



ORIGINAL ARTICLE

Outcomes of radiofrequency catheter ablation for persistent and long-standing persistent atrial fibrillation[☆]

André Azul Freitas^a, Pedro A. Sousa^{a,*}, Luís Elvas^a, Lino Gonçalves^{a,b}

^a Cardiology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

^b ICBR, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Received 20 March 2021; accepted 2 May 2021

Available online 16 May 2022



KEYWORDS

Catheter ablation;
 Persistent atrial
 fibrillation;
 Long-standing
 persistent atrial
 fibrillation;
 Tailored approach

Abstract

Objective: To assess one-year outcomes in patients with persistent and long-standing persistent atrial fibrillation (AF) treated by catheter ablation.

Methods: A retrospective observational study was conducted of consecutive patients referred for catheter ablation of persistent or long-standing persistent AF between May 2016 and October 2018. Patients underwent two different ablation strategies: pulmonary vein isolation (PVI) plus complex fractionated atrial electrograms (CFAE) (from May 2016 to June 2017) or a tailored approach (from July 2017 to October 2018). The overall recurrence rate at one year was analyzed. The secondary endpoint was arrhythmia recurrence according to the type of AF (persistent vs. long-standing persistent AF) and according to the ablation strategy employed.

Results: During the study period, 67 patients were included (40% with long-standing persistent AF). During a mean follow-up of 16±6 months, 27% of the patients had arrhythmia recurrence. Patients with long-standing persistent AF had a higher recurrence rate than those with persistent AF (44.4% vs. 15%, p=0.006), while patients who underwent a tailored approach presented better outcomes than those undergoing PVI plus CFAE ablation (17.5% vs. 40.7%, p=0.024). Ablation strategy (HR 6.457 [1.399-29.811], p=0.017), time in continuous AF (HR 1.191 [1.043-1.259], p=0.010) and left atrial volume index (HR 1.160 [1.054-1.276], p=0.002) were independent predictors of arrhythmia recurrence.

Conclusion: Catheter ablation is an effective treatment for patients with persistent and long-standing persistent AF. Patients with persistent AF and those undergoing a tailored approach presented lower arrhythmia recurrence.

© 2022 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

[☆] This article is the subject of two Editorial Comments, which reflect the views of two arrhythmologists and are published in alphabetical order of their authors.

* Corresponding author.

E-mail address: peter@chuc.min-saude.pt (P.A. Sousa).

PALAVRAS-CHAVE

Ablação por cateter;
FA persistente;
FA persistente de
longa duração;
Abordagem
individualizada

Resultados da ablação por radiofrequência na fibrilhação auricular persistente e persistente de longa duração

Resumo

Objetivo: Avaliar os resultados a um ano da ablação por cateter na fibrilhação auricular (FA) persistente e persistente de longa duração.

Métodos: Estudo retrospectivo observacional de doentes referenciados para a ablação de FA persistente e persistente de longa duração de maio de 2016 a outubro de 2018. Os doentes foram submetidos a duas estratégias: isolamento de veias pulmonares (PVI) e ablação de eletrogramas auriculares fracionados e complexos (CFAE) (de maio de 2016 a junho de 2017) ou a uma abordagem individualizada (de julho de 2017 a outubro de 2018). Foi avaliada a taxa de recidiva a um ano de seguimento. Os objetivos secundários consistiram na avaliação da taxa de recidiva de acordo com o tipo de FA (persistente *versus* persistente de longa duração) e de acordo com a estratégia de ablação realizada.

Resultados: Durante o período de estudo, 67 doentes foram incluídos (40% dos quais com FA persistente de longa duração). Durante o seguimento médio de 16 ± 6 meses, observou-se recorrência de arritmia em 27% dos doentes. Os doentes com FA persistente de longa duração apresentaram uma maior taxa de recidiva comparativamente aos doentes com FA persistente (44,4% *versus* 15%, $p=0,006$). Por sua vez, os doentes submetidos a uma abordagem individualizada apresentaram uma menor recidiva de arritmia, em comparação com os doentes submetidos a PVI+CFAE (17,5% *versus* 40,7%, $p=0,024$). A estratégia de ablação (HR 6,457 [1,399–29,811] $p=0,017$), o tempo em FA (HR 1,191 [1,043–1,259] $p=0,010$) e o volume indexado da aurícula esquerda (HR 1,160 [1,054–1,276] $p=0,002$) foram preditores independentes de recidiva de arritmia.

Conclusão: A ablação por cateter é um procedimento eficaz em doentes com FA persistente e persistente de longa duração. Doentes submetidos a uma ablação individualizada e doentes com FA persistente apresentaram uma menor taxa de recidiva.

