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CLINICAL RESEARCH

Catheter ablation of atrial fibrillation in transthyretin and light-chain cardiac amyloidosis: results from the multicentre *AMYL-AF* study

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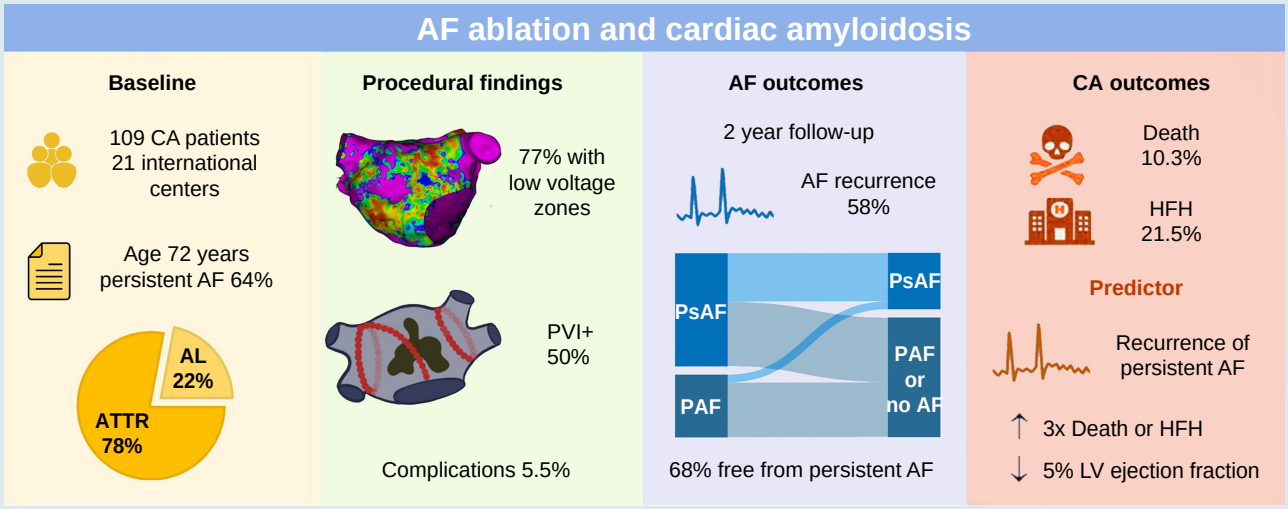
Aims Atrial fibrillation (AF) is highly prevalent among cardiac amyloidosis (CA) patients and contributes significantly to their morbidity and mortality. Evidence regarding AF ablation efficacy and safety in CA patients remains limited. The aim of our study is to evaluate baseline characteristics, clinical course and outcomes of AF ablation in a series of patients with transthyretin (ATTR) or light-chain (AL) CA from a multicentre international registry.

Methods and results Patients with CA who underwent AF ablation were included. Co-primary endpoints were: (i) atrial arrhythmia (AA) recurrence; (ii) a composite endpoint of all-cause mortality and heart failure hospitalization (HFH). 109 patients (mean age 72.4 ± 7.4 years, females 17.4%, persistent AF 64.2%, ATTR 78%, AL 22%) were included. Radiofrequency, cryo-balloon and pulsed-field ablation were performed in 67%, 15% and 18% of patients, respectively; 49.5% received pulmonary vein isolation plus additional ablations. Low voltage zones were documented in 34 out of 44 patients undergoing electro-anatomical mapping (77.3%). During a median follow-up of 22.7 months, 63 patients (58.3%) experienced AA recurrence (32.4% persistent AF recurrence), with no significant differences between CA subtypes (ATTR 59.5% vs. AL 54.2%, log-rank $P = 0.55$). The composite endpoint of HFH and all-cause death occurred in 27 patients (25%). Recurrence of persistent AF was associated with three-fold higher risk (OR 2.9, $P = 0.02$) of the composite endpoint.

Conclusion CA patients undergoing AF ablation present high prevalence of persistent AF. Freedom from AA after AF ablation is achieved in 42% of patients after a two-year follow-up. Patients with persistent AF recurrence have a three-fold higher risk of HFH and death.

Graphical Abstract



AF, atrial fibrillation; AL, immunoglobulin light-chain; ATTR, transthyretin; CA, cardiac amyloidosis; HFH, heart failure hospitalization; LV, left ventricle; PAF, paroxysmal AF; PsAF, persistent AF; PVI, pulmonary vein isolation.

Keywords Atrial fibrillation • Cardiac amyloidosis • Ablation • Pulmonary vein isolation

What's new?

- In transthyretin (ATTR) or light-chain (AL) CA patients undergoing AF ablation, freedom from atrial arrhythmias was achieved in 42% after a median 23-month follow-up, with similar outcomes across CA subtypes.
- The composite endpoint of heart failure hospitalization (HFH) and all-cause death after AF ablation occurred in 25% of patients.
- Recurrence of persistent AF was independently associated with a three-fold higher risk of HFH or death.

