Long-Term Clinical Course of Patients After Termination of Ventricular Tachyarrhythmia by an Implanted Defibrillator

Arthur J. Moss, MD; Henry Greenberg, MD; Robert B. Case, MD; Wojciech Zareba, MD, PhD; W. Jackson Hall, PhD; Mary W. Brown, MS; James P. Daubert, MD; Scott McNitt, MS; Mark L. Andrews, BBS; Adam D. Elkin, BA; for the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) Research Group

Background—The implanted cardioverter defibrillator (ICD) improves survival in high-risk cardiac patients. This analysis from the MADIT-II trial database examines the long-term clinical course and subsequent mortality risk of patients after termination of life-threatening ventricular tachyarrhythmias by an ICD.

Methods and Results—Life-table survival analysis was performed, and proportional hazards regression analysis was used to evaluate the contribution of baseline clinical factors and time-dependent defibrillator therapy to mortality during long-term follow-up. Of 720 patients with an ICD (average follow-up 21 months), 169 patients received 701 antiarrhythmic device therapies for ventricular tachyarrhythmias. Few baseline characteristics distinguished patients who received appropriate ICD therapy for their first ventricular tachyarrhythmic episode. The probability of survival for at least 1 year after first therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) was 80%. The hazard ratios for the risk of death due to any cause in those who survived appropriate therapy for termination of VT and VF were 3.4 (P<0.001) and 3.3 (P=0.01), respectively, compared with those who survived without receiving ICD therapy, with a high frequency of heart failure and late nonsudden cardiac death after first successful ICD therapy for VF.

Conclusions—Successful appropriate therapy by an ICD for VT or VF is associated with 80% survival at 1 year after arrhythmia termination. These patients are at increased risk for heart failure and nonsudden cardiac death after device termination of VT or VF and should receive special attention for the prevention and management of progressive left ventricular dysfunction during long-term follow-up. (Circulation. 2004;110:3760-3765.)

Key Words: tachycardia ■ fibrillation ■ heart-assist device ■ cardioversion ■ defibrillation

The implanted cardioverter defibrillator (ICD) is effective in improving survival in high-risk cardiac patients, with a reduction in mortality risk ranging from 30% to 54%.1-5 The lifesaving benefit achieved with the ICD is due to a reduction in sudden cardiac death.6 In the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II), all the implanted devices had the capability for antitachycardia pacing to terminate reentrant ventricular tachycardia (VT) with appropriately timed pacemaker stimuli and the ability to deliver an internal shock for termination of fast VT or ventricular fibrillation (VF). The implanted devices also stored records of all therapy delivered by the ICD, and this information was routinely retrieved by device interrogation at regular follow-up visits during the course of the study. This study details the long-term clinical course and subsequent mortality risk of patients after successful termination of life-threatening ventricular tachyarrhythmias by the ICD.

Methods

Study Subjects

The MADIT-II trial7 prospectively enrolled 1232 patients with a myocardial infarction 1 month or more before entry and with an ejection fraction of 0.30 or less. Of the 742 patients randomized to the ICD arm of the trial, 720 subjects actually received an implanted defibrillator, and this latter group is the cohort utilized in the present study.

Follow-Up and End Points

Patients were scheduled for clinical follow-up at 3-month intervals after enrollment, and data concerning arrhythmias and device therapy were obtained at the time of device interrogation at each follow-up visit. The retrieved electrograms were reviewed by the 2 members of the Electrocardiographic Core Laboratory (WZ and JPD). Ventricular tachyarrhythmic episodes were categorized as VT or VF on the basis of rate and morphology and by the type of device therapy (antitachycardia pacing or shock) that terminated the tachyarrhythmia. In patients with multiple tachyarrhythmic episodes,
each discrete episode was counted when it was separated from a prior episode by more than 5 minutes.

An independent End-Point Committee established before initiation of the trial reviewed all mortality events using a variation of the Hinkle-Thaler clinical classification system. This committee determined, to the extent possible, the cause of death (cardiac or noncardiac) and the mode of cardiac death (sudden or nonsudden).

ICD Devices
During the course of the MADIT-II trial, several different US Food and Drug Administration–approved Guidant defibrillator devices were used, all of which had the capability of delivering antitachycardia pacing and shock therapy. Programming of the defibrillator was left to the discretion of the implanting cardiologist. Antitachycardia pacing function was activated (turned on) in 59% of the patients at the time of device implantation. No investigational devices were used. The implanted devices included the VENTAK AV series, the VENTAK Mini series, and the VENTAK Prizm series (Guidant Corporation). Four hundred six patients received a single-chamber unit, and 314 received a dual-chamber unit. For the most part, the defibrillator devices were set at a 2-zone configuration with a VT zone set at 180 bpm and a VF zone at 210 bpm; defibrillation was set with a 10-J safety margin.

