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ORIGINAL ARTICLE

Nuclear imaging and echocardiographic findings in hypertrophic cardiomyopathy with and without ATTR-CM

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Abstract

Aims Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) often experience delayed diagnosis, which may detrimentally impact clinical outcomes. This study aimed to assess the frequency of use of planar scintigraphy with and without single-photon emission computed tomography (SPECT) in patients with hypertrophic cardiomyopathy (HCM) screened for ATTR-CM in the TTRACK study. Variability in readings based on different readers, tests and radiotracers used in cardiac nuclear imaging, and differences in echocardiogram findings between patients with and without ATTR-CM were explored.

Methods Patients aged ≥50 years with HCM (left-ventricular wall thickness ≥15 mm without an identified cause) underwent diagnostic technetium-99m [^{99m}Tc]Tc-DPD [3,3-diphosphono-1,2-propanodicarboxylic acid], -PYP [pyrophosphate] and -HMDP [hydroxymethylene diphosphonate]–labelled planar bone scintigraphy with or without SPECT. Cardiac-versus-bone uptake on images was visually graded (Perugini, 0–3) by onsite and central readers (discrepancies resolved by consensus). Patients with grade 1–3 cardiac uptake underwent monoclonal protein testing.

Results Of 766 eligible patients (mean age ± standard deviation, 72.3 ± 10.6 years, 69.6% male), 691 (90.2%) had planar imaging alone and 75 (9.8%) planar plus SPECT imaging. Cardiac uptake was observed on imaging in 245 patients (32.0%); grades 1, 2 and 3 were assigned in 37 (4.8%), 34 (4.4%) and 174 (22.7%), respectively. Initial cardiac uptake grading for planar scintigraphy by onsite readers was strongly concordant with consensus decisions [κ coefficient, 0.84 (95% confidence interval 0.81–0.88)]. Grading for planar versus SPECT imaging was very strongly concordant [0.93 (95% confidence interval 0.86–1.00)]; discordant findings were only observed with [^{99m}Tc]Tc-PYP. Compared with patients with no cardiac uptake, patients with ATTR-CM had a lower mean left ventricular (LV) ejection fraction (55.7% vs. 61.4%; $P < 0.001$), higher mean LV mass index (179.0 vs. 155.6 g/m^2; $P < 0.01$), a higher rate of preserved apical strain (73.4% vs. 57.9%; $P < 0.05$) and differences in hypertrophic pattern ($P < 0.001$), such as a higher rate of concentric hypertrophic pattern (77.5% vs. 38.8%;). Clinical overlap between patients with ATTR-CM and those without cardiac uptake was high.

Conclusions In this real-world study, a high level of concordance was seen in cardiac uptake grading on planar versus SPECT imaging, with discordant findings only observed with [^{99m}Tc]Tc-PYP. The findings support the use of these imaging tools to facilitate ATTR-CM screening in clinical practice. Further studies should investigate differences across tracers used in ATTR-CM screening. NCT03842163.

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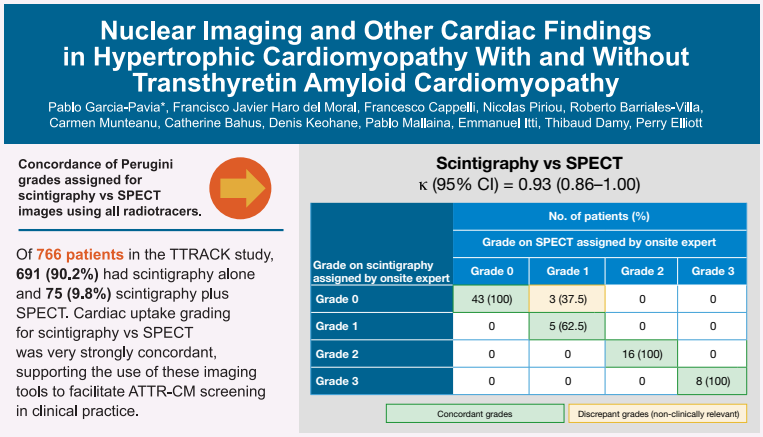
Graphical Abstract



Keywords echocardiogram; hypertrophic cardiomyopathy; scintigraphy; SPECT; transthyretin amyloid cardiomyopathy

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Introduction

Cardiac amyloidosis is a rare disease characterized by the extracellular deposition of misfolded proteins in the heart and other organs and tissue.[1–3] Cardiac amyloidosis is most frequently caused by the misfolding of either monoclonal immunoglobulin light-chain amyloid produced in bone marrow plasma cell disorders or transthyretin (TTR) amyloid synthesized predominantly in the liver in wild-type and variant TTR amyloidosis.[3] Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal, progressive condition with a heterogeneous clinical presentation that may mimic other, more common cardiac conditions, including hypertrophic cardiomyopathy (HCM).[4–7] Although the natural history of ATTR-CM is variable, the prognosis associated with untreated disease has been traditionally considered to be poor, with a median reported survival of 2.6 years in patients with the V122I genotype and 3.6 years in patients with wild-type TTR cardiac amyloidosis.[8,9]

