

Atrial fibrillation progression and management: A 5-year prospective follow-up study

Carlo Pappone, MD, Andrea Radinovic, MD, Francesco Manguso, MD, Gabriele Vicedomini, MD, Giuseppe Ciconte, MD, Stefania Sacchi, MD, Patrizio Mazzone, MD, Gabriele Paglino, MD, Simone Gulletta, MD, Simone Sala, MD, Vincenzo Santinelli, MD

From the Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan, Italy.

BACKGROUND Few data on atrial fibrillation (AF) progression from the first paroxysmal episode are available.

OBJECTIVE The purpose of this study was to assess the progression of AF not due to potentially reversible causes in patients treated according to current guidelines recommendations that also include catheter ablation.

METHODS Among 402 screened patients with first AF, 106 patients (mean age 57.5 years) were selected and followed for 5 years. Of these patients, 54 had lone AF and 52 had comorbidities.

RESULTS Fifty patients (61.1% with lone AF) had no further recurrence after 5 years. The remaining 56 patients within 19 months after the first episode developed recurrent paroxysmal AF requiring long-term antiarrhythmic drug therapy, which was continued in 45 patients and was stopped because of intolerance/failure in 11 patients who underwent catheter ablation. AF became persistent in 24 of the 45 patients on antiarrhythmic drug therapy and then permanent in 16, of whom 6 had refused catheter

ablation at the time of persistence. No AF recurrences or AF progression occurred after ablation. Kaplan-Meier curves demonstrated that patients with comorbidities were more likely to progress than were those with lone AF ($P < .001$) and that patients who underwent catheter ablation were at lower risk for progression to permanent AF than were those on antiarrhythmic drug therapy ($P = .029$). Age, diabetes, and heart failure ($P < .001$) predict final progression to permanent AF.

CONCLUSION Patients with first AF and comorbidities are at higher risk for rapid progression to permanent AF, and age, diabetes, and heart failure are independent predictors. Catheter ablation rather than antiarrhythmic drug therapy is beneficial in eliminating recurrences delaying arrhythmia progression.

KEYWORDS Arrhythmia; Atrial fibrillation; Risk factors; Catheter ablation

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Introduction

At present, no prospective data on atrial fibrillation (AF) progression and management according to recent AF guideline recommendations are available.^{1,2} Published data on AF progression mainly derive from retrospective analyses³⁻⁶ or survey data registries.⁷ To date, no prospective information that includes a potential influence of catheter ablation is available. Accordingly, the purpose of this prospective study was to report additional data on AF progression and management, which includes catheter ablation as an alternative to conventional antiarrhythmic drug therapy.

Methods

Study population

All consecutive patients admitted to the emergency department with a first episode of paroxysmal AF were recruited for this 5-year prospective follow-up study. Final inclusion

required ECG confirmation of the arrhythmia and verification of the episode as the first recognized AF event for the individual without previous antiarrhythmic drug therapy. Patients with arrhythmia due to potentially reversible causes, such as acute or recent (<6 months) myocardial infarction, recent cardiac surgery, New York Heart Association class III-IV heart failure, severe valvular heart disease requiring surgery, uncontrolled hypertension, acute pulmonary disease, Wolff-Parkinson-White syndrome, a history of long QT syndrome, Brugada syndrome, pericarditis, substance abuse, electrolyte imbalance, hyperthyroidism, or hypothyroidism, were excluded from the study. Patients with hepatic disease, contraindication to anticoagulation therapy, or any condition making survival unlikely for 1 year also were excluded. All patients gave written informed consent to participate in the study. The study protocol was approved by the local ethics committee.

