Electrical Storm Presages Nonsudden Death
The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial

Derek V. Exner, MD, MPH; Sergio L. Pinski, MD; D. George Wyse, MD, PhD;
Ellen Graham Renfroe, RN; Dean Follmann, PhD; Michael Gold, MD, PhD; Karen J. Beckman, MD;
James Coromilas, MD; Scott Lancaster, MS; Alfred P. Hallstrom, PhD; and the AVID Investigators

Background—Electrical storm, multiple temporally related episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF), is a frequent problem among recipients of implantable cardioverter defibrillators (ICDs). However, insufficient data exist regarding its prognostic significance.

Methods and Results—This analysis includes 457 patients who received an ICD in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial and who were followed for 31±13 months. Electrical storm was defined as ≥3 separate episodes of VT/VF within 24 hours. Characteristics and survival of patients surviving electrical storm (n=90), those with VT/VF unrelated to electrical storm (n=184), and the remaining patients (n=183) were compared. The 3 groups differed in terms of ejection fraction, index arrhythmia, revascularization status, and baseline medication use. Survival was evaluated using time-dependent Cox modeling. Electrical storm occurred 9.2±11.5 months after ICD implantation, and most episodes (86%) were due to VT. Electrical storm was a significant risk factor for subsequent death, independent of ejection fraction and other prognostic variables (relative risk [RR], 2.4; 95% confidence interval [CI], 1.3 to 4.2; P=0.003), but VT/VF unrelated to electrical storm was not (RR, 1.0; 95% CI, 0.6 to 1.7; P=0.9). The risk of death was greatest 3 months after electrical storm (RR, 5.4; 95% CI, 2.4 to 12.3; P=0.0001) and diminished beyond this time (RR, 1.9; 95% CI, 1.0 to 3.6; P=0.04).

Conclusions—Electrical storm is an important, independent marker for subsequent death among ICD recipients, particularly in the first 3 months after its occurrence. However, the development of VT/VF unrelated to electrical storm does not seem to be associated with an increased risk of subsequent death. (Circulation. 2001;103:2066-2071.)

Key Words: defibrillation ■ heart failure ■ tachycardia ■ fibrillation

Compared with antiarrhythmic drugs, implantable cardioverter defibrillator (ICD) therapy reduces mortality in patients at high risk for arrhythmic death, especially those with depressed left ventricular function and ventricular fibrillation (VF) or ventricular tachycardia (VT).1–4 Recurrent arrhythmias occur in 40% to 60% of ICD recipients over the initial 3 years of follow-up, and multiple temporally related episodes of VT/VF occur in 10% to 20% of patients.5,6 However, the prognostic significance of recurrent ventricular arrhythmias7–9 including multiple recurrent episodes,5,6 is unclear. Whether ICD recipients who experience electrical storm (≥3 distinct episodes of VT/VF within a 24-hour period) are at increased risk of subsequent death remains controversial. Further, it is unclear if electrical storm is a contributing factor to, or a marker of, increased mortality. Finally, whether the development of electrical storm identifies ICD recipients at a transiently higher risk of death and thus in whom therapies aimed at altering heart failure progression, recurrent ischemia, or recurrent arrhythmias should be considered10–19 is of obvious clinical significance.

The present analysis sought to determine the prognostic significance of electrical storm in patients receiving an ICD in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Specifically, we sought to assess the independent prognostic impact of electrical storm, both in the initial 3 months after its occurrence and long-term. The 3-month window was chosen a priori to identify whether a clinically meaningful window for intervention existed.

Methods

Patients presenting with VF, VT with syncope, or VT with hemodynamic compromise and a left ventricular ejection fraction <0.40 were eligible for enrollment in AVID, but those with stable VT, unexplained syncope and inducible VT, ventricular arrhythmias secondary to a correctable cause, prior VT or VF already treated with
IMPLANTABLE CARDIOVERTER DEFIBRILLATOR = 507

Antiarrhythmic drug = 509

Died prior to hospital discharge = 9
Did not receive defibrillator as planned = 7
Device with limited storage capability = 34

Study population = 457

This analysis included 457 randomized patients who were discharged alive from the hospital with a defibrillator capable of advanced storage.

