Bundle Branch Block and Benefit from Cardiac Resynchronization Therapy

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“Don’t worry about failures, worry about the chances you miss when you don’t even try”

Jack Canfield

Contents

Abbreviations

ACC	American College of Cardiology
ACE-I	Angiotensin converting enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BUN	Blood urea-nitrogen
CABG	Coronary artery bypass graft
CARE-HF	Cardiac Resynchronization – Heart Failure
CHF	Congestive heart failure
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CPT	Current Procedural Terminology
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy defibrillator
CVD	Cardiovascular disease
ECG	Electrocardiogram
ECHOCRT	Echocardiography Guided Cardiac Resynchronization Therapy
ESC	European Society of Cardiology
ESRD	End-stage renal disease
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HF	Heart failure
HR	Hazard ratio
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
ICD-9	International Classification of Diseases, 9th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IOM	Institute of Medicine
IVCD	Intraventricular conduction delay
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy
ms	milliseconds
MRI	Magnetic resonance imaging
NCDR	National Cardiovascular Data Registry
NIH	National Institutes of Health
NYHA	New York Heart Association

PCI	Percutaneous coronary intervention
PMA	Premarket approval application
PRC	Procedure Code
PTCA	Percutaneous transluminal coronary angioplasty
QRSa	QRS amplitude
QRSd	QRS duration
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial
RBBB	Right bundle branch block
REVERSE	Resynchronization Reverses Remodeling in Systolic left Ventricular Dysfunction Trial
RV	Right ventricle
SMD	Standardized mean difference
U.S.	United States

CHAPTER I
Introduction

INTRODUCTION

Heart failure has emerged as a significant public health problem with an estimated prevalence of approximately 2% (5.1 million heart failure patients) and incidence of 825.000 new cases per year in the United States (U.S) according to 2010 data.[1] The morbidity and mortality are high as well. In 2010, heart failure accounted for almost 58.000 deaths in the U.S.[1] Furthermore, the costs associated with heart failure are tremendous, 30.7 billion dollars per year, making it one of the most expensive diseases in the world.[1] Important to note, however, is that even though heart failure is more prevalent among men (2.5% vs. 1.8%) the mortality is higher in women (58% vs. 42% of heart failure deaths).[1]

Heart failure is a disease with a progressive course characterized by a severe reduction in pump function and left ventricular (LV) dilation. This leads to patients experiencing shortness of breath, fatigue, edema, and a reduced capacity to perform normal daily activities. LV dilation in heart failure can be caused by multiple factors, including an abnormal electrical conduction in the hearts' ventricles. In normal conduction, the electrical wave front starts at the sinus node, propagates through the atrioventricular node, and eventually activates the heart muscle in the right- and left ventricle via the rapidly conducting His-Purkinje system leading to a simultaneous contraction of the heart walls (Figure 1). When the electrical activation in one of the ventricles is blocked ("bundle branch block"), the heart muscle cannot be activated through the rapid His-Purkinje system anymore. The most common conduction disorder in patients with heart failure is a left bundle branch block (LBBB).[2] In this case the electrical conduction in the left bundle branch is blocked and activation occurs rapidly in the right bundle branch, but spreads relatively slowly to the left via the myocardial cells of the interventricular septum, and on to the myocardium of the LV free wall[3] (Figure 1). This inefficient LV activation leads to the LV septal wall and the LV lateral wall contracting dyssynchronously, thereby reducing pump function. When this situation persists, the LV will undergo significant remodeling primarily characterized by LV dilation and further reduction in pump function causing more severe heart failure symptoms.

CARDIAC RESYNCHRONIZATION THERAPY

An important device therapy for patients with heart failure and reduced pump function, who are on optimal medical therapy, is biventricular pacing, more commonly called cardiac resynchronization therapy (CRT). The goal of CRT is to restore pumping efficiency by simultaneously pacing the endocardial RV septum and epicardial LV free wall, thereby correcting the dyssynchronous contraction of both walls ("resynchronization") (Figure 2). While CRT reduces heart failure symptoms, hospitalizations, and mortality and improves ventricular remodeling and quality of life,[4-8] unfortunately not every patient that is implanted with a CRT device will derive benefit. However, these patients are still at risk for potential complications of the procedure (e.g. lead dislodgement, infection). It is estimated that, based on the different definitions for "benefit" or "response", approximately 30% of patients do not derive any significant positive effect while others may even be harmed by CRT treatment.[9-18] It is therefore imperative to select patients that are most likely to benefit while associated risks are minimized. So far, female sex,[19-22] non-ischemic cardiomyopathy[11] and LBBB[17,18] have been shown to be important predictors of benefit while atrial fibrillation[11] has been associated with a worse prognosis after CRT.

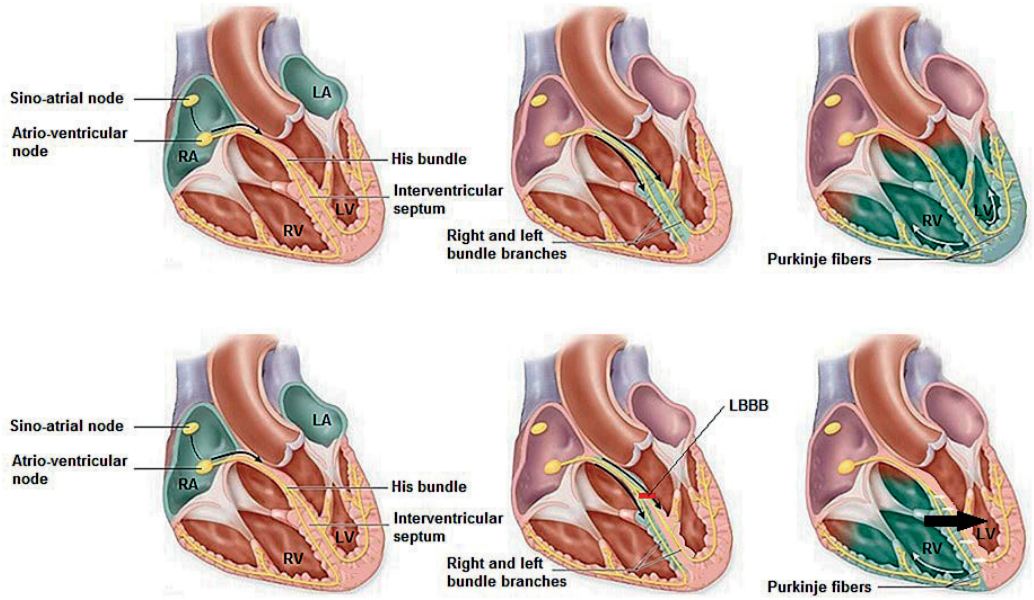

Figure 1. *Schematic representation of normal electrical activation of the heart (top) and activation with left bundle branch block (LBBB, bottom); the green area indicates the area that is electrically activated. In normal conduction, activation in the right ventricle (RV) and left ventricle (LV) occurs simultaneously through the rapidly conducting Purkinje fibers. In LBBB, activation of the RV occurs first through the Purkinje fibers but spreads relatively slowly to the LV (black arrow) with latest activation of the LV free wall. RA: right atrium; LA: left atrium.*

Both current U.S. and European professional society guidelines for CRT assign a Class I indication (highest recommendation) to patients with a LBBB and QRS duration equal to or greater than 150 milliseconds (ms).[23,24] Patients with LBBB and QRS duration of 120-149 ms receive a Class IIa indication (benefit significantly outweighs the risk) in U.S. guidelines[23] but a Class I recommendation in the European guidelines.[24] Patients without LBBB either receive a Class IIa or IIb indication, depending on QRS duration and New York Heart Association (NYHA) heart failure symptom class.[23,24]

LEFT BUNDLE BRANCH BLOCK

Since CRT aims at correcting the delay in activation between the LV septal and LV free wall, the presence of a truly significant delay between both walls is necessary for CRT to exert its benefits. The most ideal example of such a delay is LBBB, in which the LV septum is activated approximately 100 ms earlier than the LV free wall. However, there are multiple definitions of LBBB and it has been demonstrated that approximately one-third of patients diagnosed by conventional LBBB criteria (which usually require a QRS duration of 120 ms or more) do not have activation consistent with a true LBBB.[25-28] Furthermore, women have smaller ventricles and shorter baseline QRS duration than men[29] and may therefore also have a true LBBB at a shorter QRS duration. New LBBB criteria were recently proposed to account for this difference between both sexes and require a QRS duration greater than 130 ms in women and greater than 140 ms in men along with mid-QRS notching or slurring.[28] In

this thesis the effect of LBBB related to sex on benefit from CRT will be thoroughly investigated.

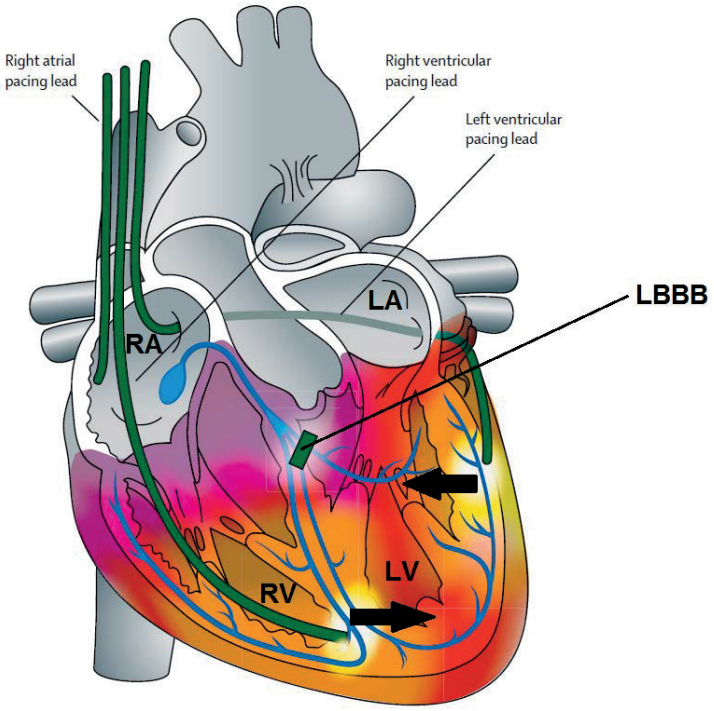

Figure 2. *Schematic representation of cardiac resynchronization therapy (CRT) in left bundle branch block (LBBB) using three pacing leads: right atrial (RA) lead, endocardial right ventricular (RV) lead, and epicardial left ventricular (LV) lead. Simultaneous pacing of the RV and LV results in a correction of the abnormal LV activation in LBBB (black arrows). The RA lead is used to either detect normal activation in the atria or pace the right atrium. LA: left atrium.*

NON-LEFT BUNDLE BRANCH BLOCK

Professional society guidelines do not distinguish between right bundle branch block (RBBB) and non-specific intraventricular conduction delay (IVCD) in patients without LBBB and indicate that the benefits of CRT treatment outweigh the potential risks in the patients without LBBB.[23,24] However, in non-LBBB the activation of the LV through the His-Purkinje system is normal and a significant delay between LV septal and LV free wall contraction likely absent. As a consequence, overdriving normal His-Purkinje activation of the LV with LV epicardial pacing may be inefficient or even harmful in patients without LBBB. In this thesis the effect of CRT in non-LBBB and, more specifically, RBBB and IVCD will be investigated.

SEX-DIFFERENCES IN POTENTIAL BENEFIT FROM CRT

Women have been underrepresented in clinical trials, especially those in the cardiovascular arena.[30,31] Even though heart failure mortality is higher in women than in men,[1] in trials for CRT women only accounted for approximately 20% of enrollees. The results of clinical trials, and the professional society guidelines that are primarily based on

these trials, therefore mainly reflect outcomes in men. However, certain differences between women and men, including anatomy and physiology, can result in CRT performing better or worse in either sex. An example was given earlier regarding women having smaller ventricles and therefore may also more often have LBBB than men. By not having enough women in clinical trials, which creates a critical information gap in terms of efficacy and safety of CRT, it is difficult to detect potential sex-differences. This thesis mainly focuses on sex-differences in CRT effectiveness and investigates reasons for these potential differences.

AIMS OF THIS THESIS

The general aim of the research conducted and reported in this thesis is to explore which patients are most likely to benefit from CRT. This mainly focuses on ventricular conduction disorders (i.e. LBBB, RBBB, and IVCD), sex-differences in the definition of these conduction disorders, and how other (sex-specific) factors influence CRT response.
The specific research questions are:

- How do patients with different ventricular conduction disorders (LBBB, RBBB, and IVCD) respond to CRT?
- Do women benefit more from CRT than men?
- What is the reason for a potential greater benefit from CRT in women?
- Are there other (sex-related) factors that predict benefit from CRT?

OUTLINE OF THIS THESIS

In **chapter 2**, data from multiple clinical trials was used to evaluate the difference in benefit from CRT between women and men. An investigation of CRT effect in a large real-world population included in a national registry for implantable defibrillators, including the differences by sex, is presented in **chapter 3**. **Chapter 4** builds upon this by evaluating the difference in benefit between CRT and ICD in subgroups by sex, QRS morphology and QRS duration. In **chapter 5**, health care claims data is used to investigate benefit from CRT in patients with solely RBBB. **Chapter 6** discusses the overall results of this thesis, compares them to existing literature and puts the findings into a broader perspective.

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CHAPTER II
Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data

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ABSTRACT

Importance: Women were underrepresented in cardiac resynchronization therapy (CRT) trials for heart failure (making up about 20% of enrollees). Combining individual-patient data from multiple clinical trials would enable assessment of CRT benefit in women.

Objective: To evaluate whether women with left bundle branch block (LBBB) benefit from CRT-defibrillators (CRT-D) at a shorter QRS duration than men with LBBB do.

Design, Setting and Participants: Individual-patient data was pooled from three CRT-D vs implantable cardioverter defibrillator (ICD) trials (4076 patients) enrolling predominantly patients with New York Heart Association (NYHA) class II heart failure and follow-up to 3 years. The effect of CRT-D compared with ICD on outcomes was assessed using random effects Cox proportional hazards.

Main Outcomes and Measures: Time to heart failure event or death (primary) and death alone (secondary).

Results: Women benefited from CRT-D more than men. The main difference occurred in patients with LBBB and a QRS of 130 to 149 milliseconds. In this group, women had a 76% reduction in heart failure or death (absolute CRT-D to ICD difference, 23%; hazard ratio [HR], 0.24, [95% CI, 0.11-0.53]; p<.001) and a 76% reduction in death alone (absolute difference 9%; HR, 0.24, [95% CI, 0.06-0.89]; p=.03), while there was no significant benefit in men for heart failure or death (absolute difference 4%; HR, 0.85 [95% CI, 0.60-1.21]; p=.38) or death alone (absolute difference 2%; HR, 0.86 [95% CI, 0.49-1.52]; p=.60). Neither women nor men with LBBB benefited from CRT-D at QRS shorter than 130 milliseconds, while both sexes with LBBB benefited at QRS of 150 milliseconds or longer.

Conclusions and Relevance: In this population of patients with primarily mild heart failure, women with LBBB benefited from CRT-D at a shorter QRS duration than men with LBBB. This is important because recent guidelines limit the class I indication for CRT-D to patients with LBBB and QRS of 150 milliseconds or longer. While guidelines do give a class IIa indication to patients with LBBB and a QRS of 120 to 149 milliseconds, the present findings are important to communicate because women are less likely to receive CRT-D than men are. This study exemplifies the potential public health and regulatory science value of combining data from multiple clinical trials submitted to the FDA.

INTRODUCTION

As recently outlined by the U.S. Food and Drug Administration (FDA)[1] in the Federal Register, regulatory science research that combines clinical data submitted to FDA has the potential to generate new knowledge and facilitate innovation. One area where this can have value is in determining the safety and efficacy of medical products in patient subgroups that were underrepresented in individual clinical trials, a critical area identified in the 2012 FDA Safety and Innovation Act.[2]

Cardiac resynchronization therapy (CRT) is a heart failure therapy that improves heart failure symptoms, decreases hospitalizations and reduces mortality.[3-7] Some studies have shown that women may benefit more than men from CRT[8-11]; however, women were underrepresented in CRT trials (making up only about 20% of enrollees), as has been true for other devices,[12] making it difficult to thoroughly assess sex differences. Recent study-level meta-analyses of CRT trials demonstrated that benefit from CRT may be limited to a more restrictive patient population (specifically, patients with a left bundle branch block [LBBB] and QRS ≥150 milliseconds) than that enrolled in the original clinical trials.[13,14] Consequently, 2012 professional society guidelines limited the class I indication for CRT to patients with LBBB and QRS of 150 milliseconds or longer.[15] However, the study-level meta-analyses were unable to assess sex differences because of lack of individual-patient data.

Heart size and QRS duration are generally smaller in women compared to men,[16] and recent work has suggested that sex-specific QRS duration criteria for LBBB better predict CRT response.[17,18] We pooled individual-patient data from 3 large CRT-defibrillator (CRT-D) vs implantable cardioverter defibrillator (ICD) trials enrolling predominantly patients with mild heart failure to test the hypothesis that women with LBBB defined by conventional electrocardiographic (ECG) criteria benefit from CRT-D at a shorter QRS duration than men with LBBB do.

METHODS

This study was approved by the FDA Research in Human Subjects Committee. Informed consent was obtained from patients in the original trials. The inclusion criteria for this meta-analysis required that the included study be a randomized clinical trial comparing CRT-D vs ICD in primarily patients with mild heart failure (New York Heart Association [NYHA] class II), that it report heart failure and mortality outcomes, and that individual-patent data from the study had been submitted to the FDA as a part of a premarket approval application (PMA). Randomized clinical trials performed in patients with moderate to severe heart failure (NYHA class III or IV)[6,7] were not included because the FDA indications for CRT in these patients differ from those in patients with mild heart failure. In addition, the trials that included more severe heart failure were older trials, and the participants in their control groups received only optimal medical therapy, not an ICD as in the more recent trials. Furthermore, the FDA does not have all patient-level data from the older trials in NYHA class III and IV heart failure.

Three trials met the criteria for inclusion in this meta-analysis: the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[3] the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT),[4] and the Resynchronization Reverses Remodeling in Systolic left Ventricular Dysfunction Trial (REVERSE)[5] (Table 1). The data from these trials were presented and discussed at 2 FDA panel meetings.[19,20] For the purpose of the present analysis, it was assumed that data

obtained from different manufacturers' CRT-D systems were poolable. Potential differences between the sponsors' devices were not considered.

Table 1. Inclusion Criteria and Characteristics of Published Trials

Trial Characteristic	REVERSE[5]	MADIT-CRT[3]	RAFT[4]
Year	2008	2009	2010
Patients, No.	610	1820	1798
Patients included in meta-analysis, No.	593	1820	1663
Design	CRT on vs CRT off (2:1)[a]	CRT-D vs ICD (3:2)	CRT-D vs ICD (1:1)
Inclusion criteria	NYHA class I/II, LVEF ≤40%, QRS ≥120 ms	NYHA class I/II, LVEF ≤30%, QRS ≥130 ms	NYHA class II/III, LVEF ≤30%, QRS ≥120 ms[b]
Primary end point	HF composite response	Death or HF	Death or HF
Follow-up, median, y	1.1	2.2	4.7
Age, mean, y	63	65	66
Men, %	79	74	83
LVEF, mean, %	27	24	23
Ischemic cardiomyopathy, %	55	55	67
NYHA heart failure class, %	I, 18 II, 82	I, 15 II, 85	II, 80 III, 20
QRS duration, mean, ms	153	158	158
LBBB, %	77	70	66
Diabetes mellitus, %	22	30	37
Hypertension, %	52	63	51
Atrial fibrillation or atrial flutter, %	0	12	13
Creatinine, mg/dL	1.1	1.2	1.3
β-Blockers, %	95	93	90
ACE-I or ARB, %	97	98	97
Randomization	Randomized	Randomized	Randomized
Blinding	Double-blind	Open label	Double-blind

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; ms, milliseconds; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Trial.

SI conversion factors: To convert creatinine to µmol/L, multiply values by 88.4.

[a] Of which 84% of patients had a defibrillator.

[b] Or paced QRS of 200 ms or longer.

The current analysis included all patients enrolled in MADIT-CRT (n=1820), all patients in RAFT without a pacemaker at baseline (n=1663), and all patients from REVERSE with data on QRS morphology (n=593). We combined the key patient characteristics from all trials (Table 2). The presence of LBBB was defined as reported in each trial using conventional ECG criteria. Time to heart failure event or death (primary) and time to death alone (secondary) were the defined end points. For MADIT-CRT, the definition for heart failure as specified in the MADIT-CRT primary end point was used: heart failure event responsive to oral or intravascular decongestive therapy on an inpatients or outpatient basis.[3] For RAFT and REVERSE, heart failure event was defined as heart failure leading to hospitalization.[4,5] Because the 3 trials had different median follow-up times (MADIT-CRT, 2.2 years; RAFT, 4.7 years; and REVERSE, 1.1 years) and the number of patients in subgroups significantly decreased during follow-up, all follow-up was censored at 3 years. Of note, while US patients in REVERSE were only followed up for 1 year, non-US patients were followed for 2 years,[21] and the full length of follow-up for REVERSE patients was used.

Statistical Analysis

To address potential differences of CRT-D effect across trials, we used mixed-effects Cox proportional hazards analysis, with and without sex-by-treatment interactions, to calculate the risk for specified end points in the overall population and in subgroups by sex,

LBBB, QRS duration, and heart failure etiology (ischemic vs nonischemic). Random effects trial intercept models were used to combine data from all trials in a 1-stage individual-patient data meta-analysis. Cumulative survival curves were created by the Kaplan-Meier method. Patients with LBBB were divided into groups defined by 10-millisecond QRS duration intervals. Analysis was repeated using the QRS groups 120 to 129, 130 to 149 and 150 milliseconds or longer, as QRS durations of 120, 130 and 150 milliseconds have been the thresholds used in FDA indications and/or professional society guidelines for CRT-D. In addition, we performed multivariable analysis, adjusting for ischemic etiology, atrial fibrillation and/or flutter, and cardiac medications; we modeled QRS duration in LBBB as a continuous variable with smoothed splines. For patients without LBBB, analysis by sex was performed in 2 QRS groups: shorter than 150 milliseconds and 150 milliseconds or longer. All statistical analyses were performed using the "coxme package" (version 2.2.3) for R (version 3.0.0) (additional details provided in the Supplement). Ninety-five percent CIs are reported for all hazard ratios (HRs), and 2-sided $p<.05$ were considered significant for interaction analyses.

RESULTS

Of the 4076 patients included in this pooled analysis, 3198 (78%) were men, and 878 (22%) were women (Table 2). Women were more likely than men to have LBBB (85% vs 68%) and less likely to have ischemic cardiomyopathy (33% vs 67%). The majority of both women and men had NYHA class II heart failure (87% and 82%, respectively).

In women, CRT-D resulted in a 60% relative reduction in heart failure or death (CRT-D to ICD HR, 0.40; absolute difference, 15%) and 55% relative reduction in death alone (absolute difference, 6%), compared with only 26% and 15% relative reductions (absolute differences, 7% and 2%) in the 2 end points, respectively, in men (Figure 1). Subgroup and interaction analysis revealed that there were significant differences in the efficacy of CRT-D by sex in patients with LBBB, QRS shorter than 150 milliseconds, and nonischemic heart failure etiology (Figure 1). Of note, there was no benefit from CRT-D in patients without LBBB, women or men (Figure 1), regardless of QRS duration (eFigure 1 in the Supplement), although the CIs in women were wide.

Sex Differences in Efficacy of CRT-D in Patients With LBBB

All patients with LBBB were divided into groups based on 10-millisecond QRS duration intervals (eTable 2 in the Supplement). There was no difference in outcomes between the CRT-D and ICD groups in either women or men with LBBB at QRS durations of 120 to 129 milliseconds. However, in women with LBBB, there was an 85% relative reduction in heart failure event or death at QRS of 130 to 139 milliseconds and a 69% relative reduction with QRS of 140 to 149 milliseconds. In men, there was no difference between CRT-D and ICD in either of these QRS duration groups. Above 150 milliseconds, CRT-D benefited both women and men with LBBB.

Table 2. Patient Characteristics by Sex in the Total and LBBB Populations

Characteristic	Total Population		LBBB Population	
	Women (n = 878)	Men (n = 3198)	Women (n = 749)	Men (n = 2182)
Treatment arm, No. (%)				
CRT-D[a]	497 (57)	1823 (57)	422 (56)	1236 (57)
ICD	381 (43)	1375 (43)	327 (44)	946 (43)
Age, mean (SD), y	64 (10)	65 (10)	64 (10)	65 (10)
LVEF, mean (SD), %	24 (6)	24 (6)	23 (6)	23 (6)
NYHA HF class, No. (%)				
I	41 (5)	326 (10)	29 (4)	170 (8)
II	763 (87)	2623 (82)	654 (87)	1822 (84)
III	74 (8)	249 (8)	66 (9)	190 (9)
Ischemic cardiomyopathy, No. (%)	293 (33)	2141 (67)	215 (29)	1315 (60)
LBBB, No. (%)	749 (85)	2182 (68)	749 (100)	749 (100)
QRS duration, mean (SD), ms	157 (20)	157 (22)	159 (19)	163 (22)
Non-LBBB, No. (%)	129 (15)	1016 (32)	-	-
QRS duration, mean (SD), ms	143 (16)	145 (19)	-	-
Comorbidities, No. (%)				
Diabetes mellitus[b]	258 of 851 (30)	990 of 3075 (32)	218 of 723 (30)	650 of 2086 (31)
Hypertension[b]	480 of 803 (60)	1716 of 3044 (56)	412 of 679 (61)	1132 of 2051 (55)
Atrial fibrillation or atrial flutter[b]	54 of 870 (6)	335 of 3165 (11)	43 of 742 (6)	217 of 2164 (10)
Creatinine, mean (SD), mg/dL	1.0 (0.3)	1.3 (0.5)	1.0 (0.3)	1.3 (0.6)
Medications, No. (%)				
β-blockers	823 (94)	2928 (92)	704 (94)	2007 (92)
ACE-I or ARB	845 (96)	3076 (96)	722 (96)	2104 (96)
Trial, No. (%)				
MADIT-CRT[3]	453 (52)	1367 (43)	394 (53)	887 (41)
RAFT[4]	295 (34)	1368 (43)	253 (34)	1042 (48)
REVERSE[5]	130 (15)	463 (14)	102 (14)	253 (12)

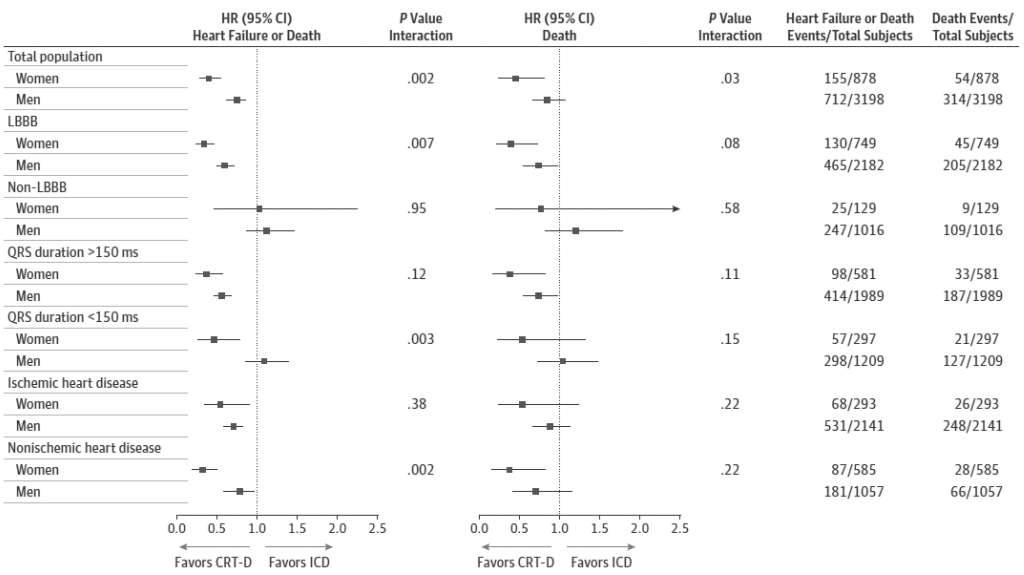
Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; CRT-D, cardiac resynchronization therapy–defibrillator; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; ms, milliseconds; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Trial.

[a] In REVERSE, 16% did not receive a defibrillator.

[b] Numbers do not sum to group totals due to missing data on these variables.

SI conversion factors: To convert creatinine to µmol/L, multiply by 88.4.

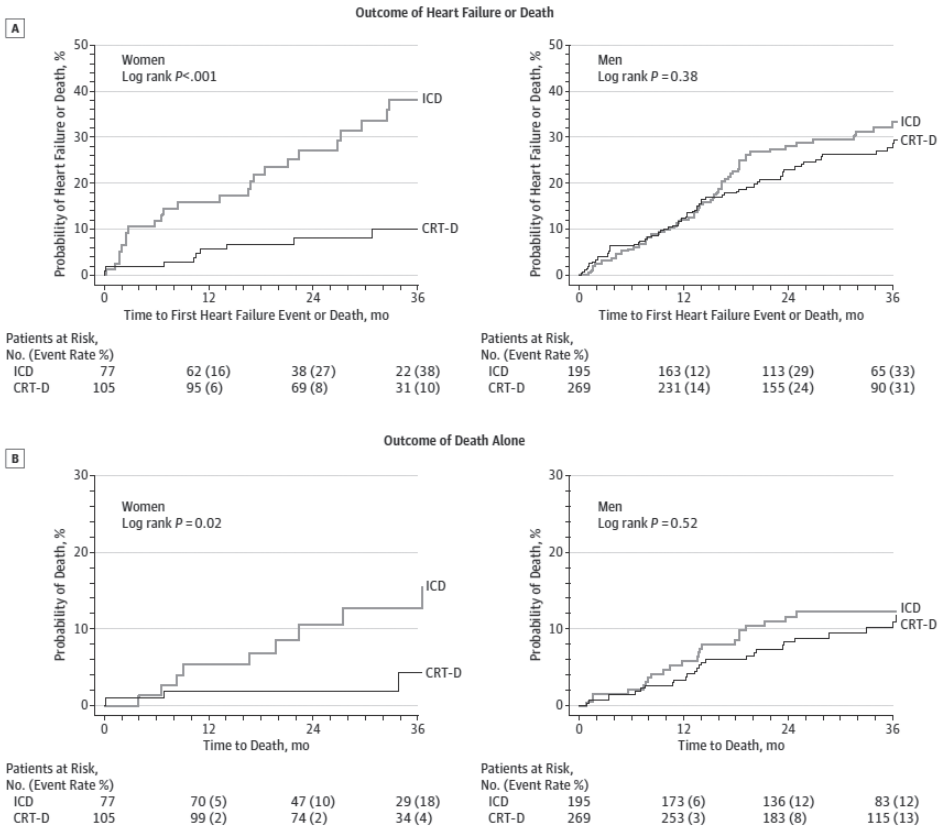
Figure 1. CRT-D to ICD HRs for Outcomes by Sex in the Total Population



CRT-D indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; ms, milliseconds. *P* values represent sex-by-treatment interactions. Number of events and total subjects are listed for each subgroup. See eTable 1 in the Supplement for exact numbers.

Figure 2 shows Kaplan-Meier graphs for patients with LBBB in the QRS duration range of 130 to 149 milliseconds. Women had a 76% relative reduction in heart failure or death (absolute difference, 23%; HR, 0.24 [95% CI, 0.11-0.53]) and a 76% relative reduction in death alone (absolute difference, 9%; HR, 0.24 [95% CI, 0.06-0.89]) from CRT-D. In contrast, in men with LBBB and QRS duration of 130 to 149 milliseconds, CRT-D did not have a significant effect on heart failure or death (absolute difference, 4%; HR, 0.85 [95% CI, 0.60-1.21]) or death alone (absolute difference, 2%; HR, 0.86 [95% CI, 0.49-1.52]). Interaction analysis in LBBB with QRS of 130 to 149 milliseconds revealed that the difference in treatment efficacy between women and men was significant for the end point of heart failure or death (p=.003), but not for death alone (p=.10). eFigure 2 and eFigure 3 in the Supplement show Kaplan-Meier curves for women and men with LBBB in the other QRS duration categories (QRS 120-129 and ≥150 milliseconds). With LBBB and QRS of 150 milliseconds or longer, both women and men had a significant reduction in heart failure or death (women HR, 0.33 [95% CI, 0.21-0.52], absolute difference, 16%; men HR, 0.47 [95% CI, 0.37-0.59], absolute difference, 14%) and death alone (women HR, 0.36 [95% CI, 0.16-0.82], absolute difference, 5%; men HR, 0.65 [95% CI, 0.47-0.91], absolute difference, 4%). eFigure 4 in the Supplement shows spline curves for QRS duration modeled as a continuous variable in women and men with LBBB.

