Stepwise ablation approach versus pulmonary vein isolation in patients with paroxysmal atrial fibrillation: Randomized controlled trial

Massimiliano Faustino, MD,*†1 Carmine Pizzi, MD,‡1 Tullio Agricola, MD,†
Borejda Xhyheri, MD,‡ Grazia Maria Costa, MD,‡ Maria Elena Flacco, MD,§‖
Lorenzo Capasso, MD,§¶ Giancarlo Cicolini, MD,** Enrico Di Girolamo, MD,††
Luigi Leonzio, MD,†† Lamberto Manzoli, MD§¶‡‡‖

From the *Cardiology Department, Private Hospital "L. Pierangeli," Pescara, Italy, †Electrophysiology
Operating Unit, Cardiovascular Department, "Spirito Santo" Hospital, ASL Pescara, Pescara, Italy,
‡Department of Specialised, Experimental and Diagnostic Medicine, University of Bologna, Bologna, Italy,
§Department of Medicine and Aging Sciences, University of Chieti, Chieti, Italy, ¶EMISAC, CeSi Biotech,
Chieti, Italy, **Nursing Department, ASL Lanciano-Vasto-Chieti, Chieti, Italy, ††Cardiology Department, ASL
Lanciano-Vasto-Chieti, Chieti, Italy, ‡‡Regional Healthcare Agency of Abruzzo, Pescara, Italy, and ‖Local
Health Unit of Pescara, Pescara, Italy.

BACKGROUND Pulmonary vein isolation (PVI) is a central procedure for the treatment of paroxysmal atrial fibrillation (PAF). However, in patients with PAF and structural atrial disease, PVI may fail and cause progressive atrial remodeling, often leading to persistent/permanent atrial fibrillation.

OBJECTIVE We performed a prospective, single-blind, 2-center randomized controlled trial to compare the efficacy of PVI alone with that of PVI plus stepwise ablation in achieving sinus rhythm and nonatrial arrhythmia inducibility in patients with PAF refractory to antiarrhythmic therapy.

METHODS Patients were randomized to perform a first catheter ablation procedure either through PVI alone or through PVI plus substrate modification in stepwise ablation. Data were recorded at 3, 6, and 12 months after both ablation procedures. Patients who experienced atrial fibrillation/atrial tachycardia (AF/AT) recurrence were encouraged to undergo repeat ablation using the technique of the first ablation procedure.

RESULTS A total of 150 patients were enrolled (mean age 62.8 ± 8.7 years; 92 (61.3%) men; 104 (69.3%) hypertensive; AF mean duration 10.7 months), with 75 patients in each group. After 12 months of the first procedure, patients who were converted to sinus

rhythm using stepwise ablation showed a significantly lower rate of AF/AT recurrence (26.7%) than did those who were treated using PVI alone (46.7%; P < .001). Similar results were observed in the 52 patients who underwent a second catheter ablation procedure. After adjusting for several potential confounders, the hazard ratio of 12-month AF/AT recurrence after the first ablation procedure was 0.53 (95% confidence interval 0.30–0.91) for those treated using stepwise ablation.

CONCLUSION In addition to PVI, stepwise ablation achieving sinus rhythm and nonatrial arrhythmia inducibility has relevantly improved the clinical outcome of the PAF control strategy.

KEYWORDS Paroxysmal atrial fibrillation; Catheter ablation; Pulmonary vein isolation; Stepwise ablation; Randomized controlled trial

ABBREVIATIONS AF = atrial fibrillation; **AT** = atrial tachycardia; **CFAE** = complex fractionated atrial electrogram; **CL** = cycle length; **ECG** = electrocardiogram; **INR** = international normalized ratio; **PAF** = paroxysmal atrial fibrillation; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **SR** = sinus rhythm

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Introduction

Atrial fibrillation (AF) is the most common abnormal heart rhythm, affecting approximately 4% of the population 60 years and older.[1] A common form of AF is paroxysmal atrial fibrillation (PAF), which occurs when an AF episode terminates on its own in less than 7 days.[1] In patients with PAF, the arrhythmogenic activity usually originates in the muscle sleeves of the pulmonary veins (PVs), which in turn may trigger and perpetuate the arrythmias,[1,2] often leading to persistent or permanent AF.[1,2]

To control PAF in patients with no structural heart disease and maintain sinus rhythm (SR) over time, the current

[1]The first 2 authors contributed equally to this work.

cornerstone strategy is pulmonary vein isolation (PVI).[2,3] However, in patients with PAF and structural atrial disease, PVI may be unsuccessful and even explain the recurrences and the development of "new" arrhythmias,[4,5] turning into further atrial remodeling. Hence, especially in the setting of patients refractory to prophylactic treatment with antiarrhythmic drugs, alternative approaches have been suggested, including complex fractionated atrial electrogram (CFAE) ablation[6–8] or linear ablation,[9] which can be used in addition to PVI or alone. To date, however, the relative benefit and success of the stepwise ablation in the setting of PAF has not been fully evaluated.

A prospective, single-blind, 2-center randomized controlled trial was performed to compare the efficacy of PVI alone with that of stepwise ablation in achieving SR and nonatrial arrhythmia inducibility in patients with PAF refractory to antiarrhythmic therapy.

