Identification of Patients Most Likely to Benefit From Implantable Cardioverter-Defibrillator Therapy
The Canadian Implantable Defibrillator Study

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Background—Patients with resuscitated ventricular tachyarrhythmias (ventricular tachycardia/ventricular fibrillation) benefit from implantable cardioverter-defibrillators (ICDs) compared with medical therapy. We hypothesized that the patients who benefit most from an ICD are those at greatest risk of death.

Methods and Results—In the Canadian Implantable Defibrillator Study (CIDS), 659 patients with resuscitated ventricular tachyarrhythmias were randomly assigned to receive an ICD or amiodarone and were then followed for a mean of 3 years. There were 98 and 83 deaths in the amiodarone and ICD groups, respectively. We used multivariate Cox analysis to assess the impact of baseline parameters on the mortality in the amiodarone group. Reduced left ventricular ejection fraction, advanced age, and poor NYHA status identified high-risk patients (\(P < 0.0001\) to 0.0009). Quartiles of risk were constructed, and the mortality reduction associated with ICD treatment in each quartile was assessed. There was a significant interaction between risk quartile and the ICD treatment effect (\(P = 0.011\)). In the highest risk quartile, there was a 50% relative risk reduction (95% CI 21% to 68%) of death in the ICD group, whereas in the 3 lower quartiles, there was no benefit. Patients who are most likely to benefit from an ICD can be identified with a simple risk score (\(\geq 2\) of the following factors: age \(\geq 70\) years, left ventricular ejection fraction \(\geq 35\)%, and NYHA class III or IV). Thirteen of 15 deaths that were prevented by the ICD occurred in patients with \(\geq 2\) risk factors.

Conclusions—In CIDS, patients at highest risk of death benefited most from ICD therapy. These can be identified easily on the basis of age, poor ventricular function, and poor functional status. (Circulation. 2000;101:1660-1664.)

Key Words: arrhythmia n death, sudden n survival n trials n risk factors

Sudden cardiac death is a major cause of death and most often is due to ventricular tachyarrhythmias. Three recent randomized clinical trials have provided considerable evidence of increased survival in patients with resuscitated ventricular tachycardia (VT) or ventricular fibrillation (VF) who received an implantable cardioverter-defibrillator (ICD) compared with those who were treated with amiodarone.1–3 The survival difference, however, was small. Given the high cost of ICD therapy, selection of patients most likely to benefit would make this therapy more cost effective.

Given the high cost and invasiveness of the procedure, it is particularly important to determine which patients are likely to benefit most from treatment with ICDs.4–6 In most situations, patients at high risk of events gain the greatest absolute benefit from a treatment because there are more events to prevent. This is true if the treatment works equally well in high- and low-risk patients. Conversely, there is reason to suspect that the ICD might not effect a large risk reduction in older patients with poor left ventricular function because a high competing risk of nonarrhythmic death would overwhelm the effect of the ICD on arrhythmic death.

The Canadian Implantable Defibrillator Study1 (CIDS) involved 659 patients who had a history of resuscitated VT or VF and who were then randomized to receive an ICD or amiodarone. The data from CIDS were analyzed to determine whether high-risk patients were more likely to benefit from treatment with ICDs or from conventional treatment with amiodarone.

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Treatment of VT and VF, like treatment of other disorders, is best targeted to appropriate individuals. The patients in these trials were marked by great heterogeneity in the risk of death and in baseline clinical variables, such as age, left ventricular ejection fraction (LVEF), functional status, burden of coronary artery disease, and presenting symptoms.
TABLE 1. Baseline Risk Factors in Cox Regression Model for All-Cause Mortality in Patients Treated With Amiodarone

