Influence of Implantable Cardioverter-Defibrillators on the Long-term Prognosis of Survivors of Out-of-Hospital Cardiac Arrest

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Background. Survivors of out-of-hospital cardiac arrest not associated with acute myocardial infarction are at high risk for recurrent cardiac arrest and sudden cardiac death. The impact of the implantable cardioverter-defibrillator on long-term prognosis in these patients is uncertain.

Methods and Results. Three hundred thirty-one survivors of out-of-hospital cardiac arrest (age, 56±13.7 years) underwent electrophysiologically guided therapy. Implantable defibrillators were placed in 150 patients (45.3%), and 181 patients (54.7%) received pharmacological and/or surgical therapy alone. Left ventricular ejection fraction was 35.2±16.6% in defibrillator recipients and 45.3±18.2% in nondefibrillator patients. Median patient follow-up was 24 months in the defibrillator group and 46 months in the nondefibrillator group. In a proportional hazards model, the independent predictors of total cardiac mortality were left ventricular ejection fraction of less than 0.40 (relative risk, 4.55; 95% confidence interval, 2.44 to 8.33; P=.0001), absence of an implantable defibrillator (relative risk, 2.70; confidence interval, 1.41 to 5.00; P=.017), and persistense of inducible sustained ventricular tachycardia (relative risk, 1.84; 95% confidence interval, 0.97 to 3.49; F=.045). The 1- and 5-year probabilities of survival free of cardiac mortality in patients with left ventricular ejection fraction of less than 0.40 were 94.3% and 69.6% with a defibrillator and 82.1% and 45.3% without a defibrillator, respectively. For patients with left ventricular ejection fraction of 0.40 or more, the 1- and 5-year probabilities of survival free of cardiac mortality were 97.7% and 94.6% with a defibrillator and 95.4% and 86.9% without a defibrillator, respectively.

Conclusions. In survivors of out-of-hospital cardiac arrest, the implantable defibrillator is associated with a reduction in cardiac mortality, particularly in patients with impaired left ventricular function.

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Key Words • heart arrest • electrophysiology • defibrillator • death, sudden • arrhythmias

Electrophysiological testing provides important prognostic information on survivors of out-of-hospital cardiac arrest,1-6 many of whom are at risk for recurrent cardiac arrest and sudden cardiac death.7-13 Patients with persistently inducible ventricular arrhythmia at predischarge electrophysiological study are at significantly higher risk for recurrent cardiac arrest and death in comparison with patients in whom inducible arrhythmias are suppressed with pharmacological and/or surgical therapy.1,13 However, in many of these patients, no effective antiarrhythmic drug regimen can be found.1,2,14,15 Furthermore, some controversy exists with regard to the prognosis of patients who exhibit no inducible arrhythmia at baseline electrophysiological study.1,16-21 Among the subgroup of patients with no inducible ventricular arrhythmia and poor left ventricular function, however, there exists a substantial risk of recurrent cardiac arrest.1,20,21 Thus, many survivors of out-of-hospital cardiac arrest are suitable candidates for treatment with implantable cardioverter-defibrillators (ICDs). In fact, this therapy is now widely applied in clinical practice and considered by some to be the treatment of choice in cardiac arrest survivors.22-24 Previous studies have reported a low incidence of sudden cardiac death in patients with life-threatening ventricular arrhythmias who receive an implantable defibrillator.25-27 However, since the introduction of the implantable defibrillator into clinical practice in the early 1980s, no large studies have specifically examined the impact of this new therapy on the long-term outcome of survivors of out-of-hospital cardiac arrest. The objective of this study was to examine the influence of the implantable defibrillator and other variables on long-term outcome in survivors of out-of-hospital cardiac arrest.

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Patient Population

The 338 patients described in this study include 276 consecutive survivors of out-of-hospital cardiac arrest...
who were referred to the Cardiac Arrhythmia Service of the Massachusetts General Hospital for electrophysiologically guided therapy from January 1978 to December 1990. In addition, all 62 consecutive patients who survived an out-of-hospital cardiac arrest and whose therapy included an ICD at the Hospital of the Good Samaritan, Los Angeles, from May 1983 to December 1990 were included in this series. In all cases, the cardiac arrest occurred when the subject was a patient in a hospital or an emergency department and external electrical defibrillation was required for resuscitation. No patient had evidence of a new Q wave myocardial infarction on serial ECGs recorded after the event. Five patients (2.7%) died of refractory ventricular arrhythmias during serial antiarrhythmic drug testing. One patient died suddenly while waiting for an ICD, and one patient (0.7%) who had received an ICD died after surgery before hospital discharge. These patients were removed from further data analysis to avoid a bias that would favor the ICD group.

