ORIGINAL RESEARCH

Sex Differences in Long-Term Outcomes With Cardiac Resynchronization Therapy in Mild Heart Failure Patients With Left Bundle Branch Block

Yitschak Biton, MD; Wojciech Zareba, MD, PhD; Ilan Goldenberg, MD; Helmut Klein, MD; Scott McNitt, MS; Bronislava Polonsky, MS; Arthur J. Moss, MD; Valentina Kutyifa, MD, PhD; on behalf of the MADIT-CRT Executive Committee

***Background*—**Previous studies have shown conflicting results regarding the benefit of cardiac resynchronization therapy (CRT) by sex and QRS duration.

***Methods and Results*—**In the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT), we evaluated long-term clinical outcome of heart failure (HF) or death, death, and HF alone by sex and QRS duration (dichotomized at 150 ms) in left bundle-branch block patients with CRT with defibrillator backup (CRT-D) versus implantable cardioverter-defibrillator (ICD) only. There were 394 women (31%) and 887 men with left bundle-branch block. During the median follow-up of 5.6 years, women derived greater clinical benefit from CRT-D compared with implantable cardioverter-defibrillator only, with a significant 71% reduction in HF or death (hazard ratio [HR] 0.29, $P<0.001$) and a 77% reduction in HF alone (HR 0.23, $P<0.001$) compared with men, who had a 41% reduction in HF or death (HR 0.59, $P<0.001$) and a 50% reduction in HF alone (HR 0.50, $P<0.001$) (all sex-by-treatment interaction $P<0.05$). Men and women had similar reduction in long-term mortality with CRT-D versus implantable cardioverter-defibrillator only (men: HR 0.70, $P=0.03$; women: HR 0.59, $P=0.04$). The incremental benefit of CRT-D in women for HF or death and HF alone was consistent with QRS <150 or >150 ms.

***Conclusions*—**During long-term follow-up of mild HF patients with left ventricular dysfunction and wide QRS, both women and men with left bundle-branch block derived sustained benefit from CRT-D versus implantable cardioverter-defibrillator only, with significant reduction in HF or death, HF alone, and all-cause mortality regardless of QRS duration. There is an incremental benefit with CRT-D in women for the end points of HF or death and HF alone.

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Key Words: cardiac resynchronization therapy with defibrillator • clinical outcomes • sex • implantable cardioverter-defibrillator • long-term survival • mild heart failure • mortality • QRS duration

Cardiac resynchronization therapy with defibrillator (CRT-D) has been shown to be associated with significant reduction in heart failure (HF) or death in mild HF patients with left ventricular ejection fraction ≤30% and QRS ≥130 ms in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT).[1] This reduction was shown to be more pronounced in women during short-term follow-up.[1,2] Subsequent study[3] and long-term follow-up of MADIT-CRT[4] revealed that the benefit was restricted to patients with left bundle-branch block (LBBB) configuration.[3]

Recently published substudies reflect differences in outcomes with implanted CRT by sex and QRS duration[2,5,6]; however, long-term data on sex-specific outcome of CRT-D by QRS duration in LBBB patients are lacking. Accordingly, the present study was carried out in patients with an LBBB ECG pattern enrolled in MADIT-CRT and was designed to evaluate (1) the long-term effect of CRT-D versus implantable cardioverter-defibrillator (ICD) only to reduce HF or death, HF alone, and death and (2) the sex-specific benefit of CRT-D to improve

From the Heart Research Follow-up Program, Division of Cardiology, Department of Medicine, University of Rochester Medical Center, Rochester, NY.

An accompanying Figure S1 is available at http://jaha.ahajournals.org/content/4/7/e002013/suppl/DC1

Correspondence to: Yitschak Biton, MD, or Valentina Kutyifa, MD, PhD, Heart Research Follow-up Program, Cardiology Division, University of Rochester Medical Center, 265 Crittenden Blvd., PO Box 653, Rochester, NY 14642. E-mails: yitschak.biton@heart.rochester.edu; valentina.kutyifa@heart.rochester.edu

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long-term outcomes by QRS duration in the mild HF patients with LBBB enrolled in MADIT-CRT.

