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UNIVERSITÀ DEGLI STUDI DI TORINO

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Word count: ... words, 2 tables, 3 figures and 29 references

Abstract word count: 242 words

Running title**:** Permanent AF following transcatheter ablation

Conflict of interest: none.

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Abstract

Background. Natural history of atrial fibrillation (AF) is characterized by gradual increase in duration and frequency of relapses until a definitive shift to permanent AF. Heart disease and comorbidities modulate AF progression, however, to date, the influence of catheter ablation on AF evolution has rarely been investigated.

Objective. Our aim is to identify long-term predictors of AF progression in a large cohort of patients undergoing transcatheter AF ablation (AFTCA).

Methods. 889 patients (mean age 57±11 years, 53.3% paroxysmal, 40.5% persistent and 6.2% long-standing AF) underwent AFTCA. All patients received pulmonary veins isolation while linear lesions and complex fractionated atrial electrograms ablation were reserved for patients with persistent/long-standing AF and/or in confirmed structural heart disease.

Results. After a median follow up of 64 (41–84) months, AF progression despite AFTCA occurred in 57 (6.4%) cases. However, AF progression was much more pronounced in patients afflicted by persistent (10%) and long-standing persistent AF (14,6%) compared to patients afflicted by paroxysmal AF (2,7%, p<0.001). Furtheremore, AF progression was more frequently reported in patients presenting with underlying comorbidities/cardiomyopathies (9.1%)compared to those presenting with lone AF (29.9%,p<0.001). At multivariate analysis, comorbidities/cardiomyopathies and baseline persistent/long-standing AF proved as independent predictors of progression (OR 11.3, CI 95% 2.6-48.0, p<0.001 and OR 1.6, CI 95% 1.2-2.1, p<0.001 respectively).

Conclusions. The presence of comorbidities/cardiomyopathies and persistent/long-standing AF seem to predict AF progression in patients undergoing AFTCA. Performing AFCTA in the paroxysmal phase of the arrhythmia may reduce progression of AF to its permanent form.

Key-words: atrial fibrillation, transcatheter ablation, long-term progression, permanent atrial fibrillation

List of abbreviations: atrial fibrillation (AF), transcatheter AF ablation (AFTCA), antral pulmonary veins isolation (PVI), transient ischemic attack (TIA).

Introduction

The presence of atrial fibrillation (AF) impairs quality of life [1] and worsens long-term prognosis[2]. Natural history of AF is characterized by a gradual shift from rare and short-lasting episodes (paroxysmal AF) to progressively more frequent and persisting relapses (persistent/permanent AF) [3]. To date, several factors including presence of comorbidities [4], underlying cardiomyopathies [5], clinical subtype [6],[7],[8] and duration [9] of the arrhythmia in patients treated with pharmacological therapy have been related to an increased risk of AF progression over time. In addition, patient and physician's belief [10],[11] plays a major role in modulating AF progression and represents an area in which biggest efforts should be invested. Although transcatheter ablation, a valuable and increasingly proposed option for symptomatic drug resistant AF [12], holds the potential to interfere and delay this process, few data are available concerning progression to permanent AF following AF transcatheter ablation (AFTCA).
The main aim of the present study is to report on long-term progression rate to permanent AF in a large cohort of patients undergoing AFTCA in a single high volume center.

Methods

Consecutive patients referred to our center between 2004 and 2010 for AFTCA have been included in this retrospective study. Clinical features of the study population, procedural and periprocedural details and follow-up data have been routinely recorded. AF progression was defined as the shift from paroxysmal or persistent/long-standing persistent AF to permanent AF. Permanent AF, according to latest ESC guidelines [13], was defined when the presence of the arrhythmia was accepted by the patient and the physician leading to a rate control strategy.

Ablation procedure. Procedural details have been reported elsewhere [14]. Briefly, ablation approach encompassed antral pulmonary veins isolation (PVI) in all cases of paroxysmal lone AF (i.e. AF in the absence of any clinical, ECG, or structural abnormality). Antral PVI with the addition of linear lesions and complex fractionated atrial electrograms ablation was performed in persistent/long-standing persistent AF and/or in confirmed structural heart disease (i.e. congenital, hypertrophic, dilated cardiomyopathy, coronary artery disease or valvular heart disease). In case of redo procedure due to paroxysmal lone AF and documented PV reconnection antral PV isolation alone was newly performed.

