



Systematic Review/Meta-analysis

Sex, Race, and Age Differences of Cardiovascular Outcomes in Cardiac Resynchronization Therapy RCTs: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is beneficial in patients who have heart failure with reduced ejection fraction or arrhythmic events. However, most randomized controlled trials (RCTs) showing survival benefits primarily enrolled older white men. This study aims to evaluate CRT efficacy by sex, race, and age in RCTs.

Methods: Five electronic databases (CINAHL, Embase, Emcare, Medline, and PubMed) were searched from inception to July 12, 2021 for RCTs with CRT in adult patients. Data were analyzed for clinical outcomes including all-cause or cardiovascular (CV) death, worsening heart failure (HF), and HF hospitalization (HFH) according to sex, race, and age.

Heart failure (HF) with reduced ejection represents a significant global burden,¹ in which cardiac resynchronization therapy (CRT) has shown therapeutic benefit in certain patients.² For instance, the Multicenter Automatic Defibrillator

RÉSUMÉ

Contexte : La thérapie de resynchronisation cardiaque (TRC) est salutaire chez les patients qui souffrent d'insuffisance cardiaque avec fraction d'éjection réduite ou qui subissent des épisodes arythmiques. Toutefois, la plupart des essais contrôlés randomisés (ECR) montrant des bienfaits en matière de survie ont été principalement menés chez des hommes blancs âgés. Cette étude vise à évaluer l'efficacité de la TRC en fonction du sexe, de la race et de l'âge des participants aux ECR.

Méthodologie : Nous avons effectué des recherches dans cinq bases de données électroniques (CINAHL, Embase, Emcare, Medline et PubMed) en ciblant une période allant de la date de leur création

Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) randomized controlled trial (RCT) found a decrease in HF events and mortality with CRT and implantable cardioverter-defibrillator (ICD) therapy in HF patients with New York Heart Association (NYHA) class I/II symptoms.³ Other notable RCTs that investigated the effectiveness of CRT include the Cardiac Resynchronization—Heart Failure (CARE-HF),⁴ Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE),⁵ Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION),⁶ Multicenter InSync Randomized Clinical Evaluation (MIRACLE),⁷ and Multisite Stimulation in Cardiomyopathy (MUSTIC)⁸ trials. However, most of these CRT RCTs have been limited to homogeneous populations comprised primarily of older white men. There is a paucity of RCT data

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Ethics Statement: This research report has adhered to the relevant ethical guidelines.

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See page S200 for disclosure information.

Results: Among six RCTs with up to moderate risk of bias, 54% (n = 3,630 of 6,682; mean age 64 years, 22% female, 8% black patients) had CRT device implantation. All-cause death (odds ratio [OR], 0.51; $P = 0.053$) was reduced in female versus male CRT patients, whereas CV death, HFH, or all-cause death with worsening HF or HFH did not differ significantly. No difference was seen in CRT patients for all-cause death and worsening HF (OR, 1.32; $P = 0.46$) among white vs black patients or for all-cause death and HFH (OR, 1.19; $P = 0.55$) among ≥ 65 versus < 65 years.

Conclusions: Whereas all-cause death was lower in female CRT patients, other reported outcomes did not significantly differ by sex, race, or age. Only 6 studies partially reported outcomes. Thus, enhanced reporting and analyses are required to overcome such paucity of data to evaluate the impact of these factors on clinical outcomes in distinct patient cohorts with CRT indication.

available to indicate the specific benefits of CRT in more diverse demographic cohorts. In fact, the relationship between sex, race, and age and CRT patient outcomes has produced mixed study results. Although some studies have reported that there is no difference in clinical cardiovascular (CV) outcomes and mortality based on race⁹ and age,¹⁰⁻¹² others suggest that CRT produces notable differences between these populations. Specifically, women may have greater reduction in all-cause death and worsening HF after CRT intervention.^{13,14} Black patients may exhibit a similar reduction in cardiac volumes, but increased risk of HF or death, when compared to white patients after CRT intervention.¹⁵ Older participants (≥ 80 years old) may have a higher mortality risk compared with younger patients after CRT intervention.¹⁶ Collectively, there is no consensus among large RCT data to inform CRT indications based on these important sociocultural factors. Therefore, this systematic review sought to investigate the effect of sex (male or female), race (white or nonwhite) and age (< 65 or ≥ 65 years old) on CV outcomes and mortality in CRT patients.

Methods

Data sources, search strategy and study eligibility

This review was conducted in accordance with the Preferred Reporting Items Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁷ and reported in adherence to relevant ethical guidelines. A search was performed from

jusqu'au 12 juillet 2021 afin de recenser les ECR menés chez des patients adultes ayant subi une TRC. Les données ont fait l'objet d'une analyse axée sur les résultats cliniques, notamment les décès toutes causes confondues ou d'origine cardiovasculaire (CV), l'aggravation de l'insuffisance cardiaque (IC) et les hospitalisations pour cause d'IC (HIC), en fonction du sexe, de la race et de l'âge des patients.

Résultats : Dans six ECR présentant un risque de biais tout au plus modéré, 54 % des patients (n = 3 630 sur 6 682; âge moyen : 64 ans, 22 % de femmes, 8 % de patients noirs) étaient porteurs d'un dispositif de RC. Les décès toutes causes confondues (rapport de cotes [RC] : 0,51; $p = 0,053$) étaient moins nombreux chez les femmes que chez les hommes parmi les patients ayant subi une TRC. En revanche, aucune différence significative entre les deux sexes n'a été relevée en ce qui concerne les décès d'origine CV, les HIC ou les décès toutes causes confondues liés à l'aggravation de l'IC ou aux HIC. Au sein de la population ayant subi une TRC, aucune différence n'a été observée quant aux décès toutes causes confondues et à l'aggravation de l'IC (RC : 1,32; $p = 0,46$) chez les patients blancs par rapport aux patients noirs. Il y avait aussi absence de différence quant aux décès toutes causes confondues et aux HIC (RC : 1,19; $p = 0,55$) chez les patients âgés de 65 ans ou plus par rapport aux patients âgés de moins de 65 ans au sein de la même population.

