International Prevalence of Transthyretin Amyloid Cardiomyopathy in High-Risk Patients With Heart Failure and Preserved or Mildly Reduced Ejection Fraction

Sergi Yun[1,2], Giovanni Palladini[3,4], Lisa Anderson[5], Eve Cariou[6], Ronnie Wang[7], Franca Angeli[8], Pablo Garcia-Pavia[9]

[1]Bio-Heart Cardiovascular Diseases Research Group, Bellvitge Biomedical Research Institute (IDIBELL), Bellvitge University Hospital, L'Hospitalet de Llobregat, Spain; [2]CIBERCV, Carlos III Health Institute, Madrid, Spain; [3]University of Pavia, Pavia, Italy; [4]Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, Pavia, Italy; [5]St George's University of London, London, UK; [6]Rangueil University Hospital, Toulouse, France; [7]Pfizer Inc, Groton, CT, USA; [8]Pfizer Inc, New York, NY, USA; [9]Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, Universidad Francisco de Vitoria, and Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain

INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) often presents as heart failure with preserved (HFpEF) or mildly reduced (HFmrEF) ejection fraction.[1-4]
- ATTR-CM is typically fatal within a few years if left untreated.[5-7]
- Historically, ATTR-CM has been underdiagnosed due to its non-specific symptoms and limited disease awareness among non-specialist clinicians.[8] Because of this, the true prevalence of ATTR-CM is unclear.
- Recent developments in non-invasive cardiac scintigraphy and the approval of disease-modifying therapy in many regions lends support towards the benefits of ATTR-CM screening among clinically at-risk patients.[9-11]
- This epidemiology study aimed to determine the international prevalence of ATTR-CM in high-risk patients with HFpEF or HFmrEF who were not clinically suspected to have ATTR-CM.

METHODS

- An international, multicenter, epidemiology study (NCT04424914).
- Enrolled patients were at risk of ATTR-CM but not currently suspected to have amyloidosis (**Table 1**).
- ATTR-CM was diagnosed using radionucleotide scintigraphy with SPECT as grade 2 or 3 cardiac uptake, or grade 1 uptake with a confirmatory biopsy.
  - Biopsies were encouraged for patients with grade 1 uptake but performed at the investigator's discretion. No patients with grade 1 uptake had a biopsy recorded.
  - All patients with cardiac uptake underwent exclusionary testing for light chain amyloidosis.
- The study was terminated early (without safety concerns) to allow dissemination of the findings.

Table 1: Key patient enrollment criteria

Inclusion criteria	Exclusion criteria
• Age ≥60 years	History of:
• History of heart failure	• HFrEF (LVEF ≤40%)
• LVEF >40%	• Amyloidosis
• End-diastolic IVST ≥12 mm	• Cardiomyopathy of known cause
• No suspicion of amyloidosis	• Severe valvular disease
	• Coronary heart disease

HFrEF=heart failure with reduced ejection fraction; IVST=interventricular septum thickness; LVEF=left ventricular ejection fraction

RESULTS

Patients

- 347 patients were enrolled at 36 centers across 8 countries and 3 continents between December 2020 and June 2023 (**Table 2**).
- 42% of patients were from specialist ATTR-CM referral centers or general centers where the investigator had a subspecialist interest in ATTR-CM (**Table 2**).
- Mean age (SD) among all patients was 78 (8.2) years, 53% were male, 86% were White, and 63% were in Europe (**Table 2**).
- Most patients had New York Heart Association functional class II symptoms (66%). Median left ventricular ejection fraction (LVEF) was 60% (quartile 1, 3: 53.0, 64.0) (**Table 3**).

Prevalence and Risk Factors

- 56 of 315 evaluable patients (18%; 95% CI: 13.7–22.5) were found to have previously undiagnosed ATTR-CM (**Figure 1**).
  - Scintigraphy results were unevaluable in 32 patients due to incomplete, poor quality, or unclear imaging. These patients are not included in the prevalence estimate.
  - Among the 56 patients diagnosed with ATTR-CM and genotype findings at the end of the study, 84% had wild-type transthyretin.
- Prevalence was higher in Europe (24%) than in North America (5%) or Asia (9%) (**Figure 2**).
- Prevalence was higher in older vs younger patients (particularly those aged ≥85 years), and in males vs females (**Figure 3**).
- The number of patients in each country was small, but there were some notable differences in demographic and clinical characteristics between regions.
  - Patients in Europe had a higher median age (31% were ≥85 years vs 17% in Asia and 7% in North America).
  - Median end diastolic interventricular septum thickness (IVST) in European countries was 14 mm vs 13 mm in other regions.
  - Median N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration was higher in most European countries than in other regions.
  - 54% of patients in Europe were male, compared with 48% in North America and 65% in Asia.
  - The proportion of patients enrolled at specialist ATTR-CM referral centers or general centers where the investigator had a subspecialist interest in ATTR-CM was 55% in Europe, 52% in Asia, and 14% in North America.
- The creation of a comparator group without ATTR-CM allowed for evaluation of risk factors.
  - These included a higher NT-proBNP concentration a higher end diastolic IVST, male sex, history of carpal tunnel syndrome, higher age, higher troponin T concentration, lower supine systolic blood pressure, and lower modified body mass index (**Table 3 and Figure 3**).

