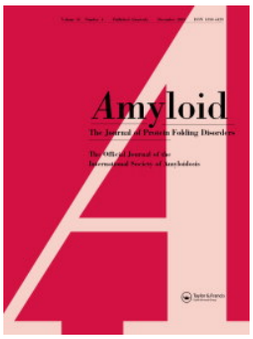

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RESEARCH ARTICLE

International prevalence of transthyretin amyloid cardiomyopathy in high-risk patients with heart failure and preserved or mildly reduced ejection fraction

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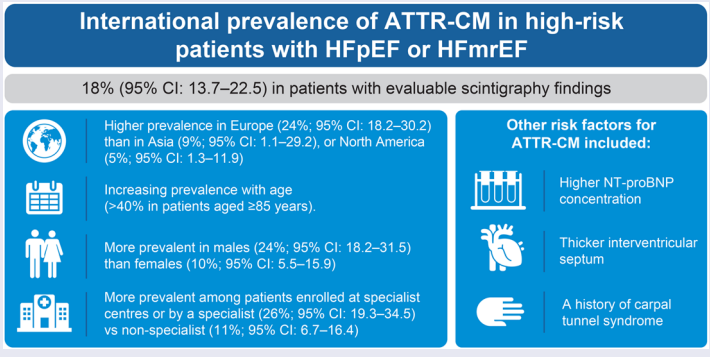
ABSTRACT

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed cause of heart failure (HF).
Methods: This epidemiology study assessed the international prevalence of ATTR-CM among patients aged ≥60 years with a history of HF, left ventricular ejection fraction (LVEF) >40%, an end-diastolic interventricular septum thickness (IVST) ≥12 mm, but without diagnosed amyloidosis, history of LVEF ≤40%, cardiomyopathy of known cause, severe valvular, or coronary heart disease. ATTR-CM was determined using cardiac scintigraphy alongside exclusionary testing for light chain amyloidosis. The study was terminated early due to slow recruitment, without safety concerns.
Results: Overall, 56/315 (18%; 95% CI: 13.7–22.5) patients with evaluable scintigraphy had ATTR-CM, with a numerically higher prevalence in: Europe (24%) *vs.* other regions (9% Asia; 5% North America); at specialist vs non-specialist centres (26% *vs.* 11%); in males *vs.* females (24% *vs.* 10%); and in older *vs.* younger patients (e.g. >40% among those ≥85 years). Other risk markers ($p<.05$) included a history of carpal tunnel syndrome, higher N-terminal pro B-type natriuretic peptide concentration, and higher end-diastolic IVST.
Conclusions: ATTR-CM was diagnosed in 18% (95% CI: 13.7–22.5) of evaluable patients with HF, LVEF >40%, and risk markers for ATTR-CM, but no previous diagnosis of amyloidosis. Recruitment bias may have contributed to regional variability. NCT04424914



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KEYWORDS
Amyloidosis; left ventricular ejection fraction; epidemiology; carpal tunnel syndrome; N-terminal pro B-type natriuretic peptide; interventricular septal thickness

Abbreviations: 6MWT: Six-minute walk test; AL: Light chain; ATTR-CM: Transthyretin amyloid cardiomyopathy; BP: Blood pressure; CI: Confidence interval; CTS: Carpal tunnel syndrome; eGFR: Estimated glomerular filtration rate; HF: Heart failure; HFmrEF: Heart failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; IVST: Interventricular septal thickness; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF:

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Left ventricular ejection fraction; mBMI: Modified body mass index; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; Q: Quartile; SD: Standard deviation; SPECT: Single photon emission computed tomography; ^{99m}Tc-DPD: ^{99m}Technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP: ^{99m}Technetium-hydroxymethylene diphosphonate; ^{99m}Tc-PYP: ^{99m}Technetium-pyrophosphate; UK: United Kingdom; USA: United States of America

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed cause of progressive heart failure (HF) that can be fatal in a median of 2–6 years if untreated [1–3]. Patients with ATTR-CM present with a range of left ventricular ejection fractions (LVEF), but most frequently with HF with preserved or mildly reduced ejection fractions (HFpEF or HFmrEF; LVEF >40%) [4–7]. The prevalence of HFpEF and HFmrEF increases with age and is most common among older people, often alongside complex clinical profiles [7,8]. Due to non-specific symptoms and limited awareness among non-specialist clinicians, ATTR-CM continues to be underdiagnosed [9]. Recent developments in non-invasive cardiac scintigraphy and the approval of tafamidis in many regions supports the benefits of ATTR-CM screening among patients with risk markers [10,11]. Delays in obtaining the correct diagnosis and treatment for patients with ATTR-CM are widely reported and detrimental to prognosis [9,12,13].

International estimates on the prevalence of ATTR-CM in patients with HFpEF or HFmrEF are lacking. A better understanding of the prevalence and risk markers for ATTR-CM will guide the identification of patient groups who may be underdiagnosed. This epidemiology study aimed to determine the international prevalence of ATTR-CM in patients with HFpEF or HFmrEF and potential risk markers for ATTR-CM, but not being clinically assessed for amyloidosis. Patients with prior diagnosis of HF with reduced ejection fraction (HFrEF) or other known aetiologies leading to HF were excluded to create an enriched population that might reasonably be expected to have received screening in clinical practice. As these patients were not evaluated for amyloidosis prior to the study, the cohort represents a potentially overlooked population that might particularly benefit from ATTR-CM screening. Supportive analyses examined differences in prevalence by region, age, sex, and clinical characteristics between patients with and without ATTR-CM.

Methods

Study design

This international multicentre epidemiology study (NCT04424914) estimated the prevalence of ATTR-CM in a subgroup of outpatients with HFpEF or HFmrEF and risk markers for ATTR-CM. It was approved by the independent review board or ethics committee at each participating centre and was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

The study initially planned to enrol up to 2000 patients worldwide, to find 200 patients with ATTR-CM. This was expected to provide a prevalence estimate with a precision of ±2.5%. Slow recruitment early in the study period may have been due to national and personal measures implemented due to the COVID-19 (SARS-CoV-2 disease) pandemic. The study was terminated early to allow dissemination of the findings with no safety concerns revealed.

Patients

To enrol in the study, patients must have been aged ≥60 years with an LVEF >40%, end-diastolic interventricular septal thickness (IVST) ≥12 mm, and a history of HF (either with a single prior HF-related hospitalisation, or without prior hospitalisation but with symptoms of volume overload or elevated intracardiac pressure that required treatment with a diuretic). Patients with a history of HFrEF (LVEF ≤40%), myocardial infarction, coronary artery bypass graft, multi-vessel obstructive coronary disease (>50% stenosis in ≥2 epicardial coronary arteries), amyloidosis (including a prior diagnosis of transthyretin or light chain (AL) amyloidosis), severe valvular heart disease, non-amyloid infiltrative cardiomyopathy, reversible cardiomyopathy, confirmed genetic hypertrophic obstructive cardiomyopathy, pericardial constriction, or muscular dystrophy were excluded. While entry criteria were designed to create an enriched population of patients at-risk of undiagnosed ATTR-CM, this study was not designed to provide full diagnostic screening [14]. Patients with any clinical findings should have received additional testing and treatment outside of the study.