Table 1. Characteristics of Patients Who Survived Electrical Storm

Electrical Storm

Amiodarone, a limited life expectancy, New York Heart Association functional class IV symptoms, or contraindications to amiodarone or ICD therapy were not eligible. A total of 1016 patients were randomly assigned to ICD or antiarrhythmic drug therapy. Of the 507 patients assigned to receive an ICD, 457 (90%) were discharged alive from the hospital with a device that had advanced storage (Figure). The survival of these 457 patients was evaluated through August 31, 1998.

ICD Therapies and Electrical Storm

A group of experienced cardiac electrophysiologists characterized ICD therapies as appropriate or inappropriate using stored electrogram data, R-R interval data, and clinical history. Electrical storm was defined a priori as the occurrence of ≥3 separate episodes of VT/VF within a 24-hour period, each separated by ≥5 minutes. ICD interventions included antitachycardia pacing, low-energy shocks, and high-energy shocks. Only patients with ≥3 discrete VT/VF episodes were classified as having electrical storm. Nontemporally distinct clusters of VT/VF were not categorized as electrical storm.

Group Categorization

A time-dependent analytic method was used wherein patients were categorized as surviving electrical storm, surviving VT/VF unrelated to electrical storm, or as either dying during an initial episode of VT/VF or having no VT/VF during follow-up. Because we sought to compare the risk of death during each time period (before VT/VF, after non-electrical storm VT/VF, and after electrical storm), patients who died during their initial episode of VT/VF and those who did not experience VT/VF were included in the same category because they contributed follow-up time to only the period before VT/VF. Remaining patients contributed follow-up time to the period before VT/VF and to the period after electrical storm and/or the period after non-electrical storm VT/VF, depending on whether they had VT/VF related or unrelated to electrical storm.

Categorization of Deaths

Deaths were categorized as cardiac or noncardiac, and cardiac deaths were subcategorized as arrhythmic or nonarrhythmic by an experienced committee that was masked to treatment assignment. Given the limitations inherent in clinical definitions of arrhythmic death, arrhythmic deaths are referred to as “sudden” in this analysis.

Window for Intervention

A 3-month window after the development of electrical storm was chosen a priori on the basis of data from prior studies to provide a clinically meaningful intervention period. Villacastin and colleagues found that patients who had clusters of ICD shocks had an excess risk of cardiac death beyond 12 months of follow-up, 2 months after the mean time to the development of these clusters (10 months). Likewise, Credner et al found a nonsignificant excess number of deaths beyond 8 months of follow-up, 4 months after the mean time to the development of electrical storm (4 months).

Statistical Analysis

Continuous baseline characteristics are presented as mean ± SD and were compared among the 3 groups using ANOVA. Pairwise comparisons were performed using Student’s t test and correcting for multiple comparisons using the Bonferroni method. Group comparisons of categorical data were evaluated using an uncorrected χ² test. Univariate Cox proportional hazards models were used to assess the significance of baseline variables with respect to outcome. Multivariate Cox models were used to adjust for important prognostic variables and baseline differences. To account for the fact that the occurrence of VT/VF, including episodes of electrical storm, are postrandomization events (ie, patients need to survive long enough to be at risk), time-dependent Cox models were used to evaluate the prognostic significance of VT/VF and the follow-up use of antiarrhythmic drugs. The Cox models were used to determine relative risk (RR) estimates and 95% confidence intervals (CI) surrounding these estimates. Analyses were performed using SIR (Scientific Information Retrieval Inc), SPSS 6.1 (SPSS Inc), and Stata: Release 6.0 statistical software.

Results

Characteristics

Characteristics of patients who survived electrical storm, those who survived VT/VF unrelated to electrical storm, and the remaining patients are shown in Table 1. Patients with electrical storm were more likely to have had VT versus VF as their index arrhythmia. Patients with electrical storm or VT/VF unrelated to electrical storm had lower mean ejection fraction values, were more likely to receive an angiotensin-converting enzyme (ACE) inhibitor or digoxin at baseline, and were less likely to have a revascularization procedure after their index arrhythmia compared with the remaining patients.

Electrical Storm

Most patients (274 of 457; 60%) had ≥1 appropriate ICD therapy for VT/VF during follow-up. Therapies for VT/VF unrelated to electrical storm accounted for two-thirds of these episodes (184 of 274; 67%); 90 patients (20%) developed electrical storm.

