Sex-specific mortality differences in heart failure patients with ischemia receiving cardiac resynchronization therapy

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Abstract

Background
Recent studies have reported prognosis differences between male and female heart failure patients following cardiac resynchronization therapy (CRT). However, the potential clinical factors that underpin these differences remain to be elucidated.

Methods
A meta-analysis was performed to investigate the factors that characterize sex-specific differences following CRT. This analysis involved searching the Medline (Pubmed source) and Embase databases in the period from January 1980 to September 2016.

Results
Fifty-eight studies involving 33445 patients (23.08% of whom were women) were analyzed as part of this study. Only patients receiving CRT with follow-up greater than six months were included in our analysis. Compared with males, females exhibited a reduction of 33% (hazard ratio, 0.67; 95% confidence interval, 0.62–0.73; \( P < 0.0001 \)) and 42% (hazard ratio, 0.58; 95% confidence interval, 0.46–0.74; \( P = 0.003 \)) in all-cause mortality and heart failure hospitalization or heart failure, respectively. Following a stratified analysis of all-cause mortality, we observed that ischemic causes \( (p = 0.03) \) were likely to account for most of the sex-specific differences in relation to CRT.

Conclusion
These data suggest that women have a reduced risk of all-cause mortality and heart failure hospitalization or heart failure following CRT. Based on the results from the stratified analysis, we observed more optimal outcomes for females with ischemic heart disease. Thus, ischemia are likely to play a role in sex-related differences associated with CRT in heart

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failure patients. Further studies are required to determine other indications and the potential mechanisms that might be associated with sex-specific CRT outcomes.

**Introduction**

Cardiac resynchronization therapy (CRT) is an effective treatment for heart failure patients exhibiting wide QRS complexes and reduced systolic left ventricular ejection fractions (LVEF). Although CRT devices are routinely implanted according to ACCF/AHA/HRS guidelines, approximately 20% of CRT patients fail to benefit from CRT [1]. Recently, sex-specific differences in relation to heart failure (HF) epidemiology, clinical presentation, response to CRT, and post-CRT prognosis have been reported. However, the mechanisms that underlie these differences are not well understood. An AHA Statistical Update from 2016 [2] reported that heart failure mortality was higher in women than men; however, no obvious sex-specific differences were observed in relation to the prevalence of heart failure. Therefore, these data suggest that sex-specific factors may cause differences in CRT response between males and females. Indeed, most studies and meta-analyses performed in this area report that women who received CRT experienced greater benefits and reduced mortality compared with men [3]. Studies evaluating the differential effects of clinical factors, including ischemic events, left bundle branch block (LBBB), age, LVEF, and atrial fibrillation on male and female clinical outcomes are limited. Thus, it is important that we attempt to identify and characterize factors that might help us to improve clinical responses to CRT for both male and female HF patients.

The aim of this meta-analysis was to assess sex-specific differences in all-cause mortality in patients who received CRT. We also aimed to examine the effect of clinical factors on sex-related outcomes.

**Methods**

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [4]. No participation of human subjects were involved in this analysis.

**Literature search**

A computer-based literature search by two reviewers (Z.H. and Z.C.) was performed to identify English-language publications listed in the Medline (Pubmed source) and Embase electronic databases from January 1980 to September 2016. The search terms and algorithm for the literature search were as follows: cardiac resynchronization therapy OR CRT OR pacemaker AND (female OR women OR gender). The detailed search strategy were uploaded in supply materials (S1 File).

**Study selection**

To further identify sex-specific differences in post-CRT prognosis, The selection of eligible studies was performed by two independent reviewers (Z.H. and Z.C.). The following studies or patients were included in this meta-analysis: (1) randomized controlled trials (RCT), prospective (PC) or retrospective (RC) studies, (2) studies that included patients with QRS ≥ 120 ms and LVEF ≤ 35%, (3) studies that compared endpoints for all-cause or any-cause mortality between males and females, (4) patients from studies with follow-up periods > 6 months. The
causes of ischemia in associated cases included ischemic cardiomyopathy, ischemic heart failure, myocardial infarction, and patients who received coronary artery bypass grafting or stent implantation. Exclusion criteria for this analysis included the following: animal studies, case reports, review articles, meta-analyses, editorials, posters and studies that did not provide primary end-points for all-cause mortality or enough data to analyze sex-related differences. Disagreement was solved by discussion with another reviewer (W.X.).

Quality assessment

The selection of eligible studies was performed by two independent reviewers (R.L. and W.D.). Since double-blinding is not possible in RCTs of pacemaker implantation, RCT study was evaluated using a modified version of the Jadad scale [5]. The quality of observational studies was assessed by Newcastle-Ottawa Quality Assessment Scale (NOS) [6], selection (a maximum of 4 points), comparability (a maximum of 2 points) and outcomes (a maximum of 3 points). To maintain quality control, only studies with more than 3 points (Jadad score) or 4 points (NOS score) were included in our analysis.

Data extraction

Two reviewers (Z.H. and X.L.) independently extracted data from the associated studies. Results were compared and any disagreements were resolved by consensus. The following characteristics pertaining to the type of study design were extracted; author identification, published year, New York Heart Association functional class (NYHA), age, QRS duration, LVEF, morbidity of ischemic cause, atrial fibrillation and LBBB, and hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality and heart failure hospitalization or heart failure. In some studies, HR was not provided straightly, so the ratio was calculated by Tierney’s [7] method published in 2007. The primary endpoint of interest was death from any cause, and the secondary endpoint was heart failure hospitalization or heart failure.

Publication bias and statistical analysis

Publication bias was assessed by author (X.Z. and W.J.) with funnel plot and by the using Stata 11.0. (Stata Corporation, College Station, TX) via Begg’s and Egger’s test of the intercept. Review Manage (RevMan) version 5.3 (Cochrane Collaboration, UK) was utilized for other statistical analyses by three authors (Z.H., Z.C. and H.Y.). HR and 95% CI values were calculated from the extracted data. All-cause mortality and heart failure hospitalization or heart failure were defined as the primary and secondary endpoints, respectively. Because of significant between-study heterogeneity, a random-effects model was employed to evaluate meta-regression models. Subgroups were categorized based on average values pertaining to age, female ratio, QRS duration, LVEF and average morbidity of ischemic events, atrial fibrillation and LBBB. The p-value of interaction was used to further investigate sex-differences among and between subgroups. P < 0.05 was considered to be statistically significant.

