Sex Differences in Device Therapy for Heart Failure: Utilization, Outcomes, and Adverse Events

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Abstract

Background: Multiple studies of heart failure patients demonstrated significant improvement in exercise capacity, quality of life, cardiac left ventricular function, and survival from cardiac resynchronization therapy (CRT), but the underenrollment of women in these studies is notable. Etiological and pathophysiological differences may result in different outcomes in response to this treatment by sex. The observed disproportionate representation of women suggests that many women with heart failure either do not meet current clinical criteria to receive CRT in trials or are not properly recruited and maintained in these studies.

Methods: We performed a systematic literature review through May 2014 of clinical trials and registries of CRT use that stratified outcomes by sex or reported percent women included. One-hundred eighty-three studies contained sex-specific information.

Results: Ninety percent of the studies evaluated included $\leq 35\%$ women. Fifty-six articles included effectiveness data that reported response with regard to specific outcome parameters. When compared with men, women exhibited more dramatic improvement in specific parameters. In the studies reporting hazard ratios for hospitalization or death, women generally had greater benefit from CRT.

Conclusions: Our review confirms women are markedly underrepresented in CRT trials, and when a CRT device is implanted, women have a therapeutic response that is equivalent to or better than in men, while there is no difference in adverse events reported by sex.

Introduction

BIVENTRICULAR PACING, a device therapy for heart failure more commonly called cardiac resynchronization therapy (CRT), reduces heart failure symptoms, improves left ventricular function, and reduces mortality.¹ CRT-pacemaker (CRT-P) devices help the heart beat in a synchronized pattern by improving the timing or resynchronize pumping action of the heart's lower chambers, while CRT-defibrillators (CRT-D) devices additionally have the ability to detect and treat fast heart rhythms and cardiac arrest. This additional feature enables automated treatment of life-threatening cardiac arrhythmias.

The American College of Cardiology/American Heart Association/Heart Rhythm Society professional society guidelines specify that CRT devices are a class 1 indication (highest recommendation, there are class 2 indications as well) for patients with an ejection fraction $\leq 35\%$ (the fraction of blood the left ventricle pumps out relative to its end-diastolic blood volume); New York Heart Association

(NYHA) heart failure class 2, 3, or 4 symptoms (scale of patient's inability to conduct physical activity); left bundle branch block (LBBB) with a QRS duration ≥ 150 ms; and sinus rhythm.² While this class 1 guideline indication is reflected in the inclusion criteria for a majority of CRT trials, the United States Food and Drug Administration (FDA) has expanded its own indication for some CRT devices to include LBBB with QRS ≥ 130 ms, ejection fraction $< 30\%$, and mild (NYHA class 2) ischemic or nonischemic, or asymptomatic (NYHA class 1) ischemic heart failure.³ Numerous studies have evaluated the effects of CRT in heart failure patients who are classified as NYHA heart failure class 3–4, patients limited or unable to carry out physical activity without discomfort.⁴ Trials have focused on optimal patient selection or the role of patient-specific predictors of device efficacy, but have not examined the potential influence of sex on CRT-P and CRT-D outcomes except in post hoc analyses.

Sex-related differences have been observed in heart failure etiology and pathophysiology, though the underlying

mechanisms are not well understood. Women diagnosed with heart failure are older, more often hypertensive and diabetic,^{5–9} and are less likely to have ischemic heart failure etiology.^{10,11} Women are also more likely to have diastolic dysfunction/diastolic heart failure, which presents with relatively preserved ejection fraction. Hence, on presentation, women may have relatively preserved ejection fraction, but worse NYHA class.^{5,7,12–16,17} There is evidence that women are treated less aggressively for heart disease in general and that they are less likely to receive guideline-recommended treatments.^{7,9,14,18,19} The American Heart Association reported that women also had a higher total mortality due to heart failure than men had.²⁰ Despite these disparities in heart failure outcomes between sex, women comprised only approximately 30% of CRT device implantations.¹⁸ Disparity in diagnosis and treatment of cardiovascular disease may be inhibiting CRT utilization in women.

