(5–7). 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); postero-lateral 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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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 dyssynchrony 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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