

Sex and Gender in Cardiac Resynchronization Therapy Cohort Studies

A systematic methodological review and meta-analysis of cohort studies

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Preface

Omar Dewidar (OD) is the student. OD conceptualized the studies and was involved in the conduct and preparation of manuscripts. Dr. George Wells is (GW) is the primary thesis supervisor. GW is the director of the Cardiovascular Research Methods Center at the University of Ottawa Heart Institute, professor in the School of Epidemiology and Public Health at the University of Ottawa, and senior scientist affiliate in the Ottawa Hospital Research Institute. Dr. Vivian Welch (VW) is the co-supervisor for this thesis. VW is director of the Methods Centre at the Bruyère Research Institute, an Associate Professor in the School of Epidemiology and Public Health at the University of Ottawa. GW and VW were involved in overseeing the protocol inception, study conduct, and preparation of thesis. Dr. David Birnie (DB) is a Thesis Advisory Committee (TAC) member. DB is a staff cardiac electrophysiologist and Deputy Division Head of Cardiology at the University of Ottawa Heart Institute and full Professor in the Division of Cardiology, Department of Medicine, at the University of Ottawa. DB served as an expert content advisor to the thesis and conduct of the studies.

Ethics approval was not required for any component of this thesis as it did not involve any human participants.

ABSTRACT

Randomized trials and cohort studies have shown sex differences in the implantation and response to Cardiac Resynchronization Therapy (CRT). Furthermore, gender roles are associated with precipitants of congestive heart failure. Cohort studies are well-suited to assessing implantation rates, long-term outcomes, and the role of sex and gender. Therefore, we systematically identified cohort studies that reported outcomes of CRT and evaluated the following: 1) prevalence and temporal changes in sex and gender reporting and analysis; and 2) sex differences in the implantation and response to CRT. Sex was increasingly considered but remained inadequately reported and analyzed. Gender was not considered in the studies. In clinical practice, fewer women received devices, despite benefiting from CRT more than men. Of note, the difference in response may be confounded by differences in the clinical profiles of men and women. There is a need for better integration of sex and gender in studies to understand better the reasons leading to the observed differences.

EXECUTIVE ABSTRACT

Landmark trials and large observational studies have found that patient sex influences the likelihood of receipt and response to Cardiac Resynchronization Therapy (CRT). However, the reasons for these differences are also not well understood. The underrepresentation of women in trials renders it challenging to assess sex differences using data from randomized trials. This creates a need to investigate observational data that reflects real-world practice and may help overcome issues of underrepresentation. Therefore, we systematically searched for cohort studies reporting clinical and safety outcomes of CRT in heart failure patients in all languages from January 2000 to June 2020. First, we evaluated the prevalence and temporal changes in sex and gender reporting analysis. Assessment of 253 studies showed that less than a third of the studies considered sex in the study design or analysed sex, but improvements were found over time. In particular, the introduction of the policy by National Institutes of Health (NIH) on Sex as A Biological Variable (SABV) in 2015 increased the integration of sex in study design and statistical models but not in analysis. Gender analysis was not mentioned in any studies. We conducted a systematic review of sex differences in implantation rate, effectiveness and safety of CRT based on the studies identified previously and further searches of references and citations of relevant systematic reviews. We found that men are more likely than women to be implanted with CRT, and women have lower mortality following CRT compared to men. Women also have echocardiographic evidence of more significant improvement and have fewer complications than men. Baseline imbalances between men and women in the studies suggest that differences may be due to left bundle branch block (LBBB) and non-ischemic cardiomyopathy (NICM), which were more commonly presented in women, as they are both strongly associated with improvements in cardiac remodeling. However, the reasons for the lower implantation rate of CRT in women compared to men were not described in the studies. To further investigate the reason for these differences, sex and gender need to be considered in study design and analysis. Furthermore, study design and analysis across sex and gender need to be explicitly reported.

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Chapter 1: Introduction

1.1 Interventions to treat congestive heart failure

There are several pharmacological and non-pharmacological therapies to improve the clinical outcome of CHF ¹. Over the past decade, significant advances in medical management of patients with CHF resulted in the establishment of cardiovascular implantable electronic devices (CIEDs) as the ideal treatments for a variety of cardiac arrhythmias². Permanent Pacemakers provide appropriate heart rate and response ³. Implantable cardioverter defibrillators (ICDs) provide ventricular shock to defibrillate ventricular fibrillation (VF) ⁴. Cardiac Resynchronization Therapy devices (CRT), also known as biventricular pacing, are the latest CIEDs aimed to reduce symptoms for CHF and improve heart ventricular function. This device exists in two types: CRT-pacemaker (CRT-P), which synchronizes the heart beating pattern through improving the pumping action the lower ventricles, and CRT-Defibrillator (CRT-D) which in addition to synchronizing heart rhythm, can detect and treat sudden cardiac death (SCD) ⁵.

1.2 Sex Differences in cardiovascular disease

There are substantial behavioral and biological differences between men and women which affect the manifestation, pathophysiology of diseases and potential therapies⁶. Congestive Heart failure (CHF); one of the most prevalent cardiovascular conditions and is the leading cause of cardiovascular morbidity and mortality in Canada and the world. In addition, some of the most profound sex differences in risk and outcomes in cardiovascular medicine exist in CHF ^{7, 8}. Sex refers to a set of biological attributes in humans and animals that determine physical and physiological features⁹. Biological differences, in part, are responsible for differences in disease manifestation, prognosis and treatment ^{10, 11}.

1.3 Gender in cardiovascular disease

Apart from sex, gender is a multidimensional concept that evolves from identities, socially constructed roles, behaviours and relations ⁹. Gender identity represents the individual's intrinsic sense of their identity. The mechanisms by which gender identity interacts with cardiovascular disease (CVD) is poorly understood, and likely mediated by other gender dimensions. Gender roles

vary greatly across cultures leading to different effects. Aspects of gender roles which may influence cardiovascular disease include occupation type, work hours, primary earner status and household responsibilities. Gender relations refer to the relationships and interactions based on their marital status, social and familial support. These factors may intersect and interact with sex to impact diagnosis, treatment and health outcomes ¹².

1.4 Rationale for investigating cohort studies

Cohort studies constitute a large portion of the evidence base on CRT. They are used to inform decisions about prognostic factors, practice variation, long-term outcomes, and determinants of behaviours and outcomes in broader populations and settings than those included in randomized trials (e.g. women, patients with multiple comorbidities, older patients and racially diverse populations)¹³. Cohort studies also represent the majority and upcoming literature published for devices and drugs that achieve market approval. Furthermore, cohort studies can be used to inform guideline development, particularly with respect to implementation issues, long-term effects, and disease prognosis¹⁴. With such a wide range of uses for evidence from cohort studies, it is crucial to understand how sex and gender are considered in cohort studies that constituted this large evidence base.

Randomized controlled trials (RCTs) are the “gold standard” for assessing the effectiveness and/or safety of a treatment ¹⁵⁻¹⁷. However, subgroup analyses to assess sex differences in RCTs are exploratory, may have inadequate study power¹⁸ and findings may be confounded by baseline profiles which differ between men and women. Furthermore, women are underrepresented in heart failure trials. Possible explanations include: difficulties in access to study sites, women perceive a greater risk of harm from trial participation, women take fewer risks and may require more than one source of input ¹⁹. Hence, observational studies may be utilized to understand sex differences.

Cohort studies may be more representative of patients seen in clinical practice since they follow a group of people over time. Design and analytical approaches such as propensity score matching, and modelling with covariates could be used to adjust for potential confounding^{20, 21}. However, cohort studies may be affected by unknown confounding. Cohort studies tend to produce

effect estimates in real-world settings²². This benefit of high external validity comes at a price of their internal validity which is poor relative to RCTs.

Since CRT were granted marketing authorization, emerging evidence on effectiveness and safety is from observational studies^{23, 24}. This paradigm is typically valid for cardiac surgery studies as evidence shows a significant reduction in the number of RCTs over the years²⁵. Cohort studies are more feasible for assessing long-term safety and effectiveness outcomes such as mortality and hospitalization²⁶. In addition, cohort studies are less likely to restrict eligibility by comorbidities, sex, age or other sociodemographic factors. In randomized studies, these patients would be excluded to minimize variation in participants and maximize the signal to noise ratio²⁷. Since cohort studies are interested in describing real-world practice and exploring reasons for variation, they are well-suited to exploring interaction of sex and gender with clinical practice and long-term outcomes.

1.5 Research Questions

Objective 1: Appraise Sex and Gender Reporting and Analysis in Cardiac Resynchronization Therapy Cohort Studies

What is the prevalence, temporal trends and impact of the 2015 NIH Sex as A Biological Variable (SABV) policy on the reporting and analysis of sex and gender in Cardiac Resynchronization Therapy?

Objective 2: Assess Sex Differences in the Implantation Rate, Clinical Effectiveness and Safety in Cardiac Resynchronization Therapy Cohort Studies

Are there sex differences in the implantation rate and response to Cardiac Resynchronization Therapy in real world settings?

1.6 Chapter Descriptions

The objectives of this thesis will be addressed in the following chapters:

- Chapter 2 provides a summary of evidence on sex differences in Cardiac Resynchronization Therapy with a focus on reported differences in implantation, efficacy and safety.

- Chapter 3 includes the protocol for the systematic review of sex differences in Cardiac Resynchronization Therapy cohort studies which describes the methods for objective 1: Appraisal of sex and gender reporting and analysis in Cardiac Resynchronization Therapy cohort studies, and objective 2: Assessment of sex differences in the Implantation rate, clinical effectiveness and safety in Cardiac Resynchronization Therapy cohort studies.
- Chapter 4 addresses objective 1 and includes a research methodology study. This study evaluates the prevalence and temporal changes in sex and gender reporting and analysis in Cardiac Resynchronization Therapy cohort studies assessing effectiveness and safety. The methodological assessment provides insights for improving sex and gender analysis and reporting in Cardiac Resynchronization Therapy studies.
- Chapter 5 addresses objective 2 and includes a systematic review and meta-analysis on sex differences in the implantation rate, effects, and safety of Cardiac Resynchronization Therapy cohort studies. The review summarizes evidence from cohort studies and elucidates possible reasons for sex differences in response to Cardiac Resynchronization Therapy.
- Chapter 6 is a discussion chapter which includes a summary of findings, integrative synthesis of thesis components and future directions.

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Chapter 2: Background

1.1 Cardiac Resynchronization Therapy in International Guidelines

Recommendations for CRT vary by geographical area and the cardiac professional society¹. However, all the guideline recommendations have been based on the eligibility criteria that have been considered for CRT clinical trials over the years. All the cardiac societies agree that patients with reduced Heart Failure (rHF) in New York Heart Association (NYHA) functional class III with left bundle branch block (LBBB) and a QRS duration ≥ 150 ms should receive CRT device. There is also consensus for CRT implantation in NYHA functional class II and ambulatory IV patients with LBBB and narrow QRS duration (120-149 ms). Disagreements persist in LBBB patients with narrow QRS (120-149 ms), patients with QRS duration <129 ms and NYHA II. Additionally, discrepancies among guidelines exist for non-LBBB patients, especially those with narrower QRS duration. So far, there are no sex-specific recommendations for heart failure treatment, but calls are in place to encourage the consideration of CRT guidelines for women and men separately²⁻⁴.

1.2 Sex Differences in the Epidemiology of Congestive Heart Failure

According to the Framingham Heart Study (FHS), the risk of CHF is similar between men and women at 40 years of age; estimated at 20% for women and 21% for men⁵. The Rotterdam Study also found a comparable risk (29% for women and 33% for men)⁶. However, apparent differences are found when the type of CHF is considered. The prevalence of preserved Heart Failure (HFpHF) has been shown to be higher in women than in men and increases with age⁷. According to a recent epidemiological study in Olmstead County, the incidence of HFpHF increased over time (40% in 2000-2003 to 52% in 2008-2010), with the proportion in women double to the proportion in men⁸. Conversely, women have been found to constitute 29% of patients with reduced Heart Failure (HFrEF) in the Swedish Heart Failure Registry⁹. In a study of 28,820 participants from four community-based cohorts, men had a two-fold higher risk of reduced Heart Failure (HFrEF) than women¹⁰. Interestingly, evidence has emerged that HFpHF varies with ethnicity, with a greater prevalence in blacks compared to whites¹¹.

1.3 Sex Disparities in Cardiac Resynchronization Therapy Implantation

There is abundant evidence that women are less likely to receive guideline-recommended treatments especially when receiving expensive treatments such as cardiac implantable devices¹²⁻¹⁷. Age and comorbidities have been identified as factors that further reduce the likelihood of receiving CRT in women¹⁸. This disparity in utilization could be explained by disparity in diagnosis. Studies have shown that women are more likely to have diastolic heart failure resulting in worse disease presentation in terms of NYHA class while having preserved ejection fraction¹⁹. This would lead to missing the need to recommend CRT for women.

1.4 Sex Differences in Cardiac Resynchronization Therapy Efficacy

Sex differences are apparent in heart failure pathophysiology and etiology; however, the mechanisms remain not well understood²⁰. Diagnosis of heart failure in women is later in life than in men. Also, women are more frequently hypertensive and diabetic compared to men²¹. Several trials have found sex differences in the effectiveness of CRT in heart failure patients. CARE-HF and COMPANION trials compared CRT-P with medical therapy and found varying effects between sexes. CARE-HF demonstrated a similar reduction in mortality and time to a cardiovascular event in women (Hazard Ratio [HR]; 0.64, 95% CI, 0.42–0.97) and men (HR; 0.62, 95% CI, 0.49–0.79) with LVEF \leq 35% and QRS $>$ 120 ms²². The COMPANION trial identified women to have a greater reduction of the composite endpoint death or hospitalization compared to men²³. This trial also assessed the ability of CRT-D to improve survival in comparison to pharmacotherapy and found a significantly improved effect in men but not in women, even though the estimates were the similar, suggesting lack of study power to assess this difference.

An international observational study (MASCOT) on advanced heart failure patients (NYHA class III-IV), LVEF \leq 35% and QRS \geq 130 ms suggested no sex differences for increased LVEF \geq 5%, however women had greater improvement in quality of life²⁴. After adjusting for cardiovascular history, women were found to have lower all-cause mortality (P=0.008), cardiac mortality (P=0.04) and hospitalization due worsening heart failure (P=0.045) compared to men. In another study limited to nonischemic cardiomyopathy advanced heart failure patients, women (n=105) had greater cardiac reverse remodelling benefits, and LVEF increase (12 \pm 13% in women versus 0.89 \pm 9.0 in % men, P=0.001) compared to men (n=107). In summary, most of the evidence suggests a greater CRT benefit for women with heart failure compared with men.

The reasons for the difference in response between men and women is not known and may be influenced by anatomical and physiological differences, or other causes. For example, approximately one third of patients diagnosed with LBBB do not have activation consistent with a true LBBB ²⁵⁻²⁸. The use of the current QRS criteria leads to the selection of women with more severe conduction delay as they tend to have ~ 5ms shorter QRS duration than men in the absence of disease ^{28, 29}. Hence, in the presence of LBBB, the net increase in the duration of QRS is greater for women than men. This discrepancy in the degree of desynchrony between men and women has led to the proposal of sex-specific criteria for LBBB ². Conversely, the absence of LBBB and smaller ventricle size in women may lead to inefficient left ventricular pump function and greater harm compared to men ³⁰. Of note, there is conflicting evidence if the QRS morphology or the duration is responsible for driving the difference in response ³¹.

Heart failure etiology may also have a role in leading to differences in response. Women have less ischemic cardiomyopathy (ICM), in turn less myocardial scar in inferolateral region (the target area for CRT implantation). The difference in viable myocardium translates to less available tissue that could be recruited by CRT, which would lead to less effective stimulation ³¹. Hence, patients with non-ischemic cardiomyopathy (NICM) exhibit greater reverse modelling than those with ICM. In contrast, a large observational study of 44,000 patients showed that sex differences persisted after separating patients by history of myocardial infection; women had significantly greater benefit compared to men ³². These findings were consistent with another study conducted in 2011 that suggest that differences in aetiology play a large but indecisive role in sex differences in CRT outcomes ³³.

1.5 Sex Differences in Cardiac Resynchronization Therapy Complications

CRT involves an invasive procedure with inherent risks. There are sex differences in complications for CRT, mostly for CRT-D. In heart failure patients randomized in the MADIT-CRT trial, perioperative adverse events were 2.5 times more likely to occur in women with CRT-D than in men ³⁴. This overwhelming difference could be explained by differences across sex in frequency of pneumothorax/hemothorax (women 4.4% versus men 0.9%) and device infections (women 2.5% versus men 0.6%). In another study, comparing CRT-D while on anticoagulation therapy versus usage of anti-coagulation therapy after device implantation, found that hematomas were more common in women (13%) compared to men (7%) ³⁵. A large retrospective analysis of

a United States nationwide CRT database found that in-hospital mortality was lower in women compared with men (0.71% versus 0.93%)¹⁵, with a non-significant difference in the length of stay post implantation of the device. Overall, women are more likely to suffer from complications post implantation than men.

1.6 Evidence for Sex Differences in Systematic Reviews of Randomized Trials

There are also conflicting findings from systematic reviews^{29,36}. An individual participant data meta-analysis (IPD-MA) of three landmark trials (REVERSE, MADIT-CRT, RAFT)³⁷⁻³⁹ investigated the effect of conventional LBBB presence and variation in QRS duration. The analysis showed that for both end points of heart failure and death alone, women with conventional LBBB and mild heart failure tended to benefit from the CRT-D at a QRS duration shorter than 150 ms, while men with conventional LBBB derive a significant benefit at QRS of 150 ms or longer²⁹. However, these findings were synthesized from studies that were composed of 80% men, so the subgroup analyses lacked power to investigate effects between sexes considering other clinical characteristics and shorter QRS durations.

Another larger IPD-MA of five trials (CARE-HF, MIRACLE, MIRACLE-ICD, REVERSE, RAFT) investigated if the effects of CRT on men and women were directly related to sex or driven by other features. Interestingly, they found that height and QRS duration predicted the ability of CRT to reduce the time to heart failure hospitalization and mortality, independent of sex. Men and women with short stature consistently showed significant benefit from CRT even at short QRS durations (<130ms). However, the analysis was incapable of differentiating if sex masks the effects of height, QRS aetiology and morphology or vice versa. Nonetheless, Linde and colleagues suggest that QRS duration is the primary predictor of CRT response. A primary limitation of this IPD-MA is that the mean age of the participants was lower than the mean age of the CHF population reported in epidemiological studies and CHF surveys. Therefore, external validity of the findings beyond the randomized trials are questionable and are inconclusive.

Several systematic reviews have assessed sex differences in CRT outcomes in cohort studies over the years⁴⁰⁻⁴³. These four reviews found a greater benefit in women compared to men. However, they were of low methodological quality as per AMSTAR 2.0 checklist (Table 1), thus their findings may not be robust.

1.7 Efforts for Improving the Reporting of Sex and Gender

The need for improving integration of sex and gender in research has been acknowledged by several international organizations. In 2015, the National Institutes of Health (NIH) released the policy Consideration of Sex as a Biological Variable (SABV) for NIH-funded biomedical Research ⁴⁴, calling for scientists to account for possible roles of sex as a biological variable in both human and animal studies by considering sex in reporting, study design and analysis. Global efforts are also in place to promote the inclusion of sex and gender in research. The Pan-American Health Organization (PAHO) and World Health Organization (WHO) have explicitly advocated for developing standards for reporting and analysis ^{45, 46} and guidance has been provided by the (Sex and Gender Equity in Research) SAGER guidelines and the Cochrane and Campbell Sex and Gender Methods Group ^{47, 48}.

The extent of sex and gender considerations in CRT studies are limited. Knowledge about where the deficiencies in considerations persist would help identify possible avenues for improvement in integrating sex and gender in research. Furthermore, evaluation of sex differences in CRT cohort studies may help generate clinical questions to investigate the source of sex differences and help eliminate the long-standing disparities in CRT.

Table 1. AMSTAR 2.0 assessment of previously conducted systematic reviews assessing sex differences in cohort studies of cardiac resynchronization therapy.

	Cheng 2014	Han 2017	Herz 2015	Yin 2017
Did the research questions and inclusion criteria for the review include the components of PICO?	More Favorable Response to Cardiac Resynchronization Therapy in Women Than in Men	Sex-specific mortality differences in heart failure patients with ischemia receiving cardiac resynchronization therapy	Sex Differences in Device Therapy for Heart Failure: Utilization, Outcomes, and Adverse Events	The impact of gender difference on clinical and echocardiographic outcomes in patients with heart failure after cardiac resynchronization therapy: A systematic review and meta-analysis
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No justification for including observational studies	No justification for including observational studies	No justification for including observational studies	No justification for including observational studies

	Cheng 2014	Han 2017	Herz 2015	Yin 2017
Did the review authors use a comprehensive literature search strategy?	MEDLINE and EMBASE + Jan 1980 to March 2014 English language No search strategy provided	MEDLINE and EMBASE + Jan 1980 to Sept 2016 English language TERM SEARCH ONLY	MEDLINE and EMBASE + Jan 1976 to May 2014 English language TERM SEARCH ONLY narrowed by adding “gender OR sex OR male OR men”	PubMed, Embase and the Cochrane Library were searched up to November 30 2016 English Language medical subject headings (MeSH)search, text word
Did the review authors perform study selection in duplicate?	Not reported	Yes	Not reported	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Not reported	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No, NO PRISMA	PRISMA provided but no reasons for exclusion reported	No	Yes, PRISMA provided

	Cheng 2014	Han 2017	Herz 2015	Yin 2017
Did the review authors describe the included studies in adequate detail?	No, Only characteristics of 9/45	No, only report characteristics for total population	No, Only characteristics of 19/56	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No ROB assessment	Yes, NOS	No ROB assessment	Yes, NOS
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No, Pooled NRSI with RCT without showing separate diamonds for each study type	No, Pooled NRSI with RCT without showing separate diamonds for each study type	No, Pooled NRSI with RCT without showing separate diamonds for each study type	No, Pooled NRSI with RCT without showing separate diamonds for each study type
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on	No	No	No	No

	Cheng 2014	Han 2017	Herz 2015	Yin 2017
the results of the meta-analysis or other evidence synthesis?				
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	No	No	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No <p>“Although significant heterogeneity was observed among the 45 available studies (I²=29.49%; 95% CI, 0–51.36%; P=0.03), little of it was explained by study design (P=0.20), percentage of women (P=0.64), sample size (P=0.87), number of events (P=0.55), duration of follow-up (P=0.22), average LVEF (P=0.70), whether risk profiles were adjusted</p>	No	No	Yes

	Cheng 2014	Han 2017	Herz 2015	Yin 2017
	(P=0.53), or whether patients with atrial fibrillation were enrolled (P=0.33) .”			
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes, “No evidence of publication bias was found in Begg test (P = 0.76) and Egger test (P = 0.68)“	No	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes
Final score	4/16	5/16	2/16	6/16

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Chapter 3. Protocol for a systematic review to identify Cardiac Resynchronization Therapy cohort studies assessing effectiveness and safety in heart failure patients

Chapter Overview

This section includes the protocol manuscript titled '*Sex differences in CRT device implantation rates, efficacy and complications following implantation: Protocol for a systematic review and meta-analysis of cohort studies*'. The protocol outlines the plan to identify CRT effectiveness and safety studies with a cohort study design using a systematic search of two databases and Web of Science repository. The protocol will guide the conduct of the sex and gender appraisal and review of the existing evidence on sex differences.

Manuscript Status

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Author Contributions

Omar Dewidar was involved in the conception of study protocol and the preparation of manuscript. Irina Podinic involved in all stages of protocol development. George Wells, Vivian Welch and David Birnie were involved in all stages of protocol development and preparation of the manuscript.

Sex differences in CRT device implantation rates, efficacy and complications following implantation: Protocol for a systematic review and meta-analysis of cohort studies

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Abstract

Introduction: There is abundant evidence for sex differences in the diagnosis, implantation and outcomes for Cardiac Resynchronization Therapy (CRT) devices. Controversial data suggesting women are less likely to receive the device regardless of the greater benefit. The aim of this review is to assess sex differences in the Implantation rate, clinical effectiveness and safety of patients receiving CRT devices.

Methods: We will conduct a systematic literature search of MEDLINE, Embase and Web of Science to identify cohort studies that meet our eligibility criteria. Title and full text screening will be conducted in duplicate independently. Eligible studies report clinical effectiveness or safety of patients receiving CRT device while providing sex-disaggregated data. Implantation rate will be extracted from the baseline characteristics tables of the studies. The effectiveness outcomes include: All cause death, Hospitalization, Peak oxygen consumption (pVO₂), Quality of life (QoL), 6 min walk test, NYHA class reduction, LVEF, Heart failure hospitalization. The complication outcomes include: Contrast-induced nephropathy, Pneumothorax, Pocket-related Hematoma, Pericardial tamponade, Phrenic nerve stimulation, Device Infection, Death, Pulmonary edema, Electrical storm, cardiogenic shock, Hypotension requiring resuscitation. Description of included studies will be reported in detail and outcomes will be meta-analyzed and presented using forest plots when feasible. Risk of Bias will be assessed using Newcastle-Ottawa Scale (NOS) by two review authors independently. GRADE approach will be used to assess the certainty of evidence.

Discussion: The aim of this review is to determine the presence of differences in CRT implantation between women and men as well as differences in clinical effectiveness, safety of CRT after device implantation. Results from this systematic review will provide important insights into sex differences in CRT devices that could contribute to the development of sex-specific recommendations and inform policy.

PROSPERO registration number: CRD42020204804

Keywords: Cardiac Resynchronization Therapy, Cardiac Implantable electronic device, efficacy, complications, Implantation, Cohort, sex differences, non-randomized studies, Systematic review

Background

There are substantial behavioral and biological differences between men and women which affect the manifestation, epidemiology and pathophysiology of diseases and potential therapies ⁶. Sex and gender affect an array of diseases including cardiovascular disease ⁷⁵. Heart failure (HF); one of the most prevalent cardiovascular diseases, is the leading cause of cardiovascular morbidity and mortality in Canada and the world and also differentially impacts men and women in terms of risk and outcomes ^{7, 8}. Biological differences cause women to more frequently experience heart failure with atypical symptoms unlike men which results in underdiagnosis ^{10, 11}.

Cardiac Resynchronization therapy (CRT), also known as Biventricular Pacing is the latest Cardiac Implantable electronic device (CIED) aimed to reduce symptoms for HF and improve ventricular function heart. This device exists in two types: CRT-pacemaker (CRT-P), which synchronizes the heart beating pattern through improving the pumping action the lower ventricles, and CRT-Defibrillator (CRT-D) which in addition to synchronizing heart rhythm, can detect and treat sudden cardiac death (SCD) ⁵. International cardiovascular guidelines have declared CRT devices as the highest recommendation (class 1 indication) for patients with left ventricular ejection fraction (LVEF) $\leq 35\%$; New York Heart Association (NYHA) heart failure classification 2,3 or 4 symptoms (scale corresponding to patient's inability to conduct physical activity); left bundle block (LBBB) with a QRS duration ≥ 150 ms; and sinus rhythm ⁷⁶.

Sex differences are apparent in heart failure pathophysiology and etiology; however, the mechanisms remain not well understood ⁴⁷. An in-depth review of observational studies and trials assessing sex differences in heart failure therapies ⁷⁷ reports controversial findings of underutilization of CRT devices in women compared to men ³⁹⁻⁴⁴ even though there is greater clinical benefit in women and diverse findings for adverse events ^{42, 60, 61}. Evidence from an Individual participant data (IPD) network meta-analysis (MA) of 3 trials ^{65, 78, 79} (n=4076) suggests that women with LBBB and QRS of 150 milliseconds or longer benefited from CRT-D more than men, with 76% reduction in heart failure ⁵⁵. However, underrepresentation of women (only 20% of the total population) and variety in follow up times (1.1, 2.2 and 4.7 years across 3 trials) proposes cautious interpretation of the results.

A systematic review of randomized and non-randomized (NRS) CRT studies (n=183) suggests that women with CRT devices tend to have better LVEF reduction <15% compared to men ⁶⁹. However, this review was conducted in 2015 and is of low quality as per AMSTAR 2 tool⁸⁰; with single database search (PubMed) in combination with study restriction via text search and absence of risk of bias (RoB) assessment, inappropriate pooling of studies for MA among other issues ⁸¹.

Most of the previous SRs and MAs have focused on RCTs. However, to better interpret the effectiveness and safety of CRT devices across sex in the usual clinical setting, we will restrict to cohort studies as the results tend to be more generalizable²⁶, implantation rates will reflect real world setting, overcome the issue of female underrepresentation in clinical trials ⁸² and spurious findings from post hoc subgroup analyses ⁸³.

The objectives of this review are to formally assess sex differences in the (1) Implantation rate, (2) clinical effectiveness and (3) safety for patients receiving CRT devices.

Methods

This protocol was developed a priori to conducting the study. Any deviations will be reported in all related publications and the PROSPERO record (CRD42020204804) will be adapted accordingly. This systematic review protocol was developed using guidance from the Cochrane handbook for Systematic review of interventions ⁸⁴ and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) ⁸⁵.

Eligibility criteria

Participants

This review will target patients ≥ 18 years eligible for de novo implantation of CRT conforming with international guidelines ⁷⁶. Studies in which the population underwent device replacement will not be included however we will consider patients that received upgrade from ICD to CRT-D.

Interventions

The intervention of the included studies will be the CRT device in addition to follow-up from time of implantation of CRT in accordance to guidelines ^{86, 87}. Follow-up methods can be conducted virtually or by in clinic visits.

Outcomes

Studies must report outcomes disaggregated by sex or compare outcomes across sex.

Implantation rate

Implantation rate will correspond to the frequency of device implantations for each sex as a proportion of the total number of implantations.

Effectiveness

The definitions for the effectiveness outcomes are reported in supplement 1 and were selected based on reporting in international clinical guidelines. Clinical efficacy outcomes include: All cause mortality, Hospitalization, Peak oxygen consumption (pVO₂), Quality of life (QoL), 6 min walk test, NYHA class reduction, LVEF, Heart failure hospitalization (Defined in Appendix file 1).

Complications

We plan to assess both clinical and mechanical complications as categorized by Krahn et al. ⁸⁸ where mechanical complications stem from mechanical effects of the surgery, while clinical complications arise from new or worsening comorbidities. All the complications to be assessed will be “major” as they will require intervention to provide therapeutic relief ⁸⁹. Complications were classified short term if they occurred within 2 months of implantation and long term if they emerged thereafter ⁹⁰. We will assess the emergence of the following device complications (Defined in Appendix file 2): Contrast-induced nephropathy, Pneumothorax, Pocket-related Hematoma, Pericardial tamponade, Phrenic nerve stimulation, Device Infection, Death, Pulmonary edema, Electrical storm, cardiogenic shock, Hypotension requiring resuscitation.

Study designs

We will include in our review cohort studies (prospective, retrospective). We will exclude Randomized studies, Case reports, case series, review articles, cross-sectional studies, surveys, qualitative or interview/focus group studies, editorials, letters, and commentaries.

Setting

No restrictions will be imposed on the type of setting.

Language

No language restriction will be applied.

Information sources

The search was conducted from the date January 1, 2000 to June 12, 2020 of the following databases: MEDLINE, EMBASE and Web of Sciences. To ensure a thorough search, we will review the reference list of relevant systematic reviews for eligible studies.

Search Strategy

With the assistance of an information specialist, we developed a comprehensive search strategy. The search strategy includes a combination of Medical Subject Headings (MeSH) and indexed terms and database-specific terms. Detailed description of the search strategies can be found in Appendix file 3.

Keywords used to develop this search are variations of the following terms: “Cardiac Implantable Electronic Device” or “Cardiac Resynchronization Therapy” or “Defibrillators” or “Implantable cardioverter defibrillator” or “heart failure” or “Cardiac failure” or “Biventricular Pacemaker”. Due to the large number of studies retrieved (> 20,000), we will use the most up-to-date cohort study search filter developed by the InterTASC Information Specialists’ Sub-Group (ISSG)⁹¹ to obtain observational studies. We also added variants of the terms: “Registry”, “Prospective” and “Retrospective” for a more comprehensive search. To further narrow our search we will use a validated heart failure search filter that retrieving studies focused on device therapy in heart failure context⁹².

Study selection and screening process

Study selection will be conducted in a blinded fashion, by two independent reviews using Covidence program ⁹³. Screening at title and abstract stage and full text stages will be completed in duplicate. Discrepancies will be resolved by discussion between reviewers followed by consensus, or a third reviewer. We will prepare a PRISMA study flow chart. Studies that assess sex differences in outcomes for patients receiving CRT devices will be selected in duplicate, independently. We plan on capturing all outcomes reported in the studies that relate to the clinical effectiveness of the device, implantation rate across sex and as well as adverse events related to complications post implantation. ICD studies with > 50% CRT-D will be considered eligible and extracted. Studies with >75% primary prevention will be extracted, and other studies will be listed with reason for exclusion (e.g. secondary prevention).

Data Collection

Data extraction will be conducted by two independent reviewers using a pretested extraction form. Conflicts will be resolved by consensus between the two reviewers or by a third reviewer. The extraction form will be developed in collaboration with a content expert based on the Data Extraction Template for Cochrane Reviews ⁹⁴. The form will be pilot tested with a random sample of 5 studies, and further developed accordingly. The extraction process will be facilitated using Microsoft Excel forms customized with extraction criteria.

Data items

The extraction form will be developed in collaboration with a content expert, and pilot tested with a random sample of 5 studies, and further developed accordingly.

Reviewers will extract data on study characteristics (name of author, publication date, journal, funding and conflict of interest), study methodology (objectives, target population, recruitment and sampling procedures, setting) participant information (baseline characteristics, device type, disease severity classification, sample size) and outcomes (definitions, time of measurement and results) (Appendix 1).

Risk of bias and quality of assessment of individual studies

We will be assessing non-randomized studies; therefore, we will be using the Newcastle-Ottawa Scale (NOS) tool to assess risk of bias ⁹⁵. Scale Items assess selection of cases and controls,

comparability of cases and controls and outcome follow up. Judgments will be made by two independent reviewers and disagreements will be resolved through discussion.

Synthesis of results

We will meta-analyze quantitative data when appropriate. We will use I^2 statistic to assess heterogeneity. An I^2 value greater than 75% would indicate high heterogeneity. An I^2 between 50 and 75 percent indicates moderate heterogeneity and calls for investigation via post hoc subgroup analysis ⁹⁶. We will conduct meta-analysis using random effects methodology using Revman ⁹⁷. When meta-analysis is inappropriate due to comparative diversity, results will be narratively reported while providing effect sizes and confidence intervals. Individual and pooled analyses will be presented using tables and forest plots respectively.

Interventions that involve implantation of CRT-P and CRT-D will be treated separately. All the extracted outcomes will be analyzed separately. Categorical outcomes will be assessed using risk ratios (95% Confidence intervals (C.I)) and continuous outcomes will be analyzed using mean differences (95% C.I) ⁹⁸.

An Intention to treat analysis method will be adopted. We will record how authors dealt with missing data and sensitivity analysis will be used to investigate the effect of missing data on the overall results. Adjusted results reported in the included studies as effect measures will be used in the analyses accordingly.

Subgroup analysis

Where feasible and appropriate, we will conduct exploratory subgroups to investigate the impact of factors on outcomes. We plan on conducting a priori subgroup analysis for the following criteria:

- Age (<65, ≥ 65)
- Type of device (CRT-D, CRT-P)
- Disease severity (NYHA class I-II, NYHA class III-IV)
- QRS morphology (LBBB, non-LBBB)
- Heart Failure etiology (Ischemic, Non-ischemic)

Sensitivity analysis

Sensitivity analysis may be considered with respect to composition of the participants or definitions of outcomes to assess the robustness of the performed meta-analysis. We will inspect publication bias using funnel plots in the case of 10 or more studies are included in our review ⁹⁹. We will display the meta-analyzed results using forest plots.

Strength of evidence assessment

We will use the GRADE framework to rate the certainty of the evidence of intervention effects ¹⁰⁰. GRADE assessment will be conducted in duplicate by two reviewers, independently. Discrepancies will be resolved by discussion or a third reviewer. Summarized results will be presented as summary of findings tables ¹⁰⁰.

Discussion

The aim of this review is to determine the presence of differences in CRT implantation between women and men as well as differences in efficacy, safety of CRT post device implantation. We anticipate our systematic review will provide important insights into sex differences in CRT devices that could eventually lead to develop sex-specific recommendations and inform policy.

A potential limitation to this review is the inability to retrieve disaggregated data for some of the included studies that do not report data in the manuscript. We will not attempt to contact authors for sex-specific data as we predict a high yield of eligible studies and anticipate little reward with contacting as it is a time-consuming process. However, our pilot search has identified several studies with disaggregated data so this will not impede the ability to conduct quantitative meta-analysis. We also acknowledge that implementing our search filters restricting by study design and heart failure topic may result in missing eligible studies, but we plan on hand searching eligible systematic reviews to ensure a complete search.

