Progression of Atrial Fibrillation After a Failed Initial Ablation Procedure in Patients With Paroxysmal Atrial Fibrillation
A Randomized Comparison of Drug Therapy Versus Reablation

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Background—The aim of this prospective randomized study was to assess whether an early reablation was superior to antiarrhythmic drug (AAD) therapy in patients with previous failed pulmonary vein isolation.

Methods and Results—Patients with paroxysmal atrial fibrillation (AF) eligible for AAD therapy or reablation after a previously failed initial pulmonary vein isolation procedure were eligible for this study and were followed up for 3 years to assess rhythm by means of an implanted cardiac monitor. After the blanking period postablation, 154 patients had symptomatic AF recurrences and were randomized to AAD (n=77) or repulmonary vein isolation (n=77). At the end of follow-up, 61 (79%) patients in the AAD group and 19 (25%) patients in the reablation group demonstrated AF progression (P<0.01). The AF% at 36 months was significantly greater in the AAD group compared with patients in the reablation group (18.8±11.4% versus 5.6±9.5%, respectively; P<0.01). In addition, 18 (23%) patients in the AAD group and 3 (4%) patients in the reablation group progressed to persistent AF (P<0.01). Furthermore, 45 (58%) of the 77 reablation group patients were free of AF/atrial tachycardia on no AADs; in contrast, in the AAD group, only 9 (12%) of the 77 patients were free of AF/atrial tachycardia (P<0.01) throughout follow-up.

Conclusions—Redo AF ablation was substantially more effective than AAD in reducing the progression and prevalence of AF after the failure of an initial ablation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01709682.

Key Words: ablation ■ antiarrhythmic drug ■ atrial fibrillation ■ atrial fibrillation progression ■ continuous implantable monitor

Atrial fibrillation (AF) represents an important public health problem. Patients with AF have an increased long-term risk of stroke, heart failure, and all-cause mortality.1-4 Catheter ablation of AF has proved effective in treating highly symptomatic patients with paroxysmal AF in comparison with antiarrhythmic drug (AAD).5-10

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The single-procedure success rate of catheter ablation is ≈60%, and performing additional ablation procedures and adding AAD therapy can increase the success rate to ≈75%.10,11 When the first ablation fails and the patient has AF recurrences, the physician must choose the optimal treatment to halt or minimize AF progression and symptom burden. There are no clinical markers that can reliably indicate the most appropriate approach. Recently, it was demonstrated that the efficacy of AAD and reablation in patients after failed initial ablation within the first year of follow-up by implantable loop recorder (ILR) were 27% and 58%, respectively.12,13 However, the degree of AF progression was not evaluated in these patients.

The advent of the technology for continuous AF monitoring made possible the rigorous definition of AF burden, computed as the measured percentage of time spent in AF during the follow-up period. The trend of daily AF burden during the follow-up period is an easy and efficient way to demonstrate the presence and evolution of arrhythmia patterns.14,15

The aim of this prospective, randomized study was to assess whether an early reablation was superior to AAD therapy (control) in patients with previous failed pulmonary vein isolation (PVI) ablation for paroxysmal atrial fibrillation (PAF), by means of the diagnostic data stored in an ILR.

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Methods

Patient Selection
Patients with a history of symptomatic PAF eligible for AAD therapy or reablation after a previous failed initial radio frequency ablation (RFA) procedure involving only PVI were eligible for this study. The study protocol was approved by the local ethics committee (State Research Institute of Circulation Pathology) and conducted in compliance with the protocol and in accordance with standard institutional operating procedures and the Declaration of Helsinki. All patients enrolled in the study provided written informed consent. The failure of the initial RFA was adjudicated when recurrences persisted after the blanking period of 3 months postablation. Patients with persistent AF or atrial flutter, inability to tolerate any AAD, amiodarone therapy within 3 months before the ablation procedure, congestive heart failure, left ventricular ejection fraction <35%, or left atrial (LA) diameter ≥60 mm were excluded from the study. Patients were randomized to AAD therapy or reablation procedure using a coded envelope system. The patients were followed up for 3 years to assess rhythm by means of an ILR.

