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Sex-Specific Mortality Risk by QRS Morphology and Duration in Patients Receiving CRT

Results From the NCDR

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ABSTRACT

BACKGROUND Prior studies have suggested that women have better outcomes than men after cardiac resynchronization therapy-defibrillator (CRT-D) implantation.

OBJECTIVES The purpose of this study was to compare mortality after CRT-D implantation by sex, QRS morphology, and duration.

METHODS Survival curves and covariate adjusted hazard ratios (HR) were used to assess mortality by sex in 31,892 CRT-D patients in the National Cardiovascular Data Registry (NCDR), implantable cardioverter defibrillator (ICD) registry between 2006 and 2009, with up to 5 years' follow-up (median 2.9 years, interquartile range: 2.0 to 3.9 years). Patients were grouped by QRS morphology and 10-ms increments in QRS duration.

RESULTS Among patients with left bundle branch block (LBBB), women had a 21% lower mortality risk than men (HR: 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$); however, there was no sex difference in non-LBBB (HR: 0.95; 95% CI: 0.85 to 1.06; $p = 0.37$). Longer QRS duration was associated with better survival in both sexes with LBBB, but not in patients without LBBB. Compared with women with LBBB and QRS of 120 to 129 ms, women with LBBB and QRS of 140 to 149 ms had a 27% lower mortality (HR: 0.73; 95% CI: 0.60 to 0.88; $p = 0.001$); this difference was 18% in men (HR: 0.82; 95% CI: 0.71 to 0.93; $p = 0.003$). Mortality in LBBB and QRS of 150 ms or longer compared with those with LBBB and QRS of 120 to 129 ms was similar between sexes (HR: 0.61 to 0.68; $p < 0.001$ for women and HR: 0.58 to 0.66; $p < 0.001$ for men). Sex interactions within 10-ms groups were not significant.

CONCLUSIONS Among patients with LBBB who received CRT-D, mortality is lower in women than men. Additionally, longer QRS duration in LBBB is associated with better survival in both sexes. In contrast, there is no sex difference in patients without LBBB, regardless of QRS duration. Further studies should include a non-CRT comparator group to confirm these findings. (J Am Coll Cardiol 2014;64:887–94) © 2014 by the American College of Cardiology Foundation.

Biventricular pacing, a therapy for heart failure, commonly referred to as cardiac resynchronization therapy (CRT), reduces mortality and heart failure hospitalizations in selected patients with left ventricular systolic dysfunction and prolonged QRS duration (1-4). However, although

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy defibrillator

FDA = U.S. Food and Drug Administration

ICD = implantable cardioverter defibrillator

LBBB = left bundle branch block

NYHA = New York Heart Association

there is an incomplete understanding of who benefits from CRT, all patients receiving CRT are subjected to potential device complications (e.g., infection, lead failure/dislodgement) and costs. Therefore, it is important to identify those patients most likely to benefit from this therapy.

Although most CRT clinical trials enrolled patients with a QRS duration of 120 ms or longer, meta-analyses found that benefit from CRT is most pronounced in patients with a left bundle branch block (LBBB) and QRS of 150 ms or longer (5,6). These observations are reflected in professional society guidelines, which limit Class I recommendations for CRT to patients with LBBB and QRS of 150 ms or longer. Patients with LBBB and QRS of 120 to 149 ms and those without LBBB are categorized as either Class IIa or IIb recommendations (7).

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In clinical trials of CRT, women only represent approximately 20% of patients; therefore, the results of both the trials and meta-analyses primarily reflect outcomes in men. Nonetheless, previous studies suggest that benefit from CRT is greater in women (8–11). This may be due to a combination of reasons, including that women are more likely to have LBBB and nonischemic cardiomyopathy, which are both associated with a better CRT response (12). Furthermore, separate analyses suggest that one-third of patients with LBBB by conventional electrocardiographic (ECG) criteria may not have true LBBB (13–16). Because women have a shorter QRS duration than men in the absence of any conduction disease (17), they can have a true LBBB at a shorter QRS duration than men (16). Previous studies suggest that sex-specific QRS duration criteria for LBBB predict a better response to CRT (18,19).

This study assessed the effect of CRT by sex in a large real-world CRT-defibrillator (CRT-D) population. The objective was to compare long-term mortality outcomes of women and men receiving CRT-D among different combinations of QRS morphology and duration.

