Shock Occurrence and Survival in 241 Patients
With Implantable Cardioverter-Defibrillator Therapy

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Background. The purpose of this study was to determine the influence of clinical characteristics on shock occurrence and survival in 241 patients with implantable cardioverter-defibrillator (ICD) therapy.

Methods and Results. Two hundred forty-one consecutive patients underwent ICD implantation between November 1982 and November 1991 and were subsequently followed for 26±22 months (intention-to-treat analysis). Actuarial incidence of “appropriate” shocks was 13%, 42%, and 63%, and the incidence of any spontaneous shocks was 15%, 51%, and 76% at 1, 3, and 5 years of follow-up, respectively. Poor left ventricular function (ejection fraction ≤30%) was associated with an earlier occurrence of both appropriate and any spontaneous ICD shocks (p=0.001). Appropriate and any spontaneous shocks occurred significantly later in patients who presented with cardiac arrest and in patients in whom only ventricular fibrillation but no uniform ventricular tachycardia was induced during preoperative programmed stimulation. In addition, amiodarone treatment at implant was associated with later occurrence of any spontaneous shocks. Cumulative survival from all-cause mortality including perioperative mortality was 84%, 62%, and 57%, and survival from arrhythmic death was 97%, 89%, and 83% at 1, 3, and 5 years, respectively. Ejection fraction ≤30% was the best predictor of both total arrhythmic death (p=0.019) and total mortality (p=0.003). Antiarrhythmic therapy with class 1 agents at implant was also associated with a higher total mortality during follow-up (p=0.023) but not with total arrhythmic death.

Conclusions. The majority of patients receive shocks during long-term follow-up. The occurrence of appropriate or any spontaneous shocks during follow-up is not associated with increased arrhythmic or total mortality consistent with effective prevention of sudden cardiac death with ICD therapy in this high-risk patient population. Although low ejection fraction is the strongest predictor of both shock occurrence and mortality during follow-up, no easy algorithm can be derived from the analyzed clinical characteristics to predict which patients will benefit most from ICD implantation. (Circulation 1993;87:1880–1888)

Key Words • implantable cardioverter-defibrillator • sudden cardiac death • ventricular tachyarrhythmias

Since the first automatic implantable cardioverter-defibrillator (ICD) developed by Michel Mirowski was implanted on February 4, 1980, more than 25,000 devices have been implanted worldwide. Many studies have demonstrated the efficacy of the ICD in preventing sudden cardiac death in patients with life-threatening tachyarrhythmias. However, there are only a few reports of outcome in large study populations with more than 200 patients.2–5 The purpose of this study was threefold: 1) to determine the actuarial incidence of shocks and mortality in a large cohort of ICD patients, 2) to identify clinical characteristics associated with the occurrence of appropriate and any spontaneous ICD shocks, and 3) to determine clinical variables associated with total arrhythmic and total mortality after ICD implantation (intention-to-treat analysis).

Methods

Patient Population

The study population consists of 241 consecutive patients who underwent initial implantation of an ICD between November 1982 and November 1991 and a total 112 generator replacements until the end of follow-up in March 1992. The clinical characteristics of the 241 study patients are summarized in Table 1. Implantation data are provided in Table 2. All patients signed written informed consent before device implantation. Implantation protocols for investigational devices were approved by the institutional review board at the University of Pennsylvania.
Follow-up

Follow-up began at the time of first ICD implantation. End points of follow-up were 1) death from any cause including perioperative mortality, 2) heart transplantation (six patients), 3) last patient visit as of March 1992. All patients were seen routinely every 1–3 months or after device discharge. One hundred ninety-one patients were followed primarily at our hospital. Follow-up evaluation of the remaining 50 patients followed primarily at other centers was completed by telephone communication with the patient and/or the patient’s physician and analysis of the response to mailed questionnaires completed by the patient’s physician. All spontaneous shocks and deaths during follow-up were classified as defined below. In 20 of the 241 patients (8%), the ICD was removed, inactivated, or not replaced after battery depletion during follow-up for the following reasons: device infection or generator skin erosion (12 patients), refusal of replacement after battery depletion (five patients), end-stage heart failure (two patients), and high defibrillation threshold at attempted generator replacement (one patient). Of note, these 20 patients are included in the survival analysis according to the intention to treat.

