Survival After Shock Therapy in Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy-Defibrillator Recipients According to Rhythm Shocked

The ALTITUDE Survival by Rhythm Study

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Objectives
This study sought to determine if the risk of mortality associated with inappropriate implantable cardioverter-defibrillator (ICD) shocks is due to the underlying arrhythmia or the shock itself.

Background
Shocks delivered from ICDs are associated with an increased risk of mortality. It is unknown if all patients who experience inappropriate ICD shocks have an increased risk of death.

Methods
We evaluated survival outcomes in patients with an ICD and a cardiac resynchronization therapy defibrillator enrolled in the LATITUDE remote monitoring system (Boston Scientific Corp., Natick, Massachusetts) through January 1, 2010. First shock episode rhythms from 3,809 patients who acutely survived the initial shock were adjudicated by 7 electrophysiologists. Patients with a shock were matched to patients without a shock (n = 3,630) by age at implant, implant year, sex, and device type.

Results
The mean age of the study group was 64 ± 13 years, and 78% were male. Compared with no shock, there was an increased rate of mortality in those who received their first shock for monomorphic ventricular tachycardia (hazard ratio [HR]: 1.65, p < 0.0001), ventricular fibrillation/polymorphic ventricular tachycardia (HR: 2.10, p < 0.0001), and atrial fibrillation/flutter (HR: 1.61, p = 0.003). In contrast, mortality after first shocks due to sinus tachycardia and supraventricular tachycardia (HR: 0.97, p = 0.86) and noise/artifact/oversensing (HR: 0.91, p = 0.76) was comparable to that in patients without a shock.

Conclusions
Compared with no shock, those who received their first shock for ventricular rhythms and atrial fibrillation had an increased risk of death. There was no significant difference in survival after inappropriate shocks for sinus tachycardia or noise/artifact/oversensing. In this study, the adverse prognosis after first shock appears to be more related to the underlying arrhythmia than to an adverse effect from the shock itself.

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Implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds) improve survival in patients with congestive heart failure or ventricular arrhythmias (1–3). However, 10% to 17% of patients in primary prevention ICD and CRT-D trials receive inappropriate or unnecessary shocks for sinus tachycardia, supraventricular tachycardia (SVT), or atrial fibrillation (AF)/atrial flutter (AFL) over the first 2 to 4 years after implant of the device (4–6). Some studies have shown that not only do patients who receive appropriate shocks for ventricular arrhythmias have an increased risk of death, but those who receive inappropriate shocks also have an increased risk of death compared with patients who do not receive any shocks (4–6). It remains unknown if the increased risk of death after inappropriate shocks is due to potentially harmful effects of ICD shocks.

Many ICD and CRT-D devices are now followed remotely from transmitters in patients’ homes. The data, including shock and rhythm data, from ICD and CRT-D devices are transmitted on a regular basis over a secure network to a central server. This provides a unique opportunity to analyze data in a large number of “real-world” ICD and CRT-D recipients.

We sought to determine if decreased survival after inappropriate shocks is due to the underlying arrhythmia or the ICD shock itself.

**Methods**

**Study design and subject participation.** The ALTITUDE project is a clinical science initiative formed to prospectively analyze data from ICD and CRT-D devices followed on a remote monitoring system (LATITUDE, Boston Scientific Corp., Natick, Massachusetts). The ALTITUDE study group consists of an independent physician leadership panel that prospectively identifies key clinical questions for analysis. De-identified patient data from the remote monitoring system were analyzed for this study.

At the time of this analysis, 127,134 patients with an ICD and a CRT-D from 1,550 centers across the United States were being followed on the LATITUDE remote monitoring system. A total of 28,398 patients received 1 or more ICD or CRT-D shock therapies. A random sample of 3,809 patients (13.4%) who experienced 1 or more spontaneous defibrillator shocks was evaluated. Patients were drawn from 2 previous studies of adjudicated shocked episodes (6,7). In the first study, a random sample of 2,000 patients who received ICD or CRT-D shocks was included. In the second study, 1,809 patients were randomly sampled from groups of patients based on ICD or CRT-D tachyarrhythmia therapy programming parameters. Further details regarding patient sampling can be found in the 2 studies referenced.

A physician panel of 7 board-certified cardiac electrophysiologists adjudicated the rhythm at the time of the shock episodes by reviewing the intracardiac electrograms stored in the ICD or CRT-D device at the time of therapy. The methods for review of the electrogams and level of agreement have been previously reported (8).

Survival status was obtained by cross-reference to the U.S. Social Security Death Index. Follow-up for vital status data was continued for 12 months after collection of study data was closed to allow for lag time in reporting. Patients without Social Security numbers were excluded from the analysis and totaled 5% of the study population.