METHODS

This study included all patients in the National Cardiovascular Data Registry (NCDR), implantable cardioverter defibrillator (ICD) registry who received a CRT-D device between January 1, 2006, and September 30, 2009 (n = 178,900). The registry, formed in 2005 with data collection beginning in 2006, contains data on all ICD and CRT-D implantations from more than 80% of hospitals in the United States (20). Patient-level clinical, demographic, and procedural information was collected using standardized data elements and definitions. The NCDR programs use a multistage data quality process, including quality checks on submitted data, outlier analysis, and medical record audits (21). The ICD Registry is used in more than 1,400 US hospitals, including almost all centers that implant cardiac rhythm devices (22).

The defined endpoint for this study was time to death from any cause obtained by linking NCDR registry files with the Social Security Death Master File. Patients were censored if they were alive at the end of the follow-up period (March 31, 2011). We excluded patients with a QRS of <120 ms or >220 ms, epicardial leads, a history of atrial fibrillation, or a prior pacemaker or ICD; those who received a CRT-D device for secondary prevention of sudden cardiac death or had missing data on sex, QRS morphology, or duration; patients who could not be linked to the Death Master File; and those who were not admitted to the hospital for the sole purpose of CRT-D implantation. Prior pacemaker or ICD (n = 66,122) and hospital admission for reasons other than CRT-D implantation (n = 50,753) accounted for most of the 147,008 exclusions (82% of all identified registry patients). Patients with QRS of greater than 220 ms were excluded due to the small number of subjects in this category and uncertainty about the accuracy of QRS duration measurement. Patients who were not admitted for the sole purpose of CRT-D implantation were excluded based on a potential confounding effect of competing factors for death. Finally, the study population was restricted to patients without atrial fibrillation, as atrial fibrillation is associated with a low rate of biventricular pacing. The U.S. Food and Drug

devices. Dr. Piña has received consulting fees/honoraria from Novartis and GE Healthcare. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services. The views expressed in this manuscript represent those of the authors, and do not necessarily represent the official views of the NCDR or its associated professional societies identified at www.ncdr.com. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Administration (FDA) Research in Human Subjects Committee and the Yale University Human Investigation Committee approved the analysis.

STATISTICAL ANALYSIS. Univariate and multivariable adjusted Cox proportional hazards analysis was used to calculate mortality risks in the total population and in groups stratified by sex, QRS duration, and QRS morphology (LBBB and non-LBBB [including right bundle branch block and nonspecific intraventricular conduction delay]). The clustering of patients within hospitals was considered in the Cox proportional hazard models by marginal model approach with the robust sandwich estimate of the covariance. The proportional hazards assumption was confirmed by log-log plotting and supremum test. Multivariable models included adjustments for all covariates in Table 1 and additionally for syncope, family history of sudden death, cardiac arrest, ventricular tachycardia, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and systolic blood pressure. LBBB and non-LBBB patients were divided into groups, defined by 10-ms increments in QRS duration. The 120- to 129-ms category was used as the reference for Cox proportional hazards analysis, and sex-by-treatment interactions were calculated within the 10-ms subgroups. Kaplan-Meier curves for the total population and separately in women and men with LBBB and non-LBBB were used to assess unadjusted comparisons of time-to-all-cause mortality in CRT-D patients across the 10-ms QRS duration groups. Missing data were rare for all variables (ranging between 0.02 and 0.61%) and were imputed by using the most common value for categorical variables and medians for continuous variables. All statistical analyses were conducted with SAS software, version 9.3 (SAS Institute, Cary, North Carolina). Ninety-five percent confidence intervals are reported for all hazard ratios, and probability values of less than 0.05 were considered statistically significant. Probability values were not adjusted for multiplicity.