Introduction

Cardiac amyloidosis (CA) is an under-recognized cause of heart failure (HF) with preserved ejection fraction in older adults, resulting from the extracellular deposition of misfolded transthyretin (ATTR) or immunoglobulin light-chain (AL) secreted by clonal plasma cells.[1,2]

Different types of arrhythmias, including bradyarrhythmias, atrial fibrillation (AF) and ventricular arrhythmias, have been reported in CA patients.[3] AF is the most common sustained arrhythmia in this population, particularly among patients with ATTR-CA (55–70% in ATTR-CA vs. 16–27% in AL-CA), leading

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to a higher risk of heart failure hospitalizations (HFH), worsening symptoms, and systemic embolism, even in the presence of adequate anticoagulation.[4–9]

The prognostic impact of AF treatment in CA patients remains debated.[10,11] Furthermore, pharmacological management of AF in CA is particularly challenging due to the frequent coexistence of bradyarrhythmias and altered hemodynamics.[2,12,13,14–16]

Catheter ablation is currently the most effective long-term rhythm control strategy for AF, and it is recommended for HF patients to reduce hospitalizations and improve survival.[12,17,18] Nevertheless, the overall poor prognosis, unique AF mechanisms, and frequent coexistence of multiple comorbidities in CA patients limit the available data regarding the efficacy and safety of AF ablation, with existing evidence limited to small studies.[10,11,19,20]

The aim of this study is to evaluate the baseline characteristics, clinical course and outcomes of AF ablation in a large series of patients with ATTR and AL-CA.

Methods

Study design and patient population

This multicentre, retrospective, observational study included all consecutive patients diagnosed with either ATTR or AL-CA who underwent index transcatheter ablation for AF between 2011 and 2025 at 21 international tertiary care centres.

The diagnosis of CA was confirmed based on the most recent international guidelines available at that time.[2] This included haematologic testing, scintigraphy, and cardiac or extracardiac histologic examination, in order to differentiate ATTR and AL-CA.

Informed consent was obtained from all subjects or their legally authorized representative. The study protocol was approved by the local ethics committee and conforms to the Declaration of Helsinki.

Procedural details

Pulmonary vein isolation (PVI) was performed using various technologies over the study period, including radiofrequency (RF), cryoballoon (CB) and, more recently, pulsed field ablation (PFA) catheters, with or without three-dimensional electroanatomical mapping (EAM).[21,22] Low voltage areas (LVA) at EAM were defined as ≥3 adjacent mapping points with a peak-to-peak amplitude ≤0.5 mV during sinus rhythm (SR) or atrial pacing, ≤0.3 mV during atrial flutter (AFL), or ≤0.24 mV during AF.[23]

Ablation of concomitant AFL, atrial tachycardia (AT), non-pulmonary vein triggers or additional substrate modification, defined as PVI plus (PVI+), was performed at the operator's discretion. Marshall plan included concomitant PVI, ethanol infusion through the vein of Marshall, and creation of mitral isthmus, roof, and cavo-tricuspid isthmus (CTI) lines.

Follow-up

Post-ablation follow-up was conducted through outpatient clinic visits or hospital records. Rhythm monitoring included 12-lead electrocardiograms, periodic 24-h or 7-day Holter monitoring, rhythm recordings from wearable devices, implantable loop recorders (ILRs) and cardiac implantable electronic devices (CIEDs) interrogation when applicable.

Antiarrhythmic drug (AAD) therapy discontinuation after the ablation procedure and management of arrhythmic recurrence during blanking period were at the discretion of the attending physician.

New or worsening atrioventricular conduction disturbances during follow-up were defined as the occurrence of a new atrioventricular block (AVB) of any grade in patients without previously documented AVB, or progression of a pre-existing AVB to a higher grade.

Study endpoints

The study endpoints were: (i) recurrence of atrial arrhythmias (AAs), defined as any episode of AF, AFL, or AT lasting >30 s, occurring after the 90-day post-ablation blanking period; (ii) composite clinical endpoint of all-cause mortality and HFH.

Statistical analysis

Continuous variables were presented as mean ± standard deviation when normally distributed or otherwise as median and interquartile range. Between group comparisons were performed with parametric (Student's *t*-test, ANOVA) or non-parametric (Mann–Whitney *U* test) test, as applicable. The comparison between categorical variables was performed with the χ^2 test and the Fisher's exact test, as indicated. Event-free survival probability was estimated using the Kaplan– Meier method. Univariate Cox regression analysis [hazard ratios (HR) and 95% confidence interval (CI)] and univariate Logistic regression analysis [odds ratios (OR) and 95% confidence interval (CI)] were used to estimate the association between baseline characteristics and arrhythmic events or clinical endpoint. A two-sided *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 109 patients with CA who underwent catheter ablation for AF were included in the study. The mean age was 72.4 ± 7.4 years, and 19 patients (17.4%) were female. Among them, 39 patients (35.8%) had paroxysmal AF, and 70 (64.2%) persistent AF. ATTR-CA was diagnosed in 85 patients (78.0%) and AL amyloidosis in 24 patients (22.0%). Baseline characteristics are reported in *Table 1*. Chronic kidney disease (eGFR < 60 mL/min) was present in 32.1% and left ventricular dysfunction (left ventricle ejection fraction [LVEF] < 50%) in 30.3%. The mean left atrial volume index (LAVI) was 45.8 mL/m^2. Among ATTR-CA patients, 24 (28.2%) were on Tafamidis therapy before ablation.

