Cost-Effectiveness of Cardiac Resynchronization Therapy in the MADIT-CRT Trial

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Cost Effectiveness of MADIT-CRT. ***Background:*** **The Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial demonstrated that cardiac resynchronization therapy (CRT) when added to the implantable cardiac defibrillator (ICD) reduces risk of heart failure or death in minimally symptomatic patients with reduced cardiac ejection fraction and wide QRS complex.**

Objectives: **To evaluate 4-year cost-effectiveness of CRT-ICD compared to ICD alone using MADIT-CRT data.**

Research Design: **Patients enrolled in the trial were randomized to implantation of either ICD or CRT-ICD in a 2:3 ratio, with up to 4-year follow-up period. Cost-effectiveness analyses were conducted, and sensitivity analyses by age, gender, and left bundle branch block (LBBB) conduction pattern were performed.**

Subjects: **A total of 1,271 patients with ICD or CRT-ICD (US centers only) who reported healthcare utilization and health-related quality of life data.**

Measures: **We used the EQ-5D (US weights) to assess patient HRQOL and translated utilization data to costs using national Medicare reimbursement rates.**

Results: **Average 4-year healthcare expenditures in CRT-ICD patients were higher than costs of ICD patients ($62,600 vs 57,050, P = 0.015), mainly due to the device and implant-related costs. The incremental cost-effectiveness ratio of CRT-ICD compared to ICD was $58,330/quality-adjusted life years (QALY) saved. The cost effectiveness improved with longer time horizon and for the LBBB subgroup ($7,320/QALY), with no cost-effectiveness benefit being evident in the non-LBBB group.**

Conclusions: **In minimally symptomatic patients with low ejection fraction and LBBB, CRT-ICD is cost effective within 4-year horizon when compared to ICD-only.** *(J Cardiovasc Electrophysiol, Vol. 24, pp. 66–74, January 2013)*

cardiac resynchronization therapy (CRT), cost-effectiveness, health-related quality-of-life (HRQOL), implantable cardioverter-defibrillator (ICD), MADIT-CRT, survival

Introduction

Heart failure (HF) with its associated morbidity and mortality remains a major unresolved public health problem in the United States. It is estimated that HF affects nearly 5 million people in the United States alone and claims more than 400,000 lives annually.[1] Patients with severe HF and wide QRS (≥120 milliseconds) benefit from cardiac resynchronization therapy (CRT).[2,3] Recently, three large clinical studies demonstrated that *prophylactic* CRT in combination with an implantable cardioverter defibrillator (CRT-ICD) can inhibit and slow down the development of HF in relatively *asymptomatic* patients with low ejection fraction (EF ≤ 30%) and wide QRS complex.[4-6] In the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial, the benefit of CRT-ICD therapy was most marked in patients with left bundle branch block (LBBB) conduction disturbance.[7,8] In September 2010, the US Food and Drug Administration approved the CRT-ICD for patients with MADIT-CRT indications who had a LBBB problem.[9]

With the growing focus on enhancing quality and efficiency of healthcare delivery system, the need for information about comparative effectiveness of alternative treatment strategies is picking up.[10] We evaluated the total in-trial healthcare costs and estimated incremental cost effectiveness ratio (ICER) of CRT-ICD therapy compared to ICD-only therapy using data from the US subgroup of MADIT-CRT population, with particular focus on those with and without LBBB problems. Finally, we examined patient and

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treatment factors that contributed to uncertainty around the ICER estimate.

Methods

Study Population

Patients of either sex who were at least 21 years of age were enrolled in the MADIT-CRT study if they had ischemic cardiomyopathy (NYHA class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an EF of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 milliseconds or more, as previously reported.[5,11] Enrollment in the study took place from December 22, 2004, through April 23, 2008, enrolling a total of 1,820 patients at 110 hospital centers, including 1,271 patients at 88 centers in the United States and 549 patients at 22 centers in Canada and Europe. The patients were randomly assigned in a 3:2 ratio to receive either CRT with an ICD (CRT–ICD group) or only an ICD (ICD-only group). Follow-up continued thereafter until June 22, 2009, when the study was terminated upon recommendation of the Data and Safety Monitoring Board due to reaching a prespecified stopping boundary. The protocol was approved by the institutional review board at each of the participating centers.

Associated cost and quality-of-life assessments were carried out alongside the main trial, with the cost study restricted to the 1,271 patients enrolled in the United States. The trial's sponsor, Boston Scientific Inc., was not involved in data collection or data analysis. The authors vouch for the accuracy and completeness of the reported findings.

Health Utilization

Patients were scheduled for follow-up visits at 1 and 3 months after randomization and at 3-month intervals thereafter. To collect information about health services utilization, patients were contacted by phone monthly. The information gathered at each contact (clinic or phone) included number of hospitalizations, emergency room and physician visits, outpatient surgeries, and diagnostic tests and procedures. When a hospitalization was reported, study staff requested patient authorizations and obtained hospital bills from the identified hospitals.

The use of prescription medications for cardiovascular problems was collected but found to be similar in the two treatment groups, and was omitted from the cost-effectiveness analysis. Because nursing home admissions in this asymptomatic population were rare, nursing home costs were also omitted from this analysis.

