Health-Related Quality of Life Consequences of Implantable Cardioverter Defibrillators

Results From MADIT II

Katia Noyes, PhD, MPH, Ethan Corona, BA,* Jack Zwanziger, PhD,† W. Jackson Hall, PhD,‡ Hongwei Zhao, DSc,‡ Hongkun Wang, PhD,§ Arthur J. Moss, MD,¶ and Andrew W. Dick, PhD‖*

Background: Implantable cardioverter defibrillators (ICDs) improve survival and extend lives of patients with severe heart disease.
Objective: We sought to evaluate the impact of ICDs on health-related quality of life (HRQOL) during the first 3 years after implantation.
Subjects: A total of 1089 patients from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) were randomized to an ICD or medical treatment only.
Measures: Health Utility Index (HUI3) at baseline, 3, 12, 24, and 36 months following randomization; survival data.
Research Design: We constructed mean profiles of HRQOL for living patients, estimated overall quality-adjusted life years (QALYs), separately by treatment arm, and calculated cumulative QALY gains/losses as the difference between the areas under the treatment specific HRQOL profiles. Multivariate fixed effect regression models were developed to impute the missing HRQOL data using baseline patient characteristics (age, gender, treatment, HUI3 score, diabetes, diuretics use, and NYHA class). Bootstrapped standard errors were calculated for the estimated differences in HRQOL gains/losses between treatment arms. Similarly, we performed subgroup analyses (by gender, age, and baseline NYHA class, blood urine nitrogen, ejection fraction, and QRS).
Results: There were no differences in QALYs loss for living patients by treatment group (-0.037, $P = 0.64$) or in overall QALYs loss by treatment group (0.043, $P = 0.37$) over 3 years. In subgroup analysis, female subjects demonstrated a trend towards greater survival benefit (0.298, $P = 0.07$) and overall QALYs (0.261, $P = 0.14$).
Conclusions: Adverse effects of the ICD on HRQOL together with lower HRQOL among survivors may offset the 3-year survival benefits of ICDs.

Key Words: implantable cardioverter defibrillator, health-related quality-of-life, survival, MADIT II

(*Med Care* 2007;45: 377–385)

During the last 20 years, implantable cardioverter defibrillators (ICDs) have become an accepted treatment of patients with life-threatening ventricular arrhythmias. Most but not all of the clinical trials (the exceptions are the CABG and DINAMIT studies[1,2]) have demonstrated the survival effect of the ICDs in patients with cardiac conditions who were at risk for sudden death. These trials found larger improvements in survival rates among subjects with worse heart functioning.[3]

Nevertheless, the survival gains come with a very high price tag, including the device and associated maintenance and medical care costs. The benefits of the ICD have been measured predominantly as survival, which is, in fact, only a proxy for welfare; a more complete measure is based on the combination of quality-adjusted life years (QALYs) and costs. The concept of health-related quality of life (HRQOL) was developed to evaluate quantitatively a person's well-being.[4,5] Utility scores reflect a person's *preferences* for health states. Thus, HRQOL and utility evaluations are different from the assessment of health states, which describe the degree to which a person is able to *function* physically, emotionally and socially, with or without help from the health care system.[6] Utilities are used as weights when calculating QALYs that capture both duration of life in a particular health state and utility of that state.[6–8] Utilities are assessed using preference-based methods.[7]

Earlier studies of quality of life associated with ICDs used nonpreference based instruments and did not provide health utilities. Of those studies, 3 reported superior quality of life in surviving ICD patients compared with patients receiving medical treatment[9,10] (MHI, the RAND Corporation's 38-item Mental Health Inventory, and NHP, Nottingham Health Profile) and[11] (SF-36), and 2 detected no such bene-

From the Departments of *Community and Preventive Medicine, ‡Biostatistics and Computational Biology, and ¶Cardiology Division, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York; †School of Public Health, University of Illinois at Chicago, Chicago, Illinois; §Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia; and ‖RAND Corporation, Pittsburgh, Pennsylvania.

Supported by CPI/Guidant Corporation, St. Paul, Minnesota. Katia Noyes was supported in part by a grant from the National Institute of Aging (K01 AG 20980).

Reprints: Katia Noyes, PhD, MPH, Department of Community and Preventive Medicine, University of Rochester, 601 Elmwood Ave., Box 644, Rochester, NY 14620. E-mail: katia_noyes@urmc.rochester.edu.

ISSN: 0025-7079/07/4505-0377

fit.[12,13] Receiving multiple shocks was associated with negative effect on quality of life.[9,10,13]

Only 1 study other than ours of ICD cost-effectiveness (CE) has used actual trial data on both costs and health preferences from the same population.[14] Published CE studies typically have combined data from various sources via modeling techniques.[15–17] As described in Zwanziger et al,[18] modeling studies are limited by the strong assumptions they require. Included in these, for example, are assumptions about the baseline HRQOL and the *causal* effect of ICD on the HRQOL while alive.