TABLE 1 Patient Characteristics by Sex in the Total and LBBB CRT-D Populations

	Total Population		LBBB	
	Women (n = 11,542)	Men (n = 20,350)	Women (n = 9,978)	Men (n = 14,174)
Demographics				
Age (yrs)	68 ± 11	69 ± 11	68 ± 11	69 ± 11
Race				
White	9,016 (78)	16,864 (83)	7,869 (79)	11,818 (83)
Black	1,644 (14)	1,894 (9)	1,339 (13)	1,283 (9)
Hispanic	611 (5)	1,049 (5)	526 (5)	722 (5)
Other	271 (2)	543 (3)	244 (2)	351 (2)
Clinical characteristics				
LVEF	24% ± 7%	24% ± 7%	24% ± 7%	24% ± 7%
NYHA functional heart failure class				
I/II	1,431 (12)	2,975 (15)	1,259 (13)	2,140 (15)
III	9,721 (84)	16,697 (82)	8,399 (84)	11,596 (82)
IV	390 (3)	678 (3)	320 (3)	438 (3)
Ischemic cardiomyopathy	4,354 (38)	13,621 (67)	3,441 (34)	8,760 (62)
LBBB	9,978 (86)	14,174 (70)		
Non-LBBB	1,564 (14)	6,176 (30)		
QRS duration (ms)	154 ± 19	153 ± 21	155 ± 18	157 ± 21
AV conduction				
Normal	9,440 (82)	14,150 (70)	8,255 (83)	10,084 (71)
First-degree block	1,979 (17)	5,733 (28)	1,624 (16)	3,823 (27)
Second-/third-degree block	123 (1)	467 (2)	99 (1)	267 (2)
Heart failure duration				
No	423 (4)	988 (5)	360 (4)	658 (5)
<3 months	1,104 (10)	2,142 (11)	931 (9)	1,471 (10)
3–9 months	1,988 (17)	3,212 (16)	1,736 (17)	2,271 (16)
>9 months	8,027 (70)	14,008 (69)	6,951 (70)	9,774 (69)
Previous valvular surgery	499 (4)	1,109 (6)	386 (4)	789 (6)
Cerebrovascular disease	1,203 (10)	2,606 (13)	986 (10)	1,733 (12)
Renal failure/dialysis	220 (2)	594 (3)	179 (2)	375 (3)
Diabetes mellitus	4,325 (38)	8,025 (40)	3,617 (36)	5,324 (38)
Hypertension	8,371 (73)	15,405 (76)	7,181 (72)	10,571 (75)
Sodium (mEq/l)	139 ± 3	139 ± 3	139 ± 3	139 ± 3
Blood urea nitrogen (mmol/l)	23 ± 13	25 ± 13	23 ± 12	24 ± 12
Creatinine (mg/dl)	1.2 ± 0.8	1.4 ± 1.0	1.1 ± 0.8	1.4 ± 0.9
Discharge medications				
Beta-blockers	10,295 (89)	17,937 (88)	8,921 (89)	12,519 (88)
Angiotensin receptor blockers	2,779 (24)	3,697 (18)	2,423 (24)	2,586 (18)
ACE inhibitors	6,969 (60)	13,366 (66)	6,059 (61)	9,386 (66)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; AV = atrioventricular; CRT-D = cardiac resynchronization therapy defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

RESULTS

The final study population included 31,892 CRT-D patients, of whom 11,542 (36%) were women and 20,350 (64%) were men (Table 1). Women were more likely than men to have LBBB (86% vs. 70%), normal atrioventricular conduction (82% vs. 70%), and nonischemic cardiomyopathy (62% vs. 33%). Overall, the majority of both women and men had New York Heart Association (NYHA) functional class III heart failure symptoms (84% and 82%).

After a median follow-up of 2.9 years (interquartile range: 2.0 to 3.9 years), 5,428 patients (17%) died. In the overall cohort, those with LBBB had a 24% lower mortality risk than those with non-LBBB (adjusted hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.72 to 0.80; $p < 0.001$). Patients with QRS durations of 120 to 129 ms had the highest mortality (Figure 1), with slightly better survival in the QRS 130- to 139-ms (HR: 0.92; 95% CI: 0.85 to 1.00; $p = 0.057$) and 140- to 149-ms groups (HR: 0.88; 95% CI: 0.81 to 0.96; $p = 0.002$). Survival was highest in patient groups with QRS of

