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12-year follow-up of catheter ablation for atrial fibrillation. A prospective multi-center, randomized study.

Short title: follow-up of catheter ablation for atrial fibrillation

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ABSTRACT

Background. Randomized and controlled study have reported the effect of catheter ablation (CA) for atrial fibrillation (AF) over a follow-up of 12-24 months.

Objective. We report on the effect of CA plus antiarrhythmic drugs in comparison with antiarrhythmic drugs alone on the maintenance of sinus rhythm over a 12-year follow-up.

Methods. We extended the follow-up of the 137 patients who were enrolled in the Catheter Ablation for the Cure of Atrial Fibrillation Study between 01st February 2002 and 30th June 2003 and randomized to antiarrhythmic drugs (control group) or antiarrhythmic drugs plus CA (ablation group). The primary end-point was time to first symptomatic or asymptomatic recurrence of atrial arrhythmia lasting > 30 seconds during the follow-up.

Results. During the follow-up 19/68 (27.9%, 95% CI 18.7-39.6%) ablation group patients and 3/69 (4.3%, 95% CI1.49-12.0 %) control group patients did not experienced any relapse of atrial tachyarrhythmia ($p< 0.001$). The Kaplan-Meier analysis to determine the probability of survival-free from atrial arrhythmias showed a statistical difference in favor of the ablation group (log-rank $p <0.001$). The effect of CA was consistent with both paroxysmal and persistent AF patients. At the multivariate Cox regression analysis belonging to control group (HR 2.95, IC 95% 1.896-4.726; $p<0.001$) and longer time since first AF episode (HR 1.004, IC 95% 1.002-1.084; $p=0.041$) were predictors of atrial tachyarrhythmias recurrence.

Conclusion. In patients with paroxysmal and persistent AF, CA significantly increased time to first recurrence of atrial arrhythmias during a 12-year follow-up.

Clinical Trial Registration: www.isrctn.com. Unique Identifier ISRCTN46898887

KEYWORDS

Atrial fibrillation; Catheter ablation; Antiarrhythmic drugs; Long-term follow-up;

Randomized study.

INTRODUCTION.

Atrial fibrillation (AF) affects 6.7 million people in the United States and Europe.[1] People with AF have impaired quality of life and suffer from severe cardiovascular complications, especially cerebrovascular embolism.[2,3]

Catheter ablation (CA) has become a standard therapy in patients with AF.[1,4-6] To date, however, randomized and controlled studies have evaluated the effect of CA in comparison with antiarrhythmic drugs over a period of 12-24 months.[4-9] Only observational studies have explored the effect of CA over longer periods.[10-20] Moreover, none of these has reported the effect of CA on progression to permanent AF beyond 10 years.

The Catheter Ablation for the Cure of Atrial Fibrillation (CACAF) Study was a randomized study involving selected patients with paroxysmal and persistent AF that assessed the comparative effectiveness of CA plus antiarrhythmic drugs and antiarrhythmic drugs alone over 1 year.[4] This study is an extended analysis of the CACAF Study, aimed at determining the effect of CA plus antiarrhythmic drugs in comparison with antiarrhythmic drugs alone on the maintenance of sinus rhythm over a 12-year follow-up.

METHODS

Study population. Briefly, the CACAF study enrolled patients with paroxysmal and persistent AF who were intolerant of antiarrhythmic drugs or in whom 2 or more antiarrhythmic drug regimens had failed. Description of trial design, eligibility criteria, sample size determination, randomization, settings where data were collected have already been reported.[4]

Enrolled patients were randomized to antiarrhythmic drug therapy alone (control group) or antiarrhythmic drug therapy plus CA (ablation group). The antiarrhythmic drug preferentially administered was amiodarone. In patients with a history of side-effects or

intolerance to amiodarone, a class IC antiarrhythmic drug was administered. The final decision was left to the physician in accordance with local practice.