Follow-up

Serial control visits with ECG, 48-hour Holter monitoring, and echocardiography were scheduled at 1, 3, and 6 months and once annually thereafter for 5 years. Patients were

Address reprint requests and correspondence: Dr. Carlo Pappone, Department of Cardiology, San Raffaele University Hospital, Via Olgettina 60, 20132 Milan, Italy. E-mail address: carlo.pappone@hsr.it. (Received July 18, 2008; accepted August 7, 2008.)

provided with a LifeWatch event monitor (LifeWatch Technologies, Rosemont, IL, USA) and were asked to record their rhythm at least 5 days per week for 3 minutes and whenever they had symptoms suggestive of AF. Rhythm transmissions were available for all patients for $84\% \pm 10\%$ of the follow-up days. Baseline evaluation included a past medical history of cardiovascular and endocrine disorders as well as a history of precipitating events. A complete blood count, urinalysis, thyroid function tests, hepatic panel, lipid profile, and serum chemical measurements were obtained at baseline and at each control visit thereafter. Transesophageal echocardiography was performed at baseline to rule out atrial thrombi and annually in patients with comorbidities. After the first paroxysmal episode, no antiarrhythmic drug therapy was administered. Recurrent symptomatic episodes were pharmacologically managed by conventional antiarrhythmic drug therapy (propafenone, flecainide, and/or sotalol as first-line drugs in patients without structural heart disease or amiodarone as a single drug or in combination in patients with structural heart disease or in case of first-line drug failure) according to AF management guidelines.^{1,2} Alternatively, in case of antiarrhythmic drug therapy failure or intolerable side effects, catheter ablation was offered. Long-term efficacy was evaluated after a 3-month blanking period in ablated patients or after a 2 week dose titration period in patients taking antiarrhythmic drug therapy. Electrical cardioversion was performed if necessary or in patients with persistent AF refractory to antiarrhythmic drug therapy. Antithrombotic therapy with warfarin (international normalized ratio [INR] 2.0–3.0) was initially applied after stroke risk assessment according to current AF guidelines recommendations.^{1,2} Patients with comorbidities or those with at least one moderate risk factor for thromboembolism regardless of AF clinical form were prescribed warfarin.^{1,2} Patients older than 60 years with lone AF received aspirin 100 mg/day. Electrical cardioversion was performed for a maximum of three attempts. Patients with recurrent AF were followed monthly in an outpatient setting.

Definitions

Paroxysmal AF was defined as recurrent AF that was self-terminating with episode durations less than 7 days. *Persistent AF* was defined as recurrent AF that was not self-terminating with episode duration greater than 7 days. *Permanent AF* was defined as AF that had been present for at least 6 months without intervening spontaneous episodes of sinus rhythm for which cardioversion was unsuccessful and subsequently not attempted. *Lone AF* was defined as AF occurring in the absence of structural heart disease, including a history of hypertension and left ventricular hypertrophy, as determined by physical examination, ECG, chest radiography, and echocardiography. *Ischemic stroke* was defined as neurologic deficit of sudden onset lasting longer than 24 hours and caused by ischemia.

Endpoint

The primary endpoint of the study was assessment of AF progression and predictors from the first-detected paroxysmal episode to permanent AF over a 5-year follow-up period. The influence of catheter ablation on arrhythmia progression in patients with recurrent paroxysmal AF also was evaluated.

Statistical analysis

Chi-square test with or without exact correction was used to measure the association for categorical variables. Independent-samples t-test or one-way analysis of variance was used for continuous variables with gaussian distribution. Mann-Whitney U-test was used to compare the different time intervals of progression. Kaplan-Meier curves were used to examine the cumulative probability of arrhythmia progression. Cox proportional hazards models with stepwise method (Backward likelihood ratio as the variable selection method) were used for multivariate analyses of progression to permanent AF. Variables such as age, ejection fraction, left atrial enlargement, diabetes mellitus, hypertension, coronary artery disease, and heart failure were included in the model. All tests of significance were two sided. $P \leq .05$ was considered significant. SPSS software for Windows (release 15.0.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Study population

