Asymptomatic or “Silent” Atrial Fibrillation
Frequency in Untreated Patients and Patients Receiving Azimilide

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Background—Asymptomatic, or “silent” atrial fibrillation could increase the risk of stroke. Little is known about the frequency of asymptomatic atrial fibrillation in patients who also have symptomatic atrial fibrillation; similarly, little is known about the effect of antiarrhythmic drug therapy on asymptomatic atrial fibrillation.

Methods and Results—Patients in sinus rhythm with a history of symptomatic atrial fibrillation or atrial flutter received placebo or azimilide (35 to 125 mg) once daily for 6 or 9 months in 4 similar double-blind trials. The end point was the first recurrence of a symptomatic ECG-documented supraventricular arrhythmia. Routine transtelephonic electrocardiograms, in the absence of symptoms, were recorded for 30 seconds every 2 weeks until patients completed follow-up or documented a symptomatic supraventricular arrhythmia. Of the 1380 patients, 489 received placebo. Among these patients receiving placebo, 303 transmitted at least one routine ECG while asymptomatic. Asymptomatic atrial fibrillation was recorded in 50 (17%) within 6 months and before recurrence of symptomatic supraventricular arrhythmia. In the 3 trials evaluating azimilide in therapeutic doses (100 and 125 mg), asymptomatic atrial fibrillation occurred in 49 of 382 (13%) receiving azimilide and 43 of 233 (18%) receiving placebo. Although drug effect on time to first asymptomatic event was not statistically significant (hazard ratio, 0.70; P=0.09), there was a 40% reduction in asymptomatic atrial fibrillation on azimilide compared with placebo (P=0.03) when repeated observations were considered.

Conclusions—Asymptomatic atrial fibrillation is common in untreated patients with a history of symptomatic atrial fibrillation (and is likely underestimated by this analysis). Azimilide may reduce the occurrence of this silent arrhythmia.

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Key Words: fibrillation ■ atrial flutter ■ antiarrhythmia agents ■ drugs

Atrial fibrillation is the most common arrhythmia that requires medical therapy and accounts for substantial morbidity and mortality, as well as for substantial health-related costs. Although most patients with atrial fibrillation are identified because they have symptoms, atrial fibrillation also may be asymptomatic; in fact, atrial fibrillation is sometimes first diagnosed when patients present with a stroke. Clinical trials of antiarrhythmic drug therapy have treated asymptomatic atrial fibrillation in different ways; some measured only symptomatic arrhythmia recurrence, whereas others considered both symptomatic and asymptomatic arrhythmias as end points and did not report them separately. Few trials have incorporated methods that capture both symptomatic and asymptomatic recurrences and discriminate between them. Because of the difficulty of documenting asymptomatic atrial fibrillation events, it has been challenging to determine whether antiarrhythmic drugs decrease the frequency of asymptomatic recurrences or increase them possibly by converting symptomatic episodes into asymptomatic ones. The 4 recent clinical trials of the class III antiarrhythmic drug azimilide permit data to be combined to address the issue of how this and perhaps other antiarrhythmic drugs affect both symptomatic and asymptomatic atrial fibrillation.

The efficacy of azimilide was studied in 4 double-blind, randomized, placebo-controlled clinical trials with almost identical trial designs. These trials demonstrated antiarrhythmic efficacy of azimilide for symptomatic atrial fibril-
lation, atrial flutter, and paroxysmal supraventricular tachycardia. Routine transtelephonic ECG recordings, recorded every 2 weeks when the patients were asymptomatic, allowed assessment of asymptomatic arrhythmias and comparison between patients receiving placebo and azimilide for this report. Only the patients with atrial fibrillation and/or atrial flutter were included in this study.

Methods

The methods for the 4 randomized, placebo-controlled clinical trials (designated SVA-1, SVA-2, SVA-3, and SVA-4) were identical except for the doses of azimilide tested, numbers of patients receiving each treatment, and length of study period. The duration of study was 270 days in SVA-1 and SVA-2 and 180 days in SVA-3 and SVA-4. The doses tested were 100 mg/d in SVA-1; 35 and 75 mg/d in SVA-2; 50, 100, and 125 mg/d in SVA-3; and 125 mg/d in SVA-4. The present study represents the analysis for a prespecified (but not primary) end point of these trials. Although data from 4 separate trials are combined, the study design similarities allow meaningful combination of the data in order to increase the statistical power of the analysis.

Entry Criteria

Male or female patients over 18 years of age were eligible if they (1) had a history of symptomatic atrial fibrillation and/or flutter, (2) were candidates for antiarrhythmic medication, (3) had documentation of their symptomatic arrhythmia by 12-lead ECG, inpatient ECG telemetry, or by transtelephonic ECG within the preceding 24 months, and (4) were in normal sinus rhythm at the onset of randomized therapy. Detailed criteria for enrollment are included in a previous study. Patients were required to give written informed consent, using a document approved by an institutional review board for clinical investigation at their study site. Procedures followed were in accordance with institutional guidelines.

