Placebo-Controlled, Randomized Clinical Trial of Azimilide for Prevention of Ventricular Tachyarrhythmias in Patients With an Implantable Cardioverter Defibrillator

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Background—Although implanted cardioverter defibrillators (ICDs) effectively treat sustained ventricular tachyarrhythmias, up to 50% of ICD recipients eventually require concomitant antiarrhythmic drug therapy to prevent symptomatic arrhythmia recurrences and hence reduce the number of device therapies.

Methods and Results—A total of 633 ICD recipients were enrolled in a randomized, double-blind, placebo-controlled study to evaluate the effect of daily doses of 75 or 125 mg of azimilide on recurrent symptomatic ventricular tachyarrhythmias and ICD therapies. Total all-cause shocks plus symptomatic ventricular tachycardia (VT) terminated by antitachycardia pacing (ATP) were significantly reduced by azimilide, with relative risk reductions of 57% (hazard ratio [HR]=0.43, 95% CI 0.26 to 0.69, P=0.0006) and 47% (HR=0.53, 95% CI 0.34 to 0.83, P=0.0053) at 75- and 125-mg doses, respectively. The reductions in all-cause shocks with both doses of azimilide did not achieve statistical significance. The incidence of all appropriate ICD therapies (shocks or ATP-terminated VT) was reduced significantly among patients taking 75 mg of azimilide (HR=0.52, 95% CI 0.30 to 0.89, P=0.017) and those taking 125 mg of azimilide (HR=0.38, 95% CI 0.22 to 0.65, P=0.0004). Five patients in the azimilide groups and 1 patient in the placebo group had torsade de pointes; all were successfully treated by the device. One patient taking 75 mg of azimilide had severe but reversible neutropenia.

Conclusions—Azimilide significantly reduced the recurrence of VT or ventricular fibrillation terminated by shocks or ATP in ICD patients, thereby reducing the burden of symptomatic ventricular tachyarrhythmia. (***Circulation*. 2004;110:3646-3654.)**

Key Words: drugs ■ cardioversion ■ defibrillation ■ antiarrhythmia agents ■ tachycardia

Implanted cardioverter defibrillators (ICDs) effectively treat sustained ventricular arrhythmias and thereby prolong life compared with antiarrhythmic drug therapy (or no antiarrhythmic drug therapy) in patients at risk for sustained ventricular tachyarrhythmias.[1–4] However, many patients with an ICD have ventricular tachyarrhythmias that may cause transiently disabling symptoms and may lead to painful ICD shocks. In patients implanted with defibrillators after sustained ventricular tachyarrhythmias, quality of life improves in many but not in those who require multiple ICD therapies.[5] Over time, 30% to 50% of ICD recipients receive antiarrhythmic drug therapy to prevent symptomatic tachyarrhythmias and to reduce the number of device therapies.[6–8] Moreover, defibrillator therapies often occur in clusters, which suggests that the recurrence of ventricular tachyarrhythmias is not randomly distributed in time.[9–11]

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No antiarrhythmic drug is currently approved by regulatory agencies in North America or Europe for use in ICD recipients. The range of currently available antiarrhythmic drugs for this indication is limited, particularly because of adverse effects. Drugs with class I action are contraindicated in patients with coronary artery disease or left ventricular dysfunction.[12] Although sotalol, a drug with class III and β-blocking action, has been shown to be effective as an

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adjunct in patients with an ICD,[6] it can cause adverse effects and complicates concomitant therapy with those β-blockers that are indicated for the large proportion of ICD patients who have congestive heart failure. The use of amiodarone is limited by multiple serious adverse effects, which accumulate over time.[13]

Azimilide dihydrochloride is an investigational antiarrhythmic drug with potassium channel (I_{Kr} and I_{Ks})–blocking properties that prolongs the cardiac action potential and refractory periods. In a pilot study in ICD patients, its use was associated with a significant reduction in the recurrence of ventricular tachycardia (VT) or ventricular fibrillation (VF) terminated by appropriate shocks or ATP therapies.[14] Additionally, use of azimilide did not affect the defibrillation or pacing thresholds of the ICD devices. The present randomized, double blind, placebo-controlled study assessed the safety and efficacy of azimilide in reducing symptomatic tachyarrhythmia recurrences and subsequent ICD therapies in patients with ICDs.