Results

Eligible trials

After duplicates removed, a total of 8160 citations were identified using the search strategy. Initially, after excluding non-relevant studies, reviews, meta-analyses, case reports, and a review of the abstracts, a total of 380 articles were identified. After quality assessment (studies with NOS score less than 4 points were excluded) and full text review, 58 studies were finally enrolled in our analysis as a result of full-text screening. The flow chart pertaining to the study
Baseline characteristics and outcomes

The fifty eight studies [8–65] that were included in this analysis reported sex-stratified relative risk estimates for all-cause mortality. A total of 34,455 individuals, 7952 (23.08%) of whom were females, were enrolled in these studies. All of the studies reported details regarding NYHA classification and 26 studies included NYHA class III-IV patients. A total of 23481 patients were categorized as NYHA class III-IV (78.40%) and 5532 individuals (18.46%) were classified as NYHA class I-II. Patients suffering from ischemia were identified in studies as those with ischemic cardiomyopathy, ischemic heart failure, myocardial infraction, and patients who received coronary artery bypass grafting or stent implantation. Mean values for age (67.19 years), QRS duration (161.46 ms) and LVEF (24.73%) were calculated from extracted data from 57, 52 and 54 studies, respectively. The average morbidity of patients with ischemic cardiomyopathy or related events, LBBB and AF was 51.39%, 72.17% and 25.48%,
respectively; these data were extracted from 54, 40 and 22 studies, respectively. Additional characteristics and associated details including the type of study and follow-up durations are shown in Table 1. A total of 23.08% of the patients in the ischemic cause group were female. Similarly, 23.34% and 22.82% of the lower and higher risk subgroups were female, respectively. A total of 22.80% of the AF group was composed of female patients; 22.55% and 23.41% of the lower and higher risk subgroups were also comprised of female patients, respectively.

After pooling data from all of the studies, most of the studies (53/58) [8–14, 16, 17, 19, 21–23, 25–55, 57–65] reported that females exhibited better outcomes post-CRT compared with males. However, significant heterogeneity was observed among the 58 available studies ($I^2 = 36$%; $P = 0.004$) and the HR for all causes mortality using random-effect models was $0.67$ (95% CI, 0.62–0.73, $P < 0.0001$, Fig 2). Begg test showed no evidence of publication bias ($P = 0.08$) rather than Egger test ($P = 0.01$), the funnel plot was shown in S1A Fig. A total of 11 studies [8, 13–15, 20, 24, 30, 38, 49, 51, 64] reported sex-related differences in relation to heart failure hospitalization or heart failure; the HR for significant heterogeneity, which was calculated using random-effect models, was $0.58$ (95% CI, 0.46–0.74, $P < 0.0001$, Fig 3) ($I^2 = 62$%; $P = 0.003$). No evidence of publication bias was found in Begg test ($P = 0.76$) and Egger test ($P = 0.68$), and the funnel plot was shown in S1B Fig. To further investigate the reliable factors that led to significant sex-related differences for all-cause mortality, the NYHA class and average values pertaining to age, female ratio, QRS duration and LVEF were used to generate subgroups. In addition, the average morbidity associated with ischemic cause, LBBB and AF were used to establish lower and higher rate subgroups. The $p$-value of interaction between the ischemic cause subgroups was 0.03, no evidence of publication bias was found in Begg test ($P = 0.81$) and Egger test ($P = 0.69$) this may lead to the sex-related differences for all-cause mortality. Furthermore, the $p$-value of interaction between AF subgroups might also suggest an association with sex-related differences; however, no significant statistical difference was observed ($P = 0.07$). Furthermore, patients with ischemia or AF exhibited a 47% or 40% increase (HR) in risk in relation to all-cause mortality, respectively (associated details are shown in the S2 and S3 Figs, respectively), the funnel plots are shown in S4 Fig. Additional factors, including the type of study ($P = 0.28$), published year ($P = 0.50$), follow-up duration ($P = 0.23$), NYHA class ($P = 0.77$), age ($P = 0.34$), female ratio ($P = 0.10$), QRS duration ($P = 0.28$), LBBB ($P = 0.66$) and LVEF ($P = 0.42$), did not appear to statistically correlate with sex-related effects (Table 2).

**Discussion**

The ACCF/AHA/HRS guidelines for CRT are based upon large clinical trials and meta-analyses of clinical trials. However, only 20% of the patients with HF that received CRT in these studies were female. This suggests that the current guidelines may be more applicable to male patients. In fact, clinical trial and meta-analysis data suggest that female patients respond better to CRT than male patients; however, there was no significant sex-related difference in relation to heart failure prevalence. More importantly, females exhibit higher mortality following HF, and were less likely to receive guideline-recommended treatment with medicine or CRT [66]. Data indicate that sex-related factors might influence the outcome of HF patients that receive CRT; however, this phenomenon has not yet been taken into account in the development of sex-specific diagnostic and treatment modalities, and we have yet to elucidate the potential clinical and molecular factors that underlie these sex-differences.

A total of 34,455 patients from 58 studies, of which 7952 (23.08%) were females, were included in our meta-analysis. For both primary and second endpoints, females exhibited a reduction of 33% and 42% in the rate of all-cause mortality and heart failure hospitalization or
Table 1. Baseline characteristics for this meta-analysis.

