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,‡] and George A. Wells, PhD[a,d,‡]

[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.

RÉSUMÉ

Contexte : Les données probantes issues des essais randomisés sont contradictoires quant aux effets de la thérapie de resynchronisation cardiaque (TRC) selon le sexe, et les différences en matière d'accès sont inconnues. À l'aide d'études de cohortes, nous avons examiné les différences en fonction du sexe pour les taux d'implantation et les résultats chez les patients recevant une TRC.

Méthodologie : Nous avons suivi un protocole prédéterminé (International Prospective Register of Systematic Reviews [PROSPERO] : CRD42020204804). Nous avons recherché dans les bases de données MEDLINE, Embase et Web of Science les études de cohortes réalisées entre janvier 2000 et juin 2020 évaluant la réponse à la TRC

Landmark randomized controlled trials (RCTs) have demonstrated that cardiac resynchronization therapy (CRT) effectively treats heart failure (HF) patients by reducing hospitalization and mortality.[1] 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.[2]

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.[3-5] The difficulty in determining if sex differences exist may be primarily due to the underrepresentation

of women in HF trials.[6] Furthermore, some studies across the globe suggest differences in utilization of CRT across sex.[7]

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.[8] 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 **M**eta-Analysis **o**f **O**bservational **S**tudies 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.

chez les patients $\geq$ 18 ans et faisant état d'informations spécifiques au sexe, peu importe la langue.

Résultats : Nous avons inclus 97 études (1 172 654 hommes et 486 553 femmes). La TRC était plus fréquemment administrée chez les hommes que chez les femmes (rapport médian de 3,16; intervalle interquartile du 25ᵉ au 75ᵉ centile : 2,48 à 3,62). Lors des analyses non ajustées, le taux de mortalité à long terme toutes causes confondues après une TRC était plus élevé chez les hommes que chez les femmes (rapport de risques instantanés [RRI] : 1,50; intervalle de confiance [IC] à 95 % : 1,38 à 1,63; $p < 0,001$). L'ajustement en fonction des facteurs de confusion n'affectait pas la force ni le sens de l'association (RRI : 1,45; IC à 95 % : 1,32 à 1,59; $p < 0,001$). Les femmes affichaient un taux d'amélioration de la fraction d'éjection ventriculaire gauche plus élevé que les hommes (RRI : 4,66; IC à 95 % : 4,23 à 5,13; $p < 0,001$). Les hommes montraient un risque plus faible de pneumothorax (risque relatif : 0,21; IC à 95 % : 0,13 à 0,34; $p < 0,001$); il n'y avait aucune autre différence quant aux complications.

Conclusions : Dans le cadre de cette méta-analyse à grande échelle, nous avons constaté que les hommes recevaient plus souvent une TRC que les femmes, mais que, après une TRC, les hommes présentaient une plus grande mortalité à long terme toutes causes confondues, et une amélioration moindre de la fraction d'éjection ventriculaire gauche par rapport aux femmes. Les raisons de cette différence dans les taux d'intégration de la TRC dans la pratique réelle restent à étudier.

Epidemiology (MOOSE) checklist.[9] 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,[10] and cohort studies[11] (Supplemental Appendix S1). We further searched the reference list and study citations of 4 relevant systematic reviews,[12-15] and we included studies identified by hand-searching using the citationchaser R package.[16]

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.[17]

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 $\geq$ 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.[18] P-curve analysis was used to investigate the extent of the impact of publication bias on the effect estimate.[19]

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.[20] The characteristics of the remaining 97 studies were extracted

(Supplemental Tables S2-S4) and included in the analyses (1,172,654 men and 486,553 women). The difference between men and women was deemed clinically important for the following characteristics. Women more often presented with nonischemic cardiomyopathy (NICM; 51% vs 30%), left bundle branch block (LBBB; 41% vs 37%), and longer QRS duration (150.28 ± 25 ms vs 155.1 ± 21 ms), compared with men (Table 1). Women less frequently presented with atrial fibrillation (AF; 34% vs 39%) or paced QRS (19% vs 30%), and they had lower serum creatinine levels (1.23 ± 0.92 mg/dL vs 1.44 ± 0.97 mg/dL) than men. Overall Newcastle–Ottawa Quality Scale scores ranged from 7 to 9 points (maximum score: 9 points) for 62 studies.

CRT implantation rate

From 97 studies, one study was excluded from this analysis due to potential selection bias (only 2 women in the study).[21] In the remaining studies, men were 3.26 times more likely to receive CRT (interquartile range [IQR], 2.47-3.59) than were women (Fig. 1). However, the sex disparity is improving over time, with a reduction in the ratio of men to women receiving the device ($P = 0.005$). A total of 58 studies reported the proportion of men and women receiving CRT device subtypes (ie, CRT-with defibrillator [D] or CRT-with pacemaker [P]). In those studies, men were also more likely to receive either of the CRT subtypes, and this finding persisted throughout the years. The median ratio of men to women receiving CRT-D was 3.37 (IQR, 2.66-4.27), higher than the ratio for those receiving CRT-P (median ratio: 2.08; IQR, 1.71-2.74). Over the past 2 decades, the sex disparity for the implantation rate of either subtype did not change ($P = 0.808$).