Methods
Study population, design, and outcomes
Between January 2007 and June 2013, at the electrophysiology units of Clinica Pierangeli and "Spirito Santo" Hospital, Pescara, Italy, we asked participation of all patients with PAF refractory to at least 1 antiarrhythmic drug, who were eligible for a first-time catheter ablation procedure (Registration number: ACTRN12614001231639). PAF was defined according to the criteria of the Task Force for the Management of Atrial Fibrillation of European Society of Cardiology/European Association for Cardio-Thoracic Surgery.[1] The exclusion criteria were persistent or permanent AF, age less than 18 years, history of heart surgery, including Maze surgery or AF transcatheter ablation, myocardial infarction, hyperthyroidism, severe kidney disease (glomerular filtration rate < 30 mL/(min $\cdot$ 1.73 m^2)), liver failure, neoplasm, drug dependency, and mental disorders. All procedures were performed by 2 investigators with similar experience (M.F. and T.A.). The study was approved by the local ethics committee, and all patients gave written informed consent.

Patients were randomly assigned to one of the following catheter ablation procedures: PVI alone or stepwise ablation. Randomization was done by the statistical unit using a computer-generated random table. After the first catheter ablation procedure, all patients were followed and data were recorded at 3, 6, and 12 months.

At baseline, as part of their clinical pathway, all patients underwent a clinical examination, laboratory examinations, and 12-lead electrocardiograms (ECGs). Transthoracic echocardiography and transesophageal echocardiography were performed in all patients before catheter ablation in order to exclude left atrial thrombus. Patients with a high risk of thromboembolism (CHA$_2$DS$_2$-VASc score ≥ 2; CHA$_2$DS$_2$-VASc = congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65–74 y, sex category) were treated with oral anticoagulant therapy (warfarin) for at least 4 weeks before ablation, with a target international normalized ratio (INR) of 2–3. Oral anticoagulant treatment was discontinued 3 days before ablation, and low-molecular-weight heparin was administered up to 12 hours before. All antiarrhythmic drugs were discontinued at least 5 half-lives before ablation, whereas amiodarone was discontinued 1 month or more before ablation.

After the first ablation procedure, all patients were examined in order to assess arrhythmia-related symptoms, adverse events, treatment adherence, and any additional therapy since the previous follow-up visit, and a 12-lead ECG was performed. Forty-eight-hour Holter monitoring was also performed every month, and in addition to clinical examinations, a structured questionnaire was administered to record arrhythmia recurrence and any other symptoms.

The primary end point of the study was the recurrence rate of AF and/or atrial tachycardia (AT) lasting more than 30 seconds after the first ablation procedure. AF was defined as a beat-to-beat variability in cycle length (CL) and a morphology with irregular fibrillatory waves on the surface ECG. AT was defined as organized atrial rhythm with a stable CL, a consistent endocardial activation sequence in both atria, and a monomorphic P wave on the surface ECG. When a patient had both AF and AT during follow-up, the recurrence mode was considered to be AF. Episodes of AF/AT occurring during the 3-month period after ablation procedures were not considered as recurrence. After a blanking period of 3 months, patients who experienced AF/AT recurrence were encouraged to repeat ablation. In order to keep patients on the same follow-up program, it was recommended that the redo ablation procedure be performed after the blanking period (3 months) and preferably at less than 6 months from the first ablation procedure. All patients who underwent the second ablation procedure continued with the follow-up and data were recorded at 3, 6, and 12 months after ablation as described above for the first procedure.

Secondary end points included incidence of periprocedural complications and procedural characteristics such as mean procedural time, fluoroscopy time, and radiofrequency time.

Electrophysiological procedures
All procedures were performed under conscious sedation with remifentanil (0.4–0.8 mg/h) and midazolam (0.02 mg/kg). Noninvasive blood pressure and oxygen saturation were monitored continuously. During the procedure, 4 catheters were introduced via the right femoral vein using lidocaine as a local anesthesia. Our catheter placement technique has previously been reported.[10] Briefly, a decapolar catheter (Inquiry, St Jude Medical Inc, St. Paul, MN) was positioned inside the coronary sinus and a tetrapolar catheter (Supreme CRD-2, St Jude Medical Inc) on the His bundle. Left atrium access was obtained by a single interatrial septal puncture with a BRK needle (St Jude Medical Inc). Subsequently, a circumferential decapolar catheter (AFocusII 10 poles with 20 mm diameter, St Jude Medical Inc) for PV mapping and the ablation catheter were positioned in the left atrium.

Ablation was performed with an open-irrigated ablation catheter (Therapy Cool Path Duo, (St Jude Medical Inc).[10] Three-dimensional electroanatomic mapping was performed using EnSite NavX software (version 8.0, St Jude Medical Inc).[11]

Surface ECGs and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (GE Prucka electrophysiological recorder, GE Healthcare, Chalfont St Giles, UK). The filter settings were set at 30–500 Hz; online callipers and a sweep speed of 100 mm/s were used.

Catheter ablation procedures

All approaches were performed under fluoroscopic and 3-dimensional mapping guidance. In the control group (PVI alone), if patients were in AF at the time of the procedure, they underwent external electrical cardioversion before ablation. The end point of the procedure was the isolation of all 4 PV antra. Radiofrequency ablation was performed after mapping the areas of interest distal to the antrum. PVI was confirmed in all patients by an entrance block.