We acknowledge that acquiring measures of effect from NRS is not always reliable due to confounding and other biases. However, several reviews have indicated that the results of NRS correspond generally with the results from trials when properly designed with appropriate accounting for covariates ¹⁰¹⁻¹⁰⁵; providing accurate estimates of effects in real-world practice

setting. In addition, Ethical issues arise with conducting RCTs primarily aimed at assessing therapies that are already implemented in health policy due to equipoise. In general, RCTs for surgical treatments are of poor methodological quality due to difficulties in randomization, incapability of blinding and small sample sizes ^{106, 107}. Therefore, treatment information is primarily obtained from NRS evidence ^{23, 24}. This paradigm remains valid for cardiac surgery studies as there is a significant reduction in the number of RCTs over the years ²⁵.

Furthermore, the absence of participant restrictions in observational studies makes them well suited to study effects on health inequities which are differences in health that are avoidable and unfair ¹⁰⁸. Patient-physician gender, patient preference and gender bias impact the choice and efficacy of cardiovascular interventions ¹⁰⁹⁻¹¹¹. The use of RCTs to investigate this question will be inadequate since researchers manipulate the enrolment of participants.”

We are aware that observational studies cannot replace RCTs as they provide high internal validity and comparability, but RCTs cannot be axiomatic. Results from both study designs can complement each other to fill gaps in clinical knowledge and contribute to decision making.

List of abbreviations

HF: Heart Failure

CRT: Cardiac Resynchronization Therapy

CIED: Cardiac Implantable electronic device

CRT-P: Cardiac Resynchronization Therapy - Pacemaker

CRT-D: Cardiac Resynchronization Therapy - Defibrillator

LVEF: Left Ventricular Ejection Fraction

LBBB: Left Bundle Block Branch

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

QoL: Quality of Life

Declarations

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Author Contribution

OD is the guarantor and prepared the manuscript. All other authors contributed to the development of the eligibility and data extraction criteria. OD developed the search criteria. All authors have read and approved the final manuscript. VW and GW are senior co-authors.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Appendix Table 1: Definitions of Efficacy outcomes

Efficacy outcomes	Definitions
6-minute walk test	Treadmill walking test to test exercise capacity in patients with chronic heart failure ¹¹² .
NYHA class reduction	Estimation of NYHA functional class ¹¹³ within six months after randomization ¹¹⁴ .
LVEF improvement	Measured using 2-dimensional Doppler-flow echocardiography ¹¹⁵ or used LV volume reduction.
Peak oxygen consumption (pVO ₂)	Measurement of peak oxygen consumption per unit time at anaerobic threshold. The improvement will be assessed from baseline to 6 months ¹¹⁶ .
Hospitalization	NA
All cause mortality	NA
Quality of life	Questionnaire developed to assess patients perception on the impact of heart failure on their daily lifestyle ¹¹⁷ .
Heart Failure hospitalization	Includes patients that were admitted to any health facility for the treatment of heart failure symptoms for more than 24 hours ¹¹⁸ .
Composite Response Endpoint	Worsened: Patient death; worsening of heart failure resulting in hospitalization; therapeutic response is considered insufficient; worsening in NYHA class relative to previous observation or moderate-marked worsening of patient global assessment score at LOCF (Last observation Carried Forward).

	<p>Improved: Patient has not worsened (as previously described) and shows improvement in NYHA class at LOCF and/or moderate-marked improvement in patient global assessment score at LOCF.</p> <p>Unchanged: No indications of worsened nor improved health of patients. ¹¹⁴</p>
<p>All-cause mortality composite outcomes</p>	<p>All-cause mortality in combination with any other outcomes</p>

Appendix Table 2: Definitions of Safety outcomes

Short term or long term	Complications	Definition
Mechanical		
Long term	Lead-related complications (i.e. Dislodgement, Lead malposition)	Presence of lead malfunction requiring reoperation ¹¹⁹ . Presence of lead malfunction requiring reoperation ¹¹⁹ .
Short term or long term	Device Infection	Hospitalization for proven CIED infection within 1 year of implantation. Infection is categorized into pocket infection, bloodstream infection, and endocarditis ¹²⁰ .
Short term	Contrast-Induced nephropath	Contrast nephropathy was defined as an increase in serum creatinine of 25% or greater within 48 h after contrast administration. Contrast nephropathy was defined as an increase in serum creatinine of 25% or greater within 48 h after contrast administration. Contrast nephropathy was defined as an increase in serum creatinine of 25% or greater within 48 h after contrast administration. Contrast nephropathy was defined as an increase in serum creatinine of 25% or greater within 48 h after contrast administration which would lead to dialysis ¹²¹ .
Short term	Pneumothorax (Related to venous access)	Complications while obtaining venous access during the index hospitalization Including the absence of lung markings over the lung field ipsilateral to the PM pocket assessed from the pre-discharge X-ray ¹²² .

Short term	Pocket-related Hematoma	Hematoma requiring further surgery, resulting in prolongation of hospitalization, or requiring interruption of oral anticoagulation therapy. Prolongation of hospitalization was defined as extended hospitalization or rehospitalization for at least 24 hours after the index surgical procedure, primarily due to the hematoma ¹²³ .
Short term	Pericardial tamponade	Slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots, or gas, as a result of effusion, trauma, or rupture of the heart ¹²⁴ .
Short term	Phrenic nerve stimulation requiring re-operation	PS tested during follow up of patients starting from maximum pacing system analyzer output, 10 V at 1.5 ms followed by a stepping down protocol. In the event of PS occurrence, its threshold is measured in all the possible pacing configurations and compared with LV pacing threshold to ensure the feasibility of biventricular stimulation. PS disappearance was defined as absence of muscular stimulation over a 20-minute observation period during respiratory changes (deep breath); LV threshold was defined as 100% stimulation during the same respiratory changes and requires reoperation ¹²⁵ .
Clinical		
Short term	Death	Clinical death was considered to be when spontaneous respirations ceased, and pulse and blood pressure disappeared. ¹²⁶ Cause of death of patients before their first outpatient visit must be established by reviewing patient charts to identify relation to procedure ¹²⁷
Short term	Electrical storm	Electric storm in patients with CRT-D is defined as ≥ 3 adequate detections of VT and/or VF in 24 h terminated with ATP or high voltage therapy (HVT), or untreated sustained VT recorded in the monitoring zone over 1 week after the implantation ¹²⁸⁻¹³¹
Short term	Pulmonary edema	NA

Short term	Cardiogenic shock	Defined as hypotension (SBP ,90 mmHg) despite adequate filling status with signs of hypoperfusion ¹³² .
short term	Hypotension requiring resuscitation	NA

Appendix Table 3: Detailed search strategy

Medline:

1. CIED or (Cardiac adj2 implant* adj2 electronic* adj2 device?).ti,ab.
2. defibrillators, implantable/ or exp pacemaker, artificial/
3. ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.
4. ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*)).ti,ab.
5. (cardioconver* or (cardio adj conver*)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp cohort studies/
8. cohort\$.tw.
9. controlled clinical trial.pt.
10. epidemiologic methods/
11. limit 10 to yr=1971-1988
12. or/7-9,11
13. (registr* or Prospective* or Retrospective*).mp.
14. 12 or 13
15. heart failure.mp.
16. ventricular dysfunction, left.sh.
17. cardiomyopathy.mp.
18. left ventricular ejection fraction.mp.
19. or/13-16
20. 6 and 14 and 19
21. limit 20 to yr="2000 -Current"

Embase:

1. CIED or (Cardiac adj2 implant* adj2 electronic* adj2 device?).ti,ab.
2. cardiac implantable electronic device/ or exp cardiac resynchronization therapy device/
3. exp biventricular implantable cardioverter defibrillator/ or exp cardiac resynchronization therapy defibrillator/ or exp dual chamber implantable cardioverter defibrillator/
4. exp defibrillator pacemaker/

5. ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.
6. ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*)).ti,ab.
7. (cardioconver* or (cardio adj conver*)).ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp cohort analysis/
10. exp longitudinal study/
11. exp prospective study/
12. exp follow up/
13. cohort\$.tw.
14. or/9-13
15. (registr* or Prospective* or Retrospective*).mp.
16. 14 or 15
17. heart failure.mp.
18. ventricular dysfunction, left.sh.
19. cardiomyopathy.mp.
20. left ventricular ejection fraction.mp.
21. or/15-18
22. 8 and 16 and 21
23. limit 22 to yr="2000 -Current"
24. (conference abstract or conference review).pt.
25. 23 not 24

Web of Science

1. TS=(CIED or (Cardiac NEAR/2 implant* NEAR/2 electronic* NEAR/2 device*))
2. TS=((biventricular NEAR/2 pacemaker*) or pace-maker*)
3. TS=((resynch* or re-synch*) NEAR/3 (cardiac or therap* or treatment* or device*))
4. TS=(cardioconver* or (cardio adj conver*))
5. 1 or 2 or 3 or 4
6. TS="heart failure"
7. TS=(left ventric* NEAR/2 "dysfunction")
8. TS=(left ventric* NEAR/2 "ejection fraction")

9. 6 or 7 or 8 or 9
10. 10 and 5
11. TS=Cohort
12. TS=longitudinal*
13. TS=prospective*
14. TS="follow up"
15. TS = registr*
16. TS = Retrospective*
17. 11 or 12 or 13 or 14 or 15 or 16
18. 18 and 11

Chapter 4: Sex and Gender reporting and analysis in Studies of Cardiac Resynchronization Therapy: A Systematic Review

Chapter Overview

Chapter 4 addresses Objective 1: Appraise sex and gender reporting and analysis in CRT cohort studies based on articles systematically identified using the protocol detailed in Chapter 3. Prior to this thesis, there was no published methodological assessment of sex and gender considerations in CRT studies or cohort studies. Our review, informed by internationally accepted guidance, provides us with insights on the extent of sex and gender integration in the study design and analysis of CRT studies while identifying where methodological improvements are needed to improve the understanding of sex and gender differences in CRT.

Manuscript Status

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Author Contributions

Omar Dewidar was responsible for the conception of study protocol, conduct of the methodological assessment of all the studies and preparation of the manuscript. The coauthors involved in conducting duplicate screening and extraction were coordinated by Omar Dewidar. Irina Podinic, Victoria Barbeau, Dilan Patel and Alba Antequera was involved in the study selection process and conduct of the methodological assessment. George Wells, Vivian Welch and David Birnie were involved in stages of the protocol inception, conduct of the review and revision of the manuscript.

Integrating Sex and Gender in Studies of Cardiac Resynchronization Therapy: A Systematic Review

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Word count: 3314

Abstract

Aims: To examine the prevalence, temporal changes, and impact of the National Institute of Health (NIH) Sex as a Biological Variable (SABV) policy on sex and gender reporting and analysis in Cardiac Resynchronization Therapy (CRT) cohort studies.

Methods and results: We searched Medline, EMBASE and Web of Science for Cohort studies reporting the effectiveness and safety of CRT in heart failure (HF) patients from January 2000 to June 2020, with no language restrictions. Segmented regression analysis was used for policy analysis. We included 253 studies. Fourteen percent considered sex in the study design. Outcome data disaggregated by sex was only reported in 17% of the studies. Of the studies with statistical models (n=173), 57% adjusted for sex. Sixty-eight percent of those reported an effect size for sex on the outcome. Sex-stratified analyses were conducted in 13% of the studies. Temporal analysis shows an increase in sex reporting in background, statistical models, study design and discussion. Besides statistical models, NIH SABV policy analysis showed no significant change in the reporting of sex in study sections. Gender was not reported or analysed in any study.

Conclusion: There is a need to improve the study design, analysis, and completeness of reporting of sex in CRT cohort studies. Inadequate sex integration in study design and analysis may potentially hinder progress in understanding sex disparities in CRT. Deficiencies in the integration of sex in studies could be overcome by implementing guidance that already exists.

Nonstandard Abbreviations and Acronyms:

CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy-Defibrillator
CRT-P	Cardiac Resynchronization Therapy-Pacemaker
LBBB	Left Bundle Branch Block
NIH	National Institute of Health
PAHO	Pan-America Health Organization
WHO	World Health Organization

SAGER	Sex and Gender Equity in Research
ICD	Implantable Cardioverter-Defibrillator
CIHR	Canadian Institute of Health Research
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
CAD	Coronary artery disease
CVD	Cardiovascular disorder

Introduction

There is important evidence for sex differences in the effectiveness and safety of Cardiac Resynchronisation Therapy (CRT)¹. The reasons remain unclear due to the underrepresentation of women in trials², but they are likely to be multi-faceted. Evidence shows that they may be due to differences in physiology, disease presentation, and gender-related behaviours^{1, 3}. These uncertainties could be elucidated by improved reporting and integration of sex and gender in studies.

Sex and gender have been poorly analysed for many years, in all fields of medical research, with few studies reporting outcomes disaggregated by sex and gender^{4, 5}. To encourage sex integration in research, the National Institutes of Health (NIH) released a funding policy in 2015, Sex as a Biological Variable (SABV), calling onto scientists to consider sex in the reporting, study design and analysis in human and animal studies⁶. Other global efforts are also in place to promote sex and gender in research^{7, 8}. In addition, the principles of sex inclusion and analysis have been prominently endorsed by cardiovascular academic societies and leading journals^{9, 10}. In this study, we define sex as biological attributes that differentiate males from females and gender as social constructs, identities and roles set by the society¹¹.

For post market approval of CRT, cohort studies are commonly used to evaluate long-term clinical outcomes, such as mortality, understanding prognostic factors and determinants, assessing practice variations and providing insight into real-world health effects, especially in populations that are under-represented in RCTs, such as women, minorities and older patients¹². Sex and gender integration in those studies could help understand the observed sex differences in response. However, there is limited information on the extent of sex and gender integration in CRT cohort studies. Thus, we assessed all the CRT cohort studies that reported clinical or safety outcomes among heart failure patients treated with CRT over the past two decades to determine the prevalence and temporal trends of sex and gender reporting and analysis.

Methods

Study protocol

This methodological study was conducted as part of a systematic review of sex differences in the clinical and safety outcomes of CRT as assessed in cohort studies (PROSPERO ID: CRD42020204804).

Searching

We developed a search strategy in collaboration with a librarian scientist for cohort studies reporting clinical and safety outcomes for CRT using combinations of both text-words and MeSH headings to capture HF¹³, cardiac devices and cohort studies (Supplementary methods 1). We validated the search strategy by searching a set of 10 studies identified in the preliminary search. MEDLINE, EMBASE and Web of Science were searched from January 2000 to June 2020 with no language restrictions.

Eligibility criteria

We included cohort studies with (comparative cohorts) or without control groups (single cohorts) that reported clinical or safety outcomes among patients with heart failure for CRT with no restrictions on publication language or outcomes. Non-English language studies were translated using google translate. Studies evaluating the efficacy of implantable cardioverter-defibrillator (ICD)s and pacemakers were not eligible. Reviews, randomized trials, cross-sectional studies, case-control studies, conference papers, editorials and letters were also excluded. Studies that were limited to single sex were also excluded from our assessment. Studies were not considered as CRT studies if they reported outcomes in patients with multiple devices, but less than 50% of the study population received CRT, and data was not disaggregated by sex as a guarantee that most of the patients assessed received CRT. We included studies that assessed participants receiving a device upgrade from ICD to CRT-D, but other device upgrades were excluded. Studies developing clinical prediction rules as their approach to analysing sex is different from studies that report clinical and safety outcomes of CRT. Such studies tend to focus on the performance of the model, rather than the effects of individual predictors. Studies that were limited to single sex were also excluded from our assessment.

Screening and data extraction form

All the articles were independently screened for inclusion and information extracted by two review authors, and discrepancies were resolved by consensus. We extracted the following study characteristics from each study: publication year, journal classification (quartile ranking based on impact factor as per Scientific Journal Rankings (SJR) where Q1 occupies the top 25% of the journals and Q4 occupies 75 to 100%¹⁴), sample size, geographic region, type of CRT, availability of control group and use of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline¹⁵.

Table 1 details the definitions of sex and gender considerations in the study sections; informed by the SAGER guidelines, guidance provided by the Cochrane and Campbell Sex and Gender Methods Group and a CIHR grant-approved project for developing health equity extension for the STROBE reporting guidelines¹⁶⁻¹⁸. We defined the reporting or analysis of gender as the reporting or analysis of how differences between men and women and gender-diverse individuals as it relates to gender constructs, identities and roles¹⁹.

Statistical models were classified into either prediction models or association models because we hypothesized that prediction models would more likely report the covariates included in the model compared with association models. Prediction models were defined as models that aimed to identify predictors that contributed to the prediction of the outcome²⁰, while models aimed to determine the aetiology of disease were categorized as association models²¹.

Statistical analysis

We present the study characteristics and prevalence of sex and gender considerations in the studies as proportions. Temporal patterns were evaluated using the Cochrane-Armitage trend test via the DescTools package²². We used segmented regression to assess whether there was a change in the reporting and analysis of sex after 2015; the date when the NIH SABV policy on sex as a biologic consideration was published. The NIH SABV date was used as a marker of possible change in considering sex and gender, since the policy from this influential funding organization and world leader in biomedical research received a great amount of attention and support in the scientific community on the importance of analysis by sex^{23, 24}. NIH is also a very influential funding organization and a world leader in biomedical research. A detailed explanation of the

segmented regression model is in Supplementary Methods 3. All analyses were performed using R software and statistical significance was determined using a 2-tail significance level of 0.05.

Results

Study selection and characteristics

Of 7518 identified studies, we included 253 studies that met our eligibility criteria (Supplementary Figure 1). Table 2 summarizes the characteristics of the included studies. Most CRT studies were conducted in Europe (57%), of prospective study design (52%) and included participants receiving a variety of cardiac devices (83%) (i.e., devices other than CRT). The majority were published in Q1 classified Journals (62%) (i.e., Top 25% of all the Journals) but only 2% reported the use of the STROBE guidelines for reporting.

Reporting in study sections

Figure 2a shows that 101 studies (40%) considered sex in the statistical model plan and analysis. In addition, Sex was poorly reported in the background of the studies (14%) and the study design and analysis plan (16%). Less than half (40%) of the studies reported the proportion of both males and females in their study characteristics (Figure 2b). Exploratory analysis shows that in all the study sections, retrospective studies considered sex more than prospective studies (Supplementary Table 1).

Over the past two decades, there has been an increase in the proportion of CRT studies that considered sex in the background ($P = 0.0065$), study design and analysis plan ($P = 0.0014$), statistical models ($P < 0.001$) and the discussion ($P < 0.001$) (Supplementary Figure 2). However, there was no significant change in the trend of reporting in the title/abstract ($P = 0.4244$) or the findings ($P = 0.0784$). Evaluation of the NIH SABV policy's impact on the consideration of sex indicates a significant change in the trend of considerations only in the statistical models (Figure 3).

Study design and analysis plan

Fifteen studies (6%) planned to balance for differences across sex in the study design (Table 3). Two studies attempted to address potential biases across sex. *A priori* planning to stratify results by sex was reported in 21 studies (8%).

Findings and analysis

Only two studies (1%) described sex in the flow of participants: from patient recruitment to study eligibility and inclusion in analysis (Table 3). Information on missing data disaggregated by sex was also reported in only two studies (1%). Five studies (2%) reported the follow time separately for each sex. Twenty-five (10%) studies reported all their outcomes stratified by sex.

Trend analysis shows significant improvements in the adjustment for sex in reporting of outcomes disaggregated by sex. Segmented regression shows that NIH SABV policy had no significant impact on the trend of disaggregating outcome data by sex (Supplementary Figure 4).

Statistical model plan and analysis

Of the included studies, 173 studies (69%) reported using statistical models in their analysis (Table 4). Even though 69% of those adjusted for sex in their analysis, only 37% planned to control for sex *a priori* in their model. Of the studies that adjusted for sex in their statistical models, 60% reported an effect size for sex. Twenty-three studies (13%) analysed males and females separately.

Fifty-four percent of the studies used prediction models in their analysis. Studies employing prediction models and association models differed significantly in terms of their planning to control for sex in their statistical model ($P = 0.003$), reporting of separate models by sex ($P = 0.002$), adjusting of models for sex ($P = 0.024$), and reporting of effect sizes for sex ($P = 0.021$).

Temporal analysis shows that CRT studies are increasingly incorporating sex in their statistical models by adjusting for it ($P < 0.001$) or assessing for interactions ($P < 0.01$) (Supplementary Figure 3). However, NIH SABV policy analysis shows no significant change in the trend of reporting of sex consideration in statistical models (Supplementary Figure 4).

Interpretation of findings

Fifty-nine studies (23%) interpreted their results while accounting for sex (Table 3). Discussion about the generalizability of the study results across sex was reported in 8%, while 6% of the studies discussed the study limitations pertaining to sex.

Analysis and reporting of gender in study sections

We assessed studies for explaining differences in risk due to gender identity, roles, and norms in the background, considering gender domains in study design, analysing the impact of gender on outcomes in the results and discussing the findings in relation to gender identity, roles and roles and norms. However, Gender was not reported or analysed in all the included studies.

Discussion

This systematic review of reporting and analysis of sex and gender in CRT studies reporting clinical and safety outcomes shows that sex reporting in all aspects of studies is improving over time but remains poorly integrated in the study design and analysis. There was no significant change in the trend of sex considerations after the introduction of the NIH SABV policy. In this study, we focused on the reporting and analysis of sex and gender, but this does not diminish the importance of other patient characteristics such as ethnicity and age, which have been previously shown to differentially impact treatment quality and health outcomes^{25, 26}. Such characteristics could be assessed for CRT in future studies.

Considering the known sex differences in aetiology, prognosis, and disease presentation in heart failure, well thought out transparent research on the impact of sex and gender in health is needed to understand sex differences in response to CRT. Systematic reviews of landmark trials have shown that women benefit from CRT more than men²⁷⁻²⁹. The reasons for the differences in response are uncertain, with evidence suggesting that sex may independently predict the response, while other evidence suggesting that sex may act as surrogate for height and QRS duration. The AdaptResponse trial, the largest randomized CRT trial with the largest proportion of women enrolled to date (41%), found that QRS duration was shorter in women regardless of height³⁰. This demonstrates how the underrepresentation of women in cardiovascular trials impedes the understanding of the observed differences.

Cohort studies could be utilized to overcome this underrepresentation as they represent data collected during routine care. The effect estimates from cohort studies may not accurately correspond to estimates from RCTs, but tend to coincide when assessing long term outcomes such as all-cause mortality³¹. Moreover, as guidelines are moving towards producing sex-specific recommendations, cohort studies will be ideal for evaluating the adherence to the guideline recommendations and real-world effectiveness of CRT¹².

Inadequate reporting threatens research reproducibility and diminishes the quality of evidence, and impedes the understanding of sex differences³². As an indicator for utilizing guidance for transparent reporting, we evaluated the proportion of CRT studies that reported the use of STROBE guidelines¹⁵. Even though STROBE is the second most cited reporting guideline, less than 10 CRT studies reported the explicit use of the reporting guideline. This may be due to unclear reporting of guideline use as indicated by Caulley and colleagues³³.

Inadequate integration of sex and gender in the study design may have impeded the efforts in place to understand these differences. The importance of transparent reporting and study design in clinical advances has been demonstrated in both basic science and clinical research to achieve accurate representation of the population³⁴. Methodological approaches to help improve the quality of evidence for sex differences such as sex-specific eligibility criteria and stratified sampling or participant matching – should be considered.

Only 13% of the studies reported independent statistical models for men and women. Depending on a single statistical model to identify sex differences overstates the value of statistical significance and inhibits the application of sex-specific definitions for clinical characteristics^{1, 35}. In addition, two out of 17 studies that conducted subgroup analyses specified that they planned to conduct such analyses. Hence, the credibility of the subgroups is doubtful, as well as the studies' ability to detect an interaction effect²⁴. Furthermore, our findings in CRT studies are comparable to an assessment of sex and gender in anaesthesia studies, indicating that adjustment for sex as a covariate in models is common in research, but reporting findings by sex is lacking³⁶.

We defined gender considerations as the reporting or the analysis of the influence of social constructs, identities and roles set by the society on the findings¹¹. Gender was not considered in any of the included studies. The direct and indirect contribution of gender in CV disease manifestation, diagnosis and treatment has been documented in the literature². For the analysis of gender, there is no standard approach for measuring gender, but validated tools have been developed. The GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond-Premature Acute Coronary Syndrome) is a tool that provides a composite measure of gender identity, constructs and roles³⁷. The application of this tool on young patients with acute coronary syndrome has shown that adverse cardiovascular outcomes are more likely to occur in individuals with personality traits and social roles traditionally ascribed to women³⁸.

Hence, the lack of gender analysis may hinder ability of scientific research to improve lives of men, women, and gender diverse people.

Sex reporting and analysis has improved over time in all the study sections which is consistent with what was found in other studies^{39, 40}. However, we did not detect an effect for the NIH SABV policy, published in June 9, 2015⁶, on the trend of sex reporting in all the study sections, except for statistical models. The lack of effect could be due to the following reasons.

First, the NIH SABV policy exerts minimal influence on the rates of sex and gender reporting and analysis⁴¹. Second, SABV may have not manifested in the cardiovascular literature. Third, we cannot differentiate if the effect is solely due to the NIH SABV policy or a combination of funding policies have preceded and succeeded it such as the CIHR's federal policy to account for sex in research in 2009, the European Association of Science Editors (EASE) gender policy mandate in 2013⁴² and the European Commission funded GENDER-NET Plus in 2017⁴³. In contrast, one could speculate that NIH funded studies would report sex better than non-NIH funded studies. However, a study analysing sex bias in neuroscience studies published in 2017 (n = 1800) found that there little to no evidence that sex bias and omission differed by reported NIH funding status.

Limitations

One inherent weakness of this study is that we only assessed what was reported in the articles. Sex and gender considerations may have been implemented but not reported, which may have led to an underestimation of their prevalence. In addition, the findings of this study may not be generalizable to other types of studies within or outside the cardiovascular field. We also did not use other methods of searching such as manual reference search or citation search to identify studies not captured by our electronic search, therefore there is a chance that some studies were missed. However, our large study sample mitigates this limitation with little possible changes in reporting prevalence and temporal change.

Conclusions

Our investigation of sex reporting and analysis in CRT cohort studies reporting clinical and safety outcomes over the past 20 years demonstrates that sex is suboptimally reported and

inadequately analysed. Improvements in the consideration of sex were observed over time, but the NIH SABV policy only impacted sex considerations in statistical models. In addition, gender considerations were absent from the studies. Funders and Journal editors can drive authors to consider sex and gender in reporting and analysis by developing policies to encourage or enforce reporting and analysis of sex and gender. This will result in improved reporting of sex and gender and scientific transparency, leading to better healthcare for all.

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Data availability

Data is available upon request to the corresponding author.

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Disclosers

Nothing to disclose.

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Figure Legends

Figure 1. Sex in Cardiac Resynchronization Therapy (CRT) cohort studies reporting clinical and safety outcomes. (A) “Title/abstract” includes the descriptive reporting of sex. (B) Presents the percentage of descriptive reporting of participant sex. * $P \leq 0.05$. *** $P \leq 0.001$. **** $P \leq 0.0001$.

Figure 2. Impact of NIH Sex as a Biological Variable (SABV) policy on the reporting of sex in the study sections of Cardiac Resynchronization Therapy (CRT) cohort studies reporting clinical and safety outcomes. Studies published in year 2020 were excluded since we did not capture all the studies published that year. Dotted lines at 2015 represent the release of National Institutes of Health (NIH) policy on including sex as a biological variable in reporting, study design and analysis. Segmented regression analysis was used to assess the impact of the NIH SABV policy on the reporting of sex considerations. ‘Title/abstract’ corresponds to title or abstract.

Table 1. Sex and gender considerations.

Study sections	Sex/Gender considerations
Title/abstract	<ul style="list-style-type: none"> ▪ Were sex/gender term used in the title or abstract?
Objective of research question	<ul style="list-style-type: none"> ▪ Was the assessment of sex/gender differences an objective of the study?
Background	<ul style="list-style-type: none"> ▪ Did the background discuss why sex/gender differences may be expected?
Study design and analysis plan	<ul style="list-style-type: none"> ▪ Did the authors have strategies to balance across sex/gender in the study design? ▪ Did the authors reference sex/gender in the study eligibility criteria? ▪ Were there any efforts to address potential bias across sex/gender? ▪ Did the authors plan to stratify results by sex/gender?
Findings and analysis	<ul style="list-style-type: none"> ▪ Was sex/gender described in flow of participants? ▪ Were reasons for non-participation reported separately for each sex/gender? ▪ Did the authors report the percentage of participants included in the study disaggregated by sex/gender? ▪ Did the authors report missing data of participant disaggregated by sex/gender? ▪ Did the authors report follow up time disaggregated by sex/gender? ▪ Were summary measures of outcome data reported separately for each sex/gender?
Statistical model plan and analysis	<ul style="list-style-type: none"> ▪ If the authors planned to use a statistical model, did they plan to control for sex/gender in analysis? ▪ If a statistical model was used in the analysis, was sex/gender adjusted for in the analysis? ▪ Were statistical models conducted separately by sex/gender?
Discussion	<ul style="list-style-type: none"> ▪ Did the authors discuss limitations pertaining to sex/gender? ▪ Did the authors discuss results pertaining to sex/gender? ▪ Did the authors consider sex/gender when discussing external validity to the general population?

Sex/gender corresponds to sex or gender. Variables were captured for sex and gender separately.

Table 2. Characteristics of included studies

n=253 (%)	
Publication year	
2000-2010	90 (36)
2011-2020	163 (64)
Journal classification	
Q1*	156 (62)
Q2 – Q4*	93 (37)
Not yet assigned	4 (1)
Objective to assess sex differences	
Primary	23 (9)
Secondary	5 (2)
Not reported	28 (89)
Cohort study type	
Comparative	126 (50)
Single	127 (50)
Cohort study design	
Prospective	131 (52)
Retrospective	122 (48)
Continent	
Europe	143 (57)
North America	55 (22)
Asia	38 (15)
South America	8 (3)
Oceania	6 (2)
International	2 (0.8)
Africa	1 (0.4)
Sample size	
<500	170 (67)
≥ 500	83 (33)

Age of participants	
< 65	97 (39)
≥ 65	155 (61)
NR	1 (0.4)
Type of cardiac device	
CRT-D only [†]	27 (11)
CRT-P only [‡]	17 (7)
Combination of devices	209 (83)
Prevention of Sudden Cardiac Arrest (SCA)	
Primary only	53 (21)
Primary and Secondary	53 (21)
Not specified	147 (58)
Report use of STROBE[§] guidelines	6 (2)

* Q: Quartile; Q1 occupies the top 25% of the journals, while Q4 occupies 75 to 100%.

[†] CRT-D: Cardiac Resynchronization Therapy-Defibrillator

[‡] CRT-P: Cardiac Resynchronization Therapy-Pacemaker

[§]STROBE: The Strengthening the Reporting of Observational Studies in Epidemiology

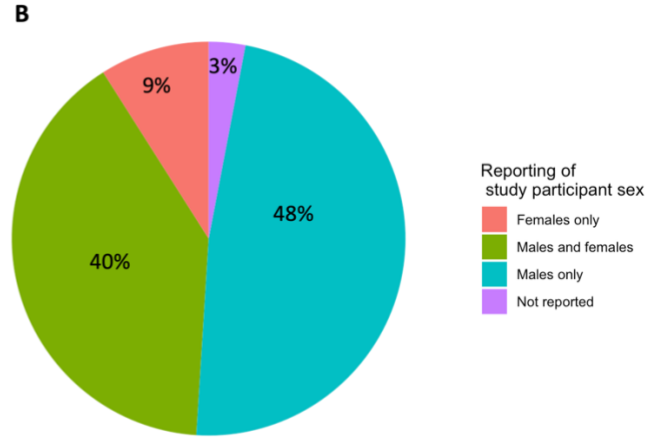
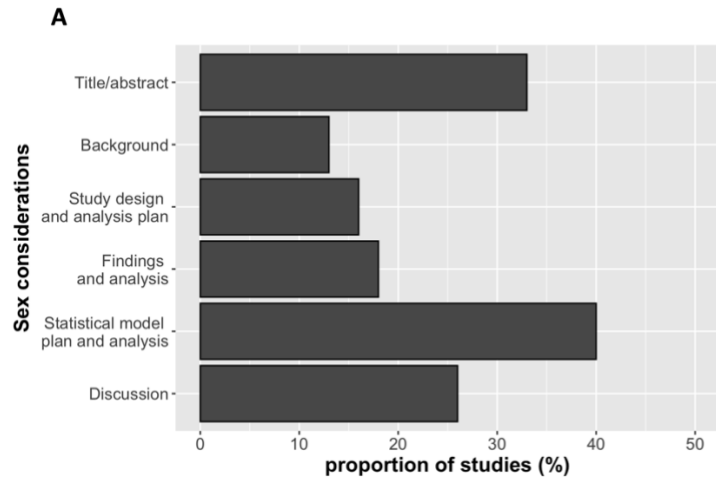
Table 3. Sex in the study sections of Cardiac Resynchronization Therapy (CRT) cohort studies reporting clinical and safety outcomes.

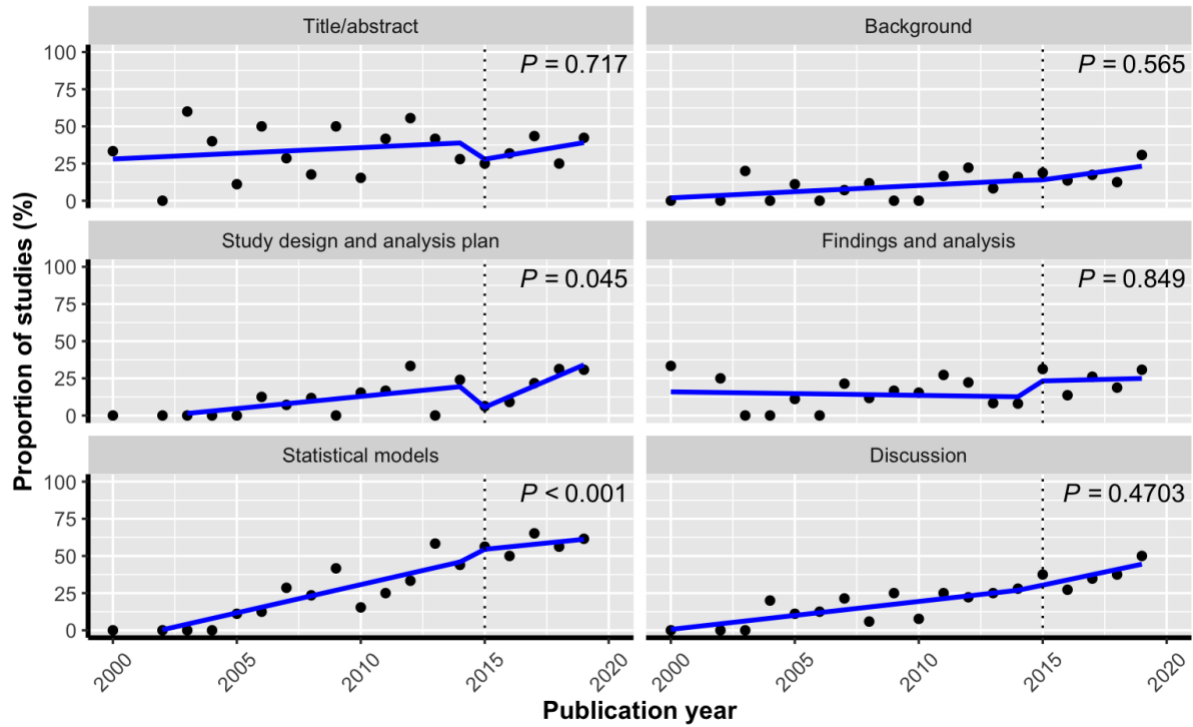
	n=253 (%)
Study design and analysis plan	
Strategies to balance across sex in study design	15 (6)
Eligibility criteria mention sex	5 (2)
Address potential bias across sex	3 (1)
Plan to stratify results by sex	21 (8)
Findings and analysis	
Sex of participants described from the process of examining eligibility to analysis	2 (1)
Reasons for non-participation reported across sex	-
Missing data disaggregated by sex	2 (1)
Follow up time disaggregated by sex	5 (2)
Report at least one outcome disaggregated by sex	17 (7)
Report all outcomes disaggregated by sex	25 (10)
Interpretation of findings	
Limitations of study pertaining to sex	15 (6)
Interpreted results while considering sex	59 (23)
Generalizability across sex	21 (8)

Table 4. Sex in the statistical analysis models of Cardiac Resynchronization Therapy (CRT) cohort studies reporting the clinical and safety outcomes.

