Cost-Effectiveness of Defibrillator Therapy or Amiodarone in Chronic Stable Heart Failure

Results From the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

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Background—In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), implantable cardioverter-defibrillator (ICD) therapy significantly reduced all-cause mortality rates compared with medical therapy alone in patients with stable, moderately symptomatic heart failure, whereas amiodarone had no benefit on mortality rates. We examined long-term economic implications of these results.

Methods and Results—Medical costs were estimated by using hospital billing data and the Medicare Fee Schedule. Our base case cost-effectiveness analysis used empirical clinical and cost data to estimate the lifetime incremental cost of saving an extra life-year with ICD therapy relative to medical therapy alone. At 5 years, the amiodarone arm had a survival rate equivalent to that of the placebo arm and higher costs than the placebo arm. For ICD relative to medical therapy alone, the base case lifetime cost-effectiveness and cost-utility ratios (discounted at 3%) were $38,389 per life-year saved (LYS) and $41,530 per quality-adjusted LYS, respectively. A cost-effectiveness ratio < $100,000 was obtained in 99% of 1000 bootstrap repetitions. The cost-effectiveness ratio was sensitive to the amount of extrapolation beyond the empirical 5-year trial data: $127,503 per LYS at 5 years, $88,657 per LYS at 8 years, and $58,510 per LYS at 12 years. Because of a significant interaction between ICD treatment and New York Heart Association class, the cost-effectiveness ratio was $29,872 per LYS for class II, whereas there was incremental cost but no incremental benefit in class III.

Conclusions—Prophylactic use of single-lead, shock-only ICD therapy is economically attractive in patients with stable, moderately symptomatic heart failure with an ejection fraction $\geq 35\%$, particularly those in NYHA class II, as long as the benefits of ICD therapy observed in the SCD-HeFT persist for at least 8 years. (Circulation. 2006;114:135-142.)

Key Words: amiodarone ■ defibrillators, implantable ■ heart failure, congestive ■ quality-adjusted life years ■ cost-benefit analysis

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mortality benefit was observed in the amiodarone arm compared with placebo (hazard ratio=1.06). Major secondary end points of the SCD-HeFT included costs and cost-effectiveness. To evaluate these outcomes, we prospectively gathered empirical resource use and cost data and conducted intention-to-treat and cost-effectiveness analyses.
Methods

Patient Population and Primary End Point Comparisons

Between September 1997 and July 2001, the SCD-HeFT randomly assigned 2521 patients, age ≥18 years with New York Heart Association (NYHA) class II or III chronic stable heart failure and a left ventricular ejection fraction ≤35% in equal proportions to placebo, amiodarone (Cordarone, Wyeth-Ayerst Pharmaceuticals, Madison, NJ), or a single-chamber (VVI) ICD programmed to shock-only mode (Medtronic, model 7223, Medtronic, Minneapolis, Minn). By protocol, therapy was initiated in the outpatient setting. Median study follow-up was 45.5 months (range, 24 to 72 months). Most patients (90%) were enrolled in the United States, with 9% in Canada and 1% in New Zealand.

Overview of Economic Analyses

A detailed research plan for the economic analysis of the SCD-HeFT was submitted to the National Heart, Lung, and Blood Institute as a companion RO1 application and was funded in 1997. The study design proposed in our application involved 3 major components: (1) collection of empirical resource use data (all patients) and hospital cost data (US patients), (2) an intention-to-treat comparison of within-study medical costs, and (3) a lifetime cost-effectiveness analysis. The cost-effectiveness analysis used empirically collected study data to make projections of lifetime costs and life expectancy beyond the end of study follow-up. A societal perspective was used, but nonmedical costs were not assessed. Because baseline employment rates were low and no differences in workforce retention by treatment were observed, productivity costs were not included. Both survival and costs were discounted at 3%. All costs were adjusted to 2003 US dollars. Because the survival in the amiodarone and placebo arms was equivalent, cost-effectiveness analysis of amiodarone therapy was not performed. Cost-effectiveness ratios for the ICD arm were expressed as the incremental lifetime costs required to add 1 extra year of life with ICD therapy relative to placebo/medical therapy alone. All patients provided informed consent, and study protocol approval was obtained from each site’s institutional review board. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Measurement of Resource Use and Calculation of Within-Trial Costs

