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Review

Sex Specific Outcomes With Cardiac Resynchronization Therapy in Patients With Symptomatic Heart Failure Having Reduced Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis ☆

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ABSTRACT

Cardiac resynchronization therapy (CRT) has emerged instrumental in managing heart failure. Notably, there is a lack of evidence of CRT efficacy among both sexes. Thus, this meta-analysis focuses on the long-term benefits of CRT in both sexes. PubMed, The Cochrane Library and clinicaltrials.gov were searched for articles from 2010 to 2024. ROB2 was used to assess risk of bias of RCTs. Newcastle Ottawa Scale was used for quality appraisal of cohorts. Meta-analysis was conducted on Revman 5.4. Out of 2722 articles, only 9 RCTs and 18 cohorts were included. Our results demonstrated that females had a significantly lower risk of composite outcomes compared to males in both RCTs (RR 0.80; 95% CI [0.68, 0.94], P = .006) and cohorts (RR 0.76; 95% CI [0.63, 0.92], P = .004). Results were similar for all-cause mortality. For heart failure hospitalization, only cohorts showed a significant lesser risk in females (RR 0.78; 95% CI [0.65, 0.93], P = .006). Left ventricular ejection fraction improved significantly in females but no differences were observed for NYHA class improvement. Males showed a 31% lower survival rate. However future trials are needed to highlight this variation.

Introduction

Cardiac resynchronization therapy (CRT) has major implications in the treatment of heart failure ranging from mild severity to more morbid and life-threatening forms, significantly deranging the patient's quality of life.[1] Several studies conducted in recent years highlight the favorable outcomes of this modality for heart failure patients, particularly those with reduced ejection fraction (HFrEF) by jump-starting a synchronous intra-ventricular rhythm and fostering remarkable results when it comes to reducing the remodeling,[2,3,4] improving the individual New York Heart Association (NYHA) classification while also cutting down the episodes of subsequent hospitalizations.[5] Despite being a favored modality with significant benefits, a point of concern arises here regarding the difference in efficacy of CRT between males and females with the latter population reporting overall better results and survival outcomes.

Numerous subsets of approaches have been applied ever since CRT became a widely accepted modality for heart failure treatment as backed by clinical guidelines, including the traditional Biventricular pacing (BVP) employed for patients with symptomatic heart failure and left bundle branch block (LBBB),[6] to more modern and accurate varieties namely His Bundle Pacing (HBP) that targets mainly the distal segments and corrects LBBB and yet another form focusing primarily on the left bundle branch area specifically.[7] However, when it comes to broadly classifying CRT, it comes in 2 forms, 1 implanted with a Pacemaker (CRT-P) and 1 with an Implantable Cardioverter-defibrillator (ICD) (CRT-D).[8] Each patient is considered for treatment according to the demographics and disease severity and prescribed 1 of the 2 forms.

The overall effectiveness of CRT for both genders is evident from the fact that many studies have shown that patients with heart failure are reported to have a lower risk of mortality or frequent hospitalizations with CRT as compared to ICD.[9] On the contrary, literature also shows no

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significant survival benefits with CRT when used in patients with mild heart failure (NYHA class II or III), widened QRS complex duration and LV malfunction, provided that the concerned patients had already received medical therapy and an ICD.[10] Of all the studies conducted to date, there exists a homogeneity in the patient population, thus making it difficult to extract results when considering certain subgroups including age, sex and race (unless 1 of these factors has been a primary focus of a study). Such examples can be found in researches conducted on the African American population in comparison with the European American and Caucasian population, highlighting that African Americans derive the same therapeutic benefits from CRT as other races.[11,12]

When addressing the sex-specific differences on the subject matter, trials such as COMPANION and CARE-HF revealed no gender specific difference in survival outcomes, whereas MADIT-CRT showed a greater benefit from CRT-D for women compared to men.[13] Compared to monotherapy, guideline-directed combination medical therapies have a better effect on all-cause mortality in both sexes. Outcomes such as all-cause mortality and hospitalization rates in females have been shown to be less than in males, despite female patients in the cohort having a higher median age than the men included in the study.[14] Despite the evidence being clinically established through preexisting literature with the aid of systematic reviews and/or meta-analyses conducted on RCTs and Cohort studies separately, a meta-analysis combining both study types hasn't been done yet, presenting a gaping clinical gap that must be filled promptly.[15–17]

In light of the aforementioned findings, we plan on conducting this systematic review and meta-analysis to provide categorical and quantitative evidence regarding the long-term benefits of CRT in women compared to the data obtained from their male counterparts. We plan on drawing a comparison between the 2 genders using statistical analysis techniques applied to the data obtained from Randomized Controlled Trials (RCTs) and Cohort studies conducted on the subject from 2010 to the date of the inception of this study. We will also explore the possible reasons for the differences obtained (if any) and discuss them thoroughly, to aid future researchers and medical practitioners belonging to the field in making evidence-based decisions when recommending CRT as a major treatment modality.