CA was performed in the right and left atria, and included circumferential ablation of the pulmonary veins, linear ablation connecting the left inferior pulmonary vein to the mitral annulus (mitral isthmus), and inferior vena cava-tricuspid annulus isthmus ablation.[4] After a one-month blanking period, patients received a transtelephonic ECG recorder, and a 30-second ECG was scheduled each day for 3 months. Moreover, patients were instructed to obtain an ECG in the event of palpitations. Standard ECG, Holter monitoring and transthoracic echocardiography were scheduled at 1, 4, 7, 10, and 13 months.

In the event of atrial arrhythmia recurrence, patients were allowed to repeat CA (ablation group) or to undergo CA (control group).

Study protocol. The study was approved by our institutional review committee, and patients gave written informed consent to be enrolled. We extended the follow-up of the 137 patients who were enrolled in the CACAF Study between 01st February 2002 and 30th June 2003 and randomized to antiarrhythmic drugs or antiarrhythmic drugs plus CA.

After the first year, patients were followed up according to local practice (at least annually), and were invited to repeat 12-lead ECG and 24-h Holter monitoring in case of symptoms. In addition, all patients were asked to perform pulse check once daily, and to report any pulse irregularity or increase in heart rate at rest. Between 1st June 2014 and 31st May 2015 they underwent an in-office examination or a phone interview, and were invited to repeat a 12-lead ECG.

End-points. The primary end-point was time to first symptomatic or asymptomatic recurrence of atrial arrhythmia lasting > 30 seconds during the follow-up.

The secondary end-points were: 1) maintenance of sinus rhythm at 12-year follow-up; 2) all-cause mortality survival.

Statistical analysis. Normality was evaluated for each variable from normal distribution plots and histograms. Descriptive statistics, i.e. proportions, means and standard deviations (for variables with normal distribution), medians and 25^{th}-75^{th} percentiles, were used to summarize the clinical data. When data were not available, the worst case (i.e. 'failure') was assumed.

Between-group comparisons were tested by means of two-sided Wilcoxon rank-sum test and Student's t test (for variables with normal distribution) for continuous variables or Chi-square test for categorical variables. The method used to calculate a confidence interval for a proportion is the Wilson score method without continuity correction. To evaluate the current probability of survival free from atrial arrhythmias and all-cause mortality survival, the Kaplan-Meier method and log-rank test were used to compare the survival curves between ablation group and control group patients.

Effects of baseline characteristics on atrial arrhythmia recurrences were evaluated with the Cox proportional hazards model. Variables tested in the model were age, gender, left atrial diameter, history of persistent AF, years since the first AF episode, CHA_2DS_2 -VASc score, and belonging to control group.

In all statistical tests, a p-value<0.05 was considered statistically significant. All statistical analyses were performed by means of SPSS, version 17.0.

RESULTS

Study population. The study groups proved to be well balanced in terms of clinical and echocardiographic characteristics, apart from the time from the first AF episode that resulted longer in the control group patients (Table 1).

Follow-up. During the study 36/69 (52.2%) control group patients received CA due to failure of antiarrhythmic drug therapy. Paroxysmal and persistent AF patients performed the same percentage of CA (76%). Among patients who performed ablation 40/104

(38.5%) patients repeated CA during follow-up: 25 patients underwent 2 procedures; 13 patients 3 procedures; and 2 patients >3 procedures. Paroxysmal AF patients (29/92, 31%) repeated CA more frequently than persistent AF patients (9/45, 20%). Major complications related to ablation were observed in 4/104 patients (3.8%): 2 patients had a pericardial effusion which required pericardiocentesis; one patient had a stroke during left atrium ablation, and another suffered transient phrenic paralysis.

During the follow-up 22/137 (16.1%) died and 18/137 (13.1%) were lost. Causes of death were: non-cardiovascular in 6, undetermined in 5, stroke in 5 (hemorrhagic in 2), cardiac arrest in 3, and heart failure in 3. The occurrence of stroke/transient ischemic attack was similar in the ablation and control groups [7/68 (10.3%) vs 6/69 (8.7%), p= 0.750]. Only one stroke was ablation-related. Of note, all but one patients who suffered a stroke/transient ischemic attack during follow-up presented paroxysmal AF on enrollment [(12/92 (13.0%) paroxysmal vs 1/45 (2.2%) persistent, p=0.042].