Study procedures

Baseline demographics and clinical characteristics were collected during screening. At the main study visit, patients underwent cardiac scintigraphy, completed the six-minute walk test (6MWT; if available), had concomitant medications recorded, completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), had New York Heart Association (NYHA) functional class assessed, provided blood for the analysis of N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin T and I concentrations, transthyretin genotyping, serum creatinine concentration for calculation of estimated glomerular filtration rate (eGFR) using the modified Modification of Diet in Renal Disease equation, and serum albumin concentration for the calculation of modified body mass index (mBMI).

All patients underwent radionuclide chest scintigraphy with both planar 2D imaging and chest single photon emission computed tomography (SPECT; or SPECT/computed tomography (3D; was preferred, if available) using a bisphosphonate biotracer (^{99m}Technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD),^{99m}Technetium-pyrophosphate (^{99m}Tc-PYP), or ^{99m}Technetium-hydroxymethylene

diphosphonate (^{99m}Tc-HMDP)) according to study-specific predefined guidelines. Images were captured at 2.5 (planar) and 3 h (SPECT) following injection of the radiotracer and quality assessed at a specialist central review facility (Calyx, Nottingham, UK). Cardiac retention and grading were determined by independent central readers at the central facility. Grading was defined as Perugini Grade 0 = absent cardiac uptake; 1 = mild uptake less than bone; 2 = moderate uptake equal to bone; 3 = high uptake greater than bone [15].

Testing for AL amyloidosis was conducted for all patients with grade 1, 2, or 3 scintigraphy uptake using standard tests (serum free-AL assay, plus serum and urine electrophoresis with immunofixation). Findings were read at a central laboratory and patients with monoclonal gammopathy of unknown significance should have undergone confirmatory biopsy. Testing for AL amyloidosis was not conducted for patients without uptake (grade 0) as this study was not designed to provide the full diagnostic testing workflow for amyloidosis. Endomyocardial biopsy to further evaluate potential ATTR-CM was recommended after the main visit for patients who had grade 1 cardiac scintigraphy findings, but performance was at investigator's discretion. Locally collected data for echocardiography, serum creatinine, albumin and troponin concentrations, and 6MWT distance could be used if obtained in the six months prior to screening. Except for central reading of scintigraphy images and laboratory tests to exclude AL amyloidosis and other gammopathies, all procedures were conducted and analysed locally by trained personnel.

Outcomes

The prespecified primary outcome was an estimate of the international prevalence of ATTR-CM in the study population. Patients with ATTR-CM were determined as those with negative AL amyloidosis findings and either grade 2 or 3 cardiac scintigraphy uptake, or grade 1 uptake and a confirmatory endomyocardial biopsy [14]. Secondary outcomes were to estimate the prevalence of ATTR-CM among enrolled patients by region, sex and age. Exploratory outcomes aimed to compare the baseline clinical characteristics of patients who did and did not have ATTR-CM, and across patient groups enrolled in different regions.

Statistical analysis

The prevalence of ATTR-CM in the overall patient population, by country, region, age and sex, was calculated using the Clopper and Pearson method and presented with 95% confidence interval. Exploratory comparisons of selected baseline and clinical characteristics between patient groups were conducted using the Chi Squared or Fisher's exact test (NYHA class, medical history), T test (supine diastolic blood pressure (BP)), or Wilcoxon rank sum test (NT-proBNP concentration, eGFR, 6MWT distance, cardiac troponin T and I concentration, mBMI, standing diastolic, standing systolic, and supine systolic BP, LVEF, end-diastolic IVST and KCCQ overall summary score). $P < .05$ was considered nominally statistically significant. Cross tabulation by geographic region is presented descriptively.

Results

Between 30 December 2020, and 2 June 2023, 421 patients with HFpEF or HFmrEF were screened. Supplemental Table 1 details the reasons for screen failure. Of these, 347 were enrolled at 36 centres across eight countries and three continents (Europe (63%), North America (31%) and Asia (7%)). The country with the highest enrolment was Spain (33%), followed by the United States of America (USA; 27%). Patients in Italy, Poland, Japan, the United Kingdom (UK), France and Canada each comprised <10% of the overall population. A total of 146 patients (42%) were enrolled at the 13 sites designated as specialist ATTR-CM referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM.

Patient characteristics

The demographics of all enrolled patients (mean age: 78 years; 53% male; 86% White) are shown in Table 1 and their clinical characteristics are shown in Table 2. Patients had a median LVEF of 60% and end-diastolic IVST of 14 mm. Most patients (66%) were NYHA class II. Median 6MWT distance was 267 m, NT-proBNP concentration was 1013 ng/L, eGFR was 56 ml/min/1.73m^2 and KCCQ Overall

Table 1. Patient demographics.

	Patients			
n (%) unless stated	All (*N* = 347)	Non-evaluable findings (*n* = 32)	Without ATTR-CM (*n* = 259)	With ATTR-CM (*n* = 56)
Age, years, mean (SD)	77.7 (8.2)	75.6 (7.5)	76.5 (7.9)	84.1 (6.6)
60–64	24 (6.9)	3 (9.4)	21 (8.1)	0
65–69	38 (11.0)	4 (12.5)	32 (12.4)	2 (3.6)
70–74	60 (17.3)	8 (25.0)	49 (18.9)	3 (5.4)
75–79	77 (22.2)	9 (28.1)	58 (22.4)	10 (17.9)
80–84	70 (20.2)	3 (9.4)	58 (22.4)	9 (16.1)
85–89	58 (16.7)	4 (12.5)	30 (11.6)	24 (42.9)
≥90	20 (5.8)	1 (3.1)	11 (4.2)	8 (14.3)
Male	183 (52.7)	11 (34.4)	130 (50.2)	42 (75.0)
Female	164 (47.3)	21 (65.6)	129 (49.8)	14 (25.0)
Race				
White	299 (86.2)	25 (78.1)	226 (87.3)	48 (85.7)
Black or African American	23 (6.6)	6 (18.8)	11 (4.2)	6 (10.7)
Asian	23 (6.6)	1 (3.1)	20 (7.7)	2 (3.6)
American Indian or Alaskan Native	1 (0.3)	0	1 (0.4)	0
Not reported	1 (0.3)	0	1 (0.4)	0
Region				
Europe	217 (62.5)	7 (21.9)	160 (61.8)	50 (89.3)
Spain	116 (33.4)	7 (21.9)	87 (33.6)	22 (39.3)
Italy	32 (9.2)	0	19 (7.3)	13 (23.2)
United Kingdom	20 (5.8)	0	12 (4.6)	8 (14.3)
France	17 (4.9)	0	12 (4.6)	5 (8.9)
Poland	32 (9.2)	0	30 (11.6)	2 (3.6)
North America	107 (30.8)	24 (75.0)	79 (30.5)	4 (7.1)
USA	94 (27.1)	24 (75.0)	67 (25.9)	3 (5.4)
Canada	13 (3.7)	0	12 (4.6)	1 (1.8)
Asia	23 (6.6)	1 (3.1)	20 (7.7)	2 (3.6)
Japan	23 (6.6)	1 (3.1)	20 (7.7)	2 (3.6)

ATTR-CM: transthyretin amyloid cardiomyopathy; SD: standard deviation; USA: United States of America.

