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Clinical Research

Prevalence of Cardiac Amyloidosis Among Elderly Patients With Recent-Onset Atrial Fibrillation: The PREVAL-ATTR Study

Paloma Remior-Pérez, MD,[a] Miriam Gómez-Molina, MD, PhD,[b] Daniel García-Rodríguez, MD,[a] María Gallego-Delgado, MD, PhD,[c,d] Laroussi Mohamed-Salem, MD,[e] Javier de Haro-del Moral, MD,[f] Fernando Hernández-Terciado, MD,[a] Daniel de Castro, MD,[a] Rocio Eiros-Bachiller, MD, PhD,[d] Fernando Dominguez, MD, PhD,[a,c,g] Esther Gonzalez-Lopez, MD, PhD,[a,c,g] Eduardo Villacorta, MD, PhD,[c,d] Domingo A. Pascual-Figal, MD, PhD,[b,c,g,h,‡] and Pablo Garcia-Pavia, MD, PhD[a,c,g,i,‡]

[a] *Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain*

[b] *Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain*

[c] *CIBERCV, Instituto de Salud Carlos III, Madrid, Spain*

[d] *Inherited Cardiac Diseases Unit, Department of Cardiology, Instituto de Investigación Biomédica de Salamanca (IBSAL), Complejo Asistencial Universitario de Salamanca, Gerencia Regional de Salud de Castilla y León (SACYL), Salamanca, Spain*

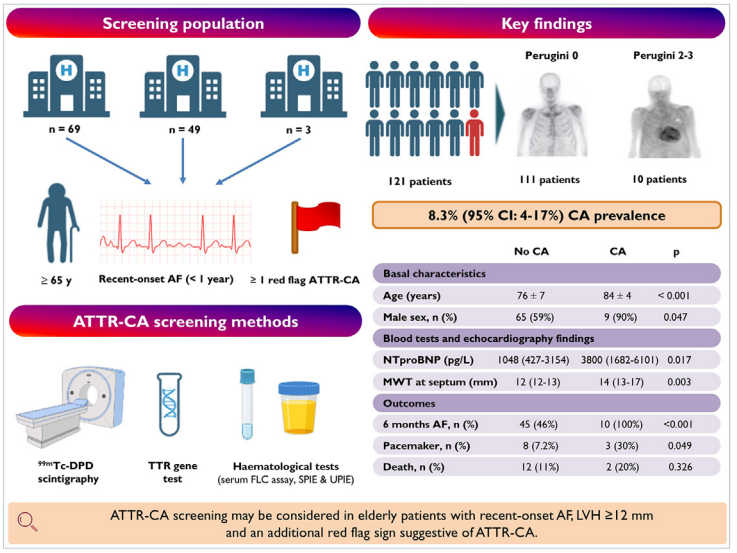
[e] *Department of Nuclear Medicine, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain*

[f] *Department of Nuclear Medicine, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain*

[g] *Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain*

[h] *Universidad de Murcia, Murcia, Spain*

[i] *Universidad Francisco de Vitoria (UFV), Pozuelo de Alarcón, Spain*



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ABSTRACT

Background: Transthyretin cardiac amyloidosis (ATTR-CA) is increasingly recognized as a treatable form of heart failure. Atrial fibrillation (AF) is common in patients with ATTR-CA. Whether recent-onset AF can be used as an early marker to identify patients with ATTR-CA has not been elucidated.

Methods: This was a prospective study conducted at 3 Spanish centres. ATTR-CA noninvasive screening was offered to patients $\geq$ 65 years of age recently diagnosed ($<$ 1 year) with nonvalvular AF and who had $\geq$ 1 echocardiographic, electrocardiographic, or clinical sign suggestive of ATTR-CA.

Results: A total of 121 patients were included (75% male, mean age 77 $\pm$ 7 years). Ten patients (8.3%; 95% confidence interval [CI],4-14.7%), were diagnosed with cardiac amyloidosis (CA): 5 with definite wild-type ATTR-CA (ATTRwt), 4 with likely ATTRwt, and 1 with undetermined CA. Compared with patients without CA, patients with CA were older (84 $\pm$ 4 vs 76 $\pm$ 7 years; $P < 0.001$), more frequently men (90% vs 59%; $P = 0.047$), presented higher median N-terminal pro-B-type natriuretic peptide (NTproBNP) (3800 pg/L, interquartile range [IQR]:1682-6101 vs 1048 pg/mL, IQR: 427-3154; $P = 0.017$) and higher left ventricular hypertrophy (LVH) (14 mm, IQR: 13-17 vs 12 mm, IQR: 12-13; $P = 0.003$). Patients with CA also showed higher rate of permanent AF (90% vs 49.5%; $P = 0.018$) and a greater need for pacemaker implantation during follow-up (30% vs 7.3%; $P = 0.049$). No differences in mortality were observed between patients with and without CA after a median follow-up of 13 months (IQR: 11-16 months).

Conclusions: Routine DPD scanning in elderly patients with recent-onset AF, LVH and an additional red flag may help to identify patients with ATTR-CA. However, larger studies evaluating this strategy in more diverse clinical settings would be required.

RÉSUMÉ

Contexte : L'amylose cardiaque à transthyrétine (ATTR-CA) est de plus en plus reconnue comme étant une forme traitable d'insuffisance cardiaque. La fibrillation auriculaire (FA) est fréquente chez les patients atteints d'ATTR-CA. Il n'a pas encore été établi si une apparition récente de FA peut être utilisée comme premier marqueur pour déceler l'ATTR-CA chez les patients.