At the 12-year follow-up examination, 29/68 (42.6%) ablation group patients and 21/69 (30.4%) control group patients were on antiarrhythmic drugs (p = 0.138). Amiodarone was the most frequently used drug (32/50, 64%), followed by 1C antiarrhythmic drugs (15/50, 30%) and sotalol (3/50, 6%). During the follow-up 12/137 patients (8.8%) presented side effects probably related to antiarrhythmic drugs: 6 patients showed thyroid dysfunction while on amiodarone, 3 had a cardiac arrest (1 on amiodarone and 2 on propafenone), and 3 received a pacemaker (2 on amiodarone and 1 on flecainide).

Similar proportions of patients in both study groups were receiving oral anticoagulants [34/68 (50.0%) ablation group vs 33/69 (47.8%) control group, p=0.799].

Time to first recurrence of atrial arrhythmia on antiarrhythmic drugs. During the follow-up 19/68 (27.9%, 95% CI 18.7-39.6%) ablation group patients and 3/69 (4.3%, 95% CI1.49-12.0 %) control group patients did not experienced any relapse of atrial

tachyarrhythmia (p< 0.001). Patients who experienced relapse belonged more frequently to control group, were slightly younger, with a longer history of AF (Table 2). The Kaplan-Meier analysis to determine the probability of survival free from atrial arrhythmias showed a statistical difference in favor of the ablation group (log-rank p <0.001, Figure 1). The effect of CA was consistent with both paroxysmal and persistent AF patients (Figure 2). At the multivariate Cox regression analysis belonging to control group (HR 2.95, IC 95% 1.896-4.726; p<0.001) and longer time since first AF episode (HR 1.004, IC 95% 1.002-1.084; p=0.041) were predictors of atrial tachyarrhythmias recurrence.

Long term maintenance of sinus rhythm. Figure 3 displays the rates of patients in sinus rhythm during the study. At the 12-year follow-up examination the rate of patients alive and in sinus rhythm was similar between the 2 study groups [31/68 (45.6%) in ablation group and 27/69 (39.1%) in control group, p = 0.348]. Among patients alive and in sinus rhythm 16.2% in ablation group and 17.4% in control group were not receiving antiarrhythmic drugs. The effect of CA was coherent in paroxysmal AF patients [22/42 (51.2%) ablation group vs 22/50 (44.0%) control group, p 0.402] and in persistent AF patients [9/26 (34.6%) ablation group vs 5/19 (26.3%) control group, p= 0.553].

A rate-control strategy was adopted in 9/68 (13.2%) ablation group patients and in 15/69 (21.7%) control group patients.

All-cause mortality survival. At the end of the follow-up the rate of patients still alive was similar between the 2 study groups too [49/68 (72.1%) in ablation group and 48/69 (69.6%) in control group, p=0.748]. A trend toward a higher total-mortality rate in the paroxysmal AF population than in the persistent AF population was observed [30/92 (32.6%) vs 10/45 (22.2%), p=0.209]. The Kaplan-Meier analysis to determine the probability of cumulative survival did not show any difference between the 2 groups (log-rank p=0.675, Figure 4).

DISCUSSION

Main outcomes. In this paper we reported the results of a prospective, multi-centre, randomized trial that investigated the efficacy of CA over more than a decade in a population of patients with paroxysmal and persistent symptomatic AF refractory to multiple antiarrhythmic drugs. Main outcomes were: 1) CA increased time to first recurrence of atrial arrhythmia; 2) the effect of CA was consistent with both paroxysmal and persistent AF patients; 3) at the multivariate analysis, belonging to control group and longer time since first AF episode were the best predictors of atrial tachyarrhythmias relapse during the follow up.

