The Cost Effectiveness of Implantable Cardioverter-Defibrillators
Results From the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II

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OBJECTIVES We sought to evaluate the cost implications of the implantable cardioverter-defibrillator (ICD), using utilization, cost, and survival data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II.

BACKGROUND This trial showed that prophylactic implantation of a defibrillator reduces the rate of mortality in patients who experienced a previous myocardial infarction and low left ventricular ejection fraction. Given the size of the eligible population, the cost effectiveness of the ICD has substantial implications.

METHODS Our research comprises the cost-effectiveness component of the randomized controlled trial, MADIT-II, based on utilization, cost, and survival information from 1,095 U.S. patients who were assigned randomly to receive an ICD or conventional medical care. Utilization data were converted to costs using a variety of national and hospital-specific data. The incremental cost-effectiveness ratio (iCER) was calculated as the difference in discounted costs divided by the difference in discounted life expectancy within 3.5 years. Secondary analyses included projections of survival (using three alternative assumptions), corresponding cost assumptions, and the resulting cost-effectiveness ratios until 12 years after randomization.

RESULTS During the 3.5-year period of the study, the average survival gain for the defibrillator arm was 0.167 years (2 months), the additional costs were $39,200, and the iCER was $235,000 per year-of-life saved. In three alternative projections to 12 years, this ratio ranged from $78,600 to $114,000.

CONCLUSIONS The estimated cost per life-year saved by the ICD in the MADIT-II study is relatively high at 3.5 years but is projected to be substantially lower over the course of longer time horizons. (J Am Coll Cardiol 2006;47:2310–8) © 2006 by the American College of Cardiology Foundation

Several clinical trials have shown that implantable cardioverter-defibrillators (ICDs) improve survival in patients with a spectrum of heart disease (1–8). The second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) (5), conducted in 1997 to 2002, had a relatively broad set of inclusion criteria that could have a major impact because 32,000 to 66,000 people in the U.S. annually fit these criteria (9,10). Three studies (10–12) have reported cost evaluations for MADIT-II–type patients, without use of cost information from the trial. This report combines patient outcome and economic data from the U.S. patients in the MADIT-II study and presents an analysis of the cost effectiveness of their ICD therapy.

METHODS

The MADIT-II study. Eligibility requirements for the MADIT-II study included a previous myocardial infarction and a left ventricular ejection fraction ≤30%, with no electrophysiological testing required. Patients were assigned randomly to receive either an ICD or conventional medical therapy (CONV), in a 3:2 ratio; approved ICD devices were those manufactured by Guidant Corporation (St. Paul, Minnesota). The enrollment procedures, clinical follow-up, and results have been described previously (5). The MADIT-II research protocol was approved by the institutional review boards of the enrolling centers; all enrolled patients gave written informed consent. Funding for the study was provided by Guidant Corporation. The authors are solely responsible for the study design, data collection, analysis, and interpretation of results.
The cost-effectiveness analysis was based on 1,095 of the 1,232 patients in the MADIT-II study, namely those from 69 U.S. centers (omitting the five European centers [n = 109], two U.S. centers [n = 14] with grossly incomplete cost data, and 14 additional patients with missing cost data). Of the 1,095 patients, there were 664 in the ICD arm and 431 in the CONV arm; 17 of the former never received an ICD, and 23 of the latter had implantations during the trial. Baseline characteristics of the patients in the cost-effectiveness substudy were much the same as for all patients (5). All-cause mortality was 90 (21%) in the CONV arm and 97 (15%) in the ICD arm (estimated hazard ratio [HR] = 0.677).

Collection of utilization information. Patients were scheduled for follow-up visits at one and three months after randomization, at three-month intervals thereafter, and were contacted by phone during each intervening month. The information gathered at each contact (clinic or phone) included:

- number and duration of physician office visits by specialty
- number and type of outpatient diagnostic tests and procedures and ambulatory surgeries
- dates and hospital name for each emergency room visit and hospitalization
- number and duration of other health care services, including nursing home admissions, physical, speech, or occupational therapies and podiatry
- medications taken since the last clinic visit.