Estimating Healthcare Costs

To translate the collected utilization data into costs, we used the methods similar to those described previously by our group.[12,13] All costs are expressed in 2008 dollars. We did not obtain indirect costs such as time lost from work, time lost from leisure, or travel costs; hence, our costs estimates represent a third-party payer perspective. Healthcare utilization imposed by the trial and associated costs were excluded from the analysis. We provided additional details of the analysis in the Supporting Information.

Hospital inpatient stay facility costs (including hospitalization for implantation)

We applied 2008 average national Medicare reimbursement rates, by Diagnosis Related Group codes (DRG), to estimate costs of inpatient admissions. To account for the difference between the ICD and CRT-ICD (including the difference in cost for defibrillator, generator, and lead systems), we added the average difference in the costs between the CRT-ICD combination and ICD device provided by Boston Scientific Inc. ($7,000, private communication) to the average DRG-based reimbursement for ICD implantation-related hospitalization.

Inpatient physician costs

Inpatient physician charges are typically not reported in hospital bills. Instead, we estimated inpatient physician costs using a multivariate regression model based on the Medicare hospital reimbursement and physician bills. We calculated the ratio between hospital component of hospitalization costs and physician-allowable charges. These relationships were used to predict the ratio of inpatient physician costs to hospital costs for each admission in the MADIT-CRT database. These predicted ratios, multiplied by the hospital DRG-based costs, were used to estimate physician costs for each admission in the study.

Emergency room and outpatient surgery costs, diagnostic tests and procedures, and physician costs

Costs of emergency room visits that did not result in a hospitalization, physician visits, and outpatient surgery costs were based on the average 2008 Medicare reimbursement for appropriate procedures, according to the Current Procedure Terminology (CPT) codes. Matching Ambulatory Procedure (APT) codes were identified and added to the CPT-based cost estimates.

Imputing Missing Utilization

If a DRG code was missing from a hospital bill, we used Centers for Medicare & Medicaid Services grouper software to assign the code to that hospitalization based on patient's birth date, admission-discharge dates, insurance, codes for primary diagnosis and other diagnoses, and codes for primary and secondary procedures. Once the DRG code was generated, the cost was assigned using the same approach as described earlier. If no additional information were available about nonimplant hospitalization except for the date of admission and discharge, we imputed cost of such hospitalization based on patient characteristics and costs of other nonimplant hospitalizations (see Supporting Information for additional details on the imputation).

Health Outcomes and Quality of Life (HRQOL), Life Years (LY), and Quality-Adjusted Life Years (QALY)

We assessed patient HRQOL using the EQ-5D instrument, a prescored health utility assessment system defined over 5 domains of health: mobility, self-care, usual activity, pain, and emotional health.[14] Before randomization and every 6 months thereafter, subjects completed the EQ-5D forms.

The primary endpoint of the MADIT-CRT trial was a nonfatal HF event or death from any cause, whichever came first, with parallel analyses based only on deaths. HF events

and deaths were adjudicated by independent committees.[5] To satisfy the standards of cost-effectiveness assessment[15] and to reflect the primary endpoint of the MADIT-CRT trial, 2 versions of life-years (LY) and QALY were reported in this study, namely, overall (unrestricted) LY and QALY, and heart-failure-free LY and QALY (with censoring of life expectancy upon occurrence of a first HF or death).

Statistical Analysis

Observed utilization and cost data were accumulated for the full trial participation period for each patient, with averages across patient groups compared by *t*-tests. Patient follow-up, crossover activity, and accumulations of HFs and death events for the full trial period were tabulated. EQ-5D scores were summarized and compared between groups by *t*-tests.

To adjust for censoring, caused by staggered entry into the study and early drop-out, further cost, life-expectancy and cost-effectiveness analyses used censored data methods to estimate these statistics over a full 4-year horizon.[16,17] Accumulated costs, life-years, and QALYs were discounted at 3% per annum, and were estimated by treatment group using the inverse probability weighting techniques that accommodate the "induced informative censoring" problem in estimating QALY and costs.[16,17] Associated variances, covariances, and resulting confidence intervals on derived quantities of interest were also obtained.

Cost-Effectiveness

To estimate the cost-effectiveness of CRT-ICD compared to ICD, we used estimated LY or QALY gain within 4 years as the effectiveness measures. The ICER is the difference in the estimated cumulative costs over a 4-year period per incremental gains in treatment effectiveness (LY or QALY) between the 2 treatment arms within 4 years. The confidence intervals for ICERs were obtained by adapting the Fieller's method to the censored data.[16]

Sensitivity Analyses

Because the MADIT-CRT study was designed to assess the effect of CRT-ICD for *prevention of HF*, in addition to *extending life*,[11] we repeated cost-effectiveness evaluation using the number of HF-free life years and quality adjusted life years as alternative outcome measures. Analyses of the subgroups with and without LBBB were done similarly. Finally, within the LBBB subgroup, we re-estimated ICER for females, males, and three age groups (under 65, 65–74, and 75 and over). For the LBBB subgroup, analyses were repeated using 1-, 2-, and 3-year horizons.