Enrollment began between January 2002 and July 2002, and the study ended in July 2007. Among 402 screened patients, 244 had potentially reversible causes and were excluded from the study. Of the 158 eligible patients, 52 declined to enter the study, and the remaining 106 patients completed the study protocol (Figure 1). Baseline clinical characteristics of the 106 patients and of those who progressed are given in Table 1. Heart failure was present in 12.2% of subjects with preserved left ventricular ejection fraction ($>50\%$) and hypertensive cardiomyopathy (7 patients) or low ejection fraction ($37.8\% \pm 6.6\%$) and idiopathic dilated cardiomyopathy (6 patients). Valvular heart disease was present in 12 (11.3%) patients: 8 with mitral regurgitation, 3 with moderate aortic stenosis, and 1 with aortic prosthesis. Among enrolled patients, 54 (age 53.3 ± 12.1 years) had lone AF, and 52 (age 62.0 ± 9.1 years) had one or multiple associated diseases (Table 2).

AF progression after the first detected paroxysmal episode

Figure 1 shows arrhythmia progression over 5-year follow-up from the first detected symptomatic paroxysmal episode to recurrent paroxysmal, persistent, and then permanent AF. During follow-up, 56 patients had recurrent paroxysmal episodes treated by conventional antiarrhythmic drug therapy, which was continued in 45 (17 with lone AF). Class IC (flecainide or propafenone) and/or III antiarrhythmic drugs, including amiodarone or sotalol (mostly in com-

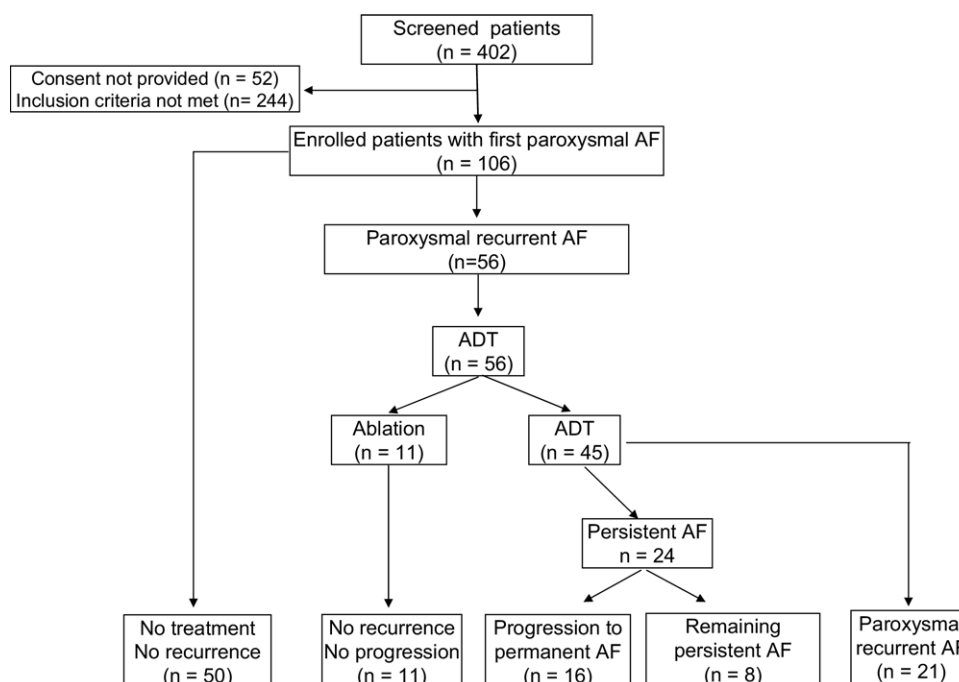


Figure 1 Flow diagram showing screening, eligibility, and enrollment of study patients. Progression from a first episode of paroxysmal atrial fibrillation (AF) to permanent arrhythmia during the 5-year follow-up is shown.

bination), were administered. Catheter ablation was offered to 11 patients (4 with lone AF) because of drug-refractory paroxysmal AF or intolerance to long-term antiarrhythmic drug therapy. No differences were found with regard to patient gender, comorbidities, left ventricular ejection fraction, left atrial diameter, and number of recurrences per month between the two groups. Patients who underwent catheter ablation did not have further AF recurrences and did not progress over a median follow-up of 40.2 months (minimum–maximum, 22–60). Oral anticoagulation therapy with warfarin was stopped 6 months after the procedure. Conversely, among the 45 patients on long-term antiarrhythmic drug therapy, 21 continued to experience recurrent paroxysmal episodes, and 24 progressed to recurrent persistent AF. Among the 24 patients with persistent episodes of AF, 8 continued to experience recurrent persistent AF, and 16 definitively progressed to permanent AF (Figure 1).

