Effect of Clinical Risk Stratification on Cost-Effectiveness of the Implantable Cardioverter-Defibrillator

The Canadian Implantable Defibrillator Study

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Background—Three randomized clinical trials showed that implantable cardioverter-defibrillators (ICDs) reduce the risk of death in survivors of ventricular tachyarrhythmias, but the cost per year of life gained is high. A substudy of the Canadian Implantable Defibrillator Study (CIDS) showed that 3 clinical factors, age ≥ 70 years, left ventricular ejection fraction ≤ 35%, and New York Heart Association class III, predicted the risk of death and benefit from the ICD. We estimated the extent to which selecting patients for ICD therapy based on these risk factors makes ICD therapy more economically attractive.

Methods and Results—Patients in CIDS were grouped according to whether they had ≥ 2 of 3 risk factors. Incremental cost-effectiveness of ICD therapy was computed as the ratio of the difference in mean cost to the difference in life expectancy between the 2 groups. Over 6.3 years, the mean cost per patient in the ICD group was Canadian (C) $87 715 versus $38 600 in the amiodarone group (C$1 = US$0.67). Life expectancy for the ICD group was 4.58 years versus 4.35 years for amiodarone, for an incremental cost-effectiveness of ICD therapy of C$213 543 per life-year gained. The cost per life-year gained in patients with ≥ 2 factors was C$65 195, compared with C$916 659 with < 2 risk factors.

Conclusions—The cost-effectiveness of ICD therapy varies by patient risk factor status. The use of ICD therapy in patients who have ≥ 2 risk factors of age ≥ 70 years, left ventricular ejection fraction ≤ 35%, and NYHA class III is C$65 195 to gain a year of life. (Circulation. 2001;104:1622-1626.)

Key Words: cost-benefit analysis ■ defibrillation ■ cardioversion ■ trials

Three recent randomized clinical trials demonstrated that implantable cardioverter-defibrillator (ICD) therapy is associated with a 28% relative reduction in the risk of death (P = 0.0006) compared with amiodarone in patients with resuscitated ventricular tachycardia (VT) or ventricular fibrillation (VF).1-4 However, defibrillator therapy comes with a substantial cost. The incremental cost-effectiveness ratio (ICER) of ICD therapy in the Canadian Implantable Defibrillator Study (CIDS) was $213,543 Canadian (C) dollars per life-year gained [approximately (US) $145 209].5 This estimate is not attractive by currently accepted standards and indicates the need to identify patient subgroups in which ICD therapy is more economically attractive.

We reported a method of risk stratification that separated patients into 4 levels of risk of death according to the baseline clinical factors of left ventricular ejection, age, and functional status.6 The benefit from ICD therapy was highest in patients at highest risk of death,6 that is, patients who had at least 2 of 3 risk factors: age ≥ 70 years, left ventricular ejection fraction (LVEF) ≤ 35%, and New York Heart Association class III. Accordingly, the ICER for ICD therapy might be more attractive in patients with the highest risk of death as assessed by clinical risk stratification. The purpose of this study was to determine whether the use of ICD therapy in patients with ≥ 2 risk factors would be economically attractive by current standards.

Methods

Overview of CIDS

In brief, 659 patients with resuscitated VT/VF or with unmonitored syncope, structural heart disease, and inducible VT/VF were randomly assigned to receive initial therapy with an ICD (n = 328) or amiodarone (n = 331) between October 1990 and January 1997. The annual risk of death from any cause in patients treated with an ICD or amiodarone was 8.3% compared with 10.2% (2P = 0.14); arrhythmic deaths were 3.0% compared with 4.5% per year in patients treated with an ICD or amiodarone (2P = 0.09). A meta-analysis of
all-cause death from the 3 ICD secondary prevention trials shows that the results of CIDS are no different to those of Antiarrhythmics Versus Implantable Defibrillators (AVID) and Cardiac Arrest Study Hamburg (CASH).4

