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ORIGINAL ARTICLE

Prevalence and characteristics of transthyretin amyloid cardiomyopathy in hypertrophic cardiomyopathy

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Abstract

Aims Recognition of transthyretin amyloid cardiomyopathy is increasing due to advances in cardiac imaging and diagnostic strategies, but questions remain regarding disease frequency and characteristics. We examined the prevalence and characteristics of transthyretin amyloid cardiomyopathy in older patients with hypertrophic cardiomyopathy of unascertained aetiology.

Methods and results TTRACK was a multicentre, non-interventional, cross-sectional epidemiologic study funded by Pfizer and conducted in 20 hospitals and medical centres in 11 countries (NCT03842163). Eligible patients were aged ≥50 years, had hypertrophic cardiomyopathy (maximal end-diastolic left ventricular wall thickness ≥15 mm on echocardiogram) without an identified genetic or alternative origin at study enrolment, and underwent ^{99m}Technetium bone scintigraphy, with or without single photon emission computed tomography (SPECT). Cardiac-versus-bone uptake on scans was visually scored from 0 to 3 (Perugini scoring). Patients with grades 1–3 underwent monoclonal protein and laboratory testing and transthyretin (*TTR*) gene sequencing. Of 766 eligible patients, 691 (90.2%) had scintigraphy alone and 75 (9.8%) scintigraphy plus SPECT. Two hundred and eight patients (27.2%) had grade 2 or 3 cardiac uptake on scintigraphy; 144 (18.8%) had grade 2 or 3 cardiac uptake and no evidence of plasma cell dyscrasia and were diagnosed with transthyretin amyloid cardiomyopathy. Of patients with transthyretin amyloid cardiomyopathy, 11 (7.6%) had a pathogenic *TTR* gene variant and 34 (23.8%), 74 (51.7%), and 35 (24.5%) had New York Heart Association class I, II, and III/IV heart failure (HF) symptoms, respectively. Clinical and laboratory diagnostic characteristics were observed in ≥90% of patients with transthyretin amyloid cardiomyopathy. The characteristics most strongly associated with transthyretin amyloid cardiomyopathy on multivariable analysis were carpal tunnel syndrome (odds ratio [OR] 54.3; $P < 0.0001$) and male sex (OR 7.9; $P < 0.0001$).

Conclusions In the TTRACK study, almost one in five patients ≥50 years of age with hypertrophic cardiomyopathy had transthyretin amyloid cardiomyopathy. Greater awareness of the frequency and characteristics of transthyretin amyloid cardiomyopathy in older patients with hypertrophic cardiomyopathy are needed to help improve early detection of this debilitating but treatable disease.

Keywords Cardiac amyloidosis; Epidemiology; Hypertrophy; Prevalence; Transthyretin amyloid cardiomyopathy

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Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disease associated with the deposition of amyloid fibrils formed by misfolded transthyretin in the heart and other tissues.[1] The disease has a broad clinical spectrum but is characterized by increased left ventricular (LV) wall thickness (WT) with preserved or impaired LV ejection fraction.[2] ATTR-CM may be linked to pathogenic variants in the transthyretin (*TTR*) gene or may be secondary to deposition of amyloid fibrils originating from native TTR. Familial (variant) ATTR-CM often affects multiple organs and can present in early middle age; nonfamilial (wild-type) ATTR-CM primarily affects the heart, with symptom onset after the age of 60 years.[2,3] The natural history of ATTR-CM is variable and dependent on type, but the prognosis is generally poor,[1] with one-third of symptomatic patients developing heart failure (HF) over 3–4 years as well as other cardiovascular complications, such as heart block and atrial fibrillation.[4] In patients presenting with HF, untreated ATTR-CM is associated with a life expectancy of approximately 2 to 6 years from diagnosis,[5] but lower mortality has recently been reported, which may be linked to greater awareness of the disease and increased diagnosis.[6]

Although ATTR-CM is a recognized contributor to HF in older adults, it continues to be misdiagnosed or diagnosed late in the disease course.[1,7] Technetium (Tc)-labelled cardiac scintigraphy and single photon emission computed tomography (SPECT) are currently recommended for the diagnosis of ATTR-CM in appropriate clinical scenarios,[8,9] but detection also requires greater awareness of the clinical presentations associated with the disease. The TTRACK study was conducted to determine the frequency and characteristics of ATTR-CM in older patients with hypertrophic cardiomyopathy (HCM) defined according to the 2014 European Society of Cardiology (ESC) guidelines and without an already identified aetiology.[10]

Methods

The principles of the Declaration of Helsinki were followed throughout the study. The study protocol, amendments, and informed consent documentation were reviewed and approved by the independent ethics committee/institutional review board for each participating centre. All patients provided written informed consent prior to study enrolment. The study is registered with ClinicalTrials.gov (NCT03842163). The investigators adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (STROBE) in reporting the study.

Study design

TTRACK is a multicentre, non-interventional, cross-sectional, epidemiologic study conducted at 20 centres in 11 countries (*Figure S1*) between July 2018 and October 2022. Inclusion criteria for the study were age ≥50 years and a clinical diagnosis of HCM as defined by the 2014 ESC guidelines[10] (maximal end-diastolic LV WT ≥ 15 mm on echocardiogram). Based on patient history or prior testing, patients were excluded if they were known to have a pathogenic sarcomere gene variant, amyloidosis, other rare disease phenocopies, or severe aortic stenosis, defined as aortic valve area <1.0 cm^2. Eligible patients underwent nuclear imaging with ^{99m}Tc-labelled bone scintigraphy, with or without SPECT, using one of the following bisphosphonate radiotracers: ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), ^{99m}Tc-pyrophosphate (PYP), or ^{99m}Tc-hydroxymethylene diphosphonate (HMDP).