Statistical Methods
Baseline characteristics of the patients who did and did not receive therapy from the implanted defibrillator were compared with the χ²
test. The event-free survival was graphically displayed according to the method of Kaplan and Meier,8 with comparisons of cumulative mortality by the log-rank test; the time origin for the before-therapy curve was the day of ICD implantation, whereas that for the posttherapy curve was the day of first ICD therapy. Multivariate Cox proportional hazards regression analysis was used to evaluate the contribution of baseline clinical factors and time-dependent defibrillator therapy to outcome during follow-up,9 with the time origin being the day of ICD implantation. The statistical software used for the analyses was SAS version 8.2, and a 2-sided probability value \( P < 0.05 \) was used for declaring statistical significance.

Results

Of the 720 patients with an implanted defibrillator, 169 patients received 1 or more successful device therapies; 281 episodes of VT were terminated by antitachycardia pacing in 147 patients, 305 episodes of VT were terminated by defibrillator shocks in 108 patients, and 115 episodes of VF were terminated by defibrillator shocks in 36 patients. The time between study entry and the first appropriate ICD therapy for a ventricular arrhythmic event is presented in Figure 1. The Kaplan-Meier graph of cumulative VT /VF events shows that at 3 years after implantation of the ICD, 35% of the patients had received at least 1 appropriate therapy for VT or VF. The numbers of patients who received 1 or more device therapies for VT and VF, grouped by the first arrhythmia terminated, are presented in Figures 2A and 2B. Patients whose initial (first) device therapy was for VT (VTi) or VF (VFi) were more likely to experience subsequent device therapies (VTs or VFs) for the same type of ventricular tachyarrhythmia (VTs/VTi \( \approx 55% \); VFs/VFi \( \approx 53% \)) than for the alternate tachyarrhythmia (VFs/VTi \( \approx 4% \); VTs/VFi \( \approx 27% \)). There were 98 patients who received 2 or more successful device therapies for ventricular tachyarrhythmias,
with 54% of the repeat episodes occurring within 24 hours, 67% within 1 week, and 93% within 6 months.

Baseline clinical characteristics of the 720 ICD-treated patients categorized by the first episode of VT (n=139) or VF (n=30) terminated by the implanted device and of those who did not experience any electrical therapy from the implanted device during follow-up (n=551) are presented in Table 1. Patients receiving successful electrical termination therapy for their first ventricular tachyarrhythmic episode had a higher New York Heart Association class at baseline than those who did not require any electrical therapy. The 30 patients who received a shock to terminate their first episode of VF during follow-up were less likely to have been inducible at baseline electrophysiological testing than those who required no electrical therapy or who received their first electrical therapy for VT. With time-dependent Cox analysis, the occurrence of an interim myocardial infarction was not a significant risk factor for appropriate ICD therapy for VT/VF (hazard ratio 1.86; 95% CI 0.86 to 4.04; P=0.12, with censoring of deaths and adjustment for relevant covariates).

Clinical Course
Hospitalization for heart failure was a frequent event after device therapy for VT or VF. At 1 year after appropriate ICD therapy for ventricular tachyarrhythmias (Figure 3), the probability of a heart failure event was 26% and 31% after first treatment for VT and VF, respectively, compared with 19% for those not yet requiring ICD therapy. The frequencies of use of dual- versus single-chamber ICD units were similar in the 3 therapy groups.

Kaplan-Meier estimates of survival after first successful device therapy are presented in Figure 4A, with a significant difference (P<0.001) in survival among the 3 curves. Survival curves after first therapy for VT or VF were similar (P=0.08), with survival close to 80% at 1 year after initial device therapy of either arrhythmia, followed by an apparent separation thereafter that involved a limited number of patients and thus had low power to detect a significant difference. Among those who received device therapy for VT or VF, survival curves were ordered by the rate of the tachycardia that required termination (Figure 4B), with decreased survival at increased tachycardia heart rates.

The 1-year rates for total mortality, cardiac death (sudden and nonsudden), and noncardiac death derived from Kaplan-Meier survival curves before and after ICD therapy for VT and VF are presented in Table 2. The 1-year rate for nonsudden death after first device therapy for VF was particularly elevated.

Effect of ICD Therapy on Subsequent Risk of Death
As a further analysis of risk after first therapy for VT or VF, a proportional hazards regression analysis was performed that allows for a change in risk of death at the time of first appropriate ICD therapy (Table 3). This analysis permits inclusion of other important risk factors for mortality in the risk model. First appropriate ICD therapy identifies more than a 3-fold increase in mortality risk, whether the therapy is for
VT or VF. Dual- versus single-chamber units, QRS duration, evidence of inducibility at the time of device implantation, and time-dependent new myocardial infarction after enrollment did not enter the risk model. Additional analyses that evaluated the change of amiodarone or β-blocker therapy from before to after the first VT/VF event revealed that these drug therapies did not have a significant effect on mortality (P<0.10 for both drugs).

