Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 19, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.06.054

Cardiac Resynchronization and Quality of Life in Patients With Minimally Symptomatic Heart Failure

Peter J. Veazie, PhD,* Katia Noyes, PhD, MPH,* Qinghua Li, MS,* W. Jackson Hall, PhD,† April Buttaccio, MPH,‡ Kelly Thevenet-Morrison, MS,* Arthur J. Moss, MD‡

Rochester, New York

Objectives This study compared the quality of life (QOL) of patients with cardiac resynchronization therapy (CRT) and an implantable cardioverter-defibrillator (ICD) to patients with an ICD only.

Background CRT with ICD is associated with a reduction in heart failure risk among minimally symptomatic patients. It is unknown whether this improves QOL.

Methods This study uses the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) data. The MADIT-CRT enrolled 1,820 patients at 110 centers across 14 countries. Patients had ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NYHA functional class II only), sinus rhythm, an ejection fraction of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 ms or more. QOL was evaluated on the 1,699 patients with baseline and follow-up measures using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Six dimensions (Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Quality of Life, and Social Limitations) and 3 summary scores (Total Symptom, Clinical Summary, and Overall Summary) were analyzed.

Results During an average follow-up of 2.4 years, the CRT-ICD group had greater improvement than the ICD-only group on all KCCQ measures ($p < 0.05$ on each scale). These differences were significant among patients with left bundle branch block conduction disturbance ($n = 1,204$, $p < 0.01$ on each scale), but not among patients without left bundle branch block ($n = 494$).

Conclusions Compared with patients with ICD only, CRT-ICD is associated with greater improvement in QOL among relatively asymptomatic patients, specifically among those with left bundle branch conduction disturbance. (J Am Coll Cardiol 2012;60:1940–4) © 2012 by the American College of Cardiology Foundation

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) showed the combined cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD), compared with ICD only, had a 34% reduction in risk of death from any cause or a nonfatal heart failure event among patients with mild heart failure (New York Heart Association [NYHA] functional classes I and II). This reduction was primarily driven by a 41% reduction in the risk of heart failure events (1). Moreover, Zareba et al. (2) and Goldenberg et al. (3) reported that CRT-ICD therapy was primarily beneficial among those with a left bundle branch block (LBBB) conduction disturbance.

In this paper, we address whether adding CRT to ICD comes at the expense of a decrease in quality of life, or whether it provides an improvement among patients with mild heart failure (NYHA functional classes I and II). We assess changes in quality of life among those with and without LBBB conduction disturbance.

Methods

Detailed information about the MADIT-CRT study design, randomization, recruitment, and outcome has been published (1,4). The MADIT-CRT trial enrolled 1,820 patients at 110 centers in 14 countries (1,271 patients in the United States) from December 22, 2004, through April 23, 2008; the trial was stopped on June 22, 2009. Patients enrolled in the study had ischemic cardiomyopathy (NYHA functional class I or II) or nonischemic cardiomyopathy (NYHA functional class II only), sinus rhythm, an ejection

From the *Department of Community and Preventive Medicine, University of Rochester Medical Center, Rochester, New York; †Department of Biostatistics and Computational Biology, University of Rochester Medical Center, Rochester, New York; and the ‡Department of Medicine, University of Rochester Medical Center, Rochester, New York. This project was funded by Boston Scientific through the MADIT-CRT project. Dr. Moss has received consulting and honorarium fees from Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 30, 2012; revised manuscript received June 15, 2012, accepted June 19, 2012.

fraction of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 ms or more.

The analyses presented here were based on 1,699 patients, which comprise the subset of the original 1,820 patients who had baseline observations and at least 1 additional observation on our outcome variables up to the close of the study.

Quality-of-life assessment. To assess quality of life, we used 6 basic scales and 3 summary scales of the Kansas City Cardiomyopathy Questionnaire (KCCQ) instrument that comprises heart failure–specific quality-of-life–related measures (5–11). The 6 basic scales included the Symptom Stability, Symptom Frequency, Symptom Burden, Physical Limitation, Quality of Life, and Social Limitation scales. The 3 summary scales included the Total Symptom, Clinical Summary, and Overall Summary scores. See the Online Appendix for a discussion of these scales.

Quality-of-life analysis. We used feasible generalized least squares (12) to estimate models of the KCCQ measures in which all variables are centered on hospital means, thereby eliminating hospital fixed effects, and multiplied by heteroskedasticity weights to account for the different numbers of subjects at each hospital.

The data were slightly different in baseline blood pressure across the arms; therefore, to reduce error variance, we adjusted analyses for baseline systolic and diastolic blood pressure levels.

