Stepwise Approach Ablation Versus Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation: Randomized Controlled Trial

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

Short title: Stepwise approach ablation efficacy: RCT.

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Abstract

**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, two-center randomized controlled trial compare the efficacy of catheter PVI alone versus PVI plus stepwise approach in achieving SR and non-atrial arrhythmias inducibility patients with PAF refractory to antiarrhythmic therapy.

**Methods:** Participants were randomized to perform a first catheter ablation either through PVI alone or through PVI plus substrate modification based upon stepwise approach. Data were recorded at 3, 6 and 12 months after both ablations. The subjects who experienced AF/AT recurrence were encouraged to repeat ablation using the same technique of the first ablation.

**Results:** 150 subjects were enrolled (mean age 62.8±8.7y; 61.3% males; 69.3% hypertensive; AF mean duration 10.7 months); 75 patients in each group. After 12 months from the first procedure, the patients who were converted to sinus rhythm using PVI plus stepwise ablation ablation showed a significantly lower rate of AF/AT recurrence (26.7%) than those who were treated using PVI alone (46.7%; p<0.001). Similar results were observed among the 52 subjects who underwent a second catheter ablation. Adjusting for several potential confounders, the hazard ratio of 12-month AF/AT recurrence after the first ablation was 0.53 (95% Confidence Interval: 0.30-0.91) for those treated using stepwise ablation.

**Conclusion:** In addition to PVI, the stepwise ablation achieving sinus rhythm and non-atrial arrhythmias inducibility has relevantly enhanced the clinical outcome of PAF control strategy.

**Registration number:** ACTRN12614001231639.

**Key words:** Paroxysmal atrial fibrillation; Catheter ablation; Pulmonary vein isolation; Stepwise ablation; RCT.

**Abbreviations and Acronyms**

AF = atrial fibrillation

AT = atrial tachycardia
Introduction

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

To control PAF in patients with no structural heart disease and maintain sinus rhythm (SR) over time, the current cornerstone strategy is PV 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 electrograms (CFAEs) 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 stepwise ablation approach in the setting of PAF has not been fully evaluated.
A prospective, single-blind, two-center randomized controlled trial was carried out to compare the efficacy of catheter PVI alone versus stepwise approach in achieving SR and non-atrial arrhythmias inducibility 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 to all patients with PAF refractory to at least one anti-arrhythmic drug, who were eligible for a first-time catheter ablation. PAF was defined according to criteria of the Task Force for the Management of Atrial Fibrillation of ESC/ECATS (1). The exclusion criteria were persistent or permanent AF, age<18y, history of previous heart surgery, including Maze surgery or AF transcatheter ablation, myocardial infarction, hyperthyroidism, severe kidney disease (glomerular filtration rate<30 mL/min/1.73 m²), liver failure, neoplasm, drug dependency and mental disorders. All procedures were carried out by two investigators with similar experience (MF and TA). The study was approved by the local Ethics Committee, and all participants gave written informed consent.

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

At baseline, as part of their clinical pathway, all patients underwent a clinical examination, laboratory exams and 12-lead electrocardiograms (ECGs). Transthoracic echocardiogram and transesophageal echocardiography were performed in all patients before catheter ablation in order to exclude left atrial thrombus. Patients having a high risk of thromboembolism (CHA2DS2-VASc score≥2) were treated with oral anticoagulant therapy (warfarin) for at least 4-week before ablation, with a target International Normalized Ratio (INR) of 2–3; weekly controls of the INR were carried out. Oral anticoagulant treatment was stopped 3 days before ablation and low-molecular-weight heparin was administered until 12 hours before. All antiarrhythmic medications were discontinued at least 5 half-lives prior to ablation whereas amiodarone was stopped ≥1 month before.
After the first ablation, 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 carried out. Forty-eight-hour Holter monitoring was also carried out every month and, in addition to clinical examinations, a structured questionnaire was administered to record arrhythmia recurrence and any other symptoms.