At each office visit or telephone contact, patients reviewed their utilization for any period they missed. Study staff contacted the named hospitals, provided the required patient authorizations, and requested the hospital bills.

Table 1 shows the completeness of the health care utilization data collected for the MADIT-II study. The largest proportion of expenditures was for hospital services with only 17 of 530 (CONV) and 25 of 1,450 (ICD) inpatient hospital bills missing. Similarly, small proportions of other utilization data were not collected. Values for missing data were imputed; for example, when hospital bills were missing, the costs were estimated using length of stay and average cost per day for that admission type.

Calculating costs and charges. The methods used to translate utilization data into costs were those used in Mushlin et al. (13), except that the costs for inpatient physician services were estimated by regression models using data from Medicare inpatient and physician bills. These models generated the predicted ratio of inpatient physician costs to hospital costs for each admission. The physician costs associated with an admission are this predicted ratio multiplied by its hospital costs.

Table 1. Data Completion, by Treatment Arm

| Type                  | CONV (n = 431) Total Follow-Up = 729 yrs | ICD (n = 664) Total Follow-Up = 1,170 yrs | All 
|-----------------------|------------------------------------------|------------------------------------------|-----------------------
|                       | Total* | Incomplete† (%) | Total* | Incomplete† (%) | Percent Service Type of Total Non-Device Costs |
| Hospitalizations      | 530    | 17 (3.21%)       | 1,450  | 25 (1.72%)       | 63.5% |
| Emergency room visits | 256    | 15 (5.86%)       | 454    | 14 (3.08%)       | 0.3%  |
| Physician visits      | 6,338  | 3 (0.05%)        | 10,582 | 0 (0.00%)        | 4.0%  |
| Outpatient tests/procedures | 6,275 | 54 (0.86%)   | 12,548 | 31 (0.25%)       | 3.4%  |
| Medications           | 6,864  | 0 (0.00%)        | 11,215 | 1 (0.01%)        | 25.2% |
| Nursing home stays    | 97     | 1 (1.03%)        | 39     | 0 (0.00%)        | 2.6%  |
| Other (e.g., home health care) | 713   | 68 (9.54%)    | 1,457  | 121 (8.30%)      | 1.0%  |

*Total number of services reported by patients. †Number of services for which a cost could not be assigned or an imputation was used.

CONV = conventional therapy arm of the trial; ICD = implantable cardioverter-defibrillator.
only their survival status was determined at closeout. Their follow-up averaged 44% of the potential number, representing a loss of 2.2% of the total follow-up days in the study.

Arm-specific discounted mean costs and survival times and the resulting incremental cost-effectiveness ratio (iCER) and associated confidence limits were estimated by methods in (15), extended to accommodate differing follow-up times for cost and survival in some patients (16). We re-estimated the iCER by the method used in the MADIT study (17), which is similar to that in Lin et al. (18).

**PROJECTING TO A 12-YEAR TIME HORIZON.** Projecting survival. To project arm-specific survival out to 12 years, using Kaplan-Meier estimates for the first 3.5 years, we used the following life-table method. We determined the average survival probability for each of 12 successive years for a subset of the U.S. population, matched by age and gender to the MADIT-II study population, using published data for the U.S. (19). This survival curve was fit almost perfectly by a quadratic hazard rate model, with hazard rate increasing at an accelerated rate over time (reflecting aging). We assumed that CONV arm patients would likewise have a quadratic hazard rate, proportional to that for the U.S. subpopulation, during the 12-year period. Using the CONV arm data (years 0 to 4), we estimated the conventional arm versus U.S. age-adjusted HR to be 4.54. Equivalently, the CONV arm survival curve is exponential on an accelerated time scale that reflects yearly increases in hazard rates for the matched U.S. subpopulation. This model fit the available data well (with two goodness of fit tests each yielding $p > 0.6$), but projections beyond 3.5 years are speculative.