Because of the broad clinical spectrum of ATTR-CM and low awareness of amyloid disease-related diagnostic red flags, most individuals with ATTR-CM do not receive a timely diagnosis.[10–12] In a patient-experience survey, a correct diagnosis was achieved within 6 months of symptom onset in only 35% and 46% of patients with hereditary and wild-type ATTR amyloidosis, respectively.[13] In a large, prospective, observational study, 42% of patients with wild-type ATTR-CM had a delayed diagnosis of at least 4 years after presenting with cardiac symptoms.[8] Many patients visited three to five different physicians before receiving a diagnosis, and more than 40% were misdiagnosed.[14] In a descriptive European study, 35% of patients with wild-type ATTR had been previously misdiagnosed with other conditions, including, most frequently, hypertensive heart disease and HCM.[15] The clinical consequences of misdiagnosis or delayed diagnosis of ATTR-CM have not been well studied, but evidence suggests detrimental effects on heart failure symptomatology, other markers of cardiac function, and quality of life.[12]

Non-invasive technetium (Tc)-labelled planar cardiac scintigraphy and single-photon emission computed tomography (SPECT) are recommended for the non-invasive diagnosis of ATTR-CM in appropriate clinical scenarios, after screening for monoclonal proteins.[3,11] The use of these nuclear imaging techniques in patients with suspected ATTR-CM has several benefits, including high sensitivity and specificity, facilitation of early diagnosis with low risk and ease of access. Although nuclear imaging has rapidly become a cornerstone of non-invasive ATTR-CM diagnosis, experience with its usage, interpretation and performance in clinical practice is limited, and comparisons across radiotracers have been seldom performed.

The TTRACK study was an international multicentre, cross-sectional, non-controlled, non-interventional epidemiologic study conducted to determine the prevalence and characteristics of ATTR-CM in older patients with HCM of unascertained aetiology. Because increased left ventricular (LV) wall thickness in ageing patients with undiagnosed ATTR-CM is often mistaken for HCM, findings from the TTRACK study may increase awareness of the broad spectrum of features that characterize amyloid disease in patients with this concomitant illness.

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In the current analyses, we examined the frequency of use of planar scintigraphy with and without SPECT imaging and the frequency of use of specific radiotracers in patients who participated in the TTRACK study. Variability in readings was evaluated based on the different readers, tests and radiotracers employed in cardiac nuclear imaging. We also explored differences in characteristics of patients with and without ATTR-CM observed on echocardiogram (echo), magnetic resonance imaging (MRI) and electrocardiogram (ECG) assessments to identify features that may raise the index of suspicion for ATTR-CM and signal the need for additional screening.

Methods

The methodology of the TTRACK study (ClinicalTrials.gov: NCT03842163) was published previously[7] (see summary in *Figure* S1). Information relevant to the current analyses is presented in the following sections.

Study population

The TTRACK study included patients ≥50 years of age who had a clinical diagnosis of HCM, as defined by the 2014 European Society of Cardiology guidelines (maximal end-diastolic LV wall thickness ≥15 mm on echocardiogram).[16] Based on patient history or previous testing, patients with known pathogenic sarcomere gene variants, amyloidosis, other rare disease phenocopies or severe aortic stenosis (defined as aortic valve area <1.0 cm^2) were excluded. Eligible patients underwent nuclear imaging with technetium-99m [^{99m}Tc]-labelled planar bone scintigraphy, with or without SPECT imaging, using the bisphosphonate radiotracers [^{99m}Tc]Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), [^{99m}Tc]Tc-pyrophosphate (PYP) or [^{99m}Tc]Tc-hydroxymethylene diphosphonate (HMDP).

Assessments

Information from cardiac assessments was obtained from eligible patients who entered the study. Cardiac evaluation included planar bone scintigraphy, with or without SPECT imaging, in all patients, and echo, MRI and ECG in patients at centres where these tests were available. SPECT imaging was optional, not mandatory, per the study protocol, conducted according to the standard of care at each centre, regardless of the radiotracer used.

An expert in nuclear medicine at each participating centre and a centralized independent expert reviewer graded cardiac uptake of radiotracers on planar scintigraphy and SPECT scans. Images with discordant grades were adjudicated by a second centralized reader; the final grade was decided by a majority consensus of three reviewers. Radiotracer uptake in the myocardium relative to bone was scored using the Perugini grading scale: Grade 0, 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).[17]

Additional follow-up testing, including serum and urine immunofixation electrophoresis and serum free light-chain assay to identify monoclonal protein abnormalities, was performed in patients with cardiac uptake graded 1, 2 or 3. Patients with Grade 2 or 3 (moderate or high) cardiac uptake were classified as having cardiac amyloidosis. Patients with cardiac amyloidosis who were negative for monoclonal protein abnormalities were categorized as having non-invasively confirmed ATTR-CM. Patients with cardiac amyloidosis who were positive for monoclonal protein abnormalities, categorized as having ATTR and a monoclonal gammopathy of undetermined significance or immunoglobulin light-chain amyloidosis, were discontinued from the study.