To quantify modeling uncertainty due to uncertainty in the estimation of costs and effectiveness, we plotted cost-effectiveness acceptance curves (CEAC).[18,19] CEAC represents the probability that the CRT-ICD arm is cost-effective compared to ICD only, conditional on different values of willingness to pay (WTP).

Results

Study Population

The study analytic sample was comprised of 1,251 patients, with 748 in the CRT-ICD group and 503 in the ICD-only group; 20 patients with no cost data reported (and limited follow-up) were omitted. Patient characteristics in the cost-effectiveness substudy reported here were similar to the characteristics of the main trial cohort, with no differences in the average age (64 $\pm$ 11 for ICD and 65 $\pm$ 11 for CRT-ICD), sex (76% male for ICD and 75% for CRT-ICD), race (91% white for ICD and 90% for CRT-ICD), diabetes (31% among ICD and 30% among CRT-ICD), heart disease severity (15.5% NYHA class I ischemic HD for ICD vs 14% for CRT-ICD, 10% NYHA class III or higher), and LBBB (71% among ICD vs 70% among CRT-ICD).[5]

During an average follow-up of 28 months, the primary endpoint of documented HF event or death, whichever occurred first, occurred in 128 (17%) of the CRT-ICD group patients and 126 (25%) of the ICD-only patients; crude death rates during follow-up were 6% and 8%, respectively (Table 1). Hazard ratios were as reported earlier.[5] The effectiveness of the CRT-ICD was greater in the subgroup of patients with LBBB, with no effect apparent in those without this conduction disturbance, as reported earlier.[5,7,8]

Resource Utilization and Costs

In-trial reported 4-year health services utilization, excluding trial-related visits, included acute care hospitalizations (more than 1 hospital admission per person with about half of the patients having an emergency room visit during the study period), outpatient physician visits (more than 12 per person), outpatient tests and procedures (more than 9 per person) and outpatient surgery (0.7 per person). Per person rates of use were similar between the treatment arms (Table 1).

Without adjusting for censoring, the costs for device plus implantation averaged $36,870 per patient in the CRT-ICD group and $29,550 in the ICD-only group (Table 2). Other device-related costs were higher in the ICD-only group ($4,280 vs $2,850), due largely to the excess crossover activity in this group (Table 2). Cardiac and non-cardiac hospitalization costs were not different between the treatment groups. Costs for emergency room visits were significantly higher in the CRT-ICD group ($350 vs $250), but amounts were low relative to other costs. Costs for outpatient diagnostic tests were higher in the ICD-only group ($2,190 vs $1,750, $P < 0.05$). Implant costs accounted for 70% or more (over 80% when combined with other device-related costs) of the total costs. The treatment group difference in total costs was $6,730.

We examined outlier costs and found them to be reasonably balanced between the 2 arms. Twelve patients had accumulated costs over $150,000 (6 from each treatment group). Among them, 3 patients received heart transplants (all from the CRT-ICD group), 1 received dialysis (ICD group), and the other extreme costs were caused by multiple implants, outpatient diagnostic test costs, or multiple hospitalizations.

Utility and Quality-Adjusted Life Years

The EQ-5D scores averaged 0.848 and 0.845 for the CRT-ICD and ICD only groups at baseline, with statistically significant improvement evident in the subsequent scores in each of the groups (Table 2). For subsequent scores, the CRT-ICD average was significantly greater than the ICD-only average in the all-patient category and in LBBB patients, but not in those without LBBB.

TABLE 1

In-Trial (Raw) Cardiac Events and Utilization

Category	All Patients (n = 1,251)		LBBB Patients (n = 859)		Non-LBBB Patients (n = 391)	
	CRT-ICD (n = 748)	ICD (n = 503)	CRT-ICD (n = 507)	ICD (n = 352)†	CRT-ICD (n = 241)	ICD (n = 150)†
Follow-Up and Crossovers, Heart Failure Events and Deaths						
Avg f-u prior to HF/D‡	28.1	26.1	29.0	26.1	26.2	26.2
Avg f-u prior to death	30.1	29.5	30.6	29.9	28.9	28.5
No. with no device	3	6	1	4	2	2
No. x-over < HF, >HF	59, 2	23, 44	43, 2	18, 32	16, 0	5, 12
Heart Failure Events and Deaths						
Primary events: HF, D	101, 27	112, 14	52, 16	88, 12	48, 11	24, 2
Total HF events§	163	183	87	132	76	51
All deaths	46	41	25	33	21	8
Total Healthcare Utilization Events						
Hospitalizations	1,090	770	–	–	–	–
Emergency room visits	481	301	–	–	–	–
Physician visits	9,318	6,234	–	–	–	–
Outpatient tests and procedures	7,066	4,630	–	–	–	–
Outpatient surgeries	528	386	–	–	–	–

†One ICD patient had LBBB status unknown and is omitted when tabled by LBBB status,
‡Avg f-u prior to HF/D = average follow-up prior to the first of a HF event, death or trial termination/withdrawal,
§Subsequent HF events are those subsequent to an initial HF event. No. x-over = number of patients who crossed over to the opposite device, classified here as occurring prior to, or after, any HF event. f-u = follow-up; HF = heart failure; LBBB = left bundle branch block.