Conclusions : Les décès toutes causes confondues étaient moins nombreux chez les femmes qui avaient subi une TRC, mais les autres résultats rapportés ne différaient pas significativement selon le sexe, la race ou l'âge des patients. Seulement six études ont signalé partiellement les résultats. Des rapports et des analyses plus détaillés sont nécessaires pour remédier à la paucité des données et ainsi permettre d'évaluer l'effet des facteurs étudiés sur les résultats cliniques au sein de cohortes distinctes de patients chez qui la TRC est indiquée.

inception to July 12, 2021 of 5 databases: CINAHL (Cumulative Index to Nursing & Allied Health Literature), Embase, Emcare, Medline (Ovid) and PubMed (non-Medline). The search strategy, developed in collaboration with an Information Specialist (M.P.) using the PICOS framework and search terms used are highlighted (Supplemental Table S1). Search terms included variations of *CRT*, *CRT pacemaker*, and *CRT defibrillator*. RCTs and their secondary analyses that had CRT as an intervention with a control or comparison group were included (even if investigating CRT without indication for HF, such as fine QRS). Studies that provided only short-term outcomes (< 12 months), involved human subjects < 18 years of age, reported on nonhuman subjects, and were published in non-English-language text were excluded from analyses. Studies that conducted secondary analyses of data already included in main trial data were also excluded unless they reported on different clinical outcomes of interest.

Data collection, data extraction and statistical analyses

Search results exported to Endnote X9 (Clarivate Analytics, Philadelphia, PA)¹⁸ were imported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia),¹⁹ and duplicate studies were removed. Two independent reviewers (B.M. and N.T.) assessed the titles, abstracts, and full-text manuscripts for study eligibility and data extraction. Data were extracted into standardized spreadsheets for first and corresponding author and funding recipient details, trial origin and enrollment sites, patient details, funding

type (peer-reviewed or industry), the intervention and control group characteristics, and 1-year event rates for CV outcomes and mortality by sex (male or female), race (white or nonwhite), and age (≥ 65 or < 65 years). Data on authorship, funding, and trial details were collected from publications or institutional websites with verification on the clinicaltrials.gov Web site as applicable; funding recipient was presumed to be the corresponding author if not explicitly reported. Article conflicts in the reviewing and extraction stages were resolved by consensus with a third reviewer (M.S.).

Thirteen studies were excluded during the data extraction stage for nondichotomized age ranges and where reported data could not be used in the analysis ([Supplemental Tables S2 and S3](#)).

We extracted reported relevant CV outcomes and mortality from the studies that met inclusion criteria. These included 1-year all-cause or CV death, HFH, or composite all-cause death, and worsening HF or HFH. No studies reported on 1-year 3-point major adverse CV events defined as composite myocardial infarction, stroke, and CV death.

