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Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial

Stefan H. Hohnloser[1]*, Hussein R. Al-Khalidi[2], Craig M. Pratt[3], Jose M. Brum[2], Daljit S. Tatla[2], Patrick Tchou[4], and Paul Dorian[5]on behalf of the SHock Inhibition Evaluation with AzimiLiDe (SHIELD) Investigators

[1] *Division of Electrophysiology, Department of Cardiology, J.W. Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany;* [2] *Procter & Gamble Pharmaceuticals, Health Care Research Center, Cincinnati, OH, USA;* [3] *The Methodist DeBakey Heart Center, Houston, TX, USA;* [4] *Cleveland Clinic Foundation, Cardiology Department, Cleveland, OH, USA; and* [5] *Division of Cardiology, St. Michael's Hospital, Toronto, Ontario, Canada*

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KEYWORDS
Azimilide dihydrochloride;
Implantable cardioverter defibrillator;
Antiarrhythmic therapy;
Ventricular tachycardia storms

Aims The purpose of this study was to assess the incidence, features, and clinical sequelae of 'electrical storm' (ES).
Methods and results This study is a prospectively designed secondary analysis of SHIELD; a randomized trial of azimilide for suppression of ventricular tachycardia/fibrillation (VT/VF) leading to implanted cardioverter defibrillator (ICD) therapies. Systematic and rigorous follow-up and blinded adjudication of ICD therapy allowed identification of all ESs ($\geq$3 separate VT/VF episodes leading to ICD therapies within 24 h). Of 633 ICD recipients, 148 (23%) experienced at least one ES over 1-year follow-up. No clinical predictors of ES were identified. Frequent VT episodes accounted for 91% of all ESs, with the remaining being VF alone or both VT plus VF. ES led to a 3.1-fold increase in arrhythmia-related hospitalization (95% CI 2.3–4.3; $P < 0.0001$) compared with patients with isolated VT/VF, and to a 10.2-fold increase (95% CI 6.4–16.3; $P < 0.0001$) compared with patients without VT/VF. Compared with placebo, azimilide (75 and 125 mg/day) reduced the risk of recurrent ES by 37% (HR = 0.63, 95% CI 0.35–1.11, $P = 0.11$) and 55% (HR = 0.45, 95% CI 0.23–0.87, $P = 0.018$), respectively. However, the reduction in time-to-first ES did not reach statistical significance by both doses (75 and 125 mg) of azimilide (HR = 0.82, 95% CI 0.56–1.19, $P = 0.29$ and HR = 0.69, 95% CI 0.46–1.04, $P = 0.07$), respectively.
Conclusion ES is common and unpredictable in ICD recipients and it is a strong predictor of hospitalization.

Introduction

Implanted cardioverter defibrillators (ICDs) prolong life when used for primary[1,2] or secondary[3] prophylaxis of sudden death in patients with various structural heart diseases. Despite a continuous improvement in technology, patients with ICDs can experience adverse events.[4] Frequent ICD shocks, whether appropriately delivered for incessant or recurrent ventricular tachycardia (VT) or fibrillation (VF), or inappropriately delivered in the absence of ventricular tachyarrhythmias, are the most common adverse events encountered after ICD implantation.[4] The clustering of VT/VF within a short period of time (i.e. three or more VT/VF episodes within 24 h) has been defined as an electrical storm (ES)[5–7] and constitutes a medical emergency.[8] Multiple shocks produce profound psychological morbidity, resulting in severely impaired quality of life.[9] Moreover, there is evidence that ES may be a harbinger of increased mortality.[7] There is a relative paucity of systematic data on ES with respect to its incidence, features, clinical profile of affected patients, and clinical sequelae. Data obtained from prospective randomized studies, in particular, are very sparse.[7]

The SHock Inhibition Evaluation with AzimiLiDe (SHIELD) trial was a double-blind, placebo-controlled randomized trial evaluating the effects of azimilide, a novel class III antiarrhythmic drug, on the frequency of device therapies in ICD patients.[10] As a pre-specified secondary efficacy endpoint of this trial, all episodes of ES, as documented by the devices, were recorded and subsequently analysed. Accordingly, the purpose of this study was to assess the incidence, features, and clinical sequelae of ES.

