomography; *TTR*=transthyretin

Table 1: Visual grading of cardiac uptake on scintigraphy[10]

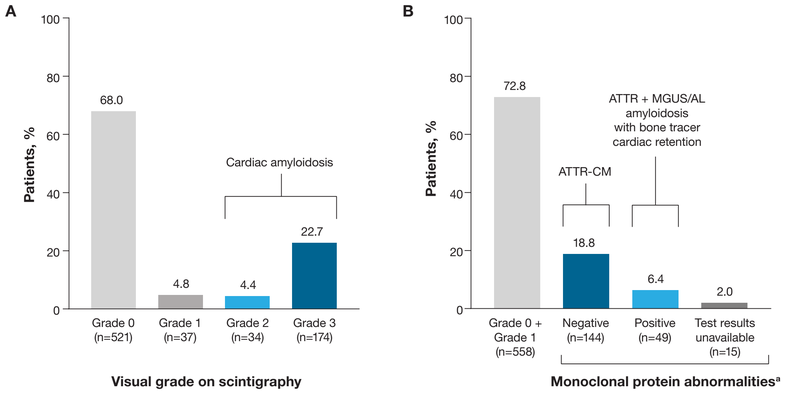
Visual grade	Level of cardiac uptake
0	No cardiac uptake
1	Mild: uptake less than bone
2	Moderate: uptake equal to bone
3	High: uptake greater than bone

RESULTS

Patient Disposition

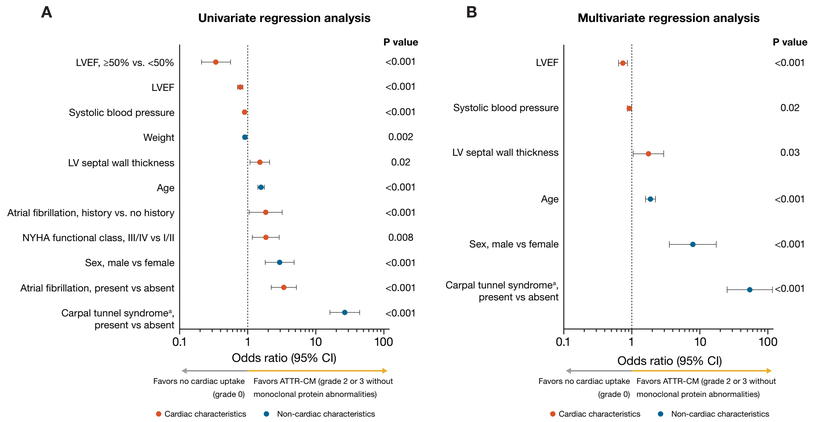
- 766 patients with scintigraphy data were eligible:
  - No cardiac uptake: n=521/766 (68.0%).
  - Cardiac uptake: n=245/766 (32.0%).
- 208/766 (27.2%) patients had moderate or high uptake and were classified as having cardiac amyloidosis (**Figure 2A**).
- 144/766 (18.8%) patients had moderate or high cardiac uptake and negative monoclonal protein findings were classified as having ATTR-CM (**Figure 2B**).

Figure 2: Patient disposition by (A) cardiac uptake on scintigraphy and (B) cardiac uptake and monoclonal protein test findings



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

Figure 3: Predictors of ATTR-CM based on (A) univariate and (B) multivariate regression analysis



[a] Unilateral or bilateral.
ATTR-CM=transthyretin amyloid cardiomyopathy; LV=left ventricular; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; OR=odds ratio

ATTR-CM Predictors (Univariate Regression)

- The strongest cardiac predictors were (**Figure 3A**):
  - Atrial fibrillation, present vs absent: odds ratio (OR) 3.4 (95% CI: 2.2–5.2).
  - Atrial fibrillation, history vs no history: OR 1.8 (95% CI: 1.1–3.2).
  - Severe heart failure, New York Heart Association functional class III/IV: OR 1.9 (95% CI: 1.2–2.9).
- The strongest non-cardiac predictors were (**Figure 3A**):
  - Carpal tunnel syndrome: OR 26.7 (95% CI: 16.1–44.1).
  - Male sex: OR 3.0 (95% CI: 1.8–4.8).

ATTR-CM Predictors (Multivariate Regression)

- The strongest cardiac predictor was (**Figure 3B**):
  - Left ventricular septal wall thickness: OR 1.8 (95% CI: 1.1–2.9).
- The strongest non-cardiac predictors were (**Figure 3B**):
  - Carpal tunnel syndrome: OR 54.3 (95% CI: 25.2–117.1).
  - Male sex: OR 7.9 (95% CI: 3.6–17.5).
  - Age: OR 1.9 (95% CI: 1.6–2.2).

CONCLUSIONS

- In the TTRACK study, nearly 19% (144/766) of patients aged ≥50 years with unexplained HCM (maximal end-diastolic left ventricular wall thickness ≥15 mm on echocardiogram)[10] had scintigraphy and monoclonal protein findings indicative of ATTR-CM.
- Carpal tunnel syndrome, male sex, advanced age, and left ventricular wall thickness were the strongest predictors of ATTR-CM on multivariate regression analysis.
- Additional information about the characteristics of ATTR-CM in older patients with unexplained HCM is needed to improve understanding and facilitate detection of this debilitating but treatable disease.

REFERENCES

1. Garcia-Pavia P, et al. Eur J Heart Fail 2021;23:895-905. **2.** Damy T, et al Eur Heart J 2016;37:1826-34. **3.** Lane T, et al. Circulation 2019;140:16-26. **4.** Grogan M, et al. Am Coll Cardiol 2016;68:1014-20. **5.** Kittleson MM, et al. J Am Coll Cardiol 2023;81:1076-126. **6.** Rozenbaum MH, et al. Cardiol Ther 2021;10:141-59. **7.** Lousada I, et al. J Card Fail 2019;25(8 suppl):S69. **8.** Elliott P, et al. Circ Heart Fail 2022;15:e008193. **9.** Elliott PM, et al. Eur Heart J 2014;35:2733-79. **10.** Perugini E, et al. J Am Coll Cardiol 2005; 46:1076-84.

DISCLOSURES

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

ACKNOWLEDGMENTS

This study was supported by Pfizer. Editorial assistance was provided by Donna McGuire of Engage Scientific Solutions and was funded by Pfizer.

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Presented at the XIX International Symposium on Amyloidosis (ISA), May 26–30, 2024, Rochester, MN, USA