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Editorial

Sex Differences in Complications and Outcomes of Cardiac Implantable Electronic Devices: Time to Evaluate Our Practice

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See article by Mohamed et al, pages 69–78 of this issue.

Cardiac implantable electronic devices (CIEDs) improve symptoms and quality of life, and reduce death from heart failure or arrhythmias. Approximately 200,000 Canadians are living with one of these devices.[1] Although there is overwhelming evidence to support their value, there is evidence of considerable variability in their use, benefits, and adverse outcomes. The study by Mohamed et al.,[2] in this edition of the *Journal,* entitled "Trends in Sex Differences in Outcomes of Cardiac Electronic Device Implantations in the United States," explores this variability for permanent pacemakers (PPMs), cardiac resynchronization therapy (CRT), and implantable cardioverter defibrillators (ICDs) through the lens of sex differences in a fairly contemporary national cohort. This analysis is timely, given the lack of robust data on sex differences in clinical trials and registries and an overall underrepresentation of women, especially in trials of ICDs,[3,4] and the suggestion that CRT may be of greater benefit in women in the setting of nonischemic cardiomyopathy and left bundle branch block.[5]

Mohamed et al.[2] used the National Inpatient Sample, the largest publicly available database of hospitalized patients in the United States, to evaluate in-hospital adverse events, major adverse cardiovascular events (MACE), all-cause mortality, and procedural complications, including bleeding, thoracic, and cardiac complications by sex and over time. Between 2004 and 2014, they identified approximately 570,000 *de novo* CIED implantations, corresponding to approximately 2.9 million hospitalizations. Women comprised 41.9% of this cohort. It was not surprising that women were older, on average by 4 years, and were less frequently admitted electively. Although baseline characteristics were almost all significantly different by sex, this is not surprising given the large sample size. The features that stand out are the notably higher rate of ischemic disease (previous myocardial infarction, ischaemic heart disease, percutaneous coronary intervention, or coronary artery bypass grafting) and the 2-fold higher incidence of ventricular tachycardia (20.1% vs 10.2%) at presentation in men compared with women. Atrial fibrillation was more common in women with an absolute difference of 4.2%, whereas the prevalence of heart failure was more common among men, with an absolute difference of 6.1%. PPMs comprised the majority of CIEDs (62.2%), followed by ICDs at 22.1%. PPMs were more likely to be implanted in women (74.7% vs 53.2%), whereas ICDs were used more frequently in men (27.7% vs 14.2%). When viewed from the perspective of CIED type, only 27% of all ICDs were implanted in women. By taking the sex composition of the cohort into account, men were almost twice as likely to receive a cardiac resynchronization therapy defibrillator (CRT-D) or an ICD compared with women. Although the proportion of women receiving a PPM did not increase over time, there were significant, but marginal, increases in ICD and CRT use in women.

With respect to adverse outcomes in the overall CIED cohort, crude rates were marginally higher in women for all outcomes: MACE, death, and procedure-related complications. However, men experienced more device-related infections. After adjustment for baseline differences, MACE and procedure-related complications remained significantly more common in women, but there was no longer a difference in death. When considered from the perspective of CIED type, women had significantly lower odds of death if they received CRT with a pacemaker or defibrillator. However, MACE and procedure-related complications remained significantly higher in women who received a PPM, a CRT-D, or an ICD. In the evaluation of time trends, an increasing trend in MACE and procedure-related complications was noted in women; however, the odds of death decreased over the same timeframe. Although these trends were statistically significant, the absolute changes were marginal.

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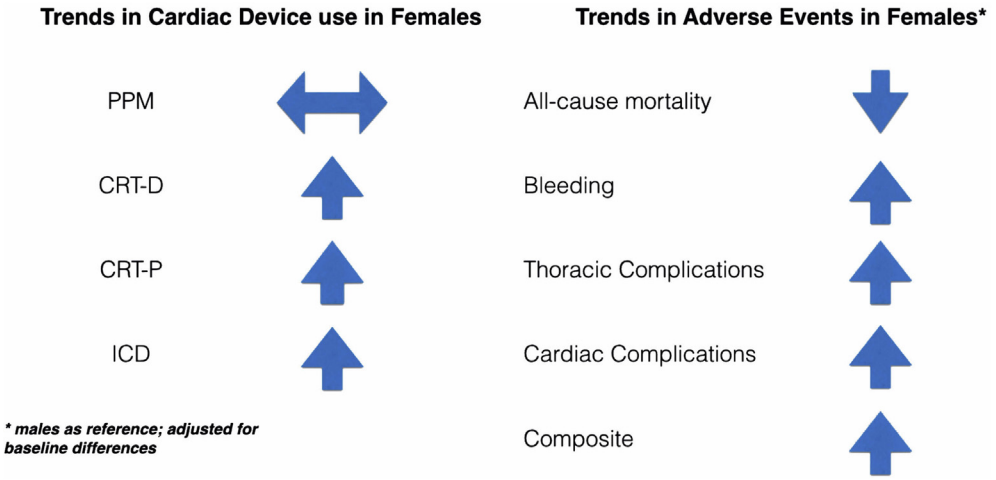

Figure 1. Trends in device use and device-related adverse events. CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; PPM, permanent pacemaker.