Methods

Patient Sample

This randomized clinical trial was undertaken in 129 sites in 9 countries, after institutional review approval at all sites, and informed consent was obtained from every patient. Patients were enrolled between September 2001 and March 2003. Patients were randomized to receive placebo or 75 or 125 mg of azimilide once daily for 1 year.

Adult patients were eligible if they had a documented episode of spontaneous sustained VT or cardiac arrest/VF (with an ejection fraction of ≤40% for the latter group) during the 42 days preceding a first ICD implant, or if they had a preexisting ICD implant and then received an ICD shock triggered by spontaneous VT or VF. They had to be randomized within 180 days after this shock or within 30 days after an initial ICD implantation.

Patients were excluded if they had New York Heart Association class IV heart failure, unstable angina, or recent (within 30 days) myocardial infarction, prolonged QTc intervals at baseline (>440 ms, with a QRS ≤120 ms) or JTc (>320 ms with a QRS >120 ms), or major cardiac or noncardiac illness. Antiarrhythmic drugs were stopped at least 5 half-lives before study drug dosing or at least for 60 days in case of prior chronic amiodarone therapy.

ICD Programming and Follow-Up

ICDs were programmed according to a strictly defined protocol, with the "floor" for VT detection specified according to the slowest documented VT rate and a ceiling set at 200 bpm. For patients with dual-chamber ICDs, at least 1 VT discriminator was enabled. Antitachycardia pacing (ATP) was programmed "on" in all patients, with a minimum of 2 attempts in the lowest detection zone, followed by shocks if necessary. Above 200 bpm, only shock therapies were programmed.

Patients were followed up for 1 year and were questioned at every visit about symptomatic arrhythmias, the timing of which was documented before ICD interrogation and documentation of arrhythmias in the data logs. Arrhythmias were identified as symptomatic on the basis of the association of patient-reported dizziness, dyspnea, palpitations, presyncope, or syncope with the date and time of recorded arrhythmia.

Study End Points

The 2 primary end points of this trial were (1) all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP and (2) all-cause shocks. The single secondary end point was all appropriate ICD therapies, defined as shocks or VT terminated by ATP. All events were adjudicated by a blinded Events Committee that evaluated all arrhythmia episodes from detailed event data logs and classified them as appropriate (due to VT or VF) or inappropriate (due to supraventricular arrhythmias or other reasons). Study oversight was provided by a Steering Committee that was independent of the study sponsor and an independent, unblinded Data and Safety Monitoring Board (Appendix).

Sample Size Calculation and Data Analysis

The sample size of this trial was estimated as the number of patients per group required to demonstrate a 30% reduction in the primary

TABLE 1. Baseline Characteristics and Concomitant Therapy During the Study (All Randomized Patients)

Category	Placebo (n=214)	Azimilide 75 mg/d (n=220)	Azimilide 125 mg/d (n=199)
Age, mean±SD, y	62±12	63±12	64±12
Female, %	7	13	10
Existing ICD, %	84	84	85
Ejection fraction ≤0.40, %	70	72	74
Ejection fraction, mean±SD	0.34±0.14	0.35±0.13	0.35±0.14
NYHA class, %			
0 or I	48	50	41
II	43	42	46
III	9	8	13
History of MI, %	66	65	62
β-Blocker usage, %	77	79	78
Aspirin, %	39	38	37
ACE, %	74	76	72
Statins, %	60	59	61
Digoxin, %	37	42	34
Spironolactone, %	14	13	16
Diuretics, %	62	62	62

NYHA indicates New York Heart Association; MI, myocardial infarction.

end point of all-cause shocks, comparing each dose of azimilide with placebo, with 90% power at a significance level of 0.0025. The sample size calculation was based on the assumption that the incidence rate per patient-year for all-cause shocks in the placebo group is 4. Accordingly, a total of 624 patients (208 patients per arm) followed up for 365 days was required.[15]

The randomization was conducted in a ratio of 1:1:1 (75 mg of azimilide, 125 mg of azimilide, and placebo); patients were stratified within a region (every country was a separate region except for the United States, which had 4 regions) by β-blocker usage, left ventricular ejection fraction (≤40% or >40%), and ICD type (existing ICD or new ICD). The strata in the stratified intention-to-treat analysis were identical to the strata in the randomization. Nine countries (United States, Canada, Germany, Poland, France, Spain, the Netherlands, Belgium, and Italy) participated in this study. A dynamic randomization scheme using Schouten's methods[16] was used through an interactive voice response system to randomize patients to treatment groups. Patients, investigators, and the sponsoring agency were blinded to the treatment assignment, and the codes were only available to the Data and Safety Monitoring Board. Blinding was maintained throughout the entire study. Patients were maintained on the originally assigned blinded therapy for 365 days (unless withdrawn for any reason), regardless of the number of intervening arrhythmia events.

