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**CLINICAL RESEARCH**
*Ablation for atrial fibrillation*

# Predictive role of early recurrence of atrial fibrillation after cryoballoon ablation

**Giuseppe Stabile [1,2,3]*, Saverio Iacopino[4], Roberto Verlato[5], Giuseppe Arena[6], Paolo Pieragnoli[7], Giulio Molon[8], Massimiliano Manfrin[9], Giovanni Rovaris[10], Antonio Curnis[11], Emanuele Bertaglia[12], Massimo Mantica[13], Luigi Sciarra[14], Maurizio Landolina[15], and Claudio Tondo[16]**

[1]Clinica Montevergine, Mercogliano, Avellino, Italy; [2]Clinica San Michele, via Montella 16, 81024 Maddaloni, Caserta, Italy; [3]Anthea Hospital, Bari, Italy; [4]Maria Cecilia Hospital, GVM Care&Research, Cotignola, Ravenna, Italy; [5]AULSS 6 Euganea, Ospedale di Cittadella-Camposampiero, Padova, Italy; [6]Ospedale delle Apuane, Massa, Italy; [7]Ospedale Careggi, University of Florence, Firenze, Italy; [8]IRCCS Sacro Cuore Don Calabria Don Calabria, Negrar, Italy; [9]San Maurizio, Bolzano, Italy; [10]ASST San Gerardo, Monza, Italy; [11]Azienda Ospedaliera Spedali Civili, Brescia, Italy; [12]Azienda Ospedaliera di Padova, Padova, Italy; [13]Ospedale Sant'Ambrogio, Milano, Italy; [14]Policlinico Casilino, Roma, Italy; [15]Department of Cardiology, Ospedale Maggiore, Crema, Italy; and [16]Heart Rhythm Centre, Centro Cardiologico Monzino IRCCS Milan, Italy

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**Aims** The aims of this study were to determine the rate and the predictors of early recurrences of atrial fibrillation (ERAF) after cryoballoon (CB) ablation and to evaluate whether ERAF correlate with the long-term outcome.

**Methods and results** Three thousand, six hundred, and eighty-one consecutive patients (59.9 ± 10.5 years, female 26.5%, and 74.3% paroxysmal AF) were included in the analysis. Atrial fibrillation recurrence, lasting at least 30 s, was collected during and after the 3-month blanking period. Three-hundred and sixteen patients (8.6%) (Group A) had ERAF during the blanking period, and 3365 patients (Group B) had no ERAF. Persistent AF and number of tested anti-arrhythmic drugs ≥2 resulted as significant predictors of ERAF. After a mean follow-up of 16.8 ± 16.4 months, 923/3681 (25%) patients had at least one AF recurrence. The observed freedom from AF recurrence, at 24-month follow-up from procedure, was 25.7% and 64.8% in Groups A and B, respectively ($P < 0.001$). ERAF, persistent AF, and number of tested anti-arrhythmic drugs ≥2 resulted as significant predictors of AF. In a propensity score matching, the logistic model showed that ERAF 1 month after ablation are the best predictor of long-term AF recurrence ($P = 0.042$).

**Conclusion** In patients undergoing CB ablation for AF, ERAF are rare and are a strong predictor of AF recurrence in the follow-up, above all when occur >30 days after the ablation.

**Keywords** Atrial fibrillation • Catheter ablation • Cryoballoon • Recurrence

## Introduction

Early recurrences of atrial fibrillation (ERAF) have been reported in up to 50% of patients within the first 3 months of AF ablation.[1–4] Although these arrhythmias do not indicate therapy failure, they are associated with a higher AF recurrence rate over the long term. The pathophysiological mechanisms of these early recurrences are various[1]: primarily incomplete isolation of the pulmonary veins (PV), acute inflammatory changes owing to energy delivery, recovery of conduction in a previously isolated PV, modification of the autonomic nervous system, changes in the atrial substrate, and delayed effect of radiofrequency (RF) ablation due to lesion consolidation. The great amount of information about ERAF has been collected in patients undergoing RF catheter ablation. In recent years, cryoballoon (CB) ablation has become the most efficient alternative to RF catheter ablation for the treatment of AF. Little is known[5–8] about ERAF incidence and clinical significance in patients undergoing CB ablation. The aims of this study were to determine the rate and the predictors of ERAF within the first 3 months after CB ablation and to evaluate whether ERAF correlate with the long-term outcome.

