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Atrial electrofunctional predictors of incident atrial fibrillation in cardiac amyloidosis

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is common in patients with cardiac amyloidosis (CA) and is a significant risk factor for heart failure hospitalization and thromboembolic events.

OBJECTIVE This study was designed to investigate the atrial electrofunctional predictors of incident AF in CA.

METHODS A multicenter, observational study was conducted in 4 CA referral centers including sinus rhythm patients with light-chain (AL) and transthyretin (ATTR) CA undergoing electrocardiography and cardiac magnetic resonance imaging. The primary end point was new-onset AF occurrence.

RESULTS Overall, 96 patients (AL-CA, n = 40; ATTR-CA, n = 56) were enrolled. During an 18-month median follow-up (Q1–Q3, 7–29 months), 30 patients (29%) had incident AF. Compared with those without AF, patients with AF were older (79 vs 73 years; $P = .001$). They more frequently had ATTR (87% vs 45%; $P < .001$); electrocardiographic interatrial block (IAB), either partial (47% vs 21%; $P = .011$) or advanced (17% vs 3%; $P = .017$); and lower left atrial ejection fraction (LAEF; 29% vs 41%; $P = .004$). Age (hazard ratio [HR], 1.059; 95% CI, 1.002–1.118; $P = .042$), any type of IAB (HR, 2.211; 95% CI, 1.03–4.75; $P = .041$), and LAEF (HR, 0.967; 95% CI, 0.936–0.998; $P = .044$) emerged as independent predictors of incident AF. Patients exhibiting any type of IAB, LAEF <40%, and age >78 years showed a cumulative incidence for AF of 40% at 12 months. This risk was significantly higher than that carried by 1 (8.5%) or none (7.6%) of these 3 risk factors.

CONCLUSION In patients with CA, older age, IAB on 12-lead electrocardiography, and reduced LAEF on cardiac magnetic resonance imaging are significant and independent predictors of incident AF. A closer screening for AF is advisable in CA patients carrying these features.

KEYWORDS Cardiac amyloidosis; Atrial fibrillation; Cardiac magnetic resonance; Electrocardiogram; Interatrial block

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Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in patients with cardiac amyloidosis (CA), which is an infiltrative cardiomyopathy characterized by the deposition of misfolded protein in the heart.[1] Two main types of CA are acknowledged: immunoglobulin light-chain (AL) and transthyretin (ATTR) CA. In AL, the amyloid fibrils are formed by a monoclonal immunoglobulin light chain produced by a

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low-proliferating bone marrow plasma cell clone. Conversely, ATTR is derived from misfolding of transthyretin protein, a carrier of thyroxine and retinol-binding protein mainly produced by the liver. ATTR is further subdivided into wild type and hereditary types, depending on the absence or presence of variants in the transthyretin gene. AF can be detected in up to two-thirds of CA patients, far more commonly in those with ATTR-CA than AL-CA.[2]

Patients with CA poorly tolerate AF occurrence, and those affected are exposed to a greater risk of heart failure hospitalizations.[3] Moreover, AF exacerbates the existing elevated risk of intracardiac thrombi and systemic embolisms in this population.[4] Therefore, early AF detection is key for timely initiation of anticoagulant therapy that in CA is not dependent on the CHA_2DS_2-VASc score.[5] Previous studies have identified certain factors associated with a greater risk for development of AF (eg, older age, advanced ATTR-CA stage, heart failure, left ventricular ejection fraction, left atrial size, and right atrial pressure).[6,7] However, none of these studies considered P-wave indices on the electrocardiogram, including assessment of interatrial block (IAB), or functional evaluation of the atria by cardiac magnetic resonance (CMR) imaging. The objective of this study was to identify baseline clinical parameters, including electrocardiographic and CMR imaging findings, to predict incident AF in a multicenter cohort of patients with AL- and ATTR-CA.

Methods

This is a multicenter observational study performed in 4 referral centers for CA in Italy: Padua University Hospital, Padua; Careggi University Hospital, Florence; SS Annunziata University Hospital, Chieti; and Trieste University Hospital, Trieste. The local regional institutional review board approved the study, and the participating centers obtained local institutional review board approvals for the retrospective collection of anonymous data. The research reported in this paper adhered to the Declaration of Helsinki as revised in 2013, and informed consent was obtained according to the local review board policies.

Abbreviations

AF: atrial fibrillation

AL-CA: light-chain cardiac amyloidosis

ATTR-CA: transthyretin cardiac amyloidosis

CMR: cardiac magnetic resonance

HR: hazard ratio

IAB: interatrial block

LAEF: left atrial ejection fraction

LAV: left atrial volume

LGE: late gadolinium enhancement

Study design and study population

All patients in sinus rhythm with a definitive diagnosis of AL- and ATTR-CA referred for a clinical CMR study between March 2017 and March 2022 were included in the study. The diagnosis of CA was established according to the European Society of Cardiology position paper.[5] Because of the small number of patients with hereditary ATTR in our cohort, we analyzed ATTR-CA patients as a unique group. Standard 12-lead electrocardiography performed within 3 months of CMR examination was necessary for inclusion. Exclusion criteria were a previous diagnosis of AF, including paroxysmal, and all standard contraindications to performance of a CMR examination as described in more detail in the Supplemental Methods.