Analyses

Descriptive statistics were used to summarize data from all assessments. The frequency of use of [^{99m}Tc]Tc-3,3-DPD, [^{99m}Tc]Tc-PYP and [^{99m}Tc]Tc-HMDP radiotracers for planar and/or SPECT imaging was analysed by the participating country (Australia, Austria, France, Italy, South Korea, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom). The frequency of cardiac uptake Grades 0 to 3 on planar scintigraphy, as well as cardiac amyloidosis and ATTR-CM categorization, was analysed by the performance of planar imaging alone versus planar plus SPECT imaging and by the individual radiotracers used for nuclear imaging.

Concordance rates were calculated for Perugini cardiac uptake Grades 0 to 3 assigned by onsite readers versus consensus decision, in addition to planar versus SPECT images for all radiotracers combined and individual radiotracers. Concordance in image grading was measured using Cohen's kappa (κ) coefficients [95% confidence interval (CI)]. Coefficients less than 0 were interpreted as discordance; coefficient ranges of 0–0.2, 0.2–0.4, 0.4–0.6, 0.6–0.8 and 0.8–1.0 were interpreted as very light, light, moderate, strong and very strong concordance, respectively. Differences in readings between Grades 0 and 1 were not considered clinically relevant as they do not have diagnostic implications; differences in readings between Grades 0 or 1 versus 2 or 3 were considered clinically relevant due to their potential impact on diagnosis.

Statistical analyses of differences in the characteristics of patients with and without cardiac amyloidosis and ATTR-CM

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seen on echo, MRI and ECG assessments were conducted using the Student's *t* test and χ^2 test for continuous and categorical variables, respectively.

Results

A plain language summary of the main study findings is included as supporting information.

In all, 766 patients [mean age ± standard deviation (SD), 72.3 ± 10.6 years, 69.6% male] who satisfied eligibility criteria and had nuclear imaging data were included in the TTRACK study.[7] Patients' demographics, family history and clinical history were summarized in a previous publication.[7] Most (90.2%) patients underwent planar scintigraphy alone, and most had scans with [^{99m}Tc]Tc-DPD or [^{99m}Tc]Tc-HMDP radiotracers (42.6% and 45.2%, respectively; *Figure 1*). Use of individual radiotracers varied widely across the 11 countries with centres participating in the study (*Figure 2*).

Cardiac amyloidosis and ATTR-CM prevalence

As reported previously, 521 (68.0%) of the 766 patients analysed had no cardiac uptake on planar/SPECT imaging; 208 (27.2%) patients with Grade 2 or 3 cardiac uptake were classified as having cardiac amyloidosis (*Figure 1*).[7] In the latter group, 144 (18.8%) patients who were negative for monoclonal gammopathy were classified as having ATTR-CM.

Among patients in the [^{99m}Tc]Tc-DPD, -PYP and -HMDP subgroups, the frequency of grade 0 cardiac uptake on planar/SPECT imaging was 79.8%, 61.7% and 58.7%, respectively, whereas the frequency of low uptake (Grade 1) was 2.1%, 27.7% and 1.2%, and high uptake (Grade 3), 17.8%, 7.4% and 31.5% (*Figure 3A*). Cardiac amyloidosis rates were 18.1%, 10.6% and 40.2% in the [^{99m}Tc]Tc-DPD, -PYP and -HMDP subgroups, respectively, and ATTR-CM rates were 11.7%, 6.4% and 26.9% (*Figure 3B*).

Concordance in nuclear image grading

The initial grades for scintigraphy scans assigned by onsite expert readers were strongly concordant with the final grades decided by consensus [κ coefficient (95% CI), 0.84 (0.81–0.88); *Table 1*]. Fifty-eight (7.6%) patients had discordant grades assigned by onsite readers versus consensus decisions. Of these, four (0.5%) patients had clinically relevant discordant grades, with images scored 0 or 1 by the onsite expert versus 2 or 3 by consensus decision. One (0.1%) patient's image received Grade 0 based on initial onsite expert review and Grade 2 based on final consensus decision; two (0.3%) images received an initial Grade 0 and a final Grade 3; and one (0.1%) image received an initial Grade 1 and a final Grade 3. Of the 58 patients with discordant grades assigned by onsite readers versus the consensus decision, 16 (2.1%), 15 (2.0%) and 27 (3.5%) patients were in the [^{99m}Tc]Tc-DPD, -PYP and -HMDP subgroups, respectively. Clinically relevant

Figure 1 Patient distribution in the TTRACK study. MGUS/AL, monoclonal gammopathy/L-chain type.