© 2022 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ It is independently associated with increased risk of death, heart failure (HF), stroke and hospitalization, and reduced quality of life.^{2–4} Catheter ablation has become a first-line treatment for symptomatic AF refractory to drugs^{5–8} and has recently demonstrated a particularly favorable impact in HF patients.^{9–14} However, there is less evidence supporting catheter ablation for persistent and long-standing persistent AF.⁵ Although various ablation strategies in addition to pulmonary vein isolation (PVI) have been employed, the recurrence rate remains significant in patients with non-paroxysmal AF.⁷ Moreover, there is a lack of national data in Portugal concerning results of catheter ablation in patients with persistent and long-standing persistent AF.

The objective of this study was to assess one-year outcomes in patients with persistent and long-standing persistent AF treated by catheter ablation.

Methods**Study design and setting**

A retrospective observational study was performed of consecutive patients referred for catheter ablation of persistent

or long-standing persistent AF between May 2016 and October 2018 in a tertiary referral center. Procedural endpoints and one-year follow-up results were assessed.

All patients provided written informed consent and the study complied with the Declaration of Helsinki.

Patient eligibility criteria

Patients were eligible for inclusion in the study if they presented drug-refractory persistent or long-standing persistent AF or intolerance to antiarrhythmic drug (AAD) therapy, and had undergone radiofrequency (RF) catheter ablation.

Persistent AF was defined as AF lasting between seven days and one year, and long-standing persistent AF as AF lasting for >1 year before a decision to attempt rhythm control was made.⁵

Exclusion criteria were age <18 years and the presence of thrombus.

Data required for cohort characterization were collected from patients' clinical records.

Electrical cardioversion was performed in all patients before intervention to reduce the time in AF, and consequently a significant number of patients were in sinus rhythm (SR) at the time of intervention.

Ablation procedure

All procedures were conducted under general anesthesia and patients suspended AAD therapy at least five half-lives before the procedure. All patients were under oral anticoagulation for at least two months prior to the procedure. In patients under vitamin K antagonists (VKAs), the medication was continued in the periprocedural period with an international normalized ratio within the 2.0–3.0 range. In patients taking non-VKAs the last drug dose was omitted. The presence of intracardiac thrombus was excluded prior to the procedure by either transesophageal echocardiography or computed tomography (CT). During the procedure, unfractionated heparin was administered immediately after transeptal puncture and adjusted as needed for a target activated clotting time >300 s. Anatomical mapping data were collected using a 3D mapping system with CARTO 3 (Biosense Webster, Irvine, CA, USA), or NavX Precision (Abbott, IL, USA) and integrated with a CT imaging reconstruction of the left atrium, when available. Ablation lines were created with point-by-point RF energy using an irrigated tip contact force-sensing catheter, in power-controlled mode with temperature limited to 43°C. Power settings varied according to the targeted region.

During the study period, patients underwent two different AF ablation strategies: PVI plus complex fractionated atrial electrogram (CFAE) ablation (Group 1), from May 2016 to June 2017; and a tailored approach (Group 2), from July 2017 to October 2018.

Group 1: pulmonary vein isolation plus complex fractionated atrial electrogram ablation

If patients were in SR in the beginning of the procedure, bipolar voltage mapping was performed (criteria for healthy and scarred tissue >0.5 mV and <0.2 mV, respectively). Left atrial (LA) voltage mapping was considered adequate when at least 500 points were collected. Wide PVI was then performed. However, if patients were in AF at the beginning of the procedure, CFAE mapping (automatic algorithms based on bipolar recordings with acquisition of dV/dT over 5 s, CFAE being defined as a mean cycle length of <120 ms) was performed, which was used to guide a wide point-by-point PVI. The detailed technique for ablating CFAE using the automated mapping software has been described and validated previously.¹⁵ The procedure terminated if conversion to SR occurred. After performing PVI, if the patient remained in AF or if it was inducible, ablation was performed in CFAE located outside the PVI lines. When AF was converted to a regular atrial arrhythmia, this was mapped and ablated. If patients were still in AF at the end of the procedure, electrical cardioversion was performed. If typical flutter was present or previously documented, a cavotricuspid isthmus (CTI) line was also created.

Group 2: tailored approach

If patients were in SR, LA bipolar voltage mapping was performed (acquiring at least 500 points). Voltage criteria for healthy and scarred tissue were >0.5 mV and <0.2 mV, respectively. Wide point-by-point PVI was then carried out. If patients were in AF at the beginning of the procedure,

PVI was performed first. Electrical cardioversion was subsequently performed if patients were still in AF after PVI, and the voltage map was obtained in SR. After PVI, low voltage areas were ablated to achieve tissue homogenization. If necessary, lines were created connecting these areas of scar. Bidirectional block was confirmed after these lines were created. If low voltage areas were absent but AF inducibility persisted, CFAE mapping was performed followed by ablation. If AF was converted to a regular atrial arrhythmia, this was mapped and ablated. Likewise, if typical flutter was present or previously documented, a CTI line was also created. If AF persisted or was still inducible at the end of the procedure, electrical cardioversion was performed.