The indication for the CMR study in the centers involved was for diagnostic purposes. Specifically, CMR was requested for clinical suspicion of cardiomyopathy or demonstration of cardiac involvement. Patients' baseline was set at the time of CMR execution at participating centers. The clinical data recorded within ±3 months from the baseline included all the following: medical history and physical examination, electrocardiography, and laboratory examinations.

Clinical data collection

Careful clinical history was collected, including New York Heart Association class and National Amyloidosis Centre stage. Electrocardiographic IAB was defined as follows: partial IAB, P-wave duration ≥120 ms without a negative deflection in the inferior leads (II, III, aVF); or advanced IAB, P-wave duration ≥120 ms and biphasic (positive/negative) morphology in the inferior leads.[8,9] Low QRS voltages were defined as QRS amplitude <5 mm (0.5 mV) in all peripheral leads, including both negative and positive components.[10] Further details about clinical evaluation, electrocardiography, and biomarkers are described in the Supplemental Methods.

CMR imaging protocol and imaging analysis

CMR imaging was performed with 1.5T systems (Magnetom Avanto [Siemens Medical Systems, Erlangen, Germany], Gyroscan NT and Intera [Philips Healthcare, Andover, MA], and CVi, HD release [GE Healthcare, Milwaukee, WI]). All images were analyzed with dedicated software (cvi42, version 5.13.7; Circle Cardiovascular Imaging Inc, Calgary, Canada). Left and right atrial end-diastolic areas, volumes, ejection fraction, and stroke volume were calculated using 4- and 2-chamber views, as reported by Petersen and coworkers.[11] For the left atrium, the biplane area-length method was used, with atrial endocardial borders manually contoured in 4- and 2-chamber views, excluding the appendage and the pulmonary veins.[12] Maximum area was contoured, as shown in the Supplemental Figure, in the frame immediately before mitral valve opening, whereas minimum area was contoured in the frame immediately after the mitral valve closure. From these, left atrial volume (LAV) was calculated by the formula volume = $(0.85 \cdot \text{area}^2)$/length. Atrial ejection fraction was derived with the formula left atrial ejection fraction (LAEF) = (LAVmax − LAVmin)/LAVmax, as previously reported.[12] For the right atrium, given the lack of multiple dedicated views, the area-length method was applied. Left and right ventricular end-diastolic volumes, ejection fractions, stroke volumes, and masses were measured from the short-axis cine images. Left ventricular late gadolinium enhancement (LGE) pattern was qualitatively classified as subendocardial and transmural.[13] Left ventricular LGE presence was qualitatively assessed in

Table 1 Baseline characteristics of population according to onset of atrial fibrillation

Variable	Overall (N = 96)	AF (n = 30)	No AF (n = 66)	*P*
Age, y	74 (66–79.5)	79 (72–82)	73 (62–77)	<.001
Sex	M: 66 (69) F: 30 (31)	M: 24 (80) F: 6 (20)	M: 42 (64) F: 14 (36)	.11
Amyloidosis type				
AL	40 (41)	4 (13)	36 (55)	<.001
ATTR	56 (59)	26 (87)	30 (45)	<.001
NYHA class				
I/II	80 (73)	27 (90)	53 (81)	.38
III/IV	16 (17)	3 (10)	13 (19)	.38
CHA_2DS_2-VASc score				
<3	50 (52)	11 (37)	39 (59)	.041
≥3	46 (48)	19 (63)	27 (41)	.041
Electrocardiogram				
LBBB	12 (13)	3 (10)	9 (14)	.62
LAFB	30 (31)	13 (43)	17 (26)	.09
RBBB	14 (15)	2 (7)	12 (18)	.14
P wave, ms	100 (90–120)	120 (88–130)	100 (88–120)	.08
PQ interval, ms	194 (162–220)	200 (174–235)	191 (159–220)	.32
QRS interval, ms	102 (90–118)	106 (90–119)	101 (90–119)	.43
Low QRS voltages	34 (35)	14 (47)	20 (30)	.12
Anterior pseudoinfarction	30 (31)	12 (40)	18 (27)	.21
Inferior pseudoinfarction	23 (24)	8 (27)	15 (23)	.68
Partial interatrial block	28 (29)	14 (47)	14 (21)	.011
Advanced interatrial block	7 (7)	5 (17)	2 (3)	.017
Blood examination				
NT-proBNP, ng/L	883 (330–1265)	1890 (966–3871)	1370 (491–2513)	.048
eGFR, mL/min/m^2	62.5 (45–78)	66 (56–79)	79 (67–91)	.046
Cardiac magnetic resonance				
LA area, cm^2	26 (21–30)	29 (25–32)	25 (20–30)	.17
RA area, cm^2	21 (18–27)	27 (20–31)	21 (18–24)	.61
LA EDVi, mL/m^2	44 (34–56)	51 (40–61)	43 (33–53)	.018
RA EDVi, mL/m^2	39 (31–53)	43 (36–61)	35 (29–45)	.014
LA EF, %	36 (26–47)	29 (24–36)	41 (28–52)	.004
LA SVi, mL/m^2	17 (12–20)	16 (12–20)	17 (12–21)	.69
RA EF, %	36 (27–48)	33 (25–42)	39 (28–49)	.38
RA SVi, mL/m^2	15 (11–20)	15 (13–19)	14 (9–20)	.11
IVS, mm	16 (14–18)	17 (15–19)	15 (14–18)	.10
LV, mass indexed, g/m^2	89 (69–115)	102 (82–134)	83 (67–105)	.045
LV EDVi, mL/m^2	73 (62–87)	82 (71–102)	71 (58–80)	.027
LV EF, %	58 (50–65)	50 (43–61)	61 (52–65)	.13
LV SVi, mL/m^2	40 (35–47)	41 (36–48)	40 (34–46)	.37
RV EDVi, mL/m^2	66 (54–79)	75 (60–84)	66 (54–77)	.97
RV EF, %	59 (52–66)	60 (49–66)	59 (53–65)	.64
RV SVi, mL/m^2	39 (33–46)	39 (36–46)	39 (33–46)	.96
LA LGE	72 (75)	28 (93)	44 (69)	.009
RA LGE	60 (63)	24 (80)	36 (57)	.031
LV LGE	89 (93)	30 (100)	59 (91)	.09
RV LGE	61 (64)	23 (77)	38 (59)	.10
Subendocardial LGE	38 (40)	13 (43)	25 (42)	.93
Transmural LGE	54 (56)	19 (63)	35 (59)	.71
Pericardial effusion	30 (31)	11 (37)	19 (29)	.47
Pleural effusion	25(26)	8 (27)	17 (26)	.96
Follow-up				
Heart failure	18 (19)	12 (40)	6 (9)	<.001
Death	17 (18)	7 (23)	10 (15)	.33
Ischemic stroke	6 (6)	4 (14)	2 (3)	.047