Medical resource use was assessed at each patient contact through the end of the study follow-up and was recorded on the study case report form. Major baseline resource consumption recorded for the protocol ICD implantation included the ICD generator and lead(s), operating room versus catheterization laboratory placement, mode of anesthesia, duration of procedure (ie, time in operating room or catheterization laboratory), time in the hospital, and all perioperative complications. Additional baseline resource consumption available for all patients included hospital admission, days in the hospital, major procedures and diagnostic tests performed, and major complications. Interval data were collected at each follow-up contact on hospitalizations (including length of stay and reason for admission), medical outpatient care (both protocol and nonprotocol), major diagnostic tests, therapy-related and cardiac disease–related complications, medication use, and use of a visiting nurse or home health aides. Custodial care or nursing home stays were also recorded.

Our original research plan called for collection of hospital bills for all patients for the first 2.5 years of study follow-up. This represented the planned minimum follow-up for all patients and allowed us to avoid the problem of censored cost data. Because of a prolonged enrollment period and a change in the minimum follow-up, as well as development of statistical methods to address censored cost data, we altered this plan in 2001 to collect all available hospital bills. Although the study initially involved only US patients, sites in Canada and New Zealand were added to improve enrollment, and these sites did not offer the hospital billing data available from fee-for-service US hospitals. We identified 5550 hospitalizations during the study, of which 495 took place in hospitals outside the United States and 508 took place in institutions in the United States that do not generate a UB-92 bill form (including VA hospitals, rehabilitation facilities, and nursing homes). Of the remaining 4547 US hospitalization episodes, we collected complete hospital billing data for 4330 (95%).

Hospital charges were converted to costs by using department-level cost-to-charge ratios from each hospital’s Medicare Cost Report for the relevant year, and physician fees were estimated from an algorithm based on case report data, using the Medicare Fee Schedule. Outpatient visits and procedures recorded on the case report form were also assigned costs from the Medicare Fee Schedule. Selected outpatient cardiac medications were assigned costs by using prices from the 2003 Red Book.

For patients in whom hospital cost data could not be obtained, we imputed costs by using regression models based on case report form resource use data and collected hospital billing data. The protocol ICD implantation and all follow-up device care related to the SCD-HeFT protocol were provided without cost to study participants. The ICD device tested in the SCD-HeFT is no longer produced. Using a proprietary database of retail ICD costs (IMS Health January 2004 Survey of 350 US hospitals), we assigned a base case cost of $17 500 for the SCD-HeFT protocol VVI-ICD system (including lead). We assumed a base case battery life of 5 years.

The institutional cost component of protocol ICD implants was estimated by using “shadow” hospital bills (ie, bills generated at our request rather than for reimbursement purposes), which we obtained on 244 of 812 ICD patients. Of these, 219 represented uncomplicated, outpatient ICD implantations, as defined by the lack of complications recorded on the case report form. The remaining 25 bills captured complicated ICD implantations, often with subsequent inpatient hospital days. Although generally similar, the groups with and without a shadow bill differed modestly in race and gender. Because the shadow bills were not collected on a random sample, we were uncertain that the estimate of procedural costs they provided was truly representative. Consequently, for uncomplicated ICD implantations, we arbitrarily chose the 75th percentile of the distribution of the costs among the 219 uncomplicated bills as a more conservative estimate than the mean or median of the cost of the implantation procedure for all uncomplicated SCD-HeFT ICD arm implantations. The hospital plus physician cost (exclusive of ICD and leads) estimated for the protocol ICD implants was $4707.

These costs were increased by 25% and 50% in sensitivity analyses to reflect both a more expensive implantation procedure as well as the selection of a more expensive ICD system. For reference, we estimated the average cost of a dual-chamber ICD at $21 760 (IMS survey, January 2004), which represents a 24% increase over the cost of the single-lead system ($17 500). For complicated ICD implantations (as identified in the case report form), a regression model using the 25 complicated bills was developed and then applied to estimate procedure cost, primarily as a function of hospital length of stay.

