Azimilide for the Treatment of Atrial Fibrillation, Atrial Flutter, and Paroxysmal Supraventricular Tachycardia: Results of a Randomized Trial and Insights on the Concordance of Symptoms and Recurrent Arrhythmias

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Azimilide Efficacy and Symptom Concordance. **Introduction:** Azimilide hydrochloride is an investigational antiarrhythmic medication that had shown evidence of efficacy in prolonging the time to recurrence of atrial fibrillation (AF) or atrial flutter (AFL) and paroxysmal supraventricular tachycardia (PSVT). This study was designed to confirm efficacy of 125 mg daily azimilide.

**Methods and Results:** The primary endpoint was ECG-documented recurrence of AF, AFL, or PSVT, followed for a maximum of 180 days. Four hundred eighty-two patients were enrolled in the United States and Canada (422 with AF or AFL and 60 with PSVT). The primary efficacy analysis included 402 patients with AF-AFL and 56 patients with PSVT. There was no significant difference in the time to first recurrence of symptomatic supraventricular arrhythmia in the AF-AFL stratum (median of 38 days for azimilide versus 27 days for placebo; hazard ratio [HR] of 1.14, P = 0.29). Similarly, there was no difference in time to recurrence in the PSVT stratum (>180 days for azimilide versus 135 days for placebo; HR = 1.28, P = 0.55). There were three deaths in the azimilide group and one in the placebo group. Four patients had nonsustained ventricular tachycardia (one torsades de pointes), all in the azimilide group. Asymptomatic recurrence was frequent in the AF-AFL group (8% with azimilide and 11% with placebo), but was absent in the PSVT group. False recurrence was common in both groups.

**Conclusion:** Azimilide 125 mg daily was not associated with significant prolongation of the time to recurrent symptomatic supraventricular arrhythmias. There was substantial discordance between symptoms and recurrence. (J Cardiovasc Electrophysiol, Vol. pp. 1-6)

atrial fibrillation, azimilide, silent atrial fibrillation, asymptomatic, false recurrence, antiarrhythmic medication

**Introduction**

Atrial fibrillation is the most common arrhythmia that requires therapy, accounting for substantial health care costs in the USA and elsewhere. Despite advances in nonpharmacologic therapy and the evidence that antiarrhythmic drug therapy does not improve survival, many patients receive medical therapy for atrial stabilization in an effort to reduce symptoms. Currently available antiarrhythmic agents are limited due to modest efficacy and substantial risk of toxicity. Azimilide dihydrochloride (azimilide) is a novel Vaughn Williams class III agent that was shown in previous studies to reduce symptomatic arrhythmia recurrence in patients with a history of atrial fibrillation (AF), atrial flutter (AFL), or paroxysmal supraventricular tachycardia (PSVT). This study was designed to further evaluate the efficacy and safety of azimilide in patients with these symptomatic supraventricular arrhythmias, employing a single dose that appeared in those previous studies to have clinical efficacy.

**Methods**

**Entry Criteria**

Male and female patients 18 years or older were eligible if they had a history of symptomatic AF, AFL, or PSVT and were candidates for antiarrhythmic medication in the judgment of their physician. An institutional review board at each site approved the protocol. Patients were required to give written informed consent for participation in the trial. Enrolling investigators were obligated to provide either 12-lead ECG or transtelephonic ECG of the arrhythmia recorded within 24 months of enrollment. The patients were required to demonstrate sinus rhythm...
immediately before initial dosing. Important exclusion criteria were: supraventricular arrhythmia (SVA) due to acute electrolyte disturbance, hyperthyroidism, pericarditis, or other reversible cause; NYHA class IV congestive heart failure; unstable angina; history of polymorphic ventricular tachycardia (including torsades de pointes) or sustained ventricular tachycardia; Wolff-Parkinson-White syndrome; resting heart rate below 50 beats per minute; history of Mobitz type II or complete heart block; current use of class I or class III antiarrhythmic drugs (and no amiodarone for 1 month); unresolved organ toxicity due to amiodarone; use of other agents that prolong QTc within five half-lives of the agent; QTc (Bazett’s) >440 ms during sinus rhythm; elevated blood pressure (systolic >160 and diastolic >100 mm Hg); severe valvular disease; history of syncope, angina, congestive failure, or sudden death associated with any arrhythmia; acute myocardial infarction, cardiothoracic surgery, or neurologic event within 2 months; implantable cardioverter-defibrillator; underlying terminal illness with life expectancy <1 year; current pregnancy or breast feeding, or plan for pregnancy within 1 year; recreational drug use or alcohol abuse; current psychosis; or significant laboratory abnormality (ALT or AST >2 times normal, BUN >50 mg/dL, creatinine >2.0 mg/dL, potassium <3.8 mEq/L, or >5.5 mEq/L).