The previously reported results from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) study demonstrate that ICD therapy saves lives.[18,19] The current study uses 3 years of HRQOL assessment data from U.S. patients in the MADIT II study to evaluate the health preferences in patients who received ICD therapy along with medical treatment compared with those on conventional medical treatment alone (hereafter referred to as ICD and CONV, respectively). The results presented here are based on actual health utility data and can provide a more accurate evaluation of the cost-utility of ICD therapy.

METHODS

Overview of Clinical Trial

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) used transvenous defibrillator systems (Guidant, St. Paul, MN). Reports detailing the methods and clinical outcomes of the clinical trial[19,20] and ICD cost per life year[18] have been published.

The trial was a controlled study that randomly assigned 1232 subjects with a prior myocardial infarction and a left ventricular ejection fraction of ≤ 0.30 to either ICD arm (n = 742) or CONV (n = 490). Enrollment occurred between July 11, 1997 and November 20, 2001 at 76 academic cardiovascular clinics in the United States (71 sites) and Europe (5 sites). Subjects were systematically followed annually for up to 4 years until the trial was stopped when a significant difference in mortality between the treatment arms was established (reduction in risk of all-cause mortality, with 95% power to detect a 37% reduction with two-sided significance level of 5%). The primary trial outcome was death from any cause. Secondary outcomes included the incidence of adverse events, economic outcomes, and HRQOL.

HRQOL analysis was based on a subset (n = 1089) of the total trial population since HRQOL questionnaires were not distributed among the subjects in European study centers (n = 109) and subjects with missing baseline HRQOL data (n = 22) were excluded from the analysis. In addition, subjects from study centers with poor data quality (n = 12) were omitted. The study used a rolling enrollment design, with subjects receiving differential follow-up time. As such, HRQOL data were right censored (at trial termination).

Health Related Quality of Life Assessment

HRQOL was measured using the Health Utility Index 3 (HUI3)[21] at baseline, and 3, 12, 24, and 36 months after randomization; any questionnaires returned after trial termination were excluded (n = 8). The HUI3 is a questionnaire that assesses HRQOL across 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort and can take values between −0.371 and 1, with −0.371 being the worst possible health state, 0 being death, and 1 being the best possible health state. The HUI3 uses a set of health preferences elicited from a sample of healthy population in Hamilton, Canada, to valuate self-reported health status of subjects in the MADIT II study.

The HUI3 was self-administered during face-to-face study visits. Subjects who did not complete the HRQOL assessment in the office at the time of visit were allowed to complete it at home and mail it back to the office before the next scheduled visit.

Analyses

Imputation of Missing HRQOL Data

Overall, 8.5% of HRQOL data were missing (290 of 3397 observations), either in the middle of the trial (56 intermittent missing, 1.6%) or at the end of an individual's enrollment (234 drop-out missing, 6.9%). Reasons for missing data were collected during the trial and varied from "subject being too sick to answer" to "form lost in the mail." An additional set of observations was missing HRQOL data even though subjects completed the HRQOL forms (69 observations from 59 patients) because of internal logical conflicts in their answers. We evaluated each of these cases and used subjects' responses on other instruments (health status of the subjects was also evaluated using nonpreference based instruments Duke Activity Status Index (DASI) and SF-12[22,23]) to resolve the internal contradictions and to allow for calculation of a total HUI3 score. These values were considered "not missing" for further analyses. For the subjects who died during the study (n = 175), HRQOL was assigned to zero for all visits subsequent to death (228 observations), until trial closing.

The missing HUI3 scores were imputed using a multivariate fixed-effects model, regressing the difference between a subject's baseline HRQOL score and a score at each subsequent visit on time, treatment, gender, age, death during the trial, death within 6 months after the HRQOL assessment, sudden death within 6 months of the HRQOL assessment, presence of diabetes, use of diuretics, and having NYHA class II–IV. Each variable was interacted with time, and death indicators were interacted with both time and treatment. We included subject-level fixed effects to capture the idiosyncratic component of each subject's HUI3 responses.

We imputed missing data by calculating predicted values using the above independent variables, all of which were observed, and the estimated individual idiosyncratic component of HRQOL. Implicit in this approach is the assumption that HRQOL data were missing at random (MAR), conditional on observed subject characteristics and the individual idiosyncratic component, similar to other studies.[24,25] All further analyses used the final dataset with imputed missing HRQOL values. We used STATA/SE Version 8.2 software for the modeling and SAS Version 8 for Windows for data

manipulations (StataCorp LP, College Station, TX; The SAS Institute, Cary, NC).

Primary Analyses

Expected Life Years

Kaplan-Meier survival estimates based on average monthly values were used to construct mean survival profiles for the both the ICD and CONV arms. The expected life years (LY) and years of life saved (YOLS), represented by the area under each profile and the difference in those areas, respectively, were calculated and discounted by 3% per annum (p.a.).[26,27]

Quality-Adjusted Life Years While Alive

Monthly HRQOL scores were estimated using linear interpolation between observed values (0, 3, 12, 24, and 36 months). The HRQOL score from the last observation was carried forward to the time of censoring or death, and set to missing thereafter. The change in HRQOL score from baseline at each point was calculated for each subject, and mean profiles were generated for each study arm. The changes in QALYs while alive, represented by the area under each arm's mean profile, were calculated and discounted by 3% p.a.