Follow up. Recurrences were detected by routine ambulatory visits (performed at 1, 3, 6months and then yearly), with collection of patients' symptoms and 24 hours Holter ECG recordings. Rhythm or rate control strategy was registered according to the referring physician's advice, as for type of antiarrhythmic drugs prescribed.

Statistical analysis. Categorical variables are reported as counts and percentages, while continuous variables as median and interquartile range (IQR). Correlations between baseline characteristics and AF progression were tested in cross tabulation tables by means of the Pearson Chi-Square or Fisher's Exact Test and by one-way ANOVA respectively for categorical and continuous variables. To test the independent correlation of these parameters with AF progression, all variables reporting a significant correlation at univariate analysis were included in a stepwise multivariate logistic regression model. Kaplan Meier curves were used to measure AF progression free survival over time stratified for lone AF or not and compared by log-rank test. A two sided p-value <0.05 was considered statistically significant; all analyses were performed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Eight hundred eighty-nine patients (mean age 57±11 years, male 78%) underwent AF ablation between January 2001 and September 2010. Baseline features of the study population are listed in Table 1. Paroxysmal AF was detected in 474 patients (53.3%), while persistent AF in 360 patients (40.5%) and long-standing AF in 55 patients (6.2%). In order to achieve stable long-term rhythm control 276 (31%) patients underwent redo procedures (Figure 1). The first redo procedure was performed after a median of 11.2 months (IQR 6.2-22.4 months) from the first transcatheter ablation.

Ablation protocol according to baseline AF classification is detailed in Table 2. The overall cumulative AF progression rate was 1.25 per 100 patient-years. AF progression occurred in 57/889 patients (6.4%) after a median follow up of 64 months (IQR 41 – 84 months), showing an increasing trend from patients with baseline paroxysmal (13/474, 2.7%), to persistent (36/360, 10.0%) and long-standing AF (8/55, 14.6%; $p<0.001$). Stratification by baseline AF subtype and lone AF is illustrated in Figure 2. Thirteen of 474 paroxysmal AF patients progressed to permanent AF despite transcatheter ablation was performed. The main reasons explaining why AF progressed to permanent in paroxysmal patients were, firstly, low compliance to the scheduled ambulatory visits, especially within asymptomatic patients, and, secondly, refusal to pursue rhythm control strategies. None of the 266 (30%) patients with lone AF progressed to permanent AF while 9.1% of the 623 patients with associated comorbidities and/or underling cardiomyopathies shifted to permanent AF (Figure 3, $p<0.001$).

At multivariate analysis (adjusted for age, hyperthyroidism, CHA_2DS_2VASc score ≥2, baseline comorbidities/cardiomyopathies, AF classification and left atrium enlargement), baseline comorbidities/cardiomyopathies and persistent/long-standing AF only emerged as

independently related to progression (OR 11.3, CI 95% 2.6-48.0 p<0.001 and OR 1.6, CI 95% 1.2-2.1 p<0.001).

Discussion

Available literature describes long term efficacy of AFTCA based on recurrences of arrhythmia episodes lasting more than 30 seconds[15]. On this basis paroxysmal, persistent and permanent AF recurrences, despite being clinically obviously different, are considered all the same. The main aim of the present study was to evaluate the progression rate of AF considering a reproducible, everyday clinical practice endpoint such as the shift to permanent AF. Our study reports a low progression rate to permanent AF in a large cohort of patients undergoing AFTCA during a long-term follow up of more than 5 years. Among patients with lone AF we don't observe any AF progression. Interestingly, within the few patients (57/623, 9.1%) in which AF progression has been documented, instead, presence of baseline comorbidities/cardiomyopathies and persistent/long-standing AF proved as independent predictors.

Atrial fibrillation's natural history is characterized by gradual episodes duration and frequency increase until a definitive shift to the permanent form of the arrhythmia[16]. This evolution, however, may be modulated by available rhythm control strategies[17], especially AFTCA[18]. This finding is indeed clinically relevant bearing in mind that recent findings support the potential protective role of rhythm versus rate control strategy on both clinical thromboembolic events[19] and cognitive performance[20]. Physician's belief directed or not towards a rhythm control strategy, in fact, is strongly associated with AF progression. This opinion is supported by a recent large cohort study of patients with newly diagnosed AF [10]. In this population, despite

lower incidence of AF progression was reported in patients treated with rhythm control strategy than in those treated with rate control strategy (164/1542, 11% vs 154/595, 26%, P < 0.001), a relevant AF progression rate was reported already after a follow up of 1 year. However, in this study, rhythm control maintenance was preferentially achieved by pharmacological therapy. Indeed, similar data on AF progression has been reported in general AF populations treated by antiarrhythmic therapy[21] with rates up to 8.6 % in 1 and 24.7% in 5 years. Few data, however, are available concerning progression to permanent AF following AFTCA. Three previous experiences[15⊥], [22], [23] reported 5 year AF progression rates following AFTCA between 0 and 2.4 %.