Quantitative variables are expressed as median value (25th–75th percentile). Qualitative variables are expressed as absolute number (%).
AF = atrial fibrillation; AL = light-chain amyloidosis; ATTR = transthyretin amyloidosis; EDVi = end-diastolic volume indexed; EF = ejection fraction; eGFR = estimated glomerular filtration rate; F = female; IVS = interventricular septum; LA = left atrial; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricular; M = male; NT-proBNP = N-terminal pro–B-type natriuretic peptide (available in 55); NYHA = New York Heart Association; RA = right atrial; RBBB = right bundle branch block; RV = right ventricular; SVi = stroke volume indexed.

Table 2 Predictors of incident atrial fibrillation during 60-month follow-up

	Univariate analysis		Multivariable analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y	1.078 (1.026–1.133)	.003	1.059 (1.002–1.118)	.042
Male sex	1.96 (0.79–4.81)	.14		
AL	0.167 (0.058–0.482)	.001		
History of stroke	0.95 (0.13–7.01)	.96		
History of heart failure	1.24 (0.59–2.61)	.58		
Hypertension	1.83 (0.89–3.71)	.10		
P wave, ms	1.01 (0.92–1.02)	.44		
PQ interval, ms	1.00 (0.99–1.01)	.84		
QRS interval, ms	1.09 (0.96–1.02)	.22		
Low QRS, voltages	2.10 (1.01–4.39)	.048		
Partial interatrial block	2.096 (1.020–4.306)	.044		
Advanced interatrial block	3.657 (1.364–9.805)	.010		
Interatrial block of any grade	3.352 (1.582–7.102)	.002	2.211 (1.03–4.75)	.041
NT-proBNP, ng/L	1 (1–1)	.09		
eGFR, mL/min/m^2	0.980 (0.962–0.999)	.039		
LA EDVi, mL/m^2	1.025 (1.001–1.049)	.041		
RA EDVi, mL/m^2	1.024 (1.004–1.045)	.019		
LA EF, %	0.961 (0.932–0.991)	.011	0.967 (0.936–0.998)	.044
RA EF, %	0.99 (0.96–1.02)	.52		
LV EDVi, mL/m^2	1.01 (0.99–1.02)	.39		
LV EF, %	0.98 (0.94–1.01)	.19		
RV EDVi, mL/m^2	1 (0.99–1.01)	.86		
RV EF, %	0.98 (0.95–1.02)	.31		
LA LGE	4.608 (1.092–19.45)	.038		
RA LGE	2.04 (0.83–5.01)	.12		

HR = hazard ratio; other abbreviations as in Table 1.

4-, 2-, and 3-chamber views. Intrareader and interreader reproducibility of left atrial indices and other details about CMR imaging protocol and postprocessing analysis are described in the Supplemental Methods.

Outcomes and statistical analysis

The primary end point was incident AF of any type (paroxysmal, persistent, or permanent) at follow-up. Secondary end points included ischemic stroke, hospitalization for heart failure, and death. All patients were followed up in the heart failure or amyloidosis outpatient clinic every 6 months. AF was diagnosed by standard electrocardiography recorded at each visit, hospitalization or emergency department admission, and 24-hour Holter electrocardiography performed yearly. AF was defined by current guidelines.[14] Survival analysis was calculated with day 1 set as the day the CMR study was performed at the referral center. End points were obtained from follow-up visits and medical records.

Correlation analysis was performed with Cox regression. For statistically continuous variables significant at multivariate Cox regression, a receiver operating characteristic curve was calculated, and the best cutoff was obtained through the Youden index. Subsequently, a score based on the presence of the detected risk factors was calculated. For both factors and score, cumulative incidence curves with Kaplan-Meier method and Gray test were drawn. Further details of statistical methods are given in the Supplemental Methods.

