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EDITORIAL COMMENT

Leaning Toward a Better Understanding of CRT in Women*

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Cardiac resynchronization-defibrillation therapy (CRT-D) is now a well-established treatment for patients with symptomatic heart failure unresponsive to optimized pharmacological therapy, including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-adrenergic blocker (1). Current indications based on American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines include patients with New York Heart Association (NYHA) functional class II to IV symptoms, left bundle branch block (LBBB), and QRS duration of 150 ms or more (2). Patients with LBBB and QRS duration of 120 to 149 ms or non-LBBB and QRS duration of 150 ms or more also have been reported to benefit from CRT-D therapy on the basis of earlier clinical trial results. Recently, the long-term results of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial demonstrated improved survival among patients with mild (NYHA functional class I or II) symptoms (3). Despite more than a decade of progress in improving implantation techniques and optimizing pacing, approximately 30% of patients still fail to respond adequately to CRT-D therapy. Given its invasive nature and the significant healthcare costs, accurate identification of those patients most likely to benefit remains a clinical challenge. Although multiple clinical trials have evaluated a myriad of echocardiographic parameters to assess ventricular dyssynchrony, these measures have generally failed to differentiate responders from nonresponders (4). The recently published ECHO-CRT (Echocardiography Guided Cardiac Resynchronization) trial confirmed the powerful predictive value of QRS duration, but not dyssynchrony measures, in identifying responsive patients (5). Despite clear-cut echocardiographic confirmation of ventricular dyssynchrony, patients with normal QRS duration (mean 105 ms) failed to benefit from CRT-D therapy.

Attention has shifted away from dyssynchrony assessment and once again refocused on QRS morphology and duration as predictors of favorable outcome (e.g., improved survival, increased exercise duration, and left ventricular reverse remodeling). Several recent clinical trials and meta-analyses have shown that the presence of LBBB is predictive of a favorable response to CRT-D (6–8). More importantly, it is now increasingly apparent that patients with significant QRS prolongation but a non-LBBB morphology may experience no benefit or even sustain harm from this treatment (9–11). When complete LBBB exists, left ventricular lateral wall activation occurs approximately 100 ms later than the interventricular septum activation due to impairment in rapid impulse conduction via the His-Purkinje system. The left ventricular pacing lead in CRT reduces this delay and restores more-synchronized activation between both ventricular walls. However, left ventricular activation remains relatively intact through the normal His-Purkinje pathway in patients with QRS prolongation and non-LBBB morphology.

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In this issue of the *Journal,* Zusterzeel et al. (12) report sex-specific mortality risk by QRS morphology and duration among a cohort of 31,892 patients who underwent CRT-D therapy and were included in the NCDR (National Cardiovascular Data Registry) Implantable Cardioverter Defibrillator (ICD)

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registry. The study population included patients with either ischemic (56%) or nonischemic cardiomyopathy (44%) and predominantly NYHA functional class III symptoms (83%) who underwent device implantation between 2006 and 2009. Unlike previously published clinical trials or registries in which women have comprised 22% to 30% of the study population, females represented 36% of this large cohort. Although mean left ventricular ejection fraction (LVEF) did not differ between men and women (mean LVEF 24 ± 7%), significantly more women had LBBB at baseline (86% vs. 70%) and a nonischemic heart failure etiology (62% vs. 33%). Among the entire cohort with complete LBBB, women had a 21% lower mortality compared with men (hazard ratio: 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$). Further, longer QRS duration with LBBB was associated with better survival in both men and women. Specifically, a QRS duration >140 ms in women and >150 ms in men was associated with the greatest survival benefit. Importantly, no benefit was observed in either sex when QRS prolongation was due to non-LBBB morphology.

In the study by Loring et al. (8) of 144,642 Medicare beneficiaries who underwent CRT-D therapy between 2002 and 2007, women composed 26% of this cohort. Unlike the present study, women who underwent CRT-D therapy had a higher rate of atrial fibrillation or flutter (48% vs. 0%), a higher incidence of ischemic cardiomyopathy (53% vs. 38%), and a lower prevalence of LBBB (53% vs. 86%). Despite substantial differences between the 2 study populations, this large registry also reported that women with complete LBBB demonstrated a substantially lower risk-adjusted mortality rate than men; furthermore, heart failure hospitalizations were decreased by 26% in women compared with 15% in men with LBBB (8).

Why would women be more responsive to CRT-D than men? Women normally have smaller left ventricular cavity dimensions and shorter baseline QRS duration. Further, women are more likely to have "true" LBBB, whereas men are more likely to have an incomplete LBBB at the lower end of the QRS prolongation spectrum (e.g., 120 to 140 ms). In addition to electrophysiological differences between sexes, ischemic cardiomyopathy remains a significantly less common cause of symptomatic heart failure in women.

Like all retrospective database analyses, the present study has several limitations. It evaluated only patients admitted for CRT-D implantation who did not have a prior pacemaker or ICD. This trial excluded patients with a prior history of atrial fibrillation, a group known to have a lower response rate to CRT-D therapy. Further, no information is provided regarding the use of aldosterone antagonists in this population. The majority of patients (83%) had NYHA functional class III symptoms, and the results should be largely confined to patients with this severity of heart failure. Given the large size of the database, the endpoint for analysis was all-cause mortality, and the exact cause of death or percent cardiovascular deaths was unknown. Finally, as with any observational study, there is a possibility of unmeasured, confounding variables, including noncardiac comorbidities. Nonetheless, this study demonstrates among real-world CRT-D recipients a striking mortality reduction among women with LBBB compared with men and, as importantly, no difference between men and women patients who exhibited substantial QRS prolongation but lack LBBB morphology. Although the extent of QRS prolongation was associated with better survival in LBBB patients, this favorable prognosis seems to plateau higher than 140 ms in women and 150 ms in men. This report adds to knowledge derived from smaller clinical trials by further identifying patients more (and less) likely to respond to CRT-D treatment. It is important to recognize that women are frequently underrepresented in clinical trials and less frequently receive invasive cardiac interventions. Limiting CRT-D therapy to individuals with LBBB and QRS duration of 150 ms or more may deprive a substantial number of women with shorter QRS duration of this beneficial treatment. Conversely, the appropriate role of CRT-D therapy in both men and women with moderately severe heart failure symptoms who lack LBBB morphology appears to require careful reevaluation.

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