The hypothesis of this study was that early reablation (test) was superior to AAD therapy (control) in patients with previous failed PVI ablation for paroxysmal AF. The primary end point of the study was progression of AF (AF burden progression; development of persistent AF) during the 3-year follow-up based on ILR findings. Progression to persistent AF was defined as a change from paroxysmal to persistent AF during the 3-year follow-up based on ILR data. Persistent AF was defined as continuous AF for ≥27 days. AF burden progression was defined as an increased AF burden >30% relative to the baseline level (before randomization) during the 3-year follow-up based on ILR data. Baseline AF burden was defined as mean AF burden during the period from 3 months after first ablation until randomization. Long-term efficacy was evaluated after a 3-month blanking period in reablated patients or after a 2-week dose titration period in patients taking AAD therapy. The secondary end points were recurrence of atrial tachyarrhythmia, including AF and atrial flutter/tachycardia, number of additional ablations, predictors of AF progression, and complications.

Repeat Ablation Procedure
All patients underwent transesophageal echocardiogram before the procedure to exclude LA thrombus. The LA and pulmonary veins (PVs) were explored through a transseptal approach. The PVs were continuously assessed for isolation using the Lasso catheter (Biosense-Webster Inc, Diamond Bar, CA). Reisolation of the PVs was performed by identifying the breakthrough sites guided by the Lasso recordings and on the mapping catheter (Navistar Thermocool, Biosense-Webster Inc, Diamond Bar, CA). Radio frequency energy was delivered at 43°C. 35 W, 0.5 cm away from the PV ostia at the anterior wall and was reduced to 43°C, 30 W, 1 cm away from the PV ostia at the posterior wall, with a saline irrigation rate of 17 mL/min. Each lesion was ablated continuously until the local potential amplitude decreased by >80% or radio frequency energy delivery exceeded 40 s.

The end point of ablation was complete PVI; this was confirmed when Lasso catheter mapping showed the disappearance of all PV potentials or the dissociation of PV potentials from LA activity. For patients with induced LA flutter, additional RFA lines were created by connecting the left inferior PV to the mitral annulus (mitral isthmus) and the roof of the LA between the 2 superior PVs, depending on the mechanism of induced flutter. In the case of registration or induction of typical atrial flutter, the cavotricuspid isthmus was ablated. Bidirectional conduction block across the lines was assessed in all patients by differential pacing.

Drug Therapy and Patient Follow-Up
In the drug therapy (control) group, recurrent episodes were pharmacologically managed by conventional AAD therapy (propafenone, 450–900 mg/d; flecainide, 200–400 mg/d; or sotalol, 160–320 mg/d) according to AF management guidelines.1 Class IC drugs were recommended as first-line agents for most patients in the absence of structural heart disease. Sotalol was recommended as a first-line agent for patients with coronary artery disease. The final choice of agent and dosage was left to the discretion of the treating electrophysiologist. In the case of AAD therapy failure or intolerable side effects, catheter ablation was offered.

In the reablation (test) group, after the procedure, all patients were treated with AADs for 6 weeks after PVI; these drugs were subsequently withdrawn, regardless of the cardiac rhythm, to prevent their influence after the blanking period.

The data stored by the ILR were collected every 3 months during the 3-year follow-up. At each follow-up visit, all AF recordings were manually reviewed to confirm automatic detections. Any erroneous designations were removed. In patients with recurrences, the telemetric data and the stored ECG were used to tailor the antiarrhythmic therapy and to guide an additional ablation procedure.