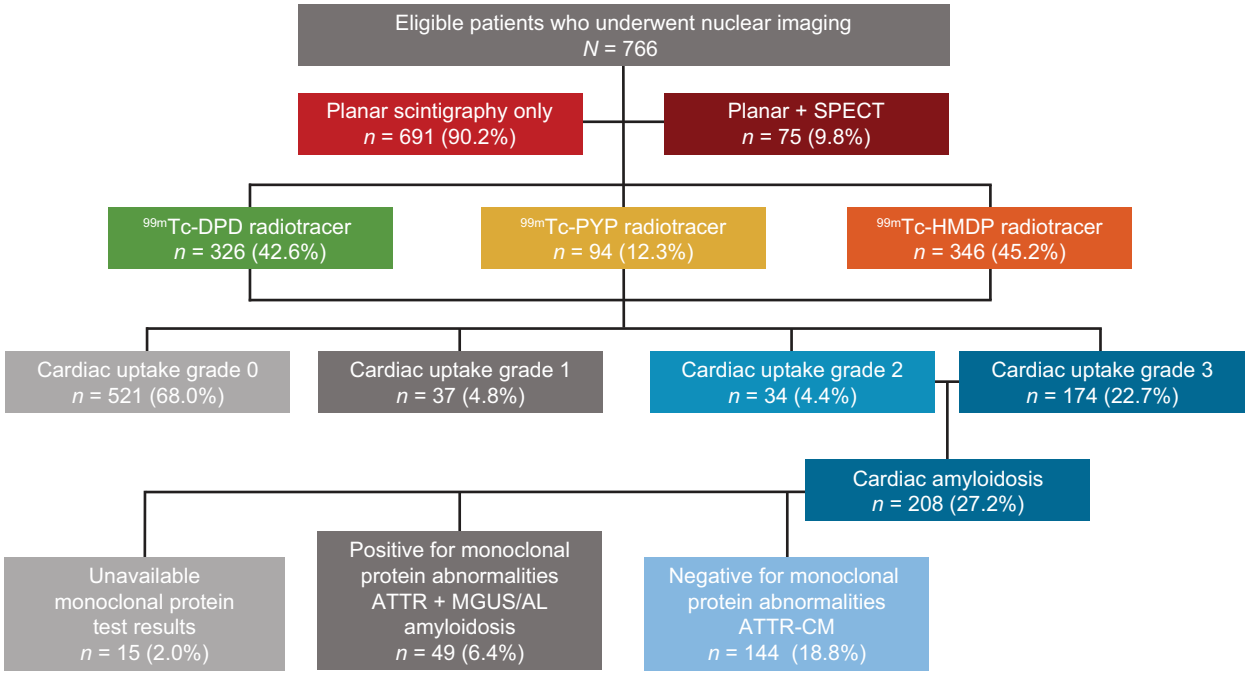

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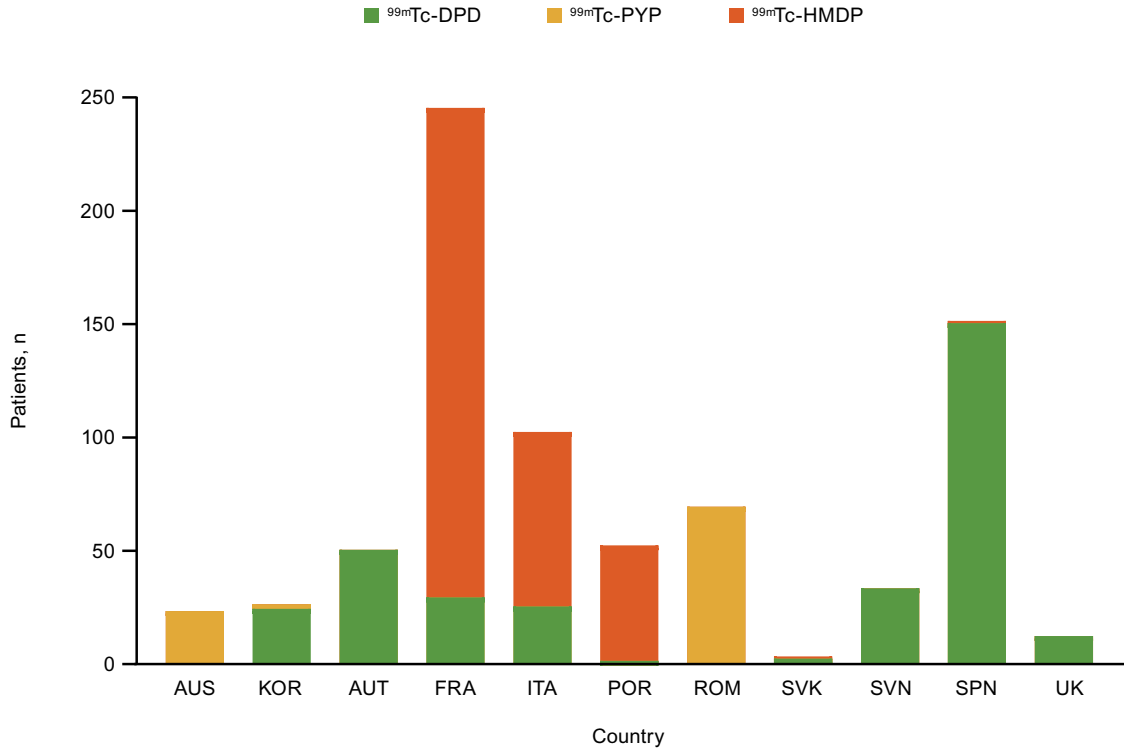
Figure 2 Distribution of individual radiotracers used for nuclear imaging by participating country. ASTL, Australia; KOR, South Korea; AUST, Austria; FRAN, France; ITLY, Italy; PORT, Portugal; ROM, Romania; SVK, Slovakia; SVN, Slovenia; SPN, Spain; UK, United Kingdom.