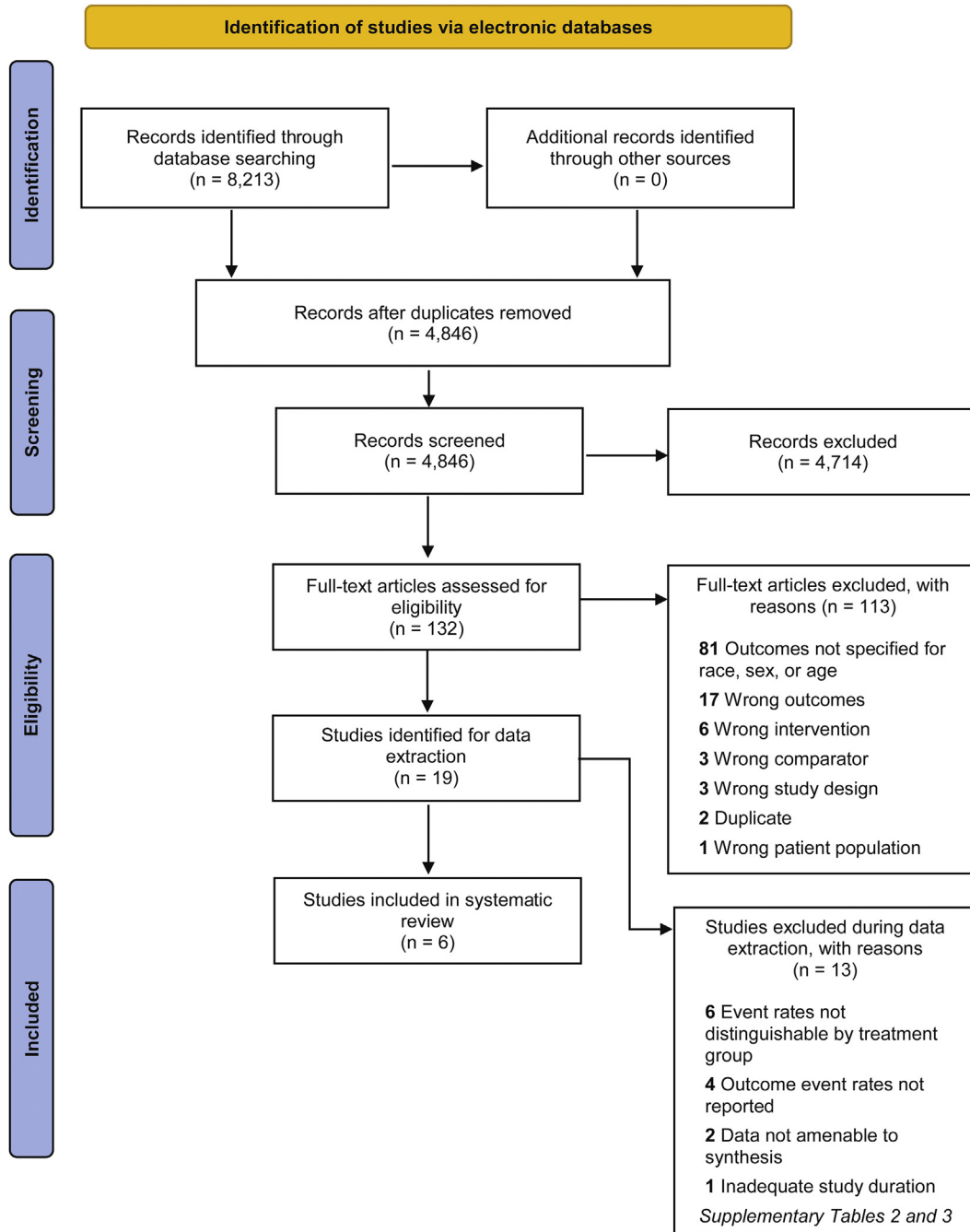


Figure 1. Study flow diagram. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol recommendations were used for study inclusion.

Table 1. Inclusion criteria and summary of included CRT RCTs in meta-analyses

| Articles eligible for data extraction* | de Waard et al. ²⁶ | Ruschitzka et al. ²⁷ | Biton et al. ²⁴ (2015) |
|--|--|---|---|
| Trial name | RAFT ⁴⁶ | Echo-CRT ²⁷ | MADIT-CRT ³ |
| Trial sites region | North America, Australia | Europe | North America, Europe |
| No. of trial sites | 34 | 115 | 110 |
| Age | NR | > 18 years | > 21 years |
| Patient population | NYHA class II or III HF, QRS duration > 120 msec, and LVEF < 30% | NYHA class II or IV HF, LVEF < 35%, indication for ICD, QRS < 130 msec, LV diastolic diameter > 55 mm, and evidence of LV desynchronization | Ischemic CM (NYHA class I or II) or non-ischemic CM (NYHA class II), sinus rhythm, LVEF < 30%, prolonged QRS > 130 msec |
| Trial subgroup | CHF | HF | CM, CHF |
| Primary outcome(s) | Composite (Death, HFH), [†] ACD, [†] HFH, [†] CV death [†] | Composite (ACD, HFH), [†] HFH | Composite (ACD, HF) |
| Secondary outcome(s) | Change in 6MWT time and MLWHFQ score | HFH, change in NYHA class, change QoL, first HFH, CV death, [†] ACD [†] | ACD, HF |
| Treatment arm | CRT-D | CRT-D | CRT-ICD |
| Control arm | ICD | ICD | ICD |
| No. of patients (treatment vs control) | 1798 (894 [†] vs 904) | 809 (404 [†] vs 405) | 1820 (1089 vs 731) |

6MWT, 6-minute walk test; ACD, all-cause death; AF, atrial fibrillation; AFAF-CRT, Ablate and Pace in Atrial Fibrillation; AV, atrioventricular; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; CV, cardiovascular; Echo-CRT, Echocardiography Guided Cardiac Resynchronization Therapy; EF, ejection fraction; HF, heart failure; HFH, HF hospitalization; LV, left ventricular; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; NYHA, New York Heart Association; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; QoL, quality of life; NR, not reported; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RCT, randomized controlled trials.

* Inclusion criteria: Study with human adult subjects ≥ 18 years of age; English language publication; RCT study design with CRT in one arm -; and at least one clinical outcome as the primary outcome must have at least one clinical outcome. Exclusion criteria: Nonhuman studies; paediatric studies; non-English-language publications; non-RCT study design (eg, observational, case study, cohort, review articles). Elanchenny et al.¹⁵ and Steffel et al.²⁸ were not included in this table, as they report secondary analyses from the same trial as Biton et al.²⁴ and Ruschitzka et al.,²⁷ respectively. However, Steffel et al. was still included in the meta-analysis for cardiovascular death, as Ruschitzka et al. did not report this outcome. Extracted data are from the original RCT or secondary analyses as indicated. Brignole et al.²⁵ and Ruschitzka et al.²⁷ were original trials, whereas Biton et al. and de Waard et al.²⁶ were secondary analyses of original trials. Brignole et al. was included in the results but was not eligible for pooled analysis, as the primary outcome was a composite not reported elsewhere in any other included study. Steffel et al. was included in the meta-analysis for outcomes where Biton et al. did not report the events from MADIT-CRT. The secondary outcomes were also not reported by either sex, race, or age, and so could not be pooled.

[†]significance at $P < 0.05$. Comparisons are between intervention and control.

Descriptive statistics were calculated for retrieved data (means) and 1-year event rates for each clinical outcome. Clinical outcomes were reported as odds ratios (ORs) and risk ratios (RRs) with a 95% confidence interval (CI). A 2-tailed P statistic was calculated at α -value of 0.05, where P values < 0.05 were considered statistically significant. Data were then analyzed using Cochrane Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, 2014),²⁰ and Forest plots were generated for RRs. Authors tested for publication bias using Funnel plots and for heterogeneity using χ^2 and I^2 tests if sufficient data points were available for each category of analyses.