Results

Study population

Of 703 patients diagnosed with CA in the 4 involved centers between March 2017 and March 2022, 140 (19.9%) underwent CMR. Of them, 96 (40 AL-CA, 56 ATTR-CA, of whom 11 had hereditary ATTR) had no previous history of AF and constituted the study population. Baseline characteristics are shown in Table 1 and in Supplemental Table 1. Intraobserver and interobserver variability of left atrial parameters on CMR is shown in Supplemental Table 2.

Incident AF and follow-up

During a median follow-up time of 18 months (Q1–Q3, 7–29 months), 30 patients (29%) had incident AF. Compared with those without AF, patients with incident AF were significantly older (79 vs 73 years); they were more frequently diagnosed with ATTR-CA (n = 26, 87%) and more frequently showed IAB, either partial (47% vs 21%; $P = .011$) or advanced (17% vs 3%; $P = .017$). Based on CMR findings, patients with incident AF had significantly higher left atrial (51 vs 43 mL/m^2; $P = .018$) and right atrial (43 vs 35 mL/m^2; $P = .014$) end-diastolic volume indexed. They also exhibited a reduced LAEF (29% vs 41%; $P = .004$) and presented more frequently with left atrial LGE (93% vs 69%; $P = .009$) and right atrial LGE (80% vs 57%; $P = .031$). Regarding secondary end points, heart failure hospitalizations (40% vs 9%; $P < .001$) and ischemic stroke (14% vs 3%; $P = .047$) were more frequent

in patients with incident AF compared with those without. Clinical characteristics of patients with ischemic stroke are reported in Supplemental Table 3. No differences in all-cause mortality between the 2 groups were observed ($P = .33$).

Predictors of incident AF

Univariable analyses and the derived multivariable model are shown in Table 2. The presence of IAB of any grade emerged as an independent predictor of incident AF (hazard ratio [HR], 2.211; 95% CI, 1.03–4.75; $P = .041$), together with age (HR, 1.059; 95% CI, 1.002–1.118; $P = .042$) and LAEF (HR, 0.967; 95% CI, 0.936–0.998; $P = .044$). These findings were further confirmed after proportional hazards assumption (Supplemental Table 4) and competing risk analysis for all-cause mortality (Supplemental Table 5). As shown in Figure 1, the hazard of experiencing incident AF progressively increased with the reduction of LAEF values. The cutoffs of LAEF and age for the prediction of incident AF, also confirmed by the receiver operating characteristic curve, were 40% (area under the curve, 0.31; $P = .004$) and 78 years (area under the curve, 0.73; $P < .001$), respectively. The presence of either LAEF <40% or age >78 years in combination with the presence of IAB of any grade conferred an increased risk for incident AF (HR, 2.64 [95% CI, 1.264–5.51; $P = .01$] and HR, 2.42 [95% CI, 1.096–5.34; $P = .029$], respectively). The increased risk also emerged for the contemporary presence of any 2 risk factors (HR, 2.19; 95% CI, 1.06–4.52; $P = .034$), but the highest risk was found in the presence of the 3 parameters (HR, 3.44; 95% CI, 1.523–7.77; $P = .003$). As shown in Figure 2, cumulative incidence of AF at 12 months was significantly higher in patients with IAB of any type (20% [95% CI, 12%–28%] vs 11.5% [95% CI, 5%–18%]; log-rank $P < .001$), age >78 years (30% [95% CI, 21%–39%] vs 8.5% [95% CI, 3%–14%]; log-rank $P = .001$), or LAEF <40% (19% [95% CI, 11%–27%] vs 10% [95% CI, 4%–16%]; log-rank $P = .021$) than without. After combination of the 3 parameters (IAB of any type, age >78 years, LAEF <40%), the highest risk of incident AF was found in the presence of all of them (40% [95% CI, 30%–50%] at 12 months) compared with 2, 1, or none (20% [95% CI, 12%–28%] vs 8.5% [95% CI, 3%–14%] vs 7.6% [95% CI, 2.3%–13%]; log-rank $P < .001$; Figure 3). Furthermore, as

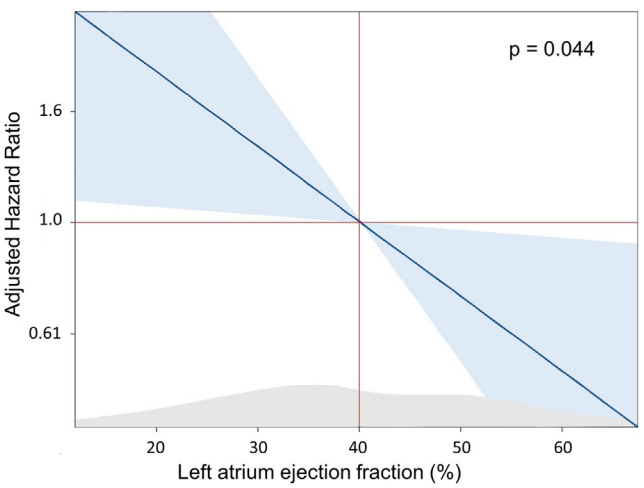

Figure 1
Hazard risk of incident atrial fibrillation according to left atrial ejection fraction, adjusted for age and interatrial block of any grade. *Light blue* = CI; *gray zone* = distribution of left atrial ejection fraction in our cohort.

