AER
Arrhythmia & Electrophysiology Review

ORIGINAL RESEARCH
Atrial Fibrillation

Ten-year Follow-up Study of Patients with Persistent Atrial Fibrillation Treated by Combined Pulmonary Vein Isolation and Complex Fractionated Electrogram Ablation

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Abstract

Aim: This study retrospectively investigated the clinical outcomes of patients with persistent AF treated with a combined approach of pulmonary vein isolation (PVI) and complex fractionated atrial electrogram (CFAE) ablation over a follow-up period of 10 years. **Methods:** A total of 73 patients with persistent and long-standing persistent AF who underwent combined pulmonary vein isolation and CFAE ablation in the first procedure were included. A complete CFAE mapping of the left atrium and coronary sinus was performed with a 3D mapping system. All CFAEs defined as electrograms with continuous activity or mean cycle length detected by the system of <80 ms were excluded. Patients were controlled regularly during the first year followed by annual control. Any documented atrial tachyarrhythmia (ATA) was regarded as a recurrence. **Results:** After index ablation, 18 (24.7%) were free of ATAs during 10-year follow-up. The proportion of atrial flutter (AFL) was 39.7%, with six typical AFL. A mean of 2.2 ± 1.2 ablation procedures were performed in each patient. After multiple procedures, 33 (45.2%) patients were free of ATA during the follow-up. The proportion of AFL was 23.2% with no typical AFL. Older age, female sex and a longer AF history were associated with ATA recurrence. **Conclusion:** A high recurrence rate of ATA was observed after index procedure of pulmonary vein isolation plus CFAE ablation in patients with persistent AF. No significant difference in freedom of ATA was found between persistent and long-standing persistent AF groups beyond 1 year. The incidence of postablation AFL was particularly high, even after multiple ablations.

Keywords

Persistent AF, pulmonary vein isolation, radiofrequency ablation, complex fractionated atrial electrograms, long-term follow-up

Received: 15 September 2024 **Accepted:** 30 December 2024 **Citation:** *Arrhythmia & Electrophysiology Review* 2025;14:e07. **DOI:** https://doi.org/10.15420/aer.2024.43

Disclosure: JC has received honoraria for lectures, travel/meeting support from and is a consultant for Biosense Webster and Johnson & Johnson. KW has received travel/meeting support from Johnson & Johnson and Medtronic. All other authors have no conflicts of interest to declare.

Funding: This study was partly supported by the Helse Vest, Norway

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions: Conceptualisation: JC; data curation: KW, CT; formal analysis: KW, CT; project administration: KW, CT; software: KW, CT; supervision: JC; writing – original draft: KW, CT; writing – review & editing: JC, ES.

Ethics: This is an observational study. The Ethics Committee of Western Norway has confirmed that no ethical approval is required. The study was performed in line with the principles of the Declaration of Helsinki.

Consent: There were patients involved in this retrospective study, but no personal individual data are presented in this manuscript.

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AF is one of the most frequently sustained cardiac arrhythmias, and its prevalence is increasing with age.[1] The current estimated prevalence in adults is 2–4%, and a 2.3-fold rise is expected due to ageing and increased screening.[2–4] AF is associated with significant morbidity and mortality, including heart failure and stroke, and thus represents a considerable burden on patients and the healthcare economy.[5] Eliminating AF and maintaining normal sinus rhythm lowers the risk of death from cardiovascular causes and reduces the risk of stroke.[6]

Pulmonary vein isolation (PVI) is the cornerstone strategy for AF ablation, regardless of its duration. Ablation for paroxysmal AF is far superior to that for persistent AF in 1-year freedom from atrial tachyarrhythmia (ATA; 70–80% versus 43–67%).[7,8] This suggests that the mechanisms driving persistent AF may differ from those of paroxysmal AF, with the development of pathological substrates in the left atrium (LA) maintaining AF even if the triggers from the pulmonary veins have been isolated.[9]

Additional strategies for substrate modification to improve clinical outcomes, such as linear lesions and complex fractionated atrial electrogram (CFAE) ablation, have been used. However, most randomised trials have failed to clearly demonstrate clinical benefits, at least primarily over a shorter follow-up of 1–2 years.[10,11] On the contrary, two meta-analyses have shown a benefit of the PVI plus CFAE approach in patients with persistent AF over a follow-up of <2 years.[12,13]

The question regarding the role and effect of CFAE ablation in persistent AF in the long term remains unanswered. This study aimed to investigate the very long-term outcomes of patients with persistent and long-standing persistent AF who underwent combined PVI and CFAE ablation during the index procedure.