Assessments

Information on demographic and baseline characteristics, family and clinical history, and cardiologic and neurologic assessments was obtained for patients who entered the study. Race and ethnicity were self-reported by patients (supporting information). Cardiologic evaluation included blood pressure measurement, bone scintigraphy, electrocardiogram, and echocardiography. Neurologic evaluation included signs/symptoms of small fibre peripheral neuropathy, autonomic dysfunction, and carpal tunnel syndrome.

Cardiac uptake of scintigraphy radiotracers was graded by a nuclear medicine expert at each centre and a centralized independent expert reviewer. The local and centralized reviewers had access only to patients' scintigraphy/SPECT images, not to any other patient information, but were not blinded to the purpose of the study. If an image received discrepant grades, it was reviewed by a second centralized reader, with the final grade determined by a consensus of 2 of the 3 readers. Radiotracer uptake in the myocardium relative to bone was scored using the 4-point Perugini grading scale: grade 0 denotes no uptake; grade 1, low uptake (cardiac uptake less than bone); grade 2, moderate uptake (cardiac uptake equal to bone); and grade 3, high uptake (cardiac uptake greater than bone).[11]

Patients with cardiac uptake graded 1, 2, or 3 (i.e., low, moderate, or high) underwent standard clinical laboratory testing and screening with serum and urine immunofixation electrophoresis (IFE), serum-free light chain (FLC) assay, and *TTR* gene sequencing. Laboratory diagnostic characteristics were defined as values outside standard reference ranges (supporting information) in patients with data from more than one laboratory blood test.

Monoclonal protein abnormalities were defined by positive IFE findings and/or an abnormal FLC ratio. Based on data

from the iStopMM study[12] and guidance from the American College of Cardiology,[8] post hoc analyses were conducted to apply redefined reference intervals for serum FLC ratios associated with varying degrees of renal impairment (supporting information).

Patients with grade 1 (low) cardiac uptake were classified as having undetermined status. Patients with grade 2 or 3 (moderate or high) cardiac uptake were classified as having cardiac amyloidosis (CA); those with grade 2 or 3 cardiac uptake and no monoclonal protein abnormalities were classified as having ATTR-CM according to guidelines for non-biopsy diagnosis of CA.[8,13,14] Patients with ATTR-CM with and without a pathogenic *TTR* gene variant were classified as having variant and wild-type ATTR-CM, respectively. Patients with grade 2 or 3 cardiac uptake and monoclonal protein abnormalities were classified as having either ATTR-CM plus monoclonal gammopathy of undetermined significance (MGUS) or light chain amyloidosis. Further testing, including biopsy in patients with grade 1 uptake or histological confirmation of the CA subtype in those with grade 2/3 uptake, was not conducted under the TTRACK study protocol due to the noninterventional nature of the study.

Statistical analyses

Assuming ATTR-CM prevalence of ~10%, a sample size of ~1500 patients was estimated to provide precision of ±1.5% in estimating disease prevalence. Due to COVID pandemic-related challenges in recruitment, and despite postponement of the study end date, 812 patients were recruited, with 766 satisfying eligibility criteria for enrolment (*Figure S2*).

Statistical analyses were conducted in all patients who satisfied eligibility criteria and underwent nuclear imaging with radionuclide bone scintigraphy. Descriptive statistics were used to analyse collected data from the assessments already mentioned in this article. Missing data were not imputed.

Concomitant signs/symptoms associated with ATTR-CM (diagnostic characteristics) were analysed using separate univariable logistic regression models for each characteristic; characteristics reaching statistical significance at the 10% level were selected for multivariable analysis. Using backward stepwise regression, characteristics not reaching statistical significance at the 5% level were removed from the multivariable model. Odds ratios (OR) with 95% confidence interval (CI) and *P*-values were calculated from the univariable and multivariable models.

Results

Patient disposition

Among the 766 patients who satisfied eligibility criteria and had nuclear imaging data in the final analysis of the TTRACK study (*Figures S1* and *S2*), scintigraphy alone was conducted in 691 (90.2%), and scintigraphy plus SPECT in 75 (9.8%). ^{99m}Tc-DPD, ^{99m}Tc-PYP, and ^{99m}Tc-HMDP radiotracers were used for nuclear imaging in 326 (42.6%), 94 (12.3%), and 346 (45.2%) patients, respectively.

Of all eligible patients with scintigraphy/SPECT data, 208 (27.2%) had CA based on moderate/high cardiac uptake on the scans (*Figure 1A*). Of these, 144 (18.8%) were identified as having ATTR-CM without evidence of monoclonal gammopathy (*Figure 1B*); 11 (7.6%) had variant ATTR-CM, and 123 (85.4%) had wild-type ATTR-CM (*Figure 1C*). The prevalence of ATTR-CM increased with increasing age, ranging from 5.2% in patients aged 50 to ≤60 years to 33.5% in those aged >80 years; disease prevalence was more than twice as high in males (22.9%) as in females (9.4%) (*Figure S3*). The most common *TTR* gene variants in patients with variant ATTR-CM were V122I (p.V142I [*n* = 4]), I68L (p.I88L [*n* = 2]), and V30M (p.V50M [*n* = 2]) (*Figure 1D*). Forty-nine (6.4%) patients had moderate/high cardiac uptake and monoclonal protein abnormalities (ATTR-CM plus MGUS or light chain amyloidosis).