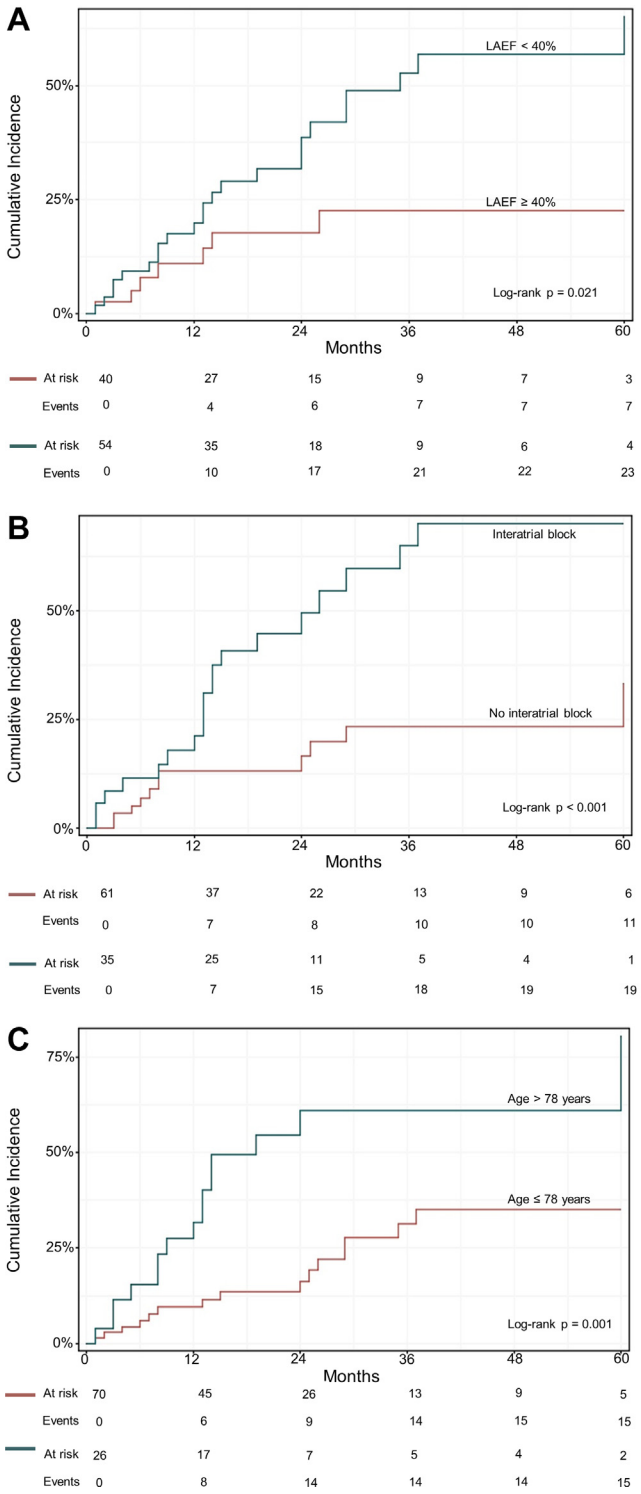

Figure 2
Cumulative incidence of atrial fibrillation according to the presence of (**A**) left atrial ejection fraction (LAEF) <40%, (**B**) interatrial block of any grade, or (**C**) age >78 years.

