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Sex disparities in the choice of cardiac resynchronization therapy device utilized: an analysis of trends, predictors and outcomes.

--Manuscript Draft--

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Abstract:	Background There is limited evidence on the influence of sex on decision to implant a cardiac resynchronization therapy device with pacemaker (CRT-P) or defibrillator (CRT-D), and the existence of sex-dependent differences in complications that may bias this decision. Methods All patients undergoing de novo CRT implantation (2004-2014) in the United States (US) National Inpatient Sample were included, stratified by device type (CRT-P and CRT-D). Multivariable logistic regression models were conducted to assess the association of female sex with receipt of CRT-D, and periprocedural complications. Results Out of 400,823 weighted CRT procedural records, the overall percentages of women undergoing CRT-P and CRT-D implantations were 41.5% and 27.2%, respectively, and these increased in comparison to males over the study period. Women were less likely to receive CRT-D (OR 0.66 95% confidence interval (CI) 0.64-0.67) and this trend remained stable throughout the study period (p=0.06). Furthermore, women were associated with increased odds of procedure-related complications (bleeding, thoracic and cardiac), compared to men, in the CRT-D group but not in the CRT-P group. Factors such as atrial fibrillation, malignancies, renal failure, advanced age (>60 years) and admission to non-urban/small hospitals favored the receipt of CRT-P over CRT-D whereas history of ischemic heart disease, cardiac arrest or ventricular arrhythmias favored the receipt of CRT-D over CRT-P. Conclusion Females were associated with persistently reduced odds of receipt of CRT-D

	compared to males over an eleven-year period. The present study identifies important factors that predict the choice of CRT device patients receive in the US healthcare system.

Keele Cardiovascular Research Group

Dear Professor Stanley Nattel, MD, Editor in Chief,

We thank the Editorial Committee and the Reviewers for their valuable comments on the manuscript entitled '*Trends of sex differences in outcomes of cardiac electronic device implantations in the United States'* and agree that these recommendations have further improved the readability of our study. We have responded to all the comments fully as outlined in the rebuttal and highlighted all changes in a marked copy of the manuscript.

We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable publication of our paper in the Canadian Journal of Cardiology.

We list our reply to the reviewer's comments in the file entitled 'Response to Reviewers' as per your instructions, in addition to a marked copy of the highlights.

Yours sincerely

Dr Mohamed Mohamed and Prof. Mamas Mamas
On behalf of submitting authors

Response to reviewers

Reviewer #1: I thank my colleagues Mohamed et al for their thoughtful responses to my concerns and suggestions. I have no further major points to raise, but I do wish to make two last minor suggestions that I leave up to the authors to decide whether they feel are helpful or not. I do not feel replies to these final suggestions are necessary.

Response: We thank you thank the reviewing for reassessing our updated manuscript, and we are delighted to know that their major concerns were addressed. We have responded to the reviewer's final suggestions below.

1. I agree with the authors that administrative data can be valuable for this type of research. The concern I raised in my point #10 was that the reference they use to a at least partially argues against the authors' point. Perhaps adding one or two more supportive references (e.g. those they cite in their RtR) might give more confidence in the importance of the results to readers less familiar with research using administrative data/.
Response: We thank the reviewer for this suggestion and the references cited in our first rebuttal were now added to the relevant section in the limitations.

2. I would consider changing the wording in the following sentence: "Female patients may have greater concerns about body image…". This could be viewed as a somewhat presumptuous statement that, I suggest, should be supported by empiric data if kept in the manuscript. The study they cite did NOT find differences in body image concerns between men and women, although that study does refer to one that suggested that YOUNGER women as a subgroup may have this concern more often. I think stating that sex differences in levels of anxiety and concerns regarding ICD implantation have been reported previously would probably be sufficient

Response: We agree with the reviewer's suggestion and we have now removed references to concerns about body image that may be viewed by some as a controversial statement.

3. Kudos to the authors on an interesting manuscript
Response: We thank the reviewer for their kind words.

Reviewer #3: I have read the new version of the manuscript with interest. The authors have significantly improved the paper according to the reviewers comments. The message appears clearer and the removal of the reference to CRT response score make it less confusing. I think that this work represents valuable information that should be published

I still have a few significant concerns:

1-My most significant remaining concerns is the lack of clarity regarding the real sample size as mentioned in my previous comment,
The authors state in the abstract: "Out of 400,832 de-novo CRT procedures analyzed" and in the results section : "A total of 400,823 de novo CRT implantation procedures were recorded". However, as clearly shown in the supplementary figure S1 this "400 823 people population" is inferred from a sample of 84 184. Although the methods used to

make this inference are probably adequate as stated in the response, it is misleading for the reader to state that 400 823 patients were analyzed. The size of the sample analyzed should be made explicit in the main text in the methods and result section rather than only in the supplement.

Response: We have made changes in the results and conclusion sections to further clarify that this is a weighted sample (quoted below and highlighted in the manuscript). We must emphasize that it is not our intention to mislead the readership or falsely inflate our sample size. We understand that even without application of discharge weight, a sample size of more than 80,000 is large enough to produce valid statistical inferences and would still be considered one of the largest analyses on this topic to date. However, we have an obligation to abide by HCUP sampling and analytical recommendations as stated in our Data User Agreement. These include the application of a sampling weight when running logistic regression models and reporting frequencies. Therefore, our analysis is only considered valid if reported using the weighted data.

Under Abstract (results subheading):

Out of 400,823 weighted CRT procedural records, the overall percentages of women undergoing CRT-P and CRT-D implantations were 41.5% and 27.2%, respectively, and these increased in comparison to males over the study period.

Under Methods (Data source subheading):

The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population.

Under Results:

A total of 84,148 individual records for de novo CRT implantation procedures were recorded between 2004 and 2014, which are representative of 400,823 estimated discharges after application of sampling weights.

Under Conclusion:

The present study is the largest to investigate sex differences in choice of CRT device type in more than 400,000 weighted hospitalization records (from 84,148 unweighted cases) for de novo CRT implantation and shows persistently lower odds of receipt of CRT-D in females compared to males over an eleven-year period.

2-In table 1, the number of patients when divided by sex are is not equal to the total numbers of patients divided by procedures (CRT-P-Male 39855 + CRT-P Female 28277 + CRT-D Male 282778 + CRT-D Female 105506 = 456 416 vs 60032 + 340791=400823). This should be verified and clarified

Response: We thank the reviewer for highlighting this important point. The sample size is indeed 400,823 as mentioned in the manuscript. As the reviewer rightly pointed out, the

individual numbers did not correspond to this total and this has now been corrected. An error in the SPSS filter function occurred when generating the individual group numbers after our analysis was complete, meaning that we the numbers reported were those prior to removing missing data. We have updated the CRT-P and CRT-D weighted values in Table 1. However, this does not affect our analysis and group numbers/percentages that were all correct and have been verified. We list below an output from SPSS shows the sample size and percentage for each study group and, as the reviewer will note, these numbers and group percentages match those in our paper (total sample size: 400,823, CRT-P vs. CRT-D: 15% vs. 85%, CRT-P-Male 35107 + CRT-P Female 22925 + CRT-D Male 246015 + CRT-D Female 94776 = 400,823).