We sought to compare survival in patients experiencing a shock by underlying rhythm at the time of shock and survival in patients with and without a shock. Two methods of analysis were pre-specified: analysis of time from first shock to death by adjudicated rhythm and matched pair analysis of patients with a shock to patients without a shock.

**Statistical methods. ANALYSIS OF TIME FROM FIRST SHOCK TO DEATH.** The first adjudicated episode for each patient was included in the analysis. Patients were grouped by adjudicated rhythm observed at the time of the first shock episode. Categories for rhythm classification were ventricular fibrillation (VF)/polymorphic ventricular tachycardia (PMVT), monomorphic ventricular tachycardia (MVT), MVT and PMVT, AFL/AFL, sinus tachycardia, SVT, nonsustained arrhythmia, and shock secondary to noise, artifact, or oversensing. Nonsustained arrhythmias were defined as arrhythmias that met device detection criteria and resulted in a shock but the arrhythmia terminated spontaneously before delivery of the shock. Kaplan-Meier and Cox proportional hazards model analyses were performed for time from first shock to death. Patients were grouped by adjudicated rhythm that resulted in the first shock, accounting for left truncation at the first LATITUDE transmission with a common censor date of January 1, 2010, to allow for complete reporting of mortality information. Cox model covariates were adjusted for age at implant and sex.

**MATCHED PAIR ANALYSIS.** For each patient with an adjudicated shock, a matching patient was identified who was known to be shock-free through the point in time when the adjudicated shock was delivered (n = 3,630). Patients were matched by age at implant, sex, device type (ICD or CRT-D), implant year, and time from implant to first remote monitoring transmission (in quarter years). In the matched analysis, 95.3% of patients with a shock were included. Each pair was categorized by one of 4 outcomes: shock patient...

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died, matched patient died, both died, or neither died. Analysis was performed independently for each adjudication category to assess the association between shock occurrence and mortality. The Cochran-Mantel-Haenszel test was used to test for homogeneity of effect across patients and time. An overall odds ratio was calculated using the Mantel-Haenszel estimator. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patients were followed up for an average of 3.1 ± 1.7 years after implant and 2.1 ± 0.4 years after a first shock. The mean age of the study group was 64 ± 13 years, and 78% were male. Patients with a CRT-D were older than patients with an ICD (Table 1), but there was no significant difference in age or sex between single-chamber and dual-chamber ICD groups. Of the 3,809 patients in the study group, 950 (24.9%) had a single-chamber ICD, 1,318 (34.6%) had a dual-chamber ICD, and 1,541 (40.5%) had a CRT-D device. Unsuccessful antitachycardia pacing preceded the first shock in 1,118 patients (29.4%). Patient characteristics were similar between the patient populations sampled from the 2 previous studies (Table 1).

Survival by rhythm at time of first shock. Patients who received a first shock for a ventricular arrhythmia had an increased risk of death during follow-up compared with those who received a first shock for a nonventricular arrhythmia (Fig. 1). Compared with patients with an ICD who received a shock for MVT, those who received a shock for PMVT or VF had an increased risk of death (hazard ratio [HR] for death: 1.35; 95% confidence interval [CI]: 1.01 to 1.81). In contrast, there was no significant difference in survival in patients with a CRT-D who received a shock for VF/PMVT compared with MVT (HR for death: 0.99; 95% CI: 0.78 to 1.28). Compared with MVT, there was a decreased risk of death during follow-up in those who received a first shock for sinus tachycardia/SVT (HR for death: 0.60; 95% CI: 0.47 to 0.76) or noise/artifact/oversensing (HR for death: 0.49; 95% CI: 0.33 to 0.73), while there was no significant difference for AF/AFL (HR for death: 0.84; 95% CI: 0.69 to 1.03). These results were similar for both patients with an ICD and patients with a CRT-D.

Table 2 details the type of rhythm at the time of subsequent shocks for the 1,982 patients who had data available on adjudicated episodes of subsequent shocks. Most patients with an appropriate shock as their first shock had a combination of both appropriate and inappropriate subsequent shocks (86.1% of patients with an appropriate shock as their first shock). In contrast, 72.2% of patients who had an inappropriate shock as their first shock only had inappropriate shocks as subsequent shocks during the study period.