Methods

Study Population

We enrolled 73 patients (aged 36–80 years) with persistent and long-standing persistent AF who underwent the first ablation procedure with complete CFAE mapping and ablation in the LA and coronary sinus. Patients without complete mapping and elimination of all CFAEs were excluded. All patients in this study were highly symptomatic and had either failed at least one antiarrhythmic drug or had contraindications (2 patients). Clinical data, such as AF history, body mass index, present hypertension and echocardiographic measurements, including LA diameter and left ventricular ejection fraction, were recorded (*Table 1*). The Ethics Committee of Western Norway confirmed that no ethical approval was required.

Ablation Procedures

All patients underwent combined PVI and CFAE ablation in their first procedure. A non-contact force-sensing irrigated ablation catheter (CoolFlex, Abbott) and a spiral mapping catheter (Inquiry Optima, Abbott) was used for all the cases. A complete CFAE mapping of the LA and coronary sinus was performed with the spiral catheter and a mapping tool provided by EnSite NavX (Abbott). The details of mapping have been described previously.[14] All CFAEs defined as electrograms with continuous activity or complex fractionated electrogram mean detected by the system of <80 ms were eliminated. After mapping, the pulmonary veins were isolated with a circumferential lesion set applied 5–10 mm away from the ostia. The endpoint of PVI was elimination of the pulmonary vein potentials with exit/entrance block. PVI was confirmed for >30 minutes after CFAE ablation was performed.

If ATA recurred, a new procedure was evaluated and performed at least 6 months after the index procedure based on clinical symptoms. Repeat procedures were not standardised, and the ablation approach was at the operators' discretion. Recurrence of paroxysmal AF was typically treated with repeat PVI alone, and persistent AF with PVI and a new CFAE ablation. Atrial tachycardias or atrial flutter (AFL) were generally treated with focal or linear lesions based on mapping results. No prophylactic linear ablation was applied if there was no AFL presented or induced, as this has not been shown to be beneficial for AF ablation.[15]

Follow-up and Data Collection

After index ablation, all patients were followed up closely with clinical evaluation, 12-lead ECG, and 24-hour Holter recordings at 3, 6 and 12 months. Thereafter, annual follow-up was conducted, and patients were instructed to contact their cardiologist or general practitioner if symptoms suggestive of arrhythmia occurred. Furthermore, the electronic health records for all patients were extensively investigated. Any documented ATA lasting >30 seconds after the 3-month blanking period was regarded as recurrence.

Statistical Analysis

The Shapiro–Wilk test was used for testing the normality of distribution. Continuous variables are presented as the mean ± SD or median (IQR), and categorical variables as count or percentage where appropriate. Comparisons between groups were undertaken with Student's t-test when normally distributed, otherwise the Mann–Whitney U-test was used. The comparison between categorical variables was performed with the χ^2 test or Fisher's exact test. Event-free survival was estimated by the Kaplan–Meier method using the log-rank test. Cox regression was used for time-dependent variables. One-way ANOVA test was used for multivariate analysis between groups. All analyses were two-tailed, and p-values of <0.05 were considered statistically significant. SPSS 29.0.1.0 (IBM) was used for all statistical analyses.

Results

Patient Characteristics and Follow-up

Of the 73 patients, eight had structural heart disease, among these, five had cardiomyopathy and three had aortic valve replacement (2 severe aortic stenosis, 1 endocarditis). A total of 23 (31.5%) patients had persistent, while 50 (68.5%) had long-standing persistent AF. The mean history of AF was 5.5 years. Four patients had undergone prior ablation for typical AFL that did not recur during the follow-up. The baseline characteristics of patients are listed in *Table 1*.