Within-study, end-of-life generator replacements were also provided without cost to ICD-arm patients, and similar methods were used to assign these costs.

For ICD crossover implantations occurring during follow-up among placebo- and amiodarone-arm patients, we used bill-based costs, when available, derived from charges and cost-to-charge correction factors, as described earlier. When bill-based costs were not available, we assigned device costs identical to those assigned for the baseline device for our base case analysis.

Physician costs of an ICD implantation and all routine follow-up ICD care were estimated by using the Medicare Fee Schedule.

Estimation of Cumulative Within-Trial Costs

A nonparametric partitioned estimator was used to estimate treatment-specific, 5-year medical costs with 6 partitions set to correspond to the intervals of follow-up used to collect economic
data: 3 months, 12 months, 2 years, 3 years, 4 years, and 5 years. Cost data were censored at the time of heart transplantation. The rates of heart transplantation did not differ among treatment groups (P=0.62).

**Estimation of ICD Costs Beyond Empirical Study Follow-Up**

For the period after the end of empirical study follow-up, we assumed in our base case analysis that routine ICD and chronic heart failure follow-up as well as the rates of device replacement with a more expensive ICD system, device-related complications, and device explantation observed during the first 5 years would remain unchanged. This assumption was modified in sensitivity analyses.

**Overview of Lifetime Cost Estimation**

Lifetime estimates of costs were based on an accumulation of the within-trial costs, post-trial long-term costs, and battery replacement costs. We used nonparametric estimates based on the empirical data to model costs within the initial 5 years. For costs after the end of empirical study follow-up, we assumed cost data observed between 12 months and 5 years would provide stable estimates of future costs. The models implicitly account for ICD-related complications observed within the SCD-HeFT follow-up. For our base case analysis, we assumed that this complication rate would be representative of the post–5-year complication rate. For the average ICD patient, this resulted in an $1186/year incremental cost.

**Modeling of Post-Trial Long-Term Costs**

To estimate costs after the initial 5 years, we constructed 2 covariate-specific regression models. The first cost model estimated the medical cost per year under the assumption that the patient survived the year. Data used to construct this model were taken from those patients randomly assigned to either placebo or ICD who survived at least 12 months after random assignment. The model included a treatment-specific intercept term for yearly costs with a linear relation for the covariates: age >65, diabetes, gender, ejection fraction ≤30%, cause of heart failure, NYHA class, QRS duration ≥120 ms, and 6-minute walk distance. Interaction terms for covariates by treatment groups were examined but not included because of a lack of statistical significance at the 0.01 level. Costs for the surviving patients varied on the basis of the patient’s characteristics.

Although an estimated 19.4% of placebo patients crossed over to ICD therapy during follow-up, for purposes of long-term cost estimation, we made the conservative assumption that no placebo patients would receive an ICD after 5 years.

The second model estimated the treatment-specific medical cost within the year of death. For this model, data were obtained from patients who died after the first year of follow-up. To construct a conservative estimate of costs for the placebo patients, we excluded yearly intervals where placebo patients were crossed over to ICD and then died. We made the assumption that deaths occurring after year 5 were similar in costs to deaths observed during this latter portion of the trial. The predicted cost of death for an ICD patient was $28,356 versus $20,714 for a placebo patient (P=0.07).

**Estimation of Life Expectancy**

Because the available follow-up time for the SCD-HeFT cohort is limited, extrapolation of survival beyond the observed study period is made feasible by modeling the hazard rate as a function of a patient’s age rather than as a function of a patient’s time since study entry (as is traditional). This approach, called “age-based” modeling, allows us to make use of all available data in an optimal fashion for extrapolation. Specifically, although the SCD-HeFT cohort has only 5 years of survival time for use in this analysis, the cohort spans more than 70 years of age. Thus, owing to both the broad range of ages and the extensive follow-up of the SCD-HeFT cohort, we have 8447 person-years of observation available for use as the basis for extrapolating observed study survival into life expectancy for each study subject. Despite these extensive data, however, we have some modeling limitations in the older ages and must extrapolate beyond the range of available data. For the SCD-HeFT cohort, we had sufficient data to estimate survival up to age 88 years. Beyond this age, we used the fact that the survival distribution for patients follows a Gompertz distribution, together with an acceleration term from the US life tables, to extrapolate the remaining survival for each study patient.