Total sample size:

CIED TYPE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	CRTP	60032	15.0	15.0	15.0
	CRTD	340791	85.0	85.0	100.0
	Total	400823	100.0	100.0	

Group absolute numbers and percentages:

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* Custom Tables.
CTABLES
  /VLABELS VARIABLES=CIEDCATEGORICAL FEMALE DISPLAY=LABEL
  /TABLE BY CIEDCATEGORICAL [C] > FEMALE [C][COUNT F40.0, ROWPCT.COUNT PCT40.1] + CI
EDCATEGORICAL
    [C][COUNT F40.0, ROWPCT.COUNT PCT40.1]
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Custom Tables

CIED TYPE								CIED TYPE			
CRTP				CRTD				CRTP		CRTD	
Indicator of sex				Indicator of sex							
Male		Female		Male		Female					
Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
35107	58.5%	24925	41.5%	246015	72.2%	94776	27.8%	60032	15.0%	340791	85.0%

3-The advanced statistical methods are beyond my level of expertise and would benefit from a specific statistical review

4-An important limitation that remains is the lack of any information regarding the indication of the device including any data on LV function and presence of conditions requiring ventricular pacing. This is now better acknowledged in the discussion "we were unable to adjust for certain important factors such as exact LV function and conditions requiring a high proportion of right ventricular pacing".

Response: We agree with the reviewer's comments in that data on exact LV function and conditions requiring a high proportion of RV pacing remain as a limitation and, as the reviewer has kindly noted, we have acknowledged them both in the limitation section and discussion. Nevertheless, we feel that our study provides insights into differences in choice of CRT subtype in a large and unselected population, and we hope that this work inspires the conduct of further prospective studies to examine the observed disparities, adjusting for potential confounders that were not fully captured in our analysis.

Sex disparities in the choice of cardiac resynchronization therapy device utilized: an analysis of trends, predictors and outcomes.

Short Title: Sex differences in choice of CRT type

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Word count (inc. abstract): 4825

Abstract

Background: There is limited evidence on the influence of sex on decision to implant a cardiac resynchronization therapy device with pacemaker (CRT-P) or defibrillator (CRT-D), and the existence of sex-dependent differences in complications that may bias this decision.

Methods: All patients undergoing de novo CRT implantation (2004-2014) in the United States (US) National Inpatient Sample were included, stratified by device type (CRT-P and CRT-D). Multivariable logistic regression models were conducted to assess the association of female sex with receipt of CRT-D, and periprocedural complications.

Results: Out of 400,823 weighted CRT procedural records, the overall percentages of women undergoing CRT-P and CRT-D implantations were 41.5% and 27.8%, respectively, and these increased in comparison to males over the study period. Women were less likely to receive CRT-D (OR 0.66 95% confidence interval (CI) 0.64-0.67) and this trend remained stable throughout the study period (p=0.06). Furthermore, women were associated with increased odds of procedure-related complications (bleeding, thoracic and cardiac), compared to men, in the CRT-D group but not in the CRT-P group. Factors such as atrial fibrillation, malignancies, renal failure, advanced age (>60 years) and admission to non-urban/small hospitals favored the receipt of CRT-P over CRT-D whereas history of ischemic heart disease, cardiac arrest or ventricular arrhythmias favored the receipt of CRT-D over CRT-P.

Conclusion: Females were associated with persistently reduced odds of receipt of CRT-D compared to males over an eleven-year period. The present study identifies important factors that predict the choice of CRT device patients receive in the US healthcare system.

Key Words: cardiac resynchronization, pacemaker, defibrillator, sex, trends, outcomes

Introduction

Cardiac resynchronization therapy (CRT) is a class I recommendation for the management of patients with symptomatic heart failure with reduced ejection fraction on guideline directed medical therapy and left bundle branch block (with a QRS duration >150 milliseconds). [1-5] Decision making can be difficult in patients with Class 2a and 2b recommendations, such as those with atrial fibrillation, right bundle branch block or QRS duration <150 msec. In these situations, device type is often based on the implanters' choice. [6]

There is limited data on differences in the rate of utilization of both CRT device types between sexes, and whether sex is independently associated with the choice of device therapy. Findings from the recently published European Society of Cardiology (ESC) CRT Survey II concluded that females are more likely to receive a CRT-P (CRT with pacemaker) than a CRT-D (CRT with defibrillator) device.[7] In the absence of any randomized control trials, this survey was the first to examine predictors of receipt of CRT-P in a European cohort of more than 10,000 patients undergoing CRT implantation between October 2015 and January 2017. However, only an estimated 11% of patients undergoing CRT were believed to have been enrolled in the survey making the findings less generalizable to the wider European population and other healthcare systems. Furthermore, it is unclear whether sex disparities in choice of CRT device type have changed from a national perspective over the years. The presence and trends of sex disparities regarding the type of CRT device as well as the difference in procedure related complications between sexes has not been evaluated in recent years.

The present study examined the proportion of females undergoing implantation of CRT-P and CRT-D devices and evaluated the independent association between sex and choice of implanted CRT device type in a nationwide cohort of de novo CRT procedures performed from January 2004 through December 2014 in the United States (US).

Methods

Data Source

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the US and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[8] NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The estimates of hospital characteristics, numbers of discharges, length of stay, and in-hospital mortality from the HCUP NIS for 2007 were highly comparable to three related data sources: the American Hospital Association (AHA) Annual Survey Database; the National Hospital Discharge Survey (NHDS) from the National Center for Health Statistics; and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS). [9, 10]

Study Design and Population

All adults (aged ≥18 years) undergoing de novo CRT implantation (CRT-P and CRT-D) during hospitalization between 2004 and 2014 were included in this study, as identified using the International Classification of Diseases, ninth revision (ICD-9) codes given in Table S1 (Supplemental Material). We excluded CRT upgrades and records with missing data on the following variables: age, elective admission, primary expected payer and median household income.

Patient characteristics, comorbidities, and clinical outcomes were extracted using the ICD-9 procedure and diagnosis codes provided in Table S1 (Supplemental Material);

procedure-related bleeding, cardiac complications (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis) and thoracic complications (composite of acute pneumothorax or hemothorax, with or without drainage, or thoracic vascular injury) were also extracted. Procedure-related bleeding was defined as any post-procedural hemorrhage or anemia after hemorrhage according to ICD-9 diagnosis codes. (Table S1)

Outcomes

The primary outcome was comparison of receipt of CRT-D compared to CRT-P between sexes. The secondary outcomes were in-hospital adverse events, including major acute cardiovascular events (MACE), all-cause mortality and procedural-related complications (bleeding, thoracic and cardiac). In-hospital MACE was defined as a composite of all-cause mortality, cardiac complications, thoracic complications and device-related infection.