In the experimental group (stepwise ablation), AF was induced by rapid atrial pacing (CL 200–300 ms) from the proximal dipoles of the coronary sinus catheter. After circumferential PVI ablation met the end point of complete isolation of all 4 PVs, the procedure was continued through electrogram-guided ablation for CFAEs if AF was still ongoing or inducible and CFAE regions were identified through visual inspection. CFAEs were defined as follows: (1) atrial electrograms that have fractionated electrograms composed of 2 or more deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period and (2) atrial electrograms with a very short CL (≤ 120 ms) averaged over a 10-second recording period. If the patient was not in AF at the end of PVI, AF induction was performed by rapid atrial pacing. Isoproterenol was administered for maintaining AF in patients with short-lasting self-terminating episodes. When AF was inducible (AF persisting ≥ 1 minute), CFAE regions were recorded and ablated.[5,6] After CFAE ablation, we revisited the areas that were initially ablated to ensure that there is no residual electrical activity. The aim of the electrogram-guided ablation was the restoration of SR. Once left atrial CFAE ablation was completed and if the right appendage CL was shorter than the left appendage CL, radiofrequency application was continued in the right atrium especially in the following sites: coronary sinus, cavotricuspid isthmus, superior vena cava, crista terminalis, and right atrial septum. The CL of AF was monitored in both the right and the left atrial appendage to help determine the optimal site of ablation. The end points of CFAE ablation were the elimination of all CFAE sites in the left and right atria and termination of AF, if AF converted into stable AT (AT lasting 1 minute) catheter ablation of this tachycardia were performed until restoration of SR. When induced, AT was due to either focal or macroreentrant mechanism.

The macroreentrant mechanism was interrupted through linear ablation including "roof line," "mitral isthmus" line, and cavotricuspid isthmus line. Linear ablation should become a part of AF ablation strategies only in the presence of macroreentrant circuits and not as a routine strategy. The end point of linear ablation was AT termination after radiofrequency energy applications and bidirectional block. After SR restoration, the induction of AF was again attempted; if the arrhythmia was not inducible, the procedure was stopped, and if AF was still inducible, ablation continued until noninducibility was achieved. AF was considered inducible if it lasted more than 1 minute. The end points at the end of stepwise ablation were SR restoration and noninducibility of AF postablation. The time of the procedure never exceeded 4 hours; if AF did not terminate after PVI, CFAE, and linear ablation, SR was restored by electrical cardioversion.

The parameters of the ablation catheter (Therapy Cool Path Duo were usually set at a maximum power of 35 W (20–25 W for ablation in the coronary sinus); maximum temperature was set at 45°C, and the irrigation flow ranged from 10 to 20 mL/min (saline 0.9% instilled with a TeruFuSIoN infusion pump, Terumo Europe NV, Leuven, Belgium). Radiofrequency was delivered for 25–60 seconds at each point.

Patients were discharged with oral anticoagulation therapy (warfarin) with a target INR of 2–3, which was continued for 3 consecutive months. The decision to discontinue oral anticoagulation therapy was based on the presence of SR and the absence of other risk factors for thromboembolism. The use of antiarrhythmic drugs was restarted after AF ablation. Class 1C drugs were recommended as first-line agents for most patients in the absence of structural heart disease. Amiodarone was prescribed in the presence of left ventricle dysfunction. In all patients, antiarrhythmic therapy was discontinued 3 months after the procedure.

Repeated electrophysiological procedures were performed for recurrent AF and/or recurrent AT. The strategy used for the second ablation procedure was comparable to the randomized strategy used in the first ablation procedure.

Sample size estimation

Assuming a 2-tailed α error of .05, a rate of withdrawals or losses to follow-up of 5%, and a hazard ratio of 0.50 of AF/AT recurrence 12 months after the first catheter ablation procedure for patients receiving stepwise ablation as compared with those receiving PVI alone,[12] 50 patients per group were required to achieve 80% statistical power. We planned to enroll 75 patients per group.

Data analysis

The differences in the AF/AT recurrence rate according to the type of ablation and other recorded variables were initially examined using the χ^2 test for categorical variables and the t test for continuous variables. Cox proportional

hazards analysis was then used to compute the adjusted relative hazards of AT and/or AF recurrence by each variable, after both the first and second ablation procedures. The dependent variable was the recurrence of either AF or AT in both models. We recorded the following variables, all of which were a priori considered for inclusion in the multivariate analysis: age, sex, body mass index, current cigarette smoking, hypertension, diabetes, dyslipidemia, ischemic heart disease, left ventricular hypertrophy, valvular heart disease, idiopathic dilated cardiomyopathy, AF duration, number of AF episodes per month, left atrial size and volume, left ventricular ejection fraction, antiarrhythmic drugs, amiodarone, β-blocker and calcium-channel blocker use, and procedural, radiofrequency, and fluoroscopy times, CFAE, and ablation complications. Covariates were selected for inclusion in the final models using a stepwise forward process with the following inclusion criteria: $P < .15$ in univariate analysis and $\geq 20\%$ change in the hazard ratio of significant predictors. Age and procedure complications were forced to entry. A minimum events-to-variable ratio of 10 was maintained in multivariate modeling to avoid overfitting, and the Schoenfeld test was conducted to check the validity of the proportional hazards assumption. Kaplan-Meier survival analysis was used to display the outcome probability over time in the 2 groups. The validity of constant incidence ratios over the follow-up period was checked using Nelson-Aalen cumulative hazard estimates. There were no missing values. A P value of $<.05$ was considered significant for all analyses that were performed using Stata, version 11.1 (Stata Corp, College Station, TX).