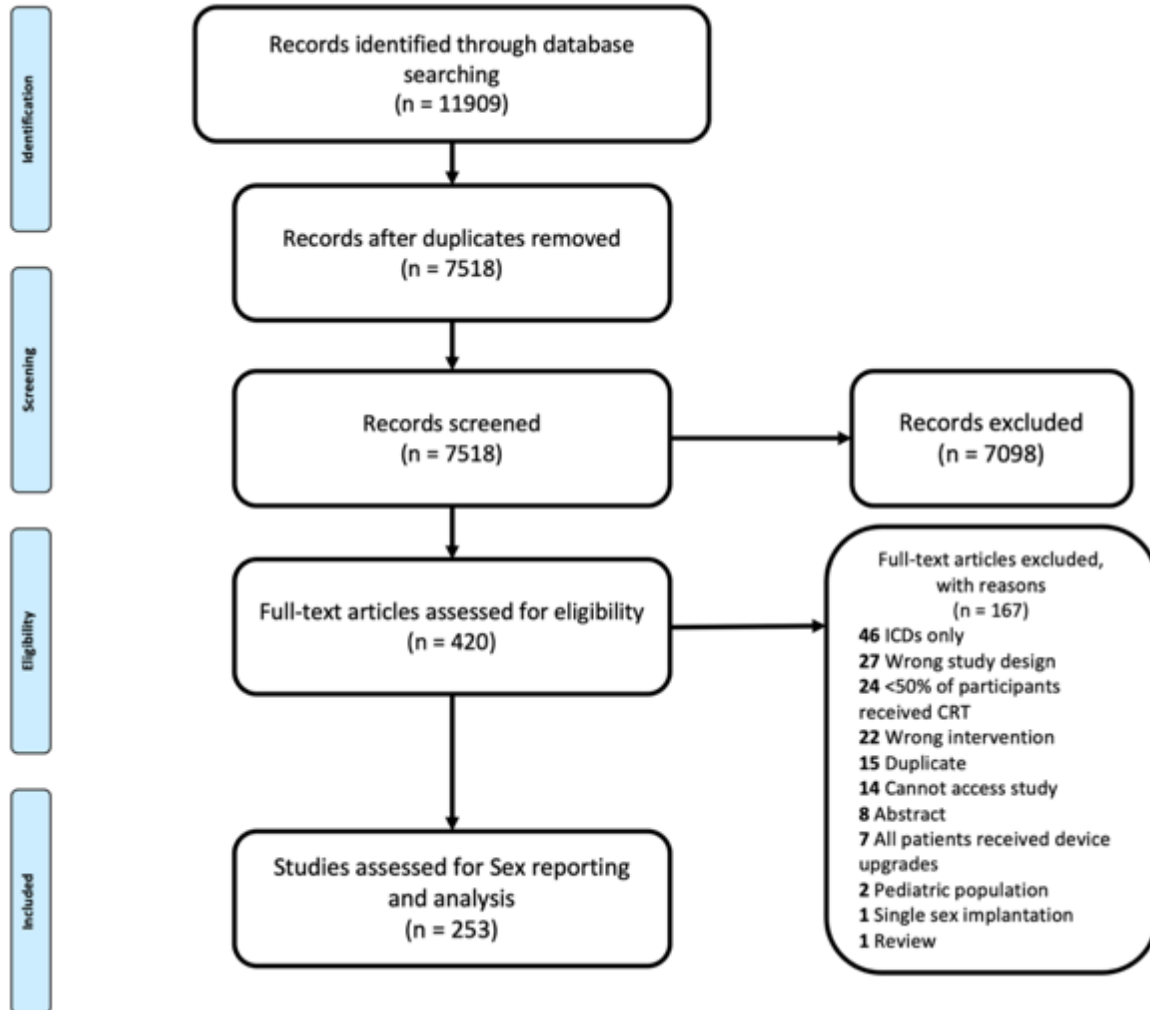
	Prediction model n = 94 (%)	Association model n = 79 (%)	<i>P-value</i>*	All models N = 173 (%)
Planned to control for sex in statistical model	24 (26)	38 (48)	0.003	63 (37)
Report separate models by sex	5 (5)	18 (47)	0.002	23 (13)
Adjusted for sex	46 (49)	53 (67)	0.024	99 (57)
Reported effect size	37 (80)	30 (57)	0.021	67 (68)

Footnote: Proportions calculated from 173 studies that included statistical models in their studies. Proportion of studies that reported an effect size calculated from the number of studies that adjusted for sex. * Fisher’s exact test.





SUPPLEMENTAL MATERIAL



Supplementary Figure 1. PRISMA chart of included studies

Supplementary methods 1: Search Strategy - Medline

1. CIED or (Cardiac adj2 implant* adj2 electronic* adj2 device?).ti,ab.
2. defibrillators, implantable/ or exp pacemaker, artificial/
3. ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.
4. ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*).ti,ab.
5. (cardioconver* or (cardio adj conver*).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp cohort studies/
8. cohort\$.tw.
9. controlled clinical trial.pt.
10. epidemiologic methods/
11. limit 10 to yr=1971-1988
12. or/7-9,11
13. (registr* or Prospective* or Retrospective*).mp.
14. 12 or 13
15. heart failure.mp.
16. ventricular dysfunction, left.sh.
17. cardiomyopathy.mp.
18. left ventricular ejection fraction.mp.
19. or/13-16
20. 6 and 14 and 19
21. limit 20 to yr="2000 -Current

Supplementary Methods 2: Data Dictionary

Extraction item	Description	Example
Is sex/gender/male/female/women/men used in the title or abstract?	The terms are mentioned of in the title/abstract.	“Women with nonischemic cardiomyopathy have a favorable prognosis and a better left ventricular remodeling than men after cardiac resynchronization therapy.” ¹⁵⁵
Does background discuss why sex/gender differences may be expected?	Authors provide any information on the differences in risk/prevalence of the disease.	“Women have also been reported to have a lower frequency of ischaemic aetiology of heart failure and more frequently a typical LBBB configuration of the QRS complex in electrocardiogram (ECG)” ¹⁵⁶
Is assessing sex/gender differences primary or secondary objective of the study?	Confirmed by explicitly stating the priority of assessing sex differences in regard to the objective.	“This large observational multicentre study compared CRT-D versus CRT-P in both men and women using several propensity score (PS) methods and a cause-of-death analysis in order to determine whether the addition of the ICD functionality to CRT devices does indeed offer a more pronounced survival benefit

		in men compared with women.” ¹⁵⁷
Does the study design have strategies to balance across sex/gender?	Authors state that they stratified sampling or matched participants by sex/gender.	“Twenty-two age- and sex matched healthy volunteers were recruited and served as the control group.” ¹⁵⁸
Does the eligibility criteria mention sex/gender/male/female?	Sex/gender mentioned in the eligibility criteria of the study population	“We excluded patients discharged with comfort care or not to home and patients with missing documentation of LVEF, CRT status on admission, race, or sex.” ⁴⁰
Are there any efforts to address potential bias across sex/gender?	Authors discussed any efforts to overcome misdiagnosis in women or men.	Table 1 159
Did they plan to stratify results by sex/gender?	Authors stated they would investigate the effect of sex on outcomes by stratifying results (raw number of events).	“We prespecified clinically important subgroups—including age, sex, race, and type of intraventricular conduction delay—combined with QRS duration, New York Heart Association class, and the presence or absence of atrial fibrillation and renal dysfunction” ¹⁶⁰
Did the authors plan to control for sex/gender in analysis?	Authors adjusted for sex/gender as a covariate in the in statistical model.	
Is sex/gender described in flow of participants?	Reported number of participants examined for eligibility, confirmed eligible, included in the study, completing	“From January 2003 to January 2005, 334 CRT devices were implanted (in

	follow-up, and analysed disaggregated by sex/gender.	66 women, 19.7%; and 268 men, 82.3%). A CRT pacemaker alone was implanted in 178 patients (53.3%) (42 women, 23.6%, 136 men, 76.4%). A CRT-ICD device was implanted in the remaining 156 patients (46.7%) (24 women, 15.3%, 132 men, 84.7%; P < 0.01 vs BIV). The criteria of the MADIT II type population ¹⁸ were fulfilled by 23.1% of women and 34.4% of men (P < 0.05). Out of 334 CRT patients, 195 (46 women, 23.6%, 149 men, 76.4%, P = NS vs implanted population) underwent complete clinical and echocardiographic assessment at baseline, at six and at 12 months follow-up” ¹⁶¹
Are reasons for non-participation described across sex/gender?	Reported reasons for non-participation at each stage disaggregated by sex/gender.	-
Does the study report participant % disaggregated by sex/gender?	Give characteristics of study participants disaggregated by sex/gender.	Table 1 ¹⁶²
Does the study report missing-data of participant disaggregated by sex/gender?	Indicated the number of participants with missing data for each variable of interest disaggregated by sex/gender.	Table 1 ¹⁶³

Does the study report follow up time disaggregated by sex/gender?	Summarised follow-up time (e.g., average and total amount) disaggregated by Sex/gender.	Table 1 162
Were results reported by sex/gender?	Report numbers of outcome events or summary measures over time disaggregated by sex/gender e.g., number of deaths reported	Table 3 163
Was Sex/gender controlled for in the analysis?	Authors adjusted for sex/gender as a covariate in the in statistical model. We captured if the effect size or the interaction p value was reported.	Table 3 163
Were statistical models conducted separately by sex/gender?	Report separate prediction/association models for males and females.	Table 3 163
Did the study discuss limitations pertaining to sex/gender?	Discuss limitations of the study, taking into account sources of potential bias or imprecision, including the direction and magnitude of any potential bias disaggregated by sex/gender.	“There was no core laboratory for LVEF measurements. Underlying differences may have existed between men and women despite stringent selection criteria for LBBB-associated idiopathic cardiomyopathy in the NEOLITH II study (Wang, Li, et al., 2018).” ¹⁶⁴
Did the study discuss results pertaining to sex/gender?	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence while considering sex/gender.	“Just to emphasis again, the beneficial effect of CRT has been consistently proved in several randomized trials, like Miracle3 (improves functional capacity and LVEF), REVERSE4

		<p>(improves LV remodeling), Care-HF5 (the first CRT trial to show survival benefit), and trials in combination with ICD like Companion6 , MADIT-CRT7 , RAFT8 (all showed survival benefit). Despite the evidence base and guidelines, CRT has been underutilized in eligible patients, with significant variation in age, gender, QRS duration, care provider, insurance status, and geographic location of practices”¹⁶⁵</p>
<p>Did the studies discuss external validity to populations or context in discussion of generalizability across Sex/gender?</p>	<p>Considering issues of possible self-selection, healthy volunteer bias, losses, generalisability (external validity) of studies across Sex/gender.</p>	<p>“In the group of 80 years patients, we observed a higher proportion of females and a higher NYHA class that reveals, as previously reported, a worse functional status in the elderly. However, mean LV diameters appeared lower in this group, probably due to the higher proportion of females.” ¹⁶⁶</p>

Supplementary Methods 3: Explanation of segmented regression Model

Segmented regression analysis equation:

$$Y = b_0 + b_1 \times Time + b_2 \times Policy + b_3 \times TimeSincePolicy + e$$

Column	Variable name	Description
Y	Sex consideration	Proportion of studies that meet the criterion (from 0 to 100)
T	Time	Time from the year 2000-2019
D	Policy	Observation pre (=0) and post (=1) NIH 2015Policy
P	Time Since Policy	Time passed since the Policy release

Beta coefficients from analysis of “Title/Summary” data:

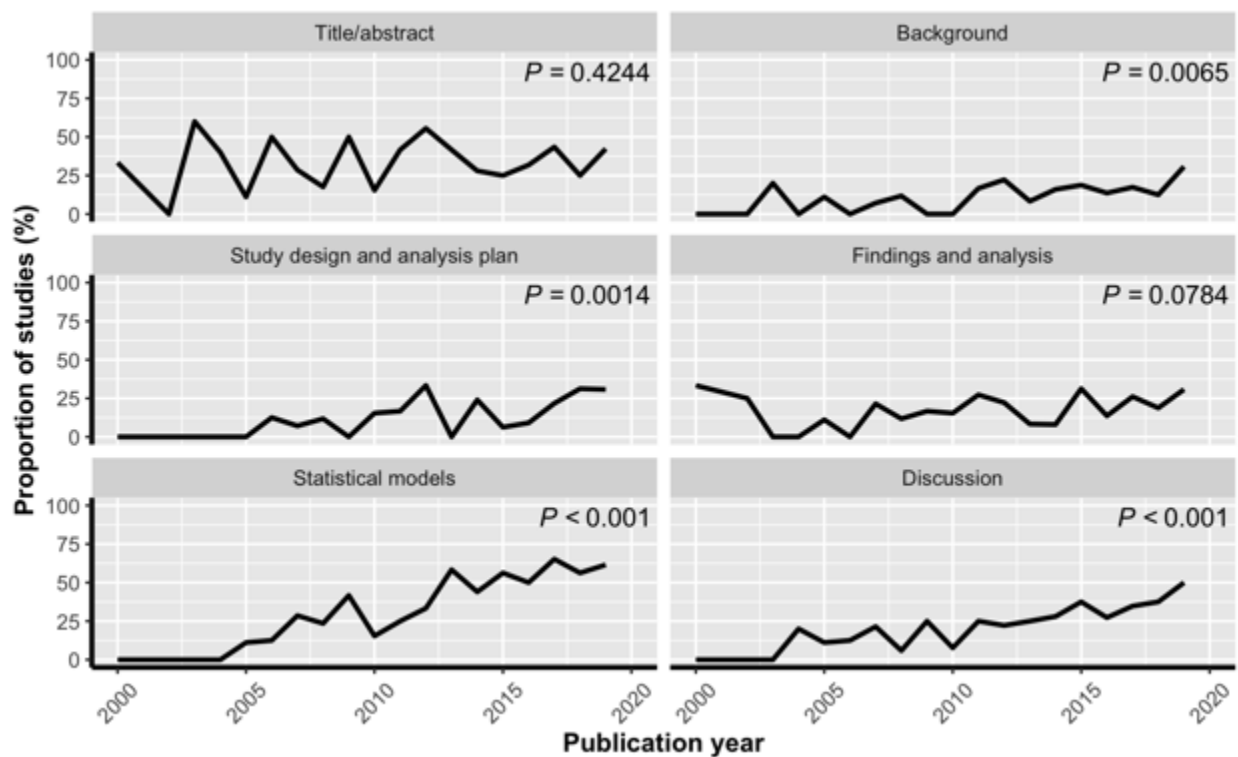
	Dependent variable Reporting of sex in title/abstract	
	Estimate	Pr(> t)
Time (b_1)	0.7704	0.489
Policy (b_2)	-13.6623	0.497
Time Since Policy (b_3)	2.00093	0.717
Constant	-1512.793	0.498

Interpretation of coefficients:

- The Time coefficient (b_1) corresponds to the proportion of studies that reported sex in Title/abstract before the policy release. The value is positive, indicating an increase in reporting of sex 0.77% per year but it is not significant.
- The Policy coefficient (b_2) indicates the change in the reporting of sex in title/abstract after the introduction of the policy. We can see a negative value of 13.6%, indicating that introduction of the NIH policy reduced the reporting of sex, however the immediate effect is not significant.
- The Time since policy coefficient (b_3) indicates that the trend has increased by 2% after the introduction of the policy. The sustained effect is positive and not significant, indicating that over each year after the policy release, the reporting of sex in title/abstract did not significantly increase.

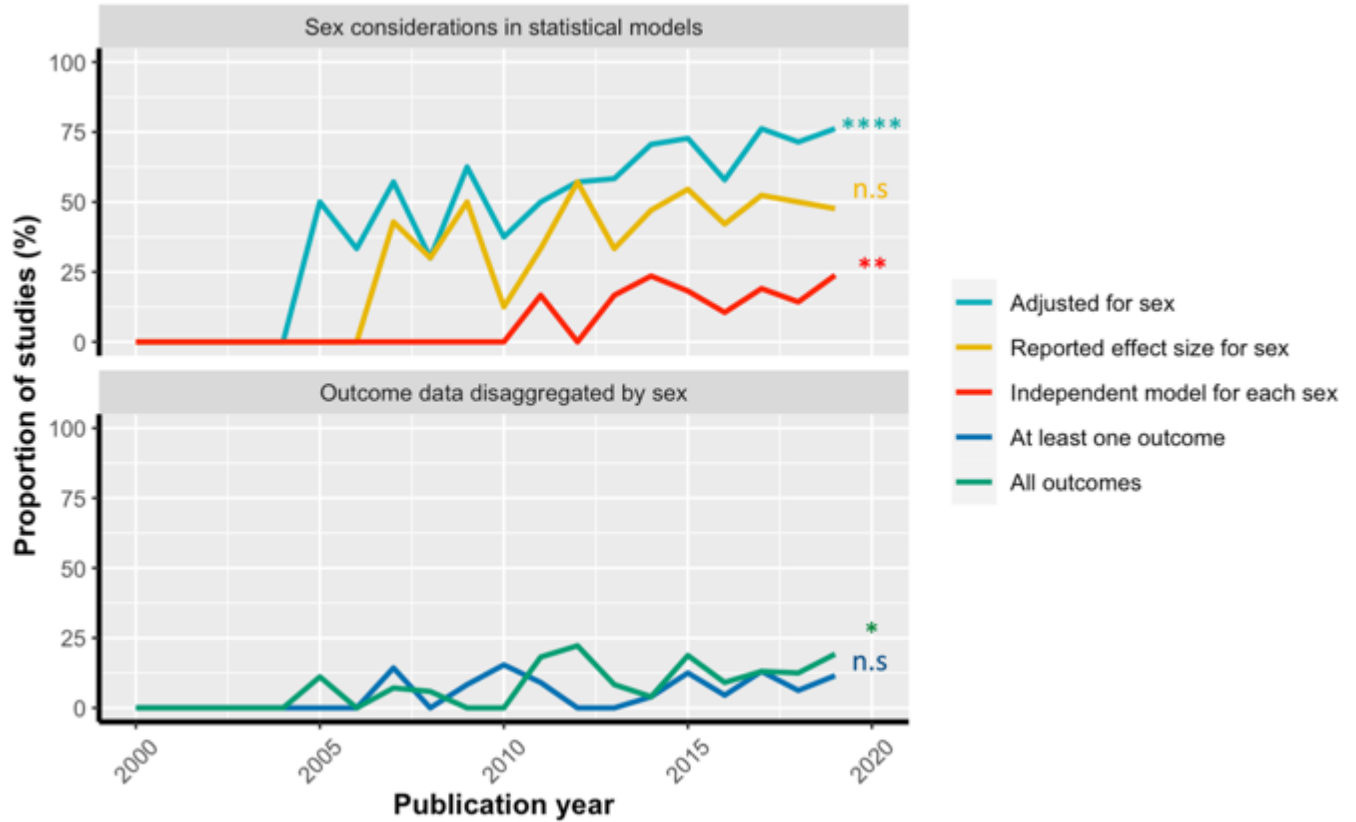
Supplementary Table 1. Sex considerations in cardiac resynchronization therapy studies stratified by study design.

Study sections	Prospective n = 133 (%)	Retrospective n = 120 (%)
Title/abstract	44 (33)	40 (33)
Background	13 (10)	21 (18)
Study design and analysis plan	13 (10)	29 (23)
Findings and analysis	20 (15)	26 (22)
Statistical model plan and analysis	46 (45)	56 (55)
Discussion	28 (21)	38 (32)

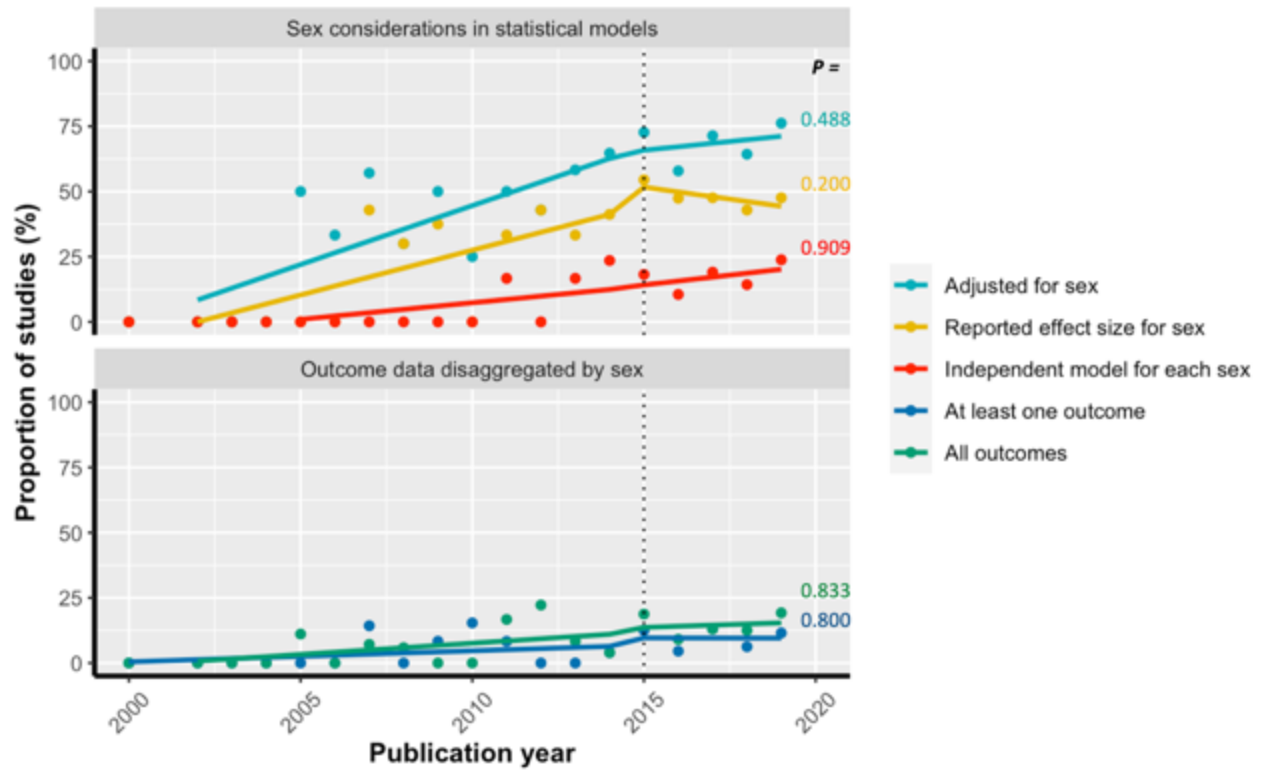


Supplementary figure 2. Temporal trends in sex considerations reported in cohort studies assessing the effectiveness and safety of Cardiac Resynchronization Therapy (CRT).

Studies published in year 2020 were excluded since we did not capture all of the studies published that year. Two sided Cochrane-Armitage test was used for trend analysis.



Supplementary figure 3. Temporal trends in sex considerations reported in statistical models and outcome data of cohort studies assessing the effectiveness and safety of Cardiac Resynchronization Therapy (CRT). Proportions for sex considerations in statistical models were calculated from the number of studies that reported the use of statistical models published per year (n=173). Studies published in year 2020 were excluded since we did not capture all of the studies published that year. Two sided Cochrane-Armitage test was used for trend analysis. n.s = non-significant. * $P \leq 0.05$. ** $P \leq 0.01$. **** $P \leq 0.0001$.



Supplementary figure 4. Impact of NIH Sex as a Biological Variable (SABV) policy on the reporting of sex considerations in statistical models and outcome data of cohort studies assessing the effectiveness and safety of Cardiac Resynchronization Therapy (CRT).

Studies published in year 2020 were excluded since we did not capture all the studies published that year. Dotted line at 2015 represent the release of the National Institutes of Health (NIH) policy on including sex as a biological variable in reporting, study design and analysis.

Segmented regression analysis was used to assess the impact of the NIH policy on the reporting of sex considerations.

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Chapter 5: Systematic Review of Sex differences in Cohort Studies of Cardiac Resynchronization Therapy

Chapter Overview

Chapter 5 addresses Objective 2: Assessment of sex differences in the Implantation rate, clinical effectiveness and safety in CRT cohort studies. Using the plan detailed in Chapter 3, we synthesize evidence from cohort studies to describe sex differences in receipt, efficacy and safety of cardiac resynchronization Therapy and identify possible reasons behind sex differences. This could help inform future studies that can help identify the reasons behind sex differences.

Manuscript Status

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Author Contributions

Omar Dewidar was involved in all stages of the protocol design, study selection and extraction of all the studies and preparation of the manuscript. The coauthors involved in conducting duplicate screening and extraction were coordinated by Omar Dewidar. Haben Dawit and Victoria Barbeau were responsible for duplicating the study selection and data collection. George Wells, Vivian Welch and David Birnie were involved in stages of the protocol inception and extraction and preparation of the manuscript.

Title: Sex Differences in Implantation and Outcomes of Cardiac Resynchronization Therapy in Real World Settings: A Systematic Review of Cohort Studies

Short Title: Sex Difference in Cardiac Resynchronization Therapy

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Correspondence:

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Key Points

Question: Are there sex differences in the implantation rate and treatment response to Cardiac Resynchronization Therapy (CRT) in patients with heart failure in real world settings?

Findings: In this systematic review and meta-analysis of cohort studies, women benefited more than men from CRT with a significant reduction in the risk of long-term all-cause mortality. However, globally, women are less likely to receive any CRT device in practice.

Meaning: These results provide evidence to support the sex disparity in CRT; more sex-based analyses are needed to investigate the cause of sex differences observed in receipt and response to CRT and develop more patient-specific selection criteria.

Abstract

IMPORTANCE: There is conflicting evidence from randomized trials on the effects of Cardiac Resynchronization Therapy (CRT) by sex and differences in access are unknown.

OBJECTIVE: To conduct a meta-analysis of cohort studies that examined sex differences in the implantation rates and outcomes in patients treated with CRT.

DATA SOURCES: MEDLINE, EMBASE and Web of Science were searched for relevant studies in all languages from January 2000 to June 2020. References and citations of eligible hand-searched studies were also searched.

STUDY SELECTION: Cohort studies were eligible if they evaluated the response to CRT in patients ≥ 18 years old and reported sex-specific information for outcomes of interest. Other study designs were excluded.

DATA EXTRACT AND SYNTHESIS: Citations were independently searched by two investigators and assessed for eligibility. Conflicts were resolved by consensus. Quality of studies was assessed by Newcastle-Ottawa scale (NOS). All meta-analyses were pooled using random effects models.

MAIN OUTCOMES AND MEASURES: Sex-specific implantation rate and any efficacy and safety outcomes. Raw number of events, unadjusted and adjusted analyses, and sex interaction analyses were used, if reported.

RESULTS: We included 97 studies (1,172,654 men and 486,553 women). Men received CRT more frequently than women (Median ratio, 3.16, 25th to 75th IQR, 2.48, 3.62). In the unadjusted analysis, men were at a higher risk of all-cause mortality after CRT compared with women (hazard ratio [HR], 1.50; 95% CI, 1.38, 1.63 [$P < .001$]). Adjustment for confounders did not affect the strength of association or direction (HR, 1.45; 95% CI, 1.32, 1.59 [$P < .001$]). Women achieved a greater rate of improvement in left ejection fraction (LVEF) compared with men (HR:

4.66; 95% CI, 4.23, 5.13 [$P<.001$]). Women were at higher risk of pneumothorax (RR: 0.21; 95% CI, 0.13, 0.34 [$P<.001$]), otherwise, there were no differences in complications.

CONCLUSIONS AND RELEVANCE: We found in this large meta-analysis that men were more likely than women to be implanted with CRT, yet men had a higher all-mortality following CRT compared to women and smaller improvement in LVEF. Reasons for this difference in implantation rates of CRT in real world practice need to be investigated.

Keywords: Cardiac Resynchronization Therapy, sex differences, implantation, sex disparity

Abbreviations:

CRT: cardiac resynchronization therapy

ICD: implantable cardioverter-defibrillator

6MWT: 6-minute walking test

HF: heart failure

NICM: Nonischemic cardiomyopathy

ICM: Ischemic cardiomyopathy

LVEF: left ventricular ejection fraction

HFH: heart failure hospitalization

NOS: Newcastle-Ottawa Scale

LBBB: Left bundle branch block

QOL: Quality of life

NYHA: New York Heart Association

Introduction

Landmark randomized controlled trials (RCT)s have demonstrated that Cardiac Resynchronization Therapy (CRT) effectively treats heart failure (HF) patients by reducing hospitalization and mortality⁶⁴. These RCTs, which all predominantly included male patients (67-83%), are the basis for CRT being classified as the highest recommendation by international cardiovascular guidelines⁷⁶.

Several RCTs have assessed sex differences as post-hoc subgroup analysis with conflicting evidence of no observed sex differences in effectiveness or CRT being more effective for women than men^{55, 62, 167}. The difficulty in determining if sex differences exist may be primarily due to the underrepresentation of women in HF trials¹⁹. Furthermore, some studies across the globe suggest differences in utilization of CRT across sex⁷⁷.

This creates a need for investigating data from observational studies which could overcome the issues of women representation, and are ideal for assessing real-world CRT implantation rates, effectiveness and adverse events¹³. In this systematic review, we pooled cohort studies reporting effectiveness and safety outcomes among patients treated with CRT to compare the implantation rate of CRT devices in men to women and evaluate the presence of sex differences in the response to CRT.

Methods

Search Strategy

The protocol for this systematic review was developed *a priori* to conducting the study (PROSPERO record: CRD42020204804). The manuscript was reported according to the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) checklist¹⁶⁸. MEDLINE, EMBASE and Web of Science were searched from January 1, 2000 to June 12, 2020, without language restrictions. Search terms were constructed by a medical research librarian combining several terms for cardiac devices, HF topic⁹² and cohort studies⁹¹ (eMethods in supplement). We further searched the reference list and study citations of 4 relevant systematic reviews⁶⁶⁻⁶⁹ and included studies identified by hand searching using citationchaser R package¹⁶⁹.

Selection of Articles

Title and abstracts and full text articles were screened independently by two investigators and discrepancies were resolved by consensus. We included pooled cohort studies reporting sex-disaggregated data for effectiveness and safety outcomes among patients treated with CRT. Non-English language studies were translated using google translate. RCTs and other observational study designs were excluded. We contacted authors for studies that were not available through our library and other online sources.

Data Extraction

Study information was extracted independently by two investigators for men and women separately when available. We collected all reported measures for our outcomes of interest defined *a priori* (PROSPERO record: CRD42020204804). When more than 1 multivariable model was reported, we selected the model with the largest number of adjustment variables. We adapted the Newcastle-Ottawa Quality Scale (NOS) as follows to provide an overall assessment for the quality of studies: Nine stars indicating “very good” quality, seven to eight stars indicating “good” quality, five to six stars indicating “satisfactory” quality, and zero to four stars indicating “unsatisfactory” quality¹⁷⁰.

Data Synthesis

We conducted four types of analyses for men vs women: (1) adjusted effect sizes (2) unadjusted effect sizes (3) Raw number of events/measures (4) interaction p-values. When possible, we compared the findings of unadjusted outcomes with adjusted to assess if estimates were biased. We planned to conduct subgroup analysis by device type, HF disease severity and age. Implantation rates were calculated as a ratio of men to women who received the device. Studies not reporting the proportion of men and women who received a type of CRT device but $\geq 90\%$ of the patient population received one type of device, the whole population of men and women in the study was considered to have received that device type. Linear regression models were used to compare trends in implantation rate for men vs women over time. Forest plots were used to calculate overall effect sizes using random effects models and conducted using Revman 5.1 (Nordic Cochrane Center). Heterogeneity was assessed using I^2 statistic and explored by subgroup analysis. Publication bias was visually inspected by funnel plots and verified by Egger’s

test¹⁷¹. P-curve analysis was used to investigate the extent of publication bias on the effect estimate¹⁷².

Results

Study Characteristics

Of the 8,504 citations screened, we identified 98 studies that met our eligibility criteria (eFigure 1, eReferences in supplement). One study had discrepancies in baseline characteristics and outcome data therefore, it was not extracted and was excluded for all analyses¹⁷³. The characteristics of the remaining 97 studies were extracted (eTable 1 & 2 in supplement) and included in the analyses (1,172,654 men and 486,553 women). Notable differences were found in the patient characteristics with women mostly presenting with nonischemic cardiomyopathy (NICM) (51 vs 30%), left bundle branch block (LBBB) (41 vs 37%) and higher QRSd (150.28 ± 25 vs 155.1 ± 21) compared to men (Table 1). Women were less likely to present with AF (34 vs 39%), paced QRS (19 vs 30%) and had lower serum creatinine levels (1.23 ± 0.92 vs 1.44 ± 0.97) than men. Overall NOS scores ranged from 7 to 9 points (maximum score, 9 points) for 62 studies.

CRT Implantation Rate

From 97 studies, one study was excluded from this analysis due to potential selection bias (only two women in the study)¹⁷⁴. In the remaining studies, men were 3.26 more likely to receive CRT (interquartile range [IQR], 2.47-3.59) compared to women (Figure 1). However, the sex disparity is improving over time, with a reduction in the ratio of men to women receiving the device ($P=.005$). Fifty-eight studies reported the proportion of men and women receiving CRT device subtypes (i.e., CRT-D or CRT-P). In those studies, men were also more likely to receive either of the CRT subtypes and this finding persisted throughout the years. The median ratio of men to women receiving CRT-D was 3.37 (IQR, 2.66-4.27), higher than those receiving CRT-P (median ratio: 2.08; IQR, 1.71-2.74). Over the past two decades, the sex disparity between the implantation rate of either subtype did not change ($P=.808$).

All-cause Mortality

Of the 97 studies included, 24 reported the raw number of events for all-cause mortality in men and women, 29 reported unadjusted effect sizes for effect of sex on all-cause mortality, and

30 reported adjusted analyses. Loring et al¹⁷⁵ reported raw, unadjusted and adjusted analyses but was excluded from meta-analyses due to being a primary source of heterogeneity. Twenty-four studies reported raw number of events, involving 221,856 men and 109,389 women. The risk of all-cause mortality was higher in man than women (Relative Risk [RR], 1.32; 95% CI, 1.27-1.37 [$P < .001$]) (eFigure 2 in supplement). Unadjusted analysis showed a greater all-cause mortality rate for men compared to women (HR, 1.50; 95% CI, 1.38-1.63 [$P < .001$]) (eFigure 3 in supplement). Direction and magnitude were similar for adjusted analysis (HR, 1.48; 95% CI, 1.32-1.66 [$P < .001$]) (Figure 2). Supplementary figure 4 shows that adjustment for LBBB and NICM did not change the results.

Comparison of studies reporting both unadjusted and adjusted estimates for all-cause mortality indicates that adjustment for covariates overall, had no effect on the estimate size or direction (eTable 3 in supplement). There was no statistically significant difference in odds ratio (OR) of all-cause mortality reported in adjusted models by 4 studies (eFigure 5 in supplement).

Eleven studies assessed the interaction of sex with all-cause mortality while adjusting for confounders. Interaction analyses shows that there are significant differences in mortality rate by sex in patients with LBBB, RBBB, ICM, AF, hypertension, history of heart failure hospitalization (HFH) and QRS wider than 150 milliseconds (eFigure 6 in supplement).

Heart Failure Hospitalization

Six studies reported outcome data for HFH stratified by sex; two studies involving 303 men and 149 women reported the raw number of patients. A non-significant difference in risk of HFH was found (RR, 1.31; 95% CI, 0.84-2.02 [$P = .23$]) (eFigure 7 in supplement). Four other studies reported the unadjusted analyses and found no difference in delaying time to HFH (HR, 1.03; 95% CI, 0.75-1.43 [$P = 0.14$]). Adjusted analysis also showed no difference (HR, 0.58; 95% CI, 0.32-1.06 [$P = .08$]) (Figure 2).

Composite outcomes

Out of the seven studies that reported the effect of sex on the composite outcome death or HFH, four studies reported an effect size for sex in their univariate analysis. Time to death or HF hospitalization was greater in man than women (HR, 1.25; 95% CI, 1.05-1.48 [$P = .01$]) (eFigure 8a in supplement), however substantial heterogeneity was present. Upon the removal of the Loring

et al¹⁷⁵ (Medicare patients) from the analysis, the pooled HR remained similar with a significant reduction in heterogeneity (HR, 1.37; 95% CI, 1.19-1.57 [$P < .001$]) (eFigure 8b in supplement). In the adjusted analysis, the difference remained significant but attenuated (HR, 1.06; 95% CI, 1.02-1.11 [$P = .005$]) (Figure 3b). In the five studies that conducted subgroup analyses by sex, there were significant differences in time to death or HFH across same characteristics as for all-cause mortality (eFigure 9 in supplement). Pooled analysis of other mortality composite outcomes consistently showed a greater risk for men compared to women (eTable 5, eFigures 10-12 in supplement).

