Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study)

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Background—Atrial arrhythmias are common early after atrial fibrillation (AF) ablation. We hypothesized that empirical antiarrhythmic drug (AAD) therapy for 6 weeks after AF ablation would reduce the occurrence of atrial arrhythmias.

Methods and Results—we randomized consecutive patients with paroxysmal AF undergoing ablation to empirical antiarrhythmic therapy (AAD group) or no antiarrhythmic therapy (no-AAD group) for the first 6 weeks after ablation. In the no-AAD group, only atrioventricular nodal blocking agents were prescribed. All patients wore a transtelephonic monitor for 4 weeks after discharge and were reevaluated at 6 weeks. The primary end point of the study was a composite of (1) atrial arrhythmias lasting more than 24 hours; (2) atrial arrhythmias associated with severe symptoms requiring hospital admission, cardioversion, or initiation/change of antiarrhythmic drug therapy; and (3) intolerance to antiarrhythmic agent requiring drug cessation. Of 110 enrolled patients (age 55±9 years, 71% male), 53 were randomized to AAD and 57 to no-AAD. There was no difference in baseline characteristics between groups. During the 6 weeks after ablation, fewer patients reached the primary end point in the AAD compared with the no-AAD group (19% versus 42%; \(P=0.005\)). There remained fewer events in the AAD group (13% versus 28%; \(P=0.05\)) when only end points of AF >24 hours, arrhythmia-related hospitalization, or electrical cardioversion were compared.

Conclusions—AAD treatment during the first 6 weeks after AF ablation is well tolerated and reduces the incidence of clinically significant atrial arrhythmias and need for cardioversion/hospitalization for arrhythmia management. (Circulation. 2009;120:1036-1040.)

Key Words: atrial fibrillation ■ ablation ■ antiarrhythmia agents

Early recurrence of atrial arrhythmias is common after atrial fibrillation (AF) ablation and does not necessarily indicate failure of the procedure.1–4 Clinical trials assessing the efficacy of AF ablation do not take into account arrhythmias occurring during the first 6 to 12 weeks after the procedure, a period that has been called the blanking period.5 However, arrhythmias occurring early after ablation can be disappointing to the patients and are often associated with bothersome symptoms that require drug adjustments, hospitalizations, or electrical cardioversion. In order to prevent these early arrhythmia recurrences, antiarrhythmic drugs (AADs) are often resumed empirically after AF ablation. However, AADs have limited efficacy6,7 and can be associated with significant side effects, including serious proarrhythmic effects.7–9 The overall benefit of AADs during the early period after atrial fibrillation has never been studied, and the role for these agents therefore remains unclear. We therefore conducted a prospective, randomized trial to test the hypothesis that empirical antiarrhythmic drug therapy during the first 6 weeks after ablation for paroxysmal atrial fibrillation would reduce the combined incidence of AF recurrence or need for cardioversion or hospitalization, as compared with a strategy of no empirical AAD therapy.

Clinical Perspective on p 1040

Methods

The trial was designed as a prospective, randomized, nonblinded study. All adult patients referred to the University of Pennsylvania...
Table 1. Suggested Antiarrhythmic Agent on the Basis of Heart Disease

<table>
<thead>
<tr>
<th>Heart Disease</th>
<th>Suggested Antiarrhythmic Agent (minimum dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LV function, no obstructive CAD</td>
<td>Propafenone (150 mg TID)</td>
</tr>
<tr>
<td>Normal LV function with CAD</td>
<td>Sotalol (80 mg BID)</td>
</tr>
<tr>
<td>Abnormal LV function</td>
<td>Sotalol (80 mg BID)</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; LV, left ventricle.

*Dose adjusted based on creatinine clearance.

for ablation of AF were screened. Exclusion criteria included persistent AF or atrial flutter, inability to tolerate any AAD, amiodarone therapy within 3 months before the ablation procedure, inability to follow-up at the study site, or participation in another clinical trial. Eligible patients provided consent before their ablation procedure and were randomized in a 1:1 fashion after ablation to either the AAD or no-AAD group using sealed envelopes. Patients who did not undergo pulmonary vein isolation as part of their ablation procedure were excluded before randomization.