Table 2. Patient clinical characteristics.

n (%) unless stated	Patients				*p* value With *vs.* without ATTR-CM
	All (*N* = 347)	Non-evaluable findings (*n* = 32)	Without ATTR-CM (*n* = 259)	With ATTR-CM (*n* = 56)	
NHYA Functional Classification, *n* (%)					
I	33 (9.5)	5 (15.6)	26 (10.0)	2 (3.6)	
II	230 (66.3)	22 (68.8)	165 (63.7)	43 (76.8)	.3006[b]
III	79 (22.8)	5 (15.6)	66 (25.5)	8 (14.3)	
IV	5 (1.4)	0	2 (0.8)	3 (5.4)	
mBMI	*n* = 213	*n* = 13	*n* = 150	*n* = 50	
Median[a] (Q1, Q3)	1083.8 (908.0, 1320.3)	1284.8 (1125.7, 1466.1)	1144.6 (972.1, 1376.4)	929.4 (800.3, 1044.2)	**< .0001**
Standing diastolic BP	*n* = 316	*n* = 32	*n* = 240	*n* = 44	
Median mmHg (Q1, Q3)	75.0 (66.0, 82.0)	78.5 (71.5, 89.5)	74.0 (65.5, 82.0)	73.5 (66.0, 80.0)	.4586
Standing systolic BP	*n* = 316	*n* = 32	*n* = 240	*n* = 44	
Median mmHg (Q1, Q3)	131.0 (118.0, 144.0)	139.0 (122.5, 155.0)	131.5 (118.0, 144.0)	129.0 (118.5, 135.0)	.2508
Supine diastolic BP	*n* = 334	*n* = 31	*n* = 249	*n* = 54	
Median mmHg (Q1, Q3)	74.0 (66.0, 83.0)	79.0 (73.0, 84.0)	73.0 (65.0, 83.0)	70.0 (65.0, 80.0)	.1278
Supine systolic BP	*n* = 334	*n* = 31	*n* = 249	*n* = 54	
Median mmHg (Q1, Q3)	132.5 (119.0, 146.0)	136.0 (127.0, 155.0)	134.0 (119.0, 146.0)	127.0 (120.0, 135.0)	**.0299**
LVEF	*n* = 346	*n* = 32	*n* = 258	*n* = 56	
Median % (Q1, Q3)	60.0 (53.0, 64.0)	60.0 (55.5, 67.0)	60.0 (52.0, 64.0)	55.0 (49.5, 62.6)	.1749
End-diastolic IVST	*n* = 344	*n* = 31	*n* = 257	*n* = 56	
Median mm (Q1, Q3)	13.5 (12.4, 15.0)	13.0 (12.0, 16.0)	13.0 (12.1, 14.7)	15.9 (14.0, 18.0)	**< .0001**
eGFR	*n* = 267	*n* = 18	*n* = 201	*n* = 48	
Median mL/min/1.73m^2 (Q1, Q3)	56.1 (40.8, 72.2)	61.0 (48.6, 69.8)	56.6 (41.4, 74.2)	51.3 (37.8, 65.3)	.1392
NT-proBNP	*n* = 322	*n* = 30	*n* = 240	*n* = 52	
Median ng/L (Q1, Q3)	1012.5 (307.0, 2097.0)	416.1 (100.0, 1335.0)	817.5 (273.5, 1850.0)	2470.0 (1230.0, 5713.5)	**< .0001**
Troponin T	*n* = 95	*n* = 2	*n* = 70	*n* = 23	
Median µg/L (Q1, Q3)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.1 (0.0, 0.1)	**.0001**
Troponin I	*n* = 83	*n* = 7	*n* = 60	*n* = 16	
Median µg/L (Q1, Q3)	0.0 (0.0, 3.0)	0.1 (0.0, 15.2)	0.0 (0.0, 4.1)	0.0 (0.0, 0.1)	.8931
KCCQ Overall Summary	*n* = 345	*n* = 32	*n* = 257	*n* = 56	
Median score (Q1, Q3)	61.5 (39.1, 79.7)	63.8 (36.7, 74.4)	61.5 (40.6, 79.7)	62.9 (33.1, 81.3)	.3941
6MWT distance	*n* = 82	*n* = 4	*n* = 54	*n* = 24	
Median m (Q1, Q3)	267.0 (205.0, 388.0)	382.5 (350.0, 396.0)	264.0 (205.0, 390.0)	250.0 (172.0, 375.0)	.7007

[a]mBMI = serum albumin concentration (g/L) × BMI.
[b]Classes I and II *vs.* III and IV.
6MWT: six-minute walk test; ATTR-CM: transthyretin amyloid cardiomyopathy; BP: blood pressure; eGFR: estimated glomerular filtration rate; IVST: interventricular septal thickness; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; mBMI: modified body mass index; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; Q: quartile.

Summary score was 62, indicating fair to good health-related quality of life [16].

All enrolled patients had a medical history of HF. Selective additional medical history relevant to ATTR-CM risk was collected (Table 3). Cardiac disorders of relevance (MedDRA preferred terms of atrial fibrillation, atrial flutter, heart block or intracardial thrombus) were present in 62% of patient's medical histories. Overall, 28% of patients had a medical history including arthroplasty, CTS, lumbar spinal stenosis or non-traumatic rotator cuff tear. Concomitant cardiovascular medications were common among patients, with 89% receiving diuretics, 75% antithrombotic agents, 68% beta-blockers and 67% agents acting on the renin-angiotensin system (Supplemental Table 2).

Though patient numbers in many countries limited the ability to resolve differences, some key demographics and clinical characteristics were descriptively explored by region (Table 4). Patient cohorts enrolled in the UK, Spain, Italy and France had the highest median age, leading to 31% of patients in Europe being ≥85 years old (7% North America; 17% Japan). Male sex was most common among patients enrolled in Italy, the UK and Japan, with 54% of patients in European countries being male, compared with 48% in North America and 65% in Japan. Racial differences were indicative of the general population in each region. Median mBMI was lowest in the UK, France and Japan, and highest in the USA and Canada.

Median end-diastolic IVST was 14 mm in all European countries, and 13 mm in Canada, the USA, and Japan. Median NT-proBNP concentration was higher in all European countries (aside from Poland), than in Canada, the USA or Japan. Median troponin T concentrations were low in cohorts from European countries, but unexpectedly high in the USA, likely due to an outlier (only 2 patients had data). Median supine systolic BP was slightly lower in Italy than in all other countries (125 *vs.* 131–135). Median baseline LVEF was similar across regions (55–65% in all countries), and 6MWT distance was similar in Europe and the USA (240–335 m in all countries) but higher in Japan (407 m). Interestingly, the proportion of patients with a medical history of CTS was highest in North America (20%) compared with Europe (10%) and Japan (9%). This difference was driven by a particularly high prevalence in Canada.

A higher proportion of participating recruitment sites in Europe (60%), compared with Japan (25%) or North America (18%), were specialist ATTR-CM referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM. This was reflected in the proportion of patients recruited from these centres in each region (European:

Table 3. Relevant medical history at baseline.