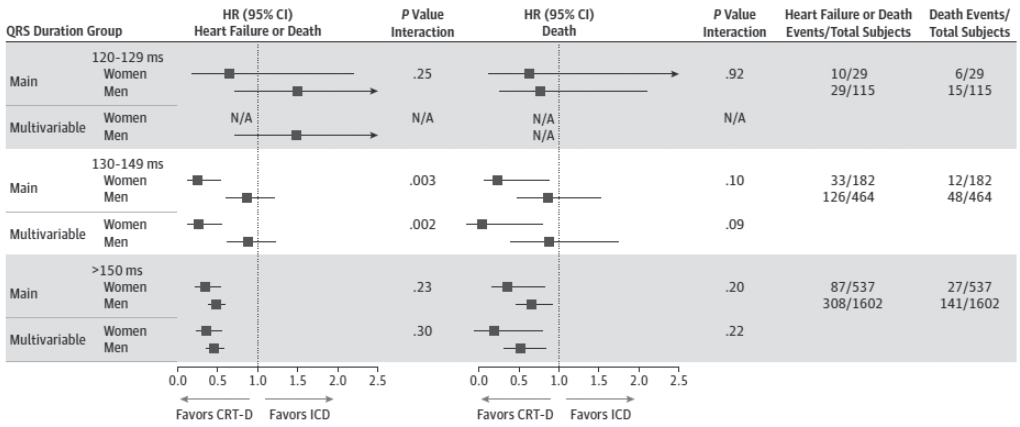
Figure 2. Kaplan-Meier Estimates of Outcomes in LBBB and QRS of 130 to 149 Milliseconds (ms) Stratified by Sex



CRT-D indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block.

Adjustment for ischemic etiology, atrial fibrillation and/or flutter, and cardiac medications did not change the results for the QRS groups 130 to 149 milliseconds and 150 milliseconds or longer, while the number of patients in the QRS group 120 to 129 milliseconds was too small for adjustment (Figure 3). eFigure 5 in the Supplement shows the results excluding patients with NYHA class III heart failure (8% of patients overall). The results for the primary end point did not change. For the secondary end point of death alone, the HR point estimates remained almost identical, but CIs widened and crossed HR of 1 in women with LBBB and QRS of 130 to 149 milliseconds and men with LBBB and QRS of 150 milliseconds or longer. In addition, no significant interaction between CRT-D treatment and the individual trials was detected.

Figure 3. CRT-D to ICD HRs for Outcomes in LBBB and QRS Duration Groups of Main and Multivariable Adjusted Analysis



CRT-D indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; ms, milliseconds. *P* values represent sex-by-treatment interactions. Number of events and total subjects are listed for each subgroup. See eTable 3 in the Supplement for exact numbers.

DISCUSSION

The primary finding of this individual-patient data analysis of 3 large randomized CRT-D trials enrolling primarily patients with NYHA class II heart failure is that women with LBBB by conventional ECG criteria derive significant benefit from CRT-D at QRS durations shorter than 150 milliseconds (specifically ≥130 milliseconds), while men with conventional LBBB derive significant benefit at QRS of 150 milliseconds or longer. These findings are true for both end points of heart failure or death and death alone. This is important because recent professional society guidelines for CRT-D only assign a class I indication to patients with LBBB and QRS of 150 milliseconds or longer.[15] These indications were based on study-level meta-analyses of published trials for which approximately 80% of enrollees were men, and it was not possible to perform robust interaction and subgroup analysis by sex and clinical characteristics due to lack of individual-patient data. Of note, guidelines do give a class IIa indication to patients with LBBB and QRS of 120 to 149 milliseconds,[15] and thus many of these patients would likely be offered CRT-D. However, considering that women receive CRT-D less often than men,[22] we believe that the current findings are important to communicate.

The question of the appropriate QRS duration threshold for selecting CRT patients was discussed extensively at the most recent FDA public advisory committee meeting on CRT-D for expanding indications to patients with NYHA class II heart failure.[20] FDA ultimately approved CRT-D for these patients with LBBB, QRS of 130 milliseconds or longer, and ejection fraction of 30% or less. The indication for Boston Scientific also includes patients with ischemic NYHA class I heart failure. The results of the present analysis are not necessarily in conflict with FDA indications because the reason for the lack of CRT-D effect in men with QRS durations of 130 to 149 milliseconds may be that most of these patients diagnosed as having LBBB by conventional ECG criteria do not have a true LBBB.[18,22] Men with a QRS shorter than 150 milliseconds and true LBBB may benefit. The FDA indications for NYHA class III and IV heart failure do not include a requirement for QRS morphology.

However, because this study included primarily patients with NYHA class II heart failure (only 8% had class III heart failure), the results cannot be used to make conclusions about patients with NYHA class III or IV heart failure.

The findings confirm prior analyses by Arshad et al[10] and Zareba et al[23] from MADIT-CRT demonstrating that women, but not men, benefited from CRT-D at QRS shorter than 150 milliseconds. However, the prior MADIT-CRT analyses did not divide patients by the presence of LBBB and QRS duration, and thus the greater benefit in women with QRS shorter than 150 milliseconds could have been explained by a higher incidence of LBBB in women. The larger sample size of patients with QRS shorter than 150 ms (1209 men and 297 women) in the present analysis allowed us to investigate the combination of LBBB presence and QRS duration in 10-millisecond intervals. Interestingly, a different individual-patient data meta-analysis that included significantly more patients with NYHA class III heart failure found that benefit from CRT became significant at a QRS of 140 milliseconds, while findings of interaction analysis by sex were not significant.[24]

The hypothesis of this study was based on the premise that patients with true, complete LBBB benefit from CRT-D. With complete LBBB, activation of the interventricular septum and left ventricular lateral wall is uncoupled, resulting in about a 100-millisecond delay between initial activation of the 2 walls. In contrast, in normal conduction or incomplete LBBB conduction delay, most of the left ventricle is activated synchronously via the rapidly conducting His-Purkinje system. The beneficial effect of CRT-D in LBBB likely derives from attenuating the dyssynchronous contraction caused by the large activation delay, while in other cases, CRT-D can overdrive nature's rapid activation of the left ventricle. The lack of CRT benefit in patients without LBBB has also been observed in recent studies.[13,22,23,25,26]

In the present analysis, LBBB was defined by the conventional criteria used in the trials. While for MADIT-CRT, the World Health Organization criteria for LBBB were used,[23] in RAFT and REVERSE, the exact definition of LBBB was not specified. In the current study, women had a higher percentage of LBBB than men (85% vs 69%). However, the difference is likely even greater because men have longer QRS durations than women[16] and are more likely to have a false-positive LBBB diagnosis.[18] New sex-specific strict LBBB criteria were proposed that require QRS of 130 ms or longer in women and 140 milliseconds or longer in men, along with mid-QRS notching and/or slurring.[18] Recent single-center studies demonstrated that patients not meeting strict LBBB criteria had a 4-fold higher rate of heart failure hospitalization or death and did not respond to CRT-D compared with patients who met the strict LBBB criteria.[17,27] The current study seems to support the use of sex-specific criteria for LBBB. Based on the strict LBBB criteria, one might expect men with QRS durations of 140 to 149 milliseconds to derive benefit; however, the present study did not involve analysis of mid-QRS notching and/or slurring. In addition, while there was no benefit for women or men with LBBB and a QRS of 120 to 129 milliseconds, the number of patients in this group was too small to make definitive statements about CRT-D efficacy.

The fact that men were more likely than women to have ischemic cardiomyopathy and atrial fibrillation, which are both associated with a worse prognosis,[28] might have contributed to a greater benefit from CRT-D in women. While controlling for these variables did not affect the results, it is difficult to differentiate the effect of LBBB vs nonischemic cardiomyopathy because, as demonstrated by a recent cardiac magnetic resonance study,[29]

complete LBBB in patients referred for ICD and CRT-D is most commonly caused by nonischemic cardiomyopathies.

The effectiveness and safety of medical products such as drugs, devices and biologics can differ between women and men due to differences in prevalence of disease, physiology, body size and a plethora of other intrinsic and extrinsic factors.[30] The FDA released a draft guidance on evaluating sex differences in device trials to improve the quality and consistency of available data regarding the performance of medical devices in both sexes. The draft guidance document discusses the importance of ensuring that representation by sex that is consistent with disease prevalence and that data from studies are appropriately analyzed for sex differences.[31] Pooling individual-patient data from multiple clinical trials in a specific product area provides an additional powerful tool to analyze sex differences.

Use of Regulatory Data in Research Studies

Data submitted to the FDA in PMAs has confidentiality protections, including that FDA cannot disclose receipt of PMAs until a decision is made or reveal trade secrets and commercial or financial information.[32] However, after the FDA issues an order approving or denying approval of any PMA, summary safety and effectiveness data are available for public disclosure.[33] An individual-patient data meta-analysis such as this one is a summary of safety and effectiveness data and is a logical mechanism for reporting safety and effectiveness in patient subgroups that are underrepresented in individual trials. Other examples of FDA regulatory science with drug trials include individual-patient data meta-analyses in patients with hepatitis C[34] and human immunodeficiency virus.[35]

While the present analysis was performed by the FDA, it is not possible for the FDA to conduct all research of this nature. Currently, nonsummary safety and efficacy data from marketing applications are not available to researchers outside the FDA. However, the FDA recently requested public comment on the "Availability of Masked and De-identified Non-Summary Safety and Efficacy Data".[1] The posting indicates that making datasets available to non-FDA experts for regulatory science research could further facilitate innovation in the development and evaluation of medical products and maximize benefit to society that patients provide by participating in clinical trials. Separately, industry,[36] academic consortiums,[37] and other medical product regulatory agencies[38] have proposed other "open data" initiatives.

Limitations

A limitation of this study is that it is a post hoc analysis of the included clinical trials, and multiple comparisons were performed. In addition, the results could have been influenced by different follow-up time between trials and larger size of MADIT-CRT[3] and RAFT[4] compared with REVERSE.[5] To partially address this, follow-up was censored at 3 years and time-to-event analysis was performed incorporating random effects by trial. It should be noted that differences between trials are a limitation of prior study-level meta-analyses. The number of patients in the LBBB and 120 to 129 milliseconds QRS duration group was small, and this particular analysis might therefore be underpowered to detect significant results. In addition, findings related to mortality should be interpreted with caution because of the low mortality rate in these patients with mild heart failure symptoms. Two large older trials including patients with more severe heart failure were not included in this analysis. These trials differed significantly from the included trials in that they did not

include an ICD control arm, enrolled predominantly patients with NYHA class III heart failure,[6,7] and in 1 trial required the presence of mechanical dyssynchrony in patients with QRS of 120 to 149 milliseconds.[7] The findings from the current study cannot be extended to more severe heart failure.

Conclusions

In summary, in an individual-patient data meta-analysis of 3 major clinical CRT trials primarily limited to patients with mild heart failure symptoms (NYHA class II), women were found to benefit from CRT-D at a shorter QRS duration than men. While current guidelines only give a class I indication for CRT-D to patients with LBBB and QRS of 150 milliseconds or longer, this analysis found that women with LBBB and QRS of 130 to 149 milliseconds have a 76% reduction in heart failure events and mortality from CRT-D. While professional society guidelines do give a class IIa indication for these patients, and thus most women in this group are likely be offered CRT-D, these findings are important to communicate because women are less likely to receive CRT-D than men. The fact that women normally have smaller ventricles and shorter QRS duration than men provides an anatomical and/or physiological explanation for the findings, but the higher rate of nonischemic cardiomyopathy in women compared with men may have also contributed. Overall, this study highlights the importance of sex-specific analysis in medical device clinical studies and the public health value of combining individual-patient data from clinical trials submitted to the FDA.

Conflict of interest disclosures
None reported.

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Role of the Sponsor
The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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INVITED COMMENTARY

The Case for Sex- and Gender-Specific Medicine

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There are numerous differences in cardiovascular disease (CVD) between men and women. Women have a higher prevalence of coronary microvascular dysfunction, heart failure with preserved ejection fraction, Tako-Tsubo syndrome (also known as stress-induced cardiomyopathy), and post–myocardial infarction depression than men. Women also have a greater sensitivity to QT-prolonging medications and higher heart failure mortality with digoxin than men.[1,2] A mounting literature further documents important sex differences in pharmacology, including response to β-blockers and angiotensin converting enzyme inhibitors.[3]

There are also important sex differences in use of cardiac devices. Implantable cardiac defibrillators (ICDs) are particularly underused in women. Among patients hospitalized for heart failure between 2005 and 2007, eligible women were less likely than men to get an ICD (27% vs 40%, $P < .001$). African Americans were also less likely to receive ICDs. While the racial disparities had disappeared by 2009, the sex disparities persisted,[4,5] possibly related to the relative lack of data in women.[6] Women are referred for heart transplant at a more severe level of heart failure, suggesting that transplantation is a less-considered option for women.[7]

The report by Zusterzeel and colleagues[8] documents an important sex difference in cardiac resynchronization therapy (CRT); in particular, they found that women experienced a greater benefit from CRT than men among those for whom the QRS interval was 130 to 149 milliseconds. In this group, women experienced a 76%reduction in heart failure and a 76% reduction in death, compared with no benefit in men. The authors appropriately conclude in this adequately powered study that among patients with mild heart failure, women with left bundle branch block benefit from CRT at a shorter QRS duration than men. Because the current US guidelines give only a class IIa recommendation (benefit >> risk, additional studies with focused objectives needed) for patients with QRS duration of 130 to 149 milliseconds, this new finding indicates that this device is likely underused in women. These results also shed light on a major contributor to the misdiagnosis and suboptimal treatment of CVD in women: guidelines are typically based on a male standard and do not address important differences in women.

The recognition that sex and gender affect the pathophysiology and expression of human disease prompted the National Institutes of Health (NIH) mandate to include both men and women in clinical studies and, when the studied health condition affects both sexes, to analyze data by sex.[9] In addition, the Institute of Medicine (IOM)[10] and others[11] provide actions items to improve CVD care for women. Where are we in 2014? Despite the NIH mandate and the IOM call for action, women remain the minority of research subjects but the majority of persons dying of CVD.[12]

Sex- and gender-specific medicine is the most ready-for-translation approach among the genomic, proteomic, and metabolomic personalized medicine approaches. While traditional medicine is evidence and guideline based (extrapolating from large trials to the whole disease population), it neglects subgroups (such as the majority subgroup of women!), and the clinical trials needed for guidelines are becoming prohibitively expensive. Personalized medicine is genome based, successful in predicting genome-based risks and responses—single gene effects—but it is currently too expensive for use in clinical care and incomplete because epigenetic modifications are not covered. Sex- and gender-specific medicine considers an important genetic difference—sex—and includes effects of lifestyle and environment transmitted by epigenetic modifications. It is known that the environment

affects the phenotype through sex-specific epigenetic modifications such as methylation patterns that are permanently modified. For example, if the fetus is exposed to severe nutrient limitation during gestation, in later life, the men and women display different epigenetic profiles,[13] which will impact future health. Sex- and gender-specific medicine is also attractive because it is easy and economical to recognize the sex of the patient and because our existing substantial body of registry and clinical trial data includes women and men.

To better understand and respond to sex and gender differences, we need initiatives to increase awareness of these differences, develop a common knowledge basis and exchange between researchers of different disciplines, develop career opportunities for young scientists, provide common training tools to introduce students early into the disciplines, and establish systematic sex- and gender- specific medicine research as an independent discipline.

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CHAPTER III
Sex-Specific Mortality Risk by QRS Morphology and Duration in Patients Receiving Cardiac Resynchronization Therapy: Results from the NCDR

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ABSTRACT

BACKGROUND Prior studies have suggested that women have better outcomes than men after cardiac resynchronization therapy-defibrillator (CRT-D) implantation.

OBJECTIVES To compare mortality after CRT-D implantation by sex, QRS morphology, and duration.

METHODS Survival curves and covariate adjusted hazard ratios (HR) were used to assess mortality by sex in 31,892 CRT-D patients in the National Cardiovascular Data Registry (NCDR), implantable cardioverter defibrillator (ICD) registry between 2006 and 2009, with up to 5 years' follow-up (median 2.9 years, interquartile range: 2.0–3.9 years). Patients were grouped by QRS morphology and 10-ms increments in QRS duration.

RESULTS Among patients with left bundle branch block (LBBB), women had a 21% lower mortality risk than men (HR 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$); however, there was no sex difference in non-LBBB (HR 0.95; 95% CI: 0.85 to 1.06; $p = 0.37$). Longer QRS duration was associated with better survival in both sexes with LBBB, but not in patients without LBBB. Compared with women with LBBB and QRS of 120 to 129 ms, women with LBBB and QRS of 140 to 149 ms had a 27% lower mortality (HR 0.73; 95% CI: 0.60 to 0.88; $p = 0.001$); this difference was 18% in men (HR 0.82; 95% CI: 0.71 to 0.93; $p = 0.003$). Mortality in LBBB and QRS of 150 ms or longer compared with those with LBBB and QRS of 120 to 129 ms was similar between sexes (HR 0.61–0.68; $p < 0.001$ for women and HR 0.58–0.66; $p < 0.001$ for men). Sex interactions within 10-ms groups were not significant.

CONCLUSIONS Among patients with LBBB who received CRT-D, mortality is lower in women than men. Additionally, longer QRS duration in LBBB is associated with better survival in both sexes. In contrast, there is no sex difference in patients without LBBB, regardless of QRS duration. Further studies should include a non-CRT comparator group to confirm these findings.

INTRODUCTION

Biventricular pacing, a therapy for heart failure, commonly referred to as cardiac resynchronization therapy (CRT), reduces mortality and heart failure hospitalizations in selected patients with left ventricular systolic dysfunction and prolonged QRS duration (1–4). However,
although there is an incomplete understanding of who benefits from CRT, all patients receiving CRT are subjected to potential device complications (e.g., infection, lead failure/dislodgement) and costs. Therefore, it is important to identify those patients most likely to benefit from this therapy.

Although most CRT clinical trials enrolled patients with a QRS duration of 120 ms or longer, meta-analyses found that benefit from CRT is most pronounced in patients with a left
bundle branch block (LBBB) and QRS of 150 ms or longer (5,6). These observations are reflected in professional society guidelines, which limit Class I recommendations for CRT to patients with LBBB and QRS of 150 ms or longer. Patients with LBBB and QRS of 120 to 149 ms and those without LBBB are categorized as either Class IIa or IIb recommendations (7).

In clinical trials of CRT, women only represent approximately 20% of patients; therefore, the results of both the trials and meta-analyses primarily reflect outcomes in men. Nonetheless, previous studies suggest that benefit from CRT is greater in women (8–11). This may be due to a combination of reasons, including that women are more likely to have LBBB and nonischemic cardiomyopathy, which are both associated with a better CRT response (12). Furthermore, separate analyses suggest that one-third of patients with LBBB by conventional electrocardiographic (ECG) criteria may not have true LBBB (13–16). Because women have a shorter QRS duration than men in the absence of any conduction disease (17), they can have a true LBBB at a shorter QRS duration than men (16). Previous studies suggest that sex-specific QRS duration criteria for LBBB predict a better response to CRT (18,19).

This study assessed the effect of CRT by sex in a large real-world CRT-defibrillator (CRT-D) population. The objective was to compare long-term mortality outcomes of women and men receiving CRT-D among different combinations of QRS morphology and duration.

METHODS

This study included all patients in the National Cardiovascular Data Registry (NCDR), implantable cardioverter defibrillator (ICD) registry who received a CRT-D device between January 1, 2006, and September 30, 2009 (n = 178,900). The registry, formed in 2005 with data collection beginning in 2006, contains data on all ICD and CRT-D implantations from more than 80% of hospitals in the United States (20). Patient-level clinical, demographic, and procedural
information was collected using standardized data elements and definitions. The NCDR programs use a multistage data quality process, including quality checks on submitted data, outlier analysis, and medical record audits (21). The ICD Registry is used in more than 1,400 US hospitals, including almost all centers that implant cardiac rhythm devices (22).

The defined endpoint for this study was time to death from any cause obtained by linking NCDR registry files with the Social Security Death Master File. Patients were censored if they were alive at the end of the follow-up period (March 31, 2011). We excluded patients with a QRS of less than 120 or more than 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 death or had missing data on sex, QRS morphology, or duration; patients who could not be linked to the Death Master File; and those who were not admitted to the hospital for the sole purpose of CRT-D implantation. Prior pacemaker or ICD (n = 66,122) and hospital admission for reasons other than CRT-D implantation (n = 50,753) accounted for most of the 147,008 exclusions (82% of all identified registry patients). Patients with QRS of greater than 220 ms were excluded due to the small number of subjects in this category and uncertainty about the accuracy of QRS duration measurement. Patients who were not admitted for the sole purpose of CRT-D implantation were excluded based on a potential confounding effect of competing factors for death. Finally, the study population was restricted to patients without atrial fibrillation, as atrial fibrillation is associated with a low rate of biventricular pacing. The US Food and Drug Administration (FDA) Research in Human Subjects Committee and the Yale University Human Investigation Committee approved the analysis.

Statistical Analysis

Univariate and multivariable adjusted Cox proportional hazards analysis was used to calculate mortality risks in the total population and in groups stratified by sex, QRS duration, and QRS morphology (LBBB and non-LBBB [including right bundle branch block and nonspecific intraventricular conduction delay]). The clustering of patients within hospitals was considered in the Cox proportional hazard models by marginal model approach with the robust sandwich estimate of the covariance. The proportional hazards assumption was confirmed by log-log plotting and supremum test. Multivariable models included adjustments for 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. LBBB and non-LBBB patients were divided into groups, defined by 10-ms increments in QRS duration. The 120- to 129-ms category was used as the reference for Cox proportional hazards analysis, and sex-by-treatment interactions were calculated within the 10-ms subgroups. Kaplan-Meier curves for the total population and separately in women and men with LBBB and non-LBBB were used to assess unadjusted comparisons of time-to-all-cause mortality in CRT-D patients across the 10-ms QRS duration groups. Missing data were rare for all variables (ranging between 0.02 and 0.61%) and were imputed by using the most common value for categorical variables and medians for continuous variables. All statistical analyses were conducted with SAS software, version 9.3 (SAS Institute, Cary, North Carolina). Ninety-five percent confidence intervals are reported for all hazard ratios, and probability values of less than 0.05 were considered statistically significant. Probability values were not adjusted for multiplicity.

RESULTS

The final study population included 31,892 CRT-D patients, of whom 11,542 (36%) were women and 20,350 (64%) were men (Table 1). Women were more likely than men to have LBBB (86% vs. 70%), normal atrioventricular conduction (82% vs. 70%), and nonischemic cardiomyopathy (62% vs. 33%). Overall, the majority of both women and men

had New York Heart Association (NYHA) functional class III heart failure symptoms (84% and 82%).

TABLE 1 Patient Characteristics by Sex in the Total and LBBB CRT-D Populations

	Total Population		LBBB	
	Women (n = 11,542)	Men (n = 20,350)	Women (n = 9,978)	Men (n = 14,174)
Demographics				
Age (yrs)	68 ± 11	69 ± 11	68 ± 11	69 ± 11
Race				
White	9,016 (78)	16,864 (83)	7,869 (79)	11,818 (83)
Black	1,644 (14)	1,894 (9)	1,339 (13)	1,283 (9)
Hispanic	611 (5)	1,049 (5)	526 (5)	722 (5)
Other	271 (2)	543 (3)	244 (2)	351 (2)
Clinical characteristics				
LVEF	24% ± 7%	24% ± 7%	24% ± 7%	24% ± 7%
NYHA functional heart failure class				
I/II	1,431 (12)	2,975 (15)	1,259 (13)	2,140 (15)
III	9,721 (84)	16,697 (82)	8,399 (84)	11,596 (82)
IV	390 (3)	678 (3)	320 (3)	438 (3)
Ischemic cardiomyopathy	4,354 (38)	13,621 (67)	3,441 (34)	8,760 (62)
LBBB	9,978 (86)	14,174 (70)		
Non-LBBB	1,564 (14)	6,176 (30)		
QRS duration (ms)	154 ± 19	153 ± 21	155 ± 18	157 ± 21
AV conduction				
Normal	9,440 (82)	14,150 (70)	8,255 (83)	10,084 (71)
First-degree block	1,979 (17)	5,733 (28)	1,624 (16)	3,823 (27)
Second-/third-degree block	123 (1)	467 (2)	99 (1)	267 (2)
Heart failure duration				
No	423 (4)	988 (5)	360 (4)	658 (5)
<3 months	1,104 (10)	2,142 (11)	931 (9)	1,471 (10)
3-9 months	1,988 (17)	3,212 (16)	1,736 (17)	2,271 (16)
>9 months	8,027 (70)	14,008 (69)	6,951 (70)	9,774 (69)
Previous valvular surgery	499 (4)	1,109 (6)	386 (4)	789 (6)
Cerebrovascular disease	1,203 (10)	2,606 (13)	986 (10)	1,733 (12)
Renal failure/dialysis	220 (2)	594 (3)	179 (2)	375 (3)
Diabetes mellitus	4,325 (38)	8,025 (40)	3,617 (36)	5,324 (38)
Hypertension	8,371 (73)	15,405 (76)	7,181 (72)	10,571 (75)
Sodium (mEq/l)	139 ± 3	139 ± 3	139 ± 3	139 ± 3
Blood urea nitrogen (mmol/l)	23 ± 13	25 ± 13	23 ± 12	24 ± 12
Creatinine (mg/dl)	1.2 ± 0.8	1.4 ± 1.0	1.1 ± 0.8	1.4 ± 0.9
Discharge medications				
Beta-blockers	10,295 (89)	17,937 (88)	8,921 (89)	12,519 (88)
Angiotensin receptor blockers	2,779 (24)	3,697 (18)	2,423 (24)	2,586 (18)
ACE inhibitors	6,969 (60)	13,366 (66)	6,059 (61)	9,386 (66)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; AV = atrioventricular; CRT-D = cardiac resynchronization therapy defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

After a median follow-up of 2.9 years (interquartile range: 2.0–3.9 years), 5,428 patients (17%) died. In the overall cohort, those with LBBB had a 24% lower mortality risk than those with non-LBBB (adjusted hazard ratio [HR] 0.76; 95% confidence interval [CI]: 0.72 to 0.80; $p < 0.001$). Patients with QRS durations of 120 to 129 ms had the highest mortality (Fig. 1), with slightly better survival in the QRS 130- to 139-ms (HR 0.92; 95% CI: 0.85 to 1.00; $p = 0.057$) and 140- to 149-ms groups (HR 0.88; 95% CI: 0.81 to 0.96; $p = 0.002$). Survival was highest in patient groups with QRS of 150 ms or longer, with similar mortality in patients with QRS of 150 to 159 ms (HR 0.74; 95% CI: 0.67 to 0.80; $p < 0.001$), QRS of 160 to 169 ms (HR 0.72; 95% CI: 0.66 to 0.79; $p < 0.001$), and QRS of 170 ms or longer (HR 0.69; 95% CI: 0.64 to 0.76; $p < 0.001$).

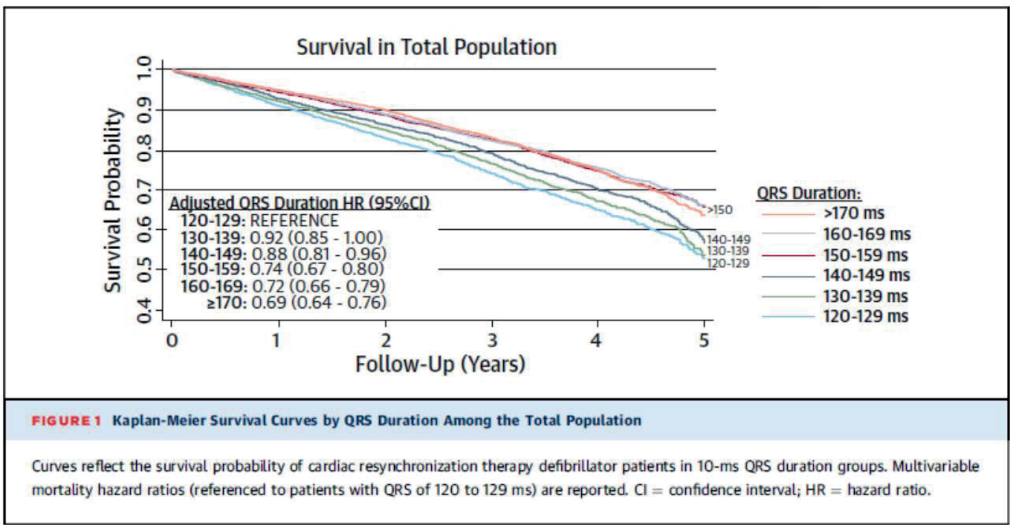


FIGURE 1 **Kaplan-Meier Survival Curves by QRS Duration Among the Total Population**

Curves reflect the survival probability of cardiac resynchronization therapy defibrillator patients in 10-ms QRS duration groups. Multivariable mortality hazard ratios (referenced to patients with QRS of 120 to 129 ms) are reported. CI = confidence interval; HR = hazard ratio.

MORTALITY IN CRT-D PATIENTS BY SEX, QRS MORPHOLOGY, AND DURATION

Overall, women had an 18% lower mortality risk compared with men (HR 0.82; 95% CI: 0.78 to 0.87; $p < 0.001$). In patients with LBBB, women had an adjusted 21% lower mortality risk than men (HR 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$). Figure 2 shows unadjusted survival curves for patients grouped by 10-ms QRS intervals, stratified by sex and QRS morphology, and the Central Illustration shows the hazard ratios for mortality separately in women and men, comparing QRS duration subgroups to a reference group with a QRS duration of 120 to 129 ms.

For both women and men with LBBB, mortality was highest in the QRS 120- to 129-ms group, with a slightly better survival in QRS of 130 to 139 ms, although this did not reach statistical significance in either women or men. In LBBB and QRS of 140 to 149 ms, women had a 27% lower mortality than those with QRS of 120 to 129 ms (HR 0.73; 95% CI: 0.60 to 0.88; $p = 0.001$), and this difference was 18% in men (HR 0.82; 95% CI: 0.71 to 0.93; $p = 0.003$); however, the difference between sexes was not statistically significant ($p = 0.30$ for interaction). With QRS duration longer than 150 ms, the lower mortality risk remained significant within the 10-ms subgroups and was similar between sexes (HR 0.61–0.68; $p < 0.001$ for women and HR 0.58–0.66; $p < 0.001$ for men). Although there were no significant sex-by-treatment interactions within the 10-ms QRS duration groups, the HR point estimates for mortality remained fairly consistent without much variation with QRS longer than 140 ms in women and 150 ms in men (Central Illustration).

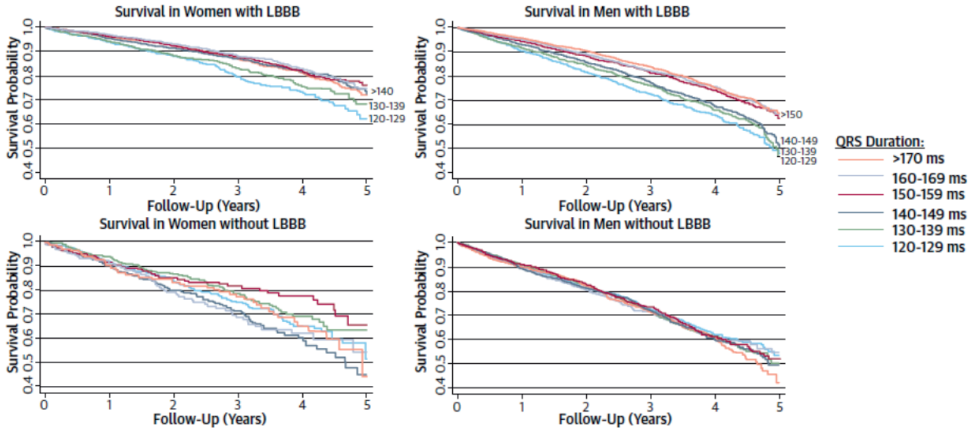


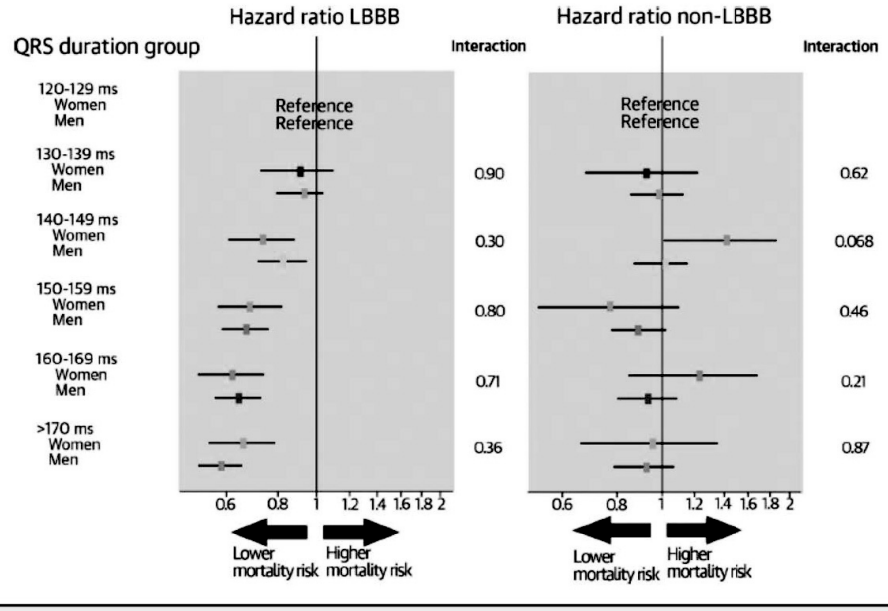
FIGURE 2 **Kaplan-Meier Survival Curves of QRS Duration Groups, Stratified by Sex and Presence of LBBB**

Curves reflect the survival probability of women **(top left)** and men **(top right)** with LBBB and women **(bottom left)** and men **(bottom right)** without LBBB in 10-ms QRS duration groups. LBBB = left bundle branch block.

