Systematic Review/Meta-analysis

Sex Differences in Implantation and Outcomes of Cardiac Resynchronization Therapy in Real-World Settings: A Systematic Review of Cohort Studies

Omar Dewidar, HBSc,a,b Haben Dawit, HBSc,a Victoria Barbeau, b David Birnie, MD, c Vivian Welch, PhD,a,b,z and George A. Wells, PhD,a,d,z

a School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
b Bruyère Research Institute, University of Ottawa, Ottawa, Ontario, Canada
c Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
d Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

ABSTRACT

Background: Evidence from randomized trials is conflicting on the effects of cardiac resynchronization therapy (CRT) by sex, and differences in access are unknown. We examined sex differences in the implantation rates and outcomes in patients treated with CRT using cohort studies.

Methods: We followed a pre-specified protocol (International Prospective Register of Systematic Reviews [PROSPERO]: CRD42020204804). MEDLINE, Embase, and Web of Science were searched for cohort studies from January 2000 to June 2020 that evaluated the response to CRT in patients ≥ 18 years old and reported sex-specific information in any language.

Landmark randomized controlled trials (RCTs) have demonstrated that cardiac resynchronization therapy (CRT) effectively treats heart failure (HF) patients by reducing hospitalization and mortality. These RCTs, which all included predominantly male patients (67%-83%), are the basis for CRT being the most strongly recommended treatment in international cardiovascular guidelines.

Several RCTs have assessed sex differences in post hoc subgroup analysis, with conflicting evidence of no observed sex differences in effectiveness vs CRT being more effective for women than men. The difficulty in determining if sex differences exist may be primarily due to the underrepresentation of women in HF trials. Furthermore, some studies across the globe suggest differences in utilization of CRT across sex.

This difficulty creates a need for investigating data from observational studies, which could overcome the issues relating to representation of women and are ideal for assessing real-world CRT implantation rates, effectiveness, and adverse events. In this systematic review, we pooled cohort studies reporting effectiveness and safety outcomes among patients treated with CRT, to compare the implantation rate of CRT devices in men vs women and evaluate the presence of sex differences in the response to CRT.

Methods

Search strategy

The protocol for this systematic review was developed a priori, ie, in advance of conducting the study (International Prospective Register of Systematic Reviews [PROSPERO] record: CRD42020204804). The article content was reported according to the Meta-Analysis of Observational Studies in...
**Results:** We included 97 studies (1,172,654 men and 486,553 women). Men received CRT more frequently than women (median ratio, 3.16; 25th to 75th interquartile range, 2.48-3.62). In the unadjusted analysis, men had a greater long-term all-cause mortality rate after CRT, compared with women (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.38-1.63; \( P < 0.001 \)). Adjustment for confounders did not affect the strength or direction of association (HR, 1.45; 95% CI, 1.32-1.59; \( P < 0.001 \)). Women achieved a greater rate of improvement in left ejection fraction compared with men (HR, 4.66; 95% CI, 4.23-5.13; \( P < 0.001 \)). Men had a lower risk of a pneumothorax (relative risk, 0.21; 95% CI, 0.13-0.34; \( P < 0.001 \)); otherwise, there were no differences in complications.

**Conclusions:** We found in this large meta-analysis that men were more often implanted with CRT than women, yet men had a higher long-term all-cause mortality following CRT, compared with women, and smaller improvement in left ventricular ejection fraction. Reasons for this difference in implantation rates of CRT in real-world practice need to be investigated.

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**Epidemiology (MOOSE) checklist.** MEDLINE, Embase, and Web of Science were searched for the time period from January 1, 2000 to June 12, 2020, without language restrictions. Search terms were constructed by a medical research librarian, combining several terms for cardiac devices, HF topic, and cohort studies. We further searched the reference list and study citations of 4 relevant systematic reviews, and we included studies identified by hand-searching using the citationchaser R package.