Definitions

Perioperative mortality was defined as death from any cause within the first 30 days after ICD implantation or before hospital discharge. Cause of death was defined as previously described by Mosteller et al; Sudden death is defined as death occurring within 1 hour of symptoms in a previously medically stable patient or death occurring during sleep or unwitnessed; tachyarrhythmic/nonsudden death is defined as death associated with sustained ventricular tachycardia persisting or recurring over a time period longer than 1 hour before death; total arrhythmic death is defined as sudden or tachyarrhythmic/nonsudden death; cardiac nonarrhythmic death is defined as a witnessed death of cardiac nature other than sudden or tachyarrhythmic/nonsudden; cardiac death is defined as death that is sudden, tachyarrhythmic/nonsudden, or cardiac nonarrhythmic; noncardiac death is defined as death resulting primarily from other causes.

Since the incidence of spontaneous shocks preceded by presyncope or syncope clearly underestimates the occurrence of ventricular tachycardia (VT) or ventricular fibrillation (VF) in ICD patients and the majority of shocks were not electrocardiographically documented, analysis of spontaneous shocks was performed for both “appropriate” shocks and any spontaneous shocks. Appropriate shocks were defined as previously described by Fogoros et al; as spontaneous ICD discharges preceded by symptoms of severe light-headedness, presyncope or syncope followed by immediate relief from these symptoms, or shocks for VT or VF as documented by Holter or telemetry monitoring or stored electrograms by the device (Ventricad Cadence). The criteria for distinguishing supraventricular
FIGURE 1. Top panel: Continuous recordings (25 mm/sec) of ventricular electrograms before and after spontaneous implantable cardioverter-defibrillator (ICD) shock for rapid ventricular tachycardia (VT) with a cycle length (CL) of 220 msec. Of note, the patient did not feel any symptoms preceding the shock. In the absence of stored electrograms by the device, this shock would not have been classified as “appropriate.” SR, supraventricular rhythm. Bottom panel: Continuous recordings (25 mm/sec) of ventricular electrograms before and after spontaneous ICD shock for rapid VT degenerating into ventricular fibrillation (VF) before a 550-V shock restored a supraventricular rhythm below the rate cutoff. Of note, the patient did not recall any symptoms nor did she recall having received a shock when she came for a routine follow-up visit. Importantly, this shock episode would also not have been classified as “appropriate” in the absence of stored electrograms by the device, although this shock most likely saved the patient’s life at this time.

ular tachycardia and VT by stored electrograms using electrogram morphology, rate, and RR interval variability have been described previously. Of note, 67 of the 241 study patients (28%) received one or more shocks for VT or VF documented by surface Holter or telemetry monitoring or stored electrograms by the device during follow-up. According to the definition above, these shocks are appropriate shocks despite the frequent absence of severe symptoms preceding the shocks for electrocardiographically documented VT (Figure 1). Any shocks were defined as any spontaneous ICD shocks other than electrocardiographically documented shocks for a non-VT rhythm or shocks in an asymptomatic patient with documented ICD generator or lead malfunction in whom the shock was most likely preceded by a non-VT rhythm, e.g., lead adapter breakage, magnet misdirection.

Statistical Methods

Data were analyzed for appropriate shocks versus no appropriate shocks, for any shocks versus no shocks, for total arrhythmic death versus no arrhythmic death, and for total death versus survival in relation to the following clinical variables: age, sex, ejection fraction, underlying heart disease, clinical presentation of the arrhythmia, result of programmed stimulation before ICD implant, coronary artery bypass grafting or subendocardial resection preceding ICD implantation, and antiarrhythmic drug treatment at implant. For the continu-ous-variable ejection fraction, subgroups were formed for patients with an ejection fraction <30% and ≥30% as suggested by the study of Kim and colleagues, who found a significantly increased risk for total arrhythmic and total mortality in patients with an ejection fraction <30%. For the continuous variable, age subgroups were formed arbitrarily at 70 years since no previous study suggested a particular cutoff for age as a predictor for spontaneous shocks, total arrhythmic, and total mortality. All analysis was performed according to the intention-to-treat principle unless specified otherwise. Values are expressed as mean±SD. Survival curves were plotted using the Kaplan-Meier method. Univariate comparison between survival curves was performed using the log-rank method for all variables listed above. A value of p<0.05 was considered significant. Variables demonstrating sufficient association with the dependent variable (occurrence of appropriate shocks, any shocks, arrhythmic death, and total mortality, respectively) at p≤0.15 were then included in a multivariate stepwise Cox proportional hazards analysis requiring p<0.05 for variable entry and p>0.10 for variable removal.