	Patient with relevant medical history, *n* (%)				
n (%) unless stated	All (*N* = 347)	Non-evaluable findings (*n* = 32)	Without ATTR-CM (*n* = 259)	With ATTR-CM (*n* = 56)	*p* value With *vs.* without ATTR-CM
Cardiac disorders					
Atrial fibrillation	183 (52.7)	15 (46.9)	136 (52.5)	32 (57.1)	.5286
Atrial flutter	22 (6.3)	0	20 (7.7)	2 (3.6)	.3894
Heart block	42 (12.1)	4 (12.5)	28 (10.8)	10 (17.9)	.1421
Intracardiac thrombus	3 (0.9)	0	3 (1.2)	0	–
Congenital, familial and genetic disorders					
Transthyretin amyloid polyneuropathy	2 (0.6)	1 (3.1)	1 (0.4)	0	–
Injury, poisoning and procedural complications					
Bicep tendon rupture	2 (0.6)	0	1 (0.4)	1 (1.8)	.3244
Ligament sprain	25 (7.2)	2 (6.3)	18 (6.9)	5 (8.9)	.5758
Muscle strain	27 (7.8)	6 (18.8)	17 (6.6)	4 (7.1)	.7745
Non-traumatic rupture of the Achilles tendon	2 (0.6)	0	1 (0.4)	1 (1.8)	.3253
Musculoskeletal and connective tissue disorders					
Lumbar spinal stenosis	23 (6.6)	4 (12.5)	16 (6.2)	3 (5.4)	1.0000
Non-traumatic rotator cuff tear	15 (4.3)	3 (9.4)	12 (4.6)	0	–
Nervous system disorders					
CTS	45 (13.0)	4 (12.5)	26 (10.0)	15 (26.8)	**.0007**
Embolic stroke	17 (4.9)	2 (6.3)	10 (3.9)	5 (8.9)	.1560
Surgical and medical procedures					
Arthroplasty	52 (15.0)	4 (12.5)	36 (13.9)	12 (21.4)	.1552
Cardiac pacemaker insertion	44 (12.7)	4 (12.5)	33 (12.7)	7 (12.5)	.9608
Implantable defibrillator insertion	10 (2.9)	1 (3.1)	8 (3.1)	1 (1.8)	1.0000

Medical history was recorded as MedDRA v26.0 preferred terms. Relevant terms were predefined prior to the start of the study.
ATTR-CM: transthyretin amyloid cardiomyopathy; CTS: carpal tunnel syndrome.

119/217 (55%); North America: 15/107 (14%); Japan: 12/23 (52%)). No patients in Poland were recruited from a specialist ATTR-CM referral centre or by an investigator with a subspecialty interest.

Prevalence

Of the 347 patients enrolled, 43% had scintigraphy undertaken with ^{99m}Tc-DPD, 37% with ^{99m}Tc-PYP, and 20% with ^{99m}Tc-HMDP. Of these, 315 had evaluable scintigraphy results at study close. Of the 32 patients with unevaluable image sets, the majority had missing SPECT (19/32) or image quality/format that was not to the standard required by the central review facility (11/32; two other cases were due to an artefact, and reason not specified). Among the 315 evaluable patients, 56 (18%; 95% CI: 13.7–22.5%) were diagnosed with ATTR-CM (Figure 1); 8 (3%) had grade 2 uptake and 48 (15%) had grade 3 uptake; all were negative for AL amyloidosis. The remaining 259 evaluable patients were not diagnosed with ATTR-CM, including 235 (75% of all evaluable patients) with grade 0 cardiac tracer uptake and 24 (8%) with grade 1 uptake but without a cardiac biopsy confirming ATTR-CM. Biopsies were recommended for patients with grade 1 uptake but performed at the investigator's discretion. No patients with grade 1 uptake had cardiac biopsy findings reported. Patients with unevaluable scintigraphy findings at study close ($n = 32$) were not included in the analysis. Among the 56 patients with ATTR-CM, 47 (84%) had wild-type transthyretin and 7 (12%) had a confirmed transthyretin gene variant (1 with I68L (p. I88L) and 6 with V122I (p. V142I)). Two patients (4%) did not have genotype findings at the time of study termination.

Secondary study outcomes evaluated the prevalence of ATTR-CM in patients from different regions, of different age and sex. The highest prevalence of ATTR-CM was found in Europe (24% (95% CI: 18.2–30.2); 50/210 patients with evaluable findings); specifically, 41% in Italy, 40% in the UK, 29% in France, 20% in Spain and 6% in Poland (Figure 2A). Prevalence in North America was 5% (95% CI: 1.3–11.9; 4/83 patients with evaluable findings); specifically, 4% in the USA and 8% in Canada. Prevalence in Asia was 9% (95% CI: 1.1–29.2; 2/22 patients with evaluable findings), with all patients enrolled in Japan. Prevalence estimates in countries and regions with smaller numbers of patients generally had wider confidence intervals, reflecting a lower certainty in the estimate.

Notably, the prevalence of ATTR-CM was higher among patients enrolled at specialist referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM than among patients enrolled at other centres (26% (95% CI: 19.3–34.5; 37/140) *vs.* 11% (95% CI: 6.7–16.4; 19/75); Figure 2B and Supplemental Table 3). Though patient numbers were small, this trend was also observed in most regional and country-specific data (Supplemental Table 3). All patients in Italy, the UK and France were from specialist referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM, with observed prevalence ranging from 29% to 41%. No patients were enrolled at these centres in Poland (0%), and a minority in the USA (11%) and Canada (38%). These countries were found to have comparatively lower ATTR-CM prevalence (4–8%).

There was a numerically higher prevalence of ATTR-CM with increasing patient age. Prevalence in patients aged 60–64 years was 0%; 65–69 years: 6%; 70–74 years: 6%; 75–79 years: 15%; 80–84 years: 13%; 85–89 years: 44%; and

Table 4. Demographics and clinical characteristics across regions.