TABLE 2

Observed Quality of Life and Follow-Up Costs by Treatment Group, for All Patients and by Left Bundle Branch Block Status

Category	All Patients (n = 1,251)		LBBB Patients (n = 859)		Non-LBBB Patients (n = 391)	
	CRT-ICD (n = 748)	ICD (n = 503)	CRT-ICD (n = 507)	ICD (n = 352)†	CRT-ICD (n = 241)	ICD (n = 150)†
Average Quality-of-Life EQ-5D Scores (x 1,000)‡						
Initial scores (SD = 134)	848	845	854	844	835	850
Subs. scores (SD = 145)	884	874	893	873	860	875
Average Costs (SDs) in Thousands of 2008 Dollars§						
Device and implant	36.87(3.1)	29.55(3.1)	36.91(3.0)	29.69(2.5)	36.78(3.5)	29.24(4.3)
Device related	2.85(10.4)	4.28(11.3)	2.71(9.8)	4.53(11.7)	3.15(11.6)	3.70(10.3)
Cardiac hosp.	2.37(15.9)	1.80(7.0)	2.11(17.4)	1.99(7.6)	2.91(12.0)	1.37(5.2)
Noncardiac hospital	1.62(5.9)	1.07(4.4)	1.52(5.5)	1.03(3.7)	1.84(6.7)	1.15(5.9)
Emergency room visits	0.35(1.0)	0.25(0.5)	0.32(0.8)	0.24(0.5)	0.42(1.3)	0.26(0.5)
Outpatient tests	1.75(3.1)	2.19(5.7)	1.57(2.4)	2.16(5.8)	2.13(4.2)	2.24(5.3)
Outpatient surgery	0.50(1.7)	0.44(1.2)	0.49(1.7)	0.41(1.2)	0.50(1.5)	0.51(1.4)
Physician visits	2.11(1.9)	2.13(2.1)	2.03(1.8)	2.15(2.0)	2.28(2.2)	2.09(2.4)
All costs	48.42(21.4)	41.69(19.9)	47.64(22.0)	42.20(20.7)	50.00(20.0)	40.55(18.0)

Implant costs include device and implantation costs limited to an initial implantation, whether in-patient or out-patient. Device related costs include any costs associated with device adjustments, explants, re-implantation, device change, or complications.
†One ICD patient had LBBB status unknown and is omitted when tabled by LBBB status.
‡Avg f-u prior to HF/D = average follow-up prior to the first of a HF event, death and trial termination/withdrawal.
No. x-over = number of patients who crossed over to the opposite device, classified here as occurring prior to, or after, any HF event.
Avg initial scores = average of all QoL scores at baseline, times 1,000; 10 CRT-ICD and 2 ICD-only patients had missing initial scores. No group differences are statistically significant.
Avg of all subsequent scores = avg (times 1,000) of all EQ-5D scores after the initial scores, whenever recorded on average, patients had 4.3 subsequent EQ-5D scores after their initial EQ-5D score. In each column, the average subsequent score is significantly greater than the average initial score. Group differences between treatments for all patients and for LBBB patients, and between LBBB and non-LBBB patients in the CRT-ICD group are statistically significant.
§For implant and all costs, differences between treatment groups are highly significant ($P < 0.001$), for all patients and for each LBBB-status subgroup. For device related and emergency room visits, differences between device groups for all patients are statistically significant ($P < 0.05$). For outpatient diagnostic tests, differences between device groups for non-LBBB patients are statistically significant ($P < 0.05$). Within each treatment group, there are no significant differences for costs between LBBB and non-LBBB groups, Approximately one-third of inpatient hospital bills were not obtained or were incomplete: 342 of 1,090 (31%) for CRT-ICD patients and 291 of 770 (38%) for ICD-only patients. LBBB = left bundle branch block.

TABLE 3

Accumulated Costs, Life Expectancies and Quality-Adjusted Life Expectancies per Patient, by LBBB Status and by Treatment Group, and Selected Incremental Cost-Effectiveness Ratios, All Within a Four-Year Horizon

Panel A: Costs and Life Expectancies Within a Four-Year Horizon

All Patients	CRT-ICD	ICD	Diff.	P	95% CI
Costs ($1,000)	62.60	57.05	5.55	0.01	1.10, 10.00
Unrestricted LY	3.61	3.54	0.07	0.11	–0.01, 0.15
Unrestricted QALY	3.16	3.07	0.10	0.05	0.00, 0.20
HF-free LY	3.29	3.02	0.26	<0.001	0.12, 0.40
HF-free QALY	2.89	2.65	0.24	<0.001	0.10, 0.38
LBBB Patients					
Costs ($1,000)	60.09	56.73	3.36	0.18	–1.54, 8.26
Unrestricted LY	3.66	3.51	0.14	0.00	0.05, 0.24
Unrestricted QALY	3.25	3.05	0.20	<0.001	0.08, 0.32
HF-free LY	3.41	2.94	0.47	<0.001	0.31, 0.63
HF-free QALY	3.04	2.58	0.46	<0.001	0.30, 0.62
Non-LBBB Patients					
Costs ($1,000)	68.10	57.60	10.50	0.07	–0.69, 21.69
Unrestricted LY	3.50	3.62	–0.12	0.14	–0.28, 0.04
Unrestricted QALY	2.97	3.13	–0.17	0.11	–0.37, 0.03
HF-free LY	3.02	3.22	–0.20	0.13	–0.45, 0.05
HF-free QALY	2.57	2.82	–0.25	0.05	–0.50, 0.00

