REFERENCES


Letters to the Editor

A Critical Reappraisal of Differences in Cardiac Resynchronization Therapy Defibrillator Effectiveness Between Men and Women in the MADIT-CRT Trial

In a recent issue of the Journal, Arshad et al. (1) reported a significantly greater reduction in death and heart failure with cardiac resynchronization therapy defibrillators (CRT-D) in women than in men. In their discussion, they described the characteristics of the patients. We wish to analyze these data more in depth. The study population shows a difference between the overall percentage of men and women, but in our opinion it is worth noting a difference in the etiology of heart failure between sexes. Over the last decades the prevalence of ischemic heart disease has been demonstrated to be similar in both sexes with increasing age (2), whereas in this study the majority of women (72%) had nonischemic heart disease, as compared with only 36% of men with nonischemic heart disease. Baseline functional and structural parameters of left ventricular function are comparable between the 2 groups. In general, patients with ischemic heart disease have a worse prognosis (3,4), and coronary artery disease is a predictor of poor response to cardiac resynchronization therapy.
Because benefits of CRT-D are mainly linked to reverse remodeling, an ischemic population will probably have a worse response and, thus, a poorer outcome. In patients with previous myocardial infarction, global scar burden and extent of viable myocardium directly correlate with remodeling after CRT (8,9). Moreover, the location of prior infarction is also important to the response. Lateral lead placement improves reverse remodeling and functional capacity compared with other locations (10); posterolateral scar, independently from the presence of LV dyssynchrony, has a negative impact on the response to CRT (11,12). A greater proportion of women in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) had a left bundle branch block, which is a predictor of response to cardiac resynchronization therapy.

In conclusion, we recognize the effectiveness of CRT-D also in relatively asymptomatic heart failure patients with a low ejection fraction and wide QRS complex, as previously demonstrated by the MADIT-CRT trial (13), but we suggest the use of a matched cohort of patients to support the hypothesis that CRT-D is more effective in women to avoid confounding bias.

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REFERENCES


Reply

We thank Dr. Durante and colleagues for their interest in our paper (1) and their comments. Ischemic cardiomyopathy remains the most common etiology of systolic heart failure (2). In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) (3), 55% of patients had ischemic cardiomyopathy and 45% had nonischemic cardiomyopathy (NICM). This substrate distribution is similar to other contemporary early stage heart failure trials (4,5). The RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) recently showed that patients with ischemic or nonischemic causes of heart failure had a similar benefit from implantable cardioverter-defibrillator–cardiac resynchronization therapy in early-stage heart failure (6).

For the sex substudy in the MADIT-CRT trial, we found 72% of the women had NICM as compared with 36% of men. Examining the NICM subgroup further, we found women had a significant reduction of the primary endpoint of heart failure and death (70%) or heart failure alone (69%), with significant interaction p values compared with men after receiving cardiac resynchronization therapy defibrillators (CRT-D). No prior study has demonstrated a significantly greater benefit from device therapy for women than men with regard to mortality or cardiac-related outcomes in an overall study population or by disease etiology.

It is possible that among patients with heart disease, the risk of heart failure is greater for women than for men, resulting in a greater benefit from preventive CRT-D therapy in women. Women might also have more dysynchrony with equivalent QRS width compared with men. Of note, left bundle branch block (LBBB) was present in 70% of the MADIT-CRT patients, with 31% of the females having LBBB in this subset. Even within the LBBB subset, women had a significantly greater benefit from CRT-D than men after adjustment for relevant covariates (7).

The findings from the MADIT-CRT trial with regard to the enhanced benefit in women when compared with men are quite strong. We doubt that a substrate matched trial of men and women might also have more dysynchrony with equivalent QRS width compared with men. Of note, left bundle branch block (LBBB) was present in 70% of the MADIT-CRT patients, with 31% of the females having LBBB in this subset. Even within the LBBB subset, women had a significantly greater benefit from CRT-D than men after adjustment for relevant covariates (7).

The findings from the MADIT-CRT trial with regard to the enhanced benefit in women when compared with men are quite strong. We doubt that a substrate matched trial of men and women with early-stage heart failure receiving CRT-D with equivalent rates of LBBB would further advance our knowledge in this area.

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