Statistical Analysis

For exploratory analysis, the cohort was stratified by device type (CRT-D, or CRT-P) and sex. Continuous variables are summarized using medians and interquartile range (IQR) and were compared using the Kruskal-Wallis test. Categorical variables are summarized as percentages and were analyzed using the chi-squared (X^2) test.

Several multivariable logistic regression models were constructed to examine the independent association between female sex and each of our outcomes of interest; first, receipt of CRT-D and second all of the procedure-related adverse events that we considered (stratified by device type). All multivariable models adjusted for differences in socioeconomic, clinical, and hospital-level covariates that may directly influence in-hospital outcomes (all variables listed in Appendix A in Supplemental Material). Trend analysis was performed using linear regression modelling with the inclusion of time (years) as a covariate for assessing sex differences in type of device use over time, and by assessing the interaction between sex and

time (years) in logistic regression analysis for clinical outcomes. All associations were summarized from the multivariable logistic regression models using odds ratios (ORs) and associated 95% confidence intervals (CIs).

All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY). Additionally, all analyses used the sampling weights provided by the AHRQ, which are required because the design of the study means that different observations may have different probabilities of selection. The sampling weights for each individual discharge were hence incorporated into the relevant SPSS commands for each analysis.

Results

A total of 400,823 de novo CRT implantation procedures were recorded between 2004 and 2014, including 60,032 CRT-P procedures (15%) and 340,791 CRT-D procedures (85%). A flow diagram illustrating the inclusion and exclusion process in the present study is presented in Figure S1 (Supplemental Material). Cases excluded due to missing variables represented 3% (n=2601 unweighted records) of the CRT de novo implantation cohort.

In the total cohort, 77% of females underwent CRT-D implantation compared to 88% of males, while the rest underwent CRT-P implantation. Within the CRT groups, females were more prevalent in the CRT-P group than the CRT-D group (41.5% vs. 27.8%). The percentage of females undergoing both CRT-P and CRT-D procedures amongst all CRT implantations has increased over the study period, but more so in the CRT-P group. Specifically, the percentage of females undergoing CRT-P was 34.9% in 2004, compared to 45.6% in 2014 (absolute difference of 10.7%), while the percentage of females undergoing CRT-D was 24.2% in 2004 compared to 29.0% in 2014 (absolute difference of 4.8%). (Figure 1)

Patients undergoing CRT-D were primarily younger with a greater burden of cardiovascular risk factors such a previous cardiac arrest, ventricular tachycardia (VT), ventricular fibrillation (VF), diabetes and a previous history of acute myocardial infarction

(AMI), percutaneous coronary intervention (PCI) and coronary artery bypass grafts (CABG). (Table 1) However, the CRT-D group had a lower prevalence of renal failure, anemias and coagulopathies. Several sex differences in patient characteristics were observed in both CRT groups. Females in both groups had significantly lower prevalence of VT, VF, renal failure and previous AMI, PCI, CABG and history of ischemic heart disease (IHD) but a much higher prevalence of non-ischemic cardiomyopathy.

Predictors of receipt of CRT-D

Female sex was independently associated with lower odds of CRT-D compared to male sex in the total cohort (OR 0.66 95% CI 0.64 - 0.67), and this finding persisted throughout the study years ($P_{interaction}$=0.06). (Table 2, Figure 2). Several other variables were predictive of receipt of CRT-D compared to CRT-P. (Table 2, Figures 3A and 3B) Older age was associated with a lower odds of CRT-D (Age (years) 61-70: OR 0.77 95% CI 0.74, 0.80; 71-80: OR 0.52 95% CI 0.50- 0.54; >80: OR 0.22 95% CI 0.21 - 0.23], p<0.001 for all). (Figure 3A) The majority of primary expected payer categories were not associated with receipt of CRT-D over CRT-P; however, privately insured patients were less likely to receive a CRT-D device (OR 0.84 [0.77, 0.91]) compared to those insured with Medicare. Furthermore, patients admitted to urban hospitals (teaching and non-teaching) and hospitals with a higher bed capacity (medium and large) were more likely to receive CRT-D (Table 2, Figure 3B).

Amongst the comorbidities, factors such as previous cardiovascular disease (acute myocardial infarction and coronary artery bypass graft), history of cardiac arrest and ventricular arrhythmias (ventricular tachycardia and fibrillation) were associated with increased odds of receipt of CRT-D whereas comorbidities such as atrial fibrillation, anemia (deficiency and chronic), renal failure and malignancy (solid tumors, metastatic cancers and lymphomas) were associated with reduced odds of receipt of CRT-D. (Table 2, Figure 3A).

In-hospital adverse outcomes

Overall, the crude rates of mortality and adverse events were higher in the CRT-P group compared to CRT-D group (MACE: 4.8 vs. 7.0%; mortality: 0.8% vs. 1.4%; procedure-related bleeding: 1.9% vs. 3.5%; thoracic and complications: 2.6% vs. 4.2% and 0.4% vs. 0.5%, respectively. (Table 3) Within the CRT-P group, the rates of MACE, mortality, procedure-related bleeding and device-related infection were lower in females compared to males, while the rate of cardiac complications was higher in females and there was no difference in thoracic complications between sexes. (Table 3, Figure S2) In contrast, in the CRT-D group, the majority of complications (MACE, procedure-related bleeding, thoracic and cardiac complications) were higher in females than in males, with the exception of mortality and device-related infections, which were lower in females. (Table 3, Figure S2)

In multivariable analysis there was a sex-related difference in outcomes in the CRT-P and CRT-D groups. The odds of MACE were higher in females undergoing CRT-D (OR 1.10 95% CI 1.06-1.14) but lower in females undergoing CRT-P implantation (OR 0.91 95% CI 0.85-0.97). (Table 4) Further, the odds of procedure-related bleeding, thoracic and cardiac complications were significantly raised in females in the CRT-D group but there was no difference between sexes in the CRT-P group. However, females in both CRT groups were associated with reduced odds of mortality (CRT-P: OR 0.70 95% CI 0.59-0.82, CRT-D: OR 0.73 95% CI 0.67-0.81).

Discussion

The current study is the largest to examine sex differences in the type of CRT device used in de novo implantations. We also present the largest analysis of predictors of receipt of CRT-D, compared to CRT-P, in a national cohort of CRT implantations in the US. Our key finding is that over a period of 11 years, among recipients of CRT, a larger proportion of females received CRT P as opposed to CRT D despite adjustment for baseline differences.

analysis demonstrates that females undergoing CRT-D implantation are at a higher risk of procedure-related complications (bleeding, thoracic and cardiac) compared to males, but no difference in these complications was observed between sexes in the CRT-P group. We also report lower mortality in females undergoing implantation of both types of CRT devices compared to males. Finally, we observe institutional disparities in choice of CRT device, where patients admitted to urban and larger bed hospitals were more likely to receive CRT D, rather than CRT P.

