

Azimilide Reduces Emergency Department Visits and Hospitalizations in Patients With an Implantable Cardioverter-Defibrillator in a Placebo-Controlled Clinical Trial

Paul Dorian, MD, FACC,* Hussein R. Al-Khalidi, PhD, FAHA,†
Stefan H. Hohnloser, MD, FACC,‡ Jose M. Brum, MD, MSc,† Preston M. Dunnmon, MD, FACC,†
Craig M. Pratt, MD, FACC,§ Michael J. Holroyde, PhD,† Peter Kowey, MD, FACC,||
on behalf of the SHIELD (SHock Inhibition Evaluation with AzimiLiDe) Investigators
*Toronto, Ontario, Canada; Cincinnati, Ohio; Frankfurt, Germany; Houston, Texas;
and Philadelphia, Pennsylvania*

- Objectives** The goal of this study was to determine whether azimilide, as compared with placebo, will reduce the number of emergency department (ED) visits and hospitalizations caused by arrhythmias or cardiac events in patients with an implantable cardioverter-defibrillator (ICD).
- Background** Patients with an ICD may require ED visits and hospitalizations because of arrhythmias, which trigger ICD therapies. The effect of adjunctive antiarrhythmic therapy on these outcomes is not known.
- Methods** A total of 633 patients with an ICD were randomized in the SHIELD (SHock Inhibition Evaluation with AzimiLiDe) trial, a blinded, placebo-controlled randomized trial of the investigational class III antiarrhythmic azimilide (75 and 125 mg/day), and, prospectively, cardiac and arrhythmic ED visits and hospitalization data were collected over 1 year.
- Results** All patients had symptomatic sustained ventricular tachycardia (72%) or ventricular fibrillation (28%) before study entry. Overall, 44% (n = 276) experienced at least 1 cardiac ED visit or hospitalization. Among 214 patients assigned to placebo, 38.3% had at least 1 arrhythmic-related ED visit or hospitalization compared with 21.8% of 220 patients assigned to 75-mg azimilide (p < 0.001) and 27.6% of 199 patients assigned to 125 mg azimilide (p < 0.05). Symptomatic ventricular tachycardia treated by antitachycardia pacing, shocks, and shocks plus symptomatic arrhythmias were significant predictors of cardiac-related ED visits or hospitalizations (relative risk: 2.0, 3.0, and 3.1, respectively). In a stepwise logistic regression model, the presence of congestive heart failure (New York Heart Association functional class II/III) was the only additional independent predictor of cardiac ED visits or hospitalizations.
- Conclusions** Azimilide significantly reduces the number of ED visits and hospitalizations in patients with an ICD at high risk of arrhythmias. (J Am Coll Cardiol 2008;52:1076–83) © 2008 by the American College of Cardiology Foundation

Implantable cardioverter-defibrillators (ICDs) reduce mortality, compared with standard medical therapy alone, when

See page 1084

used for primary (1,2) or secondary (3) prophylaxis of sudden death in patients at risk for life-threatening ventric-

ular arrhythmias. However, many patients with an ICD eventually experience multiple arrhythmic events, often within a short period of time, and develop significant symptoms and morbidity (4,5). Patients receiving frequent ICD shocks or antitachycardia pacing (ATP) for the treatment of ventricular arrhythmias are often evaluated in an emergency setting and hospitalized for stabilization of heart

*From the Division of Cardiology, St. Michael's Hospital/University of Toronto, Toronto, Ontario, Canada; †Health Care Research Center, Procter & Gamble Pharmaceuticals, Cincinnati, Ohio; ‡Department of Cardiology, Division of Electrophysiology, J.W. Goethe-University, Frankfurt, Germany; §Methodist DeBakey Heart Center, Houston, Texas; and the ||Division of Cardiovascular Diseases, Jefferson Medical College, Philadelphia, Pennsylvania. This study was supported by Procter & Gamble Pharmaceuticals,

Inc., Cincinnati, Ohio. Drs. Dorian, Hohnloser, and Pratt served on the Steering Committee for the SHIELD study and were consultants to Procter & Gamble Pharmaceuticals. Dr. Kowey served as a consultant to Procter & Gamble Pharmaceuticals, and Drs. Al-Khalidi, Brum, Dunnmon, and Holroyde are employees of Procter & Gamble Pharmaceuticals.