	AUS	KOR	AUT	FRA	ITA	POR	ROM	SVK	SVN	SPN	UK	Total
^{99m}Tc-DPD	0	24	50	29	25	1	0	2	33	150	12	326
^{99m}Tc-PYP	23	2	0	0	0	0	69	0	0	0	0	94
^{99m}Tc-HMDP	0	0	0	216	77	51	0	1	0	1	0	346
Total	23	26	50	245	102	52	69	3	33	151	12	766

Figure 3 Proportions of patients with (A) Perugini Grades 0–3 for cardiac uptake on bone scintigraphy, (B) amyloid disease by radiotracer used for bone scintigraphy.

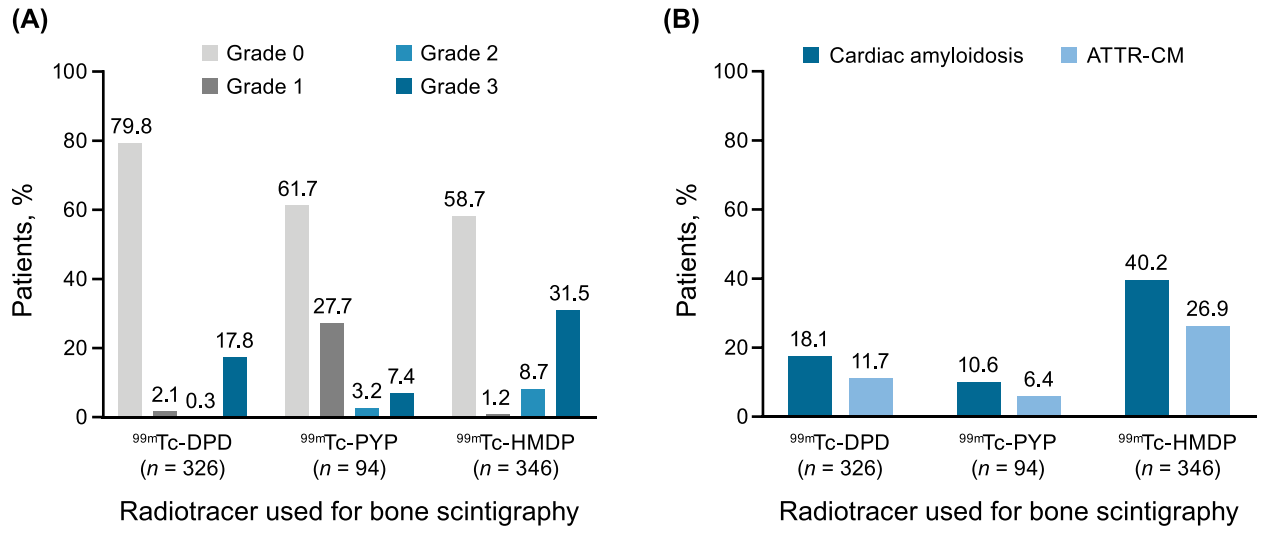


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Table 1 Concordance of Perugini grades assigned for scintigraphy images by the initial onsite reader versus the final consensus decision.

Grade assigned by onsite reader	No. of patients (%)			
	Grade assigned by consensus			
	Grade 0	Grade 1	Grade 2	Grade 3
n	521	37	34	174
Grade 0	517 (99.2)	12 (32.4)	1 (2.9)	2 (1.1)
Grade 1	4 (0.8)	25 (67.6)	0	1 (0.6)
Grade 2	0	0	30 (88.2)	35 (20.1)
Grade 3	0	0	3 (8.8)	136 (78.2)
Concordance, κ (95% CI)	0.84 (0.81–0.88)			

Note: Blue shading denotes concordant grades; light orange shading denotes non-clinically relevant discordant grades (i.e., differences in readings between Grades 0 and 1 or Grades 2 and 3); dark orange shading denotes clinically relevant discordant grades (i.e., differences in readings between Grades 0 or 1 vs. 2 or 3). Coefficient interpretation: <0 = discordance; 0–0.2 = very light concordance; 0.2–0.4 = light concordance; 0.4–0.6 = moderate concordance; 0.6–0.8 = strong concordance; and 0.8–1.0 = very strong concordance.
Abbreviation: CI, confidence interval.

discordant grades were observed in one (0.1%) patient in the [^{99m}Tc]Tc-PYP subgroup [Grade 0 (initial) and Grade 2 (final)] and 3 (0.4%) patients in the [^{99m}Tc]-HMDP subgroup [Grade 1 (initial) and Grade 2 (final), *n* = 1; Grade 0 (initial) and Grade 3 (final), *n* = 2]. No important discordances were observed with [^{99m}Tc]-DPD.

In 75 patients who underwent both types of nuclear imaging, nearly perfect agreement was observed between grading for planar versus SPECT scans [κ coefficient 0.93 (95% CI 0.86–1.00); *Table 2*]. Discordant grades were only observed in 3 (4%) patients and all were in the [^{99m}Tc]Tc-PYP subgroup [κ coefficient 0.55 (95% CI 0.15–0.96)]. The images of these three patients received Grade 0 on planar scintigraphy and Grade 1 on SPECT; the differences were not considered clinically relevant.

Table 2 Concordance of Perugini grades assigned for planar versus SPECT images using all radiotracers and individual radiotracers.