* Corresponding author. Tel: +39 348 896 0534. *E-mail address*: gmrstabile@tin.it

## What's new?

- This large, multicentre study investigated the clinical significance of early recurrences of atrial fibrillation in patients undergoing cryoballoon ablation.
- Early recurrences of atrial fibrillation, during the 3-month blanking period, are rare occurring in <10% of patients.
- Early recurrences of atrial fibrillation are a strong predictor of long-term atrial fibrillation recurrence, above all when occur >30 days after the ablation.

# Methods

## Patients' selection

The patients included in the present analysis were enrolled and followed in a network of 47 cardiology centres, which participate in the Italian ClinicalService® framework (Clinical Trial Registration Information: http://clinicaltrials.gov/ct2/show/NCT01007474), 1STOP project. This is a national medical care project aimed at evaluating and improving the use of medical therapies in the clinical practice. The project consists of a shared environment for the collection, management, analysis, and reporting of data from patients in whom Medtronic therapies have been applied.[9] Patients aged between 18 and 90 years with documented symptomatic paroxysmal or persistent AF, refractory to anti-arrhythmic therapy, were eligible for the analysis. Exclusion criteria were (i) permanent AF, (ii) New York Heart Association functional class IV, (iii) unstable angina or acute myocardial infarction within three months, (iv) need for or prior cardiac surgery within 6 months, (v) contraindication to treatment with oral anti-coagulants, and (vi) severe chronic renal or hepatic impairment.

The project was approved by each site's Medical Ethical Committee or Medical Director and conforms to the principles outlined in the Declaration of Helsinki. Each patient provided informed consent for data collection and analysis.

## Ablation procedure

After transseptal catheterization, the CB catheter was introduced into the left atrium via a 12-Fr steerable sheath (FlexCath Advance, Medtronic, Inc.). Mapping of the PVs was performed with an inner lumen mapping catheter (Achieve, Medtronic, Inc.). The mapping catheter was advanced in each PV ostia, positioned as proximal as possible to provide PV potentials recording. A 28-mm CB catheter (Arctic Front Advance, Medtronic) was advanced inflated and positioned at each PV antrum. Optimal vessel occlusion was considered to have been achieved when selective contrast injection showed the absence of contrast backflow to the atrium. When complete occlusion could not be achieved, the mapping catheter was replaced by a stiff guide wire (Amplatz Ultra Stiff, Cook Medical, Bloomington, IN, USA). The standard set of lesions includes the left superior PV treated as first, followed by the left inferior PV, right superior PV, and right inferior PV. As per nature of this project, we did not implement a standardized protocol on the number and duration of freeze nor the usage of a bonus freeze but a general strategy was shared among the centres. In case of the presence of a common ostium, the veins were treated as separate branches. Target application time was 180–240 s.

Time-to-PV isolation was defined as the time from freeze initiation to the last recorded PV potentials. If the temperature did not attain −40°C within 60 s or acceptable nadir temperature was not reached, a bonus freeze with a different occlusion was applied. The right phrenic nerve was paced from the superior cava or subclavian vein during freezing at the septal PVs. Phrenic capture was monitored by tactile feedback. In case of cessation or weakening of right hemi-diaphragm contractions, freezing was immediately terminated.[10]

## Post-ablation management and follow-up

Oral anti-coagulation was left uninterrupted on the day of the procedure for all patients and continued for at least 3 months or long term in patients with a high thromboembolic risk assessed by $CHA_2DS_2$-VASc score. Anti-arrhythmic drugs were usually discontinued ≥5 half-lives prior to ablation, except for amiodarone. Patients were scheduled for follow-up examinations 3, 6, and 12 months after the initial treatment and every 6 months thereafter. Rhythm monitoring during the follow-up visits was performed by the clinical assessment of AF recurrence, ECG and Holter monitoring according to the clinical practice of each centre. Patients were asked to provide any other ECG or Holter monitoring performed since the previous visit.