The primary endpoint 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 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 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 (3 months), the 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 the redo ablation to be performed after the blanking period (3 months) and preferably at less than 6 months from the first ablation. 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 endpoints included incidence of peri-procedural complications, procedural characteristics namely; 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). Non-invasive blood pressure and oxygen saturation were continuously monitored. During the procedure, 4 catheters were introduced via the right femoral vein using lidocaine as local anesthesia. Our catheter placement technique has previously been reported (14). Briefly, a decapolar catheter (Inquiry™ St. Jude Medical Inc., St. Paul, MN, USA) was positioned inside the coronary sinus and a tetrapolar catheter (Supreme™ CRD-2, St. Jude Medical Inc., St. Paul, MN, USA) 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 for PV mapping (AFocusIT™ 10 pole with a 20 mm diameter; St. Jude Medical Inc.) and the ablation catheter were positioned in the left atrium.

The ablation was performed with open irrigated ablation catheter Therapy Cool Path Duo™ (St. Jude Medical Inc.) (10). The 3-D electro-anatomic mapping was carried out 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 EP Recorder; GE Healthcare, Chalfont St Giles, UK). The filter settings were set for 30–500 Hz; online callipers and a sweep speed of 100 mm/s were used.

**Catheter ablations**

All approaches were carried out under fluoroscopic and 3-D 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 endpoint of the procedure was the isolation of all four 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 approach), AF was induced by rapid atrial pacing (300 to 200 msec CL) from the proximal dipols of the coronary sinus catheter. After circumferential PVI ablation met the endpoint of complete isolation of all four PV, the procedure was continued through electrogram-guided ablation for CFAEs if AF was still ongoing or inducible, regions of CFAEs were identified through visual inspection. The CFAEs were defined as follows: 1) atrial electrograms which have fractionated electrograms composed of two deflections or more and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period; 2) atrial electrograms with a very short CL (≤120 ms) averaged over a 10-s recording period. If the patient was not in AF at the end of the PVI, AF induction was performed by rapid atrial pacing. Isoproteronol was administrated for maintaining AF in patients with short lasting self-terminating episodes. When AF was inducible (AF persisting ≥ 1 min), CFAE regions were recorded and ablated(5,6). After CFAE-ablation we revisited the areas which 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 completed left atrial CFAE ablation, if the right appendage CL was shorter than the left, 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 AF CL was monitored in both the right and the left atrial appendage to help in determining the optimal site of ablation. The endpoints for CFAEs ablation were the elimination of all CFAE sites in the left and the right atria, and termination of AF if AF converted into stable AT (AT lasting ≥1 minute) activation mapping and catheter ablation of this tachycardia were performed until restoration of the SR. When induced AT was either focal or due to 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 macro-reentrant circuits and not as routine strategy. The endpoint of linear ablation was the AT termination after the 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, the ablation continued until non-inducibility. AF was considered inducible if it lasted more than one minute. The endpoints at the end of stepwise ablation were (i) SR restoration and (ii) non-inducibility of AF post-ablation. The time of the procedure never exceeded four 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™ (St. Jude Medical Inc., St.Paul, MN, USA.) were usually set at 35 W max Power (20-25 W for ablating within the coronary sinus); max 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). The radiofrequency was delivered for 25-60 seconds at each point. Patients were discharged with oral anticoagulation therapy (Warfarin) with a INR target between 2-3 that was continued for 3 consecutive months. The decision to terminate oral anticoagulation therapy was based on the presence of SR and the absence of other risk factors for thromboembolism. The use of antiarrhythmics 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 three months after the procedure.
Repeated electrophysiological procedures were carried out 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 procedure.

**Sample size estimation**

Assuming a two-tailed alpha error of 0.05, a 5% rate of withdrawals or losses to follow-up, and a hazard ratio of 0.50 of AF/AT recurrence 12 months after the first catheter ablation for the subjects receiving stepwise ablation as compared to those receiving PVI alone (12) 50 patients per group were required to achieve 80% statistical power. We planned to enroll 75 subjects per group.

**Data analysis**

The differences in the AF/AT recurrence rate according to type of ablation and other recorded variables were initially examined using chi-square 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 the 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, gender, body mass index (BMI), 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 ventricle ejection fraction, antiarrhythmics, amiodarone, beta-blocker and calcium-channel blocker use, and procedural, radiofrequency and fluoroscopy time, CFAE and ablation complications. Covariates were selected for inclusion in the final models using a stepwise forward process with the following inclusion criteria: p-value <0.15 at univariate analysis and ≥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 Schoenfeld’s test was carried out to check the validity of the proportional hazards assumption. Kaplan-Meier survival analysis was used to display the outcome probability over time in the two groups. The validity of constant incidence ratios over the follow-up was checked using Nelson-Aalen cumulative hazard estimates. There were no missing values. A p-value of <0.05 was considered significant for all analyses which were carried out using Stata, version 11.1 (Stata Corp., College Station, TX, USA, 2009).
Results

Characteristics of the patients (Table 1)

Of the 162 eligible patients contacted, 150 were enrolled (Figure 1). The baseline characteristics were evenly distributed between the two groups; the mean age was 62.8±8.7 years, 61.3% were males, 69.3% were hypertensive and the mean time of AF diagnosis was 10.7 months (min 3 months–max 24 months). Mean left atrial volume was 35.9±5.6 ml/m2.