Manuscript received March 5, 2008; revised manuscript received April 24, 2008, accepted May 21, 2008.

failure, to rule out myocardial infarction (MI) or ischemia, or for other investigations. Patients who experience these recurrent events also often receive additional antiarrhythmic therapy with drugs such as sotalol or amiodarone since there is evidence that these agents decrease the number of ICD therapies (5,6). In addition to benefits from adjunctive antiarrhythmic therapy on symptoms and quality of life, antiarrhythmic therapy that reduces recurrent events, particularly clusters of ventricular tachycardia (VT) or ventricular fibrillation (VF), may be expected to reduce health care resource consumption. However, the effect of antiarrhythmic therapy on the number and duration of hospitalizations in patients with an ICD has not been systematically investigated in a controlled clinical trial.

Azimilide dihydrochloride is an investigational class III antiarrhythmic drug that was evaluated in a randomized, double-blind, placebo-controlled study (SHIELD [SHock Inhibition Evaluation with AzimiLiDe]) to test the safety and efficacy of daily doses of azimilide in patients with an ICD and a documented history of sustained VT, VF, or cardiac arrest. In the SHIELD study, the 75-mg dose of azimilide significantly reduced the recurrence of shocks plus symptomatic arrhythmias treated by ATP, as well as arrhythmic storms (7). This study assessed the effects of azimilide treatment on the pre-specified end points of emergency department (ED) visits and hospitalizations in patients with an ICD enrolled in the SHIELD trial.

Methods

Patient population. The SHIELD trial was a randomized clinical study undertaken at 121 sites in 9 countries (U.S., Canada, Germany, Poland, France, Spain, Netherlands, Belgium, and Italy). The study design and the primary results have been reported in detail (7). The study complied with the Declaration of Helsinki. The locally appointed ethics committee approved the research protocol, and subjects provided informed consent.

In brief, patients were eligible if they had a documented episode of spontaneous sustained VT or VF (with an ejection fraction [EF] of $\leq 40\%$ for the latter group) during the 42 days preceding a first ICD implantation or had a pre-existing ICD implant and then received an ICD shock triggered by spontaneous VT or VF.

Patients were excluded if they had New York Heart Association (NYHA) functional class IV heart failure; unstable angina; or recent (within 30 days) MI, 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 that would limit survival. 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.

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 beats/min. For patients with dual-chamber ICDs, at least 1 VT discriminator was enabled. 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 beats/min, only shock therapies were programmed.

Study protocol. Randomization was conducted in a ratio of 1:1:1 to placebo or 2 doses of azimilide (75 or 125 mg once daily). Patients were stratified within a geographic region by beta-blocker usage, left ventricular EF ($\leq 40\%$ or $>40\%$) and ICD “type” (existing or new ICD). Patients were followed and maintained on the originally assigned blinded therapy for 365 days (unless withdrawn for any reason), regardless of the number of intervening arrhythmia events. In this study, ED visits and hospitalization data, including numbers of selected in-hospital treatments and procedures were pre-specified end points with case-report forms designed to prospectively collect cardiac (arrhythmic and nonarrhythmic)-related events during the blinded phase of the study. Adverse events were systematically collected using standard COding Symbols for a Thesaurus of Adverse Reaction Terms for adverse events.

Statistical analysis. Continuous baseline characteristics are presented as mean \pm SD and were compared among the groups using the Wilcoxon rank sum test. Group comparisons of categorical data were conducted using Pearson’s chi-square test. The ED visits and hospitalization data were analyzed using time-to-event analysis. The survival curves were generated using Kaplan-Meier estimates, and the log-rank statistic was used to assess the statistical significance of the observed treatment differences in the time-to-event distribution. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and the 95% confidence interval for the azimilide group to the placebo group. The Andersen-Gill mean intensity model (8) was used to analyze recurrent (i.e., multiple) ED visits and hospitalizations. This model produces a robust variance for the estimated parameter (treatment effect) and thus adjusts for the correlation between recurrent events within a patient. The Andersen-Gill mean intensity model is a generalization of Cox’s proportional hazards model (9) (i.e., if only the first event is considered, then this model is equivalent to Cox’s model). In addition, an estimated mean function (Nelson-Aalen estimator) (10) was calculated to describe recurrent events over time between treatment groups. This estimator is a simple nonparametric estimator for the cumulative hazard over time for recurrent events (it

Abbreviations and Acronyms

ATP = antitachycardia pacing
CHF = congestive heart failure
ED = emergency department
EF = ejection fraction
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
MI = myocardial infarction
NYHA = New York Heart Association
TdP = torsades de pointes
VF = ventricular fibrillation
VT = ventricular tachycardia

is an analog to the Kaplan-Meier estimator in the single event case). The plot of these estimators demonstrates whether the expected number of events is significantly different among treatment groups.

All the statistical analyses were performed using SAS statistical software, version 9.1 procedure PHREG (SAS Institute, Cary, North Carolina) in which ties were handled by the method of exact likelihood. A 2-sided p value <0.05 was considered significant.

