Cost-Effectiveness of the Implantable Cardioverter-Defibrillator
Results From the Canadian Implantable Defibrillator Study (CIDS)

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Background—In the Canadian Implantable Defibrillator Study (CIDS), we assessed the cost-effectiveness of the implantable cardioverter-defibrillator (ICD) in reducing the risk of death in survivors of previous ventricular tachycardia (VT) or fibrillation (VF).

Methods and Results—Healthcare resource use was collected prospectively on the first 430 patients enrolled in CIDS (n=212 ICD, n=218 amiodarone). Mean cost per patient, adjusted for censoring, was computed for each group based on initial therapy assignment. Incremental cost-effectiveness of ICD therapy was computed as the ratio of the difference in cost (ICD minus amiodarone) to the difference in life expectancy (both discounted at 3% per year). All costs are in 1999 Canadian dollars (C$1 ≈ US$0.65). Over 6.3 years, mean cost per patient in the ICD group was C$87 715 versus C$38 600 in the amiodarone group (difference C$49 115; 95% CI C$25 502 to C$69 508). Life expectancy for the ICD group was 4.58 years versus 4.35 years for amiodarone (difference 0.23, 95% CI 0.09 to 0.55), for incremental cost-effectiveness of ICD therapy of C$213 543 per life-year gained. ICD benefit was greater in patients with low left ventricular ejection fraction (<35%), and cost-effectiveness in this group was more attractive (C$108 484). Alternative extrapolations of survival benefit and costs to 12 years indicated cost-effectiveness in the range of C$100 000 to C$150 000 per life-year gained.

Conclusions—At C$213 543, the value for the money offered by ICD therapy is not attractive by currently accepted standards. Further research is warranted to identify the indications and patient subgroups for whom ICDs are a cost-effective use of resources. (Circulation. 2001;103:1416-1421.)

Key Words: heart-assist device ■ defibrillation ■ cardioversion ■ tachyarrhythmias ■ cost-benefit analysis

Patients surviving ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) are at high risk of death owing to recurrence of arrhythmia. Although antiarrhythmic drug therapy has been the primary treatment for this patient population, large randomized trials have raised major concerns about the lack of efficacy and proarrhythmic potential of these drugs.1,2 A device alternative to antiarrhythmic drug therapy was developed in the 1980s in the form of the implantable cardioverter-defibrillator (ICD). The ICD continuously monitors the heart, identifies malignant ventricular tachyarrhythmias, and then delivers an electrical countershock to restore normal rhythm. Although early evidence indicated that the ICD was effective in recognizing and terminating episodes of VT/VF, it is only recently that large randomized trials have demonstrated reductions in mortality compared with antiarrhythmic drug therapy.3-5

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Although ICDs may extend survival, their high cost (~$22 000 [Canadian dollars] for the hardware alone) raises questions about the cost-effectiveness of this technology. To estimate the cost per year of life gained with ICD therapy compared with drug therapy with amiodarone, we conducted a prospective cost-effectiveness study as part of a randomized trial, the Canadian Implantable Defibrillator Study (CIDS).

Overview of CIDS
The results from CIDS have been reported previously.3 In brief, 659 patients with resuscitated VF or VT or with unmonitored syncope were randomly assigned to receive initial therapy with ICD (n=328) or amiodarone (n=331). Patient enrollment occurred between October 1990 and January 1997. The primary outcome measure was all-cause mortality. The annual risk of death from any cause with

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ICD was 8.3% versus 10.2% with amiodarone \( (P = 0.14) \); arrhythmic deaths were 3.0% per year with ICD and 4.5% per year with amiodarone \( (P = 0.09) \). Although the all-cause mortality reduction in CIDS was not significant at the conventional 5% level, a subsequent analysis of pooled patient-level data on all-cause mortality from the 3 ICD secondary prevention trials (AVID [Antiarrhythmics Versus Implantable Defibrillators], CIDS,\(^4\) and CASH [Cardiac Arrest Study Hamburg])\(^5\) showed that the results of CIDS were not significantly different from those of AVID and CASH and that ICD therapy was associated with a 27% reduction in the risk of death \( (P = 0.002) \) compared with amiodarone.\(^6\)

**Cost-Effectiveness Substudy**
The economic substudy was designed to collect prospective data on resource utilization on all of the first 400 patients randomized, which was the target sample size of CIDS at initiation. Because of a change in the primary outcome from arrhythmic death to all-cause mortality, CIDS recruitment and funding was extended to a target of 650 patients, but no data were collected on resources for the additional 200 patients owing to limited funding. Hence, of the total 659 patients in CIDS, the first 430 (65%) recruited are the subject of our economic analysis, and of these patients, 212 received initial therapy with ICD and 218 with amiodarone.