| Author (year) | Type | Total | Female | NYHA I/II | NYHA III/IV | Time | Age | ICs | LBBB | QRS (ms) | AF | LVEF (%) |
|---------------|------|-------|--------|-----------|-------------|------|-----|-----|-------|----------|----|----------|
| Arshad (2011) [8] | RCT | 1089 | 248 | 1089 | - | 12 | 64 | - | - | - | 210 | - |
| Xu (2011) [9] | RC | 728 | 166 | - | 723 | 44 | 69 | 316 | 333/712 | 165 | 213 | 24 |
| Lilli (2007) [10] | RC | 195 | 46 | - | 195 | 12 | 71 | 99 | - | 153 | - | 28 |
| Mooyaart (2011) [11] | PC | 578 | 147 | - | 578 | 24 | 67 | 342 | 406 | 166 | 99 | 23 |
| Zardkoohi (2007) [12] | RC | 117 | 26 | - | 117 | 24 | 71 | 80 | - | 169 | - | 20 |
| Zabarovskaja (2012) [13] | RC | 619 | 119 | 49 | 341 | 44 | 68 | 331 | 712 | 165 | 213 | 24 |
| Cleland (2005) [14] | PC | 1298 | 308 | 69 | 1208 | 34 | 64 | 561 | - | 168 | 243 | 24 |
| Schuchert (2013) [15] | RCT | 409 | 105 | - | 409 | 12 | 67 | 165 | - | 160 | 268 | 20 |
| Yu (2005) [16] | PC | 141 | 38 | 12 | 129 | 6 | - | - | - | - | - | - |
| Auricchio (2007) [17] | PC | 1298 | 308 | 69 | 1208 | 34 | 64 | 561 | - | 168 | 243 | 24 |
| Bai (2008) [18] | PC | 542 | 124 | - | 542 | 27 | 66 | 361 | - | 162 | 268 | 20 |
| Biase (2008) [19] | PC | 395 | 99 | - | 395 | 27 | 66 | 361 | - | 162 | 268 | 20 |
| Ei-saed (2009) [20] | RC | 115 | 2 | - | 115 | 18 | 67 | 87 | - | 158 | 50 | 23 |
| Fantoni (2008) [21] | RC | 355 | 89 | - | 355 | 34 | 63 | 167 | - | 163 | - | 21 |
| Iler (2008) [22] | RC | 355 | 89 | - | 355 | 34 | 63 | 167 | - | 163 | - | 21 |
| Kronborg (2008) [23] | PC | 355 | 89 | - | 355 | 34 | 63 | 167 | - | 163 | - | 21 |
| Shalaby (2008) [24] | PC | 129 | 2 | - | 129 | 18 | 67 | 87 | - | 158 | 50 | 23 |
| Shalaby (2008) [25] | PC | 270 | 35 | 23 | 147 | 48 | 66 | 99 | - | 176 | 63 | 23 |
| Yokoi (2010) [26] | RCT | 322 | 74 | - | 322 | 27 | 66 | 361 | - | 162 | 268 | 20 |
| Miller (2011) [27] | PC | 480 | 124 | - | 542 | 27 | 66 | 361 | - | 162 | 268 | 20 |
| Prochnau (2011) [28] | PC | 338 | 88 | 32 | 306 | 27 | 65 | 170 | - | 164 | 145 | 24 |
| Van (2011) [29] | PC | 490 | 98 | - | 490 | 26 | 65 | 293 | - | 157 | - | 26 |
| Eitel (2012) [30] | PC | 219 | 40 | - | 219 | 56 | 67 | 150 | 119/151 | 180 | 61 | 23 |
| Bogale (2012) [31] | PC | 2111 | 488 | 415 | 1538 | 12 | 70 | 1006 | 1369 | 157 | 473 | 24 |
| Kreuz (2012) [32] | RC | 239 | 47 | 66 | 173 | 43 | 67 | 387 | - | 159 | 348 | 22 |
| Morani (2013) [33] | PC | 374 | 76 | 89 | 285 | 55 | 69 | 209 | - | 168 | - | 27 |
| Risum (2013) [34] | RC | 121 | 26 | - | 121 | 24 | 66 | 72 | - | 155 | - | 23 |
| Rossi (2014) [35] | RC | 330 | 66 | 99 | 231 | 55 | 62 | 135 | - | 161 | 53 | 28 |
| Gasparini (2014) [36] | PC | 3319 | 929 | 752 | 2567 | 37 | 67 | 1218 | - | 167 | 690 | 25 |
| Reitan (2014) [37] | RC | 446 | 76 | 58/398 | 340/398 | 82 | 72 | 262/435 | 280/443 | 170 | 268/446 | 25 |
| Wilcox (2014) [38] | RC | 421 | 109 | - | 411 | 25 | 66 | 198 | 240 | 161 | 73 | 27 |
| Sharma (2015) [39] | RC | 511 | 116 | 124 | 387 | 22 | 69 | 294 | - | 161 | 146 | 24 |
| Cipriani (2016) [40] | RC | 507 | 101 | 186 | 321 | 48 | 62 | 198 | 406 | 161 | 73 | 27 |
| Saxon (2006) [41] | RCT | 595 | 196 | - | 595 | 16 | 66 | 327 | 434 | 159 | - | 23 |
| Levy (2011) [42] | pC | 550 | 122 | - | 549 | 12 | 70 | 360 | - | 155 | 118 | - |
| Looi (2014) [43] | RC | 500 | 115 | 39 | 461 | 29 | 69 | 264 | - | 160 | 91 | 25 |
| Perini (2014) [44] | RC | 559 | 138 | 148 | 411 | 72 | 70 | 261 | 460 | 157 | 135 | 27 |
| Khatib (2014) [45] | PC | 600 | 122 | 135 | 465 | 36 | 67 | 253 | - | 168 | 155 | 25 |
| Hoke (2014) [46] | PC | 798 | 180 | - | 798 | 39 | 67 | 480 | - | 156 | 137 | 26 |
| Lumens (2015) [47] | PC | 191 | 50 | - | 191 | 24 | 66 | 115 | 115 | 159 | - | 24 |

(Continued)
heart failure, respectively. These results are very similar to those presented in a previous meta-analysis by Cheng [67] in 2014. However, in the latter analysis, clinical factors including follow-up duration, proportions of female patients, NYHA function class, and average LVEF were not subject to sex-related differences. Indeed, only slight sex-related differences were found between European and American cohorts. Although geographical factors may have contributed to these observations, it is difficult to further analyze the sex-specific differences due to the lack of individual participant data.

Only a limited number of studies have analyzed sex-related differences or prognosis in patients with ischemic events, LBBB, age, LVEF or other clinical factors. It is possible that difference pertaining to the presentation of ischemic events is a factor that underpins sex-specific mortality. In our analysis, to further investigate potential factors that affect sex-specific outcomes, average values pertaining to age, female ratio, QRS duration and EF, along with mean morbidity values for ischemic cause, LBBB and AF were all used to establish subgroups. In summary, as a result of this meta-analysis it was observed that female patients suffering from ischemia experienced greater benefits following CRT in comparison with males with ischemia. Clinically, ischemic cardiomyopathy (ICM) is an independent risk factor for non-response in relation to CRT. However, patients with no ischemic cardiomyopathy (NICM) have been shown to exhibit better outcomes and greater reverse remodeling compared to those with ICM [68]. We further mined the collected data and analyzed the baselines associated with patients exhibiting ischemic causes and found: (1) ischemia is more common in males than in females (83.23% vs. 16.77%) [9–14, 19, 27, 38, 49], (2) the prevalence of female patients was similar in lower and higher rate ischemic cause subgroups (23.34% vs. 22.82%), (3) Patients with ischemia exhibited a 47% increase in the rate of all-cause mortality (S2 Fig). These findings suggest that male patients have a higher risk of ischemia, which is a certain factor in relation to higher mortality. Thus, the sex ratio of patients with ischemia is an important factor underlying differences pertaining to outcomes associated with CRT. Based on the higher morbidity rates in male patients, this result may explain why females benefit more and exhibit reduced mortality following CRT in comparison with males. Similarly, Herz et al [69] observed that sex-specific differences in CRT response may be the result of differences in the progression and