All symptomatic arrhythmia events terminated by ATP and all-cause shock therapy were considered as events for the primary efficacy analysis. If multiple shocks or ATP were delivered by the device to terminate an episode of arrhythmia, they were considered to be part of 1 event. The Andersen-Gill mean intensity model[17] was used as a primary statistical methodology to analyze recurrent events; this model considers all interevent intervals, the first interval being from randomization to the first device therapy. This model, which is commonly used in analyzing data that involve multiple recurring discrete events, is based on a counting process intensity function (ie, time-transformed Poisson process), and it is a generalization of Cox's proportional hazards model[18] (ie, if the first event is considered only, then this model is equivalent to Cox's model). The Andersen-Gill is a semiparametric model that compares the distribution of all events (and interevent intervals) between groups and accounts for the correlation between the recurrent events within a subject (ie, accounts for multiple events per subject). The model explicitly does not require that interevent intervals follow an exponential or Weibull distribution.[19] Hazard ratios (HRs) for the end point in various prespecified subgroups were calculated with the Andersen-Gill mean intensity model, and a 2-sided probability value <0.05 was considered significant for all subgroup analyses.

Results

Patient Characteristics

Six hundred thirty-three patients were randomized to placebo (n=214), 75 mg of azimilide (n=220), and 125 mg of azimilide (n=199). Patients (including those who prematurely discontinued the study) were followed up for a mean (median) of 273 (367) days (range 1 to 399 days). Only 6 of the 633 randomized patients did not receive any dose of study medication (ie, withdrew consent or voluntarily withdrew from the study), 2 in each treatment group. The intention-to-treat analysis included all 633 randomized patients; however, the "on-treatment" analysis excluded these 6 patients. There were no patients lost to follow-up in the study.

Baseline characteristics and concomitant therapy during the study for all randomized patients are shown in Table 1. The majority of patients had existing ICDs, were male, and were receiving concomitant β-blockade. Mean ejection fraction for the entire cohort of 633 patients was 34±14%. There were no significant differences between groups for any baseline characteristic, except that there were more females in the 75-mg azimilide group than in the placebo group.

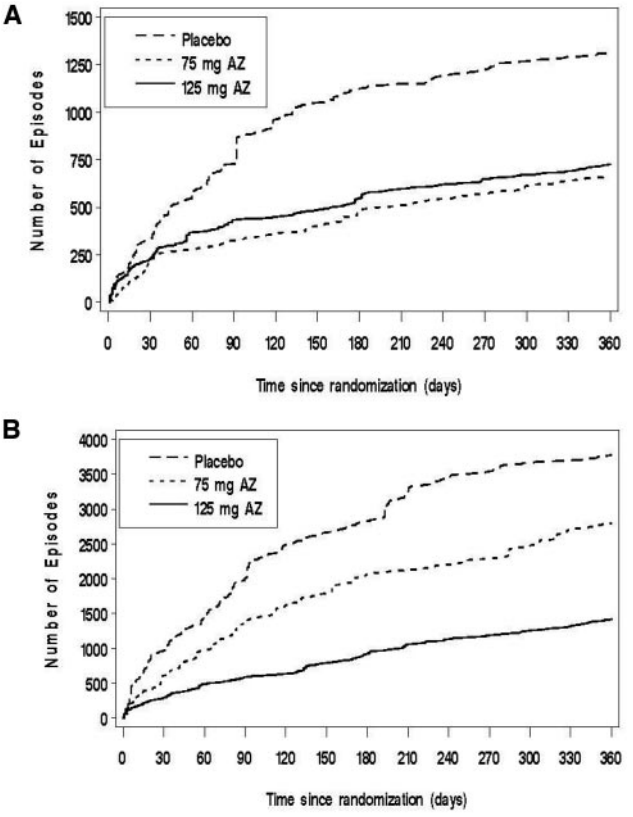

Figure 1. A, Cumulative number of arrhythmia episodes as primary end point (all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP). B, Cumulative number of episodes of VT or VF (all appropriate therapies). AZ indicates azimilide.