Randomization and Follow-Up

The investigator classified patients at the time of study entry as manifesting AF, AFL, or PSVT as their “index arrhythmia.” Patients with AF or AFL were assigned to a single stratum (AF-AFL stratum) for randomization and patients with PSVT were assigned to a separate stratum (PSVT stratum). Patients in both strata were randomly assigned in a 1:1 fashion to receive azimilide 125 mg tablets or matching placebo. The first dose of study drug until exit from the trial. Adverse events were counted if they occurred within 30 days of withdrawal from the trial for any reason. Safety variables reported here include deaths, occurrences of torsades de pointes, occurrences of other ventricular tachycardias, withdrawal from the study because of adverse events, neutropenia, and the adverse events most commonly reported by patients. Deaths were classified by the event committee using a variant of the Hinkle system.9 Serious adverse events were defined according to industry guidelines. The Data Safety Monitoring Board reviewed unblinded safety data, primarily serious adverse events, at periodic intervals.

Further analysis of the concordance of symptoms and recurrent supraventricular arrhythmias was performed for the patients who met inclusion criteria and entered the efficacy period. Asymptomatic recurrence was defined as the occurrence of supraventricular arrhythmia as recorded on the routine 30-second recording. False recurrence was defined as symptoms that were reported by the patient to represent recurrent supraventricular arrhythmia but another rhythm was documented by TTM. Both asymptomatic recurrence and false recurrence were categorized by cohort (AF-AFL or PSVT) and by treatment group (azimilide or placebo).

Study Chronology

The first and last patients were enrolled on July 2, 1998, and November 30, 1998, respectively. The last patient observation took place on June 30, 1999, and the database was locked on July 31, 1999.
Results

Study Population

A total of 482 patients were enrolled. There were 422 patients in the AF-AFL stratum; of these, 66% had a history of AF alone, 5% AFL alone, 20% both AF and AFL; 8% had a history of PSVT also. There were 60 patients with PSVT; 17% had a history of atrial fibrillation as well. The first dose was administered while the patient was in the hospital in 38 (9%) of the AF-AFL group and none of those with PSVT. Demographic and baseline characteristics for both the AF-AFL and PSVT strata were similar among the treatment groups, as were concomitant medications. Mean age was 61 years; 63% were men. A history of congestive heart failure was reported in 13%, cardiomyopathy in 6%, and valvular heart disease in 42%. Left ventricular ejection fraction measurement was not available. The only differences observed were in the PSVT stratum, where smaller numbers allowed for disproportionately higher percentage of male patients, black patients, and those with structural heart disease in the azimilide group.

Efficacy Analyses

Among the 422 AF-AFL patients, 409 entered the efficacy period, as did 57 of the 60 PSVT patients. Among the patients who entered the efficacy period, seven AF-FL patients and one PSVT patient failed to meet inclusion criteria, so they were not included in the primary efficacy analysis. Their data were included in analyses that examined all randomized patients and in safety analyses.

Primary and other efficacy analyses for the AF-FL stratum

The median time to symptomatic arrhythmia occurrence was 38 days in the azimilide group and 27 days for placebo, yielding a placebo-to-azimilide hazard ratio of 1.14 (P = 0.29, 95% confidence interval = 0.89, 1.47) (see Fig. 1A). Further analyses that measured recurrence from the first day...
of the loading period (all randomized patients) showed no difference between the two groups, nor did a comparison of the number of events that occurred during the loading period (27 events on azimilide and 34 on placebo, \( P = \text{NS} \)).

The secondary analysis of heart rate during a recurrent arrhythmia demonstrated no significant difference (119 beats per minute for azimilide vs 122 for placebo; \( P = 0.32 \)).