Other Effectiveness outcomes

Nine studies including 1,904 men and 701 women reported the mean change in left ejection fraction (LVEF) from baseline. At short term follow up (<6 months), women had larger improvements in LVEF compared to men (SMD, -7.36; 95% CI, -9.11--5.61 [$P < .001$]). However, at longer follow up (≥ 6 months) the difference diminished (eFigure 13a in supplement). Adjusted analysis shows a greater rate of LVEF improvement in women compared to men (HR, 4.66; 95% C, 4.23- 5.13 [$P < .001$]) (Figure 3a). Four studies reported the mean change in Quality of life (QOL) for 1,777 men and 528 women. The unadjusted analysis shows a greater improvement in QOL for women compared to men, but not significant (SMD: -1.38; 95% CI: -3.19 to 0.43). Little to no difference was found for improvements in New York Heart Association (NYHA) HF classification and 6MWT (Figure 3 and eFigure 13b in supplement).

Complication outcomes

We identified four studies that reported raw number of complication events. Pneumothorax was reported for 10,445 men and 3,440 women. Women had a significantly greater pneumothorax rate compared to men (HR, 0.21; 95% CI, 0.13-0.34 [$P < .001$]). There was a trend for women to be at a higher rate of lead-related complications (HR, 0.84; 95% CI, 0.67-1.04 [$P = .84$]), while trends of a higher rate of pocket related hematoma (HR, 1.79; 95% CI, 0.76-4.23 [$P = .18$]) and device infection (HR: 1.27; 95% CI: 0.82 to 1.94 [$P = .28$]) in men (Figure 4).

Subgroup analysis

Analysis of raw number of events, unadjusted and adjusted HRs, indicated no significant difference in all-cause mortality between men and women across NYHA classification, age and device subtype (eFigure 14 in supplement). Barra et al¹⁵⁷ found no significant difference in all-cause mortality between men and women. Mohamed et al^{176, 177} also found no statistically significant difference for in-hospital mortality across CRT devices.

Two studies reported adjusted all-cause mortality for patients age ≥ 75 comparing men to women (HR, 2.85; 95% CI, 1.48-5.48 [$P = .002$]) (eFigure 5b in supplement). One study reported no difference in unadjusted HR of mortality in men vs women for those < 80 or 80 years and over¹⁶⁶.

Publication Bias

Visual inspection of forest plots in addition to Egger's test for all-cause mortality from raw number events, unadjusted and adjusted analyses show evidence of asymmetry, with possible weaker association studies missing (eFigure 15 in supplement). However, P-curve analysis shows that there is no indication of data manipulation (eFigure 16 in supplement).

Discussion

In this systematic review and meta-analysis of cohort studies comparing implantation rates and response to CRT in men and women, women were three times less likely to receive the device. Compared to men, women had a lower mortality rate post CRT implantation, a greater rate of LVEF improvement and higher risk of pneumothorax.

Even though observational studies are susceptible to bias, they provide insights that have contributed greatly to understanding cardiovascular disease¹³. Observational data are optimal for investigating the delivery of interventions in practice. Thus, they can provide an accurate representation of the use of CRT in men compared to women¹⁷⁸. Furthermore, our findings confirm individual reports that CRT is implanted less frequently in women than men, especially the CRT-D⁷⁷. However, we did not detect a statistically significant difference between CRT-D and CRT-P due to imprecision from the limited number of studies.

There are several possible explanations for CRT being implanted less often in women than in men. One, sex differences in HF progression and disease presentation. Women with HF tend to present with more severe comorbidities, shorter QRS duration and furthermore, their ejection fraction is often more preserved than men ¹⁷⁹.

Two, differences in care-seeking behavior may explain the differences in implantation of CRT. Even though men are less likely to seek primary care compared to women, some studies have shown that women delay to seek emergency help, especially when experiencing heart attack symptoms ¹⁸⁰. This may be due to women believing the myth that heart attacks are a “man’s disease” ¹⁸¹. Women also tend to prioritize their social responsibilities over their own health which leads to delays in care ¹⁸².

Three, gender bias may underlie the observed disparity in addition to biological sex differences. There is evidence across health care ¹⁸³, including cardiovascular care ¹⁸⁴, that women are sometimes not offered the same treatments as men, without any medical reason, possibly be due to the unintended neglect of including women in early trials ¹⁸⁵. The extent of these differences in treatment due to gender bias is difficult to know, however, lack of understanding of sex differences generates and exacerbates gender biases ¹⁸⁶. Gender bias may exist in cardiac device treatment as it was found that less than a third of women eligible for CRT received the device ¹⁸⁷. With men being perceived by cardiologists as stronger and greater risk takers than women ¹⁸⁸, cardiologists may be hesitant with suggesting CRT implantation to women as they believe that women would less likely accept the implantation and avoid referral from onset. Furthermore, women receiving the device, were less likely to receive ICD counselling compared to men prior to implantation ¹⁸⁹. This could be explained by the effect of gender bias influencing physician’s clinical decision-making process. The potential difficulties that operators face when implanting devices may discourage them from implanting the bulkier CRT-D devices ¹⁹⁰.

The difference in all-cause mortality across sex is consistent with two meta-analyses of RCTs that found there was a better survival benefit in women compared to men ^{55, 62}. Our multi-faceted analyses of all-cause mortality confirms that sex differences are present in real world setting and not likely due to residual confounding. Thus, the explanation of the found sex

difference in mortality is likely to be multifactorial. In our studies, women more commonly presented with LBBB compared to men which has been shown to be associated with greater reduction in mortality⁵⁵. However, sensitivity analysis of studies adjusting for LBBB and HF etiology further demonstrates that the difference is not driven by differences baseline risk profiles. Linde et al found that the harms of LBBB are more pronounced in men, which may be the cause the difference in survival, irrespective of CRT⁶². Consequently, female CRT candidates may have a survival advantage *a priori* to implantation.

We found that women had greater rate of improvement in LVEF after CRT compared to men which was consistent with findings from the MADIT-CRT trial⁶³. Our findings were confirmed by both unadjusted and adjusted analyses. Since women are more likely to have NCIM than ICM, some studies have hypothesized that patients with NICM exhibit greater reverse modelling and better outcomes than those with ICM^{156, 191}. Our findings add validity to this theory as we found a pronounced survival benefit in women while NICM was more prevalent in women than men in our studies. Furthermore, men were more likely to present with AF and higher creatinine levels than women, which have both been associated with poor prognosis and high risk of mortality in patients with depressed LVEF.

Similar to previous trials^{60, 192}, we found a greater risk of pneumothorax in women compared to men. The increase in risk of pneumothorax in women, may arise due to smaller cardiovascular anatomy (i.e. chest cavity, blood vessels) that poses greater technical challenges during implantation¹⁹⁰. The choice of access (subclavian vs axillary vs cephalic) by the operator may mechanistically lead to increased risk in complications¹⁹³. Access through cephalic vein was found to be the most preferred by operators regardless of sex¹⁹⁴. The presence of comorbidities such as AF necessitate the use of single leads, in which cephalic pacing is more appropriate than axillary¹⁹⁵. However, we found that women to present with AF less than men, so the use of other access approaches may be tested to reduce risk of pneumothorax.

limitations are inherent when using observational studies for evaluating effectiveness as they lack randomization. One limitation is that differences in effect estimates across sex were driven by baseline imbalance and possible confounding due to unknown factors, especially for

unadjusted analyses. We also did not seek data from authors, which if acquired, would have enabled us to conduct more robust meta-analyses and gain further insight in cause of sex differences by acquiring more information on patient characteristics. We may have missed studies because we used two search filters due to the large yield of citations that required screening. However, we mitigated the possibility of missing studies by searching citations and reference lists of hand searched included studies and relevant systematic reviews.

Conclusions:

We found in this large meta-analysis men are more likely than women to be implanted with CRT yet women have a lower mortality following CRT compared to men and greater rate of improvement in LVEF. Reasons for this difference in implantation rates of CRT in real practice needs to be investigated. More separate analyses for men and women need to be conducted to understand the reasons for sex differences in outcomes.

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Table 1: Characteristics of included studies

Study characteristics	N of studies (Patients, No) Men/women	Men	Women
Age y, (mean±sd)	29 (998,986/433,235)	70.8±11.4	71.6±12.5
LVEF, mean, %	21 (81,041/37,490)	24.3±7.2	24.2±7.1
NYHA heart failure class, %	16 (78,788/35,431)	2.92±0.5	2.97±0.4
QRS duration, mean, ms	19 (76,008/36,369)	150.28±25	155.1±21
Comorbidities			
Diabetes, %	19 (816,637/336,656)	33	33
Hypertension, %	15 (808,867/334,600)	62	63
Creatinine (mg/dl), mean±sd	9 (73,686/35,582)	1.46±0.97	1.26±0.92
NCM, %	28 (792,044/327,479)	30	51
AF, %	19 (765,811/313,227)	41	36
LBBB, %	17 (465,132/193,905)	65	70
Paced, %	4 (21,330/11,925)	30	19
Medication			
B-Blocker, %	17 (74,767/35,036)	86	88
ACE/ARB, %	15 (74,206/34,874)	67	61
NOS quality assessment (stars), n (%)			
Very Good (9)	6 (6)		
Good (7-8)	51 (53)		
Satisfactory (5-6)	38 (39)		
Unsatisfactory (0-4)	2 (2)		

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; LBBB: Left bundle branch block; LVEF, Left

ventricular ejection fraction; AF, Atrial fibrillation; NICM, Non-ischemic cardiomyopathy; ICM: Ischemic cardiomyopathy; NOS: Newcastle Ottawa Scale

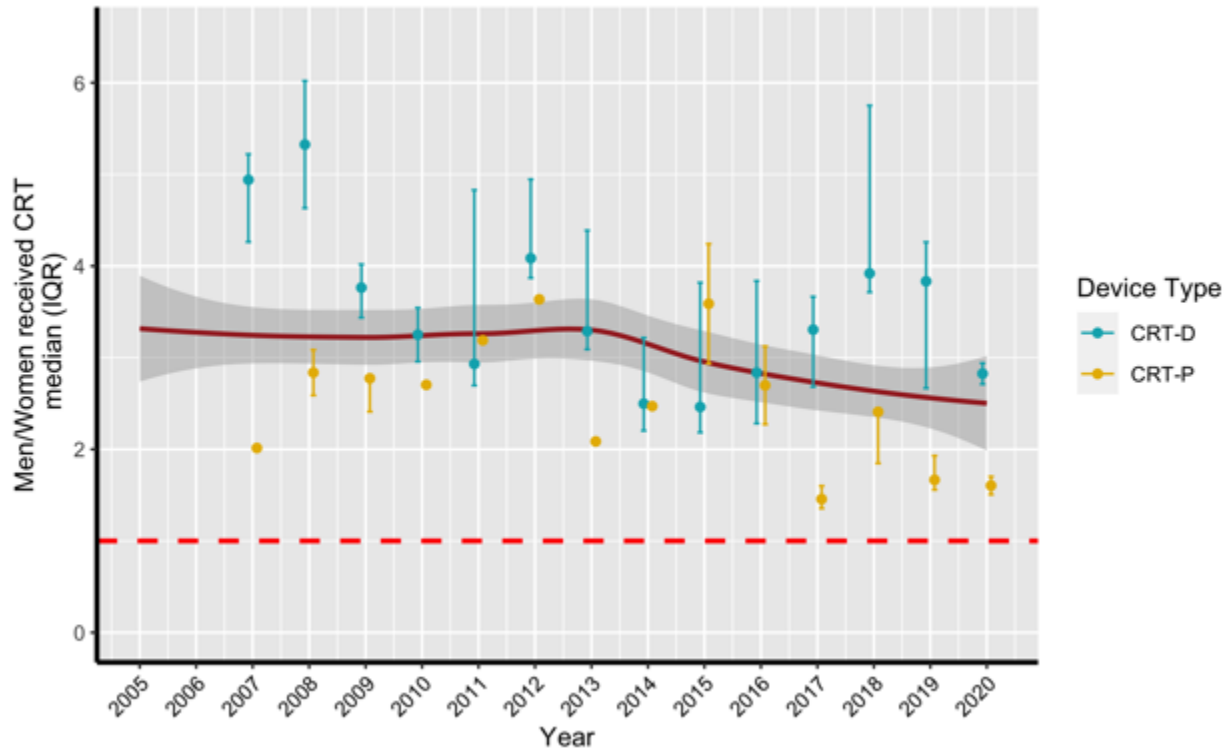


Figure 1. Ratio of men compared to women received a cardiac resynchronization therapy with (CRT-D) or without a defibrillator (CRT-P). IQR (Interquartile Range). Dotted red line corresponds to ratio of 1. Points with no intervals are ratios of single studies. One study was excluded from this analysis due to potential selection bias (conducted at the Veteran’s affairs Healthcare services). Linear regression analysis shows significant improvement in implantation ratio over time ($P = 0.005$), but no significant difference between men and women receiving either device subtype ($P = 0.808$).

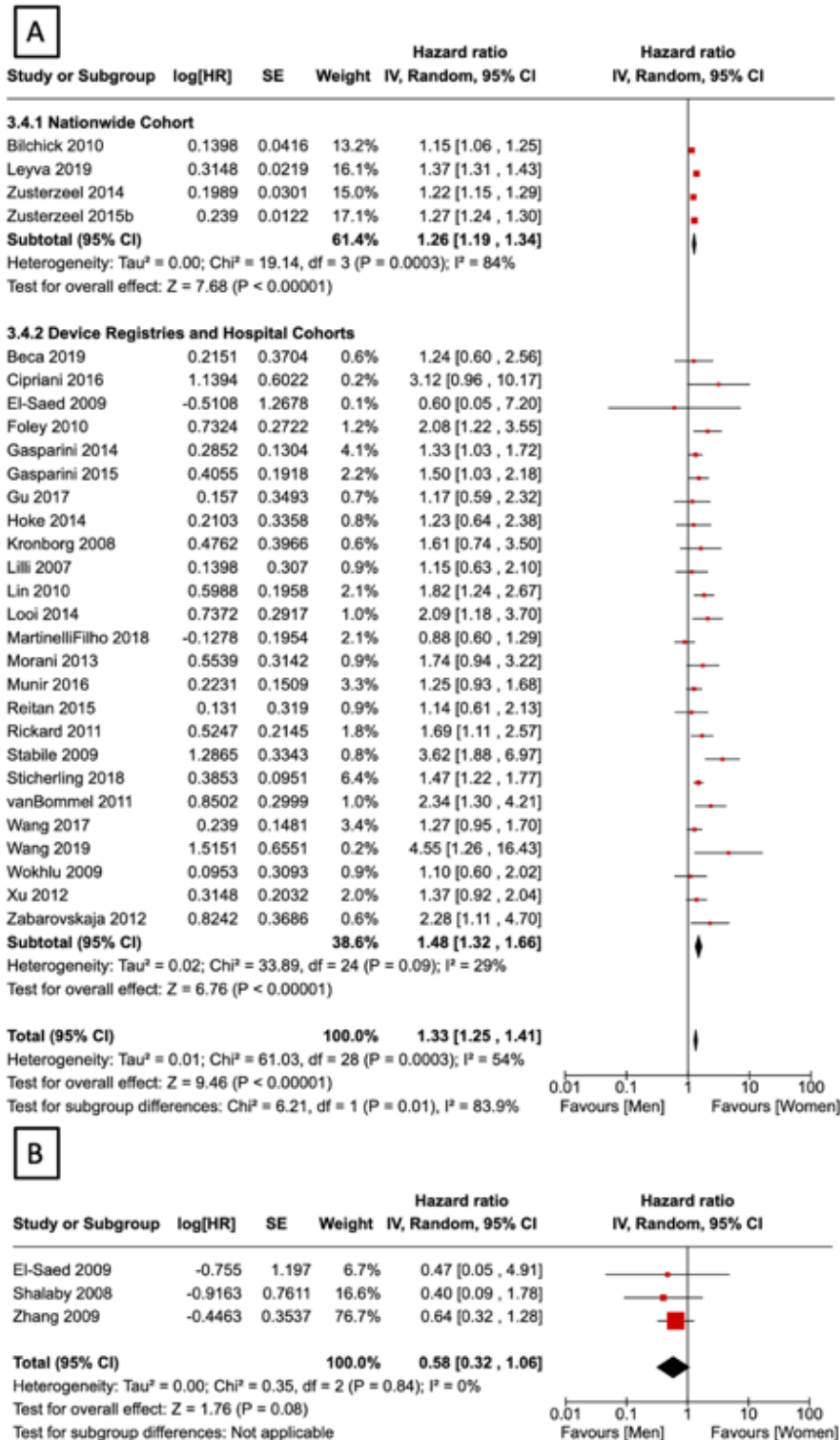
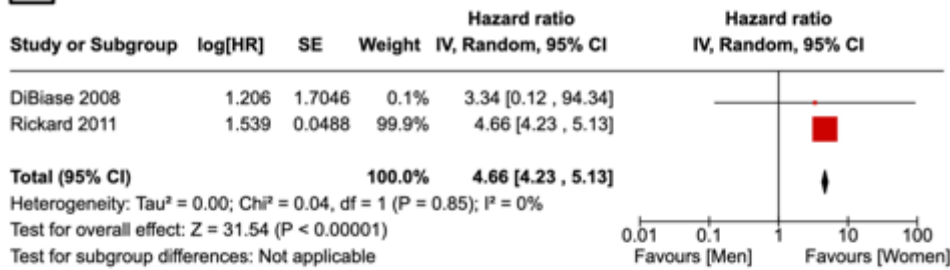
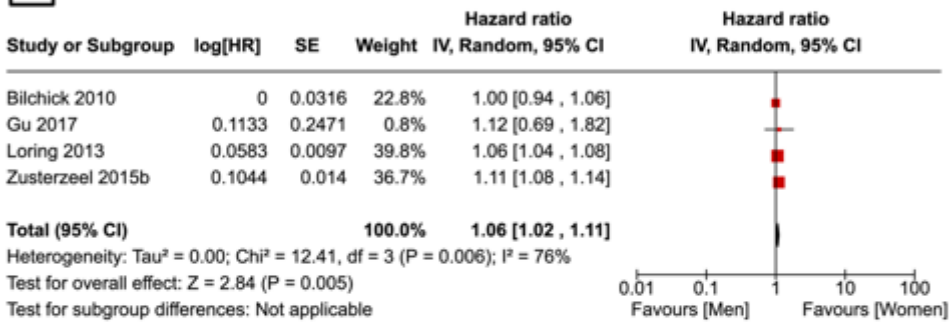


Figure 2. Adjusted all-cause mortality and Heart Failure Hospitalization. Forest plots showing adjusted (A) all-cause mortality and (B) Heart failure hospitalization when men were compared to women. IV indicates inverse variance; M-H, Mantel-Haenszel.

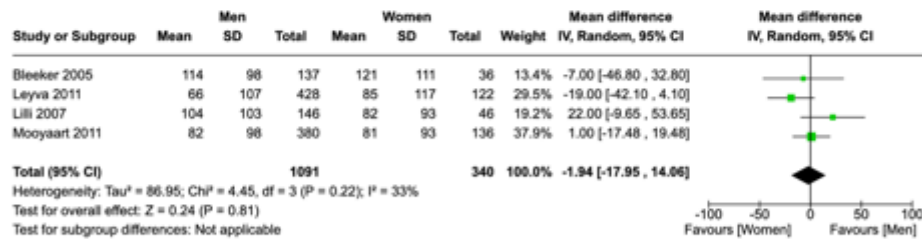
A



B



C



D

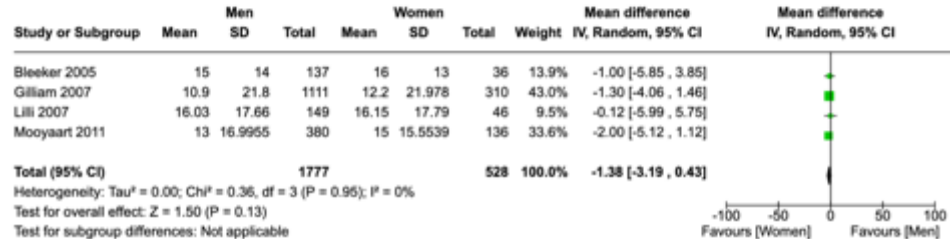
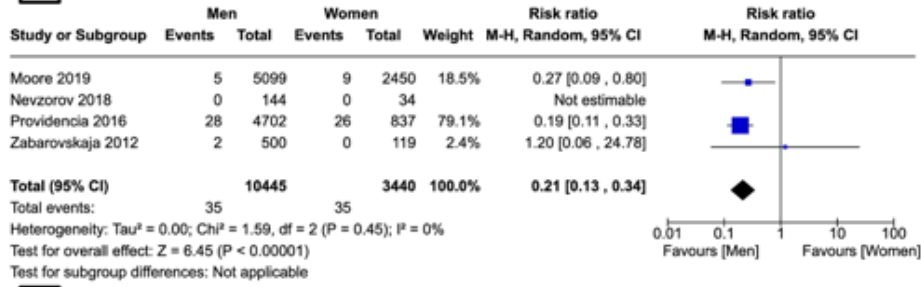
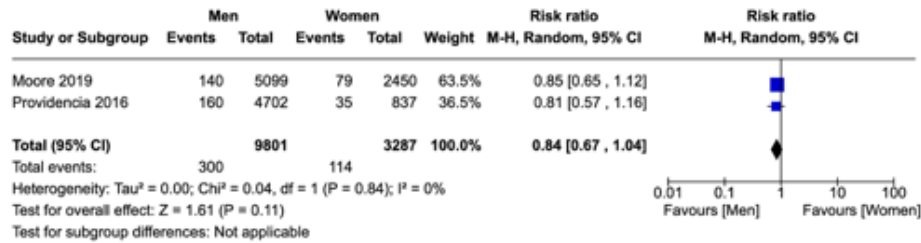


Figure 3. Other adjusted and unadjusted efficacy outcomes. Forest plots showing (A) adjusted left ventricular ejection fraction, (B) adjusted death or heart failure hospitalization, and (C) unadjusted change in quality of life score and (D) unadjusted 6-minute walking test. IV indicates inverse variance; M-H, Mantel-Haenszel.

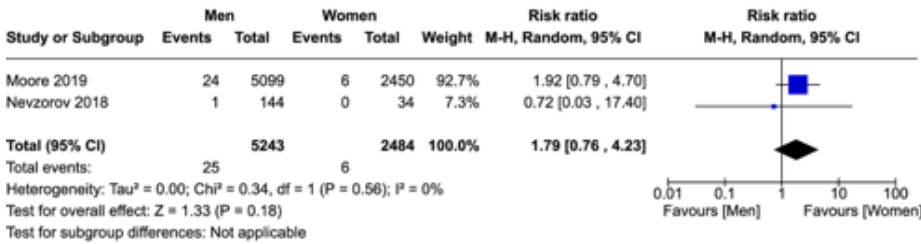
A



B



C



D

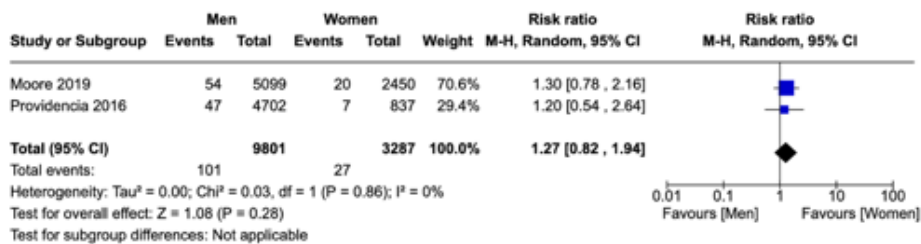


Figure 4. Unadjusted safety outcomes. Forest plots showing raw number of events for (A) Pneumothorax, (B) lead-related complications, (C) pocket related hematoma, (D) device infection. IV indicates inverse variance; M-H, Mantel-Haenszel.

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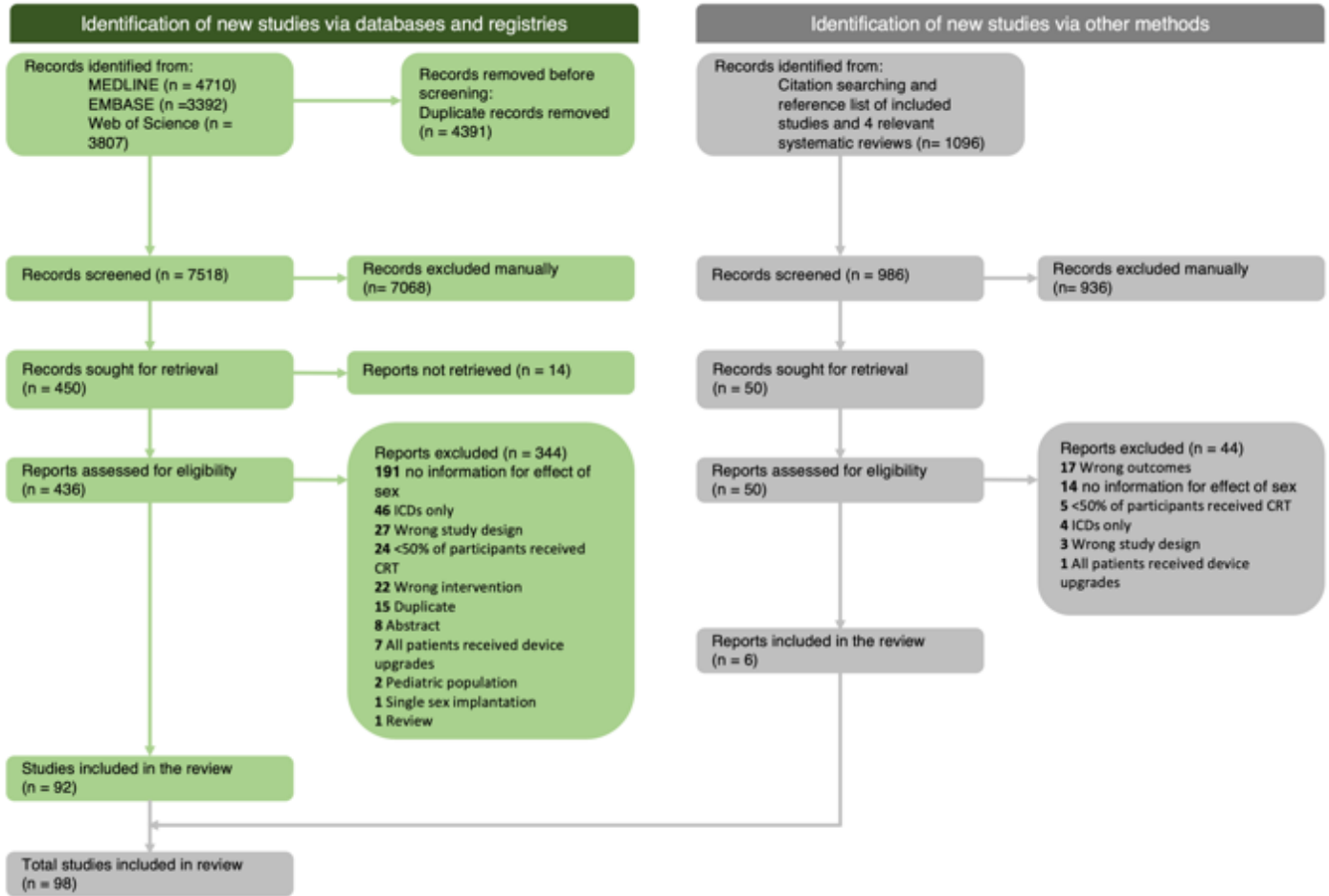
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eMethods

Detailed Search Strategy: MEDLINE

1. CIED or (Cardiac adj2 implant* adj2 electronic* adj2 device?).ti,ab.
2. defibrillators, implantable/ or exp pacemaker, artificial/
3. ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.
4. ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*)).ti,ab.
5. (cardioconver* or (cardio adj conver*)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp cohort studies/
8. cohort\$.tw.
9. controlled clinical trial.pt.
10. epidemiologic methods/
11. limit 10 to yr=1971-1988
12. or/7-9,11
13. (registr* or Prospective* or Retrospective*).mp.
14. 12 or 13
15. heart failure.mp.
16. ventricular dysfunction, left.sh.
17. cardiomyopathy.mp.
18. left ventricular ejection fraction.mp.
19. or/13-16
20. 6 and 14 and 19
21. limit 20 to yr="2000-Current



eFigure 1. PRISMA flow chart for included studies

eReferences. Bibliography of included studies

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eTable 1. Patient characteristics in included studies

Study ID	Clinical characteristics								Comorbidities								Medication				Adapted- Newcas- tle Ottawa Scale (NOS)						
	Age, mean±sd		LVEF, mean %		NYHA, mean %		QRS, mean ms		Diabetes, %		Hypertension, %		Creatinine, mean±sd mg/dl		ICM/NICM , %		AF, %		LBBB , %			Paced, %		B-Blocker, %		ACE-I/ARB, %	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		M	F	M	F	M	F
Achilli 2007	68±9		27±10		3.2±0.4		166±30		18		-		-		46/54		16		-		-		53		80		Satisfactory
Adelstein 2016	82.9±3		24.4±6.9		2.95±0.3		172		26		-		-		71/29		28		48		27		88		79		Satisfactory
Auger 2012	66±11		25±8		3.06±0.2 7		154.5±33		-		-		-		58/42		-		71		-		-		-		Satisfactory
Auricchio 2007	64±9		24±7		3.1±0.4		168±29		-		-		-		-		19		75		15		80		91		Satisfactory
Bai 2008	66.4±12		19.9±7.8		3.19±0.4		161.7±24		10		-		-		67/33		49		-		-		69		82		Good
Barra 2017	66. 8± 10	67. 9± 12	25. 7± 8	26. 7± 8	2.7 7± 0.7	2.7 8± 0.7	-		2 7	2 1	-		-		56/4 4	30/7 0	G o o d	2 9	-		-		7 7	7 6	82	82	Very good

Beca 2019	66.2±10		24.1±8		NYHA III/IV 51%		160.1±30		43	54	1.13±0.4	-	34	44	17	94	90	Satisfac tory				
Bilchick 2010	73.0±11		23.1±6		3.00±0.5		156.9±25		36	-	-	69/31		35	4 8	2 1	-	79	74	Good		
Bleeker 2005	66. 6± 11	65 ±1 1	21 ±8	21 ±7	3.1 5± 0.4	3.0 8± 0.3	173± 28	168± 35	-	-	-	62/3 8	33/6 7	-	100		-	-	-	Satisfac tory		
Boriani 2016	67±10		-		2.78±0.5		150.7±29		-	-	-	39/61		14	-	5	-	-	Satisfac tory			
Boveda 2009	71.0±9		25.0±7.1		3.1±0.29		163.2±27		-	-	-	-	41	-	-	69	91	Satisfac tory				
Cipriani 2016P	66.4±10		27.8±7		NYHA III/IV 72%		152.9±27		-	-	-	47/53		32	69	-	77	82	Satisfac tory			
Cipriani 2016	61. 0± 10	63. 6± 10	26. 7± 6	26. 6± 6	2.6 ±0. 6	2.8 ±0. 5	162. 6±29	163± 26	-	-	-	44/5 6	19/8 1	6 5	1 0	7 9	8 6	-	7 4	8 4	89	Satisfac tory
Delgado 2010	67±10		25±7		3.0±0.3		155±33		-	-	-	100		-	-	-	71	89	Good			

DiBiase 2008	67.5±12	21.6±8	NYHA III-IV 87%	QRS interval ≥120 ms 93%	27	-	>1.4 mg/dL 31%	55/45	-	-	-	76	85	Good
Doring 2018	80±4	28.4±6	2.9±0.4	154.4±19	-	-	-	52/48	22	62	100	86	90	Satisfactory
Echouffo - Tcheugui 2016	74.9±6	24.3±6	2.8±0.4	QRS ≥ 150: 56%	38	78	<2.5 mg/dL 86%	65/35	30	56	26	87	78	Good
El-Saed 2009	67±10.7	22.5±10	2.9±0.3	148.3±30	47	77	1.25±0.4	76/24	55	-	-	81	80	Good
Fantoni 2008	63±9	21.2±6	3.1±0.3	163±27	40	-	-	47/53	-	-	-	89	98	Good
Foley 2010	69.2±11	24.0±10	3.3±0.5	153.5±29	16	27	-	66/34	30	-	-	48	90	Good
Friedman 2015	75.7±6	23.3±6	3.1±0.2	77.5% QRS <170 ms	43	80	-	68/32	33	74	28	86	56	Satisfactory
Frigerio 2013	62.0±11	27.7±7	2.73±0.5	161.3±29	-	-	-	41/59	16	-	-	75	92	Good

Gasparini 2014	67±11	35±7	NYHA III-IV: 77%	167.4±27	13	-	1.43	37/63		21	-	-	58	63	Good
Gasparini 2015	66.3±11	26±7	NYHA III-IV 78%	158.2±32	25		-	-		17	89	83	80	85	Good
Gilliam 2007	69.3±11	-	3.11±0.3	-	-	-	-	-		-	-	100	-	-	Satisfac tory
Gu 2017	58.5±11	28.9±8	2.93±0.7	160.9±19	23	31	-	28/7 2	5/95	14	85	> 90%	94	77	Good
Hoke 2014	66.9±11	26.3±8	3.00	156.3±32	21	-	-	60/40		17	-	-	70	89	Good
Iler 2007	65±12	22±12	2.70±0.7	175±30	-	-	-	65/35		22	45	28	-	87	Satisfac tory
Jacobsso n 2016	69±10	23±6	2.9±0.5	169±28	35	38	1.32±0.5	63/37		49	65	20	84	93	Good
Jeevanan tham 2016	67±12	24±9	3±0.3	-	34	68	1.5±1.5	59/41		35	-	-	90	ACE: 65%; ARB: 20%	Good

Kelarijan i 2008	61 ±1 0	59 ±1 2	21 ±7	20 ±8	3.1 ±0. 3	3.1 ±0. 5	142± 15	152± 11	-	-	-	52/4 8	33/6 7	-	100	-	-	-	Satisfac tory					
Khatib 2014	66.9±10		24.8±7		2.87±0.6		167.8±32		-	-	-	42/58		25	63	-	69	72	Satisfac tory					
Khazanie 2014	77.4±7		23.4±7		-		148.9±20		42	77	1.5±1.0	66/34		36	65	-	87	72	Good					
Kobe 2017	73% < 75 yrs		26.3±7		NYHA III/IV: 79%		160		31	52	> 1.5 mg/dL 23%	-		17	84	7	-	-	Unsatis factory					
Kreuz 2012	66.7±10		25.8±10		2.7±0.5		146.2±18		31	49	1.58±0.7	58/42		39	-	-	92	95	Satisfac tory					
Kronborg 2008	65.5±10		22.5±6		3.1±0.6		146±30		17	-	-	60/4 0	37/6 3	35	-	-	54	87	Good					
Lee 2014	62.3±12		22.9±5		3.1±0.5		169.1±31		32	57	-	13/87		32	68	-	72	77	Good					
Leyva 2011	70. 1± 11	71. 3± 11	24. 4± 10	23. 5± 12	3.3 ±0. 5	3.4 ±0. 5	155. 5±29	152. 1±26	1 7	1 3	2 6	3 2	-	70/3 0	51/4 9	2 4	1 3	-	-	5 6	4 6	90	89	Satisfac tory
Leyva 2017	66.5±14		27.3±12		2.88±0.7		150.2±25		17	26	-	0/100		28	60	-	65	92	Good					
Leyva 2018																				Satisfac tory				

Leyva 2019	71. 2± 11	70. 8± 13	-	-	-	2 9	2 4	6 8	6 4	-	-	-	-	-	-	-	Good						
Liang 2020	62.1±11		30.0±5.0		2.91±0.7		160.6±31		18	37	-	7/93		14	67	-	88	94	Very good				
Lilli 2007	71. 1± 10	72. 7± 8	27. 3± 7	29. 3± 7	3.1 ±0. 6	3.2 ±0. 4	152. 8±23	153. 5±19	-	-	-	53/4 7	42/5 8	1 4	1 1	9 4	9 6	-	5 4	6 3	78	79	Good
Lin 2010	68.4±12		22.3±8		-		163.5±33		-	-	1.50±0.5	62/38		-	-	0	80	85	Good				
Looi 2014	69.1±10		24.9±8		NYHA III/IV: 92%		159.6±27		15	7	1.29±0.5	53/47		18	-	-	71	91	Satisfac tory				
Looi 2019	64. 4	64. 9	26.4±7.9		2.35±0.7		176.3±25		24	27	-	23/51		26	76	24	-	-	Satisfac tory				
Loring 2013	73. 1± 8	73. 0± 8	-	-	-	-	4 6	4 8	8 4	8 7	-	69/3 1	53/4 7	5 6	4 8	3 9	5 3	-	-	-	Good		
Lumens 2015	66±11		24±6		NYHA II/III 76%		159±27		32	-	-	60/40		0	34	-	87	85	Good				
Marijon 2015	68.8±11		Median 25.5		2.89±0.5		157.7±27		-	-	-	47/53		27	-	-	60	67	Satisfac tory				