Methodology

This review was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and the protocol was registered on PROSPERO (CRD42024584566).[18]

Search Strategy

Three databases including PubMed, The Cochrane Library, and Clinicaltrials.gov were searched for articles from 2010 to 2024 and the search was restricted to trials and observational studies only. Keywords were made using Boolean operators "OR" and "AND" and included: "Cardiac Implantable Electronic Device" OR "Cardiac Resynchronization Therapy" OR "Implantable cardioverter defibrillator" AND "Heart Failure" AND Sex difference. The search strategy for each database separately has been uploaded as supplementary table 1.

Eligibility Criteria

A prespecified criteria was employed to screen articles. The inclusion criteria were as follows:

- Studies after 2010, RCTs, and Cohort/longitudinal studies.
- Age ≥18 years, NYHA 2,3,4 HF, LVEF < 40%, has both males and females.
- conventional CRT, CRT-P, CRT-D, Biventricular pacing.
- Has any of the following outcomes: Composite of all-cause mortality and hospitalization due to HF, hospitalization due to HF and all-cause mortality separately, LVEF, NYHA improvement.
- Studies reporting gender specific outcomes.

Studies were excluded based on the following criteria:

- Studies before 2010, Reviews, SRMA, cross-sectional, conference abstracts, case-control studies, and other study types that are not RCTs or cohort studies as well studies not in English.
- NYHA 1 HF, LVEF > 40%, has only males or only females, patients having LVAD, any condition other than HF.
- ICD alone, his bundle pacing, bundle branch pacing, single ventricle pacing.
- Not reporting on outcomes such as composite of all-cause mortality and hospitalization due to HF, hospitalization due to HF and all-cause mortality separately, LVEF, NYHA improvement.
- Does not include gender specific outcomes.

Selection and Data Extraction

Articles were organized in excel and duplicates were removed. Three reviewers then independently screened and removed articles based on title and abstracts of the studies and any disagreements were solved the help of another reviewer. The remaining articles were screened by 2 reviewers independently to retrieve full text. Selection criteria were applied to articles with full texts, and studies falling under our criteria were included. This process was carried out again by 2 reviewers independently and any dispute was solved by third reviewers after discussion and reviewing reasons for exclusion or inclusion.

An excel sheet was created to extract data from final included articles and consisted of first author name, study type, trial ID in case of RCTs, location where the study was conducted, study duration, sample size for the study and intervention, mean age, ratio of males and females for the overall cohort and intervention cohort, and outcomes. Data was extracted by 2 reviewers and was double checked for discrepancies by third reviewer.

Quality Assessment

The Cochrane Risk of Bias assessment tool (ROB2) was used to assess the risk of bias in included RCTs. It has 5 domains and an overall risk column which is classified as follows: 1) Low risk: If a study has low risk in all domains[2] Some concerns: If a study has shown some concerns in 1 of the domains and rest have low risk[3] High risk: If a study has some concerns in more than 1 domain or has high risk in any of the domains.[19]

For cohort studies, the Newcastle Ottawa Scale (NOS) was used for quality appraisal. The scale consists of 3 domains namely selection, comparability and outcome. These further consist of 8 items each having a score of 1 except the item in the comparability domain which has a maximum score of 2. A score of 8-9 was considered good quality, 6-7 as fair quality and a score ≤ 5 was considered poor quality.[20]

Data Synthesis

A meta-analysis of the included studies was carried out using Revman 5.4. Mean differences (MD) with standard deviations (SD) were collected and used for meta-analysis for continuous outcomes. In studies, where SD was not reported, the Cochrane Revman calculator was used to calculate SD. For dichotomous outcomes, risk ratio was used for analysis. Data analyzed was presented using forest plots. The results throughout the paper used a 95% confidence interval (CI) and a p value < .05 was considered significant. Subgroup analysis was conducted where possible. I2 was used to assess statistical heterogeneity in results, where I2 <25%, 25%-75%, and >75% were considered as low, moderate and high heterogeneity respectively. Sensitivity analysis was carried out based on the risk of bias among studies as well as leaving 1 study out.