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.[22] 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 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).

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.[22] 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% C, 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

Table 1. Characteristics of included studies

Study characteristics	Number of studies (men/women, n)	Men	Women
Age, y	29 (998,986/433,235)	70.8 ± 11.4	71.6 ± 12.5
LVEF, %	21 (81,041/37,490)	24.3 ± 7.2	24.2 ± 7.1
NYHA heart failure class, %	16 (78,788/35,431)	2.92 ± 0.5	2.97 ± 0.4
QRS duration, ms	19 (76,008/36,369)	150.28 ± 25	155.1 ± 21
Comorbidities			
Diabetes	19 (816,637/336,656)	33	33
Hypertension	15 (808,867/334,600)	62	63
Creatinine, mg/dL	9 (73,686/35,582)	1.46 ± 0.97	1.26 ± 0.92
NICM	28 (792,044/327,479)	30	51
AF	19 (765,811/313,227)	41	36
LBBB	17 (465,132/193,905)	65	70
Paced	4 (21,330/11,925)	30	19
Medication			
β-Blocker	17 (74,767/35,036)	86	88
ACE/ARB	15 (74,206/34,874)	67	61
NOS quality assessment (stars), n (%)			
Very good (9)	6 (6)		
Good (7−8)	51 (53)		
Satisfactory (5−6)	38 (39)		
Unsatisfactory (0−4)	2 (2)		

Values in men and women columns are mean ± standard deviation, or %.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; NICM, nonischemic cardiomyopathy; ICM, ischemic cardiomyopathy; NOS, Newcastle−Ottawa Scale.

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.
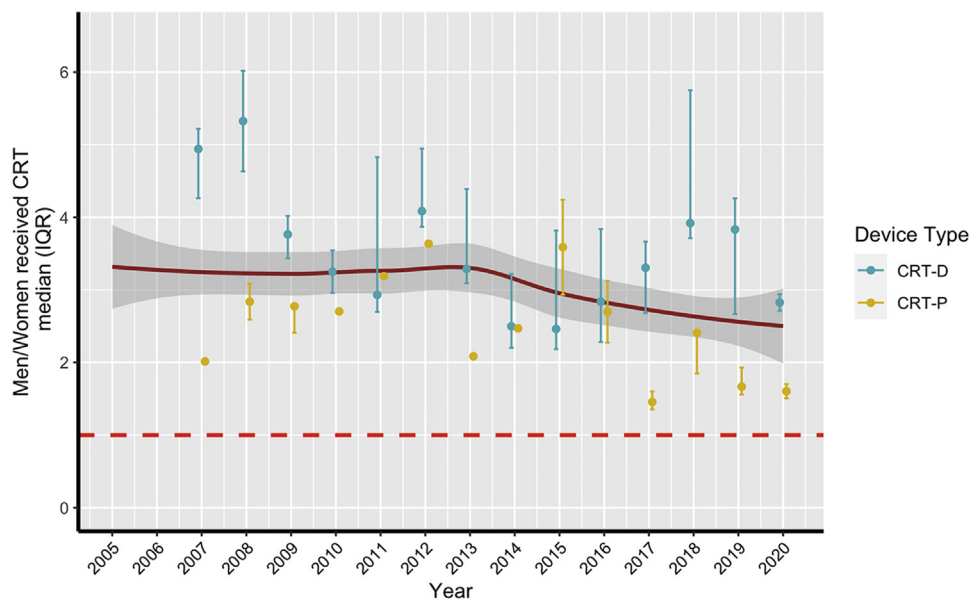
Figure 1. Ratio of men compared to women who received cardiac resynchronization therapy with a defibrillator (CRT-D) or without a defibrillator (pacemaker; CRT-P). **Dotted red line** corresponds to ratio of 1. Points with no intervals are ratios of single studies. One study was excluded from this analysis 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.