The age-based modeling approach assumes that the effect of treatment (modeled as a hazard ratio as a function of age) remains constant over time. Changes in this hazard ratio over time could have a profound effect on the lifetime survival estimates. It is therefore important to ensure that the data used for development of the extrapolation model be representative of a stable, chronic state for the cohort of interest. However, a patient’s condition at the time of study enrollment is often not reflective of this stable state (eg, patient presentation may be due to precipitating events, enrollment in a study can be biased toward more stable patients). For this reason, we chose to model the hazard of treatment as a function of time in the early study period and to develop the age-based extrapolation model on a later study period after the hazard of treatment as a function of age had more likely stabilized.

Our choice of time point for conditioning survival for the age-based model was guided by the clinical analysis. The SCD-HeFT intention-to-treat comparison of all-cause mortality revealed a difference in treatment effect for the initial 1.5 years versus later follow-up period. On the basis of these results, we chose to condition on 1.5-year survival for development of the age-based extrapolation model. Although we evaluated and found no evidence that the hazard ratio for treatment varied over time in the post-1.5-year period, there was limited power to test this effect with only 3.5 years of follow-up.

The following models were used to extrapolate life expectancy for the SCD-HeFT study population. Each model includes all variables necessary for planned subgroup analyses to allow estimation of life expectancy within subgroups reliably, including treatment effect (ICD versus placebo), NYHA II versus III, treatment by NYHA class interaction, ischemic versus nonischemic etiology, age, gender, minority status, ejection fraction, QRS duration, 6-minute walk distance, β-blocker use, and history of diabetes.

**Model 1: Observed Study Follow-Up, Random Assignment to 1.5 Years**

The initial 1.5-year survival was modeled with the Cox proportional hazards regression model, using the standard convention, where time is measured from date of random assignment.

**Model 2: Lifetime Survival Projection Beyond 1.5 Years**

For observed survival after 1.5 years and survival projections beyond the end of study follow-up, we used the Cox proportional hazards regression model with left-truncated and right-censored data to model the hazard of death as a function of age, conditional on surviving 1.5 years and adjusted for the same covariates used in model 1. Additionally, we allowed an adjustment to increase the hazard rate over time as a function of age.

**Integration of Life Expectancy Models**

Using the laws of conditional probability, these 2 models were linked together to obtain a covariate-specific lifetime survival prediction for each patient. The individual survival predictions were averaged together over all patients in both treatment groups to produce mean predicted survival estimates for each treatment group. These estimated mean survival curves were then integrated over a lifetime to produce mean life expectancy estimates (Figure 1). As an external benchmark for life expectancy estimation, we compared the 14-year estimated survival of the ischemic cardiomyopathy placebo arm subset of the SCD-HeFT with the empirical 14-year survival of 1285 patients with a history of myocardial infarction and an ejection fraction ≤0.30 referred to Duke University Medical Center for angiography. Both cohorts had a 14-year survival rate of 23%. Similar follow-up for the Duke nonischemic cohort was not available. We also compared the hazard rate of SCD-HeFT patients by age with the corresponding annual hazard for...
remain constant. This assumption was varied in extensive sensitivity analysis. For each sample, survival and cost models were refit and tested and found no evidence for significant variations in the hazard ratio within each phase. Our base case analysis modeled this survival behavior very closely and assumed that the hazard ratio for the therapy at 5 years. The overall trial hazard ratio for ICD relative to placebo arm, 10.87 years for the ICD arm (both undiscounted).