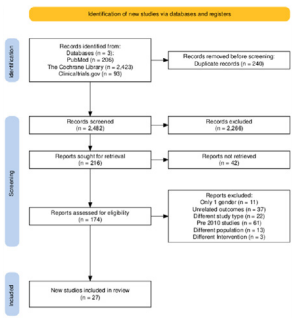

Figure 1. PRISMA flowchart for article screening and selection.

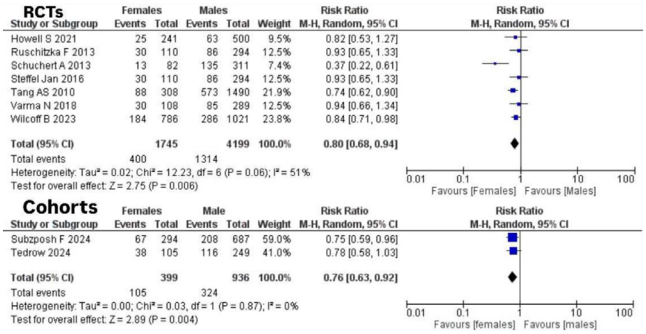

Figure 2. Forest plot showing sex difference in composite outcome.

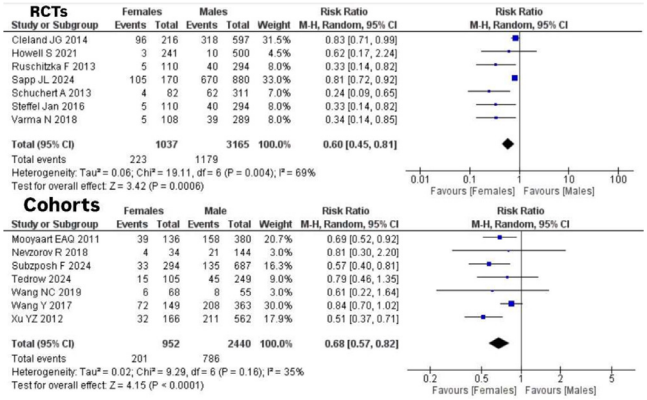

Figure 3. Forest plot presenting sex differences in mortality outcome.

Results

Our comprehensive search on the above-mentioned 3 databases yielded a total of 2722 articles, out of which 240 duplicates were removed. The remaining articles underwent title and abstract screening in which 2266 articles were removed for being irrelevant to our review. Full text of 42 articles was not found and our selection criteria were applied on the remaining 174 articles. 11 articles were removed for having only 1 gender (majorly male), 37 articles were removed for either not reporting gender specific outcomes or not reporting our pre-specified outcomes, 22 articles were removed for not being RCTs or cohorts and 61 studies were published prior to 2010. 13 studies were removed for having different population such as patients with LVAD or NYHA class 1 patients and 3 studies were removed as they didn't use CRT as the main intervention. At the end, only 27 articles were included in the review.[9,10,12,13,21-43] The screening and selection process has been summarized below in Figure 1.

Characteristics of Studies

Out of 27 included studies, 9 were RCTs and 18 were cohorts. Out of 10826 participants from the RCTs only 5970 (55.14%) patients underwent CRT implantation and comprised 4212 males (70.6%) and 1757 (29.4%) females. The mean age of the RCT population was 63.5 years. However, for cohorts, the number of participants were 42770, majorly contributed by Zusterzeel R. et al, 2014,[33] and comprised of 65.9% males and 34.1% females. CRT-D was the most prevalent resynchronization therapy used i.e., 32.2% followed by CRT-P being 16.1% and BIVP being 9.7%. CRT type was not specified in 42% of the studies. The majority i.e., 18 out of 27, of the studies had patients of NYHA 3 and 4 classifications while 4 studies had NYHA 2 and 3 class patients and only 5 study had patients from all 3 classes. The characteristics of RCTs and cohorts have been summarized in Table 1.