Ablation was deemed successful in the absence of symptomatic or asymptomatic atrial tachyarrhythmias lasting >30 s identified by surface ECG or Holter monitoring, after the blanking period (3 months). Long-term success was defined as single procedural success.

## Aim of the research

Early recurrences of AF after AF ablation have been defined as any recurrence of AF ≥30 s during the first 3 months of follow-up. In using the term ERAF, it is recognized that the early recurrence might be atrial flutter or atrial tachycardia.[1] The aims of this study were to determine the rate and the predictors of ERAF within the first 3 months after CB ablation and to evaluate whether ERAF correlate with the long-term outcome.

## Statistical analysis

Descriptive statistics were used to summarize patient characteristics. This includes mean and standard deviation, minimum, maximum, and median with the interquartile range (IQR) for continuous variables, and counts and percentages for categorical variables. Summary statistics were reported with maximum two decimals, as appropriate. Comparisons between groups have been performed using Wilcoxon's test for continuous variables, while comparisons of categorical variables have been performed by means of the $\chi^2$ test or Fisher's exact test for extreme proportions, as appropriate. Statistical tests were based on a two-sided significance level of 0.05.

The analyses of time-to-the-first event were described by means of Kaplan–Meier curves and compared between the groups by means of the log-rank test. The follow-up duration (months) will be computed from the date of the implant to the date of the last available follow-up or date of event.

The annual rates of complications were reported, together with the 95% Poisson confidence intervals (CIs). The Poisson regression model was used to calculate the incidence rate ratio (IRR), with the *d*-scale option. An IRR >1 would show a lower incidence of event in the *reference* group, while an IRR <1 would show a higher incidence of event in the *reference* group.

To find predictors for AF recurrences, a Cox regression was imputed for both univariable (the proportional hazard hypothesis has been tested) and multivariable analyses. A set of a priori defined potential predictors were assessed. Possible collinearity among these variables was tested by Spearman-rho, where a correlation coefficient >0.25 and clinical judgement determined covariate exclusion. The final set of potential predictors was then included in the multivariable model. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated for all initial potential predictors. The multivariable Cox regression model used stepwise

**Table 1 Clinical characteristic of the study population**

| Baseline characteristics | Total ($n = 3681$) | Group A ($n = 316$) | Group B ($n = 3365$) | P |
|---|---|---|---|---|
| Mean age (years) | 59.9 ± 10.5 | 60.5 ± 9.8 | 59.8 ± 10.5 | 0.614 |
| Gender (female) (%) | 26.5 | 24.4 | 26.7 | 0.372 |
| Mean BMI | 27.0 ± 4.2 | 27.3 ± 4.0 | 27 ± 4.2 | 0.110 |
| Paroxysmal AF (%) | 74.3 | 60.1 | 75.6 | <0.001 |
| Months from first AF episode | 54.1 ± 66 | 59.1 ± 60.8 | 53.6 ± 66.5 | 0.033 |
| Patients tested ≥2 AAD (%) | 42.7 | 55.1 | 41.4 | <0.001 |
| History of stroke/TIA (%) | 4.4 | 4.4 | 4.3 | 0.953 |
| Cardiac insufficiency (%) | 4.3 | 5.9 | 4.1 | 0.132 |
| Hypertension (%) | 48.8 | 49.2 | 48.7 | 0.872 |
| Coronary artery disease (%) | 6.2 | 7.8 | 6.1 | 0.238 |
| Any valve disease (%) | 5.6 | 5.6 | 5.6 | 0.987 |
| Any other CV diseases (%) | 4 | 6.3 | 3.8 | 0.036 |
| Mean $CHA_2DS_2$-VASc score | 1.4 ± 1.2 | 1.4 ± 1.2 | 1.4 ± 1.2 | 0.780 |
| Diabetes (%) | 6.0 | 7.2 | 5.9 | 0.376 |
| Chronic kidney disease (%) | 2.4 | 2.4 | 2.4 | 0.995 |
| LVEF (%) | 59.0 ±7.0 | 58.1 ± 7.2 | 59.1 ± 7 | 0.055 |
| Left atrial diameter (mm) | 41.7 ± 7.9 | 43.4 ± 7.4 | 41.6 ± 8.0 | <0.001 |
| Left atrial volume (mL) | 68.0 ± 25.9 | 74.1 ± 31.0 | 67.1 ± 25.0 | 0.115 |

