Survival Benefit of the Implantable Cardioverter-Defibrillator in Patients on the Waiting List for Cardiac Transplantation

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Background—The implantable cardioverter-defibrillator (ICD) effectively reduces sudden cardiac death in patients with severe LV dysfunction. Effect of ICD therapy on total mortality in patients on the waiting list for cardiac transplantation is still uncertain.

Methods and Results—We retrospectively analyzed 854 unselected consecutive patients (ICD therapy, n=102; 11.9%) on the waiting list for cardiac transplantation between January 1992 and March 2000. Actuarial 12-month total mortality rate on the waiting list was 24.2%; sudden cardiac death was the predominant mode of death (66.7% of total deaths). Kaplan-Meier analysis revealed improved survival for ICD (total mortality, 13.2%) compared with non-ICD (total mortality, 25.8%) patients (log rank, P=0.03). No event of sudden death occurred in ICD patients, whereas in non-ICD patients, 12-month sudden death rate was 20.1% (P=0.0001). Nonsudden death rates did not differ between ICD and non-ICD patients (P=0.16). A Cox proportional hazards model demonstrated that absence of an ICD was a powerful independent predictor of total mortality (P=0.02; relative risk, 2.22; 95% confidence interval, 1.16 to 4.17) and sudden cardiac death (P<0.0001; infinite relative risk) on the waiting list.

Conclusions—ICD therapy, because it prevents sudden cardiac death, significantly improves survival on the waiting list for cardiac transplantation. The present study supports the use of ICDs as a bridge to transplantation in patients who are at risk of sudden cardiac death. Prospective randomized trials are needed to evaluate the potential benefit of prophylactic ICD therapy as a bridge to transplantation in all patients on cardiac transplant waiting lists. (Circulation. 2001; 104[suppl I]:I-171-I-176.)

Key Words: cardioversion ♦ mortality ♦ death, sudden ♦ transplantation

Poor LV function is accepted as the most important predictor of sudden cardiac death and total cardiac mortality.1-3 Patients with end-stage heart failure listed for cardiac transplantation are at high risk of sudden cardiac death while on the waiting list.4-6 Of all deaths in patients on the waiting list, ≈70% occur suddenly.7 Implantable cardioverter-defibrillator (ICD) therapy has been shown to reduce sudden cardiac death effectively in patients with severe LV dysfunction.8-10 including those awaiting transplantation.11-13 Whether reduction in sudden cardiac death leads to improved overall survival in severe heart failure patients is still uncertain.14-16 Previous studies have argued that patients saved from sudden cardiac death by the ICD eventually may die from progression of heart failure.16 The aim of this retrospective analysis was to examine the effect of ICD therapy on mortality in patients on the waiting list for cardiac transplantation.

Methods

Patient Population

Study population consisted of 854 unselected consecutive patients placed on the Eurotransplant waiting list for cardiac transplantation at Vienna University Hospital from January 1992 through March 2000. Indication for transplantation in all patients was end-stage heart disease, with unacceptable prognosis for survival even after careful consideration of all other medical and surgical therapies.17

ICD Patients

A group of 102 patients (11.9% of the total population) received ICDs. All patients had ICDs implanted before listing for transplantation. Median time from ICD implantation to listing for transplantation was 6.7 months (range, 1 day to 77 months). A total of 64 patients (62.7%) underwent baseline electrophysiological study before ICD implantation (inducible sustained ventricular tachycardia or ventricular fibrillation in 57 patients). Indications for ICD implantation were (1) out-of-hospital cardiac arrest (n=62 patients, 60.8%) and either inducible sustained ventricular tachycardia or ventricular fibrillation not suppressed by antiarrhythmic drugs at electrophysiological study (n=29) or ICD as first-line therapy without electrophysiological study (n=33); (2) spontaneous sustained ventricular tachycardia or nonsustained ventricular tachycardia with inducible sustained ventricular tachycardia or ventricular fibrillation at electrophysiological study (n=27, 26.5%) and either inducible sustained ventricular tachycardia or ventricular fibrillation not suppressed by antiarrhythmic drugs at electrophysiological study (n=18) or ICD as...
first-line therapy without electrophysiological study (n=9); and (3) syncope (n=13, 12.7%) and either inducible sustained ventricular tachycardia or ventricular fibrillation not suppressed by antiarrhythmic drugs at electrophysiological study (n=10) or ICD as first-line therapy without electrophysiological study (n=3). Median time from presentation with out-of-hospital cardiac arrest or sustained ventricular tachycardia to listing for transplantation in these patients was 9.6 months (range, 1 to 84 months). Of the ICD patients, 42 (41.2%) received additional amiodarone therapy at time of ICD implantation.