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Mean±SD or Prevalence</th>
<th>Risk Coefficient β</th>
<th>SE (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±10</td>
<td>0.041</td>
<td>0.012</td>
<td>0.0005</td>
</tr>
<tr>
<td>Female</td>
<td>16%</td>
<td>0.014</td>
<td>0.28</td>
<td>0.96</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33±14</td>
<td>-0.043</td>
<td>0.010</td>
<td>0.0001</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>25%</td>
<td>0.034</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>10%</td>
<td>1.00</td>
<td>0.30</td>
<td>0.0009</td>
</tr>
<tr>
<td>VF or cardiac arrest</td>
<td>50%</td>
<td>-0.015</td>
<td>0.22</td>
<td>0.95</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>82%</td>
<td>-0.32</td>
<td>0.30</td>
<td>0.28</td>
</tr>
<tr>
<td>Coronary stenosis &gt;70%</td>
<td>30%</td>
<td>-0.10</td>
<td>0.25</td>
<td>0.68</td>
</tr>
<tr>
<td>Any inducible VT or VF</td>
<td>52%</td>
<td>-0.50</td>
<td>0.35</td>
<td>0.16</td>
</tr>
<tr>
<td>Inducible VF or VT &gt;200 bpm</td>
<td>38%</td>
<td>0.40</td>
<td>0.37</td>
<td>0.28</td>
</tr>
<tr>
<td>β-Blockers at discharge</td>
<td>21%</td>
<td>0.34</td>
<td>0.28</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Methods

Overview of CIDS Design

The details of CIDS have been published elsewhere.¹ ¹ There were 659 patients enrolled from 24 centers in Canada, the United States, and Australia. They were eligible for enrollment if, in the absence of acute ischemia or reversible factors, they had (1) documented VF, (2) out-of-hospital resuscitated cardiac arrest, (3) documented VT causing syncope, (4) documented sustained VT at a rate of ≥150 bpm causing presyncope or angina in a patient with LVEF ≤35%, or (5) unmonitored syncope with subsequent documentation of either spontaneous VT ≥10 seconds or inducible sustained monomorphic VT. Patients also could meet criterion 3 or 4 if they had a prior documented sustained VT and inducible sustained monomorphic VT. Among those satisfying the inclusion criteria, patients were excluded if they were judged to have excessive perioperative risk for defibrillator implantation, previous intolerance to, or failure of, amiodarone, previous use of a defibrillator, long QT syndrome, or a medical condition other than VT/VF making survival of >1 year unlikely.

Patients were randomly assigned to receive either amiodarone or an ICD and were enrolled between October 1990 and January 1997. Cointervention with other drugs was allowed in both arms at the discretion of the treating physician. The primary outcome event was death from any cause.

Analytic Approach

The cumulative mortality experiences of the 2 treatment groups were summarized as survival curves (Kaplan-Meier method)⁵ ⁶ based on the intention-to-treat principle. A multivariate risk model for survival in patients treated with amiodarone was used to identify independent predictors of death. This then was used to assign patients to 1 of 4 quartiles of increasing risk. The effect of ICD therapy on the mortality rates in each of the risk quartiles was then computed.

Survival in Amiodarone-Treated Patients

We first forced 11 variables into a Cox multivariate model⁷ ⁸ ⁹ of total survival of the amiodarone-treated patients (Table 1). Age and LVEF were continuous variables, and the remaining variables were included as indicator variables. The description of the NYHA status required 2 variables to distinguish class II from class I and classes III/IV from class I. Similarly, the description of the drug-free inducible arrhythmias required 2 variables. Using the Cox model, we calculated the risk scores for each patient as the weighted sum of the individual predictor variables. The risk scores were expressed as a distribution, and the quartiles of the distribution were identified. Applying the cut points of the quartiles allows one to define the 4 risk strata for both the amiodarone- and ICD-treated patients.

Effect of ICD by Risk Strata

Finally, we computed the mortality rates and estimated the effect of ICD therapy within each stratum. A formal test of homogeneity of treatment effect was performed across all strata.¹⁰

Other Statistical Methods

The determination of a death as a presumed arrhythmic death was according to the criteria of Hinkle and Thaler.¹² Means (±SD) and medians were calculated. Probability values are 2-sided without adjustment for multiple analyses.

Results

Overall Results

There were 331 patients assigned to receive amiodarone and 328 patients assigned to receive an ICD. There were 98 deaths in the amiodarone group and 83 deaths in the ICD group, with yearly risks of mortality of 10.2% and 8.3%, respectively (1P=0.07). There were 43 and 30 presumed arrhythmic deaths in the amiodarone and ICD groups, respectively. Of the 15 excess deaths in the amiodarone group, 13 were presumed to be arrhythmic.