* Corresponding author. Tel: +49 69 6301 7404; fax: +49 69 6301 7017.
E-mail address: hohnloser@em.uni-frankfurt.de

Methods

Patient population

This randomized clinical trial was undertaken at 121 sites in nine countries (USA, Canada, Germany, Poland, France, Spain, Netherlands, Belgium, and Italy). Following institutional review approval at all sites, informed consent was obtained from every patient. Study oversight was provided by a Steering Committee independent of the study sponsor, and an independent, unblinded Data and Safety Monitoring Board. As recently reported in detail,[10] adult patients were eligible if they had a documented episode of spontaneous sustained VT or VF (with an EF of $\leq$40% for the latter group) during the 42 days preceding a first ICD implant; or had a pre-existing ICD implant and then received an ICD shock triggered by spontaneous VT or VF. The design and final results of the SHIELD trial have been reported in detail.[10] In brief, both doses (75 and 125 mg) of azimilide yielded a significant reduction in the composite endpoint of all-cause shocks plus symptomatic arrhythmias terminated by antitachycardia pacing (ATP).[10]

Patients were excluded if they had NYHA class IV heart failure, unstable angina, or recent (within 30 days) myocardial infarction (MI), prolonged QTc intervals at baseline ($>$440 ms, with a QRS $\leq$120 ms) or JTc ($>$320 ms with a QRS $>$120 ms), or major cardiac or non-cardiac illness that would limit survival. Antiarrhythmic drugs were stopped at least five 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 b.p.m. For patients with dual chamber ICDs, at least one VT discriminator was enabled. ATP was programmed 'on' in all patients, with a minimum of two attempts in the lowest detection zone, followed by shocks if necessary. Above 200 b.p.m., only shock therapies were programmed.

Study protocol

Azimilide dihydrochloride is an investigational antiarrhythmic drug with potassium channel (I_{Kr} and I_{Ks}) blocking properties, which prolongs the cardiac action potential and refractory periods.[10,11] Randomization was conducted in a ratio of 1:1:1 to placebo or two doses of azimilide (75 or 125 mg once daily). Patients were stratified within a geographic region by beta-blocker usage, left ventricular ejection fraction (LVEF) ($\leq$40 or $>$40%) and ICD 'type' (existing ICD 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.

Definition of ES

ES was prospectively defined as $\geq$3 separate arrhythmia episodes leading to ICD therapies (ATP or shock) occurring over a single 24 h time period.[5–7] The present analysis focuses only on appropriately treated (VT/VF terminated by ATP or shock) ES episodes. If multiple shocks or ATP were delivered by the device to terminate a single episode of arrhythmia, they were considered to be part of one arrhythmic episode. Patients with $\leq$2 arrhythmia episodes within a 24 h period were defined as having isolated arrhythmia events. All events were adjudicated and classified by a blinded Events Committee who evaluated all arrhythmia episodes from detailed event data logs and device-stored electrograms.

Statistical analysis

Continuous baseline characteristics are presented as mean $\pm$ SD and were compared among the three groups using Wilcoxon sum-rank test. Group comparisons of categorical data were conducted using Pearson's χ^2 test. A stratified Andersen–Gill mean intensity model[12] was used as primary statistical methodology to analyse the recurrence of ES. The strata in this model were the following: beta-blocker usage, LVEF ($\leq$40 or $>$40%), and ICD 'type' (existing ICD or new ICD) at the time of randomization. This model produces a robust variance for the estimated parameter (treatment effect) and thus adjusting for the correlation between inter-ES intervals within a subject. The Andersen–Gill model is a generalization of Cox's proportional hazards model[13] (i.e. if only the first event is considered, then this model is equivalent to Cox's model). All adjudicated arrhythmia events fulfilling the above definition of ES were considered as episodes for the efficacy analysis. Hazard ratios for the pre-specified subgroup of 'storms' were calculated using the Andersen–Gill mean intensity model. A stratified multivariable Andersen–Gill mean intensity model was used to adjust for risk factors for ESs such as sex, congestive heart failure, and age. In addition, estimated mean function (Nelson–Aalen estimator[14]) was calculated to describe recurrent events over time between treatment groups. This estimator is a simple non-parametric estimator for the cumulative hazard over time. The plot of this estimator yields information on recurrent events expected by certain time, and whether the rate of recurrences is increasing, decreasing, or remaining constant over time. The plot also demonstrates whether the expected number of events is significantly different between treatment groups.