Results

A total of 633 patients were randomized to placebo (n = 214), 75-mg (n = 220), and 125-mg azimilide (n = 199). Baseline characteristics and concomitant drug therapy for those with at least 1 ED visit or hospitalization and those with no ED visits or hospitalization are shown in Table 1.

Overall, 44% experienced at least 1 cardiac ED visit or hospitalization. The total number of cardiac-related ED visits or hospitalizations for the placebo, 75-mg azimilide, and 125-mg azimilide groups was 211, 121, and 150, respectively, and the total arrhythmic-related ED visits or hospitalizations was 120, 63, and 71, respectively. Table 2 shows that treatment with 75-mg azimilide significantly reduces both cardiac- and arrhythmic-related ED visits or hospitalizations with relative risk reductions of 37% (log-rank p = 0.002) and 47% (log-rank p = 0.0004), respectively. Additionally, treatment with 125-mg azimilide sig-

nificantly reduced arrhythmic-related ED visits or hospitalizations with a relative risk reduction of 31% (log-rank p = 0.032). By the Kaplan-Meier estimate over 1 year (Fig. 1), 383 of 1,000 patients with an ICD assigned to placebo will have a visit to the ED or will be hospitalized 1 or more times due to an arrhythmic event, whereas only 218 of 1,000 patients assigned to 75-mg azimilide will experience these events (i.e., number needed to treat to prevent 1 such event per year = 6) (Table 2).

In addition, using the Andersen-Gill mean intensity model, recurrent cardiac ED visits or hospitalizations (i.e., taking into account both the first occurrence of ED visit or hospitalization and the subsequent admissions, correcting for unequal distribution between patients) were reduced among patients treated with 75-mg azimilide by 46% (p < 0.001) as compared with that seen in placebo-assigned patients (Fig. 2).

Among patients experiencing an ED visit or hospitalization, the majority of the events involved hospitalization. Among 276 patients with at least 1 cardiac ED visit or hospitalization, only 76 (27.5%) experienced at least 1 ED visit: 35 patients assigned to placebo, 18 patients assigned to 75 mg azimilide, and 23 patients assigned to 125 mg azimilide. Device-treated arrhythmias were strong predictors of hospitalization. Patients experiencing only symptomatic arrhythmias terminated by ATP (but no shocks), shocks only, and both shocks and symptomatic arrhythmias termi-

Table 1 Baseline Characteristics and Concomitant Medication

Category	Hospitalized			Not Hospitalized		
	Azimilide (N = 166)	Placebo (N = 110)	Overall (N = 276)	Azimilide (N = 253)	Placebo (N = 104)	Overall (N = 357)
Age (yrs), mean (SD)	65 (11.13)	64.5 (10.07)	64.8 (10.72)	64.5 (11.21)	63.3 (12.27)	64.1 (11.53)
Ejection fraction (%), mean (SD)*	31.8 (11.65)	30.4 (12.64)	31.2 (12.07)	34 (12.89)	33.7 (13.56)	33.9 (13.08)
CHF, NYHA functional class						
I	21 (12.7%)	15 (13.6%)	36 (13.0%)	36 (14.2%)	21 (20.2%)	57 (16.0%)
II	79 (47.6%)	51 (46.4%)	130 (47.1%)	105 (41.5%)	40 (38.5%)	145 (40.6%)
III*	26 (15.7%)	15 (13.6%)	41 (14.9%)	18 (7.1%)	5 (4.8%)	23 (6.4%)
Other cardiovascular characteristics						
Atrial fibrillation*	67 (40.4%)	47 (42.7%)	114 (41.3%)	68 (26.9%)	35 (33.7%)	103 (28.9%)
Myocardial infarction	106 (63.9%)	69 (62.7%)	175 (63.4%)	159 (62.8%)	72 (69.2%)	231 (64.7%)
ICD indication						
Cardiac arrest	1 (0.6%)	0 (0.0%)	1 (0.4%)	4 (1.6%)	0 (0.0%)	4 (1.1%)
VF	53 (31.9%)	29 (26.4%)	82 (29.7%)	60 (23.7%)	30 (28.8%)	90 (25.2%)
VT	112 (67.5%)	81 (73.6%)	193 (69.9%)	187 (73.9%)	74 (71.2%)	261 (73.1%)
Diabetes	39 (23.5%)	25 (22.7%)	64 (23.2%)	32 (12.6%)	23 (22.1%)	55 (15.4%)
Concomitant medications						
ACE	129 (77.7%)	82 (74.5%)	211 (76.4%)	184 (72.7%)	77 (74.0%)	261 (73.1%)
Aspirin	72 (43.4%)	45 (40.9%)	117 (42.4%)	96 (37.9%)	45 (43.3%)	141 (39.5%)
Beta-blockers	142 (85.5%)	99 (90.0%)	241 (87.3%)	214 (84.6%)	87 (83.7%)	301 (84.3%)
Digoxin*	76 (45.8%)	50 (45.5%)	126 (45.7%)	81 (32.0%)	30 (28.8%)	111 (31.1%)
Diuretics*	117 (70.5%)	87 (79.1%)	204 (73.9%)	142 (56.1%)	44 (42.3%)	186 (52.1%)
Spironolactone*	29 (17.5%)	24 (21.8%)	53 (19.2%)	31 (12.3%)	7 (6.7%)	38 (10.6%)
Statins	91 (54.8%)	63 (57.3%)	154 (55.8%)	157 (62.1%)	65 (62.5%)	222 (62.2%)