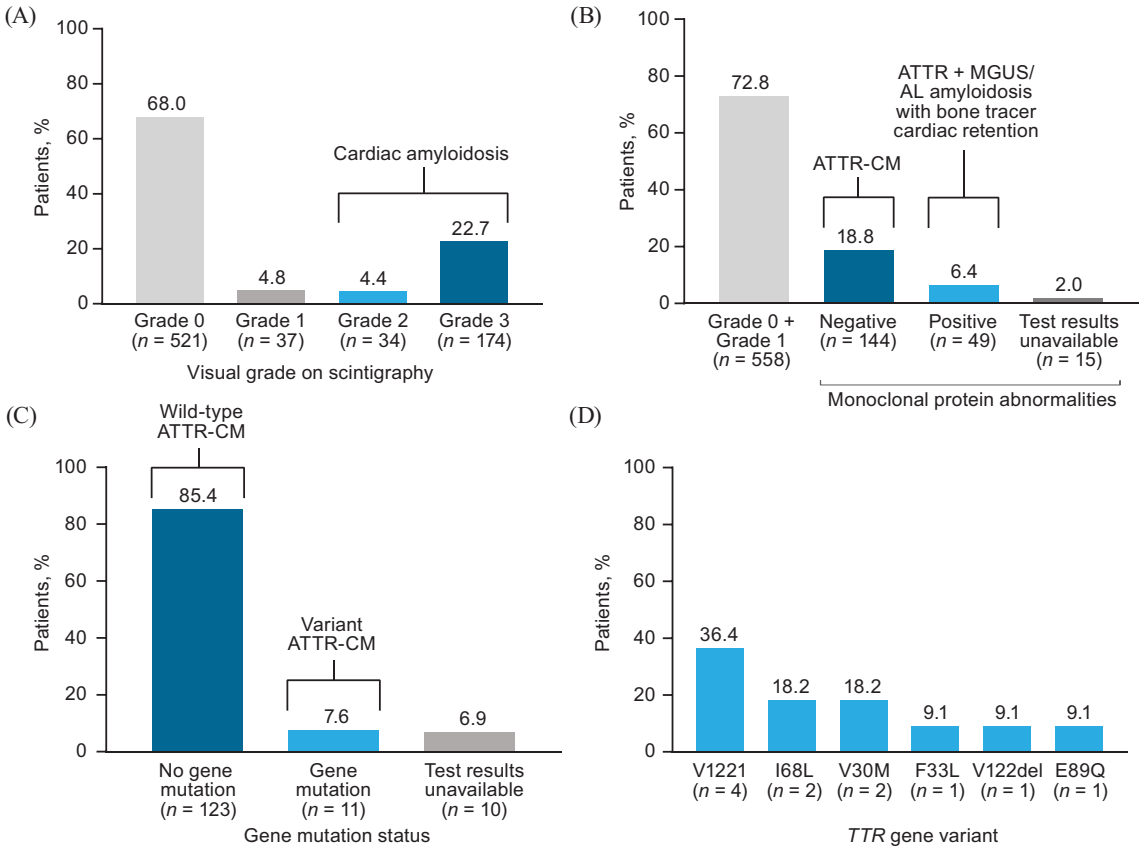
Among eligible patients who underwent scintigraphy/SPECT using ^{99m}Tc-DPD, ^{99m}Tc-PYP, and ^{99m}Tc-HMDP radiotracers, the prevalence of CA was 18.1%, 10.6%, and 40.2%, respectively. The corresponding prevalence of ATTR-CM was 11.7%, 6.4%, and 26.9%.

Of 75 patients undergoing both scintigraphy and SPECT, 25 (33.3%) patients had CA and 18 (24.0%) had ATTR-CM. Of 691 patients with only scintigraphy scans, 183 (26.5%) and 126 (18.2%) had CA and ATTR-CM, respectively. Discordant grades on scintigraphy versus SPECT were observed in 3 (4%) patients. All grading discrepancies were seen on ^{99m}Tc-PYP radiotracer-labelled images between grade 0 on scintigraphy and grade 1 on SPECT and were not considered clinically relevant.

Demographic and clinical characteristics

Patients in the overall study population were a mean (standard deviation [SD]) age of 72.3 (10.6) years, and 69.6% were men (*Table 1*). The mean age of patients with variant and wild-type ATTR-CM was 68.3 (9.3) and 78.6 (8.8) years, respectively, and 82% and 85% were men. Overall, 3.5%, 2.7%, and 93.0% of patients were Asian, Black, and White, respectively; four patients self-reported their ethnicity as Cuban, Armenian, Turk, and Algerian, and two patients chose not to provide this information. Numerical differences in some demographic features were observed in patients with moderate/high cardiac uptake versus patients with no/low cardiac uptake on imaging: patients with grade 2 or 3 uptake were older, were more often male, and had lower weight and body mass index. New York Heart Association (NYHA) functional class I, II, and III/IV symptoms, respectively, were observed in 23.8%, 51.7%, and 24.5% of patients with grade 2 or 3 uptake.

Figure 1 Patient disposition. (A) Visual grade on scintigraphy in patients with scintigraphy data (n = 766). (B) Monoclonal protein test findings in patients with scintigraphy data (n = 766). (C) *TTR* genetic test findings in patients with ATTR-CM (n = 144). (D) *TTR* gene variants in patients with variant ATTR-CM (n = 11). Complete variant names: V122I (p.V142I); I68L (p.I88L); V30M (p.V50M); F33L (p.F53L); V122del (p.V142del); E89Q (p.E109Q).



Patients with ATTR-CM differed in several respects from patients with no cardiac uptake (*Figure 2*). The greatest differences were observed in the history of carpal tunnel syndrome (39.6% vs. 5.6%) and presence of atrial fibrillation (38.2% vs. 17.0%).

Characteristics of transthyretin amyloid cardiomyopathy

Of 144 patients with ATTR-CM, 141 (97.9%), 129 (89.6%), and 139 (96.5%) had cardiologic, neurologic (polyneuropathy), or laboratory characteristics associated with ATTR-CM, respectively (*Figure 3*). Abnormal (i.e., out of reference range) levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T, and B-type natriuretic peptide (BNP) were the most common laboratory diagnostic characteristics. The prevalence of specific neuromuscular and other characteristics observed in patients with ATTR-CM is summarized in *Figure S4*.