| Author (year)       | Type | Total | Female | NYHA I/II | NYHA III/IV | Time | Age | ICs | LBBB | QRS (ms) | AF | LVEF (%) |
|---------------------|------|-------|--------|-----------|-------------|------|-----|-----|------|----------|----|----------|
| Yanagisawa (2015)   | RC   | 125   | 34     | -         | -           | 125  | 37  | 67  | 35   | 70       | 161| 14       |
| Stabile (2015)      | PC   | 216   | 60     | 93        | 123         | 17   | 69  | 95  | -    | -        | 151| 61       |
| Roubicek (2015)     | PC   | 329   | 81     | -         | 329         | 40   | 68  | 185 | 299  | 160      | 51 | 26       |
| Rickard (2015)      | RC   | 723   | 210    | -         | 723         | 60   | 67  | 439 | -    | -        | 165| 384      |
| Tayal (2015)        | PC   | 151   | 43     | 18        | 133         | 24   | 66  | 91  | 107  | 163      | -  | 25       |
| Nagy (2015)         | PC   | 93    | 21     | 12        | 81          | 24   | 67  | 46  | 84   | 160      | 26 | 30       |
| Gold (2015)         | RCT  | 353   | 83     | 281       | 66          | 6   | 63  | 200 | 217  | 153      | -  | 27       |
| Gasparini (2015)    | PC   | 5153  | 1116   | 1159      | 3994        | 39   | 66  | -   | 3441 | 158      | 899| 26       |
| Munir (2016)        | RC   | 512   | 149    | -         | -           | 41   | 81  | 264 | 236  | 154      | -  | 23       |
| Jacobsson (2016)    | RC   | 496   | 79     | -         | -           | 36   | 69  | 312 | 322  | 169      | 243| 23       |
| Cipriani (2016)     | PC   | 1122  | 247    | 316       | 806         | 12   | 66  | 527 | 774  | 153      | 356| 28       |
| Total               | -    | 33445 | 7952   | -         | -           | 18.46| 78.40| -  | 67.19 | 51.39    | 72.17| 161.47    | 25.20 | 24.73    |

ICs = ischemic causes.

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Fig 2. Forest plot for sex-specific differences in all-cause mortality of patients who received CRT.

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Table 2. Stratified analysis of hazard ratio of all-cause mortality.

| Subgroup          | No. of studies | HR   | IC   | P value of interaction |
|-------------------|----------------|------|------|------------------------|
| Study type        |                |      |      |                        |
| RCT               | 6              | 0.55 | 0.33 | 0.94                   | 0.28                    |
| PC                | 25             | 0.65 | 0.57 | 0.73                   |
| RC                | 27             | 0.72 | 0.65 | 0.80                   |
| Year              |                |      |      |                        |
| <2010             | 16             | 0.72 | 0.58 | 0.88                   | 0.50                    |
| >2010             | 42             | 0.66 | 0.60 | 0.73                   |
| Follow up         |                |      |      |                        |
| <24 (m)           | 24             | 0.72 | 0.61 | 0.86                   | 0.23                    |
| >24 (m)           | 34             | 0.65 | 0.60 | 0.71                   |
| Patients          |                |      |      |                        |
| <500 (n)          | 20             | 0.69 | 0.63 | 0.76                   | 0.58                    |
| >500 (n)          | 38             | 0.66 | 0.58 | 0.76                   |
| NYHA              |                |      |      |                        |
| I-V               | 32             | 0.66 | 0.60 | 0.74                   | 0.77                    |
| III-V             | 26             | 0.68 | 0.59 | 0.79                   |
| Age               |                |      |      |                        |
| ≤67.19 (y)        | 32             | 0.69 | 0.63 | 0.77                   | 0.28                    |
| >67.19 (y)        | 23             | 0.63 | 0.54 | 0.73                   |
| Female            |                |      |      |                        |
| ≤23.08 (%)        | 30             | 0.62 | 0.56 | 0.69                   | 0.10                    |
| >23.08 (%)        | 28             | 0.72 | 0.63 | 0.81                   |
| Ischemic          |                |      |      |                        |
| ≤51.39 (%)        | 22             | 0.74 | 0.64 | 0.86                   | 0.03                    |
| >51.39 (%)        | 31             | 0.61 | 0.55 | 0.67                   |
| QRS               |                |      |      |                        |
| ≤161.47 (ms)      | 29             | 0.72 | 0.64 | 0.81                   | 0.28                    |
| >161.47 (ms)      | 22             | 0.66 | 0.59 | 0.73                   |
| LBBB              |                |      |      |                        |
| ≤72.17 (%)        | 13             | 0.68 | 0.6  | 0.78                   | 0.65                    |
| >72.17 (%)        | 8              | 0.65 | 0.57 | 0.75                   |
| AF                |                |      |      |                        |
| ≤25.20 (%)        | 21             | 0.61 | 0.54 | 0.69                   | 0.07                    |
| >25.20 (%)        | 18             | 0.74 | 0.63 | 0.86                   |
| LVEF              |                |      |      |                        |
| ≤24.73 (%)        | 27             | 0.65 | 0.57 | 0.74                   | 0.42                    |
| >24.73 (%)        | 26             | 0.70 | 0.62 | 0.78                   |

The subgroups were based on average values pertaining to age, female ratio, QRS duration, LVEF and average morbidity of ischemic events, atrial fibrillation and LBBB. The average values for different characteristics associated with the subgroups are mentioned in Table 1.

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presentation of heart failure; however, the exact nature of the baseline characteristics associated with this study was unclear.

Other clinical factors, including AF (P = 0.07), age, published year, QRS duration, NYHA class, and LVEF, did not correlate with sex-specific differences. Similar to ischemia, permanent AF was observed as attenuating the effect of CRT [70]. Additionally, in our analysis, AF resulted in a 40% increase in the risk of all-cause mortality during follow-up, and a higher prevalence of AF was observed in males compared with females (80.47% vs. 19.53%, respectively). However, we suggest that larger sample sizes should be analyzed to confirm this result. Importantly, female patients exhibit significantly higher complication rates during follow-up [71]. Females have higher blood pressure than males; they also exhibit a higher prevalence of heart failure with preserved ejection fraction. Both of these characteristics represent independent risk factors for stroke [72]. However, sex-specific complications are difficult to evaluate in clinical trials pertaining to CRT. Furthermore, the FDA have previously reported [73] that women are underrepresented in clinical trials due to fear of fetal consequences, associated economic costs, and lack of experience and knowledge in the management of disease during study follow-up.

Of note, without correcting for sex-specific differences in overall mortality on a population level, the benefit seen in women cannot be confidently associated with CRT. In most studies, survival was better for women with heart failure compared with men. And most patients enrolled in these studies were male. For example, in Chen’s meta analysis [67], 24.1% of subjects were women, but the causes for sex disparity were not evaluated. In our analysis, the HR of higher female ratio subgroup and lower female ratio subgroup were 0.72 and 0.62 respectively, and no significantly statistical difference (p = 0.10) was observed. However, it seemed that benefit of survival was attenuated with the increasing ratio of female patients. Thus, our results can not completely exclude the possibility that sex disparity play a potential role in sex-specific differences of survival. Further clinical trials are needed to answer the question whether women get more benefits after receiving CRT.

In addition to clinical factors, physiological factors are likely to influence the occurrence of sex-specific outcomes following CRT. As a consequence of smaller body mass and reduced ventricular size, female QRS durations are 5–10 ms shorter than for men [74]. Therefore, if this sex-specific difference in relation to QRS duration is taken into account, the net increase in conductive time of ventricles may be greater for females than males, especially in patients with complete LBBB. Furthermore, if the effect of body weight on QRS duration is normalized, a standardized QRS duration would help to improve patient selection for CRT, thereby providing a better prediction of CRT response[74]. Furthermore, females often exhibit greater age-related left ventricular concentric remodeling and higher EF compared with healthy aging men. Therefore, in addition to QRS duration and EF, which were both utilized as enrollment criteria, we speculate that greater conduction disturbance, ventricular dyssynchrony, and systolic dysfunction exist in female patients with HF who received CRT.