Panel B: Selected Incremental Cost-Effectiveness Ratios (ICERs)† over 4 Years

All Patients	ICER ($1,000)	95% CI
Incremental costs for unrestricted LY.	80.91	–
Incremental costs for unrestricted QALY	58.33	–
Incremental costs for HF-free LY	21.10	3.40, 64.31
Incremental costs for HF-free QALY	22.92	1.76, 151.64
LBBB Patients	ICER ($1,000)	95% CI
Incremental costs for unrestricted LY	23.33	–10.52,‡ 106.7
Incremental costs for unrestricted QALY	16.64	–6.80,‡ 64.40
Incremental costs for HF-free LY	7.18	–3.87, 17.06
Incremental costs for HF-free QALY	7.32	–1.65, 41.26

Costs are in $1,000 (2008) and life expectancies are in years, both discounted at 3% p.a.
†For the non-LBBB patient group, all estimates of savings of life-years, and of quality-adjusted life-years, are negative, and hence no ICER calculations are appropriate. Savings in unrestricted life in the all-patient group were nonsignificant, and no ICERs are given, ‡the lower confidence limit's negativity reflects that for the cost difference, implying nonsignificant evidence of any excess cost for the estimated savings in life; however, magnitudes of negative ICERs cannot be consistently interpreted. Diff. (in accumulated costs, or in LYs or in QALYs) = [cost difference] or [life-years saved], all within 4-year horizon; HF = heart failure event; HF-free LY = heart failure-free years-of-life expected within 4 years (QAL = quality-adjusted life); LBBB = left bundle branch block, at baseline; SE(diff.) = (width of CI)/3.92; YOL = unrestricted years-of-life expected within 4 years (QAL = quality-adjusted).

After adjusting for censoring, there were no statistically significant savings in unrestricted quality-adjusted (3.16 QALY for CRT-ICD vs 3.07 QALY for ICD) or unadjusted life-years (3.61 years vs 3.54 years) for the full patient group (Table 3). Within the LBBB subgroup, there were roughly 2.4-month (0.20 years) savings in unrestricted QALYs. The non-LBBB subgroup had an estimated loss in life expectancies and QALY with CRT-ICD relative to ICD therapy, with negative values for the differences between these therapies as shown in Table 3, but not significant.

Cost-Effectiveness Analysis

After adjusting for censoring, the overall 4-year costs were $62,600, and $57,050 for the CRT-ICD group and the ICD group, respectively, for the all-patient group. The ICER comparing CRT-ICD versus ICD only was $58,330/QALY saved (Table 3). Because the savings in QALY did not reach statistical significance level of 0.05 for the unrestricted analysis, the confidence interval for this ICER was not provided here.

Within the LBBB subgroup, the costs difference was $3,360, but not statistically significant. The ICER in the LBBB subgroup was $16,640 per QALY, with a 95% confidence interval of (–$6,800/QALY, $64,400/QALY).

Sensitivity Analysis

On the basis of the CEAC (Fig. 1), there is about 40% chance that ICD-CRT option is cost-effective compared to implantation of ICD only at cost-effectiveness threshold of $50,000/QALY. If WTP to be increased to $100,000/QALY, cost-effectiveness of ICD-CRT would approach 80%.

For the all-patient analysis, the CRT-ICD group had a 2.9-month gain (0.24 years) in HF-free QALY within 4 years when compared to the ICD group (Table 3). Within the LBBB subgroup, savings in HF-free QALY were almost twice those for the full group (0.46 vs 0.24 QALY). Taking HF events into consideration, we estimated that adding CRT to ICD required extra $22,920 per heart-failure-free QALY saved for the all-patient group (95% CI: $1,730, $153,90/QALY), with a reduction to one-third that value in those with LBBB ($7,320/HF-free QALY; Table 3).

For each sex and age group studied within the LBBB subgroup, statistically significant savings in unrestricted and HF-free QALYs were found (Table S2), with estimated ICERs less than $25,000/QALY for each gender and for age groups <75 years.

Differences in accumulated costs between treatment groups are very similar regardless of the time horizon

