Heart failure (HF) is a major public health problem, with 1% to 2% of adults and $\geq 10\%$ of those aged $\geq 70$ years affected in developed countries. Advances in our understanding of this condition and in available therapies have substantially improved outcomes in patients with HF with reduced left-ventricular ejection fraction (LVEF). One such innovation is cardiac resynchronization therapy (CRT), which can improve ventricular synchrony and atrioventricular timing, and has earned its place as an evidence-based strategy to improve many of our patients’ quality of life and survival. Two types of conventional CRT devices exist: CRT defibrillators (CRT-Ds), which include an automated implantable cardioverter-defibrillator (AICD), and CRT pacemakers (CRT-P), which do not.

In this context, a study in this issue of Canadian Journal of Cardiology by Mohamed et al. raises an unsettling question: Are women disadvantaged when it comes to CRT-D implantations? Our colleagues used the National Inpatient Sample (NIS)—the largest available public database of hospitalized patients in the United States—to examine sex-based differences in the type of CRT device implanted in 84,148 de novo implantations between January 2004 and December 2014. In-hospital adverse events, including all-cause mortality, procedure-related complications (thoracic, cardiac, and bleeding), and major adverse cardiovascular events (composite of all-cause mortality, procedure-related complications, and device-related infection) were secondarily examined. The NIS is a stratified systematic random sample of inpatient discharges sorted on hospital characteristics. “Weights” provided with the dataset allow users to calculate national (“weighted”) estimates from sample (“unweighted”) estimates. This means that the sample of 84,148 discharges for CRT device implantations in the current study can be extrapolated to 400,823 discharges nationally, once the weighting is applied. After adjusting for available patient characteristics and hospital factors (see following information), 2 findings were particularly notable and warrant careful consideration: Relative to men, women were less likely to receive CRT-Ds—a finding that persisted throughout the study period—and, when they did, they were more likely to have adverse in-hospital outcomes, including procedure-related bleeding, thoracic complications, and cardiac complications (but not mortality or device-related infections). The authors also identified numerous sex-independent factors that were positively associated with CRT-D receipt such as younger age, history of ventricular tachyarrhythmias, previous acute myocardial infarction, hospital bed size, and admission to an urban hospital.

Before evaluating these findings, certain study limitations should be emphasized. First, the study relied on administrative data, using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes. As with any database of this type, concerns regarding diagnostic and procedural coding accuracy arise, which may vary among conditions. The feasibility of using this type of database for cardiac device-associated complications has been demonstrated, however, with 92% sensitivity and 100% specificity in 1 study. Second, the NIS is designed to capture inpatient data, but more than half of cardiac device implantations in the United States are performed on an outpatient basis, as can be appreciated by comparing the NIS data with that of the State Ambulatory Surgery and Services Database. Thus, the cases included in this analysis may be skewed toward relatively sicker patients and more urgent procedures. Outcomes after hospital discharge are also not captured. Third, although the authors adjusted for many potentially relevant variables—including age, race, the presence of left bundle branch block, ischemic heart disease, history of ventricular tachyarrhythmias or cardiac arrest, Elixhauser comorbidities, median household income, hospital bed size, and others—important factors remained unaccounted for (eg, measures of LV function, QRS duration, or ventricular pacing requirements). Fourth, the study’s sample size is a strength but should be...
kept in mind when interpreting “significant” findings. With this sample size, statistically significant and meaningful differences can easily mean different things.

Based on the weighted estimates in the study by Mohamed et al., 85.0% of CRT devices implanted during the study period were CRT-Ds. Of these, 27.8% were implanted in women. Women accounted for 29.9% of all patients undergoing any type of CRT implantation, meaning that 79.2% of women received CRT-Ds compared with 87.5% of men (or, conversely, that 20.8% of women received CRT-Ps compared with 12.5% of men). The fact that >70% of all CRT devices—and of CRT-Ds, specifically—were implanted in men gives one pause for thought but was described in more detail in a previous report by the same authors and has been observed in other studies, including in similar analyses using the NIS, and in other countries. Rather, the current analysis is focused on relative differences between the sexes in the type of CRT device implanted.

How do we explain this sex-based discrepancy in CRT-D implantations? The authors postulate that physicians may believe that women are more likely to respond to CRT, which could reduce the benefits of the AICD component in this patient group; that physicians may be reluctant to implant AICD leads in women because of concerns of increased risks of complications; that there may exist heightened concerns regarding bulkier generators and AICD shocks among female patients; and that patient preferences could differ between the sexes.

In studies comparing CRT-Ds with AICDs in patients with HF and reduced LVEF, women have indeed generally derived more benefit from CRT than men, although this may vary by QRS characteristics and HF symptom severity, and it may be that female sex acts as a surrogate for influential variables such as body or cardiac dimensions. The Cardiac Resynchronization-Heart Failure (CARE-HF) trial demonstrated that CRT-P reduces mortality, including sudden death, relative to medical therapy to a similar extent in both men and women. Whether CRT-D improves clinical outcomes above those of CRT-P is debated, however, especially in women. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, CRT of either type reduced mortality or hospitalization for any cause, with a more pronounced mortality benefit seen with CRT-D. No sex-related difference was evident in the mortality benefit. In contrast, others have not detected this additional benefit of CRT-D over CRT-P or have suggested a smaller benefit in women. In keeping with this, the relatively consistent finding that women with HF are less prone to ventricular tachyarrhythmias than men, which would alter the risk-to-benefit balance of the AICD component.

The finding by Mohamed et al. that women had more procedural complications from CRT-D implantation than men, especially thoracic complications, is supported by other data. The authors propose that the use of bulkier AICD leads may explain this, as women tend to have smaller blood vessels and smaller and thinner-walled ventricles. If so, adjusting for anthropometric indices or cardiac dimensions would be expected to attenuate or even eliminate this difference. Indeed, accounting for such variables has resolved sex differences in CRT outcomes in other studies. However, in the current study, women undergoing CRT-P implantations had more complications than women undergoing CRT-D implantations (6.6% vs 5.2%) and fewer complications than men undergoing CRT-P implantations (6.6% vs 7.3%). Equipment- or device-related factors are therefore unlikely to be the sole explanation, and patient selection is likely at play. Nevertheless, the authors’ suspicion that important aspects of the design and testing of medical devices may not be optimized for women is not without basis. Women accounted for approximately 1 in 5 patients in clinical trials of CRT-D submitted to the US Food and Drug Administration for premarket approval, which is comparable with their inclusion in submitted trials for other cardiovascular devices. Female inclusion is similarly low in preclinical cardiovascular studies using animals, which are often used to inform such trials. In short, efficacy and safety data for cardiovascular therapies are often of poorer quality for women than for men.

Ultimately, one must also acknowledge that sex bias may influence clinical practice, particularly when high-quality data to inform practice are lacking. It is concerning that women with HF and reduced LVEF receive AICD counselling less frequently than men, but that when they are counselled, they are as likely as men to receive AICDs. It is therefore likely that most women undergoing CRT implantations would opt for a CRT-D if it were offered.

The findings by Mohamed et al. prompt us to ask tough questions, including whether women are being undertreated with regard to CRT-D implantations. Unfortunately, given the available data, providing clear answers may be even tougher. Perhaps the fact that we still lack the facts to answer these questions properly is the clearest sign that there is a serious problem.

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