Antiarrhythmics After Ablation of Atrial Fibrillation
(5A Study)
Six-Month Follow-Up Study

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Background—We previously demonstrated that treatment with antiarrhythmic drugs (AADs) during the first 6 weeks after atrial fibrillation (AF) ablation reduces the incidence of clinically significant atrial arrhythmias and need for cardioversion or hospitalization for arrhythmia management. Whether early rhythm suppression decreases longer-term arrhythmia recurrence is unknown. We now report the 6-month follow-up data from this study.

Methods and Results—The Antiarrhythmics After Ablation of Atrial Fibrillation study prospectively randomized patients with paroxysmal AF undergoing ablation to either receive (AAD group) or not receive (no-AAD group) AAD treatment for the first 6 weeks after ablation; all patients received atrioventricular nodal blockers. Physicians were encouraged to stop the AADs after the 6-week treatment period. All patients underwent 4 weeks of transtelephonic monitoring to document asymptomatic AF and an evaluation at 6 weeks and 6 months. A total of 110 patients (71% men) aged 55 ± 9 years were randomized, with 53 to AAD and 57 to no AAD. At 6 months, there was no difference in freedom from AF between the early AAD and no-AAD groups (38/53 [72%] versus 39/57 [68%]; P=0.84). Lack of early AF recurrence during the initial 6-week period was the only independent predictor of 6-month freedom from AF (64/76 [84%] without early recurrence versus 13/34 [38%] with early recurrence; P=0.0001).

Conclusions—Although short-term use of AADs after AF ablation decreases early recurrence of atrial arrhythmias, early use of AADs does not prevent atrial arrhythmia recurrence at 6 months. Early AF recurrence on or off AADs during the initial 6-week blanking period is a strong independent predictor of long-term AF recurrence.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00408200.

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Key Words: atrial fibrillation • ablation • antiarrhythmia agents

Empirical use of antiarrhythmic drugs (AADs) after atrial fibrillation (AF) ablation is common to prevent early AF recurrences, which may be troubling for patients and often resolve with “healing” after ablation. There have been no data to support the effectiveness of such an approach. We previously demonstrated in a prospective randomized trial that treatment with AADs during the first 6 weeks after AF ablation reduced the incidence of clinically significant atrial arrhythmias and need for cardioversion or hospitalization for arrhythmia management. Whether a strategy of early rhythm suppression with AADs decreases longer-term arrhythmia recurrence is unknown.

Clinical Perspective on p 14

There is mixed evidence in the literature regarding the prognostic values of early recurrence of atrial arrhythmias within the first 6 to 12 weeks post-pulmonary vein (PV) ablation.2–4 However, prior studies have suggested that the presence of AF leads to more AF because of a variety of proposed mechanisms, including structural7–9 and electric remodeling.10,11 We hypothesize that reduction of the early recurrence of atrial arrhythmias with the use of AADs would reduce the incidence of symptomatic atrial arrhythmias during 6-month follow-up by attenuating the remodeling process. Furthermore, we seek to identify whether there are clinical predictors of AF recurrence at 6-month follow-up.

Methods

The methodology for the Antiarrhythmics After Ablation of Atrial Fibrillation (5A) study was previously described in detail.1 The 5A study was a prospective, randomized, nonblinded study that involved patients with paroxysmal AF undergoing PV ablation. Paroxysmal
AF was defined as typical episodes lasting >30 seconds and spontaneously returning to sinus rhythm within 7 days. All adult patients referred to the University of Pennsylvania (Philadelphia, PA) for ablation of paroxysmal AF were screened. Exclusion criteria included inability to tolerate any AAD, amiodarone therapy within 3 months of the ablation procedure, and participation in another clinical trial. Eligible patients were enrolled before ablation and randomized in a 1:1 fashion to the AAD and no-AAD groups immediately after the procedure.