The objective of this literature review was to examine the possibility of differential enrollment and outcomes by sex in published CRT trials and registries. We analyzed publications for reported sex differences in (1) enrollment, (2) baseline characteristics, or (3) outcomes (either effectiveness or safety endpoints). We also evaluated whether trial inclusion/exclusion criteria could potentially affect enrollment of women in each study.

Materials and Methods

Literature search

PubMed was used to search the Medline database through May 31, 2014, resulting in articles with a date range from 1976 to 2014. Three broad searches were done: (1) “cardiac resynchronization therapy OR biventricular pacing,” (2) trial names for all approved CRT-P and CRT-D systems, and (3) the trade names for approved CRT-Ds, CRT-Ps, pulse generators, and leads. The trial names searched were restricted to those which included “cardiac resynchronization therapy OR biventricular pacing.” Each search was then narrowed by adding “gender OR sex OR male OR men” (which would also capture articles with the words “female” or “women”).

Publication inclusion criteria

Publications in English of all CRT studies that reported baseline characteristics and/or outcomes by sex were included. Each publication needed to have at least one of the following outcomes (not necessarily stratified by sex): mortality, heart failure, hospitalizations due to heart failure or cardiac events, outcome complications such as device-related adverse events, improvement in NYHA heart failure class, stroke volume (the volume of blood pumped out of one ventricle of the heart with each beat), change from baseline in left ventricular end diastolic volume (LVEDV) (volume of blood in the ventricle before contraction), left ventricular end systolic volume (LVESV) (volume of blood in the ventricle after contraction) at 6 months follow-up, or ejection fraction (i.e., the stroke volume divided by the end-diastolic blood volume).

Publication exclusion criteria

We excluded all case reports, review articles, editorials, abstracts, non-human studies, trial substudies that were lim-

ited to cost effectiveness, and imaging studies that did not provide clinical or echocardiographic outcome data. Studies that focused on a subgroup of CRT eligible patients such as those with right bundle branch block, atrioventricular node ablation, or pediatric populations were not included. Studies evaluating patient reported outcomes (surveys, self-assessments, etc.) and lead-related complications were also excluded.

Abstraction

We extracted information on study design, study cohort, study size (study design, cohort and size), enrollment (inclusion)/exclusion criteria, enrollment proportions by sex, baseline characteristics (Table 1), and sex differences in effectiveness outcomes and adverse events. If raw numbers were not present or could not be calculated or were mistyped, the corresponding author of the particular study was asked to provide further information.

Measures of effectiveness and outcomes of CRT

We collected information on baseline mean values of left ventricular ejection fraction (LVEF), NYHA class, QRS duration, age, and ischemic percent by sex (Table 1). In articles where mean values of LVEF were not available, the prevalence of each class was calculated. Risk ratios for LVESV reduction were calculated using the number of nonresponders (LVESV reduction < 15%) by sex with women as the reference group.

Results

Search

The initial PubMed search returned 7,163 citations. After limiting the search using the terms “gender OR sex OR male OR men,” there were 2,191 articles. After the exclusions (e.g., duplicates, articles not in English, case reports, review articles, editorials, abstracts, non-human studies, trial substudies limited to cost effectiveness, and imaging studies), 386 manuscripts remained, resulting in 203 articles describing 183 unique studies (Fig. 1). One hundred publications provided some sex-specific information.^{13,19,21–119} Two authors were contacted for data clarification and did not respond; therefore, these studies were excluded from the results.^{103,106} Of these 100 articles, 56 included comparisons of means or risk ratio estimates of effectiveness analyses of improvement in NYHA heart failure class, ejection fraction, and left ventricular volumes.^{19,21,24,25,27–49,53–78,107} Twenty-two articles discussed sex-specific outcomes for hospitalization and death^{44,50–52,79–84,110} or death alone,^{19,28,85–94,114,116–118} 2 included device-related complications,^{120,121} and 20 included baseline characteristics stratified by sex (Fig. 1).^{19,29,50–54,89,95–100,110,114,116–118,122}