All the univariate and multivariable recurrent ESs analyses were performed using SAS® statistical software, V8.2 procedure PHREG, in which ties were handled by the method of exact likelihood (SAS Institute, Cary, NC, USA). A two-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 one ES, those with at least one episode of VT/VF but no ES, and the remaining patients are shown in *Table 1*.

Discontinuation for any reason occurred in 40% of placebo patients vs. 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 three groups. Torsade de pointes (TdP) was observed in one patient on placebo, two receiving 75 mg azimilide, and three receiving 125 mg azimilide. None were fatal and all were terminated by the ICD device. Since study discontinuation rates were substantial among the three groups, recurrence of ES was analysed separately among patients who dropped out from the study and those who completed the study. Both doses of azimilide showed consistent results (i.e. HR $<$ 1.0) as compared with placebo in both patient cohorts.

Incidence of ES

A total of 148 patients (23%) out of 633 patients randomized experienced at least one ES [after 7 (2–12.3) months of median (IQR) follow-up]: 58 (27%) were on placebo, 51 (23%) on 75 mg, and 39 (20%) on 125 mg azimilide. Among these patients, the incidence of ES was 6.5 VT/VF storms (95% CI 6.0–7.1) per patient/year of observation. There were 59 (40%) out of 148 patients whose first VT/VF episode was the start of ES, 16 (11%) patients whose second VT/VF episode was a start of ES, and 23 (16%) patients whose third episode was a start of ES. *Figure 1* shows the estimated mean functions[14] for recurrent VT/VF events over time by treatment groups. There was a larger increase in the cumulative estimated mean function over

Table 1 Baseline characteristics and concomitant therapy during the study

	Patients with ES ($n = 148$)	Patients with VT/VF episodes but no ES ($n = 235$)	Patients free of VT/VF episode ($n = 250$)	*P*-value*
Age (mean $\pm$ SD years)	62 (11)	64 (11)	63 (13)	0.27
Female, *n* (%)	12 (8)	22 (9)	30 (12)	0.41
Ischaemic heart disease, *n* (%)	105 (71)	156 (66)	177 (71)	0.50
Valvular disease, *n* (%)	58 (39)	121 (51)	90 (36)	0.002
Previous MI, *n* (%)	95 (64)	150 (64)	161 (64)	0.99
Congestive heart failure, *n* (%)	102 (69)	176 (75)	157 (63)	0.02
Idiopathic dilated cardiomyopathy, *n* (%)	76 (51)	152 (65)	118 (47)	0.0004
Syncope, *n* (%)	88 (59)	147 (63)	157 (63)	0.78
ICD indication				0.002
ICD for VF, *n* (%)	30 (20)	58 (25)	89 (36)	
ICD for VT, *n* (%)	118 (80)	177 (75)	161 (64)	
Existing ICD, *n* (%)	128 (86)	215 (91)	191 (76)	<0.0001
LVEF (SD)	0.37 ± 0.013	0.32 ± 0.014	0.35 ± 0.014	0.001
LVEF ≤ 0.40, *n* (%)	104 (70)	184 (78)	168 (67)	0.02
NYHA class 0–I, *n*(%)	64 (43)	104 (44)	126 (50)	0.27
NYHA class II, *n* (%)	71 (48)	104 (44)	100 (40)	0.29
NYHA class III, *n* (%)	13 (9)	27 (12)	24 (10)	0.65
Concomitant therapy during the study				
Beta-blocker, *n* (%)	128 (86)	208 (89)	211 (84)	0.42
Aspirin, *n* (%)	67 (45)	76 (32)	98 (39)	0.04
ACE inhibitors, *n* (%)	106 (72)	183 (78)	183 (73)	0.32
Statins, *n* (%)	83 (56)	145 (62)	151 (60)	0.54
Digoxin, *n* (%)	50 (34)	105 (45)	86 (34)	0.03
Spironolactone, *n* (%)	25 (17)	39 (17)	26 (10)	0.08
Diuretics, *n* (%)	95 (64)	159 (68)	137 (55)	0.01

*Comparison between the three groups.
n, number of patients in each group; SD, standard deviation; NYHA, New York Heart Association.