	Europe					North America		Asia
n (%) unless stated	Italy (*n* = 32)	UK (*n* = 20)	France (*n* = 17)	Spain (*n* = 116)	Poland (*n* = 32)	Canada (*n* = 13)	USA (*n* = 94)	Japan (*n* = 23)
Age, years, mean (SD)	80.8 (6.5)	83.6 (8.7)	80.4 (7.1)	81.4 (7.1)	72.2 (6.1)	71.6 (8.8)	73.0 (6.6)	77.1 (7.5)
60–64	1 (3.1)	0	1 (5.9)	2 (1.7)	5 (15.6)	5 (38.5)	9 (9.6)	1 (4.3)
65–69	1 (3.1)	2 (10.0)	1 (5.9)	4 (3.4)	3 (9.4)	1 (7.7)	23 (24.5)	3 (13.0)
70–74	1 (3.1)	1 (5.0)	0	13 (11.2)	12 (37.5)	2 (15.4)	27 (28.7)	4 (17.4)
75–79	9 (28.1)	4 (20.0)	4 (23.5)	24 (20.7)	10 (31.3)	2 (15.4)	18 (19.1)	6 (26.1)
80–84	11 (34.4)	3 (15.0)	6 (35.3)	30 (25.9)	2 (6.3)	2 (15.4)	11 (11.7)	5 (21.7)
85–89	8 (25.0)	5 (25.0)	5 (29.4)	30 (25.9)	0	0	6 (6.4)	4 (17.4)
≥90	1 (3.1)	5 (25.0)	0	13 (11.2)	0	1 (7.7)	0	0
Male	25 (78.1)	14 (70.0)	9 (52.9)	58 (50.0)	11 (34.4)	7 (53.8)	44 (46.8)	15 (65.2)
Female	7 (21.9)	6 (30.0)	8 (47.1)	58 (50.0)	21 (65.6)	6 (46.2)	50 (53.2)	8 (34.8)
Race								
White	32 (100.0)	10 (50.0)	17 (100.0)	114 (98.3)	32 (100.0)	13 (100.0)	81 (86.2)	0
Black or African American	0	10 (50.0)	0	1 (0.9)	0	0	12 (12.8)	0
Asian	0	0	0	0	0	0	0	23 (100.0)
American Indian or Alaskan Native	0	0	0	0	0	0	1 (1.1)	0
Not reported	0	0	0	1 (0.9)	0	0	0	0
LVEF	*n* = 31	*n* = 20	*n* = 17	*n* = 116	*n* = 32	*n* = 13	*n* = 94	*n* = 23
Median %	55.0	59.5	58.0	60.0	54.5	65.0	56.5	61.6
(Q1, Q3)	(47.0, 60.0)	(53.5, 63.0)	(50.0, 60.0)	(55.0, 64.6)	(49.5, 60.0)	(60.0, 65.0)	(55.0, 64.0)	(53.0, 64.6)
mBMI	*n* = 19	*n* = 18	*n* = 13	*n* = 83	*n* = 7	*n* = 6	*n* = 47	*n* = 20
Median[a]	984.4	850.0	860.4	1114.4 (972.1,	1114.0	1320.6	1284.8	960.8
(Q1, Q3)	(775.5, 1167.9)	(707.4, 1012.5)	(827.2, 1062.6)	1349.5)	(1075.6, 1507.4)	(917.7, 1722.0)	(1084.9, 1563.7)	(838.0, 1085.7)
6MWT distance	*n* = 28	*n* = 5	*n* = 15	*n* = 12	*n* = 13	*n* = 0	*n* = 8	*n* = 1
Median m	258	245	240	335	251	–	332	407
(Q1, Q3)	(211, 384)	(240, 270)	(160, 341)	(154, 410)	(230, 401)		(197, 379)	(407, 407)
End-diastolic IVST	*n* = 31	*n* = 20	*n* = 17	*n* = 114	*n* = 32	*n* = 13	*n* = 94	*n* = 23
Median mm	14.0	14.0	14.0	13.9	14.0	13.0	13.0	12.8
(Q1, Q3)	(13.0, 16.0)	(13.0, 15.5)	(12.9, 15.0)	(13.0, 15.7)	(12.0, 15.0)	(12.5, 14.0)	(12.1, 15.0)	(12.0, 14.0)
NT-proBNP	*n* = 26	*n* = 18	*n* = 17	*n* = 109	*n* = 32	*n* = 12	*n* = 85	*n* = 23
Median ng/L	1559.5	2244.5	1738.0	1500.0	470.5	672.5	296.0	1117.0
(Q1, Q3)	(833.0, 4999.0)	(1147.0, 5795.0)	(1375.0, 2509.0)	(618.0, 2609.0)	(210.0, 1210.0)	(239.0, 1595.5)	(101.0, 940.0)	(456.0, 2660.0)
Supine systolic BP	*n* = 26	*n* = 20	*n* = 16	*n* = 111	*n* = 32	*n* = 13	*n* = 93	*n* = 23
Median mmHg	125	135	133	134	131	132	134	134
(Q1, Q3)	(110, 140)	(120, 153)	(124, 145)	(119, 148)	(118, 144)	(120, 140)	(120, 144)	(110, 152)
Troponin T	*n* = 19	*n* = 12	*n* = 13	*n* = 37	*n* = 7	*n* = 0	*n* = 2	*n* = 5
Median µg/L (Q1, Q3)	0.0 (0, 0)	0.1 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	0.0 (0, 0)	–	16.5 (0, 33)	0.0 (0, 0)
History of CTS	8 (25.0)	3 (15.0)	3 (17.6)	6 (5.2)	2 (6.3)	6 (46.2)	15 (16.0)	2 (8.7)
Specialist ATTR-CM referral centre or general centre where the investigator had a subspecialist interest in ATTR-CM								
n of all sites	3/3	1/1	2/2	3/6	0/3	1/3	2/14	1/4
Patients enrolled at these centres	32 (100)	20 (100)	17 (100)	50 (43)	0 (0)	5 (38)	10 (11)	12 (52)

[a]mBMI = serum albumin concentration (g/L) × BMI.
6MWT: six-minute walk test; ATTR-CM: transthyretin amyloid cardiomyopathy; BP: blood pressure; CTS: carpal tunnel syndrome; IVST: interventricular septal thickness; LVEF: left ventricular ejection fraction; mBMI: modified body mass index; NT-proBNP: N-terminal pro B-type natriuretic peptide; Q: quartile; USA: United States of America; UK: United Kingdom.

≥90 years: 42% (Figure 2C). Prevalence was also higher in male *vs.* female patients (24% *vs.* 10%; Figure 2D). In age and sex subgroups, prevalence was nearly always numerically higher among patients enrolled at specialist referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM than among patients enrolled at other centres (Supplemental Table 3).

Exploratory statistical analyses examined baseline and clinical characteristics among patients with (*n* = 56) and without (*n* = 259) ATTR-CM (Tables 2 and 3). Several variables were significantly higher in patients with ATTR-CM, namely NT-proBNP concentration (difference between medians: 1653 ng/l; $p < .0001$), end-diastolic IVST (difference between medians: 2.9 mm; $p < .0001$) and the proportion of patients with a history of CTS (difference between groups: 17%; $p < .001$). There were no patients with evaluable scintigraphy and a medical history combining lumbar spinal stenosis, non-traumatic rotator cuff tear, CTS and arthroplasty. A combination of three conditions was reported in seven patients (one with ATTR-CM), and two conditions in 20 patients (five with ATTR-CM). At least one of these conditions was reported 41% in patients with ATTR-CM and 24% in those without. Median troponin T concentration was also significantly higher in patients with ATTR-CM *vs.* without (difference between medians: 0.1 µg/L; $p = .0001$). Supine systolic BP (difference between medians: 7 mmHg; $p = .03$) and mBMI (difference between medians: 215; $p < .0001$) were significantly lower in patients with ATTR-CM *vs.* without. Most patients with ATTR-CM were NYHA class II (77%) but there was no significant difference in classification profile between patients with and without ATTR-CM ($p = .30$). There was also no significant difference ($p > .05$) in eGFR, 6MWT distance, troponin I concentration, standing diastolic and systolic BP, supine diastolic

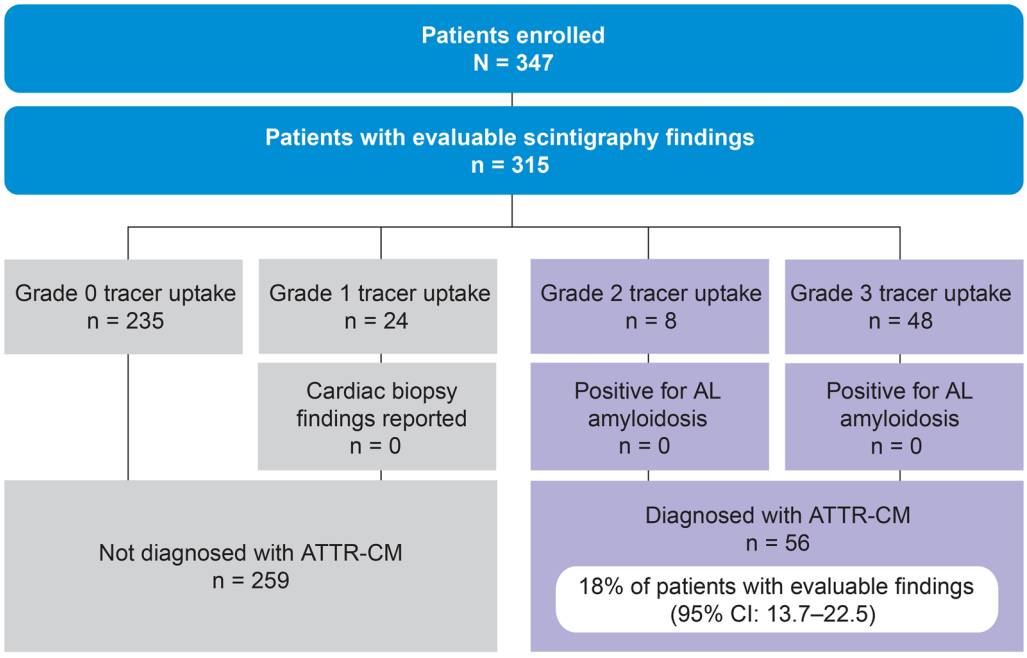

Figure 1. Prevalence of ATTR-CM in patients with HFpEF or HFmrEF.
AL: light chain; ATTR-CM: transthyretin amyloid cardiomyopathy; CI: confidence interval; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction.