Cardiac arrest was defined as sudden loss of consciousness that results from a ventricular tachyarrhythmia not associated with reversible conditions and that requires cardiopulmonary resuscitation, including external electric defibrillation, for termination. Sustained ventricular tachycardia was defined as ventricular tachycardia at rates $\geq 100$ bpm that lasts $\geq 30$ s and that requires intervention for termination. Nonsustained ventricular tachycardia was defined as $\geq 3$ consecutive ventricular premature beats at rates of $\geq 100$ bpm that last $<30$ s.

**Non-ICD Patients**

A group of 752 patients (88.1% of the total population) was not treated with ICDs.

**Follow-Up**

Patients were followed up from the date of listing for transplantation from January 1, 1992; study end points were transplantation, death on list, still awaiting transplantation on March 1, 2000, and removed from list. Table 2 shows follow-up times for patients on the waiting list. Median follow-up time in the total population was 4.7 months (range, 1 day to 52 months). Median waiting time to transplantation was 8.1 months (range, 1 day to 52 months). Waiting times to transplantation were similar between ICD and non-ICD patients.

Circumstances of death that occurred while the patient was on the waiting list were determined from hospital records and interviews with personal physicians and family members. Deaths were classified as sudden cardiac, nonsudden cardiac, and noncardiac. Sudden cardiac death was defined as death within 1 hour after onset of acute symptoms or unwitnessed, unexpected death in a patient known to have been stable within the previous 24 hours. Nonsudden cardiac death included arrhythmia-related nonsudden deaths (ie, death within 24 hours after an arrhythmic event despite initial termination of arrhythmia by ICD).

**TABLE 1. Baseline Clinical Characteristics of 854 Consecutive Patients on the Waiting List for Cardiac Transplantation**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total (n=854)</th>
<th>ICD (n=102)</th>
<th>Non-ICD (n=752)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD, %</td>
<td>11.9</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>53.7±9.7</td>
<td>53.0±9.0</td>
<td>53.8±9.8</td>
<td>0.42</td>
</tr>
<tr>
<td>Men, %</td>
<td>85.6</td>
<td>90.2</td>
<td>85.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Cardiac disease, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>36.4</td>
<td>47.0</td>
<td>35.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>60.6</td>
<td>51.0</td>
<td>61.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Other</td>
<td>3.0</td>
<td>2.0</td>
<td>3.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Arrhythmia history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>26.4</td>
<td>27.5</td>
<td>26.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>38.8</td>
<td>77.5</td>
<td>33.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syncope</td>
<td>5.4</td>
<td>18.6</td>
<td>3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest</td>
<td>11.5</td>
<td>60.8</td>
<td>4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean NYHA functional class</td>
<td>3.2±0.6</td>
<td>3.1±0.6</td>
<td>3.3±0.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAPSYS, mm Hg</td>
<td>49.7±14.9</td>
<td>44.7±14.3</td>
<td>50.4±14.8</td>
<td>0.0004</td>
</tr>
<tr>
<td>PVR, Wood U</td>
<td>2.7±1.6</td>
<td>2.4±1.2</td>
<td>2.8±1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.3±1.3</td>
<td>4.4±1.2</td>
<td>4.3±1.3</td>
<td>0.36</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>2.2±0.6</td>
<td>2.3±0.6</td>
<td>2.2±0.6</td>
<td>0.61</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>17.7±7.9</td>
<td>18.9±9.2</td>
<td>17.5±7.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral diuretics</td>
<td>96.9</td>
<td>97.1</td>
<td>96.9</td>
<td>1.00</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>96.2</td>
<td>94.1</td>
<td>96.4</td>
<td>0.27</td>
</tr>
<tr>
<td>β-blockers</td>
<td>24.3</td>
<td>33.3</td>
<td>23.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>23.4</td>
<td>41.2</td>
<td>20.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PGE₁†</td>
<td>13.0</td>
<td>10.8</td>
<td>13.4</td>
<td>0.53</td>
</tr>
<tr>
<td>Dobutamine†</td>
<td>10.9</td>
<td>11.8</td>
<td>10.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Ventricular assist device</td>
<td>3.2</td>
<td>6.9</td>
<td>2.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PAPSYS indicates pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac index; ACE, angiotensin-converting enzyme; and PGE₁, prostaglandin-E1.