Risk of Bias

The risk of bias was calculated for RCTs using ROB2 and which showed that 6 out of 9 RCTs had an overall low risk of bias while only 2 trials overall showed some concerns with all of them having some concerns in domain 1. However, only 1 study by Cleland JG et al, 2014[22] had an overall high risk of bias. The summary of the risk of bias for RCTs is given in supplementary figure 1.

Similarly, for cohorts, studies were evaluated for quality using NOS. Majority of the studies i.e., 13 out of 18 had fair quality,[6-7] while only 3 studies had good quality.[8-9] Only 2 studies by Reitan C et al, 2014 and Said F et al, 2021[31,35] had poor quality (≤5) which were used for sensitivity analysis. The detailed scores in each domain of NOS for all the included cohorts are given in supplementary table 2.

Composite Outcome

The data was obtained and analyzed for the composite of heart failure hospitalization and all-cause mortality from 7 RCTs however, only 2 cohort studies of 2024 reported on this composite outcome. For RCTs, the analysis showed that the risk of composite outcome was reduced significantly in females compared to males (RR 0.80; 95% CI [0.68, 0.94], $P = .006$). However, moderate heterogeneity was observed in the results as I2 = 51% but it was not significant ($P = .06$). Similarly in cohorts, females showed a significant reduced risk of the composite outcome compared to males (RR 0.76; 95% CI [0.63, 0.92], $P = .004$) and heterogeneity was not observed. The forest plots for both these results are given in Figure 2.

All-Cause Mortality

A total of 7 RCTs and 7 Cohorts separately reported the results of all-cause mortality in males and females. For RCTs, our analysis showed that the risk of all-cause mortality was significantly reduced in females compared to males (RR 0.60; 95% CI [0.45, 0.81], $P = .0006$) but moderate heterogeneity was observed in the results with I2 = 69%. Similarly in cohorts, the risk of all-cause mortality was reduced significantly in females compared to males (RR 0.68; 95% CI [0.57, 0.82], $P < .0001$) with mild but insignificant heterogeneity i.e., I2=35% ($P = .16$). Both results are shown below as forest plots in Figure 3.

Hospitalization for Heart Failure

Five RCTs and 5 cohorts reported results of patients undergoing hospitalization for worsening heart failure. The results were opposite across study designs with risk being more in females compared to males in RCTs (RR 1.14; 95% CI [0.92, 1.41], $P = .24$) and being less in females compared to males in cohorts (RR 0.78; 95% CI [0.65, 0.93],

Table 1
Characteristics of Included Trials and Cohorts

Trials									
Author ID	Study Design	Sample Size	Mean age (SD)	Male: Female	CRT Sample	CRT Male: Female	Outcomes	Risk of bias	Main Findings
Schuchert A. et al, 2013	Multicenter single blind RCT	393	67.78 (9.5)	311: 82	393	311:82	Change in NYHA, QOL, all-cause mortality, hospitalization for worsening HF, presence of atrial fibrillation	Some concerns	Females had a better response to CRT than males
Ruschitzka F. et al, 2013	Multicentre RCT	809	57.95 (12.75)	585: 224	404	294:110	Death, hospitalization for HF, change in NYHA, QOL	Low	CRT does not reduce the mortality in patients with systolic HF or QRSd <130ms
Sapp J. et al, 2024	Multicenter, double blind, RCT	1050	66.5 (9.2)	880:170	520	441:79	death, heart transplantation, LVAD	Low	The survival benefit associated CRT-D as compared with ICD appeared to be sustained during a median of nearly 14 years of follow-up
Tang SL. et al, 2010	Multicenter, double-blind, RCT	1798	66.15 (9.35)	1490:308	894	758:136	Mortality, heart transplant, HF hospitalization, LVAD implantation	Low	The addition of CRT to an ICD reduced rates of death and hospitalization for heart failure but also increased adverse outcomes
Cleland J. et al, 2012	RCT	813	66.5 (nil)	597: 216	409	304:105	Mortality	High	The effect of CRT on mortality observed during the randomized CARE-HF trial persisted during long-term follow-up
Steffel J. et al, 2016	International, multicenter, RCT	809	57.85[13]	585: 224	404	294:110	All cause Death, hospitalization for HF, freedom from CRT-D complications	Low	Results suggest that male sex may be a risk factor for harm by CRT in patients with narrow QRS width
Howell S. et al, 2021	Randomized, multicenter, single-blinded clinical trial	741	66[11]	500: 241	741	500:241	freedom from death and hospitalization, >15% reduction in LVESVI	Some concerns	Both sexes' response to CRT is similar. Sex differences in HF substrate, treatment and comorbidities explain sex disparities in CRT outcomes.
Varma N. et al, 2018	Randomized, prospective, double-blinded, multi-center, international trial	796	58[13]	574: 222	398	289:108	all cause deaths, hospitalizations, echocardiographic findings	Low	CRT has opposite effects among patients with heart failure with QRSd <130 ms according to LV size: worsening outcomes in patients with larger LV, but inducing beneficial effects in those with smaller LV.
Wilkoff B. et al, 2023	Global, prospective, RCT	3617	64.9[11]	2049:1568	1807	1021:786	All cause death, hospitalization for HF, unplanned invasive HF therapy, first occurrence of A fib., KCCQ	Low	Compared with conventional CRT, adaptive CRT did not significantly reduce the incidence of all-cause death or intervention for heart failure decompensation