Grade for planar scintigraphy	Grade for SPECT			
	Grade 0	Grade 1	Grade 2	Grade 3
All radiotracers				
n	43	8	16	8
Grade 0	43 (100)	3 (37.5)	0	0
Grade 1	0	5 (62.5)	0	0
Grade 2	0	0	16 (100)	0
Grade 3	0	0	0	8 (100)
Concordance, κ (95% CI)	0.93 (0.86–1.00)			
[^{99m}Tc]Tc-DPD-labelled				
n	27	2	3	5
Grade 0	27 (100)	0	0	0
Grade 1	0	2 (100)	0	0
Grade 2	0	0	3 (100)	0
Grade 3	0	0	0	5 (100)
Concordance, κ (95% CI)	1.00 (1.00–1.00)			
[^{99m}Tc]Tc-PYP-labelled				
n	4	6	0	1
Grade 0	4 (100)	3 (50)	0	0
Grade 1	0	3 (50)	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	1 (100)
Concordance, κ (95% CI)	0.55 (0.15–0.96)			
[^{99m}Tc]Tc-HMDP-labelled				
n	12	0	13	2
Grade 0	12 (100)	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	13 (100)	0
Grade 3	0	0	0	2 (100)
Concordance, κ (95% CI)	1.00 (1.00–1.00)			

Note: Blue shading denotes concordant grades; light orange shading denotes non-clinically relevant discordant grades (i.e., differences in readings between Grades 0 and 1 or Grades 2 and 3); dark orange shading denotes clinically relevant discordant grades (i.e., differences in readings between Grades 0 or 1 vs. 2 or 3). Coefficient interpretation: <0 = discordance; 0–0.2 = very light concordance; 0.2–0.4 = light concordance; 0.4–0.6 = moderate concordance; 0.6–0.8 = strong concordance; and 0.8–1.0 = very strong concordance.
Abbreviation: CI, confidence interval.

Differences in echo, MRI and ECG findings

Marked numerical differences were seen in several echo, MRI and ECG parameters between patients with ATTR-CM and those with no cardiac uptake on planar bone scintigraphy (*Table 3*). Mean (*SD*) LV mass index was higher in patients with ATTR-CM [179.0 g/m^2 (53.1)] than in those with no cardiac uptake [155.6 g/m^2 (56.9); $P < 0.01$]; LV ejection fraction was lower [55.7% (11.2) vs. 61.4% (10.2); $P < 0.001$]; and the rate of preserved apical strain was higher (73.4% vs. 57.9%; $P < 0.05$). Significant differences were also found in hypertrophic pattern between patients with ATTR-CM and those with Grade 0 cardiac uptake ($P < 0.001$), including higher rates of concentric hypertrophic pattern (77.5% vs. 38.8% for ATTR-CM vs. Grade 0) and lower rates of asymmetric hypertrophic pattern (20.4% vs. 53.1% for ATTR-CM vs. Grade 0).

On MRI, the prevalence of late gadolinium enhancement was higher in patients with ATTR-CM than no cardiac uptake (85.0% vs. 54.7%, respectively; $P < 0.001$; *Table 3*). On ECG, significant differences were found in mean (*SD*) PR interval [ATTR-CM, 197.7 (40.2) ms vs. no cardiac uptake, 179.4 (33.4) ms; $P < 0.001$] and Sokolow index [19.5 (8.6) vs. 24.7 (11.1), respectively; $P < 0.001$] and the proportion of patients with poor precordial R wave progression (48.8% vs. 21.9%; $P < 0.001$) and left bundle branch block (14.8% vs. 7.8%; $P < 0.05$).

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Table 3 Cardiac imaging and ECG results by cardiac uptake on bone scintigraphy and amyloid disease type.

Parameter	No cardiac uptake (Grade 0)	Grade 2 or 3 cardiac uptake			
		CA	*P* value (Grade 0 vs. CA)	ATTR-CM[a]	*P* value (Grade 0 vs. ATTR-CM)
Echo					
LV ejection fraction, %	61.4 (10.2)	55.2 (11.2)	<0.001	55.7 (11.2)	<0.001
LV end-diastolic diameter, mm	44.3 (8.2)	43.2 (7.9)	0.13	43.2 (7.5)	0.16
Maximal wall thickness, mm	17.6 (2.8)	17.5 (2.4)	0.73	17.9 (2.6)	0.24
LV mass index, g/m^2	155.6 (56.9)	177.0 (53.2)	<0.001	179.0 (53.1)	<0.01
Aortic valvular stenosis area[b], cm	2.2 (0.9)	2.2 (0.7)	0.93	2.3 (0.7)	0.77
LVOT obstruction, *n* (%)	95 (18.4)	22 (10.7)	<0.05	18 (12.6)	0.10
Preserved apical strain, *n* (%)	84 (57.9)	60 (69.8)	0.07	47 (73.4)	<0.05
Hypertrophic pattern, *n* (%)			<0.001		<0.001
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)	0.08	21 (14.7)	0.26
MRI					
Late gadolinium enhancement, *n* (%)	81 (54.7)	50 (87.7)	<0.001	34 (85.0)	<0.001
ECG					
PR interval, ms	179.4 (33.4)	201.7 (44.9)	<0.001	197.7 (40.2)	<0.001
QRS interval	105.8 (23.7)	106.9 (25.3)	0.60	105.4 (26.0)	0.87
Sokolow index	24.7 (11.1)	18.7 (8.6)	<0.001	19.5 (8.6)	<0.001
Poor precordial R wave progression, *n* (%)	103 (21.9)	83 (46.4)	<0.001	62 (48.8)	<0.001
Left bundle branch block, *n* (%)	37 (7.8)	23 (12.7)	0.05	19 (14.8)	<0.05
Right bundle branch block, *n* (%)	65 (13.7)	32 (17.7)	0.20	19 (14.8)	0.74
Intraventricular conduct delay, *n* (%)	44 (9.3)	32 (17.7)	<0.01	19 (14.8)	0.07