Methods

Study Population

The protocol and results of the MADIT-CRT study and the MADIT-CRT long-term follow-up registry have been detailed in prior publications.[1,4,7] In summary, 1820 patients with ischemic and nonischemic cardiomyopathy classified as having New York Heart Association (NYHA) class I or II symptoms with left ventricular ejection fraction ≤30% and QRS duration of at least 130 ms were randomly assigned to CRT-D and ICD-only treatment arms in a 3:2 ratio. All patients received optimal medical therapy for HF consisting of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers/angiotensin II inhibitors, and statins. Exclusion criteria included NYHA class III or IV symptoms, coronary artery bypass grafting surgery, percutaneous coronary intervention, or myocardial infarction within 90 days prior to enrollment; second- or third-degree heart block; atrial fibrillation 30 days prior to enrollment; and comorbidities such as uremia (blood urea nitrogen >70 mg/dL or creatinine >3.0 mg/dL) and liver failure.

In the present study, we included only MADIT-CRT patients with an LBBB ECG pattern at baseline because our previous data showed that the benefit of CRT-D was restricted to LBBB patients only.[3,4] Accordingly, the present study population comprised 1281 LBBB patients, 70% of the total patient population of MADIT-CRT.

Follow-up

MADIT-CRT was carried out from December 22, 2004, through June 22, 2009. Following the publication of the primary results,[1] a post-trial follow-up was conducted for all surviving study participants (n=1691) until September 10, 2010 (phase I of the extended follow-up). After September 10, 2010, extended follow-up was conducted in 48 of 87 US centers that agreed to participate in the long-term follow-up registry requested by the US Food and Drug Administration (coordinated by the Heart Research Follow-up Program at the University of Rochester Medical Center, Rochester, NY) and in 23 of 24 non-US centers as an investigator-initiated research project (coordinated by the Israeli Association for Cardiovascular Trials at Sheba Medical Center, Ramat Gan, Israel). A total of 854 patients were involved, 407 in the US registry and 447 in the non-US registry. Both phases of the post-trial follow-up were approved by the institutional review board of each participating center, and all patients provided written informed consent. Post-trial clinical and adverse events were obtained at 6-month intervals during follow-up.

Definitions and End-Points

Patients with an LBBB and an implanted CRT-D or an ICD-only device were divided into 2 prespecified subgroups based on their sex, male or female.

The primary end point of the current study was HF or death, whichever came first during long-term follow-up. Secondary end points included long-term HF events and long-term all-cause mortality. Three sex subgroups were prespecified: QRS <150 versus ≥150 ms, ischemic or nonischemic etiology of heart disease, and age <65 or >65 years. The end points and the subgroups are the same as those used in the original study. The analyses were performed on an intention-to-treat basis using the initial treatment assignment in the study. The rate of crossover in the long-term follow-up study was reported previously: 9% from the ICD to the CRT-D arm and 5% from the CRT-D to the ICD arm.[4]

Statistical Analysis

Categorical data are presented as frequencies and percentages, and continuous variables are presented as mean±SD. Baseline clinical characteristics were compared between sex subgroups using the χ^2 test or Fisher's exact test for dichotomous variables and the Wilcoxon signed-rank test for continuous variables.

The cumulative probability of long-term HF or death, HF events, and all-cause mortality was displayed according to the Kaplan–Meier method by treatment arm within each sex subgroup, with comparisons of cumulative event rates by the log-rank test.

Multivariable Cox proportional hazards regression analysis was used to assess the effect of CRT-D to reduce the risk of long-term combined outcome of HF or death, HF alone, and long-term all-cause mortality. The Cox model was further adjusted for relevant clinical covariates using best subset regression modeling (age, creatinine ≥1.4 mg/dL, body mass index, ischemic etiology, HF hospitalization at month prior to enrollment, QRS ≥150 ms, coronary artery bypass grafting, left ventricular end-systolic volume index at baseline, and black race). Interaction *P* values for CRT-D benefit by sex were computed and reported.

All statistical tests were 2-sided, and a *P* value of <0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4; SAS Institute).

Results

Among 1281 study patients, there were 394 women (31%) and 887 men. Baseline clinical characteristics by sex are shown in Table 1. Female patients had higher rates of black descent compared with male patients. Women more often had nonischemic etiology of cardiomyopathy and properties of more severe HF including higher frequency of prior HF hospitalizations and higher left ventricular end-systolic volume at baseline, whereas men had higher frequency of previous coronary artery bypass grafting revascularization and conduction and rhythm disturbances including atrial arrhythmias, longer PR and QRS intervals, and higher blood urea nitrogen and creatinine levels. Women were more likely prescribed digitalis and beta-blockers, whereas men were more likely prescribed statins.