Méthodologie : Il s'agit d'une étude prospective menée dans 3 établissements espagnols. Le dépistage non invasif de l'ATTR-CA a été offert à des patients de 65 ans et plus ayant récemment (au cours des 12 mois précédents) reçu un diagnostic de FA et présentant au moins 1 signe échocardiographique, électrocardiographique ou clinique évoquant l'ATTR-CA.

Résultats : Au total, l'étude comptait 121 patients (75 % hommes, âge médian de 77 $\pm$ 7 ans). Dix patients (8,3 %; intervalle de confiance [IC] à 95 % : 4-14,7 %) ont reçu un diagnostic d'amylose cardiaque : 5 patients atteints du type sauvage d'ATTR-CA (ATTRts) confirmé, 4 atteints probablement de l'ATTRts et 1 dont le type était indéterminé. Comparativement aux patients qui n'étaient pas atteints d'amylose cardiaque, ceux qui en étaient atteints étaient plus âgés (84 $\pm$ 4 *vs* 76 $\pm$ 7 ans; $p < 0{,}001$), étaient plus souvent des hommes (90 % *vs* 59 %; $p = 0{,}047$), présentaient un taux médian de propeptide natriurétique de type B N-terminal (NTproBNP) plus élevé (3800 pg/L, écart interquartile [EI] : 1682-6101 *vs* 1048 pg/ml, EI : 427-3154; $p = 0{,}017$) et une hypertrophie ventriculaire gauche (HVG) plus importante (14 mm, EI : 13-17 *vs* 12 mm, EI : 12-13; $p = 0{,}003$). Les patients atteints d'amylose cardiaque affichaient également un taux plus élevé de FA permanente (90 % *vs* 49,5 %; $p = 0{,}018$) et ont eu plus besoin d'une implantation d'un stimulateur cardiaque pendant le suivi (30 % *vs* 7,3 %;$p = 0{,}049$). Aucune différence dans le taux de mortalité n'a été observée entre les patients atteints d'amylose cardiaque et ceux qui n'en étaient pas atteints après une période de suivi médiane de 13 mois (EI : 11-16 mois).

Conclusions : Une scintigraphie au DPD régulière chez des patients âgés atteints de FA d'apparition récente, une HVG et un signal d'alarme additionnel peuvent aider à déceler des patients atteints d'ATTR-CA. Cependant, il faudrait de plus vastes études visant à évaluer cette stratégie dans des contextes cliniques plus diversifiés.

Cardiac amyloidosis (CA) is an infiltrative disease caused by the extracellular accumulation of amyloid deposits at heart level.[1,2] According to the protein composition, 9 different types of CA have been described, with amyloid light chain cardiac amyloidosis (AL-CA) and transthyretin cardiac amyloidosis (ATTR-CA) being the most prevalent forms.[1]

ATTR-CA is increasingly recognized as a treatable cause of heart failure (HF) that is particularly common in elderly individuals with frequent cardiovascular conditions such as heart failure with preserved ejection fraction (HFpEF) or severe aortic stenosis.[3-5] Several specific therapies have been developed to treat ATTR-CA, and new therapies are on the horizon.[6,7]

Early recognition of patients affected by ATTR-CA is critical because specific therapies seem to be more effective if administered early in the disease course.[8,9] Recent position papers and consensus documents recommend screening for ATTR-CA in all patients with left ventricular (LV) wall thickness $\geq$ 12 mm and 1 or more red flags or clinical scenarios suggestive of cardiac amyloidosis.[1,10] Unfortunately, despite these recommendations, a significant proportion of patients with ATTR-CA are still being diagnosed in an advanced stage of the disease.[11,12]

Heart rhythm disturbances, including atrial arrhythmias and conduction disorders, are frequently observed in patients with established ATTR-CA.[11,13,14] Among them, atrial fibrillation (AF) is the most common, with a reported prevalence of up to 70% in patients with wild-type ATTR-CA.[15,16] However, it is unknown whether AF may also represent an early manifestation of ATTR-CA that should

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‡These authors are senior co-authors.

Corresponding author: Dr Pablo Garcia-Pavia, Department of Cardiology Hospital Universitario Puerta de Hierro, Manuel de Falla, 2; 28222 Madrid, Spain. Tel.: (+ 34) 91 191 7297; fax: (+34) 91 191 7718.

E-mail: pablogpavia@yahoo.es

Twitter: @dr_pavia

See page 9 for disclosure information.

be incorporated as a new clinical scenario to suspect ATTR-CA.

This study sought to determine the percentage of patients with ATTR-CA among elderly patients with recent-onset AF and additional red flags suggestive of ATTR-CA.

Material and Methods

Study design

This was a multicentre prospective screening study conducted at 3 university hospitals in Spain (Hospital Universitario Puerta de Hierro Majadahonda, Hospital Universitario Virgen de la Arrixaca, and Complejo Asistencial Universitario de Salamanca). The study protocol was approved by the Ethic Committee of Hospital Universitario Virgen de la Arrixaca and conformed to the principles of the Helsinki Declaration. All participants provided written informed consent. The authors from each participating centre guarantee the integrity of data.

Study population

Inclusion criteria included individuals $\geq$ 65 years of age, diagnosed of nonvalvular AF during the previous year before signing the consent to participate, who met at least 1 of the following requirements: presence of end-diastolic LV wall thickness $\geq$ 12 mm measured in long paraesternal view on a transthorathic echocardiogram; complete atrioventricular block of unknown etiology or previous history of pacemaker implantation caused by cardiac conduction disturbances; low voltage pattern on electrocardiogram (ECG) defined as QRS amplitude $\leq$ 0.5 mV in all limb leads or $\leq$ 1 mV in all precordial leads; pseudo-infarction (pseudoMI) pattern on ECG defined as Q wave in $\geq$ 2 consecutive leads in the absence of coronary disease; history of carpal tunnel syndrome (CTS), lumbar spinal stenosis (LSS), or unexplained polyneuropathy.