For each KCCQ scale, we estimated 2 models: Model 1 tested the difference in the change from baseline in the CRT-ICD group compared with the change from baseline in the ICD-only group on the KCCQ scales across the 4.5 years of the study period. Model 2 tested whether the treatment effect varied across time period quintiles within the 4.5 years of the study period: joint tests were used of the interaction terms between indicators of the time quintiles and the indicator of CRT-ICD group.

LBBB subgroup analyses. We repeated the analyses of Models 1 and 2 on the LBBB and non-LBBB subgroups. We investigated whether the differences in effects were statistically different between the LBBB and non-LBBB subgroups in Model 1 by testing the interaction of the LBBB indicator and the CRT-ICD group indicator using data that included all patients.

Sensitivity analyses. See the Online Appendix for our investigation of whether date of enrollment, dying or being lost to follow-up, or the patient switching device during the study impacted the KCCQ scores differentially across study arms.

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy

ICD = implantable cardioverter-defibrillator

KCCQ = Kansas City Cardiomyopathy Questionnaire

LBBB = left bundle branch block

NYHA = New York Heart Association

Results

Patient characteristics. Table 1 shows baseline characteristics and baseline KCCQ scores of the study cohort by treatment arm and LBBB status.

Quality-of-life differences and trends. Figure 1 shows the estimated difference in effects between the CRT-ICD and ICD-only groups, and the corresponding 95% confidence

Table 1 Baseline Characteristics and KCCQ Scores by Treatment Arm and LBBB Status

	All Patients*		LBBB Patients		Non-LBBB Patients	
	ICD-Only (n = 675)	CRT-ICD (n = 1,024)	ICD-Only (n = 482)	CRT-ICD (n = 722)	ICD-Only (n = 192)	CRT-ICD (n = 302)
Characteristics						
Age, yrs	64.4 ± 10.6	64.4 ± 10.8	64.4 ± 10.8	64.1 ± 10.9	64.4 ± 10.3	65.1 ± 10.7
Female, %	24%	25%	29%	32%	12%	10%
Systolic blood pressure	120.8 ± 17.7	123.8 ± 17	121.1 ± 17.6	123.9 ± 16.6	120.1 ± 18.2	123.5 ± 17.9
Diastolic blood pressure	70.7 ± 10.4	72.3 ± 10.2	70.3 ± 10.4	72.3 ± 10.0	71.5 ± 10.4	72.3 ± 10.6
NYHA functional class I†	16%	14%	12%	11%	25%	21%
Baseline KCCQ scores‡						
Symptom stability	50.3 ± 13.9	50.3 ± 14.6	50.9 ± 13.9	50.7 ± 14.0	48.7 ± 14.0	49.2 ± 16.0
Symptom frequency	81.6 ± 19.4	81.0 ± 19.7	81.8 ± 19.4	82.0 ± 18.8	81.0 ± 19.5	78.8 ± 21.6
Symptom burden	82.7 ± 18.0	82.2 ± 18.1	83.1 ± 17.7	83.0 ± 17.1	81.7 ± 18.8	80.3 ± 20.2
Physical limitation	78.1 ± 20.6	78.8 ± 19.6	78.4 ± 20.2	79.7 ± 18.6	77.3 ± 21.7	76.6 ± 21.6
Quality of life	66.4 ± 24.4	66.4 ± 23.2	66.1 ± 24.0	66.9 ± 22.5	67.4 ± 25.7	65.4 ± 24.8
Social limitation	74.1 ± 25.5	75.4 ± 23.8	74.3 ± 25.6	76.5 ± 22.7	73.6 ± 25.3	72.7 ± 26.1
Total symptom score	82.1 ± 18.0	81.6 ± 18.2	82.5 ± 17.8	82.5 ± 17.2	81.3 ± 18.4	79.5 ± 20.1
Clinical summary score	80.2 ± 17.8	80.2 ± 17.1	80.5 ± 17.5	81.1 ± 16.4	79.4 ± 18.5	78.1 ± 18.6
Overall summary score	75.2 ± 19.1	75.6 ± 18.2	75.4 ± 18.7	76.4 ± 17.4	74.9 ± 20.2	73.7 ± 19.8

Values are mean ± SD or %. Data are from patients who had baseline blood pressure measures and at least 2 KCCQ measures, including baseline. Systolic and diastolic blood pressures are the only significantly different variables between ICD-only and CRT-ICD groups for All Patients, LBBB Patients, and Non-LBBB Patients. *One individual did not have an indicated LBBB status and is included only in the All Patients results. †The percentage for NYHA functional class II classification is 100 minus the reported percent for NHYA functional class I. ‡Some scores (at most, 5%) are missing.

