Potential Benefit From Implantable Cardioverter-Defibrillator Therapy in Patients With and Without Heart Failure

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Background—Whether patients with heart failure derive a benefit from therapy with implantable cardioverter-defibrillators (ICDs) has been questioned. The purpose of this study was to investigate whether New York Heart Association (NYHA) functional class had an impact on the potential benefit from ICD therapy as assessed from data stored in the memory of ICDs.

Methods and Results—Between 1989 and 1996, 603 patients (77% men; 59% with coronary artery disease and 16% with dilated cardiomyopathy; age, 57±13 years; ejection fraction, 44±18%) were treated with an ICD with extended memory function (storage of electrograms and/or RR intervals from treated episodes) in combination with endocardial lead systems. The stages of heart failure (NYHA functional class I through III) at implantation were correlated with overall mortality and the recurrence of fast ventricular tachyarrhythmias (>240 bpm) during follow-up. The potential benefit of the device was estimated as the difference between overall mortality and the hypothetical death rate had the device not been implanted. The latter was based on the recurrence of fast and, without termination by the devices, presumably fatal ventricular tachyarrhythmias. In the overall group, a significant difference between hypothetical death rate and overall mortality was observed (13.9%, 23.5%, and 26.6% at 1, 3, and 5 years, respectively) that suggested a benefit from ICD implantation. In patients in NYHA class I, the estimated benefit, which increased over time, was 15.2%, 29.2%, and 35.6% after 1, 3, and 5 years, respectively. In patients in NYHA class II or III, the estimated benefit increased until the third year (21.8% and 21.9%, respectively) and then remained constant until the fifth year (22.9% and 23.8%, respectively). Even those patients in NYHA class III with a history of decompensated heart failure benefited from ICD implantation.

Conclusions—Analysis of stored ECG data suggests that in patients with a history of ventricular tachycardia or ventricular fibrillation, ICD therapy may lead to a prolongation of life in NYHA classes I through III. The initial benefit is greatest in patients in NYHA class II and class III, but the estimated benefit might persist longest for patients in NYHA class I.

The implantable defibrillator (ICD) introduced by Mirowski et al in 1980 has been increasingly used for the treatment of ventricular tachycardia (VT) and fibrillation (VF) and thus for the prevention of sudden cardiac death. A remarkably low incidence of sudden death has been reported by numerous investigators. Small retrospective studies have used the incidence of “appropriate” therapies delivered by the devices to estimate the potential benefit from ICD implantation. As a more rigorous variant of this approach, we previously suggested use of the recurrence of fast (>240 bpm) ventricular tachyarrhythmias documented by the memory of the device to calculate hypothetical mortality curves. This was based on the assumption that the tachyarrhythmia would have been lethal had it not been terminated by the device. Benefit from device implantation was then estimated by comparison of the estimated and observed total mortality rates. This approach suggested a marked benefit from ICD implantation.

However, the potential of the ICD to prolong life has been challenged by the argument that although the ICD reduces the rate of sudden death, it does not reduce cardiac death or total mortality (for details, see Reference 6). The premature termination of the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial in April 1997, however, confirmed our conclusions, based on the stored ECG data and the use of the occurrence of a fast VT or VF rhythm as an end point.

Key Words: heart failure ■ prognosis ■ cardioversion ■ defibrillation
As a contribution to the ongoing discussion of whether the ICD prolongs life in patients with heart failure or merely changes the mode of death, we investigated the influence of New York Heart Association (NYHA) functional class, which has been demonstrated to be a major determinant of survival, on the potential benefit from ICD implantation.

Methods

Patient Selection
Between October 1989 and October 1996, 603 consecutive patients who were treated with an ICD with extended memory function (storage of electrograms and/or RR intervals from treated episodes) in combination with endocardial lead systems because of a history of sustained malignant ventricular tachyarrhythmia, aborted sudden death, or syncope after myocardial infarction attributable to a VT were included in the study. Written informed consent was obtained from all patients. Data for all patients had been prospectively collected in a database. Follow-up started at the time of ICD implantation. Patients who received a defibrillator for prophylactic reasons as part of the Coronary Artery Bypass Graft (CABG) Patch trial or the cardiomyopathy trial were not included.