Baseline characteristics and enrollment proportions

In the 183 unique CRT studies that were included in the current analysis, the inclusion of women ranged from 2%–60%. For a majority of the studies, inclusion criteria were LVEF ≤ 35%, QRS duration ≥ 120 ms, and NYHA class 3 or 4. Enrollment criteria for CRT did not differ by sex. Ninety percent of studies had ≤ 35% women and half of the studies

TABLE 1. BASELINE CHARACTERISTICS AND ENROLLMENT PROPORTIONS FOR PATIENTS IN THE CARDIAC RESYNCHRONIZATION THERAPY ARM OF CARDIAC RESYNCHRONIZATION THERAPY STUDIES

Author (year) (trial name) ^a	Total CRT	Male n (%)	Female n (%)	Mean LVEF (%)		NYHA (1/2/3/4)		Mean QRS (ms)		Mean age (years)		Ischemic %	
				Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Arshad et al. (2011) ¹¹⁰	1089	1367 (75)	453 (25)	24 ± 5	23 ± 5	18/82/0/0	5/95/0/0	158 ± 20	158 ± 17	65 ± 11	64 ± 11	64	28
MADIT-CRT Cleland (2005) ⁹⁵	409	596 (73)	215 (27)	26 (22–29)	25 (21–29)	6/17/65/9	4/15/62/15	165	165	65 (59–72)	66 (61–74)	–	–
CARE-HF ^b Woo (2005) ¹⁰⁰	228	309 (68)	144 (32)	percent ≥ 20% 67%	percent ≥ 20% 72%	0/0/92/8	0/0/89/11	–	–	> 65 years 54%	> 65 years 42%	66	29
MIRACLE ^c Bleeker (2005) ⁵⁴	173	137 (79)	36 (21)	21 ± 8	21 ± 7	0/0/85/15	0/0/92/8	173 ± 28	168 ± 35	66 ± 11	65 ± 11	62	33
Lilli (2007) ¹⁹	195	149 (76)	46 (24)	27 ± 7	29 ± 7	3.1 ± 6	3.1 ± 4	153 ± 23	154 ± 19	71 ± 10	73 ± 8	53	42
Zardkoobi (2007) ⁵⁰	117	91 (78)	26 (22)	19 ± 13	22 ± 9	–	–	170 ± 52	168 ± 19	71 ± 11	70 ± 10	76	38
Kelarijani (2008) ⁵³	65	50 (77)	15 (23)	21 ± 7	20 ± 7	3.1 ± 33	3.1 ± 46	142 ± 15	152 ± 11	61 ± 8	59 ± 12	52	33
Dickstein (2009) ⁹⁶	2438	1780 (73)	658 (27)	–	–	–	–	–	–	–	–	57	33
Khan (2009) ¹²²	133	101 (76)	32 (24)	–	–	–	–	–	–	–	–	41	50
Shen (2009) ²⁹	108	78 (72)	30 (27)	–	–	–	–	–	–	–	–	76	33
Tamborero (2009) ⁹⁹	25	20 (80)	5 (20)	26	23	0/0/90/10	0/0/100/0	–	–	66	66.8	55	0
Ozabalova (2010) ⁹⁸	118	90 (76)	28 (23)	–	–	–	–	–	–	59 ± 5	64 ± 7	–	–
Pfau (2010) ⁸⁹	341	258 (76)	83 (24)	20 ± 6	23 ± 9	–	–	–	–	63 ± 9	65 ± 8	–	–
van Bommel (2010) ⁵²	716	566 (79)	150 (21)	–	–	–	–	–	–	–	–	65	39
Verhaert (2010) ⁵¹	313	216 (69)	97 (31)	–	–	–	–	–	–	–	–	63	29
Mooyaart (2011) ¹¹⁴	578	431 (75)	65 (25)	0.23 ± 7	0.23 ± 7	3.1 ± 0.3	3.1 ± 0.3	166 ± 26	166 ± 22	67 ± 9	65 ± 11	67	37
Xu (2012) ¹¹⁷	728	562 (77)	166 (23)	0.24 ± 7.5	0.24 ± 7.2	3.0 ± 0.5	3.0 ± 0.4	166 ± 36	162 ± 29	69 ± 11	66 ± 11.9	64	32
Zabarovskaja (2012) ¹¹⁸	619	500 (81)	119 (19)	0.24 ± 8.6	0.24 ± 8.3	0/13/81/6	0/10/85/5	154 ± 32	160 ± 27	68 ± 10	67 ± 12	65	42
Schuchert (2013) ¹¹⁶	393	311 (79)	82 (21)	0.25 ± 6.48	0.25 ± 7.11	–	–	162 ± 26	168 ± 36	68 ± 10	67.76 ± 9.47	56	26
MASCOT Total	9875	8426 (76)	2725 (24)										