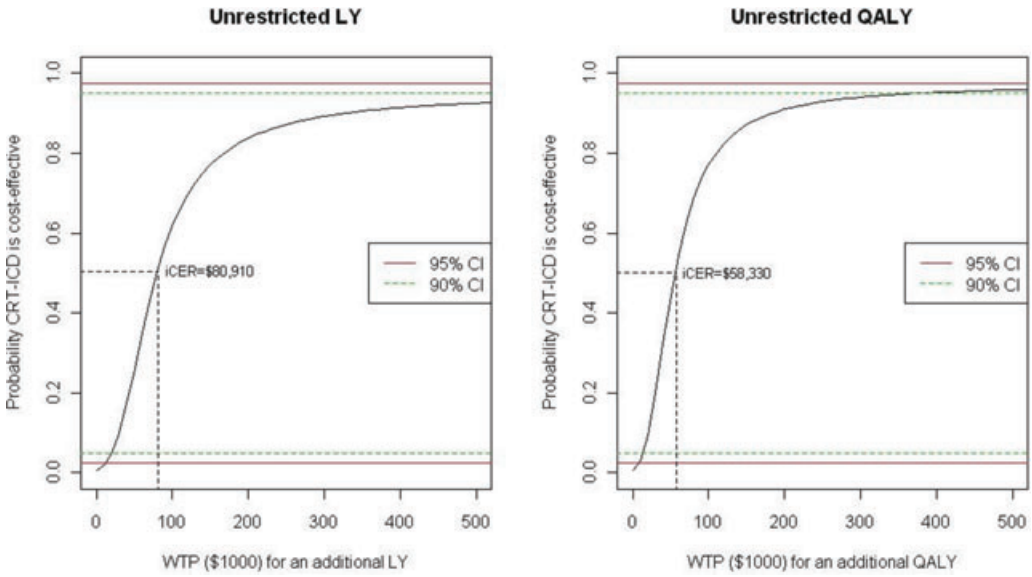

Figure 1. *Cost-effectiveness acceptance curves (CEAC).*

(1, 2, 3, and 4 year time horizons) considered with statistically significant differences only in years 1 and 2 (Figs. 2 and 3). Differences in health outcomes increased for each year with statistically significant differences every year for the HF-free outcome and for all but the first year for unrestricted life and QALY. The resulting ICERs drop substantially from year 1 to year 3 with no differences evident between years 3 and 4; all confidence intervals are, however, wide (supporting information for Figs. 2 and 3 is in Table S1 of the Supporting Information).

Discussion

This study provides evidence that CRT-ICD therapy is an economically attractive intervention in minimally symptomatic high-risk cardiac patients with low ejection fraction and wide QRS complex ($58,330/QALY). The ICER for CRT-ICD compared to ICD-only therapy in patients with LBBB was even better ($16,640/QALY). Extending study time horizons is likely to produce even more acceptable cost-effectiveness estimates because the largest difference in costs between the CRT-ICD and ICD-only treatment groups occurred early in the treatment, in the first year after implantation, due to costs associated with the device itself and implantation-related procedures, while the health benefits accumulated over time.

By assessing the relative costs and effects of various medical interventions for patients with heart disease, cost-effectiveness analysis has allowed researchers to compare the relative values of different options. Results from the first MADIT study published in 1996[11,15] demonstrated that the ICD was a cost-effective alternative to conventional medical therapy for reducing the probability of death in very high-risk patients with coronary artery disease. The cost-effectiveness study from MADIT-II[12,16] demonstrated that the ICD improved survival, but was not cost-effective short term, with an ICER of $235,000 during the in-trial time horizon of 3.5 years. However, when follow-up was projected to a 12-year time horizon, the ICER ranged from $7,000 to $114,000, depending on optimistic, neutral, or pessimistic assumptions about patient health outcomes. Similarly, the SCD-HeFT trial reported cost-effectiveness for 5 years (in-trial) of $127,500, with projections year-by-year leading to values less than $50,000 from 14 years onward.[17] On the basis of the in-trial and modeling analyses of the results of another CRT study, CARE-HF, ICD-CRT versus ICD-only device was considered potentially cost-effective at about $62,900/QALY.[20,21] The cost-effectiveness analyses from the current MADIT-CRT analysis are more economically favorable than these estimates.

It is important to recognize that CRT-ICD devices are used in addition to, not a replacement for, HF drug therapy. The favorable ICER seen in the MADIT-CRT analysis is due primarily to CRT-related reduction in first and recurrent HF events during about 28 months of follow-up. Long-term follow-up of the MADIT-CRT patients is continuing, and it is anticipated that ongoing reduction in HF will be associated with meaningful reduction in mortality over a longer time horizon, as was seen in the recent RAFT trial[6] and as has been demonstrated here for the LBBB patient subgroup.

Cost-effectiveness analysis based on the in-trial information alone has been criticized for its limited usefulness for health policy and decision-making.[22] For this reason the Panel on Cost-Effectiveness in Medicine recommends using lifetime horizon for cost-effectiveness evaluations.[15] However, growing healthcare costs and limited societal recourses have shifted priorities of the cost-effectiveness research paradigm in favor of pragmatic studies and "value of information" approach.[23–25] For this purpose, we presented the results of the ICER-time trend analysis (separate ICER for 1-, 2-, 3-, and 4-year horizon), in addition to the pattern of healthcare use associated with the ICD implantation (high up-front costs and benefits acquired over time). The results indicated that extension of time horizon from in-trial to lifelong would most likely result in an ICER *no greater* than the ICER of in-trial analysis presented here. Changes in medical technology and its diffusion over time raises a number of significant methodological challenges for lifelong cost-effectiveness assessment as well, and hence, was not undertaken here.[25–27]