In both groups, AF ablation consisted of pulmonary vein isolation and elimination of nonpulmonary vein triggers of AF. For patients in the AAD group, an antiarrhythmic agent was started on the night of the procedure in combination with an atrioventricular (AV) nodal blocking agent. Suggested agents and dosages are summarized in Table 1. Class 1C drugs were recommended as first-line agents for the majority of patients in the absence of structural heart disease. However, the final choice of agent and dosage was left to the discretion of the treating electrophysiologist. For patients in the no-AAD group, only AV nodal blocking agents were restarted after ablation, and treating electrophysiologists were instructed to avoid initiating AADs unless the patients developed atrial arrhythmias associated with severe symptoms or persisting >24 hours. All patients were restarted on intravenous heparin without bolus 6 hours after removal of the vascular sheaths, and warfarin was resumed on the night of the procedure. Patients remained hospitalized under telemetry monitoring until their international normalized ratio was ≥1.8 as per our usual practice after ablation. All antiarrhythmic treatment in-hospital and during the 6-week follow-up study period was prescribed by a study investigator.

All patients were discharged from the hospital with an auto-trigger transumbilical monitor (TTM) for 30 days and were instructed to transmit at least once daily. Monitors were capable of automatic detection and recording of asymptomatic bradycardia, tachycardia, or irregular rhythms such as AF. Patients were instructed that the antiarrhythmic treatment should not be modified by a referring physician without contacting one of the study investigators. Patients were seen for follow-up at 6 to 8 weeks after their ablation, which marked the end of the study.

The primary end point of the study was a composite of (1) atrial arrhythmias lasting >24 hours; (2) atrial arrhythmias associated with severe symptoms requiring hospital admission, cardioversion, or initiation/modification of antiarrhythmic drug therapy; and (3) intolerance to antiarrhythmic agent requiring drug cessation or change. Secondary outcome variables included each individual end point from the composite primary end point. TTM secondary end points included the total number of atrial arrhythmia episodes, the number of atrial arrhythmia episodes other than atrial fibrillation, and the number of days with any atrial arrhythmia during the monitoring period. All TTM strips were over-read by a study investigator.

Statistical Analysis

The incidence of early postablation atrial arrhythmias reported in the literature ranges from 35% to 46%. Therefore, assuming an incidence of the composite primary end point of 40% in the control group and a 50% reduction in the composite primary end point in the drug treatment group, we calculated that a total of 160 patients would have to be included in the study in order to obtain a power of 80% and with a 2-tailed α error of 0.05.

Continuous variables were analyzed using the Student t test, and dichotomous variables were analyzed using the Fisher exact test. For the primary end point of the study, analysis was based on time to a first event, with differences between groups determined by the log-rank statistic, and the time to an event plotted according to the Kaplan-Meier method.

As part of the prespecified study protocol, an interim analysis was performed after randomization of 100 patients to assess for clinical outcome and adverse events. The study could be terminated prematurely if an excess of adverse events was observed in either treatment group or if superiority of either treatment was demonstrated with a probability value <0.01 for the composite primary end point. The criteria for stopping the study met the O’Brien-Fleming boundary for significance assuming 1 interim analysis of the data. All analyses were performed with SPSS version 15.0 software (SPSS Inc., Chicago, Ill).

Results

Enrollment began in December 2006, and the last patient was randomized in March 2008. The study was terminated prematurely after analyzing data for the first 100 randomized patients, which showed a statistically significant reduction in the composite primary end point in the AAD group (P=0.001). The final data analysis included 10 additional patients who were randomized before the decision to stop enrollment was made. Overall, 475 consecutive patients were screened for the study, and 231 were excluded based on predefined exclusion criteria (persistent AF, n=183; persistent atrial flutter, n=6; receiving amiodarone, n=41; no suitable antiarrhythmic agent due to coronary artery disease and severe renal insufficiency, n=1). Therefore, 244 patients were eligible for the study, and 110 patients (47%) were enrolled. The reasons for lack of participation included patient refusal (n=101), physician refusal (n=12), unable to follow up due to distance from the study site (n=6), or enrollment in another study (n=13). Two patients were not randomized due to failure to complete the pulmonary vein isolation procedure (1 patient with nonpulmonary vein AF triggers only and 1 patient with an aborted procedure due to pericardial tamponade); the study protocol specified randomization only after a completed pulmonary vein isolation. Characteristics of the 110 randomized patients were distributed similarly between the 2 groups and are summarized in Table 2. All patients (100%) received the assigned treatment and completed the 6-week follow-up.

At the time of the procedure, 72% of patients were receiving an AAD (74% in the AAD group, 70% in the no-AAD group; P=0.7). Antiarrhythmic agents used after ablation in the active treatment group are summarized in Table 3. Overall, 60% of patients were started on a class 1C agent, 36% of the patients were started on sotalol, and only 2 patients received dofetilide. Sixty-six percent of patients were restarted on the same AAD they were taking just before ablation, and 85% of patients were started on a drug that was previously tolerated. Therefore, only 15% of patients were naïve to the AAD that was used as part of the study protocol (3 patients started on flecainide, 3 patients started on...
propafenone, and 2 patients started on sotalol). The average hospital stay after ablation was not significantly different between the AAD and no-AAD groups (2.7 versus 2.6 days, respectively; \( P=0.7 \)).