Implantation Technique
Implantation of an endocardial lead system was attempted in the patients included in the present study. Seventy-six percent of the devices were able to store RR intervals plus electrograms retrieved either from the sensing circuit or from the shocking leads, and 24% of the devices stored RR intervals from the treated episodes. Devices with only a shock counter were not used. All devices were programmed to a noncommitted mode for shock delivery.

Follow-Up
Patients were followed up in an outpatient clinic at intervals of 2 to 3 months. Study end points were the following: surgical mortality (defined as death of any cause within 30 days after operation), sudden death (defined as either death within 1 hour after the onset of symptoms or unwitnessed death occurring in previously stable patients), cardiac death (including surgical mortality), and noncardiac death.

All device discharges were classified by 2 independent cardiologists as inappropriate (that is, discharge of the device for supraventricular tachycardia or oversensing) or as appropriate on the basis of recorded electrograms, RR-interval memory before first treatment by the device, and tachycardia-related symptoms.

Recorded nonfatal events included ventricular tachyarrhythmias (of either rate) and fast ventricular tachyarrhythmias that caused device discharges, arbitrarily defined as a ventricular tachycardia >240 bpm. Because of reported data on surgery-related exacerbation of ventricular tachyarrhythmias, episodes occurring within 7 days after operation were excluded from further analysis.

When the ICD was explanted for various reasons, follow-up was continued (intention-to-treat analysis).

Statistical Analysis
SD was used as an index of dispersion of the variables measured. The Kaplan-Meier method (modification for analysis of failure time data and competing risks, as described by Kalbfleisch and Prentice) was used to generate survival curves for each group. The following end points were used: (1) VT, (2) fast VT or VF (>240 bpm), (3) sudden death, (4) total deaths, and (5) total deaths plus occurrence of fast (>240 bpm) VT representing hypothetical deaths (assuming that ICD implantation would not prevent nonarrhythmic cardiac death or noncardiac death). For calculation of hypothetical death rates, patients who died within 30 days after surgery were censored at the time of their death, thereby excluding surgical mortality from the hypothetical death rate. Benefit of implantation of an automatic defibrillator was estimated by the difference between the curves for total deaths and calculated hypothetical deaths. Cox regression was used to analyze the influence of various covariates on the occurrence of total death, fast VT, and hypothetical death. Data were analyzed on an intention-to-treat basis. Patients who underwent heart transplantation were not censored at the time of their transplant, but their follow-up was continued so that the potential benefit from ICD implantation as a bridge to transplant would be included.

Results

Patients
A total of 603 patients were considered for implantation of an ICD with storage of electrograms and/or RR intervals in combination with endocardial lead systems. There were 467 men (77%) and 136 women (23%) with a mean age of 57 ± 13 years (Table 1). Mean left ventricular ejection fraction as measured by echocardiography was 0.50 (±0.14) for patients with coronary artery disease and 0.47 (±0.13) for patients with cardiomyopathy (p < 0.05). Coronary angiography was performed in all patients. Coronary artery disease was present in 58.5% of the patients, dilated cardiomyopathy in 16.3%, arrhythmogenic right ventricular cardiomyopathy; and AAD, antiarrhythmic drugs.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Disease, %</th>
<th>All Patients</th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>58.5</td>
<td>26.1</td>
<td>66.4</td>
<td>72.0</td>
</tr>
<tr>
<td>DCM</td>
<td>16.3</td>
<td>9.9</td>
<td>18.2</td>
<td>18.3</td>
</tr>
<tr>
<td>ARVCM</td>
<td>6.5</td>
<td>19.7</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Long-QT syndrome</td>
<td>1.7</td>
<td>4.9</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>4.6</td>
<td>2.8</td>
<td>4.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Other</td>
<td>5.1</td>
<td>10.6</td>
<td>4.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Normal heart</td>
<td>7.3</td>
<td>26.1</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>Presenting arrhythmia, %</td>
<td>Cardiac arrest</td>
<td>62.7</td>
<td>69.7</td>
<td>61.9</td>
</tr>
<tr>
<td>VT (no arrest)</td>
<td>30.0</td>
<td>20.4</td>
<td>31.5</td>
<td>35.4</td>
</tr>
<tr>
<td>Medication, %</td>
<td>Digitalis</td>
<td>54.7</td>
<td>21.6</td>
<td>56.9</td>
</tr>
<tr>
<td>Diuretics</td>
<td>48.2</td>
<td>8.9</td>
<td>55.0</td>
<td>69.5</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>56.9</td>
<td>21.5</td>
<td>64.1</td>
<td>74.3</td>
</tr>
<tr>
<td>β-blockers</td>
<td>26.2</td>
<td>27.4</td>
<td>26.7</td>
<td>24.6</td>
</tr>
<tr>
<td>Class I AAD</td>
<td>1.5</td>
<td>2.2</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Class III AAD</td>
<td>17.6</td>
<td>6.7</td>
<td>19.5</td>
<td>23.6</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; CAD, coronary artery disease; DCM, dilated cardiomyopathy; ARVCM, arrhythmogenic right ventricular cardiomyopathy; and AAD, antiarrhythmic drugs.