Risk of bias and GRADE assessment

Two reviewers (H.S. and B.M.) independently assessed the risk of bias for included studies using the Cochrane risk-of-bias tool for randomized trials (RoB2).²¹ The 2 reviewers also evaluated overall methodologic bias using individual criteria as either *low*, *high*, or *some concerns* across 5 bias domains (Supplemental Figure S1), which included bias caused by (1) randomization process, (2) deviations from intended intervention, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported results. The RoB visualizing program, RobVis,²² was used to generate the summary plot to visualize the independent domains for risk of bias. Overall quality of the evidence was also assessed independently by 2 reviewers (H.S. and B.M.) with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)²³ tool. The overall quality of evidence in the

included studies was categorized as either *very low*, *low*, *moderate*, or *high*. RCTs started with high quality of evidence and were rated downward in the presence of study limitations. Studies were assigned a lower GRADE category for limitations such as risk of bias, indirectness of evidence, heterogeneity, imprecision, or publication bias.

Results

The initial literature search resulted in 8,213 records. After duplicate record removal ($n = 3,367$), 4,846 articles were screened by title and abstract from which 132 studies were assessed for eligibility. Nineteen studies were identified for potential data extraction, of which 6 studies were included (Fig. 1).^{15,24-28} Of those 6 studies, only 4^{24, 26-28} were eligible for meta-analyses, whereas the other 2^{15,25} underwent secondary exclusion but have been reported in the results (Table 1). Thirteen of the 19 studies (original trials or secondary analyses) eligible for data extraction were excluded, as they provided insufficient data to calculate event rates in our analyses (Supplemental Tables S2 and S3). Of the 6 included studies, four RCTs were evaluated to have up to moderate overall bias using the RoB2 tool for methodological quality (Supplemental Figure S1). Elanchenny et al.¹⁵ (2012) and Steffel et al.²⁸ were excluded from this analysis, as they reported on different CV outcomes from the same RCTs as Biton et al.²⁴ ([MADIT-CRT])²⁹ and Ruschitzka et al.²⁷ (the Echocardiography Guided Cardiac Resynchronization Therapy [Echo-CRT] in Heart Failure with a Narrow QRS Complex)²⁷ publications. Three studies showed some