Indeed, our aim is to evaluate the long-term progression rate to permanent AF in a large population undergoing AFTCA. Among all our patients, including those requiring repeated procedures (i.e. one out of three patients), a cumulative AF progression rate of 1.25 per 100 patient-years has been observed after a median follow up of more than 5 years. In particular, based on the present large cohort of patients, AFTCA may significantly slow/reduce AF progression, at least over a five year period, in patients without comorbidities and/or structural cardiomyopathies. Only a small percentage of these patients (2.7%) suffers AF progression if AFTCA is performed in the early paroxysmal phase of the arrhythmia. Although the optimal time to perform catheter ablation is still uncertain, it is well known that delays in treatment, after the first clinical diagnosis, will impact procedural success rates and negatively influence outcomes[24], [25], [26]. Given this, the fact that AF progression predictors are those most closely related to atrial remodelling [27,28] is not surprising. Long arrhythmia duration and underling comorbidities/cardiomyopathies (i.e. hypertension, heart failure and structural myocardial alterations) cause chronic stretch and atrial dilatation, with consequent structural remodeling of

left atrium substrate demonstrated by increased tissue fibrosis and intra-atrial conduction disturbances perpetuating the arrhythmia [29]. In fact, atrial fibrosis quantification has proved to relate to frequency and duration of AF relapses after AFTCA[30]. On the other side, sinus rhythm restoration for at least one month prior to AFTCA for persistent AF increased its efficacy [31] and may be related to reverse remodeling requiring less extensive ablation protocol.

Ongoing clinical trials (as the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation; CABANA trial) [32], whose results are expected in few years, may surely shed some light on the potential role of AFTCA in modulating AF progression.

Limitations

First, this study shares all the weaknesses of observational, non-randomized studies. Hopefully that all the procedures were performed in a single high volume centre with a standardized AFTCA approach should mitigate this limitation. Second, physician advice in proposing rhythm versus rate control strategy, which antiarrhythmic drug prescribe or ablation protocol pursue may have introduced a poorly predictable bias, however randomly distributed. Last, the overall low incidence of AF progression rate may have limited the statistical power of the multivariate analysis.

Conclusion

AF progression may successfully be delayed by AFTCA, especially within patients without structural heart disease and before AF duration itself induces atrial remodeling. Accordingly, AFTCA must be considered as soon as possible in patients afflicted by paroxysmal AF in order to limit progression to persistent/long-standing forms.

Indeed, persistent/long-standing AF and baseline cardiomyopathies/comorbidities were linked to a poorer clinical outcome and required a more aggressive protocol strategy (PVI with the addition of linear lesions and complex fractionated atrial electrograms ablation and multiple redo procedures) in order to attempt to avoid shift to permanent AF.

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Table 1. Baseline, procedural and echocardiographic features of the study population stratified by arrhythmia progression over the long-term follow up (n, % if not differently stated).

	Total n=889	**AF progression n=57**	**No AF progression n=832**	**P value**
Male sex	696 (78.3)	36 (63.2)	660 (79.3)	
Age ≥ 65 years	244 (27.4)	23 (40.4)	221 (26.6)	0.023
Hypertension	410 (46.1)	30 (52.6)	380 (45.7)	0.338
Body mass index	27±7	27±4	27±6	0.810
Diabetes mellitus	32 (3.6)	3 (5.3)	29 (3.5)	0.453
Heart Failure	43 (4.8)	6 (10.5)	37 (4.4)	0.051
Previous Hyperthyroidism	94 (10.6)	13 (22.8)	81 (9.7)	0.006
Previous Hypothyroidism	72 (8.1)	5 (8.8)	67 (8.1)	0.802
Cerebral Stroke/TIA	84 (9.4)	7 (12.3)	77 (9.3)	0.479
$CHADS_2$ score ≥ 2	143 (16.1)	15 (26.3)	128 (15.4)	0.039