Results
Characteristics of the patients
Of the 162 eligible patients contacted, 150 were enrolled (Figure 1). The baseline characteristics were evenly distributed between the 2 groups; the mean age was 62.8 ± 8.7 years, 61.3% were men, 69.3% were hypertensive, and the mean time of AF diagnosis was 10.7 months (minimum 3 months and maximum 24 months). The mean left atrial volume was 35.9 ± 5.6 mL/m^2 (Table 1).

The overall recurrence of AF/AT during the 1-year follow-up period was 36.7% (55 patients): 47% (35 patients) in the PVI group and 27% (20 patients) in the stepwise ablation group, respectively.

A second catheter ablation procedure was performed in 52 of 55 patients with AF/AT recurrence; PVI alone was performed in 33 of 35 patients, and stepwise ablation was performed in 19 of 20 patients.

Procedural data
The addition of CFAE and linear ablation significantly prolonged procedural time: in the first procedure, 105 ± 13 minutes were required for PVI alone and 148 ± 27 minutes for stepwise ablation ($P < .001$). Both fluoroscopy time and radiofrequency time were significantly longer in the stepwise ablation group ($P < .001$). Similar results were observed during the second ablation procedure (Table 2).

In the stepwise ablation group, during the first ablation procedure, at the end of PVI, AF was ongoing in 51 patients (68%) and inducible after atrial pacing in 13 patients (18.7%).

Table 1 Characteristics of the sample by type of paroxysmal AF ablation and overall

Variable	PVI (n = 75)	Stepwise ablation (n = 75)	Overall (N = 150)	P^*
Age (y)	63.4 ± 8.4	62.3 ± 9.1	62.8 ± 8.7	.4
Sex: male	44 (58.7)	48 (64.0)	92 (61.3)	.5
Body mass index (kg/m^2)	26.0 ± 2.9	25.9 ± 3.9	25.6 ± 3.4	.2
Current cigarette smoking	20 (26.7)	30 (40.0)	50 (33.3)	.08
Hypertension	56 (74.7)	48 (64.0)	104 (69.3)	.2
Diabetes	17 (22.7)	18 (24.0)	35 (23.3)	.9
Dyslipidemia	18 (24.0)	24 (32.0)	42 (28.0)	.3
Ischemic heart disease	9 (12.0)	5 (6.7)	14 (9.3)	.3
Left ventricular hypertrophy	18 (24.0)	27 (36.0)	45 (30.0)	.11
Valvular heart disease	2 (2.7)	1 (1.3)	3 (2.0)	.6
Idiopathic dilated cardiomyopathy	5 (6.7)	5 (6.7)	10 (6.7)	.9
AF duration (mo)	10.9 ± 3.2	10.5 ± 3.7	10.7 ± 3.5	.5
No. of AF episodes per month	2.2 ± 1.7	2.7 ± 1.5	2.4 ± 1.6	.09
Left atrial size (mm)	43.8 ± 2.9	44.0 ± 3.3	43.9 ± 3.1	.8
Left atrial volume (mL/m^2)	35.7 ± 5.0	36.0 ± 6.2	35.9 ± 5.6	.8
Left ventricular ejection fraction	59.3 ± 6.9	58.5 ± 7.1	58.9 ± 7.3	.5
Class I antiarrhythmic drugs	56 (74.7)	56 (74.7)	112 (74.7)	.9
Amiodarone	18 (24.0)	16 (21.3)	34 (22.7)	.7
β-Blockers	11 (14.7)	8 (10.7)	19 (12.7)	.5
Calcium channel blockers	27 (36.0)	37 (49.3)	64 (42.7)	.10
CHA$_2$DS$_2$-VASc score	2.1 ± 1.1	2.0 ± 1.3	2.1 ± 1.2	.5

Values are presented as mean $\pm$ SD or as n (%).

AF = atrial fibrillation; CHA$_2$DS$_2$-VASc score = congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65–74 y, sex category score; PVI = pulmonary vein isolation.