Electrical cardioversion was performed in 8 (14%) patients with paroxysmal episodes and in 23 (96%) patients with persistent AF. Catheter ablation was offered to 8 patients at the time of recurrent persistent AF, but all refused the procedure (6 progressed to permanent AF, and the remaining 2 patients continued to experience recurrent persistent episodes of AF). In patients who progressed to permanent AF, persistent arrhythmia recurred 25 ± 18 days after electrical cardioversion. In the final attempts, sinus rhythm was followed by frequent atrial premature depolarizations with an immediate recurrence of AF. Afterward, AF was considered as permanent, and further electrical cardioversions were not attempted. At the end of 5-year follow-up, 50 patients had no AF recurrences after the first episode, 11 remained in sinus rhythm after catheter ablation, 21 remained in paroxysmal recurrent AF, 8 patients continued to experience recurrent persistent AF (2 of whom had refused

Table 1 Clinical characteristics of patients and gradual progression of atrial fibrillation over time

	Overall (n = 106)	Paroxysmal AF (n = 56)	Persistent AF (n = 24)	Permanent AF (n = 16)
Mean age (years)	57.5 \pm 11.5	63.8 \pm 8.1	65.6 \pm 7.1	68.3 \pm 7.6
Male (%)	68 (64.2)	34 (61)	12 (50)	9 (56)
Heart failure	13 (12.2)	13 (23)	11 (46)	9 (56)
Diabetes mellitus	5 (4.7)	3 (5)	3 (13)	3 (19)
Hypertension	48 (45.3)	32 (57)	20 (83)	14 (88)
Valvular heart disease	12 (11.3)	12 (21)	11 (46)	6 (38)
Respiratory disease	3 (2.8)	3 (5)	2 (8)	2 (13)
Coronary artery disease	10 (9.4)	8 (14)	7 (29)	5 (31)
Left atrial diameter (>40 mm)	14 (13.2)	14 (25)	12 (50)	9 (56)

Data are expressed mean \pm SD or n (percentage).

AF = atrial fibrillation.

Table 2 AF progression in patients with and without lone AF

	Lone AF (n = 54)	No lone AF (n = 52)	P value
Mean age (years)	53.3 ± 12.1	62.0 ± 9.1	<.001
Male	35 (64.8)	33 (63.5)	1.000
Paroxysmal AF	21 (38.9)	35 (67.3)	.003
Persistent AF	2 (3.7)	22 (42.3)	<.001
Permanent AF	1 (1.8)	15 (28.8)	<.001
No recurrence	33 (61.1)	17 (32.7)	.003

Data are expressed as mean ± SD or n (percentage).

AF = atrial fibrillation.

catheter ablation), and 16 definitively progressed to permanent AF (6 of whom had refused catheter ablation). All patients but one who progressed to permanent AF had single or multiple comorbidities, with the most frequent being hypertension with coronary artery disease and hypertension with heart failure.

AF progression in patients with and without comorbidities

Table 2 lists the number of patients progressing to recurrent paroxysmal/persistent and permanent AF according to the presence or absence of comorbidities. Fifty-four patients had lone AF, and 52 had associated comorbidities. Patients with lone AF were younger (mean age 53.3 ± 12.1 years). Progression to recurrent paroxysmal AF was observed less often in patients with lone AF than in those with comorbidities ($P = .003$). In addition, just 2 (3.7%) of 54 patients with lone AF progressed to recurrent persistent AF, and only one of them definitively progressed to permanent AF (Table 2). Of note, no further AF recurrence after the first episode and in the absence of therapy was observed in 33 (61.1%) of 54 patients with lone AF compared with 17 (32.7%) of 52 patients with associated diseases ($P = .003$; Table 2).