Table 2: 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, mean (SD), y	77.7 (8.2)	75.6 (7.5)	76.5 (7.9)	84.1 (6.6)
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 American African	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)
Other or NR	2 (0.6)	0	2 (0.8)	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)
UK	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)
Patients enrolled at a specialist ATTR-CM referral center or general center where the investigator had a subspecialist interest in ATTR-CM				
n (%)	146 (42.1)	6 (18.8)	103 (39.8)	37 (66.1)

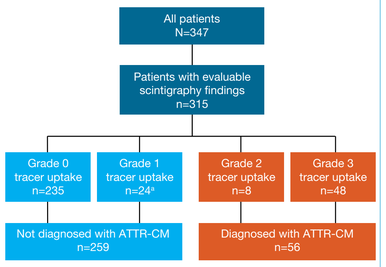
ATTR-CM=transthyretin amyloid cardiomyopathy; NR=not reported

Table 3: Clinical characteristics

	Patients				P value with vs without ATTR-CM[a]
	All N=347	Non-evaluable findings n=32	Without ATTR-CM n=259	With ATTR-CM n=56	
NYHA classification, n (%)					
I	33 (9.5)	5 (15.6)	26 (10.0)	2 (3.6)	0.3006[b]
II	230 (66.3)	22 (68.8)	165 (63.7)	43 (76.8)	
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[c]	n=213	n=13	n=150	n=50	<0.0001
Median (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)	
Supine systolic BP, mmHg	n=334	n=31	n=249	n=54	0.0299
Median (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)	
LVEF, %	n=346	n=32	n=258	n=56	0.1749
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)	
End-diastolic IVST, mm	n=344	n=31	n=257	n=56	<0.0001
Median (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)	
eGFR, mL/min/1.73 m^2	n=267	n=18	n=201	n=48	0.1392
Median (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)	
NT-proBNP, ng/L	n=322	n=30	n=240	n=52	<0.0001
Median (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)	
Troponin T, µg/L	n=95	n=2	n=70	n=23	0.0001
Median (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)	
KCCQ-OS score	n=345	n=32	n=257	n=56	0.3941
Median (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)	
6MWT distance, m	n=82	n=4	n=54	n=24	0.7007
Median (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)	
History of carpal tunnel syndrome, n (%)	45 (13.0)	4 (12.5)	26 (10.0)	15 (26.8)	0.0007

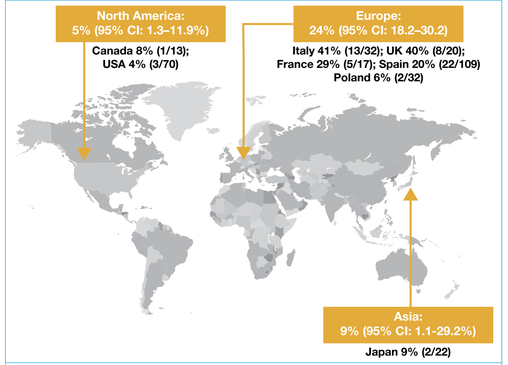
[a] P values from the chi-squared test, Fisher's exact test, *t*-test, or Wilcoxon rank sum test, as appropriate. [b] Functional classes I and II vs III and IV. [c] mBMI was calculated as serum albumin (g/L) × BMI (kg/m^2).
6MWT=6-minute walk test; ATTR-CM=transthyretin amyloid cardiomyopathy; BP=blood pressure; eGFR=estimated glomerular filtration rate; IVST=interventricular septal thickness; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LVEF=left ventricular ejection fraction; mBMI=modified body mass index; NT-pro-BNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; Q=quartile