As a contribution to the ongoing discussion of whether the ICD prolongs life in patients with heart failure or merely changes the mode of death, we investigated the influence of New York Heart Association (NYHA) functional class, which has been demonstrated to be a major determinant of survival, on the potential benefit from ICD implantation.
Follow-Up (All Patients; n=598)

<table>
<thead>
<tr>
<th>Event-Free Rates</th>
<th>1 y</th>
<th>3 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sudden death, %</strong></td>
<td>98.8</td>
<td>96.2</td>
<td>92.7</td>
</tr>
<tr>
<td><strong>All VT/VF, %</strong></td>
<td>54.7</td>
<td>41.0</td>
<td>31.7</td>
</tr>
<tr>
<td><strong>Fast VT/VF, %</strong></td>
<td>81.4</td>
<td>69.7</td>
<td>60.0</td>
</tr>
<tr>
<td><strong>Total deaths, %</strong></td>
<td>93.7</td>
<td>84.9</td>
<td>75.0</td>
</tr>
<tr>
<td><strong>Hypothetical death, %</strong></td>
<td>77.8</td>
<td>61.4</td>
<td>48.4</td>
</tr>
</tbody>
</table>

**Operative Results**

Using the endocardial lead system, a sufficiently low defibrillation threshold to allow implantation of the system was achieved in 596 patients (98.8%). In 376 patients (62.4%), a transvenous lead system was used; in 220 patients (36.5%), a transvenous lead was combined with a subcutaneous patch or array electrode. Seven patients (1.2%) did not qualify for implantation of endocardial lead systems and subsequently received epicardial defibrillation leads. All of these cases were observed before biphasic shocks were available. Devices included the CPI Ventak PRx in 64 patients, PRx II/III in 106 patients, P2/3 in 85, Mini in 61, Medtronic PCD 7216/7 in 79, Jewel in 184, Ventitrex V-100/110 in 15, Biotronik Phylax 06 in 3, Ela Defender in 1, and Teletronics Guardian ATP in 5.

**Postoperative Period**

There were 6 deaths (3 men and 3 women aged 61 ± 16 years) in the postoperative period. One patient with complex congenital heart disease and several previous surgical cardiac procedures who had a bleeding disorder because of advanced liver disease died 5 days after operation as a result of perforation of the subclavian vein that resulted in hemotherax and multiorgan failure. Two patients died of heart failure 3 and 24 days, respectively, after implantation. Another patient developed incessant VT 6 days after operation and subsequently died. This patient had had a previous episode of incessant VT seven weeks before ICD implantation. Before operation, amiodarone had been discontinued in this patient because of markedly elevated liver enzymes.

Two of the patients who did not meet the criteria for implantation of the endocardial lead system died of pulmonary embolism and adult respiratory distress syndrome, respectively, 7 and 12 days after ICD implantation with epicardial leads.