Freedom of Atrial Tachyarrhythmias after Single and Multiple Procedures

After index ablation, 35 (47.9%) patients were free of ATA at the 1-year follow-up, with 20 patients (40.0%) in the long-standing persistent group and 15 (65.2%) in the persistent AF group (p=0.033). After 4 years, 24 (32.9%) were free of ATA, 14 (28.0%) in the long-standing persistent group and 10 (43.5%) in the persistent AF group (p=0.098). After 10 years, only 18 (24.7%) were free of ATA, 11 (22.0%) in the long-standing persistent AF group and seven (30.4%) in the persistent AF group, respectively (p=0.167; *Figure 1*, left). The mean ablation time was 6,083 ± 1,483 seconds. A comparison of the total ablation time showed no difference between the ATA-free and ATA recurrence groups (*Table 1*), nor among different rhythms after single ablation (sinus rhythm: 6,080 ± 1,882, AF: 5,862 ± 1,179, AFL: 5,742 ± 1,754 and AF and AFL: 6,439 ± 1,340 seconds); thus, it is difficult to attribute the postablation AFL to the amount of CFAE ablation.

The patients in this study went through a mean of 2.2 ablation procedures during the 10-year follow-up. Among the 45 (61.6%) patients receiving multiple ablations, the mean number of ablations was 2.9 ± 1.0. A total of 20 (44.4%), 14 (31.1%), seven (15.6%) and four (8.9%) patients underwent two, three, four and five ablations, respectively. After multiple ablations, 47 patients (64.4%) were free of ATA at the 1-year follow-up, 31 (62.0%) in the long-standing persistent AF group and 16 (69.6%) in the persistent AF group (p=0.542). After 10 years and multiple ablations, 33 (45.2%) were free of ATA, 22 (44.0%) in the long-standing persistent AF group and 11 (47.8%) in the persistent AF group (p=0.708; *Figure 1*, right).

Types of Recurrent Atrial Tachyarrhythmias

In patients with ATA recurrence, AF was observed in 49 (67.1%) and 35 (47.9%) patients (p=0.019), and AFL was found in 39.1 and 23.2% of patients (p=0.005), respectively, after single and multiple procedures. Details of the ATA recurrence types are listed in *Table 2*. There were six cases with new onset of typical AFL ablated in the subsequent procedures, and no cases of typical AFL were observed after multiple procedures throughout the follow-up. Two patients received atrioventricular nodal ablation after permanent pacemaker implantation.

Predictors of Outcome

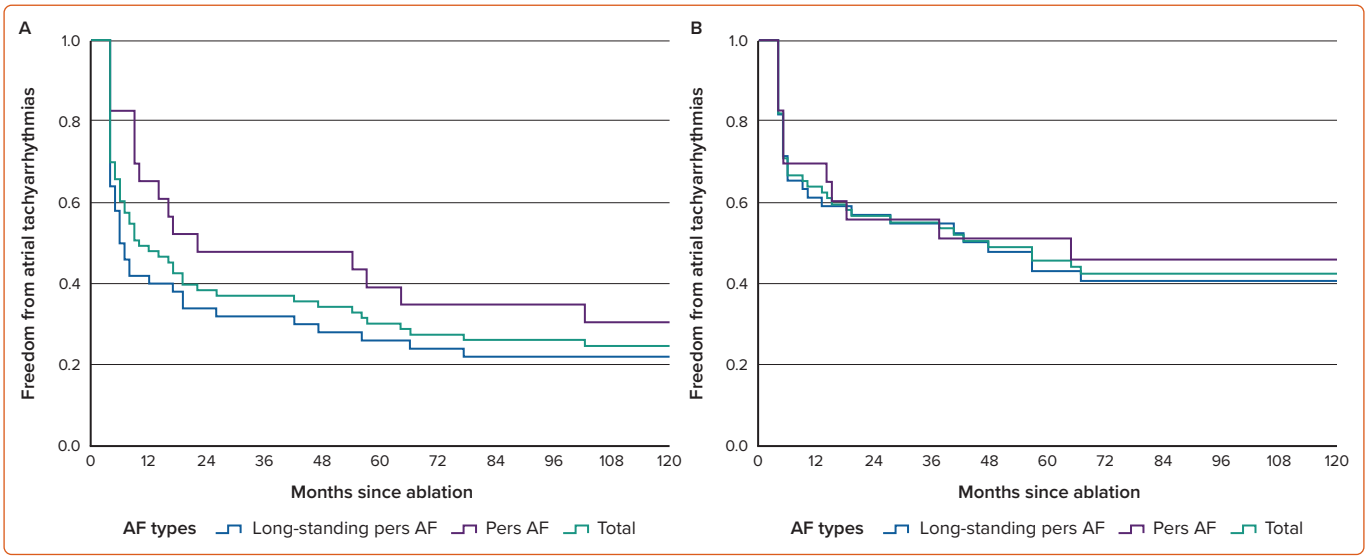
The characteristics between the recurrence and recurrence-free groups after single and multiple ablation procedures are summarised in *Table 1*. Cox regression showed that, for both single and multiple procedures,