Additional cellular and molecular systems that are conventionally regulated by estrogen, including the autonomic nervous system [75], the extracellular matrix system [76] and the renin–angiotensin–aldosterone system (RAAS) [77], also participate in cardiac remodeling in female patients with HF. Although these factors could help us to understand how the response to CRT is affected by sex-specific effects, it would be difficult to implement associated factors into clinical guidelines [78]. However, the cellular and molecular mechanisms underpinning HF represent the theoretical basis of drug therapy for associated patients. Furthermore, rational drug therapy is extremely important for patients receiving CRT. Thus, it may be possible that there is a correlation between sex and CRT as a consequence of differences in post-CRT
medicine responses. It is well known that all-cause mortality of HF patients receiving beta blockers and angiotensin converting enzyme inhibitors (ACEI) is significantly lower compared with those receiving placebo. Unfortunately, a meta-analysis [79] conducted by Kotecha reported no evidence of an interaction between beta blocker treatment effects and sex in any of the subgroups analyzed. Furthermore, Shekelle’s meta-analysis [80] revealed that women with asymptomatic LV systolic dysfunction may not have reduced mortality when treated with ACEI. However, a more recent study conducted by Kappert [81] reported a 20% lower risk for the combined cardiovascular end points in female patients with ACEI. Interestingly, similar to our finding, the latter sex-specific difference was driven primarily by a significantly lower incidence of myocardial infarction in female. This suggests that the nature of the ischemic cause plays a role in sex-related differences in relation to outcomes in HF patients. The mechanisms that underlie these differences warrant further studies to assess the relationship between molecular mechanisms and clinical effectiveness. However, in our analysis, it proved difficult to analyze sex-specific differences in relation to CRT effects without considering associated medicinal therapies.

Our meta analysis has some limitations. First, most HF studies stated that women have a survival advantage compared to men. Our analysis cannot exclude the possibility that the effects associated with ischemic patients may be due to generic survival capabilities as opposed to specific responses to CRT. Second, due to the fact that our study was limited with respect to quantitative data pertaining to sex-specific clinical factors, and the some studies included in our research with the NOS scores between 4 and 6, so the mean values and average morbidity data when categorizing the subgroups may not be so precise. Third, left ventricular lead location may influence the outcomes for HF patients receiving CRT; however, relatively little research has been conducted to investigate both location and sex-specific factors at the same time. At last, the publication bias was found in the analysis of all-cause mortality by Egger test, some small sizes studies enrolled in our analysis may be the potential reason. Thus, our results are limited and additional potential mechanisms that influence sex-related differences in CRT outcomes are still unclear.

In conclusion, similar to most clinical studies, the results from this meta-analysis suggest that female patients receiving CRT have a lower risk of all-cause mortality and heart failure or heart failure hospitalization. In addition, the occurrence of ischemia in patients might reduce the benefits associated with CRT. Furthermore, we observed that ischemia might cause differential sex-specific outcomes following CRT, especially in male patients with higher risks of ischemia. Further studies are required to elucidate the mechanisms that underpin sex-specific differences in relation to CRT.

**Supporting information**

S1 File. The details of search strategy.

(DOCX)

S2 File. PRISMA checklist for the present study.

(DOC)

S1 Table. NOS scores for the included non-RCT studies.

(DOCX)

S1 Fig. The funnel plots for all causes mortality and heart failure hospitalization or heart failure.

(TIF)
S2 Fig. Forest plot for all-cause mortality of ischemic causes for patients who received CRT. (TIF)

S3 Fig. Forest plot for all-cause mortality of atrial fibrillation for patients who received CRT. (TIF)

S4 Fig. The funnel plots for all-cause mortality of ischemic and atrial fibrillation. (TIF)

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References
1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. The New England journal of medicine. 2002; 346(24):1845–53. Epub 2002/06/14. https://doi.org/10.1056/NEJMoa013168 PMID: 12063368.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016; 133(4):e38–360. Epub 2015/12/18. https://doi.org/10.1161/CIR.0000000000000350 PMID: 26673558.
3. Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O’Callaghan KM, Carpenter JL, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA internal medicine. 2014; 174(8):1340–8. Epub 2014/08/05. https://doi.org/10.1001/jamainternmed.2014.2717 PMID: 25090172.
4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009; 6(7):e1000100. Epub 2009/07/22. https://doi.org/10.1371/journal.pmed.1000100 PMID: 19621070.
5. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996; 17(1):1–12. Epub 1996/02/01. PMID: 8721797.

6. Rostom A, Dube C, Cranney A, et al. Celiac Disease. Rockville (MD): Agency for Healthcare Research and Quality (US); 2004 Sep. (Evidence Reports/Technology Assessments, No. 104.) Appendix D. Quality Assessment Forms. http://www.ncbi.nlm.nih.gov/books/NBK35156

7. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16. Epub 2007/06/09. https://doi.org/10.1186/1745-6215-8-16 PMID: 17555882.

8. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, 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. Journal of the American College of Cardiology. 2011; 57(7):813–20. Epub 2011/02/12. https://doi.org/10.1016/j.jacc.2010.06.061 PMID: 21510317.

9. Xu YZ, Friedman PA, Webster T, Brooke K, Hodge DO, Wiste HJ, et al. Cardiac resynchronization therapy: do women benefit more than men? Journal of cardiovascular electrophysiology. 2012; 23(2):172–8. Epub 2011/09/15. https://doi.org/10.1111/j.1540-8167.2011.02168.x PMID: 21914024.

10. Lilli A, Ricciardi G, Porciani MC, Perini AP, Pieragnoli P, Musilli N, et al. Cardiac resynchronization therapy: gender related differences in left ventricular reverse remodeling. Pacing and clinical electrophysiology: PACE. 2007; 30(11):1349–55. Epub 2007/11/03. https://doi.org/10.1111/j.1540-8159.2007.00870.x PMID: 17976098.

11. Mooyaart EA, Marsan NA, van Bommel RJ, Thijssen J, Borleffs CJ, Delgado V, et al. Comparison of long-term survival of men versus women with heart failure treated with cardiac resynchronization therapy. The American journal of cardiology. 2011; 108(1):63–8. Epub 2011/05/03. https://doi.org/10.1016/j.amjcard.2011.02.345 PMID: 21529733.

12. Zardkoohi O, Nandigam V, Murray L, Heist EK, Mela T, Crencole M, et al. The impact of age and gender on cardiac resynchronization therapy outcome. Pacing and clinical electrophysiology: PACE. 2007; 30(11):1344–8. Epub 2007/11/03. https://doi.org/10.1111/j.1540-8159.2007.00869.x PMID: 17976097.

13. Zabarovskaja S, Gadler F, Braunischweig F, Stahlberg M, Hornsten J, Linde C, et al. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2012; 14(8):1148–55. Epub 2012/03/09. https://doi.org/10.1093/europace/eus039 PMID: 22399204.