The development of electrical storm was a relatively late phenomenon, with the initial episode occurring 9.2 ± 11.5 months after ICD implantation. The majority of initial episodes were attributed to multiple, temporally related episodes of VT (77 of 90 initial episodes; 86%). The remaining 14% of episodes were due to VF or a combination of VT and VF. The median number of VT/VF events in the initial electrical storm episode was 4 (range, 3 to 14). A minority of episodes (5 of 90 initial episodes; 6%) were associated with syncope. No episodes required external resuscitation.

Shocks alone were used to treat 41 of the 90 initial electrical storm episodes (46%), and the remaining 49 episodes (54%) were treated with antitachycardia pacing alone (n = 25) or a combination of shocks and antitachycardia pacing (n = 24). The therapies used to treat these episodes (shocks versus antitachycardia pacing versus shocks and antitachycardia pacing) were similar in patients with VT versus VF as their index arrhythmia (P = 0.3).

Survival and Modes of Death

There were 34 subsequent deaths among the 90 patients (38%) who survived electrical storm, 28 subsequent deaths
among the 184 patients (15%) who survived VT/VF unrelated to electrical storm, and 41 deaths among the remaining 183 patients (22%). Overall, most deaths were categorized as cardiac, nonsudden (46%); noncardiac (32%), sudden (21%), or unspecified (1%) deaths accounted for the remainder of deaths. Ten of the 34 deaths (29%) in patients who survived electrical storm occurred in the first 3 months after its development, and only 4 deaths (12%) occurred in the first month after electrical storm.

Unadjusted Risk
Before statistical adjustment, patients surviving electrical storm were at higher risk for death compared with all other patients (RR, 3.0; 95% CI, 2.0 to 4.6; \( P<0.0001 \)). This was primarily related to a higher risk for cardiac, nonsudden death (RR, 3.8; 95% CI, 2.1 to 6.9; \( P=0.0001 \)). The risk of death after electrical storm was most pronounced in the initial 3 months after electrical storm (RR, 5.6; 95% CI, 2.8 to 11.5; \( P<0.0001 \)). In contrast, patients surviving VT/VF unrelated to electrical storm had only a somewhat higher risk of subsequent death compared with patients not in this category (RR, 1.6; 95% CI, 1.1 to 2.5; \( P=0.02 \)). The use of antiarrhythmic drugs during follow-up (RR, 1.9; 95% CI, 1.2 to 2.8; \( P=0.003 \)), advancing age (RR, 1.7 per decade; 95% CI, 1.4 to 2.1; \( P<0.0001 \)), a history of diabetes (RR, 1.9; 95% CI, 1.3 to 2.8; \( P=0.002 \)), and a history of heart failure (RR, 1.8; 95% CI, 1.2 to 2.6; \( P=0.004 \)) were individually associated with a higher risk of death. Higher ejection fraction values (RR, 0.7 per 0.1; 95% CI, 0.6 to 0.9; \( P=0.0003 \)) were associated with a significantly lower risk of death. Male versus female sex (RR, 0.9; 95% CI, 0.6 to 1.5; \( P=0.8 \)) and an index arrhythmia of VF versus VT (RR, 0.9; 95% CI, 0.6 to 1.3; \( P=0.4 \)) were not significantly associated with an altered risk of death.

Independent Risk
The development of electrical storm remained associated with a subsequent risk of death, independent of age, sex, ejection fraction, history of heart failure, the follow-up use of antiarrhythmic drugs, history of diabetes, and type of index arrhythmia (RR, 2.4; 95% CI, 1.3 to 4.2; \( P=0.003 \)). Electrical storm remained independently associated with a 5.4-fold increase in the risk of death in the initial 3 months after its

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female sex, %</td>
</tr>
<tr>
<td>Heart failure symptoms</td>
</tr>
<tr>
<td>No history of heart failure, %</td>
</tr>
<tr>
<td>NYHA functional class, %</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Ejection fraction</td>
</tr>
<tr>
<td>0.29±0.10</td>
</tr>
<tr>
<td>VF index arrhythmia, %</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>History of, %</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Revascularization before index arrhythmia</td>
</tr>
<tr>
<td>Revascularization after index arrhythmia</td>
</tr>
<tr>
<td>Discharge medications, %</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Other antiarrhythmic‡</td>
</tr>
<tr>
<td>Anticoagulant</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage of patients. NYHA indicates New York Heart Association.