Effect of CRT-D on Long-term Outcomes by Sex

Kaplan–Meier survival analysis (Figure 1A and 1B) showed significant reduction in all-cause mortality events in the composite outcome of HF or death (Figure 2A and 2B) and in HF alone (Figure S1A and S1B) in men and women with LBBB treated with CRT-D versus an ICD only.

Multivariable analysis (Table 2) showed that women with CRT-D versus ICD only had significantly greater risk reduction in HF or death (hazard ratio [HR] 0.29, $P<0.001$, versus HR 0.59, $P<0.001$) and HF alone (HR 0.23, $P<0.001$, versus HR 0.50, $P<0.001$) than men, with a significant sex-by-treatment interaction ($P=0.003$ for HF or death and $P=0.008$ for HF only). Both women and men had significant mortality benefits with CRT-D versus ICD only (women: HR 0.49, $P=0.038$; men: HR 0.70, $P=0.032$; interaction $P=0.365$).

Effect of QRS Duration on Long-term CRT-D Benefit by Sex

As shown in the univariate analysis (Figure 3), women with CRT-D had significant risk reduction in HF or death with both QRS <150 and ≥150 ms compared with ICD only, whereas men showed significant benefit only from CRT-D with QRS ≥150 ms. For both subgroups, women had greater reduction of HF or death with CRT-D versus an ICD only than men, with significant sex-by-treatment interaction ($P<0.05$ for both).

Multivariable analysis (Table 3) showed consistent results. Treatment with CRT-D was associated with a greater reduction in the end point of HF alone and in the combined end point of HF or death in women compared with men. There was a significant mortality reduction in men with QRS <150 ms, but it was less prominent in those with QRS ≥150 ms (Table 3).

Table 1. Clinical and Echocardiographic Characteristics of Men and Women With Left Bundle-Branch Block

Clinical Characteristics	Men (n=887)	Women (n=394)
Age at enrollment, y	64.2±11.0	64.2±10.6
CRT-D assigned treatment	522 (59)	239 (61)
Black/African American	49 (6)	44 (11)*
BMI	28.7±4.8	28.0±6.1*
Smoking	101 (12)	33 (9)
Ischemic	476 (54)	87 (22)*
Diabetes	262 (30)	124 (32)
Hypertension	550 (62)	256 (65)
Prior CABG	250 (28)	32 (8)*
Systolic blood pressure, mm Hg	123±17	123±18
Diastolic blood pressure, mm Hg	71.6±10.0	70.9±10.6
Heart rate, bpm	67.3±10.9	70.4±10.7*
BUN, mg/dL	22.1±9.0	19.9±8.3*
Creatinine, mg/dL	1.20±0.31	0.99±0.27*
NYHA III/IV >3 months before enrollment	92 (11)	43 (11)
Past atrial arrhythmias	114 (13)	27 (7)*
Past ventricular arrhythmias	66 (8)	15 (4)*
Prior HF hospitalization	316 (36)	171 (44)*
Antiarrhythmic medication	79 (9)	8 (2)*
ACE inhibitors/ARB	854 (96)	377 (96)
Beta-blockers	824 (93)	380 (96)*
Digitalis	212 (24)	147 (37)*
Diuretics	586 (66)	287 (73)*
Statins	614 (69)	197 (50)*
PR interval, ms	202±33	187±28*
QRS duration, ms	164.6±19.9	159.5±17.3*
LVEF, %	28.4±3.4	29.4±3.4*
LVEDV indexed by BSA, mL/m^2	127.6±31.4	123.1±27.3*
LVESV indexed by BSA, mL/m^2	91.9±25.6	87.2±22.0*
LAV indexed by BSA, mL/m^2	47.4±10.2	46.6±9.9
Left ventricular dyssynchrony, ms	187±63	200±58*

Values are mean±SD and number (percentage). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.
*$P<0.05$ for the comparison of men and women.