There are inconsistencies in the recommendations of international guidelines on choice of device type (CRT-D vs. CRT-P).[11] The European Heart Rhythm Association recommends the consideration of factors such as life expectancy, severe renal failure and patient frailty status, however, in some circumstances, the decision on device type is often based on implanters' choice rather than guideline recommendations.[1, 11] Despite sex not being a factor in the choice of device type, there have been several reports on the lower rates of CRT-D implantation in females compared to males.[7, 12] However, studies to date were insufficiently powered to inform cardiologists of the trends of sex differences in the choice of device or subsequent outcomes in patients undergoing CRT-D implantation. Findings from the ESC Survey II showed that females were less likely to receive a CRT-D device in a survey of more than 10000 patients undergoing CRT implantation in Europe,[7] but these findings were limited by a small cohort that was collected over 15 months and estimated to represent only 11% of all procedures undertaken throughout this period. A study of more than 300,000 patients undergoing CRT-D implantation between 2006 and 2012 showed that women were less likely to receive CRT-D.[13] However, their trend analysis only comprised of crude rates without adjustment for baseline differences in characteristics between sexes in both device groups and, as such, appeared significant. Our study examines trends over a longer period (2004-2014) and demonstrates sex disparities in choice of CRT device, with females persistently less likely to

receive a CRT-D device compared to CRT-P over an eleven-year period, despite adjustment for all feasible baseline differences between the study groups, and shows that the trend was insignificant. However, we were unable to adjust for certain important factors such as exact LV function and conditions requiring a high proportion of right ventricular pacing. Possible explanations for the persistent sex differences in choice of CRT type could be lower referral of females for CRT, females' reduced access of to healthcare compared to men, and physicians' belief that females are better responders to CRT with improved LV reverse remodeling, as evidenced by normalization of QRS duration, and reduced longer term mortality compared to males and, therefore, less likely to experience ventricular arrhythmias requiring defibrillation, as well as patient preferences.[14-16] However, there is growing evidence to suggest that QRS duration alone is less reliable for the assessment of dyssynchrony, especially between sexes, since females have smaller left ventricles and an apparently normal QRS duration may still be dyssynchronous in relation to the right ventricle when not adjusted for LV mass.[14] An important consideration influencing the choice of device is patient preference. Female patients may have greater concerns about body image, especially with CRT-D devices that have bulkier generators, and ICD shocks. A study on sex differences in anxiety and concerns in 535 patients undergoing ICD implantation, female sex was associated with increased odds of anxiety (OR 2.60 95% CI 1.46–4.64) and concerns about ICD shocks (OR 1.81 95% CI 1.09–3.00) compared to male sex. [17] These factors may affect patient preferences and should be addressed when counselling them prior to CRT implantation.

Our study is the largest to examine and demonstrate disparities in outcomes according to sex between CRT-D and CRT-P groups, except in mortality, which was reduced in females regardless of CRT subtype. We show that there are no differences in CRT-P procedure-related complications between sexes whereas females were at a higher risk of all CRT-D procedure-related complications (bleeding, cardiac and thoracic) compared to males. The increased risk

of complications in females undergoing CRT-D insertion is possibly attributed to the use of bulky defibrillator leads relative to females, who have thinner ventricles, smaller cardiac chamber sizes, and smaller vessel size and diameter, which may, in part, explain operators' reluctance to choose CRT-D devices over CRT-P in females; however the reasons are multifactorial and include factors such as patient preferences and device indication.18-2223 While the ESC Survey II study did not demonstrate a difference in complications between CRT-P and CRT-D devices,7 their major complications did not include mechanical factors such as thoracic (pneumothorax or hemothorax), cardiac (pericardial effusion or tamponade) and vascular complications (thoracic vessels and coronary sinus vascular injuries) and were only restricted to stroke, myocardial infarction, infection, arrhythmias and worsening heart and renal failure. In contrast, a study by Barra et al. of 3008 European patients undergoing CRT implantation between 2006 and 2013 showed no significant differences in the odds of acute complications in patients undergoing CRT-D devices (OR=1.16, 95% CI 0.71-1.89, p=0.56).24 The increased risk of procedure-related complications in females undergoing CRT-D implantation observed in some studies may explain operators' reluctance to opt for CRT-D devices in females. These findings highlight the need for devices that have been designed for females (accounting for their biology, size) as much as males, and the need to increase the enrollment of females in clinical trials that establish the efficacy and safety of devices. Furthermore, risk reduction strategies such as ultrasound and echocardiography guidance for venous access and septal RV lead placements, respectively, could help reduce their risk of complications in females.

The present study reports several important predictors of receipt of CRT-D over CRT-P in a contemporary cohort of US hospitalizations. A recent study has examined factors that affect the choice of CRT device type in a European population.7 However, there are several differences between healthcare and insurance systems between both continents and the findings

from the ESC Survey II may not inform US operators of contemporary practice from a national perspective. Several predictors of receipt of CRT-D were similar between our study and the ESC Survey II such as sex, admission to a university hospital (approximately equivalent to an urban teaching hospital) and also factors in favor of receipt of CRT-P device such as atrial fibrillation.[7] While younger patients (≤75 years) were more likely to receive a CRT-P device in the ESC survey, we show that the odds of receipt of CRT-D start from an age of 60 years with an inverse relationship between age and odds of receipt of CRT-D in older age groups (61-70, 71-80 and >80 years).

Limitations

There are several limitations to our study. First, the administrative nature of the NIS database, as with any such database has limitations around the accuracy of coding with no external validation. However, the use of administrative data has been previously validated for the purpose of cardiovascular research [25], and for capturing CIED-related complications.[26] Furthermore, the NIS database has a comparable capture of patient demographics and superior geographic capture of hospitalizations in more than 25 diagnosis groups in comparison to large multistate electronic health record databases.[27] Secondly, since the NIS dataset does not provide information on pharmacotherapy, indications for CRT implantation, site of LV placement, ejection fraction, QRS duration, etiology of heart failure and operator experience, we were unable to adjust for the differences in these covariates between the study groups. We were unable to account for patient preference or consent as factors in device selection. Furthermore, due to the observational nature of these data, the results should not be interpreted as causal, but rather relate to associations that require further research. Third, our cohort includes a mixture of daycase and inpatient procedures and, therefore, may not be reflective of

simple outpatient procedures. Finally, the NIS dataset only reports in-hospital outcomes and, therefore, the present findings are not be applicable to longer term outcomes.

Conclusion

The present study is the largest to investigate sex differences in choice of CRT device type in 400,000 hospitalizations for de novo CRT implantation and shows persistently lower odds of receipt of CRT-D in females compared to males over an eleven year period. Females undergoing CRT-D implantation are at a higher risk of procedure-related complications compared to males, but no difference was found in procedure-related complications between sexes in those undergoing CRT-P implantations. The present study shows significant disparities in choice of CRT type between geographical regions and institutional levels and identifies patient factors that favor receipt of either type of device. These findings are essential to inform operators of the trends of current practice from a national perspective and drive the need for further research in to sex differences in complications in patients undergoing CRT-D implantation which may be deterring operators from offering these devices to females compared to males.

Conflicts

DB is paid modest fees by Medtronic Ltd. for educational sessions. Other co-authors have no disclosures and no relationships with the pharmaceutical industry.