Note: Values are mean (*SD*) unless otherwise specified.
Abbreviation: CI, confidence interval.
[a]Grade 2/3 on scintigraphy and no monoclonal protein abnormalities.
[b]Patients with aortic valve area <1.0 cm^2 were excluded.

Discussion

Bone-avid cardiac imaging, in tandem with monoclonal protein screening, has become a critical tool in establishing a non-invasive diagnosis of ATTR-CM.[18] However, data on current usage of non-invasive nuclear imaging tests or their interpretation and performance when evaluating ATTR-CM in the clinical practice setting are limited. In our exploratory analyses of findings from the TTRACK study, conducted in older adults with HCM of unascertained origin, we obtained detailed information about the usage of the nuclear imaging tests at 20 participating study centres located in 11 countries across three continents. We found that planar cardiac scintigraphy was accompanied by SPECT imaging in only 10% of patients in the TTRACK study. This low frequency of SPECT use is at least in part due to the absence of a requirement for the test in the study protocol, as protocol development (and study initiation) preceded the publication of clinical guidelines recommending follow-on SPECT in this clinical scenario.[11] It is important to recognize that radiotracer activity in the blood pool or ribs may be misinterpreted as tracer retention by the myocardium when interpreting planar radiotracer-labelled scans, underscoring the need for SPECT imaging in patients whose scans exhibit planar myocardial uptake.[11,19–22]

Our findings indicate that [^{99m}Tc]Tc-DPD and [^{99m}Tc]Tc-HMDP–labelled radiotracers were employed in nuclear imaging in similar proportions of patients (43% and 45%, respectively), whereas [^{99m}Tc]Tc-PYP was used in a substantially lower proportion (12%). Distribution of the radiotracers varied widely among the countries participating in the study. The three radiotracers used for bone scintigraphy have demonstrated a high level of sensitivity and accuracy in identifying ATTR-CM when combined with monoclonal protein screening to exclude light-chain amyloidosis.[22–24] Moreover, their use for ATTR-CM imaging has been recommended in multi-societal guidelines and other society position statements.[3,25] Despite this support, the individual radiotracers are not universally obtainable, as demonstrated by the regional differences in radiotracer availability reported here. Traditionally, [^{99m}Tc]Tc-PYP has been most widely used in the United States, with limited availability elsewhere, whereas [^{99m}Tc]Tc-DPD and [^{99m}Tc]Tc-HMDP are widely used in Europe.[18] However, as shown in *Figure 2*, the use of [^{99m}Tc]Tc-PYP radiotracer has spread beyond the United States, and both [^{99m}Tc]Tc-DPD and [^{99m}Tc]Tc-HMDP remain accessible in multiple European countries (France, Italy, Slovakia and Spain).

Approximately 19% of patients over 50 years of age with HCM of unascertained aetiology in the overall TTRACK population had scintigraphy and monoclonal protein test results that confirmed a diagnosis of ATTR-CM without cardiac biopsy. Some variability in ATTR-CM prevalence was seen in the current analyses based on the performance of planar

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scintigraphy with or without SPECT and the specific radiotracer used, but the clinical importance of this variability is unclear. In previously published studies of older adults with heart failure and increased LV wall thickness, 6% to 14% of patients who were screened using [^{99m}Tc]Tc-PYP or -DPD scintigraphy had ATTR-CM.[26–28] Based on their meta-analysis of ATTR-CM screening studies, Aimo et al. recently reported an estimated ATTR-CM prevalence of 12% in patients with heart failure with preserved ejection fraction and increased cardiac wall thickness and in 7% in patients with HCM.[29] Although we do not have a definitive explanation for the higher prevalence of ATTR-CM in the TTRACK study, it may be due, in part, to the exclusion of patients with known sarcomeric genetic variants.

It is interesting to note that the only discordant grades in our analyses were observed with [^{99m}Tc]Tc-PYP–labelled images. While agreement between grading for planar versus SPECT scans was almost perfect, the only discrepant grades occurred in patients who underwent nuclear imaging with [^{99m}Tc]Tc-PYP. These findings suggest that there may be important differences between radiotracers and that further studies comparing radiotracers should be conducted.