Overall Quality-Adjusted Life Years

Overall quality-adjusted life years were calculated using the same method as QALYs while alive. For deceased patients, monthly HRQOL scores were estimated using linear interpolation between the last point of support and the time of death, with HRQOL set to zero from that time forward until the end of the study time for that patient. Accumulated QALY gains/losses were calculated as described above.

Prespecified primary analyses were comparisons between treatment arms of each of these changes from baseline, discounted, and accumulated over 3 years: YOLS, QALYs while alive and overall QALYs. We focused in each on changes from baseline since average QALYs at baseline may vary between treatment arms. We used bootstrapping (1000 iterations resampled by patient) to estimate standard errors of the areas under the appropriate profiles and the estimates of incremental effectiveness; confidence intervals and *P* values were constructed by the bootstrapping percentile method.[28,29]

Evaluation of Treatment Effectiveness in Subpopulations

To assess whether key subpopulations had differential treatment effects, we estimated results for the following groups (as determined at randomization): males, females, subjects over age 65, subjects under 65 years of age, subjects in New York Heart Association functional class I or II–IV, subjects with ejection fraction of ≤25% or >25%, subjects with blood urine nitrogen >25 mg/dL or ≤25 mg/dL, and QRS duration of ≥120 milliseconds or <120 milliseconds using the same methods as above.

RESULTS

Study Population

Table 1 summarizes the baseline characteristics of the study population by treatment arm. The only statistically significant difference between the 2 groups at baseline was a higher proportion of diuretic use among CONV group patients ($P = 0.049$).

TABLE 1. Baseline Characteristics by Treatment Arm

Characteristics	ICD Group (N = 658)	Control Group (N = 431)
Means		
HUI3 score	0.637	0.646
SF-12 physical component score	36.293	36.444
SF-12 mental component score	50.505	50.419
Age (yr)	64.4	65.0
Percentages		
Male sex	83.0	84.9
Diabetes	33.6	37.0
NYHA functional class*		
I	35.6	39.2
II	32.7	32.5
III	26.0	22.3
IV	4.7	4.2
Current or former smoker	79.6	82.8
Coronary bypass surgery	59.1	56.6
Interval of >6 mo between most recent myocardial infarction and enrollment	89.6	87.3
Blood nitrogen urine >25 mg/dl	29.3	33.2
QRS interval ≥0.12 s	50.5	53.3
Hospitalized at baseline	14.7	10.9
Diuretic use at baseline	73.4	78.7†

Eligibility was limited to patients who were in NYHA class I, II, or III at the time of enrollment.

*Values reflect the highest New York Heart Association (NYHA) functional class recorded in the 3-month period before enrollment.

†$P = 0.049$; all other *P* values are >0.10.

The study population was mainly comprised of older adults, with 54% of subjects being aged 65 or older at baseline, and overwhelmingly male (84%). A number of baseline health indicators suggest that the study population was severely ill (Table 1). Baseline HUI3 scores averaged 0.641, ranging from −0.25 to 1 with a standard deviation of 0.294.

Unadjusted Survival and HRQOL Data

Table 2 summarizes the unadjusted (crude) survival and HRQOL data in the 2 arms during the study. This survival rate examines the proportions of subjects who are still alive among the subjects who were under observation at a certain time. At baseline, >10% of the patients had near-perfect health (score ≥0.95), roughly half had scores exceeding 0.7, and approximately 5% had scores nearly as bad as the score for death (scores ≤0.05). It is important to notice that since the HUI3 scores represent preferences of general population for the health states of the MADIT II subjects, these scores are likely to be lower than patients' own valuation for their health.[30–34]

The CONV arm had lower survival rates at each year after randomization compared with the ICD arm, with 66.7%

TABLE 2. Unadjusted HRQOL Data Summary

	Conventional Arm				ICD Arm			
Year (y) After Randomization	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
Survival								
n = observed at least y years	431	321	183	81	658	489	279	129
r = alive at least y years	431	290	145	54	658	455	236	99
p = proportion alive (r/n)		0.903	0.792	0.667		0.93	0.846	0.767
HUI3 scores while alive								
m = missing scores among alive		49	30	12		46	39	17
% of (r-m) scores ≥0.95	12	13	15	26	14	15	14	13
Median HUI3 score while alive	0.72	0.74	0.73	0.70	0.71	0.70	0.70	0.685
% of (r-m) scores ≤0.05	5.6	4.6	3.5	2.4	4.7	5.9	5.6	6.1
Mean HUI3 score while alive	0.646	0.659	0.667	0.678	0.637	0.627	0.622	0.601
Mean annual change in HUI3 score*		−0.012	−0.011	−0.013		−0.019	−0.027§	−0.019‡
Overall mean score including death†	0.646	0.595	0.529	0.452	0.637	0.584	0.526	0.461

HRQOL (HUI3) scores may range from 1.0 (perfect health) down to −0.371, with 0.0 considered equivalent to death. Scores were also recorded at 3 months, but are omitted from this summary table. All observations, whether survival information or HRQOL scores, are censored at trial termination. The number (n) of patients observed declines rapidly due to rolling enrollment. Later analyses replace missing scores by regression-based imputation, extend last recorded scores forward to death or end of study, interpolate to obtain monthly values, and integrate over time to obtain cumulative effects; see Methods.