**Selection of articles**

Titles and abstracts and full-text articles were screened independently by 2 investigators, and discrepancies were resolved by consensus. We included pooled cohort studies reporting sex-disaggregated data for effectiveness and safety outcomes among patients treated with CRT. Non-English language studies were translated using Google Translate. RCTs and other observational study designs were excluded. We contacted authors for studies that were not available through our library and other online sources.

**Data extraction**

Study information was extracted independently by 2 investigators, for men and women separately when available. We collected all reported measures for our outcomes of interest defined a priori (PROSPERO record: CRD42020204804; Supplemental Table S1). When more than 1 multivariable model was reported, we selected the model with the largest number of adjustment variables. We adapted the Newcastle–Ottawa Quality Scale as follows, to provide an overall assessment for the quality of studies: 9 stars to indicate “very good” quality, 7 or 8 stars to indicate “good” quality, 5 or 6 stars to indicate “satisfactory” quality, and 0-4 stars to indicate “unsatisfactory” quality.

**Data synthesis**

We conducted 4 types of analyses for men vs women, as follows: (i) adjusted effect sizes; (ii) unadjusted effect sizes; (iii) raw number of events/measures; and (iv) interaction \( P \) values. When possible, we compared findings for unadjusted vs adjusted outcomes, to assess whether estimates were biased. We planned to conduct subgroup analysis by device type, HF disease severity, and age. Implantation rates were calculated as a ratio of men to women who received the device. For studies that did not report the proportion of men and women who received a type of CRT device, but \( > 90% \) of the patient population received one type of device, the whole population of men and women in the study was considered to have received that device type. Linear regression models were used to compare trends in implantation rate for men vs women over time. Forest plots were used to calculate overall effect sizes using random effects models and were created using Revman 5.1 (Nordic Cochrane Center, Copenhagen, Denmark). Heterogeneity was assessed using the I^2 statistic and explored by subgroup analysis. Publication bias was visually inspected by funnel plots and verified by Egger’s test. \( P \)-curve analysis was used to investigate the extent of the impact of publication bias on the effect estimate.

**Results**

**Study characteristics**

Of the 8504 citations screened, we identified 98 studies that met our eligibility criteria (Supplemental Fig. S1; Supplemental Appendix S2). One study had discrepancies in baseline characteristics and outcome data; therefore, it was not extracted and was excluded for all analyses. The characteristics of the remaining 97 studies were extracted...
and 30 reported adjusted analyses. Loring et al. reported unadjusted effect sizes for effect of sex on all-cause mortality. Long-term all-cause mortality of either subtype did not change (the past 2 decades, the sex disparity for the implantation rate receiving CRT-P (median ratio: 2.08; IQR, 1.71-2.74). Over was 3.37 (IQR, 2.66-4.27), higher than the ratio for those years. The median ratio of men to women receiving CRT-D (ie, CRT-with de...192 ms (Supplemental Fig. S6; Supplemental Table S6).

Heart failure hospitalization

Six studies reported outcome data for HFH stratified by sex; 2 studies, involving 303 men and 149 women, reported the raw number of patients. A nonsignificant difference in risk of HFH was found (RR, 1.31; 95% CI, 0.84-2.02; P = 0.23; Supplemental Fig. S7). Four other studies reported the unadjusted analyses and found no difference in time to HFH (HR, 1.03; 95% CI, 0.75-1.43; P = 0.14). Adjusted analysis also showed no difference (HR, 0.58; 95% CI, 0.32-1.06; P = 0.08; Fig. 2).

Composite outcomes

Of the 7 studies that reported the effect of sex on the composite outcome of death or HFH, 4 studies reported an effect size for sex in their univariate analysis. Time to death or HF hospitalization was greater in men than women (HR, 1.25; 95% CI, 1.05-1.48; P = 0.01; Supplemental Fig. S8A), but substantial heterogeneity was present. Upon the removal of the Loring et al. data (Medicare patients) from the analysis, the pooled HR remained similar, with a significant reduction in heterogeneity (HR, 1.37; 95% CI, 1.19-1.57; P < 0.001; Supplemental Figure S8B). In the adjusted analysis, the difference remained significant but attenuated (HR, 1.06; 95% CI, 1.02-1.11; P = 0.005; Fig. 3B). In the 5 studies that conducted subgroup analyses by sex, significant differences were found in time to death or HFH across the same characteristics as for all-cause mortality (Supplemental Fig. S9). Pooled analysis of other mortality composite outcomes consistently showed a greater risk for men than for women (Supplemental Table S7, Supplemental Figs. S10-S12).