Funding

This work constitutes part of a PhD for MOM that is supported by Medtronic Ltd. Medtronic Ltd. was not involved in the conceptualization, design, conduct, analysis, or interpretation of the current study.

Statement

The manuscript has neither been published nor is currently under consideration for publication by any other journal. All authors have approved the final version of the manuscript.

References

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Figure Legends:

Figure 1. Proportions of A) CRT-P and B) CRT-D procedures over the study period*

Legend: *p<0.001 for trend; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively

Figure 2. Odds ratios (OR) of receipt of CRT-D as opposed to CRT-P in females*

Legend: *reference is male sex; **CI:** confidence interval; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; p>0.05 (non-significant for trend)

Figure 3. Patient-related (A) and non-patient-related (B) predictors of receipt of CRT-D as opposed to CRT-P in females*

Legend: *reference is male sex; **§** non-significant; † p<0.05; ‡ p<0.001; **CI:** confidence interval; OR: odds ratio; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively.

Table 1

Table 1. Patient characteristics of study groups

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
Number of weighted discharges	35107	24925		246015	94776		60032	340791	
Sociodemographic									
Age (years), median (IQR)	77(68,83)	78(69,84)	<0.001	71(62,78)	71(62,78)	0.08	77 (69,83)	71 (62,78)	<0.001
Ethnicity, %			<0.001			<0.001			<0.001
White	84.0	81.3		79.9	72.0		83.0	78.0	
Black	6.5	9.1		9.4	15.9		7.5	11.2	
Hispanic	5.3	5.4		6.2	7.5		5.3	6.4	
Asian/Pacific Islander	1.2	1.4		1.3	1.3		1.3	1.3	
Native American	0.7	0.8		0.5	0.6		0.7	0.5	
Other	2.4	2.1		2.6	2.7		2.2	2.6	
Elective Admission, %	44.5	42.9	<0.001	50.3	50.2	0.673	43.9	50.3	<0.001
Weekend admission, %	11.1	10.7	<0.001	9.0	8.9	0.429	10.9	9.0	<0.001
Primary expected payer, %			<0.001			<0.001			<0.001
Medicare	78.3	82.3		71.7	71.3		80.1	71.7	
Medicaid	3.0	3.2		4.5	6.5		3.0	5.0	
Private Insurance	15.9	12.4		20.3	19.2		14.5	20.0	
Self-pay	1.1	1.0		1.6	1.6		1.0	1.5	
No charge	0.0	0.1		0.2	0.2		0.1	0.2	
Other	1.7	0.9		1.7	1.2		1.3	1.6	
Median Household Income (Percentile), %			<0.001			<0.001			<0.001
0-25th	23.3	27.2		25.5	29.5		24.9	26.5	
26-50th	26.2	27.2		26.3	26.9		26.6	26.5	
51-75th	26.7	24.8		25.3	23.5		25.9	24.8	
76-100th	23.9	20.9		22.9	20.1		22.7	22.2	
Hospital bed size, %			<0.001			<0.001			<0.001

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
Small	9.4	10.8		8.5	8.1		10.0	8.4	
Medium	19.6	19.1		18.4	19.7		19.4	18.7	
Large	71.0	70.1		73.1	72.2		70.6	72.9	
Hospital Region, %			<0.001			<0.001			<0.001
Northeast	15.8	14.3		20.7	19.6		15.0	20.4	
Midwest	28.6	29.2		25.1	25.9		29.1	25.5	
South	39.0	40.3		37.4	38.9		39.5	37.7	
West	16.6	16.2		16.9	15.6		16.3	16.3	
Location/ Teaching status, %			<0.001			<0.001			<0.001
Rural	5.4	6.5		3.3	3.2		5.8	3.2	
Urban non-teaching	32.7	33.1		35.4	34.1		32.8	35.0	
Urban- teaching	61.9	60.4		61.4	62.7		61.4	61.8	
Length of stay (days), %			0.232			0.162			0.04
0-1	42.4	39.1		40.0	39.4		40.8	39.2	
2	10.7	10.8		9.8	10.1		9.9	10.2	
Comorbidities, %									
All-cause infection*	2.5	1.9	<0.001	1.8	1.6	<0.001	2.2	1.7	<0.001
Cardiac Arrest	1.6	1.4	0.086	2.1	2.5	<0.001	1.5	2.2	<0.001
Shock	1.7	1.5	0.032	1.9	1.6	<0.001	1.6	1.8	<0.001
LBBB	73.3	70.4	<0.001	76.0	74.1	<0.001	74.6	72.8	<0.001
Atrial Fibrillation	52.0	58.3	<0.001	36.7	29.2	<0.001	54.7	34.8	<0.001
Ventricular Tachycardia	10.2	6.0	<0.001	29.3	22.1	<0.001	8.4	27.4	<0.001
Ventricular Fibrillation	0.9	0.8	0.712	3.9	4.1	0.017	0.8	3.9	<0.001
Anemias	12.8	15.6	<0.001	9.2	11.7	<0.001	9.6	12.5	<0.001
Coagulation disorders	6.2	4.1	<0.001	4.1	3.0	<0.001	4.4	3.3	<0.001
Diabetes	29.0	27.1	0.015	33.4	34.1	0.063	32.9	32.7	0.576
Hypertension	57.1	61.4	<0.001	56.3	56.4	0.696	58.9	56.4	<0.001

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
Renal failure (chronic)	22.0	18.5	<0.001	20.2	15.9	<0.001	20.6	19.1	<0.001
Peripheral vascular disease	9.5	6.7	<0.001	9.7	6.7	<0.001	8.3	8.9	<0.001
Valvular heart disease	1.1	1.4	<0.001	0.6	0.8	<0.001	1.2	0.6	<0.001
Previous AMI	13.2	9.0	<0.001	23.9	15.5	<0.001	11.5	21.7	<0.001
History of IHD	58.9	41.4	<0.001	72.1	52.2	<0.001	51.6	66.7	<0.001
Previous PCI	10.2	8.1	<0.001	13.0	9.5	<0.001	9.4	12.1	<0.001
Previous CABG	19.7	8.9	<0.001	26.1	12.6	<0.001	15.2	22.4	<0.001
Previous CVA	4.4	5.3	<0.001	3.6	3.5	0.161	4.8	3.6	<0.001
Dyslipidemia	39.6	38.4	0.001	42.7	38.5	<0.001	39.2	41.6	<0.001
Smoking	5.2	3.7	<0.001	7.7	6.1	<0.001	4.6	7.3	<0.001
Chronic pulmonary disease/ pulmonary circulation disorders	22.1	21.7	0.569	21.2	22.6	<0.001	21.3	22.4	0.001
Hypothyroidism	8.7	21.0	<0.001	7.1	15.2	<0.001	13.9	9.3	<0.001
RA/collagen vascular diseases	1.6	3.5	<0.001	1.1	2.9	<0.001	2.4	1.6	<0.001
Liver disease	1.1	0.8	<0.001	1.1	0.8	<0.001	1.0	1.0	0.679
Fluid and electrolyte disturbances	16.2	19.1	<0.001	12.8	14.7	<0.001	17.5	13.3	<0.001
Malignancies**	3.0	2.0	<0.001	1.5	1.3	0.066	1.7	1.3	0.017
Depression and/or psychosis	4.8	8.9	<0.001	4.1	7.5	<0.001	4.2	7.8	<0.001
Paralysis and other neurological disorders	4.9	4.7	0.699	3.1	3.4	0.026	3.3	3.7	0.006
Obesity	7.2	9.0	<0.001	8.4	10.4	<0.001	8.1	8.9	<0.001
Weight loss	2.5	2.5	0.831	1.3	1.4	0.020	2.5	1.3	<0.001
Dementia	1.0	1.1	0.233	0.3	0.3	0.320	1.1	0.3	<0.001