The clinical characteristics and electrophysiological features of the 331 patients who are the subject of this report are described in Table 1. The mean age of the patients was 56.9±13.7 years. Two hundred thirty-seven patients (71.6%) had coronary artery disease as their principal cardiac abnormality, and 173 (52.0%) had suffered a previous myocardial infarction. Other cardiac abnormalities included valvular heart disease in 25 patients (7.6%), dilated cardiomyopathy in 43 patients (13.0%), congenital heart disease in 5 patients (1.5%), coronary vasospasm in 5 patients (1.5%), hypertrophic cardiomyopathy in 1 patient, and a myocardial bridge in 1 patient. In 13 patients (3.9%), no structural cardiac abnormality was detected. The mean left ventricular ejection fraction was 40.7±8.2%, and 165 patients (49.8%) had a left ventricular ejection fraction of less than 0.40. The rhythm documented at the cardiac arrest was ventricular fibrillation in 289 patients (87.3%), ventricular tachycardia in 34 patients (10.3%), and unknown in 8 patients (2.4%).

### Management

Following recovery from the presenting cardiac arrest, cardiac catheterization and coronary arteriography were performed in all except 12 patients (3.6%). Ten of these 12 patients had suffered a previous myocardial infarction. All patients underwent noninvasive assessment of left ventricular function. Electrophysiological testing was performed in the baseline drug-free state in all patients unless clinical instability made antiarrhyth-
mic drug withdrawal impossible. In 29 patients (8.8%) with critical coronary artery stenoses and/or unstable ischemic symptoms, electrophysiological testing was deferred until after coronary revascularization.

Electrophysiological studies were performed using a programmable stimulator with constant-current source delivering 2-millisecond rectangular pulses at fivefold diastolic threshold. The protocol for ventricular stimulation included introduction of single and double extrastimuli following pacing drive trains at a minimum of two basic cycle lengths (600 and 400 milliseconds) and at two right ventricular sites in all patients. In the studies before 1982, brief bursts of rapid ventricular pacing (5 to 10 beats at cycle lengths of 400 to 220 milliseconds) were used; however, in all studies since 1982, the protocol included the use of triple extrastimuli during ventricular pacing instead of burst pacing. The end point of the stimulation protocol was the induction of a sustained ventricular arrhythmia, defined as an arrhythmia lasting more than 30 seconds or causing hemodynamic deterioration requiring intervention. Before 1982 and the use of triple ventricular extrastimuli, the reproducible induction of nonsustained ventricular tachycardia was also used as an end point. Ventricular tachycardia was defined as a polymorphic ventricular tachyarrhythmia with a mean cycle length of less than 200 milliseconds.

Electrophysiological testing was performed a median of 2.5 weeks (range, 0.3 to 64 weeks) after the cardiac arrest, and in 315 patients (93.4%) the first electrophysiological study was performed within 12 weeks of the presenting cardiac arrest. At the initial electrophysiological study, 103 patients (31.1%) had no inducible ventricular arrhythmia, 52 (15.7%) had reproducible nonsustained ventricular tachycardia, 124 (37.5%) had sustained monomorphic ventricular tachycardia, and 50 patients (15.1%) had inducible polymorphic ventricular tachycardia or ventricular fibrillation.

In patients with inducible sustained ventricular arrhythmias, serial drug testing was undertaken to identify an antiarrhythmic regimen that suppressed the induced ventricular arrhythmia. A favorable drug response was defined as the induction of less than 10 repetitive ventricular complexes in response to completion of the programmed stimulation protocol. The patients underwent a mean of 1.8±1.7 drug trials (range, 0 to 8). One hundred eight patients (32.6%) did not undergo any drug trials, primarily due to the absence of an inducible arrhythmia at baseline electrophysiological study. Before the availability of the implantable defibrillator, patients were discharged on the drug regimen shown to prevent initiation of the ventricular arrhythmias induced at baseline electrophysiological study. If no drug could be identified that prevented induction of ventricular arrhythmias, drugs that rendered the arrhythmia more difficult to induce or slower in rate and better tolerated hemodynamically were used.