Results

Incidence of Appropriate and Any Spontaneous ICD Shocks

During 24±20 months of follow-up with active ICD, 135 of 241 patients (56%) received a spontaneous ICD
shock (Table 3). The mean number of any spontaneous shocks was 6±9 (range, 1–61). One hundred three of the 135 patients with any spontaneous shock (76%) received more than one shock. Appropriate ICD shocks were observed in 102 of 241 patients (42%). Of note, in 67 of the 102 patients (66%) with appropriate shocks, at least one spontaneous shock was preceded by VT or VF as documented by Holter or telemetry monitoring or stored electrograms by the device. The actuarial event-free rates for appropriate and any spontaneous shocks are listed in Table 4 and shown as Kaplan-Meier curves in Figure 2.

### Clinical Variables Associated With Appropriate and Any Spontaneous Shocks

Results of univariate and multivariate Cox analysis of clinical characteristics associated with appropriate and any spontaneous ICD shocks are shown in Table 3. Ejection fraction ≤30% was the only variable that was independently associated with earlier occurrence of both appropriate and any spontaneous ICD shocks (p=0.001, Figure 3). Appropriate and any spontaneous shocks occurred significantly later in patients who presented with a cardiac arrest and in patients in whom only VF but no uniform VT was induced during pre-

### Table 4. Event-Free Rates During Long-term Follow-up of 241 Patients With Implantable Cardioverter-Defibrillator Therapy

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>6 (n=202)</th>
<th>12 (n=163)</th>
<th>24 (n=110)</th>
<th>36 (n=67)</th>
<th>48 (n=39)</th>
<th>60 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate shocks</td>
<td>93%</td>
<td>87%</td>
<td>74%</td>
<td>58%</td>
<td>45%</td>
<td>37%</td>
</tr>
<tr>
<td>Any spontaneous shocks</td>
<td>92%</td>
<td>85%</td>
<td>67%</td>
<td>49%</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>98%</td>
<td>98%</td>
<td>94%</td>
<td>90%</td>
<td>87%</td>
<td>84%</td>
</tr>
<tr>
<td>Total arrhythmic death*</td>
<td>97%</td>
<td>97%</td>
<td>93%</td>
<td>89%</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>Total cardiac death</td>
<td>93%</td>
<td>90%</td>
<td>81%</td>
<td>72%</td>
<td>69%</td>
<td>67%</td>
</tr>
<tr>
<td>Total death (any cause)</td>
<td>89%</td>
<td>84%</td>
<td>74%</td>
<td>62%</td>
<td>59%</td>
<td>57%</td>
</tr>
</tbody>
</table>

n=number of patients followed at each point of time.

*Sudden cardiac death and tachyarrhythmic/nonsudden death (see text for further definitions).
operative programmed stimulation. In addition, amiodarone treatment at implant was independently associated with later occurrence of any spontaneous shocks. Of note, age, sex, underlying heart disease, and coronary artery bypass grafting preceding ICD implantation did not independently predict appropriate or any spontaneous shocks.

Mortality in 241 Study Patients

During total follow-up of 26±22 months, 73 of 241 patients (30%) died, including eight patients who died within 4 weeks after implantation or before hospital discharge. No patient died during ICD implantation. The cause of early postoperative death was electromechanical dissociation in three patients, massive pulmonary emboli in two patients, and refractory congestive heart failure with recurrent VT, respiratory failure, and myocardial infarction in one patient each. Including early postoperative mortality, the cause of death during total follow-up was sudden death in 17 patients (7%), arrhythmic/non-sudden death in two patients (1%), cardiac/nonarrhythmic death in 31 patients (13%), and noncardiac death in 23 patients (9%). Actuarial survival data are provided in Table 4, and Kaplan-Meier curves for survival from sudden death, total cardiac death, and total death are shown in Figure 4. Of note, the actuarial incidence of death in Table 4 and Figure 4 includes 12 of 20 patients with ICD removal or inactivation for the reasons listed above who died during further follow-up (intention-to-treat analysis). Importantly, four of the 17 patients with sudden death during follow-up died after device inactivation or removal without replacement. Thus, only 13 of 241 patients (5%) experienced sudden death with active ICD during follow-up.

Clinical Characteristics Associated With Arrhythmic Death and Total Mortality

Results of univariate and multivariate Cox analysis of clinical characteristics associated with total arrhythmic and total death are shown in Table 5. Ejection fraction ≤30% was the only variable associated with total arrhythmic death (p=0.019) for both univariate and multivariate analysis. Total mortality was also independently associated with an ejection fraction ≤30% (p=0.003, Figure 5). In addition, treatment with type I antiarrhythmic agents but not amiodarone treatment was associated with a higher total mortality (p=0.023) but not with total arrhythmic death. None of the remaining variables including age, sex, underlying heart disease, clinical presentation of the arrhythmia, result of programmed stimulation before ICD implantation, or preceding revascularization was associated with an increase or decrease in arrhythmic or total mortality during follow-up. Of note, the survival curves of patients who received appropriate or any spontaneous shocks were not significantly different from the curves of patients who did not receive shocks (Table 5).
Time From First ICD Discharge to Death

Thirty-nine of 102 patients (38%) who received appropriate shocks during follow-up died during further follow-up. Mean survival after the first appropriate shock for the 39 patients who died until the end of total follow-up was 12±13 months (range, 0–63 months). Mean survival after the first appropriate ICD shock until the end of total follow-up for all 102 patients who received appropriate shocks was 20±21 months (range, 0–94 months).