In CRT-D patients without LBBB, there was no difference in adjusted mortality risk between sexes (HR 0.96; 95% CI: 0.86 to 1.06; p = 0.36) and no relation between QRS duration and mortality (Central Illustration). When all multivariable models were repeated with adjustment for discharge medications, the results did not change. The full multivariable adjusted models can be found in the online appendix (Online Tables 2 and 3 for women and men with LBBB and Online Tables 4 and 5 for women and men without LBBB).

DISCUSSION

In this large, real-world population of patients in the NCDR ICD Registry with left ventricular systolic dysfunction and predominantly NYHA functional class III heart failure symptoms who were treated with CRT-D, we found that women with LBBB have a lower mortality risk than men with LBBB. Among all patients with LBBB, longer QRS duration was associated with a better survival, although this lower mortality risk plateaued at a QRS duration longer than 140 ms in women and longer than 150 ms in men. In contrast, in the non-LBBB population, no sex-based differences in mortality were found and mortality risk was similar regardless of QRS duration. While in previous studies selected patient populations were
included and women were underrepresented, the present analysis included a more diverse and real-world CRT-D population with a larger proportion of women.



CENTRAL ILLUSTRATION **Multivariable Hazard Ratios for Mortality in LBBB and non-LBBB QRS Duration Groups by Sex**

Points reflect hazard ratios for all-cause mortality in LBBB **(left)** and non-LBBB **(right)** in 10-ms QRS duration groups for women and men. **Lines** indicate 95% confidence bounds. Sex-by-treatment interaction probability values are reported for every QRS duration category. See Online Table 1 for exact numbers. LBBB = left bundle branch block.

SEX DIFFERENCES IN THE PHYSIOLOGY OF DYSSYNCHRONY AND RESYNCHRONIZATION THERAPY

Recent studies and meta-analyses have shown that the presence of LBBB is predictive of a positive response to CRT (6,23), whereas patients with non-LBBB may experience no benefit or even harm from therapy (12,24–28). When the left bundle branch is completely blocked, the left ventricular lateral wall is activated approximately 100 ms later than the interventricular septum due to the impairment of electrical propagation in the rapidly conducting His-Purkinje system (Fig. 3). The left ventricular pacing lead in CRT reduces this delay and resynchronizes
the activation between both walls, thereby improving cardiac output and mechanical efficiency.
In patients without LBBB, the left ventricular activation via the His-Purkinje system is rapid and considered normal. For these reasons, CRT may be more effective in patients with LBBB than in patients without LBBB.

Because women have smaller ventricles and shorter baseline QRS duration than men (17), they are more likely to have a true LBBB compared with men, who are more likely to have a false-positive LBBB diagnosis at the lower end of the QRS duration prolongation spectrum (16). Single-center studies have evaluated stricter LBBB criteria accounting for sex differences in QRS duration, requiring a QRS of 130 ms or longer in women and 140 ms or longer in men together with mid-QRS notching/slurring (16). These studies found that

patients who met these stricter criteria have lower risks of heart failure hospitalizations and mortality with CRT compared with those not meeting the criteria (18,19).

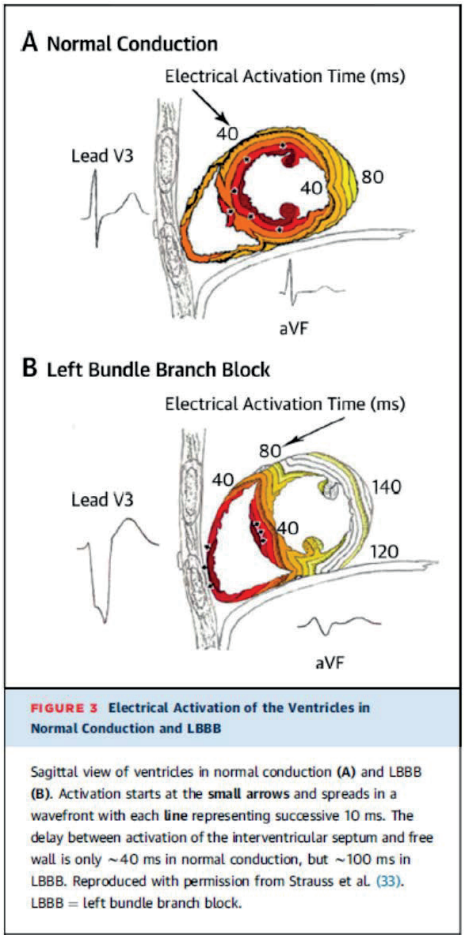


FIGURE 3 Electrical Activation of the Ventricles in Normal Conduction and LBBB

Sagittal view of ventricles in normal conduction **(A)** and LBBB **(B)**. Activation starts at the **small arrows** and spreads in a wavefront with each **line** representing successive 10 ms. The delay between activation of the interventricular septum and free wall is only ~40 ms in normal conduction, but ~100 ms in LBBB. Reproduced with permission from Strauss et al. (33). LBBB = left bundle branch block.

In addition to these electrophysiological differences, other factors may contribute to the greater response to CRT in women. Previous studies demonstrated that ischemic cardiomyopathy and atrial fibrillation are associated with a worse prognosis in CRT patients (12). In the present study, women indeed had a lower rate of ischemic cardiomyopathy than men, although patients with atrial fibrillation were excluded. Although the difference in the etiology of left ventricular systolic dysfunction could have contributed to the higher survival in women, our multivariable models controlled for this variable. In addition, it is difficult to separate the contribution of LBBB and ischemic cardiomyopathy to the observed outcomes as LBBB in CRT-D patients is usually caused by nonischemic pathologies (29).

The present findings complement the existing literature addressing the relationship between CRT-D and survival as a function of QRS morphology and duration. A study from the NCDR ICD Registry found that among patients receiving CRT-D, those with LBBB and longest QRS duration had a lower mortality risk than those without LBBB or shorter QRS

duration (25). Another study from the ICD Registry comparing outcomes between patients receiving CRT-D with those receiving ICD in a propensity-matched cohort found the lowest rates of hospitalization for cardiovascular causes and heart failure with CRT in the stratum of patients with LBBB and QRS duration longer than 150 ms (30). However, in addition to determining the relationship between sex and mortality in groups according to QRS morphology and duration, the present study evaluated mortality in 10-ms QRS duration groups, demonstrating that the survival benefit of CRT extends to shorter QRS duration groups among women as compared with men. Interestingly, although a recently conducted meta-analysis that also primarily included NYHA functional class III heart failure patients found that patients with QRS of 140 ms or longer benefited from CRT regardless of conduction type or sex (31), Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) substudies found that women with QRS shorter than 150 ms, but not men with QRS shorter than 150 ms, benefited from therapy (8,28). Additionally, in the recently published extended follow-up of MADIT-CRT, it was found that the survival benefit associated with CRT-D in patients with LBBB was independent of QRS duration and did not differ by sex; however, that analysis included fewer women and primarily patients with NYHA functional class II heart failure symptoms (32). Other published studies of CRT effect, including QRS morphology and QRS duration, have not performed separate analyses in women and men (5,6,24,25).

Limitations

This study did not include an ICD comparator group. Therefore, we were unable to evaluate the true effectiveness of CRT-D therapy. Multiple comparisons were performed; however, a Bonferroni correction for the 10 comparisons in LBBB women and LBBB men would not change the significance of the results ($p < 0.005$ for all LBBB). These data only represent patients who were admitted for the sole purpose of CRT-D implantation and did not have a prior pacemaker or ICD. It is possible that entry errors or missing data may have resulted in misdiagnosis of baseline characteristics, including QRS morphology and QRS duration. However, extensive data quality checks for the NCDR registries are in place and previous work has demonstrated that the participant average raw accuracy of data abstraction for the NCDR ICD registry is approximately 91% (21). The majority of patients in this cohort (83%) had NYHA functional class III heart failure symptoms, and thus the results are largely limited to that population. The endpoint for this analysis was all-cause mortality; the exact cause of death was not known. In addition, this is an observational study in which there is the possibility of confounding by unmeasured variables, including non-cardiac comorbidities; however, the most important potential confounders were part of the baseline characteristics (QRS morphology, QRS duration, ejection fraction, and NYHA heart failure functional class).

Conclusions

This study demonstrated that among real-world CRT-D recipients with predominantly NYHA functional class III heart failure, mortality risk in women with LBBB is lower than in men with LBBB, although there is no risk difference between female and male patients without LBBB. Furthermore, longer QRS duration is associated with better survival in patients with LBBB only. This favorable prognosis seems to plateau with QRS longer than 140 ms in women and 150 ms in men. Differences in baseline characteristics, patient

selection for the procedure, and biological effects of CRT therapy on left ventricular synchronization may contribute to the observed differences by sex and QRS duration. Further studies comparing CRT-D with a comparator ICD group may help elucidate these findings.

Conflict of interest disclosures
Dr. Masoudi is the Senior Medical Officer and Chair of the Science and Quality Oversight Committee of the National Cardiovascular Data Registry (NCDR). Dr. Curtis receives research and salary support under contract with the ACC NCDR. Dr. Curtis holds equity interest in Medtronic, a maker of cardiac devices. Dr. Piña receives consulting fees/honoraria from Novartis and GE Healthcare.

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INVITED COMMENTARY

Learning Toward a Better Understanding of CRT in Women

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Cardiac resynchronization-defibrillation therapy (CRT-D) is now a well-established treatment for patients with symptomatic heart failure unresponsive to optimized pharmacological therapy, including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-adrenergic blocker (1). Current indications based on American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines include patients with New York Heart Association (NYHA) functional class II to IV symptoms, left bundle branch block (LBBB), and QRS duration of 150 ms or more (2). Patients with LBBB and QRS duration of 120 to 149 ms or non-LBBB and QRS duration of 150 ms or more also have been reported to benefit from CRT-D therapy on the basis of earlier clinical trial results. Recently, the long-term results of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial demonstrated improved survival among patients with mild (NYHA functional class I or II) symptoms (3). Despite more than a decade of progress in improving implantation techniques and optimizing pacing, approximately 30% of patients still fail to respond adequately to CRT-D therapy. Given its invasive nature and the significant healthcare costs, accurate identification of those patients most likely to benefit remains a clinical challenge. Although multiple clinical trials have evaluated a myriad of echocardiographic parameters to assess ventricular dyssynchrony, these measures have generally failed to differentiate responders from nonresponders (4). The recently published ECHOCRT (Echocardiography Guided Cardiac Resynchronization) trial confirmed the powerful predictive value of QRS duration, but not dyssynchrony measures, in identifying responsive patients (5). Despite clear-cut echocardiographic confirmation of ventricular dyssynchrony, patients with normal QRS duration (mean 105 ms) failed to benefit from CRT-D therapy.

Attention has shifted away from dyssynchrony assessment and once again refocused on QRS morphology and duration as predictors of favorable outcome (e.g., improved survival, increased exercise duration, and left ventricular reverse remodeling). Several recent clinical trials and meta-analyses have shown that the presence of LBBB is predictive of a favorable response to CRT-D (6–8). More importantly, it is now increasingly apparent that patients with significant QRS prolongation but a non-LBBB morphology may experience no benefit or even sustain harm from this treatment (9–11). When complete LBBB exists, left ventricular lateral wall activation occurs approximately 100 ms later than the interventricular septum activation due to impairment in rapid impulse conduction via the His-Purkinje system. The left ventricular pacing lead in CRT reduces this delay and restores more-synchronized activation between both ventricular walls. However, left ventricular activation remains relatively intact through the normal His-Purkinje pathway in patients with QRS prolongation and non-LBBB morphology.

In this issue of the Journal, Zusterzeel et al. (12) report sex-specific mortality risk by QRS morphology and duration among a cohort of 31,892 patients who underwent CRT-D therapy and were included in the NCDR (National Cardiovascular Data Registry) Implantable Cardioverter Defibrillator (ICD) registry. The study population included patients with either ischemic (56%) or nonischemic cardiomyopathy (44%) and predominantly NYHA functional class III symptoms (83%) who underwent device implantation between 2006 and 2009. Unlike previously published clinical trials or registries in which women have comprised 22% to 30% of the study population, females represented 36% of this large cohort. Although mean left ventricular ejection fraction (LVEF) did not differ between men and women (mean LVEF 24 ±7%), significantly more women had LBBB at baseline (86% vs. 70%) and a

nonischemic heart failure etiology (62% vs. 33%). Among the entire cohort with complete LBBB, women had a 21% lower mortality compared with men (hazard ratio: 0.79; 95% CI: 0.74 to 0.84; $p < 0.001$). Further, longer QRS duration with LBBB was associated with better survival in both men and women. Specifically, a QRS duration >140 ms in women and >150 ms in men was associated with the greatest survival benefit. Importantly, no benefit was observed in either sex when QRS prolongation was due to non-LBBB morphology.

In the study by Loring et al. (8) of 144,642 Medicare beneficiaries who underwent CRT-D therapy between 2002 and 2007, women composed 26% of this cohort. Unlike the present study, women who underwent CRT-D therapy had a higher rate of atrial fibrillation or flutter (48% vs. 0%), a higher incidence of ischemic cardiomyopathy (53% vs. 38%), and a lower prevalence of LBBB (53% vs. 86%). Despite substantial differences between the 2 study populations, this large registry also reported that women with complete LBBB demonstrated a substantially lower risk-adjusted mortality rate than men; furthermore, heart failure hospitalizations were decreased by 26% in women compared with 15% in men with LBBB (8).

Why would women be more responsive to CRT-D than men? Women normally have smaller left ventricular cavity dimensions and shorter baseline QRS duration. Further, women are more likely to have “true” LBBB, whereas men are more likely to have an incomplete LBBB at the lower end of the QRS prolongation spectrum (e.g., 120 to 140 ms). In addition to electrophysiological differences between sexes, ischemic cardiomyopathy remains a significantly less common cause of symptomatic heart failure in women.

Like all retrospective database analyses, the present study has several limitations. It evaluated only patients admitted for CRT-D implantation who did not have a prior pacemaker or ICD. This trial excluded patients with a prior history of atrial fibrillation, a group known to have a lower response rate to CRT-D therapy. Further, no information is provided regarding the use of aldosterone antagonists in this population. The majority of patients (83%) had NYHA functional class III symptoms, and the results should be largely confined to patients with this severity of heart failure. Given the large size of the database, the endpoint for analysis was all-cause mortality, and the exact cause of death or percent cardiovascular deaths was unknown. Finally, as with any observational study, there is a possibility of unmeasured, confounding variables, including noncardiac comorbidities. Nonetheless, this study demonstrates among real-world CRT-D recipients a striking mortality reduction among women with LBBB compared with men and, as importantly, no difference between men and women patients who exhibited substantial QRS prolongation but lack LBBB morphology. Although the extent of QRS prolongation was associated with better survival in LBBB patients, this favorable prognosis seems to plateau higher than 140 ms in women and 150 ms in men. This report adds to knowledge derived from smaller clinical trials by further identifying patients more (and less) likely to respond to CRT-D treatment. It is important to recognize that women are frequently underrepresented in clinical trials and less frequently receive invasive cardiac interventions. Limiting CRT-D therapy to individuals with LBBB and QRS duration of 150 ms or more may deprive a substantial number of women with shorter QRS duration of this beneficial treatment. Conversely, the appropriate role of CRT-D therapy in both men and women with moderately severe heart failure symptoms who lack LBBB morphology appears to require careful reevaluation.

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Conflict of interest disclosures

Dr. Dec has reported that he has no relationships relevant to the contents of this paper to disclose.

LETTER TO THE EDITOR

Some Caveats about QRS Duration in Patients Receiving Cardiac Resynchronization Therapy

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J Am Coll Cardiol. 2015;65(5):514-515

To the Editor:

Zusterzeel et al reported in the September 2, 2014 issue of the *Journal* (1) on the predictive merits of QRS morphology and QRS duration (QRSd) following implementation of cardiac resynchronization therapy (CRT), analyzing 31,892 patients from the National Cardiovascular Data Registry (NCDR), Implantable cardioverter defibrillator (ICD) registry. They found that among patients with left bundle branch block (LBBB) mortality is lower in women than men, but this is not the case for patients with non-LBBB QRS morphologies, regardless of the QRSd; in both genders, longer QRSd in the LBBB cohorts, was associated with lower mortality for both men and women; women with LBBB and QRSD of 140 - 159 ms, had a lower mortality than men with similar QRS morphology and QRSd, although this was not the case in patients with QRSd of ≥ 150ms.

Women have shorter QRSd than men, and this has been often attributed to their smaller ventricles (1); however there is another mechanism producing additional shortening of the QRSd, which is QRS amplitude (QRSa)-dependent, and leads to an *apparent* shortening of the QRSd (2-4). Accordingly, if QRSd is corrected for the corresponding QRSa in the patients of the NCDR, the results might be different than reported herein. In addition, attributing the mortality improvement in patients receiving CRT only to the QRS morphology (i.e, LBBB) and the QRSd, underemphasizes the issue of the effectiveness of the CRT, based on the appropriate positioning of the left ventricular (LV) epicardial pacing leads, and the timing of the stimulation of the LV and right ventricle; regarding the later, perhaps data on the CRT biventricular pacing-based QRSd (5), if available in the NCDR, may enhance the value of the authors' contribution.

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REPLY:
Some Caveats about QRS Duration in Patients Receiving Cardiac Resynchronization Therapy

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Reply:

We thank Dr. Madias for his interest in our analysis[1] and his comments regarding QRS amplitude as well as the role of LV lead positioning in terms of response to cardiac resynchronization therapy (CRT). QRS amplitude could be important but is not available in the National Cardiovascular Data Registry (NCDR) ICD Registry and adjustment for QRS amplitude is not currently done in the selection of patients for CRT. In addition, determining the influence of QRS amplitude on QRS duration in women and men receiving CRT is difficult as the amplitude can be influenced by multiple factors that may also differ between sexes. We acknowledge that, in addition to having left bundle branch block (LBBB), appropriate left ventricular (LV) lead placement and timing of LV stimulation is important but also not available in the NCDR.

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1. Zusterzeel R, Curtis JP, Caños DA, et al. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: results from the NCDR. J Am Coll Cardiol. 2014;64:887-94.

CHAPTER IV
Cardiac Resynchronization Therapy in Women Versus Men: Observational Comparative Effectiveness Study from the National Cardiovascular Data Registry

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ABSTRACT

Background: Women have been underrepresented in trials of cardiac resynchronization therapy-defibrillators (CRT-D). Previous studies suggest that women benefit from CRT-D at shorter QRS duration than men and that there may be no benefit of CRT-D in patients without left bundle branch block (LBBB) regardless of patient sex.

Methods and Results: We compared sex-specific death risk in 75,079 patients with New York Heart Association (NYHA) Class III or IV heart failure, reduced left ventricular ejection fraction and prolonged QRS duration (≥120 ms) receiving either CRT-D or implantable-defibrillator (ICD) in subgroups according to QRS morphology and 10 ms increments in QRS duration. We applied propensity score weighting to control for differences between treatments. Among patients with LBBB, women receiving CRT-D had a lower relative death risk than those receiving ICD (absolute difference 11%, hazard ratio [HR]=0.74 [95%-CI 0.68-0.81]). In men, the lower mortality with CRT-D vs. ICD was less pronounced (absolute difference 9%, HR=0.84 [0.79-0.89]) (sex*device interaction p=0.025). In those without LBBB, the mortality difference was modest and did not differ between women and men (absolute difference 3%, HR=0.88 [0.79-0.97] in women and absolute difference 2%, HR=0.95 [0.91-0.998] in men; interaction p=0.17). In subgroups according to QRS duration, CRT-D was associated with better survival in both sexes with LBBB and QRS ≥130 ms while there was no clear relation between QRS duration and survival in patients without LBBB regardless of patient sex.

Conclusions: In a large real-world population CRT-D was associated with a lower mortality risk in both sexes with LBBB, though more pronounced among women. Only among those with LBBB, both sexes had better survival with longer QRS duration. The mortality differences in patients without LBBB were attenuated in both sexes.

Key words: Cardiac resynchronization therapy, QRS morphology, QRS duration, sex, gender.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure symptoms, hospitalizations and mortality while improving quality of life in selected patients with heart failure with reduced ejection fraction and electrocardiographic evidence of ventricular dyssynchrony.[1-5] The benefits of CRT, however, are not uniform and depend upon both QRS morphology and QRS duration.[6, 7] Current professional society guidelines reserve the highest recommendation for CRT-defibrillator (CRT-D) implantation in patients with heart failure with reduced ejection fraction, a left bundle branch block (LBBB) and QRS ≥150 milliseconds (ms) (Class I recommendation).[8] The recommendations for those without LBBB are more equivocal (Class IIa or IIb recommendation dependent on QRS duration).[8]

In available analyses of clinical trials and observational data, women tend to do better with CRT-D than men.[9-11] One possible explanation for this is that women more often have a LBBB, associated with a better CRT response. However, electrophysiology and preclinical studies have shown that approximately one-third of patients diagnosed with LBBB by conventional ECG criteria do not have endocardial activation consistent with a true LBBB,[12-14] confirming an inherent difficulty of diagnosing LBBB. Since women have smaller hearts and a shorter QRS duration at baseline compared to men,[15] they may also have a true LBBB at a shorter QRS duration than men. To account for these differences between women and men stricter ECG LBBB criteria were proposed that require a QRS ≥130 ms in women and ≥140 ms in men, along with mid QRS notching and/or slurring.[13]

A prior study of three randomized clinical CRT-D trials in primarily mild heart failure patients (New York Heart Association [NYHA] Class II) showed that women with a LBBB and QRS duration ≥130 ms had a mortality benefit from CRT-D while men with LBBB benefited at QRS ≥150 ms.[16] However, in a large real-world population of only CRT-D patients included in the National Cardiovascular Data Registry (NCDR®) implantable cardioverter-defibrillator (ICD) Registry (primarily NYHA Class III), it was observed that both women and men had a lower mortality risk with LBBB and QRS ≥140 ms.[17]

It is difficult to assess the real-world performance of CRT-D when only a narrowly selected patient population is available (clinical trials) or when a standard ICD group is not included. The objective of the current analysis was to compare long-term mortality outcomes between real-world CRT-D and ICD patients among subgroups by sex, bundle branch block and QRS duration in the NCDR ICD Registry in NYHA Class III or IV heart failure.

METHODS

This study was approved by the U.S. Food and Drug Administration (FDA) Research in Human Subjects Committee and the Yale University Human Investigation Committee. It included all patients in the NCDR ICD registry™ who received a first time CRT-D or ICD implant between January 1, 2006, and March 31, 2010, had NYHA Class III or IV heart failure symptoms, and QRS duration between 120 and 220 ms (n=86,967). Demographics and covariates were collected using standardized data elements in the NCDR including all variables in Table 1 and additionally: syncope, family history of sudden death, cardiac arrest, ventricular tachycardia, previous myocardial infarction, previous cardiac procedures (including percutaneous coronary intervention and coronary artery bypass graft) and systolic blood pressure. Post discharge medications were also available. QRS morphology was defined by the criteria used in the NCDR.[18]

The outcome for this analysis was time to all-cause mortality obtained by linking NCDR registry files with the Social Security Death Master File. The following patients were excluded from the analysis: patients with a missing ICD type (either single chamber, dual chamber or CRT-D) (n=723), epicardial leads (n=9,326), missing data for sex, QRS duration or bundle branch block type (n=61) and patients that were unable to be linked to the social security administration death master file or had a death date before implant date (n=1,778). Only patients with NYHA Class III or IV were included because patients with NYHA Class I or II heart failure were not part of professional society guidelines and FDA indications for use of CRT-D between 2006-2010. In addition, the specific NYHA Class was a strong predictor of CRT-D use within the total population of NYHA Class I-IV heart failure patients, making it difficult to apply propensity score analysis to account for measured confounders and selection bias. Patients with QRS >220 ms were excluded because of the small number of subjects in this category.

Statistical Analysis

Patients were stratified by sex, bundle branch block type and QRS duration in 10 ms increments. To account for potential treatment selection bias and to control for differences in case-mix between CRT-D and ICD we used inverse probability treatment weighting based on the propensity score. Propensity scores were calculated using logistic regression incorporating all covariates and with receiving CRT-D (versus ICD) as the outcome resulting in the predicted probability of receiving CRT-D based on these covariates. Weighted propensity scores were then calculated by weighting each patient who received CRT-D by the inverse of the probability that the patient would be selected for CRT-D, as well as weighting each patient who received ICD by the inverse of the probability that the patient would be selected for ICD. To stabilize the weights, we used the marginal probability of receiving CRT-D as standard weights can be highly variable.[19] Weighted propensity score analysis was then repeated, re-weighting all baseline characteristics in all subgroups. Standardized differences after weighting were calculated to ensure balanced treatment groups with respect to baseline characteristics. CRT-D and ICD groups were considered balanced when the standardized difference <10% as this indicates insignificant differences in covariates between groups.[20] Time-to-all-cause mortality data are presented using propensity score weighted Kaplan-Meier survival curves for the total cohort and subgroups, and weighted Cox proportional hazards models were used to assess mortality risk between CRT-D and ICD including weighted sex-by-treatment interactions. The proportional hazards assumption was assessed by including a time*device interaction and was found non-significant in all models. Missing data were rare for all variables (between 0.008 and 0.58%) and were imputed by the most common value for categorical variables and medians for continuous variables.[21] Separate analysis was conducted sub-stratifying the non-LBBB group into right bundle branch block (RBBB) and non-specific intraventricular conduction delay (IVCD). All statistical analyses were conducted with SAS software, version 9.3 (SAS institute, Cary, NC). Ninety-five percent confidence intervals are reported for all hazard ratios and a pre-specified p-value <0.05 (not adjusted for multiplicity) was considered statistically significant.

RESULTS

The total study cohort consisted of 75,079 patients of which 23,744 (32%) were women and 51,335 (68%) were men. Approximately 84% of patients received a CRT-D and 16% received ICD. The proportion of ICD recipients decreased over time (from 18% in 2006 to 13% in 2010). The most pronounced differences between CRT-D and ICD groups in the unweighted sample included LBBB and ischemic cardiomyopathy (Online Table 1). After subsequent inverse probability treatment weighting, the CRT-D and ICD groups in both sexes were balanced indicated by standardized differences <10% for all variables (Table 1). This was also true for CRT-D and ICD groups in all other stratified analyses (Online Tables 2 and 3). In the overall weighted cohorts, the main baseline differences between sexes included women (compared to men) having more LBBB (81% vs. 61%), non-ischemic cardiomyopathy (55% vs. 30%) and normal atrio-ventricular conduction (79% vs. 69%), while they had less atrial fibrillation/flutter (23% vs. 34%) (Table 1). The majority had NYHA Class III heart failure symptoms (93% of both women and men). The mean follow-up for the overall cohort was 2.5±1.3 years while the median follow-up was 2.5 years (interquartile range: 1.5-3.6 years).

The overall mortality rate in the total weighted cohort of CRT-D and ICD patients was lower in women than in men (Figure 1). After a mean follow-up of 2.5 years, female patients with CRT-D had a lower mortality risk than those with an ICD (absolute CRT-D to ICD difference 11%, hazard ratio [HR]= 0.77, 95% confidence interval [CI] 0.72-0.82, p<0.001). Men with CRT-D also had a lower mortality compared to those with an ICD, but this was less pronounced than in women (absolute difference 7%, HR=0.88, CI 0.85-0.92, p<0.001). This mortality difference between sexes was significant (p<0.001 for sex*device interaction).

Mortality in Patients with Left Bundle Branch Block

Among patients with LBBB, a similar pattern as for the total cohort – a lower mortality in women compared to men - was observed; however the overall lower mortality associated with CRT-D vs. ICD was greater than in the total cohort (Figure 2). Both women and men with LBBB had a lower mortality risk with CRT-D compared to ICD (absolute difference 11%, HR=0.74, CI 0.68-0.81, p<0.001 for women and absolute difference 9%, HR=0.84, CI 0.79-0.89, p<0.001 for men), but with a greater effect in women (p=0.025 for interaction). Although none of the patients with LBBB and QRS 120-129 ms had a lower mortality risk with CRT-D compared with ICD, both women and men with LBBB and a QRS ≥130 ms had a significantly lower mortality risk (Figure 3). While this lower mortality rate persisted in women with longer QRS durations 150-170 ms, the upper confidence limit just crossed HR=1 for men. There were no significant device interactions by sex within any of the QRS duration groups (Figure 3).

Mortality in Patients without Left Bundle Branch Block

Women and men without LBBB had a slightly lower mortality rate with CRT-D compared to ICD (absolute difference 3%, HR=0.88, CI 0.79-0.97, p=0.014 for women and absolute difference 2%, HR=0.95, CI 0.91-0.998, p=0.042 for men) (Figure 2). There was no statistical difference in the relationship between CRT-D and mortality between sexes (p=0.17 for interaction); women without LBBB did not seem to confer any additional mortality risk difference compared to men without LBBB.

Table 1. Propensity Score Weighted Patient Characteristics by Sex in CRT-D and ICD Populations

	Women			Men		
	CRT-D (n=20379)[a]	ICD (n=3383)[a]	SMD (%)[b]	CRT-D (n=42560)[a]	ICD (n=8837)[a]	SMD (%)[b]
Demographics						
Age (years), mean ± SD	70±11	70±11	0.00	70±11	70±12	0.00
Race						
White	15521 (76%)	2574 (76%)	-0.17	34861 (82%)	7239 (82%)	0.00
Black	3165 (16%)	533 (16%)	0.59	4157 (10%)	864 (10%)	0.03
Hispanic	1162 (6%)	191 (6%)	-0.19	2303 (6%)	489 (6%)	0.51
Other	530 (3%)	85 (3%)	-0.61	1238 (3%)	246 (3%)	-0.74
Clinical characteristics						
Admission for procedure	13746 (68%)	2315 (68%)	2.07	27263 (64%)	5724 (65%)	1.48
LVEF[c] (%), mean ± SD	24±7	24±8	-0.04	24±7	24±8	-0.03
NYHA[d] heart failure class						
III	18930 (93%)	3158 (93%)	1.86	39352 (93%)	8144 (92%)	-1.15
IV	1449 (7%)	225 (7%)	-1.86	3207 (8%)	693 (8%)	1.15
Ischemic cardiomyopathy	9114 (45%)	1528 (45%)	0.89	29494 (69%)	6149 (70%)	0.60
Left bundle branch block	16342 (80%)	2726 (81%)	0.98	25867 (61%)	5425 (61%)	1.25
Non-left bundle branch block	4036 (20%)	657 (19%)	-0.98	16693 (39%)	3412 (39%)	-1.25
QRS duration (ms), mean ± SD	152±21	152±20	-0.02	152±21	152±21	-0.02
AV[e] conduction						
Normal	16050 (79%)	2653 (78%)	-0.83	29371 (69%)	6091 (69%)	-0.19
First degree block	3673 (18%)	623 (18%)	0.98	11145 (26%)	2292 (26%)	-0.58
Second/Third degree block	655 (3%)	107 (3%)	-0.22	2044 (5%)	454 (5%)	1.57
Heart failure duration[f]						
Unknown	679 (3%)	106 (3%)	-1.16	1949 (5%)	393 (5%)	-0.62
<3 months	2662 (13%)	454 (13%)	1.05	5903 (14%)	1193 (14%)	-1.07
3-9 months	3160 (16%)	527 (16%)	0.23	5886 (14%)	1259 (14%)	1.20
>9 months	13878 (68%)	2296 (68%)	-0.50	28821 (68%)	5992 (68%)	0.18
Atrial fibrillation/flutter	4720 (23%)	792 (23%)	0.56	14547 (34%)	3041 (34%)	0.49
Previous valvular surgery	1440 (7%)	255 (8%)	1.78	3525 (8%)	724 (8%)	-0.34
Cerebrovascular disease	2721 (13%)	461 (14%)	0.83	6680 (16%)	1368 (16%)	-0.60
Renal failure/dialysis	667 (3%)	104 (3%)	-1.09	1906 (5%)	395 (5%)	-0.07
Diabetes mellitus	8456 (42%)	1381 (41%)	-1.37	18052 (42%)	3709 (42%)	-0.90
Hypertension	15722 (77%)	2602 (77%)	-0.59	33521 (79%)	6958 (79%)	-0.08
Sodium level (mEq/L), mean ± SD	139±4	139±4	0.00	138±4	138±4	0.01
Blood urea nitrogen level (mmol/L), mean ± SD	25±15	26±15	0.00	27±15	27±16	0.00
Creatinine (mg/dL), mean ± SD	1.3±1	1.3±1	-0.01	1.5±1	1.5±1	0.00
Discharge medications						
Beta-blockers	17895 (88%)	2897 (86%)	-6.44	37052 (87%)	7523 (85%)	-5.59
Angiotensin receptor blockers	4592 (23%)	696 (21%)	-4.76	6991 (16%)	1248 (14%)	-6.39
ACE-inhibitors	11984 (59%)	2001 (59%)	0.73	26723 (63%)	5604 (63%)	1.29

[a] Represents weighted numbers and frequencies after propensity score inverse probability treatment weighting; [b] SMD indicates standardized mean difference [c] NYHA indicates New York Heart Association; [d] LVEF indicates left ventricular ejection fraction; [e] AV indicates atrio-ventricular; [f] indicates the duration of symptoms since initial diagnosis of heart failure

There also was no clear mortality risk difference with CRT-D in non-LBBB women or men within any of the 10 ms QRS duration groups, except for women with QRS 150-159 ms (Figure 3).