Other effectiveness outcomes

Nine studies, including a total of 1904 men and 701 women, reported the mean change in left ejection fraction (LVEF) from baseline. At short-term follow-up (< 6 months), women had larger improvements in LVEF compared to men (standardized mean difference, −7.36; 95% CI, −9.11 to −5.61; P < 0.001). However, at longer follow-up times (≥ 6 months), the difference diminished (Supplemental Fig. S13A). Adjusted analysis shows a greater rate of LVEF improvement in women compared to men (HR, 4.66; 95% CI, 4.23-5.13; P < 0.001; Fig. 3A). Four studies reported the mean change in quality of life, for a total of 1777 men and 528 women. The unadjusted analysis shows a greater but not significant improvement in quality of life for women compared to men (standardized mean difference: −1.38; 95% CI: −3.19 to 0.43). Little to no difference was found for improvements in New York Heart Association HF classification and 6-minute walk test (Fig. 3 and Supplemental Fig. S13B).

Complication outcomes

We identified 4 studies that reported the raw number of complication events. A pneumothorax was reported for analyses showed significant differences in mortality rate by sex, in patients with LBBB, right bundle branch block, ischemic cardiomyopathy (ICM), AF, hypertension, history of heart failure hospitalization (HFH), or QRS interval longer than 150 ms (Supplemental Fig. S6; Supplemental Table S6).

Long-term all-cause mortality

Of the 97 studies included, 24 reported the raw number of events for all-cause mortality in men and women, 29 reported unadjusted effect sizes for effect of sex on all-cause mortality, and 30 reported adjusted analyses. Loring et al. reported raw, unadjusted, and adjusted analyses, but this study was excluded from meta-analyses due to its being a primary source of heterogeneity. A total of 24 studies reported the raw number of events, involving 221,856 men and 109,389 women. The risk of all-cause mortality was higher in men than women (relative risk [RR], 1.32; 95% confidence interval [CI], 1.27-1.37; P < 0.001; Supplemental Fig. S2). Unadjusted analysis showed a greater all-cause mortality rate for men compared to women (hazard ratio [HR], 1.50; 95% CI, 1.38-1.63; P < 0.001; Supplemental Fig. S3). Direction and magnitude were similar for adjusted analysis (HR, 1.48; 95% CI, 1.32-1.66; P < 0.001; Fig. 2). Supplemental Figure S4 shows that adjustment for LBBB and NICM did not change the results.

Comparison of studies reporting both unadjusted and adjusted estimates for all-cause mortality indicates that adjustment for covariates, overall, had no effect on the estimate size or direction (Supplemental Table S5). There was no statistically significant difference in odds ratio (OR) of all-cause mortality, reported in adjusted models in 4 studies (Supplemental Fig. S5).

Eleven studies assessed the interaction of sex with all-cause mortality, while adjusting for confounders. Interaction...
10,445 men and 3440 women. Men had a significantly lower risk of a pneumothorax compared to women (RR, 0.21; 95% CI, 0.13-0.34; \( P < 0.001 \)). There was a trend for men to have a lower rate of lead-related complications (HR, 0.84; 95% CI, 0.67-1.04; \( P = 0.84 \)), with trends of a higher rate of pocket-related hematoma (HR, 1.79; 95% CI, 0.76-4.23; \( P = 0.18 \)) and device infection (HR, 1.27; 95% CI, 0.82 to 1.94; \( P = 0.28 \); Fig. 4).