(*continued on next page*)

Table 1 (*continued*)

Cohorts									
Author ID	Study Design	Sample Size	Mean age (SD)	Male: Female	CRT Sample	CRT Male: Female	Outcomes	NOS score	Main Findings
Rickard J. et al, 2015	Retrospective cohort	662	66.7 (11.7)	466: 196	424	294:130	Mortality, LVAD implantation or heart transplant	7	Males showed less improvement in LVEF compared to females
Varrias D. et al, 2022	Cohort	592	67.75 (12.56)	417: 175	592	417:175	All-cause mortality	7	Women show greater increase in LVEF than men
Wang Y. et al, 2017	Prospective cohort	512	81.3(4.11)	363: 149	512	363:149	All-cause mortality	7	Women with CRT show better survival than men with CRT
Xu YZ. Et al, 2011	Retrospective cohort	728	66.7(11.4)	562: 166	728	562:166	Improvements in NYHA, LVEF	6	Women are underrespresented in CRT studies, but both genders attained similar benefits from CRT
Nevzorov R. et al, 2018	Cohort	178		144:34:00	178	144:34	All-cause mortality, readmission, complication rates	6	No gender related differences were found, but higher complication rate of CRT in women
Reitan C. et al, 2014	Retrospective Cohort	446	72.1 (9.7)	370: 76	309	253:56	All-cause mortality	5	Overall survival rate was better for women
Kirubakaran et al, 2012	Retrospective Cohort	164	67[13]	128: 36	164	128:36	HF hospitalization, NYHA improvement	7	Male gender was a predictor of poor response to CRT
Zusterzeel R. et al 2014	Retrospective Cohort	31892	68.5[11]	20350: 11542	31892	20350:11542	All-cause mortality	7	In NYHA class III heart failure, women had lower mortality risk than men
Theuns D. et al, 2019	Cohort	1282	67	974;308	1282	974:308	Mortality at 3 years	6	No significant difference between the genders
Said F. et al, 2021	Cohort	240 (MARC) and 818 (Belgian)	66.5 (9.7) for MARC and 72.0 (10.3) for Belgian	Marc= 146: 87 - Belgian = 556:262	240 (MARC) and 818 (Belgian)	702:349	Echocardiographic markers, change in NYHA class, LVEF and LVESF	5	Women showed greater echocardiographic response to CRT
Varma N. et al, 2017	Cohort	130	61[11]	58:72	130	58:72	Increase in LVEF	7	Females had a greater incidence of response to CRT
Wang NC. Et al, 2019	Cohort	123	62.4 (13.1)	55: 68	123	55:68	Adverse clinical events, all-cause mortality	7	Men have higher risk of mortality after CRT than women
Mooyart EAQ. Et al, 2011	Retrospective Cohort	578	67[10]	431: 147	578	431:147	Echocardiographic markers of response, NYHA improvement, 6MWT, survival	7	Women showed better long-term survival after CRT than men
Beela SA. Et al, 2019	Retrospective Cohort	1058	64[11]	804: 254	1058	804:254	All-cause mortality, reduction in LVEF >15 %	8	Both genders show similar response to CRT after balancing baseline characteristics
Looi KL. et al, 2014	Single-center cohort	500	68.5 (9.6)	385:115	500	385:115	NYHA improvement, all-cause mortality	7	Female gender was a significant predictor of survival
Subzposh F. et al, 2024	International, multicenter, cohort	1778	68 (12.5)	1203: 575	1778	1203:575	All-cause mortality and HF hospitalization	8	Women had favorable outcomes after CRT than men
Tedrow U. et al, 2024	Prospective multicenter cohort	539	70.9 (-)	376:163	539	376:163	HF hospitalization and all-cause mortality	8	Men and women had similar outcomes
Leyva F. et al, 2010	Prospective cohort	550	70.4 (10.7)	428: 122	550	428:122	NYHA improvement, 6MWT, CVS death, death from any cause, death/hospitalization from MACE	7	Women are associated with lower morbidity and mortality after CRT