$^*\chi^2$ test for categorical variables; t test for continuous variables.
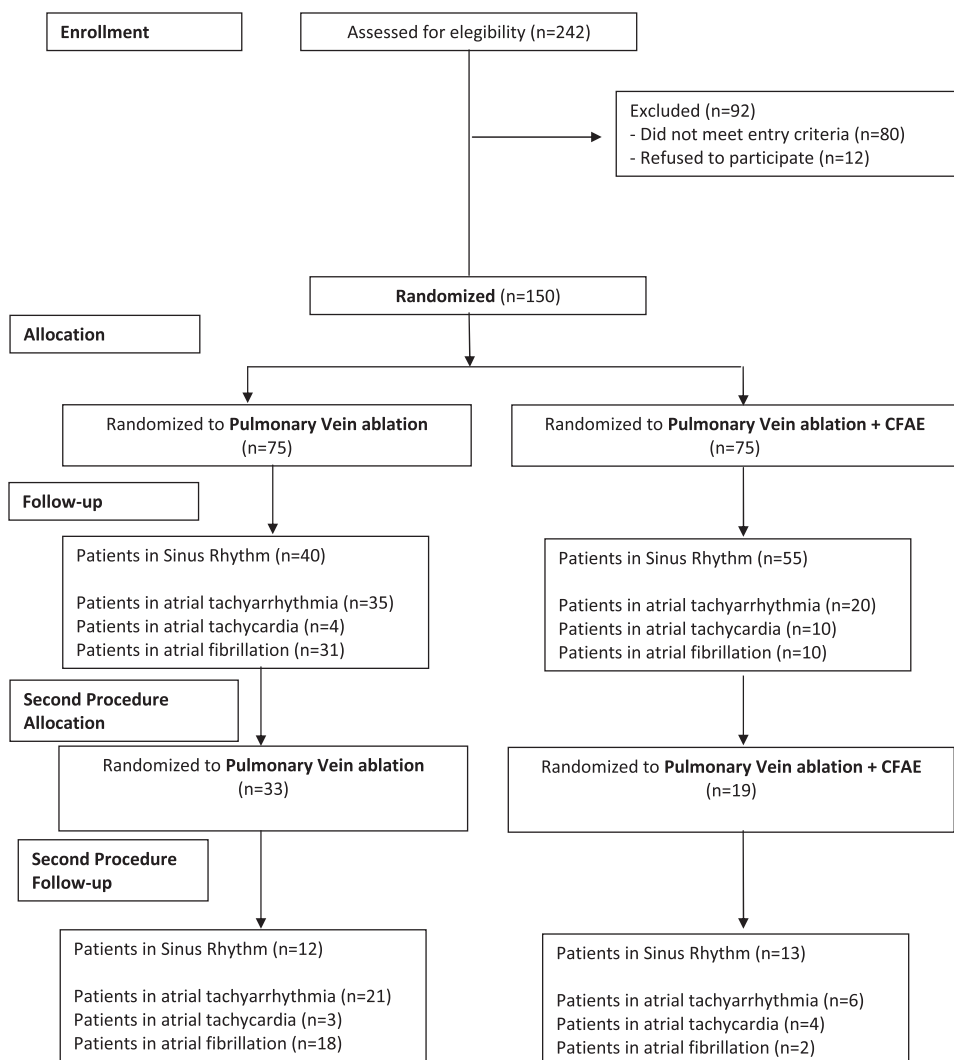
Figure 1   Study design flowchart (CONSORT flow diagram). CFAE = complex fractionated atrial electrogram.

CFAEs were detectable and ablated in 64 patients (85.3%). CFAE regions were mostly located in the roof, anterior wall, and mitral annulus (Table 3). After CFAE ablation, AT was inducible in 45 patients, with a focal mechanism in 33 patients and a macroreentrant mechanism in 12 patients. Of the 12 macroreentrant ATs, 9 circuits were identified in the perimitral isthmus, 3 circuits in the Cavotricuspid isthmus (CVT) isthmus, and 0 in the left atrial roof. All macroreentrant ATs were terminated successfully after linear radiofrequency ablation. In the remaining 33 ATs, a focal mechanism was demonstrated and subsequently ablated. The mean mapped CL of the focal AT was 285 ± 39 ms. Of those 33 ATs, 14 originated from the anterior wall, 6 from the posterior wall, 7 from the floor, 4 from the interatrial septum, and 2 from the left atrial appendage. At the end of the stepwise ablation strategy, 75 patients (100%) were in SR using radiofrequency applications without any following arrhythmia inducibility.

In patients undergoing a second ablation procedure (52 of 150), we documented persistence of complete PVI in 23 of 33 patients in the PVI group and 14 of 19 patients in the

stepwise ablation group. All patients with PV reconnections underwent redo PVI.

In the stepwise ablation group, at the end of redo PVI, AF was ongoing in 16 patients and induced in 1 patient. Thus, 17 patients received adjunctive CFAE ablation (Table 3). After CFAE ablation, AT occurred in 9 patients, with a focal mechanism in 4 patients and a macroreentrant mechanism in 5 patients. Two macrocircuits originated from the perimitral isthmus, 2 from the cavotricuspid isthmus, and 1 from the left atrial roof. All ATs were ablated following the aforementioned scheme. After the first and second catheter ablation procedures, no patient required direct current shock.

The overall rate of complications was 10.0% of the 150 patients after the first ablation procedure and 5.8% of the 52 patients after the redo ablation procedure. The most common complications were femoral hematoma (n = 9) and pericarditis (n = 4). Two episodes of cardiac tamponade requiring pericardiocentesis were reported in patients receiving stepwise ablation. No significant differences in the rate of complications were observed across the 2 groups after either the first or the second ablation procedure.