Martinelli Filho 2018	61.4±12		25.3±7		NYHA Class III/IV 84%		163.3±27		30		54		-		32/68		18		92		-		82		88		Satisfactory
Masoudi 2014	74.6±6		25±6		2.68±0.6		149±20		38		78		1.40±0.9		64/36		32		68		-		86		78		Good
Miller 2011	Median 68.9±12		Median 20±10		-		Median 168±28		-		-		-		534/47		40		-		-		-		-		Good
Mohamed 2019*	73	77	-		-		-		2	2	6	6	-		58/4	38/6	3	4	-		-		-		-		Good
									8	8	3	7			2	2	6	1									
Mohamed 2020	71	71 ^{\$}	-		-		-		3	3	5	5	-		71/2	50/5	3	3	7	7	-		-		-		Very good
									3	3	6	7			9	0	9	5	6	3							
Moore 2019	71.5±12	73.6±13	-		-		-		2	1	3	3	-		37/6	23/7	-		-		-		-		-		Good
									1	7	7	5			3	7											
Mooyart 2011	67±9	65±1	23±7	23±7	3.1±0.3	3.1±0.3	166±26	166±22	2	1	-		-		67/3	37/6	2	1	6	8	-		6	6	89	87	Satisfactory
									4	8					3	7	0	0	8	1			9	5			
Morani 2013	69±10		27±5		2.9±0.6		168±31		30		49		1.41±0.8		56/44		28		-		-		74		72		Good

Munir 2016	83±3		28±5		NYHA III/IV: 100%		154±16		33		76		1.30±0.2		-		-		46		29		77		77		Satisfac tory
Nagy 2015	67±7		29.7±6		NYHA III/IV 87%		160±20		31		51		-		49/51		27		90		-		91		94		Satisfac tory
Nevzoro v 2018	66. 9± 11	67. 8± 13	27. 1± 8	24. 4± 9	3.1 ±0. 3	3.0 ±0. 2	146± 21	148± 22	4 2	3 5	6 5	7 7	1.3 9 ±0. 6	1.1 6± 0.5	79/2 1	38/6 2	4 5	3 5	5 7	7 7	-		6 7	7 7	53	47	Satisfac tory
Ozabalov e 2010	59. 4± 5	64. 4± 7	-		2.9 ±0. 4	2.9 5± 0.3	160.3±25		-		-		-		33/6 7	25/7 5	2 0	1 4	100		-		85		-		Good
Perini 2013	70±9		26.8±6		2.84±0.6		157.3±26		31		59		-		47/53		47		66		18		83		91		Satisfac tory
Pfau 2009	62. 5± 9	64. 5± 8	20 ±6	23 ±9	3.01±0.5 3		-		-		36		-		46/54		21		100		-		82		97		Un- satisfac tory
Prochnau 2011	63.9±9		23.6±7		3.24±0.7		176±30		-		-		-		34/66		25		87		-		91		97		Good

Providencia 2016	62.6±11	62.0±12	26.7±7	27.0±9	2.41±0.7	2.50±0.7	-	-	-	-	64/36	40/60	25	19	-	-	84	88	82	80	Good
Reitan 2015	69.6±10		25±7		2.83±0.6		168±28	32	46	1.33±0.7	57/43		47	66	18	83	91		Very good		
Rickard 2011	66.3±12		21.9±8		-		159.1±31	37	59	1.36±0.5	58/42		52	39	27	84	80		Good		
Risum 2012	65.7±10		22.5±8		2.9±0.4		155±22	-	-	-	60/40		0	66	-	87	90		Good		
Rolink 2009	69		-		-		-	-	-	-	-		29	-	-	73	77		Satisfactory		
Roubicek 2015	67.6±9		26±6		3.00		160±20	-	-	0.96 (IQR 0.79-1.16)	56/44		16	91	99	99	99		Satisfactory		
Shalaby 2008	66.5±12		22.6±10		3.0±0.4		155.8±30	42	66	1.3±0.6	64/36		44	-	-	76	79		Good		
Sharma 2015	68.5±12		24±7		NYHA III/IV 76%		161±28	40	75	1.5±0.8	58/42		-	-	-	88	ACE: 61%; ARB: 20%		Satisfactory		

Shen 2010	69.9±10		20.4±7		NYHA III-IV 100%	165.4±27		39		54		-		66/34		0		75		-		91		ACE: 57% ARB: 31%	Satisfac tory		
Sjoblom 2015	64±11		26±11		2.56±0.6	-		29		47		-		64/3 6	53/4 7	4 2	2 3	40		-		95		-	Good		
Smit 2011	65±11		24±12		2.99±0.4	164±30		23		42		-		50/50		22		-		-		74		94	Satisfac tory		
Stabile 2009	68.8±8		26.5±7		3.22±0.4	-		-		-		-		49/51		22		100		-		-		-	Good		
Stabile 2015	69±10		29±7		2.85±0.6	151±25		25		58		-		44/56		28		100		-		6 9	6 6	-	Good		
Sticherlin g 2018	64 ± 11	64 ± 11	-		2.4 9± 0.7	2.6 2± 0.6	131± 34	132± 33	2 0	1 6	-		1.3 ± 0.8	1.1 ± 0.6	69/3 1	47/5 3	2 2	1 4	-		-		-	-	Satisfac tory		
vanBom mel 2011	65.5±10		25.5±8		3.1±0.3	156.7±32		-		-		1.15±0.4 3		60/40		91		-		-		69		91	Satisfac tory		
Varma 2014	59 ±1 3	61 ±1 1	18 ±7	21 ±7	2.93±0.4		161± 26	160± 18	2 6	3 3	5 6	5 0	-		0/100		3 2	2 7	100		-		8 5	8 4	87	90	Good

Varma 2017	61 ±1 1	61 ±1 1	17 ±7	21 ±7	NYHA III-IV 87%		170± 23	160± 16	2 4	2 9	5 3	5 3	-	0/100	3 3	2 8	100	-	8 4	8 2	91	90	Very good				
Varma 2017b (Survival)	70. 3 ±1 3	72. 2± 14	-		NYHA III-IV 87%		-	-	-	-	-	-	-	-	-	-	>98%	-	-	-	-	Good					
Wang 2017	81. 5± 4	81. 0± 4	25. 1± 6	24. 4± 6	-		160± 27	151± 23	2 6	3 4	7 2	7 3	1.5 1± 0.6	1.2 9 ±0. 5	-	-	4 3	7 9	3 0	2 6	7 6	7 9	78	77	Good		
Wang 2019	60. 3± 13	64. 1± 13	23. 0± 7	22. 7± 6	2.7 5± 0.5	2.8 1± 0.4	167± 15	160± 17	2 9	2 5	6 4	4 9	1.1 6± 0.6	0.9 6 ±0. 4	0/100	2	6	100	9 8	9 9	9 5	9 6	95	91	Good		
Wilcox 2014	68. 7± 13	69. 3± 14	24. 7± 7	25 ±7	-		134. 5±38	127. 6±36	3 6	3 4	6 2	6 4	1.5 0± 0.8	1.3 0± 0.8	76/2 4	58/4 2	3 4	2 7	-	-	-	-	-	-	Good		
Wokhlu 2009	68.5±11		23±7		3.0±0.5		166.6±34		-		-		1.5±0.6		62/38		31		45		33		83		80		Good

Xu 2012	69. 4± 11	66. 0± 12	23. 5± 8	23. 9± 7	3.0 ±0. 5	3.0 ±0. 4	166. 4±36	162. 1±29	-	-	1.5 0± 0.6	1.2 0± 0.5	64/3 6	32/6 8	3 2	2 0	4 2	6 3	3 1	2 1	8 7	8 8	83	78	Satisfac tory		
Yanagisa wa 2015	67.2±11		26.1±7		NYHA IV 11%		160.5±26		34	32	-		28/72		11	56	-		87		71		Satisfac tory				
Yokoshik i 2017	68.18±1 1.6		27.4±9.6		2.81±0.6		154.10±30		31	41	1.48±1.5		27/73		13	-	-		75		65		Satisfac tory				
Yu 2005	64.2±11		24.8±8		3.0±0.5		156.1±37		-	-	-		48/52		-	-	-		75		91		Good				
Zabarovs kaja 2012	68 ±1 0	67 ±1 2	24 ±9	24 ±8	2.9 3± 0.4	2.9 4± 0.4	154± 32	160± 27	2 9	1 9	-		65/3 5	42/5 8	5 1	3 9	-		-		-		-	-	Good		
Zardkooh i 2007	70. 8± 11	70. 2± 10	19 ±1 3	22 ±9	-		170± 52	168± 19	3 8	4 0	4 1	4 0	1.7 0± 1	1.6 0± 1	76/2 4	38/6 2	-		-		-		8 4	7 6	55	56	Satisfac tory
Zhang 2009	64.4±13		26.7±8		3.14±0.4		134.4±34		-	-	-		44/56		11	-	-		-		-		-	-	Good		
Zhang 2015	57. 3± 13	62. 5± 8	30. 4± 4	29. 9± 4	2.76±0.6		162. 3±28	167. 8±19	20	12	-		19/8 1	17/8 3	11	86	100	100	100		100		Good				
Zusterzee 1 2014	69 ±1 1	68 ±1 1	24 ±7	24 ±7	2.8 1± 0.4	2.8 5± 0.4	153± 21	154± 19	4 0	3 8	7 6	7 3	1.4 ±1. 0	1.2 ±0. 8	67/3 3	38/6 2	0	7 0	8 6	3 0	1 8	8 8	8 9	66	60	Very good	

Zusterzee 1 2015	70 ±1 1	70 ±1 1	24 ±7	24 ±7	3.0 8± 0.3	3.0 7± 0.3	152. 0±21	152. 0±21	4 2	4 2	7 9	7 7	1.5 0± 1	1.3 0± 1	69/3 1	45/5 5	3 4	2 3	6 1	8 0	-	8 7	8 8	63	59	Very good
Zusterzee 1 2015b (Compara)	90%>65		-	-	-	-	48	88	-	-	46	84	-	-	-	-	-	-	-	-	-	-	-	-	-	Satisfac tory

eTable 2. Additional information on characteristics of included studies.

Study ID	Cohort study type	Data Source	Country	Number of participants		Long term Follow-up (months) Median ± SD		Inclusion	Exclusion	Funding information
				Men	Women	Men	Women			
Achilli 2007	Retrospective	The InSync/InSync ICD Italian Registry.,	Italy	963	218	14±11		i) symptomatic chronic HF (NYHA class III-IV), (ii) left ventricle ejection fraction (EF) ≤ 35% on echocardiography, (iii) QRS duration.130 ms, (iv) at least one hospitalization for HF within the 12 months prior to device implantation	-	-
Adelstein 2016	Prospective	Registry of the University of Pittsburgh	USA	189	69	52±36 months		Age ≥80 years old, (ii) LV ejection fraction (LVEF), ≤ 35%, (iii) New York Heart Association (NYHA) class II-IV HF, (iv) QRS duration	-	E.C.A. receives research support from Medtronic and St. Jude Medical. J.L. and A.D.A. have no disclosures. S.J. receives research

		Medical Center					≥ 120 ms, and (v) no prior sustained or hemodynamically significant ventricular tachyarrhythmia (i.e. primary prevention indication).		support from Medtronic. D.S. receives research support from Medtronic and St. Jude Medical. J.G. receives research support from Biotronik, Medtronic, and St. Jude Medical. N.C.W. receives research support from Boston Scientific. S.S. receives research support from Boston Scientific, Medtronic, and St. Jude Medica
Auger 2012	Retrospective	Leiden University Medical Centre	The Netherlands	441	139	34	Patients with New York Heart Association (NYHA) functional class III or IV heart failure symptoms despite optimal medical therapy, LVEF, ≤35%, and QRS duration, ≥ 120 ms were selected for CRT	Patients with recent myocardial infarction (< 3 months) and decompensated heart failure requiring continuous intravenous therapy were excluded from	D.A. is financially supported by the 'Programme de bourse de perfectionnement et de fellowship du Centre Hospitalier de l'Université de Montréal (CHUM) et de la Fondation du CHUM'. S.H.E. is financially supported by the Ministry of Health Training Scholarship, Singapore. T.G.W. is financially supported by the Research Fellowship of the European Society of Cardiology

									the present analysis		
Auricchio 2007	Prospective	Registries from 4 European institutions	Italy	805	255	34			Moderate to severe HF caused by LVSD (EF \leq 35%) and QRS duration \geq 120ms; Hospitalized \geq 1 time in the previous year	-	Not reported
Bai 2008	Prospective	Cleveland Clinic	USA	418	124	27.05 \pm 17.89			1) moderate-to-severe symptomatic CHF (New York Heart Association [NYHA] class III or IV) refractory to optimal pharmacological therapy, (2) left ventricular ejection fraction (LVEF) \leq 35%, and (3) wide QRS complex (QRS duration $>$ 120 ms).	-	Grant of the Italian Society of Cardiology (SIC), Medtronic, Boston Scientific, and St. Jude Medical
Barra 2017	Prospective	French, British and Swedish	Multinational	4149	1158	40.8 \pm 28	43.4 \pm 29		Ischaemic or non-ischaemic dilated cardiomyopathy and no history of sustained ventricular arrhythmias	-	-

		Hospital centers								
Beca 2019	Retrospective	Nova Scotia ICD Registry	Canada	277	65	52.8±37.3	Two patient cohorts were identified for comparison. The de novo CRT-D group included patients with New York heart association (NYHA) Class II/III HF, left ventricular ejection fraction (LVEF) 35%, and QRS duration ≥130 ms (or ≥200ms if chronically paced) with a successful CRT-D implantation. The upgrade CRT-D group included those with the same criteria but had a pre-existing ICD or pacemaker.	patients who underwent primary prevention ICD implantation for arrhythmogenic right ventricular cardiomyopathy, ion channelopathies, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, or other indications were excluded	This project has been supported in part by the MagdyBasta Research in Medicine Studentship awarded to BogdanBeca in 2016. The funding source had no involvement in study design, collection, or analysis, in the interpretation of data, writing of the report, or decision to submit the article for publication	

								from this analysis, as were non-residents of Nova Scotia.	
Bilchick 2010	Retrospective	Medicare Implantable Cardioverter-Defibrillator Registry	USA	10866	4080	40	Patients included all had a QRSd of at least 120 ms and a left ventricular ejection fraction (LVEF) ≤ 0.35 . Patients with New York Heart Association (NYHA) HF class less than III or IV at the time of implantation were included because the NYHA classification provides a limited assessment and class scores significantly fluctuate over time in patients.	-	Funding was provided by an internal grant from the University of Virginia
Bleeker 2005	Retrospective	University Medical Center	Netherlands	137	36	21 \pm 14	The following selection criteria for CRT were applied: moderate-to-severe	Patients with a recent myocardial	-

							heart failure [New York Heart Association (NYHA) Class III or IV], LV ejection fraction (LVEF) \leq 35%, and QRS duration $>$ 120 ms with left bundle branch block configuration	infarction ($<$ 3months) or decompensated heart failure	
Borini 2016	Prospective	Web-based registry called RERAI (Registry of Emilia Romagna on Arrhythmia Interventions)	Italy	535	174	50.5 \pm 17	Mild to severe HF (NYHA class II-IV) and left ventricular ejection fraction \leq 35%	Device replacement and upgrades of a previous implant were excluded from the present analysis.	-

Boved a 2009	Prospe ctive	The Mona Lisa study	France	133	65	11.5±1.4	All patients were 18 years old with the following criteria for CRT-P implantation according to the current guidelines when the study was designed: New York Heart Association (NYHA) functional class III or IV, QRS duration 120 ms, left ventricular ejection fraction (LVEF) ≤ 0.40, and on optimal medical therapy. In addition, intra- and/or interventricular dyssynchrony was confirmed by echocardiography and tissue Doppler imaging in all patients.	Exclusion criteria included conventional recommendations for treatment with a CRT-D upon inclusion, 16 patients in whom transplantation was anticipated as preferable, unexplained syncope, myocardial infarction, 60 days before inclusion, non-optimal pharmacologic treatment,	This study was sponsored by Guidant, a Boston Scientific Company. We are indebted to the patients who participated in the Mona Lisa Study for their outstanding commitment and cooperation and to all study staff and investigators at the clinical sites. We thank Ludovic Trinquart (INSERM Centre d'Investigations E'pide'miologiques , Ho^pital Europe'en Georges Pompidou, Paris, France) for having reviewed statistical analysis of Mona Lisa study. Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov . Unique identifier NCT00180531 .
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								and coronary disease that might be treated by revascularization, and estimated life-expectancy, 6 months in patients with concomitant pathology.	
Cipriani 2016P	Retrospective	Italian Heart Transplant Centers	Italy	875	247	38.6±48	received Medtronic CRT defibrillator (CRT-D) in accordance with implantable cardioverter-defibrillator (ICD) and CRT guideline [HF in New York Heart Association (NYHA) class II, III, or IV, depressed ventricular function (left ventricular ejection fraction,	patients with mitral valve prolapse or flail, mitral valve repair or replacement before CRT implantation were excluded	This research was performed within the framework of the Italian Clinical Service, a project funded by Medtronic Italia, an affiliate of Medtronic Inc. No other funding sources were involved in the research.

							LVEF, ≤ 35%), and wide QRS complex >120 ms)]		
Cipriani 2016	Retrospective	Italian Heart Transplant Centers	Italy	405	102	48	All patients received CRT alone (CRT-P) or in combination with an implantable cardioverter-defibrillator (ICD) (CRT-D)	-	-
Delgado 2010	Prospective	Leiden University Medical Center	The Netherlands	341	56	21±66	patients were selected for CRT according to the presence of depressed LV ejection fraction (35%), together with NYHA functional class III or IV and QRS duration on the surface ECG120 milliseconds. The criteria to define ischemic heart failure were the presence of significant coronary artery disease (50% stenosis in 1 or more of the major epicardial coronary arteries)	Patients with recent myocardial infarction (3 months) or decompensated heart failure were excluded.	Drs Delgado, Marsan, and Nucifora are financially supported by the research Fellowship of the European Society of Cardiology and the European Association of Percutaneous Cardiovascular Interventions

							and/or a history of myocardial infarctions with ECG evidence of prior myocardial infarction.		
DiBiase 2008	Prospective	Cleveland Clinic and at Fondazione Cardio centro	Multinational	299	99	52.8±29	Indication to CRT was defined by functionality York Heart Association (NYHA) class III-IV despite medical treatment optimized according to currently available guidelines, LVEF ≤ 35% of ischaemic and non-ischaemic origin, ventricular conduction delay (QRS duration > 120 ms)	Patients who had a major cardiovascular event in the previous 6 weeks were not considered for CRT and included in the present registry.	Dr Luigi Di Biase is a Research Fellow supported by a grant from the Italian Society of Cardiology (SIC)
Dorin 2018	Prospective	Heart Center Leipzig	Germany	119	58	26±19	Aged ≥75 years; underwent de novo implantation of either a CRT-P or CRT-D; must have an established indication for CRT and	patients implanted with a CRT-P for antibradycardia pacing in the presence of mildly to	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

							primary preventive ICD therapy	moderately impaired LVEF and those implanted with a CRT-D for secondary prevention of SCD	
Echouffo-Tcheu gui 2016	Retrospective	NCDR-ICD Registry	USA	12408	6020	Up to 72 months follow-up	Identified patients aged , ≥ 65 years, with an LVEF of $\leq 35\%$ and a QRS duration of ≥ 120 ms, admitted to the hospital for the first-time CRT-D implantation between January 1, 2006, and December 31, 2009.	Excluded participants with an LVEF of $>35\%$ (n=34864), with a QRS duration of <120 ms (n=60726), not undergone their first CRT-D implantation (n=47083),	The Implantable Cardioverter-Defibrillator Registry is an initiative of the American College of Cardiology Foundation.

								<p>admitted for reasons other than device implantation (n=16363), had undergone an epicardial lead placement (n=925), had a previous placement of a pacemaker or an ICD (n=8245), had an implantation for secondary prevention (n=877), underwent a coronary artery bypass graft</p>	
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								surgery or percutaneous coronary intervention during the implantation hospitalization (n=46), and had myocardial infarction within 40 days before the index discharge (n=252).	
El-Saed 2009	Retrospective	Veterans Affairs (VA) Pittsburgh Healthcare System	USA	113	2	17.5±6.5	All patients, older than 21 years, meeting standard clinical indications who underwent transvenous pectoral implantation of CRT-D were included in the database (n=173).	As we intended to exclude patients who had a clinical diagnosis of a recent (<= 30 d) acute	-

								coronary syndrome, acute decompensation of chronic heart failure (CHF), revascularization procedure, or surgery	
Fantoni 2008	Retrospective	University Hospital of Magdeburg	Germany	266	89	34±29	At the time of implantation, all patients presented with New York Heart Association (NYHA) functional class III or IV despite stable (N3 months) optimized medical therapy, severe left ventricular systolic dysfunction of any etiology (ejection fraction, ≤35%, end-diastolic diameter >55 mm) and	-	-

							ventricular conduction disturbances (QRS-duration, ≥ 120 ms).		
Foley 2010	Retrospective	Good Hope Hospital	UK	248	74	36.66	underwent CRT device implantation in a single centre	-	Medtronic Inc and St Jude Medical provided funding for fellowships during the course of this study
Friedman 2015	Retrospective	NCDR ICD Registry (National registry for the entire United States)	USA	6229	3296	30	fee-for-service Medicare patients ≥ 65 years old with stage 3 to 5 CKD (glomerular filtration rate [GFR] < 60 ml/min/1.73 m ² , including those on dialysis) were eligible for CRT based on contemporary indications during the study period (ejection fraction [EF] $< 35\%$, QRS > 120 ms, New York Heart Association [NYHA] functional class III/IV); and could be linked to Medicare claims data.	were admitted during a non-elective hospitalization, were enrolled in the ICD registry at the time of generator change, required an epicardial lead, or had a prior pacemaker or defibrillator	-

Frigerio 2013	Retrospective	Niguarda-Ca'Granda Hospital	Italy	264	66	49	patients should have survived at least 6 months after CRT device implantation and have undergone a follow-up echocardiographic evaluation at 6,Ä12 months.	-	S. Bisetti and C. Campo are employees of Medtronic Italia. The other authors report no relevant relationships to the contents of this paper to disclose.
Gasparini 2014	Prospective	MULIN study	Multinational	2534	785	37±39	moderate to severe HF (New York Heart Association [NYHA] class II-ambulatory IV), QRS duration,≥120 ms, and LV ejection fraction (LVEF),≤35%despite maximum tolerated pharmacologic therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, B-blockers, aldosterone antagonists, and	Patients undergoing upgrade to CRT from conventional pacemakers and patients with primary valvular disease were excluded	The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

							diuretics for at least 2 months. Patients in NYHA class II who had a recent HF hospitalization were also included.		
Gasparini 2015	Retrospective	European centres	Multinational	4037	1116	39	systolic HF in NYHA class III or ambulatory (or II in the case of a recent hospitalization because of HF), LVEF, $\leq 35\%$ and QRS, ≥ 120 ms, despite maximum tolerated pharmacological therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers, beta-adrenergic blockers, diuretics, and spironolactone for at least 2 months.	contraindications to cardiac pacing; myocardial infarction or acute coronary syndrome within the previous 3months; severe structural valvular heart disease; and the presence of co-morbidities likely to curtail	M.G. is a member of the advisory board of Medtronic. C.K. is a statistical consultant for Medtronic. C.L. has received consulting fees and research grants from Medtronic, Sorin, St Jude Medical, Biotronik, and Boston Scientific. M.L. has received consulting fees for Medtronic, Boston Scientific, St Jude Medical, and Sorin. A.A. has received consulting fees and research grants from Medtronic, Sorin, Biotronik, ERB Systems, Abbott, and Cordis. M.S. has received consulting fees and research grants from Medtronic, St. Jude Medical, and Biotronik. G.B.

								survival to 12 months or less.	has received speaker fees for Medtronic. A.P. is on the advisory boards of Medtronic and Sorin. F.L. has received consulting fees and research grants from Medtronic, Sorin, St Jude Medical, and Boston Scientific
Gilliam 2007	Prospective	HF-HRV Registry (129 centers)	USA	1111	310	11.3	Capable of maintaining outpatient follow-up visits and were over the age of 18. Study participation required a programmed pacing mode of VDD or DDD	Patients were excluded if rate-responsive pacing (i.e., chronic atrial fibrillation patients) was required.	This trial is sponsored in full by Boston Scientific CRM.
Gu 2017	Retrospective	Fuwai Hospital	China	215	97	45.84	DHCM was defined as LV systolic dysfunction [left ventricular ejection fraction (LVEF) < 50%] in the presence of (1) unexplained LV hypertrophy or (2) previous documentation of	The patients were excluded if LV dysfunction was secondary to one of the following:	-

						<p>unexplained LV hypertrophy on echocardiography, or (3) proven familial HCM with at least one relative who had an unequivocal diagnosis. The diagnosis of the ICM was based on LV systolic dysfunction and a clinical history of prior myocardial infarction, prior percutaneous coronary intervention, or prior coronary bypass surgery, or evidence of clinically significant coronary stenosis (at least 75% narrowing of at least one of the three major coronary arteries), similarly to the assignment used in large CRT trials</p>	<p>hyper-tension (> 160/100 mmHg), history of alcohol abuse (> 100 g alcohol/day), tachycardia-induced cardiomyopathy, Corpulmonale, diseases of pericardium, or congenital heart dis-eases.</p>	
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Hoke 2014	Retrospective	Department of Cardiology of the Leiden University Medical Center	The Netherlands	618	180	38.6±29	Patients underwent CRT device implantation according to the presence of LV ejection fraction (EF) , ≤35%, a QRS duration ,≥120 ms, and New York Heart Association (NYHA) functional class II to IV heart failure symptoms, despite optimal medical therapy. ¹⁰ The cause of heart failure was considered ischemic in the presence of significant coronary artery disease (> 50% stenosis in ,≥ 1 major epicardial coronary artery) on coronary angiography and a history of myocardial infarction or revascularization.	Patients with decompensated heart failure before the implantation or recent myocardial infarction (<3 months) were excluded	Department of Cardiology of Leiden University Medical Centre received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, Lantheus Medical Imaging, St. Jude Medical, Edwards Life Sciences & GE Healthcare. Dr Delgado received consulting fees from St. Jude Medical and Medtronic.
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Iler 2007	Retrospective	Cleveland Clinic	USA	255	80	27±15	Symptomatic New York Heart Association (NYHA) functional classes II to IV congestive heart failure that was refractory to conventional pharmacologic therapy	-	The current study was performed without funding
Jacobsson 2016	Retrospective	Tertiary care center	Sweden	417	79	24	Inclusion criteria were HF with dilated or ischemic cardiomyopathy, optimal pharmacologic HF treatment and QRS duration ≥120 ms, meeting standard guideline criteria for CRT implantation	Patients with “nonstandard” CRT indication or with failed CRT implant were excluded, as were patients without available digital baseline (preimplant) electrocardiogram (ECG).	This research was supported in part by grant #1R01HL118277 from national Institute of Health (Bethesda, MD) (LGT). This research was supported by grants from the Swedish Heart-Lung Foundation (R.B., P.G.P.), by Per Westling Memorial Fund (R.B.), Knut and Alice Wallenberg Fund (R.B.), the Maggie Stephen Fund (R.B.) and by governmental funding of clinical research within the Swedish National Health Service (R.B., P.G.P.)

Jeevantham 2016	Prospective	University of Kansas	USA	407	151	12.6±5	All patients who underwent CRT implantation at University of Kansas between 2000 and 2009 were reviewed from a prospective CRC registry and patients who had pre and post CRT renal function studied were included in our study.	All patients who underwent CRT implantation at University of Kansas between 2000 and 2009 were reviewed from a prospective CRC registry and patients who had pre and post CRT renal function studied were included in our study.	No financial support provided to the current study for any of the authors.
Kelarijani 2008	Prospective	Heart Hospital	Poland	50	15	6	Patients were included in the study if they had severe congestive HF that was symptomatic (New York	-	-

							Heart Association [NYHA] class III or IV) despite optimal drug therapy including diuretics, angiotensin-converting enzyme inhibitors, B-blockers, spironolactone, and angiotensin agonists at the maximum tolerated dosage, and had left ventricular (LV)dysfunction with ejection fraction (LVEF) $\leq 35\%$, and QRS duration $> 120\text{ms}$ with left bundle branch block configuration.		
Khatab 2014	Prospective	Thorax Institute, Hospital Clinic	Spain	468	132	36 \pm 29	All patients with symptomatic heart failure (NYHA class II-IV) despite optimal drug therapy, LVEF, $\leq 35\%$, and QRS duration >120 ms were	-	This study was supported in part by a Thematic Networks in Health Cooperative Research grant [REDSINCOR RD 06/0003/008] from the Spanish Health Ministry, Madrid, Spain, and a grant for

							included, as well as patients with LVEF, ≤ 35% with complete atrioventricular block who received a pacemaker or defibrillator and were in functional class II or higher, regardless of QRS duration		recognized research groups from AGAUR: Agència de Gestió d'Ajuts Universitaris i de Recerca, [2009 SGR 1104].
Khazanie 2014	Retrospective	(ADHERE) and the National Cardiovascular Data Registry's Implantable Cardioverter Defibrillator (ICD) Registry.	USA	50775	3584	36	We included patients from the ICD Registry who were admitted between April 1, 2006, and December 31, 2009, and underwent CRT-D implantation during the hospital stay. To ensure comparability with the ADHERE population, we only included patients from the ICD Registry who were admitted primarily for heart failure and not specifically for the device implantation	We excluded patients who received CRT-D for secondary prevention or had an epicardial lead placement. We included patients from ADHERE who were admitted between	This study was funded under contract HHS A290200500321 (Duke University Developing Evidence to Inform Decisions About Effectiveness [DEcIDE] Center) from the Agency for Healthcare Research and Quality as part of the DEcIDE program. The project was also supported, in part, by grant number U19HS021092 from the Agency for Healthcare Research and Quality. Dr Khazanie was supported, in part, by grant

								January 1, 2002, and March 31, 2006, and did not receive an ICD during the hospital stay. We excluded patients from ADHERE who underwent defibrillation during admission.	T32HL069749 from the National Heart, Lung, and Blood Institute.
Kobe 2017	Prospective	German Participating centers	Germany	734	222	15.4	patients undergoing CRT operation	-	-
Kreuz 2012	Retrospective	University hospital	Germany	192	47	43±30	Implantation of CRT-D	-	-
Kronborg 2008	Retrospective	Aarhus University Hospital	Denmark	144	35	61	included consecutive patients treated at Aarhus University Hospital, Skejby	-	This study was supported by the Danish Heart Foundation (07-4-B695-A1464-22378).

							from January 1, 1997 to December 31, 2002. Patients undergoing upgrade of conventional devices to CRT in the period were also included.		
Lee 2014	Retrospective	Samsung Medical Center, Gangneung Asan Hospital, and Hanmaeum General Hospital	Korea	27	20	17.5	New York Heart Association (NYHA) function class III/IV symptoms despite optimal medical therapy due to either ischemic or nonischemic cardiomyopathy with a left ventricular (LV) ejection fraction, $\leq 35\%$ and a QRS duration, ≥ 120 ms	-	-
Leyva 2011	Prospective	Good Hope Hospital	UK	428	122	25.2	Patients who successfully underwent CRT device implantation	-	-
Leyva 2017	Prospective	Good Hope	UK	154	98	45.6	All patients underwent successful CRT device	Exclusion criteria	Prof. Leyva has held consultancies with and has received research

		Hospital and Queen Elizabeth Hospital					implantation and pre-implantation CMR from July 2002 to January 2017.	included a history of myocardial infarction, coronary revascularization, or diagnosis of ischemic cardiomyopathy on the basis of other investigations (e.g., nuclear imaging); the ischemic pattern of the scar on CMR; a diagnosis of hypertrophic or restrictive cardiomyopathy	funding from Medtronic, Boston Scientific, St. Jude Medical, and Liva Nova. Dr. Patel has received speaking honoraria from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose
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								y, primary valvular disease, sarcoidosis, amyloidosis, or myocarditis made on the basis of CMR or another investigation (e.g., echocardiograp hy, cardiac biopsy, and/or positron emission tomography); and NICM and scar patterns other than MWF	
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								(patchy or subepicardial)	
Leyva 2018	Retrospective	Good Hope Hospital and Queen Elizabeth Hospital	UK	1146	404	56.4 (IQR, 28.8-84)	All Patients were recruited from two centres	-	This study was funded by an unrestricted educational grant from Boston Scientific.
Leyva 2019	Retrospective	All public Hospitals	UK	32840	10890	26.4	first CRT device implantation	-	This study was funded by an unrestricted educational grant from Boston Scientific.
Liang 2020	Retrospective	Hospital	China	157	65	36	1) moderate-to-severe heart failure despite optimal medical treatment including angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), b-blocker, and spironolactone; 2) QRS duration ≥ 120 ms; and 3) LVEF $\leq 35\%$	1) upgrade from a cardiac pacemaker or implantable cardioverter defibrillator (ICD) to a CRT device; 2) implantation of CRT-D device for secondary	This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

								prevention of sudden cardiac death (SCD)	
Lilli 2007	Prospective	University hospital and general hospital	Italy	149	46	27.7	Advanced HF (NYHA III-IV functional class) secondary to dilated cardiomyopathy of any etiology; LVEF < 40%; QRS duration, ≥ 120 ms.	surgically correctable significant valvular disease, suspected acute myocarditis, acute coronary syndrome within three months, or symptoms amenable to revascularization.	-
Lin 2010	Retrospective	Mayo Clinic	USA	384,	98	36.45±26.5 5	Underwent implantation of a CRT device	Underwent implantation of a CRT device	Dr D.L.H. has the following conflicts: Educational speaking; Medtronic, Boston Scientific, St

									Jude Medical,Sorin/ELA, Sponsored research; Medtronic, Boston Scientific, StJude Medical, Steering committee; Medtronic, Advisory board;Boston Scientific, Sorin/ELA, St Jude Medical. None of the otherauthors has any conflicts
Looi 2014	Retrospective	Tertiary referral centre (Papworth Hospital)	UK	385	115	29±14	patients implanted with either CRT-D or CRT-P	-	-
Looi 2019	Retrospective	Hospitals in Northern New Zealand	New Zealand	135	42	12	de novo CRT-pacemaker (CRT-P) and CRT-defibrillator (CRT-D), all upgrades from pacemakers to CRT-P or CRT-D, upgrades of implantable cardioverter-defibrillators (ICD) to CRT-D using transvenous or epicardial	Same day admissions	The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

							left ventricular (LV) lead placement were included. Presentation to hospital requiring an overnight stay.		
Loring 2013	Prospective	Centers for Medicare & Medicaid Services	USA	1074 75	3716 7	28±23	Medicare patients who received CRT-D and were continuously enrolled in Medicare Part A (inpatient hospital coverage) and B (outpatient medical coverage) for ≥ 6 months before CRT-D implantation	-	-
Lumens 2015	Prospective	University of Pittsburgh Medical Center	USA	141	50	24	The study group began with 210 consecutive New York Heart Association Class II to IV HF patients with QRS duration ,≥ 120 ms and LVEF , ≤ 35% referred for CRT with routine indications.	echocardiographic images were unsuitable for quantitative strain analysis.	Dr Lumens received a grant within the framework of the Dr E. Dekker program of the Dutch Heart Foundation (NHS-2012T010). Dr Gorcsan received research grant support from Biotronik, GE, Medtronic, St. Jude Medical, and Toshiba. Dr Prinzen received research grants from Medtronic, Boston Scientific, EBR Systems,

									Biological Delivery Systems (Johnson & Johnson), MSD, and Proteus Biomedical. Dr Schwartzman received research grants from Medtronic, Boston Scientific, and Biosense.
Marijon 2015	prospective	multicentre registry	France	1266	370	22.19±6	all CRT recipients	-	CeRtiTuDe was funded by grants from the French Institute of Health and Medical Research (INSERM) and from the French Society of Cardiology. A specific research grant support was funded specifically for the certitude cohort study from Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical. Funding to pay the Open Access publication charges for this article was provided by the French Society of cardiology
MartinielliFi	Retrospective	Heart Institute of the	Brazil	276	150	28.8±26	inclusion criteria were age over 18 years and systolic heart failure caused by CCC	-	-

Iho 2018		University of Sao Paulo					(diagnosed by two serologic tests), patients with DCM and ICM, under optimized medical therapy		
Maso udi 2014	Retros pective	NCDR- ICD	USA	2552	993	36	65 years or older; were admitted specifically for first-time device implantation; were discharged home between 1 April 2006 and 31 December 2009; were enrolled in fee-for-service Medicare at discharge; and might be considered for CRT-D on the basis of a history of heart failure, an LVEF of 0.35 or less, and a QRS duration at least 120 ms	We excluded patients who received device therapy for secondary prevention, received epicardial leads, were admitted for reasons other than device implantation, had coronary revascularization during the index admission, had	Agency for Healthcare Research and Quality

								a prior ICD pacemaker, or had a myocardial infarction within 40days before the index discharge,	
Miller 2011	Retrospective	Brigham and Women, Ås Hospital	USA	357	123	67.92	The target population was patients in whom CRT was being initiated	excluding those with prior history of CRT	Amy Leigh Miller: NIH/NHLBI T32 Training Grant
Mohamed 2020	Retrospective	The National Inpatient Sample (NIS) is the largest publicly available	USA	281122	119701	-	All adults (age \geq 18 years) undergoing de novo CRT implantation (CRT-P or CRT-D) during hospitalization from 2004 to 2014 were included in this study, as identified by the International Classification	We excluded CRT upgrades and records with missing data on the following variables: age, elective	This work constitutes part of a PhD for M.O.M. that is supported by Medtronic. Medtronic was not involved in the conceptualization, design, conduct, analysis, or interpretation of the present study.

		all-payer database					of Diseases, Ninth Revision (ICD-9) codes given in Supplemental Table S1.	admission, primary expected payer, and median household income	
Mohamed 2019	Retrospective	The National Inpatient Sample (NIS) is the largest publicly available all-payer database	USA	1637 121	1178 492	-	All adults (aged ≥ 18 years) undergoing de novo CIED implantation (PPM, CRT-P, CRT-D, or ICD) during hospitalization	Records with missing data on the following variables: age, executive admission, primary expected payer, median household income, and hospital size (number of	This work constitutes part of a PhD for Dr Mohamed Mohamed that is supported by Medtronic Ltd. Medtronic Ltd was not involved in the conceptualization, design, conduct, analysis, or interpretation of the current study

								beds) and location.	
Moore 2019	Prospective	Australian Admitted Patient Collection and New Zealand National Minimum Dataset (All public and most private sector hospitals and day procedure centers in New Zealand)	Australia	5099	2450	-	All patients aged > 18 years undergoing a new PPM, ICD, or CRT implant (acute or elective) from 2010 to 2015 were included	CIED implant was a device replacement or upgrade; Patients undergoing CIED implantation during the same hospital admission as other procedures (early complications could not be separated from the outcome of CIED implant-related events;	This research is funded by grants from the HCF Research Foundation, The National Heart Foundation of Australia, The University of Adelaide, and The Hospital Research Foundation.

