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

Running title: Leong-Sit et al: 5A Study Six Month Follow-up

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Abstract:

**Background**–We previously demonstrated that treatment with antiarrhythmic drugs (AADs) during the first 6-weeks after 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 5A 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 AV nodal blockers. Physicians were encouraged to stop the AADs following the 6-week treatment period. All patients underwent 4-weeks of transtelephonic monitoring to document asymptomatic AF and evaluation at 6 weeks and 6 months. 110 patients (age 55 ± 9 yrs, 71% male) were randomized, 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%) vs 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 vs. 13/34 (38%) with early recurrence; p=0.0001).

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

**Clinical Trial Registration Information**–http://www.clinicaltrials.gov; Unique Identifier: NCT00408200.

**Key words:** atrial fibrillation, ablation, antiarrhythmic agents
Introduction

Empiric use of antiarrhythmic drugs following atrial fibrillation (AF) ablation is commonly used to prevent early AF recurrences which may be troubling for patients and often resolve with “healing” after ablation. Previously, there were no data to support the effectiveness of such an approach. We previously demonstrated in a prospective randomized trial that treatment with antiarrhythmic drugs (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.

There is mixed evidence in the literature regarding the prognostic values of early recurrence of atrial arrhythmias within the first 6-12 weeks post-pulmonary vein ablation. However, prior studies suggest that the presence of AF leads to more AF due to a variety of proposed mechanisms including structural and electrical remodeling. 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. The 5A study was a prospective, randomized, non-blinded study involving patients with paroxysmal AF undergoing pulmonary vein ablation. Paroxysmal atrial fibrillation was defined as typical episodes lasting greater than 30 seconds and spontaneously returning.
to sinus rhythm within 7 days. All adult patients referred to the University of Pennsylvania for ablation of paroxysmal AF were screened. Exclusion criteria included inability to tolerate any antiarrhythmic drug, amiodarone therapy within 3 months of the ablation procedure, and participation in another clinical trial. Eligible patients were enrolled prior to ablation and randomized in a 1:1 fashion to the Antiarrhythmic Drug (AAD) and No Antiarrhythmic Drug (No-AAD) groups immediately after the procedure.

Patients from both groups underwent proximal antral pulmonary vein (PV) isolation guided by intracardiac echocardiogram and circular multipolar electrode catheter recording with a procedural endpoint 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 while the No-AAD group received no antiarrhythmic agents. Both groups received AV 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: 1) normal LV function with no obstructive coronary artery disease (CAD) - propafenone 150mg tid or flecainide 100mg bid, 2) normal LV function with CAD – sotalol 80mg bid, and 3) abnormal LV function – sotalol 80mg bid or dofetilide 500mcg bid. No patients were treated with amiodarone. Physicians were encouraged to stop the AADs following the 6-week treatment period.

The primary endpoint was 6-month freedom from atrial arrhythmias defined as asymptomatic or symptomatic AF, atrial flutter, or atrial tachycardia. The first 6 weeks post-ablation were considered a “blanking period” and any recurrences during this time period 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. Patients were all seen in the office at 6 weeks and 6 months for a detailed
history and electrocardiogram. Patients were also sent a monitor or asked to obtain an
electrocardiogram 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.

**Statistical analysis**

Results were reported as mean ± standard deviation (SD) where applicable. The primary analysis
on the 6-month outcome was performed using Fisher’s exact test on an intention to treat basis followed
by a secondary “per protocol” analysis which excluded patients who remained on antiarrhythmic
medications beyond the designated 6 week treatment period. Unadjusted analyses with normally-
distributed continuous variables (age, BMI, and LA diameter) were analyzed using the Student t-test and
non-normal continuous variables (prior AF duration, number of prior AADs, procedure duration,
number of RF applications, fluoroscopy time) were analyzed using the Wilcoxon rank sum. Unadjusted
analyses for categorical variables (gender, prior AF ablation, history of hypertension, coronary disease,
sleep apnea, and presence of non-PV triggers) were analyzed using Fisher’s exact test.

A multivariable logistic regression model was used to assess for predictors of 6-month freedom
from AF. Gender, prior AF ablation, left atrial enlargement (> 40mm), history of hypertension, coronary
artery disease, obstructive sleep apnea, presence of non-pulmonary vein triggers, long procedure
duration (≥ 5 hour), early AF recurrence (within 6 weeks of the ablation), and randomization arm were
coded as binary covariates. Duration of AF diagnosis (< 2 years, 2-10 years, ≥ 10 years) and body mass
index (< 25 kg/m2, 25-30 kg/m2, ≥ 30 kg/m2) were included as ordinal nested covariates while 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 v9.2 (SAS Institute Inc.) with a p-value < 0.05 considered statistically significant.

Results

As previously detailed, 244 patients were screened and 110 patients (age 55 ± 9 yrs, 71% male) enrolled between December 2006 and March 2008. Exclusions were due to 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 1). Patients randomized to AAD were started on flecainide in 18/53 (34%) patients, propafenone in 14/53 (26%), sotalol in 19/53 (36%), and dofetilide in 2/53 (4%). 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 group (38/53, 72%) and No-AAD group (39/57, 68%); p=0.84. Of those free of AF at 6 months, 3/53 (6%) in the AAD group remained on an antiarrhythmic agent while 4/57 (7%) in the No-AAD group had been started on an AAD (Figure 1). In the AAD group, the 3 patients remained on an AAD because of recurrent AF episodes during the early 6-week post ablation period, although none had recurrent AF after week six. In the no AAD group, two patients were started on an AAD for early AF occurrences and two patients were started on an AAD because of symptomatic atrial premature beats (no AF episodes were recorded). The primary outcome analysis was repeated omitting the patients who were continued on an AAD in the AAD group. After omission of these patients, the results were unchanged and there was no difference between the AAD group (35/50,
70%) and the No-AAD group (39/57, 68%) with respect to freedom from atrial arrhythmias at 6 months (p=1.0).