Occurrence of the composite primary end point during the 6-week follow-up period was significantly lower in the AAD group compared with the no-AAD group (19% versus 42%; \( P=0.005 \), Table 4). The Figure shows the Kaplan-Meier comparison for occurrence of the primary end point. Even when considering only elements of the composite primary end point that had dramatic clinical impact (arrhythmias lasting >24 hours, hospitalizations for atrial arrhythmias and cardioversions), there was still a reduction of events in the AAD group compared with the no-AAD group (13% versus 28%; \( P=0.05 \)). Three patients in the AAD group experienced side effects presumably related to the antiarrhythmic agent, requiring drug cessation. These side effects consisted of a skin rash, severe fatigue, and recurrent severe headaches. There was no statistically significant difference in the occurrence of the primary end point in patients undergoing their first AF ablation procedure compared with those undergoing a repeat ablation procedure (34% versus 22%; \( P=0.34 \)).

TTM strips were available for 96% of patients. During the 30-day monitoring period, a median of 37 ECG strips were transmitted per patient, with no significant difference between groups. The presence of nonsustained atrial arrhythmias recorded on TTM did not differ significantly between the AAD and no-AAD groups (53% versus 51%; \( P=0.84 \)). However, organized atrial arrhythmias (atrial flutter or atrial tachycardia) were significantly more common in the AAD group (28% versus 11%; \( P=0.02 \)). There was no significant difference in the incidence of spontaneous termination of these organized atrial arrhythmias between groups (73 versus 50%; \( P=0.35 \)).

### Discussion

The results of the current study show that in patients with paroxysmal atrial fibrillation undergoing pulmonary vein isolation, empirical use of AADs for 6 weeks after the procedure significantly reduces the occurrence of clinically significant atrial arrhythmias, including those requiring cardioversion or hospitalization. Most importantly, this reduction is obtained without significantly increasing the occurrence of serious drug side effects. The results of this study suggest that a uniform approach of empirical AAD therapy after ablation is likely to result in patient benefit in the early postablation period without increasing morbidity.

The incidence of atrial arrhythmias in the placebo group of our study was in line with that of the published literature.\(^2,4,10\)

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### Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>AAD Group (n=53)</th>
<th>No-AAD Group (n=57)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>47</td>
<td>53</td>
<td>0.57</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>43</td>
<td>53</td>
<td>0.33</td>
</tr>
<tr>
<td>History of right atrial flutter</td>
<td>34</td>
<td>33</td>
<td>0.94</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13</td>
<td>12</td>
<td>0.88</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>13</td>
<td>12</td>
<td>0.88</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4</td>
<td>2</td>
<td>0.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8</td>
<td>4</td>
<td>0.35</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; LA, left atrium; and LVEF, left ventricular ejection fraction.

### Table 3. Antiarrhythmic Drugs Used in the AAD Group (n=53)

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Patients (%)</th>
<th>Average Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>18 (34)</td>
<td>206±54, mg</td>
</tr>
<tr>
<td>Propafenone</td>
<td>14 (26)</td>
<td>479±115, mg</td>
</tr>
<tr>
<td>Sotalol</td>
<td>19 (36)</td>
<td>194±41, mg</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>2 (4)</td>
<td>500±0 mcg</td>
</tr>
</tbody>
</table>

### Table 4. Occurrence of the Composite Primary End Point in the AAD and no-AAD Groups

<table>
<thead>
<tr>
<th>Event Type</th>
<th>AAD (n=53)</th>
<th>No-AAD (n=57)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia lasting &gt;24 hours or cardioversion</td>
<td>2</td>
<td>15</td>
<td>0.0012</td>
</tr>
<tr>
<td>Adverse effect of AAD</td>
<td>3</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>10 (19)</td>
<td>24 (42)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The \( P \) value for the composite primary endpoint was obtained using log-rank analysis. The \( P \) values for components of the composite primary end point were obtained using the Fisher exact test.