Other Subgroup Sex Differences in CRT-D Benefit in LBBB Patients

We further assessed other possible prespecified subgroup differences in the long-term benefit of CRT-D for the end point

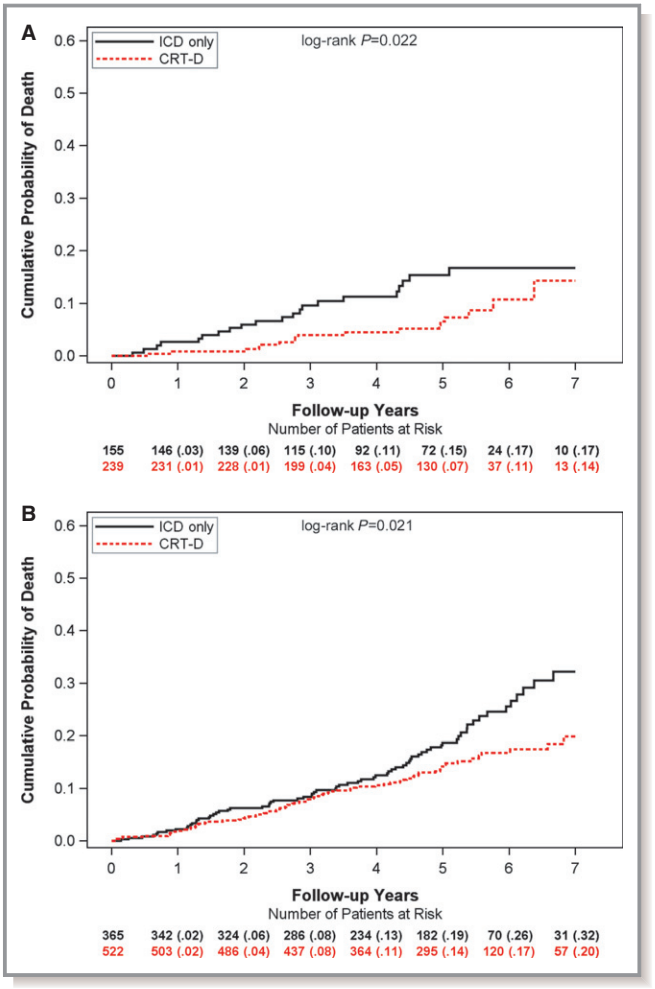

Figure 1. Cumulative probability of death by treatment arm in women (A) and men (B). The numbers in the parentheses indicates Kaplan–Meier event rates. CRT-D indicates cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator.

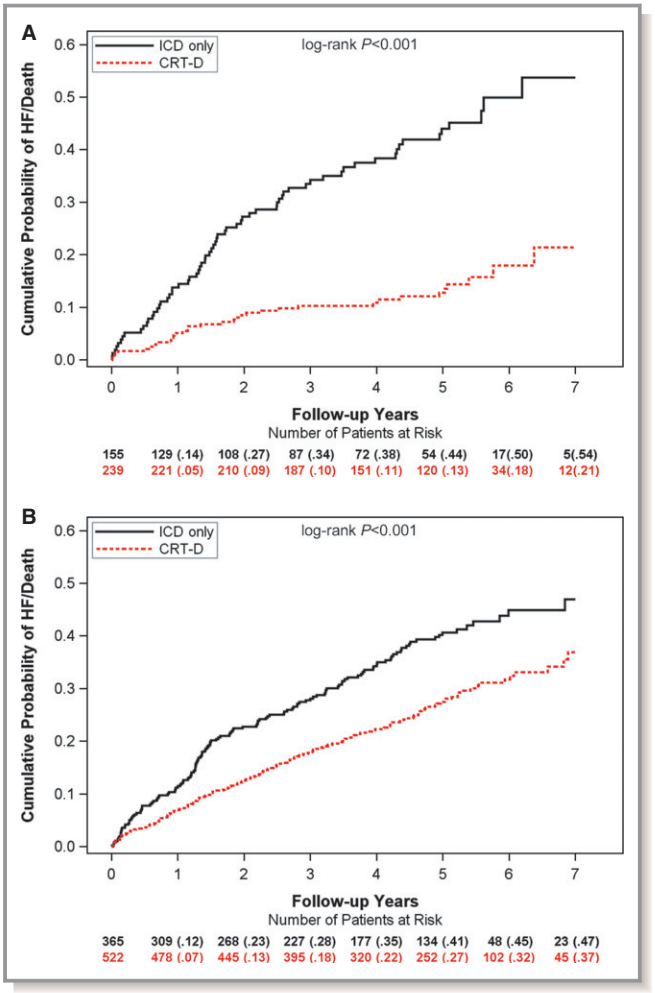

Figure 2. Cumulative probability of HF or death by treatment arm in women (A) and men (B). The numbers in the parentheses indicates Kaplan–Meier event rates. CRT-D indicates cardiac resynchronization therapy with defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator.

of HF or death between men and women with LBBB (Figure 3). This analysis showed that the incremental long-term benefit of CRT-D was more pronounced and statistically significant among patients with nonischemic cardiomyopathy and among younger patients, whereas among patients with ischemic cardiomyopathy and in older patients (aged ≥65 years), there was no statistically significant difference between men and women in the long-term benefit of CRT-D (Figure 3).