*__All-cause infection__: Composite of septicemia, viremia and bacteremia; **including hematological malignancies (e.g. lymphoma and leukemia); **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **IQR:** interquartile range; **AMI:** acute myocardial infarction; **IHD:** ischemic heart disease; **CABG:** coronary artery bypass graft; **PCI:** percutaneous coronary intervention; **CAD:** coronary artery disease; **LBBB:** left bundle branch block

Table 2. Multivariable analysis of predictors of receipt of CRT-D Device*

Predictor	**OR [95% CI]**
Female sex	0.66 [0.64, 0.67]
Age (Years)	
≤60 (reference)	
61-70	0.77 [0.74, 0.80]
71-80	0.52 [0.50, 0.54]
>80	0.22 [0.21, 0.23]
Primary payer	
Medicare (reference)	
Medicaid	1.03 [0.98, 1.09]
Private Insurance	0.94 [0.91, 0.97]
Self-pay	0.92 [0.84, 1.00]
No charge	1.33 [0.99, 1.78]
Shock	1.01 [0.93, 1.08]
Cardiac Arrest	1.09 [1.01, 1.18]
Ventricular Tachycardia	4.09 [3.97, 4.22]
Ventricular Fibrillation	4.37 [3.99, 4.79]
Dyslipidemia	1.04 [1.02, 1.06]
Atrial Fibrillation	0.53 [0.52, 0.54]
Thrombocytopenia	0.82 [0.74, 0.90]
Previous AMI	1.56 [1.52, 1.61]
Previous PCI	0.95 [0.92, 0.98]
Previous CABG	1.21 [1.17, 1.24]
Previous CVA	0.89 [0.85, 0.93]
Family history of CAD	1.01 [0.95, 1.07]
Alcohol abuse	0.97 [0.89, 1.05]
Deficiency anemias	0.84 [0.82, 0.87]
Chronic blood loss anemia	0.85 [0.76, 0.95]
RA/collagen vascular diseases	0.81 [0.76, 0.86]
Chronic pulmonary disease	0.94 [0.91, 0.96]
Coagulopathy	1.00 [0.92, 1.09]
Depression	0.87 [0.83, 0.91]
Diabetes	1.11 [1.09, 1.14]
Drug abuse	1.06 [0.93, 1.20]
Hypertension	0.94 [0.92, 0.96]
Hypothyroidism	0.89 [0.86, 0.91]
Liver disease	0.88 [0.80, 0.97]
Lymphomas	0.65 [0.59, 0.72]
Fluid and electrolyte disturbances	0.83 [0.81, 0.85]
Metastatic cancer	0.52 [0.44, 0.62]
Other neurological disorders	0.80 [0.76, 0.84]
Paralysis	0.89 [0.81, 0.99]
Peripheral vascular disease	0.99 [0.96, 1.03]
Pulmonary circulation disorder	0.54 [0.47, 0.62]

Renal failure (chronic)	0.89 [0.85, 0.96]
Solid tumor without metastases	0.76 [0.70, 0.83]
Valvular heart disease	0.81 [0.74, 0.90]
Weight loss	0.64 [0.60, 0.69]
Dementia	0.53 [0.47, 0.60]
Hospital bed size	
Small (reference)	
Medium	1.19 [1.15, 1.23]
Large	1.26 [1.23, 1.31]
Hospital Region	
Northeast (reference)	
Midwest	0.65 [0.63, 0.67]
South	0.66 [0.64, 0.68]
West	0.74 [0.72, 0.77]
Location/ Teaching status	
Rural (reference)	
Urban non-teaching	1.96 [1.87, 2.05]
Urban- teaching	1.72 [1.65, 1.80]

*Indicator is receipt of CRT-P adjusting for the above variables and calendar year.
As an example, odds ratio of 0.56 favors receipt of CRT-P over CRT-D; CI: Confidence Interval; **OR:** Odds ratio; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **IQR:** interquartile range; **AMI:** acute myocardial infarction; **CABG:** coronary artery bypass graft; **PCI:** percutaneous coronary intervention; **CAD:** coronary artery disease.

Table 3. In-hospital clinical outcomes according to device type

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (% of cohort)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.8)**	**Female (27.2)**	**p-value**	**CRT-P (15.0)**	**CRT-D (85.0)**	**p-value**
MACE, %*	7.3	6.6	0.002	4.7	5.2	<0.001	7.0	4.8	<0.001
All-cause mortality, %	1.6	1.1	<0.001	0.8	0.6	<0.001	1.4	0.8	<0.001
Procedure-related bleeding, %	3.6	3.3	<0.001	1.8	2.1	<0.001	3.5	1.9	<0.001
Thoracic complications, %	4.1	4.4	0.065	2.3	3.3	<0.001	4.2	2.6	<0.001
Cardiac complications, %	0.4	0.5	0.025	0.3	0.6	<0.001	0.5	0.4	<0.001
Device-related infection, %*	1.8	1.1	<0.001	1.6	0.9	<0.001	1.5	1.4	0.021

*__MACE:__ Composite of mortality, thoracic complications, cardiac complications, and device-related infection; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively

Table 4. Odds ratios (OR) of in-hospital outcomes in females (vs. males)

	CRT-P	**CRT-D**
	OR [95% CI]	**OR [95% CI]**
MACE*	0.91 [0.85,0.97]	1.10 [1.06,1.14]
All-cause mortality	0.70 [0.59,0.82]	0.73 [0.67,0.81]
Procedure-related bleeding	1.00 [0.91,1.10]	1.23 [1.17,1.31]
Thoracic complications	1.04 [0.96,1.13]	1.39 [1.33,1.45]
Cardiac complications	1.10 [0.87,1.39]	1.69 [1.50,1.90]