On univariable regression analysis, the cardiac characteristics most strongly associated with ATTR-CM were atrial fibrillation (atrial fibrillation present vs. absent, OR 3.4 [95% CI 2.2–5.2]; history vs. no history of atrial fibrillation, OR 1.8 [95% CI 1.1–3.2]) and advanced HF (NYHA functional class III/IV, OR 1.9 [95% CI 1.2–2.9]); the noncardiac characteristics most strongly associated with the disease were carpal tunnel syndrome (OR 26.7 [95% CI 16.1–44.1]) and male sex (OR 3.0 [95% CI 1.8–4.8]) (*Figure 4A*). Laboratory parameters (creatinine, BNP, NT-proBNP, troponin I, and troponin) were not significantly associated with ATTR-CM on univariable regression analysis. On multivariable regression analysis, LV septal WT (OR 1.8 [95% CI 1.1–2.9]) was the cardiac characteristic most strongly associated with ATTR-CM, and carpal tunnel syndrome (OR 54.3 [95% CI 25.2–117.1]), male sex (OR 7.9 [95% CI 3.6–17.5]), and age (OR 1.9 [95% CI 1.6–2.2]) were the non-cardiac characteristics most strongly associated with ATTR-CM (*Figure 4B*).

Discussion

In this analysis of data from the TTRACK study, nearly one in five patients aged ≥50 years with HCM defined based on the 2014

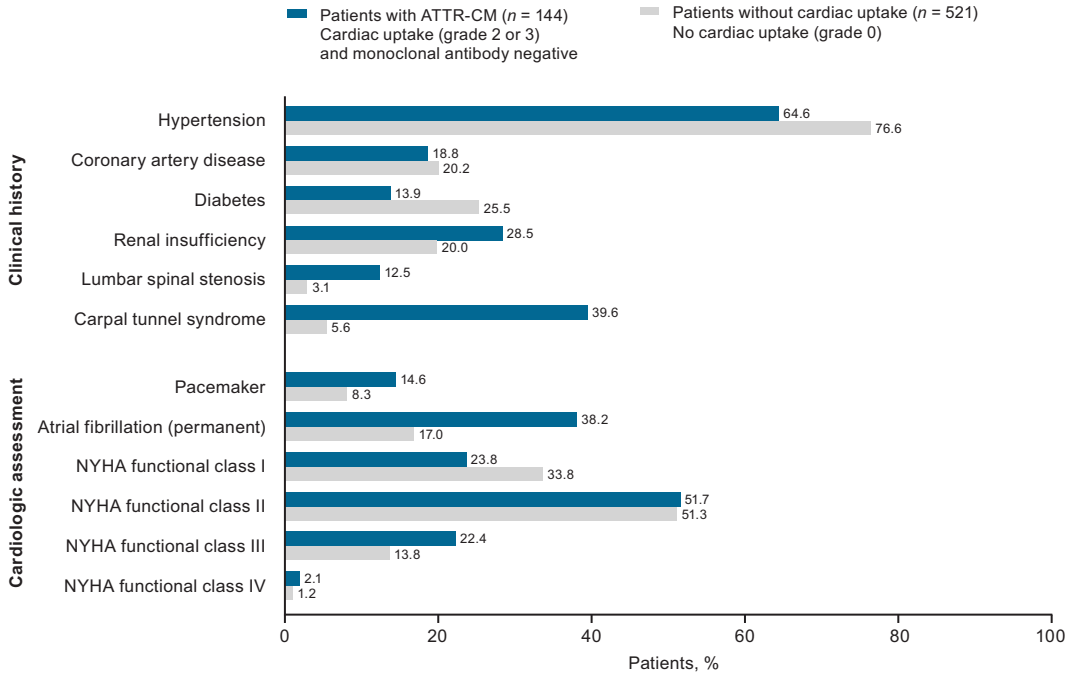
Table 1 Patient demographics and family history, and clinical characteristics by cardiac uptake grade on bone scintigraphy