To project survival in the ICD arm, we used three alternative, but related, methods, depending on the choice of the HR relative to CONV. For each, the HR at year 3.5 was fixed at 0.677, the data-based estimate. The three scenarios for the ICD HR relative to CONV were:

1) ICD1, where HR remains the same as that observed during the trial;
2) ICD2, where HR increases linearly after 3.5 years so that at 12 years ICD survivors have the same risk as do CONV survivors, which is consistent with an assumption that the beneficial advantage of the ICD declines, relative to a CONV population with patients at risk of sudden cardiac death gradually dying off;
3) ICD3, where HR increases faster after 3.5 years so that the survival curves meet at 12 years, which is consistent with an assumption of greater mortality risk among survivors in the ICD arm than in the CONV arm after 7.1 years.

Because of linear changes over the course of time, the ICD2–3 models have cubic hazard rates.

**Projecting costs.** We first conducted regression analyses of monthly patient-specific costs (undiscounted and excluding device, implantation, and replacement costs for ICD-arm patients). The regression model consisted of arm-specific random effects for patients (excluding initial and death costs), and arm-specific fixed effects for costs in the first month and for the six-month period before death. We originally considered more detailed initial costs and death costs, and time trends in monthly costs, but we found these to be small and statistically insignificant.

We then used the fitted regression model to project monthly costs beyond 3.5 years, multiplying the estimated arm-specific monthly costs (discounted) by the estimated probability of survival through that month, using the corresponding survival models. Because time trends could not be identified, cost projections for survivors do not increase with age, except that death costs become more likely with increasing death rates. In the projections, we added in generator replacement costs of $27,414, based on generator and associated medical cost data from 32 early replacements. Replacement costs, appropriately discounted, were assumed to take place at years 5 and 10; to assess sensitivity to this assumption, we considered a 7-year replacement period for the ICD1 scenario.

**Projecting the iCER.** For any time point horizon, the projected iCER is obtained as the differential (ICD minus CONV) projected discounted accumulated cost up to the horizon, divided by the corresponding projected discounted years-of-life saved (YOLS). We limited projections to 12 years because assumptions about long-term survival, ICD effects, and costs become increasingly tenuous the longer the projection, but this period should be long enough to capture much of the potential lifetime implications. (This choice also avoided ending at generator replacement times, multiples of 5 [or 7] years.)

**SUBGROUP AND SENSITIVITY ANALYSES.** We analyzed the following:

1) comparing patients in several clinically significant subgroups;
2) including, for the survival component of the analysis, the 137 patients with no cost data, bringing the total number of patients to 1,232;
3) removal of the costs of electrophysiologic testing from all ICD arm patients (because this generally is not required for an ICD implantation but was recommended in the MADIT-II protocol);
4) reduction of the initial and replacement ICD device costs by 50%.

We examined outlier costs and found them to be reasonably balanced between the two arms. However, 10 patients in the ICD arm had heart transplants whereas none of the patients in the CONV arm did. For these 10 hospitalizations, costs averaged $117,800 but did not constitute the extreme cost hospitalizations, nor was the effect large when averaged over all ICD-arm patients or over all months of follow-up.
RESULTS

Primary analyses. Table 2 summarizes the medical care use and costs for patients in each arm. On average, the device and associated implantation costs for ICD patients who received an implant totaled $32,578. Average monthly costs were higher for ICD patients—including the costs of any device-related adverse events ($1,489 vs. $1,357)—with all utilization categories, particularly inpatient hospital services ($813 vs. $735), contributing to the difference. Costs were substantially higher in the six months before a patient’s death. None of the differences in monthly costs between treatment arms were statistically significant.

Table 3 presents the within-trial results. At 3.5 years, there was a $39,200 (discounted) accumulated cost difference between the two arms. Patients in the ICD arm are expected to live two months longer within 3 years (0.167 discounted YOLS). The iCER was $235,000/YOLS, with a 95% confidence interval of $121,000 to $1,212,000/YOLS, the very large upper limit reflecting the small lower limit on YOLS (0.033 years). The iCER calculated by the alternative methodology (18), as in the MADIT study (17), was $230,000/YOLS. The calculated iCERs over time appear in Figure 1.