Exclusion criteria included refusal to participate; presence or history of significant valvular disease, defined as moderate or severe left valvular stenosis or regurgitation or valvular prostheses in any location; AF triggered by external or reversible causes as hypo/hyperthyroidism, pulmonary embolism, hypothermia, ischemia, myocarditis, or after cardiac or thoracic surgery.

Patients with recent diagnosis of nonvalvular AF were recruited by cardiologists from the outpatient clinics, cardiology inpatients, emergency departments, or during elective electrical cardioversion (ECV) procedures at participating institutions between December 2019, and May 2022. Patients who met the eligibility requirements without exclusion criteria were offered participation in the study.

Individuals who accepted to participate underwent a ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) bone scintigraphy. The standardized protocol at the 3 centres consisted of injecting 370 to 740 MBq (10-20 mCi) of ^{99m}Tc-DPD followed by imaging 3 hours later. Single photon emission computed tomography (SPECT) to confirm that myocardial tracer retention was performed in patients who exhibited any degree of cardiac uptake in planar images. Those without tracer uptake in planar images did not undergo SPECT.

In patients with a positive ^{99m}Tc-DPD scintigraphy, both transthyretin (TTR)-gene sequencing and hematologic monoclonal free light chain screening was undertaken. Hematologic tests included serum free light chain (FLC) assay (Freelite Assay, Binding Site, Birmingham, UK) and serum and urine immunofixation. Interpretation of FLC ratio intervals was made according to the estimated glomerular filtration rate (eGFR).[17]

A definite diagnosis of wild type ATTR-CA (ATTRwt) was established noninvasively in the presence of a grade 2 or 3 myocardial uptake on ^{99m}Tc-DPD cardiac scintigraphy, negative blood and urine tests for monoclonal free light chain, and absence of variants in the TTR gene, according to current consensus documents.[1,10] In patients with grade 2 or 3 myocardial uptake on ^{99m}Tc-DPD scintigraphy and any monoclonal FLC abnormality who did not undergo endomyocardial biopsy (EMB), a multidisciplinary team of cardiologists experts in amyloidosis and hematologists reviewed their clinical data and the information about their clinical course during follow-up, and patients were classified as likely ATTRwt or undetermined CA.

Data collection

Demographic information and clinical characteristics including AF-related data, laboratory tests, ECG and echocardiographic parameters, and current medications were collected from medical records at inclusion. Information on outcomes was obtained from hospital or primary care medical records.

AF-related data included date of diagnosis, AF type (paroxysmal or persistent), CHA2DS2-VASc score, stroke-prevention strategy, symptom-management strategy (rate control vs rhythm control), the use of antiarrhythmic drugs, performance of pharmacologic/electrical cardioversion or pulmonary vein isolation (PVI). PVI was considered effective if sinus rhythm persisted 3 months after the procedure as previously described.[18]

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Cardiac biomarkers included N-terminal pro-brain natriuretic peptide (NT-proBNP, pg/L) and ultra-sensitive troponin I (μg/L). ECG measures were obtained from the closest available ECG to the inclusion date. Left ventricular hypertrophy (LVH) was considered based on Sokolow criteria.[19] Low voltage and pseudoMI patterns were defined using the aforementioned inclusion criteria.

The degree of ^{99m}Tc-DPD myocardium uptake was compared with the uptake of rib bones and graded according to the Perugini visual scale: 0 (no cardiac uptake and normal rib bone uptake), 1 (cardiac uptake $<$ rib bone uptake), 2 (cardiac uptake $=$ rib bone uptake), and 3 (cardiac uptake $>$ rib bone uptake).[20] Final interpretation of ^{99m}Tc-DPD images was performed on SPECT.

Statistical analysis

Categorical variables were expressed as number and percentage (%). Continuous variables with normal distribution were presented as mean and standard deviation (SD), whereas nonparametric variables were given as median and interquartile range (IQR). The normality assumption was verified using the Kolmogorov-Smirnov test or the Shapiro-Wilk test, depending on the size of each group.

Categorical data were analyzed using Fisher's exact test. Differences between quantitative variables were performed using unpaired Student's *t*-test for parametric variables and Mann-Whitney U test for non-normally distributed variables. A 2-sided P value < 0.05 was considered statistically significant. Median follow-up was estimated using the reverse Kaplan-Meier method. All statistical analysis was performed using SPSS statistical software version 23 (IBM Corporation, Armonk, NY).

Results

A total of 137 patients with new-onset AF accepted to participate in the study during the inclusion period. Of them, 16 individuals (12%) were excluded because they withdrew consent (n = 9), did not undergo ^{99m}Tc-DPD scintigraphy (n = 6), or did not meet the inclusion criteria (1 individual). Figure 1 shows the study flowchart.

Overall study cohort

The final study cohort comprised 121 patients. A total of 118 patients were enrolled at Hospital Universitario Puerta de Hierro and Hospital Universitario Virgen de la Arrixaca, whereas only 3 individuals were enrolled at Complejo Asistencial Universitario de Salamanca, as this centre started the trial much later than the other 2. Mean age was 77 ± 7 years, and 74 (75%) were men. Remarkably, 52 (43%) patients had history of HF (35 [67, 3%] HFpEF), and 8 (7%) patients had permanent pacemakers at inclusion.

The median NT-proBNP was 1265 pg/L (IQR: 464-3792), and mean eGFR was 67.9 ± 22.3 mL/min. Median left ventricular ejection fraction (LVEF) was 59% (IQR: 51%-63%), and median LV maximal wall thickness (MWT) at the septum and at posterior wall were 12 mm (IQR: 12-13) and 11 mm (IQR: 9-12), respectively. Median left atrium (LA) volume was 55 mL/m^2 (IQR: 40-72).