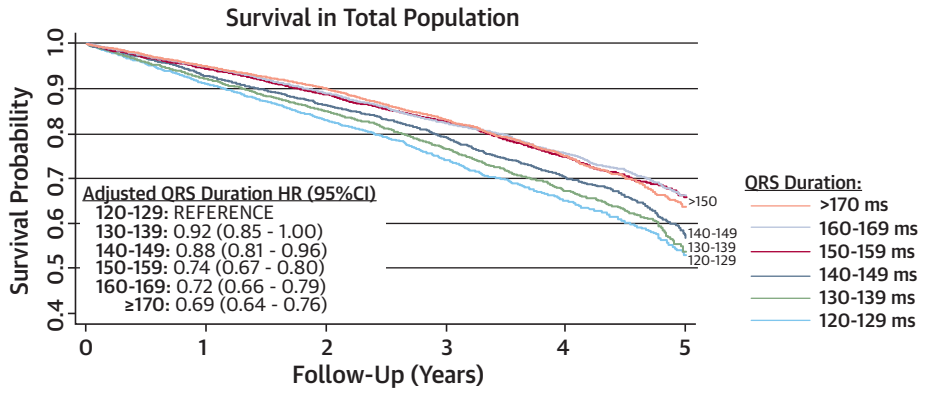


FIGURE 1 Kaplan-Meier Survival Curves by QRS Duration Among the Total Population

Curves reflect the survival probability of cardiac resynchronization therapy defibrillator patients in 10-ms QRS duration groups. Multivariable mortality hazard ratios (referenced to patients with QRS of 120 to 129 ms) are reported. CI = confidence interval; HR = hazard ratio.

150 ms or longer, with similar mortality in patients with QRS of 150 to 159 ms (HR: 0.74; 95% CI: 0.67 to 0.80; $p < 0.001$), QRS of 160 to 169 ms (HR: 0.72; 95% CI: 0.66 to 0.79; $p < 0.001$), and QRS of 170 ms or longer (HR: 0.69; 95% CI: 0.64 to 0.76; $p < 0.001$).

MORTALITY IN CRT-D PATIENTS BY SEX, QRS MORPHOLOGY, AND DURATION. Overall, women had an 18% lower mortality risk compared with men (HR: 0.82; 95% CI: 0.78 to 0.87; $p < 0.001$). In patients with LBBB, women had an adjusted 21% lower mortality risk than men (HR: 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$). Figure 2 shows unadjusted survival curves for patients grouped by 10-ms QRS intervals, stratified by sex and QRS morphology, and the Central Illustration shows the hazard ratios for mortality separately in women and men, comparing QRS duration subgroups to a reference group with a QRS duration of 120 to 129 ms. For both women and

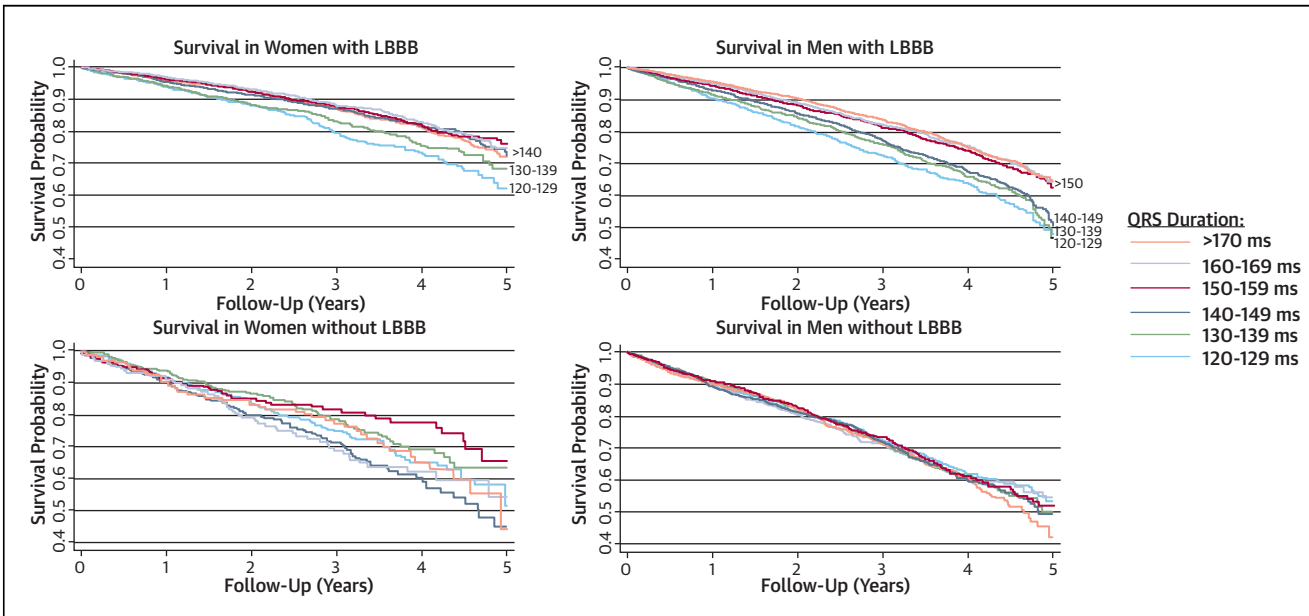
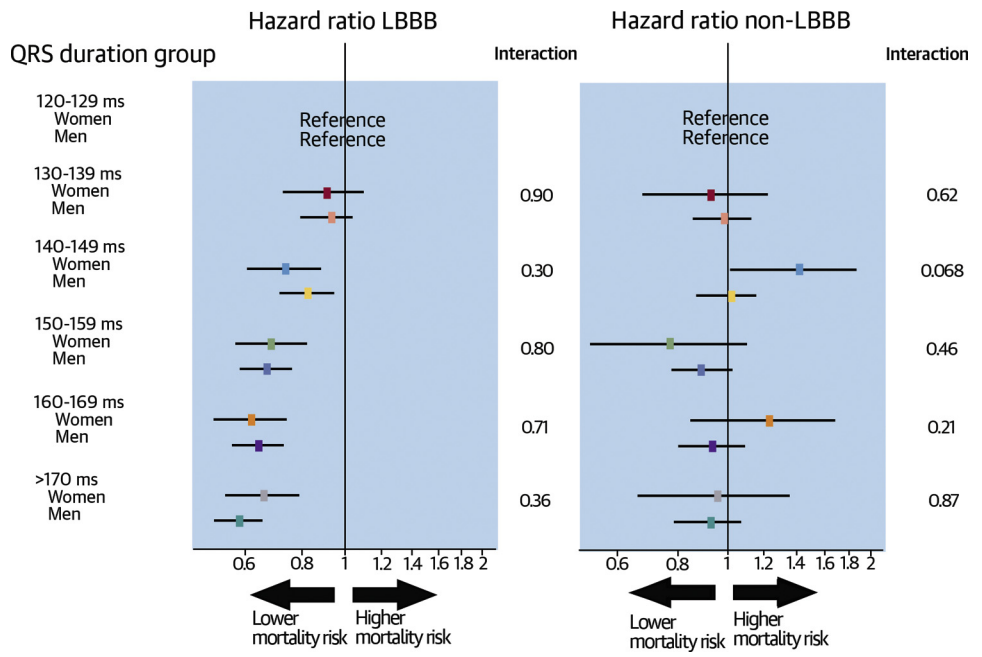