Subgroup analyses were conducted according to the protocol, with analysis performed for the following subgroups: gender, age, blood pressure, weight, congestive heart failure, ischemic heart disease, valvular disease, atrial enlargement, structural heart disease, prior cardioversion, digoxin, and smoking. All results were consistent with the primary efficacy analysis.

**Primary efficacy and secondary analyses for the PSVT stratum**

The median time to symptomatic arrhythmia occurrence was >180 days in the azimilide group and 135 days for placebo, yielding a placebo-to-azimilide hazard ratio of 1.28 (\( P = 0.55, 95\% \) confidence interval = 0.57, 2.89) (see Fig. 1B). As in the AF/FL group, further analyses that included the loading phase demonstrated no difference in overall time to recurrence and no difference in risk during the loading period.

The secondary analysis of heart rate during a recurrent arrhythmia demonstrated a significant difference with rate of 130 beats per minute on azimilide and 171 on placebo (\( P = 0.003 \)).

**Safety**

Safety data were collected for all patients who received study drug and data were collected for 30 days after withdrawal from the study. Three patients receiving azimilide (1.2%) and one receiving placebo (0.4%) died during the study. Three of the deaths were classified as cardiac arrhythmic (two azimilide and one placebo). Considering time on treatment, the mortality rates were 5.7 versus 2.0 deaths per 100 years for azimilide and placebo, respectively (\( P = \text{NS} \)).

Adverse events were reported in 66% of azimilide and 58% of placebo patients. Investigators withdrew 15 (6%) azimilide patients and six (2%) of placebo patients from the study due to adverse events (\( P = \text{NS} \)). The most frequent events for both groups were asthenia, headache, and respiratory infection (each reported in 10% of azimilide-treated patients). Serious adverse events (including the four deaths described above) were reported in 17 azimilide patients and nine placebo patients. There was one documented episode of torsades de pointes, occurring in an azimilide patient during surgery to repair an abdominal aortic aneurysm; this resulted in ventricular fibrillation that was treated satisfactorily with countershock. Three azimilide patients were reported to experience nonsustained ventricular tachycardia. Symptomatic ventricular ectopic beats were reported in one patient taking azimilide and one receiving placebo. Syncope was reported in only one patient receiving placebo. Agranulocytosis was observed in one patient receiving azimilide; this resolved after withdrawal of the drug.

Prolongation of the QTc (as measured by routine 12-lead ECG) beyond baseline was observed throughout the study in the patients receiving azimilide, with mean prolongation of 10.6% at 6 months, compared with 0.8% in patients receiving placebo. Four patients (all receiving azimilide) were withdrawn for QTc prolongation, with QTc intervals ranging from 499 to 608 ms, as measured in a blinded fashion post hoc by the event committee.

**Asymptomatic and False Recurrence**

Asymptomatic recurrence of a supraventricular arrhythmia in the AF-FL group was seen in 17 of 202 patients (8%) on azimilide and in 22 of 200 (11%) receiving placebo. In contrast, there were no episodes of asymptomatic recurrence in the PSVT stratum, with 29 patients receiving azimilide and 27 receiving placebo (see Fig. 2).

False recurrence was common in all groups, as shown in Figure 2. Among patients with AF-AFL receiving placebo, 62 of 200 (31%) provided such recordings. Similar frequency of false recurrence was observed among the patients receiving azimilide, with 72 of 202 (36%) providing a total of 192 events where recurrence was reported but no index supraventricular arrhythmia was reported. Most of these patients (49 of 72) and most recordings (101 of 192) demonstrated sinus

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**Figure 2.** Frequency of asymptomatic and false recurrence in study groups.
rhythm without ectopic beats. Next most common rhythms recorded were sinus with premature supraventricular beats (26 patients) and sinus with premature ventricular beats (11 patients). The most common symptom was palpitations, reported in 81% of the patients receiving placebo and 74% of those receiving azimilide. Patients in the PSVT cohort also manifested false recurrence. Among the combined azimilide and placebo patients, 32 of 56 (57%) reported a total of 110 false recurrences. As with the AF/AFL cohort, the most frequent symptom was palpitations, reported in 91% of patients with false recurrence.

Discussion

Main Study Results

The primary result of this study is that azimilide failed to reduce the recurrence of AF/FL or PSVT. Trends toward prolongation of the time to symptomatic recurrence were seen, but the degree of effect was not clinically important.