Figure 1: Prevalence of ATTR-CM



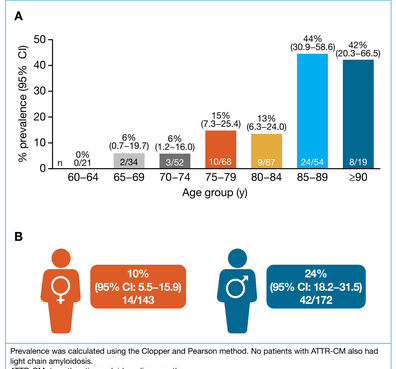
[a] No patients with grade 1 uptake had a recorded cardiac biopsy.
Prevalence was calculated using the Clopper and Pearson method. No patients with ATTR-CM also had light chain amyloidosis.
ATTR-CM=transthyretin amyloid cardiomyopathy

Figure 2: Prevalence by region



Prevalence was calculated using the Clopper and Pearson method.

Figure 3: Prevalence by (A) age and (B) sex



Prevalence was calculated using the Clopper and Pearson method. No patients with ATTR-CM also had light chain amyloidosis.
ATTR-CM=transthyretin amyloid cardiomyopathy

CONCLUSIONS

- Internationally, 18% of evaluable high-risk patients with HFpEF or HFmrEF were found to have previously undiagnosed ATTR-CM.
- Prevalence was higher in Europe (24%) than North America (5%) or Asia (9%), and this regional variability may be due to recruitment bias or differences in regional patient characteristics.
- Some previously identified risk factors were confirmed in this study, most notably a higher NT-proBNP concentration and end diastolic IVST, male sex, a higher age, and a history of carpal tunnel syndrome.
- ATTR-CM is frequently underdiagnosed and disease-modifying treatment is most effective when given early in the disease course.
- Findings from our study support the identification of patients at risk of ATTR-CM, allowing those with previously undiagnosed disease to receive effective treatment.

REFERENCES

1. Garcia-Pavia P, et al. Eur Heart J 2021;42. **2.** Shah SJ, et al. JAMA Cardiol 2024;9:25-34. **3.** Martyn T, et al. JACC Heart Fail 2022;10:689-91. **4.** Zhou Q, et al. Front Cardiovasc Med 2021;8:678121. **5.** Ruberg FL, et al. J Am Coll Cardiol 2019;73:2872-91. **6.** Grogan M, et al. J Am College Cardiol 2016;68:1014-20. **7.** Gillmore JD, et al. Eur Heart J 2018;39:2799-806. **8.** Maurer MS, et al. Circ Heart Fail 2019;12:e006075. **9.** Tahara N, et al. ESC Heart Fail 2022;9:251-62. **10.** Maurer MS, et al. N Engl J Med 2018;379:1007-16. **11.** Elliott P, et al. Circ Heart Fail 2022;15:e008193.

DISCLOSURES

SY: Speaker in scientific meetings for AstraZeneca, Bristol Myers Squibb, Rovi, and Pfizer; funding from Bristol Myers Squibb, Rovi, and Pfizer for scientific meeting expenses; and his institution received research grants/educational support from AstraZeneca, Novartis, Vifor, and Pfizer. **GP:** Advisory board for Argobio, GlaxoSmithKline, Janssen, Protego, and Prothena, and honoraria from Janssen, Pfizer, Prothena, Sebia, and Siemens. **LA:** Speaker in scientific meetings for Alnylam, Pfizer, and Vifor; advisory board for Akcea, Alnylam, AstraZeneca, and Pharmacosmos; consultancy for Pfizer; and her institution received research grants/educational support from AstraZeneca and Pfizer. **EC:** Nothing to disclose. **RW and FSA:** Employees of Pfizer and hold stock or stock options. **PGP:** Speaker in scientific meetings for Alnylam, BridgeBio, Ionis, Intellia, AstraZeneca, Novo Nordisk, and Pfizer; funding from Alnylam and Pfizer for scientific meeting expenses; consultancy fees from Alnylam, Attralus, BridgeBio, Neuroimmune, AstraZeneca, Novo Nordisk, Alexion, Intellia, and Pfizer; and his institution received research grants/educational support from Alnylam, BridgeBio, AstraZeneca, Novo Nordisk, Intellia, and Pfizer.

ACKNOWLEDGMENTS

This study was supported by Pfizer. Medical writing support was provided by Jennifer Bodkin of Engage Scientific Solutions and was funded by Pfizer.

Electronic Poster

Please scan this QR code with your smartphone app to view a copy of this poster. If you don't have a smartphone, access the poster via the internet at: https://scientificpubs.congressposter.com/p/7dgzji68rx121uay

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