*\( P<0.01 \), †\( P<0.05 \).
‡Includes sotalol.
was associated with a somewhat higher risk of death before therapy (ie, shocks and/or antitachycardia pacing). Most of these studies focused on shocks rather than any ICD methods of analysis (ie, non–time-dependent). Further, most adjustment for comorbid illness, or the use of inappropriate methods of analysis (ie, non–time-dependent) did not take into account the fact that the increased risk of subsequent death was most prominent in the first 3 months after electrical storm and approached baseline afterward.

Prior studies assessing the prognostic significance of VT/VF unrelated to electrical storm have provided conflicting results. Older studies furnished conflicting evidence on the relationship between ICD shocks and myocardial injury. Recurrent episodes of VF are also associated with increased intracellular myocardial calcium levels. Recent studies have shown that multiple shocks lead to elevations in cardiac troponin levels, which are indicative of minor degrees of myocardial injury, and more likely to receive a β-blocker (76%). Further, electrical storm occurred earlier in their patients (4 ± 4 months) than in AVID (9.2 ± 11.5 months). Finally, the method of analysis used in their study (ie, non–time-dependent) did not take into account the fact that patients need to survive long enough to be at risk for the development of VT/VF. Thus, on the basis of the strengths of the present analysis, electrical storm does seem to identify ICD recipients at higher risk of nonsudden mechanisms of death, particularly in the initial 3 months after its occurrence.

### TABLE 2. Transient and Lingering Risk of Death: Multivariate Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time-dependent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient (3-month) risk</td>
<td>5.4 (2.4 to 12.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Residual (lingering) risk</td>
<td>1.9 (1.0 to 3.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Antiarrhythmic drug use</td>
<td>1.2 (0.8 to 2.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Other VT/VF</td>
<td>1.0 (0.6 to 1.6)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.7 (1.4 to 2.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0 (1.3 to 3.0)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Ejection fraction (per 0.1)</td>
<td>0.7 (0.6 to 0.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.8 (0.5 to 1.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>1.2 (0.8 to 1.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>VF index arrhythmia</td>
<td>1.4 (0.9 to 2.1)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Development (Table 2). After the initial 3 months, the lingering risk of death was only marginally significant. Further, the risk of death during the initial 3 months after electrical storm was significantly higher than the risk beyond 3 months ($\chi^2$=5.25 for difference between models; $P$=0.02). The development of VT/VF unrelated to electrical storm was not independently associated with a significant alteration in the risk of subsequent death.

A secondary sensitivity analysis that evaluated the transient risk of death in the first month after electrical storm was also performed. The independent risks of death during (RR, 3.6; 95% CI, 1.1 to 12.2) and beyond (RR, 3.8; 95% CI, 0.16 to 9.6) the first month after electrical storm were similar. However, given the small number of deaths (n=4) in the first month after electrical storm, this analysis had limited power.

### Discussion

The occurrence of multiple clustered episodes of VT/VF independently identifies defibrillator recipients at increased risk of subsequent death. Most of this excess risk was attributable to cardiac, nonsudden mechanisms. The risk of death after electrical storm is greatest in the initial 3 months. Thus, the development of electrical storm identifies ICD recipients who warrant close follow-up, consideration of antiaarrhythmic therapy, and/or consideration of other therapies aimed at reducing nonsudden, presumably nonarrhythmic, mechanisms of death.

### Previous Research

Prior studies assessing the prognostic significance of VT/VF unrelated to electrical storm have provided conflicting results. However, many of these studies were limited by relatively small sample sizes, an inability to distinguish between appropriate versus inappropriate shocks, insufficient adjustment for comorbid illness, or the use of inappropriate methods of analysis (ie, non–time-dependent). Further, most of these studies focused on shocks rather than any ICD therapy (ie, shocks and/or antitachycardia pacing).

In the present analysis, VT/VF unrelated to electrical storm was associated with a somewhat higher risk of death before adjustment for prognostic factors such as ejection fraction but no significant excess risk after adjustment. Thus, the development of VT/VF unrelated to electrical storm is not independently associated with an increased risk of subsequent death, but it may be a marker for comorbid illness. In contrast, the development of electrical storm was associated with a significantly elevated risk of death, both before and after adjustment for important prognostic variables. Moreover, the increased risk of subsequent death was most prominent in the first 3 months after electrical storm and approached baseline afterward.