A

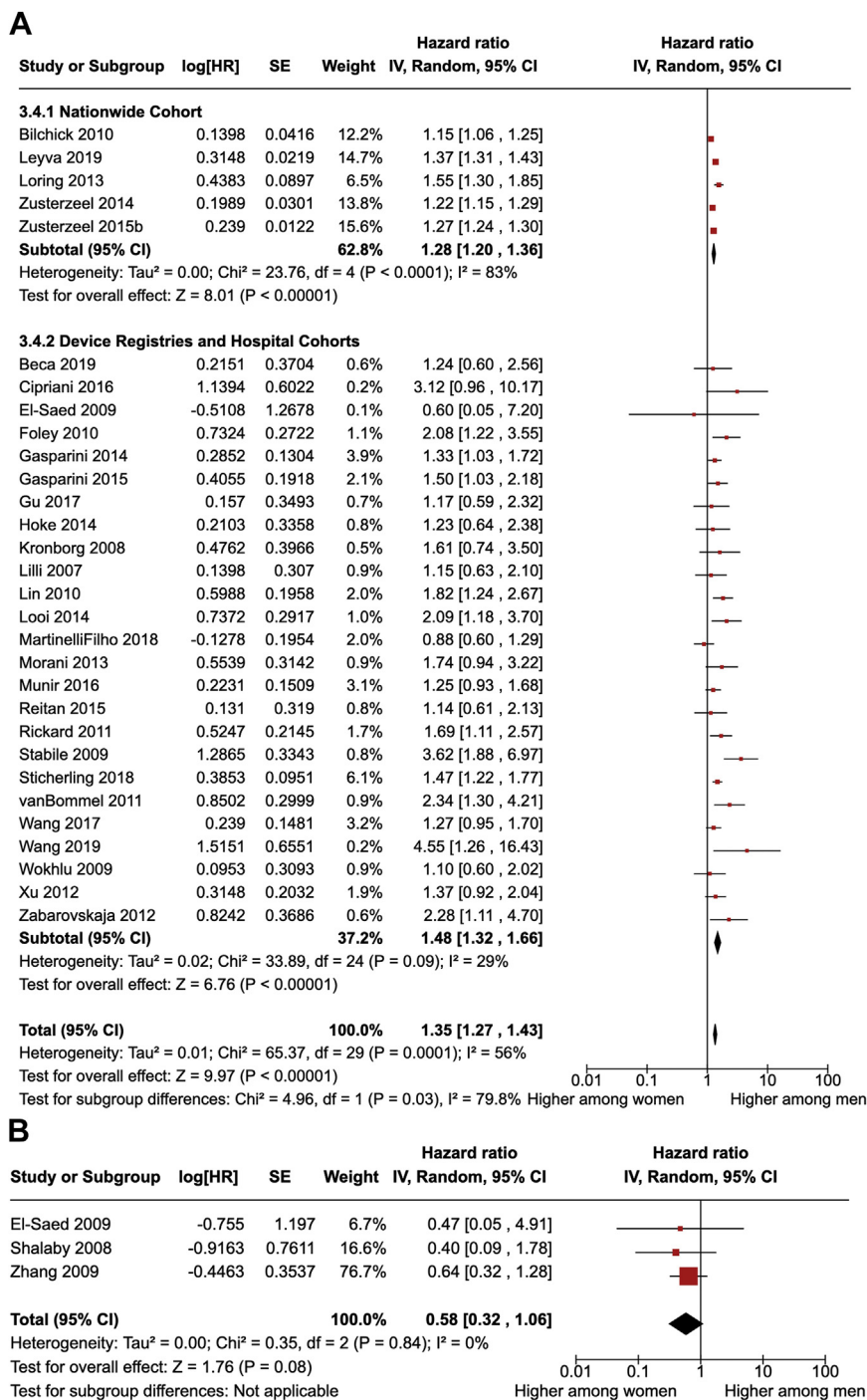| Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Random, 95% CI
3.4.1 Nationwide Cohort				
Bilchick 2010	0.1398	0.0416	12.2%	1.15 [1.06 , 1.25]
Leyva 2019	0.3148	0.0219	14.7%	1.37 [1.31 , 1.43]
Loring 2013	0.4383	0.0897	6.5%	1.55 [1.30 , 1.85]
Zusterzeel 2014	0.1989	0.0301	13.8%	1.22 [1.15 , 1.29]
Zusterzeel 2015b	0.239	0.0122	15.6%	1.27 [1.24 , 1.30]
Subtotal (95% CI)			62.8%	1.28 [1.20 , 1.36]
Heterogeneity: Tau² = 0.00; Chi² = 23.76, df = 4 (P < 0.0001); I² = 83%				
Test for overall effect: Z = 8.01 (P < 0.00001)				
3.4.2 Device Registries and Hospital Cohorts				
Beca 2019	0.2151	0.3704	0.6%	1.24 [0.60 , 2.56]
Cipriani 2016	1.1394	0.6022	0.2%	3.12 [0.96 , 10.17]
El-Saed 2009	-0.5108	1.2678	0.1%	0.60 [0.05 , 7.20]
Foley 2010	0.7324	0.2722	1.1%	2.08 [1.22 , 3.55]
Gasparini 2014	0.2852	0.1304	3.9%	1.33 [1.03 , 1.72]
Gasparini 2015	0.4055	0.1918	2.1%	1.50 [1.03 , 2.18]
Gu 2017	0.157	0.3493	0.7%	1.17 [0.59 , 2.32]
Hoke 2014	0.2103	0.3358	0.8%	1.23 [0.64 , 2.38]
Kronborg 2008	0.4762	0.3966	0.5%	1.61 [0.74 , 3.50]
Lilli 2007	0.1398	0.307	0.9%	1.15 [0.63 , 2.10]
Lin 2010	0.5988	0.1958	2.0%	1.82 [1.24 , 2.67]
Looi 2014	0.7372	0.2917	1.0%	2.09 [1.18 , 3.70]
MartinelliFilho 2018	-0.1278	0.1954	2.0%	0.88 [0.60 , 1.29]
Morani 2013	0.5539	0.3142	0.9%	1.74 [0.94 , 3.22]
Munir 2016	0.2231	0.1509	3.1%	1.25 [0.93 , 1.68]
Reitan 2015	0.131	0.319	0.8%	1.14 [0.61 , 2.13]
Rickard 2011	0.5247	0.2145	1.7%	1.69 [1.11 , 2.57]
Stabile 2009	1.2865	0.3343	0.8%	3.62 [1.88 , 6.97]
Sticherling 2018	0.3853	0.0951	6.1%	1.47 [1.22 , 1.77]
vanBommel 2011	0.8502	0.2999	0.9%	2.34 [1.30 , 4.21]
Wang 2017	0.239	0.1481	3.2%	1.27 [0.95 , 1.70]
Wang 2019	1.5151	0.6551	0.2%	4.55 [1.26 , 16.43]
Wokhlu 2009	0.0953	0.3093	0.9%	1.10 [0.60 , 2.02]
Xu 2012	0.3148	0.2032	1.9%	1.37 [0.92 , 2.04]
Zabarovskaja 2012	0.8242	0.3686	0.6%	2.28 [1.11 , 4.70]
Subtotal (95% CI)			37.2%	1.48 [1.32 , 1.66]
Heterogeneity: Tau² = 0.02; Chi² = 33.89, df = 24 (P = 0.09); I² = 29%				
Test for overall effect: Z = 6.76 (P < 0.00001)				
Total (95% CI)			100.0%	1.35 [1.27 , 1.43]
Heterogeneity: Tau² = 0.01; Chi² = 65.37, df = 29 (P = 0.0001); I² = 56%				
Test for overall effect: Z = 9.97 (P < 0.00001)				
Test for subgroup differences: Chi² = 4.96, df = 1 (P = 0.03), I² = 79.8%				