Analysis dividing the non-LBBB cohort into patients with either RBBB (n=9,209) or IVCD (n=10,212) was conducted. In RBBB there was no lower mortality with CRT-D and no difference between women and men (absolute difference 1%, HR=0.98, CI 0.83-1.16, p=0.82 in women and absolute difference 1%, HR=0.97, CI 0.90-1.05, p=0.44 in men; p=0.90 for interaction). With IVCD, there was no lower mortality risk with CRT-D in men (absolute difference 4%, HR=0.93, CI 0.86-1.01, p=0.076); however, women with IVCD had a slightly lower mortality risk with CRT-D (absolute difference 7%, HR=0.76, CI 0.65-0.88, p<0.001; p=0.02 for sex*device interaction in IVCD) (Figure 4).

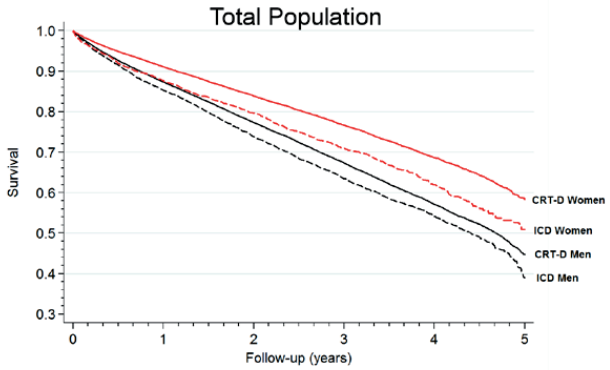

Figure 1. Propensity Score Weighted Kaplan-Meier Analysis of CRT-D vs. ICD by Sex in the Total Cohort. Curves indicate survival of CRT-D (solid lines) vs. ICD (dashed lines) patients in women (red) and men (black) after propensity score weighting in the total cohort.

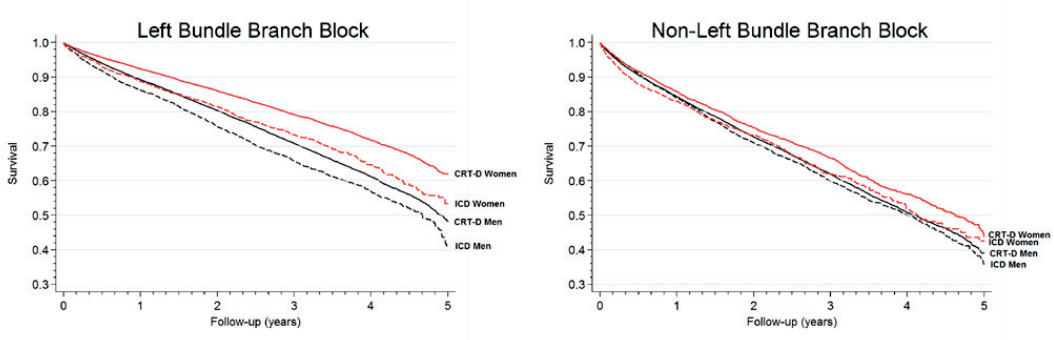

Figure 2. Propensity Score Weighted Kaplan-Meier Analysis of CRT-D vs. ICD by Sex in LBBB and non-LBBB. Curves indicate survival of CRT-D (solid lines) vs. ICD (dashed lines) in women (red) and men (black) after propensity score weighting in left bundle branch block (left) and non-left bundle branch block (right).

DISCUSSION

In this observational analysis of a large real-world cohort of patients with NYHA Class III or IV heart failure and reduced ejection fraction, we found that, compared with ICD, CRT-D was associated with a greater difference in mortality in women than in men but this lower mortality risk was more evident in both male and female patients with LBBB. Among all

LBBB patients, both women and men generally had lower mortality risks with QRS ≥130 ms; however the mortality difference associated with CRT-D was greater in women. In the non-LBBB cohort, there was no mortality risk difference between CRT-D and ICD in women or men with RBBB, or in men with IVCD. The finding that there appears to be reduced mortality in patients with LBBB and QRS 130-150 ms is important since professional society guidelines for CRT only assign a Class I recommendation to patients with LBBB and QRS ≥150 ms.[8]

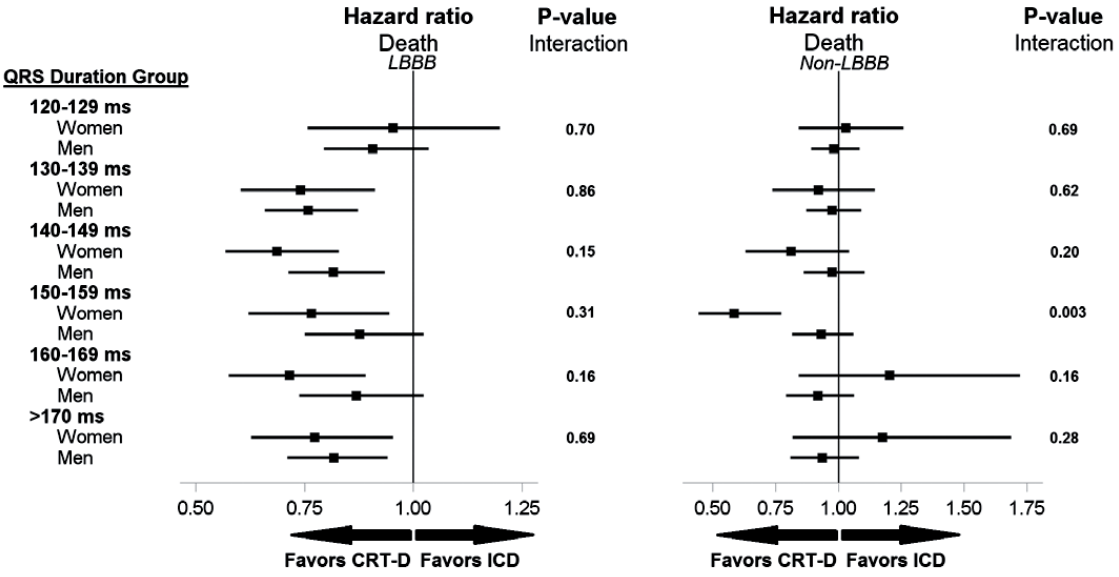

Figure 3. Propensity Score Weighted Mortality Hazard Ratios by Sex for QRS Duration Groups in LBBB and non-LBBB. Points reflect CRT-D to ICD mortality hazard ratios in 10 ms QRS duration groups in women and men after propensity score weighting for LBBB (left) and non-LBBB (right). Lines reflect 95% confidence intervals and sex*device interaction p-values are reported for every QRS duration group. Vertical lines indicate no difference between CRT-D and ICD (HR=1). See Online Table 4 for exact numbers.

That CRT is effective in LBBB has been shown in recent meta-analyses of clinical trials[7, 16, 22] while other studies have suggested that CRT is less effective or can even be harmful in patients without LBBB.[7, 23-28] One-third of patients diagnosed with LBBB by conventional criteria, however, do not have endocardial activation consistent with a true LBBB[12-14] supporting the challenges in diagnosing LBBB on the surface ECG. In addition, because women have smaller ventricles and a shorter QRS duration at baseline compared with men[15] they may also have a true LBBB at a shorter QRS duration ≥120 ms than men. Recent stricter LBBB criteria accounting for this difference between women and men, requiring a QRS ≥130 ms in women and ≥140 ms in men along with mid-QRS notching or slurring,[13] have shown to be associated with lower risks of mortality and heart failure hospitalization with CRT.[29, 30]

A previous individual-patient data meta-analysis of three large pre-market clinical trials primarily enrolling NYHA Class II heart failure patients found that women with LBBB benefited from CRT-D compared to ICD with QRS ≥130 ms while men with LBBB benefited

with QRS ≥150 ms.[16] The present study showed that both women and men with CRT-D had a lower mortality risk with LBBB and QRS ≥130 ms compared to those with an ICD. However, patients in this study were not part of a selected clinical trial patient population and primarily had NYHA Class III heart failure symptoms. In addition, men with LBBB and QRS 130-139 ms may have had a lower mortality risk with CRT-D because ICD patients with shorter QRS duration were sicker compared to CRT-D patients (discussed further below).

Other factors that may have contributed to a greater CRT effect in women compared with men are the higher rate of non-ischemic cardiomyopathy and lower rate of atrial fibrillation/flutter, factors that have been associated with a better response to CRT.[31] Adjustment for these variables, however, still did not explain the differences between women and men. Interestingly, a previous study of only CRT-D recipients in the NCDR observed that both women and men with LBBB and QRS ≥140 ms had a lower mortality risk,[17] and a separate meta-analysis showed a beneficial CRT effect in patients with QRS ≥140 ms in which sex was not predictive, although neither was bundle branch block type.[22] The extended follow-up of MADIT-CRT also showed that there was no difference between women and men with LBBB.[32] Separate studies that evaluated the effect of CRT by sex have shown slightly different results,[9, 22, 28] while other published analyses on CRT by bundle branch block type and QRS duration have not included sex-specific analysis.[6, 7, 23, 25, 33]

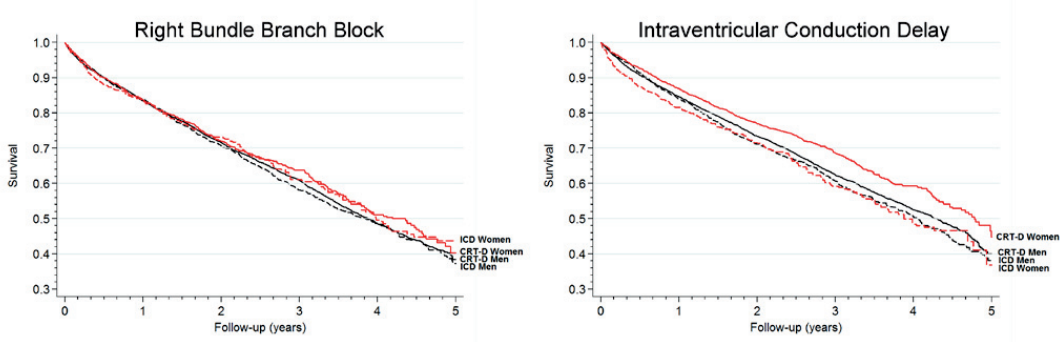

Figure 4. Propensity Score Weighted Kaplan-Meier Analysis of CRT-D vs. ICD by Sex in RBBB and IVCD. Curves indicate survival of CRT-D (solid lines) vs. ICD (dashed lines) in women (red) and men (black) after propensity score weighting in right bundle branch block (left) and non-specific intraventricular conduction delay (right).

In this analysis, we observed that patients without LBBB receiving CRT-D had a lower mortality risk than non-LBBB ICD patients, although the difference was small (absolute risk difference of 2% in men and 3% in women). A small beneficial effect of CRT has also been observed for certain patients without LBBB in previous studies and may be caused by multiple factors.[34, 35] A recent post-hoc analysis of MADIT-CRT found that patients with non-LBBB that had extremely long PR intervals at baseline benefited from CRT. This suggests that optimizing atrio-ventricular delay may provide some benefit in these patients.[35] However, when we evaluated RBBB and IVCD patients in the non-LBBB cohort we did not observe a lower mortality risk for women or men with RBBB and men with IVCD while there was a slightly lower mortality in women with IVCD. Of note, we did not observe a consistent lower mortality risk in the total non-LBBB cohort across QRS duration (Figure 3).

We observed that ICD patients with shorter QRS duration were sicker as they had more ventricular tachycardia, ischemic heart disease and a higher rate of heart failure

hospitalization in the previous 6 months compared to ICD patients with a longer QRS duration (data not shown). This may have contributed to men with LBBB and QRS 150-159 and 160-169 ms only trending towards a lower mortality risk with CRT-D and why LBBB men with a CRT-D and shorter QRS duration had lower mortality than LBBB men with CRT-D and longer QRS duration.

Limitations

This was an observational study in primarily NYHA Class III heart failure patients, and we were not able to assess the relationship between CRT-D and survival outside of this patient population. In addition, this study was not able to comment on other clinical events such as hospitalization for heart failure or heart failure symptom status. Furthermore, multiple comparisons were performed and p-values were not adjusted for multiplicity potentially influencing statistical significance. However, with a conservative Bonferroni correction p-values would still be significant ($p < 0.001$ for all comparisons in LBBB). Entry errors or missing data may have resulted in misdiagnosis of baseline characteristics including QRS morphology and QRS duration; however, prior analysis has shown that data accuracy for the NCDR ICD Registry is approximately 91%.[36] Although important cardiac covariates (NYHA Class, ejection fraction, bundle branch block type and QRS duration) were included in the analysis and propensity score weighting was used to balance characteristics between CRT-D and ICD groups, there is the possibility of unmeasured patient characteristics influencing all-cause mortality since non-cardiac competing factors for death were not included and propensity score weighting does not adjust for unobserved variables. Even though the proportion of ICD recipients was relatively low (~16%) and decreased over time, there may have been temporal selection bias as some ICD patients in this study would receive CRT-D instead of ICD according to contemporary practice. Finally, unmeasured characteristics may have contributed to treatment selection bias in choosing CRT-D vs. ICD.

Conclusions

In a large real-world population of CRT-D and ICD patients with primarily NYHA Class III heart failure, CRT-D was associated with a significantly lower mortality risk in women than in men and this lower mortality risk increased for both sexes with a LBBB. In non-LBBB, there was a much smaller effect of CRT-D and no difference between sexes. Furthermore, only among LBBB patients both women and men had lower mortality risks with QRS ≥130 ms while QRS duration had no effect on mortality in non-LBBB. RBBB patients did not experience a mortality risk benefit regardless of sex. Potential unmeasured patient characteristics not adjusted for by propensity score weighting may have influenced the results.

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Disclosures

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CHAPTER V
Comparative Effectiveness of Cardiac Resynchronization Therapy Defibrillators vs. Standard Implantable Defibrillators in Left- and Right Bundle Branch Block Medicare Patients

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ABSTRACT

Purpose: To assess the comparative effectiveness of CRT-defibrillators (CRT-D) versus standard implantable defibrillators (ICD) separately in left bundle branch block (LBBB) and right bundle branch block (RBBB) patients.

Methods: We analyzed Medicare records from CRT-D and ICD recipients from 2002-2009 that were followed up for up to 48 months. ICD patients were propensity-score matched to CRT-D patients. In LBBB, 1:1 matching with replacement resulted in 54,218 CRT-D and 20,763 ICD patients, and in RBBB 1:1 matching resulted in 7,298 CRT-D and 7,298 ICD patients.

Results: In LBBB, CRT-D had a 12% lower risk of heart failure (HF) hospitalization or death (hazard ratio [HR]: 0.88 [95%CI: 0.86-0.90]) and 5% lower death risk (HR: 0.95 [0.92-0.97]) compared to ICD. In RBBB, CRT-D had a 15% higher risk of HF hospitalization or death (HR: 1.15 [1.10-1.20]) and 13% higher death risk (HR: 1.13 [1.07-1.18]). Sensitivity analysis revealed that accounting for unmeasured covariates might lead to increased benefit with CRT-D in LBBB and no difference in RBBB.

Conclusions: In a large Medicare population, CRT-D was associated with lower mortality in LBBB, but higher mortality in RBBB. These findings should be interpreted with caution as propensity scores do not adjust for unmeasured confounders.

INTRODUCTION

As part of the US Food and Drug Administration's (FDA) responsibility to monitor the products it regulates, the Agency, together with the Centers for Medicare & Medicaid Services (CMS), launched the SafeRx Initiative. Its purpose continues to be the development of methods for the assessment of medical therapy safety and effectiveness in large real-world populations using Medicare and Medicaid claims databases. While the initial pre-market approval of medical products usually requires a well-conducted randomized clinical trial, some questions cannot always be answered in the premarket setting and this is one area where post-market analysis of claims data can be of value.

Cardiac resynchronization therapy (CRT), either alone or in combination with an implantable cardioverter defibrillator (ICD, CRT-D), is an increasingly used therapy for heart failure and has been shown to reduce heart failure symptoms, heart failure hospitalizations and mortality while improving quality of life.[1-3] Current professional society guidelines for CRT give a Class I indication to patients with left bundle branch block (LBBB) and a QRS duration ≥150 ms while patients without LBBB receive either a Class IIa or Class IIb recommendation indicating that in these patient groups the benefits outweigh the risks.[4] The guidelines were largely based on randomized clinical trials; however, the majority of patients included in the CRT trials had a LBBB while only a small sample of non-LBBB patients were included. Thorough investigation of the CRT effect in patients with right bundle branch block (RBBB) is difficult because they were highly underrepresented and part of a selected population based on clinical trial inclusion criteria. In support of the SafeRx Initiative, a study was conducted to evaluate the effect of CRT-D in a large real-world population. The objective was to assess the comparative effectiveness of CRT-D versus ICD separately in LBBB and RBBB patients.

MATERIAL AND METHODS

Patient Cohort and Covariates

This study was approved by the US Food and Drug Administration Research in Human Subjects Committee and the Centers for Medicare & Medicaid Services. It included all Medicare patients who received a primary prevention CRT-D (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] procedure code '00.51') or ICD device (ICD-9-CM procedure code '37.94') between July 1, 2002 and September 30, 2009 who were also continuously enrolled in Medicare Part A (inpatient hospital coverage) and B (outpatient medical coverage) ≥12 months prior to implantation. The following patients were excluded from further analysis: patients with an ICD-9 code for ventricular fibrillation, ventricular flutter, cardiac arrest or sudden cardiac arrest as part of secondary prevention and patients with end-stage renal disease or hypertrophic cardiomyopathy (Supplemental Methods).

The presence of preexisting comorbidities and other covariates (Table 1) was assessed through ICD-9 codes in a 12-month look back window while demographics were determined using the Medicare enrollment database. To account for other competing factors for death, we also included the Charlson comorbidity score. The Charlson score is a score to predict 10-year mortality based on whether a patient has certain health conditions,[5] further explanation can be found in the online appendix (Supplemental Methods).

To further specify the cohort to only include incident CRT-D and ICD patients with LBBB or RBBB and a primary prevention implant we used ICD-9 procedure codes (PRC) and current procedural terminology (CPT) codes used for maintenance and follow-up of patients with CRT-D and ICD devices (patients without an ICD-9 code for LBBB or RBBB were excluded). Patients were excluded if they either had a maintenance code or a cohort defining event (CRT-D or ICD implantation code) in the 12 months before implantation, indicating a previous device implant. All codes used for cohort determination and the assessment of preexisting comorbidities can be found in the online appendix (Online Tables 1 and 2).

Study Endpoints

The defined endpoints for this study were 1) heart failure hospitalization or death and 2) all-cause mortality. All-cause mortality was determined by using the Medicare Master Beneficiary Summary File from CMS, which documents the date of death for all enrolled patients assessed from the Social Security Administration. Heart failure hospitalization was defined as having an ICD-9 code for heart failure as the primary diagnosis on an inpatient claim. Patients were censored if they did not reach the endpoint after a maximum of 48 months of follow-up or if they were no longer continuously enrolled in Medicare Part B.

Statistical Analysis

Propensity score matching was performed separately in LBBB and RBBB patients to reduce potential treatment selection bias and differences in baseline characteristics between CRT-D and ICD patients. A multivariable logistic regression model including all variables listed in Table 1 was used to calculate the propensity score. LBBB ICD patients were 1:1 matched (with replacement) to LBBB CRT-D patients and RBBB ICD patients were 1:1 matched to RBBB CRT-D patients using a 0.1 caliper width. Standardized mean differences were calculated to ensure that there were no significant differences between CRT-D and ICD patients. Treatment groups were considered balanced when the standardized mean difference was <0.10 as this has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups.[6] Kaplan-Meier curves and multivariable Cox proportional hazards models were generated to compare the effect of CRT-D to ICD in both LBBB and RBBB patients.

Sensitivity analyses were conducted for both endpoints to investigate the potential influence of unmeasured confounders by introducing an unobserved covariate into the model based on three parameters – relative risk, treatment distribution and prevalence – and determine which combination of these parameters would change the results significantly after matching CRT-D and ICD populations. Relative risk was defined as the probability of the endpoint (either heart failure hospitalization or death, or death alone) in CRT-D patients with the introduced covariate vs. the probability of the endpoint in CRT-D patients without the introduced covariate. Treatment distribution was defined as the ratio of the proportion of CRT-D patients with the introduced covariate to the proportion of ICD patients with the introduced covariate while prevalence was the frequency of the covariate in the total population. Probabilities of receiving the unobserved covariate were calculated based on combinations of these three parameters for patients within a given endpoint and treatment group (CRT-D or ICD). These probabilities were then used to conduct Bernoulli

trials to determine whether a subject had the covariate.[7] Statistical analyses were performed using SAS statistical software (Version 9.3, Cary, NC) and STATA (Version 11, College Station, TX). All reported 95% confidence intervals and p-values are two-sided.

RESULTS

After propensity score matching the cohort consisted of 54,218 CRT-D and 20,763 ICD patients with LBBB and 7,298 CRT-D and 7,298 ICD patients with RBBB. There were no significant differences between CRT-D and ICD treatment groups in LBBB or RBBB indicating that they were properly balanced (Table 1). However, there were some differences between the matched LBBB and RBBB populations. RBBB patients more often were men, had diabetes, previous myocardial infarction, ischemic cardiomyopathy, atrial fibrillation, peripheral vascular disease, ventricular tachycardia, a higher Charlson score and a higher PTCA/CABG procedure rate compared to LBBB patients. Follow-up data were available for a median of 32 months in LBBB and 24 months in RBBB.

Heart Failure Hospitalization or Death in Propensity Score Matched Patients

The rate of heart failure hospitalization or death was lower in LBBB patients compared to RBBB patients (51.2% vs. 58.6%). In LBBB, unadjusted heart failure hospitalization or death was lower for CRT-D than ICD (50.1% vs. 54.0%) while this relation was reversed in patients with RBBB (60.8% vs. 56.4%) (Figure 1A).

Multivariable adjusted Cox proportional hazards models were determined separately in patients with LBBB and RBBB. In LBBB, CRT-D patients had a 12% lower risk for heart failure hospitalization or death (hazard ratio [HR]=0.88, 95% confidence interval [CI] 0.86-0.90) compared to ICD, while in RBBB, CRT-D patients had a 15% higher risk (HR=1.15 [1.10-1.20]) than ICD patients. The full multivariable adjusted models can be found in the online appendix (Online Tables 3 and 4 for LBBB and RBBB respectively).

Mortality in Propensity Score Matched Patients

Similar results as for the combined endpoint of heart failure hospitalization or death were observed for the endpoint of all-cause mortality. After a maximum follow-up of 48 months, 32,317 patients (36.1% of the combined LBBB and RBBB matched populations) had died and all-cause mortality was lower in LBBB patients compared to RBBB patients (34.9% vs. 42.3%). In LBBB, the unadjusted mortality rate was lower in CRT-D than in ICD patients (40.3% vs. 44.2%), while in RBBB this was reversed demonstrating a higher mortality rate in CRT-D than in ICD patients (35.8% vs. 34.5%) (Figure 1B).

Multivariable adjusted models showed that in LBBB, CRT-D patients had a 5% lower risk of death than ICD patients (HR=0.95 [0.92-0.97]), while in RBBB, CRT-D patients had a 13% higher death risk (HR=1.13 [1.07-1.18]) compared to ICD patients. The full multivariable adjusted models can be found in the online appendix (Online Tables 5 and 6 for LBBB and RBBB respectively).

Table 1. Baseline Characteristics of LBBB and RBBB Patients After Propensity Score Matching

	Matched Left Bundle Branch Block					Matched Right Bundle Branch Block				
	CRT-D		ICD		SMD	CRT-D		ICD		SMD
	N	%	N	%		N	%	N	%	
	54,218		**20,763**			**7,298**		**7,298**		
Gender										
Male	36,357	67%	13,877	67%	0.01	6,218	85%	6,217	85%	0.00
Age										
0-64	5,625	10%	2,181	11%	0.00	758	10%	771	11%	0.01
65-69	8,625	16%	3,348	16%	0.01	1,123	15%	1,129	16%	0.00
70-74	12,319	23%	4,733	23%	0.00	1,634	22%	1,628	22%	0.00
75-79	13,915	26%	5,259	25%	0.01	1,901	26%	1,872	26%	0.01
80-84	10,065	19%	3,846	19%	0.00	1,401	19%	1,436	20%	0.01
85+	3,669	7%	1,393	7%	0.00	481	7%	462	6%	0.01
Race										
Black	4,418	8%	1,755	9%	0.01	591	8%	594	8%	0.00
Other	1,616	3%	620	3%	0.00	250	3%	246	3%	0.00
White	48,184	89%	18,386	89%	0.01	6,457	89%	6,458	89%	0.00
Charlson Score										
Charlson Score 0	639	1%	212	1%	0.02	70	1%	63	1%	0.00
Charlson Score 1	5,931	11%	2,306	11%	0.01	537	7%	517	7%	0.01
Charlson Score 2	9,649	18%	3,756	18%	0.01	1,044	14%	1,025	14%	0.01
Charlson Score 3	10,625	20%	4,027	19%	0.01	1,397	19%	1,410	19%	0.00
Charlson Score 4+	27,374	51%	10,461	50%	0.00	4,250	58%	4,283	59%	0.01
Health Conditions										
Diabetes	25,482	47%	9,745	47%	0.00	3,776	52%	3,791	52%	0.00
Mitral/Aortic Valve Disorder	31,642	58%	12,047	58%	0.01	4,217	58%	4,181	57%	0.01
Hypertension	47,407	87%	18,144	87%	0.00	6,540	90%	6,523	89%	0.01
Myocardial Infarction	21,299	39%	8,171	39%	0.00	3,871	53%	3,875	53%	0.00
Ischemic Heart Disease	32,445	60%	12,449	60%	0.00	4,979	68%	4,962	68%	0.00
Tricuspid/Pulmonary Valve Disorder	8,734	16%	3,408	16%	0.01	1,273	17%	1,273	17%	0.00
Atrial Fibrillation	24,630	45%	9,299	45%	0.01	3,691	51%	3,664	50%	0.01
Prior Heart Failure Hospitalization	15,826	29%	6,024	29%	0.00	2,013	28%	1,934	27%	0.02
Prior Stroke	2,724	5%	1,063	5%	0.00	462	6%	462	6%	0.00
Peripheral Vascular disease	11,965	22%	4,652	22%	0.01	2,000	27%	2,000	27%	0.00
Ventricular Tachycardia	19,236	36%	7,348	35%	0.00	3,310	45%	3,283	45%	0.01
PTCA	1,888	4%	686	3%	0.01	416	6%	411	6%	0.00
CABG	5,047	9%	1,921	9%	0.00	971	13%	975	13%	0.00

CRT-D = Cardiac resynchronization therapy defibrillator; ICD = Implantable cardioverter defibrillator; SMD = Standard mean difference; PTCA = Percutaneous transluminal coronary angioplasty; CABG = Coronary artery bypass graft; Ventricular tachycardia includes non-sustained ventricular tachycardia

Figure 1A.

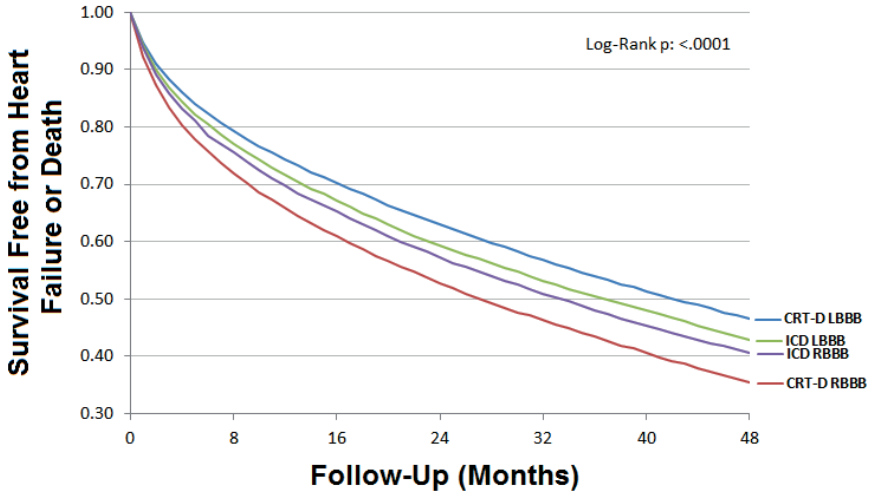

Figure 1B.

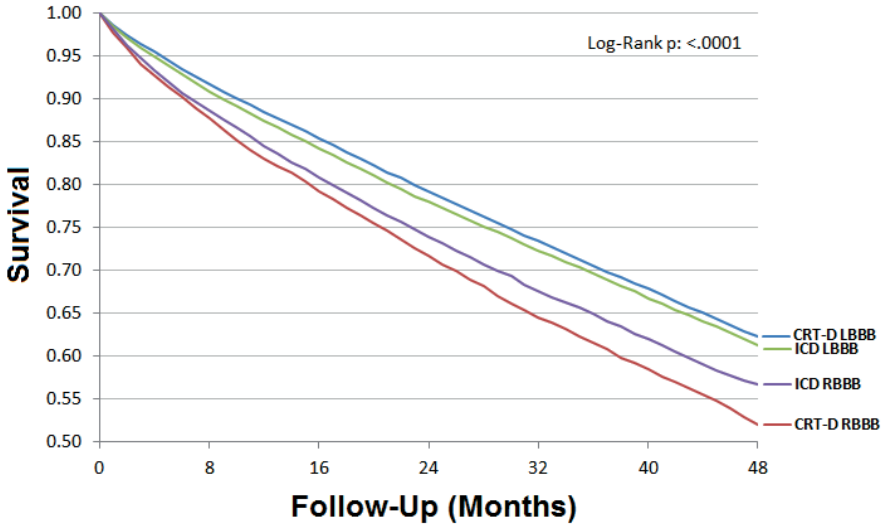

Figure 1. A. Kaplan-Meier graphs of freedom from heart failure hospitalization or death in propensity score matched LBBB and RBBB patients. **B**. Kaplan-Meier graphs of survival in propensity score matched LBBB and RBBB patients.

Sensitivity Analysis

Sensitivity analyses introducing an unobserved covariate into the already matched LBBB and RBBB populations were conducted to evaluate the potential influence of unmeasured confounders. First, the prevalence of the already included covariates was determined (Online Table 7A and B for LBBB and RBBB respectively). Prior heart failure hospitalization had a higher prevalence in CRT-D patients compared to ICD patients; therefore, it would have a chance of changing the results if not already included. Since prior heart failure hospitalization had an overall prevalence of approximately 30% and covariates have a higher impact on model results when their prevalence is higher, we chose an overall prevalence of 40% (=0.40) for our unobserved covariate.

As an example Figure 2 shows that for the outcome of heart failure hospitalization or death in RBBB, the treatment effect significantly reversed (CRT-D associated with a lower risk of outcome) when the relative risk for heart failure hospitalization or death of the introduced covariate was at least 1.8 with a treatment distribution of at least 1.7. For LBBB, Online Figure 1 shows a similar hazard ratio graph for the whole spectrum of relative risks and treatment distributions while Online Figures 2 and 3 show hazard ratios and 95% confidence intervals for respectively LBBB and RBBB (also for other prevalence numbers). Sensitivity analysis for the endpoint of death alone showed similar trends as for the endpoint of heart failure hospitalization or death (Online Figures 4-7). The figures include areas where there was no significant difference between CRT-D and ICD treatment groups. Increasing the prevalence of the covariate in the total population had no major effect on the results of sensitivity analyses.

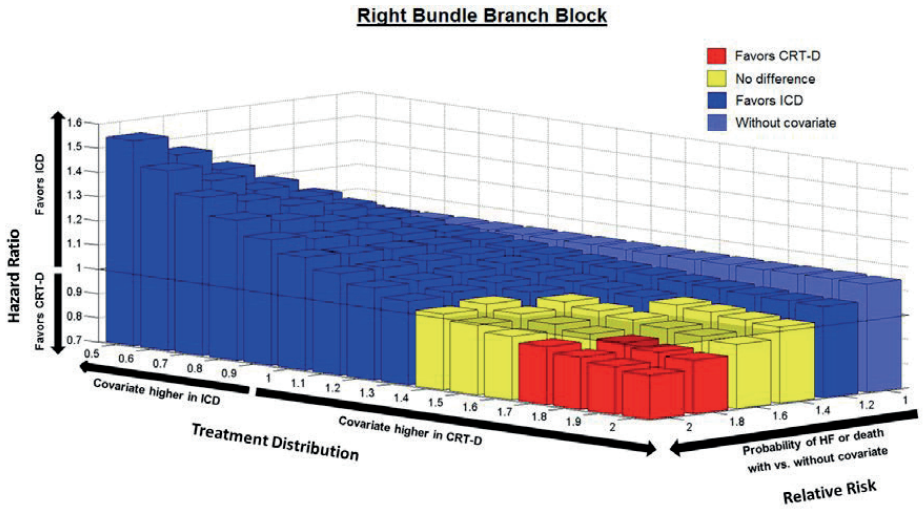

Figure 2. Adjusted hazard ratios for heart failure hospitalization or death (bar height) for an introduced covariate with a prevalence of 40% in RBBB, divided by treatment distribution (horizontal axis, range 0.5-2 – illustrates the effect of various distributions of the covariate within both treatment groups) and relative risk of heart failure or death (depth axis, range 1-2 – illustrates the effect of increasing probability of heart failure hospitalization or death due to the covariate). Plane indicates no difference between CRT-D and ICD (HR=1).