Primary Study End Points

The stratified intention-to-treat analysis showed that recurrent all-cause shocks plus symptomatic arrhythmias terminated by ATP (the primary end points; Figure 1A) were significantly (at the level of $\alpha=0.0025$) reduced by 75 mg of azimilide (compared with placebo), with a relative risk reduction of 57% (HR=0.43, 95% CI 0.26 to 0.69, $P=0.0006$; Table 2). In patients taking 125 mg/d azimilide, the relative risk reduction was 47% (HR=0.53, 95% CI 0.34 to 0.83, $P=0.0053$). Azimilide 75 and 125 mg/d reduced the recurrence of the primary end point of all-cause shocks with relative risk reductions of 28% and 17%, respectively, but these did not achieve statistical significance (Table 2). The results of on-treatment analysis of the primary end points were similar to the intention-to-treat analysis. There was no statistically significant difference between the 2 doses of azimilide with respect to the relative risk reduction.

Secondary Study End Point

The recurrence of all appropriate ICD therapies (shocks or ATP), representing all ICD-terminated VT and VF events as adjudicated by the Events Committee, was significantly reduced among patients taking both 75 and 125 mg/d azimilide with a relative risk reduction of 48% (HR=0.52, 95% CI

TABLE 2. Recurrent Symptomatic Arrhythmias (Shocks or ATP), Stratified Intention-to-Treat Analysis

End-Point Treatment	N	n (%)	Total Events	HR	95% CI	P
All-cause shocks plus symptomatic tachyarrhythmias terminated by ATP*						
Placebo	214	124 (58)	1459			
Azimilide 75 mg	220	114 (52)	665	0.43	0.26 to 0.69	0.0006
Azimilide 125 mg	199	100 (50)	737	0.53	0.34 to 0.83	0.0053
All-cause shocks*						
Placebo	214	113 (53)	613			
Azimilide 75 mg	220	106 (48)	472	0.72	0.47 to 1.10	0.13
Azimilide 125 mg	199	91 (46)	480	0.83	0.55 to 1.24	0.36

N indicates number of patients randomized to treatment group; n(%),number and percentage of patients who experienced at least 1 event.

*Primary end points.

0.30 to 0.89, $P=0.017$) and 62% (HR=0.38, 95% CI 0.22 to 0.65, $P=0.0004$; Table 3), respectively. All the primary and secondary analyses above were also conducted with an unstratified Andersen-Gill mean intensity model, and the results were qualitatively and quantitatively very similar. Appropriate ICD therapies represented 91% of all-cause ICD therapies. Although there was a trend to a larger effect with the higher dose of azimilide, the difference in the relative risk reduction between the 2 doses was not statistically significant ($P=0.054$).

Additional Analyses

Figure 1B illustrates the cumulative number of appropriately treated ICD episodes over follow-up time in the 3 treatment groups, demonstrating a stepwise arrhythmia reduction with 75 and 125 mg of azimilide. Expressed as the total number of ventricular tachyarrhythmia episodes adjusted for patient-years of exposure, by intention-to-treat analysis, the incidence of ventricular arrhythmia episodes appropriately treated by the ICD was reduced from 25.1 (95% CI 24.3 to 25.9) events per patient-year in the placebo group to 17.1 (95% CI 16.5 to 17.7) events per patient-year in the 75-mg azimilide group and 9.6 (95% CI 9.1 to 10.1) events per patient-year in the 125-mg azimilide group. All-cause shocks were reduced from ≈4 (95% CI 3.6 to 4.2) shocks per patient-year in the placebo group to 2.8 (95% CI 2.6 to 3.1) shocks per patient-year in the 75-mg azimilide group and 3.3 (95% CI 2.9 to 3.5) shocks per patient-year in the 125-mg azimilide group. None of the above 95% CIs for the incidence of all-cause shocks for both azimilide doses overlap with the corresponding placebo CIs, which suggests a statistically significant difference ($P<0.05$) from placebo; however, this analysis, unlike the Andersen-Gill mean intensity model, assumes that the events are independent.