Patients from both groups underwent proximal antral PV isolation guided by intracardiac echocardiogram and circular multipolar electrode catheter recording with a procedural end point of isolation of PVs and elimination of provokable non-PV triggers of AF. The AAD group received an antiarrhythmic agent starting on the night of the ablation for a duration of at least 6 weeks, whereas the no-AAD group received no antiarrhythmic agents. Both groups received atrioventricular nodal blocking agents. The choice of antiarrhythmic agent was up to the treating physician, but suggested agents were based on the presence of structural heart disease as follows: (1) normal left ventricular (LV) function with no obstructive coronary artery disease (CAD), propafenone 150 mg TID or flecainide 100 mg BID; (2) normal LV function with CAD, sotalol 80 mg BID; and (3) abnormal LV function, sotalol 80 mg BID or dofetilide 500 μg BID. No patients were treated with amiodarone. Physicians were encouraged to stop the AADs after the 6-week treatment period.

The primary end point was 6-month freedom from atrial arrhythmias defined as asymptomatic or symptomatic AF, atrial flutter, or atrial tachycardia. The first 6 weeks postablation were considered a blanking period, and any recurrences during this time were recorded but did not contribute to the 6-month outcome. All patients left the hospital with a 30-day transtelephonic monitor to document early AF occurrences and underwent a second 30-day monitor at 6 months. All patients were seen in the office at 6 weeks and 6 months for a detailed history and ECG. Patients also were sent a monitor or asked to obtain an ECG for any symptomatic AF occurrences during the 6-month period after ablation. For the purposes of this study, any documented AF episode after the blanking period lasting >1 minute was considered a recurrence of AF.

Results are reported as mean±SD where applicable. The primary analysis on the 6-month outcome was performed using Fisher exact test on an intention-to-treat basis followed by a secondary per-protocol analysis that excluded patients who remained on antiarrhythmic medications beyond the designated 6-month treatment period. Unadjusted analyses with normally distributed continuous variables (age, body mass index [BMI], and left atrial [LA] diameter) were analyzed using the Student t test, and nonnormal continuous variables (prior AF duration, number of prior AADs, procedure duration, number of radiofrequency applications, fluoroscopy time) were analyzed using the Wilcoxon rank sum. Unadjusted analyses for categorical variables (sex, prior AF ablation, history of hypertension, coronary disease, sleep apnea, and presence of non-PV triggers) were analyzed using Fisher exact test.

A multivariable logistic regression model was used to assess predictors of 6-month freedom from AF. Sex, prior AF ablation, LA enlargement (>40 mm), history of hypertension, CAD, obstructive sleep apnea, presence of non-PV triggers, long procedure duration (>5 hours), early AF recurrence (within 6 weeks of the ablation), and randomization arm were coded as binary covariates. Duration of AF diagnosis (<2 years, 2 to 10 years, ≥10 years) and BMI (<25 kg/m², 25 to 30 kg/m², ≥30 kg/m²) were included as ordinal nested covariates, whereas age was included as a continuous covariate. Clinically pertinent covariates were forced into the model regardless of statistical significance followed by stepwise selection for the remaining covariates using a threshold P value of 0.25 for inclusion in the model. Analyses were conducted using SAS version 9.2 (SAS Institute Inc; Cary, NC) statistical software, with a P<0.05 considered statistically significant.

Results
As previously detailed,1 244 patients were screened, and 110 patients (71% men) aged 55±9 years were enrolled between December 2006 and March 2008. Exclusions were because of lack of patient consent or use of amiodarone within 3 months of randomization. There were 53 patients randomized to AAD and 57 to no AAD. There were no differences in baseline characteristics between groups (Table). Eighteen (34%) of the patients randomized to AAD were started on flecainide, 14 (26%) on propafenone, 19 (36%) on sotalol, and 2 (4%) on dofetilide. Six-month follow-up was complete (100%). At 6 months follow-up, there was no difference in freedom from symptomatic and asymptomatic atrial arrhythmias between the AAD (38/53; 72%) and the no-AAD (39/57; 68%) groups (P=0.84). Of those free of AF at 6 months, 3 (6%) in the AAD group remained on an antiarrhythmic agent, whereas 4 (7%) in the no-AAD group were started on an AAD (Figure 1). In the AAD group, 3 patients remained on an AAD because of recurrent AF episodes during the early 6-week postablation period, although none had recurrent AF after week 6. In the no-AAD group, 2 patients were started on an AAD for early AF occurrences, and 2 patients were started on an AAD because of symptom-
Wijffels et al. initially described the mechanism of atrial electric remodeling in goats, supporting the clinical observation that “AF begets more AF.” These authors found that even short periods of rapid atrial rate led to a shortening of refractory period that facilitated the maintenance of AF. Further human studies also found that new-onset, short-lived AF reduced effective refractory periods and prolonged conduction times in the atria and PVs. We therefore hypothesized that a reduction in early AF after ablation would lead to fewer late recurrences by preventing the remodeling process. However, despite the suppression of early atrial arrhythmia recurrence with a 6-week course of AADs, the present study did not demonstrate any difference in clinical outcome.