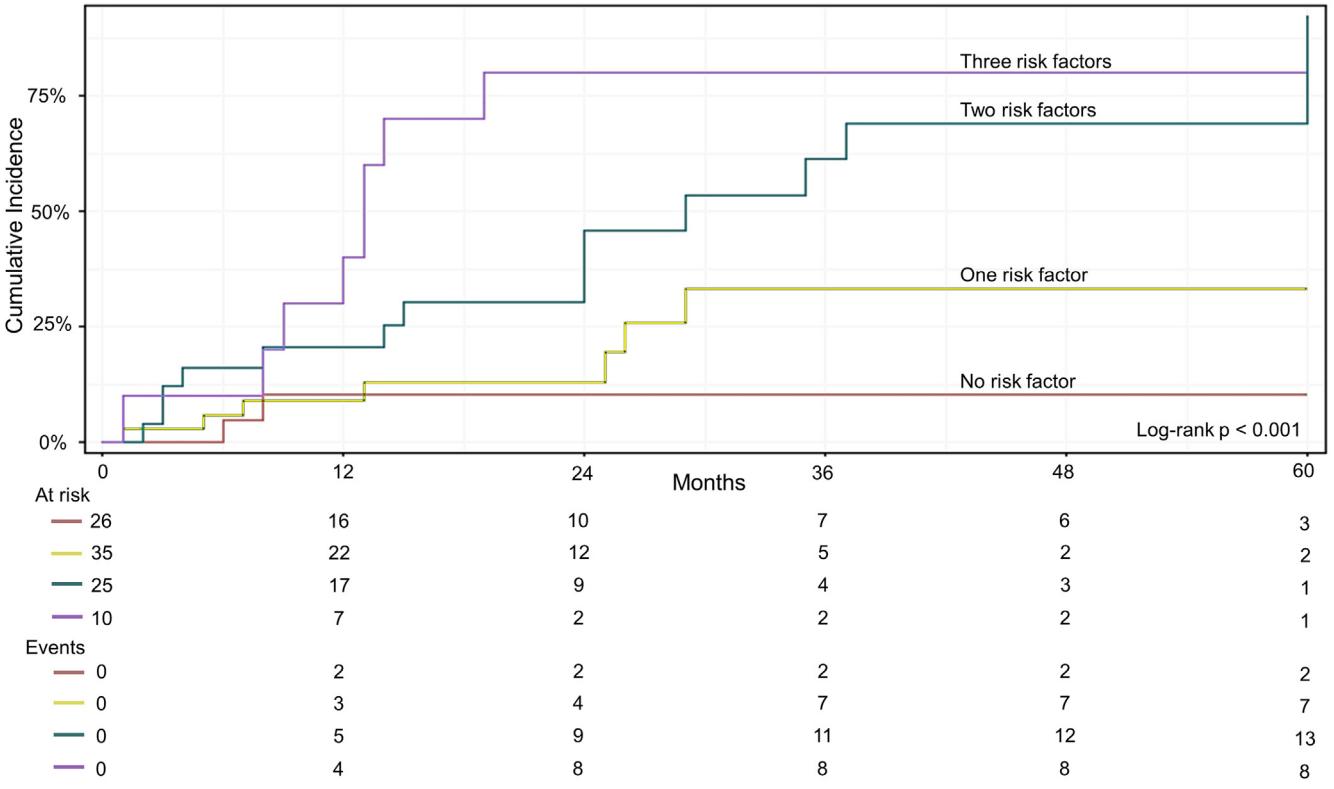

Figure 3
Cumulative incidence of atrial fibrillation according to the different combined presence of left atrial ejection fraction <40%, interatrial block of any grade, and age >78 years.

shown in Figure 4, age >78 years, IAB of any type, and LAEF <40% showed incremental predictive value when sequentially added to a basal model (ie, absence of any of the 3).

Discussion

This study was designed to investigate the electrical and functional predictors of incident AF in patients with CA by electrocardiography and CMR imaging. The main findings were as follows. First, electrocardiographic IABs, either partial or advanced, are frequent in patients with CA, being detected in 29% and 7% of our cohort, respectively. Second, during a median 1.5-year follow-up, new-onset AF occurred in almost one-third of sinus rhythm patients with CA. Third, IABs and LAEF calculated by CMR emerged as independent predictors of incident AF. Fourth, in the individual CA patient, the combined presence of IAB (any type), age >78 years, and LAEF <40% led to the highest risk of incident AF.

AF is the most frequent arrhythmia in CA, with a prevalence ranging from 15% to 88% of patients and incidence up to 15% per year.[6,15–17] In our study, which included only sinus rhythm CA patients undergoing CMR, we observed an incidence of about 18% per year. This rate is in keeping with that of Sanchis and coworkers,[16] who observed 36% new-onset AF during a 2-year follow-up (15% per year), but differs from that of Longhi and coworkers,[6] who conversely reported 2.1% per year. The differences encountered may reasonably be due to different study sample size and CA subtype distribution, in particular a higher prevalence of wild-type ATTR in our cohort.

In patients with CA, AF is a significant contributor of heart failure symptoms and a well-established risk factor for stroke[6,18] and bradyarrhythmias worthy of pacemaker implantation.[19] Identifying prognostically relevant markers of AF is therefore crucial to allow early diagnosis and to prompt all strategies that in turn may prevent the risk for development of heart failure hospitalizations and thromboembolic events. Age, male sex, ATTR-CA, renal function, and atrial remodeling were previously demonstrated as significant predictors of AF in CA.[6,7,17,20–22] Our results are consistent with this, in particular with regard to age and ATTR subtype. The major novelty, however, is represented by the prognostic role of IABs and CMR LAEF as independent predictors of incident AF in CA. IABs are associated with AF and stroke in the general population[23] and have been associated with reduced left atrial function on echocardiography of patients with CA.[24] In our CA cohort, partial IAB was detected in 29% of patients and advanced IAB in 7%, both more frequently in ATTR-CA than in AL-CA. From a pathogenetic point of view, tissue abnormalities involving the myocardium of the atria, such as fibrosis and amyloid deposition, may contribute to IAB and AF occurrence and perpetuation by altering the normal pattern of propagation and inducing discontinuous slow conduction, which plays a key role in the context of reentrant circuits.[25–27]