Predictors of Total Mortality in Amiodarone-Treated Patients

The variables tested in the Cox risk model are shown in Table 1. The mean age of the patients was 64±10 years, and the mean LVEF was 33±14%. Sixty-five percent of the patients were in NYHA class I, 25% were in NYHA class II, and 10% were in NYHA class III/IV. Only 3 variables were significant predictors of all-cause mortality in the amiodarone-treated patients (Table 1). These were increasing age (P=0.0005), decreasing LVEF (P=0.0001), and NYHA functional class III or IV (P=0.0009). These 3 risk factors then were incorporated into a Cox model that predicted the risk of total mortality, and the patients were divided into 4 equally sized quartiles of ascending risk of death. This produced a clear gradient of risk across 4 risk quartiles, with little difference between the 2 central quartiles. There were 7, 20, 23, and 48 deaths in the 4 risk quartiles, with annual mortality rates of 2.7%, 7.7%, 8.3%, and 30.1%, respectively (Table 2 and Figure 1).
Effect of ICD Therapy on Survival

The effect of ICD therapy in each of the 4 risk quartiles is shown in Table 2. The largest treatment effect with ICD therapy was in the highest risk quartile, in which there was a 50% relative risk reduction in the patients treated with ICDs (95% CI 21% to 68%). There was no significant treatment effect in the 3 lower risk quartiles, and all had wide CIs. To test whether the treatment effect of the ICD was significantly greater in high-risk patients, we performed a formal test of homogeneity over the 4 quartiles. This was strongly significant at \( P = 0.015 \). There was no significant difference in the ICD benefit among strata 1, 2, and 3 (\( P = 0.14 \)) but a highly significant difference in the treatment effect between the highest risk stratum and the other 3 strata (\( P = 0.011 \)). In the combined 3 lower risk strata, there were 50 and 49 deaths in patients who received amiodarone and ICDs, respectively. In the highest risk stratum, there were 48 and 34 deaths in patients who received amiodarone and ICDs, respectively. Of the 15 excess deaths in the patients who received amiodarone in the entire study, 14 occurred in the highest risk quartile.

These differences in reduction of risk of death by ICD therapy are depicted in the Kaplan-Meier survival curves in Figure 2. In the 3 lower risk quartiles, the yearly death rates were 6.3% and 6.5% in patients receiving amiodarone and ICDs, respectively. In the highest risk quartile, the yearly death rates were 30.1% and 14.4% in patients receiving amiodarone and ICDs, respectively. The relative risk reduction with ICDs was 50% (95% CI 21% to 68%). There was no significant treatment effect in the 3 lower risk quartiles, and all had wide CIs.

Derivation of a Risk Score

Although consideration of risk quartiles helps to understand how ICD therapy is interacting with risk factors, it is of
limited use in clinical situations. We developed a simple risk score indicating the benefit from ICD therapy based on the 3 significant risk factors. The 3 factors were based on the results of the Cox modeling. The 3 factors were age $\geq$ 70 years, LVEF $\leq$ 35%, and NYHA class III or IV. Twenty-five percent of patients had no risk factors, 51% had 1 of the factors, and 24% had 2 or 3 factors. The risk score produces a difference of risk between the groups with 0 to 1 and 2 to 3 risk factors. There were 55 and 53 deaths in patients with $\leq$ 1 factor who were treated with amiodarone and an ICD, respectively. In comparison, there were 43 and 30 deaths in patients with $\geq$ 2 factors ($P=0.18$). There was an 8% (95% CI –35% to 37%) relative risk reduction of death in patients with $\leq$ 1 risk factor who received an ICD and a 29% (95% CI –14% to 55%) relative risk reduction of death in patients with $\geq$ 2 risk factors who were treated with an ICD. Therefore, patients who are more likely to benefit from ICD therapy can be identified by consideration of simple clinical variables.

Discussion

The principal finding of this analysis of the CIDS data is that patients who are most likely to benefit from receiving an ICD are also those at highest overall risk of death. Patients in the highest risk group were older, had poor left ventricular systolic function, and had poor functional status. They can be identified by using a simple risk score: patients who are more likely to benefit are those with at least 2 of the following: age $\geq$ 70 years, LVEF $\leq$ 35%, and presence of NYHA class III or IV. Therefore, although the absolute mortality is highest in this group of older and sicker patients, they also receive the highest benefit from receiving a defibrillator. Patients at lower risk of death, ie, those who are younger and with less functional and systolic impairment, are also less likely to benefit from receiving an ICD.