Implanted Monitoring Device
In most patients, the ILR (Reveal XT, Medtronic Inc, Minneapolis, MN) was implanted on the day of the primary ablation procedure. The ILR continuously classifies the heart rhythm of the patient. This classification is made through the analysis of the beat-to-beat variability of cardiac cycles on a 2-minute ECG strip. The device stores the amount of AF per day (daily AF burden, hours in AF in 1 day) and the AF burden of the overall follow-up period, defined as the percentage of time spent in AF (AF%).15,16 In addition, the ECG is stored for visual confirmation of AF episodes. By accumulating data from multiple follow-up sessions, it is possible to discern the trend in the AF burden over 3 years.

The Reveal XT was implanted in the parasternal area of the chest. The requirement for defining the exact final position was an R-wave amplitude ≥0.4 mV assessed through the Vector Check.

Patients were provided with the Patient Assistant, a tool that allows each patient to store the ECG through the implanted device during symptoms; data were collected to analyze heart rhythm during symptomatic events.

Definition of Responders
Patients with an AF% ≤0.5% were considered AF-free (responders), whereas those with an AF% >0.5% were classified as patients with AF recurrences (nonresponders). This cutoff of 0.5% corresponds to a maximum cumulative time in AF of 3.6 hours in 1 month and to >99.5% of the time spent in sinus rhythm during the overall follow-up period.12,14 AF was visually verified by investigators through the analysis of the stored ECGs and all follow-up visits. ILR interpretations were made by physicians not aware of the randomized ablation treatment.

Definition of HATCH Score
The HATCH score has been proposed as predictive of AF progression in pharmacologically treated AF patients.13 The HATCH acronym stands for hypertension (1 point), age ≥75 years (1 point), transient ischemic attack or stroke (2 points), chronic obstructive pulmonary disease (1 point), and heart failure (2 points).

Statistical Analysis
Because there are no prior data to provide basis for sample size calculations, we used an estimate of a 10% difference in treatment outcomes, yielding a projected sample size of 154 patients (assuming χ=0,0.5, β=0.20). Results are expressed as mean±SD or as absolute values and percentages, as appropriate. Continuous variables were compared by Student t test or ANOVA with repeated measures comparisons. The Mann–Whitney U test was used if normal distribution criteria were not met. χ2 analysis for categorical variables was used for comparisons between characteristics of patients. Kaplan–Meier analysis was performed to determine the probability of success, estimated as the percentage of AF freedom. Differences in arrhythmia-free survival were assessed using the log-rank test. Logistic regression analysis was used to evaluate independent predictors for AF burden progression and...
progression to persistent AF. Variables included in the logistic regression model were selected from baseline characteristics (Table). All reported $P$ values were based on 2-sided tests, and a $P<0.05$ was considered significant. All statistical calculations were performed using the SPSS version 13.0 software (SPSS Inc, Chicago, IL).

### Results

All patients with a history of symptomatic PAF underwent the primary RFA between November 2007 and January 2009. Of the 742 patients, 171 (23%) had recurrent AF and were eligible for repeat ablation. Of these patients, 154 (91%) patients had symptomatic AF recurrences after the blanking period postablation and were enrolled in this study and randomized to AAD therapy ($n=77$) or reablation ($n=77$; Figure 1). There were 17 patients who were excluded when inclusion criteria were not met or consent was not provided. Overall, in the AAD group, 79% of patients were started on a class IC agent (68% propafenone 579±205 mg/d; 11% flecainide 255±88 mg/d), and 21% of the patients were started on sotalol (210±76 mg/d).

In the AAD group, 68 patients (88%) were restarted on the same AAD they were taking just before first ablation. Clinical characteristics of each group were similar (Table). The average time from first ablation to randomization was 6.8±2.2 months (median=6) and 7.4±2.1 months (median=7) in AAD therapy and reablation groups ($P=0.12$), respectively. The ILR was implanted 6.7±2.3 months (median=6) before randomization (mostly on the day of the primary ablation procedure). Despite the fact that ILR was implanted before randomization, all patients had reached the primary end point of the study (AF progression or 3 years of follow-up after randomization) within the battery life of the ILR.