The overall recurrence of AF/AT during the one 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 was undertaken in 52/55 patients with AF/AT recurrence; PVI alone was conducted in 33/35 patients and stepwise ablation was performed in 19/20 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 the stepwise ablation (p<0.001). Both fluoroscopy and radiofrequency times were significantly longer in the stepwise ablations group (p<0.001).

Similar results were observed during the second ablation (Table 2).

In the stepwise ablation group, during the first ablation, at the end of PVI, AF was ongoing in 51(68%) patients and inducible after atrial pacing in 13(18.7%) patients. CFAE 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. Among the 12 macroreentrant AT, 9 circuits were identified in the perimitral isthmus, 3 circuits in CVT isthmus, none 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 recording isochrone maps with a centrifugal activation from a focal site, and subsequently ablated. The mean mapped CL of the focal AT was 285±39 ms. Of those, 14 originated from the anterior wall, 6 from posterior wall, 7 in the floor, 4 from interatrial septum and 2 in left atrial appendage. At the end of the stepwise ablation strategy, 75(100%) patients were in SR using RF applications without any following arrhythmias inducibility.
In patients undergoing a second ablation procedure (52/150) we documented persistence of complete PVI in 23/33 patients in the PVI group, and 14/19 patients in the stepwise ablation group. All patients with PV reconnections underwent redo PVI.

In the stepwise ablation group, at the end of re-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, 4 with a focal mechanism and 5 with a macro-reentrant mechanism. The macrocircuits originated 2 from the perimital isthmus, 2 from the cavotricuspid isthmus and 1 from left atrial roof. All ATs were ablated following the aforementioned scheme. After first and second catheter ablation, no patient required DC-shock.

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

**AF/AT recurrence after the first and the second ablations**

During the follow up, the overall recurrence rates were 36.7%(55/150) and 51.9%(27/52), 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. Regarding the first procedure, after the blanking period (3-month of follow-up), 40.0% (30/75) of the patients who received PVI alone experienced a recurrence as compared to 20.0% (15/75) of those who received stepwise ablation (p<0.001). At the end of the target follow-up (12 months), the above rates were 46.7%(35/75) and 26.7%(20/75), respectively (p<0.001). AT occurred more frequently in patients treated with the stepwise procedure; 10/20 AT occurred in the stepwise group vs 4/35 in the PVI group.

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

Multivariate analyses confirmed univariate results: the patients who received stepwise ablation were significantly more likely to maintain SR during the follow-up as compared to subjects 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%CI:0.30-0.91) for the subjects in the stepwise ablation group, as compared to PVI alone (Table 3). Similar results were observed after the second ablation. According to Kaplan-Meier survival analysis, after both the first and second ablation, the probability of outcome was higher among patients receiving PVI alone throughout the follow-up (Figure 2).

The only other independent predictor of AF/AT recurrence after the first ablation was the left ventricle ejection fraction (EF); for each 1% increase of EF, the adjusted hazard ratio of AF/AT recurrence was 0.96 (95%CI: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 one anti-arrhythmic 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. However, in the stepwise approach the rate of AF/AT recurrence at any time point significantly decreased. The benefit of the substrate modification in addition to PVI seemed substantial after 12 months of follow-up; 90.7% of the subjects receiving stepwise ablation maintained SR, compared to 69.3% in the PVI group, even after adjusting for potential confounders or mediators including age, gender, 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 procedure, incomplete isolation of a previously PVI was found in roughly one-third of the population, while in the remaining patients AF re-occurred even if complete PVI was demonstrated.