*P for ICD vs non-ICD patients.
†Continuous intravenous administration.
ICD patients were seen at regular intervals to monitor device system function. Circumstances of shock delivery were evaluated, and number of discharges while the patient was on the waiting list was documented. Appropriate shocks were defined as previously described by Fogoros et al\textsuperscript{19} as spontaneous ICD discharges preceded by symptoms of severe lightheadedness, presyncope or syncope, or shocks for ventricular tachycardia or ventricular fibrillation as documented by Holter monitoring or stored ECGs by the device.

### Statistical Analysis

Numeric data are expressed as mean±SD. Comparisons between groups were calculated by use of \( \chi^2 \) test for categorical variables and Student’s \( t \) test for continuous variables. Follow-up times were described as medians by use of the inverse Kaplan-Meier estimator. Survival curves were generated with the Kaplan-Meier method and were compared by use of the log rank test. Effects of baseline characteristics on total mortality and sudden and nonsudden cardiac death were evaluated with the Cox proportional hazards model. In one of the present Cox proportional hazards models, a breakdown of the standard maximum likelihood method occurs, because at each failure time, a linear combination of the covariates is the largest of all covariate values in the risk set at the time. This condition is known as monotone likelihood.\textsuperscript{20} As a consequence, ≥1 parameter estimate is infinite. In the case of monotone likelihood, probability values were calculated by likelihood ratio method.\textsuperscript{20} For all analyses, a \( P \) value <0.05 was considered significant (statistical package SAS 6.12, SAS Inc).

### Results

#### Baseline Characteristics

Table 1 describes clinical characteristics of the patient population at time of listing for transplantation. Mean age was 53.7±9.7 years, and 85.6% of the patients were men. Underlying cardiac disease was coronary artery disease in 36.4% and idiopathic dilated cardiomyopathy in 60.6%. All patients had advanced symptomatic heart failure (mean New York Heart Association functional class, 3.2±0.6) and severely impaired LV systolic function (mean LV ejection fraction, 17.7±7.9%).

Baseline characteristics were similar between ICD and non-ICD patients except for incidence of coronary artery disease (higher in ICD patients) and idiopathic dilated cardiomyopathy (higher in non-ICD patients); patient history of nonsustained ventricular tachycardia, syncope, and out-of-hospital cardiac arrest (higher in ICD patients); pulmonary pressures (higher in non-ICD patients); and use of \( \beta \)-blockers, amiodarone, and ventricular assist devices (higher in ICD patients).

While on the transplant waiting list, 66 of 102 ICD patients (64.7%) received a spontaneous ICD shock. Median number of spontaneous ICD shocks per patient was 4 (range, 1 to 385). Appropriate ICD shocks were observed in all 66 patients.

#### Outcome

See Table 2 for outcome in patients on the waiting list. A total of 57% of patients underwent cardiac transplantation, and 20.4% died while on the waiting list. Most deaths on the waiting list were sudden deaths (66.7%). No sudden deaths occurred in ICD patients. Arrhythmia-related nonsudden death occurred in 3.9% of ICD patients. Actuarial total mortality on the waiting list for the entire study population was 16.2%, 24.2%, and 39.4% at 6, 12, and 24 months, respectively. A significant difference that favored ICD patients existed in total mortality between ICD and non-ICD patients (\( P=0.03; \) Figure 1), with a 12-month mortality rate of 13.2% in ICD patients and 25.8% in non-ICD patients.