The difference in the area under the 2 treatment lifetime survival curves was taken to obtain the incremental survival of the ICD arm. The empirical SCD-HeFT survival data showed an ICD-placebo hazard ratio with 2 distinct phases. In the first phase, lasting approximately 18 months, the hazard ratio was essentially 1.0, and the survival curves overlapped. In the second phase, lasting for the remaining 3.5 years, the hazard ratio averaged 0.66, and the survival curves diverged to yield a 7% absolute survival advantage for ICD therapy at 5 years. The overall trial hazard ratio for ICD relative to placebo of 0.77 represents a weighted average of theses 2 phases. We tested and found no evidence for significant variations in the hazard ratio within each phase. Our base case analysis modeled this survival behavior very closely and assumed that the hazard ratio for the second phase, representing the period of ICD survival benefit, would remain constant. This assumption was varied in extensive sensitivity analyses (see below).

Patient Utilities
We assessed patient-specific utilities by structured interview by using the time trade-off instrument at baseline, 3 months, 12 months, and at 30 months or end of study follow-up (whichever came sooner). Interviews were performed by each site coordinator after being trained by the Economics and Quality of Life Coordinating Center Project Leader. Patients were asked how much of a life expectancy they would trade for their current state of health they would attribute to excellent health. Responses were converted to a utility weight ranging from 0 (equal to death) to 1 (equal to excellent health). There was no difference in utilities by intention-to-treat and values were stable over the study follow-up and decreases it thereafter, relative to our base case analysis (see Estimation of Life Expectancy, above).

The discount rate was varied between 0% and 5%. Subgroup Analysis
Two major prespecified subgroup comparisons were performed: NYHA class II versus III, and ischemic versus nonischemic. Eight additional prespecified subgroups were examined: age, gender, race, ejection fraction, QRS duration, diabetes, \( \beta \)-blocker use, and 6-minute walk test results.

Statistical Descriptors and Comparisons
Cost and resource use data were presented as means because they better represent per-patient program costs than median values. Treatment groups were compared by intention-to-treat for cumulative 5-year costs. Intention-to-treat analyses were performed by using nonparametric methods that adjust for censored data.

Base Case Analysis
Within-Study Costs
Over 5 years of follow-up, there was no evidence that ICD patients had significantly more hospitalizations, major cardiac procedures, or outpatient visits than the placebo arm (Table 1 and Table 2). The estimated cumulative medical costs (hospital costs plus physicians' fees) at 5 years averaged $42,971 for the placebo arm, $49,338 for the amiodarone arm (\( P=0.08 \) relative to placebo), and $61,938 for the ICD arm (\( P<0.0001 \) relative to placebo).

As shown in Figure 2, costs for amiodarone and placebo increased at a faster rate due to crossover to ICD therapy. The 5-year crossover rates in the amiodarone and placebo patients were 18.1% and 19.4%, respectively.

Life Expectancy
For our base case, we projected a life expectancy from the time of random assignment in the SCD-HeFT of 10.87 years for ICD-treated patients and 8.41 years for patients receiving used to calculate incremental costs, incremental life expectancy, and cost-effectiveness. Using these data we also calculated 95% confidence intervals for costs, survival, and the incremental cost-effectiveness ratio.

Sensitivity Analyses
We examined 3 major variations on our base case assumption that the relative hazard reduction with ICD therapy would continue over the lifetime of the cohort. First, we examined the effect on the cost-effectiveness ratio of varying the time horizon over which the ICD continued to provide incremental survival benefits, from 5 to 20 years. This analysis assumed that the ICD remained fully effective until the specified follow-up termination point and that incremental costs were accrued only to that point. Second, we varied the assumed hazard ratio for the ICD arm versus the placebo arm beyond empirical follow-up between 0.5 and 1.20. A post–5-year ICD hazard ratio of 1.0 is equivalent to the assumption that all the sudden deaths preventable by an ICD have been depleted by 5 years. A hazard ratio >1.0 would be observed if there was a late acceleration of mortality from ICD relative to placebo. Third, we examined the effect on cost-effectiveness of assuming that the SCD-HeFT net average ICD-placebo hazard ratio of 0.77 was constant from the time of random assignment through the end of cohort survival. This assumption improves ICD efficacy during the first 1.5 years of follow-up and decreases it thereafter, relative to our base case analysis (see Estimation of Life Expectancy, above).