	Grade 0 (n = 521)	Grade 1 (n = 37)	Grade 2 (n = 34)	Grade 3 (n = 174)	All eligible (n = 766)
Demographics					
Age, mean (SD), years	69.5 (10.1)	72.3 (10.5)	80.3 (9.6)	79.1 (8.5)	72.3 (10.6)
Age range, years, *n* (%)					
50 to ≤60	104 (20.2)	6 (16.2)	1 (2.9)	5 (2.9)	116 (15.3)
61 to ≤70	159 (30.9)	10 (27.0)	4 (11.8)	20 (11.5)	193 (25.4)
71 to ≤80	166 (32.3)	13 (35.1)	11 (32.4)	54 (31.0)	244 (32.1)
>80	85 (16.5)	8 (21.6)	18 (52.9)	95 (54.6)	206 (27.1)
Sex, *n* (%)					
Male	340 (65.3)	23 (62.2)	26 (76.5)	144 (82.8)	533 (69.6)
Female	181 (34.7)	14 (37.8)	8 (23.5)	30 (17.2)	233 (30.4)
Weight, median (IQR), kg	78.0 (67.0–90.0)	85.0 (79.0–96.0)	74.5 (67.0–82.0)	72.0 (66.0–80.0)	76.0 (67.0–88.0)
BMI, median (IQR), kg/m^2	27.4 (24.5–31.4)	30.8 (27.4–35.8)	26.0 (23.7–28.7)	25.4 (23.6–27.6)	26.9 (24.2–30.6)
Race/ethnicity, *n* (%)					
Asian	19 (3.6)	1 (2.7)	0	7 (4.0)	27 (3.5)
Black	15 (2.9)	0	0	6 (3.4)	21 (2.7)
White[a]	481 (92.3)	36 (97.3)	34 (100.0)	161 (92.5)	712 (93.0)
Other[b]	6 (1.2)	0	0	0	6 (0.8)
Family history, *n* (%)					
Parent with cardiomyopathy	39 (7.5)	5 (13.5)	0	6 (3.4)	50 (6.5)
Parent with sudden cardiac death	21 (4.0)	3 (8.1)	1 (2.9)	6 (3.4)	31 (4.0)
Parent with polyneuropathy	2 (0.4)	0	0	0	2 (0.3)
Clinical history/characteristics, *n* (%)[c]					
Hypertension	399 (76.6)	36 (97.3)	21 (61.8)	110 (63.2)	566 (73.9)
Coronary artery disease	105 (20.2)	15 (40.5)	6 (17.6)	40 (23.0)	166 (21.7)
Diabetes mellitus	133 (25.5)	19 (51.4)	9 (26.5)	24 (13.8)	185 (24.2)
Renal insufficiency	104 (20.0)	7 (18.9)	9 (26.5)	52 (29.9)	172 (22.5)
Carpal tunnel syndrome	29 (5.6)	3 (8.1)	9 (26.5)	69 (39.7)	110 (14.4)
Lumbar spinal stenosis	16 (3.1)	0	3 (8.8)	21 (12.1)	40 (5.2)
Maximal end-diastolic LV WT, median (IQR), mm	17.0 (15.0–19.0)	16.0 (15.0–18.0)	16.0 (15.0–18.0)	17.0 (16.0–19.0)	17.0 (15.0–19.0)
Echo parameters, mean (SD)[c]					
LV ejection fraction, %	61.4 (10.2)	54.1 (12.4)	53.4 (12.0)	55.6 (11.0)	59.3 (11.0)
LV end-diastolic diameter, mm	44.3 (8.2)	43.8 (7.8)	43.5 (8.7)	43.2 (7.8)	44.0 (8.1)
Maximal WT, mm					
LV	17.6 (2.8)	17.0 (3.1)	16.8 (2.0)	17.7 (2.5)	17.6 (2.7)
At septum	16.9 (2.7)	16.4 (3.1)	16.6 (1.9)	17.3 (2.8)	17.0 (2.7)
Posterior wall	12.6 (2.8)	14.3 (2.4)	14.3 (2.7)	15.2 (3.0)	13.4 (3.0)
LV mass index, g/m^2	155.6 (56.9)	156.7 (93.4)	162.4 (32.7)	179.3 (55.6)	161.3 (59.8)
Aortic valvular stenosis					
Area[d], cm	2.2 (0.9)	2.5 (0.9)	2.1 (0.8)	2.3 (0.7)	2.3 (0.8)
Gradient, mmHg	10.8 (12.9)	7.5 (5.7)	8.3 (7.4)	6.0 (4.6)	9.3 (11.0)
Maximal aortic velocity, m/s	1.8 (1.0)	1.6 (0.5)	2.1 (2.2)	1.4 (0.5)	1.7 (1.0)
LVOT obstruction[e], *n* (%)	95 (18.4)	4 (11.1)	3 (8.8)	19 (11.1)	121 (16.0)
Preserved apical strain, *n* (%)	84 (57.9)	2 (50.0)	9 (69.2)	51 (69.9)	146 (62.1)
Hypertrophic pattern, *n* (%)					
Apical	33 (6.4)	2 (5.6)	0 (0.0)	4 (2.4)	39 (5.2)
Concentric	200 (38.8)	20 (55.6)	28 (82.4)	131 (77.1)	379 (50.1)
Asymmetric	274 (53.1)	10 (27.8)	5 (14.7)	32 (18.8)	321 (42.5)
Mixed	9 (1.7)	4 (11.1)	1 (2.9)	3 (1.8)	17 (2.2)
Pericardial effusion, *n* (%)	58 (11.2)	8 (21.6)	6 (17.6)	27 (15.7)	99 (13.0)
ECG parameters, mean (SD)	Grade 0 (n = 497)	Grade 1 (n = 37)	Grade 2 (n = 30)	Grade 3 (n = 160)	All eligible (n = 724)
Heart rate, b.p.m.	68.9 (14.0)	73.9 (17.3)	74.8 (19.8)	72.9 (13.6)	70.3 (14.5)
Sinus rhythm, *n* (%)	399 (83.0)	21 (60.0)	19 (63.3)	95 (60.9)	534 (76.1)
PR interval, ms	179.4 (33.4)	183.3 (42.7)	200.3 (45.8)	202.1 (45.0)	184.4 (37.7)
QRS interval	105.8 (23.7)	104.3 (25.5)	106.4 (28.9)	107.0 (24.7)	106.0 (24.2)
Sokolow index	24.7 (11.1)	20.8 (9.7)	19.9 (10.6)	18.5 (8.2)	22.9 (10.7)
Pseudo–MI pattern, *n* (%)	71 (15.1)	9 (25.7)	8 (27.6%)	50 (33.1)	138 (20.1)
Poor precordial R wave progression, *n* (%)	103 (21.9)	13 (37.1)	12 (41.4%)	71 (47.3)	199 (29.1)
Left bundle branch block, *n* (%)	37 (7.8)	4 (11.4)	4 (13.8%)	19 (12.5)	64 (9.3)
Right bundle branch block, *n* (%)	65 (13.7)	4 (11.4)	4 (13.8%)	28 (18.4)	101 (14.6)
Intraventricular conduct delay, *n* (%)	44 (9.3)	4 (11.4)	6 (20.7%)	26 (17.1)	80 (11.6)

BMI, body mass index; IQR, interquartile range; LVOT, left ventricular outflow tract; MI, myocardial infarction; WT, wall thickness.
[a]Patients of White and Portuguese origin.

[b]Four patients self-reported ethnicity as Cuban, Armenian, Turk, and Algerian; two patients chose not to provide race or ethnicity information.
[c]Unless otherwise noted.
[d]Patients with aortic valve area <1.0 cm^2 were excluded.
[e]As defined by individual centres (not by study protocol).

Figure 2 Prevalence of clinical characteristics. Proportions of patients with clinical characteristics based on clinical history and cardiological assessment among those with HCM who had ATTR-CM and those without cardiac uptake on scintigraphy.