Matched comparison to no-shock group. The number of patients matched by adjudicated rhythm and number of deaths in the matched analysis are shown in Table 3. Within each rhythm group, the time of follow-up was not different between the shock group and no-shock group (p = NS). There was an increased risk of death during follow-up in patients who received an appropriate shock (HR: 2.82; 95%
CI: 2.46 to 3.24) or inappropriate shock (HR: 1.81; 95% CI: 1.53 to 2.13) compared with a matched group who did not receive a shock. Compared with patients without a shock, patients with a shock had an increased risk of death if the shock was for a ventricular arrhythmia (HR: 2.10; 95% CI: 1.54 to 2.86 for VF/PMVT; p < 0.0001) or AF/AFL (HR: 1.61; 95% CI: 1.17 to 2.21; p = 0.003) (Fig. 2). However, there was no significant difference in survival for patients who received a shock for sinus tachycardia/SVT (HR: 0.97; 95% CI: 0.68 to 1.37; p = 0.86), noise/artifact/oversensing (HR: 0.91; 95% CI: 0.50 to 1.67; p = 0.76), or nonsustained arrhythmias (HR: 2.17; 95% CI: 0.86 to 5.70; p = 0.11) compared with the no-shock group. For patients who received an inappropriate shock, only shocks for AF/AFL were associated with an increased risk of death. The number of patients in the nonsustained arrhythmia group was small, resulting in large CIs that overlapped with the HRs for other groups.

**Discussion**

Patients with an ICD or CRT-D who receive an appropriate or inappropriate shock have an increased risk of death compared with those who did not receive a shock. The primary finding of this study is that the risk associated with inappropriate shock is limited to those receiving shocks for AF/AFL. Those who received an inappropriate shock for “benign rhythms” (sinus tachycardia or SVT) or nonarrhythmia events (noise, artifact, and oversensing) had similar survival to those who did not receive a shock. These data suggest that increased long-term mortality after a shock is due to the underlying arrhythmia as opposed to the shock itself.

Previous studies have shown an increased risk of death in patients who receive inappropriate shocks compared with those without a shock. The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) found that in patients who survived more than 24 h after a shock, there was an increased risk of death whether shocks were appropriate (HR: 3.0) or inappropriate (HR: 1.6) (5). The rate of survival more than 24 h after initial shock is similar to that in our study, in which patients had to survive their first shock for data to be transmitted via the ICD home remote monitoring system and be included in the study. In a previous ALTITUDE study, we reported an increased risk of death after appropriate or inappropriate shocks compared with patients who never received a shock (6). This current study provides more detailed insight into survival based on the underlying rhythm at the time of an ICD shock. This allowed us to evaluate the association between survival after inappropriate shocks for atrial arrhythmias and survival after inappropriate shocks triggered by “benign” conditions (noise, artifact, and oversensing). The increased risk of death after inappropriate shocks reported in previous studies raised the question if the ICD shock itself may cause enough harm to increase a patient’s risk of death. There are studies on animals and a small number of patients suggesting that markers of myocardial damage increase after high-energy shocks for termination of VF (9,10). However, the effect of myocardial damage and cardiac output after a transthoracic shock during normal sinus rhythm varies by patient (11). Whether or not a small degree of myocardial injury can affect a patient’s survival has been debated. The findings of our study provide new evidence to support the concept that the ICD shock itself does not increase the risk of death.

The recent MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy) study found that conventional ICD detection and therapy...
programming resulted in a greater number of ICD therapies and increased mortality (12). Does this contradict the findings of our study? There are a couple of key differences in the 2 studies. The increase in first ICD therapies with conventional programming in MADIT-RIT compared with high-rate therapy and delayed therapy groups was primarily due to increased episodes of antitachycardia pacing, while first shock episodes were not significantly different between groups. This suggests that unnecessary antitachycardia pacing increases mortality, possibly due to induction of ventricular arrhythmias. Our study was limited to patients who received ICD shocks, not antitachycardia pacing therapy alone. In addition, the survival analysis in MADIT-RIT included deaths during or immediately after the first ICD therapy. Our study looked at the long-term effects of an inappropriate ICD shock in patients who survived the initial ICD shock. Combining the results of the 2 studies, it could be concluded that unnecessary antitachycardia pacing may increase mortality, whereas unnecessary shocks for sinus tachycardia, SVT, or noise/artifact/oversensing do not appear to affect long-term survival.

Why was AF/AFL the only nonventricular arrhythmia associated with increased mortality after a shock? Some population studies have demonstrated an association between AF and increased mortality, regardless of the presence or absence of an ICD shock (13–16). The increased risk of death in patients who receive an ICD shock for AF is most likely secondary to the underlying substrate and comorbidities associated with AF. Receiving a shock due to rapid ventricular rates in the setting of AF/AFL may be a marker for patients of inadequate doses of beta-blocker medications or indicate that atrioventricular nodal blockade is inadequate in the setting of sympathetic activation associated with worsening heart failure. Rapid ventricular rates may lead to worsening ventricular function and heart failure. In addition, some patients convert to sinus rhythm with an ICD shock. If they are not on anticoagulation therapy at the time of conversion, there may be an increased risk of stroke or other thromboembolic event. This may contribute to an increased risk for death after a shock.