$CHA_2DS_2Vasc \geq 2$	335 (37.7)	32 (56.1)	303 (36.4)	0.004
Structural Cardiomyopathy	197 (22.2)	30 (52.6)	167 (20.1)	<0.001
Lone AF	266 (29.9)	0 (0.0)	266 (32.0)	<0.001
Paroxysmal AF	474 (53.3)	13 (22.8)	461 (55.4)	<0.001
Persistent AF	360 (40.5)	36 (63.2)	324 (38.9)	
Long-standing Persistent AF	55 (6.2)	8 (14.0)	47 (5.6)	
Ablation Protocol				
PVI	198 (22.3)	7 (12.3)	191 (23.0)	0.141
PVI + linear lesions	500 (56.2)	38 (66.6)	462 (55.5)	
PVI + linear lesions + CFAE	191 (21.5)	12 (21.1)	179 (21.5)	
Echocardiography				
Left Atrium AP diameter (mm)	46 ± 7	50 ± 7	46 ± 6	<0.001
Left Atrium SI diameter (mm)	61 ± 8	68 ± 7	61 ± 8	<0.001

List of abbreviation: AF, atrial fibrillation. AP, antero-posterior. CFAE complex fractionated atrial electrograms. PVI, pulmonary vein isolation. SI, supero-inferior. TIA, transient ischemic attack.

Table 2. Ablation protocol according to baseline atrial fibrillation classification (n, % if not differently stated).

Ablation protocol*	Paroxysmal AF 474 pts (53%)		Persistent AF 360 pts (41%)		Long standing AF 55 pts (6%)	
	Lone AF 163 pts (34%)	AF 311 pts (66%)	Lone AF 91 pts (25%)	AF 269 pts (75%)	Lone AF 12 pts (22%)	AF 43 pts (78%)
PVI	75 (46%)	96 (31%)	19 (21%)	8 (3%)	0 (0%)	0 (0%)
PVI + Linear lesion	70 (43%)	177 (57%)	52 (57%)	174 (65%)	3 (25%)	24 (56%)
PVI + Linear lesion + CFAE	18 (11%)	38 (12%)	20 (22%)	87 (32%)	9 (75%)	19 (44%)

*Including redo procedures. List of abbreviation: AF, atrial fibrillation. PVI, pulmonary vein isolation. CFAE complex fractionated atrial electrograms.

Figure's legend

Figure 1. Redo AF ablation procedures during follow-up.

Figure 2. Stratification of lone atrial fibrillation by baseline clinical classification.

Figure 3. Kaplan Meier curves concerning AF progression free survival over time stratified for lone AF.