Values are n (% of patients in category and treatment group). *p < 0.05 (overall category comparisons between hospitalized and not hospitalized).

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; ICD = implantable cardioverter-defibrillator; N = number of patients in treatment group; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Cumulative Incidence of Cardiac and Arrhythmic-Related ED Visits or Hospitalizations

End Point Treatment	N	n (%)	Total ED Visits and Hospitalizations	Hazard Ratio	95% CI	Log-Rank p Value
All cardiac-related ED/hospitalization						
Placebo	214	110 (51.4%)	211			
Azimilide 75 mg	220	77 (35.0%)	121	0.63	(0.47–0.85)	0.0020
Azimilide 125 mg	199	89 (44.7%)	150	0.85	(0.64–1.13)	0.2535
Arrhythmic-related ED/hospitalization						
Placebo	214	82 (38.3%)	120			
Azimilide 75 mg	220	48 (21.8%)	63	0.53	(0.37–0.76)	0.0004
Azimilide 125 mg	199	55 (27.6%)	71	0.69	(0.49–0.97)	0.0320

CI = confidence interval; ED = emergency department; N = number of patients in treatment group; n (%) = number and percentage of patients in category and treatment group.

nated by ATP all had a significantly increased risk for a cardiac-related ED visit or hospitalization compared with patients without arrhythmias, with relative risks of 2.0, 3.0, and 3.1, respectively (Table 3). In addition, patients experiencing only symptomatic arrhythmias terminated by ATP, shocks only, and both shocks and symptomatic arrhythmias terminated by ATP had a significantly increased risk for an arrhythmic-related ED visit or hospitalization compared with patients without arrhythmias with a relative risk of 4.2, 7.8, and 9.9, respectively. Figure 3 illustrates the cumulative incidence of arrhythmic-related ED visits and hospitalizations in patients with no appropriate ICD therapies due to symptomatic arrhythmias, therapies for isolated arrhythmic events, and therapies for electrical storms (defined as ≥ 3 appropriate therapies in 24 h [5]). Of the 339 patients who experienced symptomatic arrhythmias (treated with shocks and/or ATP), 195 (58%) patients required a hospital visit. Of these 195 patients, 150 (77%) required a hospitalization within 24 h of their arrhythmic event. In these patients, 75-mg azimilide reduced cardiac-related ED visits or hospitalization occurring within 24 h of arrhythmic events by 28%. There were 137 patients with at least 1 nonarrhythmic-related ED visit or hospitalization (50 in placebo, 41 in

75-mg azimilide, and 46 in 125-mg azimilide) who experienced a total of 228 nonarrhythmic-related ED visits or hospitalizations (91 in placebo, 58 in 75-mg azimilide, and 79 in 125-mg azimilide). The comparison between 75-mg azimilide and placebo was statistically significant (HR: 0.57, 95% confidence interval: 0.37 to 0.90; $p = 0.0145$) using the Andersen-Gill mean intensity model.

In a stepwise multivariate logistic regression model controlling for treatment and other relevant risk factors (gender, age ≥ 65 years vs. < 65 years, EF $< 35\%$ vs. $\geq 35\%$, congestive heart failure [CHF], previous MI, new or existing ICD, and beta-blocker usage), only the presence of CHF (NYHA functional class II/III) was an independent predictor of cardiac ED visits and hospitalizations.

Hospitalizations due to CHF were recorded on the adverse events log; among 48 patients who were hospitalized at least once due to CHF (22 in placebo, 11 in 75-mg azimilide, and 15 in 125-mg azimilide), there were a total of 61 hospitalizations (27 in placebo, 14 in 75-mg azimilide, and 20 in 125-mg azimilide). The CHF hospitalization comparison between 75-mg azimilide and placebo was statistically significant ($p < 0.05$, Fisher exact test).