Table 1: Basic Patient Characteristic and Outcomes after 10-year Follow-up

Variable	Total (n=73)	Single Procedure (n=73)				Multiple Procedures (n=73)			
		ATA-free (n=18)	ATA Recurrence (n=55)	p-value*	Univariate Cox	ATA-free (n=33)	ATA Recurrence (n=40)	p-value*	Univariate Cox
Age (years)	59.4 ± 8.1	56.8 ± 6.7	60.0 ± 8.4	0.116	0.054	56.56 ± 8.6	61.7 ± 7.0	0.006	0.005
Women	9 (12.3%)	0 (0)	9 (16.4%)	0.101	0.002	2 (6.1)	7 (17.5)	0.171	0.044
AF history (years)	6.8 ± 7.1	4.5 (1.9–7.3)	7.6 (2.1–10.3)	0.139	0.006	5.7 (2–7)	7.8 (2.1–10.0)	0.226	0.043
BMI	27.3 ± 4.0	28.1 (26.7–30.3)	27.0 (24.4–28.6)	0.102	0.340	27.5 (25.0–29.0)	27.1 (24.4–28.9)	0.357	0.587
Hypertension (%)	30 (41.1)	8 (44.4)	22 (40)	0.787	0.517	13 (39.4)	17 (42.5)	0.816	0.803
Left atrium (cm)	4.5 ± 0.7	4.8 (4.4–5.2)	4.4 (4.0–5.0)	0.136	0.088	4.5 (3.8–5.0)	4.5 (4.1–5.0)	0.684	0.949
LVEF (%)	53.2 ± 9.0	52.3 ± 11.4	53.5 ± 8.2	0.633	0.531	52.6 ± 9.4	53.7 ± 8.8	0.625	0.573
AF type				0.560	0.198			0.840	0.720
Persistent	23 (31.5%)	7 (38.9)	16 (29.1)			11 (33.3)	12 (30.0)		
Long-standing persistent	50 (68.5%)	11 (61.1)	39 (70.9)			22 (66.7)	28 (70.0)		
AF lasting duration before ablation (years)	2.5 (1.0–3.0)	1.8 (1.0–3.0)	2.7 (1.0–4.0)	0.302	0.133	2.2 (1.0–3.0)	2.8 (0.9–4.0)	0.885	0.330
Total ablation time (s)	6,083 ± 1,483	6,080 ± 1,882	6,085 ± 1,330	0.992	0.626	6,063 ± 1,558	6,101 ± 1,439	0.919	0.685

*Data are presented as mean ± SD, median (IQR) or n (%). *Compared between atrial tachyarrhythmia-free and atrial tachyarrhythmia recurrence groups. ATA = atrial tachyarrhythmias; LVEF = left ventricular ejection fraction.*

Figure 1: Kaplan–Meier Curves for All Study Patients, Subgroups of Persistent and Long-standing Persistent AF



A: After index procedure. B: After multiple ablation procedures. Pers = persistent.