Coronary artery revascularization, with coronary artery bypass graft surgery (94 patients) or percutaneous coronary angioplasty (5 patients), was performed in 99 patients (29.9%) with evidence of significant coronary artery stenoses and reversible myocardial ischemia. In five suitable patients, map-guided left ventricular aneurysmectomy was undertaken, and six patients had valvular surgery. From 1983 on, placement of an ICD was recommended at both institutions in patients who had survived an out-of-hospital cardiac arrest and who continued to have a sustained ventricular arrhythmia inducible at electrophysiological study despite pharmacological and/or surgical therapy. Placement of an implantable defibrillator was also generally recommended for patients who had no inducible sustained ventricular arrhythmias at baseline electrophysiological study and who did not have critical coronary artery disease requiring revascularization or another reversible cause for the cardiac arrest.

Characteristics of Recipients of the Implantable Defibrillator

Implantable defibrillators were placed in 150 patients (45.3%) — 89 at Massachusetts General Hospital and 61 patients at the Hospital of the Good Samaritan, Los Angeles. One patient who received an implantable defibrillator and died before hospital discharge is not included in this analysis. One hundred eighty-one patients (54.7%) were treated without implantable defibrillators. Table 1 compares the clinical features of the patients who received an implantable defibrillator with those who were treated without a defibrillator. Patients receiving implantable defibrillators had significantly lower ejection fractions, higher pulmonary capillary wedge pressures, a lower incidence of coronary artery disease and coronary revascularization following the cardiac arrest, a higher incidence of inducible ventricular tachycardia at predischarge electrophysiological study, and a lower incidence of β-adrenoceptor antagonist use than did patients who did not receive a defibrillator. Table 2 compares the clinical features of defibrillator recipients at Massachusetts General Hospital and Hospital of the Good Samaritan. Patients who received implantable defibrillators at Massachusetts General Hospital and Hospital of the Good Samaritan showed statistically significant differences in only two variables: the number of patients receiving antiarrhythmic drugs at the time of the cardiac arrest (11.2% versus 47.5%, respectively; P=.0001) and the number of drug trials undertaken before defibrillator implantation (2.0±1.7 versus 1.4±1.4, respectively; P=.04). In particular, there were no significant differences in left ventricular ejection fraction, the incidence of coronary artery disease or prior myocardial infarction, and the use of coronary revascularization or β-adrenoceptor antagonist therapy between the defibrillator recipients at the two institutions.

Patient Follow-up

Personal or telephone contact was made with all patients, or their physicians or family members, and the circumstances of any deaths were investigated to determine the probable cause. Recurrent cardiac arrest was defined as sudden collapse in a patient with previously stable circulatory function that required defibrillation for restoration of consciousness. Sudden cardiac death was defined as death occurring as a result of recurrent cardiac arrest or within 1 hour of the development of symptoms in a previously stable patient or an un witnessed death in a patient known to be stable in the preceding 24 hours. Nonsudden cardiac death was defined as death due to progressive heart failure or recurrent myocardial infarction and/or with preceding symptoms of more than 1 hour in duration.
table 2. Clinical and Electrophysiological Features of the ICD Recipients