Analyses of pooled study data have found that patients with shock therapy for VT/VF have higher rates of mortality than patients with VT/VF terminated by antitachycardia pacing therapy (17). However, ventricular arrhythmias are triggered by various mechanisms. VF/PMVT is more likely than MVT to be triggered by acute myocardial ischemia or infarction (17,18). VF/PMVT is unlikely to terminate with antitachycardia pacing, thus necessitating an ICD shock for termination. In contrast, MVT is more likely to terminate with antitachycardia pacing (19). MVT can be triggered by a simple premature ventricular contraction or couplet without more serious coexisting circumstances. This may

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original Count</th>
<th>Matched Count</th>
<th>No-Shock Group</th>
<th>Shock Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF/polymorphic VT</td>
<td>614</td>
<td>579</td>
<td>14.0% (81/579)</td>
<td>25.4% (147/579)</td>
</tr>
<tr>
<td>Monomorphic VT</td>
<td>1,372</td>
<td>1,319</td>
<td>17.6% (232/1,319)</td>
<td>25.7% (339/1,319)</td>
</tr>
<tr>
<td>Polymorphic and monomorphic VT</td>
<td>253</td>
<td>245</td>
<td>12.7% (31/245)</td>
<td>28.6% (70/245)</td>
</tr>
<tr>
<td>Atrial fibrillation and flutter</td>
<td>694</td>
<td>667</td>
<td>13.3% (89/667)</td>
<td>19.0% (127/667)</td>
</tr>
<tr>
<td>Sinus tachycardia or SVT</td>
<td>645</td>
<td>603</td>
<td>13.3% (80/603)</td>
<td>12.9% (78/603)</td>
</tr>
<tr>
<td>Nonsustained arrhythmia</td>
<td>53</td>
<td>50</td>
<td>16.0% (8/50)</td>
<td>30.0% (15/50)</td>
</tr>
<tr>
<td>Noise/artifact/oversensing</td>
<td>178</td>
<td>167</td>
<td>16.8% (28/167)</td>
<td>15.6% (26/167)</td>
</tr>
</tbody>
</table>

Values are n or % (n/N). Mean follow-up was 3 years.

Abbreviations as in Table 1.

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### Figure 2

**Risk of Death After First Shock Compared With No-Shock Matched Group**

Mantel-Haenszel odds ratio of death after first shock based on the rhythm that resulted in the shock. The last 3 rhythm categories are inappropriate shocks. Of these, only shocks for atrial fibrillation or atrial flutter were associated with an increased risk of death compared with no-shock matched controls. Data are presented in a log axis format. MVT = monomorphic ventricular tachycardia; NSVT = nonsustained ventricular tachycardia; PMVT = polymorphic ventricular tachycardia; SVT = supraventricular tachycardia; VF = ventricular fibrillation.
result in an association between ventricular arrhythmias that require shocks and coexisting conditions that trigger shocks (i.e., myocardial ischemia or acute infarction). This makes it difficult to uncouple the type of ICD therapy for the ventricular arrhythmia from the underlying coexisting cardiac state. Patients with ventricular rhythms may be more susceptible to a small degree of myocardial injury from a shock compared with patients who receive a shock for a nonventricular arrhythmia (5,20). In a recent single-center study, induced arrhythmias have also been compared with shocks for VT/VF and were not associated with an increased risk of mortality. This implicates the coexisting conditions at the time of the arrhythmia rather than the shock (21).

Study limitations. The limitations of this study include limited available clinical data regarding patient comorbidities to allow for further adjusted analysis. No data were available on patient medications. This also limited the matching process to patient age, sex, device type, year of implant, and time from implant to first remote transmission. Devices were from a single manufacturer and limited to patients enrolled in a remote monitoring system. Patients had to survive their first ICD shock to perform a subsequent remote transmission and be included in this study. As a result, this study analyzed the long-term survival of patients who survived their first shock.

Conclusions

Compared with no shock, those who received a first shock for ventricular arrhythmia or AF had an increased risk of death. There was no significant difference in survival after an inappropriate shock for sinus tachycardia/SVT or noise/artifact/oversensing compared with no shock. In this study, the adverse prognosis after shock therapy is more related to the underlying arrhythmia than to a long-term adverse effect from the shock itself.

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REFERENCES


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