Table 2   Outcomes of the sample by type of paroxysmal AF ablation and overall

Variable	PVI	Stepwise ablation	Overall	P^*
First catheter ablation procedure	n = 75	n = 75	n = 150	
Procedural time (min)	105 ± 13	148 ± 27	–	<.001
Fluoroscopy time (min)	13.9 ± 2.0	29.2 ± 15.8	–	<.001
Radiofrequency time (min)	37.3 ± 8.9	58.9 ± 19.3	–	<.001
Ablation complications	6 (8.0)	9 (12.0)	15 (10.0)	.4
AF/AT recurrence 6 mo after ablation	34 (45.3)	18 (24.0)	52 (24.7)	.006
AF/AT recurrence 12 mo after ablation	35 (46.7)	20 (26.7)	55 (36.7)	<.001
Second catheter ablation procedure	n = 33	n = 19	n = 52	
Procedural time (min)	104 ± 14	145 ± 31	–	<.001
Fluoroscopy time (min)	13.8 ± 3.0	28.3 ± 15.1	–	<.001
Radiofrequency time (min)	36.3 ± 9.8	57.8 ± 17.8	–	<.001
Ablation complications	2 (6.1)	1 (5.3)	3 (5.8)	.9
AF/AT recurrence 6 mo after ablation	17 (51.5)	4 (21.0)	21 (40.4)	.031
AF/AT recurrence 12 mo after ablation	21 (63.6)	6 (31.6)	27 (51.9)	.026

Values are presented as mean ± SD or as n (%).

AF = atrial fibrillation; AT = atrial tachycardia; PVI = pulmonary vein isolation.

AF/AT recurrence after the first and second ablation procedures

During follow-up, the overall recurrence rates were 36.7% (55 of 150) and 51.9% (27 of 52) after the first and the second procedure, respectively (Table 2).

The AF/AT recurrence rate significantly differed by ablation type at all time points and after both procedures. In the first procedure, after the blanking period (3 months of follow-up), 40.0% of the patients who received PVI alone (30 of 75) experienced a recurrence as compared with 20.0% of those who received stepwise ablation (15 of 75) (P < .001). At the end of the target follow-up (12 months), the above rates were 46.7% (35 of 75) and 26.7% (20 of 75), respectively (P < .001). AT occurred more frequently in patients treated with the stepwise ablation; 10 of 20 AT occurred in the stepwise group vs 4 of 35 in the PVI group.

At the end of follow-up after the second ablation procedure, the proportion of reoccurrence of AT/AF was doubled in the PVI group (Table 2).

Multivariate analyses confirmed the results of univariate analyses: patients who received stepwise ablation were significantly more likely to maintain SR during the follow-

Table 3   Breakdown of the anatomical sites of termination of AF or AT by complex fractionated atrial electrograms after the first and the second ablation procedure

Site of AF/AT termination	AF after the first ablation procedure (n = 75)	AF after the second ablation procedure (n = 19)
Anterior wall	16	2
Posterior wall	7	2
Floor	8	2
Roof	14	0
Interatrial septum	5	0
Pulmonary veins	31	5
Coronary sinus	19	2
Mitral isthmus	10	5
Tricuspid isthmus	4	2
Left atrial appendage	3	2

AF = atrial fibrillation; AT = atrial tachycardia.

up period than those who received PVI alone. After the first procedure, the Cox proportional hazards analysis showed an adjusted hazard ratio of AF/AT recurrence of 0.53 (95% confidence interval 0.30–0.91) for the patients in the stepwise ablation group compared with those in the PVI group (Table 3). Similar results were observed after the second ablation procedure. According to Kaplan-Meier survival analysis, after both the first and second ablation procedures, the probability of outcome was higher in patients receiving PVI alone throughout the follow-up period (Figure 2).

The only other independent predictor of AF/AT recurrence after the first ablation procedure was the left ventricular ejection fraction; for each 1% increase in ejection fraction, the adjusted hazard ratio of AF/AT recurrence was 0.96 (95% confidence interval 0.93–0.99) (Table 4).

Discussion

In the setting of PAF, to our knowledge, this study is the first randomized trial to compare PVI alone vs stepwise ablation in patients refractory to at least 1 antiarrhythmic drug. Both types of strategies were safe and showed a high efficacy in maintaining SR, with more than 75% of the patients maintaining SR at the end of follow-up after the second ablation procedure. However, in the stepwise ablation the rate of AF/AT recurrence at any time point decreased significantly. The benefit of substrate modification in addition to PVI seemed substantial after 12 months of follow-up; 90.7% of the patients receiving stepwise ablation maintained SR, compared with 69.3% of patients in the PVI group, even after adjusting for potential confounders or mediators including age, sex, ejection fraction, mean AF duration and mean episodes per week, coronary artery disease, left ventricular hypertrophy, valvular heart disease, and atrial size.