Progression times

Recurrent paroxysmal AF developed in a median time of 19 months (minimum–maximum, 1–59) after the first episode. Thereafter, the arrhythmia progressed to recurrent persistent form within 34 months (minimum–maximum, 12–57) and definitively progressed to the permanent form after 44.5 months (minimum–maximum, 18–60). The median interval between onset of recurrent paroxysmal and persistent AF was 26.5 months (range 1–38 months), which was longer than the median interval from onset of persistent to permanent AF (10 months, range 1–24; $P < .001$). Therefore, arrhythmia progression accelerated once AF became persistent.

Silent AF recurrences and progression

Intensive transtelephonic recordings (1,113 ± 132 per patient) revealed that among patients with recurrent paroxysmal or persistent AF, 11 (19.6%) of 56 patients and 6 (25%) of 24 patients, respectively, had asymptomatic arrhythmia recurrences. AF transition remained asymptomatic in 13

patients (9 at the time of recurrent paroxysmal AF, 4 at the time of persistent AF, and in 3 of the patients when AF became permanent).

Morbidity and mortality

During 5-year follow-up, new-onset heart failure, hypertension, newly diagnosed coronary artery disease, or worsening coronary artery disease did not develop in any patient. Baseline clinical characteristics of patients with and without comorbidities remained stable as documented by serial clinical visits, ECG, and echocardiography. However, during transition to persistent/permanent AF, cardiovascular and cerebrovascular events developed in 6 and 3 patients, respectively.

Cardiovascular events

During mean follow-up of 29.8 ± 9.3 months (range 16–39 months), 6 patients (mean age 69.2 ± 8.4 years, range 58–83 years; four females) with heart failure and preserved left ventricular function had worsening of heart failure during recurrent episodes of persistent arrhythmia at rapid ventricular rate (115 ± 15 bpm). Catheter ablation was offered as an alternative to antiarrhythmic drug therapy at the time of recurrent persistent AF, but all six patients refused the procedure. Once these patients progressed to permanent AF, three died suddenly (age 65, 68, and 74 years; two females), all with hypertensive cardiomyopathy and on amiodarone therapy. In these three patients, the last attempt at cardioversion for recurrent persistent AF was performed by a 200-J biphasic external shock, which restored sinus rhythm but was followed by frequent atrial premature depolarizations and immediate recurrence of AF.

Cerebrovascular events

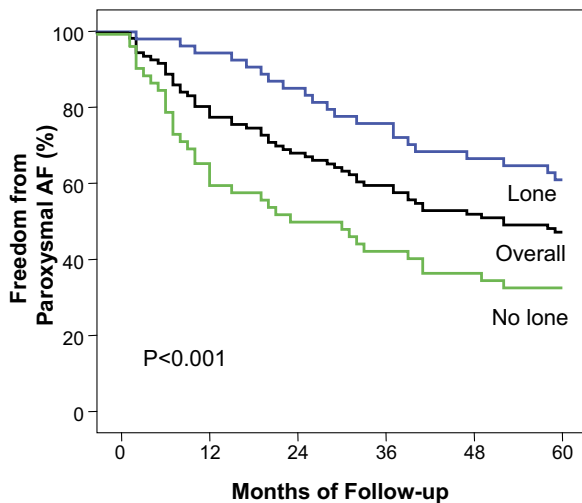
Ischemic stroke occurred in three patients with more than two risk factors for stroke (all of these patients had CHADS [congestive heart failure, hypertension, age >75 years, diabetes, stroke] score of 3: age >75 years, hypertension, and diabetes). Ischemic events developed while patients were taking subtherapeutic doses of warfarin (INR 1.72, 1.91, and 1.54) and during persistent AF.