FIGURE 2 Kaplan-Meier Survival Curves of QRS Duration Groups, Stratified by Sex and Presence of LBBB

Curves reflect the survival probability of women **(top left)** and men **(top right)** with LBBB and women **(bottom left)** and men **(bottom right)** without LBBB in 10-ms QRS duration groups. LBBB = left bundle branch block.



CENTRAL ILLUSTRATION **Multivariable Hazard Ratios for Mortality in LBBB and non-LBBB QRS Duration Groups by Sex**

Points reflect hazard ratios for all-cause mortality in LBBB **(left)** and non-LBBB **(right)** in 10-ms QRS duration groups for women and men. **Lines** indicate 95% confidence bounds. Sex-by-treatment interaction probability values are reported for every QRS duration category. See Online Table 1 for exact numbers. LBBB = left bundle branch block.

men with LBBB, mortality was highest in the QRS 120- to 129-ms group, with a slightly better survival in QRS of 130 to 139 ms, although this did not reach statistical significance in either women or men. In LBBB and QRS of 140 to 149 ms, women had a 27% lower mortality than those with QRS of 120 to 129 ms (HR: 0.73; 95% CI: 0.60 to 0.88; $p = 0.001$), and this difference was 18% in men (HR: 0.82; 95% CI: 0.71 to 0.93; $p = 0.003$); however, the difference between sexes was not statistically significant ($p = 0.30$ for interaction). With QRS duration longer than 150 ms, the lower mortality risk remained significant within the 10-ms subgroups and was similar between sexes (HR: 0.61 to 0.68; $p < 0.001$ for women and HR: 0.58 to 0.66; $p < 0.001$ for men). Although there were no significant sex-by-treatment interactions within the 10-ms QRS duration groups, the HR point estimates for mortality remained fairly consistent without much variation with QRS longer than 140 ms in women and 150 ms in men (**Central Illustration**).