In patients who underwent a second ablation procedure, incomplete isolation of a previous PVI was found in roughly one-third of the population, while in the remaining patients, AF recurred even if complete PVI was demonstrated.
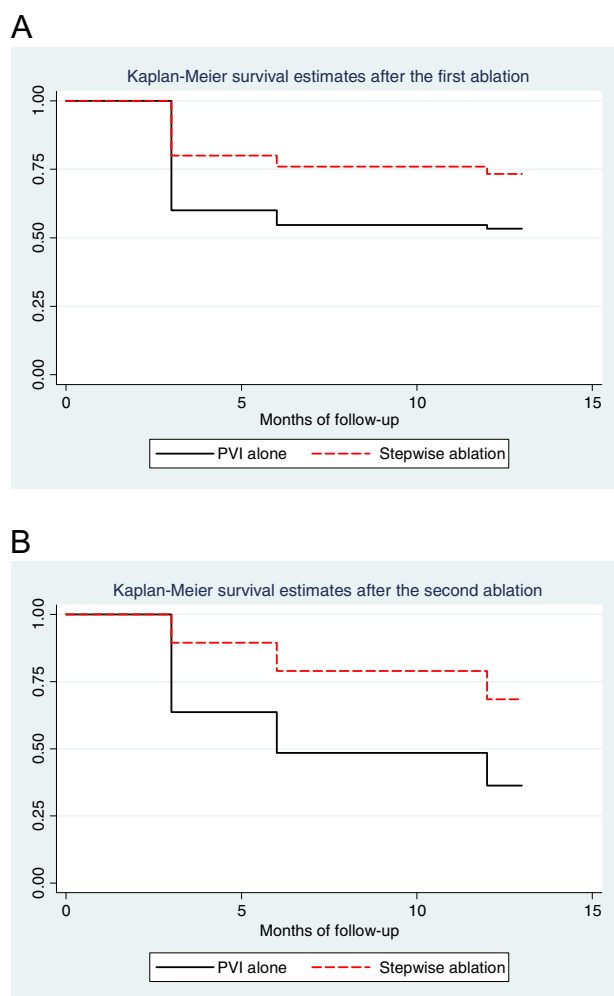
A

Kaplan-Meier survival estimates after the first ablation

— PVI alone   - - - - Stepwise ablation

B

Kaplan-Meier survival estimates after the second ablation

— PVI alone   - - - - Stepwise ablation

Figure 2   A: Kaplan-Meier survival estimates of time to first arrhythmia recurrence after the first ablation procedure. **B:** Kaplan-Meier survival estimates of time to first arrhythmia recurrence after the second ablation procedure. PVI = pulmonary vein isolation.

A potential explanation for the observed findings is that circumferential PVI may eliminate triggers/initiators or a primary driving mechanism of PAF that occurs in the muscle

sleeves of the PVs. Once initiated from a trigger, PAF will not be maintained if the appropriate substrates are not present. The atria of patients with PAF present different patterns during electroanatomic mapping,[5,6] mainly owing to atrial myocardial fibrosis, which is significantly increased in patients with PAF as compared with those in SR.[5,6]

Many studies have demonstrated AF inducibility after PVI,[15–18] with rates ranging from 7% to 56%.[12,13] The noninducibility of sustained AF after PVI was associated with lower recurrence rates of AF and a better clinical outcome[12,13]; thus, AF inducibility has been suggested as a marker for identifying patients who may benefit from additional substrate modification.[14,15] In the literature,[6–8] it has long been demonstrated that PVI is sufficient to treat the vast majority of patients with PAF and no structural heart disease. The nonsuperiority of PVI plus CFAE ablation as compared to PVI alone has been demonstrated in patients with PAF.[7,8] PVI plus CFAE ablation might be superior to PVI alone only in a particular subset of patients, in whom AF was still inducible after PVI during long-term follow-up.[7] It has been reported that additional lesions after PVI increase the success rate of freedom from arrhythmia.[9] A possible explanation for this result is that linear ablation will likely interrupt the macroreentrant circuit of AT.[19,20]

To date, no study has addressed the issue of a stepwise ablation approach in patients with PAF in the subgroup of patients with inducible AF after PVI. Our data suggest that stepwise ablation correlates with better outcomes in terms of AT/AF recurrence.[12] In the stepwise group, ablation was guided using restoration of SR and noninducibility of atrial arrhythmias at the end of the procedure. The inducibility was used to deliver additional ablation through CFAE and/or linear ablation. However, we consider that the optimal PAF ablation procedure consists of performing the minimal set of lesions associated with a successful outcome in a given patient in order to achieve the best efficacy to safety ratio. In our study, this end point was possible to achieve in all patients in the stepwise ablation group, and the repeated procedure was required only in

Table 4   Adjusted hazard ratios of AT or AF recurrence by each variable

Variable	Crude HR (95% CI)	P*	Adjusted HR (95% CI)	P*
After the first ablation procedure (n = 150)				
Stepwise ablation vs PVI	0.54 (0.31–0.94)	.028	0.53 (0.30–0.91)	.023
Age, 1-y increase	1.03 (1.00–1.06)	.072	1.03 (0.99–1.06)	.15
Sex: male	1.60 (0.90–2.87)	.11	1.72 (0.95–3.11)	.071
Left ventricular ejection fraction, 1% increase	0.97 (0.93–1.00)	.047	0.96 (0.93–0.99)	.036
Ablation complications	0.90 (0.36–2.27)	.8	1.10 (0.43–1.82)	.8
After the second ablation procedure (n = 52)				
Stepwise ablation vs PVI	0.40 (0.16–1.00)	.050	0.37 (0.15–0.95)	.038
Age, 1-y increase	0.99 (0.94–1.05)	.8	0.98 (0.93–1.04)	.6
Sex: male	0.75 (0.34–1.64)	.5	–	NS
Left ventricular ejection fraction, 1% increase	1.02 (0.97–1.08)	.4	–	NS
Ablation complications	1.75 (0.41–7.43)	.5	1.99 (0.46–8.61)	.4

To limit overfitting, we reduced the covariates to be included in the model predicting AF/AT recurrence after the second ablation procedure. None of the variables excluded from the table were significant.