Procedural data

As reported in *Table 2*, RF ablation was performed in 73 patients (67.0%), CB ablation in 16 (14.7%) and PFA in 20 (18.3%). Patients who underwent RF ablation had more frequently persistent AF (75.3% in RF group vs. 50.0% in PFA group vs. 31.3% in CB group, $P < 0.01$). Baseline characteristics were otherwise comparable between the PFA and thermal energy groups (*Table 2*). Fifty-five patients (50.5%) underwent PVI only, while the remaining 49.5% received PVI plus additional left atrial (LA) ablation.[24,25] A total of 44 patients (40.4%) underwent EAM. Of these, 34 (77%) had LVA. The most common atrial site of LVA was the anterior wall (55.8%), followed by the interatrial septum (44.1%) and the posterior wall (41.1%).

Patients with LVA were more often treated with a PVI + strategy as compared to patients with no LVA (70.6% vs. 50%), specifically targeting low voltage regions. The Marshall plan was performed in 9 patients (8.3%), including 7 with evidence of LVA at EAM and 2 without.

The most frequent PVI + strategy for patients with no LVA at EAM ($n = 10$) was posterior box isolation (30%), followed by posterior mitral line as part of the Marshall plan (20%).

Overall, 42 patients (38.5%) underwent CTI ablation during the index procedure. Of them, 35 (32.1%) underwent CTI ablation due to documented typical AFL, while it was part of the

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Table 1 Baseline characteristics

Baseline clinical data	ALL (*n* = 109)	ATTR-CA (*n* = 85)	AL-CA (*n* = 24)	*P*-value
Age, mean ± SD	72.4 ± 7.4	73.0 ± 7.0	70.1 ± 8.5	0.14
Male sex, *n* (%)	90 (82.6)	72 (84.7)	18 (75.0)	0.28
Paroxysmal AF, *n* (%)	39 (35.8)	30 (35.3)	9 (37.5)	0.79
Persistent AF, *n* (%)	70 (64.2)	55 (64.7)	15 (62.5)	0.79
Early persistent AF, *n* (%)	59 (54.1)	45 (52.9)	14 (58.3)	0.28
Long-standing persistent AF, *n* (%)	11 (10.1)	10 (11.8)	1 (4.2)	0.28
eGFR (mL/min/1.73 m^2), mean *(SD)*	65.8 (18.1)	65.3 (17.6)	67.6 (19.5)	0.54
CKD (egfr < 60 mL/min/1.73 m^2), *n* (%)	35 (32.1)	29 (34.1)	6 (25.0)	0.38
HF hospitalization, *n* (%)	38 (34.9)	30 (35.3)	8 (33.3)	0.83
Arterial hypertension, *n* (%)	68 (62.4)	54 (63.5)	14 (58.3)	0.59
LVEF, %, mean (SD)	54.8 (9.1)	53.4 (9.0)	59.3 (7.6)	0.002
LVEF<50%, *n* (%)	33 (30.3)	29 (34.1)	4 (16.7)	0.10
LAVi, mL/m, mean (SD)	45.8 (14.0)	45.4 (13.3)	47.3 (16.4)	0.59
BMI, kg/m^2, mean (SD)	26.1 (3.6)	26.3 (3.1)	25.6 (5.3)	0.57
DM II, *n* (%)	18 (16.5)	16 (18.8)	2 (8.3)	0.21
TIA/Stroke, *n* (%)	14 (12.8)	10 (11.8)	4 (16.7)	0.43
CAD, *n* (%)	23 (21.1)	19 (22.4)	4 (16.7)	0.53
CHA_2DS_2-VA score, mean (SD)	3.0 (1.4)	3.1 (1.4)	2.7 (1.7)	0.31
Carpal tunnel syndrome, *n* (%)	47 (43.1)	43 (50.6)	4 (16.7)	0.003
SND, *n* (%)	8 (7.3)	6 (7.1)	2 (8.3)	0.84
II-III AVB, *n* (%)	6 (5.5)	5 (5.9)	1 (4.2)	0.74
CIED, *n* (%)	24 (22.0)	19 (22.4)	5 (20.8)	0.85
PM, *n* (%)	11 (10.1)	8 (9.4)	3 (12.5)	0.67
ICD; *n* (%)	8 (7.3)	8 (9.4)	0 (0)	0.40
CRT, *n* (%)	5 (4.6)	3 (3.5)	2 (8.3)	0.33
Tafamidis*, *n* (%)	24 (22.0)	24 (28.2)	0 (0)	
AAD, *n* (%)	61 (56.0)	46 (54.1)	15 (62.5)	0.44
LAAC, *n (%)*	2 (1.8%)	1 (1.2%)	1 (2.9%)	0.33

Continuous variables are shown as mean ± SD. Discrete variables are presented as *n*, (%). *: ATTR subset.
Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; AVB, atrio-ventricular block; BMI, body mass index; CAD, coronary artery disease; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DM II, diabetes mellitus type II; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LAAC, left atrial appendage closure; LAVi, left atrium volume indexed; LVEF, left ventricle ejection fraction; PM, pacemaker; SD, standard deviation; SND, sinus node dysfunction, TIA, transient ischaemic attack.

Marshall plan strategy in 7 patients (6.4%). Procedural details are reported in *Table 3*.

Periprocedural complications occurred in 6 patients: 2 groin haematomas, 3 intraprocedural cardiac tamponades after ablation, and one acute HF immediately following ablation.