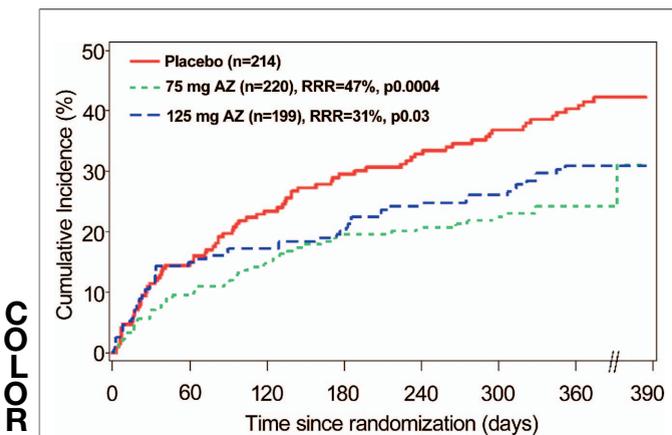


Figure 1 Kaplan-Meier Cumulative Incidence of Cardiac Arrhythmic-Related ED Visits and Hospitalizations

AZ = azimilide; ED = emergency department; RRR = relative risk reduction.

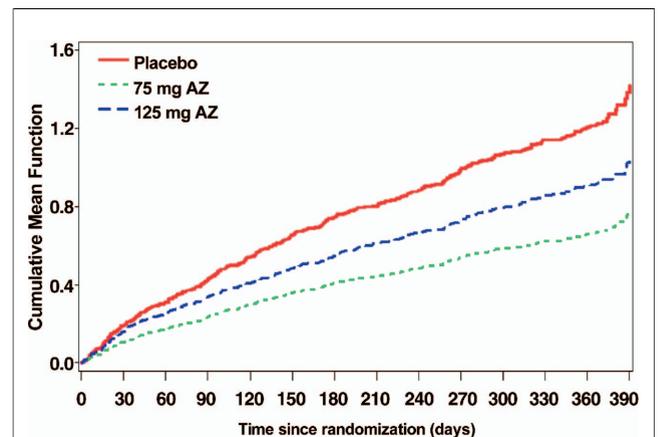


Figure 2 Cumulative Risk of Recurrent Cardiac-Related ED Visits or Hospitalizations Over Time by Treatment Group

The slope of each curve represents the estimated rate of total cardiac-related ED visits or hospitalizations within each group. Abbreviations as in Figure 1.

Table 3 Relationship Between Defibrillator Therapy and Cardiac-Related ED Visits or Hospitalizations

End Point	Hospitalization, n (%)	RR* (95% CI)	p Value†
Patients who experienced shocks (n = 213)	135 (63.0%)	3.0 (2.3–3.9)	<0.00001
Patients who experienced both shocks plus symptomatic ATP (n = 98)	64 (65.0%)	3.1 (2.3–4.1)	<0.00001
Patients who experienced only symptomatic ATP (n = 28)	12 (43.0%)	2.0 (1.2–3.3)	0.017
Patients with no arrhythmic events (n = 217)	46 (21.0%)		

*Relative risk (RR) is calculated for each end point versus patients with no arrhythmic events; †Fisher exact test.
ATP = antitachycardia pacing; other abbreviations as in Table 2.

Patients who were hospitalized had a lower EF (mean 31% vs. 34%), higher NYHA functional class (62% in class II/III vs. 47%), and more prevalent arrhythmic events (41% atrial fibrillation vs. 29%) at baseline, and were more likely to have cardiomyopathy (61% vs. 50%) than those with no hospitalization.

Discontinuation of blinded therapy for any reason occurred in 40% of placebo patients versus 36% of patients receiving 75-mg azimilide, and in 35% of those receiving 125-mg azimilide. The incidence of patient withdrawal due to adverse events was similar across the 3 groups. Torsades de pointes (TdP) was observed in 1 patient on placebo, 2 receiving 75-mg azimilide, and 3 receiving 125-mg azimilide. None were fatal, and all were terminated by the ICD device. The mean QTc intervals at baseline and post-baseline (week 2) were 406 and 412, 403 and 432, and 409 and 442 for placebo, 75-mg azimilide, and 125-mg azimilide, respectively.

There were a total of 20 (3%) deaths in this study, 7 (3%) among placebo patients, 6 (3%) among patients on 75-mg azimilide, and 7 (4%) among patients on 125-mg azimilide.