Study endpoints

The primary endpoint was one-year arrhythmia recurrence in patients referred for non-paroxysmal AF ablation, defined by the documentation of at least 30 s of atrial arrhythmia, irrespective of symptoms, in accordance with the expert consensus statement on catheter and surgical ablation of atrial fibrillation.¹⁶

We also assessed one-year freedom from arrhythmia according to the strategy employed and the AF pattern (persistent or long-standing persistent).

Follow-up

After the index procedure, patients were followed for a minimum of 12 months. Patients were assessed before discharge and at three, six and 12 months after the procedure. Transthoracic echocardiography and 24-hour Holter monitoring were performed before discharge. Information collected during follow-up included a 12-lead electrocardiogram and a 24-hour Holter at each appointment. Seven-day Holter monitoring was performed at least once per year and a transthoracic echocardiogram at six or 12 months. At discharge AAD therapy was prescribed according to patient characteristics and operators' decision. The first three months post-procedure were considered as a blanking period. Recurrence of atrial fibrillation was defined as the documentation of at least 30 s of atrial fibrillation, atrial tachycardia, or atrial flutter, irrespective of symptoms, in accordance with the expert consensus statement on catheter and surgical ablation of atrial fibrillation¹⁶ and a previously ineffective but tolerated class I or class III (sotalol) drug was the preferred option. Anticoagulation strategy after the first three months was based on the CHA₂DS₂Vasc and HAS-BLED scores.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM, Armonk, New York). Categorical variables are expressed as frequencies and percentages and continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) for variables with or without normal distribution, respectively. The chi-square test was used to assess differences between categorical variables and the Student's t test or the Wilcoxon test were

Table 1 Characteristics of patients with persistent and long-standing persistent AF undergoing catheter ablation.

	Total (n=67)	Persistent AF (n=40, 60%)	Long-standing persistent AF (n=27, 40%)	p	Group 1 (n=27, 40%)	Group 2 (n=40, 60%)	p
Age, years	59±11	58±11	62±10	0.13	60±12	60±10	0.88
Male	39 (58%)	21 (53%)	18 (67%)	0.32	17 (63%)	22 (55%)	0.80
Time since AF diagnosis, months	45 (16-85)	18 (12-37)	85 (70-120)	<0.001	64 (18-83)	44 (14-88)	0.80
Continuous AF duration, months	10 (7-19)	8 (6-9.8)	20 (18-28)	<0.001	10 (8-24)	10 (7-19.8)	0.34
Body mass index, kg/m ²	29.2±4.4	29.3±4.6	29.0±4.1	0.81	28.6±5.3	29.3±3.7	0.41
Hypertension	44 (65.7%)	23 (57.5%)	21 (77.8%)	0.028	14 (51.9%)	30 (75%)	0.17
Dyslipidemia	31 (46.3%)	17 (42.5%)	14 (51.9%)	0.60	10 (37%)	21 (52.5%)	0.12
Diabetes	9 (13.4%)	6 (15%)	3 (11.1%)	0.47	2 (7.4%)	7 (17.5%)	0.15
Stroke history	3 (4.5%)	1 (2.5%)	2 (7.4%)	0.55	1 (3.7%)	2 (5%)	0.98
Heart failure	31 (46.3%)	14 (35%)	17 (63%)	0.033	12 (44.4%)	19 (47.5%)	0.79
NYHA I	11 (35.5%)	6 (42.9%)	5 (29.4%)		4 (33.3%)	7 (36.8%)	
NYHA II	18 (58.1%)	6 (42.9%)	12 (70.6%)		7 (58.3%)	11 (57.9%)	
NYHA III	2 (6.5%)	2 (14.3%)	0		1 (8.3%)	1 (5.3%)	
Hyperthyroidism	5 (7.5%)	3 (7.5%)	2 (7.4%)	0.99	3 (11.1%)	2 (5%)	0.37
Hypothyroidism	7 (10.4%)	4 (10%)	3 (11.1%)	0.88	3 (11.1%)	4 (10%)	0.88
Creatinine clearance, ml/min	107±39.7	111±37.9	99.9±42.9	0.32	112.7±51.4	103±30.1	0.40
BNP at admission	128±219	112±161	137±250	0.66	129±160	127±253	0.96
CHA ₂ DS ₂ VASc score	2.1±1.3	1.9±1.4	2.4±1.2	0.08	1.9±1.2	2.2±1.3	0.90
HASBLED score	1.3±0.9	1.1±0.8	1.7±0.9	0.002	1.3±1	1.3±0.9	0.46
LA volume index, ml/m ²	45±10	42±10	49±9	0.004	45±11	44±10	0.90
LVEF, mean	49±14%	48±12	49±17	0.91	55±10	46±15	0.90
• LVEF<40%	14 (20.1%)	9 (22.5%)	5 (18.5%)	0.26	4 (14.8%)	10 (25%)	0.57
Only PVI performed	21 (31%)	14 (35%)	7 (26%)	0.07	9 (33%)	12 (30%)	0.32
Patients with low voltage areas beyond PV	35 (52%)	21 (53%)	14 (52%)	0.73	12 (44%)	23 (58%)	0.15
Atrial arrhythmia recurrence	18 (26.9%)	6 (15%)	12 (44.4%)	0.006	11 (40.7%)	7 (17.5%)	0.024