Figure 1

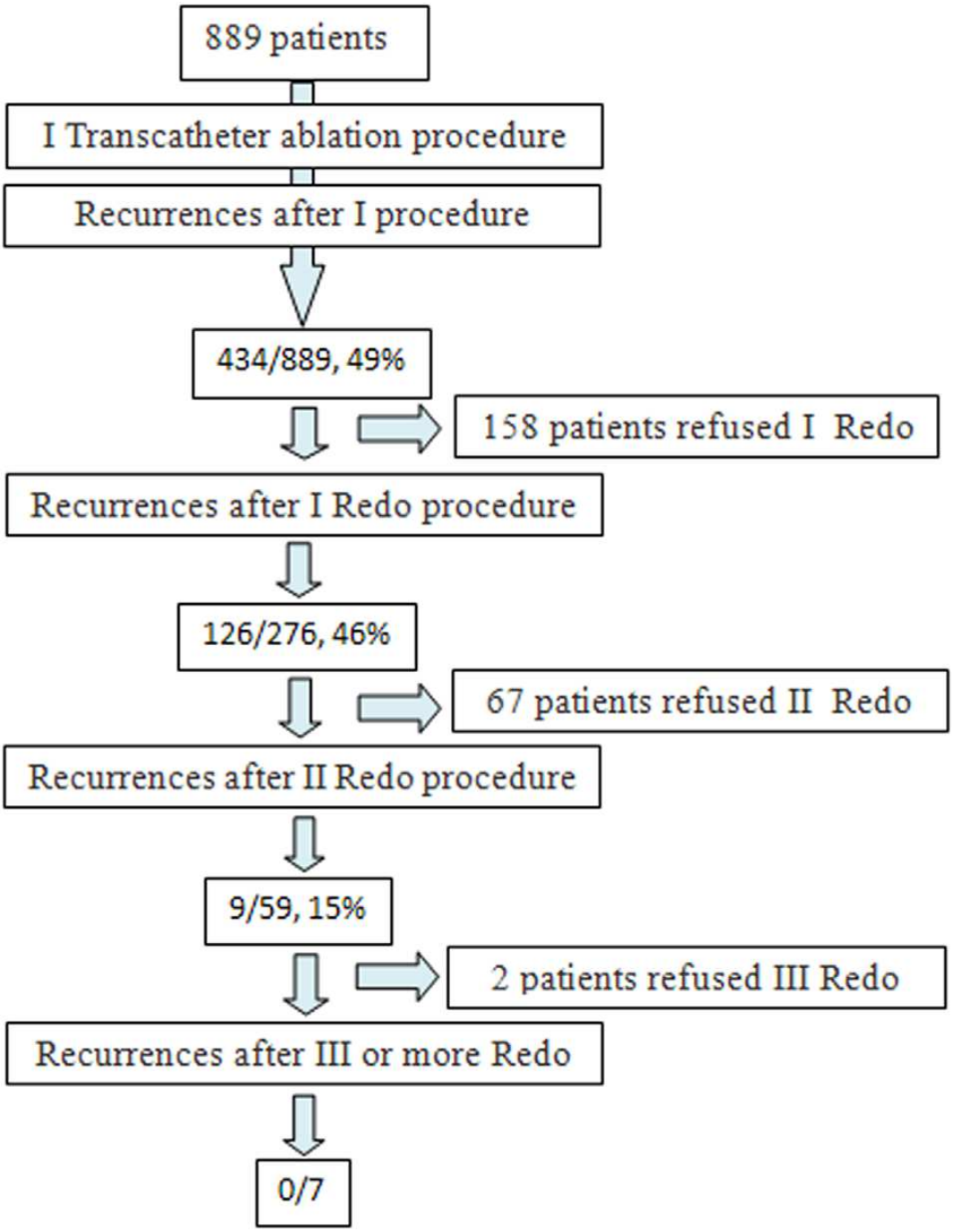

889 patients
I Transcatheter ablation procedure
Recurrences after I procedure
434/889, 49%
158 patients refused I Redo
Recurrences after I Redo procedure
126/276, 46%
67 patients refused II Redo
Recurrences after II Redo procedure
9/59, 15%
2 patients refused III Redo
Recurrences after III or more Redo
0/7