Projecting to a 12-year time horizon. Figure 2 displays actual survival for the first 3.5 years and projects it 12 years after randomization for the CONV arm and for the three ICD scenarios described previously. At year 12, projected survival is 25.7%, 19.5%, or 13.4%, depending on the assumptions and the arm; the corresponding YOLS values (discounted) at year 12 are 1.048, 0.871, and 0.665 for ICD1 to ICD3, respectively.

The cost projections are based on a regression analysis of undiscounted monthly cost data that found three cost components: 1) initial month cost (estimated as $10,335, plus device cost of $21,713, for ICD arm patients and $1,142 for CONV arm patients); 2) average monthly costs subsequently ($1,186 for ICD, $1,033 for CONV—with no evidence of increase over time); and 3) 6-month prior-to-death additional costs of $29,236 ($15,130 in the last month, $3,970 and $1,098 in each of for months 2 to 4 and 5 to 6, respectively). Death costs were highly variable and without statistically significant differences between arms, but we used arm-specific monthly costs to achieve a better fit.

Figure 3 displays discounted cumulative costs, actual values until 3.5 years and projected values beyond, based on the same four assumed trajectories. Projected values, based on the regression formulae, also are plotted for the period up to 3.5 years, demonstrating the quality of their fit. Periodic increases in costs for the ICD occur when replacement devices are implanted; otherwise, the increases in the two arms are almost parallel. The three ICD curves largely overlap until year 10. At year 12, discounted cumulative costs were $180,300, $177,400, and $173,700 for the ICD1 to ICD3 scenarios, as opposed to $97,900 for the CONV arm.

Table 3. Accumulated Discounted Costs, Discounted Life Expectancy, and the iCER, at 3.5 Years

<table>
<thead>
<tr>
<th></th>
<th>CONV (n = 431)</th>
<th>ICD (n = 664)</th>
<th>Difference</th>
<th>95% CI†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discounted total costs*</td>
<td>44.9</td>
<td>84.1</td>
<td>39.2</td>
<td>29.9–48.5</td>
</tr>
<tr>
<td>Life expectancy*</td>
<td>2.725</td>
<td>2.892</td>
<td>0.167</td>
<td>0.033–0.301</td>
</tr>
<tr>
<td>iCER†</td>
<td>235</td>
<td>235</td>
<td>121–1,212</td>
<td></td>
</tr>
</tbody>
</table>

*Per patient, within 3.5 years, in thousands of dollars of costs and in years of life expectancy, discounted at 3% p.a. The life-expectancy difference is the years-of-life saved. (Incremental cost-effectiveness ratio (iCER), in thousands of dollars per year-of-life saved; iCER = ratio of differences, (line 1)/(line 2). †Confidence interval (CI) for iCER computed by Fieller’s (16) method, using variances and covariance of the differences.

Table 2. Average Costs and Utilization, by Treatment Arm

<table>
<thead>
<tr>
<th>Type</th>
<th>CONV (n = 431)</th>
<th>ICD (n = 664)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defibrillator Device‡</td>
<td>N/A</td>
<td>$22,284</td>
</tr>
<tr>
<td>Implantation‡</td>
<td>N/A</td>
<td>$10,294</td>
</tr>
<tr>
<td>Average monthly costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (per month)</td>
<td>$1,357†</td>
<td>$1,489†</td>
</tr>
<tr>
<td>Hospital (per month)</td>
<td>$735</td>
<td>$813</td>
</tr>
<tr>
<td>Medications (per month)</td>
<td>$367</td>
<td>$390</td>
</tr>
<tr>
<td>Nursing home (per month)</td>
<td>$24</td>
<td>$49</td>
</tr>
<tr>
<td>Other§ (per month)</td>
<td>$231</td>
<td>$237</td>
</tr>
<tr>
<td>Costs associated with death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average monthly costs for 6 months prior to death</td>
<td>$6,706 (n = 64)</td>
<td>$8,477 (n = 67)</td>
</tr>
<tr>
<td>Hospitalizations‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number per yr</td>
<td>0.80</td>
<td>1.03</td>
</tr>
<tr>
<td>Days per yr</td>
<td>5.28</td>
<td>6.81</td>
</tr>
</tbody>
</table>