AAD, anti-arrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; $CHA_2DS_2$-VASc score, congestive heart failure (+1), hypertension (+1), age ≥75 (+2), diabetes (+1), stroke (+2), vascular disease (+1), age 65–74 (+1), and sex (female) (+1); CV, cardiovascular; TIA, transient ischaemic attack.

selection with entry 0.30, stay criteria 0.10, and AF as the dependent variable. The *c*-statistic was used as the main accuracy measure and reported together with the multivariable model's results, if applicable. In addition, a logistic model was used to search predictors for AF recurrence, without time effect. Both univariable and multivariable results were shown, together with the correspondent *c*-statistic.

A propensity score matching was performed to reduce the bias due to confounding variables that could be found in an estimate of the effect obtained simply comparing outcomes among patients with and without ERAF.

The SAS software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses.

# Results

## Study population

The analysis included 3681 consecutive patients. Among them, 316 patients (8.6%) (Group A) had ERAF and 3365 patients (Group B) had no ERAF. Their main baseline clinical characteristics are shown in *Table 1*. All patients underwent only CB PV isolation during the index procedure. Of 316 patients with ERAF, 10 patients had atrial tachycardia, 1 patient had an atrial flutter, and the remaining AF. Overall, 905 (24.6%) patients were on anti-arrhythmic drug during the blanking period: 98/316 (31%) patients in the Group A and 807/3365 (24%) patients in the Group B. Of the whole population, 10.1% patients were implanted and followed up with an implantable loop recorder, and 56.4, 55.3, and 48.5% of patient had a Holter monitoring at 6-, 12-, and 24-month follow-up, respectively.

## Predictors of early recurrences of atrial fibrillation

*Table 2* summarizes the predictors of ERAF at univariable and multivariable analyses. The parameters resulting as significant predictors of ERAF were persistent AF, number of tested anti-arrhythmic drugs ≥2 and patients in anti-arrhythmic drug during the blanking period, in multivariable analysis.

## Follow-up data

After a mean follow-up of 16.8 ± 16.4 months, 923/3681 (25%) patients had at least one AF recurrence. The observed freedom from AF recurrence, at 24-month follow-up, was 25.7% (19.5–32.4%) and 64.8% (62.4–67.0%) in Groups A and B, respectively ($P < 0.001$) (*Figure 1*). At univariable and multivariable analyses, ERAF, persistent AF, and number of tested anti-arrhythmic drugs ≥2 resulted as significant predictors of AF recurrence during follow-up (*Table 3*).

Overall, 253/3681 (6.9%) patients with atrial arrhythmia relapses underwent a second ablation procedure: 65 (20.6%) in the Group A and 188 (5.6%) in the Group B, $P < 0.001$.

In 2733 patients with paroxysmal AF, unadjusted freedom from AF recurrence at 12 months was 43% and 81.4% in the Groups A and B, respectively ($P < 0.001$), while in the 947 patients with persistent AF, unadjusted freedom from AF recurrence at 12 months was 30.7% and 73% in the Groups A and B, respectively ($P < 0.001$) (*Figure 2*).