14. Schuchert A, Muto C, Maounis T, Frank R, Ella RO, Polauck A, et al. Gender-related safety and efficacy of cardiac resynchronization therapy. Clinical cardiology. 2013; 36(11):683–90. Epub 2013/10/10. https://doi.org/10.1002/clc2.2003 PMID: 24105909.

15. Ciepland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. The New England journal of medicine. 2005; 352(15):1539–49. Epub 2005/03/09. https://doi.org/10.1056/NEJMoa050496 PMID: 15753115.

16. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation. 2005; 112(11):1580–6. Epub 2005/09/08. https://doi.org/10.1161/CIRCULATIONAHA.105.538272 PMID: 16144994.

17. Auricchio A, Metra M, Gasparini M, Lamp B, Klersy C, Curnis A, et al. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. The American journal of cardiology. 2007; 99(2):232–8. Epub 2007/01/16. https://doi.org/10.1016/j.amjcard.2006.07.087 PMID: 17223424.

18. Bai R, Di Biase L, Elayi C, Ching CK, Barrett C, Philips K, et al. Mortality of heart failure patients after cardiac resynchronization therapy: identification of predictors. Journal of cardiovascular electrophysiology. 2008; 19(12):1259–65. Epub 2008/07/18. https://doi.org/10.1111/j.1540-8167.2008.01234.x PMID: 18631272.

19. Di Biase L, Auricchio A, Soriente A, Civello K, Klersy C, Faletra F, et al. The magnitude of reverse remodelling irrespective of aetiology predicts outcome of heart failure patients treated with cardiac resynchronization therapy. European heart journal. 2008; 29(20):2497–505. Epub 2008/06/03. https://doi.org/10.1093/eurheartj/ehn221 PMID: 18515806.

20. El-Saied 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. Clinical cardiology. 2009; 32(11):E33–8. Epub 2009/10/10. https://doi.org/10.1002/clc.20490 PMID: 19816874.
21. Fantoni C, Regoli F, Ghanem A, Raffa S, Klersy C, Sorgente A, et al. Long-term outcome in diabetic heart failure patients treated with cardiac resynchronization therapy. European journal of heart failure. 2008; 10(3):298–307. Epub 2008/02/26. https://doi.org/10.1016/j.ejhf.2008.01.006 PMID: 18296111.

22. Iler MA, Hu T, Ayyagari S, Callahan TDT, Civello KC, Thal SG, et al. Prognostic value of electrocardiographic measurements before and after cardiac resynchronization device implantation in patients with heart failure due to ischemic or nonischemic cardiomyopathy. The American journal of cardiology. 2008; 101(3):359–63. Epub 2008/02/02. https://doi.org/10.1016/j.amjcard.2007.08.043 PMID: 18237600.

23. Kronborg MB, Mortensen PT, Kirkfeldt RE, Nielsen JC. Very long term follow-up of cardiac resynchronization therapy: clinical outcome and predictors of mortality. European journal of heart failure. 2008; 10(8):796–801. Epub 2008/07/16. https://doi.org/10.1016/j.ejhf.2008.06.013 PMID: 18619900.

24. Shalaby A, Voigt A, El-Saed A, Saba S. Usefulness of pulmonary artery pressure by echocardiography to predict outcome in patients receiving cardiac resynchronization therapy heart failure. The American journal of cardiology. 2008; 101(2):238–41. Epub 2008/01/08. https://doi.org/10.1016/j.amjcard.2007.07.064 PMID: 18179413.

25. Stabile G, Solimene F, Bertaglia E, La Rocca V, Accogli M, Scaccia A, et al. Long-term outcomes of CRT-PM versus CRT-D recipients. Pacing and clinical electrophysiology: PACE. 2009; 32 Suppl 1: S141–5. Epub 2009/03/11. https://doi.org/10.1111/j.1540-8159.2008.02271.x PMID: 19250079.

26. Zhang Q, Yip GW, Chan YS, Fung JW, Chan W, Lam YY, et al. Incremental prognostic value of combining left ventricular lead position and systolic dyssynchrony in predicting long-term survival after cardiac resynchronization therapy. Clin Sci (Lond). 2009; 117(11):397–404. Epub 2009/04/02. https://doi.org/10.1042/CS20080580 PMID: 19335338.

27. Delgado V, van Bommel RJ, Bertini M, Borleffs CJ, Marsan NA, Arnold CT, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation. 2011; 123(1):70–8. Epub 2010/12/22. https://doi.org/10.1161/CIRCULATIONAHA.110.945345 PMID: 21733535.

28. Lin G, Gersh BJ, Greene EL, Redfield MM, Hayes DL, Brady PA. Renal function and mortality following cardiac resynchronization therapy. European heart journal. 2011; 32(2):184–90. Epub 2010/11/12. https://doi.org/10.1093/eurheartj/ehq403 PMID: 21068051.

29. Pfau G, Schilling T, Koziyan A, Lux A, Gottle A, Huth C, et al. Outcome after implantation of cardiac resynchronization/defibrillation systems in patients with congestive heart failure and left bundle-branch block. Journal of cardiothoracic and vascular anesthesia. 2010; 24(1):30–6. Epub 2009/10/06. https://doi.org/10.1053/j.jvca.2009.07.009 PMID: 19800818.

30. Foley PW, Chailil S, Khadjoii K, Irwin N, Smith RE, Leyva F. Left ventricular reverse remodelling, long-term clinical outcome, and mode of death after cardiac resynchronization therapy. European journal of heart failure. 2011; 13(1):43–51. Epub 2010/11/06. https://doi.org/10.1093/eurjhf/hfq182 PMID: 21051462.

31. Miller AL, Kramer DB, Lewis EF, Koplan B, Epstein LM, Tedrow U. Event-free survival following CRT with surgically implanted LV leads versus standard transvenous approach. Pacing and clinical electrophysiology: PACE. 2011; 34(4):490–500. Epub 2011/04/06. https://doi.org/10.1111/j.1540-8159.2010.03014.x PMID: 21463344.

32. Prochnau D, Kuehnert H, Heinke M, Figulla HR, Surber R. Left ventricular lead position and nonspecific conduction delay are predictors of mortality in patients during cardiac resynchronization therapy. The Canadian journal of cardiology. 2011; 27(3):363–8. Epub 2011/04/22. https://doi.org/10.1016/j.tca.2010.12.066 PMID: 21507801.

33. Rickard J, Brennan DM, Martin DO, Hsieh E, Tang WH, Lindsay BD, et al. The impact of left ventricular size on response to cardiac resynchronization therapy. American heart journal. 2011; 162(4):646–53. Epub 2011/10/11. https://doi.org/10.1016/j.ahj.2011.07.008 PMID: 21982656.

34. Shen X, Nair CK, Holmberg MJ, Moos AN, Koruth J, Wang F, et al. Impact of left atrial volume in prediction of outcome after cardiac resynchronization therapy. International journal of cardiology. 2011; 152(1):19–27. Epub 2010/07/14. https://doi.org/10.1016/j.ijcard.2010.06.016 PMID: 20621370.