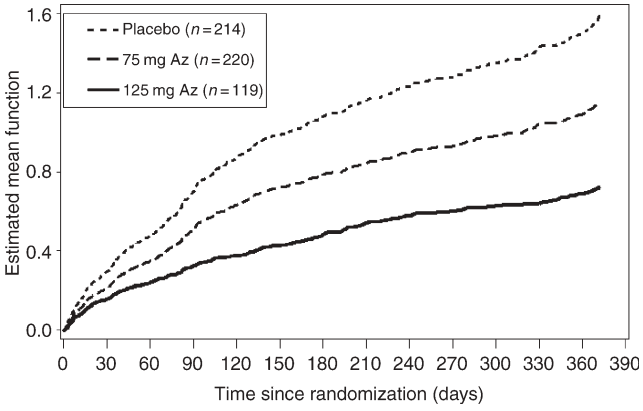

Figure 1 Estimated mean functions for recurrent VT/VF events over time by treatment groups. *Y*-axis represents the cumulative mean function, *X*-axis the follow-up duration in days. The slope of each curve represents the rate of VT/VF recurrences within each group. AZ, Azimilide.

time in placebo patients as compared with patients on either dose (75 or 125 mg) of azimilide.

Of the 148 patients with at least one ES episode, 66 (45%) experienced one ES, 31 (21%) had two, and 51 (34%) had three or more ESs during the observation period. The median (IQR) number of VT/VF episodes per ES was 5 (3–11) as described in *Table 2*.

There were a total of 568 ES episodes, of which 41 (7%) were treated by ICD shocks only (total of 246 shocks delivered), 396 (70%) were treated by ATP only (total of 3987 ATP delivered), and the remaining 131 (23%) were treated by both shocks and ATP delivery (total of 515 shocks and 1264 ATPs delivered).

Clinical features of ES

The first ES episode occurred within a mean of 3 months after study enrolment (94 ± 105 days, median 47 days). The 568 ES episodes with a total of 6012 VT/VF episodes (i.e. VT/VF rhythms treated) consisted of 519 (91%) VT storms with a total of 5512 VT events, 4 (1%) VF storms with a total of 15 VF events treated, and the remaining 45 (8%) were VT and VF storms with a total of 395 VT and 90 VF events. From the 485 patients who did not experience ES, 235 had one or more isolated arrhythmic events leading to device therapy. ES was precipitated by new or worsened congestive heart failure in 13 (9%) patients and by electrolyte disturbances in 6 (4%). In the remaining patients, there was no identifiable precipitating cause for ES. As shown in *Table 1*, there were some differences in clinical characteristics of patients with and without ES. However, on univariate and multivariable analyses including all available relevant risk factors, there were no independent predictors of ES.

Effects of azimilide on ES

The stratified intent-to-treat analysis showed that recurrent ES terminated by ATP or shocks were reduced by 75 mg azimilide (when compared with placebo) with a relative risk

Table 2 Andersen–Gill mean intensity model: analysis of ES (stratified intent-to-treat analysis)

Treatment	*n*	*n* (%)	Number of ES	Total VT/VF episodes	Median (IQR) VT/VF episodes per ES	Median (IQR) follow-up (days)	HR (95% CI)	AG *P*-value
Placebo	214	58 (27)	259	3116	6 (4–12)	366 (122–372)	1.0	
75 mg azimilide	220	51 (23)	198	2112	5 (3–11)	367 (155–371)	0.59 (0.33–1.06)	0.07532
125 mg azimilide	199	39 (20)	111	784	5 (3–8)	367 (141–371)	0.45 (0.24–0.86)	0.01622

n, the number of patients randomized to each treatment group; *n* (%), the number and percentage of patients with at least one ES; IQR, inter-quartile range (25–75th); HR, hazard ratio; AG, Andersen–Gill mean intensity model.