**Measurement of Resource Utilization**
The study viewpoint was a (provincial) government healthcare payer. We collected patient-specific data on length of hospital stay (ward and intensive care); ICD implants and generator replacements; and cardiac surgical procedures, major diagnostic procedures, outpatient physician visits, and diagnostic procedures. Resource use was collected at baseline (randomization), 2 months, 6 months, 12 months, and every 6 months thereafter.

**Valuation of Resources**
Price weights for hospital resources, including ICD implantation, are from a patient-level itemized costing system known as the Ontario Case Costing Project\(^8,9\) (specifically, from a large teaching hospital in southwest Ontario that was a CIDS investigating hospital). 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 costed using relevant physician fee codes from the Ontario Health Insurance Program.\(^10\) Study drugs such as amiodarone were costed based on hospital pharmacy acquisition cost. All costs are reported in 1999 Canadian dollars, and the approximate currency conversion factor is C$1 = US$0.65.

**Life Expectancy**
Effectiveness was defined in terms of the gain in years of life associated with ICD therapy during the trial. Gain in life expectancy was measured as the difference in mean survival times from the Kaplan-Meier survival curves and was analogous to the treatment effect over the 6.3 years of follow-up.\(^11\) A fixed duration of follow-up was taken for life expectancy and cost comparisons and set at 2310 days (6.3 years), which was the time, from randomization, of the last observed death in either group.

**Statistical Methods**
We computed the difference in the mean cost per patient between treatment groups; because cost data were nonnormally distributed, a 95% CI was estimated by the resampling technique of bootstrapping.\(^12,13\) We used the method of Lin et al\(^14\) to adjust expected cost estimates for censoring in follow-up. Standard errors for Kaplan-Meier mean survival times were used to compute a 95% CI for the gain in life expectancy. To determine the cost-effectiveness of ICD therapy, we computed the incremental cost-effectiveness ratio: the ratio of the difference (ICD versus amiodarone) in mean cost (economic study subsample) to the difference in life-years gained (full CIDS sample). Several sources of uncertainty in our estimates were explored: (1) sampling variation was quantified by bootstrap methods to calculate a 95% CI for cost-effectiveness; (2) subgroup analysis was done by left ventricular ejection fraction (LVEF) greater or less than 35%; (3) variation in discount rate was examined; and (4) variation in the cost of ICD devices and hospital length of stay for implantation was explored.

To examine the cost-effectiveness of the ICD over a longer time frame, the CIDS survival and cost data were modeled out to 12 years with 3 different survival assumptions, going from most favorable to the ICD to least:

1. Benefit continues: survival curves continue to diverge. Exponential models were fitted to the observed survival data \( (R^2 = 0.9) \), with constant annual hazard of 8.3% (ICD) and 10.2% (amiodarone).
2. Benefit equivalent: survival curves remain parallel. Beyond the trial, the ICD group was assumed to experience the same hazard rate (10.2%) as the amiodarone group, so survival curves track parallel and no further treatment effect accrues.
3. Benefit declines: survival curves converge. Beyond the trial, the ICD group is assumed to have a higher hazard rate (12.4% per year), such that cumulative survival is equal at 12 years.

The mean monthly cost after initial hospital discharge, by treatment group and weighted by survival probabilities, was used to estimate expected costs beyond the trial. We did not explicitly model the replacement of device generators or the future use of ICDs among patients assigned to amiodarone.

**Results**

**Mortality and Life Expectancy**
In CIDS, there were 98 deaths among 331 patients assigned to amiodarone (10.2% per year) and 83 deaths among the 328 patients assigned to ICD (8.3% per year), a relative risk reduction in all-cause mortality of 19.7% (95% CI \(-7.7\% to 40\%\). Life expectancy (mean survival) over the 6.33 years of follow-up was 4.65 years with amiodarone and 4.91 years with ICD, a difference of 0.26 years. Discounted to present value at 3% per year, this is a gain in survival of 0.23 years (95% CI \(-0.09 to 0.55\) in favor of ICD.

**Resource Utilization and Price Weights**
Table 1 summarizes resources and price weights used for estimating costs. Mean length of initial hospital stay was longer for ICD patients (4.7 days of intensive care plus 12.0 days on the ward, where intensive care comprises a mix of time on monitored ward, step-down facility, and intensive care unit) than amiodarone (2.0 days intensive care, 8.3 days ward). In the 6.3 years after initial hospital stay, there were 708 hospital readmissions among 212 ICD patients (3.3 per patient) versus 584 readmissions in 218 amiodarone patients (2.7 per patient).