*__MACE:__ Composite of mortality, thoracic complications, cardiac complications, and device-related infection; CI: confidence interval; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively

graphical abstract

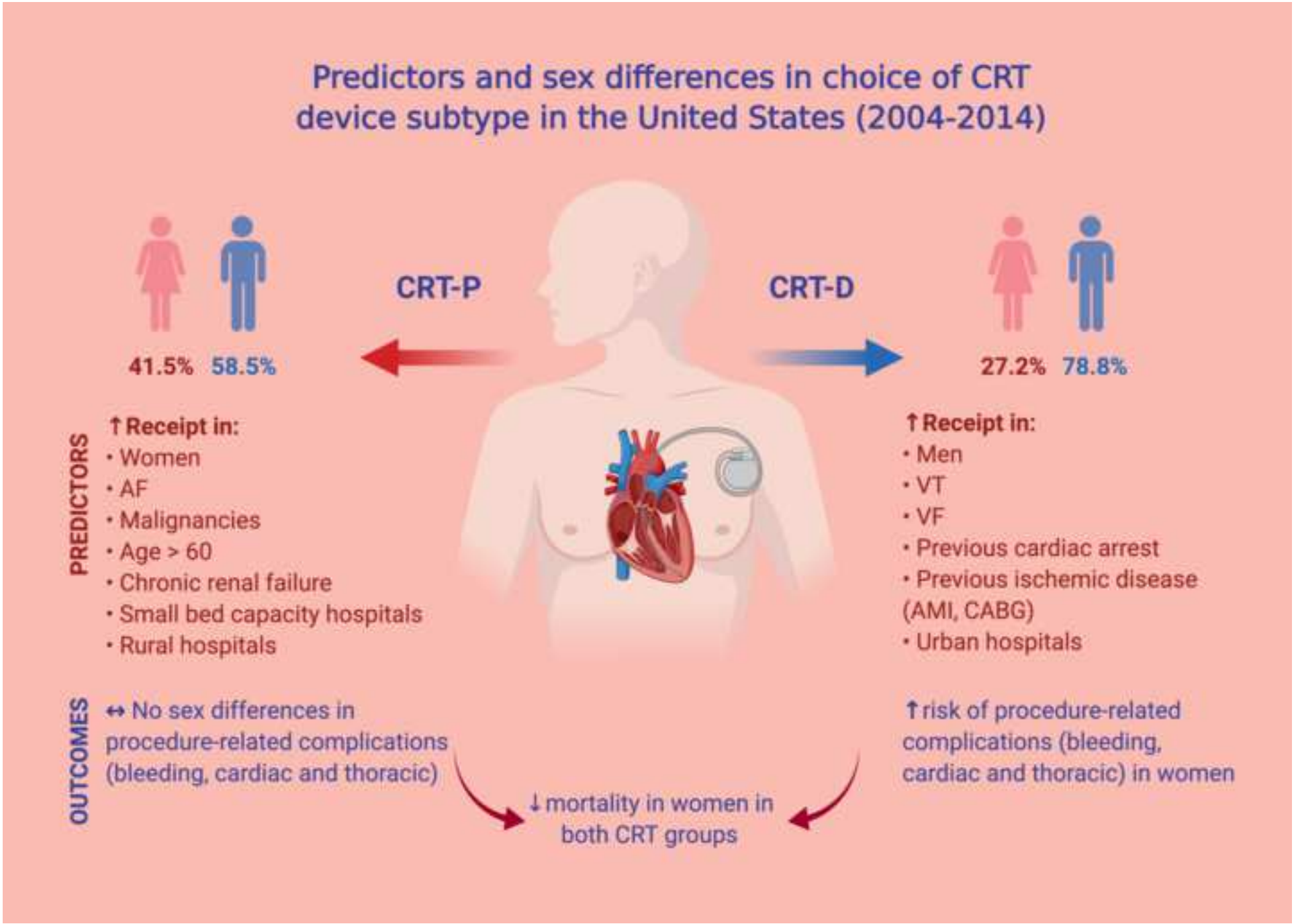