A potential explanation for the observed findings is that circumferential PVI may eliminate triggers/initiators or a primary driving mechanism of PAF which occur in the muscle sleeves of the pulmonary veins. Once initiated from a trigger, PAF will not be maintained if the appropriate substrates are not present. The atria of patients with PAF present very different patterns during electroanatomic mapping (5,6), mainly due to atrial myocardial fibrosis which is significantly increased in patients with PAF as compared to 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 non-inducibility 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 that may benefit from additional substrate modification (14,15). In the literature it has long been demonstrated that PVI is sufficient to treat the great majority of patients with PAF and no structural heart disease (6-8). It is demonstrated the non-superiority of CFAE+PVI ablation as compare to PVI alone in patients with PAF (7,8). PVI plus CFAE ablation might be only superior to PVI alone in a particular subset of patients, meaning those with still inducible AF 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 macro re-entrant 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 term of AT/AF recurrence (12). In the stepwise group, ablation was guided using restoration of SR and non-inducibility 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 endpoint was possible to reached in all patients in stepwise approach group and repeated procedure were required only in 19 patients in stepwise ablation group versus 33 patients in PVI group.

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

The success rate of PVI alone in this study was lower than those reported in other RCTs (2,3,16). This might be explained by the older age and higher prevalence of hypertension, diabetes and 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, two recent studies, 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 (19,20). There are some potential explanations for such a discrepancy: the STAR AF II trial did not compare PVI to a stepwise ablation approach, and the outcome at the end of the first ablation was not sinus rhythm restoration and non-inducibility of further atrial arrhythmias (19). In the second study, CFAE was not performed in the right atrium, the procedure in stepwise approach 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 approach (20).

**Limitations**

This study has some limitations which must be considered in interpreting the results. First, the follow-up lasted one 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-h Holter recording during follow-up, asymptomatic episodes cannot be excluded. Methods to identify CFAEs, although similar to the ones described by Nademanee, 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. demonstrated a high correlation between software and visual identification of the CFAEs areas. In addition, the initial description of defragmentation relied on visual identification of fragmented electrograms (21). Third, the current study defined structural atrial disease as the inducibility or 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 creating by stepwise approach could represent an anatomical substrate for later arrhythmias. Fifth, this study was done over a 6 year time span, a time frame in which there may have been several improvements in techniques and equipment. We did use however the same technique and equipment during the entire study period. Finally, the present study reflects the experience of two centers only.

**Conclusions**

In conclusion, beyond PVI, the stepwise ablation achieving SR and non-atrial arrhythmias inducibility has relevantly enhanced the clinical outcome of PAF control strategy. However, this approach had led to additive overall procedure and/or fluoroscopy times as compared PVI approach. However further randomized
clinical trial are required to develop patient tailored approach for substrate modification owning to the specific nature of 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 versus stepwise approach in patients with paroxysmal atrial fibrillation remains poorly understood. In our prospective randomized study, we evaluated two different ablation strategies in patients with paroxysmal atrial fibrillation: pulmonary vein isolation versus stepwise ablation. Single-procedure efficacy was high in all groups, and stepwise approach significantly enhance the single-procedure efficacy. Moreover, in those patients with arrhythmia recurrence who underwent repeat ablation, the benefit of the substrate modification in stepwise ablation seemed substantial as compared with pulmonary vein isolation. These findings suggest that use of stepwise ablation in patients with paroxysmal atrial fibrillation before the progression to the persistent form may improve outcome. However, the true value of stepwise approach in patients with paroxysmal atrial fibrillation remains to be determined in a large prospective randomized trial.

Figure Legend

Figure 1. Study design flowchart (CONSORT FLOW DIAGRAM)