								Patients discharged against medical advice; Patients lacking at least 90 days of follow-up to allow post-discharge outcomes to be assessed.	
Mooyart 2011	Prospective	On-going registry	Belgium	380	136	34±25	New York Heart Association (NYHA) class III or IV despite optimal pharmacologic treatment, QRS duration \geq 120 ms, and left ventricular (LV) ejection fraction \leq 35%	-	-

Morani 2013	Prospective	Contact Italian Registry	Italy	298	76	55±17	patients with mild or severe symptomatic chronic HF (NYHA class II-IV) despite pharmacological therapy, LVEF, ≤ 35%, sinus rhythm, and a wide QRS complex (≥ 120 ms in NYHA III-IV patients, ≥150 ms in NYHA II) on base-line evaluation.	Patients with recent myocardial infarction (3 months) or with decompensated HF were excluded.	-
Munir 2016	Retrospective	Hospitals of the University of Pittsburgh Medical Center (UPMC)	USA	363	149	40.8±37	All patients belonged to New York Heart Association (NYHA) class III/IV for HF symptoms, had QRS duration 120 milliseconds, and LVEF ≤ 35%.	Not reported	Medtronic and St. Jude Medical
Nagy 2015	Prospective	Heart and Vascular Center, Semmelw	Hungary	72	21	24	The inclusion criteria included: symptomatic heart failure [New York Heart Association (NYHA) II-IV a functional class] treated	Exclusion criteria were malignancies, diagnosed inflammatory	This work was supported by Hungarian Foundation Programs: János Bolyai Research Scholarship of the Hungarian Academy of Sciences (GSZ, LG) and the

		eis University					with maximal tolerated medical therapy for at least 3 months prior to inclusion; LV ejection fraction (LVEF) below 35%; QRS duration wider than 120 ms (measured on surface electrocardiogram using the widest QRS complex from II, V1 and V6 leads)	diseases and primary genetic cardiomyopathies.	Hungarian Scientific Research Foundation (OTKA 105555). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Nevzorov 2018	Retrospective	Medical Center	Israel	144	34	12	New York Heart Association (NYHA) function class III/IV receiving optimal medical therapy, left ventricular ejection fraction (LVEF) , ≤ 35%, and QRS width ≥ 120 ms.	-	-
Ozablove 2010	Prospective	University Hospital	Czech Republic	90	28	12	chronic heart failure, depression of LV systolic function with EF <30% with optimal pharmacological	acute inflammatory disease of any etiology, acute	-

							medication for more than three months, presence of left Tawar's shoulder block (LBBB) on the ECG and spread of QRS complex> 120 ms on the ECG	myocardial infarction or stroke in the last three months, patients did not cooperate, had blood clotting disorders, acute bleeding, had unclear anemia.	
Perini 2013	Retrospective	Italian Centres	Italy	421	138	30±27	All enrolled patients had been implanted according to current International Guidelines: moderately or severely symptomatic HF despite optimal medical treatment, severe systolic dysfunction of left ventricle (LV)with ejection fraction	-	L.P. is a consultant for Medtronic, Inc.; Boston Scientific Corporation; St Jude Medical, St Paul, Minnesota; and Sorin, Milano, Italia. The other authors have no disclosures to be declared.

							(EF), $\leq 35\%$ and prolonged QRS (≥ 120 ms).		
Pfau 2009	Retrospective	Otto-von-Guericke-University Magdebur	Germany	258,	83	24 \pm 6	All patients who underwent CRT-D implantation at the University Hospital Magdeburg between 1996 and 2005 were included.	-	-
Prochnau 2011	Prospective	Hospital	Germany	121	22	19	A total of 143 consecutive heart failure patients with an LV ejection fraction of 35% or less and a QRS duration ≥ 120 milliseconds on electrocardiogram (ECG) or permanent right ventricular pacing were included in our study	Patients with a recent (≤ 3 months previous) myocardial infarction or with revascularization-correctable coronary artery disease were excluded.	-
Proviencia 2016	Retrospective	DAI-PP study (Defibrilla	France	4702	837	33 \pm 64	At least 18 years old at the time of ICD implantation, all patients with ischemic	Having an ICD implant for secondary	The study was funded by public sources, including the French Institute of Health and Medical

		<p>teur Automatique Implantable Prevention Primaire; NCT0199 2458)Registry</p>				<p>cardiomyopathy or nonischemic cardiomyopathy, implanted with an ICD (biventricular, single chamber, or dual chamber) in the setting of primary prevention</p>	<p>prevention purposes or for primary prevention without structural heart disease (including Brugada, long QT syndrome, among others) or structural heart disease other than ischemic or nonischemic cardiomyopathy (hypertrophy cardiomyopathy, noncompaction cardiomyopathy</p>	<p>Research (INSERM) and the French Society of Cardiology, and was coordinated by Clinique Pasteur, Toulouse and the Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, in France.</p>
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								y, and arrhythmogenic right ventricular dysplasia.	
Reitan 2015	Retrospective	Tertiary referral university hospital	Sweden	589,	116	58.9	all consecutive patients receiving CRT implants	Patients with unsuccessful left ventricular lead implant or immediate explant (within 2 months of implant, e.g., due to systemic infection) and patients aged less than 18 years at the time of implant were excluded from the analysis, as	Dr. Platonov and Dr. Borgquist were supported by governmental funding of clinical research within the Swedish National Health Service. Dr. Platonov was also supported by a grant from the Swedish Heart and Lung Foundation. Dr. Bakos has received research grants from Lund University in cooperation with Skane University Hospital.

								were patients with secondary prophylactic implantable cardioverter-defibrillator (ICD) indication	
Rickard 2011	Retrospective	Cleveland clinic	USA	475	193	50.4	For inclusion, patients had the following characteristics: first implantation of a CRT device at our institution, New York Heart Association functional class II to IV symptoms on optimal medical therapy, a pre-CRT echocardiogram with an LVEF, ≤ 40%, and a US social security number.	-	No extramural funding was used to support this work.
Risum 2012	Prospective	Duke University	Multinational	95	26	Max 48	these subjects comprised a consecutive cohort of	Subjects were excluded if	-

		Medical Center and Gentofte University Hospital					patients with LVEF, ≤35%, QRSduration, ≥120 ms, and New York Heart Association II-IV functional class, despite optimal pharmacological therapy. Overall, 131 patients were identified (71 patients from Duke University Medical Center, Durham, NC, USA, between 2004 and 2006 and 60 patients from Gentofte University Hospital, Copenhagen, Denmark, between 2006 and 2007)	they had significant primary valve disease, atrial fibrillation, or acute coronary syndrome or revascularization within 3 months of the baseline echocardiography	
Rolin k 2009	Retrospective	Hospital	Netherlands	83	36	18±45	New, York heart association (NYHA) class III or IV heart failure, left ventricular ejection fraction < 30%, a wide QRS complex and/or LV desynchrony at echocardiography (a	Patients with right bundle branch block were excluded.	-

							measurement of septal to lateral delay on tissue doppler imaging on top of the signal at echocardiography).		
Roubicek 2015	Retrospective	Regional Hospital Liberec	Czech Republic	248	81	37.2±25	CRT was indicated according to current guidelines of the European Society of Cardiology: symptomatic chronic HF despite optimal medical therapy, with LV ejection fraction ≤35% and QRSd≥120 ms.13 Patients were included when they had spontaneous atrioventricular conduction, left bundle branch block (LBBB) or intraventricular conduction delay (IVCD) according to the Strauss criteria,14 and when QLV	We excluded patients who underwent early (<1 year after the enrolment) reimplantation of the LV lead or electric reposition of the multipolar lead. Patients with delayed reimplantation of the LV lead (n=10) were included, and	Dr Kautzner is a member of scientific advisory board for Biosense Webster, Boston Scientific, Medtronic, St Jude Medical, and received speaker's honoraria from Biosense Webster, Biotronik, Boston Scientific, Hansen Medical, Medtronic, and St Jude Medical. Dr Polasek reports receiving lecture fees from St. Jude Medical and Medtronic. The other authors report no conflicts.

							measurement was available at the index CRT procedure. Several patients (n=14) with a surgically implanted LV lead were also included; these had either an LV lead implanted during previous open heart surgery or a video-thoracoscopically implanted LV lead because of technical failure of the transvenous approach.	original QLV at the index implantation was considered relevant.	
Shala by 2008	Retrospective	Tertiary hospitals	USA	235	35	19.4±9	Patients meeting standard clinical indications who underwent the implantation of CRT-capable defibrillator systems were included in the database	Patients who did not undergo baseline echocardiography 6 weeks before the implantation date were not included.	-

Sharma 2015	Retrospective	Massachusetts General Hospital Heart Center	USA	395	116	Median 21.9	all patients receiving CRT	There were 3 patients with hyperthyroidism, which was too small a number for relevant analysis, and so these patients were excluded from the study; 1 of these 3 patients was on amiodarone.	-
Shen 2010	Retrospective	Creighton University Medical Center	USA	73	27	17.3±10.6	The criteria for bi-ventricular pacemaker implantation is according to ACC/AHA 2005 Guideline: [12] included 1) left ventricular ejection fraction (LVEF) ≤ 35%; 2) New York Heart Association	Patients with atrial fibrillation and mitral stenosis were excluded.	-

							(NYHA) class III–IV; 3) QRS duration (QRSD) \geq 120 ms; and 4) Optimal pharmaceutical regimen established prior to implant. QRSD in all patients was measured from surface electrocardiograms using the widest QRS complex in leads II, V1 and V6 on a 12 lead surface electrocardiogram (ECG).		
Sjoblom 2015	Retrospective	Four tertiary care hospitals	Sweden	713	152	35 \pm 18	All patients who had a primary preventive ICD implanted because of heart failure, defined as LVEF \leq 35%	Patients with a history of previous sustained ventricular arrhythmias, cardiac arrest, Brugada and Long QT syndromes	-

								familial cardiomyopathies, such as arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy.	
Smit 2011	Prospective	University Medical Center Groningen	The Netherlands	250	88	27±19	Eligibility criteria for CRT were based on the standard guidelines and included New York Heart Association functional class III or IV despite optimal pharmacological treatment, left ventricular ejection fraction ≤35%, left ventricular end-diastolic diameter ≥55 mm, and QRS duration ≥130 ms.	-	This study was supported by unrestricted educational grants from Medtronic, Biotronik, and St Jude Medical. V.G. reports receiving grant support from Medtronic, Biotronik, and St Jude Medical.

Stabile 2009	Prospective	five Italian medical centers (Maddaloni, Mercogliano, Mirano, Tricase, Frosinone)	Italy	179	54	57.5,	59.1	All patients were enrolled according to the following criteria: (1) chronic HF with New York Heart Association (NYHA) functional classes II-IV; (2) left ventricle (LV) ejection fraction (EF), ≤ 35% on echocardiography, (3) QRS duration, ≥ 120 ms with left bundle brunch block morphology.	-	-
Stabile 2015	Prospective	five Italian medical centers (Maddaloni, Mercogliano, Mirano, Tricase,	Italy	179	54	18±9		In the present analysis, we included all patients who were in sinus rhythm at the time of CRT implantation and presented with left bundle branch block (LBBB).	excluded patients undergoing replacement of a CRT device or an upgrade from a pre-existing device to CRT	-

		Frosinone)								
Stiche rling 2018	Retros pective	Registry data from 14 centres in 11 European countries	Multinat ional	4076	957	33±29		Patients with ischaemic or non-ischaemic cardiomyopathy, a primary prevention ICD and a LVEF ≤ 35%	-	EU-CERT-ICD is funded by the European Commission within the 7th Framework Programme under Grant Agreement n602299.
vanBo mmel 2011	Retros pective	single- center registry	The Netherla nds	392	98	26±21		all patients referred for CRT implantation	-	Medtronic, Biotronik, Boston Scientific, BMS Medical Imaging, St. Jude Medical, Edwards Life Sciences, and GE Healthcare
Varm a 2014	Retros pective	Cleveland Clinic	USA	107	105	2.5± 2	2.7± 2	Patients with nonischemic cardiomyopathy (NICM)	significant coronary artery disease (1 or more of 450% obstruction on coronary arteriogram, prior coronary bypass surgery, or	-

									percutaneous coronary intervention and clinical history of myocardial infarction)	
Varm a 2017	Retrospective	Heart and Vascular Institute	USA	58	72	26.4±15.6		Patients with only non-ischemic cardiomyopathy (NICM) and true LBBB	-	-
Varm a 2017b (Survival)	Retrospective	Device implant registration at St. Jude Medical, Inc, the Merlin.net RM, system, the 2012 American	USA	1745 53	9491 8	2.9± 0.7	2.9± 0.6	Patients implanted with CIEDs capable of automatic radio frequency-enabled RM	patients enrolled in a clinical trial or with a follow-up duration <90 days	This research was funded by St. Jude Medical, Inc.

		Community Survey of the US Census, and the US Social Security Death Index Master File							
Wang 2017	Retrospective	University of Pittsburgh Medical Center	USA	363	149	45.7	Aged ≥ 75 years at the time of the implant were included in this study. All patients had New York Heart Association Class III/IV heart failure symptoms, a QRS duration of ≥ 120 ms, and an LV ejection fraction of $\leq 35\%$	-	-

Wang 2019	Retrospective	University of Pittsburgh Medical Center	USA	55	68	72.4±52	LBBB, NICM	-	Research funding from NHLBI (SS), Boston Scientific (SS) and Medtronic (EA, SS).
Wilcox 2014	Prospective	IMPROVE HF, a prospective observational cohort of patients being treated at outpatient cardiology (including multispecialty) practices.	USA	5485	2261	-	LVEF ≤ 35%; primary or secondary diagnosis of HF or prior myocardial infarction with left ventricular systolic dysfunction; aged ≥ 18 years	Patients were not eligible to participate in the IMPROVE HF if they were not expected to survive for 12 months because of medical conditions other than HF or had undergone heart transplant surgery.	Medtronic Inc. (Minneapolis, MN) provided material and financial support for the IMPROVE HF. Outcome Sciences performed data abstraction and checks, stored site-specific and aggregate data, and provided benchmarked quality-of-care reports to participating sites with funding from Medtronic. The authors had full access to the data, had complete control and authority over manuscript preparation and the decision to publish, and take responsibility for data and manuscript integrity. This manuscript was submitted to Medtronic before submission for

									publication, and all authors have read and agreed to the written content.
Wokh lu 2009	Retrospective	Mayo Clinic	USA	399	106	31.2±39	Indications for CRT were HF symptoms despite optimal medical therapy (NYHA class II or greater), left ventricular ejection fraction (LVEF) ≤ 35%, and QRS duration ≥ 120 ms with the exception of select patients with < QRS 120 ms.	-	-
Xu 2012	Retrospective	Mayo Clinic	USA	562	166	44.4 (IQR 22.8-63.6)	left ventricular ejection fraction (LVEF) of ≤ 35% or less, New York Heart Association (NYHA) functional class-III or class-IV, QRS duration of 120 milliseconds (ms) or longer and were unresponsive to optimal medical therapy.	-	-

Yanag isawa 2015	Retros pective	Nagoya University Hospital	Japan	91	34	37. 2±22	patients with heart failure who underwent CRT-D	-	-
Yokos hiki 2017	Retros pective	Japan Cardiac Device Treatment Registry (JCDTR) (378 medical facilities in Japan)	Japan	535	182	21±12	All patients with implantation of CRT for primary prevention	-	-
Yu 2005	Prospe ctive	2 university hospitals	The Netherla nds	103	38	23.17±16.3 7	The inclusion criteria included severe symptomatic heart failure despite optimized medical therapy, LV systolic dysfunction with an LV ejection fraction (EF) < 40%, and QRS duration >	Two patients died (1 refractory heart failure, 1 sudden cardiac death) before the 3- to 6- month	-

							120 ms. Serial echocardiographic studies with tissue Doppler imaging (TDI) were performed before and 3 to 6 months after CRT to assess LV reverse remodeling.	echocardiographic follow-up; therefore, data for these patients were excluded from the current analysis.	
Zabar ovskaj a 2012	Retrospective	University Hospital	Sweden	500	119	44±26.2	Patients who received CRT alone (CRT-P) or in combination with an implantable cardioverter-defibrillator (ICD) (CRT-D)	Patients included in a trial on atrioventricular junction ablation and pacing for permanent atrial fibrillation, and children	F.G. has received speakers' and consultant fees from Medtronic Inc., Kista, Sweden, and St. Jude Medical, Inc., Jaërfa'lla, Sweden. F.B. has received funding from Medtronic Inc., Kista, Sweden and speakers' fees from Medtronic Inc., Kista, Sweden, St. Jude Medical, Inc., Jaërfa'lla, Sweden, and Vitatron Inc., Kista, Sweden. J.H. has received speaker' fees from Medtronic Inc., Kista, Sweden, St. Jude Medical, Inc., Jaërfa'lla, Sweden and Vitatron Inc., Kista,

									Sweden. C.L. has received funding from Medtronic Inc., Kista, Sweden and speakers' fees from Medtronic Inc., Kista, Sweden, St. Jude Medical, Inc., Ja'rfälla, Sweden, and Vitatron Inc., Kista, Sweden. L.H.L. has received consultant fees from St. Jude Medical, Inc., Ja'rfälla, Sweden.
Zardkoohi 2007	Retrospective	Massachusetts General Hospital	USA	91	26	12	New York Heart Association (NYHA) Class III or IV, left ventricular ejection fraction (LVEF) ≤ 35%, and QRS duration ≥ 120 ms. All patients were on optimal medical therapy for CHF before CRT.	-	-
Zhang 2009	Prospective	University hospital	China	88	31	39±24	The inclusion criteria for CRT included refractory HF despite optimal medical therapy, LV systolic	Four patients died (one refractory HF, two sudden	This study was supported by a research grant from Li Ka Shing Institute of Health Sciences.

							<p>dysfunction with ejection fraction, $\leq 40\%$, and QRS duration ≥ 120 ms.</p> <p>Coronary heart disease was confirmed in 52 patients (44%), who had past history of myocardial infarction and/or positive findings on coronary angiogram or underwent percutaneous coronary intervention.</p>	<p>cardiac death (SCD), and one pneumonia) before the three-month follow-up, and were excluded from analysis as there was no echocardiographic follow-up data.</p>	
Zhang 2015	Prospective	First Affiliated Hospital of Xinjiang Medical University, China	China	57	23	24	<p>The study inclusion criteria were as follows: 1) heart failure was primarily caused by either ischemic or non-ischemic cardiomyopathy; 2) pre-implantation QRS duration ≥ 120 ms; 3) NYHA heart failure status stage \geq II, and 4) LVEF $\leq 35\%$.</p>	<p>1) heart failure was primarily caused by either valvular heart disease or metabolic disease; 2) QRS duration < 120 ms; 3) QRS complex</p>	-

								showing complete RBBB; and 4) an anticipated survival time < 2 years.	
Zuster zeel 2014	Retros pective	NCDR National Cardiovas cular Data Registry (NCDR)	USA	2035 0	1154 2	34.8±17	Received a CRT-D device	We excluded patients with a QRS of <120 ms or >220 ms, epicardial leads, a history of atrial fibrillation, or a prior pacemaker or ICD; those who received a CRT-D device for secondary prevention of sudden cardiac	This project was conducted under a contract between the American College of Cardiology (ACC) and the U.S. Food and Drug Administration (FDA) and was supported by the FDA Office of Women, Health and by a research fellowship from the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the FDA.

								death or had missing data on sex, QRS morphology, or duration; patients who could not be linked to the Death MasterFile; and those who were not admitted to the hospital for the sole purpose of CRT-D implantation.	
Zuster zeel 2015	Retros pective	National Cardiovas cular Data Registry (NCDR)	USA	4256 0	2037 9	30±19	It included all patients in the NCDR ICD registry who received a first time CRT-D or ICD, had NYHA class III or IV heart failure	patients with a missing ICD type, epicardial leads (n=9326),	This study was funded by the Food and Drug Administration (FDA) Office of Women’s Health through a contract awarded to the American College of Cardiology. In addition,

							symptoms, and had QRS duration between 120 and 220 ms.	missing data for sex, QRS duration or bundle branch block type, and patients who were unable to be linked to the Social Security Death Master File or had a death date before implant date	this study was supported by a research fellowship from the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the FDA. The implantable cardioverter defibrillator Registry is an initiative of the American College of Cardiology Foundation with partnering support from the Heart Rhythm Society
Zuster zeel 2015b	Retros pective	Medicare claims data	USA	62 669	26 908	32	It included all Medicare patients who received primary prevention CRT-D (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] procedure code, "00.51,") or ICD	Patients with an ICD-9 code for ventricular fibrillation, ventricular flutter, cardiac arrest, or sudden cardiac	This project was supported by the SafeRx Project, a joint initiative of the CMS (Baltimore, Maryland), USFDA (Silver Spring, Maryland), and the US Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation and by

							device (ICD-9-CM procedure code, "37.94," from July 1, 2002, to September 30, 2009, who were also continuously enrolled in Medicare Part A (inpatient hospital coverage) and B (outpatient medical coverage) 12 months before implantation	arrest as part of secondary prevention and patients with end-stage renal disease or hypertrophic cardiomyopathy	a research fellowship from the Oak Ridge Institute for Science and Education (Oak Ridge, Tennessee) through an interagency agreement between the US Department of Energy and the USFDA. Acumen LLC is a contractor to CMS. The authors have no conflicts of interest to disclose
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eTable 3. Variables Adjusted in the Adjusted Analyses From the Included Studies

Study ID	Outcome (s)	Adjusted Variables
Achilli 2007	Death from any cause (<80 year old)	ICM, NYHA IV, EF, LVEDD, LVESD, Chronic AF, No B Blocker
Auricchio 2007	Combined event: death from any cause, urgent heart transplantation, or left ventricular assist device implantation.	Cox regression was used to assess the prognostic role of type of implanted device and control for possible confounders, such as age, gender, left ventricular ejection fraction, etiology, QRS duration, functional New York Heart Association class, presence of permanent atrial fibrillation, and implanting center.
Bai 2008	all-cause death	age, gender, cardiomyopathy etiology, comorbidities, NYHA, class (III or IV), LVEF, LV end-diastolic diameter, QRS duration (120 ms <QRS ≤160 ms or QRS >160 ms), medications, and type of biventricular device (CRT-P or CRT-D).
Beca 2019	Mortality	Device Upgrade, Age, Creatinine, LVEF, Diabetes, Hypertension, Peripheral Vascular Disease, B-Blocker, ACE, Presence of Paced QRS, History of AF
Bilchick 2010	death or HF hospitalization All-cause mortality	A Cox proportional hazards model was used to assess the statistical significance of LBBB morphology as a predictor of survival, adjusted for the concurrent effects of differences in patient demographics, clinical history, clinical characteristics, device information, and the other previously described covariates
Boriani 2016	death/cardiac transplant	Age, Unplanned, urgent hospitalization, NYHA class III (reference: class II), NYHA class IV (reference: class II), CCI
Cipriani 2016	All-cause mortality	LVEF, B blocker, LVEDV, LVESV
DiBiase 2008	LVEF	CAD, Age, NYHA III-IV, Preimplant LVEF, Diabetes, COPD, SVT, Creatinine, Beta blockers, ACE, Aldactone, Loop, QRS>120ms, CRT-D, Centre
Echouffo-2016	All-cause mortality	age, sex, cause of HF (ischemic versus nonischemic cardiomyopathy), levels of kidney function (no chronic kidney

Tcheugui 2016		disease [CKD], CKD stage 3, CKD stage 4, and end-stage renal disease or dialysis, defined on the basis of estimated glomerular filtration rate), race (non-Hispanic black versus nonblack), and QRS/LBB categories (LBBB/QRS of >150 ms, LBBB/QRS of 120–149 ms, no LBBB/QRS of >150 ms, and no LBBB/QRS of 120–140 ms)
El-Saed 2009	heart failure hospitalization & All-cause mortality	Age, Black Race, NYHA class, LVEF (per 5%), Ischemic CM, Hypertension, Diabetes, current smoking, AF History, Statins use, Creatinine (per 0.1 mg/dL), BMP (>= 492 pg/mL)
Fantoni 2008	end-point death, urgent heart transplantation and implantation of a left ventricular assist device after CRT	Diabetes, age, aetiology, NYHA IV, LVEF, Rhythm, QRS duration, Renal dysfunction, Beta blockers, Epicardial lead, CRT-D
Foley 2010	cardiovascular death/hospitalizations for HF All-cause mortality Death from any cause/hospitalizations for MACE	Accordingly, these included LV reverse remodelling, beta-blocker use, etiology of HF, and presence of chronic atrial fibrillation.
Gasparini 2014	All cause mortality	Age, QRS, NYHA class, presence of atrial fibrillation, device type, ischemic etiology, LVEF, volumes, and NYHA class.
Gasparini 2015	All-cause mortality	Age, LVEF, AF, CRT-D, CAD, NYHA, Diabetes
Gu 2017	All-cause mortality Total mortality of HF hospitalization	LAD, IDCM, ICM

Hoke 2014	All-cause mortality	Age, ICM, AF, Diabetes, 6 min walk score, GFR, LVESVi
Jeevana ntham 2016	All-cause mortality	adjusting for age, gender, diabetes, hypertension, coronary artery disease, smoking, change in LVEF by 5%, atrial fibrillation and hyperlipidemia.
Khazan ie 2014	All-cause mortality	(age, sex, and race) and clinical characteristics (atrial fibrillation/flutter, cerebrovascular disease, chronic lung disease, diabetes mellitus, hypertension, ischemic heart disease, previous myocardial infarction, renal failure dialysis, protein-calorie malnutrition, dementia, disability, major psychiatric disorders, chronic liver disease, blood urea nitrogen, EF, QRS duration, serum creatinine, serum sodium, systolic blood pressure, and admission urgency) as covariates
Kobe 2017	All-cause death (Age < 75) All-cause death (Age >= 75)	Coronary heart disease, Chronic disease, sinus rhythm, QRS
Kronbo rg 2008	All-cause mortality	Age, IHD, NYHA, LVEF
Leyva 2019	Total Mortality or HF Hospitalization Total Mortality	Age, Hypertension, Diabetes, CKD, MI, CRTD
Lilli 2007	Overall mortality	Age, etiology, NYHA class, QRS, baseline EDVi, ESVi, EF, and use of ACE-I/ARBs and β -blockers
Lin 2010	All cause mortality	NICM, EF, GFR, Hgb, Na
Looi 2014	All-cause mortality	Age, ICM, Hypertension, Sodium, Creatine, ACE, B blocker, CRT-D

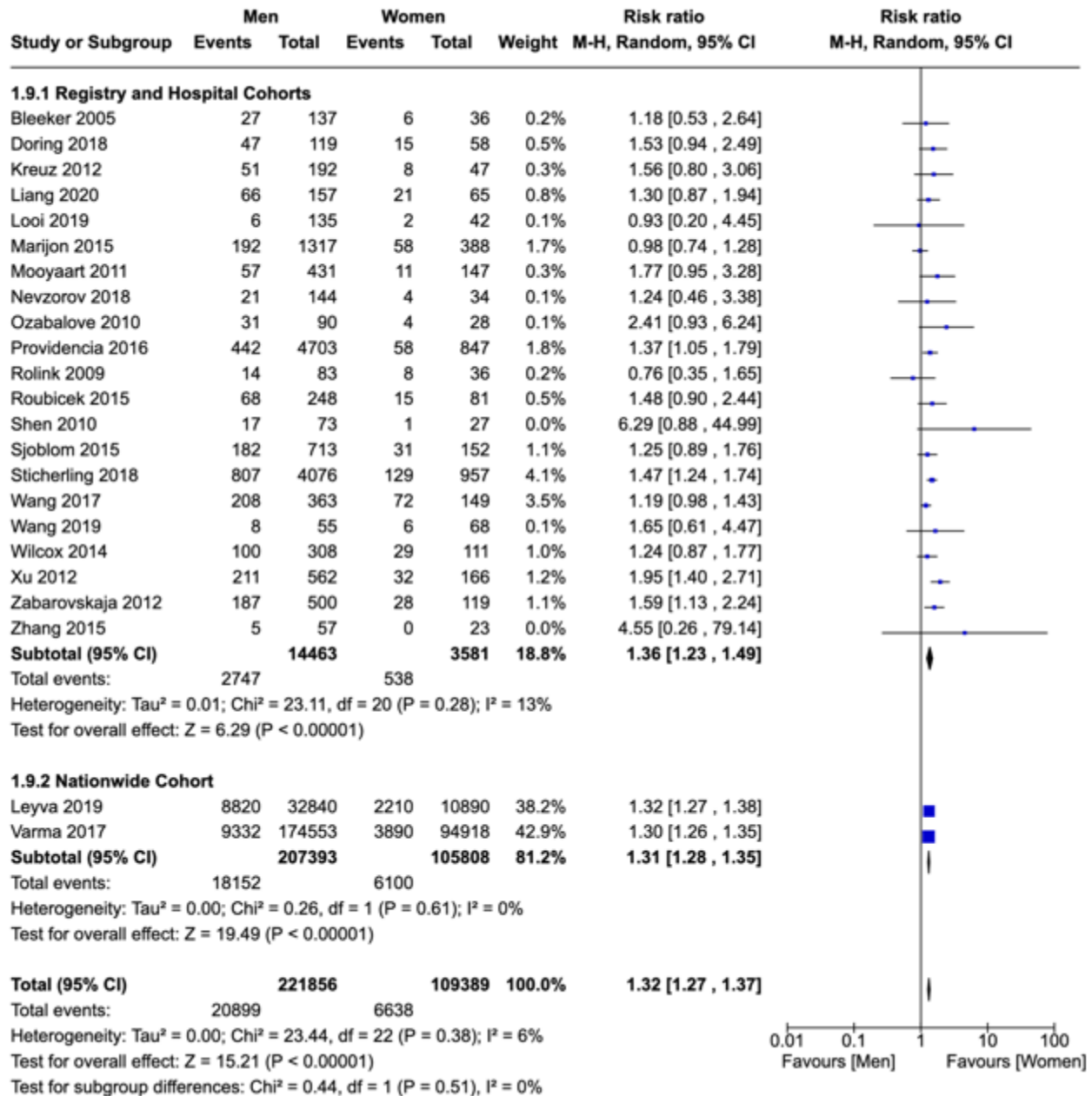
Loring 2013	Death Death or HF hospitalization	MI, Hypertension, LBBB, RBBB, ICM, Diabeties, AF, Stroke, Prior HF hospitalization, ESRD, Charlson score, age and year of CRT-D implantation.
Martine IliFilho 2018	Death	Cardiomyopathy, Age, NYHA, AF, Hypertension, Diabetes, Renal Disease, BBB, LVEF, LVEDD, RV dysfunction, MR, Beta-blocker therapy
Miller 2011	Time to death, ventricular assist device (VAD) implantation, or orthotopic heart transplant was the primary outcome.	Effects of age, EF, history of atrial arrhythmia, and type of cardiomyopathy
Mohamed 2019	All-Cause Mortality (In hospital)	age, race, weekend admission, primary expected payer, median household income, dyslipidemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass graft (CABG), history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents including stroke and transient ischemic attacks (CVA), family history of coronary artery disease (CAD), thrombocytopenia, history of cardiac arrest, ventricular tachycardia and fibrillation, all-cause infection and Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anemias, chronic blood loss anemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal

		failure, solid tumor without metastasis, valvular heart disease, and weight loss).
Mohamed 2020	All-cause mortality (in hospital)	age, race, weekend admission, primarily expected payer, median household income, dyslipidemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass graft (CABG), history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents including stroke and transient ischemic attacks (CVA), family history of coronary artery disease (CAD), thrombocytopenia, history of cardiac arrest, ventricular tachycardia and fibrillation, left bundle branch block (LBBB), non-ischemic cardiomyopathy, and Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anemias, chronic blood loss anemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, solid tumor without metastasis, valvular heart disease and weight loss.
Moore 2019	All-cause mortality (In hospital)	patient age, acute or elective (planned) status of the procedure, device- type (PPM, ICD, CRT) as well as patient with comorbidities. Comorbidities were derived using the Condition Category (CC) classification system that is widely used to derive patient comorbidities from routinely collected hospital data
Mooyart 2011	all-cause mortality and cardiac transplantation	Age, Etiology, Diabetes, GFR, AF, NYHA, 6 min walking test, LVEF