AF: atrial fibrillation; BNP: brain natriuretic peptide; LA: left atrial; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; pulmonary veins; PVI: pulmonary vein isolation.

used to compare continuous variables with or without normal distribution, respectively. The Kolmogorov-Smirnov test was used to test for normality of distribution of continuous variables. Cox regression was used to assess hazard ratios of variables regarding atrial fibrillation recurrence. Multivariate analysis was performed using the forward stepwise method. Kaplan-Meier curves and the log-rank test were used to assess and compare freedom from arrhythmia recurrence during follow-up. Statistical significance was accepted for p values <0.05.

Results

Baseline characteristics and procedural details

During the enrollment period, a total of 67 patients fulfilled our inclusion criteria and were included in this study (58% male, mean age 59±11 years). Their main baseline characteristics and echocardiographic parameters are described in Table 1. Forty percent of the patients had long-standing persistent AF. Mean LA volume index was 45±10 ml/m² and mean left ventricular ejection fraction was 49±14%.

Although electrical cardioversion had been performed before ablation, 57% of patients were in AF at the beginning of the procedure. Low voltage areas beyond the pulmonary veins were present in 52% of patients, covering a median area of 14.5 (IQR 3.2-27.1) cm². Almost one third of patients (31%) only underwent PVI. At the end of the procedure, 73% of patients were in SR and the others required electrical cardioversion to restore SR. Approximately half of the patients (49%) were discharged without AAD. Procedural details are presented in Table 2.

Mean follow-up was 16±6 months. After one procedure, atrial arrhythmia recurrence was observed in 27% of the patients (60% of them under AAD) (Figure 1). The majority of the recurrences were in atrial fibrillation (55%).

Persistent vs. long-standing persistent atrial fibrillation

Patients with long-standing persistent AF had a longer history of AF (85 vs. 18 months, p<0.001), longer continuous AF duration (20 vs. 8 months, p<0.001), more hypertension (77.8% vs. 57.5%, p=0.028), more HF (63% vs. 35%, p=0.033), an enlarged left atrium (49 ml/m² vs. 42 ml/m², p=0.004)

Table 2 Procedural characteristics.

	n (%)
<i>At the beginning of the procedure</i>	
AF, n (%)	38 (57%)
Sinus rhythm, n (%)	29 (43%)
CFAE ablation, n (%)	8 (12%)
Scar homogenization, n (%)	18 (29%)
CTI line, n (%)	19 (28%)
Lines (other than CTI), n (%)	31 (46%)
Median low voltage area beyond PV, cm ²	14.8 (3.2-27.1)
<i>At the end of the procedure</i>	
SR, n (%)	49 (73%)
Need for cardioversion, n (%)	18 (27%)
AF still induced, n (%)	19 (33%)
Mean procedure time, min	133±55
Mean ablation time, min	29±6
Mean fluoroscopy time, min	7±3
Mean fluoroscopy dose, µGy/m ²	454±283

AF: atrial fibrillation; CFAE: complex fractionated atrial electrograms; CTI: cavotricuspid isthmus; PV: pulmonary veins; SR: sinus rhythm.

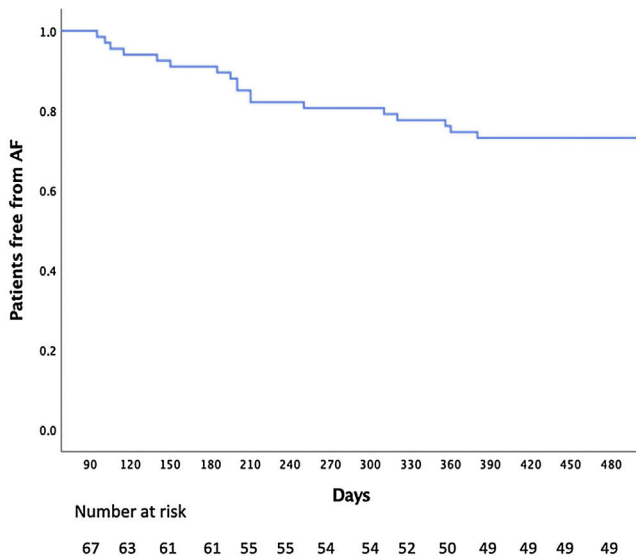


Figure 1 Freedom from atrial arrhythmia over time. Recurrence was observed in 27% of patients at 16±6 months of follow-up. AF: atrial fibrillation.