In CRT-D patients without LBBB, there was no difference in adjusted mortality risk between sexes (HR: 0.96; 95% CI:0.86 to 1.06; $p = 0.36$) and no relation between QRS duration and mortality (**Central Illustration**). When all multivariable models were repeated with adjustment for discharge medications, the results did not change. The full multivariable adjusted models can be found in the Online Appendix (Online Tables 2 and 3 for women and men with LBBB and Online Tables 4 and 5 for women and men without LBBB).

DISCUSSION

In this large, real-world population of patients in the NCDR ICD Registry with left ventricular systolic dysfunction and predominantly NYHA functional class III heart failure symptoms who were treated with CRT-D, we found that women with LBBB have a lower mortality risk than men with LBBB. Among all patients with LBBB, longer QRS duration was associated with a better survival, although this lower mortality risk plateaued at a QRS duration longer than 140 ms in women and longer than 150 ms in men. In contrast, in the non-LBBB population, no sex-based differences in mortality were found and mortality risk was similar regardless of QRS duration. While in

previous studies selected patient populations were included and women were underrepresented, the present analysis included a more diverse and real-world CRT-D population with a larger proportion of women.

SEX DIFFERENCES IN THE PHYSIOLOGY OF DYSSYNCHRONY AND RESYNCHRONIZATION THERAPY. Recent studies and meta-analyses have shown that the presence of LBBB is predictive of a positive response to CRT (6,23), whereas patients with non-LBBB may experience no benefit or even harm from therapy (12,24–28). When the left bundle branch is completely blocked, the left ventricular lateral wall is activated approximately 100 ms later than the interventricular septum due to the impairment of electrical propagation in the rapidly conducting His-Purkinje system (**Figure 3**). The left ventricular pacing lead in CRT reduces this delay and resynchronizes the activation between both walls, thereby improving cardiac output and mechanical efficiency. In patients without LBBB, the left ventricular activation via the His-Purkinje system is rapid and considered normal. For these reasons, CRT may be more effective in patients with LBBB than in patients without LBBB.

Because women have smaller ventricles and shorter baseline QRS duration than men (17), they are more likely to have a true LBBB compared with men, who are more likely to have a false-positive LBBB diagnosis at the lower end of the QRS duration prolongation spectrum (16). Single-center studies have evaluated stricter LBBB criteria accounting for sex differences in QRS duration, requiring a QRS of 130 ms or longer in women and 140 ms or longer in men together with mid-QRS notching/slurring (16). These studies found that patients who met these stricter criteria have lower risks of heart failure hospitalizations and mortality with CRT compared with those not meeting the criteria (18,19).

In addition to these electrophysiological differences, other factors may contribute to the greater response to CRT in women. Previous studies demonstrated that ischemic cardiomyopathy and atrial fibrillation are associated with a worse prognosis in CRT patients (12). In the present study, women indeed had a lower rate of ischemic cardiomyopathy than men, although patients with atrial fibrillation were excluded. Although the difference in the etiology of left ventricular systolic dysfunction could have contributed to the higher survival in women, our multivariable models controlled for this variable. In addition, it is difficult to separate the contribution of LBBB and ischemic cardiomyopathy to the observed outcomes as LBBB in CRT-D patients is usually caused by nonischemic pathologies (29).