BP, LVEF and KCCQ-OS score in patients with and without ATTR-CM.

Discussion

Among evaluable patients with HFpEF or HFmrEF and risk markers for ATTR-CM, but not being evaluated for amyloidosis, this international epidemiological study found an 18% prevalence of ATTR-CM. Though this was not designed to be a screening study, this prevalence is consistent with that reported in smaller, usually single-centre analyses of broadly similar enriched populations, indicating potential for underdiagnosis of patients with risk markers in real-life clinical settings [17–22]. We additionally confirmed some previously identified risk markers for ATTR-CM in an international population, including male sex, a history of CTS, higher age, higher NT-proBNP concentration, higher troponin T concentration, higher end-diastolic IVST, lower supine systolic BP, and lower mBMI [9,13,23,24]. We also identified a higher prevalence among patients enrolled at specialist centres, or a centre where the investigator had a subspecialist interest in ATTR-CM, than among patients enrolled at other centres. Overall findings highlight the value of risk markers and encourage further targeted screening of patients who may have undiagnosed ATTR-CM.

A diagnosis of ATTR-CM is often reached through a process of exclusion, and the condition remains underdiagnosed [9,12,14,25]. The signs and symptoms of ATTR-CM are often indistinguishable from other causes of HF, and diagnostic delays have been common due to the poor awareness among non-specialist clinicians and the requirement for cardiac biopsy [9]. The development and improved access to non-invasive cardiac scintigraphy has greatly improved the feasibility of ATTR-CM screening, which is of greater importance now that a disease-modifying treatment is available [10,11,14]. Prompt diagnosis of ATTR-CM is important because of its progressive nature, where early initiation of disease-modifying therapy is associated with the best clinical outcomes [26]. Improved screening efforts have led to increasing ATTR-CM prevalence estimates in recent years, but despite an increase in use of diagnostic scintigraphy, 9% of image sets in this study were deemed uninterpretable by the central lab. Since this study required strict image standardisation, this proportion is expected to be lower in clinical practice, but highlights the need for increased awareness of good imaging practices [27,28].

A meta-analysis of five observational studies in Spain and the USA recently suggested that 11% of patients with HFpEF have ATTR-CM; however, the precise international and regional prevalence remains uncertain [17]. The five studies included in the meta-analysis each enrolled 58–286 patients and all but one study utilised scintigraphy for diagnosis. Prevalence reported in the individual studies ranged from 5–19% ($n = 3$–19 patients with ATTR-CM in each). In another study conducted in Minnesota, USA, using scintigraphy with SPECT/CT, 6% of 286 patients ≥60 years old with an LVEF ≥40% and end-diastolic IVST ≥12 mm were found to have ATTR-CM [18]. In European analyses with similar methodology to our study, regional prevalence estimates have been slightly higher. Prevalence was 18% among 49 French patients aged >65 years and with LVEF >45% [19], 13% among 120 Spanish patients ≥60 years old with LVEF ≥50% and IVST ≥12 mm [20], and 15% among 86 Swedish patients with HF of unknown cause and an IVST >14 mm [21]. In a multicentre Spanish study of 453 patients aged ≥65 years with HF, IVST >12 mm, NYHA class II-IV, diuretic treatment and an NT-proBNP concentration

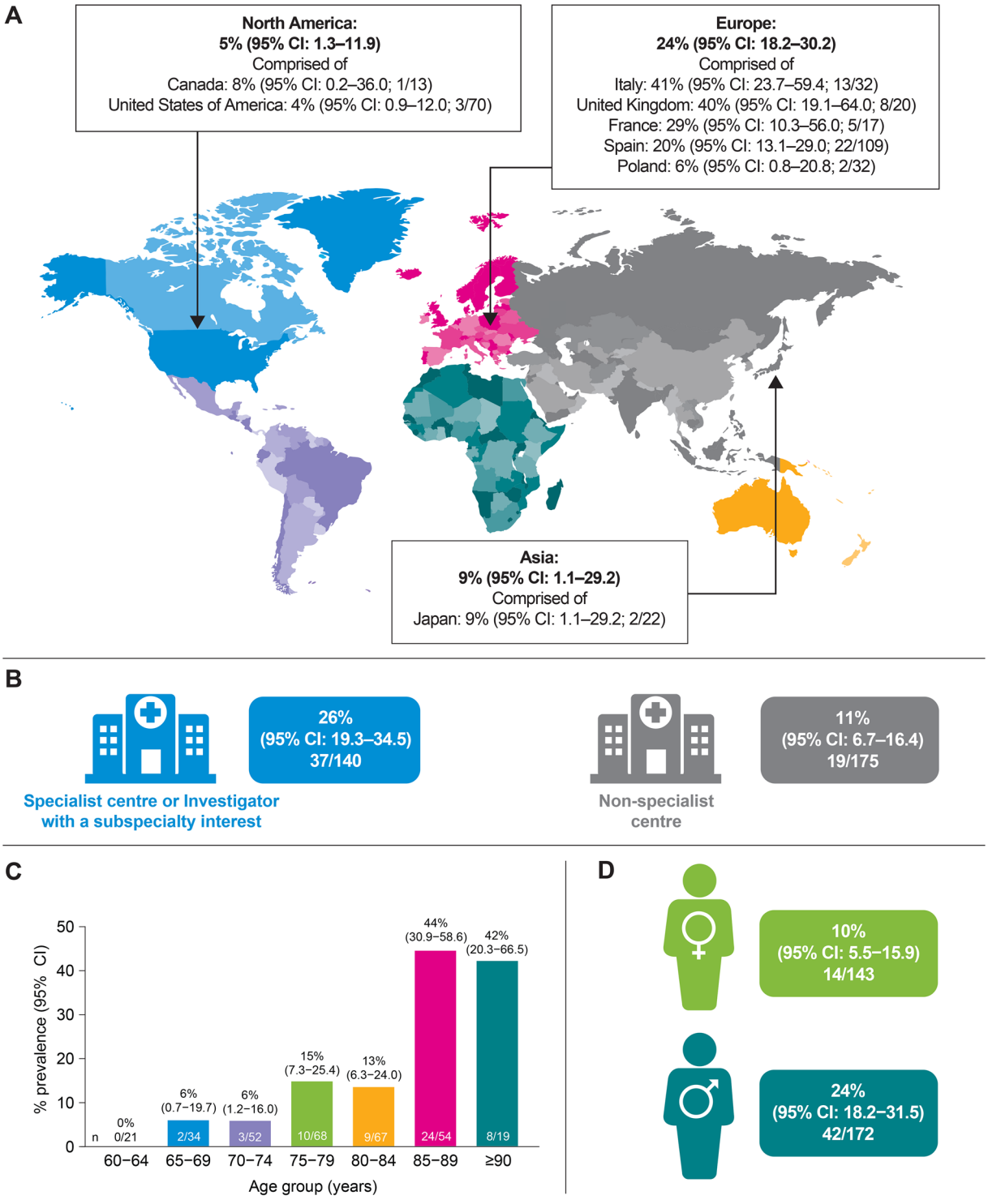

Figure 2. Prevalence of ATTR-CM in evaluable patients with HFpEF or HFmrEF by (A) region, (B) setting, (C) age, and (D) sex.
ATTR-CM; transthyretin amyloid cardiomyopathy; CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