AF outcomes

Follow-up data were available in 108 patients (99.1%). During a median follow-up of 22.7 (9.8–47.7) months (31.1 months in RF [IQR 11.7–47.0] patients, 44.3 months in CB [IQR 16.9–70.6], 8.8 months in PFA [IQR 5.6–16.2]), recurrence of AAs after ablation was observed in 63 patients (58.3%) (*Figure 1*). Among these, 56 patients (51.9%) experienced AF recurrence, 7 (6.5%) ATs and 12 (11.1%) AFL. Persistent AF occurred in 32.4% of cases (*Figure 1C*).

Univariate Cox regression analysis (*Figure 2*) did not find any predictor of AA recurrence. Specifically, there was no difference in AA recurrences between AF subtype (paroxysmal vs. persistent) and CA subtype (ATTR vs. AL) (*Figure 1A and B*). Moreover, no statistically significant differences in terms of AA recurrences were observed between patients with and without low voltage areas at EAM (54.5% vs. 40%, respectively; $P = 0.42$).

Overall, 50 patients (46.3%) were on AAD during post-ablation follow-up, compared with 61 patients (56.0%) before ablation. AA recurrence rate was similar between patients on and off AAD therapy during follow-up (27, 54.0% vs. 36, 62.1%, respectively; $P = 0.40$).

Although PFA showed lower recurrence rate compared with thermal energy (50.0% vs. 60.2%), no significant association was found in multivariate logistic regression (OR 1.1, $P = 0.78$).

Data about continuous rhythm monitoring using implantable device (i.e. CIEDs, ILRs) were available for 33 patients (30.6%). Of them, 11 had no AF recurrence (burden 0%), and 12 presented persistent AF recurrence (burden 100%). In the remaining 10 patients, the mean AF burden during follow-up was 43%.

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Table 2 Baseline characteristics stratified by ablation source

Baseline characteristic stratified by ablation source	CB (*n* = 16)	PFA (*n* = 20)	RF (*n* = 73)	*P*-value
Age, mean (SD)	70.9 ± 8.7	74.1 ± 8.6	72.2 ± 6.8	0.43
ATTR-CA, *n* (%)	12 (75.0)	14 (70.0)	59 (80.1)	0.56
Male sex, *n* (%)	13 (81.3)	13 (65.0)	64 (87.7)	0.06
Persistent AF *n* (%)	5 (31.3)	10 (50.0)	55 (75.3)	0.001
eGFR (mL/min/1.73 m^2), mean (SD)	65.2 (14.8)	63.6 (24.8)	66.6 (16.4)	0.79
Arterial hypertension, *n* (%)	12 (75.0)	12 (60.0)	44 (60.3)	0.53
LVEF, %, mean (SD)	57.4 (9.6)	55.8 (9.7)	54.0 (8.8)	0.36
LAVi, mL/m^2, mean (SD)	37.9 (5.5)	47.1 (17.1)	46.8 (13.7)	0.13
DM II, *n* (%)	4 (25.0)	5 (25.0)	9 (14.3)	0.25
TIA/Stroke, *n* (%)	2 (12.5)	1 (5.0)	11 (15.1)	0.49
CAD, *n* (%)	4 (25.0)	5 (25.0)	14 (19.2)	0.78
CHA2DS2-VA score, mean (SD)	2.8 (1.5)	3.3 (1.9)	2.9 (1.3)	0.57

Continuous variables are shown as mean ± SD. Discrete variables are presented as *n*, (%).
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DM II, diabetes mellitus type II; eGFR, estimated glomerural filtration rate; LAVi, left atrium volume indexed; LVEF, left ventricle ejection fraction; SD, standard deviation; TIA, transient ischaemic attack.

Table 3 Procedural characteristics

LVZ	ALL (*n* = 109)	ATTR (*n* = 85)	AL (*n* = 24)	*P*-value
LVZ, *n* (%)	34 (31.2)	29 (34.1)	5 (20.8)	0.22
LVZ, % (SD)	21.9 (17.6)	22.9 (17.7)	7 (NA*)	
Energy source				
RF, *n* (%)	73 (67.0)	59 (69.4)	14 (58.3)	0.31
PFA, *n* (%)	20 (18.3)	14 (16.5)	6 (25.0)	0.36
CB, *n* (%)	16 (14.7)	12 (14.1)	4 (16.7)	0.77
Ablation strategy				
PVI only, *n* (%)	55 (50.5)	45 (52.9)	10 (41.7)	0.36
Cavo-tricuspid isthmus, *n* (%)	42 (38.5)	33 (38.8)	9 (37.5)	0.87
Posterior box, *n* (%)	35 (32.1)	26 (30.6)	9 (37.5)	0.54
Superior vena cava, *n* (%)	5 (4.6)	3 (3.5)	2 (8.3)	0.33
Anterior mitral line, *n* (%)	12 (11.1)	11 (12.9)	1 (4.2)	0.22
Posterior mitral line, *n* (%)	21 (19.3)	15 (17.6)	6 (25)	0.44
Roof line, *n* (%)	14 (12.8)	9 (10.6)	5 (20.8)	0.19
Marshall Plan, *n* (%)	9 (8.3)	7 (8.2)	2 (8.3)	1.00
Complications, *n* (%)	6 (5.5)	6 (7.1)	0 (0)	

Energy sources and ablation lesion are described.
Discrete variables are presented as *n* (%). *Data available only for one patient.
Abbreviations: AL, immunoglobulin light-chain; ATTR, transthyretin; CB, cryoballoon; LVZ, low voltage zones; PFA, pulsed-field ablation; PVI, pulmonary vein isolation; RF, radiofrequency.