Sensitivity analyses on the cost side varied the cost of the initial ICD implantation, the frequency and cost of battery replacement, and the long-term cost of having an ICD (including late complications such as lead fractures).

Results

Bootstrap Analysis
We performed 1000 resamplings with replacement from the combined SCD-HeFT ICD and placebo arms to estimate the percentage of replications with cost-effectiveness ratios <$50,000 and <$100,000 per life-year saved for the base case cost-effectiveness analysis. For each sample, survival and cost models were refit and used to calculate incremental costs, incremental life expectancy, and cost-effectiveness. Using these data we also calculated 95% confidence intervals for costs, survival, and the incremental cost-effectiveness ratio.
medical therapy alone, yielding an incremental life expectancy of 2.46 years without discounting and 1.63 years discounting at 3% (95% confidence interval, 0.66 to 3.10).

Projected Lifetime Costs
On the basis of the projected life expectancy of each study patient, the lifetime costs of the ICD arm were $158 840, and the costs for the placebo arm were $79 028. Thus, the base case lifetime incremental cost for the ICD strategy was $79 812 without discounting and $62 420 discounting at 3% (95% confidence interval, $46 532 to $88 443).

Cost-Effectiveness
Discounting at 3% yielded an incremental cost to save a life-year with ICD therapy of $38 389 (95% confidence interval, $25 217 to $80 160). Results were sensitive to the amount of extrapolation beyond the empirical 5-year trial data: $127 503 per life-year at 5 years, $88 657 per life-year at 8 years, and $58 510 per life-year at 12 years. In 1000 bootstrap repetitions of our base case model, the cost-effectiveness ratio was under $50 000 per life-year saved in 79% of samples and under $100 000 in 99% (Figure 3). With discount rates of 5% and 0%, the cost-effectiveness ratio was $43 512 and $32 510 per life-year added, respectively.

Cost Utility
At 1 year, the mean time trade-off–derived utility weight was 0.85 for both the ICD arm and the placebo arm ($P = 0.96$). Values were unchanged in both arms at 30 months. Weighting survival by the utility data yielded a cost-utility ratio of $41 530 per quality-adjusted life-year.

Sensitivity Analyses

Differences in Late Benefit With ICD Therapy
As shown in Figure 4, if the base case model projected at least 8 years of follow-up benefits and costs, the cost-effectiveness ratio would fall below $100 000 per life-year added. If the costs and benefits are continued out to 14 years, the cost-effectiveness ratio falls below $50 000 per life-year added.

Figure 5 demonstrates the effect of varying the relative benefit of ICD therapy after 5 years on cost-effectiveness of ICD therapy while continuing the cost stream of the ICD arm as in the base case model. If the absolute benefit of ICD therapy was held constant at the level observed at the end of SCD-HeFT follow-up (ie, ICD versus placebo hazard ratio forced to 1.0, indicating no additional lives saved by ICD therapy), the cost-effectiveness ratio increased to $98 771.

If a constant hazard ratio of 0.77 for ICD versus placebo is assumed from the time of random assignment (rather than the 2-phase hazard ratio observed empirically), the incremental cost-effectiveness ratio is $57 696 per life-year saved.

ICD Costs
Increasing initial device plus implantation cost by 25% or 50% yielded cost-effectiveness ratios of $41 814 and $45 239 per life-year added, respectively. Increasing the post–5-year costs of the ICD arm by 50% to reflect the possibility of a substantial increase in late complications (eg, infections, lead fractures, and other problems) increased the cost-effectiveness ratio to $52 072. Increasing the cost of 5-year battery replacements by 25% (equal to the current cost of a dual-chamber ICD) increased the cost-effectiveness ratio to

<table>
<thead>
<tr>
<th>TABLE 1. Selected Within-Trial Resource Use (Cumulative 5-Year Estimates)</th>
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<tbody>
<tr>
<td>Resource Use</td>
</tr>
<tr>
<td>Hospitalizations, n</td>
</tr>
<tr>
<td>Length of stay, days</td>
</tr>
<tr>
<td>Diagnostic cardiac catheterizations (per 100)</td>
</tr>
<tr>
<td>Percutaneous coronary interventions (per 100)</td>
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<tr>
<td>Coronary artery bypass graft surgeries (per 100)</td>
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<tr>
<td>Emergency department visits, n</td>
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<td>Nonprotocol doctor visits, n</td>
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Numbers are adjusted for censoring.