Forty-seven of 135 patients (35%) who received any spontaneous shocks during follow-up died during further follow-up. Mean survival after the first shock for the 47 patients who received any spontaneous shocks and died later during follow-up was 13±13 months (range, 0–63 months). Mean survival after the first spontaneous ICD shock for all 135 patients who received any shock was 21±20 months until the end of follow-up (range, 0–94 months).

Discussion

Prevention of sudden cardiac death with ICD therapy has already been well documented.2–5,7,13–23 The present study of 241 consecutive patients who underwent ICD implantation for life-threatening ventricular tachyarrhythmias confirms the efficacy of ICD therapy in sudden cardiac death prevention by the following ob-

![Graph of survival rates (Kaplan-Meier) for total death in patients with an ejection fraction (EF) >30% and patients with an ejection fraction ≤30% (p=0.003).](image)
servation: 1) the actuarial 5-year incidence of appropriate shocks in 63% of patients and of any spontaneous shocks in 76% of patients, 2) the time from the first appropriate or any spontaneous shock to death with a mean of 12 months or 13 months, respectively, with no difference in total arrhythmic and total survival for patients with and without spontaneous shocks, and 3) the low incidence of sudden cardiac death during follow-up in 13 of 241 patients (5%) with active ICD (follow-up, 24±20 months) and 17 of 241 patients (7%) during total follow-up of 26±22 months according to the intention-to-treat analysis. The multivariate analysis of clinical characteristics associated with spontaneous shocks, total arrhythmic death, and total mortality may have important implications for future clinical trials.

**Incidence of Spontaneous Shocks**

The incidence of appropriate shocks defined as shocks preceded by presyncope or syncope clearly underestimates the true incidence of shocks for ventricular tachyarrhythmias (Figure 1). Conversely, the incidence of any spontaneous ICD shocks, excluding shocks for documented non-VT rhythm or device malfunction, clearly overestimates the true incidence of shocks for VT or VF. Therefore, both appropriate and any spontaneous shocks were analyzed in this study. Using this approach, the true incidence of shocks for ventricular tachyarrhythmia recurrence is most likely in the area between the two Kaplan-Meier curves for freedom of appropriate and any spontaneous shocks (Figure 2). Of note, the actuarial 5-year incidence of appropriate shocks in 63% of patients in our study is very similar to the findings of other investigators ranging from 62% in the study from Gross and colleagues to 69% in the report of Fogoros et al. and Tchou et al.

**Effect of Ejection Fraction on Shock Occurrence and Survival**

Poor left ventricular function (ejection fraction ≤30%) was the only clinical variable in our study that was independently associated with all four dependent variables, i.e., earlier occurrence of appropriate and any spontaneous shocks (Figure 3) and higher total arrhythmic and total mortality (Table 5). However, the predictive value of preserved left ventricular function at implant for remaining shock free during follow-up is low, since 51% of patients with an ejection fraction >30% are estimated to receive appropriate shocks during 5-year follow-up (Figure 3). These findings are similar to the results of Levine and colleagues, who found an ejection fraction ≤25% predictive for earlier ICD discharge and shorter survival after ICD discharge. Our results also confirm the finding of Kim and colleagues that an ejection fraction <30% is associated with a higher total arrhythmic and total mortality after ICD implant. In our study, patients who died during the early postoperative period after ICD implantation (3%) tended to have a lower ejection fraction of 27±11% as compared with 31±12% in patients who survived the early postoperative period. However, the difference in ejection fraction was not significant because of the small number of patients who died early postoperatively in our study. Similar to our results, a recent multicenter study reported by Mosteller and colleagues revealed a significant, inverse correlation between perioperative mortality (3%) and left ventricular ejection fraction; patients who died perioperatively had a mean ejection fraction of 26% versus 34% in survivors of ICD implantation.