female sex (p=0.002 and p=0.044) and AF history (p=0.006 and p=0.043) were associated with 10-year outcomes of ATA recurrence. AF history of 4 years was used as a cut-off, and Kaplan–Meier analysis demonstrated a significantly lower success rate after multiple procedures for those with long-standing AF history >4 years (p=0.04), but such difference was not statistically significant after the index ablation (p=0.097; *Figure 2*). Age was associated with outcomes only after multiple ablations (p=0.005). The lasting duration of AF before ablation was not associated with ATA recurrence. There was no correlation between total ablation time and outcomes for either single or multiple procedures.

Discussion

Main Findings

At 10-year follow-up after a single PVI plus CFAE ablation procedure, only 24.7% of the patients were arrhythmia-free. After multiple procedures (mean 2.2), the rate of ATA-free survival increased to 54.8%. A statistically significant difference in ATA-free survival between persistent and long-standing persistent AF groups was found only at 1 year after the index procedure, not during further follow-up. The incidence of postablation AFL was 39.7 and 23.2% after index and multiple procedures, respectively.

Challenges of CFAE

As AF progresses from paroxysmal to non-paroxysmal, the atria undergo both structural and electrical remodelling with areas of fibrosis and slow conduction. These changes may result in heterogeneity of electrical conduction, termed anisotropy.[16] CFAE has been assumed to indicate such areas of slow conduction, wave-front collisions and anchor points for re-entrant circuits driving AF.[17] Nademanee et al. introduced CFAE ablation as a new functional target in adjunct to the traditional approach of PVI, and reported an excellent outcome of stand-alone CFAE ablation without PVI

Table 2: Types of Arrhythmia Recurrence After 10-year Follow-up

Rhythms During Follow-up	Index Ablation, n (%)	Multiple Ablations, n (%)	p-value
Sinus rhythm	18 (24.7%)	33 (45.2%)	0.009
AF	26 (35.6%)	23 (31.5%)	0.599
Atrial flutter	6 (8.2%)	5 (6.9%)	0.754
Both AF and atrial flutter	23 (31.5%)	12 (16.4%)	0.033

with maintenance of sinus rhythm in >90% of patients over a follow-up period of 1 year, which has been difficult to reproduce since.[18,19] Oral et al. reported significantly inferior results, with 33% being free of ATA at 14 ± 7 months after single ablation, and 57% after multiple procedures in patients with persistent AF.[20]

The outcomes over a very long-term follow-up have always been missing. An earlier study from our group reported an ATA-free survival of 57.6 % over a mean follow-up time of 40 ± 14 months in a cohort of non-paroxysmal AF patients ablated with PVI and CFAE; however, 54.5% of patients received multiple ablations.[21] The outcomes are quite similar, and the minor differences can likely be attributed to the proportion of patients with long-standing persistent AF and follow-up time. We observed several late AF recurrences, some even after an extremely long-term follow-up. We assume that both suboptimal ablation and natural progression of the disease may play important roles during such a long period, but attribution is difficult due to the limit of study design.[22]

Two meta-analyses comparing PVI only and PVI plus CFAE showed higher rates of ATA-free survival, but only for persistent AF and not for paroxysmal AF.[12,13] This observation is in line with the theory that paroxysmal AF is mainly driven by triggers in the pulmonary veins and, thus, are less substrate-dependent in contrast to persistent AF.

The discrepancies in outcomes after CFAE ablation can be explained by multiple factors. There is a lack of definitive consensus on the concept of CFAE, including definition (criteria), mapping (visual inspection versus automated detection), ablation strategy and endpoint (electrogram silencing versus defragmentation). Once CFAE has been defined, ablation can be performed with the aim of either regularising (defragmenting) or abolishing (silencing) the electrograms. The differences in these two strategies are likely to impact both AF recurrence and the onset of postablation AFL. It is not clear how much CFAE ablation (how high the frequency of CFAE and how big the CFAE area should be ablated) is sufficient.