The key exclusion criteria were angina at rest; unstable angina; symptoms of heart failure at rest; history of torsade de pointes; patients who received nontherapeutic doses of azimilide (35 mg and 75 mg in SVA2 and 50 mg in SVA3) were not considered when testing for a treatment effect.

Data Analysis and Statistical Methods

Patients with documented atrial fibrillation and/or atrial flutter were entered into the 4 trials. Consistent with prior reports, the entire stratum of patients with atrial fibrillation and/or atrial flutter is considered for this present analysis.

Transtelephonic monitor electrocardiograms observed every 2 weeks were considered to be an "asymptomatic event" if they showed atrial fibrillation. Electrocardiograms typical for atrial flutter and paroxysmal supraventricular tachycardia were not considered in these analyses (although additional analysis showed that inclusion of these arrhythmias as end points did not affect the results—see below). Only data through 26 weeks of follow-up were considered for these analyses, since 2 of the 3 studies that used the therapeutic doses of azimilide (100-mg and 125-mg azimilide doses lasted only 26 weeks. In addition, patients who received nontherapeutic doses of azimilide (35 mg and 75 mg in SVA2 and 50 mg in SVA3) were not considered when testing for a treatment effect.

Two types of analyses were conducted to assess the effect of azimilide on asymptomatic atrial fibrillation. The first analysis was based on time-to-event and was similar to the underlying study design of the clinical trials from which the data were obtained. The second analysis used repeated measures, in which each patient was followed until study completion (the symptomatic end point was reached, the patient withdrew, or the entire follow-up period was completed with no end point documented), and may have contributed multiple asymptomatic atrial fibrillation events over the course of the study. When data from more than one study were combined, “study” was used as a stratification variable to adjust for differences between placebo groups. SAS/STAT software was used to perform all statistical analyses.

For the time-to-event analysis, the outcome was the first documented occurrence of asymptomatic atrial fibrillation. The Kaplan-Meier life-table method was used to summarize the distribution of the time to first recorded event for each treatment group, and proportional hazards modeling was used to calculate the hazard ratio (azimilide-placebo) with 95% confidence intervals for each treatment group. Follow-up data from patients who withdrew from the trials were censored at the time they withdrew. Data from patients who did not have any asymptomatic atrial fibrillation within 26 weeks had their follow-up data censored at 26 weeks. The log-rank test was used to test for equality among placebo groups across the 4 studies.

For the repeated-measures analysis, a Poisson log-linear regression model with repeated subject effects was used to estimate the expected number of patients demonstrating asymptomatic atrial fibrillation events per call. The model used categoric variables for treatment and to control for study. An exchangeable correlation structure was used to account for within-patient correlation. The scale parameter and deviance criteria were used to assess the goodness-of-fit of the model.

Results

Patient Population

Patients (n=1380) with atrial fibrillation or flutter were enrolled in the 4 studies (mean age, 63±12 years; 66% men). Structural heart disease, as defined previously, was present in 73% of patients, with 13% having a history of congestive heart failure and 28% having ischemic heart disease. Direct current cardioversion had been performed in 35% of the patients.
Time to Occurrence of Asymptomatic Atrial Fibrillation in Patients Receiving Placebo

Among the 4 studies, 489 patients received placebo. Of this total, 303 patients contributed at least one routine ECG in the absence of symptoms (an “asymptomatic ECG”), 154 patients completed the study by having a symptomatic end point arrhythmia before any routine transtelephonic ECG was recorded, and 32 patients withdrew from the study before transmitting a routine ECG. Of the 303 patients receiving placebo who were contributing an asymptomatic ECG, atrial fibrillation was recorded in 50 (17%) and at least 1 asymptomatic atrial fibrillation event was recorded within the first 4 weeks in 35 (12%). The corresponding Kaplan-Meier estimates of the proportions (of patients) with at least 1 asymptomatic event within 4 weeks and 26 weeks were 0.13 and 0.21, respectively (Figure 1). Looking at the 4 trials individually, asymptomatic atrial fibrillation was present in 10% to 20% of patients; the log-rank test did not indicate a significant study effect (P=0.41) when applied to these placebo groups.

Comparison of Patients Receiving Azimilide With Patients Receiving Placebo

The patients who received azimilide in doses of 100 mg or 125 mg daily in SVA-1, SVA-3, and SVA-4, were evaluated for occurrence of asymptomatic atrial fibrillation. They were compared with the patients receiving placebo from those same studies. Asymptomatic atrial fibrillation was seen in 49 of 382 (13%) patients taking azimilide compared with 43 of 233 (18%) of the patients taking placebo in the same trials (Figure 2). The estimated hazard ratio for the time to first occurrence was 0.70 (95% CI=[0.46,1.06]; P=0.09).