The 30-day mortality rate was 1% for all patients and 0.7% for patients qualifying for implantation of the endocardial lead system. Five of the 6 patients who died perioperatively had been in NYHA functional class III and 1 had been in class II. The mean ejection fraction was 35 ± 7% (range, 24% to 43%).

**Long-Term Follow-Up**

During follow-up of 26 ± 19 months, there were 71 deaths. Nineteen deaths that occurred 2 to 62 months after implantation were sudden, resulting in a sudden death rate of 1.2%.

**Influence of Heart Failure Class on Recurrence of Tachyarrhythmias, Survival, and Survival Benefit From ICD Implantation**

To evaluate the influence of heart failure on survival and survival benefit from ICD implantation, the severity of heart failure (NYHA class I, II, and III) at the time of implantation was correlated with total mortality, the recurrence of fast ventricular tachyarrhythmias (>240 bpm) during follow-up, and the calculated hypothetical death rate had the device not been implanted.

**NYHA Class I**

As shown in Table 1, 142 patients were in NYHA class I at the time of implantation. One patient died 14 months after implantation because of metastatic lung cancer. Another patient died suddenly 28 months after implantation. The device had been explanted 6 months before because of an infection. The patient who had not had a ventricular tachyarrhythmia after implantation of the device refused...
reimplantation of the device. A postmortem examination was not available in this patient. There were no nonarrhythmic cardiac deaths. However, fast ventricular tachyarrhythmias that would have presumably been fatal unless terminated by the devices recurred in 32 patients, resulting in a recurrence rate of fast VT or VF of 15.2%, 29.5%, and 36.1% after 1, 3, and 5 years, respectively. Using the occurrence of fast ventricular tachyarrhythmias and deaths of any cause, we calculated a hypothetical death rate (had the device not been implanted) of 15.2%, 31.9%, and 38.2% at 1, 3, and 5 years. The recurrence rate for ventricular tachyarrhythmias of either rate was 26.4%, 45.1%, and 52.0%. The estimated survival benefit derived from implantation of the defibrillator steadily increased from 15.2% at 1 year to 29.2% at 3 years and 35.6% at the end of the 5-year observation period and showed no sign of reaching a plateau (Figure 2A; Table 4).

NYHA Class II

There were 286 patients in NYHA class II at the time of implantation (Table 1). Among 32 deaths, 7 occurred suddenly 2 to 47 months after implantation, resulting in a sudden death rate of 1.2%, 3.2%, and 5.2% after 1, 3, and 5 years, respectively. There were 19 nonsudden cardiac deaths and 6 noncardiac deaths, resulting in a total mortality rate of 5.1%, 13.0%, and 24.3% after 1, 3, and 5 years, respectively. One hundred forty-four patients had recurrences of ventricular tachyarrhythmias, resulting in a recurrence rate of 46.7%, 57.9%, and 66.9% after 1, 3, and 5 years, respectively. The rate for the occurrence of fast ventricular tachyarrhythmias that would have presumably been fatal if not terminated by the devices (n = 64 patients) was 17.5%, 28.7%, and 38.2% after 1, 3, and 5 years, respectively. The hypothetical death rate was 20.3%, 34.8%, and 47.2% at 1, 3, and 5 years, respectively. For these patients, the estimated survival benefit imposed by implantation of the defibrillators increased until 3 years and then plateaued up to the end of the observation period (22.9% at 5 years) (Figure 2B).