There are many potential explanations for the observed finding. One is that AF occurrences were not sufficiently long enough to allow electric or structural remodeling or to prevent the reverse remodeling after ablation that can occur with maintenance of sinus rhythm the majority of the time. Another is that immediate postablation atrial arrhythmias are primarily due to inflammatory changes that resolved after 6 weeks. Finally, it is likely that the driving force of recurrent AF after ablation is PV reconnection, which is unaffected by early AF recurrences.

Prognostic Significance of Early AF Recurrence
A common clinical dictum is that early AF recurrence after ablation often is due to “irritability” and of little prognostic importance. We found that early AF recurrence is the single best predictor of future AF recurrence. Although some (38%) patients with early atrial arrhythmias do improve, these data suggest that particular vigilance is required in monitoring patients with early AF recurrence. One also may be hesitant to withdraw anticoagulation therapy in such patients given the poor long-term prognosis. In contrast, patients without early atrial arrhythmias can be encouraged that longer-term AF freedom is likely.

Lellouche et al. found that in patients with atrial arrhythmias within 1 month of ablation of persistent AF, 91% had longer-term AF recurrence after a mean follow-up of 11 months. Koyama et al. found that early recurrence within 30 days of ablation corresponded to a 6-month freedom from AF of 30%. As evidence builds for the prognostic value of early AF recurrence, further studies are warranted to elucidate the possible benefit of early repeat ablation in such instances.

Limitations
As with all AF outcome studies, monitoring of arrhythmia recurrence was subject to practical limitations. Patient symptoms and transtelephonic monitoring at 6 weeks and 6 months may not capture all AF recurrences, but the relative importance of brief asymptomatic episodes is debatable.

Conclusions
Although short-term use of AADs after ablation of AF decreases the early recurrence of atrial arrhythmias, there was no effect on arrhythmia recurrence at 6 months. However, this observation should not dissuade the use of AADs in the early postablation period. It remains clear that the early
short-term use of AADs decreases morbidity by reducing symptomatic episodes and the need for cardioversion or hospitalization. AF recurrence during the initial 6-week blanking period is a strong independent predictor of long-term AF recurrence. Particular vigilance for late AF recurrence is warranted in these patients, and continuation of anticoagulation, if indicated, should be considered.

Disclosures
None.

References

CLINICAL PERSPECTIVE
In patients with paroxysmal atrial fibrillation (AF) undergoing pulmonary vein ablation, the use of antiarrhythmic medications in the first 6 weeks postprocedure has been shown to decrease early recurrence of atrial arrhythmias in a randomized controlled trial (the Antiarrhythmics After Ablation of Atrial Fibrillation study). In the present study, we extended follow-up of the original study to see whether maintenance of sinus rhythm early after ablation translated into a reduction of AF at 6 months. Patients randomized to early use of antiarrhythmic medications had the same 6-month freedom of symptomatic and asymptomatic atrial arrhythmias as those randomized to no postprocedure antiarrhythmic medications. Interestingly, the study found that early recurrence of AF was the only independent predictor of late recurrence. These observations argue that the pathophysiology of early recurrence may be altered by antiarrhythmic medications, but later recurrence is likely due to a different mechanism, such as chronic reconnection of the pulmonary veins. However, the study findings should not dissuade the use of antiarrhythmic drugs in the early postablation period. It remains clear that the early short-term use of antiarrhythmic drugs decreases morbidity by reducing symptomatic episodes and the need for cardioversion or hospitalization. In addition, particular vigilance for late AF recurrence should occur in patients with early AF occurrence after ablation, and continuation of anticoagulation, if indicated, should be considered.
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