Proportion of Patients in Atrial Fibrillation on Each Routine Recording

In addition to considering the time to first occurrence of asymptomatic atrial fibrillation, we examined the proportion of patients with atrial fibrillation at the time of each routine transtelephonic ECG (Figure 3). With the first recording at week 2, 20 of 231 (9%) of the patients receiving placebo had atrial fibrillation compared with 21 of 379 (6%) of the patients receiving 100 mg or 125 mg azimilide. Subsequent proportions could include patients who previously demonstrated atrial fibrillation, although the overall number of patients enrolled was reduced over time (because of completion with a symptomatic recurrence or withdrawal for other reasons). The percentage of patients with asymptomatic atrial fibrillation was lower in the azimilide group for all but 2 time points (Figure 3). When considering repeated observations (ie, ECGs within patients), the Poisson model showed a significant treatment effect (P=0.03) and an estimated 40% (95% CI=[5%, 63%]) reduction in the occurrence of asymptomatic AF for patients in the azimilide treatment group.

Study Group and End Points

As above, only atrial fibrillation was considered to be an end point of this analysis. However, when asymptomatic arrhythmia events with transtelephonic ECGs typical for atrial flutter were included in the current study, only 4 additional patients contributed events, and the results did not change materially. Of these 4 patients, 2 were receiving therapy and 2 received placebo, so no trend was seen in terms of possible azimilide...
effect on the recurrent arrhythmia. Asymptomatic paroxysmal supraventricular tachycardia was not observed.

Discussion
This report has two important messages. First, in a population of patients with a history of symptomatic atrial fibrillation or atrial flutter, asymptomatic atrial fibrillation is commonly seen (=1 of 5 patients) before a symptomatic recurrence of any supraventricular arrhythmia is detected. Therefore, in evaluating stroke risk in patients with a history of atrial fibrillation, the absence of symptoms should not be interpreted as the absence of atrial fibrillation. Second, some antiarrhythmic drugs (such as azimilide) may reduce the frequency of asymptomatic atrial fibrillation. The antiarrhythmic drug azimilide (at doses of 100 mg and 125 mg daily) has been shown to be effective in reducing the frequency of recurrent symptomatic arrhythmias in patients with atrial fibrillation and/or atrial flutter.11,12 The drug’s potential adverse effects include an incidence of torsade de pointes of 0.9% and an incidence of severe neutropenia (absolute neutrophil count <500 cells/μL) of 0.2% at the therapeutic doses.12 A reduction in the occurrence of asymptomatic atrial fibrillation must not be assumed to reduce the risk of stroke and therefore should not be seen as reducing the need for anticoagulation, however.

Our study used systematic procedures for capturing asymptomatic arrhythmias by recording a 30-second electrocardiographic “snapshot” every 2 weeks. This methodology probably underestimated the occurrence of these events, such that the true frequency of asymptomatic atrial fibrillation is higher than the 17% by 26 weeks that we documented in untreated patients. Even so, this statistic of 1 in 6 patients having asymptomatic atrial fibrillation within 6 months is a low-end estimate and represents important information for the practicing physician.

Asymptomatic Atrial Fibrillation in Untreated Patients
Unrecognized or asymptomatic atrial fibrillation has long been recognized as a finding with important implications for the occurrence of stroke. In the Framingham study, an early report demonstrated that among patients with stroke associated with atrial fibrillation, the arrhythmia was newly diagnosed in 24%.6 A subsequent report from Framingham showed newly diagnosed atrial fibrillation on admission in 18% of patients with atrial fibrillation–related stroke and subsequent diagnosis of paroxysmal atrial fibrillation within 14 days in another 4.4%.7 Although these reports did not specify that the atrial fibrillation was asymptomatic, it was not bothersome enough to prompt medical attention. In the Canadian Registry, 142 (21%) of 674 patients with atrial fibrillation were asymptomatic.16 Page et al4 demonstrated that asymptomatic atrial fibrillation (runs of ≥30 seconds) was found to occur 12 times more frequently than symptomatic recurrences in a cohort of 8 highly selected patients with known symptomatic atrial fibrillation who were receiving no antiarrhythmic therapy. Another study examined the frequency of atrial arrhythmias recorded by a dual chamber pacemaker in patients with conduction disease or sinus nodal dysfunction. Of 354 patients, 104 (29%) demonstrated asymptomatic supraventricular arrhythmias within 28 days of implantation; 76 of these had never previously been documented to have any atrial arrhythmia.17

Asymptomatic Atrial Fibrillation in Patients Receiving Medical Therapy
The occurrence of asymptomatic atrial fibrillation in the context of antiarrhythmic drug therapy is recognized but has received little systematic study. If antiarrhythmic drugs make atrial fibrillation less symptomatic by slowing the heart rate during arrhythmias or shortening periods of arrhythmia, then antiarrhythmic therapy might simply convert symptomatic arrhythmia episodes into asymptomatic ones.18–21 Wolk et al,18 using 24-hour ambulatory monitors in patients with paroxysmal atrial fibrillation treated with propranolol and propafenone, showed that atrial fibrillation was frequent among patients who remained asymptomatic on this therapy; 4 of 18 (22%) patients receiving propranolol and 7 of 26 (27%) receiving propafenone recorded atrial fibrillation without symptoms.