Figure 2 shows the HR and 95% CIs for all appropriate therapies for 75 and 125 mg of azimilide for various prespecified subgroups. The efficacy of both doses of azimilide was consistent across all subgroups.

Approximately 7% (670 episodes) of all ICD therapies were classified (534 by the Event Committee and 136 by investigators) as inappropriate therapies, and 24% of all patients received at least 1 inappropriate device therapy. Of the 534 episodes classified by the Event Committee as inappropriate therapies, 82% of therapies were in response to supraventricular tachyarrhythmia or atrial fibrillation. The initial rhythms detected for all inappropriate therapies in the 3 groups are listed in Table 4. Although there appeared to be more atrial fibrillation episodes during treatment with 75 mg/d azimilide than with placebo, and fewer episodes of atrial fibrillation, atrial flutter, and atrial tachycardia occurred during treatment with azimilide 125 mg/d than with placebo, the episodes were unevenly distributed between patients. Analysis adjusted for the number of events per patient did not show a significant effect of either azimilide dose on inappropriate therapies.

Time Course of Arrhythmia Recurrences

In contrast to what would be expected if interevent intervals were randomly distributed over time (ie, if they followed an exponential distribution), ventricular tachyarrhythmia events terminated by shocks or ATP were highly clustered, with 79% of the interevent intervals in the placebo group being less than 1 day, compared with 73% and 57% for azimilide 75 and 125 mg/d, respectively. The distribution of interevent

TABLE 3. Recurrent Appropriate ICD Therapies (Shocks or ATP), Stratified Intention-to-Treat Analysis

Treatment	N	n (%)	Total Events	HR	95% CI	P
Placebo	214	136 (63)	3936			
Azimilide 75 mg	220	136 (61)	2849	0.52	0.30 to 0.89	0.017
Azimilide 125 mg	199	111 (55)	1436	0.38	0.22 to 0.65	0.0004

N indicates number of patients randomized to treatment group; n (%), number and percentage of patients who experienced at least 1 event.

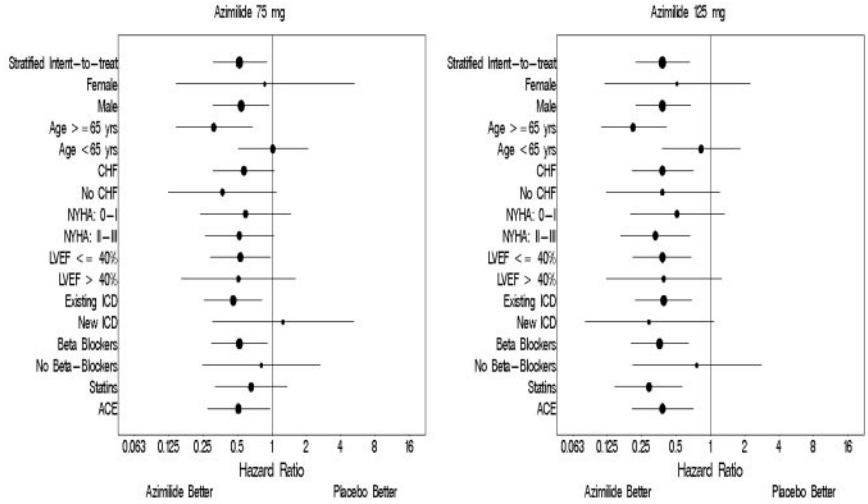

Figure 2. HRs and 95% CIs for various prespecified subgroups for all appropriate ICD therapies (shocks or ATP) for azimilide 75 mg/d vs placebo and azimilide 125 mg/d vs placebo. CHF indicates congestive heart failure; NYHA, New York Heart Association; and LVEF, left ventricular ejection fraction.

intervals was altered in the presence of azimilide 75 and 125 mg/d, as illustrated in Figure 3. All 3 interevent interval curves were significantly different from an exponential model (ie, time to first event) when the Kolmogorov-Smirnov test was used.[20]

Tolerability and Safety of Azimilide

Adverse events are listed in Table 5. Discontinuation for any reason occurred in 40% of placebo patients versus 36% of patients receiving azimilide 75 mg/d and 35% of those receiving azimilide 125 mg/d. The incidence of patient withdrawal due to adverse events was similar across the 3 groups. Torsade de pointes was observed in 1 patient taking placebo, 2 receiving 75 mg of azimilide, and 3 receiving 125 mg of azimilide. None of these cases were fatal, and all were terminated by the ICD device. Of the 5 patients with torsade de pointes who were taking azimilide, 4 were male and 1 was female. The last recorded (closest to torsade de pointes event) QTc was 458±40 ms (at the visit before the adverse event). The time from azimilide initiation to occurrence of torsade de pointes for these 5 patients was 2, 16, 33, 99, and 152 days, respectively.