Cost-Effectiveness Analysis
The main economic substudy of CIDS was previously reported4 and consisted of a prospective cost-effectiveness analysis of 430 (65%) of the 659 randomly assigned patients. The study viewpoint was that of a Canadian provincial government health care payer. We collected patient-specific data on length of hospital stay (ward and intensive care), ICD implants and generator replacements, cardiac surgical procedures, outpatient physician visits, and diagnostic procedures. Resource data were collected at the time of random assignment; at 2 and 6 months after random assignment; and every 6 months thereafter. Price weights for hospital resources, including ICD implantation, were from a patient-level–itemized costing system known as the Ontario Case Costing Project5,6 derived from a large teaching hospital in southwestern Ontario that was a participant in CIDS. Costs for ICD generators and leads were based on current Canadian market prices and Ontario Ministry of Health reimbursement levels. Physician services for procedures were estimated with the use of relevant physician fee codes from the Ontario Health Insurance Program.7 Amiodarone costs were based on hospital pharmacy acquisition costs. All costs are reported in 1999 Canadian dollars; the approximate currency conversion factor is $1 = US$0.67.

Effectiveness was defined in terms of the gain in years of life associated with ICD therapy during the trial in the entire study population of 659 patients. Gain in life expectancy was measured as the difference in mean survival times from the Kaplan-Meier survival curves and is analogous to taking the difference between the areas under the survival curves for the two treatment groups.8 A fixed duration of follow-up was taken for the life expectancy and cost comparisons and was set at 2310 days (6.3 years), which was the time from random assignment to the last observed death.

Statistical Methods
We computed the difference in the mean cost and mean survival per patient between treatment groups. To determine the cost-effectiveness of ICD therapy, we computed the ICER, which is the ratio of the difference (ICD versus amiodarone) in mean cost (economic study subsample) to the difference in life-years gained (full CIDS sample). The resampling technique of bootstrapping9,10 was used to estimate the 95% confidence intervals of the incremental cost-effectiveness ratio. Expected cost and life-year estimates were adjusted for censoring10,11 and discounted at an annual rate of 3%.

Subgroup Analyses
First, we estimated the ICER in patients with 0, 1, 2, or 3 of the risk factors that we have previously reported to predict a benefit from ICD therapy.4 These risk factors were age ≥70 years, LVEF ≤35%, and NYHA functional class III.

Second, we compared the ICERs for 2 groups of patients: a group defined as “unlikely to benefit” (having <2 risk factors) and a “likely-to-benefit” group (having ≥2 risk factors). In the CIDS risk-analysis substudy, we reported that 87% of the deaths were concentrated in the 25% of the population identified with these factors.6

For each subgroup, the uncertainty of the ICER is presented in the form of cost-effectiveness acceptability curve.13 Acceptability curves present the cumulative probability of an intervention’s ICER ratio as a function of threshold values (λ) for what society might be willing to pay for a life-year. Therefore, from our acceptability curves, the probability that ICD therapy is “cost-effective” (ie, has ICER <λ) can be found for any threshold value of society’s willingness to pay for a life-year gained. The acceptability curves are based on 1000 bootstrapped ICER replicates generated for each subgroup. For each subgroup, we also calculated 95% confidence intervals for ICERs on the basis of the 1000 bootstrapped ICER replicates.

Sensitivity analysis was performed to explore the robustness of the cost-effectiveness estimates. We estimated ICERs while varying the discount rate, the cost of ICD devices, and the length of hospital stay for implantation. To examine the cost-effectiveness of ICD therapy over a longer time frame, the survival and cost data were modeled out to 12 years with 3 survival assumptions. To implement each assumption, exponential survival curves were fitted for both the ICD and amiodarone groups, with the use of the observed survival data:

(1) Benefit continues: Survival curves continue to diverge. Exponential models were fitted to the observed survival data ($R^2 > 0.9$) with constant annual mortality rate of 8.3% (ICD) and 10.2% (amiodarone).

(2) Benefit equivalent: Survival curves remain parallel. Beyond the trial, the ICD group is assumed to have the same annual mortality rate (10.2%) as the amiodarone group, so survival curves are parallel, and no further treatment effect accrues.

(3) Benefit declines: The survival curves converge. Beyond the trial, the ICD group is assumed to have a higher annual mortality rate (12.4% per year) such that cumulative survival is equal at 12 years.