Higher among women   Higher among men

B

Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Random, 95% CI
El-Saed 2009	-0.755	1.197	6.7%	0.47 [0.05 , 4.91]
Shalaby 2008	-0.9163	0.7611	16.6%	0.40 [0.09 , 1.78]
Zhang 2009	-0.4463	0.3537	76.7%	0.64 [0.32 , 1.28]
Total (95% CI)			100.0%	0.58 [0.32 , 1.06]
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%				
Test for overall effect: Z = 1.76 (P = 0.08)				
Test for subgroup differences: Not applicable				

Higher among women   Higher among men

Figure 2. Adjusted all-cause mortality and heart failure hospitalization. Forest plots showing adjusted (**A**) all-cause mortality and (**B**) heart failure hospitalization when men were compared to women. CI, confidence interval; df, degrees of freedom; HR, hazard ratio; IV, inverse variance; SE, standard error.

Mohamed et al.[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 ≥ 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 ≥80 years.[26]

Publication 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).
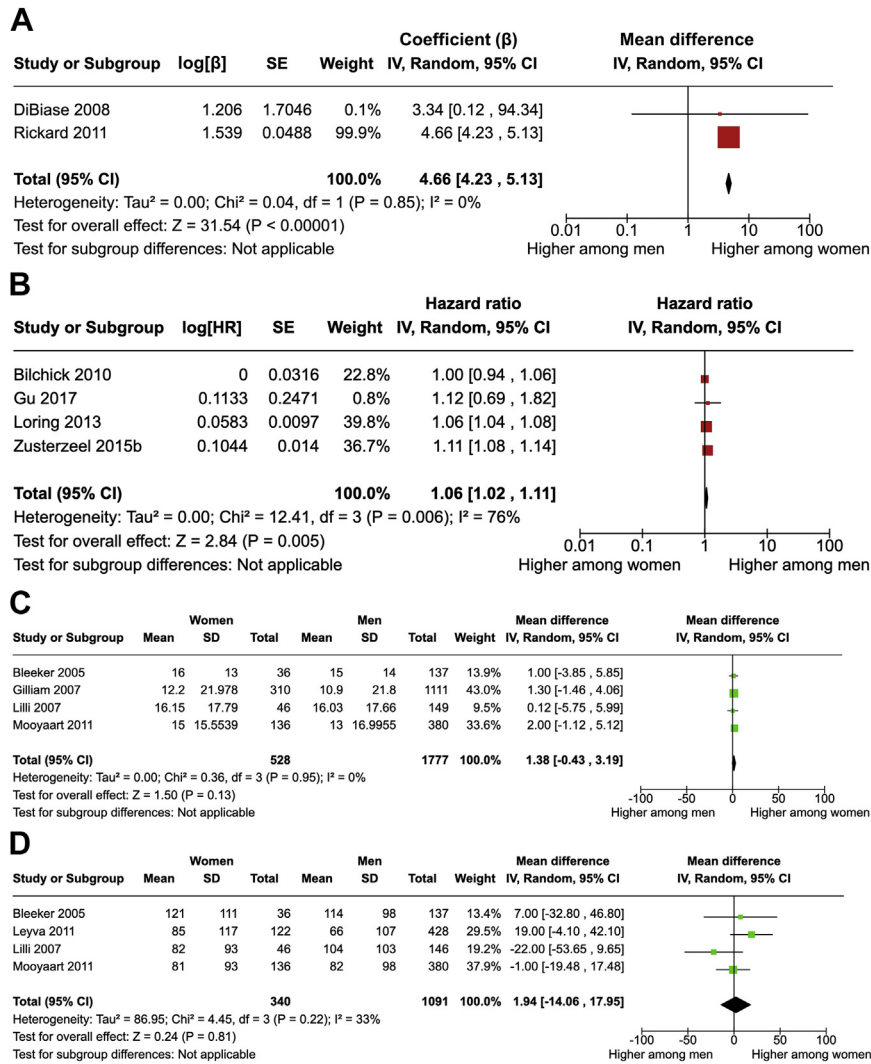
A