#### AF Burden Progression

At the end of follow-up, 61 (79%) patients in the AAD group and 19 (25%) patients in the reablation group demonstrated AF% progression ($P<0.01$) at follow-up duration of 18.1±5.8 months (range, 10–35 months) and 16.1±9.1 months (range, 4–33 months), respectively ($P=0.24$). Patients in AAD therapy

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AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LAD, left atrial diameter; and LVEF, left ventricular ejection fraction.

Figure 1. Study design and patient flow. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; and PVI, pulmonary vein isolation.
and reablation groups had similar AF burden at randomization (15.6±5.2% and 14.2±4.9%, respectively; P=0.11; Figure 2). At 3 months after study therapy, the AF% dramatically decreased in both groups, but AF% was significantly higher in the AAD group than the reablation group (3.3±2.6% and 1.9±2.4%, respectively; P<0.01). In the AAD group, AF% significantly increased during follow-up compared with patients of reablation group: at 36 months AF% was 18.8±11.4% and 5.6±9.5%, respectively (P<0.01).

Progression to Persistent AF
At the end of follow-up, 18 (23%) patients in the AAD group and 3 (4%) patients in the reablation group had progressed to persistent AF before further ablation (P<0.01) at 23.9±6.2 months (range, 12–34 months) and 25.1±3.1 months (range, 22–28 months), respectively (P=0.76). In the AAD group, progression was silent in 8 patients, whereas in the remaining 11 patients the arrhythmia exhibited a mixed pattern (both symptomatic and asymptomatic); in the reablation group all 3 patients exhibited a mixed pattern.

Crossovers and Intention-to-Treat Analyses
At the 36-month follow-up examination, 45 (58%) of the 77 reablation group patients were free of AF/AT on no AADs. In contrast, in the AAD group, only 9 (12%) of the 77 patients were free of AF/AT (P<0.01; Figure 3).

In the AAD group, 43 patients (56%) with recurrent AF crossed over to undergo reablation (second ablation). The reasons for crossover were sustained episodes of AF recurrences associated with AAD failure. The mean time to second ablation was 15.8±10.1 months (range, 6–28 months). Two patients required a third ablation procedure.

In the reablation group, 21 of the patients with AF recurrences required treatment with AAD; the remaining 11 patients with AF recurrences underwent a third ablation procedure.

By intention-to-treat analysis, at the 36-month follow-up examination after crossover and all additional reablation procedures, 50 (65%) of the 77 reablation group and 35 (45%) of the 77 AAD group patients were free of AF/AT (P=0.02, log-rank test).

Predictors of AF Burden Progression
On multivariate logistic regression analysis, reablation strategy (odds ratio [OR]=0.09; 95% confidence interval [CI], 0.04–0.18; P<0.01), age >60 years (OR=2.1; 95% CI, 1.1–4.1; P=0.04), AF duration >5 years (OR=3.3; 95% CI, 1.7–6.3; P<0.01), hypertension (OR=3.1; 95% CI, 1.5–6.3; P<0.01), diabetes mellitus (OR=4.6; 95% CI, 1.3–16.9; P=0.02), and HATCH score ≥2 (OR=11.6; 95% CI, 1.5–92.5; P=0.02) were independent predictors of AF burden progression.

The mean HATCH score was 0.5±0.8. The mean HATCH score was higher among patients with AF burden progression (0.8±0.9) than without progression (0.1±0.3, P<0.01). The HATCH score was ≥2 in 1 of 74 patients (1%) without AF burden progression and in 11 of 80 patients (14%) with progression (P<0.01).
Predictors of Progression to Persistent AF
On multivariate logistic regression analysis, only reablation strategy (OR=0.13; 95% CI, 0.04–0.47; \(P<0.01\)) and diabetes mellitus (OR=3.5; 95% CI, 1.1–11.3; \(P=0.04\)) were independent predictors of progression to persistent AF.