At initial hospital stay, 196 ICDs were implanted among 212 patients randomized to receive ICD (92.5%) in our economic substudy, and 2 ICDs were implanted in the amiodarone group, rate of implantation that are the same as in the total CIDS population. Subsequent to initial hospitalization, there were 73 ICD generator replacements in the ICD group and 4 in the amiodarone group; there were also 36 new ICD implantations in the amiodarone group ("crossovers") and 12 new implants in the ICD group (5 patients who had not received a device at initial hospital stay and 7 patients in whom the ICD was explanted and a new device reimplanted.)

The hospital and physician services cost of implanting an intravenous ICD were estimated to be C$39 093, of which C$22 000 was the cost of the device. Similarly, a generator...
replacement procedure cost C$29,012, including the device. Only 33 implants (5%) in CIDS were by thoracotomy early in the trial. We therefore decided to cost all implants as intravenous ICD procedures (current practice and 95% of CIDS cases) and used current (rather than historical) prices for all device hardware.

Expected Cost per Patient
Mean costs per patient are presented in Table 2. The initial hospital cost was greater in patients assigned to ICD (C$48,874) than in those given amiodarone (C$7,927), a difference of C$40,948 (95% CI C$38,457 to C$43,374). The main factors contributing to this cost difference were ICD implantation costs (C$36,142 versus C$359) and hospital stay (C$10,583 versus C$5,875) for the ICD and amiodarone groups, respectively. Including follow-up costs over the 6-year period, the cumulative expected cost per patient was C$87,715 for ICD and C$38,600 for amiodarone, a difference of C$49,115 (95% CI C$25,502 to C$69,508). The distribution of cost by follow-up time for both treatment groups is shown in the Figure.

Incremental Cost-Effectiveness
The incremental cost-effectiveness of ICD therapy is C$213,543 per life-year gained (Table 3), this being the additional cost (C$49,115) divided by the gain in life expectancy (0.23 years). The lower bound of the bootstrap 95% CI for cost-effectiveness is C$88,187 per life-year gained; the upper bound is arbitrarily large because the confidence interval includes a region in which amiodarone is dominant (less costly and more effective).

Sensitivity Analyses and Extrapolations
As shown in Table 4, if the cost of the ICD hardware were C$16,000 (rather than C$22,000), the cost-effectiveness would fall to C$191,929 per life-year gained. Our observed length of hospital stay for initial ICD implantation reflects practice during the 1990s, and this stay has been declining; however, the sensitivity analysis shows that even at an extreme value of 1-day stay, ICD cost-effectiveness is still high at C$170,284 per life-year gained. When costs are discounted to present value at 3% per year but effects are not discounted, then cost-effectiveness is C$191,383. In the CIDS-AVID-CASH pooled analysis,7 the treatment-by-subgroup interaction on LVEF was significant (P=0.01); in Table 4, we show that cost-effectiveness in CIDS by LVEF ≥35% is C$108,484, with amiodarone being dominant (less costly, more effective) in patients with LVEF ≥35%. Finally, Table 4 also shows the results of our 3 extrapolations of survival and cost to 12 years, and these indicate that cost-effectiveness is in the range of C$100,000 to C$150,000 per life-year gained, depending on the assumed duration of the treatment benefit.

Discussion
In this prospective economic evaluation, conducted within a randomized trial comparing ICD and amiodarone, we calculated the additional cost per patient assigned to ICD over a period of 6.3 years and the gain in life expectancy and found the incremental cost-effectiveness to be C$213,543 per life-year gained (≈US$145,209). By contemporary benchmarks of cost-effectiveness, this would not be considered good value for money.15 Our study also indicates that there are key areas of uncertainty and variability in this estimate of cost-effectiveness.
effectiveness; the data should be interpreted in the context of other ICD studies and with careful attention to limitations and potential biases.