*Equals (difference from baseline)/y, limited to the r-m patients with scores available on both occasions, and hence for patients surviving at least y years.

†Mean HRQOL score (among n patients) after setting scores for dead = 0.

‡$P < 0.10$.

§$P < 0.05$.

of CONV subjects with 3-year potential exposure surviving compared with 76.7% of ICD subjects.

The HRQOL experience of the 2 arms was more complicated. While the mean HRQOL score while alive declined in the ICD arm, it increased over time in the CONV arm. This changes, however, when looking only at the data of subjects that survived to a given year. The mean per year change in the HRQOL score from baseline for the ICD arm significantly declined at 2 years (−0.027, $P = 0.02$) but was not significant at 3 years (−0.019, $P = 0.08$). There was no significant decline in the HRQOL for survivors in the CONV arm (averaged −0.012 each year, with P values ranging from 0.27 to 0.42) suggesting that individuals with relatively high HRQOL were more likely to survive, without any changes in HRQOL over time, resulting in the increase in the mean HRQOL over time in the CONV arm. There were no statistically significant differences in the mean per year changes from baseline between the 2 groups. Meanwhile, for the survivors in the ICD arm the HRQOL was declining over time. Overall, the increased survival among patients in the ICD arm was offset by worsened HRQOL among ICD survivors, while the reduced survival in the CONV arm was offset by the elimination of those with the lowest HRQOL.

Primary Analyses

The left side of Figure 1 presents the actual mean group profiles for survival, QALYs while alive, and overall QALYs. Figure 1a presents the survival benefit of the ICD, as seen earlier in MADIT II studies,[18,19] but now limited to the 3-year span of this study. Figure 1c shows that surviving CONV patients have a steady HRQOL while the HRQOL for surviving ICD patients gradually declines, on average. When scoring death as HRQOL = 0, the average HRQOL declined (Fig. 1e) due only to mortality in the CONV patients, but due to both mortality and declining values for HRQOL while surviving for ICD patients; the result is a slope of approximately 0.06 QALYs per year, or 0.005 per month, (on average) in each treatment arm.

Of primary interest, for each treatment arm, are the changes from baseline in each of these curves. The 3 parts (b, d, and f) on the right side of Figure 1 show these changes, with the shaded areas between them being the accumulating differences between the 2 arms.

Table 3 details the accumulated QALY outcomes relative to baseline at 3 years, discounted at 3% annually and undiscounted.[7] Patients in the ICD arm were expected to have 0.123 discounted years (1.5 months) more than patients in the CONV arm over 3 years of treatment. Although the point estimate was negative, there was no statistically significant difference in the discounted QALYs loss between the 2 arms (−0.037, SE = 0.072, $P = 0.64$) before adjustment for survival. The difference in the discounted overall QALYs loss between the 2 arms (0.043, SE = 0.073, $P = 0.37$) was positive but not statistically different from zero over 3 years. To examine the impact of the negative HRQOL scores, we replaced them with 0 but this did not substantively change the results.

Although the results are imprecisely estimated, the differences in QALY between the treatment arms are also small. Computing confidence bounds, we find that the overall QALY difference is positive with confidence of 82% and the effect size exceeds 2 quality-adjusted months with the confidence of 7.6%.

Subgroup Analysis

For each of the key subgroups, the accumulated differences between the ICD and CONV arms at 3 years are presented in Table 4. Point estimates of the effects were often