T4 Table 4 shows the number of intensive care unit days per
T5 patient/year, and Table 5 shows the number of in-hospital cardiac procedures and treatments (injection or infusion) in the 75-mg azimilide and placebo patients. More placebo-

treated patients required at least 1 in-hospital cardiac procedure than 75-mg azimilide-treated patients (90 vs. 60; p = 0.001), including more in-hospital treatments (61 vs. 34; p < 0.001).

We have not done a cost-benefit analysis since the study was conducted in multiple countries and sites with different resource consumptions and costs. However, we have collected sufficient data on hospitalizations and in-hospital procedures to allow a reasonable estimate of the cost savings expected to be associated with azimilide treatment for any particular jurisdiction or health care system.

For example, the data in Table 4 show that over 1 year of follow-up there were 1,638 hospitalization days (7.65 days per patient) observed among 214 placebo-assigned patients and 815 hospitalization days (3.70 days per patient) observed among 220 patients assigned to 75-mg azimilide. This corresponds to a net reduction of 3.95 hospitalization days (including a reduction of approximately 1 intensive care unit day) per patient per year.

Additional cost savings associated with reduced in-hospital procedures are even more difficult to calculate, since we did not record details of in-hospital tests or procedures. Table 5, however, allows some estimate of the resource consequences of the additional tests and procedures associated with the additional hospitalizations in the placebo group.

Discussion

The main findings of this study are that ED visits and hospitalizations are very common in patients with an ICD and a prior history of VT or VF. Kaplan-Meier estimates suggest that 383 of 1,000 patients with an ICD will have an ED visit or hospitalization every year. Azimilide, which significantly reduces both the proportion of patients and the number of episodes of symptomatic arrhythmias treated by ATP or shock therapy (7), also substantially reduces the number of ED visits and hospitalizations, hospital days, and in-hospital cardiac procedures.

Although ICDs clearly reduce mortality in patients at high risk for life-threatening ventricular arrhythmias (11–14), patients with ICDs often receive appropriate, but potentially unpleasant defibrillator therapies, which can impair quality of life (15–18). It would be anticipated that many patients with symptomatic arrhythmias leading to

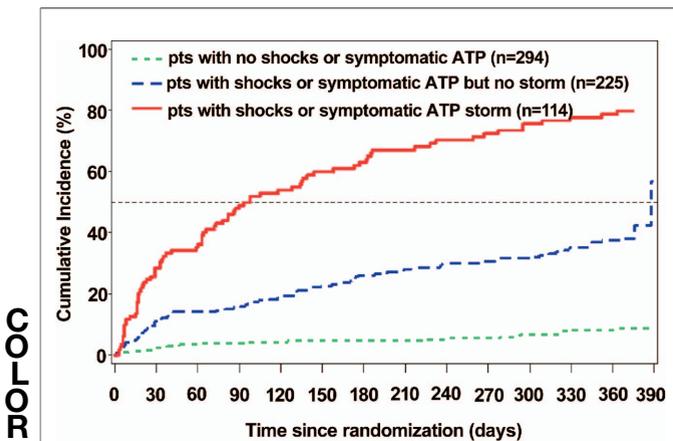


Figure 3 Kaplan-Meier Cumulative Incidence of Cardiac Arrhythmic-Related ED Visits and Hospitalizations

ATP = antitachycardia pacing; ED = emergency department; ICD = implantable cardioverter-defibrillator.

TOP-OC

Table 4 Cardiac-Related ED Visits or Hospitalizations and ICU Stays

Category	ED Visits or Hospitalizations Admissions		ICU Admissions	
	Placebo (n = 214) Pt-Yrs = 157	75-mg Azimilide (n = 220) Pt-Yrs = 167	Placebo (n = 214) Pt-Yrs = 157	75-mg Azimilide (n = 220) Pt-Yrs = 167
Total number of hospitalizations	211	121	62	35
Number of hospitalizations per patient	1.0	0.6	0.3	0.16
Number of total days	1,638	815	347	131
Number of total days per hospitalization	7.8	6.7	5.6	3.7

ED = emergency department; ICU = intensive care unit.

ICD therapy would seek unscheduled medical visits in an ED, and may be hospitalized if their physicians felt that additional investigations or treatments were necessary. The incidence of such ED visits and hospitalizations has not, however, been well documented in prior studies.

In the main SHIELD study, total ICD therapies for symptomatic arrhythmias (shocks plus symptomatic ATP) were reduced by 57%, and all-cause shocks reduced by 28% in patients treated with 75-mg azimilide compared with that seen with placebo (7). The proportion of patients in the SHIELD study who had shocks plus symptomatic arrhythmias terminated by ATP and shocks alone was 58% and 53%, respectively, for placebo and 52% and 48%, respectively, for 75-mg azimilide. Cardiac-related ED visits or hospitalizations were reduced by 37% (HR: 0.63) in the current study, and arrhythmic-related ED visits or hospitalizations were even further reduced by 75-mg azimilide (HR: 0.53): the proportion of patients visiting the ED or hospitalized for cardiac reasons decreased from 51% to 35%.