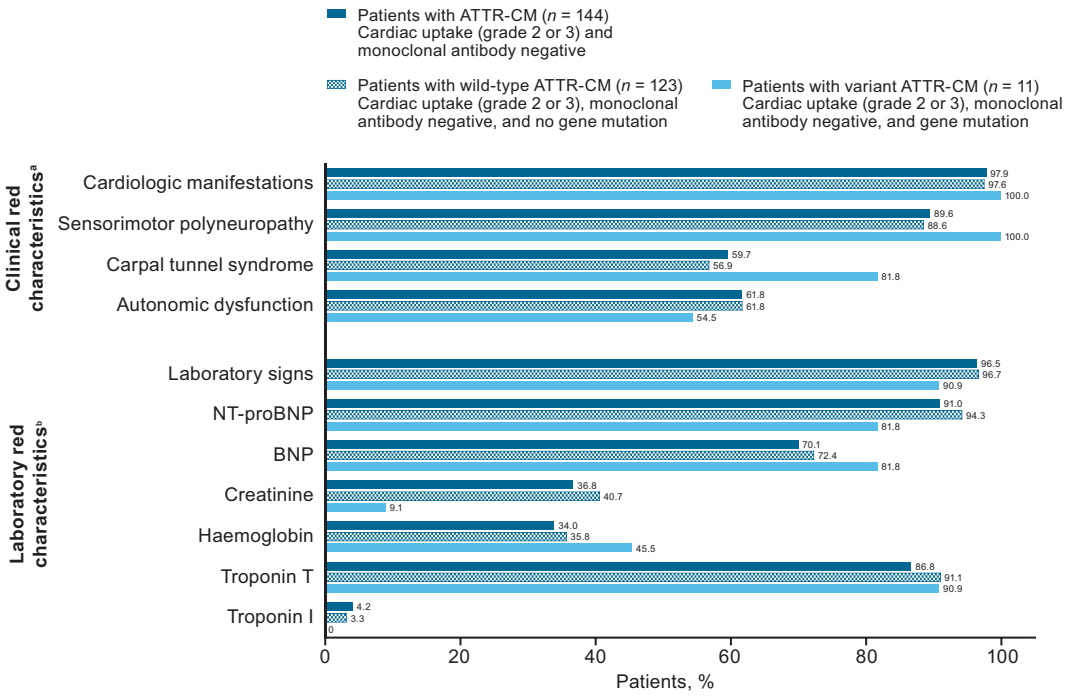
ESC guidelines[10] and without a previously identified aetiology had scintigraphy findings consistent with a diagnosis of ATTR-CM, with an additional 6% of patients having a positive scan in the presence of a monoclonal gammopathy. Cardiologic, neurologic, and laboratory diagnostic characteristics were present in approximately nine of ten patients with ATTR-CM. The characteristics most strongly associated with ATTR-CM were carpal tunnel syndrome, male sex, LV septal WT, and age.

Epidemiology of transthyretin amyloid cardiomyopathy

The TTRACK study is the first study to examine ATTR-CM prevalence in older patients with HCM. In a previous prospective study, Damy et al. investigated the prevalence of variant ATTR-CM in 298 adult (aged >18 years) patients with LV WT ≥ 15 mm of unknown aetiology.[15] They discovered 5% of patients had variant ATTR-CM, all of whom were ≥59 years of age. A lower prevalence of variant ATTR-CM has also been reported in other similar studies using a genetic screening strategy in HCM.[16,17] In the TTRACK study, we investigated the prevalence of variant and wild-type ATTR-CM in patients with a clinical diagnosis of HCM, after applying a minimum age threshold of 50 years. Approximately 19% of patients in this population had ATTR-CM, and among those with the disease, ~8% had variant ATTR-CM (or ~1% of the entire TTRACK study population). Importantly, classical echocardiographic signs described in HCM, such as asymmetric hypertrophy and LV outflow tract obstruction, were observed in patients with ATTR-CM in our cohort (in 20% and 13%, respectively), underscoring the need for clinicians to consider ATTR-CM in patients ≥50 years of age with HCM, irrespective of atypical echocardiography findings.

Our finding that approximately one in five patients aged ≥50 years with HCM had ATTR-CM supports heightened suspicion and screening of patients with signs and symptoms associated with the disease in the community setting and is consistent with published reports in other common clinical scenarios. In a Spanish prospective study of patients ≥60 years of age hospitalized due to HF with preserved ejection fraction (HFpEF) and increased LV WT ≥ 12 mm, 16 of 120 (13%) patients screened using ^{99m}Tc-DPD scintigraphy had ATTR-CM based on moderate to high cardiac uptake.[18] More recently, in a co-

Figure 3 Prevalence of clinical and laboratory diagnostic characteristics. Proportions of patients with clinical and laboratory diagnostic characteristics among those with either type of ATTR-CM, wild-type ATTR-CM, and variant ATTR-CM. [a]At least one diagnostic characteristic in the category. [b]Laboratory values out of reference range, defined as: creatinine <0.51 mg/dL or >1.18 mg/dL (<45 μmol/L or >104 μmol/L); haemoglobin <11.5 g/dL or >16.0 g/dL (<115.0 g/L or >160.0 g/L); BNP > 100 pg/mL (>100 ng/L); NT-proBNP >125 pg/mL (>125 ng/L); troponin I > 26 pg/mL (>0.03 μg/L); and troponin T > 14 pg/mL (>0.01 μg/L).



hort of Swedish patients with HF who had a mean age of 76 years and increased myocardial WT (intraventricular septum >14 mm), Lindmark et al. reported that 25 of 174 (14%) had wild-type ATTR-CM after screening with DPD scans.[19] In a US population-based cohort study examining the prevalence of ATTR-CM in ambulatory patients ≥60 years of age with HFpEF and ventricular WT ≥ 12 mm, 18 of 286 (6%) patients had ATTR-CM based on ^{99m}Tc-PYP scanning, with prevalence rising to 10% in the 149 older men included in the study.[20] Finally, in an Italian prospective study, Merlo et al. found that ATTR-CM was diagnosed in 51 of 217 patients (24%) who were ≥55 years of age, had non-dilated, hypertrophic (interventricular WT ≥ 12 mm in women and ≥13 mm in men) hearts with preserved LV ejection fraction, and had ≥1 echocardiographic characteristic suggestive of amyloid cardiomyopathy.[21]