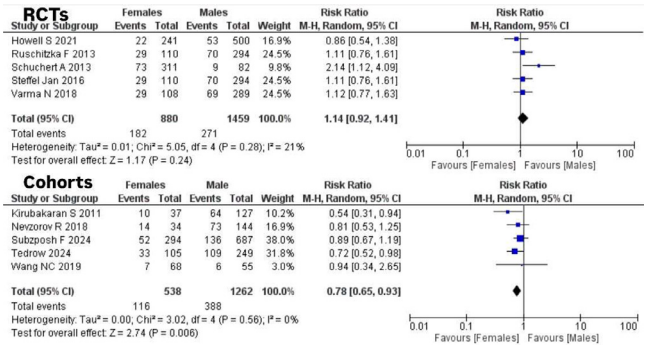

Figure 4. Forest plot showing sex differences in hospitalization due to heart failure.

$P = .006$) with low and zero heterogeneity for RCTs and cohorts respectively. However, the results were significant only for cohorts as shown by forest plots in Figure 4.

LVEF% and NYHA Class Improvement

Only the cohorts included in the meta-analysis provided significant insights LVEF% and its effect on the improvement of NYHA class. The LVEF% increased significantly more in females compared to males calculated using mean difference (MD -3.05; 95% CI [-4.69, -1.41], $P = .0003$). No significant difference was found for improvement in NYHA class between males and females (0.07; 95% CI [-0.10, 0.23], $P = .43$). The statistical heterogeneity was high for both results being 82% and 77% for LVEF% and NYHA class respectively. The forest plots for these results are given in supplementary figure 2.

Survival Analysis

The survival hazard ratios for mortality were mainly observed in cohorts showing males significantly having 31% less chances of survival compared to females but with moderate statistical heterogeneity (HR 0.69; 95% CI [0.58, 0.82], $P < .0001$) as shown in supplementary figure 3.

Sensitivity Analysis

Sensitivity analysis was carried out for outcomes having significant heterogeneity. For all-cause mortality in RCTs, the heterogeneity did not improve upon removing high-risk RCTs. However, after the removal of the high-risk RCT along with the study having a big population Sapp JL et al, 2024,[9] the heterogeneity disappeared i.e., I2=0% and the risk was reduced even further in females (RR 0.34; 95% CI [0.22, 0.52], $P <$ .00001).

Leave 1 out sensitivity analysis did not improve heterogeneity for LVEF% and the results did not change as well however, despite no change in results for NYHA as well, the heterogeneity disappeared after removal of Xu YZ et al, 2012.[29] Similarly, results did not change for survival analysis either after removing poor quality studies but the heterogeneity became insignificant (I2 = 52%, $P = .05$) with the removal of Zusterzeel R, et al 2014 in leave 1 out analysis.[33]

Discussion

We conducted a meta-analysis on 9 RCTs and 18 cohorts to determine how sex affects the efficacy of CRT, by comparing clinical and cardiovascular outcomes among both sexes. Our analysis showed that females have a significantly lower risk for composite outcome, all-cause mortality and heart failure hospitalization, after CRT implantation. LVEF improvement was significant in females than in males, while survival analysis showed that males are 31% less likely to survive than females. The difference in NYHA class improvement was insignificant between both sexes.