#### Table 2. Follow-Up and Outcome

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total (n=854)</th>
<th>ICD (n=102)</th>
<th>Non-ICD (n=752)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, mo</td>
<td>4.7</td>
<td>6.8</td>
<td>4.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Transplantation, mo</td>
<td>8.1</td>
<td>9.6</td>
<td>7.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Transplantation, n (%)</td>
<td>487 (57.0)</td>
<td>60 (58.8)</td>
<td>427 (56.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Death on list, n (%)</td>
<td>174 (20.4)</td>
<td>12 (11.8)</td>
<td>162 (21.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sudden cardiac</td>
<td>116 (66.7)</td>
<td>0 (0)</td>
<td>116 (71.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nonsudden cardiac</td>
<td>51 (29.3)</td>
<td>10 (83.3)</td>
<td>41 (25.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>7 (4.0)</td>
<td>2 (16.7)</td>
<td>5 (3.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Still awaiting transplantation, n (%)</td>
<td>42 (4.9)</td>
<td>9 (8.8)</td>
<td>33 (4.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Removed from list, n (%)</td>
<td>151 (17.7)</td>
<td>21 (20.6)</td>
<td>130 (17.3)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*Time values are expressed as median. Mode of death is expressed as percentage of total deaths.

\( P \) for ICD vs non-ICD patients.

\( \chi^2 \) test for continuous variables.

Figure 1. Comparison of total survival between ICD and non-ICD patients on waiting list for cardiac transplantation. Error bars indicate 95% confidence interval. Number of patients at risk in follow-up period is shown in parentheses at selected time points.
No sudden cardiac deaths occurred in ICD patients; sudden cardiac death rate in non-ICD patients increased progressively throughout follow-up and was 12.1%, 20.1%, and 31.7% at 6, 12, and 24 months, respectively (P < 0.0001; Figure 2). In contrast, nonsudden cardiac death rates were similar between ICD and non-ICD patients (P = 0.16; Figure 3).

Multivariate Predictors of Mortality

**Total Study Population**
As shown in Table 3, total mortality was most powerfully predicted by the need for continuous intravenous inotropic support (P = 0.0004). Absence of an ICD (P = 0.02), age (P = 0.03), male sex (P = 0.01), nonsustained ventricular tachycardia in patient history (P = 0.01), and absence of β-blocker treatment (P = 0.04) were also directly related to total mortality.

The most powerful independent predictor of sudden cardiac death was absence of the ICD (P < 0.0001). Absence of β-blocker treatment also was related directly to sudden cardiac death (P = 0.03). Presence of an ICD (P = 0.02) and need for continuous intravenous inotropic support (P = 0.02) were strongest predictors of nonsudden cardiac death.

**ICD Patients**
In ICD patients, total mortality was most strongly predicted by cardiac output (P = 0.002) and pulmonary vascular resistance (P = 0.009; Table 4). Need for continuous intravenous inotropic support (P = 0.03) also was related directly to total mortality in ICD patients.

Discussion
ICD therapy significantly improves survival among patients on the waiting list for cardiac transplantation because it prevents sudden cardiac death.

In patients with end-stage heart failure, cardiac transplantation currently is the only therapeutic option for long-term survival. Sudden cardiac death constitutes a major threat to survival for patients who are awaiting cardiac transplantation. In the present study, sudden cardiac death was the predominant mode of death among patients on the waiting list, accounting for 66.7% of total deaths. Our finding is similar to that of a recent study by Nagele et al.7 Decrease in pump failure death among patients on the waiting list is a result of medical therapy tailored to hemodynamic demands and use of ventricular assist devices as a bridge to cardiac transplantation. As a consequence, a shift from pump failure death to sudden death as the predominant mode of death while on the waiting list for cardiac transplantation.
Waiting list was observed. Therefore, the main aim of ICD therapy while a patient is on the waiting list for cardiac transplantation is short-term survival until transplantation by prevention of sudden cardiac death.