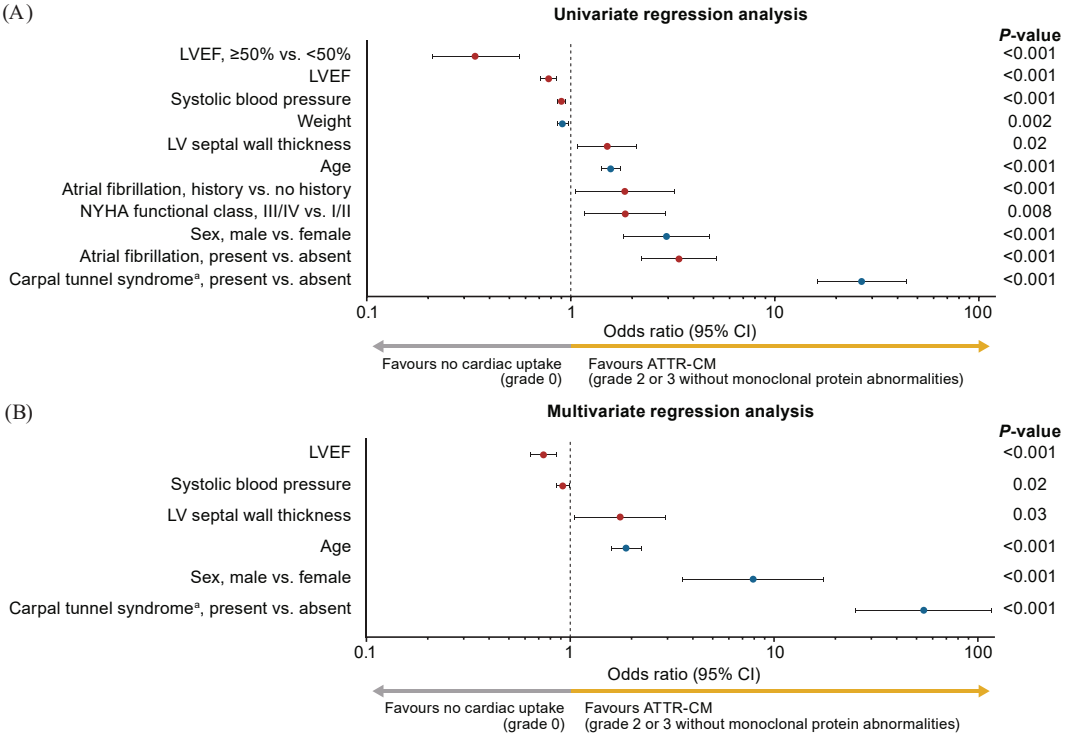
Findings from a recent meta-analysis of ATTR-CM screening studies showed an estimated prevalence of ATTR-CM of 12% among patients with HFpEF and increased cardiac WT.[22] Of note, in the two ATTR-CM screening studies conducted in patients with HCM identified in this meta-analysis, the reported prevalence of ATTR-CM was 7%. The higher prevalence found in the TTRACK study may be attributed to the inclusion of patients with HCM who were ≥50 years of age and exclusion of those who already were identified as having a known sarcomeric genetic variant.

Diagnostic characteristics of transthyretin amyloid cardiomyopathy

Nearly one-quarter of the patients with ATTR-CM in this study had no HF symptoms (NYHA functional class I), which highlights the importance of recognizing non-cardiovascular diagnostic characteristics in patients with LV hypertrophy. In a recent, large, retrospective cohort study, Kharoubi et al. found that non-cardiovascular events occurred more frequently as initial manifestations of ATTR-CM than cardiovascular events.[23] For example, non-cardiovascular signs/symptoms (e.g., carpal tunnel syndrome) were reported first in patient histories in 39% and 42% of those with variant ATTR-CM and wild-type ATTR-CM, respectively. We did not investigate temporal trends in the TTRACK study; however, in Kharoubi et al.,[23] patients who initially presented with non-cardiovascular events received a diagnosis of ATTR-CM significantly later than those presenting with cardiovascular events.

Many of the early signs and symptoms associated with ATTR-CM in the current study have been incorporated into diagnostic algorithms, with the goal of improving early diagnosis.[7,24–28] Notably, in patients with HFpEF referred for ^{99m}Tc-PYP scintigraphy, Davies et al. developed and validated a simple score comprised of 6 demographic, clinical, and echocardiographic variables (i.e., age, male sex, hypertension

Figure 4 Diagnostic characteristics associated with ATTR-CM. Association between diagnostic characteristics and ATTR-CM based on (A) univariable and (B) multivariable regression analysis. Red symbols denote cardiac characteristics; blue symbols denote non-cardiac characteristics. [a]Unilateral or bilateral.



diagnosis, ejection fraction, posterior WT, and relative WT) to predict increased ATTR-CM risk.[29] Within a range of −1 to 10, scores ≥6 indicated elevated risk warranting additional testing. In a *post hoc* analysis, 88% and 85% of patients with CA and ATTR-CM, respectively, in the TTRACK population had scores ≥6 (mean [SD] scores: 7.5 [1.5] and 7.4 [1.5]), suggesting the tool's potential utility in older patients with HCM of unascertained aetiology.