Side effects of antiarrhythmic drug therapy

Intolerable side effects occurred in 22 patients during treatment with flecainide in 5 patients, propafenone in 5, sotalolol in 7, and amiodarone in 5.

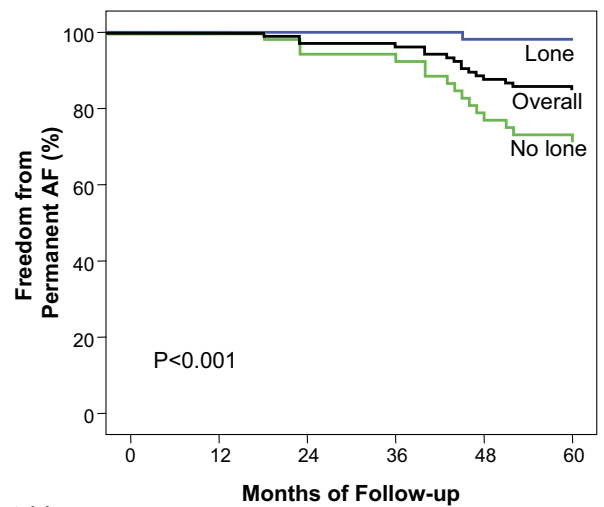
Risk factors of progression

Kaplan-Meier curves showed that patients with comorbidities were more likely to progress to recurrent paroxysmal/persistent and permanent AF than were those with lone AF (Figures 2–4). Multivariate analysis demonstrated that age ($P < .001$), diabetes mellitus ($P < .001$), and heart failure ($P < .001$) predicted progression to permanent AF (Table 3). Patients with drug-intolerant or drug-refractory paroxysmal recurrent AF who underwent catheter ablation were at lower risk for progression to permanent AF than were those on antiarrhythmic drug therapy ($P = .029$ by log rank test; Figure 5).



No. at risk	Months of Follow-up					
	0	12	24	36	48	60
Lone	54	51	46	41	37	33
Overall	106	82	72	63	56	50
No lone	52	31	26	22	19	17

Figure 2 Cumulative probability of progression from a first paroxysmal episode to recurrent paroxysmal atrial fibrillation (AF) over a 5-year follow-up period after enrollment. Kaplan-Meier curves are stratified according to the presence or absence of lone AF. $P < .001$ calculated by log rank test.



No. at risk	Months of Follow-up					
	0	12	24	36	48	60
Lone	54	54	54	54	53	53
Overall	106	106	103	102	93	90
No lone	52	52	49	48	40	37

Figure 4 Cumulative probability of progression from a first paroxysmal episode to permanent atrial fibrillation (AF) in patients with or without lone AF. $P < .001$ calculated by log rank test.

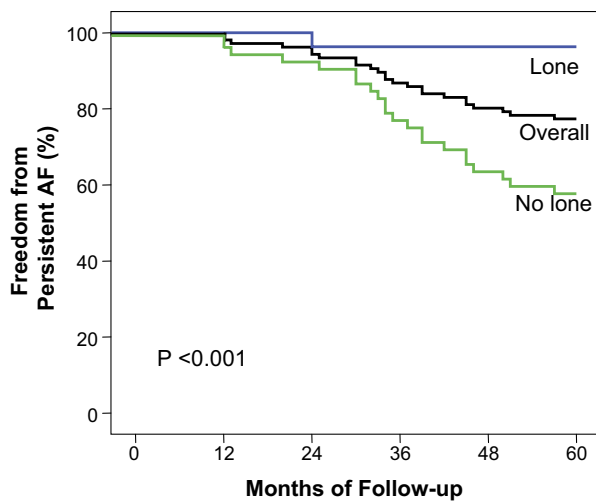
Discussion

According to current guidelines for classification and management, AF is characterized by different clinical forms depending on its clinical presentation and course, in all probability reflecting different stages with multiple mechanisms.^{1,2} Frequently, a first episode is due to a reversible cause, and in most cases after treatment of the underlying disease AF will not recur and no therapy is required.^{1,2} However, in other patients, the first episode may not be due

to a reversible cause, and recurrent transient or persistent episodes may develop over time. To our knowledge, this is the first prospective long-term study providing additional data on AF progression and predictors of progression from the first detected symptomatic paroxysmal episode not due to potentially reversible causes in patients with and without comorbidities. The potential influence of catheter ablation on AF recurrences and arrhythmia progression also was evaluated.