Figure 1

Click here to access/download;Figure;Figure 1.tiff

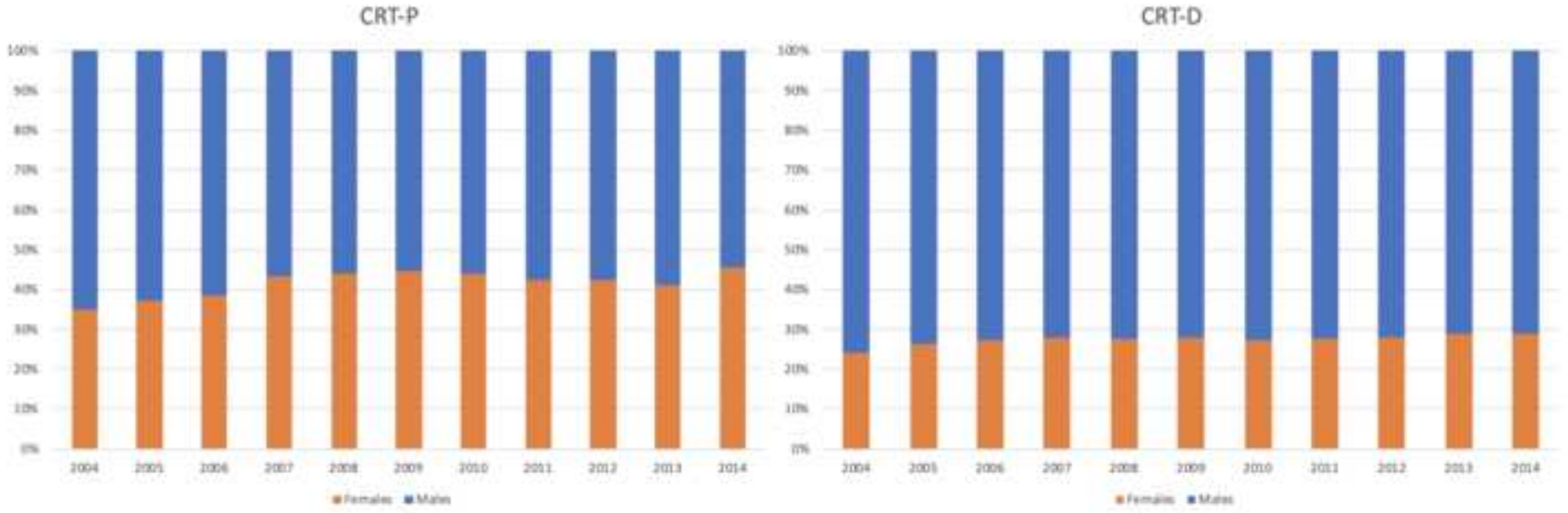

Figure 2

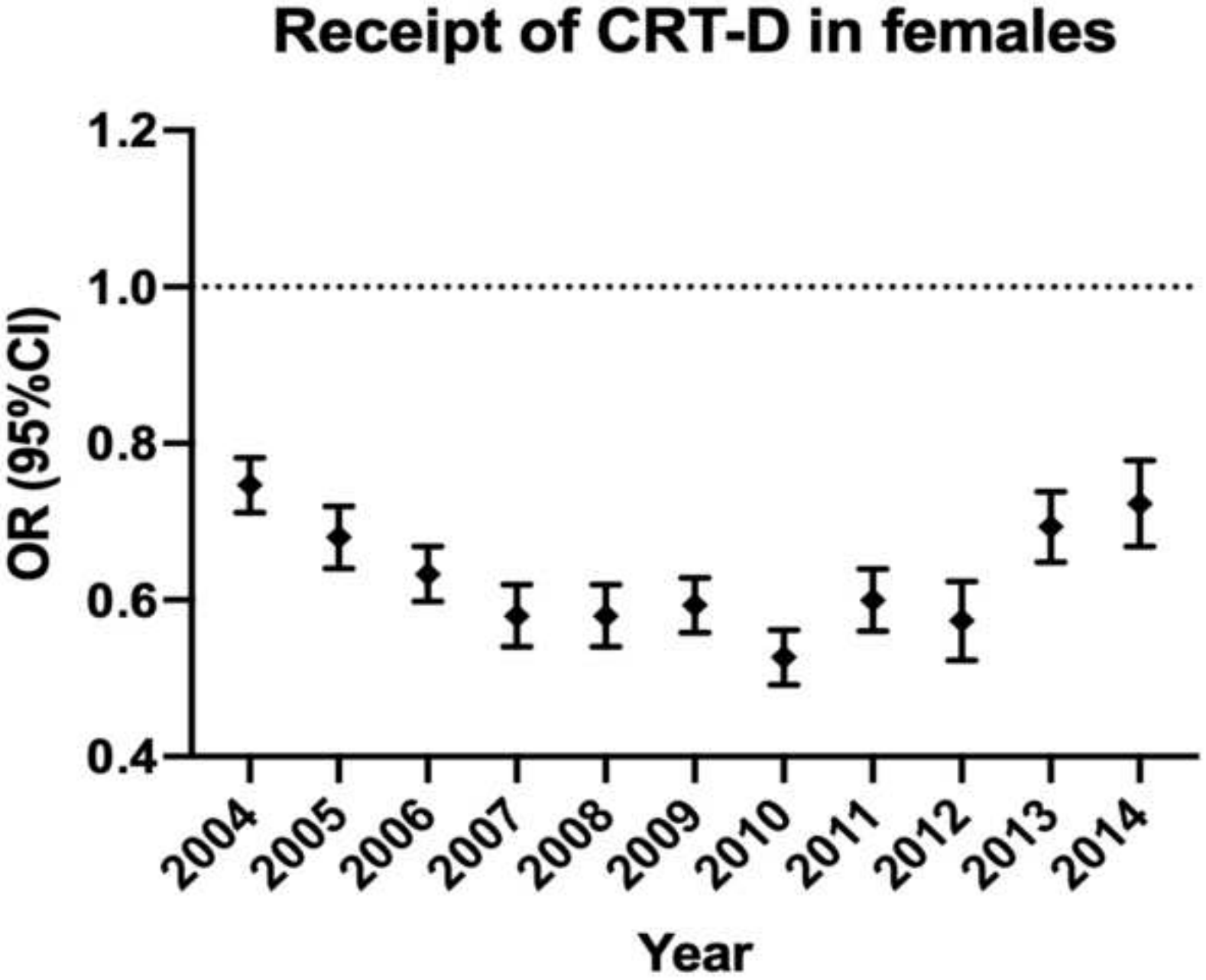

Figure 3A

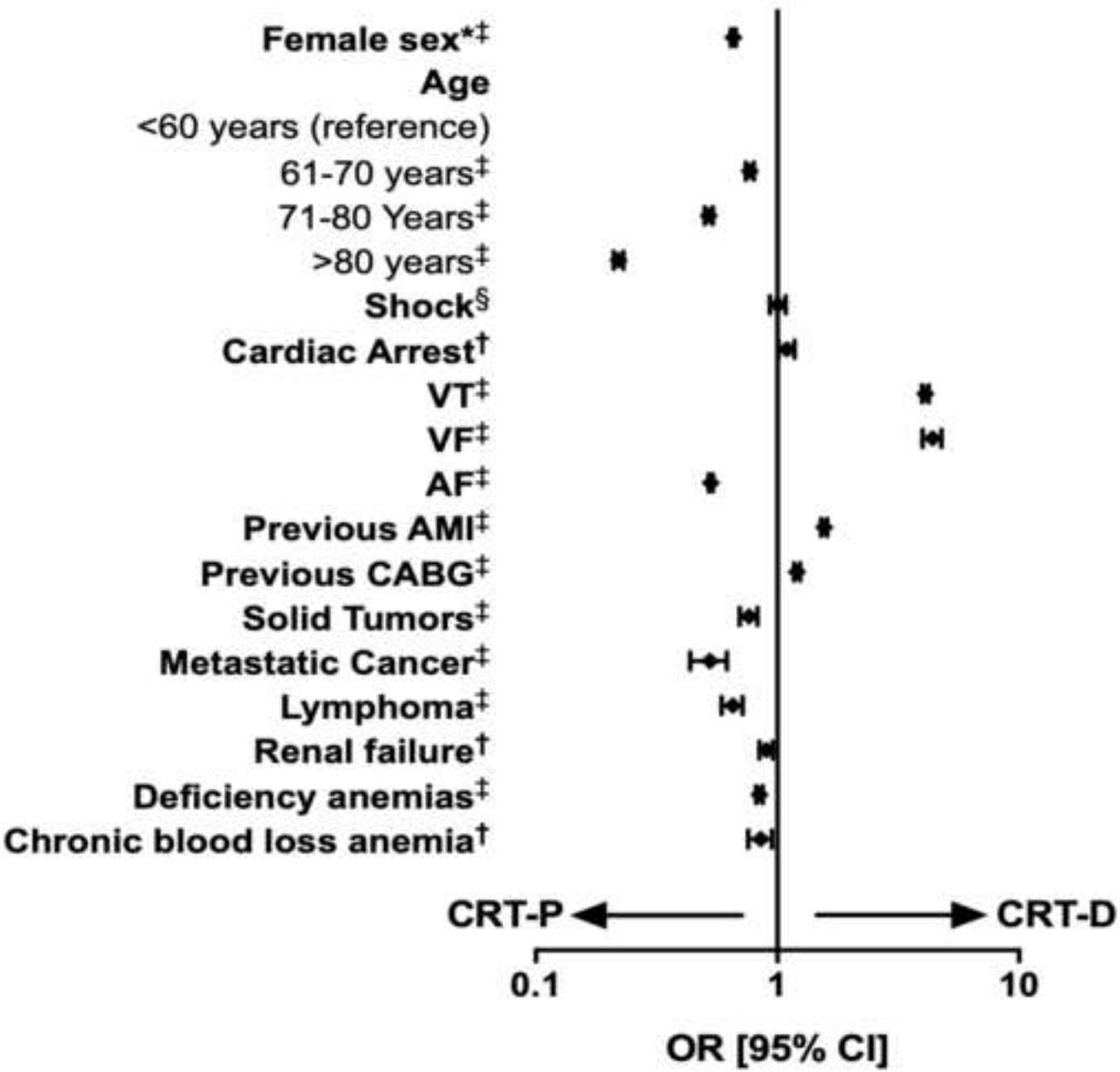

Figure 3B