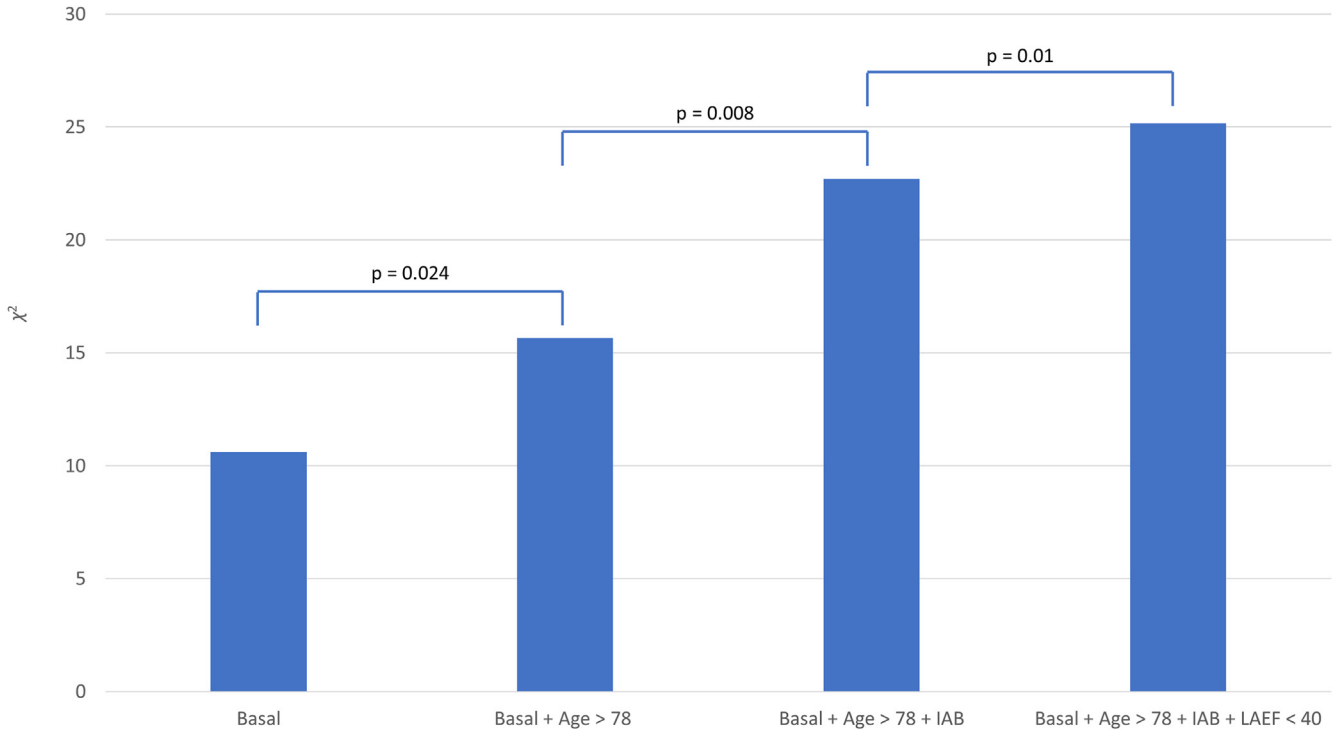

Figure 4
Incremental prognostic value of age >78 years, interatrial block (IAB) of any grade, and left atrial ejection fraction (LAEF) <40%, when sequentially added to a basal model.

Structural and functional changes in the left atrium are well-known risk factors for AF development in the general population.[28] In particular, elevated LAV and decreased left atrial reservoir and conduit functions measured with feature-tracking CMR have been associated with incident AF.[29] In patients with CA, impairment of left atrial contractile function evaluated with CMR imaging is common, is not influenced by CA cause, and is associated with poor outcome.[30] Our data seem concordant and confirm the prognostic role of left atrial dysfunction because of both atrial infiltration by amyloid fibrils and atrial volume and pressure overload due to restrictive hemodynamics, which could lead to atrial fibrosis, resulting in further atrial electrical heterogeneity favoring AF onset.[27,31]

Finally, the presence of IAB together with old age and reduced LAEF was associated with the highest risk of incident AF in patients with CA, both AL and ATTR related. Therefore, our results strongly support the combined use of electrocardiography and CMR, not only to assess QRS voltages, amyloid burden, and disease severity but also to stratify the risk of patients for development of AF during follow-up. High-risk patients could undergo close and long-term monitoring with implantable devices or be encouraged to wear smart technologies for a systematic screening of AF[32] (Graphical Abstract).

Limitations

This study has some limitations. First, it is retrospective and multicentric, with a relatively small population that allows limited statistical power and does not allow a comprehensive, systematic analysis of factors associated with AF onset. Furthermore, an in-depth separate analysis of AL-CA and ATTR-CA subpopulations was not possible. Nevertheless, the strictness of the inclusion criteria is to be considered. CMR for diagnostic purposes is not mandatory in the diagnostic pathway, and the high prevalence of AF at diagnosis of patients significantly and inevitably restricted the recruitable population. Second, despite the availability of data about disease-modifying therapy, the exiguous number of patients treated does not allow assessment of a possible impact on the risk of arrhythmia onset. Third, as mentioned, the unavailability of continuous rhythm monitoring devices limited our sensitivity to detect subclinical and asymptomatic AF events. However, therapeutic management of infrequent and short AF episodes in the general population is still a debated topic in the literature.[33,34] Fourth, although data regarding cardiac troponin levels have been collected, significant heterogeneity between centers emerged, caused by poor standardization and high variability in assays (regular sensitivity or high sensitivity) and troponin type (T or I) use over time, so these data were omitted from the analysis. Consequently, we could not apply the Mayo Clinic staging system to better characterize the disease severity of patients with AL-CA.

Conclusion

In patients with AL-CA and ATTR-CA, IABs are common and together with advanced age and reduced LAEF on CMR are independent predictors of incident AF. Patients with these

features might benefit from closer AF screening strategies during follow-up.