Discussion

In this MADIT-CRT long-term follow-up substudy, we extended the knowledge regarding the sex–QRS duration interaction and its implications for outcomes among patients with LBBB configuration. First, we showed that although only women with CRT-D in the trial experience gained a benefit for HF or death and HF alone with QRS duration >150 or <150 ms, in the long term, both sexes gained HF or death, HF alone, and mortality risk reductions regardless of QRS duration. Second, women had more pronounced benefit with CRT-D in HF or death and HF alone, and this effect was consistent regardless of QRS duration. Third, men with QRS <150 ms compared with men with QRS ≥150 ms derived less pronounced benefit from CRT-D with reduction in HF or death and HF alone, but they had significantly lower long-term mortality.

Optimizing patient selection for CRT is an ongoing challenge. Guidelines[8,9] emphasize the use of left ventricular ejection fraction ≤35%, LBBB morphology, and QRS duration ≥150 ms as major clinical variables for selection criteria with CRT in mild HF patients. There are conflicting data for CRT outcome regarding the importance of QRS duration versus QRS morphology. Cleland et al[10] suggested that QRS duration is more important for CRT outcomes than QRS

Table 2. Multivariable Models to Assess Treatment Effect by Sex of CRT-D Versus ICD Alone on All-Cause Mortality, HF Only, and HF or Death

End Point	No. Events Women/Men	Women (n=394)			Men (n=887)			Interaction *P* Value
		HR	95% CI	*P* Value	HR	95% CI	*P* Value	
All-cause mortality								
CRT-D vs ICD adjusted*	35/142	0.49	0.25 to 0.96	0.038	0.70	0.50 to 0.97	0.032	0.365
HF only								
CRT-D vs ICD adjusted*	77/203	0.23	0.14 to 0.38	<0.001	0.50	0.38 to 0.66	<0.001	0.008
HF or death								
CRT-D vs ICD adjusted*	93/274	0.29	0.19 to 0.44	<0.001	0.59	0.47 to 0.75	<0.001	0.003

CRT-D indicates cardiac resynchronization therapy with defibrillator; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator.
*Adjusted for treatment arm, age, creatinine ≥1.4, body mass index, ischemic etiology, congestive HF hospitalization at month prior to enrollment, QRS ≥150 ms, coronary artery bypass grafting, left ventricular end-systolic volume index at baseline, black race, sex, and sex-by-treatment interaction.

morphology; however, they enrolled patients with mild to severe HF in their study, and the study had different control arms (ICD or optimal medical therapy). Bryant et al[11] showed in a meta-analysis that only patients with QRS >150 ms benefit from CRT, but they did not address QRS morphology in their analysis, which also included both randomized and nonrandomized studies of patients with mild to severe HF. In contrast, the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study investigators showed that LBBB morphology was more important than QRS duration, and QRS duration did not significantly predict outcomes in the multivariable analysis.[12] Zusterzeel et al[13] performed a patient-level meta-analysis combining data from recent randomized trials available at the US Food and Drug Administration and showed that only patients with LBBB morphology benefited from CRT. They also found that women had better outcomes with CRT with shorter QRS duration (130 to 149 ms), whereas men had no such