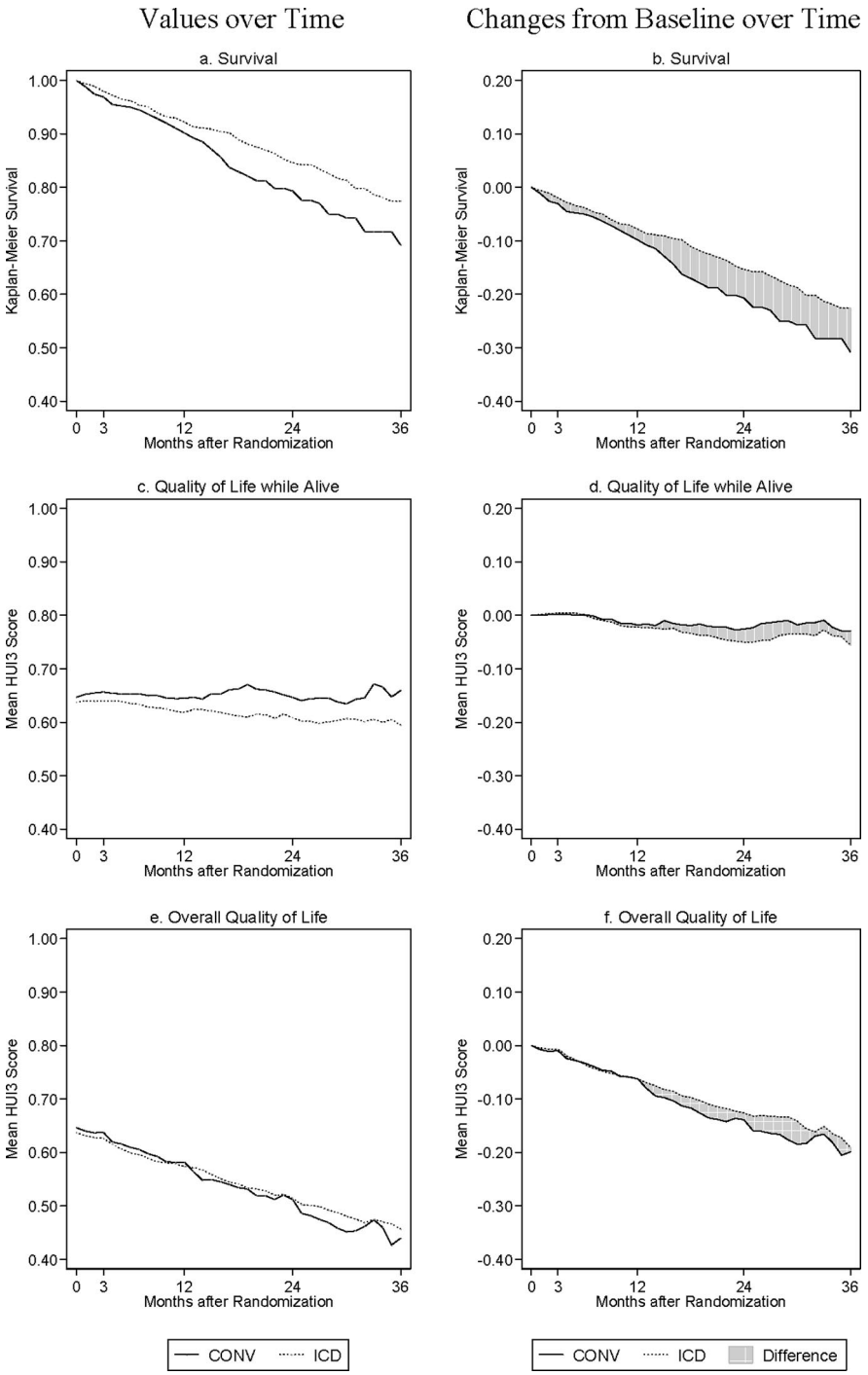

FIGURE 1. Mean group profiles: primary analyses. The left panel represents plots for (a) survival; (c) quality of life while alive; (e) quality of life adjusting for survival, separately for each treatment arm (solid line: conventional treatment only, dotted line: ICD). The right side presents changes from-baseline in these, with shading for the accumulating difference in changes between the 2 treatment arms: (b) survival; (d) quality of life while alive; (f) quality of life adjusting for survival, separately for each treatment arm (solid line: conventional treatment only, dotted line: ICD, shaded area: accumulated difference).

larger for the higher risk subjects than for the lower risk subjects, and the direction of the effects was generally consistent with the primary results: positive for survival and expected overall QALYs, and negative for expected QALYs while alive. The only statistically significant treatment effect among the subgroups, however, were modest improvements in survival for ICD subjects over CONV subjects for those age 65 years and older (0.192, SE = 0.087, $P = 0.02$), for those in NYHA classes II–IV (0.144, SE = 0.078, $P = 0.04$), and for those with QRS interval longer than 120 milliseconds (0.167, SE = 0.083, $P = 0.03$). No other significant differences were found.

One noteworthy subgroup was women. Though not significantly different from zero, female subjects statistically had the largest estimated benefits in survival (0.298, SE = 0.168, $P = 0.07$) and in overall QALYs (0.261, SE = 0.203, $P = 0.14$). There were no other subgroups for which the overall QALY effects were substantively large. Computing

TABLE 3. Primary Analyses: Life Years and Accumulated Quality Adjusted Life Year (QALY)* Changes at 3 Years

Cumulative Losses in	CONV	ICD	Difference†	*P*‡	95% CI‡
Undiscounted					
Life years	0.470	0.341	0.129	0.02	0.021 to 0.257
QALYs while alive	0.040	0.079	−0.039	0.64	−0.181 to 0.115
Overall QALYs	0.322	0.277	0.045	0.37	−0.087 to 0.220
Discounted (at 3% p.a.)					
Life years	0.450	0.327	0.123	0.02	0.020 to 0.246
QALYs while alive	0.039	0.076	−0.037	0.64	−0.173 to 0.110
Overall QALYs	0.309	0.266	0.043	0.37	−0.084 to 0.212

All changes are accumulated from baseline to 3 years.
*Overall QALYs include those who have died, scoring HRQOL as 0.
†CONV minus ICD.
‡*P* values and 95% confidence intervals were based on standard errors determined by bootstrapping.