In addition, we found noteworthy numerical differences in the proportions of patients in the [^{99m}Tc]Tc-DPD, [^{99m}Tc]Tc-PYP and [^{99m}Tc]Tc-HMDP subgroups, respectively, who had Grade 3 cardiac uptake (17.8%, 7.4%, 31.5%) or ATTR-CM (11.7%, 6.4%, 26.9%). In small studies of [^{99m}Tc]Tc-DPD, [^{99m}Tc]Tc-PYP and [^{99m}Tc]Tc-HMDP, myocardial radiotracer uptake had high sensitivity and specificity in distinguishing biopsy-confirmed ATTR-CM from other causes of cardiomyopathy and no clinical heart disease.[17,30–32] In a large, international, multicentre study conducted in patients referred for suspicion of cardiac amyloidosis who underwent cardiac scintigraphy with the three radiotracers, Gillmore et al.[23] found myocardial radiotracer uptake (Grades 1–3) had a sensitivity and specificity of $>$99% and 86%, respectively, for ATTR-CM diagnosis. However, to our knowledge, only one study has directly compared the diagnostic utility of the radiotracers in cardiac amyloidosis. Based on their comparative analyses of [^{99m}Tc]Tc-DPD and [^{99m}Tc]Tc-PYP in a small study of patients with cardiac amyloidosis, Park et al. observed that the disease severity of cardiac amyloidosis was detected better by [^{99m}Tc]Tc-DPD scans than [^{99m}Tc]Tc-PYP scans, whereas sensitivity in identifying amyloid involvement was higher with [^{99m}Tc]Tc-PYP scans.[33] This study did not analyse the concordance between planar and SPECT imaging. Given our exploratory findings and the scarcity of comparative analyses, additional research may be warranted to compare the performance of specific radiotracers employed for nuclear imaging for cardiac amyloidosis and ATTR-CM.

The timely diagnosis of ATTR-CM remains a challenge, in part because its signs and symptoms often overlap with other common cardiac conditions and red flags remain undetected, even in clinical scenarios that warrant a high index of suspicion. In the current analyses, we examined echo, MRI and ECG findings in patients with HCM with and without ATTR-CM to help identify characteristics that should raise clinical suspicion of the amyloid disease. Although noteworthy differences in several parameters were observed, none appeared to be definitive. These findings suggest that diagnostic evaluation of older patients with HCM of unascertained origin should not be limited by the assumption that HCM alone is responsible for their presentation. Broader screening for amyloid disease with scintigraphy may be warranted in this population.

The limitations of the TTRACK study have been previously described in detail.[7] Selection bias was possible due to several factors, including the lack of genotyping for sarcomere gene variants and variability in enrolment/screening practices. As mentioned, follow-on SPECT with planar scintigraphy was not required by study protocol, and the low frequency of its use may have introduced possible selection bias and/or otherwise influenced our findings. Our analyses of ATTR-CM prevalence by planar scintigraphy versus planar scintigraphy plus SPECT and by the individual radiotracers used were exploratory, and the clinical relevance of the differences observed is unclear. In addition, due to the absence of information on biopsies and their results in the presence of monoclonal gammopathy, and the absence of longitudinal follow-up offering some final diagnoses, the TTRACK study does not provide information on light-chain amyloidosis. Although light-chain amyloidosis is rare, this limitation likely had an impact on study results. Similarly, our study does not provide data on other aetiologies of LV hypertrophy, including conditions such as sarcomeric HCM and hypertension.

Conclusions

The TTRACK study was the first study to examine ATTR-CM prevalence in older patients with a clinical diagnosis of HCM. The primary findings of this large, multinational, epidemiologic study underscored the importance of potential screening for ATTR-CM in patients aged $\geq$50 years with HCM in the absence of a known cause and raised awareness of the red flags associated with amyloid disease to help improve the chances for early detection.[7] In the current exploratory analyses, we observed a high level of concordance in cardiac uptake grading by onsite versus central readers and on planar versus SPECT imaging, but notable differences in amyloid disease prevalence based on the individual radiotracer used. The high level of concordance found in nuclear image grading by planar versus SPECT imaging supports the use of these imaging tools to facilitate ATTR-CM screening in clinical practice. The radiotracer-related differences in amyloid disease prevalence warrant additional investigation of the comparative performance of the radiotracers used for ATTR-CM diagnosis. We

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also found differences in echo, MRI and ECG findings in older patients with HCM with and without ATTR-CM, although these differences did not appear to be definitive. Because differences in cardiac imaging and ECG parameters in older patients with HCM with and without ATTR-CM were unexceptional, broader ATTR-CM screening should be considered in this population regardless of these findings.

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Conflict of interest statement

Dr Garcia-Pavia reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bridgebio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, Intellia and Pfizer; consulting fees from Alexion, Akcea, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bayer, 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. Dr 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. Dr Piriou has received consultancy fees from Pfizer and speaker fees from Alnylam and Pfizer. Dr Barriales-Villa has received consultancy fees from Alnylam, Amicus, Bristol Myers Squibb, Chiesi, Cytokinetics, Pfizer and Sanofi. Dr Cappelli has received honoraria for advisory board participation from Akcea, Alnylam, AstraZeneca, Bayer, Pfizer and Novo Nordisk; and unconditional research grants from Pfizer. Ms Bahus, Ms Munteanu, Dr Keohane and Dr Mallaina are employees of Pfizer and hold Pfizer stock/stock options. Dr Elliott has received consultancy fees from Alnylam, AstraZeneca and Pfizer, and educational grants from Pfizer.

Role of the funder/sponsor

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

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. TTRACK study flow.
Data S1. Supplementary Information.

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