35. Smit MD, Maass AH, Hilleges HL, Wiestfeld AC, Van Veldhuisen DJ, Van Gelder IC. Prognostic importance of natriuretic peptides and atrial fibrillation in patients receiving cardiac resynchronization therapy. European journal of heart failure. 2011; 13(6):543–50. Epub 2011/02/19. https://doi.org/10.1093/eurjhf/hfr066 PMID: 21330294.

36. Van Bommel RJ, Mollema SA, Borleffs CJ, Bertini M, Ypenburg C, Marsan NA, et al. Impaired renal function is associated with echocardiographic nonresponse and poor prognosis after cardiac resynchronization therapy. Journal of the American College of Cardiology. 2011; 57(5):549–55. Epub 2011/01/29. https://doi.org/10.1016/j.jacc.2010.06.060 PMID: 21272745.
37. Eitel C, Wilton SB, Switzer N, Cowan K, Exner DV. Baseline delayed left ventricular activation predicts long-term clinical outcome in cardiac resynchronization therapy recipients. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014; 16(11):1603–9. https://doi.org/10.1093/europace/euu058 PMID: 24681763

38. Reitan C, Bakos Z, Platonov PG, Höijer CJ, Brandt J, Wang L, et al. Patient-assessed short-term positive response to cardiac resynchronization therapy is an independent predictor of long-term mortality. Europace. 2014; 16(11):1603–9. https://doi.org/10.1093/europace/euu058 PMID: 24681763

39. Wilcox JE, Fonarow GC, Zhang Y, Albert NM, Curtis AB, Gheorghiade M, et al. Clinical effectiveness of cardiac resynchronization and implantable cardioverter-defibrillator therapy in men and women with heart failure: findings from IMPROVE HF. Circulation Heart failure. 2014; 7(1):146–53. Epub 2013/11/02. https://doi.org/10.1161/CIRCHEARTFAILURE.113.00789 PMID: 24178311.

40. Sharma AK, Vegh E, Orencole M, Miller A, Blendea D, Moore S, et al. Association of hypothyroidism with adverse events in patients with heart failure receiving cardiac resynchronization therapy. The American journal of cardiology. 2015; 115(9):1249–53. Epub 2015/03/07. https://doi.org/10.1016/j.amjcard.2015.01.559 PMID: 25743211.

41. Cipriani M, Landolina M, Oliva F, Ghio S, Vargiu S, Rordorf R, et al. Women with nonspecific cardiomyopathy have a favorable prognosis and a better left ventricular remodeling than men after cardiac resynchronization therapy. J Cardiovasc Med (Hagerstown). 2016; 17(4):291–8. Epub 2014/09/16. https://doi.org/10.2459/JCM.0000000000000187 PMID: 25222077.

42. Saxton LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation. 2006; 114(25):2766–72. Epub 2006/12/13. https://doi.org/10.1161/CIRCULATIONAHA.106.642892 PMID: 17159063.

43. Leyva F, Foley PW, Chalil S, Irwin N, Smith RE. Female gender is associated with a better outcome after cardiac resynchronization therapy. Pacing and clinical electrophysiology. 2011; 34(1):82–8. Epub 2011/01/11. https://doi.org/10.1111/j.1540-8159.2010.02909.x PMID: 21214589.

44. Looi KL, Gajendragadkar PR, Khan FZ, Elsik M, Begley DA, Fynn SP, et al. Cardiac resynchronisation therapy: pacemaker versus internal cardioverter-defibrillator in patients with impaired left ventricular function. Heart. 2014; 100(10):794–9. Epub 2014/04/03. https://doi.org/10.1136/heartjnl-2014-305537 PMID: 24691411.

45. Paoletti Perini A, Bartolini S, Pieragnoli P, Ricciardi G, Perrotta L, Valleggi A, et al. CHADS2 and CHA2DS2-VASc scores to predict morbidity and mortality in heart failure patients candidates to cardiac
resynchronization therapy. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014; 16(1):71–80. Epub 2013/07/06. https://doi.org/10.1093/europace/eut190 PMID: 23828875.

52. Khalid M, Tolosana JM, Trucco E, Borras R, Castel A, Berruezo A, et al. EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors. European journal of heart failure. 2014; 16(7):802–9. Epub 2014/05/28. https://doi.org/10.1002/ejhf.102 PMID: 24863467.

53. Hoke U, Putter H, Van Der Velde ET, Schalij MJ, Delgado V, Bax JJ, et al. Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. Circulation Cardiovascular quality and outcomes. 2014; 7(3):437–44. Epub 2014/05/16. https://doi.org/10.1161/CIRCOUTCOMES.113.000821 PMID: 24823954.

54. Lumens J, Tayal B, Walmsey J, Delgado-Montero A, Huntjens PR, Schwartzman D, et al. Differentiating Electromechanical From Non-Electrical Substrates of Mechanical Discoordination to Identify Responders to Cardiac Resynchronization Therapy. Circulation Cardiovascular imaging. 2015; 8(8): e003744. Epub 2015/09/05. https://doi.org/10.1161/CIRCIMAGING.115.003744 PMID: 26338877.

55. Yanagisawa S, Inden Y, Shimano M, Yoshida N, Ishikawa S, Kato H, et al. Impact of cardiac resynchronization therapy-defibrillator implantation on the association between body mass index and prognosis in patients with heart failure. Journal of interventional cardiac electrophysiology: an international journal of arrhythmias and pacing. 2015; 43(3):269–77. Epub 2015/05/25. https://doi.org/10.1007/s10840-015-0015-3 PMID: 26003807.

56. Stable G, D’Onofrio A, Pepi P, De Simone A, Santamaria M, Caico SI, et al. Interlead anatomic and electrical distance predict outcome in CRT patients. Heart rhythm. 2015; 12(11):2221–9. Epub 2015/05/24. https://doi.org/10.1016/j.hrthm.2015.05.020 PMID: 26001509.

57. Roubicek T, Wichterle D, Kucera P, Nedbal P, Kupec J, Sedlakova J, et al. Left Ventricular Lead Electrical Delay Is a Predictor of Mortality in Patients With Cardiac Resynchronization Therapy. Circulation Arrhythmia and electrophysiology. 2015; 8(5):1113–21. Epub 2015/09/05. https://doi.org/10.1161/CIRCEP.115.003004 PMID: 26342653.

58. Rickard J, Bassiouny M, Tedford RJ, Baranowski B, Spragg D, Cantillon D, et al. Long-term outcomes in patients with ambulatory New York heart association class III and IV heart failure undergoing cardiac resynchronization therapy. The American journal of cardiology. 2015; 115(1):82–5. Epub 2014/12/11. https://doi.org/10.1016/j.amjcard.2014.09.052 PMID: 25491007.