A notable strength of the study is the comparison of different types of procedural complications across different device types in the same patient cohort. Although procedure-related bleeding was mildly increased, the majority of complications in women compared with men were mechanical, relating to thoracic (pneumothorax, hemothorax, vascular injury) or cardiac complications (tamponade, hemopericardium, pericardial effusion, pericardiocentesis). This may relate to anatomic differences, such as smaller vessels and chest cavities, and lower body weight. However, the precise mechanisms leading to complications are ill defined, and this report provides further impetus for more detailed exploration. For thoracic complications, are subclavian or axillary approaches being used more than cephalic relative to men? The opposite, if anything, should be true, because women had a higher proportion of atrial fibrillation necessitating a single lead, which is better suited to cephalic pacing. Likewise, for cardiac complications, is apical lead position being favoured over septal pacing, and if so for what reason?

The absence of excess procedure-related complications in women for a cardiac resynchronization therapy pacemaker (CRT-P), but not an ICD or a PPM, is intriguing but quite possibly the play of chance, given this is the least commonly used device type evaluated, with only 2.4% of patients overall, 2.3% of men, and 2.4% of women receiving CRT-P. ICD leads are associated with increased mechanical complications and perforation, particularly in women as observed in the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT).[5] However, there is no reason that a standard pacing system would be associated with complications, yet a more complex pacing system (CRT-P) would not.

The higher rate of device-related infections in men corroborates recent findings from the Danish National Registry in which male sex independently predicted infection.[6] Unequal distribution of comorbidities and higher use of complex devices in men are potential explanations. However, the present analysis extends the Danish study and dispels the latter possibility by demonstrating excess infection associated with male sex consistently across all device types. The reason for these sex differences is thus unclear, although it has been reported that bacterial skin colonization differs by sex.[7]

The lower volume of CRT-D and ICD in women compared with men is congruent with clinical trials and registries. This may appropriately reflect a smaller population of eligible women, with less heart failure and ventricular arrhythmia indications. Nevertheless, another report using the National Inpatient Sample also observed decreased odds of CRT-D vs CRT-P implants in women compared with men, despite women having more predictors of ICD efficacy.[8] Overuse in men, an alternative potential explanation, is unlikely based on analysis from the National Cardiovascular Data Registry in which women receiving devices were equally likely to meet trial enrollment criteria.[9] Finally, under-referral of eligible women or differences in patient preferences may also contribute and merit further exploration.

This transatlantic collaboration is to be congratulated for furthering our understanding of sex differences in device complications. They evaluated a representative, large cohort of patients followed over 10 years, with a much higher proportion of women than has been observed in clinical trials. The inclusion of time trends is a welcome addition to the literature, revealing unexpected worsening despite advances in implantation techniques and training. Several limitations also merit consideration and are appropriately acknowledged by the authors. Foremost, in terms of deciphering the observed disparities in uptake, is the lack of information regarding appropriateness and indication in terms of primary vs secondary. The analysis is also limited to in-hospital outcomes, whereas long-term outcomes and quality of life are not only most important to patients, but would provide further insights into the risks and benefits of CIED use in both sexes. Last, the analysis relies on administrative data, which lacks important clinical information but is an approach that has high sensitivity (> 80%) and specificity (100%) in the Canadian healthcare system,[10] with likely similar performance in the US setting.

In this analysis of approximately 570,000 CIEDs over 10 years, women had higher rates of procedure-related adverse events, with the exception of infections, but in-hospital

mortality rates did not differ by sex (Figure 1). Of note, although the adverse event rates increased significantly in women over this time period, mortality rates actually declined, although in all cases the absolute changes were small. Nevertheless, this is a call for further research to identify techniques that will reduce the excess burden of adverse events in women who receive CIEDs and to address the excess device-related infections observed in men, irrespective of device type. The lower use of CRT-D and ICD in women is consistent with prior studies and raises the question of inequitable access to these devices. This issue remains unresolved because neither this study nor previous work is able to discern whether this consistent and persistent finding is due to lower referral rates in women, patient preference, or even overuse in men. Alternatively, the lower rates may be entirely appropriate if there are truly fewer women with the relevant indications for device use. Although this study focuses on outcomes during the index hospitalization, there is also a need to evaluate adverse events in longer-term follow-up. Perhaps most important, the findings should prompt all implanters to evaluate their practice and ensure that techniques to reduce mechanical complications are used whenever possible.

Disclosures

The authors have no conflicts of interest to disclose.

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