During follow-up, 25 patients underwent a first re-do procedure, 6 patients a second re-do procedure and 3 patients even a third re-do procedure. Among 25 patients who underwent a re-do procedure, PVs were durably isolated in 18 (72%). All patients with PVs reconnection were treated with RF during index procedure. Notably, only 2 of them underwent PV re-isolation alone, whereas the remaining 23 received additional left and right atrial ablations, based on EAM findings.

Clinical outcomes

During follow-up, the composite clinical endpoint of all-cause mortality and HFH was reported in 27 patients (25.0%). Specifically, HFH was reported in 23 (21.5%) and death in 11 (10.3%).

At Univariate Logistic regression analysis (*Figure 3*), only the recurrence of persistent AF during follow-up was associated with the composite endpoint (OR 2.9, $P = 0.02$) (*Figure 4A*). This association was confirmed in a multivariable analysis adjusted

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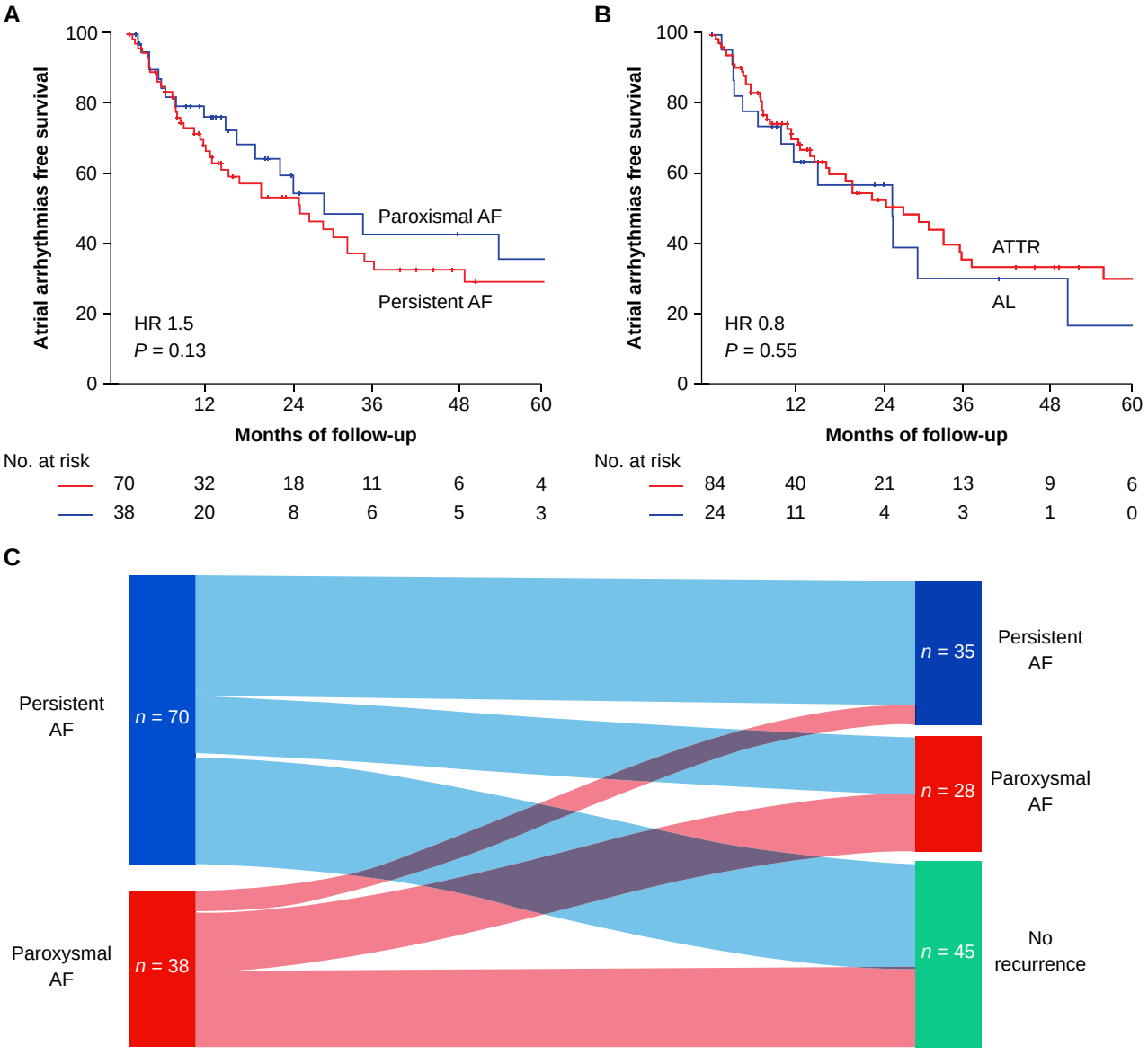

Figure 1 Kaplan-meier analysis of AA recurrence and AF burden evolution following AF ablation. Top panel: the graph depicts the Kaplan-Meier analysis for arrhythmic recurrence stratified by (*A*) paroxysmal or persistent atrial fibrillation and (*B*) ATTR or AL cardiac amyloidosis. Bottom panel (*C*): Sankey diagram illustrates the improvement of AF burden following ablation: most patients achieved a reduction from persistent AF to paroxysmal or no AF, and from paroxysmal AF to no AF. AF, atrial fibrillation; AL, immunoglobulin light-chain; ATTR, transthyretin; HR, hazard ratio.

for relevant covariates ($P = 0.05$, OR 2.57; Supplementary material online, *Figure S1*). Patients free from recurrence of persistent AF exhibited higher LVEF during follow-up (median 55% vs. 50%, $P = 0.02$) (*Figure 4B*).