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LBBB = left bundle branch block; NYHA = New York Heart Association.

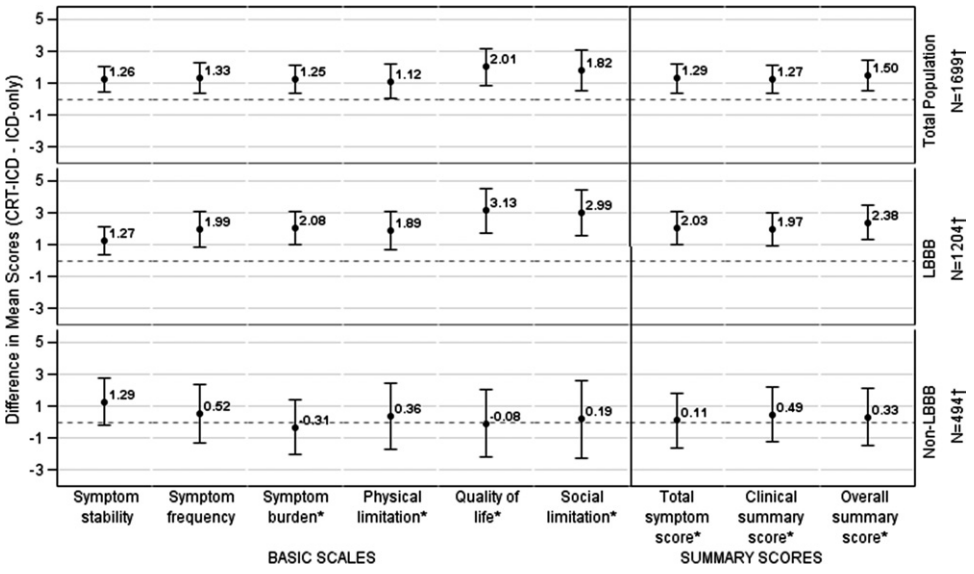

Figure 1 **Differences in Effect and 95% CIs, for Each KCCQ Measure**

Differences in effect is defined as the change from baseline for the cardiac resynchronization therapy–implantable cardioverter-defibrillator (CRT-ICD) group minus change from baseline for the ICD-only group. Results are adjusted for baseline systolic and diastolic blood pressure levels. *Significantly different effects between the LBBB and non-LBBB subgroups; †Up to 5% of patients were omitted due to missing data. CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Questionnaire; LBBB = left bundle branch block.

intervals, from Model 1 for each KCCQ measure, adjusted for baseline systolic and diastolic blood pressure levels. A positive value means the CRT-ICD group had a larger effect (i.e., change from baseline) in KCCQ scores than the ICD-only group. The first panel depicts estimates for the entire study population. The second panel depicts the estimates for the LBBB subgroup. The third panel depicts estimates for the non-LBBB subgroup, which were not significant for each measure. The interactions between the LBBB indicator and ICD-CRT group indicator, estimated using all patients, were significantly different between the LBBB and non-LBBB subgroups for all KCCQ measures ($p < 0.05$) except for the Symptom Severity and Symptom Burden scales ($p = 0.91$ and $p = 0.06$, respectively).

The analysis of Model 2, using the entire study population, resulted in rejecting the hypothesis that the treatment effect does not vary by time for each KCCQ measure (significant at the 0.05 level), except for the Physical Limitation, Symptom Frequency, and Symptom Stability scales, which were not significant. The significant findings on these joint tests suggested that a difference in effect exists for at least 1 of the time quintiles. However, we cannot rule out that at least 1 time quintile had no difference (the joint test of the hypothesis that at least 1 parameter was 0 was insignificant for each measure—all tests had p values >0.49). The LBBB subgroup analysis of Model 2 resulted in in the same inferences, but results of Model 2 applied to the non-LBBB subgroup were not significant for each measure.

Figure 2 shows the mean Overall Summary score of the KCCQ among the LBBB subgroup for each 6-month period between enrollment and Year 3. Table 2 shows the sample sizes for each of these time periods by treatment group. Similar to the preceding analyses, these differences based on the non-LBBB subgroup were not statistically significant, whereas those based on the full sample fell in between.