Study or Subgroup	log[β]	SE	Weight	Coefficient (β) IV, Random, 95% CI
DiBiase 2008	1.206	1.7046	0.1%	3.34 [0.12 , 94.34]
Rickard 2011	1.539	0.0488	99.9%	4.66 [4.23 , 5.13]
Total (95% CI)			**100.0%**	**4.66 [4.23 , 5.13]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 31.54 (P < 0.00001)
Test for subgroup differences: Not applicable

Mean difference IV, Random, 95% CI — 0.01 0.1 1 10 100 — Higher among men / Higher among women

B

Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Random, 95% CI
Bilchick 2010	0	0.0316	22.8%	1.00 [0.94 , 1.06]
Gu 2017	0.1133	0.2471	0.8%	1.12 [0.69 , 1.82]
Loring 2013	0.0583	0.0097	39.8%	1.06 [1.04 , 1.08]
Zusterzeel 2015b	0.1044	0.014	36.7%	1.11 [1.08 , 1.14]
Total (95% CI)			**100.0%**	**1.06 [1.02 , 1.11]**

Heterogeneity: Tau² = 0.00; Chi² = 12.41, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable

Hazard ratio IV, Random, 95% CI — 0.01 0.1 1 10 100 — Higher among women / Higher among men

C

Study or Subgroup	Women Mean	SD	Total	Men Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Bleeker 2005	16	13	36	15	14	137	13.9%	1.00 [-3.85 , 5.85]
Gilliam 2007	12.2	21.978	310	10.9	21.8	1111	43.0%	1.30 [-1.46 , 4.06]
Lilli 2007	16.15	17.79	46	16.03	17.66	149	9.5%	0.12 [-5.75 , 5.99]
Mooyaart 2011	15	15.5539	136	13	16.9955	380	33.6%	2.00 [-1.12 , 5.12]
Total (95% CI)			**528**			**1777**	**100.0%**	**1.38 [-0.43 , 3.19]**

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable

Mean difference IV, Random, 95% CI — -100 -50 0 50 100 — Higher among men / Higher among women

D

Study or Subgroup	Women Mean	SD	Total	Men Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Bleeker 2005	121	111	36	114	98	137	13.4%	7.00 [-32.80 , 46.80]
Leyva 2011	85	117	122	66	107	428	29.5%	19.00 [-4.10 , 42.10]
Lilli 2007	82	93	46	104	103	146	19.2%	-22.00 [-53.65 , 9.65]
Mooyaart 2011	81	93	136	82	98	380	37.9%	-1.00 [-19.48 , 17.48]
Total (95% CI)			**340**			**1091**	**100.0%**	**1.94 [-14.06 , 17.95]**

Heterogeneity: Tau² = 86.95; Chi² = 4.45, df = 3 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

Mean difference IV, Random, 95% CI — -100 -50 0 50 100 — Higher among men / Higher among women

Figure 3. Other adjusted and unadjusted efficacy outcomes. Forest plots showing (**A**) adjusted change in left ventricular ejection fraction, (**B**) adjusted death or heart failure hospitalization, (**C**) unadjusted improvement in quality of life score and (**D**) unadjusted improvement in 6-minute walk test. Effect estimates for change in left ventricular ejection fraction calculated from beta-coefficients obtained from multivariable linear regression models. CI, confidence interval; HR, hazard ratio; IV, inverse variance; SD, standard deviation; SE, standard error.