AF progression and progression times: Evidence supporting early rhythm control

Among 106 patients with an initially first detected paroxysmal episode of AF not due to transient causes, 50 (47%) patients did not have any AF recurrences and remained in stable sinus rhythm over 5 years; 66% of these patients had lone AF. These findings suggest that patients without comorbidities after the first paroxysmal episode usually have a good outcome and do not require any treatment. However, in patients with comorbidities, AF frequently progresses to recurrent AF, and in many of these patients final arrhythmia progression develops despite antiarrhythmic drug therapy or



No. at risk	Months of Follow-up					
	0	12	24	36	48	60
Lone	54	54	52	52	52	52
Overall	106	104	100	92	88	82
No lone	52	50	48	40	36	30

Figure 3 Cumulative survival of progression from a first paroxysmal episode to persistent atrial fibrillation (AF) in patients with or without lone AF. $P < .001$ calculated by log rank test.

Table 3 Cox regression analysis of factors associated with progression to permanent AF in 106 patients with first episode of AF

	Regression coefficient	P value	Adjusted hazard ratio	95% Confidence interval
Age	0.179	<.001	1.196	1.103–1.296
Heart failure	2.416	<.001	11.202	3.914–32.059
Diabetes mellitus	2.855	<.001	17.369	3.751–80.432

AF = atrial fibrillation.

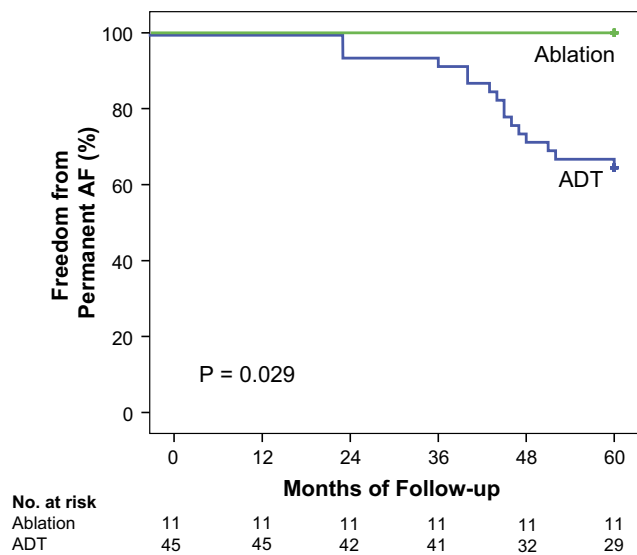


Figure 5 Cumulative probability to progress to permanent atrial fibrillation (AF) among patients with drug-refractory paroxysmal recurrent AF or intolerant to antiarrhythmic drug therapy who underwent catheter ablation and patients on long-term antiarrhythmic drug therapy.