Life expectancy was calculated as the area under the survival curves (observed and extrapolated) under each survival benefit assumption. To estimate costs for extrapolation beyond the trial, the mean monthly follow-up costs (excluding initial hospitalization) conditional on survival were estimated for each treatment group, based on the trial data. These costs were weighted by the survival probabilities at the beginning of each month determined by each of the 3 benefit assumptions.

Results
Of the 659 patients in CIDS, there were 168 patients with no risk factors, 331 patients with 1 risk factor, 145 patients with 2 risk factors, and 15 patients with 3 risk factors (Table 1). Patients with more risk factors were older, had lower LVEF, and had reduced functional status. Total costs were similar in patients who were randomly assigned to receive an ICD in each of the 4 clinical risk groups and were similar in patients who were randomly assigned to receive amiodarone in each of the 4 groups (Table 1). Total costs were higher in patients who were randomly assigned to receive an ICD.

Patient survival was shorter in those with more risk factors, regardless of treatment assignment.6 There were larger absolute and relative benefits and a relative lower cost per life-year gained associated with ICD therapy in patients with more risk factors. The overall (base) cost was C$213 543 per life-year gained. The cost per life-year gained for patients with 1, 2, and 3 risk factors was C$238 388, C$96 718, and C$23 344, respectively.

Figure 1 shows the cost-effectiveness acceptability curves for subgroups with 0, 1, 2, and 3 risk factors. For any value of λ (society’s maximum willingness to pay for a life year), it is the subgroup with 3 risk factors in which ICD therapy has the largest probability of being cost-effective (that is, the probability of ICER <λ). If λ is C$100 000, the probability of ICD therapy being cost-effective, expressed as a percentage, is 1%, 9%, 53%, and 88% for the subgroups with 0, 1, 2, and 3 risk factors, respectively.

When the group results were dichotomized according to the presence of <2 or ≥2 risk factors (Table 2), there were 499 patients (76%) who were grouped in the unlikely-to-benefit group and 160 patients (24%) who were grouped in the likely-to-benefit group.6 Although costs were higher in patients assigned to ICD rather than to amiodarone therapy, there was little variation in cost per patient when stratified by...
risk groups. ICD treatment increased life expectancy by 0.06 years compared with 0.66 years in patients in the unlikely-to-benefit and likely-to-benefit groups, respectively. The cost per life-year gained was $916 659 in the subgroup with ≥2 risk factors and $65 195 in the subgroup with <2 risk factors. The 95% confidence intervals of the ICER in all subgroups included cost-effect pairs in which ICD is dominated (ICD more costly and less effective).

Figure 2 presents the acceptability curves for subgroups with <2 and ≥2 risk factors. If λ is $100 000, the probability of ICD treatment being cost-effective is 1% and 73% for the subgroups with <2 and ≥2 risk factors, respectively. For the λ value of $200 000, the probability that ICD treatment is cost-effective is 16% and 86% for the 2 subgroups. For the λ of $50 000, the probability of ICD treatment is cost-effective is 0% and 29% for the subgroups with <2 and ≥2 risk factors, respectively.

To explore the robustness of these cost-effectiveness estimates, we performed sensitivity analyses (Table 2). Increasing and decreasing direct ICD costs to $26 000 and $16 000, respectively, had little effect on the relative difference in ICERs between the groups. For example, the cost per life-year gained in the subgroup with <2 risk factors for direct

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**TABLE 1. Baseline Characteristics, Overall Treatment Costs, and Survival in Patients Grouped According to The Number of CIDS Risk Factors**