**Discussion**

This study highlights the clinical course of patients after receipt of appropriate electrical conversion therapy for life-threatening ventricular tachyarrhythmias from an ICD. Few baseline characteristics distinguished patients who did and did not go on to develop ventricular tachyarrhythmias after device implantation. Eighty percent of patients who had their first episode of VT or VF terminated by the ICD were alive 1 year later. The rate of the ventricular tachyarrhythmia at the time of electrical termination was related to the subsequent clinical course, with faster VT/VF rates associated with higher subsequent mortality. These findings suggest that the extent and severity of the underlying myocardial disease process that provides the electrophysiological substrate for the ventricular tachyarrhythmia are important factors that influence both the rate of the tachyarrhythmia and subsequent outcome.

It would be inappropriate to conclude that each of the ICD discharges for VT recorded here represents the prevention of a lethal event. Many of the VT episodes would probably have terminated spontaneously, although some would have progressed to VF. Thirty patients had an initial device therapy for VF, and clearly these interventions were lifesaving. Interruption of VT early in the clinical course may postpone VF occurrence in patients susceptible to sudden death.

It is known that defibrillation shocks can cause myocardial damage, and the magnitude of the delivered joules may be a factor contributing to the development of heart failure and subsequent nonsudden cardiac death. We are unable to determine the relative contribution of defibrillation-related myocardial injury and intrinsic substrate remodeling to the clinical course that follows defibrillation. Dual-chamber pacemaker units were used in ~40% of the patients. Although such units may increase the probability of heart failure in vulnerable patients as a result of dysynchronous right ventricular pacing, we do not have evidence that dual-chamber units contributed to mortality, because the type of device (single versus dual chamber) did not make a significant contribution to the risk model.

A few prior studies have reported on the clinical course of patients after appropriate ICD therapy. In 1998, Bocker et al showed that defibrillation therapy was associated with prolongation of life in patients with a spectrum of cardiac disease and prior ventricular tachyarrhythmias, with the potential benefit estimated as the difference between overall mortality and a hypothetical death rate had the device not been implanted. The overall 1-year survival in the cohort studied by Bocker et al was 94%, with considerably lower survival in those who received ICD therapy for fast VT or VF. The relevant report from the Antiarrhythmics Versus Implantable Defibrillators trial involved secondary prevention with focus on ICD therapy for electrical storm. The development of

### TABLE 2. One-Year Mortality Rates Before and After First Terminated Ventricular Tachyarrhythmia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Therapy (n=720)</th>
<th>VT (n=139)</th>
<th>VF (n=30)</th>
<th>1-Year</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths</td>
<td>31</td>
<td>23</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality, %</td>
<td>6</td>
<td>18</td>
<td>20</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiac death, %</td>
<td>5</td>
<td>15</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsudden cardiac death</td>
<td>3</td>
<td>8</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiac death, %</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are 1-year mortality rates derived from Kaplan-Meier cumulative probability of type-specific mortality, with P value for all-cause mortality from the log-rank statistic comparing the 3 groups. Data on the subtypes of death were not subjected to statistical tests owing to overlap with all-cause mortality or small numbers of deaths.

### TABLE 3. Risk of Death After Appropriate ICD Therapy for Ventricular Tachyarrhythmias*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-dependent risk factors†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First therapy for VT</td>
<td>3.4</td>
<td>1.9–5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First therapy for VF</td>
<td>3.3</td>
<td>1.3–8.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Other risk factors‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen ≥25 mg/dL</td>
<td>2.3</td>
<td>1.4–3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No β-blockers</td>
<td>2.2</td>
<td>1.4–3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA II-IV</td>
<td>1.5</td>
<td>0.9–2.5</td>
<td>0.13</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association.

*Based on a proportional hazards model with 2 time-dependent risk factors.
†Time-dependent risk factors allow for a change in risk of death at the time of first appropriate ICD therapy for VT or VF.
‡These 3 variables are the only baseline covariates that entered the risk model at P<0.15. Time-dependent interim myocardial infarction occurring after enrollment did not enter the risk model. The hazard ratio values are the risk of death per unit of time among patients with the higher-risk partitions of the dichotomized variables compared with that among patients who had the lower-risk partitions of the variables.
electrical storm was associated with an elevated risk of death, but a similar increased risk was not substantiated in patients who developed VT/VF.

The present findings are derived from the MADIT-II primary prevention trial, which involved patients with coronary heart disease and an ejection fraction ≤0.30. The clinical course after defibrillator therapy in patients with higher ejection fractions and in patients with nonischemic cardiomyopathy may be different from what we observed. We have no stored postmortem interrogation data among patients who died after defibrillator therapy, so we have no direct information on the rate of unsuccessful termination of life-threatening arrhythmias.

The present study highlights the long-term clinical course of patients who received 1 or more successful terminations of life-threatening ventricular tachyarrhythmias by the ICD. Appropriate firing of an implanted device identifies patients at increased risk for subsequent heart failure and nonsudden cardiac death, and this group of patients should receive special attention for the prevention and management of progressive left ventricular dysfunction.

Acknowledgment
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References
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