Regarding the type of AF at the time of inclusion, 63 (52%) individuals had paroxysmal AF, and 58 (48%) had persistent AF. Rhythm control was the preferred management strategy over rate control (67.8% vs 32.2%). Pharmacologic cardioversion and ECV were performed in 22 (18%) and 29 (24%) patients, respectively. PVI was performed in 12 (10%) individuals and was effective in 11 (92%).

Patients' characteristics at inclusion along with the number of cardiac amyloid red flags qualifying for the study are shown in Table 1 and Table 2, respectively.

During a median follow-up of 13 months (IQR: 11-16), 14 (12%) patients died, 7 (5.8%) were hospitalized because of HF, and 6 (5%) had strokes. The main cause of death was noncardiovascular (n = 9, 64%). Evolution to permanent AF 6 months after the diagnosis of AF and at the end of the follow-up occurred in 55 (51%) and 64 (53%) patients, respectively. Eleven (9%) patients required permanent pacemaker implantation during follow-up for a total of 19 patients (16%) in the cohort with pacemakers at the end of follow-up.

ATTR-CA prevalence

^{99m}Tc-DPD scintigraphy showed no myocardial uptake (Perugini 0) in 111 (91.7%) individuals, 4 (3.3%) had moderate uptake (Perugini 2), and 6 (5%) had severe myocardial uptake (Perugini 3). All individuals with grade 2 or 3 uptake underwent TTR genetic screening and all results were negative for TTR gene variants. Among these 10 individuals with grade 2 or 3 cardiac uptake, 5 had normal FLC ratios without monoclonal protein in serum and urine immunofixation (definite ATTRwt), whereas 5 showed altered FLC ratios (3 individuals) or a positive monoclonal protein in either serum or urine immunofixation (4 and 2, respectively). Histologic confirmation of CA subtype could not be obtained in any of the 5 patients with monoclonal hematologic tests abnormalities, as they refused EMB because of advanced age or comorbidities. Expert evaluation considering their clinical evolution led to classification of 4 subjects as likely ATTRwt and 1 (patient 5) as undetermined CA. Detailed characteristics of all patients with cardiac uptake on scintigraphy are presented in Table 3 and Table 4.

Based on these results, prevalence of CA in patients with recent-onset AF and red flags suggestive of ATTR-CA in our study was 8.3% (95% confidence interval [CI], 4%-14.7%).

When analyzing prevalence of CA according to the underlying red flags, LSS had the highest diagnostic yield, as 1 of the 3 patients with LSS was diagnosed with CA (33%). The diagnostic rates for the other red flags were as follows: 25% (1 of 4) for CTS, 16% (4 of 25) for low-voltage pattern, 13% (1 of 8) for atrioventricular conduction disease, and 11% (2/18) for pseudoMI pattern (Table 4). Prevalence of CA according to the number of red flags in patients with LVH, revealed a prevalence of 5.6% in patients with no additional red flags, 15.4% in those with 1 additional red flag, 16.7% with 2 additional red flags, and 50% with 3 additional red flags (Table 2).

Patients with CA vs patients with negative scintigraphy

Patients with CA were older (84 ± 4 vs 76 ± 7 years; $P < 0.001$) and more often male (90% vs 59%; $P = 0.047$). We did not find significant differences in comorbidities (including HF), clinical characteristics, and ATTR-CA red flags between the 2 groups (Table 1).

Patients with CA presented a higher median NT-proBNP (3800 pg/mL, IQR: 1682-6101 vs 1048 pg/L, IQR: 427-3154; $P = 0.017$) and a trend toward worse eGFRs (57 ± 24 vs 69 ± 22 mL/m^2; $P = 0.093$).

Both cohorts exhibited similar baseline ECG features and LVEF (58% [IQR: 51-63] vs 62% [IQR: 53-68]; $P = 0.168$) but patients with CA appeared to have larger LA (72 mL/m^2 [IQR: 48-102] vs 55 mL/m^2 [IQR: 39-71]; $P = 0.062$). LV MWT at the septum and at posterior wall was significantly increased in patients with CA (14 mm [IQR: 13-17] vs 12 mm [IQR: 12-13]; $P = 0.003$ and 14 mm [IQR: 12-18] vs 11 mm [IQR: 9-12]; $P = 0.002$, respectively).

The use of rate control drugs was frequent in patients with CA (70% were treated with beta blockers and 10% with calcium channel blockers). There were not statistical differences regarding the type of AF, the CHADS-VASc score, and the anticoagulation rate between the 2 groups.

During follow-up, 12 (11%) patients with negative ^{99m}Tc-DPD scintigraphy and 2 (20%) patients with CA died ($P = 0.326$). HF admissions and stroke events occurred only in patients from the negative scintigraphy group. Permanent AF was more prevalent both at 6 months after AF diagnosis