NYHA Class III

There were 175 patients in NYHA class III at the time of implantation (Table 1). Among these patients, there were 37 deaths, 11 of which occurred 5 to 62 months after implantation and were classified as sudden, resulting in a sudden death rate of 2.5%, 6.8%, and 16.4% after 1, 3, and 5 years, respectively. There were 22 nonsudden cardiac deaths and 4 noncardiac deaths (total mortality rate of 13.8%, 28.6%, and 44.1% after 1, 3, and 5 years, respectively). During follow-up, 100 patients (57.1%) had recurrences of ventricular tachyarrhythmia (recurrence rate of 59.5%, 73.4%, and 100% after 1, 3, and 5 years, respectively). The rate of occurrence of fast ventricular tachyarrhythmias that would have presumably been fatal if not terminated by the devices (n = 47 patients) was 23.3%, 34.0%, and 45.7% after 1, 3, and 5 years, respectively. The hypothetical death rate was 31.6%, 50.5%, and 67.9% at 1, 3, and 5 years. Similar to patients in NYHA class II, the estimated survival benefit imposed by implantation of the defibrillators increased until 3 years and

### Table 3: Actuarial Event-Free Rates During 5 Years of Follow-Up Stratified by Disease and Left Ventricular Ejection Fraction

<table>
<thead>
<tr>
<th></th>
<th>CAD (n=353)</th>
<th>DCM (n=98)</th>
<th>LVEF &gt;40% (n=316)</th>
<th>LVEF ≤40% (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 3</td>
<td>Year 1</td>
<td>Year 3</td>
</tr>
<tr>
<td>Sudden death, %</td>
<td>98.7</td>
<td>95.9</td>
<td>97.3</td>
<td>93.9</td>
</tr>
<tr>
<td>All VT/VF, %</td>
<td>50.7</td>
<td>39.0</td>
<td>47.3</td>
<td>31.2</td>
</tr>
<tr>
<td>Fast VT/VF, %</td>
<td>82.1</td>
<td>71.5</td>
<td>77.7</td>
<td>68.5</td>
</tr>
<tr>
<td>Total deaths, %</td>
<td>93.0</td>
<td>81.6</td>
<td>90.4</td>
<td>80.7</td>
</tr>
<tr>
<td>Hypothetical death, % (fast VT/VF or death from any cause)</td>
<td>78.0</td>
<td>61.7</td>
<td>70.9</td>
<td>52.7</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; and LVEF, left ventricular ejection fraction.
then plateaued (17.8% at 1 year, 21.9% at 3 years, and 23.8% at 5 years, respectively) (Figure 2C).

Influence of Covariates on Survival
Cox regression was used to investigate the influence of various covariates (age; ejection fraction; NYHA class; underlying disease; presenting arrhythmia; treatment with digitalis, diuretics, ACE inhibitors, β-blockers, class I antiarrhythmic drugs, or class III antiarrhythmic drugs; and type of ICD memory) on total death, the occurrence of fast VT, VT of any rate, and hypothetical death. In a univariate model, older age, lower ejection fraction, higher NYHA class, and treatment with digitalis, diuretics, ACE inhibitors, and class III antiarrhythmic drugs were correlated with higher total death. Older age, lower ejection fraction, higher NYHA class, and treatment with digitalis, diuretics, ACE inhibitors, and class III antiarrhythmic drugs were correlated with greater recurrence of VT of any rate. Lower ejection fraction, higher NYHA class, treatment with digitalis and diuretics, and absence of treatment with class III antiarrhythmic drugs were correlated with a greater recurrence of fast VT. Lower ejection fraction, higher NYHA class, and treatment with digitalis, diuretics, or ACE inhibitors were correlated with a higher hypothetical death rate. Most of these variables failed to reach significance in a multivariate model (Table 5). A low NYHA class was a predictor of a low total death rate and a low incidence of VT of any rate but not of a low rate of fast ventricular tachyarrhythmia that would presumably have been fatal without device intervention. Ejection fraction provided additional information regarding total death but not VT or fast ventricular tachyarrhythmias.

In patients in NYHA III (Figure 3), the subgroup with an ejection fraction \(<30\% (n=84) had a slightly but not significantly greater recurrence rate for ventricular tachyarrhythmias of any rate than the 91 patients with an ejection fraction \(\geq 30\% (66.4\% and 81.5\% at 1 and 3 years versus 53.2\% and 66.8\%, respectively). Low ejection fraction did not predict recurrences of fast ventricular tachyarrhythmias (27.3\% and 41.9\% at 1 and 3 years, respectively, versus 14.5\% and 30.5\%), or the hypothetical death rate had the device not been implanted (36.4\% and 54.2\% at 1 and 3 years, respectively, versus 26.8\% and 47.1\%).