TABLE 4. Subgroup Analyses: Life Years and Accumulated Discounted* Quality Adjusted Life Year (QALY) Differences Between ICD and Conventional Arms at 3 Years

	Change in Life Years			Change in QALYs While Alive			Change in Overall QALYs		
Subgroup	Difference	SE†	*P*	Difference	SE†	*P*	Difference	SE†	*P*
Age, years									
≥65	0.192	0.084	0.02	−0.075	0.091	0.46	0.045	0.096	0.46
<65	0.035	0.068	0.61	0.004	0.105	0.95	0.042	0.113	0.62
NYHA									
II–IV	0.144	0.078	0.04	0.029	0.096	0.72	0.108	0.093	0.18
I	0.106	0.082	0.18	−0.124	0.098	0.19	−0.054	0.121	0.83
QRS									
≥120 ms	0.167	0.083	0.03	−0.122	0.104	0.24	−0.013	0.103	0.97
<120 ms	0.074	0.081	0.33	0.045	0.097	0.65	0.088	0.106	0.34
BUN									
>25 mg/dl	0.250	0.125	0.05	−0.068	0.133	0.65	0.034	0.135	0.70
≤25 mg/dl	0.067	0.059	0.21	−0.026	0.081	0.71	0.054	0.088	0.41
LVEF									
≤25%	0.115	0.072	0.11	0.002	0.087	0.96	0.083	0.090	0.19
>25%	0.143	0.097	0.11	−0.123	0.116	0.32	−0.055	0.128	0.76
Gender									
Female	0.298	0.168	0.07	0.049	0.186	0.77	0.261	0.203	0.14
Male	0.096	0.060	0.11	−0.057	0.074	0.46	0.006	0.079	0.79

The subgroup with greater mortality is listed first in each dichotomy.
*Results are discounted 3% p.a. from randomization.
†Standard errors (SE) and *P* values were determined by bootstrapping.

lower confidence bounds similar to the main results, we find that the overall QALY benefit for women is positive with 93% confidence, exceeds 1 month with 86% confidence, exceeds 3 months with 60% confidence, and exceeds 6 months with 16% confidence.

DISCUSSION

There is strong evidence from the MADIT II study that ICD therapy extends life, but the ICD provides little or no quality of life benefits. While our results demonstrate that there is considerable variability in the estimates of the QALY effects, it is unlikely ($P < 0.05$) that the benefit is greater than 2 quality-adjusted months (0.167 QALY) after 3 years of therapy. Our survival results differ slightly from previously published results (estimated 2 months gain within 3.5 years)[18] because our analysis was limited to a 3-year follow-up period.

There are several plausible explanations for the lack of QALY benefit of the ICDs in contrast with the substantial survival benefit. The mean HRQOL for the MADIT II sample at baseline is only about 0.64. Thus, even if HRQOL while alive remained constant and unaffected by the ICD, the value of the survival benefit in terms of QALYs would be reduced by nearly 40%, that is 1.5 months of survival benefit would be

reduced to 1 month. It is important to note here that various tools for HRQOL elicitation are known to result in different estimates of health utility[35] and that the general public values the same health states lower than patients living in these health states.[30–34] For the purpose of cost-effectiveness evaluation, the Panel on Cost-Effectiveness[6] recommends using health preferences of general population, as assessed by the HUI3. Although the HUI3 is a widely accepted measure of HRQOL, it was not designed to address cardiovascular issues, and it may be too blunt to reflect subtle but important benefits of the ICD.

The survival benefit of ICD may be greater for those at higher risk of death and those with worse health status.[3] Over time, this effect could reduce the average HRQOL among those with the ICD compared with those in the CONV group, and consequently reduce the magnitude of any QALY effect. This is precisely the HRQOL pattern shown in Table 2, and we found similar (though limited) evidence in the more complex analyses that, conditional on survival, patients who received medical treatment only (CONV) had better HRQOL. Though the effects were not statistically significant, the relative reduction in quality of life while alive for those in the ICD arm did contribute to a reduced overall QALY effect for this group. This finding was consistent across subpopulations and acted to reduce the life year survival benefit in terms of QALYs. The magnitude of the survival (life years) benefit is large, but combined with the loss in QALYs while alive, the resulting gain in expected QALYs (including survival) is positive but small and not statistically significant.

The ICD device may cause a reduction in the HRQOL. Goldenberg et al[37] showed that the ICD reduces the risk of sudden death but increases the likelihood of later heart failure events. The ICD may also generate psychologic problems, with deleterious effects on HRQOL. Studies have demonstrated that 30–50% of ICD recipients experience fear, anxiety, or depression following ICD implantation.[38–40] Both appropriate and inappropriate shocks may diminish HRQOL by contributing to patient's anxiety.[41,42] The extent to which each of these factors offsets the survival benefit, however, requires further study.

A major limitation of this study is the relatively short time horizon of the HRQOL evaluation. Implantation of an ICD is associated with considerable upfront costs while the benefits are accrued over time. The limited time horizon of the HRQOL evaluation could result in a significant underestimation of the lifetime benefit of the ICD, particularly if the survival benefit is maintained. Another potential limitation is the choice of the HRQOL instrument in the MADIT II study. We limit the analysis here to a 3-year within trial time horizon QALY evaluation. Because our study demonstrates no significant difference in QALYs gained between the ICD and CONV arms over the 3-year study period, we made the decision not to extend the time horizon with long-term projections. Such out-of-sample projections of QALY benefits would rely heavily on unsupported assumptions that would substantially increase the uncertainty around the QALY estimates.

