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.

Key Words: atrial fibrillation  ablation  antiarrhythmia agents
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 symptomatic or asymptomatic 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-week treatment period. Unadjusted analyses with normally distributed continuous variables (age, body mass index [BMI], and left atrial [LA] diameter) were analyzed using the Student 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\textsuperscript{10} 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\textsuperscript{11} 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\textsuperscript{12} 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\textsuperscript{13} 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...

---

**Discussion**

We found that despite the reduction in events at 6 weeks with antiarhythmic therapy prescribed immediately after AF ablation, there was no difference in 6-month outcome afforded by empirical AAD therapy. Therefore, antiarhythmic therapy after ablation can still be recommended on a symptomatic basis but does not improve long-term AF freedom.
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 therefore is warranted in these patients, and continuation of anticoagulation, if indicated, should be considered.

Disclosures

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.
Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study): Six-Month Follow-Up Study
Peter Leong-Sit, Jean-Francois Roux, Erica Zado, David J. Callans, Fermin Garcia, David Lin, Francis E. Marchlinski, Rupa Bala, Sanjay Dixit, Michael Riley, Mathew D. Hutchinson, Joshua Cooper, Andrea M. Russo, Ralph Verdino and Edward P. Gerstenfeld

*Circ Arrhythm Electrophysiol.* 2011;4:11-14; originally published online November 13, 2010; doi: 10.1161/CIRCEP.110.955393

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/4/1/11

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Circulation: Arrhythmia and Electrophysiology* is online at:
http://circep.ahajournals.org//subscriptions/