<table>
<thead>
<tr>
<th>No. of Risk Factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>168</td>
<td>331</td>
<td>145</td>
<td>15</td>
</tr>
<tr>
<td>ICD</td>
<td>92</td>
<td>163</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>76</td>
<td>168</td>
<td>78</td>
<td>9</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>59 (8)</td>
<td>62 (10)</td>
<td>70 (8)</td>
<td>75 (4)</td>
</tr>
<tr>
<td>LVEF, %, mean (SD)</td>
<td>50 (11)</td>
<td>30 (12)</td>
<td>26 (8)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>33</td>
<td>41</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>67</td>
<td>54</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>5</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Mean cost per patient, C$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>85 495</td>
<td>91 756</td>
<td>81 976</td>
<td>73 278</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>36 502</td>
<td>39 304</td>
<td>39 192</td>
<td>33 651</td>
</tr>
<tr>
<td>Difference</td>
<td>48 992</td>
<td>52 452</td>
<td>42 784</td>
<td>39 628</td>
</tr>
<tr>
<td>Mean survival per patient, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>5.00</td>
<td>4.64</td>
<td>3.91</td>
<td>3.51</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5.40</td>
<td>4.42</td>
<td>3.47</td>
<td>1.81</td>
</tr>
<tr>
<td>Difference</td>
<td>−0.40</td>
<td>0.22</td>
<td>0.44</td>
<td>1.70</td>
</tr>
<tr>
<td>Cost per life-year gained, C$ (95 CI)</td>
<td>(488 138, dom)</td>
<td>(75 825, dom)</td>
<td>(31 456, dom)</td>
<td>(6345, dom)</td>
</tr>
</tbody>
</table>

Factors are age ≥70 years, LVEF ≤35%, and NYHA class III. The treatment effect of ICD therapy vs amiodarone therapy in an intention-to-treat analysis was heterogeneous (P = 0.011). There were no significant differences in costs among groups.

dom indicates that ICD therapy is dominated by amiodarone therapy (ICD less effective, more costly).

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**Figure 1.** Acceptability curves for subgroups of patients with 0, 1, 2, and 3 risk factors. ICER indicates incremental cost-effectiveness ratio; λ, society’s maximum willingness to pay for a life-year.

**Figure 2.** Acceptability curves for subgroups of patients with <2 and ≥2 risk factors. ICER indicates incremental cost-effectiveness ratio; λ, society’s maximum willingness to pay for a life-year.
TABLE 2. Incremental Cost per Life-Year Gained in Patients Grouped According to CIDS Risk Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity Analysis, Cost per life-year gained, C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD costs</td>
<td>$26 000</td>
</tr>
<tr>
<td></td>
<td>$16 000</td>
</tr>
<tr>
<td>Length of initial stay (ICD)</td>
<td>15 d</td>
</tr>
<tr>
<td></td>
<td>10 d</td>
</tr>
<tr>
<td></td>
<td>5 d</td>
</tr>
<tr>
<td></td>
<td>1 d</td>
</tr>
<tr>
<td>Discount rate per year</td>
<td>0% effects, 3% costs</td>
</tr>
<tr>
<td></td>
<td>6% effects, 6% costs</td>
</tr>
<tr>
<td>Extrapolation to 12 y</td>
<td>Benefit continues</td>
</tr>
<tr>
<td></td>
<td>Benefit equivalent</td>
</tr>
<tr>
<td></td>
<td>Benefit declines</td>
</tr>
</tbody>
</table>

Treatment with an ICD provided a 29% risk reduction in death in patients with ≥2 risk factors (CL 14%, 55%) and no significant effect in patients with <2 risk factors. To test the robustness of the estimates, we varied the initial ICD costs, the length of the initial hospital stay in patients who received an ICD, the discount rates, and the persistence of the benefit of ICD therapy compared with amiodarone therapy. n indicates number of patients. Costs are in Canadian dollars. dom indicates that ICD therapy is dominated by amiodarone therapy (ICD less effective, more costly).

ICD costs of $26 000 and $16 000 were $992 237 and $828 569, respectively. Similarly, varying the length of hospital stay in the ICD group between 1 and 15 days did not alter the conclusions. Finally, varying the discount rates for both effects and costs did not change the relative difference between the subgroup with <2 risk factors and the subgroup with ≥2 risk factors. To evaluate the sensitivity of the ICER estimates to whether the relative benefit of ICD therapy continues, is fixed, or declines, we extrapolated the costs and effectiveness to 12 years under each of these conditions. Regardless of the assumption about the persistence of relative benefit of ICD therapy, there is an 8- to 10-fold-higher cost-effectiveness ratio for ICD therapy in the subgroup with <2 risk factors. In the sensitivity analysis, we found no conditions under which ICD therapy had a cost per life-year gained < $320 000 in the subgroup with <2 risk factors and no conditions under which ICD therapy had a cost per life-year gained > $72 000 in the subgroup with ≥2 risk factors. Therefore baseline clinical factors that identify patients at high risk for death also identify patients with the lowest incremental cost-effectiveness ratios for ICD therapy.