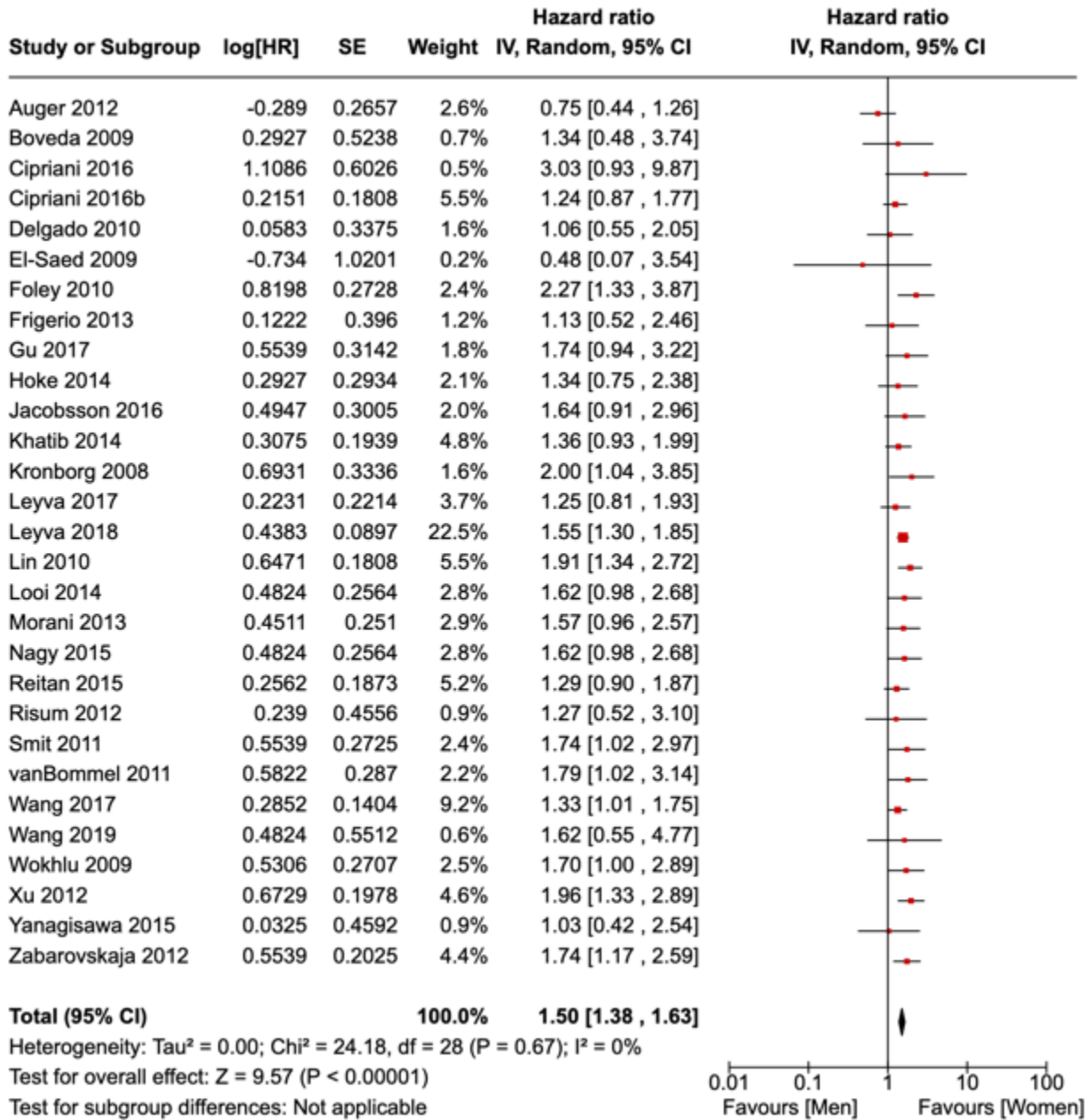
Morani 2013	All-cause mortality	Age (>70yrs), ICM, Diabetes, GFR, CRT-P, LV lead, B-blocker, Class III anti arrhythmic use, Digoxin use, Nitrate use
Munir 2016	All-cause mortality	age at implant, gender, prior myocardial infarction, use of anticoagulation, pre-implant LVEF, QRS morphology, and differences in prescribed medical therapy (digoxin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE/ARB), statins, and antiarrhythmic drugs)
Prochnau 2011	Mortality	Age, ICM, Worse NYHA III, Sustained VT/VF, LVEF, QRS, Nonspecific Conduction delay, AF, Permanent right ventricular pacing, LV lead, ICD-backup
Reitan 2015	All-cause Mortality	Age, ICM, NYHA class I-II, QRS duration greater than 150ms, Hypertension, LVEF, B blocker use, ACE, Loop diuretic use, Anticoagulant use, ECG other than LBBB, AF, previous pacemaker/ICD, CRT-D vs CRT-P, Creatinine, Hb
Rickard 2011	Change in LVEF	LVEF pre-CRT, LVEDD pre-CRT, QRS duration pre, RBBB, ACE or ARB, Epicardial Lead
Rickard 2011	All-cause mortality	Pre-CRT LVEDD, LVEF pre-CRT, QRS duration pre, ICM, COPD, Serum Creatinine, Serum Hb, ACE
Shalaby 2008	death or cardiac transplantation heart failure hospitalization	Age, Race, NYHA, LVEF< QRS, ICM, Diabetes, Smoking, AF, Creatinine, Statins, B blocker, ACE, Left atrial size, MR, SPAP
Sharma 2015	HF hospitalization, left ventricular assist device, cardiac transplant, and all-cause death	Creatinine, Hypothyroidism, Diabetes, ACE, Digoxin
Shen 2010	Death	ICM, LAVI, MR>moderate, LVRF, Beta-blocker, Time difference between TDI and PW

Stabile 2009	All-cause mortality	QRS duration, ≥ 160 m, Age > 70 -year, CRT, Ischemic heart, New York Heart Association functional class IV, LVEF, ≤ 25 , Atrial fibrillation
Sticherling 2018	All-cause mortality	ICM, LVEF < 25 , CRT-D, Age
vanBommel 2011	All-cause mortality	NYHA functional class, eGFR, LVEF, MR grade
Wang 2017	All cause mortality	Age, prior myocardial infarction, Charlson index, pre-implant left ventricular ejection fraction, QRS width, QRS morphology, and angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker use.
Wang 2019	All cause mortality	Age, QRS, LVEDD index
Wokhlu 2009	All-cause mortality	Age, ICM, NYHA, Chronic AF, Hemoglobin, RBBB, IVCD, QRS < 120 , Paced, Lateral or posterior Lead location, All other positions
Xu 2012	All-Cause Mortality	Older age at CRT implant, worse NYHA class, and higher creatinine level predicted poorer survival, whereas NICM, LBBB, LV lead placement in the lateral position, and higher hemoglobin level provided survival benefit after CRT"
Zabarovskaja 2012	All-cause mortality	Age, CRT-ICD. ICM, MAP, NYHA, Weight, EF, Aortic stenosis, Mitral insufficiency, Diabetes, Hb, GFR
Zhang 2009	HF hospitalisation	Age, Sinus Rhythm, ICM, LVESV, LVEF, QOL, NYHA
Zusterzeel 2015b	HF or Death All-Cause Mortality	CRT-D, Age, Race, Charlson Score, Diabetes, Mitral or Aortic Valve Disorder, Hypertension, MI, Coronary Heart Disease, Tricuspid or Pulmonary Valve Disorder, AF, Prior HF Hospitalization, Prior Stroke, VT,

Zusterz eel 2014	All-Cause Mortality	All covariates in Table 1 and additionally for syncope, family history of sudden death, cardiac arrest, ventricular tachycardia, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and systolic blood pressure.
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eFigure 2. Forest plot for all-cause mortality using raw number of events

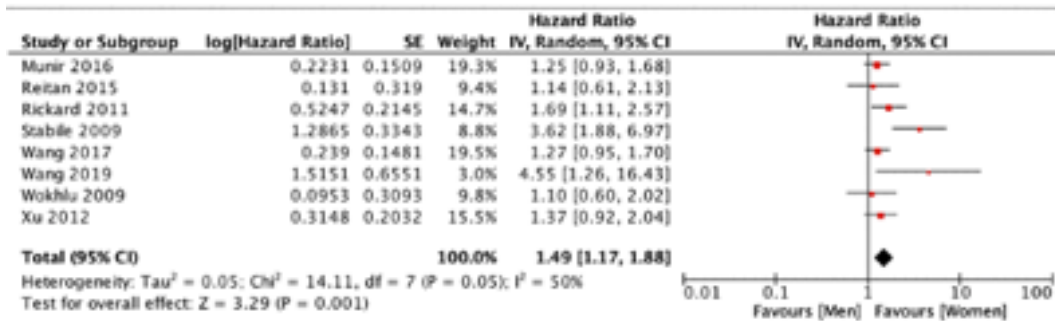


eFigure 3. Forest plot for all-cause mortality using unadjusted analyses

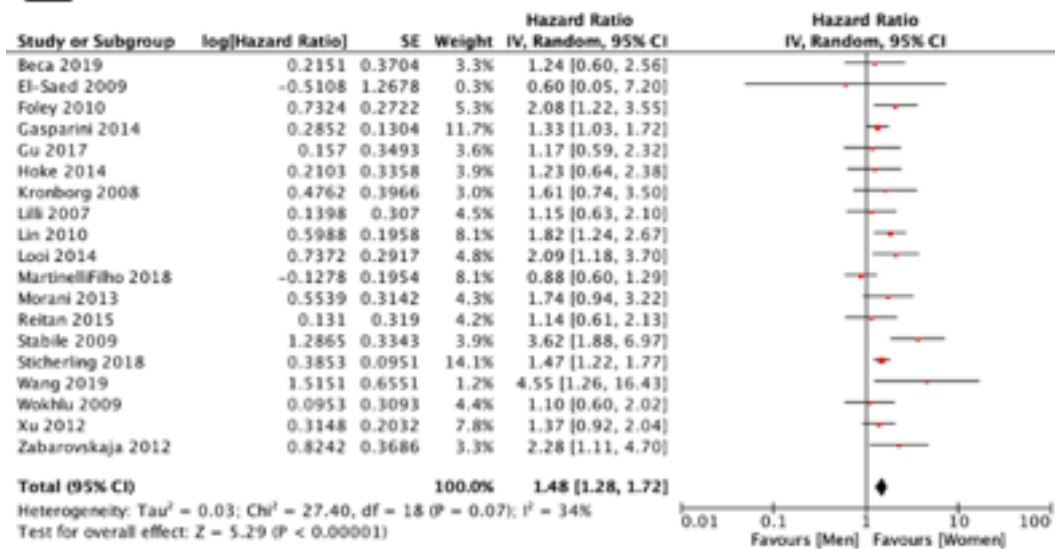
eTable 4. Comparison of adjusted and unadjusted estimates for outcomes of interest.

Outcome	Unadjusted analysis			Adjusted analysis			P value
	N of studies	HR (95% CI)	I ² %	N of studies	HR (95% CI)	I ² %	
All-cause mortality							
All studies	28	1.50 (1.38, 1.63)	0	26	1.48 (1.32, 1.66)	29	0.59
Studies that reported both adjusted and unadjusted estimates	16	1.52 (1.34, 1.73)	36	16	1.48 (1.26, 1.73)	43	0.77
HF Hospitalization	4	1.03 (0.75, 1.43)	46	3	0.58 (0.32, 1.06)	0	0.1
HF Hospitalization or Death	4	1.25 (1.05, 1.48)	69	4	1.06 (1.02, 1.11)	76	0.08
Death/ Cardiac Transplantation	2	1.51 (1.01, 2.27)	14	2	1.63 (1.10, 2.44)	0	0.79
Death/Transplant/LVAD therapy	2	1.22 (1.02, 1.45)	0	2	1.77 (1.23, 2.55)	0	0.07

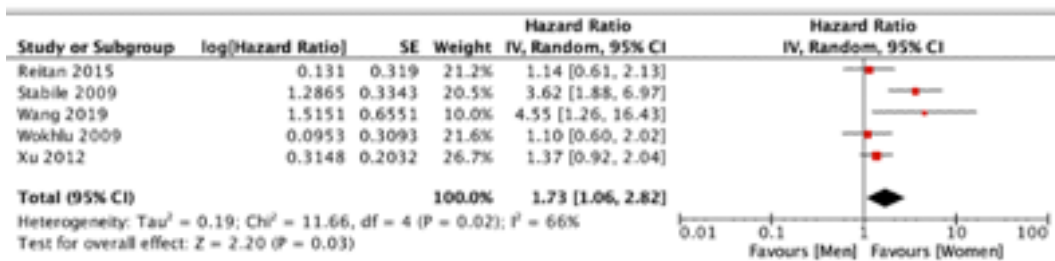
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B

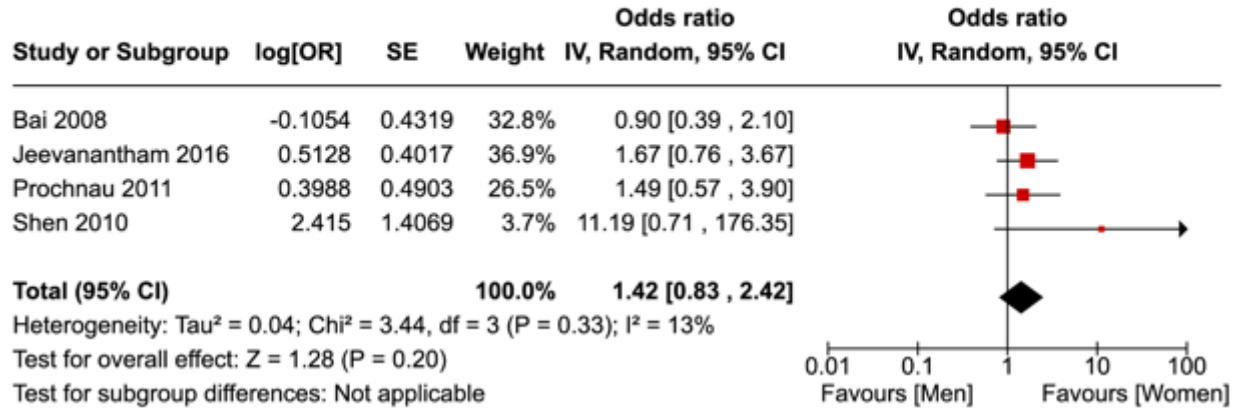


C

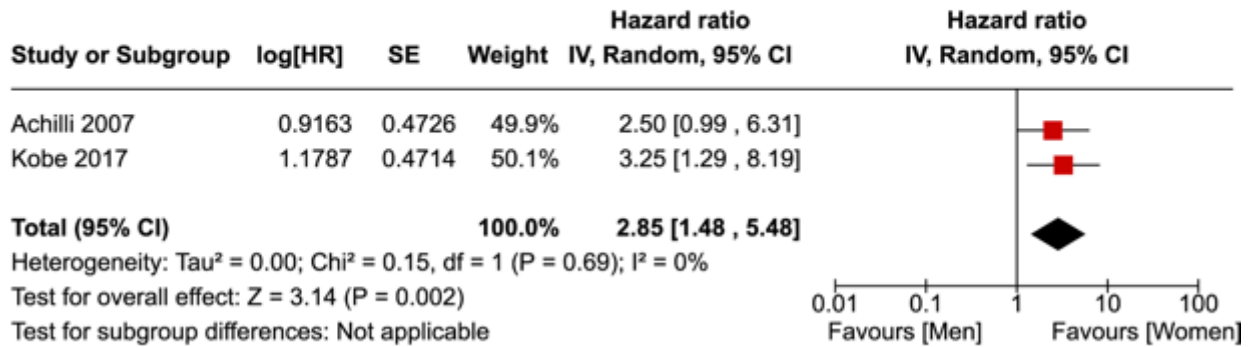


eFigure 4. Forest plot for all-cause mortality using studies adjusted for LBBB and Cardiomyopathy. (A) left bundle branch block (LBBB), (B) cardiomyopathy type and (C) both LBBB and cardiomyopathy type

A

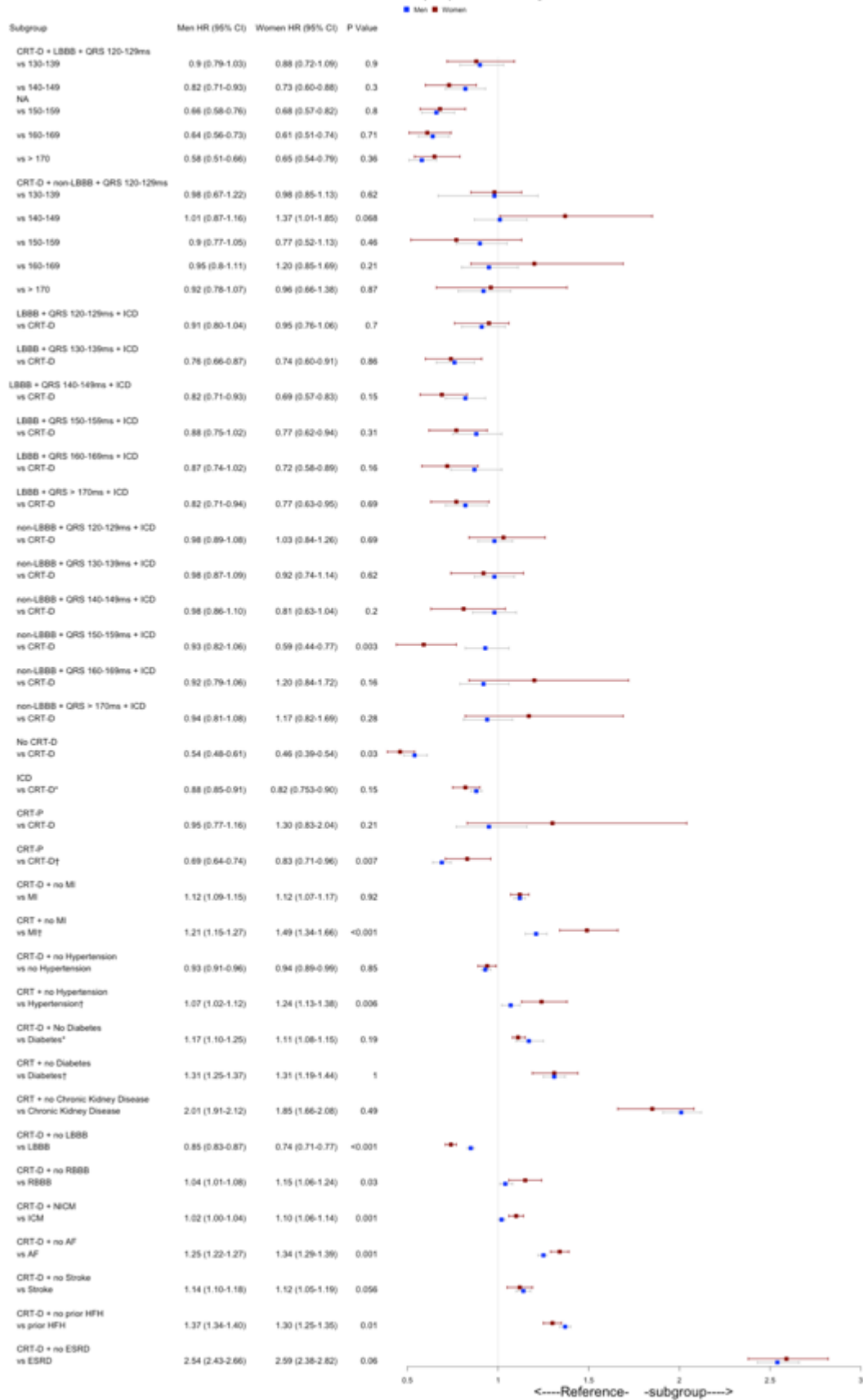


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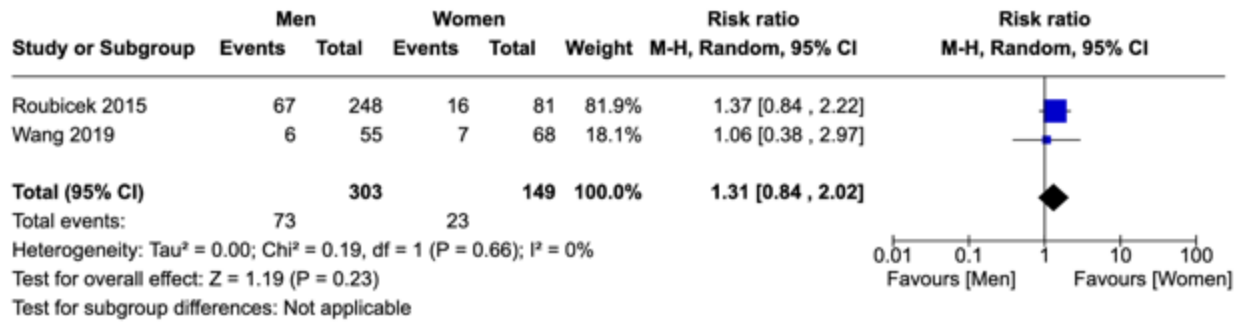
eFigure 5. Forest plot for adjusted odds of all-cause mortality and patients ≥75 years. (A) adjusted odds of all-cause mortality and (B) Hazard ratios of patients ≥75 years.

Hazard Ratio (HR) for Mortality

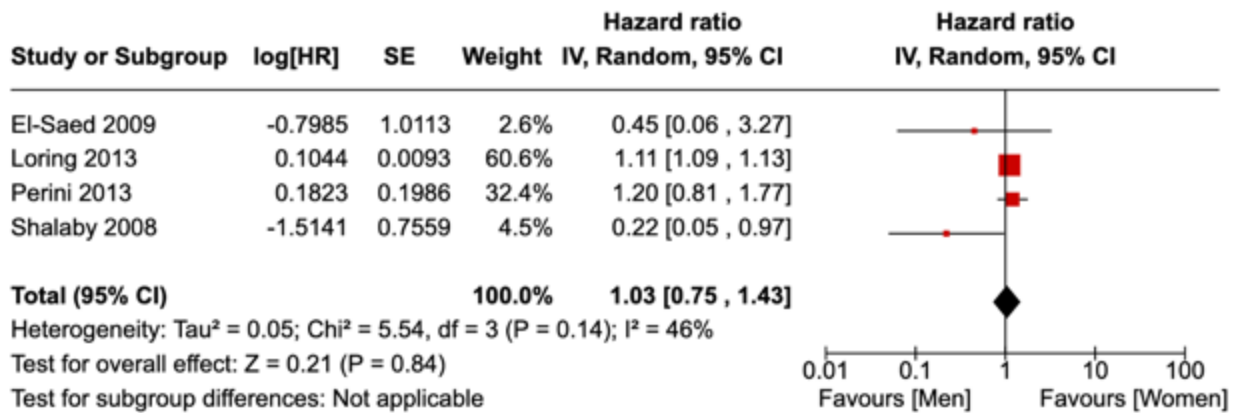


eFigure 6. Forest plots of within sex analyses for all-cause mortality. * Pooled effect sizes from 2 studies. † studies cannot be pooled with the other studies conducting the same comparison due substantial heterogeneity in study and patient characteristics. CRT-D: Cardiac Resynchronization Therapy-Defibrillator; LBBB: Left Bundle Branch Block; ICD: Implantable cardioverter-defibrillator; MI: Myocardial Infarction; RBBB: Right Bundle Branch Block; NICM: Non-Ischemic Cardiomyopathy; ICM: Ischemic Cardiomyopathy; AF: Atrial Fibrillation; HFH: Heart Failure Hospitalization; ESRD: End-stage Renal Disease.

A

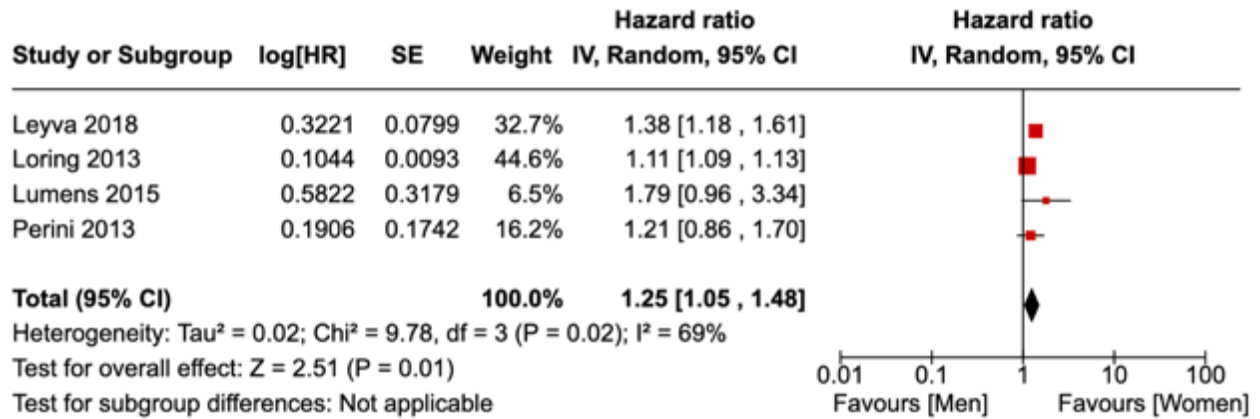


B

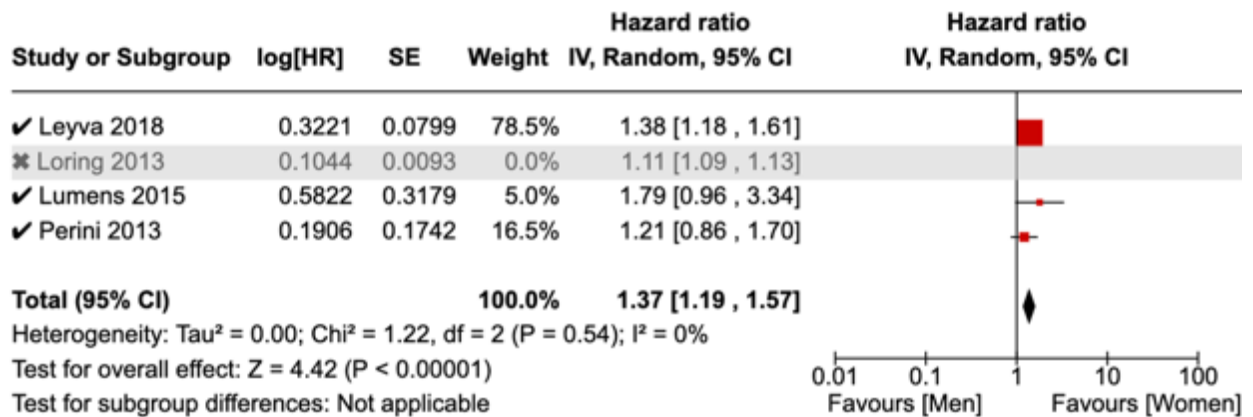


eFigure 7. Forest plots for HF Hospitalization using raw number of events and univariate analyses. (A) raw number of events and (B) univariate analyses.

A

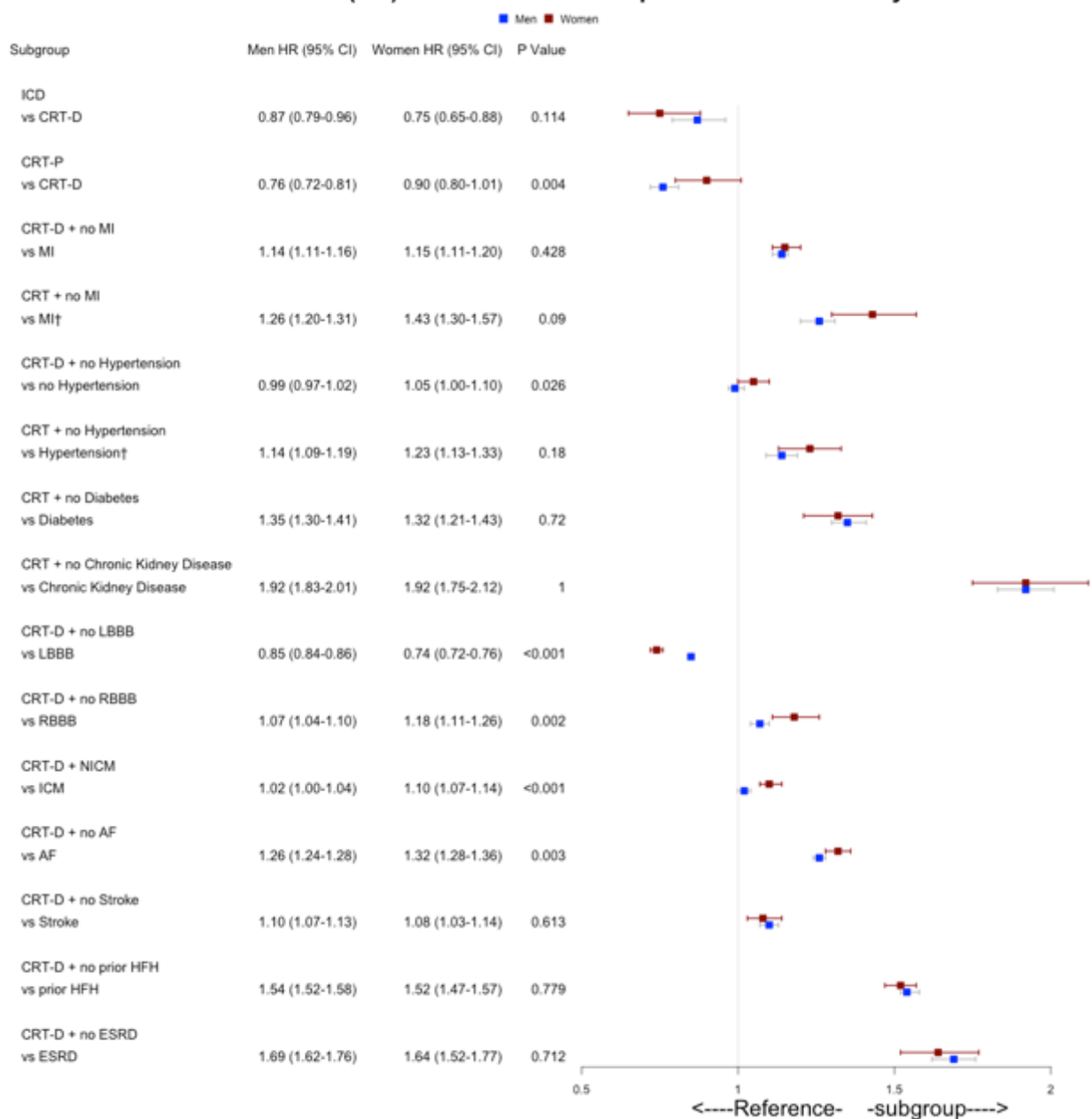


B



eFigure 8. Forest plot for Death or HF Hospitalization using univariate analyses of (A) all studies, (B) and after sensitivity analysis.

Hazard Ratio (HR) for Heart failure Hospitalization or Mortality



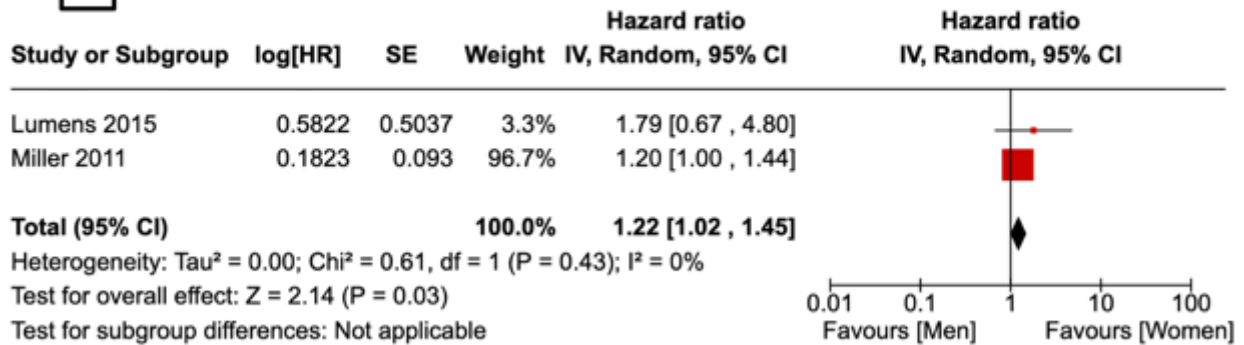
eFigure 9. Forest plots of Within sex analysis for Death or Heart failure Hospitalization. † studies cannot be pooled with the other studies conducting the same comparison due substantial heterogeneity in study and patient characteristics. CRT-D: Cardiac Resynchronization Therapy-Defibrillator; CRT-P: Cardiac Resynchronization Therapy-Pacemaker; LBBB: Left Bundle Branch Block; ICD: Implantable cardioverter-defibrillator; MI: Myocardial Infarction; RBBB: Right Bundle Branch Block; NICM: Non-Ischemic Cardiomyopathy; ICM: Ischemic

Cardiomyopathy; AF: Atrial Fibrillation; HFH: Heart Failure Hospitalization; ESRD: End-stage Renal Disease.

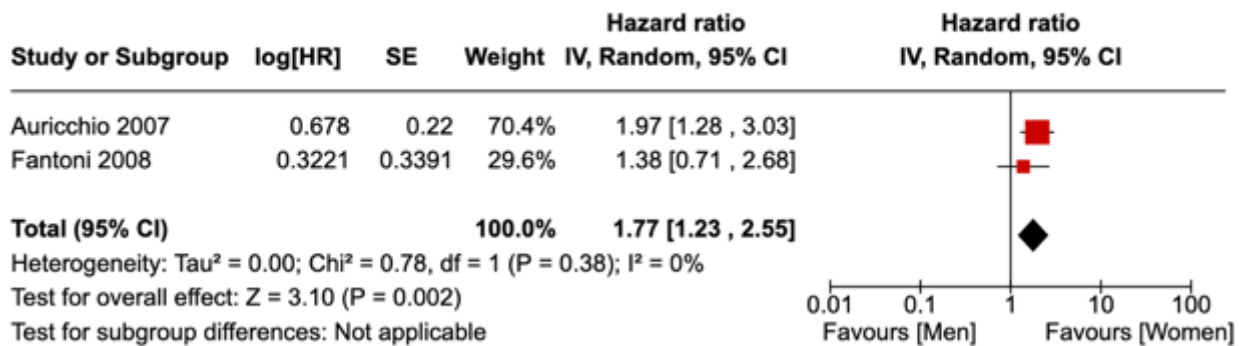
eTable 5. Incompletely reported within sex analysis

Study ID	Reference group	vs subgroup	Outcome	Effect size unit	Men Effect size 95% C.I	Women Effect size 95% C.I	p value interaction term
Masou di 2014	ICD	CRT-D	HF hospitalization	HR	0.85 (0.74–0.99)	0.61 (0.49–0.77)	0.49
Yokoshi 2017	CRT-P	CRT-D	HF hospitalization or death	HR	Not reported	Not reported	0.66
Leyva 2019	not clear	Age (per year) + CRT	Total Mortality	HR	1.03 (1.03–1.04)	1.03 (1.02–1.03)	1
	not clear	Age (per year) + CRT	HF hospitalization or death	HR	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1
Doring 2018	CRT-P	CRT-D	Mortality	RR	Not reported	Not reported	0.32
Liang 2020	CRT-D	CRT-P	Mortality	HR	Not reported	Not reported	Not reported
Wilcox 2014	No CRT-P/CRT-D	CRT-P/CRT-D	Mortality	OR	0.59 (0.33–1.06)	0.44 (0.22–0.90)	0.4441
	No ICD/CRT-D	ICD/CRT-D	Mortality	OR	0.71 (0.57–0.87)	0.65 (0.49–0.85)	0.5966
Loring 2013	Not black + CRT-D	Black + CRT-D	Mortality	HR	Not reported	Not reported	0.007
	Not black + CRT-D	Black + CRT-D	Death	HR	Not reported	Not reported	0.081

A

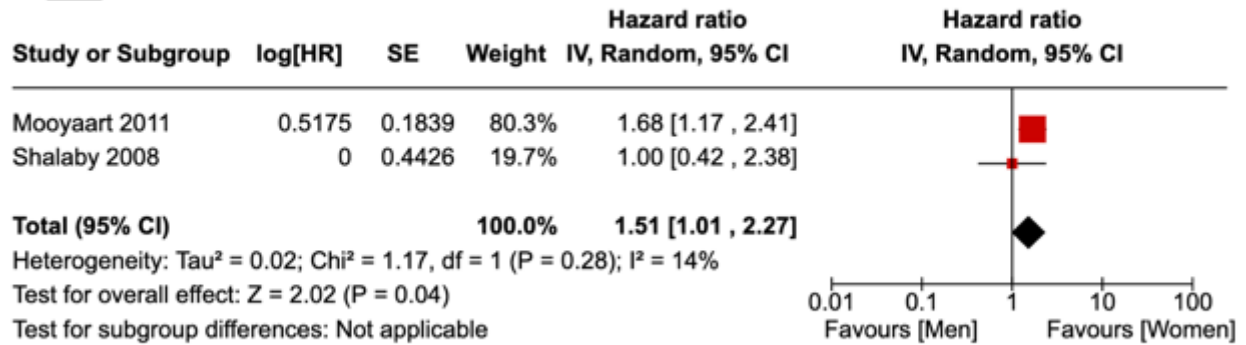


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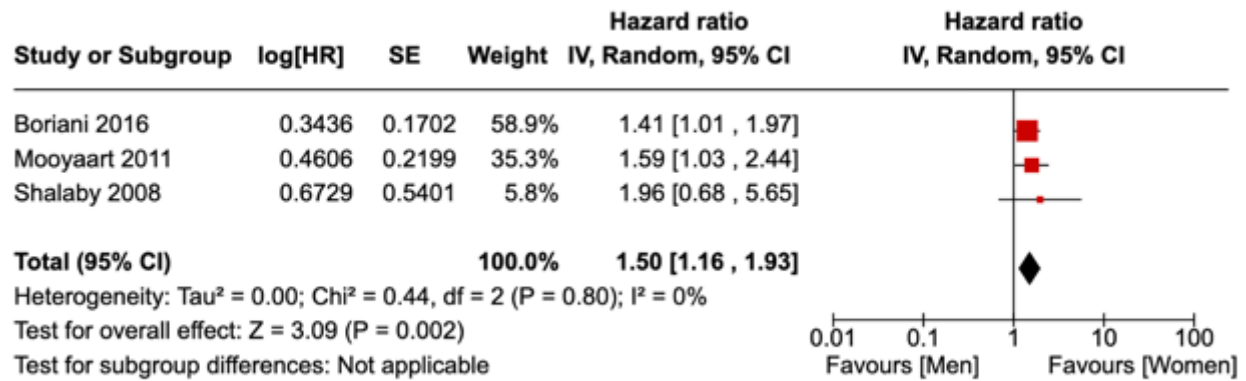


eFigure 10. Forest plots for death or LVAD therapy or heart transplant using (A) unadjusted and (B) adjusted estimates.