59. Tayal B, Gorcsan J, Delgado-Montero A, Marek JJ, Haugaa KH, Ryo K, et al. Mechanical Dysynchrony by Tissue Doppler Cross-Correlation is Associated with Risk for Complex Ventricular Arrhythmias after Cardiac Resynchronization Therapy. Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography. 2015; 28(12):1474–81. Epub 2015/09/08. https://doi.org/10.1016/j.echo.2015.07.021 PMID: 26342653.

60. Nagy VK, Szeplaki G, Apor A, Kutyifa V, Kovacs A, Kosztin A, et al. Role of Right Ventricular Global Longitudinal Strain in Predicting Early and Long-Term Mortality in Cardiac Resynchronization Therapy Patients. PloS one. 2015; 10(12):e0143907. Epub 2015/12/25. https://doi.org/10.1371/journal.pone.0143907 PMID: 26700306.

61. Gold MR, Daubert C, Abraham WT, Ghio S, St John Sutton M, Hudnall JH, et al. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. Heart rhythm. 2015; 12(3):524–30. Epub 2014/12/03. https://doi.org/10.1016/j.hrthm.2014.11.014 PMID: 25490860.

62. Gasparini M, Klezsy C, Leclercq C, Lunati M, Landolina M, Auricchio A, et al. Validation of a simple risk stratification tool for patients implanted with Cardiac Resynchronization Therapy: the VALID-CRT risk score. European journal of heart failure. 2015; 17(7):717–24. Epub 2015/04/24. https://doi.org/10.1002/ejhf.269 PMID: 25903349.

63. Munir MB, Althouse AD, Rijal S, Shah MB, Abu Daya H, Adelstein E, et al. Clinical Characteristics and Outcomes of Older Cardiac Resynchronization Therapy Recipients Using a Pacemaker versus a Defibrillator. Journal of cardiovascular electrophysiology. 2016; 27(6):730–40. Epub 2016/02/10. https://doi.org/10.1111/jce.12951 PMID: 26856440.

64. Jacobsson J, Borgquist R, Reitan C, Ghafoori E, Chatterjee NA, Kabir M, et al. Usefulness of the Sum Absolute QRST Integral to Predict Outcomes in Patients Receiving Cardiac Resynchronization Therapy. The American journal of cardiology. 2016; 118(3):389–95. Epub 2016/06/07. https://doi.org/10.1016/j.amjcard.2016.05.017 PMID: 27265674.

65. Cipriani M, Lunati M, Landolina M, Proclemer A, Boriani G, Ricci RP, et al. Prognostic implications of mitral regurgitation in patients after cardiac resynchronization therapy. European journal of heart failure. 2016; 18(8):1060–8. Epub 2016/07/15. https://doi.org/10.1002/ejhf.569 PMID: 27412374.
66. Alaeddini J, Wood MA, Amin MS, Ellenbogen KA. Gender disparity in the use of cardiac resynchronization therapy in the United States. Pacing and clinical electrophysiology. PACE. 2008; 31(4):468–72. Epub 2008/04/01. https://doi.org/10.1111/j.1540-8159.2008.01016.x PMID: 18373766.

67. Cheng YJ, Zhang J, Li WJ, Lin XX, Zeng WT, Tang K, et al. More favorable response to cardiac resynchronization therapy in women than in men. Circulation Arrhythmia and electrophysiology. 2014; 7(5):807–15. Epub 2014/08/26. https://doi.org/10.1161/CIRCEP.113.001786 PMID: 25146838.

68. Sutton MG, Plappert T, Hilipsch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation. 2006; 113(2):266–72. Epub 2006/01/13. https://doi.org/10.1161/CIRCULATIONAHA.104.520817 PMID: 16401777.

69. Herz ND, Engeda J, Zusterzeel R, Sanders WE, O’Callaghan KM, Strauss DG, et al. Sex differences in device therapy for heart failure: Utilization, outcomes, and adverse events. Journal of Women’s Health. 2015; 24(4):261–71. https://doi.org/10.1089/jwh.2014.4980 PMID: 25793483.

70. Ferreira AM, Adragao P, Cavaco DM, Candeiias R, Morgado FB, Santos KR, et al. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation. Europe: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2008; 10(7):809–15. Epub 2008/05/31. https://doi.org/10.1093/europe/jun135 PMID: 18511438.

71. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobb S, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. Journal of the American College of Cardiology. 2007; 49(5):572–7. Epub 2007/02/06. https://doi.org/10.1016/j.jacc.2006.10.047 PMID: 17276181.

72. Poli D, Antonucci E. Epidemiology, diagnosis, and management of atrial fibrillation in women. International journal of women’s health. 2015; 7:605–14. Epub 2015/06/20. https://doi.org/10.2147/IJWH.S45925 PMID: 26089706.

73. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, et al. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. American heart journal. 2009; 157(4):754–62 e2. Epub 2009/04/01. https://doi.org/10.1016/j.ahj.2008.12.016 PMID: 19332206.

74. Taneja T, Mahnert BW, Passman R, Goldberger J, Kadish A. Effects of sex and age on electrocardiographic and cardiac electrophysiological properties in adults. Pacing and clinical electrophysiology: PACE. 2001; 24(1):16–21. Epub 2001/03/03. PMID: 11227963.

75. Mitoff PR, Gamm D, Ivanov J, Al-hesayen A, Azevedo ER, Newton GE, et al. Cardiac-specific sympathetic activation in men and women with and without heart failure. Heart. 2011; 97(5):382–7. Epub 2010/09/30. https://doi.org/10.1136/hrt.2010.199760 PMID: 20876737.

76. Pedram A, Razandi M, O’Mahony F, Lubahn D, Levin ER. Estrogen receptor-beta prevents cardiac fibrosis. Mol Endocrinol. 2010; 24(11):2152–65. Epub 2010/09/09. https://doi.org/10.1210/me.2010-0154 PMID: 20810711.

77. Sandberg K, Ji H. Sex differences in primary hypertension. Biology of sex differences. 2012; 3(1):7. Epub 2012/03/16. https://doi.org/10.1186/2042-6410-3-7 PMID: 22417477.

78. Zusterzeel R, Seizelmann KA, Sanders WE, O’Callaghan KM, Canos DA, Vernooy K, et al. Toward Sex-Specific Guidelines for Cardiac Resynchronization Therapy? Journal of cardiovascular translational research. 2016; 9(1):12–22. Epub 2015/12/15. https://doi.org/10.1007/s12265-015-9663-z PMID: 26659647.

79. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, et al. Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. BMJ. 2016; 353:i1855. Epub 2016/04/22. https://doi.org/10.1136/bmj.i1855 PMID: 27098105.

80. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. Journal of the American College of Cardiology. 2003; 41(9):1529–38. Epub 2003/05/14. PMID: 12742294.

81. Kappert K, Bohm M, Schmieder R, Schumacher H, Teo K, Yusuf S, et al. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEnd) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation. 2012; 126(8):934–41. Epub 2012/07/26. https://doi.org/10.1161/CIRCULATIONAHA.111.086660 PMID: 22829023.