This has not been reported previously, despite assessment of the effects of covariables on treatment effect in the ICD studies that showed a positive treatment effect.\(^1\text{-}^3,13\) This may be because previous reports used univariate analyses, whereas we chose a multivariate analysis to allow for the interaction of variables. In the main CIDS univariate analysis, neither age, LVEF, nor poor functional status interacted significantly with the treatment effect of ICDs.

As expected, the ICD functioned almost solely to prevent arrhythmic death. It is noteworthy that several clinical variables did not predict increased mortality in patients treated with amiodarone. These nonpredictive factors include markers of hemodynamically unstable ventricular arrhythmias, such as syncope, presenting cardiac arrest or VF, and inducible unstable VT or VF. One explanation for this might lie in the ability of amiodarone to slow the rate of VT. Patients with relatively preserved LVEF might tolerate these slower tachyarrhythmias, whereas patients with reduced ejection fraction would deteriorate rapidly. In contrast, the ability of ICDs to terminate ventricular tachyarrhythmias within seconds would prevent the progression to an unstable and fatal arrhythmia in patients regardless of ejection fraction. This would explain the higher relative risk reduction in patients with reduced ejection fraction and poor functional status. It may also be that the study was underpowered to detect these effects.

These findings were quite unexpected. Not only do they suggest that older sicker patients are most likely to benefit from receiving an ICD, but they also suggest that 75% of patients do not benefit from receiving an ICD as first-line therapy. If confirmed, these findings may have broad implications for the provision of therapy for patients with resuscitated VT/VF. ICD therapy is considerably more expensive than treatment with amiodarone, and detailed cost-effectiveness studies have suggested that ICDs prolong life, with an incremental cost of $27 000 to $114 000 per life-year saved.\(^4\text{-}^6\) These estimates assume that all patients eligible for these studies receive ICDs. In the present study, we show that a subgroup of patients appears to receive virtually all the benefit from ICDs. If so, the cost-effectiveness of treating patients other than those in this subgroup with defibrillators might be very high.

There are particular points of this analysis that require comment. First, we adopted the primary outcome of the main CIDS analysis, which was all-cause mortality rather than presumed arrhythmic mortality. This was for 2 reasons: (1) there were persistent concerns that ICDs might, in some patients, simply change the cause of death from sudden arrhythmic death to nonsudden hemodynamic death; and (2) we also recognized the limitations of the various criteria for presumed arrhythmic death,\(^13\) which have been confirmed by comparing the deemed modes of death by using the Hinkle-Thaler criteria\(^19\) with the recorded terminal electrograms and trend plots in ICDs in patients who died in CIDS.\(^14\) Second, we did not control for interventions, and there may be undetected effects between unselected variables and those in the analysis. Third, these are results from a single study. Although the 3 risk factors achieved a high degree of statistical significance, it is possible that others were missed because of the small sample size, biases inherent in single studies, or other factors inherent in a retrospective analysis of this sort. Despite the high degree of statistical significance of the effect of these findings, the conclusions do require confirmation. Finally, this was not a placebo-controlled trial with a control arm that lacked any treatment. Therefore, we cannot rule out the possibility that some of benefit of the ICD in the CIDS, Antiarrhythmics Versus Implantable Defibrillators (AVID),\(^3\) and Cardiac Arrest Study Hamburg (CASH) studies was due to a harmful effect of amiodarone.

Although it is tempting to speculate that 2 of the factors, poor LVEF and poor functional status, are both markers of an inability to tolerate any recurrent VT, the physiological explanation of the effect of age is not readily apparent. Given that poor LVEF predicted a benefit from ICD therapy in both CIDS\(^15\) and AVID,\(^16\) many physicians might choose to use ICD therapy in patients with VT/VF and diminished LVEF.

Appendix

The following investigators participated in the Canadian Implantable Defibrillator Study: St. Michael’s Hospital, Toronto, Ontario: P. Dorian, D. Newman, J. Mitchell, M. Greene; Hamilton Health Sciences Corp, Hamilton, Ontario: S. Connolly, C. LeFeuvre, J. Kwasney, S. Morino; Institute de Cardiologie de Montreal, Montreal, Quebec: D. Roy, M. Dubuc, M. Talajic, B. Thibault; Calgary General Hospital, Calgary, Alberta: R. Sheldon, M. Koshman;
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