and a higher HASBLED score (1.7 vs. 1.1, p=0.002) compared with patients with persistent AF (Table 1). There were no differences between the groups concerning the presence of low-voltage areas beyond the pulmonary veins (53% for persistent AF vs. 52% for long-standing persistent AF, p=0.73). Although the proportion of patients who underwent PVI only was numerically higher in the persistent group, this did not reach statistical significance (35% for persistent AF vs. 26% for long-standing persistent AF, p=0.07).

During follow-up, patients with long-standing persistent AF had a higher recurrence rate (44.4% vs. 15%, p=0.006) than patients with persistent AF (Figure 2).

Comparison between ablation strategies

There were no significant differences between the baseline characteristics of patients treated by the different ablation strategies, including in the proportion of long-standing persistent AF patients (44.4% for PVI plus CFAE vs. 37.5% for a tailored strategy, p=0.57), the proportion of patients who underwent PVI only (33% for PVI plus CFAE vs. 30% for a tailored strategy, p=0.32) and the presence of low-voltage areas (44% for PVI plus CFAE vs. 58% for a tailored strategy, p=0.15) (Table 1).

Patients undergoing a tailored approach had a lower arrhythmia recurrence rate than patients treated by PVI plus CFAE (17.5% vs. 40.7%, p=0.024) (Figure 2).

Predictors of recurrence

The predictors of recurrence are detailed in Table 3. Multivariate modeling indicated that continuous duration of AF (hazard ratio [HR] 1.191 [1.043-1.259], p=0.010), ablation strategy (HR 6.457 [1.399-29.811], p=0.017) and LA volume index (HR 1.160 [1.054-1.276], p=0.002) were associated with a higher risk of arrhythmia recurrence.

Complications

There was one case of moderate pericardial effusion, without need for pericardiocentesis, only requiring more days of hospitalization.

Discussion

To our knowledge, this is the first Portuguese study assessing the outcomes of catheter ablation in patients with persistent and long-standing persistent AF. The main findings of this study are: (i) catheter ablation is an effective treatment in these patients, with an overall success rate of 73% at 16±6 months of follow-up with one procedure; (ii) the tailored approach presented better arrhythmia-free survival; and (iii) patients with long-standing persistent AF had worse outcomes than patients with persistent AF.

The pathophysiological mechanisms responsible for electrical and structural remodeling of the atria in persistent AF are not fully understood,¹⁷ and consequently the optimal ablation strategy remains unclear. According to the recent European guidelines, PVI remains the goal even in patients with persistent AF.⁵ The evidence for this derives mainly from the STAR AF II study, in which performing either linear ablation or CFAE ablation in addition to PVI did not significantly improve freedom from AF, compared to PVI alone.^{16,18} However, in our study, overall arrhythmia-free survival with only one procedure was 73% at 16 months of follow-up, which is better than the results obtained in STAR AF II.¹⁸ This is in line with the results of other studies.^{12,19–22} Nevertheless, the use of contact-force sensing catheters,^{9,23,24} indices for predicting lesion formation,^{25,26} multielectrode mapping catheters²⁷ and new activation mapping software^{28–30} may have contributed to the results obtained in our study.

The tailored approach was superior to the PVI plus CFAE ablation strategy. Although some studies have reported good