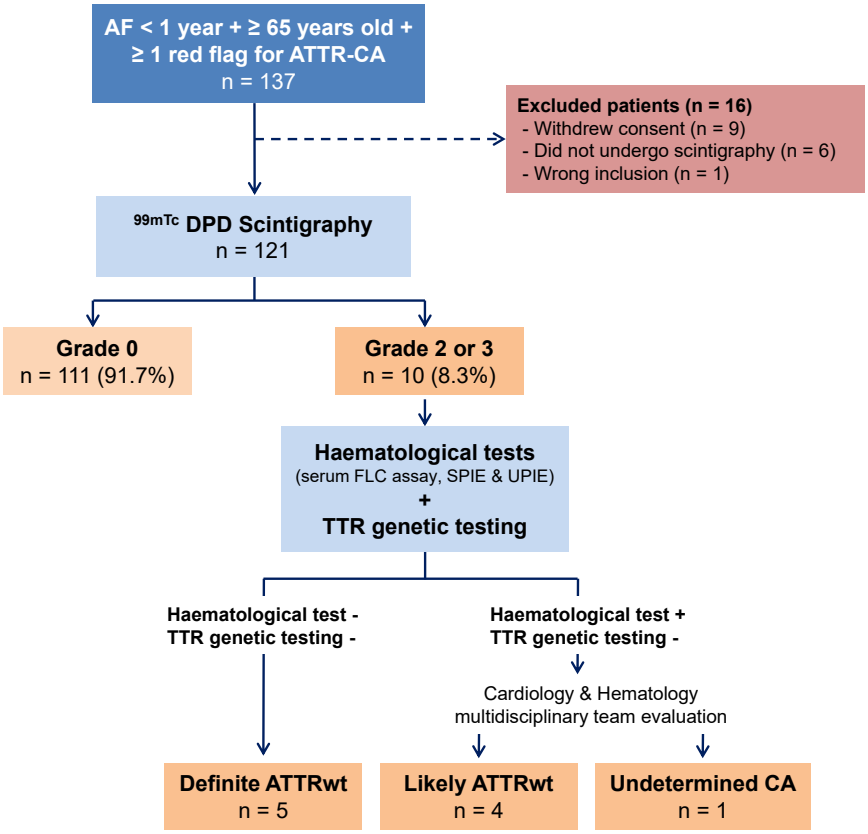

Figure 1. Study flowchart. AF, atrial fibrillation; ATTR-CA, transthyretin cardiac amyloidosis; ATTRwt, wild-type transthyretin cardiac amyloidosis; CA, cardiac amyloidosis; FLC, free light chain; SPIE, serum protein electrophoresis and immunofixation; UPIE, urine protein electrophoresis and immunofixation.

(100% vs 46%, $P < 0.001$), and at last follow-up (90% vs 50%, $P = 0.018$) in patients with CA. Patients with CA also exhibited higher rates of permanent pacemaker implantation (30% vs 7%, $P = 0.049$) at last follow-up.

Discussion

This study examined the prevalence of CA among elderly patients with recent diagnoses of nonvalvular AF and with an additional red flag for ATTR-CA. Using a noninvasive scintigraphy-based protocol, CA (mostly ATTRwt) was recognized in 8.3% of the study population. Patients diagnosed with CA were more frequently men, older than 80 years of age, with moderate LVH, and with higher rates of permanent AF and a higher need for permanent pacemaker implantation during follow-up. These results have implications when defining clinical scenarios for ATTR-CA screening and for management of AF.

Implications for ATTR-CA screening

ATTR-CA is a progressive, life-threatening disorder often misdiagnosed or diagnosed late. Although the exact prevalence of ATTR-CA is not clearly known, it seems to be greater than previously reported.[21] The development of cost-effective and noninvasive diagnostic tools such as cardiac/^{99m}Tc-DPD scintigraphy have contributed to facilitate the diagnosis.[22] Current specific treatments have shown to improve survival and functional capacity in this population, especially in early stages.[23] Hence, early accurate diagnosis is key to improve outcomes in these patients.

The 8.3% prevalence found in our cohort is similar to that reported in a recent meta-analysis in other frequent clinical settings such as HFpEF (12%), HF with reduced or mildly reduced ejection fraction (10%), severe aortic stenosis (8%), and hypertrophic cardiomyopathy phenotype (7%).[21] CA screening is now recommended among subjects $\geq$ 65 years of age and some of these frequent clinical scenarios in the presence of a LVH of $\geq$ 12 mm.[1] Given the similar prevalence obtained in our study, we believe that recent-onset AF could become a new clinical scenario to consider ATTR-CA screening.

Of note, our results contrast with a recent single-centre US study of 65 patients $\geq$ 60 years old with AF of indeterminate duration and with LVH, in which ATTR-CA screening detected only 1.5% prevalence.[24] Key differences between both studies that probably explain the disparity in the results are the difference in AF duration (recent-onset in our study vs indeterminate duration in the US study) and the inclusion in our study of additional red flags suggestive of ATTR-CA besides LVH.

Adverse long-term prognosis associated with ATTR-CA could have influenced the timing of AF onset for ATTR-CA screening, as it is unlikely that patients with long-standing AF would suffer from unrecognized ATTR-CA.