The mean HATCH score was higher among patients whose AF progressed (1.3±0.7) and did not progress to persistent AF (0.3±0.7; \(P=0.01\)). The HATCH score was \(\geq 2\) in 9 of 133 patients (7%) without AF progression and in 3 of 21 patients (14%) with progression to persistent AF (\(P=0.23\)). On multivariate analysis, the HATCH score (OR=2.3; 95% CI, 0.7–9.3; \(P=0.24\)) was not predictive of progression to persistent AF.

New LA Tachycardia
By intention-to-treat analysis, in the reablation group, new LA tachycardia developed in 4 (5%) patients who also had AF recurrences. In the AAD group, new left AT developed in 2 (3%) patients after crossover and repeat RFA. All patients with AT required ablation, which was successfully performed. Only macroreentrant AT was documented with residual gaps along ablation lines.

Complications
By intention-to-treat analysis, there were no serious complications, except cardiac tamponade in 2 patients (3%) who were assigned to reablation and in 1 patient (1%) who was assigned to AADs after crossover and repeat RFA. All patients recovered successfully after immediate pericardiocentesis. No procedure-related late complications were observed. In the group assigned to AADs, 49 (64%) patients discontinued taking AADs because of lack of efficacy or adverse events. Transient ischemic attacks occurred in 3 patients (4%) in the reablation group and in 4 patients (5%) in the AAD therapy group.

Discussion
The main finding of this study is that after the failure of the first catheter ablation procedure for PAF, a redo ablation was more effective at eradicating recurrent AF than treatment with AAD. In this randomized controlled clinical trial, we observed that (1) the AF progression rate was considerably higher in patients randomized to AAD (79%) use compared with patients treated with a second ablation procedure (25%); (2) the AF burden significantly increased on AAD during follow-up compared with patients of reablation group (18.8±11.4% versus 5.6±9.5%, respectively); and (3) there was a much greater rate of progression to persistent AF if AAD was used rather than redo ablation (23% versus 4%, respectively).

Leong-Sit et al.\(^\text{11}\) found that despite the reduction in events at 6 weeks with AAD therapy prescribed immediately after AF ablation, there was no difference in freedom from AF between the early AAD and no-AAD groups in 6-month outcomes; therefore, AAD therapy after ablation can still be recommended on a symptomatic basis but did not improve long-term AF freedom.

In another study, it was shown that comorbidities contribute to AF recurrence despite AAD. Long-term maintenance of sinus rhythm by AAD therapy was unachievable in 53% of patients with safety profiles that were less than ideal because of comorbidities.\(^\text{19}\) In contrast to our study, this study was non-randomized and without ILR; therefore, it did not evaluate AF burden progression.

However, differences in the follow-up periods and in the monitoring techniques are important limiting factors to assess the effectiveness in maintaining sinus rhythm. In the vast majority of trials, the monitoring strategy was based on intermittent ECG monitoring, leading to an underestimation of AF recurrences, as demonstrated by Charitos et al.\(^\text{20}\)

To the best of our knowledge, this is the first study to randomly assess the rhythm control options after a first ablation failure, demonstrating the superiority of reablation versus AAD as accurately determined by comprehensive monitoring over extended follow-up. In fact, we found that freedom from AF at the end of the 36-month follow-up period was several-fold higher in patients treated with a reablation (58%) compared with patients treated with AAD (12%). In addition, AF progression was suppressed by reablation, but progressed in patients treated with AAD.

The rate of AF progression described in past studies varied between 8% and 22% after 1 year of follow-up, depending on the rhythm-monitoring methods used and definitions.\(^\text{21,22}\) Various factors were associated with AF progression, including valvular disease, alcohol consumption, age, LA dimension and enlargement over time, stroke, and heart failure. Our study found that after correcting for confounders, patients aged >60 years, long history of AF, hypertension, diabetes mellitus, and high HATCH score were more likely to have progressive AF, irrespective of treatment approach. Importantly, however, the treatment approach also had a profound independent impact on AF progression and was far superior for reablation versus AAD.