The relatively large reduction in ED visits and hospitalizations by azimilide, taken together with the substantial reduction in symptomatic arrhythmias terminated by ATP and the more modest decrease in shocks from the ICD, suggests that patients experiencing frequent symptomatic arrhythmias terminated by ATP are often seeking medical intervention. In patients with symptomatic arrhythmias terminated by ATP, but no shock therapy, cardiac ED visits and hospitalizations were increased by 2-fold, and arrhythmic-related ED visits and hospitalization 4.2-fold, over the no-therapy group. Although we

did not record the specific reasons for nonarrhythmic hospitalizations in the hospitalizations database, these were reduced by 43% (HR: 0.57) in the 75-mg azimilide group, an observation that may be related to the observed reduction in CHF hospitalizations reported in the adverse effects data logs.

Patients are particularly likely to be hospitalized if they have frequent clusters of arrhythmic events, so-called “electrical storm.” Such patients are particularly prone to adverse effects on quality of life (19,20) and have been reported to have high short-term mortality (5,12,19,21–23). Treatments that reduce the probability of “electrical storm” may be expected to reduce hospitalization, but this has not been well documented in controlled clinical trials. Antiarrhythmic therapy has previously been reported to reduce the likelihood of arrhythmias requiring ICD intervention. In a randomized, open-label study of beta-blockers versus amiodarone or sotalol, the antiarrhythmic drugs reduced shock risk (amiodarone + beta-blockers vs. beta-blockers, HR: 0.27, $p < 0.01$, and sotalol vs. beta-blockers, HR: 0.61, $p < 0.06$) (6). In a prior study, sotalol reduced the risk of shocks versus placebo (HR: 0.61, $p < 0.001$) (24). In the SHIELD study, approximately 1 of 4 patients experienced at least 1 “electrical storm,” and 75-mg azimilide significantly reduced storms of symptomatic arrhythmias (HR: 0.49, $p = 0.012$) (5).

Patients who were hospitalized had a lower EF, higher NYHA functional class, and more prevalent arrhythmic events at baseline than those with no hospitalization. As expected, the majority (61%) of ED visits and hospitalizations in patients experiencing electrical storms occurred

Table 5 Frequency of In-Hospital Procedures by Treatment

Procedure Description	Placebo (n = 214)	75-mg Azimilide (n = 220)	125-mg Azimilide (n = 220)
Coronary artery catheterization and/or biopsy	18 (15)	11 (11)	13 (13)
Diagnostic ultrasound of heart*	72 (49)	27 (19)	37 (28)
Electrophysiologic studies and ablation*	17 (16)	9 (7)	10 (6)
Injection or infusion of therapeutic or prophylactic substance*	555 (61)	349 (34)	368 (41)
Intubation of respiratory tract	11 (8)	4 (4)	7 (5)
Other nonoperative cardiac and vascular diagnostic procedures	47 (27)	16 (12)	41 (16)
Others	49 (28)	29 (24)	40 (24)
Pulmonary artery wedge*	36 (8)	2 (2)	2 (2)
Overall*	805 (90)	447 (60)	518 (63)

Values are number of incidences (number of patients). * $p < 0.05$ (3-way comparisons between treatment groups).

within 24 h of the event (data not shown) demonstrating a close temporal relationship between an arrhythmic symptomatic event treated by ICD and the medical context.

Symptomatic arrhythmias and ICD shocks are a frequent cause of ED/hospital visits. In the EURID (German ICD Registry) study, 3,394 patients studied for 1 year experienced 1,691 cardiac ED/hospital visits of which 61.3% were arrhythmic (20). Additionally, several studies indicate that ICD therapies triggered by arrhythmias may result in increased hospital visits. For example, the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) studies have shown that the time to first rehospitalization was significantly shorter in patients with ICDs than the control patients (13,14). In addition, ICD-delivered shocks or pacing may increase the risk of CHF, which was suggested by the MADIT-II and the DAVID (Dual Chamber and VVI Implantable Defibrillator) trials (13,25). Although the presence of an ICD is associated with better survival, it is also associated with an increased risk of rehospitalization (26).