reduction of 41% [HR = 0.59, 95% CI (0.33–1.06), $P = 0.075$, *Table 2*]. In patients on 125 mg azimilide, the relative risk reduction was 55% [HR = 0.45, 95% CI (0.24–0.86), $P = 0.016$]. However, the reduction in time-to-first ES did not reach statistical significance by both doses (75 and 125 mg) of azimilide (HR = 0.82, 95% CI 0.56–1.19, $P = 0.29$ and HR = 0.69, 95% CI 0.46–1.04, $P = 0.07$), respectively. In a multivariable Andersen–Gill mean intensity model after adjusting for risk factors of sex, CHF, and age (<65 years vs. ≥65 years), ES were reduced by 75 mg azimilide (when compared with placebo), with a relative risk reduction of 37% (HR = 0.63, 95% CI 0.35–1.11, $P = 0.11$). In patients on 125 mg azimilide, the relative risk reduction was 55% (HR = 0.45, 95% CI 0.23–0.87, $P = 0.018$). Although the incidence of ES due to shocks was relatively small (total of 88 episodes), both azimilide doses (75 and 125 mg) resulted in a reduction in ES due to shocks (53%, $P = 0.04$ and 26%, $P = 0.37$, respectively).

Clinical implications of ES

As shown in *Figure 2A*, 82% of the patients who experienced at least one ES were admitted to the Emergency Room (ER) or hospital for cardiovascular (arrhythmic or non-arrhythmic) reasons at least once during study follow-up with a median time to hospital admission of 105 days when compared with 70% of the patients who experienced isolated VT/VF episodes with a median time to hospital admission of 381 days (HR = 2.2, 95% CI 1.7–2.9; log-rank $P < 0.0001$) and 47% of the patients who did not experience any VT/VF episodes with a median time to hospital admission of more than 388 days (HR = 4.2, 95% CI 3.1–5.8; log-rank $P < 0.0001$). Seventy-one patients with ES (48%) needed immediate (within 24 h) hospitalization, 78 (53%) patients with ES needed hospitalization within a week, and 82 (55%) patients within 2 weeks. In addition, 6 (4%) patients were hospitalized 24 h prior to their ES, 13 (9%) patients 48 h, and 16 (11%) patients 72 h prior to their ES. Of 276 re-hospitalized patients, 45 (16%) were hospitalized for ES. Excluding these 45 patients from the analysis showed that ES patients were still at higher risk for hospitalization when compared with patients with isolated VT/VF events (HR = 1.64, 95% CI 1.2–2.2; log-rank $P = 0.0019$) and to those without any VT/VF event (HR = 3.1, 95% CI 2.2–4.4; log-rank $P < 0.0001$).

In addition, 43 (29%) of 148 patients who experienced at least one ES had their hospitalization prior to their first ES. Thus, we conducted an analysis excluding these patients; the remaining ES patients ($n = 105$) continued to have a significantly higher risk of being hospitalized compared with patients with isolated VT/VF events (HR = 1.8, 95% CI 1.3–2.5; log-rank $P = 0.0001$) and to patients without any VT/VF event (HR = 3.4, 95% CI 2.4–4.8; log-rank $P < 0.0001$).