*Costs are expressed in 2001 dollars and are not discounted. †Including the costs associated with device-related adverse events on an intent-to-treat basis. There were 262 such events in the ICD arm versus 10 in the CONV arm. ‡For inpatient implantations, implantation costs were estimated by the average costs incurred for implants in one- or two-day admissions. Listed figures are estimates for the 647 ICD arm patients who received implants; when averaged over all 664 ICD arm patients, the cost is $10,030 (multiplying by 647/664). Device costs were based on list prices for the model implanted and are for the 647 patients with implants; when averaged over all 664 ICD arm patients, device costs are $21,713. Device and implantation costs for 23 CONV patients who had ICDs implanted during the trial are included in CONV average monthly costs. §Including physician visits, outpatient diagnostic and therapeutic procedures, ambulatory surgery, and home care. Including only those who survived 6 months past randomization. ¶Excluding one- or two-day admissions for ICD implantations and two days of longer implantation admissions. Abbreviations as in Table 1.
be negative. For each of these four pairs of subgroups, the subgroup with the higher mortality risk had the higher YOLS and lower iCER. However, none of the comparisons of differences between arms within a pair are statistically significant.

Reinstatement of the 137 patients with no cost data led to an estimated iCER of $211,000/YOLS (95% confidence interval $116,000 to $673,000) (16). The reduced iCER and upper confidence limit is due to greater ICD effectiveness found in the European centers and the increased sample size but assumes similar patterns of survival and costs across patient groups with and without cost data.

Removing the costs of initial electrophysiologic studies, for the 506 patients in the ICD arm who had them (average costs = $1,259), reduced the iCER at 3.5 years to $229,000/YOLS, a 2.6% reduction. Reducing ICD device costs by 50% resulted in an iCER of $166,000/YOLS at 3.5 years, a 29% reduction.

**DISCUSSION**

Both the effectiveness and cost-effectiveness results from randomized controlled trials are intended to provide information for clinical policy. The results of this study reveal a dilemma in presenting cost-effectiveness results from such trials. Whereas the effectiveness results are largely self-sufficient, demonstrating that the ICD reduces mortality for the MADIT-II study population, the cost-effectiveness data are more difficult to interpret. The cost and benefit data are observed for a relatively short period, whereas it is lifetime costs and benefits that policymakers need to calculate the true cost effectiveness of an intervention. A further complication is that, for interventions like the MADIT-II study where the incremental costs are largely the result of the initial intervention but benefits continue to accrue, iCER falls rapidly with time horizon (20). Thus, the within-trial iCER is a poor estimate of the lifetime value. This dilemma was not as acute for previous ICD trials because their within-study iCERs were much lower; their projected iCERs were not as significant in interpreting their policy implications (17,21,22). For example, the MADIT study cost for four-year iCER was $27,000/YOLS (17) resulting from a combination of a much greater YOLS and higher costs in the CONV patients. The MADIT-II study results bring both the need for, and uncertainty of, these projections clearly to the fore.

Significant issues are certainly at stake. Implantable cardioverter-defibrillators have been shown to substantially reduce the number of sudden cardiac deaths (1–8), but their costliness makes it essential that they be targeted to populations for whom they confer substantial benefits. Using the Centers for Medicare and Medicaid Services estimates (9) of the MADIT-II study population in the U.S. (55,000 to
65,000 new cases yearly), our 12-year projections of incremental costs ($78,600 to $114,000) suggest additional annual expenditures in excess of $5 billion.