Figure 2. A) Kaplan–Meier estimates of time to first arrhythmia recurrence after the first ablation procedure. B) Kaplan–Meier estimates of time to first arrhythmia recurrence after the second ablation procedure.
Table 1. Characteristics of the sample by type of paroxysmal atrial fibrillation ablation and overall.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PV1 (n=75)</th>
<th>Stepwise ablation (n=75)</th>
<th>Overall (n=150)</th>
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<tr>
<td>Mean age, years (SD)</td>
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<td>62.3(9.1)</td>
<td>62.8(8.7)</td>
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<td>Mean Body Mass Index, kg/m^2 (SD)</td>
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</tr>
<tr>
<td>Current cigarette smoking, %</td>
<td>26.7</td>
<td>40.0</td>
<td>33.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>74.7</td>
<td>64.0</td>
<td>69.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>22.7</td>
<td>24.0</td>
<td>23.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>24.0</td>
<td>32.0</td>
<td>38.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>12.0</td>
<td>6.7</td>
<td>9.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>24.0</td>
<td>36.0</td>
<td>30.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Valvular heart disease, %</td>
<td>2.7</td>
<td>1.3</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy, %</td>
<td>6.7</td>
<td>6.7</td>
<td>6.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean AF duration, months (SD)</td>
<td>10.9(3.2)</td>
<td>10.5(3.7)</td>
<td>10.7(3.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean number of AF episodes, per month (SD)</td>
<td>2.2(1.7)</td>
<td>2.7(1.5)</td>
<td>2.4(1.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean left atrial size, mm (SD)</td>
<td>43.8(2.9)</td>
<td>44.0(3.3)</td>
<td>43.9(3.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean left atrial volume ml/m^2 (SD)</td>
<td>35.7(5.0)</td>
<td>36.0(6.2)</td>
<td>35.9(5.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean ejection fraction (SD)</td>
<td>59.3(6.9)</td>
<td>58.5(7.1)</td>
<td>58.9(7.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Class I antiarrhythmics, %</td>
<td>74.7</td>
<td>74.7</td>
<td>74.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Amiodarone, %</td>
<td>24.0</td>
<td>21.3</td>
<td>22.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>14.7</td>
<td>10.7</td>
<td>12.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Calcium channel blockers, %</td>
<td>36.0</td>
<td>49.3</td>
<td>42.7</td>
<td>0.10</td>
</tr>
<tr>
<td>CHA2DS2-VASc score (SD)</td>
<td>2.1(1.1)</td>
<td>2.0(1.3)</td>
<td>2.1(1.2)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

CHA2DS2-VASc score=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65-74 years, Sex category score; CFAEs=Complex fractionated atrial electrograms. AF=Atrial fibrillation; AT=trial tachycardia;

*Chi-square test for categorical variables; t-test for continuous variables.
Table 2. Outcomes of the sample by type of paroxysmal atrial fibrillation ablation and overall.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PVI</th>
<th>Stepwise ablation</th>
<th>Overall</th>
<th>p *</th>
</tr>
</thead>
<tbody>
<tr>
<td>First catheter ablation</td>
<td>(n=75)</td>
<td>(n=75)</td>
<td>(n=150)</td>
<td></td>
</tr>
<tr>
<td>Mean procedural time, min. (SD)</td>
<td>105(13)</td>
<td>148(27)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time, min. (SD)</td>
<td>13.9(2.0)</td>
<td>29.2(15.8)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiofrequency time, min. (SD)</td>
<td>37.3(8.9)</td>
<td>58.9(19.3)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ablation complications, %</td>
<td>8.0</td>
<td>12.0</td>
<td>10.0</td>
<td>0.4</td>
</tr>
<tr>
<td>AF/AT recurrence 6 months after ablation, %</td>
<td>45.3</td>
<td>24.0</td>
<td>34.7</td>
<td>0.006</td>
</tr>
<tr>
<td>AF/AT recurrence 12 months after ablation, %</td>
<td>46.7</td>
<td>26.7</td>
<td>36.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second catheter ablation</td>
<td>(n=33)</td>
<td>(n=19)</td>
<td>(n=52)</td>
<td></td>
</tr>
<tr>
<td>Mean procedural time, min. (SD)</td>
<td>104(14)</td>
<td>145(31)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time, min. (SD)</td>
<td>13.8(3.0)</td>
<td>28.3(15.1)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiofrequency time, min. (SD)</td>
<td>36.3(9.8)</td>
<td>57.8(17.8)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ablation complications, %</td>
<td>6.1</td>
<td>5.3</td>
<td>5.8</td>
<td>0.9</td>
</tr>
<tr>
<td>AF/AT recurrence 6 months after ablation, %</td>
<td>51.5</td>
<td>21.0</td>
<td>40.4</td>
<td>0.031</td>
</tr>
<tr>
<td>AF/AT recurrence 12 months after ablation, %</td>
<td>63.6</td>
<td>31.6</td>
<td>51.9</td>
<td>0.026</td>
</tr>
</tbody>
</table>

For abbreviations see Table 1.
Table 3. Breakdown of the anatomical sites of termination of atrial fibrillation (AF) or atrial tachycardia (AT) by Complex fractionated atrial electrograms, after the first and the second procedure.