During follow-up, 31 patients (36.5% of ATTR-CA) started treatment with Tafamidis.

Eighteen patients (16.7%) developed new or worsening atrioventricular conduction disturbances during follow-up. Seven patients (6.5%) were diagnosed with sinus node dysfunction.

During follow-up, 23 patients (21.3%) required CIED implantation [19 ATTR patients (22.6%) and 4 AL patients (16.7%)]. Specifically, one patient received a cardiac resynchronization therapy with defibrillator (CRT-D) as part of an 'ablate and pace' strategy, three patients underwent implantable cardioverter defibrillator (ICD) implantation, and the remaining patients received a pacemaker (PM) due to *de novo* or worsening AVB or sinus node dysfunction. Of the latter, 5 were on AAD during follow-up, which may have contributed to bradyarrhythmias. The need for CIED implantation was significantly higher in patients who experienced AA recurrence compared with those who maintained SR (28.9% vs. 11.1%, $P = 0.03$). Patients with persistent AF at baseline had significantly higher CIED implantation rates during follow-up compared with those with paroxysmal AF (30.0% vs. 5.3%, $P < 0.01$).

Two patients (1.9%) on oral anticoagulation experienced ischaemic stroke during follow-up, one with AA recurrence and

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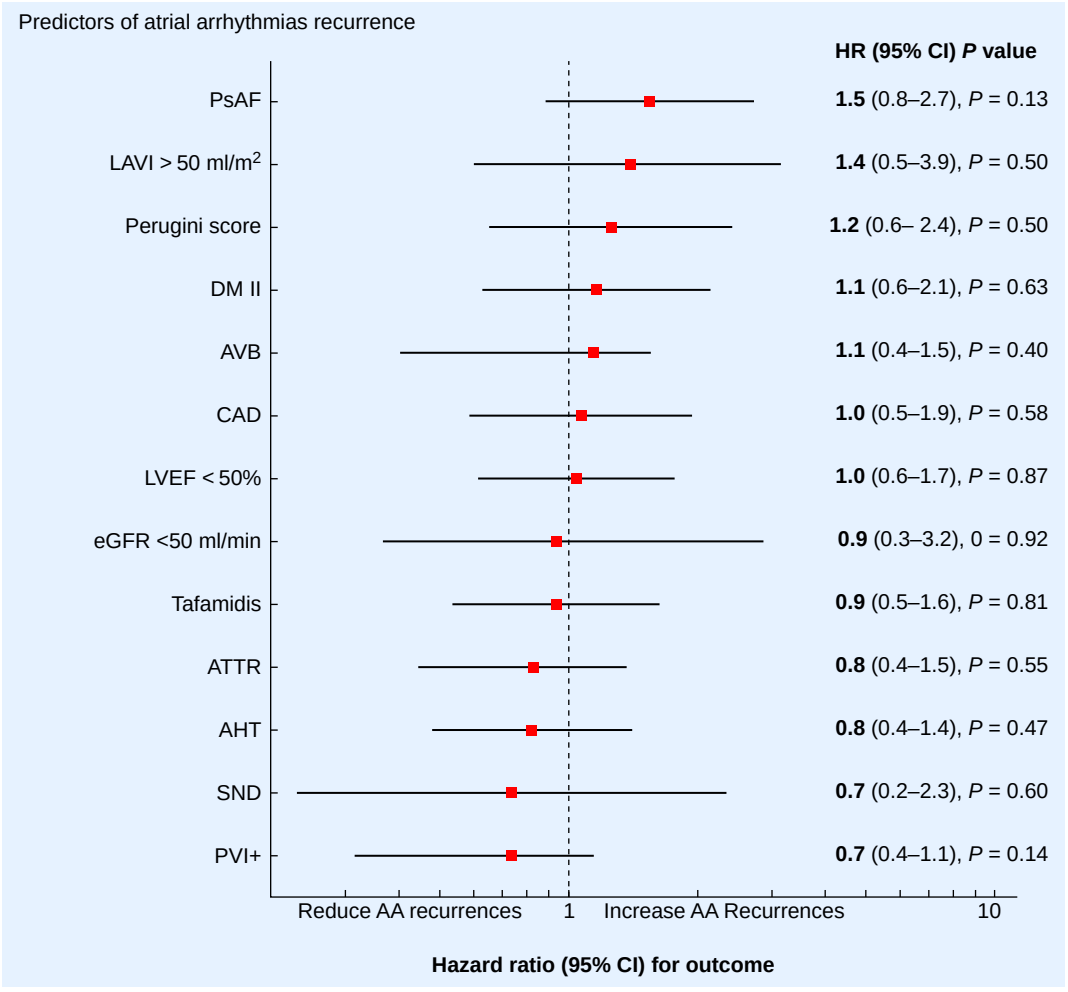