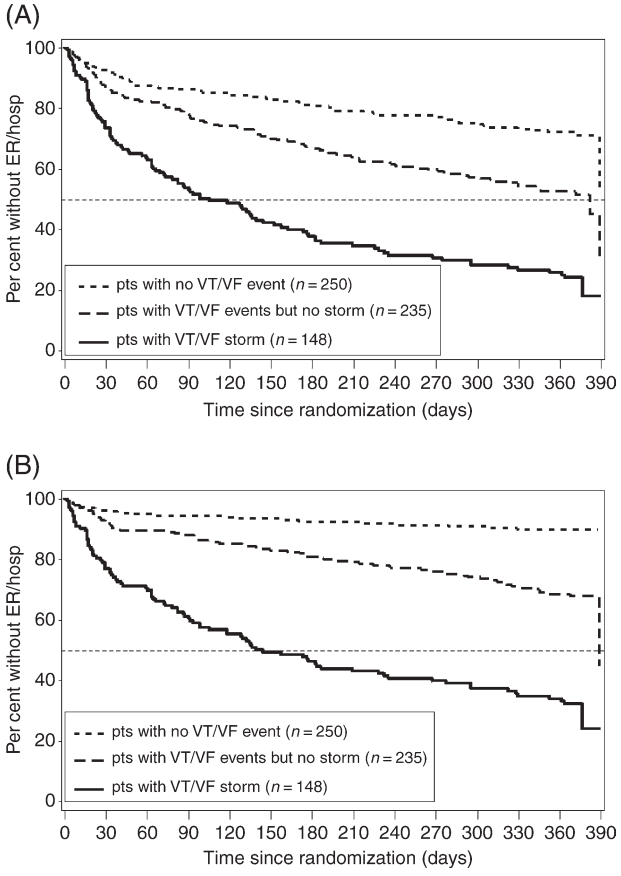

Figure 2 (*A*) Kaplan–Meier estimates of time-to-first cardiac ER/hospitalization visits among patients who experienced VT/VF ES, patients with VT/VF episodes but no ES, and those without VT/VF episode. (*B*) Kaplan–Meier estimates of time-to-first arrhythmic ER/hospitalization visits among patients who experienced VT/VF ES, patients with isolated VT/VF episodes but no ES, and those without VT/VF episode.

Figure 2B shows that 76% of the patients who developed VT/VF storms were admitted to the hospital for cardiac arrhythmic reasons at least once during the 1 year of study follow-up with a median time to hospital admission of 144 days, when compared with 55% of the patients who experienced isolated VT/VF episodes with a median time to hospital admission of 388 days (HR = 3.1, 95% CI 2.3–4.3; log-rank $P < 0.0001$) and 10% of the patients who did not experience any VT/VF episodes with a median

time to hospital admission of more 329 days (HR = 10.2, 95% CI 6.4–16.3; log-rank $P < 0.0001$).

A total of 20 (3%) deaths occurred in this study, 4 (2.7%) among patients who experienced at least one VT/VF ES, 10 (4.3%) among those who have had isolated VT/VF episodes but did not experience ES, and 6 (2.4%) in the remaining patients. The majority (75%) of these deaths was cardiac, and among the cardiac deaths, 73% were non-arrhythmic. In addition, there were six TdP in this study, 4 (2.7%) among patients who experienced at least one VT/VF ES and 2 (0.9%) among those who have had isolated VT/VF episodes but did not experience ES. None of these TdP led to death and all were terminated by the device.

Discussion

Main findings

The present study reveals several new findings regarding the occurrence of ES in ICD patients. Our observations demonstrate that approximately every fifth patient in this study who underwent ICD placement for VT/VF experienced an episode of ES within a 12-month period, an incidence which is higher than that reported from uncontrolled observational studies. A substantial proportion of patients will suffer from repeated ES episodes. The majority of ES consists of VT episodes, is frequently treated with ATP and shocks, and usually occurs without identifiable precipitating causes. Patients experiencing ES episodes are significantly at higher risk to be hospitalized than those with only sporadic VT/VF episodes. Of note, azimilide, a new class III antiarrhythmic compound, significantly reduces ES episodes in a dose-dependent manner.

Previous studies on ES

ES in ICD recipients has been the focus of only a few prior studies. Many of these studies are limited by relatively small sample sizes comprising selected patient populations,[5,15] a lack of blinded adjudication of episodes of ES according to stored ICD electrograms, and by the fact that they focused on shocks only rather than on any ICD therapy (i.e. shock and ATP). In fact, all but one study[7] were uncontrolled observational single-centre reports. The incidence of ES has been variously described as 10–28% during variable follow-up durations of 13–33 months. Exner *et al.*[7] reported data on ES derived from the largest ICD secondary prevention trial, the AVID study. Of the 457 patients assigned to receive an ICD, ES defined as $\geq$3 VT/VF episodes in 24 h occurred in 20% of their patients. The majority of storms were due to multiple temporally related episodes of VT (86%), a finding that is confirmed in the present series.