Even though we did not obtain the area sizes of CFAE ablation, the total ablation time can be assumed to be related to the amount of CFAE ablation more than the PVI. Our data did not support any association between the total ablation times and outcomes. Regardless of these challenges, the STAR AF II trial, demonstrating that additional ablations, including CFAE, were not superior to PVI alone, has led to an abandonment of many extra-PVI targets, especially adjunct CFAE ablation.[10]

Notably, these investigations, including the present study, were performed by a non-contact-force ablation catheter, and this factor might have an impact on clinical outcomes. A recent review and meta-analysis by Pranata et al. confirms this finding with the observation of similar recurrence rates between PVI only and ablation beyond PVI over 1 year follow-up, focusing on the high-power short-duration ablation method with the newest contact-force catheter.[23] Despite the negative results reported by several studies, it is still worth investigating how these patients receiving combined PVI and CFAE ablation perform during very long-term follow-up.

Postablation AFL

We report a remarkably high incidence of postablation AFL, even after multiple ablation procedures. This is in line with other studies revealing a high rate of postablation AFL after atrial substrate modification beyond PVI (40% after 3 months, 56% after 9 months).[24,25] Macro-re-entry can result from gaps in the ablation lines, and focal atrial tachycardias can originate from discrete sites. Theoretically, the risk of proarrhythmia could be proportionally higher with more ablation, since it creates more scar and slow-conduction regions.

All mechanisms of AFL, including macro-re-entry, small-loop re-entry and micro-re-entry, were observed. All lesion sets, both PVI and CFAE in the index procedure, and linear lesions in many repeat ablations could lead to postablation AFL, but their individual contribution is difficult to quantify. Noticeably, many of these postablation arrhythmias may be the consequence of progressive AF organisation caused by the creation of slow conduction areas during CFAE ablation when these were only defragmented instead of fully silenced. It has been reported that in patients presenting for a repeat procedure after ablation of persistent AF, the occurrence of atypical AFL is associated with a better outcome compared with recurrent persistent AF.[25] These results suggest that AFL might be considered as a step towards sinus rhythm.