Figure 2 Predictors of AA recurrence after AF ablation in CA patients. The graph illustrates HR for each variable, with the dotted line indicating HR = 1.00. Perugini Score in bone scintigraphy was defined as follows: Grade 0: absence of tracer myocardial uptake and normal bone uptake; Grade 1: myocardial uptake in a lower degree than at bone level; Grade 2: similar myocardial and bone uptake; and Grade 3: myocardial uptake greater than bone with reduced/absent bone uptake. AHT, arterial hypertension; ATTR, transthyretin amyloidosis; AVB, atrio-ventricular block; CAD, coronary artery disease; CI, confidence interval; DM II, diabetes mellitus type II; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAVI, left atrium volume indexed; LVEF, left ventricle ejection fraction; PsAF, persistent atrial fibrillation; PVI+: pulmonary vein isolation plus additional ablations; SND, sinus node dysfunction.

one without, with a baseline CHA_2DS_2VA score of 8 and 5 points, respectively. Oral anticoagulation was discontinued in one patient during follow-up, due to a prior intracranial bleeding event while on oral anticoagulant therapy. This patient underwent concomitant left atrial appendage closure at the time of the index AF ablation.

Discussion

This is the largest cohort of patients with either ATTR or AL-CA undergoing AF ablation reported so far. The main findings of the study are the following: (i) patients with CA referred for AF ablation have high prevalence of persistent AF and advanced atrial remodelling; (ii) catheter ablation of AF in patients with CA has an overall high recurrence rate (58%) after a median follow-up of two years, although persistent AF recurs only in 32%; (iii) patients with persistent AF recurrence have three-fold higher risk of HFH and death.

Atrial arrhythmia recurrences

Likely due to the generally poor prognosis and distinct underlying pathophysiological mechanisms, CA patients with AF are less likely to be referred for ablation. Therefore, data on the efficacy and safety of AF ablation in CA is limited.[20] Early reports by Tan et al. described outcomes of AAs ablation in 5 patients with both AL and ATTR-CA undergoing PVI.[26] More recently, observational data from small cohorts (18 and 53 patients) have suggested very high recurrence rates after PVI alone, up to 86% at 6 months, although patients often reported symptomatic improvement.[27,28] Overall, recurrence rates after AF ablation reported in literature vary widely, ranging from 43% to 83%, due to variations in inclusion criteria, techniques, and CA stages.[20,29,30]

In our study, we observed a rate of AA recurrence of 58.3% over a median follow-up of about 2 years, highlighting the challenges of achieving rhythm control in both ATTR and AL-CA. Conversely, it is relevant to note that although the recurrence rate was high, the majority of the patients had an improvement

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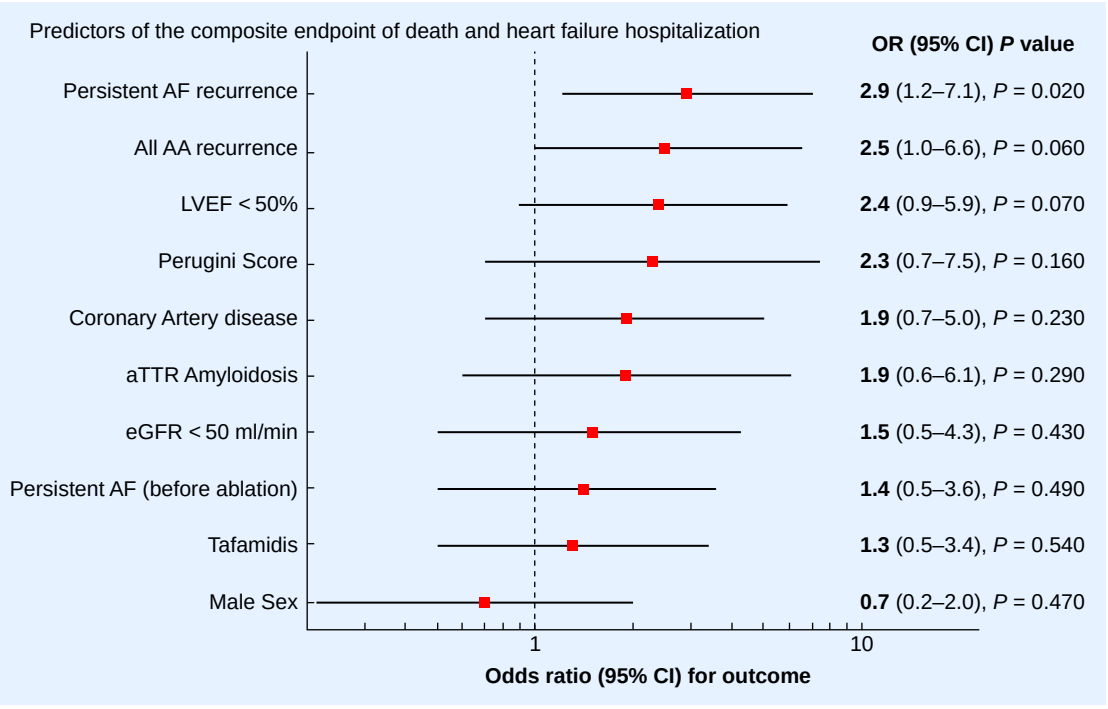

Figure 3 Univariate analysis: predictors of composite clinical endpoint of death and heart failure hospitalization (HFH) after AF ablation in CA patients. The graph illustrates OR for each variable, with the dotted line indicating OR = 1.00. AA, atrial arrhythmias; AF, atrial fibrillation; ATTR, transthyretin amyloidosis; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction; OR, odds ratio.

in AF burden and a conversion of AF form (from persistent AF to paroxysmal AF or no AF, and from paroxysmal AF to no AF) was documented in 54% of patients (*Figure 1C*).[31] Additionally, the number of patients with persistent AF after 2 years from the ablation was only 32%.