<table>
<thead>
<tr>
<th></th>
<th>All patients with ICD (n=150)</th>
<th>Patients with ICD from MGH (n=89)</th>
<th>Patients with ICD from HGS (n=61)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56.8±13.3</td>
<td>55.7±13.4</td>
<td>58.3±13.2</td>
<td>.2341</td>
</tr>
<tr>
<td>CAD (No., %)</td>
<td>91 (60.7)</td>
<td>53 (59.6)</td>
<td>38 (62.3)</td>
<td>.7354</td>
</tr>
<tr>
<td>No. of vessels CAD</td>
<td>1.5±1.3</td>
<td>1.6±1.4</td>
<td>1.4±1.3</td>
<td>.6114</td>
</tr>
<tr>
<td>Prior myocardial infarction (No., %)</td>
<td>77 (51.3)</td>
<td>41 (46.1)</td>
<td>36 (59.0)</td>
<td>.0951</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35.2±16.6</td>
<td>35.1±17.5</td>
<td>35.4±15.4</td>
<td>.9320</td>
</tr>
<tr>
<td>LV aneurysm (No., %)</td>
<td>28 (18.7)</td>
<td>14 (15.7)</td>
<td>14 (23.0)</td>
<td>.2649</td>
</tr>
<tr>
<td>Antiarrhythmic drugs at CA (No., %)</td>
<td>39 (26.0)</td>
<td>10 (11.2)</td>
<td>29 (47.5)</td>
<td>.0001</td>
</tr>
<tr>
<td>Baseline EPS (No., %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inducible SMVT</td>
<td>63 (42.0)</td>
<td>34 (38.2)</td>
<td>29 (47.5)</td>
<td>.1385</td>
</tr>
<tr>
<td>Inducible VF/PMVT</td>
<td>23 (15.3)</td>
<td>17 (19.1)</td>
<td>6 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>11 (7.3)</td>
<td>9 (10.1)</td>
<td>2 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Noninducible</td>
<td>51 (34.0)</td>
<td>28 (31.5)</td>
<td>23 (37.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.4)</td>
<td>1 (1.1)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>PredischARGE EPS (No., %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inducible SMVT</td>
<td>62 (41.3)</td>
<td>30 (33.7)</td>
<td>32 (52.5)</td>
<td>.1156</td>
</tr>
<tr>
<td>Inducible VF/PMVT</td>
<td>21 (14.0)</td>
<td>14 (15.3)</td>
<td>7 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>12 (8.0)</td>
<td>9 (10.1)</td>
<td>3 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Noninducible</td>
<td>47 (31.3)</td>
<td>29 (32.6)</td>
<td>18 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (5.4)</td>
<td>7 (8.3)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>No. of drug trials</td>
<td>1.7±1.6</td>
<td>2.0±1.7</td>
<td>1.4±1.4</td>
<td>.0411</td>
</tr>
<tr>
<td>Coronary revascularization (No., %)</td>
<td>33 (22.0)</td>
<td>22 (24.7)</td>
<td>11 (18.0)</td>
<td>.3315</td>
</tr>
<tr>
<td>LV surgery</td>
<td>3 (2.0)</td>
<td>2 (2.2)</td>
<td>1 (1.6)</td>
<td>.7939</td>
</tr>
<tr>
<td>β-Blocker therapy (No., %)</td>
<td>37 (24.7)</td>
<td>26 (29.2)</td>
<td>11 (18.0)</td>
<td>.1187</td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up (mo)</td>
<td>24</td>
<td>21.5</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; MGH, Massachusetts General Hospital; HGS, Hospital of the Good Samaritan; CAD, coronary artery disease; LV, left ventricular; EF, ejection fraction; CA, cardiac arrest; EPS, electrophysiological study; SM, sustained monomorphic; PM, polymorphous; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Values are mean±1 SD.

*P values are two-sided from unpaired t tests or χ^2 analysis for comparison of MGH with HGS patients.

Patients with implantable defibrillators were seen at regular intervals for monitoring of device function. The circumstances of any defibrillator discharges were assessed to determine the probable reason for the discharges. Spurious shocks (ie, ICD discharges considered to be due to device malfunction, probable sinus tachycardia, or documented supraventricular arrhythmias) were not included in the reported defibrillator discharge count.

Follow-up is complete for all except five patients for whom only partial data are available. These five patients were censored from the analysis at the time of last contact.

Statistical Analysis

Baseline patient characteristics are expressed as median, mean±SD, or proportion and summarized in Table 1. Comparisons between groups in these tables were made using unpaired t tests, χ^2 analysis, or Fisher's Exact Test.