One patient had severe neutropenia on the azimilide 75-mg/d dose and recovered after drug withdrawal. The overall number of deaths was similar in the 3 groups. Selected adverse events reported in the present study are listed in Table 6. The incidence of adverse events reported as new or worsening heart failure was lower in azimilide-treated patients than in those taking placebo (16% in the placebo group, 9% in the azimilide 75-mg/d group [$P<0.05$ compared with placebo], and 11% in the azimilide 125-mg/d group).

As illustrated in Table 5, most discontinuations were due to adverse events, at the patient's request or investigator's discretion, with a slight nonsignificant excess in the placebo group. The incidence rate of cardiac hospitalization in the placebo group was 105±8 hospitalizations per 100 patient-years versus 62.4±6.2 with azimilide 75 mg/d ($P=0.0023$) and 85.3±7.6 with azimilide 125 mg/d ($P=0.20$). Similarly, cardiac-related emergency department visits were reduced from 35.4±4.8 emergency department visits per 100 patient-years for those taking placebo to 14.7±3.1 emergency department visits per 100 patient-years for those taking azimilide 75 mg/d ($P=0.012$) and 19.6±3.7 emergency department visits per 100 patient-years for those taking azimilide 125 mg/d ($P=0.20$).

TABLE 4. Initial Rhythm Detected for All Inappropriate ICD Therapies

Initial Rhythm	Placebo (Total=257 Events, 57 pts)	Azimilide 75 mg (Total=283 Events, 50 pts)	Azimilide 125 mg (Total=130 Events, 42 pts)
Sinus tachycardia	13 (5%)	17 (6%)	20 (15%)
No. of patients with this rhythm	9	11	13
Atrial fibrillation	83 (32%)	108 (38%)	26 (20%)
No. of patients with this rhythm	20	17	9
Atrial flutter	30 (12%)	32 (11%)	4 (3%)
No. of patients with this rhythm	2	6	1
Atrial tachycardia or SVT	85 (33%)	82 (29%)	38 (29%)
No. of patients with this rhythm	19	16	13
Other	46 (18%)	44 (16%)	42 (32%)
No. of patients with other rhythms	27	21	19

Total indicates total number of inappropriate therapies in each group; pts, patients with inappropriate events; and SVT, supraventricular tachycardia.

Patients may have experienced more than 1 rhythm and may be included in more than 1 category.

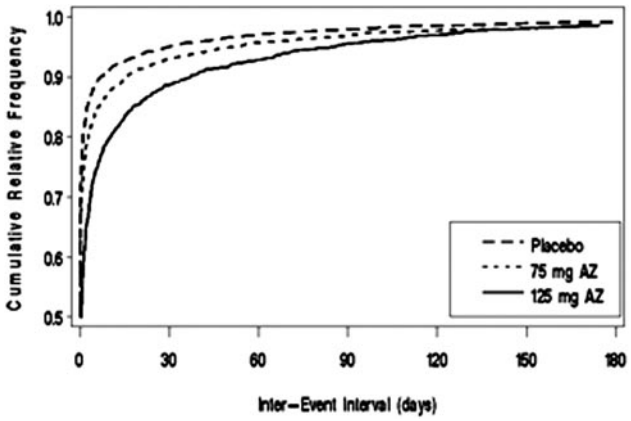

Figure 3. Interevent intervals for all appropriate ICD therapies (shocks or ATP) for placebo and azimilide (AZ) groups.