Tolerability of azimilide was generally good, with predictable QT prolongation and infrequent torsades de pointes. Of the four deaths reported, three were sudden and two of these were in the azimilide group. A previous study in high-risk patients postmyocardial infarction demonstrated no effect of azimilide on mortality.9

Prior studies, entitled SVA 1, 2, and 3, had shown variable efficacy of azimilide,3,5,10 although SVA-3, the only study that had previously studied the effect of azimilide 125 mg daily, showed a significant effect with a hazard ratio of 1.58.5 Partial results of the study presented in this article previously were incorporated into a combined analysis of all four SVA studies, showing a dose-dependent benefit of azimilide in prolonging the time to recurrence of AF/FL.3 That article included a combined subgroup analysis suggesting that patients who had ischemic heart disease and/or congestive heart failure might derive the greatest benefit from azimilide therapy. Since that high-risk group of patients has limited options for antiarrhythmic drug action and had previously been shown to derive a neutral mortality effect from azimilide,9 further study was undertaken to further define the drug effect in this population. Studies in patients with and without structural heart disease and those post cardioversion did not show significant benefit to azimilide.11,12

This is the second study to evaluate the antiarrhythmic effect of azimilide on the recurrence of SVA in patients with symptomatic PSVT. The previous report of 193 patients with PSVT provided a hazard ratio of 2.35 at 100 mg and 1.28 at 125 mg; although only the 100 mg comparison was statistically significant, a combined analysis (100 mg with 125 mg) showed a significant prolongation of time to recurrence (P = 0.02).8 Our data provide an identical hazard ratio as the previous experience with 125 mg daily, confirming a modest (but not significant) effect on recurrence. The secondary analysis, demonstrating a significant slowing of the heart rate during recurrent arrhythmia, is of questionable clinical significance.

Concordance of Symptoms with Arrhythmia Recurrence

Asymptomatic, or silent, AF has become well recognized in recent years. In a population of patients with established symptomatic AF, asymptomatic recurrence has been shown to occur up to 12 times more frequently than symptomatic recurrence.8 In the first three azimilide trials, asymptomatic recurrence was evaluated in similar fashion with this study, with 17% on placebo and 11% on azimilide (100 or 125 mg) demonstrating asymptomatic AF before having a documented symptomatic recurrence. This study confirms frequent asymptomatic recurrence, although somewhat lower at 11% on placebo and 8% on azimilide. The lower rates in this study may relate to the shorter follow-up that resulted from earlier symptomatic recurrence or may suggest a lower overall frequency of silent AF. Even the lower event rate observed in this study suggests that a far greater frequency would be documented if monitoring were continuous (as opposed to just 30 seconds every 2 weeks). It should be noted that asymptomatic recurrence has been reported in patients following ablation for AF. Although one study suggested that this was uncommon,13 further studies suggest that asymptomatic recurrence occurs frequently following ablation.14,15

False recurrence in patients with AF and PSVT has been described.16 In SOPAT (Suppression of Paroxysmal Atrial Tachyarrhythmias Trial), using a protocol that included daily TTM recordings, AF was only present in 37% of symptom-triggered ECG recordings.17 False recurrence has also been reported in patients post ablation; one study that included daily and symptomatic TTM transmissions for 6 months post ablation, 11% of the recordings in sinus rhythm were accompanied by symptoms consistent with recurrence AF.18 Our study provides additional insight regarding patients who have not undergone ablation. ECG documentation was available for all episodes (assuming a functional ECG event recorder) and demonstrated that one patient in three who has AF or AFL will report a false recurrence before a true symptomatic recurrence would be experienced. This phenomenon of false recurrence should dictate prudence in considering changes in therapy based on self-reported recurrence. It is noteworthy that patients with PSVT who previously and in this study have been shown to be free of silent recurrence, nevertheless have false recurrence before they demonstrate true recurrence in over half of the patients studied, suggesting that clinicians should not make therapeutic decisions about PSVT recurrence based on symptom reporting alone.

Conclusion

The SVA-4 trial did not show a statistically significant or clinically important effect in reducing recurrence of symptomatic AF/FL or PSVT. The results expand our understanding of the concordance of symptoms and recurrence of supraventricular arrhythmias.

References

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