<table>
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<th>TABLE 2. Within-Trial Costs (Cumulative 5-Year Estimates)</th>
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<td>Cost</td>
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<td>Medication costs†</td>
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*Includes ICD and lead.
†Includes study drug.
$41,782 per life-year added. Simultaneously increasing initial costs by 25%, battery replacement costs by 25%, and follow-up ICD costs by 50% yielded a cost-effectiveness ratio of $58,892 per life-year added. Increasing battery longevity to 7 years with other base case assumptions unchanged yielded a cost-effectiveness ratio of $32,525 per life-year added.

Subgroup Analyses
With the NYHA by treatment interaction term observed in the SCD-HeFT, the cost-effectiveness ratio for ICD therapy was $29,872 per life-year in the NYHA class II patients. In NYHA class III, ICD therapy had equivalent clinical outcomes to medical therapy and was significantly more expensive. Cost-effectiveness ratios for additional subgroups are shown in Table 3.

Discussion
The use of a conservatively programmed, single-lead ICD in addition to state-of-the-art medical therapy in patients with stable, moderately symptomatic heart failure increased health benefits at a cost comparable to that of other expensive therapies judged economically attractive. To facilitate such assessments, many use benchmarks of $50,000 or less per life-year added as a metric of good value for money and $100,000 or more per life-year as inadequate value for...
TABLE 3. Incremental Cost-Effectiveness Ratios by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Undiscounted</th>
<th>Discounted 3%</th>
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<td>NYHA class with interaction*</td>
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<tr>
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</table>

*Assuming an interaction between treatment and heart failure class.

money. In bootstrap analysis of our base case results, the cost-effectiveness ratio for the ICD arm was below this latter threshold in 99% of 1000 samples (Figure 3).

Sensitivity Analyses

As with coronary bypass surgery, much of the cost of ICD therapy is borne up front, whereas the survival benefits are accrued gradually over years. Although the specific results of our analysis do depend on assumptions about the duration and magnitude of ICD benefits beyond the empirical SCD-HeFT follow-up, sensitivity analyses demonstrate that a variety of more conservative assumptions still yield a cost-effectiveness ratio below $100,000 per life-year. For example, the cost-effectiveness ratio falls below this threshold if we are willing to assume that the relative benefits of the SCD-HeFT continue for at least 2 years beyond the last SCD-HeFT follow-up (Figure 4) or alternatively that they are preserved for the lifetime of the study cohort without further augmentation or attenuation after 5 years (Figure 5).

The ICD-placebo hazard ratio for the SCD-HeFT of 0.77 represents a weighted average of 2 components: The 70% of patients who were in NYHA class II had a 46% reduction in hazard with ICD, whereas the 30% of patients who were in class III had no survival benefit. If we impose a hazard ratio of 0.77 from the time of random assignment and use it for extrapolation of life expectancy, the resulting cost-effectiveness ratio is $57,696 per life-year saved.

Comparison With Other ICD Trials With Economic Data

Three of the major secondary prevention trials of ICD therapy involving patients who have had sudden death or malignant ventricular arrhythmias have published cost-effectiveness analyses. Results ranged from highly economically attractive for the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I) to economically unattractive in the Canadian Implantable Defibrillator Study (CIDS; sponsored by Medtronic) and the Antiarrhythmics Versus Implantable Defibrillators (AVID) results between $50,000 and $100,000 per life-year. These studies differ from the present one in the risk level of the patients and their life expectancy, the absolute benefit provided by the ICD, the type and cost of the ICD and its method of implantation, and the length of follow-up. Of the primary prevention ICD trials, several analyses using the MADIT-II clinical results have found a cost-effectiveness ratio around $50,000 using assumptions similar to those in this study.