Long term sinus rhythm maintenance after single AF ablation. Randomized clinical trials and meta-analyses have clearly demonstrated the superiority of CA over antiarrhythmic drugs in maintaining sinus rhythm.[4-9,21] These data are consistent in paroxysmal AF population,[5,7] but less in persistent and long-term persistent AF patients.[4,6,9] However, the follow-up duration of these studies was limited to 12-24 months. Several observational studies have explored the effect of CA over a longer period.[10-19, 20] If the dream is to treat AF patients with a single procedure, maintenance of sinus rhythm seemed acceptable in both paroxysmal and persistent AF patients, although a progressive decline in efficacy was observed (Table 3). AF recurrence rates ranged between 3.0 and 9.0% per year after a single procedure, and proved higher in persistent AF patients.[13,18,19] Only one randomized controlled clinical trial followed up patients for 4 years.[22] In that study, Pappone et al. prolonged the follow-up of the 198 patients enrolled in the APAF trial. Their intention-to-treat analysis showed that 72.7% of patients in the ablation arm and 56.5% of those initially randomized to AADs were free of recurrent atrial arrhythmias (P=0.017) at 4 years.

In our study CA in adjunction to antiarrhythmic drugs allowed to avoid atrial arrhythmias recurrences, after 12-year, in 27.9% of patients after a single procedure. Of interest, the effect is consistent with both paroxysmal and persistent AF patients. This result is substantially worse than that recently reported by Gokoglan et al, who found a 58.7% of recurrence-free survival without antiarrhythmic drugs among a population of paroxysmal AF patients.[20] The inclusion of persistent AF in our study population, and the difference in the ablation techniques among the 2 series, could explain the different results.

Progression to permanent AF. Permanent AF is associated with a higher risk of total mortality than the other forms of AF.[23] Paroxysmal and persistent AF naturally progress towards permanent AF at an estimated rate of 7% to 20% per year.[24-26] The impact of CA or antiarrhythmic drugs on such progression has been poorly investigated. In the United States arm of the RECORD AF Study, progression to the permanent form at 1 year was greatly slowed in patients randomized to the rhythm control group.[26] The rate of progression to permanent AF was 3% per year in paroxysmal patients and 18% in persistent AF patients. In our study, we observed an unexpected high proportion of sinus rhythm (45.6%) at 12-year follow-up in patients randomized to CA. Among paroxysmal AF patients, the proportion of those in sinus rhythm rose to 51.2%. The price of this result is that 29.4% of these patients underwent > 2 ablations, and that the majority of them were still receiving antiarrhythmic drugs. Although a history of persistent AF usually negatively affects the maintenance of sinus rhythm, the proportion of patients alive and in sinus rhythm after 12 years was acceptable even in persistent AF patients (44.0%).

All-cause mortality survival. AF is a progressive condition associated with increased mortality and morbidity. Survival has been found to be better among paroxysmal AF patients than among patients with permanent AF, but clearly lower than in patients with persistent AF. This observation was consistent in both external comparisons with the

general population and in internal comparisons with patients suffering from other types of AF.[23]

In several clinical contexts, sinus rhythm maintenance by means of antiarrhythmic drugs has already proved to be unsuccessful in increasing survival.[27] A *posthoc* analysis of the AFFIRM study clearly showed that antiarrhythmic drugs were not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of antiarrhythmic drugs are offset by their adverse effects.[28]

CA has been proposed as an effective method of maintaining sinus rhythm with fewer adverse effects.[21] To date, however, only one retrospective controlled study has investigated the role of CA on survival in comparison with antiarrhythmic drugs.[29] After a median follow-up of 900 days, the Kaplan-Meier analysis showed that the observed survival of ablated patients was longer than among patients treated medically, and not different from that expected in healthy persons of the same gender and age.[28]

In our study, only a slightly trend toward a higher total-mortality rate in the paroxysmal AF population than in the persistent AF population was observed, whereas the rate of patients still alive was similar between the two study groups.

Cerebrovascular accidents. AF-related cardiovascular morbidity is mainly due to thromboembolic complications and heart failure.[30] In our patients, the incidence of severe heart failure was negligible, while almost 1% per year suffered from cerebrovascular accidents. In line with the findings on mortality, paroxysmal AF patients were more frequently hit by these events than persistent AF patients. Although CA reduced AF recurrences, it did not overcome this complication. The main reason for this failure could be related to the withdrawal of oral anticoagulation after successful ablation in patients asymptomatic for palpitations. This strategy, which was widely adopted at the

beginning of the 2000's, could lead to an excess of embolic complications in ablated patients.