A logrank test and Cox proportional hazards model were used to examine the predictors of cardiac mortality, sudden and nonsudden cardiac death, total mortality, and time to defibrillator discharge (excluding spurious shocks). For each of these analyses, patients who did not experience the event of interest were censored at the time of their death or last follow-up. The variables examined are listed in Table 3, and each was analyzed separately to determine which had a significant effect on each type of failure. All variables were then analyzed using stepwise multiple regression to select the jointly influential predictors (see Table 5). The estimate for the relative risk for failure and 95% confidence limits for the relative risk were calculated for each significant predictor from the proportional hazards model. Analyses were performed using BMDP Statistical Software 1990 version, and Kaplan-Meier survival

Table 3. Causes of Death for Patients With and Without ICDs

<table>
<thead>
<tr>
<th></th>
<th>Patients with ICD</th>
<th>Patients without ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>150</td>
<td>181</td>
</tr>
<tr>
<td>No. of deaths (% of patients)</td>
<td>29 (19.3)</td>
<td>62 (34.3)</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>31.1±23.8</td>
<td>49.2±39.1</td>
</tr>
<tr>
<td>Sudden cardiac death (No., %)</td>
<td>5 (3.3)</td>
<td>26 (14.4)</td>
</tr>
<tr>
<td>Nonsudden cardiac death (No., %)</td>
<td>15 (10.0)</td>
<td>22 (12.2)</td>
</tr>
<tr>
<td>Noncardiac death (No., %)</td>
<td>9 (6.0)</td>
<td>14 (7.7)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator.
curves were constructed using SAS. In the figures, survival curves were truncated at 84 months because of the relatively small numbers of patients with prolonged follow-up, but all information was used in the analyses. For all analyses, a two-tailed $P<.05$ was considered statistically significant.

## Results

The 331 patients discharged from hospital after recovery from an out-of-hospital cardiac arrest were followed for an average of 40±23 months (median, 35; range, 1 to 151 months). Antiarrhythmic medications (excluding $\beta$-adrenoceptor antagonists) were prescribed at hospital discharge in 122 nondefibrillator patients (62.4%) and 68 defibrillator patients (45.3%) ($P<.0001$). At the time of follow-up, 240 patients (72.5%) were still living, and 91 patients (27.5%) had died. Twenty-nine of 150 patients (19.3%) with defibrillators died during a mean follow-up period of 31±24 months (median, 24 months), and 62 of 181 patients (34.3%) without defibrillators died during a mean follow-up period of 49±39 months (median, 46 months). Mortality rates from sudden and nonsudden cardiac death as well as noncardiac death for defibrillator and nondefibrillator patients are listed in Table 3.

### Predictors of Mortality

**Cardiac mortality.** All variables analyzed as predictors of cardiac mortality and total mortality are listed in Table 4. The $P$ values displayed are those derived from a logrank test of each variable considered alone. The statistically significant predictors from a Cox multivariate survival analysis and the relative risks and 95% confidence limits are displayed in Table 5. The results described below are derived from the multivariate regression model.

The stepwise multivariate survival analysis demonstrated that cardiac mortality was most powerfully predicted by left ventricular ejection fraction of less than 0.40 ($P<.0001$). Other significant predictors in the multivariate regression model included the absence of an implantable defibrillator ($P=.017$) and the presence of inducible ventricular tachycardia at predischarge electrophysiological study ($P=.045$). A subgroup analysis was made of 204 patients with known status regarding past history of congestive heart failure and in whom a measurement of pulmonary capillary wedge pressure was available. For this group, a past history of congestive heart failure was an additional significant independent predictor of total cardiac mortality ($P=.04$) in the regression model.

The cardiac survival of patients with and without implantable defibrillators, stratified by left ventricular ejection fraction of less than 0.40 versus 0.40 or more, are shown in Fig 1. This figure indicates the survival advantage of patients with an implantable defibrillator in both patients with left ventricular ejection fraction of less than 0.40 and those with left ventricular ejection fraction of 0.40 or more, although the magnitude of survival benefit is greater in the low ejection fraction group.

**Sudden Cardiac Death**

The most powerful independent predictor of sudden cardiac death in a multivariate Cox regression model was the absence of the implantable defibrillator ($P=.006$). The estimated relative risk for sudden cardiac
death in patients without an implantable defibrillator compared with patients with an implantable defibrillator was 6.25 (95% confidence interval, 2.13 to 20.00). The estimated actuarial risk for sudden cardiac death at 1 and 5 years was 1.5% and 3.7% for defibrillator patients and 5.7% and 19% for nondefibrillator patients. Additional significant predictors in the model included persistently inducible ventricular tachycardia at the predischarge electrophysiological study (relative risk, 3.75; 95% confidence interval, 1.56 to 9.00; $P=.006$) and left ventricular ejection fraction of less than 0.40 (relative risk, 2.63; 95% confidence interval, 1.15 to 5.88; $P=.03$).