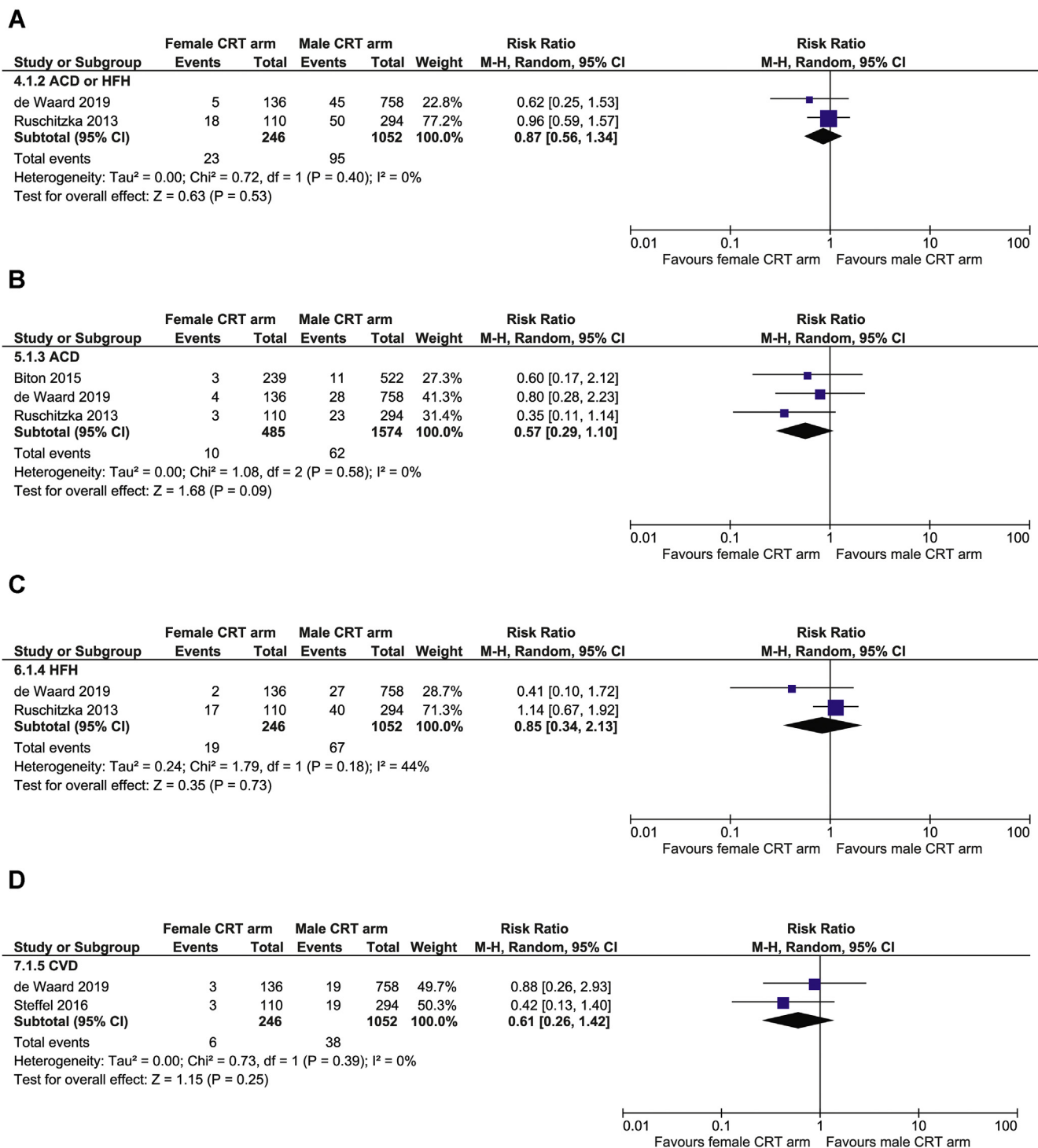


Figure 2. Cardiovascular outcomes and mortality between treatment arms by sex in CRT RCTs. Shown are Forest Plot analyses for cardiovascular outcomes and mortality by sex for all-cause death or HFH (**A**), all-cause death (**B**), HFH (**C**), and CV death (**D**). ACD, all-cause death; CRT, cardiac resynchronization therapy; CVD, cardiovascular death; HFH, HF hospitalization; RCTs, randomized controlled trials.

concerns²⁴⁻²⁶ overall, whereas 1 study showed low risk of bias.²⁷ The RobVis²² summary plot to visualize the risk of bias domains for the 4 studies is shown ([Supplemental Figure S1](#)), wherein bias caused by deviations from the intended intervention was most concerning, as various

stakeholders could not be blinded to implant procedure and/or study methodology. Funnel plot analyses highlighting limited publication bias on clinical outcomes are shown for sex ([Supplemental Figure S2](#)), but not for race or age because of limited data on clinical outcomes for such analyses. Chi

Table 2. Study patient characteristics by sex, race, and age from included CRT RCTs

| Characteristic | CRT arm (n = 3,630) | Comparator arm (n = 3,052) |
|----------------|---------------------|----------------------------|
| Age (y) | | |
| Mean | 63.7 ± 4.8 | 63.8 ± 4.7 |
| Median | 67 | 66 |
| Sex (% of n) | | |
| Male | 72.6 ± 8.5 | 71.6 ± 8.5 |
| Female | 22.4 ± 8.5 | 28.4 ± 8.5 |
| Race (% of n)* | | |
| White | 90.4 | 90.7 |
| Black | 8.0 | 7.7 |

CRT, cardiac resynchronization therapy; RCTs, randomized controlled trials.

* Data on nonwhite patients other than black patients were not reported.

square and I^2 tests highlight variable heterogeneity, often low to moderate, depending on the reported clinical outcome (Fig. 2). However, the observed low-to-moderate heterogeneity is likely a consequence of the limited studies eligible for meta-analysis. GRADE assessment for quality of the evidence was deemed high for the included studies.

Study patient demographics

Of the 6,682 patients enrolled in the 6 included studies, 3,630 patients (54%) in the treatment arm with an implanted CRT device were compared with 3,052 patients (46%) in the control arm. Baseline patient characteristics were relatively uniform across the studies (Table 2): The CRT and control groups primarily comprised whites (90% vs 91%) and men (73% vs 72%) who both had a mean age of 64 ± 5 years. Importantly, race and age data were particularly limited for our analyses, as only Elanchenny¹⁵ reported race-based data for white and black patients but not other nonwhite ethnic groups, and only Ruschitzka et al.²⁷ reported data for age ≥ 65 and < 65 years.

Cardiovascular outcomes and mortality by sex, race, and age

Total event numbers across the 6 studies were derived for all relevant clinical outcome measures. Event numbers were

observed to be consistently higher in the comparator arm for nearly all outcomes, except for CV death, which were higher in the CRT treatment arm. CV outcomes data were variably reported as ORs by sex ($n_{\text{studies}} = 4$), race ($n_{\text{studies}} = 1$), and age ($n_{\text{studies}} = 1$) as summarized in Tables 3, 4, and 5. Only CV outcomes data by sex were eligible for meta-analysis from 4 studies and has been reported as RRs in Figure 2 for CRT arm comparisons, and in Supplemental Figures S3 and S4 for treatment and control comparisons. Data were reported by outcome to avoid double counting event rates from the same study.

Variable odds were reported for associated risk of CV outcomes and mortality for between-sex comparisons in the CRT arm. Outcomes with data from only 1 study was reported by Brignole et al.²⁵ for HF death, HFH, or HF (OR, 1.30; 95% CI [0.17, 10.05]; $P = 0.80$) and Biton et al.²⁴ for all-cause death and worsening HF (OR, 0.69; 95% CI [0.36, 1.35]; $P = 0.28$).

Outcomes eligible to be pooled included all-cause death and HFH (OR, 1.04; 95% CI [0.64, 1.68], $P = 0.87$; $n_{\text{studies}} = 2$), HFH (OR, 1.23; 95% CI [0.73, 2.09]; $P = 0.44$; $n_{\text{studies}} = 2$) or CV death (OR, 0.67; 95% CI [0.28, 1.60]; $P = 0.36$; $n_{\text{studies}} = 2$), all of which were not significant (Table 3). A modest decrease in all-cause death (OR, 0.51; 95% CI [0.26, 1.01]; $P = 0.053$, $n_{\text{studies}} = 3$) was observed in women compared with their male counterparts (Table 3).