Our work builds on the cost analysis by Zwanziger and colleagues[18] who reported that 3.5 years after device implantation, ICD patients accumulated $39,200 more in associated expenses than conventionally treated patients. Since we find no statistically significant QALY benefits (with the point estimates being small and imprecisely estimated), the 3-year incremental cost effectiveness ratio (ICER) would have an unbounded confidence interval. Using the costs estimates reported by Zwanziger and colleagues[18] and our estimates of the ICD effect confidence bounds, we concluded that the 3-year ICER would fall above $235,000/QALY with 95% confidence.

According to our estimates above, is the quality-adjusted ICER of the ICD within acceptable limits? We cannot say because acceptable limits are not being set for limited horizons. Because we have found such a small and uncertain effect in 3 years, we are not able to make long-term projections.

By contrast, the SCD-HeFT cost study[14] has projected the lifetime quality-adjusted ICER to be $41,530/QALY, however, little detail has been provided about their assumptions and methods. Their time trade-off assessment of quality is reported as 0.85 per year of life, and claimed to be constant over time and over treatment groups, whereas our utility-based assessment averages 0.64 at baseline with some modest change over time. Mark and colleagues[14] provide no information for a 3-year horizon and we provide none for lifetime; their 5-year estimates are influenced greatly by whether or not a generator replacement is included ($126,664/QALY ICER without replacement, $208,192/QALY ICER with). Because of that, only comparisons at the intermediate horizons of 6 and 12 years are possible.[14,18]

At 6 years, the MADIT II[18] and SCD-HeFT[14] projections of ICER are both approximately $150,000 per life year saved. But the 12-year projections (MADIT II) are higher than those from SCD-HeFT, say $80,000 versus $60,000 when a continuing ICD effect is assumed. Our quality adjustments (roughly 0.64) are substantially lower than theirs (0.85), which would inflate any quality-adjusted ICER more than theirs are inflated (crudely, by 1/0.64 vs. 1/0.85). In fact, their reported lifetime ICER is only inflated by a divisor of 0.924 (lifetime ICER of $38,389 before quality adjustment and $41,530 after). It can be argued that this would seem to imply that either quality of life increases considerably above 0.85 in survivors in both arms or else quality of life in ICD-arm patients exceeds that in placebo patients over extended lifetimes. Neither of these assumptions is consistent with our in-trial data, nor would it seem to be with theirs as summarized in Mark et al.[14] Still, quality adjustment will certainly increase incremental costs per year-of-life saved, possibly by 50% or more. This leads us to believe that lifetime quality-adjusted costs per quality-adjusted life year saved, as measured in the MADIT II population, will likely exceed $100,000.

The results of our main and subgroup analyses have important implications for policy and clinical practice. With the number of treatment options growing every year, most health insurance plans, including federal- and state-sponsored plans like Medicare and Medicaid, are more willing to incor-

porate scientific evidence when making decisions about covered services and drug formularies.[43,44] While other factors, including equity, political power, and medical ethics, may play an important role in the decision making process, evidence of clinical effectiveness and cost-effectiveness of ICD for various population groups is valuable. In situations in which more than 1 treatment option is available, each with different benefits and side-effect profiles, making the right choice may depend not only on medical judgment but also on patient preferences. Evidence of the ICD QALY benefit in addition to its survival benefits may aid physician-patient discussions when making these treatment decisions, allowing for a more complete discussion of the long-term health consequences of ICD therapy.

ACKNOWLEDGMENTS

The authors thank the patients in the study and the investigators and coordinators of the MADIT II Data Center directed by Mary W. Brown.