Study limitations. The study has several potential limitations. This analysis was not planned at the outset of the CACAF Study, and may therefore suffer from hidden biases and other unidentified confounders.

The number of patients we could not contact at the end of follow-up is low but not negligible: this could have influenced the results of the study.

The number of patients randomized to control group who performed CA after failure of antiarrhythmic therapy could have increased sinus rhythm persistence and survival in this population.

CA techniques are continuously evolving. The anatomical approach to pulmonary vein ablation adopted in the CACAF Study did not require the use of a circular mapping catheter to document electrical isolation of the veins. This, could have reduced the efficacy of CA.

A systematic collection of procedural results of the repeated CA was not available. Thus, we couldn't explore the cause of failure of previous ablation (reconnection, incomplete line of block, non-pulmonary vein trigger).

The presence of patients with persistent AF in our population could have hampered the long term result of CA in comparison to other studies.

After the first year, patients underwent clinical follow-up according to local practice. Sinus rhythm maintenance was based mainly on the last ECG. Without routine ambulatory monitors and ECGs, estimation of long-term arrhythmia recurrences and sinus rhythm rates could be overestimated due to the inability to detect subclinical arrhythmias.

Indications for anticoagulation during and after CA have changed over the years. Thus, the rate of embolic complications observed in the ABL group might have been different if

current recommendations had been followed.

Conclusions. Our results demonstrated that in patients with paroxysmal or persistent symptomatic AF, refractory to multiple antiarrhythmic drugs, CA increased time to first recurrence of atrial arrhythmia even after 12 months. The effect of CA was consistent with both paroxysmal and persistent AF patients.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves of survival-free from atrial arrhythmyas for the total population. Blue line=control group; red line= ablation group.

Figure 2. Kaplan-Meier curves of survival-free from atrial arrhythmyas for paroxysmal AF population (A) and persistent AF population (B). Blue line=control group; red line= ablation group.

Figure 3. Rates of patients in sinus rhythm during the study. Blue bar=control group; red bar= ablation group.

Figure 4. Kaplan-Meier curves of cumulative survival for the total population. Blue line=control group; red line= ablation group.

TABLES

Table 1. Clinical and echocardiographic characteristics of the study population.

	Total (n=137)	Control group (n=69)	Ablation group (n=68)	p value
Paroxysmal AF, n [%]	92 [67.1%]	50 [72.5%]	42 [61.2%]	0.190
Male gender, n [%]	81 [59.1]	44 [63.8]	37 [54.4]	0.275
Age, years	62.2 ± 9.8	62.3 ± 10.7	62.2 ± 8.9	0.97
Years since first AF episode	5 (2-10)	5 (3-10)	3 (2-7)	0.033
Cardiopathy, n [%]	86 [62.8]	43 [62.3]	43 [63.2]	0.824
LA A-P diameter, mm	45.6 ± 5.3	45.4 ±5.5	46.0 ±5.0	0.510
LVEF, %	60 (55-65)	59.5 (55-63.5)	60 (55-65)	0.232
CHA_2DS_2 VASc score, n [%]				
0	43 [31.4]	20 [29.0]	23 [33.8]	0.171
1	45 [32.8]	23 [33.3]	22 [32.4]	
2	19 [13.9]	12 [17.4]	7 [10.3]	
3	22 [16.1]	8 [11.6]	14 [20.6]	
4	7 [5.1]	4 [8.7]	1 [1.5]	
5	1 [0.7]	0 [0]	1 [1.5]	

Data are presented as mean+SD, medians (25^{th}-75^{th} percentiles) or percentages (%). AF: atrial fibrillation; LA A-P: left atrial antero-posterior diameter; LVEF: left ventricular ejection fraction.