## Propensity score matching

Results on the after-propensity score set showed that the population analysed is composed by 560 patients divided into two groups (280 patients in each group) (*Table 4*), according to the ERAF occurrence

**Table 2 Univariable and multivariable analyses on predictors of ERAF**

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR | *P*-value | HR | *P*-value |
| Gender (male) | 1.13 (0.87–1.46) | 0.359 | 1.12 (0.85–1.47) | 0.415 |
| Age at first ablation (years) | 1.01 (1.00–1.02) | 0.224 | 1.00 (0.99–1.02) | 0.471 |
| Persistent atrial fibrillation | 2.12 (1.69–2.65) | <0.001 | 2.20 (1.73–2.80) | <0.001 |
| Months from first AF episode | 1.00 (1.00–1.00) | 0.292 | | |
| Number of tested AAD ≥2 | 1.55 (1.23–1.96) | <0.001 | 1.48 (1.17–1.88) | 0.001 |
| Hypertension | 1.05 (0.84–1.32) | 0.649 | | |
| Left atrial diameter (mm) | 1.01 (1.00–1.02) | 0.003 | | |
| Left atrial volume (mL) | 1.01 (1.00–1.02) | 0.029 | | – |
| AAD during blanking period | 1.55 (1.22–1.97) | <0.001 | 1.31 (1.02–1.69) | 0.036 |

AF, atrial fibrillation; AAD, anti-arrhythmic drugs; HR, hazard ratio.

during blanking period. During the entire follow-up period, 209/560 (37%) patients had at least one AF recurrence.

The observed freedom from AF recurrence, at 24-month follow-up, was 26.5% (19.9–33.7%) and 60.9% (51.8–68.7%) in Groups A and B, respectively ($P < 0.001$). The parameters resulting as significant predictors of AF recurrence were the ERAF [HR 3.19 (2.34–4.34), $P < 0.001$] and persistent AF [HR 1.34 (1.01–1.78), $P = 0.044$].

To evaluate the best cut-off value for ERAF that predicts long-term AF recurrence, we divided patients by different cut-offs of time to ERAF. The Logistic model showed that 'having ERAF during blanking period and after 1 month (within 3 months)' predicted AF after the blanking period both in univariable ($P = 0.043$) and multivariable (0.049) models (*Table 5*).

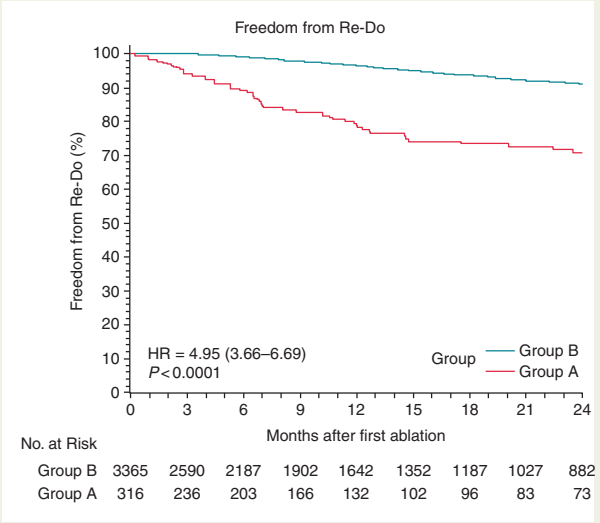


**Figure 1** Kaplan–Meier estimation of the time to AF recurrence after the blanking period in the two study groups. The HR and *P*-value reported are referred to the 24-month follow-up. AF, atrial fibrillation; HR, hazard ratio.

# Discussion

The present study demonstrates that ERAF, during the blanking period, occur in <10% of patients undergoing CB ablation for AF, and are more frequent in patients with persistent AF, with a number of tested anti-arrhythmic drugs ≥2, and on anti-arrhythmic drug during the blanking period. ERAF are a strong predictor of AF recurrence in the follow-up, above all when they occur >30 days after the ablation.

ERAF, after AF ablation, has been defined as any recurrence of atrial tachyarrhythmias lasting ≥30 s during the first 3 months of follow-up.[1] They have been widely described since early year of PV isolation[2–4] in patients undergoing RF catheter ablation and occur in up to 50% of patients.[11–13] Few data are available on patients undergoing CB ablation. Andrade *et al.*,[14] in 163 patients enrolled in the STOP AF trial, and treated with first-generation CB, found that ERAF occurred in ≈50% of patients and were strongly associated with late recurrence. More recently, with second-generation CB, a lower incidence, ≈20%, of ERAF has been reported in small series.[5–7,15,16] In our large, multicentre study, we found that ERAF occurred in only 8.6% of patients and were more frequent in patients with persistent AF, patients who tested at least two anti-arrhythmic drugs or patients on AAD during the blanking period.