DISCUSSION

This study included a large number of real-world Medicare beneficiaries receiving CRT-D and ICD devices. The findings suggest that in propensity score matched cohorts CRT-D (compared to ICD) is associated with a 12% lower risk of heart failure hospitalization or death and 5% lower mortality in LBBB patients, while in RBBB patients there is a 15% higher risk of heart failure hospitalization or death and 13% higher mortality. Sensitivity analysis further suggests that accounting for unmeasured confounders might lead to increased benefit with CRT-D in LBBB and no difference between CRT-D and ICD in RBBB. These findings are valuable as current professional society guidelines for CRT include a Class IIa or IIb recommendation for patients without LBBB indicating that the benefit of CRT outweighs the risks in this group.[4] The indications for non-LBBB patients were primarily derived from clinical trials that included a narrowly selected patient population and only included a small number of non-LBBB patients.[4] The present study, however, assessed the comparative effectiveness of CRT-D vs. ICD in a large real-world RBBB population.

That CRT can be harmful was recently shown in the EchoCRT trial which enrolled patients with systolic heart failure (ejection fraction ≤35%) and a QRS duration <130 ms. In that population CRT did not reduce the rate of death or hospitalization for heart failure and actually increased mortality (HR=1.81 [1.11-2.93]).[8] For CRT in non-LBBB patients, recent meta-analysis,[9] substudies of clinical trials[10-12] and single-center studies[13-15] have shown mixed results. However, these analyses were underpowered to evaluate the effect of CRT in solely RBBB due to the limited number of RBBB patients that were included. While the results of the current analysis confirm previous findings by Bilchick et al. in a Medicare CRT-D only population,[13] to the best of our knowledge the present study is the first to evaluate the effect of CRT-D compared to ICD alone in a large real-world RBBB population.

In the present analysis, we observed important baseline differences between the LBBB and RBBB populations. RBBB patients were more often of male sex, more frequently had diabetes, myocardial infarction and ischemic cardiomyopathy, atrial fibrillation, peripheral vascular disease, a higher Charlson score, more ventricular tachycardia and higher rates of PTCA and CABG procedures. This indicates that RBBB patients are generally sicker than LBBB patients and that RBBB patients more often have comorbidities associated with a worse response to CRT. These factors primarily include ischemic cardiomyopathy and atrial fibrillation.[16] A previous study demonstrated that in patients eligible for ICD implantation, ischemic cardiomyopathy was associated with a higher scar burden and that RBBB patients had significantly larger scar size than LBBB patients.[17] The large myocardial scar may be one explanation of why RBBB patients have worse outcomes with CRT-D. Also, RBBB patients were more often men and they have been shown to have a worse response to CRT than women.[18-21] The fact that RBBB patients might be sicker is also supported by the fact that in the current study mortality in RBBB ICD patients was higher than in LBBB ICD patients (40.3% vs. 35.8%). However, after multivariable adjustment for all these factors in the matched populations, CRT-D was still associated with worse outcomes in RBBB, suggesting that CRT may have adverse effects in RBBB patients.

Monitoring the Safety and Effectiveness of Medical Devices using Claims Data

The current study used Medicare claims data to assess the effectiveness of CRT-D therapy. The advantage of using this data source is the ability to assess real-world performance in a large patient population. However, the unavailability of some covariates,

in particular NYHA heart failure class, QRS duration, and ejection fraction in this analysis, is a factor that limits the use of such data for CRT-D effectiveness assessment. One way to account for this is to evaluate whether other unobserved covariates might influence the results of claims data analysis by performing a sensitivity analysis simulating outcomes after the introduction of such an unobserved covariate, as was done in this study.

In the present analysis of LBBB patients, there was a 5% lower mortality risk with CRT-D and this is less than has been observed in clinical trials. However, sensitivity analysis demonstrated that when introducing an unobserved covariate, in this case for example NYHA heart failure Class, the benefit of CRT-D in patients with LBBB may increase and there may be no difference between CRT-D and ICD in RBBB. Based on the analysis by Bilchick et al., CRT-D patients more likely had NYHA Class III/IV heart failure symptoms and they had an approximately 1.6 fold increase in mortality compared to patients with Class I/II symptoms.[13] Based on a different analysis by Hammill et al., ICD-patients were less likely to have Class III/IV heart failure.[22] For our sensitivity analysis, this resulted in an approximately 1.7 fold higher proportion of NYHA Class III/IV in CRT-D patients compared to ICD patients (calculated treatment distribution of 1.7). With a pre-specified prevalence of 40%, a 1.6 relative risk of death and a treatment distribution of 1.7, there was a 15% lower mortality risk in LBBB (HR=0.85 [0.83-0.88]) and no difference between CRT-D and ICD in RBBB (HR=1.00 [0.95-1.05]) (Online Figures 4 and 5). Another explanation of why there only is a 5% lower mortality risk in LBBB patients may be that the current study cohort included a more diverse, older (>65 years) and sicker patient population compared to clinical trials and thus the effect of CRT-D is expected to be worse.

This study had certain limitations. The determination of CRT-D or ICD implantation, baseline characteristics and endpoints in this study relied on ICD-9 codes and Medicare billing data. It is possible that errors in entry or coding may have resulted in the misdiagnosis of baseline characteristics. However, previous work has shown that adjudication of Medicare claims resulted in a change in less than 3% of claims.[23] Additionally, it is possible that the CRT-D and ICD implants included in this analysis were not a patients' first device implant. This was minimized by cleaning the cohort for additional device maintenance codes. The 12-month look back period did not allow for the assessment of the presence of other comorbidities than those observed in the 12 months before the implantation date. Furthermore, although a large number of variables were available for propensity score estimation, we were not able to assess the effect of QRS duration, NYHA class or ejection fraction other than through simulations of sensitivity analysis due to the absence of this data in the Medicare database. Sensitivity analysis revealed that it is possible that the results could change if additional unobserved covariates were measured.

Conclusions

The results of this study demonstrated that, in a large Medicare population of real-world CRT-D and ICD recipients, CRT-D was associated with a lower risk of heart failure hospitalization or death and lower mortality in patients with LBBB, but higher risk of heart failure hospitalization or death and higher mortality in RBBB patients. Accounting for NYHA heart failure class, QRS duration or ejection fraction, which are not captured in the Medicare database and not adjusted for by propensity scores, may result in no risk difference in RBBB.

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Disclosures
None.

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CHAPTER VI
Discussion

INTRODUCTION

Although cardiac resynchronization therapy (CRT) can be a very effective treatment for patients with heart failure and reduced pump function,[1-5] not every patient that had a CRT device implanted benefits. However, patients are still subjected to potential complications (e.g. infection, lead dislodgement). Furthermore, there is a significant cost associated with implantation and the treatment of any of these complications. It is therefore imperative to select those patients that are most likely to benefit while minimizing potential risks and complications. The general aim of this thesis was to explore which patients are most likely to benefit from CRT by evaluating how different ventricular conduction disorders, the sex-differences in these ventricular conduction disorders and other (sex-specific) factors influence response. In this chapter, the overall results of this thesis, a comparison to existing literature and the broader perspective of the findings will be discussed.

CURRENT PROFESSIONAL SOCIETY GUIDELINES FOR CRT

Current professional society guidelines for CRT implantation are not very different between continents. In general, guidelines reserve a Class I indication (highest recommendation) for patients in sinus rhythm, left ventricular ejection fraction (LVEF) ≤35%, left bundle branch block (LBBB) and QRS duration ≥150 milliseconds (ms).[6,7] Contrary to the American College of Cardiology (ACC) Foundation/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines,[6] the European Society of Cardiology (ESC) guidelines also give patients with the same characteristics but a QRS duration between 120 and 150 ms the highest recommendation for CRT.[7] Patients without LBBB receive a Class IIa or IIb indication, meaning that CRT respectively should be considered or may be considered, depending on New York Heart Association (NYHA) heart failure symptoms Class and QRS duration (Figure 1). In general, the U.S. guidelines are more conservative than the European guidelines.

NYHA Class	ACC/AHA/HRS	ESC	ACC/AHA/HRS	ESC	ACC/AHA/HRS	ESC
I					LVEF ≤30% QRS ≥150 ms LBBB Ischemic cardiomyopathy	
II	LVEF ≤35% QRS ≥150 ms LBBB Sinus rhythm	LVEF ≤35% QRS 120-150 and >150 ms LBBB	LVEF ≤35% QRS 120-149 ms LBBB Sinus rhythm	LVEF ≤35% QRS >150 ms non-LBBB	LVEF ≤35% QRS ≥150 ms non-LBBB Sinus rhythm	LVEF ≤35% QRS 120-150 ms non-LBBB
III / ambulatory IV	LVEF ≤35% QRS ≥150 ms LBBB Sinus rhythm	LVEF ≤35% QRS >150 ms LBBB	LVEF ≤35% QRS 120-149 ms LBBB Sinus rhythm	LVEF ≤35% QRS >150 ms non-LBBB	LVEF ≤35% QRS 120-149 ms non-LBBB Sinus rhythm	LVEF ≤35% QRS 120-150 ms non-LBBB

Figure 1. *U.S. and European professional society guidelines for CRT.[6,7] All patients are required to have heart failure and optimal medical treatment. Green indicates a Class I, yellow Class IIa and orange Class IIb recommendation for CRT. In all other cases CRT is not recommended. Indications for CRT in patients with atrial fibrillation or those with a conventional pacemaker indication are not included in this figure. NYHA: New York Heart Association; ACC/AHA/HRS: American College of Cardiology/American Heart Association/Heart Rhythm Society; ESC: European Society of Cardiology; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block.*

QRS MORPHOLOGY AND QRS DURATION IN BENEFIT FROM CRT

Left Bundle Branch Block

The professional society guidelines for CRT are based on one or more randomized clinical trials or meta-analyses of clinical trials. However, women were underrepresented in clinical trials for CRT (making up only about 20% of enrollees) and, since the main results reflect outcomes in men, the guidelines therefore contain an information gap on the appropriate use of CRT in women. In chapter 2 it was shown that in patients with primarily NYHA Class II heart failure symptoms, women benefit significantly more from CRT-defibrillators (CRT-D) compared with standard implantable defibrillators (ICD) than men do. One of the reasons for this may be that women more often have a true left bundle branch block (LBBB) than men do at shorter QRS durations (e.g. <150 ms) because women also have shorter QRS durations in the absence of LBBB.

Multiple criteria for LBBB currently exist in both European[8] and U.S.[9] guidelines. Commonly, these conventional criteria include a QRS duration ≥120 ms with a negative QRS complex in V1 and the absence of q-waves in lateral ECG leads. However, previous studies have shown that approximately one-third of patients diagnosed with LBBB by the conventional criteria do not have activation consistent with a true, complete LBBB.[10-13] Only with a complete LBBB, in which there is about a 100 ms delay between electrical activation of the interventricular septum and the left ventricular (LV) free wall resulting in an uncoupling between both walls, there will be a dyssynchrony more amenable to CRT treatment (Figure 2).

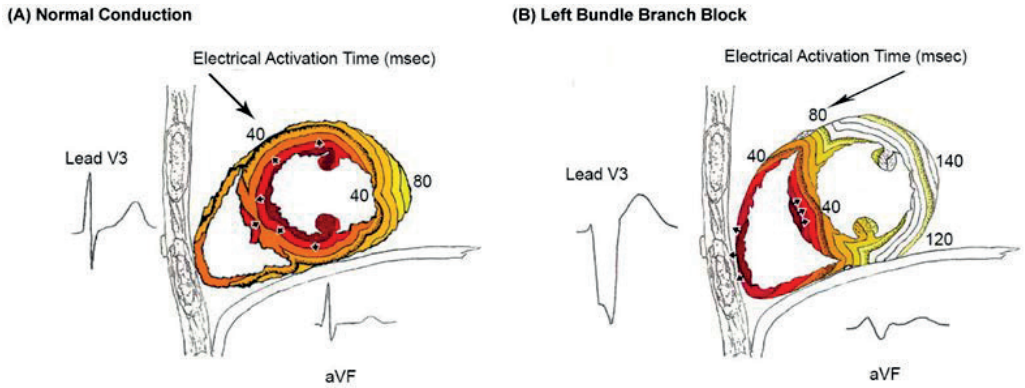

Figure 2. *Saggital view of ventricles in normal conduction (A) and left bundle branch block (B). Activation starts at the small arrows and spreads in a wavefront with each line representing 10 ms. The delay between activation of the interventricular septum and LV free wall is only about 40 ms in normal conduction, but about 100 ms in LBBB. Reproduced with permission from Strauss et al.*[13]

Women have smaller ventricles and an approximately 5 ms shorter QRS duration than men in the absence of cardiac conduction disease.[14] With a true LBBB however, this difference between women and men approximately doubles to 10 ms. Based on this difference between sexes, new strict criteria for LBBB were proposed that require a QRS duration ≥130 ms in women and ≥140 ms in men along with mid-QRS notching and/or slurring in two contiguous ECG leads I, aVL, V1, V2, V5 or V6.[13] The strict LBBB criteria were not only shown to correlate well with mechanical dyssynchrony on echocardiography[15] and

magnetic resonance imaging (MRI)[16] but it was also demonstrated in prior single-center studies that patients not meeting the strict criteria for LBBB had a 4-fold higher rate of heart failure hospitalization or death and did not respond to CRT-D compared with patients who met the strict LBBB criteria.[17,18] Furthermore, a simulation study revealed that mid-QRS notching is necessary to distinguish LV hypertrophy, LV dilation, incomplete LBBB or a combination of these, which can all be diagnosed as LBBB by the conventional criteria, from a truly complete LBBB.[19] It is reasonable to believe that patients with these kinds of conduction disorders, not meeting strict LBBB criteria, will lack a CRT response. In chapter 2 it was demonstrated that women had a 76% lower risk for heart failure hospitalization or death and a 76% lower risk for death alone with CRT-D (compared to ICD) when they had a conventional LBBB and QRS duration of 130-149 ms. Men in this category derived no benefit at all. Both women and men derived a significant and comparable benefit from CRT-D with conventional LBBB and QRS duration ≥150 ms while no patients, regardless of sex, benefited with conventional LBBB and QRS duration of 120-130 ms. The research presented in chapter 2 of this thesis further supports the use of sex-specific criteria for the diagnosis of LBBB.

Cardiac Resynchronization Therapy in the Daily Clinical Setting

Contrary to the analysis in chapter 2, in which only clinical trial patients were included, the study in chapter 3 included a large real-world population of CRT-D recipients with NYHA Class III heart failure symptoms. It was demonstrated that in these CRT-D patients mortality was highest in those with a QRS duration of 120-129 ms. The mortality was slightly lower in patients with a QRS duration of 130-139 ms and decreased further in those with QRS duration of 140-149 ms. However, in all CRT-D patients, the lower mortality was relatively consistent and plateaued in those with a QRS duration ≥150 ms (Figure 3). This 150 ms threshold for CRT use has been mentioned in earlier studies[20,21] and was the main reason behind the Class I recommendation in professional society guidelines.[6,7] However, in chapter 3 we also demonstrated that LBBB was the main discriminator of a positive CRT response. It is likely that a longer QRS duration in general indicates more LV dyssynchrony and may therefore also more often indicate a true LBBB. We observed that women with LBBB had a 24% lower mortality risk with CRT-D compared to men with LBBB and CRT-D. This may be explained by the differences mentioned earlier in the presence of LBBB in women at a shorter QRS duration than in men. Figure 3 shows that women had a relatively consistent lower mortality with LBBB and QRS duration ≥140 ms while this was ≥150 ms in men.

In chapter 4, a direct comparison between real-world CRT-D and ICD patients, also with primarily NYHA Class III heart failure, was performed. Here, we observed similar results as in chapters 2 and 3; LBBB was the main discriminator for response and women with LBBB had a better response than men with LBBB. In women with CRT-D, there was a 26% lower relative risk with CRT-D compared with ICD, while this difference was 16% in men. However, contrary to the findings in chapter 2 and 3, both sexes had a lower mortality with LBBB and QRS duration ≥130 ms with no clear differences between women and men across QRS duration groups. Chapter 5 was aimed at a similar comparison of CRT effect and found that in a large real-world population CRT-D was associated with a lower mortality in patients with LBBB.

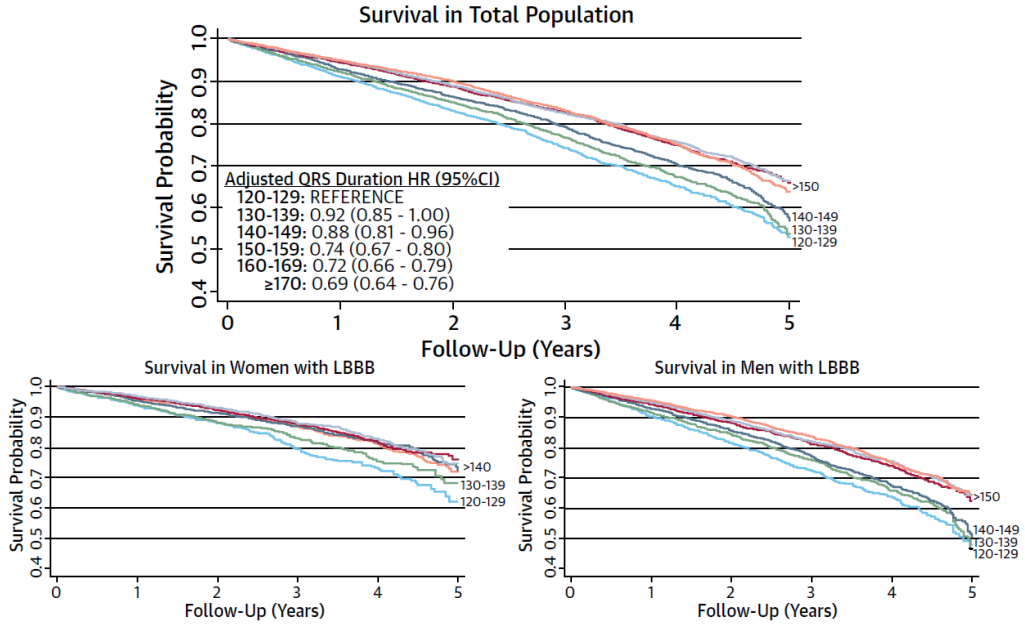

Figure 3. *Survival probability of CRT-D in 10 ms QRS duration groups in the total population (top), LBBB women (bottom left) and LBBB men (bottom right). Multivariable hazard ratios are reported. CI: confidence interval; HR: hazard ratio.*

Cardiac Resynchronization Therapy, Left Bundle Branch Block, and NYHA Class

While in the chapter 2 study primarily patients with NYHA Class II heart failure symptoms were included, patients in the studies included in chapters 3-5 mainly had NYHA Class III heart failure. Although NYHA Class can be a subjective measure of heart failure severity, based on the results from these different chapters it does seem to influence CRT response. This was demonstrated by a greater mortality benefit in patients with a LBBB in chapter 2 compared to the patients with a LBBB in chapters 3-5. Furthermore, we observed that QRS duration in conventionally defined LBBB is an important predictor of CRT benefit in both NYHA Class II and III, with a larger difference between women and men in Class II versus Class III. However, it is also reasonable to expect that patients included in clinical trials (chapter 2 – NYHA Class II) do better than those who receive CRT-D therapy in a daily clinical setting (chapter 3-5 – NYHA Class III). In general we can conclude that not only patients with LBBB and QRS duration ≥150 ms respond to CRT, but also a significant number of patients with a LBBB and QRS of 130-150 ms.

There have been multiple studies that evaluated CRT benefit in the presence of LBBB, mostly in patients with NYHA Class III heart failure. The most influential ones have been meta-analyses of clinical trials and large registry studies. Sipahi et al. demonstrated that only patients with a LBBB benefit from CRT[22] while a second analysis showed that patients in general benefited from CRT with a QRS duration ≥150 ms,[20] possibly explained by the higher incidence of LBBB in the patients with QRS ≥150 ms. In a large registry study by Peterson et al.[23] and another by Masoudi et al.[24] it was shown that patients with LBBB and QRS ≥150 ms generally respond better to CRT-D in terms of mortality and hospital readmission for heart failure compared to patients with a LBBB and QRS <150 ms, or those

with only QRS <150 ms (without mention of LBBB). Cleland et al., however, found that in their meta-analysis patients benefited with a QRS ≥140 ms regardless of the presence of LBBB.[25] Even though most of these analyses have indicated that LBBB is an important predictor for CRT response, only a few studies have been conducted that actually assessed potential sex-differences in benefit from CRT with the presence of LBBB or shorter vs. longer QRS duration (most of these studies have only assessed the general difference in CRT effect between both sexes). The meta-analysis by Cleland et al. found that neither sex nor its interaction with LBBB were additional predictors to QRS duration in benefit from CRT.[25] Two MADIT-CRT subanalyses showed that overall women, but not men, benefited from CRT-D at a QRS duration <150 ms[26,27] while the recently published long-term extended follow-up of MADIT-CRT found that mortality with CRT-D in patients with LBBB was not dependent on QRS duration and did not differ by sex.[28] However, this analysis may have been underpowered because only a limited number of patients participated in the extended follow-up study.

Non-Left Bundle Branch Block

Patients without a LBBB were underrepresented in clinical trials for CRT. It is likely that in patients without a true LBBB the electrical activation of the left ventricle through the His-Purkinje system is normal and that there will not be a conduction delay between the septum and the LV free wall, regardless of patient sex. In this case, CRT pacing of the epicardial LV free wall will overdrive the normal activation through the His-Purkinje system of the LV and may therefore result in an inefficient pattern of activation and pump function or may even cause harm. This should be distinguished from a fascicular block which may also cause a delay in LV activation but only by approximately 20 ms as opposed to 100 ms with a true LBBB.

The study presented in chapter 2 demonstrated that there was no difference between CRT-D and ICD in terms of heart failure hospitalization or death and death alone in the patients with non-LBBB, in neither women nor men with NYHA Class II heart failure. Chapter 3 also demonstrated that, among patients with primarily NYHA Class III, there were no sex-differences with CRT-D in non-LBBB. In addition, there was no relationship between QRS duration and mortality in female or male patients without LBBB (Figure 4). In chapter 4, in which a direct comparison between real-world CRT-D and ICD recipients was performed among patients with NYHA Class III heart failure, we were able to evaluate the effect of CRT-D on mortality in patients with right bundle branch block (RBBB) and non-specific intraventricular conduction delay (IVCD) separately.

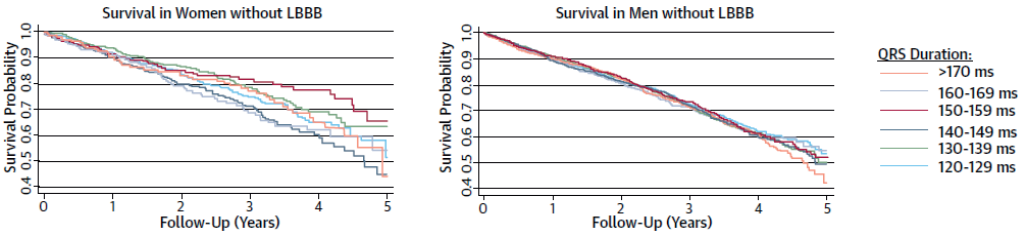

Figure 4. *Survival probability of CRT-D in 10 ms QRS duration groups in non-LBBB women (left) and non-LBBB men (right).*

Even though there was a slightly lower mortality with CRT-D for both women and men within the total non-LBBB group in chapter 4, both women and men with a RBBB did not benefit from CRT-D and in chapter 5 it was found that the mortality among the patients with a CRT-D was actually higher than in those with a standard ICD, indicating that CRT-D therapy in RBBB may even be harmful. However, in the chapter 5 analysis some important cardiac covariates were missing (e.g. QRS duration, ejection fraction, NYHA Class) and sensitivity analysis introducing an unobserved covariate (e.g. NYHA Class) demonstrated that there may be no difference in heart failure hospitalizations or mortality between CRT-D and ICD in RBBB. With regard to patients with an IVCD, the results are much less clear. It was demonstrated in chapter 4 that men with an IVCD (QRS ≥120 ms but not LBBB or RBBB) did not do better with a CRT-D compared with an ICD while women only had a slightly lower mortality with CRT-D in IVCD. Overall, from these four studies we can conclude that there can be some patients with non-LBBB that may do slightly better with CRT, but that patients with solely a RBBB do not benefit from CRT regardless of sex, QRS duration or NYHA Class. This is important because patients are still subjected to potential complications and to higher costs associated with a CRT-D implantation while an ICD alone would seem preferable. Also, the professional society guidelines include an indication for patients with a general non-LBBB but there is no specification of RBBB or IVCD.[6,7]

Prior sub-analyses of CRT trials and smaller single or multi-center studies have shown mixed results in patients without LBBB, and there have not been any studies thoroughly considering the potential sex-differences among them. A sub-analysis of the MADIT-CRT trial showed that patients with non-LBBB, RBBB and IVCD did not derive any additional benefit with CRT-D as compared to ICD alone.[27] The REVERSE and RAFT trials showed similar results.[29,30] A meta-analysis of 4 CRT trials by Sipahi et al. (including MADIT-CRT, RAFT, COMPANION and CARE-HF) also demonstrated no benefit from CRT (versus ICD or optimal medical therapy alone) in the patients with non-LBBB morphology[22] which was again confirmed in a large registry study by Masoudi et al.[24] Bilchick et al. actually found a higher mortality in CRT-D patients with RBBB.[31] Only in the smaller single-center study by Rickard et al., about half of patients with non-LBBB responded to CRT in terms of echocardiographic outcome (LVESV reduction ≥10%),[32] while another small study by Marek et al. showed that in 151 CRT patients, LV lead placement in the area of latest activation in non-LBBB was associated with similar outcomes as in those with a conventionally defined LBBB.[33] Furthermore, Strauss et al. have shown that patients with RBBB have a larger amount of scar in their LV (associated with ischemic cardiomyopathy) than those with a LBBB,[34] adding another explanation of CRT non-response in RBBB. Finally, a small beneficial effect of CRT treatment was observed for non-LBBB patients with extremely long PR intervals at baseline in MADIT-CRT indicating a potential role for AV delay optimization.[35]

Overall, these different studies demonstrate that benefit from CRT is uncommon in patients without a LBBB (and especially those with solely RBBB) likely caused by the fact that these patients do not have clear LV dyssynchrony. However, optimizing the AV-interval and LV lead placement while assessing scar size can potentially help some patients with non-LBBB that do have some sort of dyssynchrony, for example patients with a RBBB+LAFB. This may also occur in the setting of large anteroseptal infarcts,[34] which has been shown to predict poor response to CRT.[36-39]

OTHER (SEX-SPECIFIC) FACTORS INFLUENCING CRT RESPONSE

Even though QRS morphology and QRS duration are important in the selection of patients for CRT, other factors (additionally) determine CRT response. Previous studies showed that atrial fibrillation significantly reduces response to CRT[40] and atrial fibrillation is more common in men than in women. The reduced response is likely due to the irregular ventricular activation as biventricular pacing in atrial fibrillation with His bundle ablation was found to be effective.[41] In addition, the presence of scar in the LV was shown to be associated with a worse CRT response, especially if it was located in the area of LV lead placement.[42] Not only did patients with RBBB have more scar than those with LBBB,[34] but also men generally had more scar than women.[42] Finally, LV lead position should likely be tailored with regards to the native LV electrical activation pattern with the latest activated area as its ideal location.

Adjustment for atrial fibrillation (in chapters 2, 4 and 5) and ischemic cardiomyopathy (in chapters 2-5) in multivariable statistical models was not able to explain the difference in CRT response between women and men or between the different QRS morphologies, indicating that QRS morphology by itself is important for the selection of patients receiving CRT. Of note, in addition to QRS morphology and QRS duration, other important factors for improving benefit from CRT include the appropriate treatment for atrial fibrillation,[41] assessment of scar in ischemic cardiomyopathy[36-39] and determination of LV lead position.[39]

USE OF REGULATORY, REGISTRY AND CLAIMS DATA IN SEX-SPECIFIC ANALYSIS

The studies in this thesis have used different data sources, from clinical trial data needed for the approval of CRT devices by the Food and Drug Administration (FDA) to daily clinical setting national registry and claims data. The differences between these sources are evident from the results in this thesis, and one data source may be more limited than the other (e.g. claims data). Subjects enrolled in clinical trials are part of a narrowly selected patient population who are expected to do better than those who receive CRT based on broader criteria used in a daily clinical setting. However, using both these data sources is important for the detection of potential sex-differences in safety and/or efficacy of medical products. Patients will be able to benefit more if clinical trial and registry data can be put to broader use.

As mentioned before, only 20% of enrollees in CRT trials were women, and thus the results primarily reflect outcomes in men. Also, the professional society guidelines for CRT generally limit the highest indication for CRT to those patients with LBBB and QRS duration ≥150 ms irrespective of sex. However, in chapters 2-4 we concluded that the benefit from CRT was greater in women than in men and that both sexes can benefit when their QRS duration is less than 150 ms. This is one example of sex-differences in medical therapy efficacy, but there are more. Women have a higher prevalence of heart failure with preserved ejection fraction and a greater sensitivity to QT-prolonging medications than men, while there are also cardiac diseases that almost only occur in women (e.g. Tako-Tsubo).[43,44] However, there does not seem to be any sex-specific therapy for any of these conditions. A cause may be the lack of data for women, which should be considered a serious knowledge gap. This not only calls for a higher enrollment rate of women in CRT

trials and cardiovascular trials, but also for clinical trials in general. Potential reasons why women are not enrolled in clinical trials may include the lack of understanding about sex-differences in disease etiology or pathophysiology, potential side-effects to the fetus, family responsibilities or unintentional exclusion of women due to clinical trial inclusion and exclusion criteria.[45] Furthermore, research studies should report sex-specific outcomes if possible, even when this was not a primary objective of the analysis. Only in this way can potential sex-differences be detected, can we increase awareness of these differences and encourage enrollment of women, and can we move to truly personalized medicine.

FUTURE PERSPECTIVES

CRT is a very effective treatment for many heart failure patients with systolic dysfunction. However, a standardized approach applied to all potential candidates may not be desirable as it is uncertain that patients will derive benefit from CRT treatment. QRS morphology has been the most powerful predictor for benefit so far and should always be assessed before one even starts thinking about CRT. Especially LBBB has become more important as in the patient with a LBBB benefit seems much greater. However, there are too many different definitions for LBBB and efforts should be made to improve the ECG LBBB criteria, possibly by comparing these to a gold standard (which does not exist right now). The criteria by Strauss et al.[13] are a step in the right direction to achieve this goal. Furthermore, given the differences in CRT safety and efficacy between women and men, these differences should be highlighted and more often reported in all research studies (not only for CRT) because anatomy and physiology can differ between sexes. Daily clinical assessments should take a patients' sex into account while at the same time the professional society guidelines for CRT could be improved by including definitions for LBBB, sex-specific indications for CRT, and a more detailed description of non-LBBB. Clinical trials, which are the basis of guidelines and are considered the gold standard, should include a representative patient population (e.g. consistent with disease prevalence) so that more information can be gained and patients can be treated better and on a more individual level. In addition, clinicians implanting CRT devices or those determining the indications for CRT still have to take into account other characteristics such as the amount and the location of scar, the presence of atrial fibrillation or other factors that may result in a lower percentage of biventricular pacing in CRT, and LV lead position. Lastly, the value of CRT in patients with non-typical conduction disorders, such as RBBB+LAFB, and that of other forms of resynchronization, such as endocardial pacing, needs to be determined. Overall, there is a need for an integrated approach to these complex patients which includes a team of general cardiologists, cardiac electrophysiologists and experts in cardiac imaging.

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CHAPTER VII
Conclusions and summary

CONCLUSIONS AND SUMMARY

CRT is a very effective therapy for patients with heart failure and systolic dysfunction. It can improve quality of life while reducing mortality and heart failure hospitalizations. However, benefit from CRT is not universal and patients are subjected to potential serious complications and costs associated with the procedure. It is therefore imperative to select those patients that are most likely to benefit while minimizing risks. The studies in this thesis demonstrate that CRT is especially effective in patients with a LBBB. However, we found that women benefit significantly more than men and that this difference between sexes increases with the presence of LBBB. Furthermore, patients can benefit from CRT with LBBB and QRS durations shorter than 150 ms (more specifically 130-150 ms). The presence of a true LBBB seems to be the most important predictor of benefit and, because women have shorter QRS duration, this is likely more common in women than in men. Patients without LBBB generally do not respond well to CRT, while there was no benefit from CRT in RBBB, regardless of a patients' sex or QRS duration. The lower rate of atrial fibrillation and ischemic cardiomyopathy in women may contribute to a greater response to CRT as compared to men. Scar location, LV lead position and CRT device settings are other factors that may influence outcomes. Overall, this thesis provides evidence that in the decision to implant a CRT device a patients' sex, QRS morphology and QRS duration should be considered. Furthermore, this thesis highlights the importance of sex-specific analysis in clinical research studies and the importance of a higher enrollment of women in clinical trials.