Comparing patients with recurrent AF to those free of AF at 6 months, age (54.8 vs. 55.7 years, p=0.645) gender (70 vs. 71% male, p=1.000), mean prior AF duration (74 vs. 77 months, p=0.697), number of prior AADs (1.6 vs. 1.6, p=0.949), prior AF ablation (27% vs. 24%, p=0.810), body mass index (29 vs. 30 cm2/kg, p=0.489), left atrial diameter (4.3 vs. 4.2 cm, p=0.697), presence of comorbidities (hypertension (52 vs. 49%, p=1.000), coronary artery disease (21 vs. 10%, p=0.116), sleep apnea (12 vs. 13%, p=1.000)) and procedural variables (procedure duration (5.5 vs. 5.3 hours, p=0.706), RF applications (103.7 vs. 103.8, p=0.715), fluoroscopy time (82 vs. 88 mins, p=0.459), non-PV AF triggers (12 vs. 8%, p=0.483) were not associated with 6-month AF freedom. Lack of early AF recurrence during the initial 6-week “blanking” period was the only predictor of 6-month freedom from AF. Of the 76 patients without early AF recurrence during the 6-week blanking period, 64 (84%) were free of AF at 6 months. Of the 34 patients with early AF recurrence during the 6-week blanking period, only 13 (38%) were free of AF at 6 months. (p<0.001, Figure 2).

A multivariable logistic regression was performed to look for predictors of 6 month recurrence of AF. The only statistically significant predictor recurrence of AF at 6 months was early AF recurrence with an odds ratio of 16.4 (95% confidence interval 4.6-58.1, p<0.001).

Discussion

We found that despite the reduction in events at 6-weeks with antiarrhythmic therapy prescribed immediately following AF ablation, there was no difference in 6-month outcome afforded by empiric
AAD therapy. Therefore, antiarrhythmic therapy after ablation can still be recommended on a symptomatic basis, but does not improve long term AF freedom.

Wijffels et al \(^{10}\), initially described the mechanism of atrial electrical remodeling in goats, supporting the clinical observation that “AF begets more AF”. Wijffels found that even short periods of rapid atrial rate led to a shortening or atrial refractory period that facilitated the maintenance of AF. Further human studies \(^{11}\) also found that new-onset, short-lived AF reduced effective refractory periods and prolonged conduction times in the atria and pulmonary veins. 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, this 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 to allow electrical or structural remodeling, or to prevent the reverse remodeling after ablation that can occur with maintenance of sinus rhythm the majority of the time. Second is that immediate post-ablation 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 is often 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 patients (38%) with early atrial arrhythmias do improve, these data suggest that particular vigilance is required in monitoring patients with early AF recurrence. One may also 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 a month of ablation of persistent AF, 91% had longer term AF recurrence after a mean follow-up of 11 months \(^{12}\). Koyama et al. found that early recurrence within 30 days of ablation corresponded to a 6 month freedom from AF of 30% \(^{13}\). 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**

While 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 post-ablation 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 therefore warranted in these patients, and continuation of anticoagulation, if indicated, should be considered.
Conflict of Interest Disclosures: None

References:


### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>AAD group (n=53)</th>
<th>No AAD group (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>56 ± 8</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Mean AF duration (months)</td>
<td>71 ± 68</td>
<td>81 ± 65</td>
</tr>
<tr>
<td>Mean number prior AADs</td>
<td>1.7 ± 1.1</td>
<td>1.5 ± 0.9</td>
</tr>
<tr>
<td>History of previous AF ablation (%)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>61 ± 8</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Mean LA diameter (cm)</td>
<td>4.3 ± 0.7</td>
<td>4.1 ± 0.6</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Hypertension 47 % 53 %
- Hyperlipidemia 43 % 53 %
- h/o Right atrial flutter 34 % 33 %
- Coronary Artery Disease 13 % 12 %
- Sleep apnea 13 % 12 %
- Chronic Obstructive Pulmonary Disease 4 % 2 %
- Diabetes 8 % 4 %

Data presented as mean ± 1SD=standard deviation; AF=atrial fibrillation; LVEF=left ventricular ejection fraction; LA=left atrium
Figure Legends:

Figure 1. Percentage of patients with freedom from atrial fibrillation 6-months after ablation. There was no significant difference in outcome between patients randomized to early antiarrhythmic drug therapy (Early AAD) compared to those randomized to no antiarrhythmic therapy (no Early AAD).

Figure 2. The only predictor of freedom from atrial fibrillation at 6-months was lack of early AF occurrence during the 6-week “blanking” period. Of those without early AF occurrences, 84% remained free of AF at 6-months compared to only 38% AF freedom in those with early AF occurrences.
N=110
p=0.84

Early AAD
n=53
72%

No Early AAD
n=57
68%
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