In patients with a history of decompensation, recurrences of ventricular tachyarrhythmias of any rate (62.7\% and 84.8\% at 1 and 3 years, respectively) were slightly but not significantly more frequent than in those patients without a history of decompensation before ICD implantation (54.0\% and

Table 4. Actuarial Event-Free Rates During 5 Years of Follow-Up Stratified by NYHA Class

<table>
<thead>
<tr>
<th>NYHA I (n=142)</th>
<th>NYHA II (n=286)</th>
<th>NYHA III (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 3</td>
</tr>
<tr>
<td>Sudden death, %</td>
<td>100.0</td>
<td>98.5</td>
</tr>
<tr>
<td>All VT/VF, %</td>
<td>73.6</td>
<td>54.9</td>
</tr>
<tr>
<td>Fast VT/VF, %</td>
<td>84.8</td>
<td>70.5</td>
</tr>
<tr>
<td>Total deaths, %</td>
<td>100.0</td>
<td>97.4</td>
</tr>
<tr>
<td>Hypothetical death, % (fast VT/VF or death from any cause)</td>
<td>84.8</td>
<td>68.1</td>
</tr>
</tbody>
</table>

Figure 3. Actuarial survival rates for freedom from death of any cause, sudden death, fast ventricular tachyarrhythmia (>240 bpm), VTs of any rate, and hypothetical death rate (Hypoth. Death) for patients in NYHA functional class III. A, Ejection fraction \(\geq 30\%; B, ejection fraction \(\leq 30\%; C, no prior decompensation; and D, history of decompensated heart failure.
63.1% at 1 and 3 years, respectively). In addition, there was a slightly higher recurrence rate of fast ventricular tachyarrhythmias in those patients with (30.4% and 43.7% at 1 and 3 years, respectively) versus those without (17.0% and 27.7% at 1 and 3 years, respectively; risk ratio, 0.51; 95% CI, 0.28 to 0.93; \( P < 0.03 \) previous decompensation. Of note, patients with a history of decompensated heart failure had a higher total mortality rate (23.2% and 43.5% at 1 and 3 years, respectively, versus 7.3% and 19.4%; risk ratio, 0.43; 95% CI, 0.23 to 0.80; \( P = 0.008 \)) and a higher hypothetical death rate (43.5% and 67.1% at 1 and 3 years, respectively, versus 20.8% and 38.9%; risk ratio, 0.45; 95% CI, 0.27 to 0.72; \( P = 0.001 \)) than those without such history. There was a marked difference between hypothetical death rates and total mortality rate (ie, a benefit from device therapy) both in patients without and those with a history of decompensated heart failure, which indicates a benefit from ICD implantation even in these groups with the worst prognosis.

**Discussion**

The results of this study provide strong evidence that patients with a history of cardiac arrest or VT refractory to drug therapy benefit from implantation of an automatic cardioverter-defibrillator. The findings in the present study are in accordance with earlier findings from our group\(^5\) as well as from other groups who suggest a favorable outcome after ICD implantation. In a study by Sweeney et al.\(^12\) NYHA functional class was the strongest predictor of total mortality in a very sick population of patients evaluated for transplantation. This was confirmed by the present study, which showed the highest mortality rate in the group of patients in NYHA class III and a history of decompensation before ICD implantation. However, defibrillator implantation led to an improvement even in this group of patients.

In a small study of 68 patients, Kim et al.\(^13\) assessed the influence of left ventricular dysfunction on outcome after ICD implantation. They found that many of the nonsudden deaths were causally related to arrhythmias. However, because epicardial defibrillation lead systems were used in that study, ICD implantation was associated with a high surgical mortality rate (11%) in patients with an ejection fraction \(< 30\%\). With endocardial defibrillation lead systems used in combination with biphasic devices, ICD implantation should currently be associated with a mortality rate of \(< 1\%\). Therefore, conclusions from the study by Kim et al.\(^13\) should be drawn with caution. In the present study, arrhythmia-related nonsudden deaths were a rare finding. NYHA functional class proved to be a better predictor of outcome than left ventricular ejection fraction.