### Subgroup analysis

Analysis of raw number of events, and unadjusted and adjusted HRs, indicated no significant difference in all-cause mortality between men and women across New York Heart Association classification, age, and device subtype (Supplemental Fig. S14). Barra et al.\(^{23}\) found no significant difference in all-cause mortality between men and women.

![Figure 1](image-url)  
**Figure 1.** Ratio of men compared to women who received cardiac resynchronization therapy with a defibrillator (CRT-D) or without a defibrillator (pacemaker; CRT-P). **Dotted red line** corresponds to ratio of 1. Points with no intervals are ratios of single studies. One study was excluded from this analysis due to potential selection bias (conducted at the Veteran’s Affairs Healthcare Services). Linear regression analysis shows significant improvement in implantation ratio over time (\( P = 0.005 \)), but no significant difference between men and women receiving either device subtype (\( P = 0.808 \)). IQR, interquartile range.
Mohamed et al.\textsuperscript{24,25} also found no statistically significant difference for in-hospital mortality across CRT devices. Two studies reported adjusted all-cause mortality for patients age \( \geq 75 \) years, comparing men to women (HR, 2.85; 95% CI, 1.48-5.48; \( P = 0.002; \) Supplemental Fig. S5B). One study reported no difference in unadjusted HR of mortality in men vs women for those aged < 80 years and those aged \( \geq 80 \) years.\textsuperscript{26}

**Publications bias**

Visual inspection of forest plots in addition to Egger’s test for all-cause mortality from raw number of events, and unadjusted and adjusted analyses show evidence of asymmetry, with possible weaker-association studies missing (Supplemental Fig. S15). However, \( P \)-curve analysis shows that there is no indication of data manipulation (Supplemental Fig. S16).
Discussion

In this systematic review and meta-analysis of cohort studies comparing implantation rates and response to CRT in men and women, women were implanted with the device 3 times less often. Compared to men, women had a lower mortality rate post-CRT implantation, a greater rate of LVEF improvement, and a higher risk of a pneumothorax. Even though observational studies are susceptible to bias, they provide insights that have contributed greatly to understanding of cardiovascular disease. Observational data are optimal for investigating the delivery of interventions in practice. Thus, they can provide an accurate representation of the use of CRT in men compared to women. Furthermore, our findings confirm individual reports that CRT with implantation is used less frequently in women than men, especially CRT-D. However, we did not detect a statistically significant difference between use of CRT-D and CRT-P, possibly owing to imprecision from the limited number of studies. The higher rate of CRT-P implantation in women may be explained by the predominance of NICM in women, for which it is associated with a similar mortality benefit as implantation with CRT-D. Differences in CRT subtype may not exist.

The prevalence of women with HF eligible for CRT varies by region and guideline indications, ranging from 25% to 45%. According to an evaluation of 2 Canadian cohorts in 2006, women accounted for 45% of patients with HF eligible for CRT in a hospital, but only 28% of HF patients in a clinic. Similarly, in the United Kingdom, 41% of patients with HF eligible for CRT were women. In contrast, more recent evaluations in a Canadian clinic and 2 Belgium hospitals found that only 28% of women presenting with HF met the CRT eligibility criteria. Therefore, the finding that women undergo implantation less often than men may have several explanations. One is sex differences in HF progression and disease presentation—women with HF tend to present with
more severe comorbidities and shorter QRS duration, and their ejection fraction is often more preserved than that of men. A second possibility is that differences in care-seeking behaviour explain the differences in CRT implantation. Even though men are less likely to seek primary care compared to women, some studies have shown that women delay seeking emergency help, especially when experiencing heart attack symptoms. This may be due to women believing the myth that heart attacks are a “man’s disease.” Women also tend to prioritize their social responsibilities over their own health, which leads to delays in care.