Discussion

The results of this study provide evidence that CRT-ICD is associated with better improvement in heart failure–specific quality of life than ICD-only among minimally symptomatic patients. Specifically, better effects were found among the CRT-ICD group with respect to all KCCQ measures we evaluated. These findings were statistically evident among patients with LBBB but not discernible among those without this conduction disturbance. Evidence suggests that the difference between groups varies across time since enrollment, particularly during the first 2 years.

The KCCQ scores range from 0 through 100 points. The magnitudes of treatment-assignment effects on changes in the KCCQ measures reported here are on the order of approximately 1 to 3 points. Spertus et al. (13) found that differences of 5 points on KCCQ Overall Summary score correspond to changes in patient heart failure status that were judged by cardiologists to be small in terms of clinical changes. Changes in patient clinical heart failure status judged to be large by cardiologists corresponded to changes

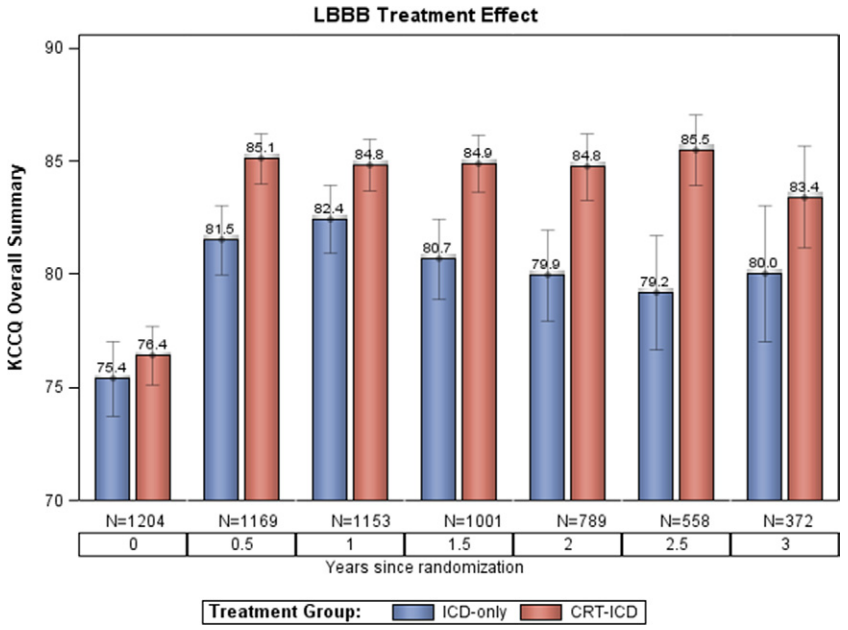

Figure 2 **Average Overall Summary Score (With 95% CI) by Treatment Status Among LBBB Patients for Every 6 Months From Randomization to 3 Years**

Each difference between CRT-ICD and ICD-only groups is statistically significant except at baseline and year 3. Sample sizes for each group are shown in Table 2. Abbreviations as in Figure 1.

in KCCQ Overall Summary scores of between 20 and 25. Flynn et al. (14) found a 5-point change in the KCCQ overall score was associated with a 2.50-ml/kg change in peak Vo_2 and a 112-m change in 6-min walking distance; they judged these changes to be clinically meaningful. What is not clear, however, is how patients, rather than cardiologists and researchers, would deem the difference in life experiences, rather than clinical indicators, that correspond to the differences in effects that we observed. This is an important factor for providers assisting patients to attain the patients' goals, particularly for patients who value the quality of their life experiences (15).

There is insufficient previous research on minimally symptomatic patients (i.e., research restricted to NYHA functional class I and II) to provide a direct comparison for our results. The aforementioned studies by Spertus et al. (13) and Flynn et al. (14) evaluated sicker patient groups that include NYHA functional classifications greater than II. This is true of other studies that evaluate KCCQ measures as well. For example, Myers et al. (16), Sullivan et al. (16), Ekman et al. (17), Eurich et al. (6), Heidenreich et al. (18), and Soto et al. (19), each found associations between KCCQ measures and relevant outcomes, but each were assessing a sicker patient population (including NHYA functional classes III and/or IV). Because the MADIT-CRT patient population is minimally symptomatic, with baseline KCCQ scores starting in the upper half of the scale range, changes in KCCQ measures are expected to be lower than among patients with worse initial scores (20). Consequently, any quality-of-life improvement is notable, but

Table 2 **Sample Size by LBBB Type and Treatment Group Across Years in the Study From Randomization (Year 0) Through Year 3**