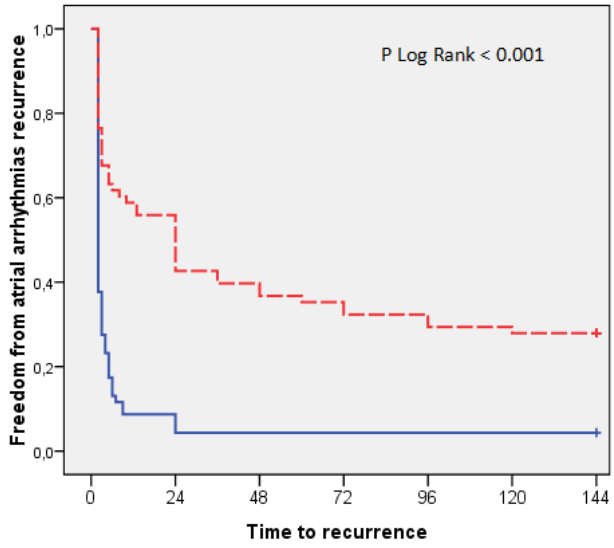
Table 2. Predictors of atrial tachyarrhythmias relapse on multivariate Cox regression.

	Total (n=137)	No AF relapses (n=22)	AF relapses (n=115)	p value univariate analisys	p value Cox analisys
Paroxysmal AF, n [%]	92 [67.1%]	18 [81.8%]	74 [64.3%]	0.110	0.088
Male gender, n [%]	81 [59.1]	12 [54.5]	69 [60.0]	0.633	0.665
Age, years	62.2 ± 9.8	65.6 ± 7.6	61.5 ± 10.1	0.038	0.153
Years since first AF episode	5 (2-10)	3 (2-5)	5 (3-10)	0.028	0.041
Cardiopathy, n [%]	86 [62.8]	14 [63.6]	72 [63.2]	0.966	0.806
LA A-P diameter, mm	45.6 ± 5.3	45.0 ±5.4	45.8 ±5.2	0.537	0.405
LVEF, %	60 (55-65)	59.0 (55-64.2)	60.0 (55-65)	0.703	0.326
CHA_2DS_2 VASc score, n [%]				0.613	0.732
0	43 [31.4]	6 [27.3]	37 [32.2]		
1	45 [32.8]	5 [22.7]	40 [34.8]		
2	19 [13.9]	4 [18.2]	15 [13.0]		
3	22 [16.1]	6 [27.3]	16 [13.9]		
4	7 [5.1]	1 [4.5]	6 [5.2]		
5	1 [0.7]	0 [0.0]	1 [0.9]		
Control group	69 [50.4]	3[4.3]	66 [95.7]	<0.001	<0.001

Data are presented as mean+SD, medians (25^{th}-75^{th} percentiles) or percentages (%). AF: atrial fibrillation; LA A-P: left atrial antero-posterior diameter; LVEF: left ventricular ejection fraction.

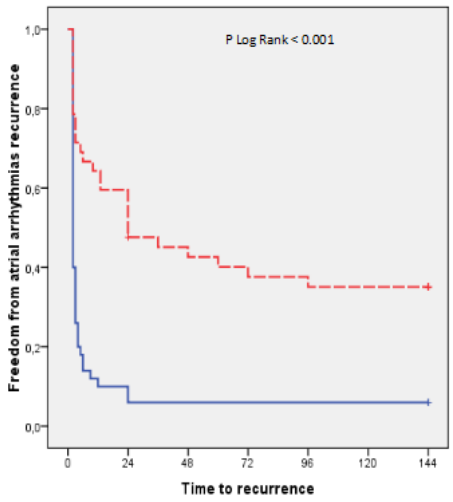
Table 3. Previous studies on the long-term effect of a single AF ablation procedure.

Author	Patients (N)	Paroxysmal AF (%)	Follow-up (months)	Relapse after a single procedure (%)
Pappone[5]	99	100	48	27
Fiala[10]	110	100	48	43
Bertaglia[11]	229	58	50	55
Hussein[12]	831	69	55	33
Ouyang[13]	161	100	57	53
Barghava[14]	1404	52	57	27
Tzou[15]	239	85	60	64
Weerasooriya[16]	100	63	60	71
Sawhney[17]	71	100	63	44
Steinberg[19]	445	72	66	22
Gokoclan[21]	513	100	144	41