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.[8] 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.[27] Furthermore, our findings confirm individual reports that CRT with implantation is used less frequently in women than men, especially CRT-D.[7] 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.[28,29] 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%.[30-33] 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.[32] Similarly, in the United Kingdom, 41% of patients with HF eligible for CRT were women.[31] 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.[30,33] Thus, 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
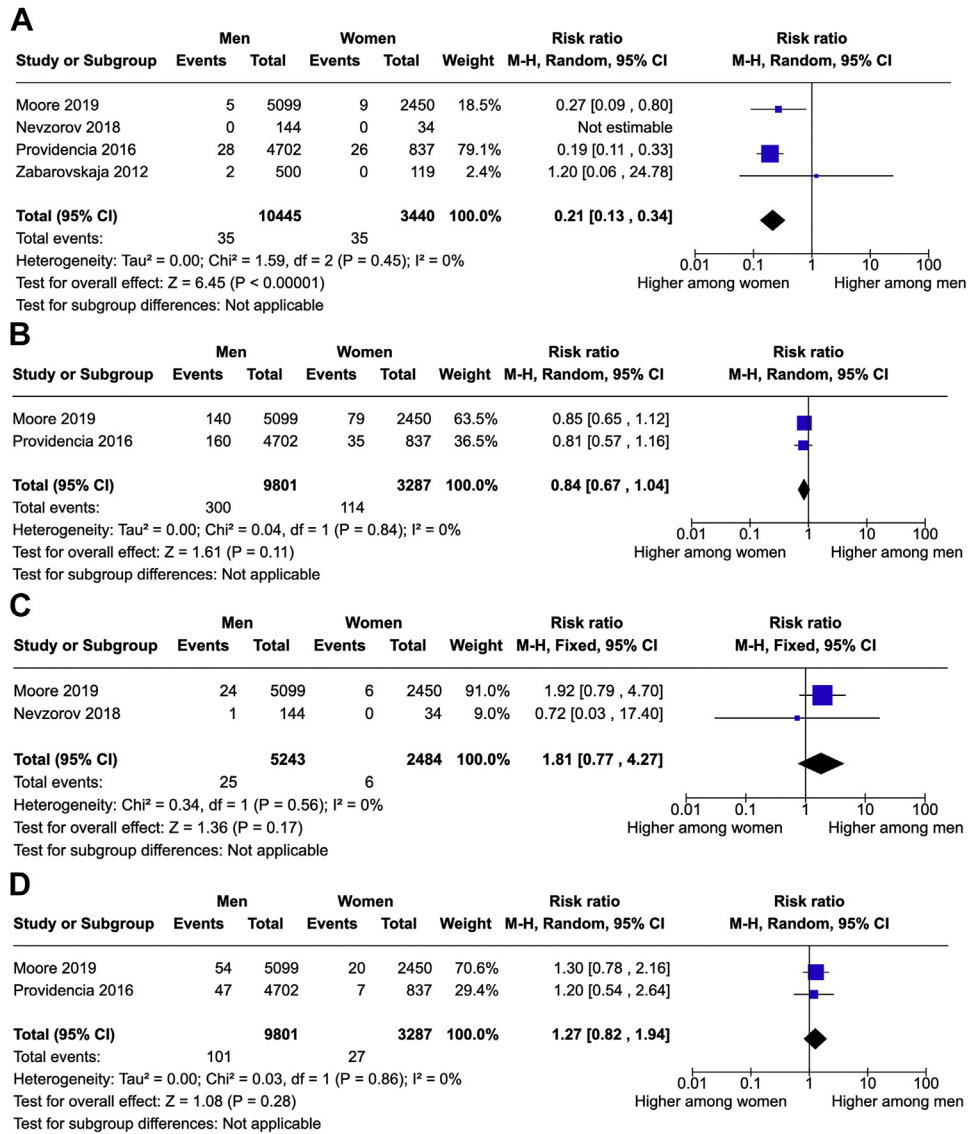
Figure 4. Unadjusted safety outcomes. Forest plots showing raw number of events for (**A**) pneumothorax, (**B**) lead-related complications, (**C**) pocket-related hematoma, and (**D**) device infection. CI, confidence interval; M-H, Mantel-Haenszel.

more severe comorbidities and shorter QRS duration, and their ejection fraction is often more preserved than that of men.[34] 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.[35] This may be due to women believing the myth that heart attacks are a "man's disease."[36] Women also tend to prioritize their social responsibilities over their own health, which leads to delays in care.[37]

A third possibility is that gender bias underlies the observed disparity, in addition to biological sex differences. There is evidence across healthcare arenas,[38] including cardiovascular care,[39] 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.[40] 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.[41] 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.[42] Given that cardiologists perceive men as being stronger and more likely to take risks than women,[43] 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.[44] This difference may be explained by the effect of gender bias on physicians' clinical decision-making process. The potential difficulties that operators face when implanting devices may discourage them from implanting the bulkier CRT-D devices.[45] On the other hand, women may be refusing implantation of an implantable cardioverter–defibrillator because

of body image concerns relating to scars and the size of the device under the skin.[46]

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.[3,4] 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.[3] 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.[4] 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 **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT) trial.[47] 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.[48,49] 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,[50,51] 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.[45] The choice of access (subclavian vs axillary vs cephalic) by the operator may mechanistically lead to an increased risk of complications.[52] Ultrasound or contrast-guided axillary vein puncture, as well as cephalic cutdown, may reduce the risk of a pneumothorax.[53-55] 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.[56]

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.