**Effect of Antiarrhythmic Drug Treatment at the Time of ICD Implantation**

Treatment with amiodarone at implantation was independently associated with later occurrence of any spontaneous shocks, but there was no significant difference in the occurrence of appropriate shocks in patients with and without amiodarone at implantation (Table 3). This finding may merely reflect differences in patient selection for amiodarone therapy at implantation that were not accounted for by the clinical variables listed in Table 3, such as frequency and hemodynamic tolerance of the clinical VT and intolerance or failure of other antiarrhythmic agents. Treatment with class 1 antiarrhythmic drugs at implantation was associated with a higher total mortality but not with sudden death or total arrhythmic death (Table 5). Of note, the lack of increased sudden death or total arrhythmic death rate in patients with class 1 agents at implantation excludes a causal relation between the increased total mortality and potential proarhythmic effects of class 1 agents. Differences in patient characteristics other than the variables listed in Table 5 may also account for the higher nonarrhythmic mortality of patients with class 1 agents at implantation. Furthermore, treatment with specific antiarrhythmic drugs at the time of ICD implantation by no means represents a stable clinical variable during long-term follow-up. Antiarrhythmic drug treatment was discontinued, started, or altered in many patients according to the clinical judgment of the patients' physician for the following reasons: 1) side effects during follow-up, 2) frequency of documented or suspected recurrences of ventricular tachyarrhythmias, 3) control of supraventricular tachyarrhythmias during follow-up, and 4) patient's compliance.

**Effect of the Clinical Presentation and Result of Programmed Stimulation Before ICD Implantation**

Of note, both appropriate and any spontaneous shocks occurred significantly later in patients who presented with a cardiac arrest before ICD implantation than in patients who presented with syncope or VT without syncope. In addition, appropriate and any spontaneous shocks occurred significantly later in patients who had only rapid polymorphic VT or VF induced before ICD implantation. Both findings may be due to differences in the electrophysiological substrate in patients with cardiac arrest and only inducible polymorphic VT or VF as compared with patients with inducible uniform VT presenting with VT with or without syncope. Similar to the results of Levine and colleagues and Veltri et al., clinical presentation and result of programmed stimulation before ICD implantation in our study did not influence survival in patients with ICD therapy.

**Other Variables**

Similar to the results of Levine and colleagues and Reiter et al., we found no difference in shock occurrence or survival curves among patients with coronary artery disease, nonischemic cardiomyopathy, valvular or congenital heart disease, and primary electrical disease,
although the latter group was too small for subgroup analysis. However, Gross and colleagues\textsuperscript{24} and Zilo et al\textsuperscript{29} found a higher incidence of shocks in patients with coronary disease. This difference may in part be due to differences in patient population as well as the lack of multivariate analysis in both studies. Similar to the results of Levine and coworkers\textsuperscript{3} and Meyerburg et al\textsuperscript{14}, age and sex of patients in our study were not independently associated with shock occurrence or survival after ICD implantation (Tables 3 and 5). In contrast to the finding of Levine and colleagues\textsuperscript{3} that coronary bypass surgery at the time of ICD implantation was associated with later occurrence of appropriate ICD shocks, we did not find differences in shock occurrence in patients with and without coronary bypass surgery preceding ICD implantation. This difference may also be due to differences in patient population in both studies. All patients who underwent coronary bypass surgery preceding ICD implantation in our study had a remote myocardial infarction generating the "anatomic substrate" for arrhythmia recurrence, which is unlikely to be altered by revascularization.\textsuperscript{30} Coronary artery bypass grafting, however, may reduce the role of ischemia for triggering tachyarrhythmias in these patients to a level comparable to patients with a remote myocardial infarction who did not need revascularization, resulting in a similar incidence of shocks during follow-up in both groups in our study.

Limitations of the Study

This study was retrospective and uncontrolled. Similar to all previously published follow-up studies of large patient populations with ICD therapy, electrocardiographic documentation of the rhythm preceding spontaneous ICD shocks was not available in the majority of cases. Shock analysis was, therefore, performed for appropriate and any spontaneous shocks as discussed above. Of note, 67 of 135 patients in our study (50\%) who received any spontaneous shocks during follow-up had VT or VF preceding one or more spontaneous shocks documented by Holter or telemetry monitoring or stored electrograms by the device.

Conclusions

The majority of patients receive shocks during long-term follow-up after ICD implantation. The occurrence of appropriate or any spontaneous shocks during follow-up is not associated with increased arrhythmic or total mortality consistent with effective prevention of sudden cardiac death with ICD therapy in this high-risk patient population. Although low ejection fraction is the strongest predictor of both shock occurrence and mortality during follow-up, no easy algorithm can be derived from the analyzed clinical characteristics to predict which patients will benefit most from ICD implantation. The results of this study warrant further investigation and may have important implications for future prospective studies with ICD therapy.

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