Sweeney et al.\(^12\) retrospectively studied the impact of ICD implantation on survival of 291 consecutive patients evaluated for cardiac transplantation. Fifty-nine of their patients had received an ICD because of malignant ventricular tachyarrhythmias refractory to other forms of treatment. They were compared with 179 patients without antiarrhythmic treatment at the time of transplant evaluation and 53 patients who were taking antiarrhythmic drugs for various reasons, including 26 with a history of cardiac arrest or sustained ventricular fibrillation. Sudden death rates were lowest in the ICD group, intermediate in the group with no antiarrhythmic treatment, and highest in the drug-treatment group. Nonsudden death rates did not differ between groups. The effect of

<table>
<thead>
<tr>
<th>TABLE 5. Risk Ratio and 95% CI for Various Covariates on Total Death, Hypothetical Death, Occurrence of Fast Ventricular Tachyarrhythmias, and Occurrence of Any Ventricular Tachyarrhythmias in a Cox Proportional Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>All VT</td>
</tr>
<tr>
<td>NYHA I (reference category: NYHA III)</td>
</tr>
<tr>
<td>(0.352–0.884)</td>
</tr>
<tr>
<td>NYHA II (reference category: NYHA III)</td>
</tr>
<tr>
<td>(0.580–0.986)</td>
</tr>
<tr>
<td>EF</td>
</tr>
<tr>
<td>(0.958–0.991)</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Class I AAD</td>
</tr>
<tr>
<td>(0.152–0.690)</td>
</tr>
<tr>
<td>Class III AAD</td>
</tr>
<tr>
<td>(1.095–3.365)</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; AAD, antiarrhythmic drugs. Values are risk ratio (95% CI) and probability values.
the reduction in sudden deaths on the total mortality rate was
marginalized by the high nonsudden death rates observed in
the present study and was not statistically significant. How-
ever, the patients included in the study by Sweeney et al12 had
severe heart disease, with a mean NYHA functional class of
3.4±0.7. Assignment of the patients to the different treatment
arms was based on arrhythmia history rather than
randomization.

In a study of 64 patients with left ventricular ejection
fraction ≤30%, Mehta et al14 observed a similar survival rate
in users and nonusers of the ICD. This indicates that ICD
therapy in patients experiencing recurrences of sustained VT
or VF was associated with a survival comparable to that of
patients who did not have any subsequent spontaneous
recurrent VT or VF. This would suggest elimination of the
arrhythmic death component of the total mortality rate in
these patients. Information on the functional status of these
patients is not available.

The recently published Multicenter Automatic Defibrilla-
tor Implantation Trial (MADIT)15 included patients with an
ejection fraction ≤35% and nonsustained VTs. One third of
the patients were in NYHA functional class I, and two thirds
were in functional class II or III. Compared with conventional
antiarrhythmic therapy (in most patients, amiodarone), pro-
phylactic ICD implantation led to significantly improved
survival. The benefit from ICD implantation did not decrease
over time but increased until 2 years and then remained
constant. This was similar to our observations in NYHA class
II and III patients. However, in patients in NYHA functional
class I, the estimated benefit continued to increase up to 5
years. This suggests that the benefit from ICD implantation
might be sustained for the longest amount of time for patients
with mild or no functional impairment. However, because
recurrence rates for VT and for fast ventricular tachyarrhythmias are higher for patients with heart failure, the
initial benefit is likely to be greater for the latter patients.

Data from the AVID trial,16 which was prematurely
stopped because of the superiority of ICD implantation over
antiarrhythmic drug treatment with amiodarone or sotalol in
patients with symptomatic VT or aborted sudden cardiac
death, suggests a greater benefit for patients with a low
ejection fraction. However, the follow-up was relatively
short, and the data do not exclude the possibility that the
benefit might be sustained longer in patients with better
myocardial function.