To date, no data are available to support expanded use of ICD therapy to improve overall short-term survival for patients on the waiting list for cardiac transplantation. Previous studies have indicated efficacy of ICD therapy in highly selected patients with malignant ventricular arrhythmias awaiting cardiac transplantation, although the number of patients was low in all studies (n = 14 to 16).11–13 These patients had a high incidence of appropriate ICD discharges, and no patient died suddenly while on the waiting list. In a retrospective analysis, Sweeney et al21 found that ICD therapy in patients on the waiting list for cardiac transplantation (n = 32) improved neither overall nor sudden death–free survival compared with patients with or without antiarrhythmic drug treatment. Grimm et al22 analyzed the influence of ICD therapy on mortality in 228 consecutive patients on the waiting list for cardiac transplantation. They demonstrated a survival benefit of ICD therapy for selected patient subgroups of survivors of sudden cardiac death and patients with high-grade ventricular arrhythmias on Holter ECG. Recommendations for expanded use of ICD therapy in unselected patients on the waiting list could not be given, because the absence of ICD therapy was only a marginally significant predictor of mortality for the entire study population in multivariate analysis.

In the present study, patients who received ICD therapy had a significantly improved survival rate while on the waiting list for cardiac transplantation compared with patients who did not receive ICD therapy. Reduction in mortality rates among patients who had ICD therapy was a result of complete prevention of sudden cardiac death. Multivariate regression analysis demonstrated that absence of an ICD is a powerful independent predictor of sudden cardiac death (P < 0.0001) and total mortality (P = 0.02) among patients on the waiting list. Interestingly, the presence of an ICD developed predictive value for nonsudden death. An explanation is that the elimination of sudden death resulted in nonsudden death as the only possible mode of death in ICD patients, given that sudden and nonsudden death were reciprocally dependent variables in the regression model. Previous studies have indicated that in severe heart failure patients (not listed for transplantation), the survival benefit conferred by the ICD appears to be restricted to the early follow-up period.23,24 Studies have suggested that the risk of pump failure death, which increases over time, may offset the early survival benefit due to the effective prevention of sudden death.25,26 In contrast, among patients listed for cardiac transplantation, progression of heart failure symptoms leads to a higher priority status on the waiting list. Multivariate analysis in the present study also demonstrated that in ICD patients, mortality on the waiting list is predicted by progression of heart failure (ie, increase in pulmonary pressures, low cardiac output, and need for continuous intravenous inotropic support). Consequently, urgent transplantation or implantation of an assist device (in 7 ICD [6.9%] versus 20 non-ICD [2.7%] patients; P = 0.03) may effectively protect ICD patients with hemodynamic deterioration from pump failure death. This is reflected in the fact that we did not observe an increased incidence of pump failure death among ICD patients in the present study. All ICD patients with combined ICD and ventricular assist device therapy had ventricular assist device implantation (6 Novacor, 1 Thoratec) after ICD implantation with refractory hemodynamic deterioration as ventricular assist device indication. One patient experienced multiple ICD discharges under ventricular assist device therapy due to documented ventricular tachycardia. No spontaneous ICD shocks were observed in the other 6 patients with combined ICD and ventricular assist device therapy.

Limitations to the Present Study

The present study has several important limitations; it was retrospective, and treatment of ventricular arrhythmias was uncontrolled and nonrandomized. In addition, baseline variables were not entirely comparable between ICD and non-ICD patients. ICD patients were highly selected; all ICD patients had manifest evidence of a spontaneous arrhythmia. However, imbalances were corrected for in the multivariate model. The exact rhythm at the time of cardiac arrest (tachyarrhythmia or electromechanical dissociation) could not be determined with certainty.

The present analysis demonstrates that the use of ICDs, because it prevents sudden cardiac death, is associated with an improved overall survival rate among patients on the cardiac transplant waiting list. Our analysis also supports the use of ICDs as a bridge to transplantation in patients who are accepted onto cardiac transplant waiting lists and who have had an arrhythmic event that identifies them as being at risk. Finally, the present analysis raises questions regarding the benefit of prophylactic ICD implantation in all patients on cardiac transplant waiting lists that will require evaluation in prospective randomized trials.

References

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