SAMENVATTING (VOOR NIET-MEDICI)

Hartfalen is een chronische ziekte die vaak voorkomt. Deze ziekte wordt gekarakteriseerd door een verminderde pompfunctie en verwijding van de linker hartkamer (ventrikel). Dit leidt tot symptomen bestaande uit onder andere kortademigheid, vermoeidheid, opgezette ledematen en een verminderd vermogen tot het uitvoeren van dagelijkse activiteiten. Het sterftecijfer van hartfalen is hoog evenals de kosten die samenhangen met de behandeling ervan. Niet onbelangrijk: er sterven jaarlijks meer vrouwen dan mannen aan deze ziekte. De verwijding van de linker ventrikel bij hartfalen kan onder andere worden veroorzaakt door een abnormale elektrische impulsgeleiding in het hart, zoals bij een linkerbundeltakblok (LBTB). Bij LBTB is de snelle fysiologische impulsgeleiding in de linker ventrikel geblokkeerd die er normaal voor zorgt dat er een gelijktijdige samentrekking plaatsvindt van beide hartwanden (dyssynchronie) en het hart efficiënt kan pompen.

Cardiale resynchronisatietherapie (CRT) is een pacemakertherapie die als doel heeft het herstellen van de dyssynchrone contractie door correctie van de elektrische impulsgeleiding. Hiermee kan een betere pompfunctie van het hart worden bereikt en kan de verwijding van de linker ventrikel deels of volledig worden teruggedraaid. Helaas is CRT niet effectief bij alle patienten met hartfalen. Ongeveer een derde van de patiënten, die CRT ontvingen, ondervinden geen verbetering maar worden wel blootgesteld aan de mogelijke complicaties en geconfronteerd met kosten van deze procedure. Het is daarom van belang om patiënten te selecteren waarbij er enige zekerheid bestaat dat ze zullen verbeteren na de implantatie.

De resultaten, verzameld in dit proefschrift, laten zien dat CRT inderdaad een effectieve therapie is voor patiënten met hartfalen en een verminderde pompfunctie. Het proefschrift laat zien dat patiënten met een LBTB het meeste baat hebben. Vrouwen hebben meer profijt van CRT dan mannen. Dit verschil wordt alleen maar groter in de aanwezigheid van een LBTB (**HOOFDSTUK 2-4**). Echter, vrouwen krijgen deze therapie helaas minder vaak aangeboden dan mannen aangezien de klinische richtlijnen zijn gebaseerd op studies waarin niet genoeg vrouwen waren betrokken (**HOOFDSTUK 2**). Hierdoor bestaat er een tekort aan informatie over de veiligheid en effectiviteit voor deze patiënten. Tevens bestaan er meerdere criteria voor het diagnosticeren van LBTB waarbij is aangetoond dat ongeveer een derde van de gediagnosticeerde LBTB patiënten geen typisch elektrisch activatiepatroon vertoont behorende bij een LBTB. Vrouwen hebben een anatomisch kleiner hart dan mannen en hebben vanwege deze reden waarschijnlijk ook eerder een LBTB dan mannen. Waarschijnlijk hebben vrouwen daardoor ook meer baat bij CRT. Bij de patiënten met hartfalen zonder LBTB kan geen goede respons op CRT worden verwacht (**HOOFSTUK 2-4**). CRT bij patiënten met een rechterbundeltakblok (RBTB), waarbij de impulsgeleding in de rechter ventrikel is geblokkeerd, moet worden ontraden, ongeacht het geslacht van de patiënt (**HOOFDSTUK 4-5**). Andere factoren die een rol kunnen spelen bij de effectiviteit van CRT tussen vrouwen en mannen is de aanwezigheid van boezemfibrilleren en een eerder hartinfarct. Beide zijn factoren die de respons op CRT kunnen verminderen. Beide factoren komen ook vaker voor bij mannen.

Een van de belangrijke conclusies van dit proefschrift is dat bij de beslissing tot het implanteren van een CRT het geslacht van de patiënt in ogenschouw moet worden genomen. Verder bevat dit proefschrift de belangrijke boodschap dat er meer vrouwen in

klinisch onderzoek moeten worden betrokken en dat onderzoeksstudies aparte uitkomsten voor vrouwen en mannen zouden moeten rapporteren.

CHAPTER VIII
Valorization: Improving the Safety and Efficacy of Medical Device Therapy in Women: Case Study Heart Failure Devices

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ABSTRACT

An information gap on medical device safety and effectiveness exists when not enough women are included in many clinical trials, which can make it difficult to detect sex-specific results. In this article we discuss potential reasons for the underrepresentation of women, and the regulatory research conducted by the U.S. Food and Drug Administration (FDA) used in supporting regulatory decisions. We demonstrate that important differences in cardiovascular device performance between women and men exist. Furthermore, concrete steps are outlined on the possible ways these sex-specific results can be detected and how a recent FDA Action Plan and Guidance Document aim at encouraging diverse participation in clinical trials and the appropriate analysis thereof.

Introduction

Through its pre-market review process, usually in the form of clinical trials, the U.S. Food and Drug Administration (FDA) makes every effort to assure that high-risk medical devices are effective and associated risks have been minimized before they are approved to enter the market. However, women have historically been underrepresented in many clinical trials, as is also true for other patient subgroups. This especially pertains to clinical trials investigating certain cardiovascular devices, many of which often carry a high risk to patients and have the potential to save or sustain life.

Certain differences between women and men, including physiology and anatomy, can result in medical devices performing better or worse. When participants in clinical trials reflect a diverse, real-world population (females and males, young and old, various racial and ethnic backgrounds, and patients with differing comorbid diseases and conditions), and when subgroup data from clinical trials and other data sources are appropriately analyzed, much more information can be known about the product and more relevant clinical data can be reported. However, an information gap exists on the safety and effectiveness of medical devices when not enough women are included in clinical trials, making it difficult to detect potential sex-specific outcomes.

To ensure that regulatory decisions are based on science, it is one of FDA's missions to conduct regulatory science. Regulatory science is defined as: "developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products".[1,2] In this report, we utilize regulatory science research to evaluate cardiac resynchronization therapy (CRT), a device-based therapy for patients with heart failure, as an example to describe significant differences in device safety and efficacy between women and men. Furthermore, we refer to how these sex-specific results can potentially be detected and reported.

Cardiac Resynchronization Therapy for Heart Failure in Women

More than 800,000 patients in the U.S. develop heart failure each year.[3] The mortality associated with heart failure is significant making it an important public health issue. Furthermore, heart failure mortality has been shown to be higher in women than in men.[3] Therefore, appropriate, and perhaps sex-specific, therapy is of vital importance. CRT is such a therapy for patients with heart failure and has been shown to significantly improve heart failure symptoms, decrease hospitalizations and reduce mortality.

In clinical trials for CRT, women only represented approximately 20% of patients. The effects of CRT are therefore primarily based on the results in men, as well as the current clinical guidelines for the implantation of CRT devices.[4] The regulatory research studies we conducted that are described in this report were aimed at assessing potential differences in CRT efficacy between sexes. We used various data sources including analysis of CRT clinical trial data and data from patients included in a national registry for implantable defibrillators.

For the analysis of pre-market clinical trials we combined individual patient data from three CRT trials. The trials were submitted to FDA as part of pre-market approval applications (PMAs) for CRT. By performing such an individual-patient data meta-analysis the FDA found that women have a significantly lower mortality after receiving CRT than men.[5] Patients of both sexes with a left bundle branch block (LBBB), an electrical conduction disorder in the heart, benefited most. However, women did so at a shorter QRS

duration (time to complete electrical activation of the heart) than men. In patients with a LBBB and shorter QRS duration, women had a 76% reduction in heart failure or death while men did not derive any benefit. With LBBB and longer QRS duration, both sexes benefited equally from CRT.[5]

A second and third FDA analysis used data from real-world CRT recipients included in a national implantable defibrillator registry (the National Cardiovascular Data Registry [NCDR] ICD Registry operated by the American College of Cardiology).[6,7] In these two studies, it was shown that women had a lower mortality risk with CRT compared to men, and that this difference between sexes increased in the presence of a LBBB, similar as in the meta-analysis. However, as opposed to the meta-analysis there was no difference by QRS duration between women and men. Both sexes benefited at shorter as well as longer QRS durations.[6]

That women benefit more from CRT compared to men is important since women are less likely than men to receive CRT treatment. This also indicates that this device may be underused in women. One of the reasons why women have greater benefit with CRT is that they have smaller hearts and may therefore more often have a LBBB than men.[8] This, however, does not only pertain to CRT. There may be multiple reasons why women and men respond differently to medical device therapy, both in terms of safety and efficacy. These may be attributable to intrinsic factors (e.g. genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g. diet, sociocultural issues, environment) or even interactions between these factors.[9] This regulatory research highlights the importance of combining clinical trial data and using multiple data sources for the detection of potential sex- and other subgroup differences in medical device clinical studies.

This deficiency of sex-specific information creates difficulties in assessing the safety and effectiveness of devices in CRT therapy as well as interpreting data from device trials in general. The regulatory science performed by the FDA demonstrates that there can be important differences in device performance between women and men, both in pre-market trials as well as in real-world use. Therefore FDA recommends that in general, study enrollment should be based on representative proportions of women and men (consistent with, for example, disease prevalence) and that data from both pre-market and post-market medical device studies are appropriately analyzed for potential sex-specific results.

Developments and Recommendations to Enhance Participation of Women

There can be multiple reasons why women may be underrepresented in clinical trials for medical devices. These may include a lack of understanding about main obstacles to female participation or about sex-differences in disease etiology and pathophysiology, fear of potential fetal consequences, avoidance of female patients due to the perception that it takes more time and money to recruit them, there may be family responsibilities limiting a woman's ability to participate, or clinical study in- and exclusion criteria may simply unintentionally exclude women.[9] As a result, the FDA has recently been looking at ways to encourage greater inclusion of women and other demographic subgroups in medical device clinical trials and how to appropriately analyze the clinical data for potential sex-specific results.

FDA published an Action Plan – mandated by Congress - for the implementation of Section 907 of the FDA Safety and Innovation Act (FDASIA), the section concerning the demographic subgroup data from clinical trials.[10] This Action Plan contains

recommendations for improving the quality, transparency, and diversity of available data on women, as well as other demographic subgroup populations. It also references the regulatory science research discussed in this report as an example of how this can be achieved.[10] In addition, FDA published a Sex-Gender Guidance document that provides a clear framework for how to analyze and communicate data on women in medical device clinical trials.[9] The final guidance includes recommendations on encouraging appropriate representation by sex in clinical studies of devices and explains that data from such studies should be appropriately analyzed by sex. Both the complete Action Plan and final guidance can be accessed through the FDA website (Action Plan: http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf and final guidance: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf)).

Raising Awareness and Stakeholder Input

The research community needs to become more aware of the historical underrepresentation of women and other demographic subgroups in certain clinical trials where study outcomes can differ between sexes, races and ages. The regulatory research studies on CRT treatment for heart failure presented in this report can serve as an example of how such studies can be conducted and reported. Next to increasing awareness, this will hopefully also translate into the inclusion of more diverse populations in future clinical trials.

The FDA and sponsors of medical products cannot complete this effort alone. There is a need for stakeholder input to achieve the goal of including a more diverse patient population in clinical trials and appropriate analysis of data for potential sex-specific results. FDA plans to continue its interactions with all interested groups to achieve this important goal and improve the public health.

Conclusions

There can be important differences in medical device performance between patients from different demographic subgroups (e.g. women) sometimes underrepresented in certain clinical trials, leading to an important information gap regarding the safety and efficacy of these devices. By continuous multi-stakeholder input, barriers to clinical trial enrollment for demographic subgroups can be addressed and diverse participation encouraged. The implementation of the 907 FDASIA Action Plan will provide a first step towards achieving this goal.

Acknowledgements
Disclaimer: The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Disclosures: None.

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CHAPTER IX
Acknowledgements/Dankwoord

Wie had ooit gedacht dat dit proefschrift er uiteindelijk echt zou komen? Schijnbaar velen, maar ikzelf niet. En toch is het er dan! Gebaseerd op een fantastisch avontuur in de Verenigde Staten, ik had het voor geen goud willen missen. Deze tijd heeft mij in alle opzichten zoveel gebracht, ik heb ontzettend veel geleerd, tegenslagen gehad en overwonnen, gelachen, gereisd, fantastische kansen gekregen en fantastische mensen leren kennen die ik nu absoluut niet meer zou kunnen missen en waarvan ik er een paar persoonlijk wil bedanken.

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En nu terug naar waar het allemaal om begonnen was, de kliniek….

CHAPTER X
Curriculum Vitae

Robbert Zusterzeel werd op 19 februari 1988 geboren in Weert. Hij voltooide in 2006 zijn middelbare VWO opleiding aan Scholengemeenschap Sint Ursula te Horn. In hetzelfde jaar begon hij aan de geneeskunde opleiding aan de Universiteit Maastricht. Deze opleiding voltooide hij in 2012 waarna hij verhuisde naar de Verenigde Staten voor een aangeboden research fellow positie in de cardiologische electrofysiologie bij de Food and Drug Administration (FDA) te Washington DC. In datzelfde jaar startte hij zijn promotietraject onder begeleiding van Prof. dr. Gorgels aan de Universiteit Maastricht en Dr. Strauss bij de FDA. Het grootse gedeelte van zijn tijd als promovendus bracht hij door bij de FDA met het verrichten van onderzoek naar de verschillen in effectiviteit van cardiale therapieen tussen mannen en vrouwen. In 2014 werden de resultaten van zijn promotieonderzoek en zijn directe collega's beloond met 4 afzonderlijke prijzen van de FDA. Tevens ontving hij de "Young Investigator Award" en is hij co-principal investigator van 4 andere FDA projecten waarbij hij ook andere studenten begeleid. De resultaten van zijn promotieonderzoek staan beschreven in dit proefschrift en werden gepresenteerd op grote internationale en nationale congressen.

CHAPTER XI
Publications

Original Research

1. Zusterzeel R., ter Bekke RMA., Volders PGA., Leijten FMM., van den Wijngaard A., Serroyen J., Gorgels, APM. **Right-Ventricular Enlargement in Arrhythmogenic Right-Ventricular Cardiomyopathy Is Associated with Decreased QRS Amplitudes and T-Wave Negativity**. Ann Noninvasive Electrocardiol. 2013 Nov;18(6):555-63.
2. Zusterzeel R., Selzman KA., Sanders WE., Canos DA., O'Callaghan KM., Carpenter JL., Pina IL., Strauss DG. **Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data**. JAMA Intern Med. 2014;174(8):1340-1348.
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Abstracts and Conference Proceedings

1. Zusterzeel R., ter Bekke RMA., Volders PGA., Leijten FMM., van den Wijngaard A., Serroyen J., Gorgels, APM. **Right-Ventricular Enlargement in Arrhythmogenic Right-Ventricular Cardiomyopathy Is Associated with Decreased QRS Amplitudes and T-Wave Negativity.**
   Oral presentation at Imaging and Electrical Technologies meeting (March 2012, Bratislava, Slovakia)
2. Zusterzeel R., Canos DA., Selzman KA. **Cardiac Resynchronization Therapy – A Cardiac Device with a Gender Gap in Outcomes**.
   Oral presentation at the US Food and Drug Administration Health of Women Workshop (June 2013, Silver Spring, MD)

3. Zusterzeel R. **Cardiac Resynchronization Therapy: Towards Selection of Patients that Benefit.**
   Oral presentation at the US Food and Drug Administration Science Seminar (September 2013, Silver Spring, MD)
4. Zusterzeel R., Canos DA., Sanders WE., Silverman H., MaCurdy TE., Worrall CM., Kelman J., Strauss DG. **Cardiac Resynchronization Therapy is Associated with Increased Mortality in Right Bundle Branch Block Patients**. Circulation. 2013;128:A15233.
   Oral presentation at American Heart Association Scientific Sessions (November 2013, Dallas, TX)
5. Zusterzeel R., Curtis JP., Canos DA., Sanders WE., Selzman KA., Pina IL., Spatz ES., Bao H., Ponirakis A., Varosy PD., Masoudi FA., Strauss DG. **Sex-Specific Mortality Risk by QRS Morphology and Duration in Patients Receiving Cardiac Resynchronization Therapy: Results from the NCDR®**. JACC. 2014;63(12):SA719.
   Moderated poster presentation at American College of Cardiology Scientific Sessions (March 2014, Washington, DC)
6. Zusterzeel R. **Bundle Branch Block and Benefit from Cardiac Resynchronization Therapy.**
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   Oral presentation at American Heart Association Scientific Sessions (November 2014, Chicago, IL)
8. Yousuf O., Zusterzeel R., Sanders WE., Dekmezian C., Silverman H., MaCurdy TE., Nazarian S., Berger R., Marinac-Dabic D., Canos DA., Strauss DG. **Trends in the Utilization and Outcomes of Medicare Beneficiaries Undergoing Catheter Ablation for Ventricular Tachycardia**. Circulation. 2014;130:A18117.
   Oral presentation at American Heart Association Scientific Sessions (November 2014, Chicago, IL)

CHAPTER XII
Supplements

SUPPLEMENT TO CHAPTER II
Cardiac Resynchronization Therapy in Women: US Food and Drug Administration Meta-analysis of Patient-Level Data

eMethods

R Commands for Calculating Random Intercept Models for CRT-D Effect Across Trials

The "coxme" library for R was used to determine random effects.[1,2] The following model codes were used:

1. Determining sex-by-treatment interactions in random intercepts for CRT-D effect across trials by subgroups:
library(coxme);
coxme(formula = Surv(time-to-event, event)[a] ~ treatment[b] + sex[c] + sex-by-treatment interaction[d] + (1|trial)[e], data = data[f])

2. Determining random intercepts for CRT-D effect across trials in women and men by subgroups:
library(coxme);
coxme(formula = Surv(time-to-event, event)[a] ~ treatment[b] + (1|trial)[c], data = data[d])

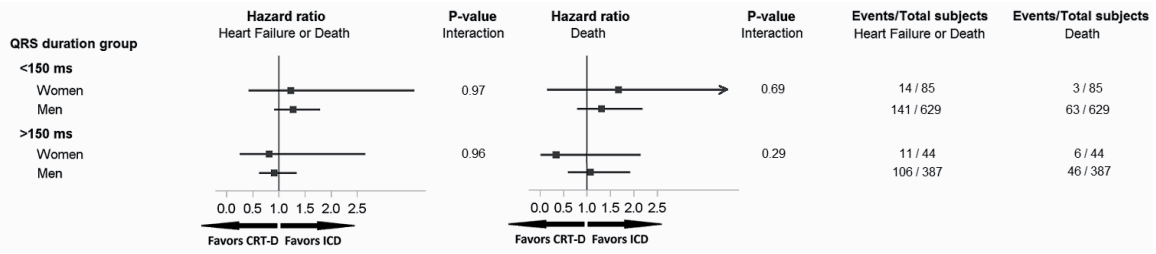
[a] Time-to-event and event include one of either end points (heart failure event or death and death alone)
[b] Treatment includes the CRT-D vs. ICD variable for all models
[c] Sex includes either female or male
[d] Sex-by-treatment interaction includes the sex variable multiplied by the treatment variable
[e] Indicates the random intercept per trial
[f] Data includes the specific subgroups for women and men separately (total database, LBBB, non-LBBB, QRS <150 ms, QRS ≥150 ms, ischemic heart failure etiology, non-ischemic heart failure etiology, LBBB-120-129, LBBB-130-139, LBBB-140-149, LBBB-150-159, LBBB-160-169, LBBB-170-179, LBBB ≥180, LBBB-130-149, LBBB ≥150)

eTable 1. CRT-D to ICD Hazard Ratios for Outcomes by Sex in the Total Population

	Hazard Ratio (95% CI) Heart Failure or Death		P-value Interaction	Hazard Ratio (95% CI) Death		P-value Interaction
Total population						
Women	0.40	(0.28 - 0.55)	0.002	0.45	(0.25 - 0.80)	0.03
Men	0.74	(0.63 - 0.85)		0.85	(0.68 - 1.06)	
Left bundle branch block						
Women	0.33	(0.23 - 0.47)	0.007	0.39	(0.21 - 0.74)	0.08
Men	0.60	(0.50 - 0.72)		0.68	(0.52 - 0.90)	
Non-Left bundle branch block						
Women	1.02	(0.46 - 2.25)	0.95	0.76	(0.20 - 2.94)	0.58
Men	1.12	(0.87 - 1.45)		1.21	(0.83 - 1.78)	
QRS duration >150						
Women	0.37	(0.24 - 0.57)	0.12	0.38	(0.18 - 0.81)	0.11
Men	0.56	(0.46 - 0.68)		0.71	(0.54 - 0.93)	
QRS duration <150						
Women	0.46	(0.27 - 0.78)	0.003	0.53	(0.22 - 1.32)	0.15
Men	1.09	(0.87 - 1.38)		1.03	(0.72 - 1.47)	
Ischemic heart disease						
Women	0.55	(0.34 - 0.90)	0.38	0.54	(0.24 - 1.23)	0.22
Men	0.70	(0.59 - 0.83)		0.87	(0.68 - 1.06)	
Non-ischemic heart disease						
Women	0.32	(0.20 - 0.50)	0.002	0.37	(0.16 - 0.81)	0.22
Men	0.79	(0.59 - 1.06)		0.70	(0.43 - 1.14)	

CRT-D to ICD hazard ratios including 95% confidence intervals for heart failure event or death (left) and for death alone (right) in subgroups separately in women and men. P-values represent sex-by-treatment interactions. This is the same information that is displayed in Figure 1.

eFigure 1. CRT-D to ICD Hazard Ratios for Outcomes in non-LBBB QRS<150 and ≥150 ms Groups by Sex



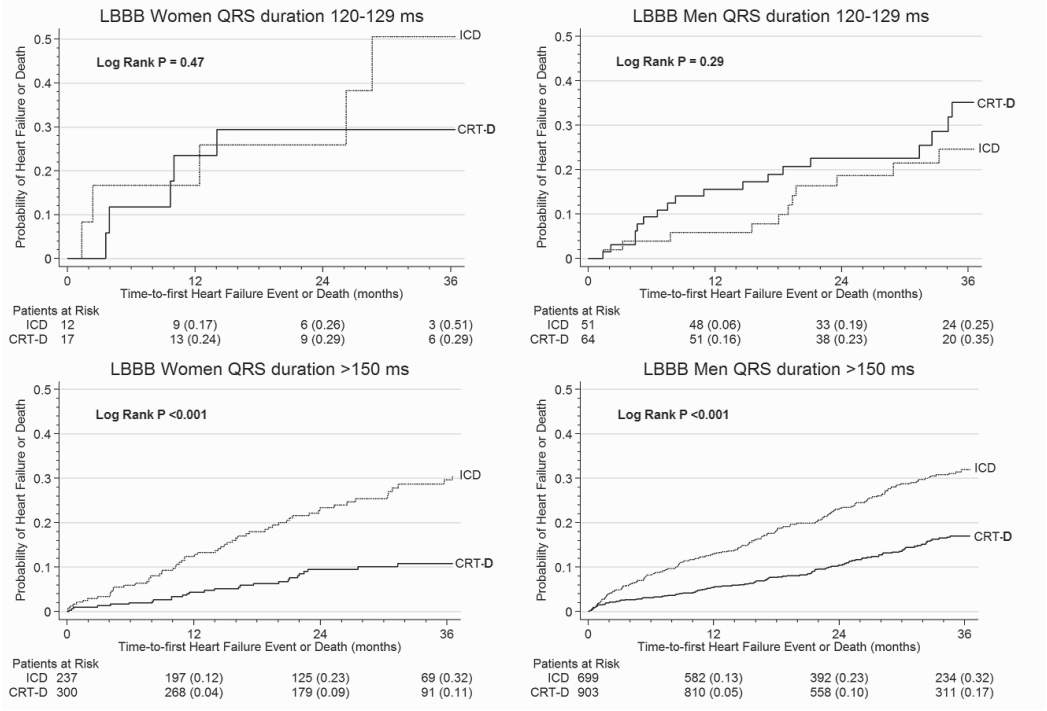
Points reflect CRT-D to ICD hazard ratios for heart failure event or death (left) and for death alone (middle) in subgroups separately in women and men for non-LBBB patients. Solid lines indicate 95% confidence intervals. P-values represent sex-by-treatment interactions. Number of events and total subjects are listed for each subgroup.

eTable 2. CRT-D to ICD Hazard Ratios for Heart Failure Event or Death in LBBB QRS Duration Intervals by Sex

	Hazard Ratio (95% CI)			
QRS duration	Heart Failure or Death			
intervals (ms)	Women		Men	
120-129	0.64	(0.18 - 2.20)	1.49	(0.70 - 3.16)
130-139	0.15	(0.03 - 0.69)	0.77	(0.44 - 1.34)
140-149	0.31	(0.12 - 0.77)	0.92	(0.58 - 1.45)
150-159	0.20	(0.08 - 0.49)	0.56	(0.32 - 0.97)
160-169	0.44	(0.21 - 0.93)	0.41	(0.27 - 0.64)
170-179	0.29	(0.07 - 1.11)	0.51	(0.30 - 0.87)
≥ 180	0.38	(0.15 - 0.97)	0.44	(0.30 - 0.64)

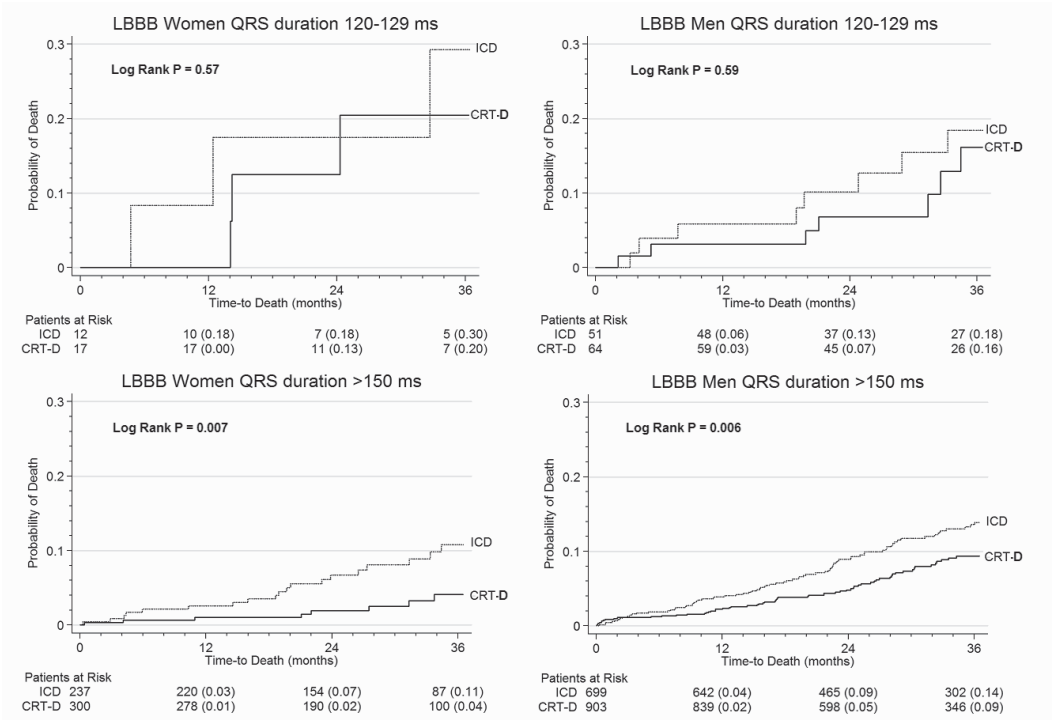
CRT-D to ICD hazard ratios including 95% confidence intervals for heart failure event or death in women (left) and men (right) across QRS duration intervals.

eFigure 2: Kaplan-Meier Estimates of Heart Failure or Death in LBBB Stratified by Sex in QRS 120-129 and ≥150 ms



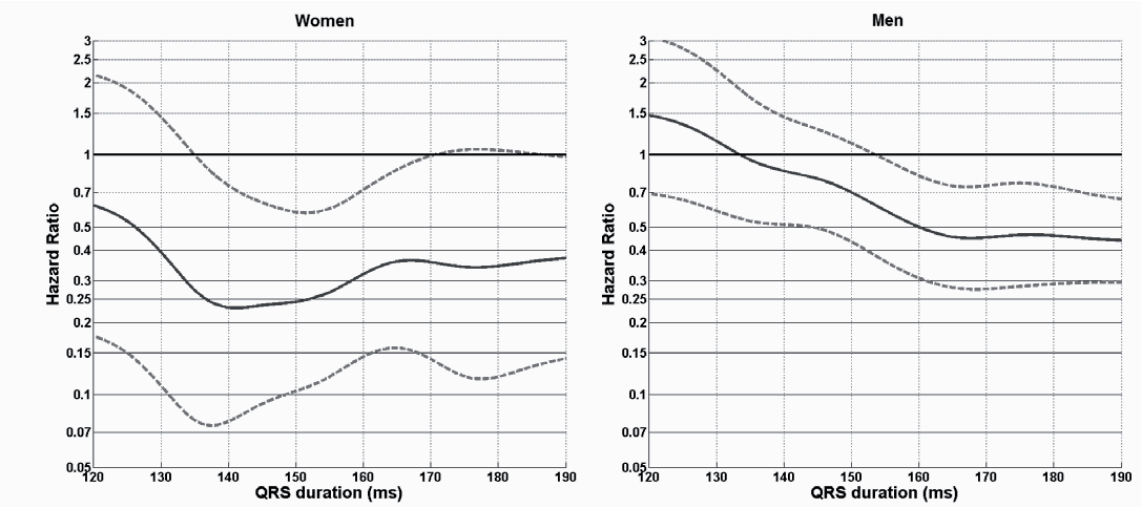
Curves reflect the probability of heart failure event or death in women (left) and men (right) with CRT-D (solid line) or ICD (dotted line) in QRS duration 120-129 (top) and ≥150 ms (bottom). Log rank P-values are listed on each graph. The number of patients remaining (and event rate) is listed at each year of follow-up.

eFigure 3: Kaplan-Meier Estimates of Death in LBBB Stratified by Sex in QRS 120-129 and ≥150 ms



Curves reflect the probability of death in women (left) and men (right) with CRT-D (solid line) or ICD (dotted line) in QRS duration 120-129 (top) and ≥150 ms (bottom). Log rank P-values are listed on each graph. The number of patients remaining (and event rate) is listed at each year of follow-up.

eFigure 4: Smoothed Spline Analysis for Women and Men with LBBB using QRS Duration as a Continuous Variable



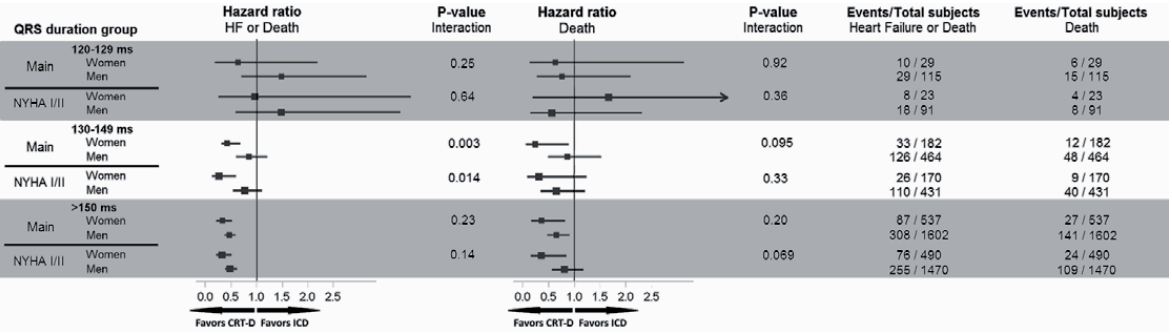
Curves reflect the CRT-D to ICD hazard ratio (blue) and 95% confidence intervals (red) for heart failure event or death in women (left) and men (right) with left bundle branch block using QRS duration as a continuous variable. The black horizontal line indicates hazard ratio = 1.

eTable 3. CRT-D to ICD Hazard Ratios for Outcomes in LBBB and QRS Duration Groups of Main and Multivariable Adjusted Analysis by Sex

QRS Duration Group		Hazard Ratio (95% CI) Heart Failure or Death		P-value Interaction	Hazard Ratio (95% CI) Death		P-value Interaction
	120-129 ms						
Main	Women	0.64	(0.18 - 2.20)	0.25	0.63	(0.13 - 3.13)	0.92
	Men	1.49	(0.70 - 3.16)		0.76	(0.27 - 2.09)	
Multivariable	Women	N/A	N/A	N/A	N/A	N/A	N/A
	Men	1.48	(0.70 - 3.14)		N/A	N/A	
	130-149 ms						
Main	Women	0.24	(0.11 - 0.53)	0.003	0.24	(0.06 - 0.89)	0.095
	Men	0.85	(0.60 - 1.21)		0.86	(0.49 - 1.52)	
Multivariable	Women	0.23	(0.10 - 0.53)	0.002	0.22	(0.06 - 0.83)	0.087
	Men	0.86	(0.60 - 1.22)		0.90	(0.50 - 1.61)	
	≥150 ms						
Main	Women	0.33	(0.21 - 0.52)	0.23	0.36	(0.16 - 0.82)	0.20
	Men	0.47	(0.37 - 0.59)		0.65	(0.47 - 0.91)	
Multivariable	Women	0.33	(0.21 – 0.53)	0.30	0.34	(0.14 - 0.83)	0.22
	Men	0.44	(0.35 - 0.55)		0.62	(0.45 - 0.87)	

CRT-D to ICD hazard ratios including 95% confidence intervals for heart failure event or death (left) and for death alone (right) in subgroups separately in women and men for the main and multivariable adjusted analysis. P-values represent sex-by-treatment interactions. This is the same information that is displayed in Figure 3.

eFigure 5. CRT-D to ICD Hazard Ratios for Outcomes in LBBB and QRS Duration Groups of Main and NYHA I/II Analysis by Sex



Points reflect CRT-D to ICD hazard ratios for heart failure event or death (left) and for death alone (middle) in subgroups separately in women and men for the main analysis and NYHA class I and II patients. Solid lines indicate 95% confidence intervals. P-values represent sex-by-treatment interactions. Number of events and total subjects are listed for each subgroup.

eReferences

1. R: A Language and Environment for Statistical Computing. 2013; http://www.R-project.org. Accessed April 15, 2013.
2. Package 'coxme' for R. 2013; http://cran.r-project.org/web/packages/coxme/coxme.pdf. Accessed April 15, 2013.