Because ERAF do not definitively indicate therapy failure over the long-term, the first 3 months after ablation is also referred to as the blanking or therapy stabilization period. The current expert Consensus Statement[1] defines the success of an ablation procedure as 'freedom from atrial tachyarrhythmias after removal from anti-arrhythmic drug therapy as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure', and current guidelines[17] recommend that repeat ablation, because of recurrence of arrhythmia following ablation, should be considered after 3 months post-ablation. Nevertheless, early recurrences have been shown to predict arrhythmia recurrences late after catheter ablation of AF in some patients[1,5,11,13] and some concern exist on the length of the blanking period.[18] In our study, ERAF were the stronger predictor of late AF recurrence, above all when they occur after the first month after ablation. Other studies have called into question the 90-day cut-off value of the blanking period. Willems *et al.*[11] studied 401 patients with paroxysmal AF undergoing PV isolation. They found

**Table 3 Univariable and multivariable analyses on predictors of AF recurrence after the blanking period**

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR | *P*-value | HR | *P*-value |
| Group (A) | 3.67 (3.08–4.37) | <0.001 | 4.38 (3.51–5.45) | <0.001 |
| Gender (male) | 0.90 (0.77–1.04) | 0.159 | 0.93 (0.73–1.19) | 0.564 |
| Age (years) | 1.01 (1.00–1.01) | 0.019 | 1.01 (1.00–1.02) | 0.271 |
| Persistent atrial fibrillation | 1.59 (1.37–1.84) | <0.001 | 1.54 (1.24–1.92) | <0.001 |
| Months from first AF episode | 1.00 (1.00–1.00) | 0.260 | | |
| Number of tested AAD 2+ | 1.32 (1.13–1.53) | <0.001 | | |
| Hypertension | 1.15 (1.00–1.33) | 0.048 | | |
| Left atrial diameter (mm/m$^2$) (continuous) | 1.39 (1.16–1.67) | <0.001 | | |
| Any other CV disease | 1.23 (0.89–1.70) | 0.216 | | |
| Left ventricurar ejection fraction | 0.99 (0.98–1.00) | 0.227 | | |
| AAD during blanking period | 1.22 (0.98–1.52) | 0.074 | | |

AAD, anti-arrhythmic drugs; CV, cardiovascular.