Subgroup Analyses

Results in major prespecified subgroups were consistent with our overall results (Table 3). In the case of NYHA class, however, there was a significant interaction of treatment with NYHA class, such that NYHA class II had a 46% relative hazard reduction with ICD, whereas NYHA class III had no significant benefit from ICD therapy. According to this interaction, use of ICD therapy in NYHA class II is very economically attractive, whereas there would be no reason to consider its use in NYHA class III (equal effectiveness and higher cost relative to placebo). The Defibrillators In Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) and MADIT II did not observe a similar trend, however. Although the issue remains controversial and cannot be settled by an economic analysis, the evidence for economic attractiveness of ICD therapy parallels the clinical results in the SCD-HeFT and is most compelling for NYHA class II.

Limitations

The major limitation of this analysis is the inability to empirically validate the extent and magnitude of ICD benefits beyond the 5-year follow-up in the SCD-HeFT. Thus, decision making at both the clinical and policy level must occur in the face of these residual uncertainties.

The estimated survival for trial patients beyond empirical SCD-HeFT follow-up was based on life table methods that use the age of the patient rather than the time in study as the basis for estimation. Although we have shown that our survival results are reasonable as judged against empirical Duke Databank data and US life table data, there are no
benchmark data that provide survival estimates beyond 5 years specifically for the SCD-HeFT heart failure population treated with contemporary medical therapy.

We did not explicitly consider the use of cardiac resynchronization therapy in the SCD-HeFT population. Although the device costs are relatively well defined (mean cost including lead of $33 500), there is no consensus about the incremental benefits over ICD therapy alone.

Conclusions
Prophylactic implantation of conservatively programmed, single-lead ICDs in patients with stable, moderately symptomatic heart failure (particularly those in NYHA class II) with an ejection fraction ≤35% is an economically efficient way to increase health benefits in this population assuming that the observed benefits of ICD therapy in the SCD-HeFT persist for at least 8 years.

Acknowledgments
The authors thank Judy Stafford for statistical programming expertise, Heather Read for economic data collection, and Melanie Daniels for editing. The authors are also greatly indebted to the extraordinary team of investigators and site coordinators who enrolled, cared for, and followed the SCD-HeFT patients. Finally, we are grateful to the SCD-HeFT patients for agreeing to participate in our study.

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Disclosures
Dr Mark has received speaking fees from Medtronic. Dr Bardy has served as a consultant to Guidant and has received speaking fees from Medtronic; he is a founder of, board member of, consultant to, and equity holder in Cameron Health. Dr Lee has received speaking fees from Guidant and Medtronic. Dr Poole has received speaking fees from Guidant and Medtronic. Dr Al-Khatib has received honoraria from Guidant and Medtronic. The other authors report no disclosures.

References

CLINICAL PERSPECTIVE
The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) compared survival benefits of conservatively programmed, single-lead implantable cardioverter-defibrillators (ICDs) or amiodarone with placebo in patients with chronic, stable, moderately symptomatic heart failure and an ejection fraction ≤35%. ICD therapy produced a statistically significant 7% absolute reduction in all-cause mortality rates over 5 years, whereas no significant mortality benefit was observed in the amiodarone arm compared with placebo. We examined the economic implications of these results and found that prophylactic use of single-lead, shock-only ICD therapy is economically attractive in the SCD-HeFT patient population, particularly those in NYHA class II, as long as the benefits of ICD therapy observed in the SCD-HeFT persist for at least 8 years.

Disclosures
The other authors report no fees from Guidant and Medtronic. Dr Al-Khatib has received fees from Guidant and Medtronic. Dr Poole has received speaking and equity holder in Cameron Health. Dr Lee has received speaking fees from Guidant and has received speaking fees from Medtronic; he is a founder of, board member of, consultant to, and equity holder in Cameron Health. Dr Lee has received speaking fees from Guidant and Medtronic. Dr Al-Khatib has received honoraria from Guidant and Medtronic.
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