TABLE 6. Number of Patients Experiencing Common Adverse Events (All Randomized Patients)

	Placebo (n=214)		Azimilide 75 mg (n=220)		Azimilide 125 mg (n=199)	
Event	n	%	n	%	n	%
Asthenia	17	8	19	9	19	10
Heart failure*	34	16	19	9	21	11
Dizziness	22	10	30	14	16	8
Chest pain	19	9	10	5	16	8
Dyspnea	15	7	17	8	12	6
Anxiety	9	4	8	4	8	4
Heart block	3	1	1	<1	2	1
Bradycardia	3	1	5	2	2	1
Myocardial infarction	4	2	2	1	0	0

*$P<0.05$ for comparison of azimilide 75 mg/d vs placebo.

Discussion

Main Findings

Azimilide significantly reduced the recurrence of VT or VF episodes terminated by shocks or ATP therapies, thereby reducing the total symptomatic arrhythmia and ICD therapy burden. The recurrence of all-cause shocks was reduced by azimilide, but the reduction did not reach conventional levels of statistical significance. This may be explained in part by the fact that the presence or absence of shock therapy is not only determined by the presence and rate of arrhythmia but also by the way in which the ICD is programmed. Changing the rate windows for tachycardia detection and the number and type of ATP trains will lead to a change in the recurrence of shocks, independent of any change in the recurrence or cycle length of the arrhythmias themselves. This makes comparison of these results to published data on ICD shock reduction with other antiarrhythmics difficult. In the present study, the substantial decline in the total number of VT events after azimilide was accompanied by a reduction in the number of cardiac-related emergency department visits and hospitalizations.

Although the risk reduction in the primary end point was greater with the 75- than with the 125-mg/d dose of azimilide, the effects of 75 versus 125 mg were not significantly different. Although the study was not powered to show a difference between the 2 doses with regard to the primary end point, the effect of 125 mg of azimilide was greater than that of the 75-mg dose with respect to the secondary end point of all appropriate therapies (the difference between the 2 doses, using the Andersen-Gill model, was of borderline significance at $P=0.054$).

The present study represents the most comprehensive evaluation performed to date to measure the effect of an antiarrhythmic drug on all forms of ICD therapies. This study focus was on symptomatic ICD therapies to define the patient benefit of azimilide therapy. The SHock Inhi-

TABLE 5. Adverse Events for All Randomized Patients

Category	Placebo (n=214)	Azimilide 75 mg (n=220)	Azimilide 125 mg (n=199)
No. (%) of patients withdrawn:			
For any reason	86 (40)	78 (36)	69 (35)
Due to an AE	46 (22)	43 (20)	42 (21)
Due to patient request	14 (7)	12 (6)	8 (4)
Due to investigators' discretion	15 (7)	9 (4)	10 (5)
Due to QTc prolongation	0 (0)	3 (1)	2 (1)
Due to other reasons*	11 (5)	11 (5)	7 (4)
No. (%) patients with AEs	169 (79)	174 (79)	153 (77)
No. (%) of patients with SAEs	88 (41)	75 (34)	91 (46)
No. (%) of patients with torsade de pointes	1 (0.5)	2 (1)	3 (2)
No. (%) of patients with severe neutropenia	0 (0)	1 (0.5)	0 (0)
Deaths, n (%)	7 (3)	6 (3)	7 (4)

AE indicates adverse event; SAE, serious adverse event.

*Other reasons for patient withdrawal included protocol violation, severe neutropenia, death, and withdrawal before dosing.

bition Evaluation with AzimiLiDe (SHIELD) design included unique aspects: (1) uniform ICD programming as described; (2) exploration of a dose range of azimilide; (3) unique statistical methodology; and (4) an attempt to capture the entire symptomatic tachyarrhythmia burden.

Previous Studies

At present, no antiarrhythmic drug is approved by regulatory agencies for use with an ICD. The therapeutic options to prevent ventricular tachyarrhythmia recurrence in patients with an ICD are limited. Class I drugs are generally contraindicated, because most patients with ICDs have ischemic heart disease and left ventricular dysfunction, and both are associated with a predisposition to drug-induced proarrhythmia and worsening of heart failure.[12]

Sotalol, an antiarrhythmic drug with class III and β-blocking activity, has previously been associated with a reduction in the number of all-cause shocks in ICD patients in an analysis using time to first all-cause shock or death as the primary end point[6]; however, the effect of sotalol on all appropriate therapies in patients with an ICD was not reported. In separate studies, sotalol and azimilide showed no adverse effect on mortality in early post–myocardial infarction patients.[21,22] The use of sotalol may complicate the coadministration of potentially more effective β-blockers (such as carvedilol, metoprolol, or bisoprolol), which have been established to reduce mortality in patients with left ventricular systolic dysfunction and congestive heart failure.