With such large additional expenditures at stake, clinical policymakers, whether physicians making treatment decisions or insurers making coverage decisions, must consider the cost-effectiveness results in their considerations despite their inherent uncertainty. The iCER at 3.5 years, the time horizon for the MADIT-II study, was $235,000/YOLS. The relatively high estimate of the iCER is largely the result of the high initial cost of implantation and the relatively small YOLS, the latter partially reflecting the underlying heterogeneity of the MADIT-II study population and the significant risks of nonarrhythmic death (40% of the classifiable deaths in CONV patients were assigned to other causes) (23). The heterogeneity in response appears clearly in the subgroup analyses. Although the study was not designed for this purpose, these analyses suggest that the iCER is more favorable in higher-risk subgroups. It would be important to confirm this finding in other studies and over a longer time horizon.

Given the limited usefulness of the within-trial iCER in informing policy, we developed three projection scenarios to represent the uncertainties implicit in any attempt to assess the longer term effects of ICD implantation: ICD1, where the protective effect continues unabated—optimistic considering that other causes of death will have an increasing role with aging; ICD2, where it gradually disappears; and ICD3, where the ICD death rate grows to surpass that in the conventional arm—which is pessimistic, with cumulative mortality “catching up” at 12 years (8 years in Weiss et al. [24]). We projected costs as if the data-based regression formula applies into the future. The corresponding iCERS at 12 years ranged from $78,600 to $114,000/YOLS. Given the uncertainties in knowledge currently available, particularly on the long-term survival curve for the MADIT-II study population, there is no guarantee that the “true” iCER would fall in that range.

The BlueCross-BlueShield study (11), a recent revision of it (12), and a recent Duke study (10) provide useful comparisons, using different methodologies applied to previously published MADIT-II study survival results. The BCBS Markov decision model approach (11) was based on the MADIT-II study cause-specific mortality data but with cost data taken from non-MADIT study sources. Lifetime iCER was estimated to be $36,700/YOLS, with corresponding values at 3.5 and 12 years, decreasing from $178,900 to $49,600/YOLS (G. Sanders, personal communication, November 2004). Their model-based 3.5-year iCER was 24% lower than our fully data-based value. Our ICD1 scenario with a seven-year replacement period provides the most direct comparison of their 12-year estimates,
both assuming a continuing protective effect. Their $49,600/YOLS is lower than our estimate ($66,700/YOLS) by a similar proportion (26%).

The recent revision (12) used all-cause mortality, some revision of costs (derived from non-MADIT study sources), and a five-year replacement period, and estimated a $39,000/YOLS lifetime iCER. Their cost projections, for both arms, remain substantially below our patient-based values, with $57,500 (2005 dollars) lifetime costs in the control group substantially lower than even our $97,900 (2001 dollars) at 12 years (and we have not allowed for any increase in costs with aging).

The Duke study (10) was based on up to 15 years of cost and survival data for a MADIT-II study-eligible group of Duke University Medical Center patients. The ICD “comparison group” experience was generated assuming an HR of 0.69 forever and non-ICD costs identical to those for non-ICD patients. Lifetime and 12-year iCERs were