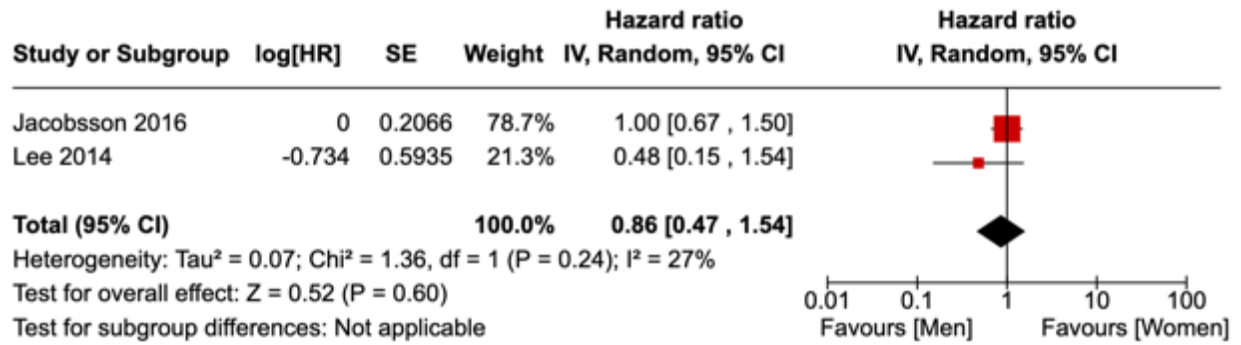
A



B



eFigure 11. Forest plot for death or heart transplant using (A) unadjusted and (B) adjusted estimates.



eFigure 12. Forest plot for death or heart transplant or HF hospitalization using univariate analyses

eTable 6. Studies comparing men to women for effectiveness outcomes

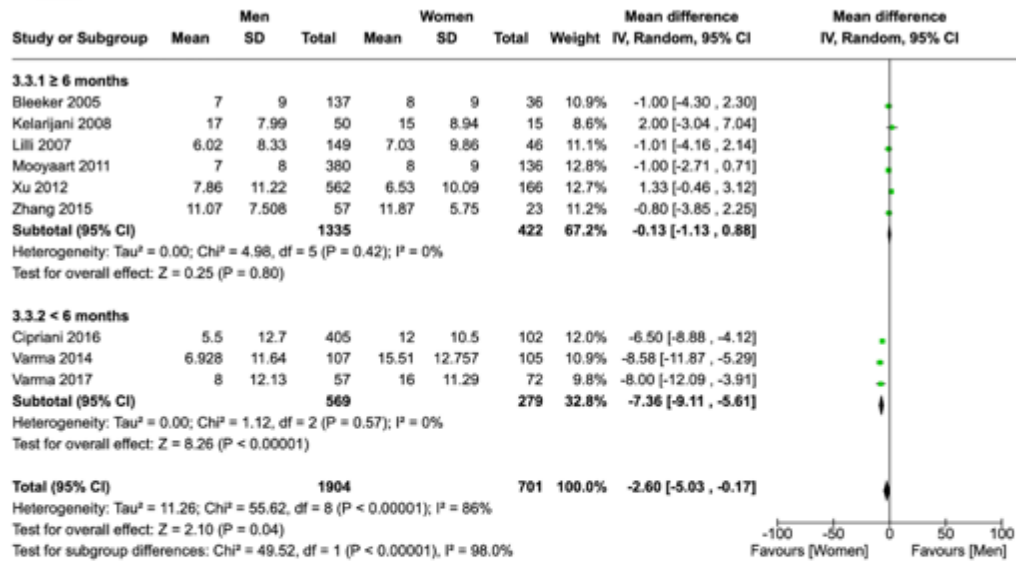
Study ID	Outcome	Covariate adjustment (adjusted vs unadjusted)	Effect estimate unit	Effect estimate (95% CI)
Loring 2013	All-cause mortality	Raw	RR	1.15 (1.14, 1.16)
		Unadjusted	HR	1.26 (1.24, 1.28)
		Adjusted	HR	1.55 (1.30, 1.85)
Shen 2010	All-cause mortality	Unadjusted	OR	7.89 (1, 62.53)
	All-cause mortality	Adjusted	OR	11.19 (0.71, 176.12)
Miller 2011	Death/Orthotopic Heart transplant/LVAD Therapy	adjusted	HR	1.1 (0.9, 1.4)
Sharma 2015	Death/Heart transplant/HF hospitalization/LVAD Therapy	Unadjusted	HR	0.69 (0.48, 0.998)
	Death/Heart transplant/HF hospitalization/LVAD Therapy	Adjusted	HR	0.64 (0.428, 0.963)
Foley 2010	Cardiovascular death/hospitalizations for HF	Unadjusted	HR	0.39 (0.23, 0.66)
	Cardiovascular death/hospitalizations for HF	Adjusted	HR	0.42 (0.24, 0.72)
	Death from any cause/Hospitalizations for MACE	Adjusted	HR	0.58 (0.38, 0.88)
Stabile 2015	Death/Cardiovascular hospitalization	Unadjusted	HR	0.53 (0.28, 1.00)
Moore 2019	In hospital all-cause mortality	Adjusted	OR	0.67 (0.26, 1.74)

Kobe 2017	All-cause death (Age < 75)	Adjusted	HR	0.94 (0.53, 1.64)
Adelstein 2016	mortality \geq 80 years	Unadjusted	HR	1.30 (0.85, 1.96)

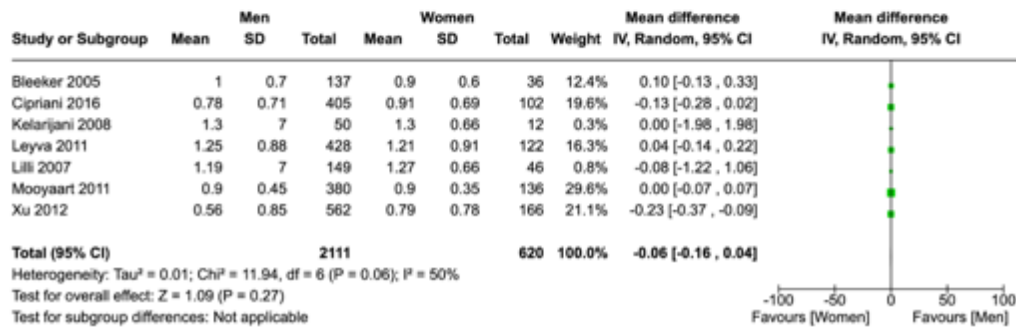
OR: Odds Ratio

HR: Hazard Ratio

A

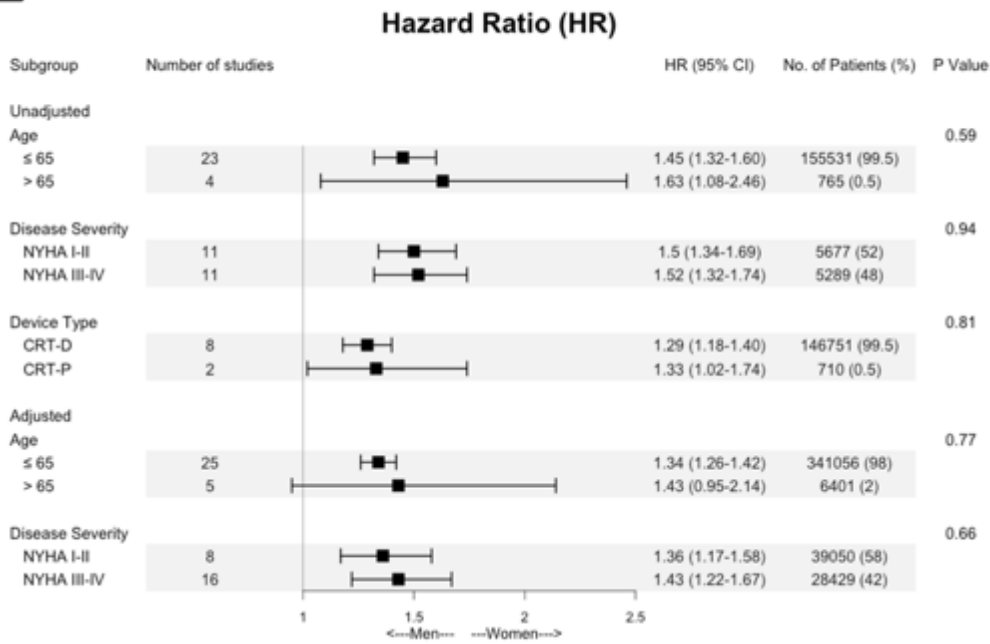


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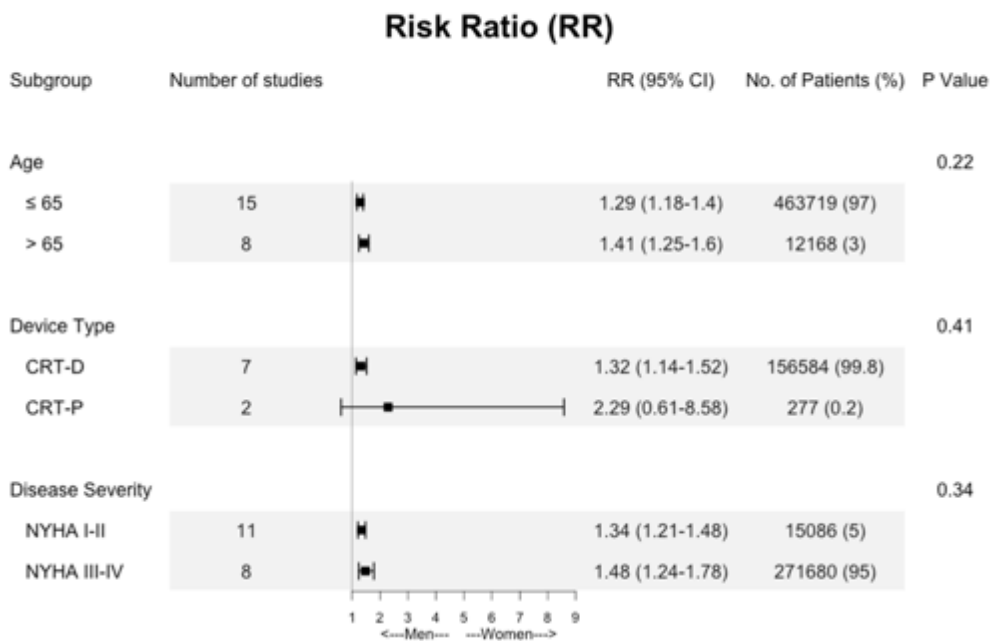


eFigure 13. Forest plots for change in (A) Left Ventricular Ejection Fraction (LVEF), (B) New York Heart Association (NYHA) using raw measures.

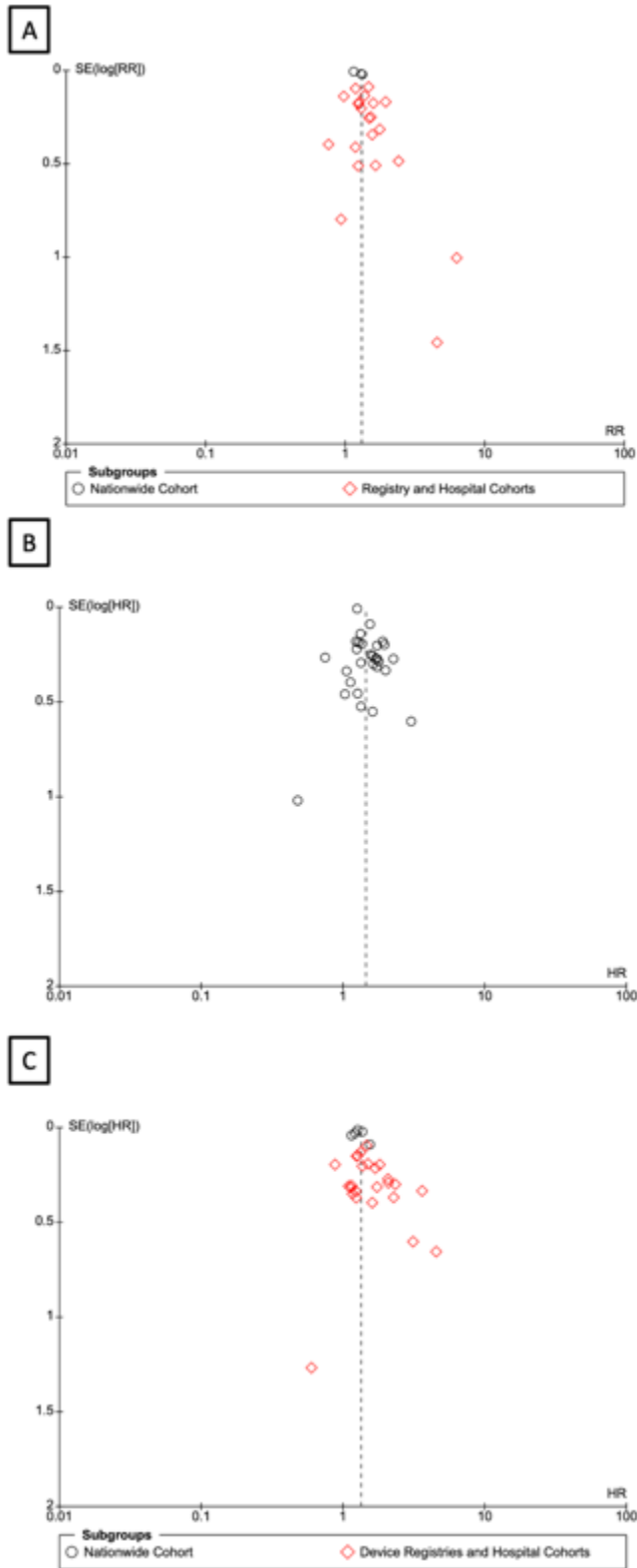
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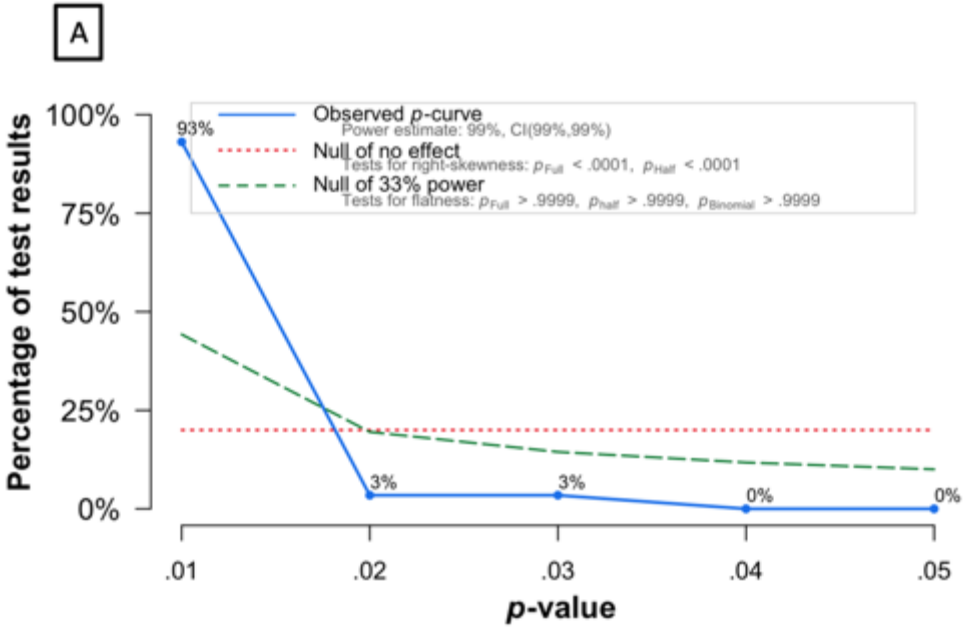
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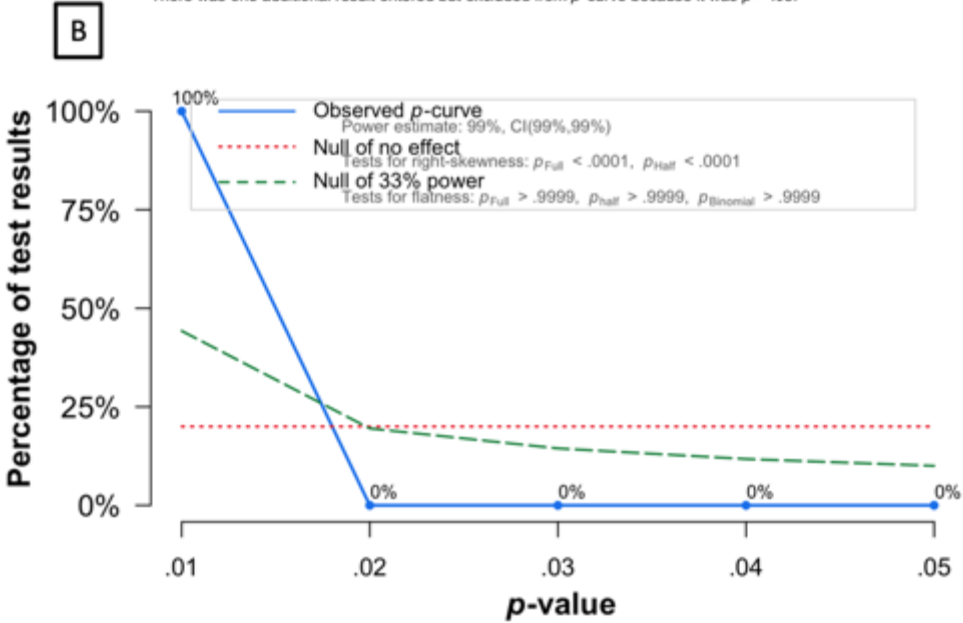
eFigure 14. Sex differences on the risk of all-cause mortality according to patient characteristics. (A) Pooled hazard ratios reported from unadjusted and adjusted models using generic inverse variance method. (B) Risk ratios calculated from raw number of events using Mantel-Hanzel method.



eFigure 15. Funnel plots for all-cause mortality comparing men to women. (A) raw number of events, (B) unadjusted estimates (C) adjusted estimates.



Note: The observed p-curve includes 29 statistically significant ($p < .05$) results, of which 29 are $p < .025$. There was one additional result entered but excluded from p-curve because it was $p > .05$.



Note: The observed p-curve includes 29 statistically significant ($p < .05$) results, of which 29 are $p < .025$. There was one additional result entered but excluded from p-curve because it was $p > .05$.

eFigure 16. P-curve analysis for all-cause mortality. (A) Unadjusted estimates and (B) adjusted estimates. Both figures show right skewness, so results are not the product of publication bias and p-hacking alone.

Further explanation of P-curve analysis:

P-Curve analysis is an alternative procedure to trim and fill to assess publication bias to determine if the true effect is present behind the collected data. This method assumes that publication bias may arise from data manipulation to obtain statistical significance rather than not publishing non-significant results.

P-Curve plot: The plot in blue represents the proportion of the effect sizes with $p < 0.05$ included in our analysis. The number of studies used in the meta-analysis determine the power of the P-curve analysis. The greater the power, the more likely you will find significant p value lower than 0.01. the conducted analyses were of high power (99%, 95 CI, 99%-99%); almost all of the p values were $p < 0.01$. P values for Right skewness test and flatness test were $p < 0.01$ and $p > 0.999$ respectively. Indicating that the data is significantly right-skewed, which suggest that there is a “true” effect present.

Chapter 6: Discussion

6.1 Principal findings

The purpose of this thesis was to explore sex and gender reporting and analysis in CRT cohort studies. The plan for the search strategy and methods of screening, data collection and analysis were described in a protocol (accepted with Systematic Reviews), included as the first article of this thesis.

In the second article, I conducted a methodology study of analysis and reporting of sex and gender in cohort studies of CRT. Following screening, 253 cohort studies of CRT met the eligibility criteria. Reporting of sex anywhere in the article was found in less than half of the studies. Temporal analysis showed that reporting of sex considerations increased over time in background, study design, statistical models and discussion, but not in the findings and analysis. Over half of the studies adjusted for sex in multivariable models, but separate analysis of men and women was rarely conducted. The reporting of sex in the study design and analysis in statistical models increased after 2015, which corresponds to when the NIH SABV policy was introduced. No cohort studies mentioned consideration of the influence of gender norms or roles in analysis or interpretation of results.

In the third article, a systematic review and meta-analysis of sex-disaggregated data in cohort studies of CRT was conducted to evaluate sex differences in implantation and response to CRT in real world settings. As described in the protocol, this systematic review included studies identified in the previous methods study and searched for additional studies in relevant systematic reviews and through citation-tracking. Following this search process, 97 studies met the eligibility criteria. Meta-analysis of sex-disaggregated data found that women were less likely than men to receive CRT-D or CRT-P devices in real-life practice. This finding is in alignment with reports of underutilization of CRT in women, for reasons that remain uncertain ¹. Our review also shows that women benefit from CRT more than men, with a notable mortality difference verified by adjusted and unadjusted analyses. The sex difference analyses were robust to sensitivity analysis of estimates adjusted for LBBB and cardiomyopathy, which are for other potential reasons for sex differences. In terms of safety, women were at higher risk of pneumothorax compared to men following CRT. Even though analysis of complications was conducted using unadjusted data, it remains consistent with findings from trials ^{2,3}. Even with these sensitivity analyses, it is not

possible to rule out the possibility that sex differences are confounded by other factors which were not known, measured or not included in the models. Figure 1 summarizes the findings of the questions and conclusions of this thesis.

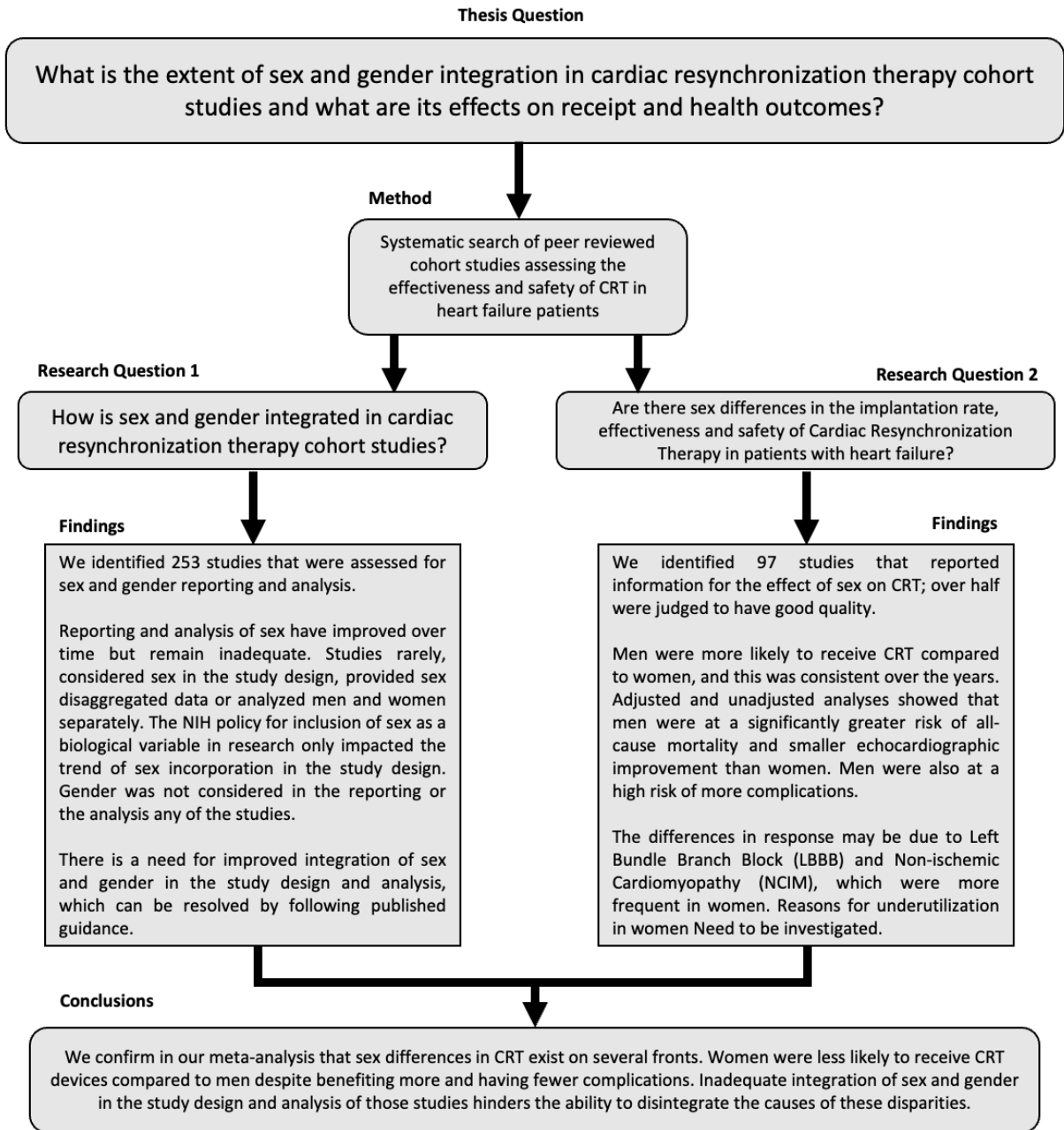


Figure 1. Illustration of thesis questions.

6.2 Integrative synthesis

Incorporation of sex and gender in research is required in order to achieve more rigorous and ethical science ⁴. In CRT research, sex differences have been consistently reported, rendering it even more important to consider sex in the conduct and reporting of the studies. Despite the availability of several comprehensive resources for incorporating sex and gender in analysis, such as Sex and Gender-based Analysis (SGA+), the Sex and Gender Equity in Research (SAGER), Stanford gendered innovations and Canadian Institute of Health Research (CIHR) training modules, the reporting of sex and gender remains poor. The role of the investigators in the poor reporting and analysis of sex in the studies when conducting research warrants further investigation. Tools such as reporting guidelines have been shown to increase the transparency in reporting ⁵, but there is no reporting guideline for sex, gender and other equity considerations in observational studies. Thus, the current work on sex and gender reporting will be used to inform a reporting guideline about health equity, including sex, gender and other identity factors in observational studies.

In addition to investigators, funders and journal editors also have a role in promoting the conduct of transparent research related to sex and gender. Funding agencies such as CIHR have endorsed the need for sex and gender integration in the study design ⁶⁻⁸, which has led to improved incorporation in studies^{9, 10}. There are campaigns for journal editors to provide explicit guidance in addition to enforcing policies to induce proper reporting of sex and gender in studies ^{10, 11}.

It is important to note that the methodology study identified 253 studies that potentially could have had information on CRT effectiveness across sex, however only half reported some information on the effects across sex. Comparison of sex considerations between prediction models and association models confirmed our hypothesis that prediction models tend to report analysis across sex more often than association models. We also identified that identifying model covariates through measuring statistical significance of baseline characteristics is a more favored investigation style compared to identifying covariates *a priori*. Therefore, there is no insight into covariates that may be important to include in analysis.

The absence of the sex disaggregated information on eligibility criteria for CRT, number of patients lost to follow up and reasons for non-participation impeded investigation of factors which could influence the difference in implantation of CRT between men and women. Possible reasons for difference in implantation may include differences in CHF presentation and

progression, women being less likely to seek emergency care or gender bias in CRT clinical practice. Furthermore, evidence from our review, in addition to reviews of trials, shows that women significantly benefit from CRT more than men. This raises a health equity issue that requires immediate investigation.

A possible solution for improving receipt of CRT implantation in women is to implement sex-specific eligibility criteria. It has been previously proposed to set a lower QRS duration cut-off criterion for LBBB in women to improve the likelihood of CRT receipt¹². A recent randomized trial set different threshold for men and women for QRS (QRS duration ≥ 140 ms in men, ≥ 130 ms in women) and was able to include the highest percentage of female patients in their study (43.3%)¹³. In other landmark trials, restrictions to the population by LBBB have been in place which may have played a role in the underrepresentation of women, as women with heart failure tend to present more frequently with LBBB. Considering these factors in the study design and reporting of trials will help improve the proportion women's representation in CHF studies and trials¹⁴. Moreover, explicitly stating the definitions and eligibility criteria applied for men and women may help explain the observed difference in response.

Baseline characteristics for men and women were only reported separately in 22 of the 97 studies. This is also a missed opportunity to investigate differences in baseline characteristics that may help in interpreting findings. With the limited information from these 22 studies, there was a notable difference in NCIM, LBBB, QRS duration, paced patients and AF between and women. However, it is uncertain whether these differences were present in the other studies.

Several systematic reviews of meta-epidemiological studies comparing estimates from non-randomized studies (NRS) and RCTs showed mixed results and unpredictability in the direction^{15, 16}. The confounding bias tends to affect the treatment effect estimate through risk of bias, which results in an overestimate of treatment effect compared to RCT, or high external validity that diminishes internal validity and reduces the treatment effect compared to RCT. In general, NRS that account for known relevant confounders¹⁷⁻²¹; provide estimates of effects that are comparable to RCTs. Furthermore, differences in context, follow-up period and patient characteristics were identified as sources of disagreement^{15, 16}. Nonetheless, we are aware NRS cannot replace RCTs, and RCTs cannot be axiomatic. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group suggests that the quality of observational studies may be rated up in the presence of the following conditions: large magnitude

of effect, evidence of effectiveness in the form of a dose-response gradient between intervention and outcome and assumption that residual confounding supports inferential effects of the intervention²². Hence, results from both NRS and RCT study designs can complement each other to fill gaps in clinical knowledge and contribute to decision making.

With only half of the cohort studies considering sex in analysis and reporting, meta-analysis in the third article in Chapter 4 found sex differences in the receipt and response of CRT in cohort studies. Assessing the interaction of sex with other patient and clinical characteristics may help inform sex-specific eligibility criteria and clinical recommendations.

Even though gender was not considered in the studies, that does not deem it of less importance or exclude its possible role in widening sex disparities. Gender is recognized as the social determinant of cardiovascular disease and may interact with sex to influence health outcomes²³. Several studies have also shown that patient-physician gender, patient preference and gender bias have a role in the choice and efficacy of interventions²⁴⁻²⁶. We would like to reiterate the importance of collecting information on gender^{4, 27, 28}. We are aware that there is no gold standard approach for data collection on gender, but we suggest collecting using gender-related measures as proposed by Nielsen et al.²⁹. The tool presents 7 gender-related variables as key aspects of gender that could be used in clinical and population research: caregiver strain, work strain, independence, risk-taking, emotional intelligence, social support, and discrimination.

6.3 Practical considerations for resolving sex/gender disparities CRT

Based on our findings, the following is a set of practical considerations that investigators conducting research on CRT should consider in producing evidence that may help inform practice and policy to mitigate sex disparities:

1. Report sex-disaggregated information for patient follow up time and reasons for non-participation;
2. Use sex-specific eligibility criteria for recruitment of heart failure patients;
3. Report sex-disaggregated information for baseline characteristics;
4. Conduct within-sex analyses to identify optimal targets for CRT for men and women and possible mechanistic causes for sex differences; and
5. Collect and analyze patient gender information.

6.4 Future directions

This thesis has established that there is ample evidence to conclude the presence of sex difference in the receipt and response to CRT. In addition to our systematic review of cohort studies, we have identified two IPD-MAs that have demonstrated a mortality benefit for women^{30,31}. This work adds to the evidence for long lasting sex disparities in cardiovascular care among other types of care³². Therefore, it is vital for funding agencies and journal editors to mandate the proper consideration of sex and gender in the study design and analysis of cohort studies.

To understand the current standards of heart failure treatment for men and women, we plan to assess the extent of integrating sex evidence into clinical guidelines pertaining to CRT. This study would help elucidate the uptake of sex into CRT guidelines based on evidence identified from our systematic review which is vital for translating findings into practice.

We plan to survey international guidelines from the following societies and organizations:

- Canadian Cardiology Society
- European Society of Cardiology/European Heart Rhythm society of Cardiology
- Canadian Heart Rhythm Society
- Heart Rhythm Society
- American College of Cardiology/American Heart Association
- Asian Pacific Heart Rhythm Society
- Cardiac Society of Australia and New Zealand
- British Cardiovascular Society

Due to the inconsistencies in how the guidelines are written, we plan to screen guidelines with text positive for “Cardiac Resynchronization Therapy” or “CRT” to determine eligibility. We adapted a framework previously developed by Tannenbaum et al³³ to classify recommendations reported in the guidelines (Figure 2). The absence of sex-specific recommendations can range from missed opportunities to provide women with the additional benefit gained from CRT, to increased risk in complications such as pneumothorax. It would be important to also note the type of evidence used in the guidelines (RCT v cohorts vs SRs) as that might help explain the extent of integration of sex in the guidelines.

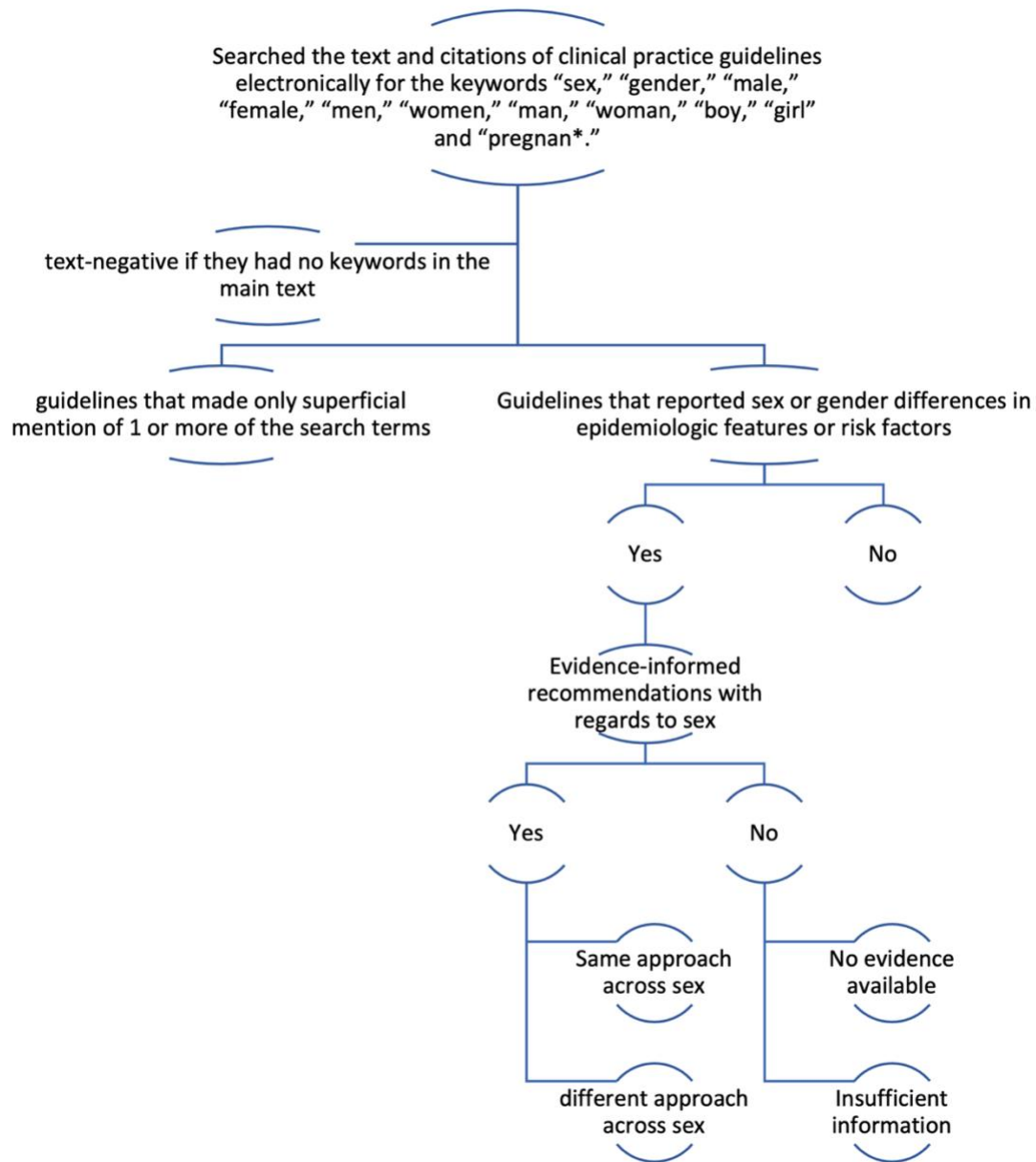


Figure 2. Framework for classifying sex considerations in clinical guidelines.

6.5 Conclusion

Sex and gender are important factors that need to be considered in study design, analysis and interpretation of CRT studies. This thesis demonstrates sex differences in receipt and response to CRT which may be due to women presenting with LBBB and NCIM more than men. Cohort studies should conduct within sex analyses to investigate the effect or interaction of sex with CRT in LBBB and NCIM populations on health outcomes. Patient gender information should also be

collected and analysed in studies. In addition, more adequately designed trials with proper integration of sex and gender in the study design and analysis need to be conducted and explicitly reported to verify the presence of sex differences in response to CRT.

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