SUPPLEMENT TO CHAPTER III

Sex-Specific Mortality Risk by QRS Morphology and Duration in Patients Receiving Cardiac Resynchronization Therapy: Results from the NCDR

Online Table 1. Multivariable Hazard Ratios for Mortality in LBBB and non-LBBB QRS Duration Groups by Sex

	Hazard Ratio	(95% CI)	P-value	Hazard Ratio	(95% CI)	P-value
QRS duration group	LBBB		For HR	Non-LBBB		For HR
120-129 ms						
Women	REFERENCE			REFERENCE		
Men	REFERENCE			REFERENCE		
130-139 ms						
Women	0.88	(0.72 – 1.09)	0.25	0.90	(0.67 – 1.22)	0.50
Men	0.90	(0.79 – 1.03)	0.12	0.98	(0.85 – 1.13)	0.77
140-149 ms						
Women	0.73	(0.60 – 0.88)	0.001	1.37	(1.01 – 1.85)	0.04
Men	0.82	(0.71 – 0.93)	0.003	1.01	(0.87 – 1.16)	0.92
150-159 ms						
Women	0.68	(0.57 – 0.82)	<0.001	0.77	(0.52 – 1.13)	0.18
Men	0.66	(0.58 – 0.76)	<0.001	0.90	(0.77 – 1.05)	0.19
160-169 ms						
Women	0.61	(0.51 – 0.74)	<0.001	1.20	(0.85 – 1.69)	0.31
Men	0.64	(0.56 – 0.73)	<0.001	0.95	(0.80 – 1.11)	0.49
>170 ms						
Women	0.65	(0.54 – 0.79)	<0.001	0.96	(0.66 – 1.38)	0.81
Men	0.58	(0.51 – 0.66)	<0.001	0.92	(0.78 – 1.07)	0.29

Multivariable all-cause mortality hazard ratios including 95% confidence intervals for LBBB (left) and non-LBBB (right) in 10 ms QRS duration groups for women and men. P-values for all hazard ratios (HR) are reported. See Figure 3 of the main text for interaction p-values.

Online Table 2. Multivariable Model for Women with LBBB

Variables	HR (95% CI)	P-value
QRS duration		
120-129	Reference	
130-139	0.884 (0.715 - 1.092)	<.0001
140-149	0.725 (0.597 - 0.880)	
150-159	0.682 (0.567 - 0.820)	
160-169	0.612 (0.508 - 0.739)	
≥170	0.650 (0.535 - 0.789)	
Age		
<50	1.110 (0.789 - 1.562)	<.0001
50-59	Reference	
60-69	1.429 (1.157 - 1.764)	
70-79	1.941 (1.600 - 2.355)	
≥80	3.082 (2.500 - 3.800)	
Race		
White non-hispanic	Reference	
Black non-hispanic	1.147 (0.985 - 1.335)	0.2923
Hispanic	0.931 (0.720 - 1.204)	
Other	0.940 (0.654 - 1.352)	
Syncope	1.196 (1.003 - 1.426)	0.0462
Family History of Sudden Death	0.657 (0.488 - 0.884)	0.0055
CHF Duration		
No	Reference	
<3 months	1.414 (0.929 - 2.154)	0.023
3-9 months	1.372 (0.910 - 2.071)	
>9 months	1.564 (1.061 - 2.306)	
NYHA Class - Current Status		
I/II	Reference	
III	1.321 (1.100 - 1.587)	0.0003
IV	1.782 (1.341 - 2.368)	
Cardiac arrest	0.579 (0.283 - 1.184)	0.1344
Ventricular Tachycardia	1.207 (1.031 - 1.412)	0.0192
Ischemic Heart Disease	1.416 (1.212 - 1.654)	<.0001
Previous Myocardial Infarction	1.122 (0.972 - 1.296)	0.1146
Previous CABG	1.169 (1.011 - 1.353)	0.0357
Previous PCI	1.084 (0.955 - 1.230)	0.2137
Previous Valvular Surgery	1.146 (0.899 - 1.460)	0.2716
Cerebrovascular Disease	1.244 (1.071 - 1.444)	0.0042
Diabetes	1.216 (1.095 - 1.351)	0.0003
Hypertension	1.037 (0.912 - 1.179)	0.581
Renal Failure-Dialysis	2.092 (1.586 - 2.759)	<.0001
AV Conduction		
Normal	Reference	

1st degree heart block only	1.206 (1.059 - 1.372)	0.0142
Heart block 2nd or 3rd degree (not paced)	1.149 (0.739 - 1.787)	
LVEF		
<20%	1.636 (1.318 - 2.030)	<.0001
20%-30%	1.141 (0.940 - 1.384)	
>30%	Reference	
Creatinine Level		
<1	Reference	
1-2	1.130 (0.999 - 1.279)	0.0001
>2	1.703 (1.335 - 2.172)	
BUN Level		
≤25	Reference	
26-50	1.363 (1.205 - 1.542)	<.0001
>50	2.099 (1.688 - 2.610)	
Sodium Level		
<135	1.453 (1.224 - 1.724)	<.0001
135-145	Reference	
>145	1.615 (1.179 - 2.212)	
Systolic BP		
<110	1.279 (1.107 - 1.477)	0.0008
≥110	Reference	

CHF indicates Congestive heart failure; NYHA indicates New York Heart Association; CABG indicates Coronary Artery Bypass Graft; PCI indicates Percutaneous Coronary Intervention; AV indicates atrio-ventricular; LVEF indicates left ventricular ejection fraction; BUN indicates blood-urea nitrogen.

Online Table 3. Multivariable Model for Men with LBBB

Variables	HR (95% CI)	P-value
QRS duration		
120-129	Reference	
130-139	0.898 (0.785 - 1.027)	<.0001
140-149	0.815 (0.713 - 0.931)	
150-159	0.663 (0.581 - 0.758)	
160-169	0.639 (0.557 - 0.732)	
≥170	0.583 (0.513 - 0.662)	
Age		
<50	0.978 (0.768 - 1.245)	<.0001
50-59	Reference	
60-69	1.262 (1.097 - 1.451)	
70-79	1.707 (1.485 - 1.962)	
≥80	2.558 (2.207 - 2.965)	
Race		
White non-hispanic	Reference	
Black non-hispanic	1.104 (0.976 - 1.248)	0.4532
Hispanic	0.985 (0.831 - 1.167)	
Other	0.971 (0.755 - 1.249)	
Syncope	1.095 (0.970 - 1.235)	0.141
Family History of Sudden Death	0.896 (0.743 - 1.079)	0.2473
CHF Duration		
No	Reference	
<3 months	0.976 (0.791 - 1.205)	0.0169
3-9 months	1.003 (0.827 - 1.217)	
>9 months	1.134 (0.947 - 1.357)	
NYHA Class - Current Status		
I/II	Reference	
III	1.440 (1.280 - 1.621)	<.0001
IV	1.896 (1.541 - 2.333)	
Cardiac arrest	0.826 (0.550 - 1.240)	0.3568
Ventricular Tachycardia	1.068 (0.959 - 1.189)	0.2343
Ischemic Heart Disease	1.210 (1.079 - 1.358)	0.0011
Previous Myocardial Infarction	1.091 (0.999 - 1.191)	0.0539
Previous CABG	1.055 (0.970 - 1.147)	0.2093
Previous PCI	0.976 (0.903 - 1.056)	0.5501
Previous Valvular Surgery	1.083 (0.934 - 1.256)	0.2929
Cerebrovascular Disease	1.292 (1.177 - 1.419)	<.0001
Diabetes	1.222 (1.139 - 1.311)	<.0001
Hypertension	0.976 (0.898 - 1.061)	0.5754
Renal Failure-Dialysis	1.741 (1.480 - 2.049)	<.0001
AV Conduction		
Normal	Reference	

1st degree heart block only	1.125 (1.045 - 1.211)	0.0025
Heart block 2nd or 3rd degree (not paced)	0.882 (0.694 - 1.123)	
LVEF		
<20%	1.541 (1.335 - 1.780)	<.0001
20%-30%	1.178 (1.039 - 1.337)	
>30%	Reference	
Creatinine Level		
<1	Reference	
1-2	1.017 (0.908 - 1.139)	<.0001
>2	1.553 (1.311 - 1.839)	
BUN Level		
≤25	Reference	
26-50	1.494 (1.377 - 1.621)	<.0001
>50	2.199 (1.880 - 2.573)	
Sodium Level		
<135	1.310 (1.169 - 1.467)	<.0001
135-145	Reference	
>145	1.059 (0.776 - 1.445)	
Systolic BP		
<110	1.334 (1.217 - 1.462)	<.0001
≥110	Reference	

CHF indicates Congestive heart failure; NYHA indicates New York Heart Association; CABG indicates Coronary Artery Bypass Graft; PCI indicates Percutaneous Coronary Intervention; AV indicates atrio-ventricular; LVEF indicates left ventricular ejection fraction; BUN indicates blood-urea nitrogen.

Online Table 4. Multivariable Model for Women without LBBB

Variables	HR (95% CI)	P-value
QRS duration		
120-129	Reference	
130-139	0.903 (0.668 - 1.219)	0.0113
140-149	1.367 (1.012 - 1.846)	
150-159	0.767 (0.521 - 1.130)	
160-169	1.198 (0.847 - 1.694)	
≥170	0.956 (0.664 - 1.375)	
Age		
<50	1.208 (0.731 - 1.994)	0.0001
50-59	Reference	
60-69	1.079 (0.748 - 1.555)	
70-79	1.157 (0.815 - 1.642)	
≥80	1.985 (1.352 - 2.912)	
Race		
White non-hispanic	Reference	
Black non-hispanic	0.991 (0.752 - 1.306)	0.8625
Hispanic	0.828 (0.519 - 1.320)	
Other	1.152 (0.486 - 2.733)	
Syncope	1.057 (0.743 - 1.504)	0.7574
Family History of Sudden Death	1.059 (0.609 - 1.839)	0.8399
CHF Duration		
No	Reference	
<3 months	1.087 (0.561 - 2.107)	0.2814
3-9 months	1.040 (0.562 - 1.923)	
>9 months	1.314 (0.742 - 2.327)	
NYHA Class - Current Status		
I/II	Reference	
III	1.457 (0.998 - 2.128)	0.0312
IV	2.074 (1.201 - 3.583)	
Cardiac arrest	0.822 (0.369 - 1.830)	0.6312
Ventricular Tachycardia	1.242 (0.923 - 1.670)	0.1531
Ischemic Heart Disease	1.491 (1.068 - 2.083)	0.019
Previous Myocardial Infarction	1.073 (0.845 - 1.364)	0.5618
Previous CABG	1.064 (0.827 - 1.370)	0.6277
Previous PCI	0.972 (0.754 - 1.254)	0.8275
Previous Valvular Surgery	0.939 (0.686 - 1.286)	0.694
Cerebrovascular Disease	0.950 (0.712 - 1.266)	0.7242
Diabetes	1.281 (1.039 - 1.579)	0.0206
Hypertension	1.083 (0.851 - 1.378)	0.5182
Renal Failure-Dialysis	1.472 (0.884 - 2.451)	0.1376
AV Conduction		
Normal	Reference	

1st degree heart block only	1.213 (0.974 - 1.510)	0.0221
Heart block 2nd or 3rd degree (not paced)	2.251 (1.147 - 4.417)	
LVEF		
<20%	1.790 (1.213 - 2.641)	0.0013
20%-30%	1.198 (0.841 - 1.706)	
>30%	Reference	
Creatinine Level		
<1	Reference	
1-2	1.466 (1.152 - 1.866)	<.0001
>2	2.568 (1.716 - 3.842)	
BUN Level		
≤25	Reference	
26-50	1.657 (1.317 - 2.086)	<.0001
>50	2.224 (1.521 - 3.252)	
Sodium Level		
<135	1.646 (1.228 - 2.206)	0.0014
135-145	Reference	
>145	1.748 (0.874 - 3.495)	
Systolic BP		
<110	1.149 (0.889 - 1.483)	0.2885
≥110	Reference	

CHF indicates Congestive heart failure; NYHA indicates New York Heart Association; CABG indicates Coronary Artery Bypass Graft; PCI indicates Percutaneous Coronary Intervention; AV indicates atrio-ventricular; LVEF indicates left ventricular ejection fraction; BUN indicates blood-urea nitrogen.

Online Table 5. Multivariable Model for Men without LBBB

Variables	HR (95% CI)	P-value
QRS duration		
120-129	Reference	
130-139	0.978 (0.846 - 1.131)	0.6319
140-149	1.008 (0.873 - 1.163)	
150-159	0.902 (0.773 - 1.053)	
160-169	0.945 (0.803 - 1.111)	
≥170	0.918 (0.784 - 1.074)	
Age		
<50	0.903 (0.637 - 1.279)	<.0001
50-59	Reference	
60-69	1.322 (1.105 - 1.581)	
70-79	1.726 (1.454 - 2.048)	
≥80	2.589 (2.159 - 3.106)	
Race		
White non-hispanic	Reference	
Black non-hispanic	1.217 (1.050 - 1.410)	0.0374
Hispanic	0.899 (0.728 - 1.110)	
Other	0.996 (0.782 - 1.270)	
Syncope	1.054 (0.895 - 1.242)	0.5254
Family History of Sudden Death	0.929 (0.727 - 1.186)	0.5527
CHF Duration		
No	Reference	
<3 months	1.036 (0.801 - 1.340)	0.0037
3-9 months	1.092 (0.850 - 1.403)	
>9 months	1.280 (1.029 - 1.594)	
NYHA Class - Current Status		
I/II	Reference	
III	1.334 (1.140 - 1.561)	<.0001
IV	1.855 (1.441 - 2.389)	
Cardiac arrest	1.142 (0.757 - 1.723)	0.5257
Ventricular Tachycardia	0.971 (0.855 - 1.103)	0.6506
Ischemic Heart Disease	1.220 (1.036 - 1.435)	0.0168
Previous Myocardial Infarction	1.028 (0.915 - 1.154)	0.646
Previous CABG	1.016 (0.913 - 1.132)	0.7691
Previous PCI	0.950 (0.856 - 1.053)	0.3273
Previous Valvular Surgery	1.138 (0.931 - 1.390)	0.2079
Cerebrovascular Disease	1.196 (1.059 - 1.351)	0.004
Diabetes	1.256 (1.144 - 1.378)	<.0001
Hypertension	0.881 (0.790 - 0.982)	0.0217
Renal Failure-Dialysis	2.002 (1.640 - 2.444)	<.0001
AV Conduction		
Normal	Reference	

1st degree heart block only	1.039 (0.942 - 1.147)	0.7413
Heart block 2nd or 3rd degree (not paced)	1.021 (0.797 - 1.308)	
LVEF		
<20%	1.630 (1.366 - 1.945)	<.0001
20%-30%	1.333 (1.149 - 1.548)	
>30%	Reference	
Creatinine Level		
<1	Reference	
1-2	1.042 (0.908 - 1.195)	<.0001
>2	1.489 (1.215 - 1.824)	
BUN Level		
≤25	Reference	
26-50	1.567 (1.407 - 1.746)	<.0001
>50	2.259 (1.859 - 2.746)	
Sodium Level		
<135	1.237 (1.061 - 1.442)	0.0246
135-145	Reference	
>145	1.058 (0.719 - 1.556)	
Systolic BP		
<110	1.333 (1.183 - 1.501)	<.0001
≥110	Reference	

CHF indicates Congestive heart failure; NYHA indicates New York Heart Association; CABG indicates Coronary Artery Bypass Graft; PCI indicates Percutaneous Coronary Intervention; AV indicates atrio-ventricular; LVEF indicates left ventricular ejection fraction; BUN indicates blood-urea nitrogen.

SUPPLEMENT TO CHAPTER IV

Cardiac Resynchronization Therapy in Women Versus Men: Observational Comparative Effectiveness Study from the National Cardiovascular Data Registry

Table 1. Patient Characteristics by Sex in the Total CRT-D and ICD Populations

	Women		Men	
	CRT-D (n=20394)	ICD (n=3350)	CRT-D (n=42589)	ICD (n=8746)
Demographics				
Age (years), mean ± SD	70±11	70±12	70±11	70±12
Race				
White	15654 (77%)	2440 (73%)	35175 (83%)	6899 (79%)
Black	3071 (15%)	611 (18%)	4045 (10%)	955 (11%)
Hispanic	1141 (6%)	209 (6%)	2151 (5%)	618 (7%)
Other	528 (3%)	90 (3%)	1218 (3%)	274 (3%)
Clinical characteristics				
Admission for procedure	14073 (69%)	1921 (57%)	28058 (66%)	4804 (55%)
LVEF[a] (%), mean ± SD	24±7	25±9	23±7	25±9
NYHA[b] heart failure class				
III	18963 (93%)	3087 (92%)	39363 (92%)	8098 (93%)
IV	1431 (7%)	263 (8%)	3226 (8%)	648 (7%)
Ischemic cardiomyopathy	8842 (43%)	1769 (53%)	29134 (68%)	6439 (74%)
Left bundle branch block	16980 (83%)	2051 (61%)	27745 (65%)	3439 (39%)
Non-left bundle branch block	3414 (17%)	1299 (39%)	14844 (35%)	5307 (61%)
QRS duration (ms), mean ± SD	153±19	147±20	153±21	146±21
AV[c] conduction				
Normal	16144 (79%)	2564 (76%)	29404 (69%)	6018 (69%)
First degree block	3679 (18%)	598 (18%)	11207 (26%)	2246 (26%)
Second/Third degree block	571 (3%)	188 (6%)	1978 (5%)	482 (5%)
Heart failure duration[d]				
Unknown	531 (3%)	282 (8%)	1330 (3%)	1053 (12%)
<3 months	2578 (13%)	512 (15%)	5700 (14%)	1433 (16%)
3-9 months	3228 (16%)	451 (13%)	6027 (14%)	1063 (12%)
>9 months	14057 (69%)	2105 (63%)	29532 (69%)	5197 (60%)
Atrial fibrillation/flutter	4584 (22%)	913 (27%)	14245 (33%)	3265 (37%)
Previous valvular surgery	1417 (7%)	255 (8%)	3530 (8%)	721 (8%)
Cerebrovascular disease	2669 (13%)	499 (15%)	6427 (15%)	1609 (18%)
Renal failure/dialysis	626 (3%)	154 (5%)	1730 (4%)	559 (6%)
Diabetes mellitus	8346 (41%)	1511 (45%)	17997 (42%)	3772 (43%)
Hypertension	15663 (77%)	2657 (79%)	33442 (79%)	6989 (80%)
Sodium (mEq/L), mean ± SD	139±4	138±4	138±4	138±4
Blood urea nitrogen (mmol/L), mean ± SD	25±15	26±16	27±15	27±16
Creatinine (mg/dL), mean ± SD	1.2±1	1.3±1	1.5±1	1.6±1
Discharge medications				
Beta-blockers	17946 (88%)	2836 (85%)	37131 (87%)	7379 (84%)
Angiotensin receptor blockers	4624 (23%)	647 (19%)	7052 (17%)	1198 (14%)
ACE-inhibitors	12021 (59%)	1942 (58%)	26808 (63%)	5415 (62%)

[a] NYHA indicates New York Heart Association; [b] LVEF indicates left ventricular ejection fraction; [c] AV indicates atrioventricular; [d] indicates the duration of symptoms since initial diagnosis of heart failure

Table 2. Unweighted and Weighted Patient Characteristics by Bundle Branch Block Type in Men with CRT-D and ICD

	Men, LBBB, Unweighted			Men, LBBB, Weighted		
Variables	**ICD only**	**CRT-D**	**P-value**	**ICD only (N=3464)**	**CRT-D (N=27734)**	**% Standardized difference**
Demographic						
Age						
<50	212 (6.2%)	1401 (5.0%)	<.0001	176 (5.1%)	1433 (5.2%)	-0.44
50-59	367 (10.7%)	3432 (12.4%)		416 (12.0%)	3380 (12.2%)	-0.56
60-69	841 (24.5%)	7145 (25.8%)		887 (25.6%)	7099 (25.6%)	0.03
70-79	1211 (35.2%)	9875 (35.6%)		1244 (35.9%)	9864 (35.6%)	0.7
≥80	808 (23.5%)	5892 (21.2%)		742 (21.4%)	5958 (21.5%)	-0.17
Race						
White non-hispanic	2751 (80.0%)	23082 (83.2%)	<.0001	2875 (83.0%)	22975 (82.8%)	0.37
Black non-hispanic	373 (10.8%)	2523 (9.1%)		313 (9.0%)	2571 (9.3%)	-0.81
Hispanic	224 (6.5%)	1383 (5.0%)		186 (5.4%)	1433 (5.2%)	0.86
Other	91 (2.6%)	757 (2.7%)		91 (2.6%)	754 (2.7%)	-0.59
Clinical Characteristics						
Admission for this procedure	2022 (58.8%)	18834 (67.9%)	<.0001	2344 (67.7%)	18557 (66.9%)	1.62
Syncope	487 (14.2%)	2908 (10.5%)	<.0001	357 (10.3%)	3007 (10.8%)	-1.78
Family Hx Sudden Death	146 (4.2%)	1013 (3.7%)	0.0822	126 (3.7%)	1031 (3.7%)	-0.35
CHF Duration						
No	365 (10.6%)	816 (2.9%)	<.0001	124 (3.6%)	1038 (3.7%)	-0.83
<3 months	533 (15.5%)	3641 (13.1%)		456 (13.2%)	3713 (13.4%)	-0.66
3-9 months	451 (13.1%)	3981 (14.3%)		507 (14.6%)	3945 (14.2%)	1.19
>9 months	2090 (60.8%)	19307 (69.6%)		2377 (68.6%)	19037 (68.6%)	-0.08
NYHA Class - Current Status						

III	3172 (92.2%)	25734 (92.8%)	0.2729	3202 (92.4%)	25706 (92.7%)	-1.02
IV	267 (7.8%)	2011 (7.2%)		263 (7.6%)	2028 (7.3%)	1.02
Cardiac arrest	125 (3.6%)	407 (1.5%)	<.0001	58 (1.7%)	469 (1.7%)	-0.05
Atrial Fibrillation/Flutter	1224 (35.6%)	8641 (31.1%)	<.0001	1100 (31.8%)	8777 (31.6%)	0.23
Ventricular Tachycardia	932 (27.1%)	5739 (20.7%)	<.0001	703 (20.3%)	5917 (21.3%)	-2.59
Ischemic Heart Disease	2308 (67.1%)	17837 (64.3%)	0.0011	2265 (65.4%)	17925 (64.6%)	1.59
Previous MI	1806 (52.5%)	13687 (49.3%)	0.0004	1747 (50.4%)	13784 (49.7%)	1.48
Previous CABG	1358 (39.5%)	10404 (37.5%)	0.0232	1346 (38.9%)	10470 (37.8%)	2.28
Previous PCI	1054 (30.6%)	8255 (29.8%)	0.2791	1046 (30.2%)	8284 (29.9%)	0.7
Previous Valvular Surgery	294 (8.5%)	2292 (8.3%)	0.5634	282 (8.1%)	2299 (8.3%)	-0.54
Cerebrovascular Disease	585 (17.0%)	4014 (14.5%)	<.0001	501 (14.5%)	4089 (14.7%)	-0.77
Diabetes	1390 (40.4%)	11179 (40.3%)	0.8863	1375 (39.7%)	11176 (40.3%)	-1.24
Hypertension	2726 (79.3%)	21548 (77.7%)	0.0328	2690 (77.7%)	21588 (77.8%)	-0.43
Renal Failure-Dialysis	201 (5.8%)	1030 (3.7%)	<.0001	136 (3.9%)	1096 (4.0%)	-0.11
AV Conduction						
Normal	2368 (68.9%)	19431 (70.0%)	<.0001	2427 (70.1%)	19390 (69.9%)	0.31
1st degree heart block only	883 (25.7%)	7247 (26.1%)		892 (25.8%)	7228 (26.1%)	-0.69
Heart block 2nd or 3rd degree (not paced)	188 (5.5%)	1067 (3.8%)		145 (4.2%)	1116 (4.0%)	0.81
LVEF						
<20%	717 (20.8%)	6253 (22.5%)	<.0001	773 (22.3%)	6203 (22.4%)	-0.11
20%-30%	2255 (65.6%)	18756 (67.6%)		2355 (68.0%)	18693 (67.4%)	1.25
>30%	467 (13.6%)	2736 (9.9%)		336 (9.7%)	2838 (10.2%)	-1.8
QRS duration						
120-129	674 (19.6%)	2861 (10.3%)	<.0001	384 (11.1%)	3134 (11.3%)	-0.65
130-139	482 (14.0%)	3548 (12.8%)		450 (13.0%)	3586 (12.9%)	0.14
140-149	583 (17.0%)	4422 (15.9%)		545 (15.7%)	4450 (16.0%)	-0.83

150-159	521 (15.1%)	4573 (16.5%)		553 (16.0%)	4527 (16.3%)	-1.01
160-169	515 (15.0%)	5001 (18.0%)		625 (18.0%)	4911 (17.7%)	0.85
>=170	664 (19.3%)	7340 (26.5%)		908 (26.2%)	7125 (25.7%)	1.16
Creatinine Level						
<1	595 (17.3%)	4552 (16.4%)	0.0002	573 (16.5%)	4577 (16.5%)	0.11
1-2	2424 (70.5%)	20363 (73.4%)		2529 (73.0%)	20265 (73.1%)	-0.13
>2	420 (12.2%)	2830 (10.2%)		362 (10.4%)	2891 (10.4%)	0.05
BUN Level						
≤25	2064 (60.0%)	16454 (59.3%)	0.1033	2058 (59.4%)	16465 (59.4%)	0.07
26-50	1102 (32.0%)	9295 (33.5%)		1155 (33.3%)	9247 (33.3%)	-0.03
>50	273 (7.9%)	1996 (7.2%)		252 (7.3%)	2021 (7.3%)	-0.07
Sodium Level						
<135	431 (12.5%)	3290 (11.9%)	0.4634	411 (11.9%)	3311 (11.9%)	-0.24
135-145	2968 (86.3%)	24154 (87.1%)		3014 (87.0%)	24119 (87.0%)	0.13
>145	40 (1.2%)	301 (1.1%)		39 (1.1%)	304 (1.1%)	0.3
Systolic BP						
<110	585 (17.0%)	4904 (17.7%)	0.3345	617 (17.8%)	4882 (17.6%)	0.53
≥110	2854 (83.0%)	22841 (82.3%)		2847 (82.2%)	22852 (82.4%)	-0.53
ACE-inhibitors	2163 (62.9%)	17601 (63.4%)	0.5335	2231 (64.4%)	17563 (63.3%)	2.24
Angiotensin Receptor Blockers	470 (13.7%)	4681 (16.9%)	<.0001	491 (14.2%)	4665 (16.8%)	-7.32
Beta Blockers	2917 (84.8%)	24318 (87.6%)	<.0001	2970 (85.7%)	24286 (87.6%)	-5.36

Variables	Men, Non-LBBB, Unweighted			Men, Non-LBBB, Weighted		
	ICD only	CRT-D	P-value	ICD only (N=5308)	CRT-D (N=14839)	% Standardized difference
Demographic						
Age						
<50	313 (5.9%)	622 (4.2%)	<.0001	248 (4.7%)	684 (4.6%)	0.28
50-59	633 (11.9%)	1731 (11.7%)		632 (11.9%)	1744 (11.8%)	0.51
60-69	1367 (25.8%)	3922 (26.4%)		1390 (26.2%)	3897 (26.3%)	-0.17
70-79	1876 (35.3%)	5381 (36.3%)		1906 (35.9%)	5342 (36.0%)	-0.21
≥80	1118 (21.1%)	3188 (21.5%)		1132 (21.3%)	3172 (21.4%)	-0.12
Race						
White non-hispanic	4148 (78.2%)	12093 (81.5%)	<.0001	4263 (80.3%)	11942 (80.5%)	-0.42
Black non-hispanic	582 (11.0%)	1522 (10.3%)		565 (10.6%)	1560 (10.5%)	0.4
Hispanic	394 (7.4%)	768 (5.2%)		314 (5.9%)	861 (5.8%)	0.48
Other	183 (3.4%)	461 (3.1%)		166 (3.1%)	476 (3.2%)	-0.41
Clinical Characteristics						
Admission for this procedure	2782 (52.4%)	9224 (62.1%)	<.0001	3178 (59.9%)	8845 (59.6%)	0.52
Syncope	871 (16.4%)	1681 (11.3%)	<.0001	664 (12.5%)	1875 (12.6%)	-0.38
Family Hx Sudden Death	195 (3.7%)	521 (3.5%)	0.5784	193 (3.6%)	535 (3.6%)	0.19
CHF Duration						
No	688 (13.0%)	514 (3.5%)	<.0001	317 (6.0%)	878 (5.9%)	0.22
<3 months	900 (17.0%)	2059 (13.9%)		767 (14.4%)	2171 (14.6%)	-0.53
3-9 months	612 (11.5%)	2046 (13.8%)		694 (13.1%)	1957 (13.2%)	-0.34
>9 months	3107 (58.5%)	10225 (68.9%)		3530 (66.5%)	9832 (66.3%)	0.53

NYHA Class - Current Status						
III	4926 (92.8%)	13629 (91.8%)	0.0199	4915 (92.6%)	13674 (92.2%)	1.68
IV	381 (7.2%)	1215 (8.2%)		393 (7.4%)	1164 (7.8%)	-1.68
Cardiac arrest	219 (4.1%)	307 (2.1%)	<.0001	133 (2.5%)	384 (2.6%)	-0.53
Atrial Fibrillation/Flutter	2041 (38.5%)	5604 (37.8%)	0.3630	2016 (38.0%)	5649 (38.1%)	-0.17
Ventricular Tachycardia	1791 (33.7%)	3551 (23.9%)	<.0001	1383 (26.0%)	3902 (26.3%)	-0.57
Ischemic Heart Disease	4131 (77.8%)	11297 (76.1%)	0.0104	4080 (76.9%)	11361 (76.6%)	0.71
Previous MI	3368 (63.5%)	9193 (61.9%)	0.0480	3317 (62.5%)	9246 (62.3%)	0.36
Previous CABG	2539 (47.8%)	7071 (47.6%)	0.7955	2555 (48.1%)	7089 (47.8%)	0.72
Previous PCI	1822 (34.3%)	5322 (35.9%)	0.0468	1916 (36.1%)	5263 (35.5%)	1.3
Previous Valvular Surgery	427 (8.0%)	1238 (8.3%)	0.5042	432 (8.1%)	1228 (8.3%)	-0.53
Cerebrovascular Disease	1024 (19.3%)	2413 (16.3%)	<.0001	926 (17.5%)	2553 (17.2%)	0.65
Diabetes	2382 (44.9%)	6818 (45.9%)	0.1888	2424 (45.7%)	6779 (45.7%)	-0.04
Hypertension	4263 (80.3%)	11894 (80.1%)	0.7523	4260 (80.2%)	11899 (80.2%)	0.15
Renal Failure-Dialysis	358 (6.7%)	700 (4.7%)	<.0001	282 (5.3%)	785 (5.3%)	0.09
AV Conduction						
Normal	3650 (68.8%)	9973 (67.2%)	0.0720	3604 (67.9%)	10038 (67.6%)	0.53
1st degree heart block only	1363 (25.7%)	3960 (26.7%)		1398 (26.3%)	3915 (26.4%)	-0.1
Heart block 2nd or 3rd degree (not paced)	294 (5.5%)	911 (6.1%)		306 (5.8%)	885 (6.0%)	-0.86
LVEF						
<20%	838 (15.8%)	2900 (19.5%)	<.0001	979 (18.4%)	2758 (18.6%)	-0.38
20%-30%	3437 (64.8%)	10069 (67.8%)		3586 (67.6%)	9973 (67.2%)	0.76