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The Figure. Kaplan-Meier curves showing freedom from the primary end point on the y axis vs time during the study in weeks on the x axis for the AAD and no-AAD groups. The 2 curves diverge early on and remain separated for the duration of the study.
As described in numerous studies, early recurrence of atrial arrhythmias after pulmonary vein isolation is common and does not necessarily indicate failure of the procedure. Some of these arrhythmias may be the result of incomplete pulmonary vein isolation, recovery of conduction in a previously isolated pulmonary vein, or arrhythmogenic foci outside the pulmonary veins. However, these mechanisms would also be expected to correlate also with long-term recurrence. Possible explanations for the transient increase in arrhythmogenicity after pulmonary vein isolation include postablation pericarditis, increased levels of circulating catecholamines, and progression of lesion formation during the early weeks after ablation.

The antiarrhythmic agent and dose was chosen to provide a therapeutic benefit and uniformity among our large group of prescribing physicians. Class IC agents are often well tolerated and effective at therapeutic doses. It is possible that higher use of Sotalol or Dofetilide may have led to a larger number of adverse or proarrhythmic reactions. Amiodarone use before ablation was excluded, because this agent may have antiarrhythmic effects for months after drug cessation. Although antiarrhythmic use after ablation was not long enough to expose patients to the risk of amiodarone toxicity, the delay in onset of action as well as patient and physician preference led no physicians to prescribe this agent after ablation. AV nodal blocking agents were prescribed to all patients in both the antiarrhythmic and no antiarrhythmic ablation. AV nodal blocking agents were prescribed to all patients in both the antiarrhythmic and no antiarrhythmic ablation. AV nodal blocking agents were prescribed to all patients in both the antiarrhythmic and no antiarrhythmic ablation. AV nodal blocking agents were prescribed to all patients in both the antiarrhythmic and no antiarrhythmic ablation. AV nodal blocking agents were prescribed to all patients in both the antiarrhythmic and no antiarrhythmic ablation.

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Limitations
It is possible that use of antiarrhythmic agents merely delayed the eventual AF recurrence until after antiarrhythmic agents were stopped. We think this is unlikely, as numerous studies have documented resolution of arrhythmias after the early postablation period. It is also possible that some of these patients may have had spontaneous resolution of their AF if the option of antiarrhythmic drugs or cardioversion were not provided. However, due to both patient anxiety and physician preference for sinus rhythm to promote reverse electrical remodeling after ablation, it is difficult to withhold these options from patients and physicians after an ablation procedure. Patients with persistent atrial fibrillation were excluded from the study; caution should be taken before expanding the results of this study to persistent AF patients.

Finally, it was our practice during the study to continue heparin after ablation until the international normalized ratio reached 1.8; the average hospital stay after AF ablation at our center was therefore approximately 2.5 days. In a center where discharge occurs on the day after ablation, initiation of a new antiarrhythmic agent may require extending the postablation hospitalization. It is important to note, however, that the vast majority of patients (85%) were prescribed an AAD that was tolerated before ablation and that initiation of a class IC agent does not typically require inpatient hospitalization. Therefore, even in a center where discharge occurs the day after ablation, >90% of patients can be placed on antiarrhythmic therapy without extending the hospital stay.

Conclusions
AAD treatment during the 6 weeks after ablation for paroxysmal AF reduces the risk for early recurrence of atrial arrhythmias and the need for hospitalization or cardioversion. This effect was obtained without significantly increasing the risk of serious side effects associated with AADs. Given the burden of these early arrhythmia recurrences, patients should be treated with AADs for the first 6 weeks after ablation.

Acknowledgments
We thank the electrophysiology fellows John D. Harding, MD, Christopher F. Liu, MD, Sandhya Dhruvakumar, MD, and Roger Fan, MD, for helping to consent patients participating in the study and our physician assistants and nurse practitioners for help with patient recruitment and follow-up. We also thank Anthony Killian, RN, for performing the study randomization.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Early recurrence of atrial fibrillation after pulmonary vein isolation, although not necessarily indicating failure of the procedure, can be associated with bothersome symptoms and lead to the need for cardioversion or hospital visits. Antiarrhythmic drugs are commonly used during the early period after ablation in order to prevent early arrhythmia recurrences, but the benefits of this approach have never been formally studied. The Antiarrhythmics After Ablation of Atrial Fibrillation (5A) Study randomized patients with paroxysmal atrial fibrillation to empirical use of antiarrhythmic drugs or no antiarrhythmic drugs for the first 6 weeks after pulmonary vein isolation. In the 5A Study, antiarrhythmic therapy significantly reduced the risk of early recurrence of atrial arrhythmias and the need for hospitalization or cardioversion. There was no difference in the length of hospitalization, and only 3 patients had an adverse reaction to drug therapy. This demonstrates that use of antiarrhythmic therapy for the initial 6 weeks after ablation is likely to result in fewer symptoms and reduced cost of care.
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