The atrioventricular nodal–blocking agent digoxin likewise demonstrated a reduction in symptomatic paroxysmal atrial fibrillation in terms of prolongation of the median time to first and second arrhythmia recurrence.21 However, 24-hour ambulatory monitors did not confirm a reduction of frequency or duration of atrial fibrillation or of ventricular rate. The authors concluded that the most plausible explanation for the reduction of symptoms, despite a failure to demonstrate a change in arrhythmia, was that digoxin was causing atrial fibrillation to become asymptomatic as the result of either changes in ventricular rate or regularity.

Relative Effect of Azimilide on Symptomatic and Asymptomatic Atrial Fibrillation
Our study was not designed to compare the efficacy of azimilide in treating symptomatic versus asymptomatic events. However, the meta-analysis of efficacy of azimilide in treating symptomatic recurrence provides some insight to the relative efficacy of azimilide.12 In that analysis, the hazard ratio (HR) for symptomatic recurrence on placebo versus azimilide was 1.34 for 100 mg/d and 1.32 for 125 mg/d. Expressed as azimilide to placebo HRs, the effects in the Connolly analysis are 0.75 and 0.76, respectively. Indeed, these HR values are comparable to the value of 0.7 that we describe for asymptomatic AF during therapy with 100 or 125 mg/d of azimilide, suggesting the effect on asymptomatic and symptomatic recurrence may be similar.

In addition, qualitative inspection of Figures 1 and 2 shows a relatively steep drop-off in the curves, consistent with early recurrence of asymptomatic atrial fibrillation in both treated and untreated patients. The shape of these curves is comparable to the curve generated in a previous report on the effect of azimilide on symptomatic atrial fibrillation,12 suggesting additional similarities between time to first event evaluations of symptomatic and asymptomatic atrial fibrillation and perhaps similar azimilide efficacy for these two end points.

Clinical Implications
This study confirms that asymptomatic atrial fibrillation occurs commonly among patients who are candidates for antiarrhyth-
mic drug therapy. These asymptomatic periods of atrial fibrillation add to the atrial fibrillation “burden” and contribute to continued stroke risk and possibly to atrial remodeling. This study also suggests that some antiarrhythmic drugs do not increase the occurrence of asymptomatic atrial fibrillation and may decrease it, as was shown here for the investigational drug azimilide. Until the role of antiarrhythmic drug therapy in reducing the risk of stroke has been studied more thoroughly, clinicians should continue to use anticoagulation as the primary method to reduce stroke risk in these patients.

**Limitations**

Our study used data from 4 studies designed primarily to evaluate occurrence of symptomatic arrhythmias. As such, there may be patient selection or other processes that influence the estimates of asymptomatic occurrence or treatment effects in important ways not accounted for in our analyses.

The likelihood that we have underestimated the true frequency of asymptomatic atrial fibrillation is addressed above. Despite the limitation of underestimating the frequency of asymptomatic atrial fibrillation, this is the largest systematic study published examining the frequency of asymptomatic atrial fibrillation in untreated patients and those receiving antiarrhythmic therapy. In addition, although studies from implanted devices have the potential advantage of assessing frequency and duration of atrial fibrillation over an extended period of time, they cannot characterize the frequency in the majority of patients with atrial fibrillation (with no indication for a pacemaker or implantable cardioverter-defibrillator).

Patients with a history of atrial fibrillation, atrial flutter, or both were combined in these studies to be as inclusive as possible and to recognize that atrial fibrillation and flutter overlap significantly. Since the risk of stroke with atrial flutter is less well established, we did not include asymptomatic atrial flutter in this current study. In our set of asymptomatic arrhythmia events, only 4 episodes of flutter were observed, and inclusion of flutter in the analysis made no difference in the conclusions. There were no episodes of asymptomatic paroxysmal supraventricular tachycardia, consistent with a previous study.

**Conclusions**

Asymptomatic atrial fibrillation occurs commonly in patients with symptomatic atrial fibrillation and atrial flutter and is likely to be even more common than we have shown. During therapy with the investigational antiarrhythmic drug azimilide, there was a trend toward reduced asymptomatic atrial fibrillation.

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**References**


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