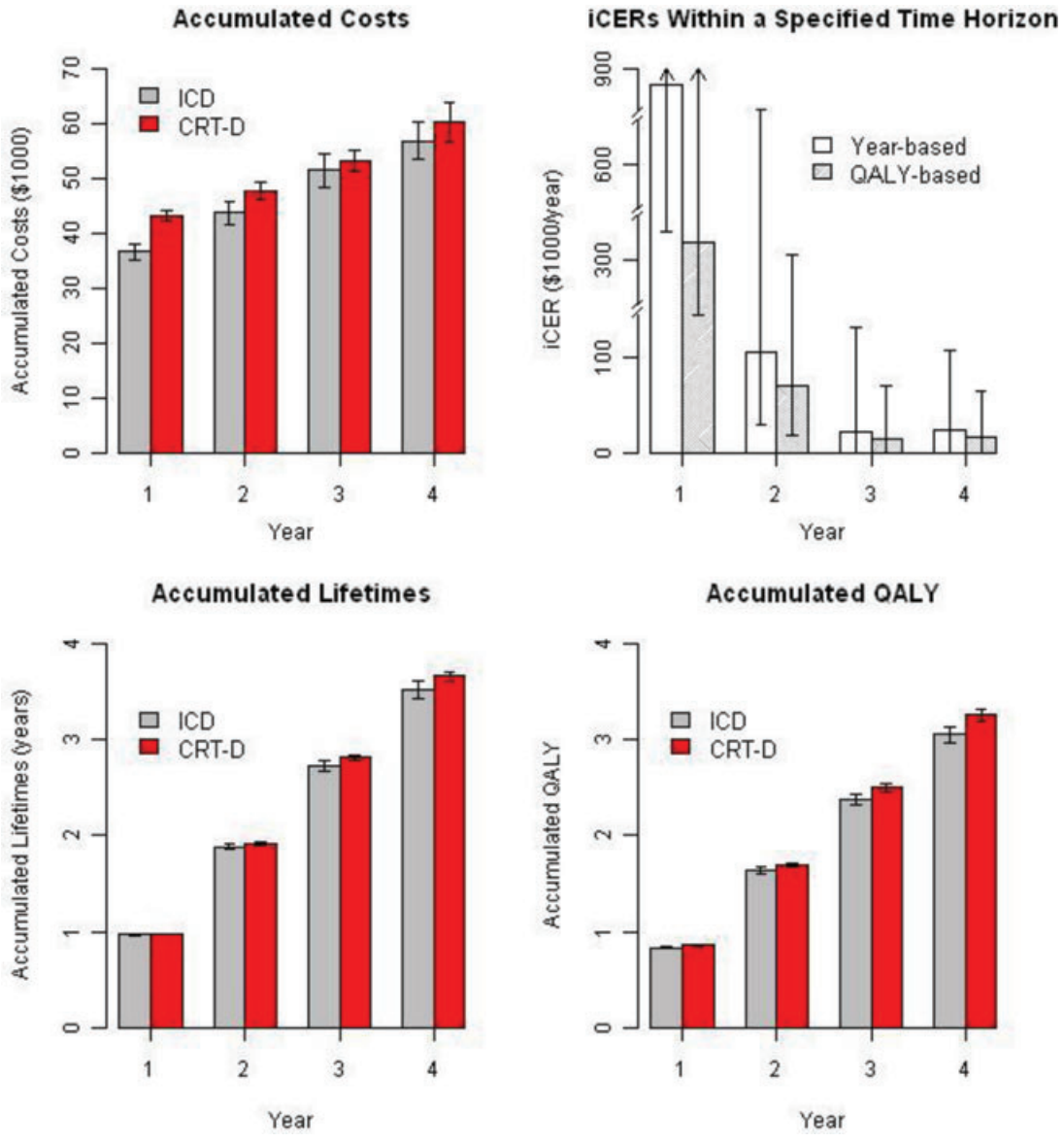

Figure 2. *Accumulated costs, lifetimes, quality-adjusted life years (QALY) and resulting incremental cost-effectiveness ratios (ICERs), unrestricted by heart failure events, for left bundle branch block (LBBB) patients, by active device and by years.*

One major limitation of this economic evaluation is that inpatient bills were missing or incomplete in approximately one-third of the hospitalizations. On the basis of the available data, we developed several imputation procedures to come up with the best matching DRG codes and to minimize the impact of missing billing information on the cost-effectiveness computations. We also observed a substantial variation in the way CRT-ICD and ICD devices were implanted, reimbursed, and monitored/serviced among different study sites. Although some sites had patients predominantly receiving devices on inpatient basis, other allowed some outpatient implantation procedures, with some sites having a majority of devices implanted in an outpatient setting. Quality of care and financial implications of these variations are not known. More research is needed to understand reasons for practice variation across hospitals regarding device implantation.