^a“–” indicates not reported. “ms” indicates milliseconds.

^bTrial name included if applicable.

^cNew York Heart Association (NYHA) class as reported by patient.

^dWoo et al. did not include mean LVEF or age. Instead, the percentage of men and women with LVEF ≥ 20% and whose age is > 65 years are presented. CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction.

FIG. 1. Study selection flow chart.

had $\leq 23\%$ women (Fig. 2). Twenty studies reported baseline characteristics by sex (Table 1).^{19,29,50–54,89,95–100,110,114,116–118,122} Ejection fraction, QRS duration, and age were similar between men and women in studies that reported these enrollment characteristics. The proportion of ischemic heart failure etiology was higher in men for 15 out of 17 studies that reported it.

Effectiveness outcomes

Six studies reported data on NYHA class improvement from baseline to 6 months.^{25,53,54,57,64,71} There were no differences between sexes on improvement in NYHA class. Regarding LVESV, women did, however, have an overall higher proportion of LVESV reduction (risk ratio = 1.12 [95% CI: 0.99–1.26]) (Fig. 3). Sixteen studies showed that the proportion of LVESV reduction $\geq 15\%$ was larger in females than males at various follow-ups.^{23–25,27,31,32,34,36,37,39,42,45–48,92,123} Yu et al. randomized patients to right ventricular pacing ($n=88$, 56% male) or biventricular pacing ($n=89$, 53% male).⁷⁸ In this study, a subgroup analysis was done at 12 months and it was found that CRT improved ejection fraction in both sexes (compared with right ventricular pacing alone). However, women had a better average ejection fraction in both groups (57% in the right ventricular and 64% in the CRT group)

compared with men (53% and 61%, respectively).⁷⁰ Of note, right ventricular pacing alone is not a standard therapy used in CRT trials or indications.

Hospitalization and mortality

Many articles assessing the possible sex differences in hospitalization or death were included in this review.^{19,22,28,44,50,52,79–81,83,85–94,107,110,114,118} There were 42 studies that reported CRT heart failure hospitalization or death using hazard ratios; 83% of the outcomes showed a greater benefit in women. More specifically, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial enrolled 1820 heart failure patients randomly assigned (3:2 ratio) to CRT-D ($n=1089$) or standard implantable defibrillators (ICD) alone ($n=731$). Patients eligible to receive ICD based on clinical guidelines were enrolled.⁸⁸ The study found that all patients had a greater benefit from CRT-D therapy. However, women had a greater benefit from CRT-D than men, including when patients were analyzed by disease etiology and LBBB.^{1,110} Women with LBBB had a lower risk of death or hospitalization than men with LBBB ($p=0.01$). The study exhibited more improvement in left ventricular ejection fraction for women with CRT-D than

FIG. 2. Cumulative proportion of enrollment of women in cardiac resynchronization therapy studies ($n=183$). Half of the studies showed $\leq 23\%$ women in their respective analyses. Ninety percent of the studies included $\leq 35\%$ women.