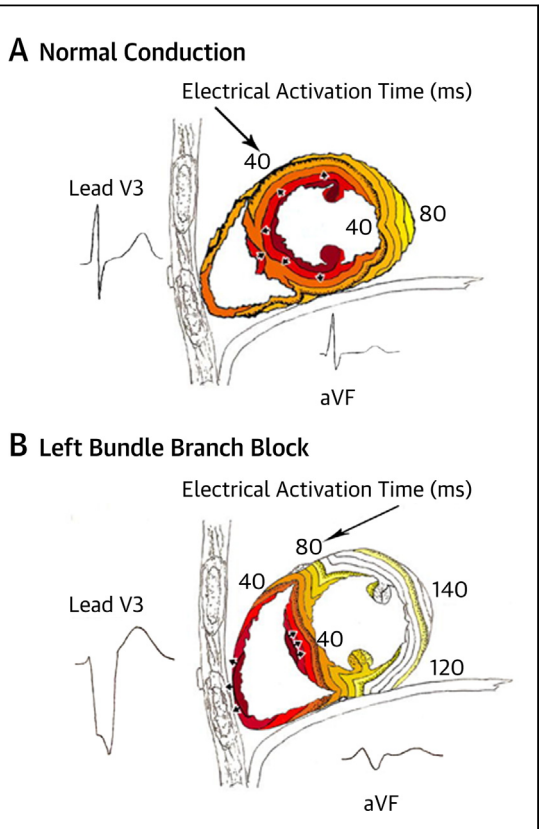


FIGURE 3 Electrical Activation of the Ventricles in Normal Conduction and LBBB

Sagittal view of ventricles in normal conduction **(A)** and LBBB **(B)**. Activation starts at the **small arrows** and spreads in a wavefront with each **line** representing successive 10 ms. The delay between activation of the interventricular septum and free wall is only ~40 ms in normal conduction, but ~100 ms in LBBB. Reproduced with permission from Strauss et al. (33). LBBB = left bundle branch block.

The present findings complement the existing literature addressing the relationship between CRT-D and survival as a function of QRS morphology and duration. A study from the NCDR ICD Registry found that among patients receiving CRT-D, those with LBBB and longest QRS duration had a lower mortality risk than those without LBBB or shorter QRS duration (25). Another study from the ICD Registry comparing outcomes between patients receiving CRT-D with those receiving ICD in a propensity-matched cohort found the lowest rates of hospitalization for cardiovascular causes and heart failure with CRT in the stratum of patients with LBBB and QRS duration longer than 150 ms (30). However, in addition to determining the relationship between sex and mortality in groups according to QRS morphology and duration, the present study evaluated mortality in

10-ms QRS duration groups, demonstrating that the survival benefit of CRT extends to shorter QRS duration groups among women as compared with men. Interestingly, although a recently conducted meta-analysis that also primarily included NYHA functional class III heart failure patients found that patients with QRS of 140 ms or longer benefited from CRT regardless of conduction type or sex (31), Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) substudies found that women with QRS shorter than 150 ms, but not men with QRS shorter than 150 ms, benefited from therapy (8,28). Additionally, in the recently published extended follow-up of MADIT-CRT, it was found that the survival benefit associated with CRT-D in patients with LBBB was independent of QRS duration and did not differ by sex; however, that analysis included fewer women and primarily patients with NYHA functional class II heart failure symptoms (32). Other published studies of CRT effect, including QRS morphology and QRS duration, have not performed separate analyses in women and men (5,6,24,25).

STUDY LIMITATIONS. This study did not include an ICD comparator group. Therefore, we were unable to evaluate the true effectiveness of CRT-D therapy. Multiple comparisons were performed; however, a Bonferroni correction for the 10 comparisons in LBBB women and LBBB men would not change the significance of the results ($p < 0.005$ for all LBBB). These data only represent patients who were admitted for the sole purpose of CRT-D implantation and did not have a prior pacemaker or ICD. It is possible that entry errors or missing data may have resulted in misdiagnosis of baseline characteristics, including QRS morphology and QRS duration. However, extensive data quality checks for the NCDR registries are in place and previous work has demonstrated that the participant average raw accuracy of data abstraction for the NCDR ICD registry is approximately 91% (21). The majority of patients in this cohort (83%) had NYHA functional class III heart failure symptoms, and thus the results are largely limited to that population. The endpoint for this analysis was all-cause mortality; the exact cause of death was not known. In addition, this is an observational study in which there is the possibility of confounding by unmeasured variables, including noncardiac comorbidities; however, the most important potential confounders were part of the baseline characteristics (QRS morphology, QRS duration, ejection fraction, and NYHA heart failure functional class).

CONCLUSIONS

This study demonstrated that among real-world CRT-D recipients with predominantly NYHA functional class III heart failure, mortality risk in women with LBBB is lower than in men with LBBB, although there is no risk difference between female and male patients without LBBB. Furthermore, longer QRS duration is associated with better survival in patients with LBBB only. This favorable prognosis seems to plateau with QRS longer than 140 ms in women and 150 ms in men. Differences in baseline characteristics, patient selection for the procedure, and biological effects of CRT therapy on left ventricular synchronization may contribute to the observed differences by sex and QRS duration. Further studies comparing CRT-D with a comparator ICD group may help elucidate these findings.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Multiple clinical factors should be considered when selecting candidates for cardiac resynchronization therapy, including sex, QRS morphology, and QRS duration.

TRANSLATIONAL OUTLOOK: The mechanisms responsible for the differential response to cardiac resynchronization therapy in women and men, which may include biological effects, patient characteristics, or patient selection for device implantation, require elucidation.

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APPENDIX For supplemental tables, please see the online version of this article.