Table 1. Baseline characteristics and outcomes of patients included in the study

	Total (n = 121)	Negative scintigraphy (n = 111)	CA (n = 10)	*P* value
Demographics				
Age, years	76.7 (± 7.3)	76.1 (± 7.2)	84.3 (± 3.9)	< 0.001
Male	74 (61.2)	65 (58.6)	9 (90.0)	0.047
Clinical features				
Hypertension	92 (76.0)	86 (77.5)	6 (60.0)	0.249
Diabetes	40 (66.9)	36 (32.4)	4 (40.0)	0.728
Dyslipidemia	65 (53.7)	61 (55.0)	4 (40.0)	0.511
Heart failure	52 (43.0)	46 (41.4)	6 (60.0)	0.324
Heart failure admission	36 (29.8)	31 (27.9)	5 (50.0)	0.161
Peripheral artery disease	4 (3.3)	4 (3.6)	0 (0.0)	0.705
Coronary artery disease	21 (17.4)	19 (17.1)	2 (20.0)	0.684
Stroke	18 (14.9)	16 (14.4)	2 (20.0)	0.643
Carpal tunnel syndrome	4 (3.3)	3 (2.7)	1 (10.0)	0.295
Lumbar spinal stenosis	3 (2.5)	2 (1.8)	1 (10.0)	0.230
Polyneuropathy	0 (0.0)	0 (0.0)	0 (0.0)	-
Chronic kidney disease	24 (19.8)	23 (20.7)	1 (10.0)	0.685
Pacemaker at baseline	8 (6.6)	8 (7.2)	0 (0.0)	1.000
AF features				
Type				0.327
Paroxysmal	63 (52.1)	56 (50.5)	7 (70.0)	
Persistent	58 (47.9)	55 (49.5)	3 (30.0)	
CHADS-VASc score	4 (3-5)	4 (3-4)	4 (3-5)	0.371
Anticoagulation	114 (94.2)	105 (94.6)	9 (90.0)	0.462
Rhythm control	82 (67.8)	77 (69.4)	5 (50.0)	0.497
Pharmacologic cardioversion	22 (18.2)	21 (18.9)	1 (10.0)	0.687
Effective*	15 (68.2)	14/21 (66.7)	1/1 (100)	1.000
Electrical cardioversion	29 (24.0)	29 (26.1)	0 (0.0)	0.115
Effective*	24 (82.8)	24/29 (82.8)	-	-
Pulmonary vein isolation	12 (9.9)	12 (10.8)	0 (0.0)	0.596
Effective*	11 (91.7)	11/12 (91.7)	-	-
Antiarrhythmic drugs	34 (28.1)	33 (29.7)	1 (10.0)	0.279
Blood test				
Creatinine mg/dL	0.97 (0.77-1.22)	0.96 (0.76-1.20)	1.14 (0.92-.33)	0.124
eGFR, mL/min/1.73 m^2	67.88 (± 22.26)	68.90 (± 21.92)	56.56 (± 24.01)	0.093
NTproBNP, pg/L	1265 (464-3792)	1048 (427-3154)	3800 (1682-6101)	0.017
Ultrasensitive troponin I, µg/L†	31 (17-98)	31 (17-107)	44 (19-71)	0.981
ECG				
PR interval, ms‡	185 (± 36)	183 (± 36)	207 (± 16)	0.270
QRS duration, ms	96 (86-114)	97 (86-116)	91 (84-108)	0.408
Left/right bundle branch block	19 (15.7)	17 (15.3)	2 (20.0)	0.656
Low voltage	25 (20.8)	21 (19.1)	4 (40.0)	0.214
LVH	11 (9.2)	10 (9.1)	1 (10.0)	1.000
PseudoMI pattern	18 (15.0)	16 (14.5)	2 (20.0)	0.645
Echocardiography				
LVEF, %	59 (51-63)	58 (51-63)	62 (53-68)	0.168
Left atrium diameter, cm	4.5 (± 0.7)	4.5 (± 0.7)	4.5 (± 0.7)	0.844
Left atrium volume, mL/m^2	55 (40-72)	55 (39-71)	72 (48-102)	0.062
MWT at septum, mm	12 (12-13)	12 (12-13)	14 (13-17)	0.003
MWT posterior wall, mm	11 (9-12)	11 (9-12)	14 (12-18)	0.002
LV wall thickness ≥ 12 mm	105 (86.8)	95 (85.6)	10 (100.0)	0.356
Pericardial effusion	5 (4.1)	4 (3.6)	1 (10.0)	0.355
Outcomes				
Death	14 (11.6)	12 (10.8)	2 (20.0)	0.326
Heart failure admission	7 (5.8)	7 (6.3)	0 (0.0)	0.538
Stroke	6 (5.0)	6 (5.4)	0 (0.0)	0.589
AF 6 months postdiagnosis§	55 (51.4)	45 (46.4)	10 (100.0)	< 0.001
Permanent AF	64 (52.9)	55 (49.5)	9 (90.0)	0.018
Pacemaker	11 (9.2)	8 (7.2)	3 (30.0)	0.049

Values are n (%), mean (± SD) or median (IQR), unless otherwise indicated. Denominators are specified when overall data is missing.

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; ARNI, angiotensin-receptor neprilisyn inhibitor; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; MWT, maximal wall thickness; pseudoMI, pseudo-infarction; SD, standard deviation.

* Effectivity rate of sinus rhythm restoration among patients who underwent pharmacologic/electrical cardioversion or pulmonary vein isolation.

† n valid = 92.

‡ n valid = 4.

§ n valid = 117 (4 patients died before 6 months).

Table 2. Number of cardiac amyloid red flags and CA diagnostic rate according to the presence of LVH

	Total (n = 121)	Negative scintigraphy (n = 95)	CA (n = 10)	CA diagnostic rate
No LVH	16	16	0	0/16 = 0%
+ 1 red flag	12 (75.0%)	12 (75.0%)	-	-
+ 2 red flags	4 (25.0%)	4 (25.0%)		
LVH	105	95	10	10/105 = 9.5%
+ no red flags	71 (67.6%)	67 (70.5%)	4 (40.0%)	4/71 = 5.6%
+ 1 red flag	26 (24.8%)	22 (23.2%)	4 (40.0%)	4/26 = 15.4%
+ 2 red flags	6 (5.7%)	5 (5.3%)	1 (10.0%)	1/6 = 16.7%
+ 3 red flags	2 (1.9%)	1 (1.1%)	1 (10.0%)	1/2 = 50.0%

CA, cardiac amyloidosis; LVH, left ventricular hypertrophy ≥ 12 mm.

Demographic characteristics of our population are consistent with the reported classical ATTRwt phenotype characterized by male predominance in elderly adults. The male preponderance seen in our cohort could also be related with the higher prevalence of AF in men.[25] Given the advanced age of patients with CA found in our study, screening for CA in patients with recent-onset AF and additional factors suggestive of CA, may be limited to patients ≥ 75 years.