Nonsudden Cardiac Death

With a multivariate Cox regression model, nonsudden cardiac death was most strongly predicted by a left ventricular ejection fraction of less than 0.40 ($P<.0001$); additional significant predictors in the model were age ($P=.013$) and absence of inducible ventricular fibrillation at baseline electrophysiology study ($P=.029$).

Total Mortality

The multivariate Cox regression model revealed a left ventricular ejection fraction of less than 0.40 as the most powerful predictor of total mortality ($P<.0001$). The other independent predictors of total mortality were age ($P=.002$) and inducible sustained monomorphic ventricular tachycardia at predischarge electrophysiological testing ($P=.008$). The absence of an implantable defibrillator was a marginally significant independent predictor ($P=.06$). Survival curves for total mortality, stratified by left ventricular ejection fraction of 0.40 or more versus less than 0.40, are displayed in Fig 2 and show a survival advantage for defibrillator patients in comparison with nondefibrillator patients within each subgroup, although the magnitude of the difference is greater in the low ejection fraction group.

Defibrillator Discharges

Defibrillator discharges were experienced by 86 patients (57.3%) with implantable defibrillators, including 48% of patients with no inducible arrhythmia at baseline electrophysiological study, 68.3% of patients with inducible sustained monomorphic ventricular tachycardia, and
47.8% of patients with inducible ventricular fibrillation or polymorphous ventricular tachycardia over a mean follow-up of 31±24 months. The median time to the first discharge was 7 months (range, 1 to 52 months), and the median number of discharges per patient (excluding discharges documented to be due to device malfunction or supraventricular arrhythmias) was four discharges. Defibrillator discharges were experienced by 64 of 95 patients (67.4%) with left ventricular ejection fraction of less than 0.40 and 20 of 55 patients (36.4%) with left ventricular ejection fraction of 0.40 or more (P=.0003).

In a multivariate Cox regression model, the most powerful predictor of time to defibrillator discharge was a left ventricular ejection fraction of less than 0.40 (P=.001). The presence of a left ventricular aneurysm also independently predicted defibrillator discharges (P=.033), and the results of the predischarge electrophysiological study added no incremental predictive information in this group.

**Comparison of Outcome of Defibrillator Patients With Nondefibrillator Inducible/Suppressed Patients**

In patients with left ventricular ejection fraction of 0.40 or more, the probability of survival free of all-cause mortality for patients without implantable defibrillators whose arrhythmias had been rendered noninducible with pharmacological or surgical therapy was similar to that of patients with implantable defibrillators at 1 and 3 years and poorer than that of defibrillator patients at 5 years (Table 6). In patients with poor ventricular function (ejection fraction of less than 0.40) whose arrhythmias were suppressed with drugs or surgical therapy, total mortality was higher at 1 and 5 years and comparable at 3 years to that observed in patients treated with defibrillators (Table 6). Patients without defibrillators and with persistently inducible ventricular arrhythmias at hospital discharge experienced higher mortality rates than did defibrillator recipients at all points during the follow-up (Table 6). This analysis specifically excludes all patients (n=103) who had no inducible arrhythmia at baseline electrophysiological study. The powerful independent contribution of the left ventricular ejection fraction to survival in each of these subgroups is evident in Table 6.

**Discussion**

In this study of 331 survivors of out-of-hospital cardiac arrest who underwent electrophysiologically guided therapy, the only significant independent predictors of both sudden cardiac death and total cardiac mortality were left ventricular ejection fraction of less than 0.40, the presence of inducible ventricular tachycardia at predischarge electrophysiological study, and the absence of an implantable defibrillator (Table 5). Furthermore, based on the multivariate survival analysis, the presence of more than one of these adverse predictors indicated a multiplicative risk for cardiac mortality. For example, the relative risk for cardiac mortality in a patient with left ventricular ejection fraction of less than 0.40 and no implantable defibrillator was 12.29. Survival analysis showed that the risk of sudden cardiac death was significantly lower in out-of-hospital cardiac arrest survivors receiving implantable defibrillators than in patients without defibrillators, regardless of left ventricular function. Absence of an implantable defibrillator was also an independent predictor of cardiac mortality in this study, although the major difference in total cardiac mortality between patients with and without implantable defibrillators occurred in the subgroup with a left ventricular ejection fraction of less than 0.40.