AF = atrial fibrillation; AT = atrial tachycardia; CI = confidence interval; HR = hazard ratio; NS = not significant (and not included in the final model); PVI = pulmonary vein isolation.

19 patients in the stepwise ablation group vs 33 patients in the PVI group.

Patients who underwent stepwise ablation required longer time for fluoroscopy. However, the stepwise procedure already had a higher success rate as compared with PVI alone after the first procedure, turning hypothetically in a lower need for repeated procedures. Consequently, the lifetime accumulated exposure to radiation in patients with AF ablation may, in theory, be lower in these patients.[17] Moreover, the extensive radiofrequency ablation procedure and longer procedure time may contribute to impaired atrial function[18] and concur with the 2 cardiac tamponade episodes recorded in the stepwise ablation.

The success rate of PVI alone in this study was lower than that reported in other randomized controlled trials.[2,3,16] This might be explained by the older age, higher prevalence of hypertension and diabetes, a higher left atrial mean size of our sample, and, at least in part, by the use of a strict evaluation of atrial arrhythmia recurrences (48-hour Holter every month). Furthermore, 2 recent studies[19,20] that used PVI alone or together with extensive ablation in patients with persistent AF have reported dissimilar findings, suggesting no additional clinical benefits in patients undergoing a more extensive ablation procedure. There are some potential explanations for such a discrepancy: the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) trial[19] did not compare PVI with a stepwise ablation, and the outcome at the end of the first ablation procedure was not SR restoration and noninducibility of further atrial arrhythmias. In the second study,[20] CFAE was not performed in the right atrium, the procedure in stepwise ablation lasted less than 60 minutes, and AF was terminated in only about 50% of the patients at the end of the ablation procedure in the stepwise ablation.[20]

Study limitations

This study has some limitations that must be considered in interpreting the results. First, follow-up lasted 1 year, which is a reasonable time to detect AT recurrence but does not allow definitive conclusions. Second, asymptomatic recurrences of AF are common, and although all patients underwent regular visits with 48-hour Holter recording during follow-up, asymptomatic episodes cannot be excluded. Methods to identify CFAEs, although similar to the ones described by Nademanee et al,[7] may be operator dependent because they are based on visual evaluation.[7] In this study, software analysis tools to identify CFAEs were not applied. However, Scherr et al[21] demonstrated a high correlation between software and visual identification of the CFAE regions. In addition, the initial description of defragmentation relied on visual identification of fragmented electrograms. Third, the present study defined structural atrial disease as the inducibility of persistent atrial arrhythmias after PVI and we did not made use of any techniques (cardiovascular magnetic resonance and electroanatomic voltage mapping) to define it. Fourth, the relatively short term of follow-up does not exclude that the area of scar tissue created by the stepwise ablation could represent an anatomical substrate for later arrhythmias. Fifth, this study was performed over a period of 6 years, a time frame in which there may have been several improvements in techniques and equipment. However, we did use the same technique and equipment during the entire study period. Finally, the present study reflects the experience of 2 centers only.

Conclusion

Beyond PVI, the stepwise ablation procedure achieving SR and nonatrial arrhythmia inducibility has relevantly improved the clinical outcome of the PAF control strategy. However, stepwise ablation had required major overall procedure time and/or fluoroscopy times as compared with the PVI approach. However, further randomized clinical trials are required to develop a patient-tailored approach for substrate modification owing to the specific nature of the underlying heart disease.

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CLINICAL PERSPECTIVES

Pulmonary vein isolation remains the optimal strategy in patients with paroxysmal atrial fibrillation. The coexistence of structural heart disease in patients with paroxysmal atrial fibrillation can make pulmonary vein ablation less effective. Actually, there is no evidence to support the application of pulmonary vein isolation plus substrate-based ablation targeting abnormal or fractionated electrograms, linear lesions to compartmentalize and/or organize atrial activation, and combinations of these treatments in a stepwise fashion. However, the impact of pulmonary vein isolation vs stepwise approach on patients with paroxysmal atrial fibrillation remains poorly understood. In our prospective randomized study, we evaluated 2 ablation strategies in patients with paroxysmal atrial fibrillation: pulmonary vein isolation vs stepwise ablation. Single-procedure efficacy was high in all groups, and the stepwise approach significantly improved the single-procedure efficacy. Moreover, in patients with arrhythmia recurrence who underwent repeat ablation, the benefit of substrate modification in stepwise ablation seemed substantial as compared with pulmonary vein isolation. These findings suggest that the use of stepwise ablation in patients with paroxysmal atrial fibrillation before its progression to the persistent form may improve outcome. However, the true value of the stepwise approach in patients with paroxysmal atrial fibrillation remains to be determined in a large prospective randomized trial.