Cardiac biomarkers are frequently increased in patients with CA. In our CA cohort, median NT-proBNP was 3800 pg/L (IQR: 1682-6101). These values were slightly higher than those reported in most ATTR-CA studies but lower than those reported in patients with ATTRwt identified in HFpEF screening studies.[4,26-28] This discordance might be explained by the fact that although all our patients with CA had AF (a factor associated with increased NtproBNP), not all had previous diagnoses of HF.

In most ATTRwt cohorts, LVH severity ranges from moderate to severe values (16-17 mm). In a recent Italian study on the prevalence of CA among patients with a suggestive echocardiogram defined as LVH at septum (≥ 12 mm in women and ≥ 13 mm in men), normal LVEF, and typical CA echocardiographic features, the median MWT was 16 mm (IQR: 15-18) among the 51 patients with ATTR-CA.[27,28] Similarly, another study analyzing echocardiographic findings in 766 individuals with ATTRwt reported a mean MWT of 16 mm at both septum and posterior wall.[29] Interestingly, in our study, LVH in patients with CA was less severe (median MWT at both septum and posterior wall of 14 mm), possibly reflecting an earlier stage of the disease.

European Society of Cardiology (ESC) recommendations for CA screening require the presence of LVH ≥ 12 mm with at least 1 additional risk factor suggestive of CA. Notably, 87 of the 121 patients (71.9%) included in our study would not have met the criteria for CA screening because of the absence of LVH ≥ 12 mm or additional red flags. Furthermore, of the 105 patients with LVH, 71 patients (67.6%) had no additional red flags, and 4 of these (5.6%) were diagnosed with CA, highlighting the need for additional criteria—such as recent-onset AF—to consider CA screening in this population of patients.

Prevalence of conduction disorders is high among patients with ATTR-CA, particularly in the hereditary form. In our study, only 20% of patients with CA had left/right bundle branch block (L/RBBB); QRS was mainly narrow (91 ms, IQR: 84-108 ms); and none of the patients with CA had pacemakers at baseline reflecting the early grade of disease. In contrast, 3 patients with CA (30%) required permanent pacemaker implantation during follow-up, highlighting the greater tendency to develop conduction disturbances. This complication is particularly relevant in patients with unrecognized CA, as rate-control medications are often used in elderly patients with AF.

Because of the limited number of patients with CA identified in our study, we could not conduct a multivariable analysis to determine characteristics independently associated with CA in this population.

We explored the performance of a recently described ATTR-CA screening score (T-Amylo) obtained by multivariate analysis.[30] T-Amylo score includes 5 items (age, gender, CTS, diastolic interventricular septum thickness, and low QRS voltage) and ranges from 0 to 11 points. Although the score showed good diagnostic accuracy in patients with hypertensive cardiomyopathy, severe aortic stenosis, or HFpEF, it was not able to identify patients with CA correctly when applied to our study population. Only 1 patient with CA in our cohort showed a score > 7 (threshold proposed to screen for CA), despite that patients with ATTR-CA had significantly higher scores than those without ATTR-CA (median score 6 points [IQR: 4-6] vs 3 points [IQR: 2-4]; $P < 0.001$).

Implications for AF

AF is the most prevalent atrial arrhythmia in patients with CA.[15,25] Previous studies have reported up to 70% of AF in ATTR-CA, being more frequent among patients with ATTRwt compared with the hereditary form.[15,16,31] One suggested explanation for this higher prevalence is that patients with ATTRwt tend to be older, predominantly male, and with more comorbidities. Despite this high rate of AF in this population, no impact on overall mortality has been observed in the literature.[16,31,32]

Early diagnosis of ATTR-CA in patients with recent-onset AF could have a crucial impact on management of AF, especially regarding rhythm control and anticoagulation therapy.

Rhythm-control strategy was barely implemented in our CA population despite that maintenance of sinus rhythm has been associated with better survival in ATTR-CA.[16] Adequate recognition of patients with recent-onset AF who suffer from CA is particularly important in patients who would undergo ECV, as this procedure is associated with more complications in this population, and intracardiac thrombi are frequent despite adequate anticoagulation.[33,34] ECV was not performed in any of the patients with CA in our study. A