Appendix

Supplementary data

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References

1. Fontana M, Ćorović A, Scully P, et al. Myocardial amyloidosis: the exemplar interstitial disease. JACC Cardiovasc Imaging 2019;12(pt 2):2345–2356.
2. Martini N, Sinigiani G, De Michieli L, et al. Electrocardiographic features and rhythm disorders in cardiac amyloidosis. Trends Cardiovasc Med. Published online February 24, 2023.
3. Thakkar S, Patel HP, Chowdhury M, et al. Impact of arrhythmias on hospitalizations in patients with cardiac amyloidosis. Am J Cardiol 2021;143:125–130.
4. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, et al. High prevalence of intracardiac thrombi in cardiac amyloidosis. J Am Coll Cardiol 2019;73:1733–1734.
5. 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;42:1554–1568.
6. Longhi S, Quarta CC, Milandri A, et al. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. Amyloid 2015;22:147–155.
7. Donnellan E, Wazni OM, Hanna M, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. JACC Clin Electrophysiol 2020;6:1118–1127.
8. Bayés de Luna A, Platonov P, Cosio FG, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol 2012;45:445–451.
9. Baranchuk A, Villuendas R, Bayes-Genis A, et al. Advanced interatrial block: a well-defined electrocardiographic pattern with clinical arrhythmological implications. Europace 2013;15:1822.
10. Cipriani A, De Michieli L, Porcari A, et al. Low QRS voltages in cardiac amyloidosis: clinical correlates and prognostic value. JACC CardioOncol 2022;4:458–470.
11. Petersen SE, Khanji MY, Plein S, et al. European Association of Cardiovascular Imaging expert consensus paper: a comprehensive review of cardiovascular magnetic resonance normal values of cardiac chamber size and aortic root in adults and recommendations for grading severity. Eur Heart J Cardiovasc Imaging 2019;20:1321–1331.
12. Kanagala P, Arnold JR, Cheng AS, et al. Left atrial ejection fraction and outcomes in heart failure with preserved ejection fraction. Int J Cardiovasc Imaging 2020;36:101–110.
13. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2015;132:1570–1579.
14. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498.
15. Bukhari S, Khan SZ, Bashir Z. Atrial fibrillation, thromboembolic risk, and anticoagulation in cardiac amyloidosis: a review. J Card Fail 2023;29:76–86.
16. Sanchis K, Cariou E, Colombat M, et al. Atrial fibrillation and subtype of atrial fibrillation in cardiac amyloidosis: clinical and echocardiographic features, impact on mortality. Amyloid 2019;26:128–138.
17. Mints YY, Doros G, Berk JL, et al. Features of atrial fibrillation in wild-type transthyretin cardiac amyloidosis: a systematic review and clinical experience. ESC Heart Fail 2018;5:772–779.
18. Bukhari S, Barakat AF, Eisele YS, et al. Prevalence of atrial fibrillation and thromboembolic risk in wild-type transthyretin amyloid cardiomyopathy. Circulation 2021;143:1335–1337.
19. Porcari A, Rossi M, Cappelli F, et al. Incidence and risk factors for pacemaker implantation in light-chain and transthyretin cardiac amyloidosis. Eur J Heart Fail 2022;24:1227–1236.
20. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. Age (Dordr) 2009;31:27–38.
21. Henein MY, Suhr OB, Arvidsson S, et al. Reduced left atrial myocardial deformation irrespective of cavity size: a potential cause for atrial arrhythmia in hereditary transthyretin amyloidosis. Amyloid 2018;25:46–53.
22. Choi YJ, Kim D, Rhee TM, et al. Left atrial reservoir strain as a novel predictor of new-onset atrial fibrillation in light-chain-type cardiac amyloidosis. Eur Heart J Cardiovasc Imaging 2023;24:751–758.
23. Tse G, Wong CW, Gong M, et al. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2018;250:152–156.
24. Lindow T, Lindqvist P. The prevalence of advanced interatrial block and its relationship to left atrial function in patients with transthyretin cardiac amyloidosis. J Clin Med 2021;10:2764.
25. Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur Heart J 2013;34:2731–2738.
26. Cheniti G, Vlachos K, Pambrun T, et al. Atrial fibrillation mechanisms and implications for catheter ablation. Front Physiol 2018;9:1458.
27. Miragoli M, Glukhov AV. Atrial fibrillation and fibrosis: beyond the cardiomyocyte centric view. Biomed Res Int 2015;2015:798768.
28. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493–505.
29. Habibi M, Samiei S, Ambale Venkatesh B, et al. Cardiac magnetic resonance–measured left atrial volume and function and incident atrial fibrillation: results from MESA (Multi-Ethnic Study of Atherosclerosis). Circ Cardiovasc Imaging 2016;9:e004299.
30. Aquaro GD, Morini S, Grigoratos C, et al. Electromechanical dissociation of left atrium in patients with cardiac amyloidosis by magnetic resonance: prognostic and clinical correlates. Int J Cardiol Heart Vasc 2020;31:100633.
31. Xintarakou A, Tzeis S, Psarras S, et al. Atrial fibrosis as a dominant factor for the development of atrial fibrillation: facts and gaps. Europace 2020;22:342–351.
32. Svennberg E, Tjong F, Goette A, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. Europace 2022;24:979–1005.
33. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP study): a randomised controlled trial. Lancet 2021;398:1507–1516.
34. Kirchhof P, Toennis T, Goette A, et al. Anticoagulation with edoxaban in patients with atrial high-rate episodes. N Engl J Med 2023;389:1167–1179.