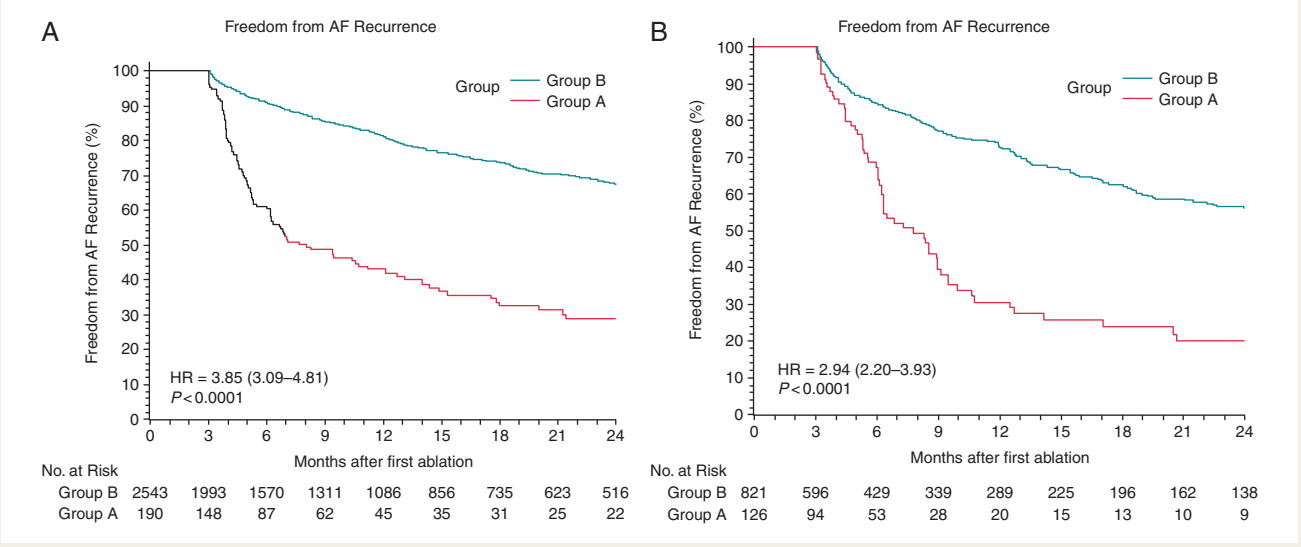


**Figure 2** Kaplan–Meier estimation of the time to AF recurrence after the blanking period in patients with paroxysmal (left) and persistent AF (right). The HR and *P*-value reported are referred to the 12-month follow-up. AF, atrial fibrillation; HR, hazard ratio.

that >90% of patients with ERAF during the third month post-ablation experience late recurrence by 1 year. The ROC curve associated with the greatest discriminatory potential was 50 days (Youden index 0.58). Alipour *et al.*,[12] studying 636 patients with paroxysmal and persistent AF, further decrease this cut-off to 23 days, beyond which time ERAF predicted late recurrence. However, overall sensitivity and specificity at 23 days were only 69.2 and 61.2%, respectively. Our data, collected in a population undergoing CB ablation, although with significantly lower incidence of ERAF, are therefore similar to those collected in patients undergoing RF catheter ablation, challenging the conventional 3-month blanking. Similarly, Mugnai *et al.*[5] in 331 patients with paroxysmal AF undergoing CB found that when ERAF occurred later than 1.5 months, patients systematically experienced a late recurrence. This concern has been recently confirmed by Yamashita *et al.*[19] that, based on serial magnetic resonance imaging, found that atrial ablation lesions are often fully mature before the typical 90-day blanking period, which could support more timely clinical decision making for arrhythmia recurrence. Moreover, compared with RF, cryoablation shows less systemic inflammatory reaction, mainly due to less endothelial damage and surface thrombosis,[20] thus further reducing the chance of ERAF. Based on all these evidence and the results of our study, a shorter blanking period, 30–45 days, seems to be more appropriate to detect ERAF that do not predict long-term recurrences. However, in the absence of randomized clinical trials with head-to-head comparisons of redo procedures after a conventional vs. shorter blanking period, earlier repeat ablation cannot be routinely recommended.

**Table 4 Clinical characteristic of the propensity score matching study population**

| Baseline characteristics | TOTAL ($n = 560$) | Group A ($n = 280$) | Group B ($n = 280$) | P |
|---|---|---|---|---|
| Mean age (years) | 60.1 ± 9.9 | 59.9 ± 9.9 | 60.3 ± 9.8 | 0.752 |
| Gender (female) (%) | 24.6 | 24.3 | 25.0 | 0.845 |
| Mean BMI | 27.6 ± 4.3 | 27.8 ± 4.5 | 27.4 ± 4.0 | 0.617 |
| Paroxysmal AF (%) | 59.6 | 59.6 | 59.6 | 1.000 |
| Months from first AF episode | 57.8 ± 66.4 | 56.0 ± 71.0 | 59.5 ± 61.5 | 0.151 |
| Patients tested ≥2 AAD (%) | 56.1 | 56.8 | 55.4 | 0.733 |
| History of stroke/TIA (%) | 3.8 | 3.2 | 4.3 | 0.499 |
| Cardiac insufficiency (%) | 5.6 | 4.7 | 6.5 | 0.355 |
| Hypertension (%) | 51.5 | 54.5 | 48.6 | 0.162 |
| Coronary artery disease (%) | 7.0 | 6.4 | 7.5 | 0.657 |
| Any valve disease (%) | 5.4 | 5.0 | 5.7 | 0.700 |
| Any other CV diseases (%) | 6.1 | 5.4 | 6.8 | 0.479 |
| Mean $CHA_2DS_2$-VASc score | 1.5 ± 1.2 | 1.5 ± 1.2 | 1.5 ± 1.3 | 0.783 |
| Diabetes (%) | 8.5 | 9.7 | 7.3 | 0.331 |
| Chronic kidney disease (%) | 3.1 | 3.5 | 2.6 | 0.579 |
| LVEF (%) | 58.4 ± 7.4 | 58.8 ± 7.5 | 58.0 ± 7.3 | 0.417 |
| Left atrial diameter (mm) | 42.6 ± 6.9 | 42.0 ± 6.3 | 43.1 ± 7.3 | 0.065 |
| Left atrial volume (mL) | 72.2 ± 27.5 | 66.8 ± 18.6 | 75.4 ± 31.3 | 0.221 |