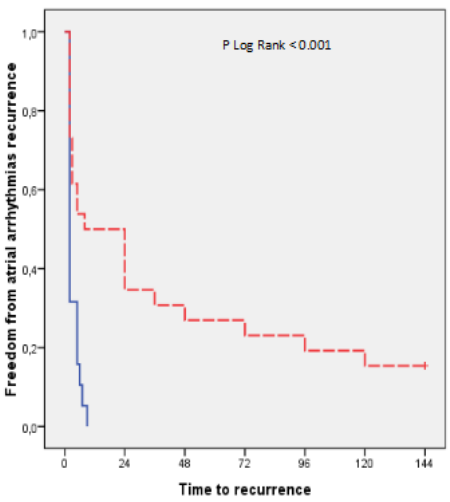
Ablation	68	29	25	22	20	19	18
Control	69	3	3	3	3	3	3

A

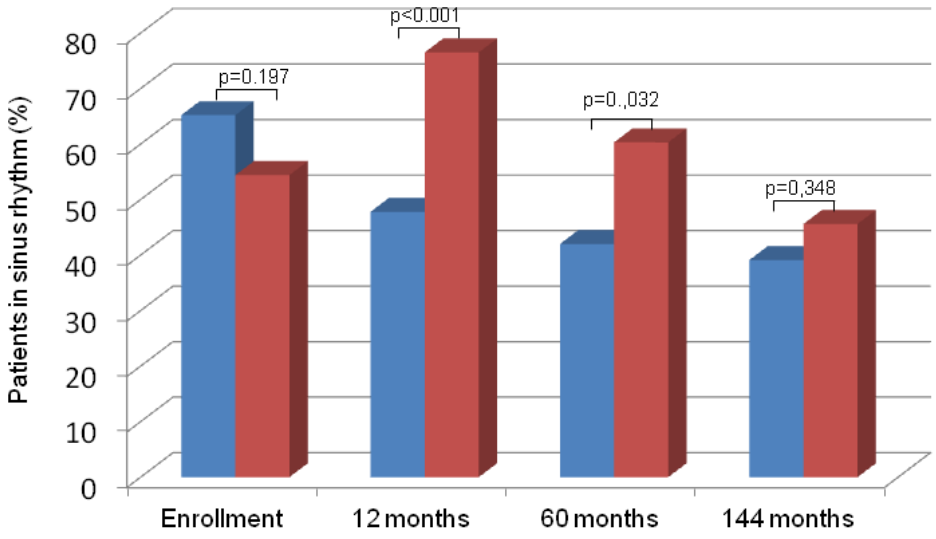


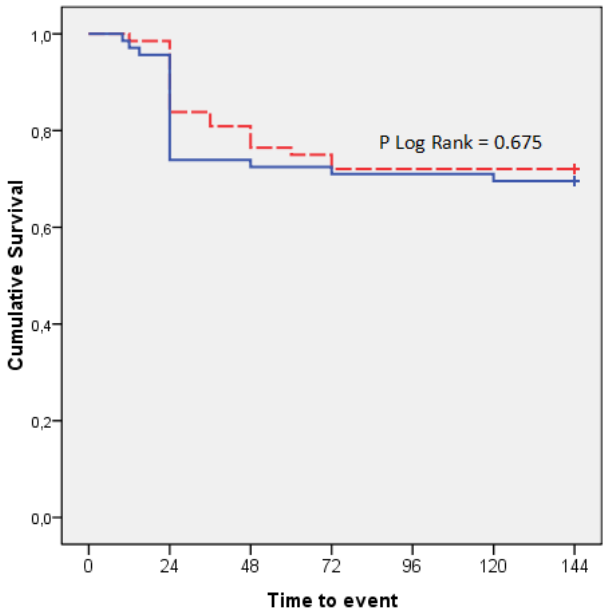
Ablation	42	20	18	16	15	15	15
Control	50	3	3	3	3	3	3

B



Ablation	26	9	7	6	5	4	4
Control	19	0	0	0	0	0	0


Patients in sinus rhythm (%)
80
70
60
50
40
30
20
10
0
p=0.197
p<0.001
p=0.,032
p=0,348
Enrollment
12 months
60 months
144 months



Ablation	68	57	52	49	49	49	49
Control	69	51	50	49	49	48	48