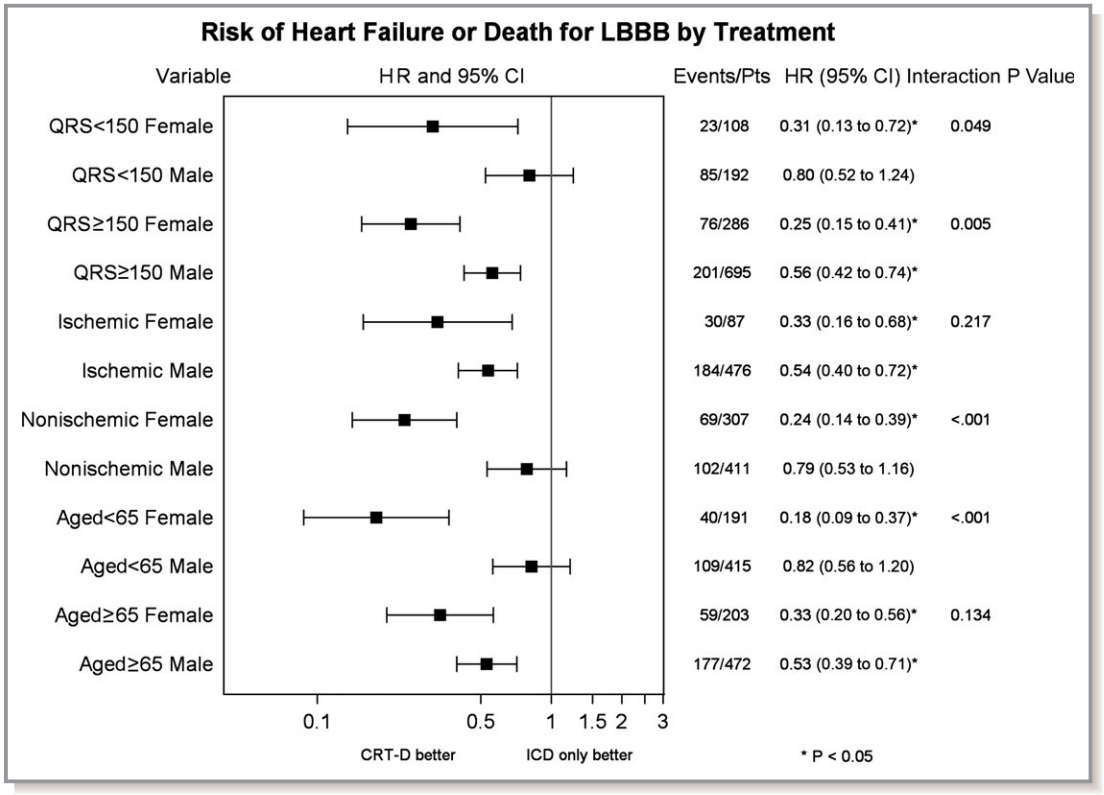

Figure 3. Forest plot shows risk of heart failure or death event by sex according to treatment group in subgroups of patients. CRT-D indicates cardiac resynchronization therapy with defibrillator; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block.

Table 3. Multivariable Models to Assess the Treatment Effect by Sex and QRS Duration of CRT-D Versus ICD Alone on All-Cause Mortality, HF Only, and HF or Death

	Women (n=394)				Men (n=887)				
End Point	No. Events/No. Patients	HR*	95% CI	*P* Value	No. Events/No. Patients	HR*	95% CI	*P* Value	Interaction *P* Value
All-cause mortality									
QRS <150 ms	9/108	0.65	0.17 to 2.45	0.525	37/192	0.42	0.21 to 0.83	0.013	0.564
QRS ≥150 ms	26/286	0.45	0.21 to 0.98	0.044	105/695	0.77	0.52 to 1.13	0.184	0.224
HF only									
QRS <150 ms	19/108	0.22	0.08 to 0.58	0.002	66/192	0.67	0.40 to 1.11	0.122	0.048
QRS ≥150 ms	58/286	0.24	0.14 to 0.42	<0.001	137/695	0.41	0.29 to 0.58	<0.001	0.107
HF or death									
QRS <150 ms	22/108	0.32	0.14 to 0.76	0.010	83/192	0.65	0.41 to 1.03	0.066	0.159
QRS ≥150 ms	71/286	0.27	0.17 to 0.45	<0.001	191/695	0.55	0.41 to 0.73	<0.001	0.018

CRT-D indicates cardiac resynchronization therapy with defibrillator; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator.
*Adjusted for treatment arm, age, creatinine ≥1.4, body mass index, ischemic etiology, congestive HF hospitalization at month prior to enrollment, coronary artery bypass grafting, left ventricular end-systolic volume index at baseline, black race, sex, and sex-by-treatment interaction.

benefit. It should be noted that Zusterzeel et al did not investigate long-term CRT outcomes by sex.

In our study, we emphasized the current knowledge of CRT-D results by sex and QRS duration, and with a long patient follow-up, we can confirm that both men and women with mild HF and LBBB morphology derived impressive benefit with CRT-D, regardless of QRS duration; in particular, women had a pronounced benefit. Importantly, we could show that men and women with LBBB and QRS <150 or >150 ms benefited from CRT-D with long-term cardiac resynchronization. Our data show that in mild HF patients with depressed left ventricular ejection fraction, LBBB configuration is the most important factor for predicting effectiveness of CRT-D therapy, whereas QRS duration is of less importance.