>600 pg/mL (during stable HF; LVEF was ≥50% in 74%), scintigraphy with SPECT/CT or biopsies diagnosed ATTR-CM in 20% [22]. Despite enrolling fewer patients than originally planned, our study is larger than many of those mentioned above and recruited internationally. Our finding of 18% prevalence among evaluable patients with HFpEF or HFmrEF and risk markers for ATTR-CM is broadly comparable to previous regional studies, which we believe adds important data to the current understanding. Together, these studies suggest that significant proportions of patients with ATTR-CM and displaying risk markers are not being screened in clinical practice.

Though the division of data by region resulted in low patient numbers, our secondary analysis showed numerically higher prevalence in Europe than in North America or Japan. Exploratory cross tabulation showed several risk markers for ATTR-CM were most common among European cohorts, demonstrating them to be a more 'at-risk' than

those in North America or Japan. These factors included higher age, end-diastolic IVST and NT-proBNP concentration. Though enrolled patients were previously evaluated for amyloidosis, we saw trends throughout our data for higher prevalence in cohorts enrolled in specialist ATTR-CM referral centres or general centres where the investigator had a subspecialist interest in ATTR-CM, suggesting that centre bias contributed to our findings. Over half of patients enrolled in Europe were from these centres. For these reasons, the numerical differences in regional prevalence should be interpreted with caution.

While the overall patient population in this study was broadly representative of previous characterisations, the proportion of patients with ATTR-CM who were female (25%) was higher than has been typically reported. Most patients had a wild-type transthyretin genotype (84% of those with ATTR-CM), which has historically been most predominantly diagnosed in males [13,29,30]. Underdiagnosis of ATTR-CM in females has been suggested to be partly caused by a lack of consideration of smaller body size when considering echocardiographic measures such as IVST; however, all patients in this study had an IVST ≥12 mm [31]. Since patients enrolled in this study had not been previously evaluated for amyloidosis, these findings may reflect differences in the clinical presentation of ATTR-CM and lower levels of suspicion in the assessment of women with heart failure. Many of the most well-known signs and symptoms may be more prominent in men [32,33].

Our study design allowed creation of a 'control' group, which was derived from the same enriched population but were without ATTR-CM. This permitted exploratory evaluation of risk markers that has not been possible in many epidemiology studies. Previously proposed risk markers for ATTR-CM are diverse but include older age (typically >60 years); increased IVST in the absence of hypertension; increased extracellular volume; conduction defects; arrhythmias; apical sparing on longitudinal strain imaging; discrepancies between left ventricular thickness and QRS voltage; intolerance to standard HF therapies; elevated troponin and NT-proBNP concentrations; orthopaedic conditions such as lumbar spinal stenosis or bicep tendon rupture; CTS; polyneuropathy and gastrointestinal symptoms [8,9,13,14,17,18,20,23,24,34,35]. The previously discussed meta-analysis of five single-centre studies found patients with ATTR-CM were significantly more likely to be male, without diabetes mellitus, have low voltage criteria on electrocardiogram, and have a higher age, NT-proBNP concentration, left ventricular mass, posterior wall thickness, and IVST than those without ATTR-CM [17]. Several of the risk markers identified in other studies were also seen in our study, where patients with ATTR-CM were significantly more likely to be male, have a history of CTS, a higher age, NT-proBNP and troponin T concentration, IVST, and a lower supine systolic BP and mBMI than patients not diagnosed with ATTR-CM. Of these, the most clinically obvious differences were seen for age (especially < *vs.* ≥85 years), NT-proBNP concentration, IVST, and a history of CTS. Interestingly, several previously reported musculoskeletal risk markers were present in similar proportions of patients with and without ATTR-CM in our study. The majority of patients with a medical history including ≥2 or more conditions of lumbar spinal stenosis, non-traumatic rotator cuff tear, arthroplasty and CTS did not have ATTR-CM, which may reflect the relative commonality of these conditions in an ageing population. Our findings on risk markers support the development of more effective screening for ATTR-CM [35].

Limitations

There were some limitations to the study, including that it was terminated before the planned sample size was reached (2000 patients) and does not have power to provide precise prevalence estimates. The study was also not designed to provide full diagnostic screening for amyloidosis and additional testing conducted outside of the study (for example, AL testing in patients with grade 0 uptake) was not captured. Similarly, biopsies were performed at the discretion of the investigator, and the lack of reported findings may indicate that the value was not considered sufficient for patients to endure an invasive procedure. This may mean that some patients with grade 1 uptake had ATTR-CM but were not included in our prevalence estimates. Moreover, although we had sparse genotyping data for patients with negative scintigraphy, there may be individuals in this group who have a variant transthyretin genotype and clinical signs of cardiomyopathy that may benefit from additional testing. Conversely, due to our enriched population, our observed prevalence may be higher than would be expected in a broader population of patients with HFpEF or HFmrEF.

A further limitation is that 32 (9%) patients had unevaluable scintigraphy findings, mostly due to incomplete (19/32) or inadequate quality (11/32) imaging for central lab requirements. As this study had strict image requirements to ensure consistent interpretation and re-imaging was not possible, it is likely that the proportion of patients with unevaluable imaging is higher than would be observed in normal clinical practice. The ATTR-CM statuses of these patients were unknown, and they were not included in the prevalence estimates to avoid bias.

Our examination of regional prevalence was likely affected by centre bias. Demographics of patients in the geographical vicinity of each participating site likely contributed to the overall population profile and low enrolment led to poor representation of some minority groups. We also noted relevant differences in baseline characteristics by region, and unequal proportions of patients were recruited from specialist centres or general centres where the investigator had a subspeciality interest in ATTR-CM. Despite strict criteria, some centres may have enrolled more restrictive cohorts than others. Our enrolment criteria also excluded patients with LVEF ≤40%, which would have prevented the identification of some patients with ATTR-CM; for example, a significant proportion of patients with V112I variant ATTR-CM have LVEF ≤40% [36]. Further, the majority of measures were collected locally, with potential for methodological differences.

To improve disease screening, future studies identifying the most effective combinations of risk markers for ATTR-CM are warranted. Though we did not have complete data with which to analyse, the association between ATTR-CM prevalence and Mayo score, or perhaps imaging modalities (i.e. SPECT vs SPECT/CT), may have been interesting additional evaluations in our study population.