REFERENCES

1. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary artery bypass graft (CABG) patch trial investigators. *New Eng J Med*. 1997;337:1569–1575.
2. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *New Engl J Med*. 2004;351:2481–2488.
3. Moss AJ. Implantable cardioverter defibrillator therapy. The sickest patients benefit the most. *Circulation*. 2000;101:1638–1640.
4. Leplege A, Hunt S. The problem of quality of life in medicine. *JAMA*. 1997;278:47–50.
5. Testa MA, Simmonson DC. Assessment of quality in life outcomes. *New Engl J Med*. 1996;334:835–840.
6. Gold MR, Siegel JE, Russell LB, et al. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
7. Drummond MF, O'Brien BJ, Stoddart GL, et al. *Methods for Economic Evaluation of Health Care Programmes*. Oxford, UK: Oxford University Press; 1997.
8. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population health. *Ann Rev Public Health*. 2002;23:115–134.
9. McCready MJ, Exner DV. Quality of life and psychological impact of implantable cardioverter defibrillators: focus on randomized controlled trial data. *Card Electrophysiol Rev*. 2003;7:63–70.
10. Irvine J, Dorian P, Baker B, et al. Quality of life in the Canadian implantable defibrillator study (CIDS). *Am Heart J*. 2002;144:282–289.
11. Newman DM, Dorian P, Paquette M, et al. Effect of an implantable cardioverter defibrillator with atrial detection and shock therapies on patient-perceived, health-related quality of life. *Am Heart J*. 2003;145:841–846.
12. Kamphuis HCM, deLeeuw JRJ, Derksen R, et al. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery. *Europace*. 2003;5:381–389.
13. Schron EB, Exner DV, Yao Q, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation*. 2002;105:589–594.
14. Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the sudden cardiac death in heart failure trial (SCD-HeFT). *Circulation*. 2006;114:135–142.
15. Al-Khatib SM, Anstrom KJ, Eisenstein EL, et al. Clinical and economic implications of the multicenter automatic defibrillator implantation trial-II. *Ann Intern Med*. 2005;142:593–600.
16. Technology Evaluation Center, Blue Cross-Blue Shield Association. Special report: cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population. Blue Cross-Blue Shield Association; 2004:1–23.
17. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med*. 2005;353:1471–1480.
18. Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the multicenter automatic defibrillator implantation trial (MADIT)-II. *J Am Coll Cardiol*. 2006;47:2310–2318.
19. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.
20. Moss AJ, Daubert JP, Weal H. Multicenter automatic defibrillator implantation trial II (MADIT II): design and clinical protocol. *Ann Noninvasive Electrocardiol*. 1999;4:83–91.
21. Furlong WJ, Feeny DH, Torrance GW, et al. The health utility index (HUI) system for assessing health-related quality of life in clinical studies. *Ann Med*. 2001;33:375–384.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
23. Alonso J, Permanyer-Miralda G, Cascant PBC, et al. Measuring functional status of chronic coronary patients. Reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). *Eur Heart J*. 1997;18:414–419.
24. Noyes K, Dick AW, Holloway RG. Dynamic changes in cost-effectiveness: comparing pramipexole and levodopa in early Parkinson's disease. *Pharmacoeconomics*. 2005;23:1257–1270.
25. Engels JM, Diehr P. Imputation of missing longitudinal data: a comparison of methods. *J Clin Epi*. 2003;56:968–976.
26. Ramsey SD, McIntosh M, Sullivan SD. Design issues for conducting cost-effectiveness analyses alongside clinical trials. *Ann Rev Public Health*. 2001;22:129–141.
27. Noyes K, Dick AW, Holloway RG, et al. Pramipexole vs Levodopa as initial treatment for Parkinson's Disease: a randomized clinical-economic trial. *Med Decis Making*. 2004;24:472–485.
28. Efron B, Tibshirani R. Bootstrap measures of standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci*. 1986;1:54–77.
29. Davison A, Hinkley D. *Bootstrap Methods and Their Applications*. Cambridge, MA: Cambridge University Press; 1997.
30. Epstein MA, Hall JA, Tognetti J, et al. Using proxies to evaluate quality of life. *Med Care*. 1989;27:S91–S98.
31. Naiman J, Levine S. Evaluating the impact of medical care and technologies on the quality of life: a review and critique. *Soc Sci Med*. 1981;15F:107–115.
32. Sackett DL, Torrance GW. The utility of different health states as perceived by the general public. *J Chronic Dis*. 1978;31:697–704.
33. Slevin ML, Stubbs L, Plant HJ, et al. Attitude to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. *BMJ*. 1990;300:1458–1460.
34. Boyd NF, Sutherland HJ, Heasman ZK, et al. Whose utilities for decision analysis? *Med Decis Making*. 1990;10:58–67.
35. Franks P, Hanmer J, Fryback DG. Relative disutilities of 47 risk factors and conditions assessed with seven preference-based health status measures in a national U.S. sample: toward consistency in cost-effectiveness analyses. *Med Care*. 2006;44:478–485.
36. Deleted in proof.
37. Goldenberg I, Moss AJ, Hall WJ, et al. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation*. 2006;113:2810–2817.
38. Sola CL, Bostwick JM. Implantable cardioverter-defibrillators, induced anxiety, and quality of life. *Mayo Clin Proc*. 2005;80:232–237.
39. Dunbar SB, Warner CD, Purcell JA. Internal cardioverter defibrillator device discharge: experiences of patients and family members. *Heart Lung*. 1993;22:494–501.

40. Sears SE, Conti JB. Understanding implantable cardioverter defibrillator shocks and storms: medical and psychosocial considerations for research and clinical care. *Clin Cardiol*. 2003;26:107–111.
41. Carroll DL, Hamilton GA. Quality of life in implanted cardioverter defibrillator recipients: the impact of a device shock. *Heart Lung*. 2005;34:169–178.
42. Wallace RL, Sears SF, Lewis TS, et al. Predictors of quality of life in long-term recipients of implantable cardioverter defibrillators. *J Cardiopulm Rehabil*. 2002;22:278–281.
43. Stevenson LW. Implantable cardioverter-defibrillators for primary prevention of sudden death in heart failure: are there enough bangs for the bucks? *Circulation*. 2006;114:101–103.
44. Gillick MR. Medicare coverage for technological innovations—time for new criteria? *N Eng J Med*. 2004;350:2199–2202.