FIG. 3. Meta-analysis of male and female reduction in left ventricular end systolic volume $\geq 15\%$ for cardiac resynchronization therapy at 6-months follow-up.

for men in the total population ($p=0.001$) as well as stratified by LBBB ($p<0.01$) and ischemic heart disease ($p<0.01$). Similarly, women had a greater reduction in LVESV and LVEDV when compared with men overall ($p<0.001$ in both scenarios), by LBBB ($p=0.002$ and $p=0.001$, respectively), and by ischemic heart disease ($p<0.05$ and $p=0.05$, respectively).¹¹⁰

The Management of Atrial Fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT) study analyzed 393 NYHA class 3/4 patients and found that, after adjusting for cardiovascular history, women had lower all-cause mortality ($p<0.001$), less cardiac death ($p=0.04$), and fewer hospitalizations for heart failure compared with men.¹¹⁶ The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial studied CRT among patients with mild heart failure from multiple centers and consisted of a preplanned long term follow up for up to 5 years. Using the Cox proportional hazards model, Gold et al. (2013) found women to have a larger survival rate compared with men after 5 years of follow up (hazard ratio [HR]: 0.07, $p=0.009$).¹¹² In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, however, Bristow et al. compared optimal pharmacologic treatment (OPT) versus both CRT-P and CRT-D for all-cause death or hospitalization over 12 months and found mixed results in health outcomes between sexes.⁸¹ When compared with OPT, the CRT-P HR for all-cause hospitalization or death was 0.82 (95% CI: 0.68–1.00) in men and 0.80 (95% CI: 0.58–1.09) in women as compared with 0.76 (95% CI: 0.62–0.92) in men and 0.93 (95% CI: 0.68–1.27) in women with CRT-D. For all-cause death only, the benefit (in HRs) from CRT-D in women was 0.59 (95% CI: 0.32–1.11) and 0.66 (95% CI: 0.47–0.92) in men.⁸¹ Nineteen single-armed prospective and retrospective cohort studies found that heart failure hospitalization or death occurred in men more than in women.^{28,44,52,79,83,86,87,90,91,93,94,107,111,114,115,117,118} Some studies, however, found that there were no sex differences in mortality and that men were less likely to experience adverse events compared with women, but these findings were not statistically significant.^{80,109}

Device-related complications

Two articles included data on device-related complications.^{120,121} Romeyer-Bouchard et al. analyzed 303 patients implanted with CRT (56 female, 18%). With a mean follow-up of 31 months, 13 male (5%) and no female patients developed a device-related infection.¹²¹ Ghanbari et al. studied 123 (32 female, 26%) patients with a CRT and evaluated them at discharge, 15 days, and 30 days post procedure. Four women (13%) and 6 men (7%) had documented presence of hematomas postoperatively.¹²⁰

Discussion

We performed a systematic literature review through May 2014 of clinical trials and registries of CRT use that stratified outcomes by sex or reported percent women included. The studies reviewed suggest women are under-represented and, when implanted, CRT results in therapeutic outcomes in women that are equivalent or better than those observed in men. Half of the studies showed $\leq 23\%$ of women included in their respective trials and 90% of the studies showed an inclusion of women $\leq 35\%$. Our results are similar to the Healthcare Cost and Utilization Project data, which indicate women comprised 30% of initial CRT device implantations.¹⁸