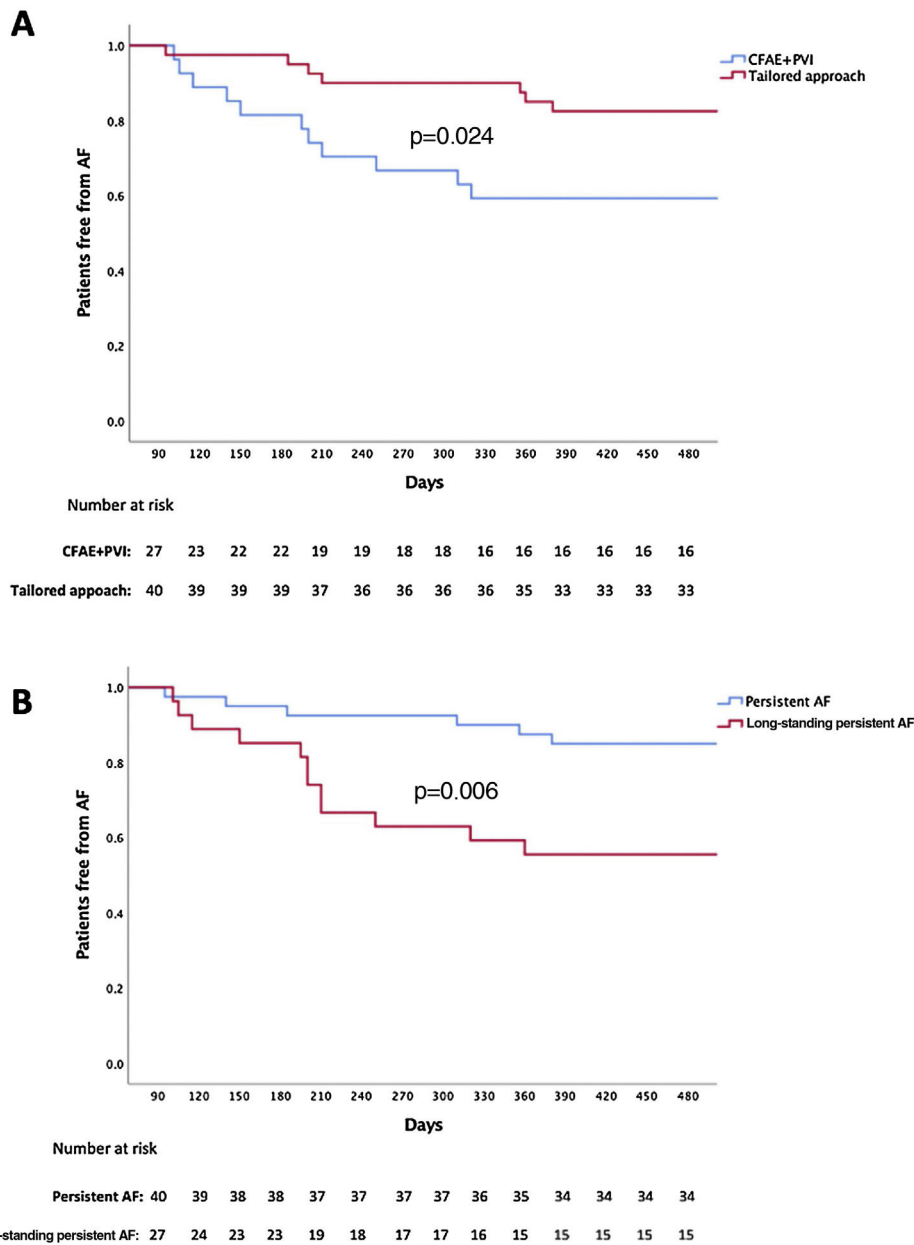


Figure 2 Freedom from atrial arrhythmia over time, according to strategy employed (A) and to type of atrial fibrillation (B). AF: atrial fibrillation; PVI+CFAE: pulmonary vein isolation plus complex fractionated atrial electrogram ablation.

outcomes with CFAE ablation, these results have been difficult to reproduce.^{16,31-33} Although our results with PVI plus CFAE ablation were superior to those obtained in other studies,³⁴ the tailored approach led to 82.5% freedom from arrhythmia in patients with persistent and long-standing persistent AF, suggesting that an individualized approach was superior to PVI plus CFAE ablation, in line with reports from other groups.³⁵ However, we should point out that the two strategies were performed at different times, hence the above-mentioned technological developments may have contributed to the differences observed. Nevertheless, despite this, the tailored approach remained an independent predictor of freedom from arrhythmia. Since the DECAAF study, evidence has emerged correlating the degree of atrial fibrosis with arrhythmia recurrence after AF

ablation.³⁶⁻⁴⁰ It therefore seems logical to target these low-voltage areas when they are present. Several studies have shown improved outcomes after ablation of low-voltage areas in addition to PVI.⁴⁰⁻⁴³ Moreover, in our study, this approach meant that 30% of patients did not undergo ablation beyond PVI, avoiding excessive ablation, as supported by the results of the STABLE-SR trial.⁴²

Our study also adds to the evidence that the longer in AF, the worse the outcome. Patients with long-standing persistent AF presented a significantly worse outcome than those in persistent AF, in line with the findings of previous studies.^{16,34,44} Also, in our study, patients with long-standing persistent AF were more likely to present hypertension, HF and an enlarged left atrium, all of which have been reported as independent predictors of recurrence.^{5,16}

Table 3 Univariate and multivariate predictors of recurrence.