The absence of an implantable defibrillator was only a marginally significant predictor of total mortality in this study (Table 5). This observation is not surprising in that the implantable defibrillator is designed only to terminate life-threatening ventricular arrhythmias and thereby reduce mortality from sudden death. Because ventricular tachycardia and fibrillation are the most common causes of sudden death, it is anticipated that the defibrillator would represent the most powerful determinant of sudden death–free survival (Table 5). However, sudden deaths comprise only 46% of all cardiac deaths and 34% of total deaths in this study. Thus, to demonstrate a more significant impact of the defibrillator on total mortality, it would be necessary to study a larger patient population. The likelihood of finding such a benefit is suggested by the marked (70 to 80%) reduction in sudden death associated with the defibrillator in this relatively small sample. The impact of the defibrillator on total mortality in this study is further compounded by an overrepresentation in the defibrillator group of patients with poor ventricular function (Table 1). Left ventricular ejection fraction, the most powerful independent predictor of cardiac and total mortality, was significantly lower in the defibrillator group than in patients without defibrillators.
ventricular arrhythmia fraction of 0.40 or more. Despite this bias and the anticipated increase in nonsudden cardiac deaths due to pump dysfunction in defibrillator recipients, a reduction in total mortality was observed in the defibrillator group. These observations are consistent with the findings of a recent retrospective case-control study in which the use of the implantable defibrillator in patients at risk for sudden death was associated with an improved probability of survival.29

In this study, a similar percentage of patients in the defibrillator and nondefibrillator groups had no inducible ventricular arrhythmia at baseline electrophysiology study. Therefore, the improved outcome with defibrillator placement cannot be attributed to an overrepresentation in the defibrillator group of patients with no inducible arrhythmias, who in some studies have been shown to have a more favorable prognosis. Furthermore, the percentage of patients with ventricular fibrillation as the first rhythm documented at the time of cardiac arrest and with inducible polymorphous ventricular tachycardia or ventricular fibrillation at baseline electrophysiology study was similar in the two patient groups, making overrepresentation of patients with ischemically mediated primary ventricular fibrillation among the defibrillator population an unlikely explanation for the enhanced survival in this group. The improved outcome in the defibrillator recipients occurred despite the presence of significantly lower left ventricular ejection fractions, higher pulmonary capillary wedge pressures, a higher incidence of inducible ventricular tachycardia at predischarge electrophysiological study, and a lower incidence of coronary artery revascularization and β-adrenoceptor antagonist therapy in the defibrillator group. Although the defibrillator group had a lower incidence of coronary artery disease, the incidence of prior myocardial infarction was the same in both populations. While the precise impact of these population differences on outcome cannot be determined in this retrospective analysis, most known predictors of an adverse outcome, except the presence of coronary artery disease, were biased against the implantable defibrillator group.

Surgical mortality was low (one patient, 0.7%) in this study. Defibrillator discharges were predicted by reduced left ventricular ejection fraction, as has also been reported by Levine and colleagues, but absence of coronary revascularization was of marginal significance as a predictor of defibrillator discharges in our study. Spurious shocks due to supraventricular arrhythmias, sinus tachycardia, or device malfunction remained a troublesome problem in follow-up care of some of these patients, requiring adjustment of antiarrhythmic drug regimens and causing psychological morbidity. Infection led to removal of the entire ICD system in one patient, seven patients required rehospitalization for lead malfunction, and two patients required pulse generator repositioning. The ICD was removed at the time of cardiac transplantation in three patients and inactivated at the request of two terminally ill patients, both of whom died shortly thereafter.

The morbidity of antiarrhythmic drug therapy is difficult to assess. Nearly a fourth of the patients in the study were taking antiarrhythmic drugs at the time of the presenting cardiac arrest. Because 60% of these patients had inducible ventricular arrhythmias at baseline drug-free electrophysiological study, it is likely that in many cases the cardiac arrest represented a failure of the particular drug rather than a proarrhythmic response. However, there is rising concern about the potential for arrhythmogenic effects and increased mortality with class I antiarrhythmic drugs, particularly among patients with left ventricular dysfunction. Of the patients treated initially with antiarrhythmic drugs alone, two were successfully resuscitated from a second cardiac arrest and subsequently received an implantable defibrillator. Eleven patients were readmitted to the hospital with symptomatic sustained ventricular tachycardia; six are alive at follow-up (including two patients who received an ICD) and five died predominantly due to nonsudden cardiac death. Antiarrhythmic drug therapy was frequently used in patients with defibrillators to prevent or control the rate of supraventricular arrhythmias and to reduce the frequency of recurrent ventricular arrhythmias and defibrillator discharges.