Table 5 summarizes the cost-effectiveness estimates from the CIDS, AVID, and MADIT (Multicenter Automatic Defibrillator Implantation Trial) trials. Our data are similar to a preliminary report on cost-effectiveness from the AVID trial. The AVID study, like CIDS, was in secondary prevention and randomized 1013 VT/VF survivors to ICD or amiodarone, showing a 31% relative risk reduction in mortality at 3 years \( P = 0.02 \). Over a 3-year time horizon, estimated gain in life expectancy was 0.23 years with an additional cost of C$40,618, for cost-effectiveness of C$169,240 per life-year gained. The AVID cost-effectiveness estimate has several limitations: (1) it is a preliminary estimate based on 87% of patients; (2) it uses hospital charges, which are typically higher than costs; (3) it is based on a short time horizon of only 3 years; and (4) because the trial was stopped early, the resulting estimate of treatment effect is likely to be inflated. The other trial-based ICD economic evaluation is from the MADIT trial in primary prevention, in which 196 survivors of acute myocardial infarction with LVEF \(<35\%\) and inducible VT were randomized to ICD or antiarrhythmic drug therapy. Over a 4-year period, the gain in life expectancy was 0.80 years with an additional cost of C$31,782, for cost-effectiveness of C$39,764 per life-year gained. In summary, both trials of ICD in VT/VF survivors (secondary prevention) estimate cost-effectiveness to be in excess of C$150,000 per life-year gained, whereas in primary prevention for those at high risk of arrhythmic death, the cost-effectiveness is more attractive at C$39,764 per life-year gained, largely because the survival benefit was 3 times greater than in the secondary prevention trials.

Secondary analyses from AVID, MADIT, and CIDS all indicate that patients with lower LVEF have a greater survival benefit from ICD therapy than those with better left ventricular function. This finding that “the sickest patients benefit the most” has important implications for cost-effectiveness and patient selection for ICD therapy. In the sensitivity analysis of our economic evaluation (Table 4), we showed that patients with LVEF \(<35\%\) had cost-effectiveness of C$108,484 per life-year gained, whereas in

<table>
<thead>
<tr>
<th>TABLE 2. Mean Costs per Patient by Treatment Group (3% Discounting and Adjusted for Censoring)</th>
<th>Mean Cost per Patient, C$</th>
<th>Difference, * C$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICD (n=212)</strong></td>
<td><strong>Amiodarone (n=218)</strong></td>
<td>(n=212)</td>
</tr>
<tr>
<td>Initial hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (excluding procedures)</td>
<td>10,583</td>
<td>5,875</td>
</tr>
<tr>
<td>ICD implantation costs</td>
<td>36,142</td>
<td>39</td>
</tr>
<tr>
<td>Other tests and procedures</td>
<td>2,138</td>
<td>1,564</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11</td>
<td>129</td>
</tr>
<tr>
<td>Total initial hospital costs (95% CI)</td>
<td>48,874</td>
<td>79,27</td>
</tr>
<tr>
<td>Follow-up costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (excluding procedures)</td>
<td>19,696</td>
<td>16,032</td>
</tr>
<tr>
<td>ICD implantation costs</td>
<td>2,442</td>
<td>6,553</td>
</tr>
<tr>
<td>ICD generator replacement</td>
<td>13,142</td>
<td>788</td>
</tr>
<tr>
<td>Emergency room costs</td>
<td>1,593</td>
<td>2338</td>
</tr>
<tr>
<td>Outpatient visits/procedures</td>
<td>93</td>
<td>72</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1031</td>
<td>4419</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs</td>
<td>491</td>
<td>119</td>
</tr>
<tr>
<td>Total cost per patient (95% CI)</td>
<td>87,715</td>
<td>38,600</td>
</tr>
</tbody>
</table>

*ICD minus amiodarone.
patients with LVEF $\geq 35\%$, there is no mortality benefit and amiodarone therapy is more cost-effective. In patients for whom benefits are greater, the cost-effectiveness is more attractive. It is evident from our data that ICD cost-effectiveness is sensitive to the time horizon chosen for the analysis. For a comparison of ICD versus drug therapy, a short time horizon arguably biases against ICD because there is an initial bolus of cost for one group (ICD), but survival benefits accrue over time. To explore this issue, we undertook 3 survival and cost extrapolations using 3 different assumptions: survival curves beyond the trial continue to diverge, track parallel, or converge by year 12. These projections gave extrapolated 12-year cost-effectiveness in the range of C$100 000 to C$150 000 per life-year gained. It should be noted, however, that our extrapolation of costs is simple and does not explicitly model risk functions for recurring resource use, such as generator replacement. Further extrapolative modeling of ICD cost and effect data similar to the work undertaken by Owens et al$^{22}$ would be valuable.