electrical cardioversion. Of interest, patients who underwent catheter ablation did not have further AF recurrences and did not progress over years. These findings confirm that comorbidities contribute to AF development, but they also suggest that control of recurrent AF by catheter ablation may be of benefit in contrasting final arrhythmia progression even in patients with comorbidities. In the present study, long-term maintenance of sinus rhythm by antiarrhythmic drug therapy was unachievable in many patients with safety profiles that were less than ideal considering patients with frequent concomitant comorbidities. The long-term efficacy of catheter ablation, as observed in the present study, suggests an early rhythm control strategy at the time of symptomatic recurrent paroxysmal AF expanding upon previous randomized studies, which reported a short-term superiority of catheter ablation compared with antiarrhythmic drug therapy.⁸⁻¹¹ However, whether long-term efficacy of catheter ablation will also result in mortality benefits in patients with AF requires larger randomized multicenter studies. Elimination of recurrent AF by catheter ablation may lead to improved survival by reducing the likelihood of new-onset heart failure and worsening of heart failure in patients with preexisting heart failure due to AF-induced tachy-cardiomyopathy, both of which contribute to an increased mortality rate, as was seen in three patients in this series who refused catheter ablation. The present study also shows that progression time was longer from the first episode to recurrent AF (either paroxysmal or persistent) than the time from the persistent to the permanent form, which indicates that final arrhythmia progression accelerates once AF became persistent. These data demonstrate that AF slowly progresses to persistent forms, supporting an early rhythm control strategy before recurrent episodes of AF become persistent.

Predictors of AF progression

Kaplan-Meier curves showed that risk of progression to permanent AF is higher among patients with comorbidities, which indicates a significant role of associated diseases in modulating arrhythmia progression. Multivariate analysis demonstrated that age, heart failure, and diabetes mellitus were independent predictors of arrhythmia progression, and diabetes was the strongest risk factor for progression. These findings emphasize the role of heart failure and metabolic diseases, not only in AF development^{12,13} but most importantly in modulating AF progression, which is associated with increased risk for morbidity and mortality.

Silent progression of first AF

It is well known that episodes of AF, regardless of its clinical form, can be undetected and asymptomatic in many patients.¹⁴ However, silent transition from one form to another and its incidence have never been reported. In the present study, AF progression remained silent in 13 patients as documented by intensive daily ECG monitoring, and diabetes and hypertension were the most common associated diseases. These findings are important in terms of pathophysiology and therapy, suggesting that oral anticoagulation therapy in patients at risk should be continued regardless of the presence of symptoms.

Comparison with previous studies

Most previous studies on AF progression were retrospective, referred to previous guidelines recommendations, and did not include catheter ablation,³⁻⁷ which can influence progression rates and complications. A short-term survey study based on registries analysis performed in a series of patients with first detected, paroxysmal, persistent and permanent AF, all followed for 1 year, presented no data on long-term efficacy of catheter ablation compared with antiarrhythmic drug therapy.⁷

Adverse events during progression

During follow-up, baseline clinical characteristics of almost all patients remained stable. New-onset heart failure, hypertension, or newly diagnosed coronary artery disease or worsening of coronary artery disease did not occur in any patient. Adverse events developed during progression to persistent/permanent AF in nine patients. Heart failure worsening occurred in six patients during persistent episodes of AF despite preserved cardiac function. After AF became permanent, three of these patients died suddenly, suggesting that in patients with heart failure, progression to permanent AF may be associated with high mortality risk. Cerebrovascular events occurred in three patients with at least two risk factors for stroke during silent persistent episodes of AF in whom warfarin doses were subtherapeutic (INR <2), emphasizing the need to better optimize anticoagulation therapy.

Study limitations

Patients with potentially reversible causes were excluded from the study. Therefore, the results of this study cannot be

transferred to other patient populations with first detected paroxysmal AF. According to current guidelines recommendations, catheter ablation was performed only in patients who had drug-refractory AF or who were intolerant to antiarrhythmic drug therapy. However, the purpose of this study was not to compare catheter ablation with long-term antiarrhythmic drug therapy, which requires a randomized long-term controlled study, but to assess arrhythmia progression according to current guidelines for management.

Conclusion

This prospective study provides new insights into AF progression and shows that over 5-year follow-up, patients with lone AF are less likely to progress from the first detected episode to permanent AF. Age, diabetes mellitus, and heart failure predict final progression, which indicates a significant role of underlying heart disease in modulating such progression. Catheter ablation may be of benefit in preventing AF recurrences and delaying final AF progression, but larger randomized studies are required to confirm this preliminary experience.

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