Study Limitations

The primary limitations of this study are its retrospective design and the shorter duration of follow-up in the defibrillator group. Because treatment was not randomly allocated, undetected biases may have influenced the selection of patients for ICD and drug therapy and thereby affected the results. However, the two groups of patients were highly comparable in most respects, and those differences that were present and known to influence outcome in this population were, with the exception of the incidence of coronary artery disease, biased against the defibrillator group. The impact of coronary artery disease on outcome in this study is difficult to assess. ICD recipients were less likely than nonrecipients to have coronary artery disease (62% vs 81%), although the incidence of prior myocardial infarction was the same in both groups, and ventricular function was significantly worse in the ICD group (Table 1). Furthermore, although cardiac mortality was higher in patients with ischemic heart disease versus other diagnoses, the presence of coronary artery disease was not an independent predictor of mortality from any cause in this study (Table 5). Nevertheless, it is possible that the lower incidence of coronary artery disease as well as shorter follow-up contributed to a more favorable outcome in the ICD group.

Because the use of implantable defibrillators in this study did not commence until 1983, less information regarding long-term outcome is available in the defibrillator group. Another potential source of bias is the pooling of defibrillator recipients from two institutions. Patients from the Hospital of the Good Samaritan were more likely to be taking antiarrhythmic drugs at the time of the initial cardiac arrest than were ICD recipients from Massachusetts General Hospital. However, no significant differences were detected between the two groups of patients among variables known to predict cardiac and total mortality. Furthermore, the institution of origin was not a predictor of sudden death, nonsudden cardiac death, or total mortality in this study.
Implications for Patient Management

Survivors of out-of-hospital cardiac arrest comprise a heterogeneous patient population in whom an individualized approach must be taken toward diagnosis and management. Treatment should be directed at the underlying structural heart disease, especially advanced ischemic heart disease. In patients with inducible ventricular arrhythmias, attempts to suppress these arrhythmias with antiarrhythmic drugs are appropriate. However, in many patients, no effective antiarrhythmic drug regimen can be defined. In these patients, placement of an implantable defibrillator is supported by the results of this study. The optimal treatment for patients without inducible ventricular arrhythmias is unknown.

It is evident that many patients in this group remain at high risk for recurrent cardiac arrest and sudden death. Furthermore, the absence of an inducible arrhythmia at electrophysiological study leaves the physician without an objective end point to guide the selection of pharmacological therapy. A decision regarding defibrillator placement in this patient group must be based on the presence or absence of other treatable factors, most notably, reversible myocardial ischemia, which clearly is causally related to the cardiac arrest in patients with normal or near-normal ventricular function. At present, patients with an episode of aborted sudden death who manifest no inducible arrhythmia at electrophysiological study and no well-defined reversible cause are appropriate candidates for defibrillator implantation. The fact that this subset of patients receives appropriate defibrillator discharges at a rate comparable to that of other patient groups confirms their ongoing risk for recurrent cardiac arrest.

The limited number of patients and the retrospective design of this study do not permit firm conclusions to be drawn regarding the relative efficacy of suppressive antiarrhythmic drug therapy compared with that of the implantable defibrillator. Nevertheless, in patients with impaired ventricular function, our observations suggest improved survival in the defibrillator group. Furthermore, we observed no significant difference in outcome at 1 and 3 years in patients with well-preserved ventricular function and inducible arrhythmias that were suppressed with pharmacological and/or surgical therapy compared with patients with inducible arrhythmias who were treated with an implantable defibrillator. A trend toward improved survival in the defibrillator group was present at 5 years, however. In this subset of patients, the optimal therapy for achieving long-term survival ultimately must be defined by a prospective trial in which patients with suppressible arrhythmias are randomly assigned to suppressive pharmacological therapy or an implantable defibrillator.

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