It is well known that inherent physiological sex differences of abnormal conduction exist. It has been suggested that women have shorter QRS duration than men in the absence of any conduction disturbance.[14,15] In our study, women had significantly shorter baseline QRS durations, but they gained even greater clinical benefit from CRT-D than men, suggesting that women may have more dyssynchrony, at shorter QRS durations, that leads to better response with CRT-D. This is in alignment with a previous retrospective study[6] restricted to NYHA class III or IV patients with LBBB and nonischemic cardiomyopathy showing that men experienced echocardiographic volume reductions with CRT only at QRS duration >150 ms, whereas women had an echocardiographic response both >150 and <150 ms. In this study, however, data on outcomes of HF and mortality were not provided.

Another study evaluating registry data[5] compared mortality risk with CRT among patients with NYHA class III by QRS morphology and duration. They showed that women with LBBB had greater mortality reductions than men and that longer QRS durations were correlated with better outcome in both women and men; however, it should be noted that no control group was available to appreciate the magnitude of effect of QRS duration on outcomes, and the follow-up in this study was relatively short (median of 2.9 years). In the present study, we confirmed these results on sex-specific long-term outcomes with CRT-D, and we emphasized that women with LBBB derived significantly greater mortality or HF reduction with CRT-D compared with ICD only than men.

Interestingly, in our study, women aged <65 years had greater benefit from CRT-D versus an ICD than men, but the groups had similar results with age >65 years. We speculate that this difference in outcomes may be related to other significant comorbidities in the older women that may result in competing modes of death or worsening of HF mortality.

Several baseline differences between men and women may have contributed to the differences in long-term outcomes in our study. Men were more likely to have higher creatinine levels, ischemic cardiomyopathy, and prior atrial tachyarrhythmias, characteristics that are related to worse prognosis in HF.

Our study has certain limitations. First, women had different baseline clinical characteristics than men; however, our findings were consistent after adjustment for these covariates and across subgroups. Second, when assessing outcomes in men and women with QRS <150 ms, we may have had limited statistical power because of the relatively smaller number of patients with QRS <150 ms in our study and the lower event rate in these subgroups. Third, MADIT-CRT was not originally designed to assess reduction of mortality alone with CRT-D; therefore, it may not be

adequately powered for the end point of mortality, especially when evaluating subgroups. Last, unknown confounders could not be taken into consideration. Nevertheless, this study is one of the largest randomized controlled CRT-D trials in patients with mild HF using a control group of ICD patients that has such long-term follow-up. In addition, we had a relatively large proportion of women, almost one-third of the total patient population, and that is much higher than most other clinical trials.

Conclusions

In this MADIT-CRT long-term follow-up study, we showed that in patients with LBBB configuration, both men and women gained sustained reductions in HF or death, HF alone, and mortality with CRT-D therapy regardless of QRS duration. Women had more pronounced benefit in outcomes for HF or death and HF alone compared with men. Consequently, we believe that clinical decisions regarding CRT-D use should be based on QRS morphology rather than QRS duration.