Conclusion

This international epidemiological study found the prevalence of ATTR-CM among evaluable patients with HFpEF or HFmrEF and risk markers for ATTR-CM, not being evaluated for amyloidosis, to be 18% (95% CI: 13.7–22.5). Additional analyses confirmed several of the previously reported risk markers for ATTR-CM, including male sex, older age, a history of CTS, higher NT-proBNP concentration, and higher end-diastolic IVST. These findings further highlight the need for increased awareness of risk markers for ATTR-CM and more intensive screening of patients displaying them.

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Disclosure statement

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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.

References

[1] Ruberg FL, Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872–2891. doi: 10.1016/j.jacc.2019.04.003.

[2] Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol. 2016;68(10):1014–1020. doi: 10.1016/j.jacc.2016.06.033.

[3] Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39(30):2799–2806. doi: 10.1093/eurheartj/ehx589.

[4] Garcia-Pavia P, Fine N, Weissman NJ, et al. Patients with transthyretin amyloid cardiomyopathy may have preserved, mildly reduced, or reduced ejection fraction. Eur Heart J. 2021;42(Supplement_1):ehab724.0717. doi: 10.1093/eurheartj/ehab724.0717.

[5] Shah SJ, Fine N, Garcia-Pavia P, et al. Effect of tafamidis on cardiac function in patients with transthyretin amyloid cardiomyopathy: a post hoc analysis of the ATTR-ACT randomized clinical trial. JAMA Cardiol. 2024;9(1):25–34. doi: 10.1001/jamacardio.2023.4147.

[6] Martyn T, Saef J, Dey AR, et al. Racial and genetic differences in presentation of transthyretin amyloid cardiomyopathy with impaired left ventricular function. JACC Heart Fail. 2022;10(9):689–691. doi: 10.1016/j.jchf.2022.06.006.

[7] Zhou Q, Li P, Zhao H, et al. Heart failure with mid-range ejection fraction: a distinctive subtype or a transitional stage? Front Cardiovasc Med. 2021;8:678121. doi: 10.3389/fcvm.2021.678121.

[8] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591–602. doi: 10.1038/nrcardio.2017.65.

[9] Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi: 10.1161/circheartfailure.119.006075.
[10] Tahara N, Lairez O, Endo J, et al. ^{99m}Technetium-pyrophosphate scintigraphy: a practical guide for early diagnosis of transthyretin amyloid cardiomyopathy. ESC Heart Fail. 2022;9(1):251–262. doi: 10.1002/ehf2.13693.
[11] Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007–1016. doi: 10.1056/NEJMoa1805689.
[12] Rozenbaum MH, Large S, Bhambri R, et al. Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy. J Comp Eff Res. 2021;10(11):927–938. doi: 10.2217/cer-2021-0071.
[13] Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail. 2019;7(8):709–716. doi: 10.1016/j.jchf.2019.04.010.
[14] Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021;42(16):1554–1568. doi: 10.1093/eurheartj/ehab072.
[15] Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol. 2005;46(6):1076–1084. doi: 10.1016/j.jacc.2005.05.073.
[16] Spertus JA, Jones PG, Sandhu AT, et al. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. J Am Coll Cardiol. 2020;76(20):2379–2390. doi: 10.1016/j.jacc.2020.09.542.
[17] Magdi M, Mostafa MR, Abusnina W, et al. A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. Am J Cardiovasc Dis. 2022;12(3):102–111.
[18] AbouEzzeddine OF, Davies DR, Scott CG, et al. Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. JAMA Cardiol. 2021;6(11):1267–1274. doi: 10.1001/jamacardio.2021.3070.
[19] Bennani Smires Y, Victor G, Ribes D, et al. Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. Int J Cardiovasc Imaging. 2016;32(9):1403–1413. doi: 10.1007/s10554-016-0915-z.
[20] González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015;36(38):2585–2594. doi: 10.1093/eurheartj/ehv338.
[21] Lindmark K, Pilebro B, Sundström T, et al. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. ESC Heart Fail. 2021;8(1):745–749. doi: 10.1002/ehf2.13110.
[22] Ruiz-Hueso R, Salamanca-Bautista P, Quesada-Simón MA, et al. Estimating the prevalence of cardiac amyloidosis in old patients with heart failure-barriers and opportunities for improvement: the PREVAMIC study. J Clin Med. 2023;12(6):2273. doi: 10.3390/jcm12062273.
[23] Chander Mohan J, Dalal J, Chopra VK, et al. Suspecting and diagnosing transthyretin amyloid cardiomyopathy (ATTR-CM) in India: an Indian expert consensus. Indian Heart J. 2022;74(6):441–449. doi: 10.1016/j.ihj.2022.11.006.
[24] Gertz M, Adams D, Ando Y, et al. Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. BMC Fam Pract. 2020;21(1):198. doi: 10.1186/s12875-020-01252-4.
[25] Rozenbaum MH, Large S, Bhambri R, et al. Impact of delayed diagnosis and misdiagnosis for patients with transthyretin amyloid cardiomyopathy (ATTR-CM): a targeted literature review. Cardiol Ther. 2021;10(1):141–159. doi: 10.1007/s40119-021-00219-5.
[26] Elliott P, Drachman BM, Gottlieb SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. Circ Heart Fail. 2022;15(1):e008193. doi: 10.1161/circheartfailure.120.008193.
[27] Damy T, Bourel G, Slama M, et al. Incidence and survival of transthyretin amyloid cardiomyopathy from a French nationwide study of in- and out-patient databases. Orphanet J Rare Dis. 2023;18(1):345. doi: 10.1186/s13023-023-02933-w.
[28] Lauppe R, Liseth Hansen J, Fornwall A, et al. Prevalence, characteristics, and mortality of patients with transthyretin amyloid cardiomyopathy in the Nordic countries. ESC Heart Fail. 2022;9(4):2528–2537. doi: 10.1002/ehf2.13961.
[29] Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. Circulation. 2016;133(3):282–290. doi: 10.1161/CIRCULATIONAHA.115.018852.
[30] Kroi F, Fischer N, Gezin A, et al. Estimating the gender distribution of patients with wild-type transthyretin amyloid cardiomyopathy: a systematic review and meta-analysis. Cardiol Ther. 2021;10(1):41–55. doi: 10.1007/s40119-020-00205-3.
[31] Patel RK, Ioannou A, Razvi Y, et al. Sex differences among patients with transthyretin amyloid cardiomyopathy – from diagnosis to prognosis. Eur J Heart Fail. 2022;24(12):2355–2363. doi: 10.1002/ejhf.2646.
[32] Bruno M, Castaño A, Burton A, et al. Transthyretin amyloid cardiomyopathy in women: frequency, characteristics, and diagnostic challenges. Heart Fail Rev. 2021;26(1):35–45. doi: 10.1007/s10741-020-10010-8.
[33] Aimo A, Panichella G, Garofalo M, et al. Sex differences in transthyretin cardiac amyloidosis. Heart Fail Rev. 2024;29(2):321–330. doi: 10.1007/s10741-023-10339-w.
[34] Nativi-Nicolau JN, Karam C, Khella S, et al. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. Heart Fail Rev. 2022;27(3):785–793. doi: 10.1007/s10741-021-10080-2.
[35] Huda A, Castaño A, Niyogi A, et al. A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy. Nat Commun. 2021;12(1):2725. doi: 10.1038/s41467-021-22876-9.
[36] Saef J, Martyn T, Ray Dey A, et al. Changes in left ventricular ejection fraction and clinical trajectories of transthyretin cardiac amyloidosis with systolic dysfunction. J Clin Med. 2023;12(23):7250. doi: 10.3390/jcm12237250.