Differences in the progression and presentation of heart failure between men and women are possible factors for the disproportionate enrollment of women in CRT trials and differences in CRT response by sex. Fewer women with heart failure may meet CRT study inclusion criteria due to ejection fraction $>35\%$ or QRS <120 ms.⁹ The EuroHeart Failure Survey illustrates that roughly 39% of men but only 20% of women with heart failure had an ejection fraction $<35\%$.¹⁶ Also, CRT is only considered for use among heart failure patients with systolic dysfunction, but this condition is more frequently observed in men.^{5,7,12–16,124} Women with heart failure and preserved systolic function are excluded from receiving CRT and participating in clinical trials.¹²⁵

Men and women also differ in how they respond to CRT. Ischemic cardiomyopathy has been linked to less effective reverse remodeling in CRT patients,^{37,62,76,100,126} and men with heart failure are much more likely to have an ischemic etiology.^{10,11,127} Although many of these studies did not evaluate sex differences in patients with LBBB, the higher prevalence of LBBB among women is a potential explanation for differences in CRT response, as it has been shown that response to CRT is better in patients with a LBBB.^{19,28} While the MADIT-CRT trial showed this benefit and reported outcomes based on sex and disease etiology, we were not able to compare this to other studies since they did not include analysis by etiology and LBBB.

While we found both sexes had a similar improvement in NYHA class, women had a higher proportion of LVESV reduction. This may in part be due to women having higher prevalence of nonischemic cardiomyopathy, as previously discussed, and less dense areas of scar.^{128,129} The similarity in NYHA heart failure class improvement between sexes despite a difference in LVESV reduction supports the notion that LVESV is likely not a direct measure of clinical symptoms or long term outcome. Furthermore, a more standardized clinical assessment of LV volumes and function among women and men, possibly based on body surface area, should be considered.

To further elucidate why the enrollment of women has proven to be consistently low and how responses to cardiovascular devices differ in women compared with men, the sex-related differences of baseline characteristics such as sinus rhythm, ischemia, NYHA heart failure class, QRS duration, LBBB, and comorbidities should be examined in future studies.

In order to better understand sex-related differences in CRT response and baseline characteristics the FDA is changing its expectations regarding inclusion of women in clinical trials for development of cardiovascular devices. Women have historically been excluded and underrepresented in clinical trials for a myriad of reasons including fear of fetal consequences for women who might become pregnant, perception that more time and money are required to recruit women, lack of experience and knowledge in the manifestations and progression of disease in women, and family responsibilities for women limiting the amount of time commitment necessary for study follow-ups.¹³⁰ This is detrimental to patients, because when clinical studies fail to enroll a substantial enough proportion of women, they are unable to identify differences between subgroups' responses to treatment if there is a lack of data in the subgroups of interest. In response, the FDA released a final guidance on the importance of focusing on sex differences in device trials in order to enhance the quality and quantity of reliable data in the response to treatment in both sexes.¹³⁰ The increase in female participants in trials may help gather more information on devices in women; however, obtaining data to assess sex-related differences must be a primary study objective in order to best understand the disease and the performance of the device in women.

This review has some limitations. Our search only found words embedded in the text, which inadvertently excludes articles with the terms "sex," "male," or "female" in tables or graphs, which are stored as images. There is also a lack of standardization of definitions and terminology for heart

failure from one study to another. The studies did not differentiate whether, when eligible for CRT, one sex was offered CRT more often than the other, nor did they state whether men or women were more likely to refuse it. This difference in participation rates could influence study outcomes. Studies also did not report comparisons of men and women whose baseline characteristics were made equivalent. Many CRT studies did not consider the impact of sex on outcomes, and therefore, data presented in this review represents only a subset of the CRT data as a whole.

Conclusions

In summary, this systematic review found that women, compared with men, demonstrate responses to CRT that are equivalent or better in device effectiveness, heart failure events, and mortality while adverse events are similar between women and men; however, women are underrepresented in clinical trials and cohort studies. This study highlights the importance in decreasing sex disparities in patient enrollment for trials, as well as the need to include sex-specific analysis when testing cardiovascular devices.

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