Study Limitations
Several aspects of the present study on the impact of ICDs on
sudden death and total mortality require further comment. Study
patients served as their own control subjects. Only patients who
received an ICD capable of storing electrograms and/or cycle
lengths before device therapy were included. The end point used
in this study was a surrogate end point. We calculated hypothet-
cial death rates using occurrence rates of fast and presumably
life-threatening tachyarrhythmias and all observed deaths as-
suming that ICD implantation does not prevent deaths from
heart failure or noncardiac deaths. Because surrogate end points
such as the occurrence of fast ventricular tachyarrhythmias
might be used in future studies of antiarrhythmic drug efficacy
with defibrillator backup in all patients,17 the cutoff rate of 240
bpm, which was chosen arbitrarily, should be evaluated within a
prospective mortality trial.

Because slower tachycardias might be hemodynamically
tolerated for a certain time, only fast VTs (>240 bpm) were
included in the analysis of projected survival without the
ICD. However, overestimation of the benefit conferred by
ICD therapy cannot be excluded, because a minority of
patients might have survived a fast ventricular tachyarrhythmia long enough to obtain medical attention. On
the other hand, it is quite possible that patients with a
tachycardia slower than 240 bpm might have died from their
arrhythmia. This is true especially for patients with advanced
heart failure, who might not tolerate a slower tachycardia
long enough to obtain medical attention. For these patients,
the benefit from ICD implantation might have been underes-
timated. The majority of fast ventricular tachyarrhythmias
were terminated with the first shock, ie, within 6 to 10
seconds. Although it cannot be completely ruled out that a
few of these tachycardias might have terminated spontane-
ously, spontaneous termination of fast VTs or VF beyond a
period of 10 seconds is rare. Thus, a significant overestima-
tion of the benefit from device implantation seems unlikely.

On the other hand, it cannot be fully excluded that some
tachycardias that started at a slower rate might have acceler-
ated had they been allowed to last longer.

This study was a retrospective analysis. However, end
points had been selected before inclusion of the vast majority
of the patients after the usefulness of this evaluation had been
demonstrated in our previous study5 based on 107 patients
who were also included in the present evaluation. In case of
a patient’s death, every effort was made to clarify the
circumstances. To minimize the bias imposed by classifica-
tion of deaths, total mortality, and not cardiac death, was used
to calculate the impact of ICD implantation.

Although the majority of the devices stored electrograms,
≈23% stored only cycle lengths from the treated episodes,
which had the potential for misinterpretation of shocks.
However, the vast majority of spurious shocks can be
detected with the cycle-length memory of the devices. In
addition, the type of device memory did not influence results
in the multivariate model.

Episodes occurring within 7 days of surgery were excluded
from the analysis. Because we have previously shown that
there is a perioperative exacerbation of ventricular
tachyarrhythmias even in patients with a nonthoracotomy
lead system,10 failure to exclude this period would lead to an
overestimation of the benefit derived from ICD implantation.

Conclusions
First, this study shows the usefulness and appropriateness of
use of hypothetical death rates based on the memory of
modern devices to estimate the benefit of ICD therapy. This
approach gives much greater certainty than other surrogate
dead end points such as device shocks. This has recently been
discussed.13 The results were confirmed by the recent, pre-
maturely terminated AVID trial. Second, this surrogate end
d point of fast ventricular tachyarrhythmia with a rate >240
bpm might be a useful criterion to assess the benefit of newer
antiarrhythmic drugs, using the already implanted ICDs to safely assess their effects. Third, our study shows that the benefit of ICD therapy depends on the severity of the underlying heart failure. Even in NYHA class III, benefit was still preserved. On the basis of these findings, use of the ICD appears appropriate for treatment of ventricular tachyarrhythmias in patients with and without heart failure and even in patients with advanced heart failure provided they have a realistic chance of transplantation. The benefit from ICD implantation might last the longest for patients without heart failure or with mild heart failure. However, the initial benefit is likely to be greater for patients with more advanced disease.

References
Potential Benefit From Implantable Cardioverter-Defibrillator Therapy in Patients With and Without Heart Failure
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