A third possibility is that gender bias underlies the observed disparity, in addition to biological sex differences. There is evidence across healthcare arenas, including cardiovascular care, that women are sometimes not offered the same treatments as men, without any medical reason, possibly due to the unintended oversight of not including women in early trials. The extent to which these differences in treatment are due to gender bias is difficult to know; however, lack of understanding of sex differences generates and exacerbates gender biases. Gender bias may exist in cardiac device treatment, as it was found that less than a third of women eligible for CRT received a device. Given that cardiologists perceive men as being stronger and more likely to take risks than women, they may be hesitant to suggest CRT implantation for women, believing that women would be less likely to accept the implantation, and therefore they avoid referral from onset. Furthermore, women receiving the device, were less likely, compared with men, to receive counselling relating to implantable cardioverter-defibrillators prior to implantation.

Figure 4. Unadjusted safety outcomes. Forest plots showing raw number of events for (A) pneumothorax, (B) lead-related complications, (C) pocket-related hematoma, and (D) device infection. CI, confidence interval; M-H, Mantel-Haenszel.
of body image concerns relating to scars and the size of the device under the skin. The difference in the risk of all-cause mortality across sex is consistent with 2 meta-analyses of RCTs that found a better survival benefit of CRT in women compared to men. Our multifaceted analyses of all-cause mortality confirms that sex differences are present in the real-world setting and are not likely due to residual confounding. Thus, the explanation of the found sex difference in mortality is likely to be multifactorial. In our studies, women more commonly presented with LBBB, compared with men, which has been shown to be associated with greater reduction in mortality. However, sensitivity analysis of studies adjusting for LBBB and HF etiology further demonstrates that the difference may be driven by differences in baseline risk profiles other than LBBB and HF etiology. Linde et al. found that the harms of LBBB are more pronounced in men, which may be the cause of the difference in survival, irrespective of CRT. Consequently, female CRT candidates may have an a priori survival advantage before implantation.

We found that women had a greater rate of improvement in LVEF after CRT, compared with men, consistent with findings from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Our findings were confirmed by both unadjusted and adjusted analyses. Given that women are more likely to have NCIM than ICM, some studies have hypothesized that patients with NICM exhibit greater reverse modelling and better outcomes than those with ICM. Our findings add validity to this theory, as we found a pronounced survival benefit in women, and NICM was more prevalent in women than in men in our studies. Furthermore, men were more likely to present with AF and higher creatinine levels than were women, both of which have been associated with poor prognosis and high risk of mortality in patients with depressed LVEF.

Similar to previous trials, we found a lower risk of a pneumothorax in men, compared with women. The increase in risk of a pneumothorax in women may be due to their having smaller cardiovascular anatomic features (ie, chest cavity, blood vessels), which poses greater technical challenges during implantation. The choice of access (subclavian vs axillary vs cephalic) by the operator may mechanistically lead to an increased risk of complications. Ultrasound or contrast-guided axillary vein puncture, as well as cephalic cutdown, may reduce the risk of a pneumothorax. In the presence of AF, it is possible that because an atrial lead is not implanted, the cephalic approach was used more often. Given that women had AF less often, more leads were required, and subclavian access was probably used more often, increasing the risk of a pneumothorax.

Limitations are inherent when using observational studies for evaluating effectiveness, as they lack randomization. One limitation is that differences in effect estimates across sex may have been driven by baseline imbalance and possible confounding due to unknown factors, especially for unadjusted analyses. We also did not seek data from authors; if acquired, these data, by providing more information on patient characteristics, would have enabled us to conduct more-robust meta-analyses and gain further insight into the cause of sex differences. We may have overlooked studies, because we used 2 search filters owing to the large number of citations that required screening. However, we mitigated the possibility of overlooked studies by searching citations and reference lists of included studies and relevant systematic reviews.

Conclusions
We found in this large meta-analysis that men more frequently undergo implantation with CRT than do women, yet women have lower mortality following CRT, compared with men, and a greater rate of improvement in LVEF. Reasons for this real-world difference in CRT implantation rates need to be investigated. More separated analyses for men vs women need to be conducted to illuminate the reasons for sex differences in outcomes.

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**Supplementary Material**

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