Meta-analysis by male vs female sex for CRT arm comparisons all favored nonsignificantly toward female CRT arms, including all-cause death or HFH (RR, 0.87; 95% CI [0.56, 1.34]; $P = 0.53$, $\chi^2 = 0.72$, $df = 1$, $I^2 = 0\%$, $n_{\text{subjects}} = 1,298$, $n_{\text{studies}} = 2$), all-cause death (RR, 0.57; 95% CI [0.29, 1.10]; $P = 0.09$, $\chi^2 = 1.08$, $df = 2$, $I^2 = 0\%$, $n_{\text{subjects}} = 2,059$, $n_{\text{studies}} = 3$), HFH (RR, 0.85, 95% CI [0.34, 2.13]; $P = 0.73$, $\chi^2 = 1.79$, $df = 1$, $I^2 = 44\%$, $n_{\text{subjects}} = 1,298$, $n_{\text{studies}} = 2$), and CV death (RR, 0.61; 95% CI [0.26, 1.42]; $P = 0.25$, $\chi^2 = 0.73$, $df = 1$, $I^2 = 0\%$, $n_{\text{subjects}} = 1,298$, $n_{\text{studies}} = 2$) (Fig. 2). Meta-analysis between treatment and control arms for male sex all yielded nonsignificant differences, including all-cause death or HFH (RR, 0.96; 95% CI

Table 3. Clinical outcomes by sex in CRT RCTs

| Clinical Outcome* | Total | Male sex | Female sex | Odds ratio [95% CI] | P value |
|-------------------------|----------|----------|------------|---------------------|---------|
| CRT arm | | | | | |
| HF death, HFH, or HF† | 4/50 | 2/28 | 2/22 | 1.30 [0.17, 10.05] | 0.80 |
| All-cause death and HF† | 49/761 | 37/522 | 12/239 | 0.69 [0.36, 1.35] | 0.28 |
| All-cause death or HFH | 118/1298 | 95/1052 | 23/246 | 1.04 [0.64, 1.68] | 0.87 |
| All-cause death | 72/2059 | 62/1574 | 10/485 | 0.51 [0.26, 1.01] | 0.053 |
| HFH | 86/1298 | 67/1052 | 19/246 | 1.23 [0.73, 2.09] | 0.44 |
| CV death | 44/1298 | 38/1052 | 6/246 | 0.67 [0.28, 1.60] | 0.36 |
| Comparator arm | | | | | |
| HF death, HFH, or HF† | 8/52 | 4/29 | 3/23 | 0.94 [0.19, 4.68] | 0.94 |
| All-cause death and HF† | 66/520 | 44/365 | 22/155 | 1.21 [0.79, 2.09] | 0.50 |
| All-cause death or HFH | 120/1309 | 90/1023 | 30/286 | 1.21 [0.79, 1.88] | 0.38 |
| All-cause death | 68/1829 | 53/1388 | 15/441 | 0.89 [0.49, 1.59] | 0.69 |
| HFH | 92/1309 | 66/1023 | 26/286 | 1.45 [0.90, 2.32] | 0.12 |
| CV death | 38/1309 | 30/1023 | 8/286 | 0.95 [0.43, 2.10] | 0.90 |

CI, confidence interval; CRT, cardiac resynchronization therapy; CV, cardiovascular; HF, worsening heart failure; HFH, heart failure hospitalization; RCTs, randomized controlled trials.

* Number of events per total patients in group at 1 year unless otherwise stated.

† Brignole et al.²⁵ was the only study that reported HF death, HFH, or HF as a composite and therefore was not eligible for pooled analysis. Biton et al.²⁴ was the only study that reported all-cause death and HF as a composite and therefore was not eligible for pooled analysis.

Table 4. Clinical outcome by race in CRT RCTs

| Clinical outcome* | White race | Black race | Odds ratio [95% CI] | P value |
|-------------------|------------|------------|---------------------|---------|
| CRT arm | 79/980 | 8/87 | 1.32 [0.64, 2.72] | 0.46 |
| Comparator arm | 66/658 | 14/56 | 2.99 [1.55, 5.76] | 0.0011 |

CI, confidence interval; CRT, cardiac resynchronization therapy; HF, worsening heart failure; RCTs, randomized controlled trials.

* Number of events per total patients in group at 1 year unless otherwise stated. Only Elanchenny et al.¹⁵ provided race-based clinical outcomes data.

[0.265, 1.42]; $P = 0.84$, $\chi^2 = 2.04$, $df = 1$, $I^2 = 51\%$, $n_{\text{subjects}} = 2,075$, $n_{\text{studies}} = 2$), all-cause death (RR, 0.89, 95% CI [0.52, 1.53]; $P = 0.68$, $\chi^2 = 3.91$, $df = 2$, $I^2 = 49\%$, $n_{\text{subjects}} = 2,962$, $n_{\text{studies}} = 3$), HFH (RR, 1.01; 95% CI [0.67, 1.51]; $P = 0.97$, $\chi^2 = 1.55$, $df = 1$, $I^2 = 35\%$, $n_{\text{subjects}} = 2,075$, $n_{\text{studies}} = 2$), and CV death (RR, 0.74; 95% CI [0.27, 2.04]; $P = 0.58$, $\chi^2 = 4.04$, $df = 1$, $I^2 = 75\%$, $n_{\text{subjects}} = 2,075$, $n_{\text{studies}} = 2$) (Supplemental Figure S3). Meta-analysis between treatment and control arms for female sex also yielded nonsignificant differences, including all-cause death or HFH (RR, 1.17; 95% CI [0.71, 1.95]; $P = 0.54$, $\chi^2 = 0.41$, $df = 1$, $I^2 = 0\%$, $n_{\text{subjects}} = 532$, $n_{\text{studies}} = 2$), all-cause death (RR, 1.53; 95% CI [0.69, 3.40]; $P = 0.29$, $\chi^2 = 0.87$, $df = 2$, $I^2 = 0\%$, $n_{\text{subjects}} = 926$, $n_{\text{studies}} = 3$), HFH (RR, 1.31; 95% CI [0.62, 2.77]; $P = 0.49$, $\chi^2 = 1.26$, $df = 1$, $I^2 = 20\%$, $n_{\text{subjects}} = 532$, $n_{\text{studies}} = 2$), and CV death (RR, 1.15; 95% CI [0.40, 3.29]; $P = 0.80$, $\chi^2 = 0.08$, $df = 1$, $I^2 = 0\%$, $n_{\text{subjects}} = 532$, $n_{\text{studies}} = 2$) (Supplemental Figure S4).