Villacastin and colleagues assessed the prognostic significance of multiple, consecutive ICD discharges for VT/VF in 80 patients who were followed for 21±19 months. The 33% of patients who experienced single shocks were not at increased risk of subsequent death, but the 20% of patients surviving multiple, consecutive ICD discharges (≥2 shocks for a single arrhythmic episode) tended to have a greater risk of death (RR, 3.5; $P$=0.06). Further, the average time to the development of multiple, consecutive ICD discharges (10 months) was similar to the mean time to electrical storm in AVID (9.2 months).

More recently, Credner and colleagues assessed the prognostic significance of electrical storm in a group of 136 patients. Over 13±7 months of follow-up, 43 patients (32%) experienced ICD therapies unrelated to electrical storm, and 14 (10%) experienced electrical storm. Neither the patients who experienced VT/VF unrelated to electrical storm nor those who experienced electrical storm were significantly more likely to die compared with patients who did not have VT/VF during follow-up. Several important differences in their study versus the present analysis merit discussion. First, the present analysis included >3 times the number of patients and had substantially longer follow-up. Further, compared with AVID, the patients in Credner et al’s study had higher ejection fraction values (0.35±0.13), less ischemic heart disease (69%), and were more likely to receive a β-blocker (76%). Further, electrical storm occurred earlier in their patients (4±4 months) than in AVID (9.2±11.5 months). Finally, the method of analysis used in their study (ie, non–time-dependent) did not take into account the fact that patients need to survive long enough to be at risk for the development of VT/VF. Thus, on the basis of the strengths of the present analysis, electrical storm does seem to identify ICD recipients at higher risk of nonsudden mechanisms of death, particularly in the initial 3 months after its occurrence.

### Direct Versus Indirect Role of Electrical Storm

It is unclear whether electrical storm plays an inciting, contributing, or bystander role in the observed excess mortality. Although older studies furnished conflicting evidence on the relationship between ICD shocks and myocardial injury, recent studies have shown that multiple shocks lead to elevations in cardiac troponin levels, which are indicative of minor degrees of myocardial injury, and pathological studies have demonstrated fibrosis and acute cellular injury in the hearts of patients who had received recent shocks. Recurrent episodes of VF are also associated with increased intracellular myocardial calcium lev-
els,31,32 which in turn have been linked to progressive left ventricular dysfunction,33 cardiac apoptosis,34 and arrhythmia facilitation.32 Thus, the present analysis provides additional support to the notion that electrical storm contributes to the observed excess mortality. The similar risk of death in patients with electrical storm, before and after adjustment for other prognostic factors, further supports a causal role for electrical storm.

Window for Intervention

Because the risk of death is most prominent in the initial 3 months after electrical storm, prompt implementation or augmentation of therapies previously demonstrated to be efficacious in similar populations seems warranted. ACE inhibitors improve outcome in patients with left ventricular dysfunction,10,11 primarily via a reduction in heart failure progression. β-Blockers further reduce mortality in these patients12,13 through reductions in sudden death and heart failure progression. β-Blockers may be particularly effective in patients with electrical storm.6 Spironolactone has also been demonstrated to reduce mortality in patients with heart failure via a reduction heart failure progression.14 Coronary artery revascularization seems to be an important adjunct in patients with ischemic left ventricular dysfunction, both in terms of reducing the risk of future arrhythmias15 and in optimizing ventricular function.16 Finally, because electrical storm may be an inciting rather than a contributing factor for premature death, therapies specifically aimed at reducing nonsudden mechanisms, interventions designed to optimize ventricular function are likely to prove useful in reducing mortality. Finally, the demonstration of a discrete, 3-month window for intervention offers an opportunity to implement and evaluate established or new therapies in this population.

Clinical Implications

Apart from confirming that electrical storm is an independent risk factor for death in defibrillator recipients, the present analysis provides insights into improving their outcome. Because most of the excess mortality was attributable to nonsudden mechanisms, interventions designed to optimize ventricular function are likely to prove useful in reducing mortality. Supported by the National Heart, Lung, and Blood Institute (N01 HC-25117). Dr Exner is supported by the Canadian Institutes of Health and Research and the Alberta Heritage Foundation for Medical Research.

References


Electrical Storm Presages Nonsudden Death: The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial

Derek V. Exner, Sergio L. Pinski, D. George Wyse, Ellen Graham Renfroe, Dean Follmann, Michael Gold, Karen J. Beckman, James Coromilas, Scott Lancaster and Alfred P. Hallstrom
and the AVID Investigators

Circulation. 2001;103:2066-2071
doi: 10.1161/01.CIR.103.16.2066

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/16/2066

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/