The other limitation is that while a QALY is a standard outcome measure for cost-effectiveness evaluations and provides a common currency for measuring the extent of health gain that results from healthcare interventions, it is a far from perfect measure of outcome. Technical and methodological shortcomings of QALY for resource allocation and health policy decisions include (1) lack of clarity about whose preferences should be used (community population's or patients'); (2) inability to distinguish QALY resulting from small gain for a large population vs large gain for a few people (e.g., cure for common minor illness vs major rare disability or life-saving intervention); (3) uncertainty about the optimal approach for eliciting utility (TTO vs SG vs VAS); (4) lack of sensitivity of generic HRQOL instruments to disease-specific symptoms; (5) inability to incorporate intervention impact on informal care givers; and (6) lack of clear guidelines on WTP value.[15,28–31] In the light of this

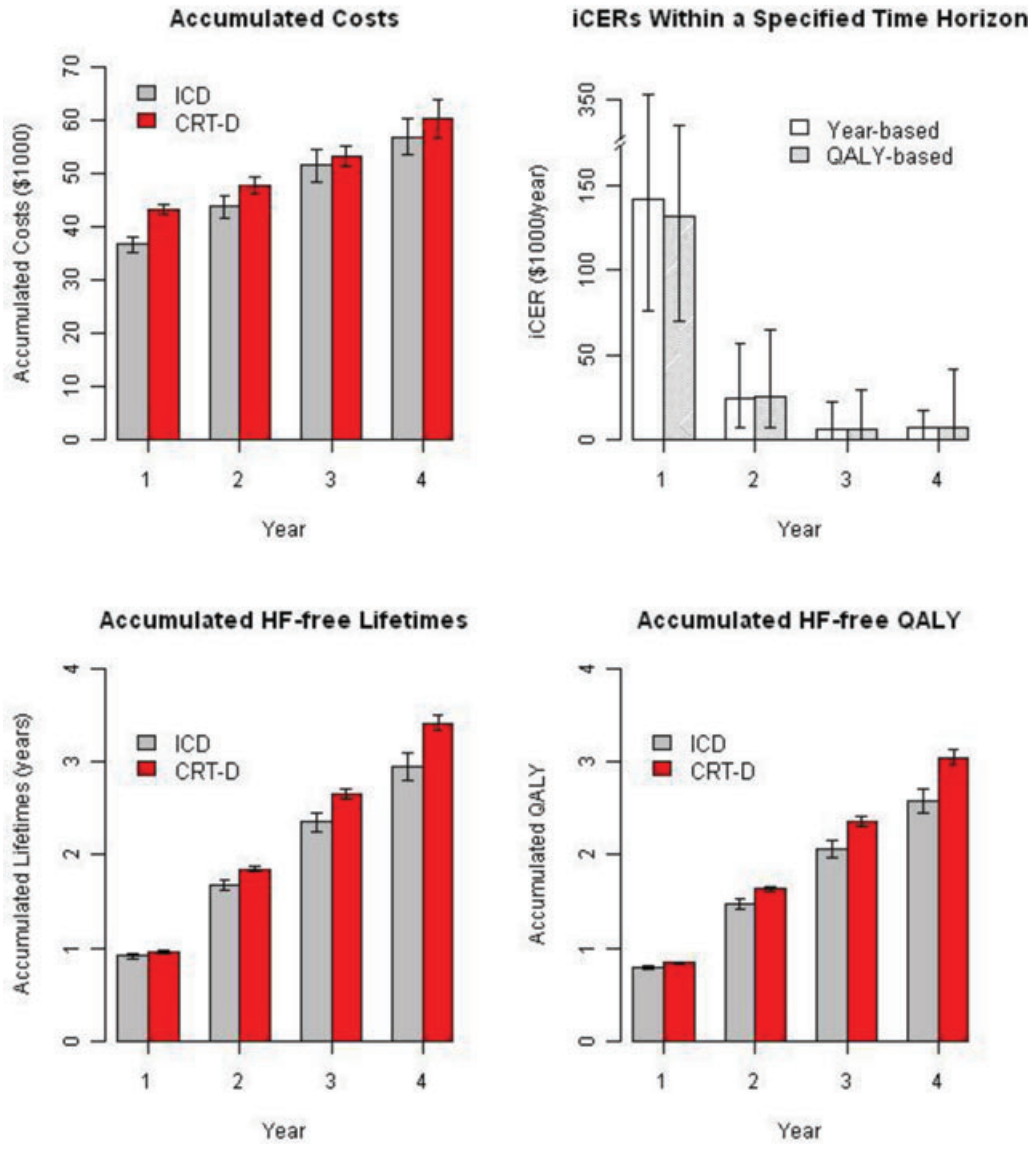

Figure 3. *Accumulated costs, lifetimes, quality-adjusted life years (QALY) and resulting incremental cost-effectiveness ratios (ICERs), limited to heart failure-free years, for left bundle branch block (LBBB) patients, by active device and by years.*

uncertainty about QALY, we chose to also present outcomes in generic units (life years) and disease-specific units (heart failure-free years).

Conclusions

In eligible patients, CRT is associated with meaningful reduction in the risk of HF, with increasing evidence of mortality reduction during longer term follow-up.[5,6] This study provides evidence that the cost of improving life expectancy with CRT in high-risk cardiac patients with LBBB is reasonable by the societal standards and is worth being covered by public health insurance plans, but with no real evidence of value in non-LBBB patients. Within the LBBB subgroup, cost-effectiveness was especially strong in females and in the age group 65–74 years—well under $25,000/QALY in each subgroup studied except the oldest age group, 75+ years of age, which is well under the currently utilized threshold of $50,000/QALY.[32,33]

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

(A) Further information on cost methods.
(B) Supporting data for Figures 2 and 3.

Table S1: Cost Effectiveness by Years in LBBB Patients
Table S2: Cost Effectiveness in Sex and Age Subgroups of the LBBB Patient Group

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