Acknowledgements

Funding Sources

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Wells G, Parkash R, Healey JS, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. CMAJ 2011;183:421-9.

2. Exner DV, Birnie DH, Moe G, et al. Canadian Cardiovascular Society guidelines on the use of cardiac resynchronization therapy: evidence and patient selection. Can J Cardiol 2013;29:182-95.

3. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med 2014;174:1340-8.

4. Linde C, Cleland JGF, Gold MR, et al. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. Eur J Heart Fail 2018;20:780-91.

5. Zweerink A, Bakelants E, Allaart CP, Burri H. Explaining sex differences in cardiac resynchronization therapy outcome. Eur J Arrhythm Electrophysiol 2020;6:17-23.

6. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. Circulation 2020;141:540-8.

7. Hsich EM. Sex differences in advanced heart failure therapies. Circulation 2019;139:1080-93.

8. Bowman L, Baras A, Bombien R, et al. Understanding the use of observational and randomized data in cardiovascular medicine. Eur Heart J 2020;41:2571-8.

9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

10. Damarell RA, Tieman J, Sladek RM, Davidson PM. Development of a heart failure filter for MEDLINE: an objective approach using evidence-based clinical practice guidelines as an alternative to hand searching. BMC Med Res Methodol 2011;11:12.

11. BMJ Best Practice. Study design search filters. Available at: https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/. Accessed December 16, 2021.

12. Cheng YJ, Zhang J, Li WJ, et al. More favorable response to cardiac resynchronization therapy in women than in men. Circ Arrhythm Electrophysiol 2014;7:807-15.

13. Han Z, Chen Z, Lan R, et al. Sex-specific mortality differences in heart failure patients with ischemia receiving cardiac resynchronization therapy. PLoS One 2017;12:e0180513.

14. Herz ND, Engeda J, Zusterzeel R, et al. Sex differences in device therapy for heart failure: utilization, outcomes, and adverse events. J Womens Health (Larchmt) 2015;24:261-71.

15. Yin FH, Fan CL, Guo YY, Zhu H, Wang ZL. The impact of gender difference on clinical and echocardiographic outcomes in patients with heart failure after cardiac resynchronization therapy: a systematic review and meta-analysis. PLoS One 2017;12:e0176248.

16. Haddaway NR, Grainger MJ, Gray CT. citationchaser: an R package and Shiny app for forward and backward citations chasing in academic searching (version 0.0.3). Zenodo 2021. Available at: https://doi.org/10.5281/zenodo.4543513. Accessed December 16, 2021.

17. Chang W-W, Boonhat H, Lin R-T. Incidence of respiratory symptoms for residents living near a petrochemical industrial complex: a meta-analysis. Int J Environ Res Public Health 2020;17:2474.

18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

19. Simonsohn U, Nelson LD, Simmons JP. p-curve and effect size: correcting for publication bias using only significant results. Perspect Psychol Sci 2014;9:666-81.

20. Madadi S, Mohimi L, Haghjoo M. Evaluation of gender differences in response to cardiac resynchronization therapy in a single heart center. Iran Heart J 2019;20:13-20.

21. El-Saed A, Voigt A, Shalaby A. Usefulness of brain natriuretic peptide level at implant in predicting mortality in patients with advanced but stable heart failure receiving cardiac resynchronization therapy 2009;32:E33-8.

22. Loring Z, Canos DA, Selzman K, et al. Left bundle branch block predicts better survival in women than men receiving cardiac resynchronization therapy long-term follow-up of similar to 145,000 patients. JACC Heart Fail 2013;1:237-44.

23. Barra S, Providência R, Duehmke R, et al. Sex-specific outcomes with addition of defibrillation to resynchronisation therapy in patients with heart failure. Heart 2017;103:753-60.

24. Mohamed MO, Volgman AS, Contractor T, et al. Trends of sex differences in outcomes of cardiac electronic device implantations in the United States 2019;36:69-78.

25. Mohamed MO, Contractor T, Zachariah D, et al. Sex disparities in the choice of cardiac resynchronization therapy device: an analysis of trends. predictors, and outcomes 2020;37:86-93.

26. Achilli A, Turreni F, Gasparini M, et al. Efficacy of cardiac resynchronization therapy in very old patients: the Insync/Insync ICD Italian Registry. Europace 2007;9:732-8.