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Disclosures

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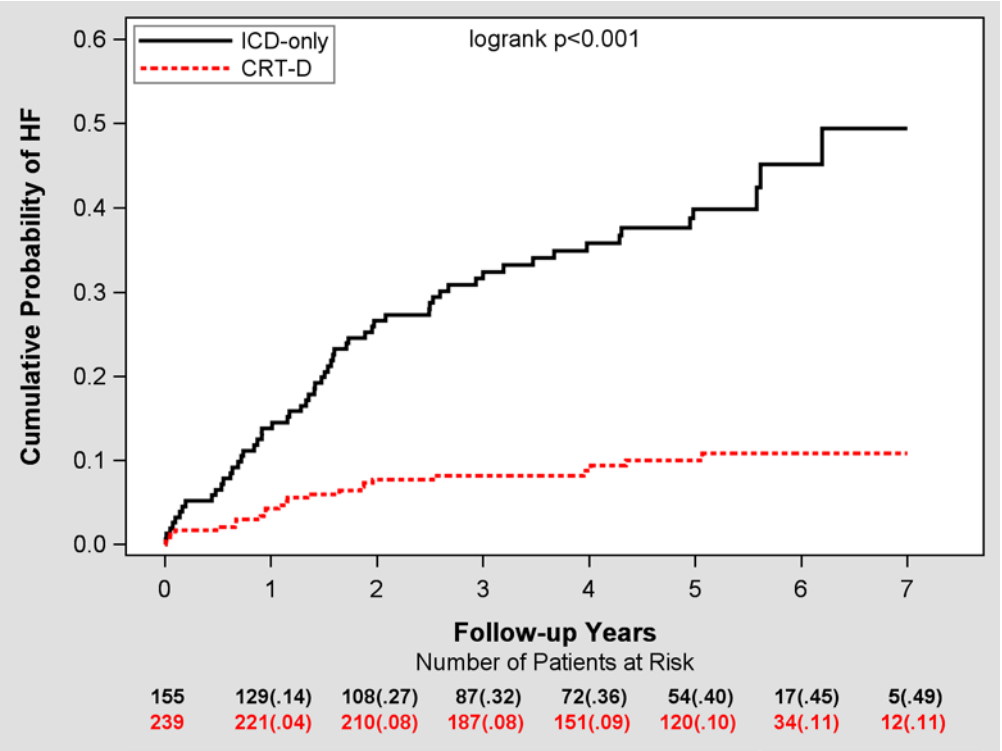
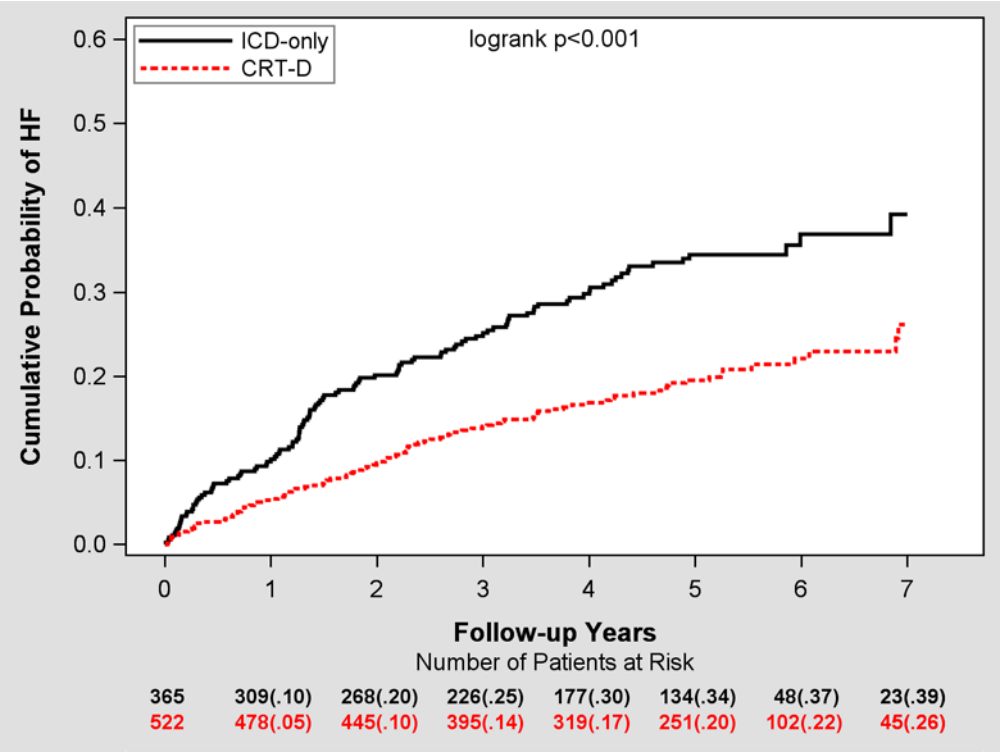
SUPPLEMENTAL MATERIAL

Figure S1. Cumulative probability of heart failure by treatment arm in Females (A) and Males (B)

A.



B.


ICD-only
CRT-D
logrank p<0.001
Cumulative Probability of HF
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
Follow-up Years
Number of Patients at Risk
365 309(.10) 268(.20) 226(.25) 177(.30) 134(.34) 48(.37) 23(.39)
522 478(.05) 445(.10) 395(.14) 319(.17) 251(.20) 102(.22) 45(.26)

Sex Differences in Long–Term Outcomes With Cardiac Resynchronization Therapy in Mild Heart Failure Patients With Left Bundle Branch Block

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