Table 3. Clinical findings in patients with ATTR-CA

	Age	Sex	LVEF (%)	MWT (mm)	eGFR (mL/min/1.73 m^2)	NT-proBNP (pg/L)	Perugini score	SPIE	UPIE	FLC ratio	TTR genetics	Histology	Final diagnosis	Clinical evolution
Patient 1	91	M	60	13	68.0	5008	2	IgMH	Negative	2.03	Negative	-	Likely ATTRwt	Alive 14 months after study inclusion without HF signs/symptoms Permanent PM during follow-up caused by sick sinus syndrome Not on disease-modifying treatment because of advanced age and comorbidities
Patient 2	82	M	35	17	80.9	7872	2	Negative	Negative	1.65	Negative	-	Definite ATTRwt	Death caused by intestinal occlusion complicated with sepsis 10 months after study inclusion Not on disease-modifying treatment because of comorbidities
Patient 3	84	M	70	19	50.1	2525	2	Negative	Negative	1.64	Negative	-	Definite ATTRwt	Permanent PM during follow-up because of AF with complete atrioventricular block Included in Cardio-TTRansform trial in February 2022; In 2024 switching to tafamidis
Patient 4	88	M	63	12	72.1	1263	2	IgGH	Negative	1.34	Negative	-	Likely ATTRwt	Alive 4 months after the study inclusion without HF signs/symptoms; treated with diflunisal
Patient 5	77	M	60	13	13.3	7011	3	IgMH	Positive	2.24	Negative	-	Undetermined CA	Death caused by metastatic skin cancer 9 months after inclusion; went into hemodialysis 8 months after inclusion; kidney transplant 12 years before inclusion; not on disease-modifying treatment because of comorbidities
Patient 6	89	M	43	13	66.6	-	3	IgAH	Positive	6.88	Negative	Negative fat biopsy	Likely ATTRwt	Alive 11 months after inclusion without HF; progressive worsening of eGFR during follow-up; not on disease-modifying treatment because of comorbidities
Patient 7	85	M	67	17	44.9	3800	3	Negative	Negative	1.15	Negative	-	Definite ATTRwt	Alive 11 months after inclusion without HF signs/symptoms Not on disease-modifying treatment because of comorbidities
Patient 8	85	M	56	14	86.4	1266	3	Negative	Negative	1.91	Negative	-	Likely ATTRwt	Alive 12 months after inclusion without HF signs/symptoms; not on disease-modifying treatment because of comorbidities
Patient 9	81	F	69	19	22.4	5190	3	Negative	Negative	1.88	Negative	-	Definite ATTRwt	Alive 6 months after inclusion without HF signs/symptoms; not on disease-modifying treatment because of comorbidities
Patient 10	86	M	68	13	52	2097	3	Negative	Negative	1.89	Negative	-	Definite ATTRwt	Alive 12 months after inclusion without HF signs/symptoms; not on disease-modifying treatment because of comorbidities

ATTRwt, wild-type transthyretin cardiac amyloidosis; CA, cardiac amyloidosis; eGFR, estimated glomerular filtration rate. F, female; FLC, free light chain; HF, heart failure; IgAH, immunoglobulin A heavy chain; IgGH, immunoglobulin G heavy chain; IgMH, immunoglobulin M heavy chain; LC, light chain; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; M, male; MWT, maximal wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker; SPIE, serum protein electrophoresis with immunofixation; TTR, transthyretin;UPIE, urine protein electrophoresis with immunofixation.

Table 4. Red flags present in patients with cardiac amyloidosis

	Carpal tunnel syndrome (n = 4)	Lumbar spinal stenosis (n = 3)	Poly-neuropathy (n = 0)	AV conduction disease (n = 8)	Low-voltage pattern (n = 25)	PseudoMI pattern (n = 18)	IVS (mm)	PW (mm)	ATTR status	Number of red flags
Patient 1	-	-	-	-	-	-	13	10	Likely ATTRwt	0
Patient 2	-	X	-	-	-	-	17	14	Definite ATTRwt	1
Patient 3	-	-	-	X	-	-	17	19	Definite ATTRwt	1
Patient 4	-	-	-	-	X	-	12	12	Likely ATTRwt	1
Patient 5	-	-	-	-	-	-	13	13	Undetermined CA	0
Patient 6	-	-	-	-	-	-	13	9	Likely ATTRwt	0
Patient 7	-	-	-	-	-	-	17	17	Definite ATTRwt	0
Patient 8	X	-	-	-	X	X	14	14	Likely ATTRwt	3
Patient 9	-	-	-	-	X	X	16	19	Definite ATTRwt	2
Patient 10	-	-	-	-	X	-	13	13	Definite ATTRwt	1

The total number of red flags in the overall population is given in brackets.
ATTRwt, wild-type transthyretin cardiac amyloidosis; AV, atrioventricular; CA, cardiac amyloidosis; IVS, interventricular septum; PW, posterior wall.

higher LA volume and the older age of these patients could have influenced rate-control preference.

Regarding anticoagulation therapy, patients with CA and AF have an increased thromboembolic risk with a greater incidence of stroke compared with the general population.[14] This risk is independent of the CHADS-VASc score that should not be used in patients with CA.[14] Therefore, adequate recognition of the coexistence of ATTR-CA in patients with recent-onset AF is important to avoid embolic events in patients of advanced age, frequently with increased bleeding risk, and in whom diagnostic and therapeutic procedures that require anticoagulation interruptions are not uncommon.[35-37]

Limitations

Despite being a multicentre study, and the largest screening study performed to date in this clinical scenario, the number of patients enrolled in our study was limited. Furthermore, selection bias cannot be excluded, as recruitment was performed exclusively by cardiologists, and only patients $\geq$ 65 years old with recent-onset AF (< 1 year) and who had an additional criterion suggestive of CA were eligible. The COVID-19 pandemic severely affected the study recruitment. For several months, it was not possible to recruit patients to the trial, and many patients who were offered the study often refused to participate in any study that required additional hospital visits.

Finally, we were not able to determine the subtype of CA in all individuals with positive cardiac uptake on scintigraphy despite that most identified individuals with CA were likely to have ATTRwt. EMB was not performed in patients who had concomitant monoclonal protein abnormalities because of patients' ages and comorbidities and because ATTRwt confirmation was unlikely to alter patients' treatments, as tafamidis was not available in Spain at the time of the study.

Conclusions

Our study highlights the importance of expanding the clinical scenarios and red flags for diagnosing ATTR-CA. A non-negligible proportion (8.3%) of selected patients with AF had diagnoses of CA. Based on our results, routine DPD scanning in patients $\geq$ 75 years of age with a recent diagnosis of AF, LVH (MWT $\geq$ 12 mm) and an additional red flag may help to identify patients with ATTR-CA. However, larger studies evaluating this strategy in more diverse clinical settings would be required. Early recognition of ATTR-CA in these individuals would allow better management of AF and would facilitate early initiation of disease-modifying therapies, which can improve their prognoses.

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Ethics Statement

The research reported in this paper adhered to the appropriate local Ethics Guidelines

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

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