### Table 4. Subgroup Analyses of Cost, Life Expectancy, and iCER, at 3.5 Years

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n*</th>
<th>Cost Difference† (SE)</th>
<th>LE Difference‡ (SE)</th>
<th>iCER</th>
<th>95% CI for iCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 yrs</td>
<td>594</td>
<td>35.3 (4.4)</td>
<td>0.266 (0.104)§</td>
<td>133</td>
<td>71–569</td>
</tr>
<tr>
<td>Age &lt;65 yrs</td>
<td>501</td>
<td>42.9 (7.4)</td>
<td>0.049 (0.079)</td>
<td>870</td>
<td>186–∞</td>
</tr>
<tr>
<td>NYHA functional class ≥II</td>
<td>677</td>
<td>33.2 (7.1)</td>
<td>0.203 (0.093)§</td>
<td>164</td>
<td>70–1,619</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>403</td>
<td>46.1 (7.0)</td>
<td>0.126 (0.099)</td>
<td>366</td>
<td>133–∞</td>
</tr>
<tr>
<td>QRS ≥120</td>
<td>558</td>
<td>46.1 (6.4)</td>
<td>0.235 (0.101)§</td>
<td>196</td>
<td>96–1,219</td>
</tr>
<tr>
<td>QRS &lt;120</td>
<td>527</td>
<td>32.0 (7.4)</td>
<td>0.096 (0.093)</td>
<td>334</td>
<td>95–∞</td>
</tr>
<tr>
<td>BUN &gt;25 mg/dl</td>
<td>337</td>
<td>36.4 (6.8)</td>
<td>0.323 (0.148)§</td>
<td>113</td>
<td>55–967</td>
</tr>
<tr>
<td>BUN ≤25 mg/dl</td>
<td>753</td>
<td>38.6 (5.9)</td>
<td>0.110 (0.071)</td>
<td>353</td>
<td>142–∞</td>
</tr>
<tr>
<td>LVEF ≥25</td>
<td>754</td>
<td>44.3 (4.7)</td>
<td>0.162 (0.085)</td>
<td>274</td>
<td>131–∞</td>
</tr>
<tr>
<td>LVEF &lt;25</td>
<td>341</td>
<td>26.1 (13.0)</td>
<td>0.178 (0.118)</td>
<td>147</td>
<td>3–∞</td>
</tr>
</tbody>
</table>

*Patients with missing baseline information omitted. †ICD minus CONV, in $1,000 (discounted). ‡ICD minus CONV, in years (discounted). §p value <2.5% for testing years-of-life saved (YOLS) = 0 vs. > 0 (YOLS = life expectancy [LE] difference)—i.e., a statistically significant treatment effect. When the YOLS is not significantly positive (and hence the incremental cost-effectiveness ratio (iCER) is not bounded above), the confidence interval (CI) is calculated under an assumption that the true YOLS is positive.

BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SE = standard error of difference; other abbreviations as in Table 1.
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$50,500/YOLS and $79,900/YOLS, respectively. Their 12-year value was almost identical to ours for ICD1 (also with a persisting ICD effect). Applying the mean of the ratios between 12-year and lifetime iCERs of these two studies (1.47) to our 12-year value suggests an estimated lifetime iCER in the $50,000 to $100,000/YOLS range.

Each of these studies assumed identical (nondevice) costs in the two arms, whereas we found higher costs in ICD survivors than in CONV survivors, possibly the result of an excess of hospitalizations for heart failure in the ICD arm (Moss et al. [5]). These discrepancies confirm the difficulties in: 1) basing estimates on data from different source, and 2) long-term extrapolations.

We have not translated into iCERS based on quality-adjusted life-years (QALYs). Some studies have done so somewhat arbitrarily, e.g., in Sanders et al. (12), it was assumed that QALYs averaged 0.80 at baseline with later reductions with aging, resulting in lifetime YOLS being reduced by a factor of 0.73 when converted to QALYs. By contrast, in the MADIT-II study, QALYs at baseline averaged only 0.64 (K. Noyes, unpublished observations, January 2006). Of necessity, iCERS in QALYs will be greater.

Using iCERS as $/QALY rather than $/YOLS leads to values higher than the conventional limit for cost effectiveness ($50,000 to 100,000 per QALY), but it is not clear whether generally accepted medical practices are, or should be, within these limits. For example, the National Heart, Lung, and Blood Institute Adult Treatment Panel III guidelines recommend cholesterol-lowering treatments with iCERS that are substantially higher than $100,000 per QALY (25). Furthermore, these limits have been challenged on conceptual grounds since they have not changed over time with per capita income and medical prices, key determinants of the value of a YOLS (26,27). Clearly, a greater consensus is needed as to a threshold value that would indicate whether or not an intervention is cost effective.

The large uncertainties that policymakers must confront can be reduced with better estimates of the ICD effects on long-term survival and on costs, especially by clinically significant subpopulations. In the interim, policy makers will have to apply the available knowledge for decisions as to how to best use this promising new technology.

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