Data for race and age could not be pooled for meta-analysis because of paucity of available data. Elanchenny et al.¹⁵ was the only study reporting any clinical outcomes by race and reported data for all-cause death and worsening HF (Table 4). Black patients experienced significantly higher rates of the composite endpoint than white patients in the control (OR, 2.99; 95% CI [1.55, 5.76]; $P = 0.0011$) vs treatment (OR, 1.32; 95% CI [0.64, 2.72]; $P = 0.46$). Ruschitzka et al.²⁷ was the only study that reported clinical outcomes by dichotomized age groups and reported data for all-cause death, HFH, and composite all-cause death and HFH by age < 65 vs ≥ 65 years (Table 5). In the CRT arm, all-cause death (OR, 1.85; 95% CI [0.84, 4.07]; $P = 0.13$), HFH (OR, 1.32, 95% CI [0.66, 2.15]; $P = 0.56$), and composite all-cause death and HFH (OR, 1.19; 95% CI [0.68, 2.07]; $P = 0.54$) were nonsignificantly higher in those ≥ 65 years

than in those < 65 years. Whereas all-cause death and HFH (OR, 1.23; 95% CI [0.70, 2.18]; $P = 0.47$) or HFH alone (OR, 1.05; 95% CI [0.58, 1.93]; $P = 0.87$) did not significantly change in the ≥ 65 vs < 65-year-old control patients, all-cause death was 6-fold higher in the older control patient cohort (OR, 6.04; 95% CI [1.91, 19.12]; $P = 0.0022$). No other race or age-based outcomes data were reported, which precluded further analysis.

Study details of trial leads and trial sites

Supplemental Table S4 summarizes the study trial characteristics. Four primary RCTs were evaluated, and outcomes data were derived from 2 primary analyses of 2 RCTs and 4 secondary analyses of 2 other RCTs. Although most trial enrollment was from the trial continent of origin, all studies reported recruitment from 4 sites in Europe, 3 sites from North America, and 2 sites each from Australia and Asia. Whether first or corresponding author, most were white men (67% of first authors, 71% of corresponding authors) from either North America (50% of first authors, 57% of corresponding authors) or Europe (50% of first authors, 43% of corresponding authors). Four studies were supported by industry (67%) and 2 by peer-reviewed grants (33%), few of which were held by nonwhites (29% Asian, 71% white) or women (29% female, 71% male) outside of North America or Europe.

Discussion

This study primarily focused on investigating CV outcomes and mortality based on sex, race, and age after CRT in patients from 6 included RCT studies. No significant sex, race, or age-specific differences in pooled clinical outcomes were observed in patients after CRT in terms of CV death or composite all-cause death with worsening HF or HFH. The strongest association was seen between female sex and a lower risk of all-cause death (OR, 0.51; $P = 0.053$). Although limited data were reported on clinical outcomes based on race or age, interesting initial observations were made between white vs black patients and patients ≥ 65 years vs < 65 years of age without CRT intervention. Further evaluation is justified for these patient populations as all-cause death with or without worsening HF were 3-fold or 6-fold higher, respectively, in the control patient cohorts of those studies. These outcomes differences were mitigated with CRT intervention.

This study also found that most CRT RCTs are conducted by white male investigators from North America or Europe, who, in turn, represent most first and corresponding authorship

Table 5. Clinical outcomes by age in CRT RCTs

| Clinical outcome* | Total | < 65 y | ≥ 65 y | Odds ratio [95% CI] | P value |
|-------------------------|--------|--------|-------------|---------------------|---------|
| CRT arm | | | | | |
| All-cause death and HFH | 67/404 | 44/278 | 23/126 | 1.19 [0.68, 2.07] | 0.54 |
| All-cause death | 27/404 | 15/278 | 12/126 | 1.85 [0.84, 4.07] | 0.13 |
| HFH | 58/404 | 38/278 | 20/126 | 1.19 [0.66, 2.15] | 0.55 |
| Comparator arm | | | | | |
| All-cause death and HFH | 59/405 | 36/264 | 23/141 | 1.23 [0.70, 2.18] | 0.47 |
| All-cause death | 16/405 | 4/264 | 12/141 | 6.04 [1.91, 19.12] | 0.0022 |
| HFH | 53/405 | 34/264 | 19/141 | 1.05 [0.58, 1.93] | 0.87 |

CI, confidence interval; CRT, cardiac resynchronization therapy; HFH, heart failure hospitalizations; RCT, randomized controlled trials.

* Number of events per total patients in group at 1 year unless otherwise stated. Nonuniform age data were not reported. Only Ruschitzka et al.²⁷ provided age-based clinical outcomes data.

for publications arising from studies as well as recipients of mostly industry-sponsored sources of funding. Collectively, these findings identify underrepresented demographics in terms of diverse patient enrollment and trial leadership and bring attention to potential for several systematic, regulatory changes to RCT design and objectives to enhance our understanding of clinical outcomes in diverse patient cohorts after CRT intervention through enhanced patient-physician concordance.