Medical technologies evolve through time, and a challenge for our study was to address the contemporary policy question of ICD cost-effectiveness using data gathered over a period of just over 6 years, when the types of devices and methods for implantation were changing. We chose to use current prices for ICD hardware and costed the implantation procedure as an intravenous procedure even though the first 5% of implants in CIDS were by thoracotomy. Our economic subsyudy sample consisted of the first 430 of the total 659 CIDS patients, and this might also induce some bias against ICD cost-effectiveness because of underlying time trends toward lower lengths of initial hospital stay for ICD implantation and greater intervals between generator replacements. However, our sensitivity analysis on ICD implantation length of stay shows that the initial hospital stay could fall to only 1 day and ICD cost-effectiveness would only fall to C$170 284 per life-year gained. Modeling future generator replacement requirements is important but complex because it is both a function of advances in technology and device firings that relate to indication and patient selection.

Another limitation of our cost-effectiveness study, which also applies to the AVID and MADIT estimates, is that patient benefits are quantified only in terms of survival gains. A more comprehensive analysis would include some preference-based measure of quality of life, such that survival could be adjusted and presented in the form of quality-adjusted life-years (QALYs).$^{23}$ The quality-of-life data that were collected within CIDS indicated that patients assigned to ICD had better functioning on 5 of the 7 domains of the Nottingham Health Profile.$^{24}$ On this basis, we anticipate that the cost per QALY for ICDs would be lower (more attractive) than the cost per life-year.

In conclusion, our estimates of the cost-effectiveness of ICD therapy bring into question whether this technology is good value for the money in survivors of VT/VF. However, ICD therapy appears to be relatively more cost-effective in patients with low ejection fraction, whether as primary or secondary prevention. Estimates of cost-effectiveness are clearly sensitive to the time horizon of analysis, and “within-trial” analyses need to be interpreted

### TABLE 3. Incremental Costs, Effects, and Cost-Effectiveness of ICD Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incremental Cost per Life-Year Gained With ICD, C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic result (base case)</td>
<td>213 543</td>
</tr>
<tr>
<td>LVEF $&lt;35%$</td>
<td>108 484</td>
</tr>
<tr>
<td>LVEF $\geq35%$</td>
<td>Amiodarone dominant*</td>
</tr>
<tr>
<td>Cost of ICD $26 000$</td>
<td>231 137</td>
</tr>
<tr>
<td>Cost of ICD $16 000$</td>
<td>191 929</td>
</tr>
<tr>
<td>Total hospital length of stay, initial ICD implantation, d</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>208 859</td>
</tr>
<tr>
<td>10</td>
<td>195 082</td>
</tr>
<tr>
<td>5</td>
<td>181 306</td>
</tr>
<tr>
<td>1</td>
<td>170 284</td>
</tr>
<tr>
<td>Discount rate per year</td>
<td></td>
</tr>
<tr>
<td>0% effects, 3% costs</td>
<td>191 383</td>
</tr>
<tr>
<td>6% effects, 6% costs</td>
<td>240 760</td>
</tr>
<tr>
<td>Extrapolation to 12 y for 3 different survival assumptions beyond trial</td>
<td></td>
</tr>
<tr>
<td>Benefit continues (survival curves diverge)</td>
<td>99 420</td>
</tr>
<tr>
<td>Benefit equivalent (survival curves parallel)</td>
<td>118 668</td>
</tr>
<tr>
<td>Benefit declines (survival curves converge)</td>
<td>149 710</td>
</tr>
</tbody>
</table>

*Less costly and more effective than ICD therapy.

ND indicates not defined; upper CI limit of cost-effectiveness consistent with amiodarone being less costly and more effective than ICD.

*ICD minus amiodarone group.
with caution. Future work to develop statistical models to extrapolate costs and effects beyond the observed trial data would be valuable.

Acknowledgments

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References

### TABLE 5. Trial-Based ICD Cost-Effectiveness Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>Time Horizon</th>
<th>Gain in Life-Years</th>
<th>Additional Cost per Patient, C$</th>
<th>Cost per Life-Year Gained, C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT</td>
<td>ICD vs conventional therapy</td>
<td>4 y</td>
<td>0.80</td>
<td>31 782</td>
<td>39 764</td>
</tr>
<tr>
<td>AVID</td>
<td>ICD vs conventional therapy</td>
<td>3 y</td>
<td>0.24</td>
<td>40 618</td>
<td>169 240</td>
</tr>
<tr>
<td>CIDS</td>
<td>ICD vs amiodarone</td>
<td>6 y</td>
<td>0.23</td>
<td>49 115</td>
<td>213 543</td>
</tr>
</tbody>
</table>
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