AAD, anti-arrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; TIA, transient ischaemic attack; $CHA_2DS_2$-VASc score, congestive heart failure (+1), hypertension (+1), age ≥75 (+ 2), diabetes (+1), stroke (+2), vascular disease (+1), age 65–74 (+1), and sex (female) (+1); CV, cardiovascular; LVEF, left ventricle ejection fraction.

**Table 5 Univariable and multivariable analyses on best cut-off value for ERAF that predicts long-term AF recurrence**

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR | P-value | HR | P-value |
| AF within blanking period ≥0.3 months | 2.18 (0.91–5.22) | 0.082 | | |
| AF within blanking period ≥0.5 months | 2.04 (1.02–4.09) | 0.052 | | |
| AF within blanking period ≥1 month | 1.67 (1.00–2.78) | 0.043 | 1.68 (1.00–2.82) | 0.049 |
| AF within blanking period ≥1.5 months | 1.46 (0.91–2.34) | 0.115 | | |
| AF within blanking period ≥2 months | 1.79 (1.10–2.90) | 0.018 | | |
| AF within blanking period ≥2.5 months | 1.25 (0.71–2.19) | 0.444 | | |

AF, atrial fibrillation; HR, hazard ratio.

## Limitations

The results of this study should be interpreted with caution due to a number of limitations. First, this is a multicentre data collection, and the ablation strategy was not standardized, including: pre-procedural imaging, oral anti-coagulant management, number and duration of freeze, and the usage of a bonus freeze. However, this observational retrospective research may provide a representative image of the real-life scenario on the usage of CB catheter for AF ablation. Secondly, sinus rhythm maintenance was based mainly on patients' symptoms, ECG and scheduled 24-h Holter monitoring. Asymptomatic or short-lasting AF episodes may have occurred unnoticed, and our success rate may have been over-estimated. Thirdly, we did not systematically collected data on redo procedures in patients with ERAF and we have no data to speculate on the mechanism underlying them. Finally, this study was not testing a prospective hypothesis, and consequently, no adjustments were formulated for the multiplicity of testing. Also, it is established that errors in confounding and bias are more common in non-prospective studies, which cannot utilize randomization or a true control arm. Consequently, these data should be viewed as a real-world snapshot of current usage practices amongst a large group of CB users in one European country.

## Conclusions

Early recurrences of atrial fibrillation, during the blanking period, occur in <10% of patients undergoing CB ablation for AF, and are more frequent in patients with persistent AF, with a number of tested anti-arrhythmic drugs ≥2, and on anti-arrhythmic drug during the blanking period. ERAF are a strong predictor of AF recurrence in the follow-

up, above all when they occur >30 days after the ablation, thus challenging the conventional 3-month cut-off for the blanking period.

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**Conflict of interest:** C.T. and R.V. received modest consultancy and speaker's fees from Medtronic. G.M. received modest consultancy fees from Medtronic and Boston Scientific and speaker's fees from Medtronic, Boston Scientific, St. Jude, and Boehringer Ingelheim. M.L. received modest speaker's fees from Boston Scientific, LivaNova (Microport), and Medtronic. All other authors have reported that they have no relationship relevant to the contents of this article to disclose.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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