27. Dreyer NA, Tunis SR, Berger M, et al. Why observational studies should be among the tools used in comparative effectiveness research. Health Aff (Millwood) 2010;29:1818-25.

28. Kutyifa V, Geller L, Bogyi P, et al. Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: results of a high-volume, single-centre experience. Eur J Heart Fail 2014;16:1323-30.

29. Witt CT, Kronborg MB, Nohr EA, et al. Adding the implantable cardioverter-defibrillator to cardiac resynchronization therapy is associated with improved long-term survival in ischaemic, but not in non-ischaemic cardiomyopathy. Europace 2016;18:413-9.

30. Lyons KJ, Podder M, Ezekowitz JA. Rates and reasons for device-based guideline eligibility in patients with heart failure. Heart Rhythm 2014;11:1983-90.

31. Nayar V, Hiari N, Prasad R, et al. Eligibility for cardiac resynchronisation therapy among patients with heart failure, according to UK NICE guideline criteria. Int J Cardiol 2013;168:4401-2.

32. McAlister FA, Tu JV, Newman A, et al. How many patients with heart failure are eligible for cardiac resynchronization? Insights from two prospective cohorts. Eur Heart J 2006;27:323-9.

33. De Sutter J, Weytjens C, Van de Veire N, et al. Prevalence of potential cardiac resynchronization therapy candidates and actual use of cardiac resynchronization therapy in patients hospitalized for heart failure. Eur J Heart Fail 2011;13:412-5.

34. Lenzen MJ, Rosengren A, Scholte op Reimer WJ, et al. Management of patients with heart failure in clinical practice: differences between men and women. Heart 2008;94:e10.

35. Herlitz J, Wireklintsundström B, Bång A, et al. Early identification and delay to treatment in myocardial infarction and stroke: differences and similarities. Scand J Trauma Resusc Emerg Med 2010;18:48.

36. Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: The Women's Heart Alliance. J Am Coll Cardiol 2017;70:123-32.

37. Moser DK, Kimble LP, Alberts MJ, et al. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on Cardiovascular Nursing and Stroke Council. J Cardiovasc Nurs 2007;22:326-43.

38. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC Med Ethics 2017;18:19.

39. Clerc Liaudat C, Vaucher P, De Francesco T, et al. Sex/gender bias in the management of chest pain in ambulatory care. Womens Health (Lond) 2018;14. 1745506518805641.

40. Hamberg K. Gender bias in medicine. Womens Health (Lond) 2008;4: 237-43.

41. Ruiz MT, Verbrugge LM. A two way view of gender bias in medicine. J Epidemiol Community Health 1997;51:106-9.

42. Hernandez AF, Fonarow GC, Liang L, et al. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. JAMA 2007;298:1525-32.

43. Daugherty SL, Blair IV, Havranek EP, et al. Implicit gender bias and the use of cardiovascular tests among cardiologists. J Am Heart Assoc 2017;6: e006872.

44. Hess PL, Hernandez AF, Bhatt DL, et al. Sex and race/ethnicity differences in implantable cardioverter-defibrillator counseling and use among patients hospitalized with heart failure: findings from the Get with the Guidelines-Heart Failure Program. Circulation 2016;134:517-26.

45. Russo AM, Daugherty SL, Masoudi FA, et al. Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: findings from the National Cardiovascular Data Registry (NCDR). Am Heart J 2015;170:330-8.

46. Frydensberg VS, Skovbakke SJ, Pedersen SS, Kok RN. Body image concerns in patients with an implantable cardioverter defibrillator: a scoping review. Pacing Clin Electrophysiol 2018;41:1235-60.

47. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011;57:813-20.

48. Beela AS, Duchenne J, Petrescu A, et al. Sex-specific difference in outcome after cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging 2019;20:504-11.

49. Xu Y-Z, Friedman PA, Webster T, et al. Cardiac resynchronization therapy: Do women benefit more than men? J Cardiovasc Electrophysiol 2012;23:172-8.

50. Jamerson D, McNitt S, Polonsky S, et al. Early procedure-related adverse events by gender in MADIT-CRT. J Cardiovasc Electrophysiol 2014;25: 985-9.

51. Peterson PN, Daugherty SL, Wang Y, et al. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. Circulation 2009;119:1078-84.

52. Chen LY, Chung MK, Allen LA, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. Circulation 2018;137:e623-44.

53. Kotsakou M, Kioumis I, Lazaridis G, et al. Pacemaker insertion. Ann Transl Med 2015;3:42.

54. Tagliari AP, Kochi AN, Mastella B, et al. Axillary vein puncture guided by ultrasound vs cephalic vein dissection in pacemaker and defibrillator implant: a multicenter randomized clinical trial. Heart Rhythm 2020;17: 1554-60.

55. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Pneumothorax in cardiac pacing: a population-based cohort study of 28,860 Danish patients. Europace 2012;14:1132-8.

56. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31: 2369-429.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.09.003.