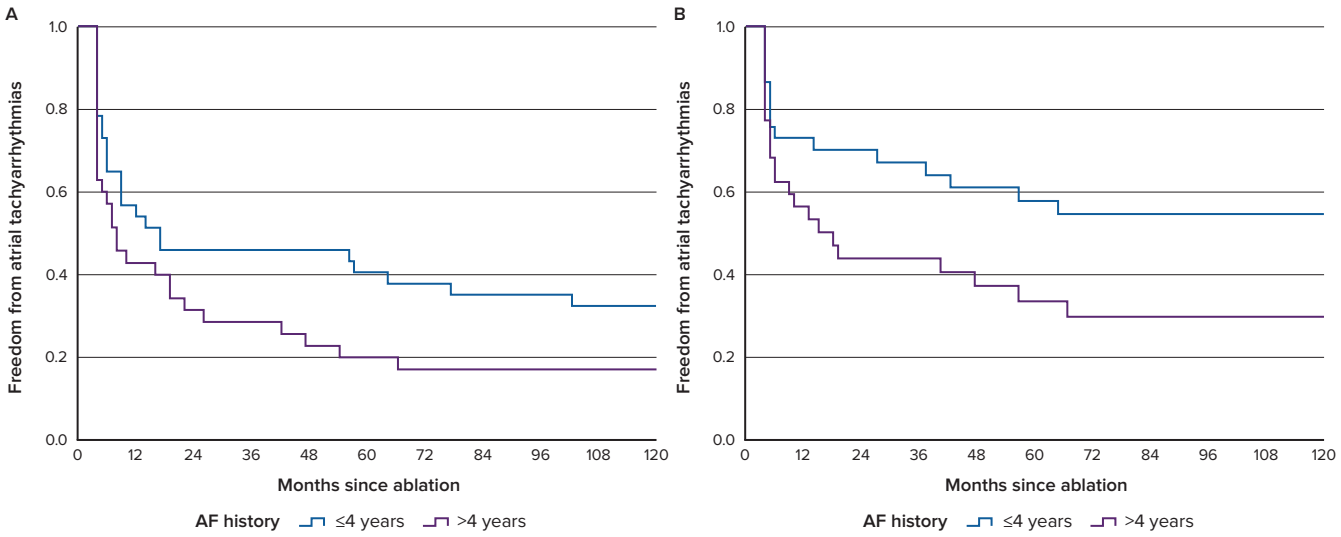
Predictors

We found that longer history of AF, older age and female sex are statistically significantly associated with worse ablation outcomes. The importance of AF history as an independent predictor of recurrence after catheter ablation is consistent with other studies.[26] Increased duration of uninterrupted AF leads to increased remodelling of atria, which makes the arrhythmia more difficult to terminate.

Age was also associated with ablation outcomes, but only for multiple procedures. This can be related to increased fibrosis observed frequently in older people, and the fact that older people are less likely to undergo multiple procedures.[9] We did not find any association between other characteristics, such as body mass index, hypertension, coronary artery disease, LA diameter or ventricular ejection fraction and outcome, even though these are established risk factors. This may be attributable to the sample size, and the fact that most patients in this study had a normal ejection fraction and only mildly dilated LA.

Female sex was associated with a worse outcome during follow-up. However, only a minority (16.4%) of the patients in this study were women, and compared with men, women were slightly older (62.8 ± 8.8 versus 58.9 ± 8.0 years) and had a longer history of AF (11.2 ± 13.4 versus 6.2 ± 5.6 years). These factors constrain us to draw a definite conclusion. In contrast, these findings are consistent with other studies reporting a lower procedural success rate for women, possibly attributable to non-pulmonary vein triggers and longer AF duration contributing to atrial remodelling.[27–29] Furthermore, female sex seems to be an independent risk factor for atrial fibrosis found in atrial cardiomyopathy.[30] From the Kaplan–Mayer curve (*Figure 1*, left), it seems that the recurrence rates of persistent and long-standing persistent AF are quite different. However, the statistical analysis shows the difference is significant only at 1-year follow-up, but not beyond

Figure 2: Kaplan–Meier Curves Comparing Patients with AF History of >4 and ≤4 Years



A: After index procedure. B: After multiple ablation procedures.

that. This may be associated with the small sample size, but in contrast, this trend may reflect the progressive nature of AF.

Limitations

This study was a retrospective cohort study, and there was less strict control during the very late period of follow-up. This may impact the results, and more frequent and regular monitoring might have been needed to further detect recurrence of arrhythmias. Therefore, some asymptomatic recurrences may not have been detected. An older version of the platform and non-contact force-sensing ablations catheters were used for most cases, and a non-high-density mapping catheter was employed due to the retrospective study design.

Unfortunately, we do not have enough information to allow us to attribute the postablation atrial flutter to the index CFAE ablation. Increased atrial debulking may occur after multiple procedures with larger encircling of the PVs and excessive ablation in the atria, but it is difficult to associate the improved results with the debulking itself because no information about scar status after procedures is available in this study. In addition, there was a relatively small number of patients in this study, especially women. This also limits the interpretation of data. A large, randomised trial with long-term follow-up (>5 years) would be needed to further elucidate this subject.

Conclusion

Patients with persistent AF who underwent PVI plus CFAE ablation in the first procedure had a high recurrence of ATA, but multiple ablation procedures might improve the outcomes. The difference in ATA freedom between persistent and long-standing persistent AF groups was demonstrated only at 1 year after the index procedure, but not during further long-term follow-up. The incidence of postablation AFL was particularly high, even after multiple ablation procedures. ❑

Clinical Perspective

- At 10-year follow-up after single-procedure combined pulmonary vein isolation and complex atrial electrogram ablation, the success rate for eliminating atrial tachyarrhythmias was low, but improved after multiple ablation procedures.
- Between patients with persistent and long-standing persistent AF, there was only a statistically significant difference in atrial tachyarrhythmia-free survival at 1 year after the index procedure, but not during further follow-up.
- A high incidence of postablation atrial flutter was observed.
- Female sex, longer AF history and older age were associated with atrial tachyarrhythmia recurrence after multiple procedures.

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