Sex differences in CV outcomes and mortality post-CRT

We reported no sex-based differences in most CV outcomes and mortality after CRT intervention in men vs women at 1 year. Although we included 4 CRT RCTs reporting on clinical outcomes dichotomized by sex, women were underrepresented in all of these studies given that they accounted for only 21%-28% of enrolled study subjects. However, all-cause death was reduced in women relative to men by half, with a *P* value approaching significance. Prior CRT studies found that women tend to have more favourable clinical and echocardiographic outcomes compared with men.^{13,14} Specifically, women may have a greater improvement in left ventricular ejection fraction and related survival benefit after CRT.³⁰ Future research needs to be adequately powered to detect true sex differences for other clinically relevant outcomes after CRT including HFH.

Race and age differences in CV outcomes and mortality post-CRT

Although we also reported no significant race or age-based differences in clinical outcomes at 1 year post-CRT intervention, these were both based on only 1 study each. Limited research has been conducted with regard to race-based clinical outcomes in CRT patients. In a subanalysis to improve the use of evidence-based heart failure therapies in the outpatient setting, no race-related differences were reported in all-cause death at 2 years post-CRT.³¹ Our findings emphasize the need to address the problematic disparities observed in CRT indication for black and other minority patients who have HF with reduced ejection fraction.^{32,33} This finding is particularly important, as only 8% of enrolled subjects were black participants in the one study reporting on race-related clinical outcomes with CRT.

Our results suggest that CRT may be beneficial in older adults ≥ 65 years of age, with the caveat that these patients may potentially experience higher rates of adverse clinical outcomes, although none were statistically significant. This finding supports prior findings that CRT remains clinically effective enough to warrant indication for implantation in this patient subgroup.^{34,35} However, this finding contrasts with those from other studies that suggest CRT implantation in populations much older than 65 years may not hold the same benefit as in younger cohorts over an individual's lifespan but still pose significant periprocedural risks.^{36,37} Additional RCTs with race- and age-specific data reporting are required to determine the risk of adverse clinical outcomes vs therapeutic benefits among our ethnically diverse and aging adult population, which are adequately powered to detect such differences after CRT. Recent cardiology trials found modest increases in the inclusion of more diverse patient populations.^{38,39} For example, it was shown that between the

years of 1996 and 2015, the mean percentage of women in published cardiology RCTs increased by 0.29% each year, whereas the mean age increased by 0.15 years.³⁸ Similarly, a review by Gong et al.⁴⁰ found that women enrollment in CV trials increased by 33% between the years of 2011 and 2015. However, certain patient subgroups continue to be underrepresented and/or underreported in most RCTs, particularly those of nonwhite race and female sex.^{38,39,41}

Clinical implications and future considerations

Underrepresentation and/or underreporting of study data by sex, race, and age persist among large RCTs evaluating the efficacy of CRT on clinical outcomes including CV sequelae and mortality. While we did not observe differences along these sociocultural demographics because of the small number of studies reporting these data, an important first step to understanding the risks vs benefits on clinical outcomes of CRT intervention in diverse patient populations would be to enhance female, nonwhite, and elderly patient enrollment. Systemic changes in study inclusion and reporting may enable investigation of the intersectionality of important demographic variables with clinical outcomes in CRT patients. Intersectionality is clinically relevant and may challenge the current RCT data reporting that has focused on few demographic characteristics, namely, male sex and white race, while largely failing to consider broader principles of equity, diversity, and inclusion in CV medicine.⁴² It is undeniable that multiple factors including cultural connectedness may interact and summate to influence CV outcomes and mortality, including a lack of sex and race-based similarities between patients and their physicians.^{43,44} The CRT RCTs reporting on clinical outcomes in this review had mostly white male principal investigators from North America and Europe, who, in turn, led knowledge dissemination through first or corresponding authorship. Previous work indicates that the physician-patient relationship is positively influenced by a shared identity (eg, sex, race), resulting in higher levels of trust, satisfaction, and intention to treatment adherence.⁴⁵ As a result, increased research team diversity, patient enrollment in clinical trials through government or industry-led incentives, and the use of patient-centered communication may help overcome existing knowledge gaps on diverse CV disease patient populations.^{40,41,45}

Limitations

No study is without limitations. In this review, the effect size of CRT on certain sex, race, or age groups must be evaluated with caution owing to the small number of included studies with sufficiently reported outcomes data. We also did not write to the study authors of the 13 excluded studies to see if they still had access to the relevant outcomes data for inclusion into this analysis. These elements precluded a more robust metaanalysis. Further, our analyses focused on the capturing event numbers at 1 year, which estimates may not always be accurate owing to some variability between studies in follow-up times and the subgroups investigated. Additionally, shorter and longer clinical outcomes were not explored, but may be warranted, alongside adequately powered studies to allow for sex, race, or age-related clinical outcomes, given the impact on resource utilization in CRT patients over their lifespan.

Conclusions

This study identifies considerable knowledge gaps in the reported efficacy of CRT on the basis of sex, race, or age for clinical outcomes and mortality. Although women may benefit from CRT in terms of a lower risk of all-cause death, the fact that most CV and mortality outcomes reported no differences requires targeted evaluation through diverse leadership dedicated toward the enrollment of distinct sex, race, and age cohorts of HF patients with reduced ejection fraction.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2021.09.005>.