Figure 2

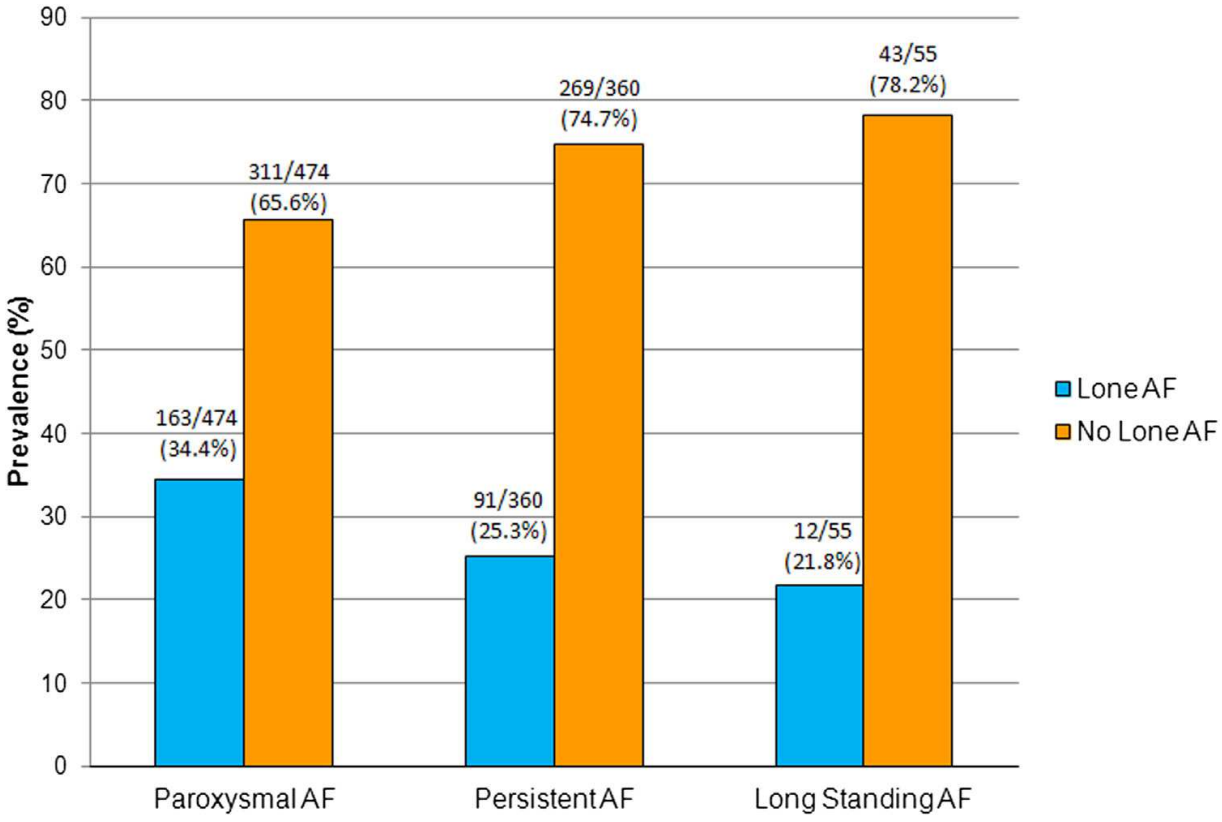
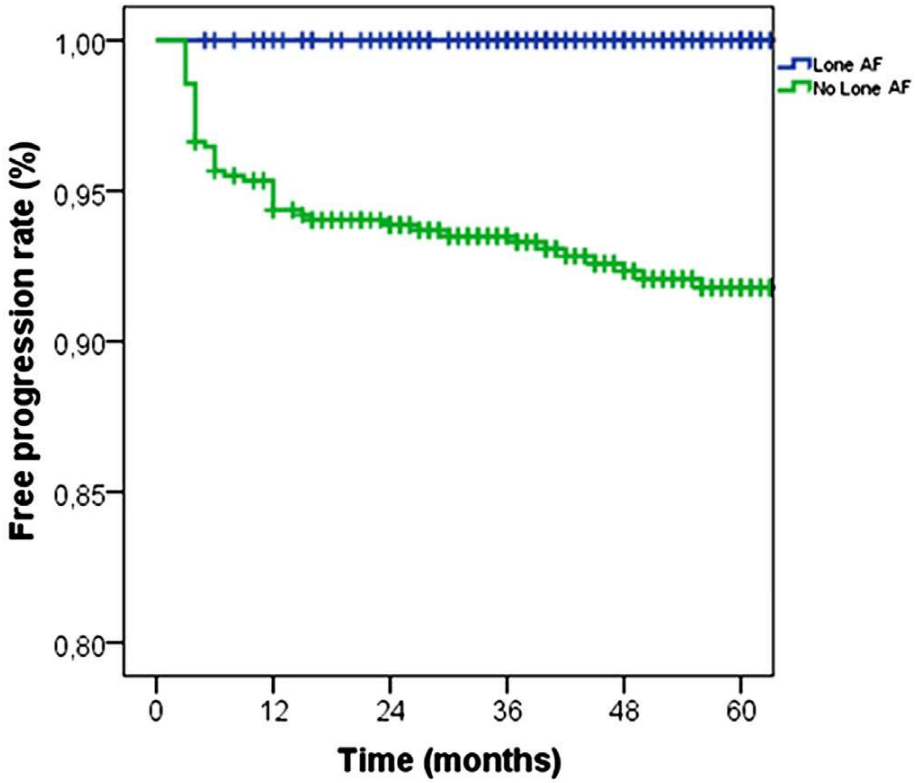

90
80
70
60
50
40
30
20
10
0
Prevalence (%)
163/474
(34.4%)
311/474
(65.6%)
91/360
(25.3%)
269/360
(74.7%)
12/55
(21.8%)
43/55
(78.2%)
Paroxysmal AF
Persistent AF
Long Standing AF
Lone AF
No Lone AF

Figure 3



No lone AF	Time (months)	0	12	24	36	48	60
	Pts at risk (n)	623	588	585	583	578	576
	Event free survival	100%	94,4%	93,9%	93,6%	92,8%	92,4%
Lone AF	Time (months)	0	12	24	36	48	60
	Pts at risk (n)	266	266	266	266	266	266
	Event free survival	100%	100%	100%	100%	100%	100%