	All Patients*			LBBB			Non-LBBB		
Year	ICD-Only	CRT-ICD	Total	ICD-Only	CRT-ICD	Total	ICD-Only	CRT-ICD	Total
0	675	1,024	1,699	482	722	1,204	192	302	494
0.5	652	998	1,650	464	705	1,169	187	293	480
1	638	985	1,623	453	700	1,153	184	285	469
1.5	535	849	1,384	391	610	1,001	143	239	382
2	421	668	1,089	305	484	789	115	184	299
2.5	292	456	748	222	336	558	70	120	190
3	196	297	498	151	221	372	45	76	121

Estimates in Figure 2 are based on the sample sizes reported in the LBBB columns. *One individual did not have an indicated LBBB status and is included only in the All Patients results. Abbreviations as in Table 1.

additional research is necessary to identify the extent that the effect sizes found in our study impact the lives of patients in this population and thereby impact treatment decisions and satisfaction.

Notwithstanding the need for future research to identify the importance to patients of the effects identified in this study, the improvement found across all KCCQ measures suggests that the clinical benefits of resynchronization therapy (1), as an adjunct to the ICD, do not come at the expense of quality of life—a finding that may be reassuring to patients. Instead, the CRT-ICD is associated with a greater increase in quality of life than ICD-only among the minimally symptomatic patients, who might otherwise have been presumed to not garner a discernible improvement.

Reprint requests and correspondence: Dr. Peter Veazie, Department of Community and Preventive Medicine, University of Rochester, 265 Crittenden Boulevard, CU (Box) 420644, Rochester, New York 14642. E-mail: peter_veazie@urmc.rochester.edu.

REFERENCES

1. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
2. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.
3. Goldenberg I, Hall WJ, Beck CA, et al. Reduction of the risk of recurring heart failure events with cardiac resynchoronization therapy. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011;58:729–37.
4. Moss AJ, Brown MW, Cannom DS, et al. Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT): design and clinical protocol. Ann Noninvasive Electrocardiol 2005;10 Suppl:34–43.
5. Cardiovascular Outcomes Inc. KCCQ Overview. 2008. Available at: http://cvoutcomes.org/pages/3214. Accessed March 3, 2010.
6. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. Health Qual Life Outcomes 2006;4:89.
7. Faller H, Steinbuchel T, Schowalter M, et al. [The Kansas City Cardiomyopathy Questionnaire (KCCQ)—a new disease-specific quality of life measure for patients with chronic heart failure]. Psychother Psychosom Med Psychol 2005;55:200–8.
8. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.
9. Miani D, Rozbowsky P, Gregori D, et al. The Kansas City Cardiomyopathy Questionnaire: Italian translation and validation. Ital Heart J 2003;4:620–6.
10. Pettersen KI, Reikvam A, Rollag A, Stavem K. Reliability and validity of the Kansas City Cardiomyopathy Questionnaire in patients with previous myocardial infarction. Eur J Heart Fail 2005;7:235–42.
11. Spertus JA, Jones PG, Kim J, Globe D. Validity, reliability, and responsiveness of the Kansas City Cardiomyopathy Questionnaire in anemic heart failure patients. Qual Life Res 2008;17:291–8.
12. Greene WH. Nonspherical disturbances—the generalized regression model. In: Greene WH. Econometric Analysis. 5th edition. Upper Saddle River, NJ: Prentice Hall 2003:191–214.
13. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707–15.
14. Flynn KE, Lin L, Moe GW, et al. Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure. Am Heart J 2012;163:88–94.e3.
15. Spertus JA. Evolving applications for patient-centered health status measures. Circulation 2008;118:2103–10.
16. Myers J, Zaheer N, Quaglietti S, et al. Association of functional and health status measures in heart failure. J Card Fail 2006;12:439–45.
17. Ekman I, Chassany O, Komajda M, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011;32:2395–404.
18. Heidenreich PA, Spertus JA, Jones PG, et al. Health status identifies heart failure outpatients at risk for hospitalization or death. J Am Coll Cardiol 2006;47:752–6.
19. Soto GE, Jones P, Weintraub WS, et al. Prognostic value of health status in patients with heart failure after acute myocardial infarction. Circulation 2004;110:546–51.
20. Chan PS, Khumri T, Chung ES, et al. Echocardiographic dyssynchrony and health status outcomes from cardiac resynchronization therapy: insights from the PROSPECT trial. J Am Coll Cardiol Img 2010;3:451–60.

Key Words: cardiac-resynchronization therapy (CRT) ■ heart failure ■ implantable cardioverter-defibrillator (ICD) ■ KCCQ ■ MADIT-CRT ■ quality-of-life.

APPENDIX

For supplementary information on the KCCQ scales and the sensitivity analyses, please see the online version of this paper.