<table>
<thead>
<tr>
<th>Site of AF/AT termination</th>
<th>AF after the 1\textsuperscript{st} procedure (n=75)</th>
<th>AF after the 2\textsuperscript{nd} procedure (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior wall</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Floor</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Roof</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Interatrial septum</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary veins</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Mitral isthmus</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Tricuspid isthmus</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Left atrial appendage</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4. Adjusted relative hazards of atrial tachycardia (AT) or atrial fibrillation (AF) recurrence according to each variable.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude HR (95% CI)</th>
<th>p*</th>
<th>Adjusted HR (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After the first ablation (n=150)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stepwise ablation vs PVI</td>
<td>0.54 (0.31-0.94)</td>
<td>0.028</td>
<td>0.53 (0.30-0.91)</td>
<td>0.023</td>
</tr>
<tr>
<td>- Age, 1-year increase</td>
<td>1.03 (1.00-1.06)</td>
<td>0.072</td>
<td>1.03 (0.99-1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>- Male gender</td>
<td>1.60 (0.90-2.87)</td>
<td>0.11</td>
<td>1.72 (0.95-3.11)</td>
<td>0.071</td>
</tr>
<tr>
<td>- Left ventricle ejection fraction, 1%-increase</td>
<td>0.97 (0.93-1.00)</td>
<td>0.047</td>
<td>0.96 (0.93-0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td>- Ablation procedure complications</td>
<td>0.90 (0.36-2.27)</td>
<td>0.8</td>
<td>1.10 (0.43-1.82)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>After the second ablation (n=52)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stepwise ablation vs PVI</td>
<td>0.40 (0.16-1.00)</td>
<td>0.050</td>
<td>0.37 (0.15-0.95)</td>
<td>0.038</td>
</tr>
<tr>
<td>- Age, 1-year increase</td>
<td>0.99 (0.94-1.05)</td>
<td>0.8</td>
<td>0.98 (0.93-1.04)</td>
<td>0.6</td>
</tr>
<tr>
<td>- Male gender</td>
<td>0.75 (0.34-1.64)</td>
<td>0.5</td>
<td>--</td>
<td>NS</td>
</tr>
<tr>
<td>- Left ventricle ejection fraction, 1%-increase</td>
<td>1.02 (0.97-1.08)</td>
<td>0.4</td>
<td>--</td>
<td>NS</td>
</tr>
<tr>
<td>- Ablation procedure complications</td>
<td>1.75 (0.41-7.43)</td>
<td>0.5</td>
<td>1.99 (0.46-8.61)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

HR=Hazard ratio; CI=Confidence Interval. PVI=Pulmonary vein isolation. NS Not significant (and not included in the final model). To limit overfitting, we reduced the covariates to be included in the model predicting AF/AT recurrence after the 2nd procedure. None of the variables excluded from the Table were significant.
Enrollment

Assessed for eligibility (n=242)

Excluded (n=92)
- Did not meet entry criteria (n=80)
- Refused to participate (n=12)

Randomized (n=150)

Randomized to Pulmonary Vein ablation (n=75)

Randomized to Pulmonary Vein ablation + CFAE (n=75)

Follow-up

Patients in Sinus Rhythm (n=40)
Patients in atrial tachyarrhythmia (n=35)
Patients in atrial tachycardia (n=4)
Patients in atrial fibrillation (n=31)

Patients in Sinus Rhythm (n=55)
Patients in atrial tachyarrhythmia (n=20)
Patients in atrial tachycardia (n=10)
Patients in atrial fibrillation (n=10)

Second Procedure Allocation

Randomized to Pulmonary Vein ablation (n=33)

Randomized to Pulmonary Vein ablation + CFAE (n=19)

Second Procedure Follow-up

Patients in Sinus Rhythm (n=12)
Patients in atrial tachyarrhythmia (n=21)
Patients in atrial tachycardia (n=3)
Patients in atrial fibrillation (n=18)

Patients in Sinus Rhythm (n=13)
Patients in atrial tachyarrhythmia (n=6)
Patients in atrial tachycardia (n=4)
Patients in atrial fibrillation (n=2)

Figure 1
Figure 2.

(A) Kaplan-Meier survival estimates after the first ablation

(B) Kaplan-Meier survival estimates after the second ablation