As demonstrated by de Vos et al.,\(^\text{17}\) the HATCH scoring system was proposed to predict the risk of progression of AF in patients receiving pharmacological therapy. The premise for proposed use of the HATCH score was early selection of patients for rhythm control therapy in an effort to prevent disease progression. Conversely, potentially harmful drugs and interventions, including cardioversion and ablation, may be avoided in patients with a high HATCH score. A confirmation could be found in the outcome of our multivariate logistic regression analysis, where an elevated HATCH was an independent strong predictor of AF burden progression.

This may confirm the lack of effectiveness of AAD in preventing AF progression in the majority of patients with multiple comorbidities. However, the HATCH score was not an independent predictor of progression to persistent AF, although AAD use and diabetes mellitus were predictive. Importantly, the use of repeat ablation as a therapeutic strategy was also a powerful negative predictor of AF burden progression and progression to persistent AF, confirming its superiority compared with alternative treatment approaches. Diabetes mellitus also predicted progression of AF, probably indicative of atrial pathology.

Limitations
The ideal choice of AAD in this circumstance is unknown, and we cannot be certain that a different strategy would not have altered our findings. It could be argued that the deck is stacked against the AAD arm because by definition, based on
current guidelines, ablation is offered when AAD therapy has failed.³ Reinroduction of a failed approach and specifically a failed AAD will inevitably be inferior. Nonetheless, this is the real-world situation that is faced after failed ablation, and the spectrum of AAD options is limited. Previously failed AADs are often resumed, and clinical experience does in fact suggest that patients can often respond to previously ineffective drug therapy. The ideal study would be similar to our design, but in patients naive to AAD, not currently supported by guidelines. The strategy usually used at repeat ablation is reisolation of the PVs, as we performed. Whether different ablation approaches may work better is unknown. The use of ILR is advantageous for completeness of AF data collection, but may detect more episodes than what many centers routinely capture using external ECG methods and does not exactly conform to Heart Rhythm Society guidelines.³

Additional limitations exist concerning drug therapy. For example, amiodarone and dofetilide were not used in this study, although they have good efficacy. In the AAD group, 88% patients were restarted on the same AAD they were taking just before first ablation. On the one hand, AAD should have been changed if there was recurrent AF. But on the other hand, often ineffective AAD before ablation become effective after. Also, continuing prior therapy eliminates the potential for poor tolerance and early discontinuation. Irrespective of that, AAD therapy was managed according to AF guidelines.³ One important limitation of this study was the time to randomization, 7 months, because patients with AF recurrences may undergo repeat ablation in an earlier time frame.

Conclusions
Our study demonstrated the superiority of a second ablation procedure compared with AAD once the first ablation fails; the use of long-term continuous ECG monitoring facilitated the objective quantification of AF burden progression and to assess AF freedom at the end of a long follow-up. In addition, we were able to show that there were several predictors of AF burden progression; use of reablation was negatively associated with progression to persistent AF. These findings support the need for consideration of a timely intervention in patients with PAF who have responded inadequately to an initial PVI.

Disclosures
Dr De Melis is an employee of Medtronic. The other authors report no conflict.

References


CLINICAL PERSPECTIVE

The aim of this prospective randomized study was to assess whether an early reablation for atrial fibrillation (AF) was superior to antiarrhythmic drug (AAD) therapy in patients with previous failed pulmonary vein isolation. The study enrolled 154 patients who had symptomatic AF recurrences after initial ablation and were randomized to AAD (n=77) or repulmonary vein isolation (n=77). AF progression at 36 months was significantly greater in the AAD group compared with patients in the reablation group (18.8±11.4% versus 5.6±9.5%; P<0.01). In addition, patients in the AAD group were much more likely to evolve to persistent AF (23% versus 4%; P<0.01). Complete freedom from AF was several-fold more likely in the reablation arm (58% versus 12%; P<0.01). We conclude that redo AF ablation was substantially more effective than AAD treatment in reducing the progression and prevalence of AF after the failure of an initial ablation.
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