The key benefits of adjunctive antiarrhythmic treatment with azimilide in this study are the reductions in the symptomatic ventricular arrhythmic burden leading to reductions in arrhythmia-related ED visits and hospitalizations. The potential risks regarding the use of this antiarrhythmic agent are severe neutropenia and TdP, together with other minor side effects. Based on the SHIELD study, approximately 165 of 1,000 patients treated with azimilide for 1 year may avoid arrhythmia-related ED visits and hospitalizations whereas 5 of 1,000 (0.5%) patients may experience severe neutropenia, and 8 of 1,000 (0.8%) may experience TdP leading to a visit to a health care facility. This study does not compare the potential strategy of starting adjunctive antiarrhythmic therapy at the time of implantation (for patients with no prior symptomatic VT or VF) versus the strategy of starting such drugs after documented VT/VF (before or after ICD implantation), but does suggest that reducing the burden of appropriate therapies from the ICD has tangible benefits beyond patient symptoms and patient acceptance of the ICD.

Acknowledgments

The authors thank Judith M. Pepin, Liz Fincher, and Zana Mariano for their assistance in the preparation of this manuscript.

Reprint requests and correspondence: Dr. Paul Dorian, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. E-mail: dorianp@smh.toronto.on.ca.

REFERENCES

1. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. *N Engl J Med* 1996;335:1933–40.
2. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
3. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. *Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J* 2000;21:2071–8.
4. DiMarco JP. Implantable cardioverter-defibrillators. *N Engl J Med* 2003;349:1836–47.
5. Hohnloser SH, Al-Khalidi HR, Pratt CM, et al. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. *Eur Heart J* 2006;27:3027–32.
6. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. *JAMA* 2006;295:165–71.
7. Dorian P, Borggrefe M, Al-Khalidi HR, et al. Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004;110:3646–54.
8. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Ser B* 2000;62:711–30.
9. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100–20.
10. Cook RJ, Lawless JF, Nadeau C. Robust tests for treatment comparisons based on recurrent event responses. *Biometrics* 1996;52:557–71.
11. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;341:1882–90.
12. Exner DV, Pinski SL, Wyse DG, et al. Antiarrhythmics Versus Implantable Defibrillators. Electrical storm presages nonsudden death: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *Circulation* 2001;103:2066–71.
13. Moss AJ, Zareba W, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.
14. Bardy GH, Lee KL, Mark DB, et al., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
15. Irvine J, Dorian P, Baker B, et al. Quality of life in the Canadian Implantable Defibrillator Study (CIDS). *Am Heart J* 2002;144:282–9.
16. Groh WJ, Bhakta D, Lowe MR, Bennett SJ. Come see the softer side of clinical outcomes: quality of life measures in implanted defibrillator trials. *J Cardiovasc Electrophysiol* 2004;15:292–4.
17. Godemann F, Butter C, Lampe F, Linden M, Werner S, Behrens S. Determinants of the quality of life (QOL) in patients with an implantable cardioverter/defibrillator (ICD). *Quality Life Res* 2004; 13:411–6.
18. Sola CL, Bostwick JM. Implantable cardioverter-defibrillators, induced anxiety, and quality of life. *Mayo Clin Proc* 2005;80: 232–7.
19. Credner SC, Klingenhoben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol* 1998;32:1909–15.
20. Gradaus R, Block M, Brachmann J, et al. Mortality, morbidity, and complications in 3344 patients with implantable cardioverter defibrillators: results from the German ICD Registry EURID. *Pacing Clin Electrophysiol* 2003;26:1511–8.
21. Sesselberg HW, Moss AJ, McNitt S, Zareba W, Daubert JP, Andrews ML. Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: a MADIT-II substudy. *Heart Rhythm* 2007;4:1395–402.
22. Verma A, Kilicaslan F, Marrouche NF, et al. Prevalence, predictors, and mortality significance of the causative arrhythmia in patients with electrical storm. *J Cardiovasc Electrophysiol* 2004;15:1265–70.
23. Villacastin J, Almendral J, Arenal A, et al. Incidence and clinical significance of multiple consecutive, appropriate, high-energy dis-

- charges in patients with implanted cardioverter-defibrillators. *Circulation* 1996;93:753–62.
24. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable defibrillator shocks by treatment with sotalol. *N Engl J Med* 1999;340:1855–62.
 25. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator—the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. *JAMA* 2002;288:3115–23.
 26. Nazarian S, Maisel WH, Miles JS, Tsang S, Stevenson LW, Stevenson WG. Impact of implantable cardioverter defibrillators on survival and recurrent hospitalization in advanced heart failure. *Am Heart J* 2005;150:955–60.

Key Words: azimilide dihydrochloride ■ recurrent events ■ implantable cardioverter-defibrillator ■ antiarrhythmic therapy ■ ventricular tachycardia storms ■ hospitalization.