Although the above-mentioned ATTR-CM risk score did not include carpal tunnel syndrome as a variable, carpal tunnel syndrome is a well-recognized risk factor for this disease, with prevalence ranging from 13% to 55% in studies of patients with wild-type ATTR-CM.[3,30,31] Recently, in a Danish registry study, the probability of amyloidosis was reported to be >12 times higher in patients undergoing surgery for carpal tunnel syndrome than in matched controls from the general population.[32] Carpal tunnel syndrome also serves as a prognostic marker in TTR-related amyloidosis, regardless of cardiac involvement, and precedes the diagnosis of CA by 5 to 9 years.[33] Given these findings, carpal tunnel syndrome was included in another recently developed prognostic model and score (the 'T-Amylo') to improve prediction capacity.[34]

The associations between male sex, age, and ATTR-CM are also well known.[35–37] However, Grogan et al. reported that 9% of patients diagnosed with wild-type ATTR-CM pre-mortem were women, rising to 31% of those diagnosed post mortem.[3] In a recent literature review of studies that included >4500 patients with ATTR-CM, 17% were women.[38] In the latter analysis, women comprised 29% and 18% of patients with variant ATTR-CM and undefined disease, respectively, compared with 9% of those with wild-type ATTR-CM. Similarly, the disease does not exclusively affect the elderly, as earlier reports include patients as young as 47 years old at diagnosis.[3,39]

Limitations

Several limitations should be considered when interpreting the findings of the TTRACK study, specifically, the prevalence and diagnostic characteristics of ATTR-CM. First, we cannot exclude a substantial selection bias. Although patients with known pathogenic sarcomere gene variants were excluded from the study, previous genotyping for these variants was not required by study protocol and this information was not collected. It is unknown how many of the participants had been previously genotyped, and accordingly we cannot determine how this could have enriched the patient population towards a more likely ATTR-CM diagnosis or affected the association between diagnostic characteristics and ATTR-CM.

Moreover, other types of selection bias may have been possible. The numbers of patients presenting to each study centre or referred from other practices, and details related to preliminary screening elsewhere, were not collected. The study protocol stipulated enrolment of consecutive patients who presented at the centres and satisfied eligibility criteria, but some variability in enrolment practices likely occurred. Although investigators at large referral/research centres enrolled primarily new patients, investigators at smaller centres may also have enrolled existing patients.

Other factors that might have influenced the observed ATTR-CM prevalence include lack of SPECT in most patients (~90%), the absence of endomyocardial biopsies in patients with scintigraphy uptake and monoclonal abnormalities, and HCM-related inclusion/exclusion criteria of the study. SPECT was not required by study protocol as study planning and initiation preceded the publication of guidelines recommending both planar and SPECT images in patients with cardiac uptake on scintigraphy.[8] ATTR-CM prevalence was higher in patients with both scintigraphy and SPECT scans than in all patients (24% vs. 19%), but the clinical relevance of these findings is unclear. Variability in findings based on the individual radiotracers used, with ATTR-CM prevalence ranging from 6% (^{99m}Tc-PYP) to 27% (^{99m}Tc-HMDP), should also be interpreted with caution. At some study centres, based on their standard of care, biopsy in patients with grade 1 uptake or histological confirmation of the CA subtype in those with grade 2/3 uptake was conducted; however, these procedures were not required under the TTRACK study protocol due to the noninterventional nature of the study. Finally, eligibility criteria stipulated that patients have HCM defined as maximal end-diastolic LV WT $\geq$ 15 mm on echocardiogram (based on 2014 ESC guidelines[10]), in the absence of known aetiologic conditions. However, given the diverse aetiology of HCM, all possible aetiologies may not have been excluded at all centres, resulting in a potentially broad population of patients with the condition participating in the study.

The desired sample size of approximately 1500 patients was not achieved in this study in large part due to the Covid pandemic. Although the final sample size of 766 patients is smaller than originally sought, it nonetheless offered a rare opportunity to examine the prevalence and clinical characteristics of ATTR-CM in a large population of patients with HCM. Finally, although the TTRACK study was conducted in 11 countries across 3 continents, with some study centres located in countries with a high number of Black patients (in whom 3–4% are carriers of V142I variant), most patients studied were White. Accordingly, our findings cannot be extrapolated to populations in other countries with different racial composition. Similarly, our results are not generalizable to populations of younger individuals (<50 years of age).

Conclusions

This large, multinational, epidemiologic study suggests ATTR-CM is underdiagnosed in patients aged ≥50 years with a clinical diagnosis of HCM. Greater awareness of the frequency and characteristics of ATTR-CM in older patients with unexplained HCM is needed to help improve early detection of this debilitating but treatable disease.

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Conflict of interest

Pablo Garcia-Pavia reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bridgebio, General Electric, Intellia, Neurimmune, Novo Nordisk, and Pfizer; and research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, Intellia, Novo Nordisk, and Pfizer. Thibaud Damy has received consulting fees from Alnylam, GlaxoSmithKline, Pfizer, and Prothena; honoraria from Alnylam, Pfizer, and Prothena; research grants from GlaxoSmithKline and Pfizer; and clinical trial support from Alnylam, Ionis, and Pfizer. Nicolas Piriou has received consultancy fees from Pfizer and speaker fees from Alnylam and Pfizer. Roberto Barriales-Villa has received speaking and consultancy fees from Alnylam, Amicus, Bristol Myers Squibb, Chiesi, Cytokinetics, Pfizer, and Sanofi. Francesco Cappelli has received honoraria for advisory board participation from Akcea, Alnylam, Pfizer, and Novo Nordisk; and unconditional research grants from Pfizer. Catherine Bahus, Carmen Munteanu, Denis Keohane, and Pablo Mallaina are employees of Pfizer and hold Pfizer stock/stock options. Perry Elliott has received consultancy fees from Alnylam and Pfizer; and educational grants from Pfizer. Pfizer contributed to the design and conduct of the study and collection and management of data. In their role as authors, employees of Pfizer were involved in the analysis and interpretation of data, preparation, review, and approval of the manuscript and the decision to submit for publication, along with their co-au-

thors. The study sponsor approved the manuscript from an intellectual property perspective but had no right to veto the publication.

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Data availability statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Patient Participation in the TTRACK Study by Country.
Figure S2. Patient Disposition in the TTRACK Study.
Figure S3. Prevalence of ATTR-CM by Age and Sex.
Figure S4. Prevalence of Neuromuscular and Other Characteristics Associated With ATTR-CM in Patients With HCM.

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