The composite outcome risk for males and females significantly differs in favor of females. It has been proven in previous studies as well[15,26]; some suggesting about 2-fold decreased risk in females.[24] A possible explanation for this disparity could be that males often have HFrEF and present at a later age with a greater number of comorbidities and a wider QRS width and females more often have LBBB and non-ischemic etiology which is proven to give better outcomes post CRT.[27,44,45] Females also receive different heart failure medication dosages owing to their smaller body surface area.[35] Moreover, females tend to have smaller LV volume which reportedly warrants better LV reverse remodeling.[46]

These factors are likely to account for the better figure of mortality in females and worse survival rate in males, as reported in our study.[38] Most studies suggest that biological history accounts for this sex discrepancy in response to CRT. Females have LV dimensions up to 20% smaller than males and preserve normal LV size in HF, while males experience undesirable remodeling, widening the heart size gap. Females are also known to have more sustainable myocardium that can be activated by CRT.[47] HF hospitalization risk for females was greater than males in the RCTs included in contrast with the cohorts. It could be attributed to the variable inclusion of females in the studies. Females tend to meet the LV function criteria (LVEF <35%) less often than males, which may affect the study outcomes by creating sex bias in some studies with a strict inclusion criterion.[17] Anyhow, females are under-represented in CRT trials due to multifactorial causes including social, psychological and stereotypical influences.[46]

The improvement in LVEF in females was significant as compared to males. Varrias et al and Tedrow et al also reported a much higher improvement seen in LVEF of females post-implantation.[27,42] A possible reason for this finding could be that females have a higher QRS area-to-volume ratio and show greater degree of LV reverse remodeling.[27,41] The improvement in NYHA class showed no significant difference between both sexes which is in accordance with Mooyaart et al's study.[38] A previous meta-analysis also reports a similar outcome regarding LVEF and NYHA class improvement between the 2 sexes. The lack of difference in NYHA class improvement could be due to minimal influence of sex disparity on secondary clinical outcomes.[46] Left bundle branch area pacing (LBBAP) CRT is promising better results for NYHA class and LVEF in those not responding to BVP-CRT but the current literature has limited data on gender related differences in outcomes.[48-50]

Our meta-analysis has some potential limitations as well. For our analysis, we only included studies with patients who underwent CRT implantation and excluded those with ICD therapy which might have resulted in exclusion of studies evaluating gender related differences in device therapy. Moreover, we did not acquire data from authors regarding more information about patient characteristics which if retrieved, would have helped us in better understanding of the cause of the sex specific differences. Male population in both RCTs (70.6%) and cohorts (65.9%) among our included studies, is more than the female population (29.45 females in RCTs and 34.1% in cohorts) which may have affected the sex specific outcomes. Furthermore, we excluded articles related to conduction system pacing (CSP)-mediated CRT due to a lack of high quality randomized controlled trials (RCTs) and large-scale cohort studies specifically CSP-CRT with sex-based outcomes. High heterogeneity in some outcomes such as LVEF improvement and NYHA class might reduce the value of results. Despite sensitivity analyses, the variability in study designs and populations might undermine the reliability of the pooled results. Due to the variability in reporting of adjusted estimates by the studies, conducting a meaningful meta-regression was not feasible which could impact the pooled estimates. Finally, due to limited data available, a subgroup analysis wasn't conducted.

This study found that male population in both RCTs and cohorts was significantly higher than the female population, highlighting the

need for strategies to encourage female participation in future trials to improve representation. Taking the results of this meta-analysis into consideration and keeping in mind the potential benefits of CRT in females, it is important for the concerned authorities to denote sex-specific guidelines for the implantation of CRT when dealing with HF patients. Females should receive an up-to-date regimen based on physiological differences in cardiovascular function when compared to males. We observed that females have a higher risk of hospitalization rates, this calls for the development of better follow up guidelines to monitor CRT outcomes focusing on sex related differences. Males can also benefit from this study as it would prompt clinicians to devise better treatment strategies for them, in accordance with the disparities reported in the outcomes.

Conclusion

In summary, the present analysis suggested that females were better able to benefit from cardiac resynchronization therapy (CRT) compared to males. In addition to a decrease in mortality in women, results revealed that left ventricular ejection fraction (LVEF %), and overall survival rates, showed significant improvements in women undergoing CRT. These improvements were noticeably higher than those observed in men. However, it is important to note that males had a decreased risk of hospitalisation according to our included RCTs, and no significant differences were observed between the 2 sexes when it came to the improvement in New York Heart Association (NYHA) class. Despite this, the enhanced response in women highlights the necessity for further research to better understand the underlying biological mechanisms driving these sex-related differences. Such insights will be crucial in developing more tailored treatment guidelines, ensuring that both male and female patients receive the most effective, personalized care and optimal outcomes from CRT.

Data availability

Data will be made available upon reasonable request by the editor.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2025.100097.

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