Discussion

Taken together, 3 randomized, clinical trials have shown that the ICD significantly reduces the likelihood of death in these patients in comparison to medical therapy. However, the widespread adoption of ICD therapy may be limited by the cost of this therapy. The incremental cost-effectiveness of ICD therapy in CIDS was C$213 543 per life-year gained. By contemporary benchmarks of cost-effectiveness, this would not be considered value for money.

ICD therapy should be more economically attractive if it is targeted to those more likely to benefit. This could be accomplished by targeting ICD therapy in patients most likely to benefit from it. Risk stratification analyses from the CIDS, the AVID, and the Multicenter Automatic Defibrillator Implantation Trial (MADIT) studies consistently show that the relative benefit of ICD therapy over medical therapy is greatest in the sickest patients. In AVID, there was no incremental benefit from ICD therapy in patients with an LVEF ≥ 35%, and in MADIT the benefit from ICD therapy was mainly in patients with an LVEF ≤ 25%. The cardioverter-defibrillator secondary prevention meta-analysis suggested that the benefit from ICD treatment might be concentrated in patients with reduced LVEF. A risk-stratification analysis in CIDS showed that >90% of the incremental benefit of ICD therapy was in the 25% of patients who had at least 2 of the 3 risk factors of age ≥ 70 years, LVEF ≤ 35%, and NYHA class III. Use of a dichotomous score of ≥2 risk factors identified the patients who would benefit from ICD therapy with 87% sensitivity and 98% specificity in CIDS and 79% sensitivity and 91% specificity in AVID. The benefit of the ICD was concentrated in 25% of patients in CIDS and in 31% of patients in AVID. Patients with ≥2 risk factors in both the CIDS and AVID studies had ≈ 50% reductions in the likelihood of death with ICD therapy, whereas the remaining patients were unlikely to benefit from ICD therapy over medical therapy.

Here we performed a cost-effectiveness analysis of patients in the CIDS who were at low or high risk of death, based on these 3 baseline parameters. This analysis shows that the incremental cost-effectiveness of ICD therapy in patients with ≥2 risk factors was C$65 195 compared with C$916 659 in patients with <2 risk factors. Thus, the incremental cost-effectiveness of ICD therapy in patients with ≥2 risk factors compares well with other generally accepted treatments such as hypertension therapy, cardiac transplantation, and the use of statins for isolated hyperlipidemia. However, these results should only be used to determine whether more resources ideally should be put toward a particular treatment and need to be considered within a framework that accounts for lost funding for other treatments in a world of fixed resources.
Limitations
This is a retrospective analysis from a single study. These conclusions require confirmation in the AVID and CASH trials. This study was exploratory and only indicates where new information about specific subgroups might be helpful. Zipes\textsuperscript{26} suggested a similar focus on specific subgroups and reviewed the limitations of the CIDS. We adopted the primary outcome of the main CIDS analysis, which was all-cause death. The ICD might, in some patients, simply change the cause of death from sudden arrhythmic death to nonsudden hemodynamic death. Furthermore, there are limitations to the criteria for presumed arrhythmic death.\textsuperscript{27}

Our Canadian costs may not be directly transferable to other countries, partly because of the differences in cost of health care resources and partly because of differences in practice patterns and resources used. For Canada-United States comparisons, it is important to note that our data relate to costs, not changes,\textsuperscript{28} the latter being usually higher. Furthermore, because we are taking differences in costs between ICD and medical therapy, these incremental differences may be applicable elsewhere.

Importantly, although the risk-stratification study showed increased relative benefit from ICD therapy in older and sicker patients, there is likely to be a limit to the ability to help aged or gravely ill patients. There were few octogenarians in the CIDS study, and it also might be that study investigators did not enroll the sickest patients. Therefore, although the reported risk stratification has internal validity and performed generally similarly in the AVID study, it may not be applicable to very aged or very ill patients.

In conclusion, ICD therapy relative to best medical therapy is more economically attractive when treating patients with ≥2 risk factors of ≥35%, age ≥70 years, and NYHA functional class III compared with treating patients with <2 of these risk factors.

Acknowledgments
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References
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