Increasing evidence indicates that the prevalence of atrial amyloidosis is greater than previously suspected, and it may be a key mechanism of atrial cardiomyopathy, defined as the presence of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.[32,33] Previous work by Oraii *et al*. emphasized that CA patients with AF often exhibit non-PV triggers, left AFLs and LA voltage abnormalities during first-time AF ablation, reflecting extensive atrial derangement due to CA-related atrial cardiomyopathy.[20,24,25] Interestingly, among the 25 patients who underwent a re-do procedure, PVs were durably isolated in 18 (72%). However, as already reported in other sub-groups of HF patients, the use of PVI plus additional ablation strategies was not associated with improved AA-free survival (*Figure 2*).[34] Further studies are needed to determine the best ablation strategy in this population.

To our knowledge, this is the first study to report PFA outcomes in CA patients.[35] However, given the shorter follow-up and the smaller cohort in the PFA subgroup, further studies are necessary to elucidate this matter.

Clinical outcomes

Despite the overall high recurrence rate of AAs following ablation in our cohort, patients with no persistent AF recurrence showed improved clinical outcomes. This aligns with previous studies in the field of AF ablation and HF with reduced LVEF, which have demonstrated that it is not the overall recurrence of AF that impacts prognosis, but rather the AF burden.[31] In the cohort of CA, as well as among patients with HF, the goal might not be the complete elimination of AF, but rather the control of its burden.[36,37] This is consistent with smaller studies showing a significant reduction in all-cause mortality after ablation in ATTR-CA patients with AF.[10,38]

We also observed that patients with persistent AF at baseline had significantly higher CIED implantation rates compared with those with paroxysmal AF, consistent with a more advanced atrial involvement and conduction system disease in persistent AF as amyloid infiltration likely contributes both to arrhythmia persistence and conduction abnormalities.

Interestingly, ATTR-CA was not significantly associated with a lower composite clinical endpoint occurrence (OR 1.9, $P = 0.29$), despite significant higher LVEF at baseline; to our knowledge, this observation has not been previously described in the literature.

Limitations

The sample size is relatively small, particularly for subgroup analysis, due to the rarity of CA and the limited number of CA patients systematically referred for AF ablation. As a retrospective, observational, multicentre study, ablation strategies and follow-up protocols were not standardized and varied among participating centres. Continuous rhythm monitoring was available only in a minority of patients, which may have led to under-detection of arrhythmic events during follow-up

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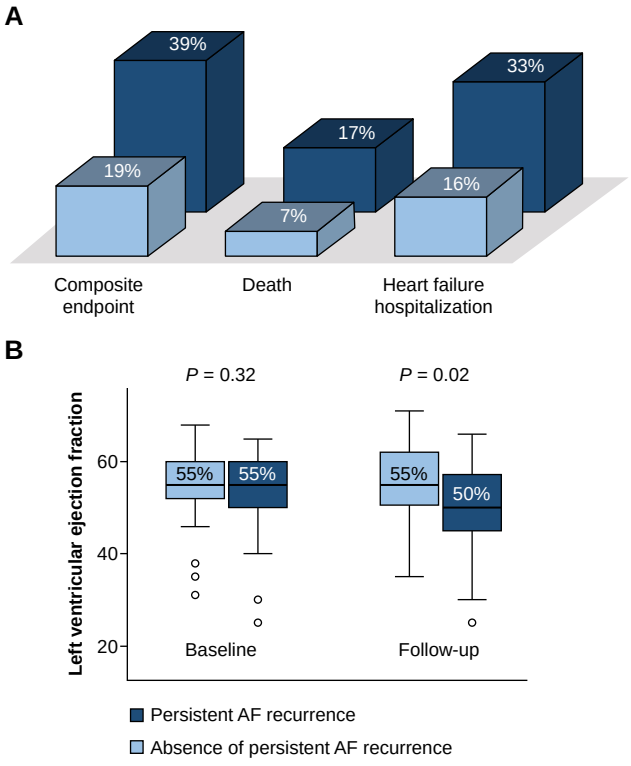

Figure 4 Clinical outcomes and left ventricular ejection fraction stratified by presence or absence of persistent AF recurrence. Panel (*A*): the graph depicts incidence of composite endpoint of death and HFH stratified by patients with and without recurrence of persistent AF. Panel (*B*): this graph displays the median left ventricular ejection fraction in patients with and without recurrence of persistent AF at baseline and at follow-up. LVEF was assessed at a median of 22.9 months [IQR 10.0–45.8] after ablation.

and limiting actual determination of AF burden. Specifically, the exact timing of persistent AF recurrence was not systematically collected. Furthermore, detailed substrate data were available only for a subset of patients. These limitations underscore the need for future prospective studies with standardized protocols and longer follow-up to confirm and expand upon our findings.

Conclusions

Patients with CA undergoing AF ablation have high prevalence of persistent AF and advanced atrial remodelling. Freedom from AA after AF ablation is achieved in 42% of patients after a median follow-up of two years. Although the high recurrence rate, a considerable proportion of patients experience AF burden reduction, and conversion from persistent to paroxysmal AF. Patients with persistent AF recurrence may have three-fold higher risk of HFH and death.

Supplementary material

Supplementary material is available at *Europace* online.

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