Several studies have attempted to identify risk factors for the development of ES. Identifiable causes such as congestive heart failure (31%) or electrolyte disorders (20%) were reported in some studies.[16] However, in the majority of events, no 'triggers' were found. Lower LVEF in patients with ES compared with ICD recipients without device therapy was also described in some reports,[7] but not in others.[5] Our results, in one of the largest series of ES patients studied, demonstrate that LV function in storm patients was slightly but significantly better than that of patients with isolated VT/VF episodes or patients without any ICD interventions. Since our study is the only one in which patients received optimal background medication for heart failure including beta-blockers in more than 80% and ACE inhibitors in ~75%, it seems that LVEF does not provide predictive power for the occurrence of ES.

Some studies have found that ES may represent a harbinger of increased mortality, particularly from non-arrhythmic cardiac death.[7] Owing to the limited observation period of this prospective study, no firm conclusions can be drawn regarding this feature of ES. However, in the study by Exner *et al.*,[7] most of the observed excess mortality occurred within the first 3 months after the storm.[7] During this time period, however, we did not observe a higher mortality rate in storm patients both compared with ICD recipients with isolated device therapies and to those never receiving any treatment from the ICD. Two explanations for this discrepancy can be offered; first, patients in the AVID study[7] had more extensive underlying heart disease as evidenced by an average LVEF of 0.29 compared with 0.37 in the present study. Secondly, 86% of our storm patients were treated with beta-blockers compared with only 43% in the Exner study.[7] Sympathetic blockade has been demonstrated to be very effective in the acute therapy of ES.[17] This treatment may also reduce cardiac mortality from ischaemia, heart failure, and possibly the fatal consequences of ES.[17]

The present study is the first to address in a systematic way other clinical implications of ES. Most notably, ES resulted in a significantly higher rate of hospital admissions, mostly and expectedly for arrhythmia-related causes. Many patients needed to be immediately hospitalized when ES occurred. Besides the unpleasant effects on quality of life related to these admissions, such hospitalizations constitute a major burden in terms of resource utilization.

Antiarrhythmic drug therapy for prevention of ES

Ours is the first study on ES, which derives its conclusions from a randomized placebo-controlled trial of antiarrhythmic drug therapy. No antiarrhythmic drug is currently approved by regulatory agencies in North America or Europe for prophylactic use in ICD recipients. As recently reported, azimilide significantly reduces the recurrence of single VT/VF episodes terminated by shocks or ATP in ICD patients.[10] This preventive effect is also borne out when the drug effect on ES is examined. Therapy with azimilide at a dose of 75 mg daily led to a 41% reduction in the risk of ES. A dose of 125 mg was accompanied by a risk reduction of 55%. Although we do not necessarily recommend the use of azimilide in all ICD recipients to prevent ES, administration of this new antiarrhythmic drug is indicated at least to prevent recurrent episodes of ES, an important and unwanted side effect of ICD therapy. The therapeutic efficacy is clinically relevant, considering the need for immediate hospitalization after experiencing recurrent ES episodes as shown in the present study, the psychological implications, and the potential detrimental effects on survival.

Limitations of the study

Since all our patients received their ICD after at least one documented episode of spontaneous VT or VF, our observation applies primarily for patients undergoing device therapy for secondary prevention of sudden cardiac death.

The results may not necessarily apply to patients receiving an ICD for primary prevention of arrhythmogenic death. In addition, about 40% of the arrhythmic episodes did not have sufficient electrograms, but did have the ICD data log.

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Conflict of interest: S.H.H., P.D., and C.M.P. served on the Steering Committee for the SHIELD study and were consultants to the Procter & Gamble Pharmaceuticals. P.T. served on the Event Committee for the SHIELD study, and H.R.Al-K., J.M.B., and D.S.T. are employees of the Procter & Gamble Pharmaceuticals.

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