Amiodarone has not been studied in a placebo-controlled, randomized trial, nor is it approved for use in patients with an ICD. Amiodarone also has a wide range of potentially serious noncardiac adverse effects,[23] the incidence of which accumulates over time.[13] Furthermore, there are recent reports suggesting that amiodarone may be associated with an increase in defibrillation thresholds.[24] This is in contrast to sotalol and azimilide, which have been shown, in separate studies, to not alter or decrease defibrillation thresholds.[14,25]

Previous Experience With Azimilide

Azimilide is an investigational agent that blocks the rapidly and slowly activating delayed-rectifier repolarizing potassium currents, I_{Kr} and I_{Ks}. In animal models, it prolongs cardiac refractoriness[26] and lowers defibrillation thresholds.[27] In a pilot study,[14] azimilide was associated with a 69% reduction in appropriate ICD therapies over an average 9-month follow-up. Maximal energy necessary for defibrillation and pacing thresholds were not altered by azimilide in this pilot study; however, the present study did not assess defibrillation or pacing thresholds in a systematic manner. This comprehensive study is consistent with efficacy results in the pilot study. In a large, placebo-controlled, randomized trial of azimilide in patients with left ventricular dysfunction after acute myocardial infarction, azimilide had no adverse effect on 1-year mortality.[22] In the current study, as well as in a previous study,[22] azimilide was well tolerated, with an adverse effect profile similar to placebo. Azimilide is associated with the infrequent occurrence (0.5%) of severe neutropenia, which occurs within the first 3 months of treatment and is reversible on drug discontinuation.

In the present study, azimilide reduced the recurrence of VT and VF episodes by ≈50% to 60% in a dose-dependent manner. This benefit was seen in all prespecified subgroups. Importantly, ≈86% of the patients were also receiving concomitant β-blocker therapy, and 75% of the patients were also receiving concomitant ACE inhibitor therapy; thus, the antiarrhythmic benefit of azimilide is over and above that provided by these cotherapies.

Patterns of Arrhythmia Recurrence

Almost all studies assessing antiarrhythmic drug efficacy, both for ventricular and atrial arrhythmias, have used the time to first event as the primary assessment of drug efficacy. However, for arrhythmias that tend to recur multiple times in an unpredictable pattern (for example, ventricular tachyarrhythmias[10,28] or atrial fibrillation[28]), the arguably more important clinical end point is the total arrhythmia burden over time, because patients with ICDs survive their arrhythmia episodes and are subject to multiple subsequent recurrences.[29] If arrhythmia recurrences, ie, the interevent intervals, do not follow an exponential distribution, then the time-to-first-event analysis will be likely to incorrectly estimate the true difference between drug-treated and control groups.[19] This can be overcome by using a mathematical model that incorporates all the events corrected for the duration of follow-up. The Andersen-Gill mean intensity model is a semiparametric model that accounts for all events, and it accounts for an uneven distribution of the number of events per patient, because a small proportion of patients may have many events. As illustrated in Figure 3, interevent intervals were highly clustered at short intervals in all patient groups, with a distribution that was significantly different from an exponential distribution. In this analysis, the number of symptomatic events was reduced by 50%, and the total number of ventricular tachyarrhythmia events among all patients was reduced from 25.1 events per patient-year with placebo to 9.6 events per patient-year with azimilide 125 mg/d.

Although recurring ventricular tachyarrhythmias that require device therapy occur in up to 50% of patients receiving an ICD within the first 1 to 2 years,[8] the annual mortality rate for ICD patients is $<$10%,[1,30] which suggests that the ICD is likely to be implanted for many years and associated with a high risk of repeated symptomatic arrhythmias during follow-up. In large part for this reason, a substantial number of patients will require antiarrhythmic therapy in the first year after implantation, increasing to 30% to 50% at 5 years; among patients who receive device therapy for symptomatic arrhythmias, the vast majority will receive antiarrhythmic drug therapy.[10] The present trial demonstrates that azimilide is an effective antiarrhythmic drug that reduced the symptomatic burden of arrhythmias with a manageable safety profile in ICD patients.

Appendix

Steering Committee

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Data and Safety Monitoring Board

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