	Univariate model		Multivariate model ^a	
	HR (95% CI)	p	HR (95% CI)	p
Age	0.986 (0.945-1.028)	0.51		
Gender (male/female)	1.982 (0.782-5.023)	0.15		
Body mass index	1.094 (0.971-1.232)	0.14		
AF history	1.006 (1.002-1.009)	0.002		
Continuous duration of AF	1.144 (1.080-1.223)	<0.001	1.191 (1.043-1.359)	0.010
Hypertension	2.610 (0.756-9.009)	0.13		
Type 2 diabetes	1.351 (0.381-4.785)	0.64		
Heart failure	1.916 (0.739-4.975)	0.18		
Hypothyroidism	0.493 (0.066-3.705)	0.49		
Hyperthyroidism	4.139 (1.353-12.658)	0.013		
CrCl	1.015 (0.975-1.025)	0.33		
BNP at admission	1.016 (1.005-1.021)	0.048		
LVEF	1.006 (0.958-1.057)	0.80		
LA volume	1.121 (1.071-1.174)	<0.001	1.160 (1.054-1.276)	0.002
CFAE ablation	2.811 (0.688-11.489)	0.15		
Presence of low voltage area beyond PV	2.714 (0.65-30.3)	0.09		
Low voltage ablation	1.966 (0.381-10.138)	0.42		
Sinus rhythm at the end of the procedure	0.267 (0.103-0.692)	0.007		
AF induced at the end of the procedure	8.137 (2.607-25.398)	<0.001		
Antiarrhythmic drug prescription at discharge	0.233 (0.076-0.710)	0.005		
PVI plus CFAE vs. tailored approach	2.832 (1.097-7.353)	0.031	6.457 (1.399-29.811)	0.017
Persistent/long-standing persistent AF	3.597 (1.346-9.609)	0.011		

AF: atrial fibrillation; BNP: brain natriuretic peptide; CFAE: complex fractionated atrial electrograms; CI: confidence interval; CrCl: creatinine clearance; HR: hazard ratio; LA: left atrial; LVEF: left ventricular ejection fraction; PV: pulmonary veins; PVI: pulmonary vein isolation.

^a Variables included in Cox regression analysis with forward selection were AF history, continuous duration of AF, hyperthyroidism, BNP at admission, LA volume, sinus rhythm at the end of the procedure, AF induced at the end of the procedure, antiarrhythmic drug prescription at discharge, PVI plus CFAE vs. tailored approach and persistent/long-standing persistent AF.

Study limitations

We acknowledge several limitations of our work. First, this was a retrospective study involving a relatively small number of patients, and therefore comparisons between subgroups and multivariate analysis may be underpowered. However, our main goal was to assess one-year arrhythmia recurrence in patients with non-paroxysmal AF ablation. Second, although both ablation strategies were clearly defined, we recognize that scar homogenization and, more importantly, CFAE ablation can be operator-dependent and these results may not be reproduced in other centers. Third, as mentioned above, the different AF strategies were performed at different times, therefore we cannot rule out that developments in AF technology in recent years may have contributed to the results obtained in this study. Fourth, systematic monitoring using implantable loop recorders could have documented a higher rate of asymptomatic atrial fibrillation recurrence. However, to minimize this possibility, every patient underwent seven-day Holter monitoring. Also, the proportion of patients with exclusively asymptomatic AF is not expected to be consistently different between the groups.

Conclusion

This study demonstrates that catheter ablation is an effective treatment for patients with persistent and long-standing persistent AF. Patients treated by a tailored approach had better arrhythmia-free survival, while those with long-standing persistent AF had worse outcomes.

Conflicts of interest

P.A.S. has received speaker fees from Biosense Webster, Boston Scientific, Medtronic and Abbott. All other authors have no conflicts of interest to declare.

References

1. Blum S, Aeschbacher S, Meyre P, et al. Incidence and predictors of atrial fibrillation progression. *J Am Heart Assoc.* 2019;8:e012554.
2. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946–52.

3. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359–64.
4. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J.* 2016;37:1591–602.
5. 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.* 2020;42:373–498.
6. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the aatac multicenter randomized trial. *Circulation.* 2016;133:1637–44.
7. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythmia Electrophysiol.* 2009;2:626–33.
8. Nielsen JC, Johannessen A, Raatikainen P, et al. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart.* 2017;103:368–76.
9. Mansour M, Calkins H, Osorio J, et al. Persistent atrial fibrillation ablation with contact force – sensing catheter: the prospective multicenter PRECEPT trial. *JACC Clin Electrophysiol.* 2020;6:958–69.
10. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;378:417–27.
11. Kelly JP, DeVore AD, Wu JJ, et al. Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from get with the guidelines-heart failure. *J Am Heart Assoc.* 2019;8:e011560.
12. Alturki A, Proietti R, Dawas A, et al. Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord.* 2019;19:18.
13. Mont L, Bisbal F, Hernández-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J.* 2014;35:501–7.
14. Virk SA, Bennett RG, Chow C, et al. Catheter ablation versus medical therapy for atrial fibrillation in patients with heart failure: a meta-analysis of randomised controlled trials. *Hear Lung Circ.* 2019;28:707–18.
15. Verma A, Novak P, Macle L, et al. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjunct strategy. *Hear Rhythm.* 2008;5:198–205.
16. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *J Arrhythmia.* 2017;33:369–409.
17. Terricabras M, Piccini JP, Verma A. Ablation of persistent atrial fibrillation: challenges and solutions. *J Cardiovasc Electrophysiol.* 2020;31:1809–21.
18. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372:1812–22.
19. Brooks AG, Stiles MK, Laborderie J, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Hear Rhythm.* 2010;7:835–46.
20. Stabile G, Bertaglia E, Senatore G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J.* 2006;27:216–21.
21. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med.* 2006;354:934–41.
22. Dong J-Z, Sang C-H, Yu R-H, et al. Prospective randomized comparison between a fixed '2C3L' approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace.* 2015;17:1798–806.
23. De Potter T, Van Herendael H, Balasubramaniam R, et al. Safety and long-term effectiveness of paroxysmal atrial fibrillation ablation with a contact force-sensing catheter: real-world experience from a prospective, multicentre observational cohort registry. *Europace.* 2018;20(f410):f418.
24. Kautzner J, Neuzil P, Lambert H, et al. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace.* 2015;17:1229–35.
25. Philips T, Taghji P, El Haddad M, et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace.* 2018;20:f419–27.
26. Dello Russo A, Fassini GM, Casella M, et al. Lesion index: a novel guide in the path of successful pulmonary vein isolation. *J Interv Card Electrophysiol.* 2019;55:27–34.
27. Anter E, Tschabrunn CM, Josephson ME. High-resolution mapping of scar-related atrial arrhythmias using smaller electrodes with closer interelectrode spacing. *Circ Arrhythmia Electrophysiol.* 2015;8:537–45.
28. Sousa PA, Barra S, António N, et al. HD Coloring for assessment of block along an ablation line. *J Cardiovasc Electrophysiol.* 2019;30:1692–3.
29. Sousa PA, Barra S, Elvas L, et al. HD coloring for atypical atrial flutter after mitral valve repair: what is the mechanism? *J Cardiovasc Electrophysiol.* 2020;31:252–5.
30. Anter E, Duytschaever M, Shen C, et al. Activation mapping with integration of vector and velocity information improves the ability to identify the mechanism and location of complex scar-related atrial tachycardias. *Circ Arrhythmia Electrophysiol.* 2018;11:e006536.
31. Nademanee K, McKenzie J, Kosar E. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol.* 2004;43:2044–53.
32. Seitz J, Bars C, Théodore G, et al. AF ablation guided by spatiotemporal electrogram dispersion without pulmonary vein isolation: a wholly patient-tailored approach. *J Am Coll Cardiol.* 2017;69:303–21.
33. Boveda S, Providência R, Defaye P, et al. Outcomes after cryoballoon or radiofrequency ablation for persistent atrial fibrillation: a multicentric propensity-score matched study. *J Interv Card Electrophysiol.* 2016;47:133–42.
34. Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythmia Electrophysiol.* 2015;8:18–24.
35. Kircher S, Arya A, Altmann D, et al. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation: a randomized study. *Europace.* 2018;20:1766–75.
36. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and

- atrial fibrillation catheter ablation: the DECAAF study. *JAMA*. 2014;311:498–506.
37. Chelu MG, King JB, Kholmovski EG, et al. Atrial fibrosis by late gadolinium enhancement magnetic resonance imaging and catheter ablation of atrial fibrillation: 5-year follow-up data. *J Am Heart Assoc*. 2018;7:e006313.
 38. Yamaguchi T, Tsuchiya T, Fukui A, et al. Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation. *J Cardiol*. 2018;72:427–33.
 39. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation. *J Am Coll Cardiol*. 2005;45:285–92.
 40. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7:825–33.
 41. Jadidi AS, Lehrmann H, Keyl C, et al. Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. *Circ Arrhythm Electrophysiol*. 2016;9:e002962.
 42. Yang B, Jiang C, Lin Y, et al. STABLE-SR (electrophysiological substrate ablation in the left atrium during sinus rhythm) for the treatment of nonparoxysmal atrial fibrillation: a prospective, multicenter randomized clinical trial. *Circ Arrhythm Electrophysiol*. 2017;10:e005405.
 43. Yang G, Yang B, Wei Y, et al. Catheter ablation of nonparoxysmal atrial fibrillation using electrophysiologically guided substrate modification during sinus rhythm after pulmonary vein isolation. *Circ Arrhythm Electrophysiol*. 2016;9:e003382.
 44. Tilz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the hamburg sequential ablation strategy. *J Am Coll Cardiol*. 2012;60:1921–9.