>30%	1032 (19.4%)	1875 (12.6%)		743 (14.0%)	2107 (14.2%)	-0.6
QRS duration						
120-129	1649 (31.1%)	2882 (19.4%)	<.0001	1207 (22.7%)	3355 (22.6%)	0.33
130-139	1068 (20.1%)	2959 (19.9%)		1054 (19.9%)	2954 (19.9%)	-0.12
140-149	819 (15.4%)	2732 (18.4%)		929 (17.5%)	2611 (17.6%)	-0.24
150-159	698 (13.2%)	2255 (15.2%)		782 (14.7%)	2173 (14.6%)	0.25
160-169	534 (10.1%)	1933 (13.0%)		650 (12.2%)	1816 (12.2%)	0.02
>=170	539 (10.2%)	2083 (14.0%)		685 (12.9%)	1930 (13.0%)	-0.3
Creatinine Level						
<1	862 (16.2%)	2226 (15.0%)	0.0271	820 (15.4%)	2269 (15.3%)	0.43
1-2	3768 (71.0%)	10820 (72.9%)		3840 (72.3%)	10750 (72.4%)	-0.23
>2	677 (12.8%)	1798 (12.1%)		648 (12.2%)	1820 (12.3%)	-0.15
BUN Level						
≤25	3059 (57.6%)	8197 (55.2%)	0.0059	2969 (55.9%)	8271 (55.7%)	0.42
26-50	1780 (33.5%)	5328 (35.9%)		1860 (35.0%)	5247 (35.4%)	-0.67
>50	468 (8.8%)	1319 (8.9%)		479 (9.0%)	1321 (8.9%)	0.4
Sodium Level						
<135	690 (13.0%)	1857 (12.5%)	0.6519	663 (12.5%)	1877 (12.6%)	-0.48
135-145	4560 (85.9%)	12827 (86.4%)		4589 (86.5%)	12803 (86.3%)	0.52
>145	57 (1.1%)	160 (1.1%)		56 (1.1%)	159 (1.1%)	-0.2
Systolic BP						
<110	986 (18.6%)	2871 (19.3%)	0.2259	1017 (19.2%)	2850 (19.2%)	-0.12
≥110	4321 (81.4%)	11973 (80.7%)		4291 (80.8%)	11988 (80.8%)	0.12
ACE-inhibitors	3252 (61.3%)	9207 (62.0%)	0.3360	3280 (61.8%)	9194 (62.0%)	-0.34
Angiotensin Receptor Blockers	728 (13.7%)	2371 (16.0%)	<.0001	754 (14.2%)	2346 (15.8%)	-4.49
Beta Blockers	4462 (84.1%)	12813 (86.3%)	<.0001	4470 (84.2%)	12802 (86.3%)	-5.81

Table 3. Unweighted and Weighted Patient Characteristics by Bundle Branch Block Type in Women with CRT-D and ICD

	Women, LBBB, Unweighted			Women, LBBB, Weighted		
Variables	**ICD only**	**CRT-D**	**P-value**	**ICD only (N=2062)**	**CRT-D (N=16973)**	**% Standardized difference**
Demographic						
Age						
<50	98 (4.8%)	810 (4.8%)	0.0997	95 (4.6%)	809 (4.8%)	-0.75
50-59	239 (11.7%)	2133 (12.6%)		256 (12.4%)	2116 (12.5%)	-0.16
60-69	522 (25.5%)	4509 (26.6%)		543 (26.3%)	4485 (26.4%)	-0.21
70-79	721 (35.2%)	6056 (35.7%)		732 (35.5%)	6045 (35.6%)	-0.25
≥80	471 (23.0%)	3472 (20.4%)		436 (21.1%)	3518 (20.7%)	1.03
Race						
White non-hispanic	1537 (74.9%)	13178 (77.6%)	0.0132	1590 (77.1%)	13122 (77.3%)	-0.46
Black non-hispanic	341 (16.6%)	2417 (14.2%)		302 (14.6%)	2461 (14.5%)	0.39
Hispanic	127 (6.2%)	951 (5.6%)		118 (5.7%)	962 (5.7%)	0.22
Other	46 (2.2%)	434 (2.6%)		52 (2.5%)	429 (2.5%)	0.04
Clinical Characteristics						
Admission for this procedure	1289 (62.8%)	11999 (70.7%)	<.0001	1450 (70.3%)	11857 (69.9%)	0.99
Syncope	289 (14.1%)	1668 (9.8%)	<.0001	213 (10.3%)	1743 (10.3%)	0.18
Family Hx Sudden Death	91 (4.4%)	620 (3.7%)	0.0764	76 (3.7%)	632 (3.7%)	-0.3
CHF Duration						
No	153 (7.5%)	435 (2.6%)	<.0001	58 (2.8%)	516 (3.0%)	-1.36
<3 months	320 (15.6%)	2092 (12.3%)		263 (12.7%)	2151 (12.7%)	0.23
3-9 months	273 (13.3%)	2714 (16.0%)		332 (16.1%)	2667 (15.7%)	1.09

>9 months	1305 (63.6%)	11739 (69.1%)		1409 (68.3%)	11639 (68.6%)	-0.53
NYHA Class - Current Status						
III	1908 (93.0%)	15846 (93.3%)	0.6155	1933 (93.8%)	15837 (93.3%)	1.82
IV	143 (7.0%)	1134 (6.7%)		129 (6.2%)	1136 (6.7%)	-1.82
Cardiac arrest	68 (3.3%)	216 (1.3%)	<.0001	28 (1.3%)	249 (1.5%)	-0.98
Atrial Fibrillation/Flutter	492 (24.0%)	3534 (20.8%)	0.0009	438 (21.2%)	3590 (21.2%)	0.21
Ventricular Tachycardia	442 (21.6%)	2533 (14.9%)	<.0001	309 (15.0%)	2646 (15.6%)	-1.64
Ischemic Heart Disease	961 (46.9%)	6795 (40.0%)	<.0001	846 (41.0%)	6917 (40.7%)	0.55
Previous MI	716 (34.9%)	5050 (29.7%)	<.0001	623 (30.2%)	5140 (30.3%)	-0.16
Previous CABG	418 (20.4%)	2734 (16.1%)	<.0001	348 (16.9%)	2812 (16.6%)	0.88
Previous PCI	483 (23.5%)	3513 (20.7%)	0.0027	434 (21.1%)	3564 (21.0%)	0.16
Previous Valvular Surgery	146 (7.1%)	1057 (6.2%)	0.1162	137 (6.6%)	1075 (6.3%)	1.21
Cerebrovascular Disease	282 (13.7%)	2088 (12.3%)	0.0599	257 (12.5%)	2114 (12.5%)	0.09
Diabetes	843 (41.1%)	6718 (39.6%)	0.1789	810 (39.3%)	6741 (39.7%)	-0.84
Hypertension	1588 (77.4%)	12929 (76.1%)	0.1969	1573 (76.3%)	12948 (76.3%)	0
Renal Failure-Dialysis	72 (3.5%)	476 (2.8%)	0.0705	56 (2.7%)	487 (2.9%)	-1
AV Conduction						
Normal	1603 (78.2%)	13678 (80.6%)	<.0001	1663 (80.6%)	13632 (80.3%)	0.81
1st degree heart block only	364 (17.7%)	2914 (17.2%)		350 (17.0%)	2922 (17.2%)	-0.65
Heart block 2nd or 3rd degree (not paced)	84 (4.1%)	388 (2.3%)		49 (2.4%)	419 (2.5%)	-0.51
LVEF						
<20%	370 (18.0%)	3433 (20.2%)	<.0001	421 (20.4%)	3395 (20.0%)	1

20%-30%	1398 (68.2%)	11889 (70.0%)		1437 (69.7%)	11854 (69.8%)	-0.29
>30%	283 (13.8%)	1658 (9.8%)		204 (9.9%)	1724 (10.2%)	-0.9
QRS duration						
120-129	263 (12.8%)	1274 (7.5%)	<.0001	167 (8.1%)	1369 (8.1%)	0.14
130-139	310 (15.1%)	2101 (12.4%)		260 (12.6%)	2149 (12.7%)	-0.1
140-149	403 (19.6%)	3267 (19.2%)		388 (18.8%)	3270 (19.3%)	-1.16
150-159	375 (18.3%)	3524 (20.8%)		418 (20.3%)	3478 (20.5%)	-0.58
160-169	340 (16.6%)	3346 (19.7%)		399 (19.3%)	3290 (19.4%)	-0.09
>=170	360 (17.6%)	3468 (20.4%)		430 (20.9%)	3418 (20.1%)	1.78
Creatinine Level						
<1	787 (38.4%)	6671 (39.3%)	0.0259	807 (39.1%)	6651 (39.2%)	-0.08
1-2	1113 (54.3%)	9313 (54.8%)		1131 (54.9%)	9300 (54.8%)	0.14
>2	151 (7.4%)	996 (5.9%)		124 (6.0%)	1023 (6.0%)	-0.13
BUN Level						
≤25	1288 (62.8%)	10957 (64.5%)	0.2007	1333 (64.7%)	10920 (64.3%)	0.71
26-50	628 (30.6%)	5034 (29.6%)		606 (29.4%)	5051 (29.8%)	-0.76
>50	135 (6.6%)	989 (5.8%)		122 (5.9%)	1003 (5.9%)	0.04
Sodium Level						
<135	240 (11.7%)	1867 (11.0%)	0.6186	224 (10.8%)	1878 (11.1%)	-0.69
135-145	1790 (87.3%)	14945 (88.0%)		1819 (88.2%)	14927 (87.9%)	0.92
>145	21 (1.0%)	168 (1.0%)		19 (0.9%)	168 (1.0%)	-0.86
Systolic BP						
<110	348 (17.0%)	2914 (17.2%)	0.8257	352 (17.1%)	2909 (17.1%)	-0.14
≥110	1703 (83.0%)	14066 (82.8%)		1709 (82.9%)	14064 (82.9%)	0.14
ACE-inhibitors	1208 (58.9%)	10082 (59.4%)	0.6775	1231 (59.7%)	10060 (59.3%)	0.87
Angiotensin Receptor Blockers	402 (19.6%)	3904 (23.0%)	0.0005	425 (20.6%)	3893 (22.9%)	-5.64
Beta Blockers	1731 (84.4%)	15017 (88.4%)	<.0001	1764 (85.6%)	14997 (88.4%)	-8.29

Variables	Women, Non-LBBB, Unweighted			Women, Non-LBBB, Weighted		
	ICD only	CRT-D	P-value	ICD only (N=1302)	CRT-D (N=3411)	% Standardized difference
Demographic						
Age						
<50	95 (7.3%)	197 (5.8%)	0.0049	81 (6.2%)	212 (6.2%)	0.01
50-59	179 (13.8%)	393 (11.5%)		159 (12.2%)	416 (12.2%)	0.13
60-69	370 (28.5%)	920 (26.9%)		347 (26.6%)	934 (27.4%)	-1.63
70-79	404 (31.1%)	1227 (35.9%)		448 (34.4%)	1177 (34.5%)	-0.18
≥80	251 (19.3%)	677 (19.8%)		267 (20.5%)	673 (19.7%)	1.9
Race						
White non-hispanic	903 (69.5%)	2476 (72.5%)	0.1981	926 (71.1%)	2439 (71.5%)	-0.82
Black non-hispanic	270 (20.8%)	654 (19.2%)		262 (20.1%)	671 (19.7%)	1.06
Hispanic	82 (6.3%)	190 (5.6%)		77 (5.9%)	201 (5.9%)	0.11
Other	44 (3.4%)	94 (2.8%)		37 (2.9%)	100 (2.9%)	-0.47
Clinical Characteristics						
Admission for this procedure	632 (48.7%)	2074 (60.7%)	<.0001	752 (57.8%)	1964 (57.6%)	0.42
Syncope	189 (14.5%)	353 (10.3%)	<.0001	148 (11.4%)	389 (11.4%)	-0.03
Family Hx Sudden Death	64 (4.9%)	131 (3.8%)	0.0933	55 (4.2%)	142 (4.1%)	0.19
CHF Duration						
No	129 (9.9%)	96 (2.8%)	<.0001	61 (4.7%)	158 (4.6%)	0.05
<3 months	192 (14.8%)	486 (14.2%)		191 (14.7%)	494 (14.5%)	0.54
3-9 months	178 (13.7%)	514 (15.1%)		192 (14.7%)	500 (14.7%)	0.23
>9 months	800 (61.6%)	2318 (67.9%)		858 (65.9%)	2258 (66.2%)	-0.59

NYHA Class - Current Status						
III	1179 (90.8%)	3117 (91.3%)	0.5609	1190 (91.5%)	3112 (91.2%)	0.83
IV	120 (9.2%)	297 (8.7%)		111 (8.5%)	299 (8.8%)	-0.83
Cardiac arrest	59 (4.5%)	91 (2.7%)	0.001	38 (2.9%)	106 (3.1%)	-0.98
Atrial Fibrillation/Flutter	421 (32.4%)	1050 (30.8%)	0.2736	415 (31.9%)	1068 (31.3%)	1.16
Ventricular Tachycardia	407 (31.3%)	679 (19.9%)	<.0001	298 (22.9%)	781 (22.9%)	-0.03
Ischemic Heart Disease	808 (62.2%)	2047 (60.0%)	0.1592	793 (60.9%)	2074 (60.8%)	0.29
Previous MI	660 (50.8%)	1624 (47.6%)	0.0468	634 (48.7%)	1659 (48.6%)	0.2
Previous CABG	424 (32.6%)	1105 (32.4%)	0.8576	431 (33.1%)	1111 (32.6%)	1.23
Previous PCI	385 (29.6%)	986 (28.9%)	0.6091	380 (29.2%)	992 (29.1%)	0.27
Previous Valvular Surgery	109 (8.4%)	360 (10.5%)	0.0273	129 (9.9%)	339 (10.0%)	-0.13
Cerebrovascular Disease	217 (16.7%)	581 (17.0%)	0.7979	221 (17.0%)	578 (16.9%)	0.05
Diabetes	668 (51.4%)	1628 (47.7%)	0.0218	637 (49.0%)	1663 (48.8%)	0.43
Hypertension	1069 (82.3%)	2734 (80.1%)	0.0856	1058 (81.3%)	2753 (80.7%)	1.55
Renal Failure-Dialysis	82 (6.3%)	150 (4.4%)	0.0065	64 (4.9%)	167 (4.9%)	0.02
AV Conduction						
Normal	961 (74.0%)	2466 (72.2%)	<.0001	942 (72.4%)	2477 (72.6%)	-0.57
1st degree heart block only	234 (18.0%)	765 (22.4%)		278 (21.3%)	723 (21.2%)	0.33
Heart block 2nd or 3rd degree (not paced)	104 (8.0%)	183 (5.4%)		82 (6.3%)	210 (6.2%)	0.49
LVEF						
<20%	224 (17.2%)	642 (18.8%)	<.0001	240 (18.4%)	629 (18.4%)	-0.1
20%-30%	834 (64.2%)	2398 (70.2%)		896 (68.9%)	2341 (68.6%)	0.48

>30%	241 (18.6%)	374 (11.0%)		166 (12.7%)	441 (12.9%)	-0.55
QRS duration						
120-129	420 (32.3%)	797 (23.3%)	<.0001	336 (25.8%)	882 (25.9%)	-0.13
130-139	296 (22.8%)	778 (22.8%)		297 (22.8%)	777 (22.8%)	0.16
140-149	210 (16.2%)	633 (18.5%)		239 (18.3%)	617 (18.1%)	0.67
150-159	151 (11.6%)	489 (14.3%)		177 (13.6%)	460 (13.5%)	0.26
160-169	118 (9.1%)	365 (10.7%)		127 (9.8%)	345 (10.1%)	-1.21
>=170	104 (8.0%)	352 (10.3%)		126 (9.7%)	330 (9.7%)	0.02
Creatinine Level						
<1	448 (34.5%)	1129 (33.1%)	0.3244	426 (32.7%)	1135 (33.3%)	-1.16
1-2	723 (55.7%)	1979 (58.0%)		757 (58.2%)	1962 (57.5%)	1.35
>2	128 (9.9%)	306 (9.0%)		119 (9.1%)	315 (9.2%)	-0.42
BUN Level						
≤25	771 (59.4%)	1952 (57.2%)	0.1523	753 (57.8%)	1971 (57.8%)	0.08
26-50	408 (31.4%)	1172 (34.3%)		438 (33.6%)	1145 (33.6%)	0.18
>50	120 (9.2%)	290 (8.5%)		111 (8.5%)	295 (8.6%)	-0.45
Sodium Level						
<135	197 (15.2%)	455 (13.3%)	0.1949	175 (13.5%)	472 (13.8%)	-1.12
135-145	1081 (83.2%)	2913 (85.3%)		1109 (85.2%)	2891 (84.7%)	1.37
>145	21 (1.6%)	46 (1.3%)		17 (1.3%)	48 (1.4%)	-0.91
Systolic BP						
<110	229 (17.6%)	664 (19.4%)	0.1542	240 (18.4%)	644 (18.9%)	-1.25
≥110	1070 (82.4%)	2750 (80.6%)		1062 (81.6%)	2767 (81.1%)	1.25
ACE-inhibitors	734 (56.5%)	1939 (56.8%)	0.8572	745 (57.3%)	1943 (57.0%)	0.6
Angiotensin Receptor Blockers	245 (18.9%)	720 (21.1%)	0.0902	259 (19.9%)	712 (20.9%)	-2.41
Beta Blockers	1105 (85.1%)	2929 (85.8%)	0.5246	1119 (86.0%)	2918 (85.6%)	1.27

Table 4. Propensity Score Weighted Mortality Hazard Ratios by Sex for QRS Duration Groups in the LBBB and non-LBBB

	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
QRS duration	LBBB		for HR	Non-LBBB		for HR
120-129 ms						
Women	0.95	0.76 – 1.06	0.678	1.03	0.84 – 1.26	0.786
Men	0.91	0.80 – 1.04	0.148	0.98	0.89 – 1.08	0.719
130-139 ms						
Women	0.74	0.60 – 0.91	0.005	0.92	0.74 – 1.14	0.450
Men	0.76	0.66 – 0.87	<0.001	0.98	0.87 – 1.09	0.656
140-149 ms						
Women	0.69	0.57 – 0.83	<0.001	0.81	0.63 – 1.04	0.102
Men	0.82	0.71 – 0.93	0.003	0.98	0.86 – 1.10	0.682
150-159 ms						
Women	0.77	0.62 – 0.94	0.012	0.59	0.44 – 0.77	<0.001
Men	0.88	0.75 – 1.02	0.095	0.93	0.82 – 1.06	0.277
160-169 ms						
Women	0.72	0.58 – 0.89	0.003	1.20	0.84 – 1.72	0.312
Men	0.87	0.74 – 1.02	0.092	0.92	0.79 – 1.06	0.246
>170 ms						
Women	0.77	0.63 – 0.95	0.016	1.17	0.82 – 1.69	0.384
Men	0.82	0.71 – 0.94	0.005	0.94	0.81 – 1.08	0.370

Inverse probability treatment weighting adjusted CRT-D to ICD hazard ratios for mortality including 95% confidence intervals and p-values for left bundle branch block (left) and non-left bundle branch block (right) in 10 ms QRS duration subgroups for women and men. The same information is presented in Figure 3 of the main text.

SUPPLEMENT TO CHAPTER V
Comparative Effectiveness of Cardiac Resynchronization Therapy Defibrillators vs. Standard Implantable Defibrillators in Medicare Patients

Supplemental Methods

Charlson Score

The Charlson score is a score to predict 10-year mortality based on whether a patient has certain health conditions. Conditions are given a score of 1 to 6 based on their associated mortality risk. Scores are calculated as follows:[5]

- 1 point each: Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, ulcer disease, mild liver disease
- 2 points each: Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, any tumor, leukemia, lymphoma
- 3 points each: Moderate or severe liver disease
- 6 points each: Metastatic solid tumor, AIDS

End Stage Renal Disease

The following two methods were used to determine whether a patient had end stage renal disease (ESRD) (only one of two criteria must be met):

- If a patient registered to be eligible to receive Medicare benefits due to ESRD in the month of implantation. This is determined by an ESRD eligibility form submitted to CMS
- If a patient received an outpatient "72X" type of billing (dialysis) claim within the month before or month after implantation.

Supplemental Tables

Table 1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Procedure Codes (PRC), Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) Codes Identifying Procedures and Comorbidities

Comorbidity	Codes	Description
Cardiac Resynchronization Therapy	00.51	Implantation of cardiac resynchronization defibrillator, total system [CRT-D]
Implantable Cardioverter Defibrillator	37.94	Implantation or replacement of automatic cardioverter/defibrillator, total system [AICD]
Ventricular Tachycardia	427.1	Ventricular tachycardia
Ventricular Fibrillation	427.41	Ventricular fibrillation
Ventricular Flutter	427.42	Ventricular flutter
Cardiac Arrest	427.5	Cardiac arrest
Sudden Cardiac Arrest	V12.53	Personal history of sudden cardiac arrest
Left Bundle Branch Block	426.3	Other left bundle branch block
Right Bundle Branch Block	426.4	Right bundle branch block
	426.51	Right bundle branch block and left posterior fascicular block
	426.52	Right bundle branch block and left anterior fascicular block
Diabetes	250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
	250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
	250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
	250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
	250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
	250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
	250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
	250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
	250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
	250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
	250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
	250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled

250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled
250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
250.81	Diabetes with other specified manifestations, type I [juvenile type], not stated as

		uncontrolled
	250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
	250.83	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
	250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
	250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
	250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
	250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled
Mitral/Aortic Valve Disorders	39.40	Mitral stenosis
	39.49	Other and unspecified mitral valve diseases
	39.60	Mitral valve stenosis and aortic valve stenosis
	39.61	Mitral valve stenosis and aortic valve insufficiency
	39.62	Mitral valve insufficiency and aortic valve stenosis
	39.63	Mitral valve insufficiency and aortic valve insufficiency
	39.68	Multiple involvement of mitral and aortic valves
	39.69	Mitral and aortic valve diseases, unspecified
	42.40	Mitral valve disorders
	42.41	Aortic valve disorders
Hypertension	401.0	Malignant essential hypertension
	401.1	Benign essential hypertension
	401.9	Unspecified essential hypertension
	402.00	Malignant hypertensive heart disease without heart failure
	402.01	Malignant hypertensive heart disease with heart failure
	402.10	Benign hypertensive heart disease without heart failure
	402.11	Benign hypertensive heart disease with heart failure
	402.90	Unspecified hypertensive heart disease without heart failure
	402.91	Unspecified hypertensive heart disease with heart failure
	403.00	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified
	403.01	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease
	403.10	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage I through

	stage IV, or unspecified
403.11	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease
403.90	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified
403.91	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
404.00	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.02	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.10	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.12	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.90	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified

	404.92	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
	404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
	405.01	Malignant renovascular hypertension
	405.09	Other malignant secondary hypertension
	405.99	Other unspecified secondary hypertension
	997.91	Complications affecting other specified body systems, not elsewhere classified, hypertension
Myocardial Infarction	410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified
	410.01	Acute myocardial infarction of anterolateral wall, initial episode of care
	410.02	Acute myocardial infarction of anterolateral wall, subsequent episode of care
	410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified
	410.11	Acute myocardial infarction of other anterior wall, initial episode of care
	410.12	Acute myocardial infarction of other anterior wall, subsequent episode of care
	410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified
	410.21	Acute myocardial infarction of inferolateral wall, initial episode of care
	410.22	Acute myocardial infarction of inferolateral wall, subsequent episode of care
	410.30	Acute myocardial infarction of inferoposterior wall, episode of care unspecified
	410.31	Acute myocardial infarction of inferoposterior wall, initial episode of care
	410.32	Acute myocardial infarction of inferoposterior wall, subsequent episode of care
	410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified
	410.41	Acute myocardial infarction of other inferior wall, initial episode of care
	410.42	Acute myocardial infarction of other inferior wall, subsequent episode of care
	410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified
	410.51	Acute myocardial infarction of other lateral wall, initial episode of care
	410.52	Acute myocardial infarction of other lateral wall, subsequent episode of care

	410.60	True posterior wall infarction, episode of care unspecified
	410.61	True posterior wall infarction, initial episode of care
	410.62	True posterior wall infarction, subsequent episode of care
	410.70	Subendocardial infarction, episode of care unspecified
	410.71	Subendocardial infarction, initial episode of care
	410.72	Subendocardial infarction, subsequent episode of care
	410.80	Acute myocardial infarction of other specified sites, episode of care unspecified
	410.81	Acute myocardial infarction of other specified sites, initial episode of care
	410.82	Acute myocardial infarction of other specified sites, subsequent episode of care
	410.90	Acute myocardial infarction of unspecified site, episode of care unspecified
	410.91	Acute myocardial infarction of unspecified site, initial episode of care
	410.92	Acute myocardial infarction of unspecified site, subsequent episode of care
	412	Old myocardial infarction
Ischemic Heart Disease	414.8	Other specified forms of chronic ischemic heart disease
	414.9	Chronic ischemic heart disease, unspecified
Tricuspid/Pulmonary Valve Disorders	424.2	Tricuspid valve disorders, specified as nonrheumatic
	424.3	Pulmonary valve disorders
Hypertrophic Cardiomyopathy	425.11	Hypertrophic obstructive cardiomyopathy
	425.18	Other hypertrophic cardiomyopathy
Atrial Fibrillation	427.31	Atrial fibrillation
Heart Failure Hospitalization*	428.0	Congestive heart failure, unspecified
	428.1	Left heart failure
	428.20	Systolic heart failure, unspecified
	428.21	Acute systolic heart failure
	428.22	Chronic systolic heart failure
	428.23	Acute on chronic systolic heart failure
	428.30	Diastolic heart failure, unspecified
	428.31	Acute diastolic heart failure
	428.32	Chronic diastolic heart failure
	428.33	Acute on chronic diastolic heart failure
	428.40	Combined systolic and diastolic heart failure, unspecified
	428.41	Acute combined systolic and diastolic heart failure

	428.42	Chronic combined systolic and diastolic heart failure
	428.43	Acute on chronic combined systolic and diastolic heart failure
	429.9	Heart failure, unspecified
Stroke	430	Subarachnoid hemorrhage
	431	Intracerebral hemorrhage
	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
	433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
	434.01	Cerebral thrombosis with cerebral infarction
	434.11	Cerebral embolism with cerebral infarction
	434.91	Cerebral artery occlusion, unspecified with cerebral infarction
Peripheral Vascular Disease	440.20	Atherosclerosis of native arteries of the extremities, unspecified
	440.21	Atherosclerosis of native arteries of the extremities with intermittent claudication
	440.22	Atherosclerosis of native arteries of the extremities with rest pain
	440.23	Atherosclerosis of native arteries of the extremities with ulceration
	440.24	Atherosclerosis of native arteries of the extremities with gangrene
	440.29	Other atherosclerosis of native arteries of the extremities
	440.4	Chronic total occlusion of artery of the extremities
	443.89	Other specified peripheral vascular diseases
	443.9	Peripheral vascular disease, unspecified
Percutaneous Transluminal Coronary Angioplasty	00.66	Percutaneous transluminal coronary angioplasty [PTCA]
	36.06	Insertion of non-drug-eluting coronary artery stent(s)
	36.07	Insertion of drug-eluting coronary artery stent(s)
Coronary Artery Bypass Graft	36.10	Aortocoronary bypass for heart revascularization, not otherwise specified
	36.11	(Aorto)coronary bypass of one coronary artery
	36.12	(Aorto)coronary bypass of two coronary

	arteries
36.13	(Aorto)coronary bypass of three coronary arteries
36.14	(Aorto)coronary bypass of four or more coronary arteries
36.15	Single internal mammary-coronary artery bypass
36.16	Double internal mammary-coronary artery bypass
36.19	Other bypass anastomosis for heart revascularization

* Only considering inpatient claims and only counting as a heart failure hospitalization if the heart failure diagnosis was the primary diagnosis

Table 2. Procedure Codes (PRC) and Current Procedural Terminology (CPT) Maintenance Codes Used for Cohort Cleaning

Codes	Description
37.76	Replacement of transvenous atrial and/or ventricular lead(s) (electrode(s))
37.97	Replacement of automatic cardioverter/defibrillator leads(s) only
89.45	Artificial pacemaker rate check
89.46	Artificial pacemaker artifact wave form check
89.47	Artificial pacemaker electrode impedance check
89.48	Artificial pacemaker voltage or amperage threshold check
89.49	Automatic implantable cardioverter/defibrillator (AICD) check
93279	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with physician analysis, review and report; single lead pacemaker system
93280	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with physician analysis, review and report; dual lead pacemaker system
93281	Programming device evaluation (in person) with iterative adjustment of the implantable device to test function of the device and select optimal permanent programmed values with physician analysis, review and report; multiple lead pacemaker system
93282	Programming device evaluation (in person) with iterative adjustment of implantable device to test function of device & select optimal permanent programmed values, review & report; single lead implantable cardioverter-defibrillator system
93283	Programming device evaluation (in person) with iterative adjustment of implantable device to test function of device & select optimal permanent programmed values, review & report; dual lead implantable cardioverter-defibrillator system
93284	Programming device evaluation (in person) with iterative adjustment of the implantable device to test function of device & select optimal permanent programmed, review & report; multiple lead implantable cardioverter-defibrillator system
93287	Peri-procedural device evaluation (in person) & programming device system parameters before or after a surgery, procedure, or test with physician analysis, review & report; single, dual, or multiple lead implantable cardioverter-defibrillator system
93288	Interrogation device evaluation (in person) with physician analysis, review and report; single, dual, or multiple lead pacemaker system
93289	Interrogation device evaluation (in person) with physician analysis, review and report; single, dual, or multiple lead implantable cardioverter-defibrillator system, including analysis of heart rhythm derived data elements
93293	Transtelephonic rhythm strip pacemaker evaluation(s) single, dual, or multiple lead pacemaker system, includes recording with and without magnet application with physician analysis, review and report(s), up to 90 days

93294	Interrogation device evaluation(s) (remote), up to 90 days; single, dual, or multiple lead pacemaker system with interim physician analysis, review(s) and report(s)
93295	Interrogation device evaluation(s) (remote), up to 90 days; single, dual, or multiple lead implantable cardioverter-defibrillator system with interim physician analysis, review(s) and report(s)
93296	Interrogation device evaluation(s) (remote), up to 90 days; single, dual, or multiple lead pacemaker system or implantable cardioverter-defibrillator system, remote data acquisition(s), transmissions receipt & technician review
33202	Insertion of epicardial electrode(s); open incision (eg, thoracotomy, median sternotomy, subxiphoid approach)
33203	Insertion of epicardial electrode(s); endoscopic approach (eg, thoracoscopy, pericardioscopy)
33215	Repositioning of previously implanted transvenous pacemaker or pacing cardioverter-defibrillator (right atrial or right ventricular) electrode
33216	Insertion of a single transvenous electrode, permanent pacemaker or cardioverter-defibrillator
33217	Insertion of 2 transvenous electrodes, permanent pacemaker or cardioverter-defibrillator
33218	Repair of single transvenous electrode for a single chamber, permanent pacemaker or single chamber pacing cardioverter-defibrillator
33220	Repair of 2 transvenous electrodes for a dual chamber permanent pacemaker or dual chamber pacing cardioverter-defibrillator
33223	Revision of skin pocket for cardioverter-defibrillator
33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or pacing cardioverter-defibrillator pulse generator
33226	Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion and/or replacement of generator)
33233	Removal of permanent pacemaker pulse generator
33234	Removal of transvenous pacemaker electrode(s); single lead system, atrial or ventricular
33235	Removal of transvenous pacemaker electrode(s); dual lead system
33241	Subcutaneous removal of single or dual chamber pacing cardioverter-defibrillator pulse generator
33243	Removal of single or dual chamber pacing cardioverter-defibrillator electrode(s); by thoracotomy
33244	Removal of single or dual chamber pacing cardioverter-defibrillator electrode(s); by transvenous extraction
33249	Insertion or repositioning of electrode lead(s) for single or dual chamber pacing cardioverter-defibrillator and insertion of pulse generator

Table 3. Multivariable Model for Heart Failure Hospitalization or Death in LBBB

Covariates	Hazard Ratio	P-Value	95% Confidence Interval
Cohort			
CRT-D	0.882	<0.001	(0.863, 0.902)
ICD	Reference		
Demographics			
Gender: Male	1.109	<0.001	(1.084, 1.134)
Age			
0-64	1.211	<0.001	(1.162, 1.262)
65-69	Reference		
70-74	1.043	0.019	(1.007, 1.08)
75-79	1.171	<0.001	(1.132, 1.211)
80-84	1.349	<0.001	(1.302, 1.397)
85+	1.64	<0.001	(1.569, 1.713)
Race			
Black	1.342	<0.001	(1.294, 1.391)
Other	1.181	<0.001	(1.116, 1.25)
White	Reference		
Charlson Score			
Charlson Score 0	0.785	<0.001	(0.68, 0.906)
Charlson Score 1	Reference		
Charlson Score 2	1.209	<0.001	(1.154, 1.267)
Charlson Score 3	1.332	<0.001	(1.272, 1.396)
Charlson Score 4+	1.765	<0.001	(1.687, 1.847)
Health Conditions			
Diabetes	1.137	<0.001	(1.112, 1.163)
Mitral/Aortic Valve Disorder	1.074	<0.001	(1.05, 1.097)
Hypertension	0.974	0.125	(0.943, 1.007)
Myocardial Infarction	1.06	<0.001	(1.037, 1.083)
Ischemic Heart Disease	1.167	<0.001	(1.141, 1.193)
Tricuspid Pulmonary Valve Disorder	1.052	<0.001	(1.024, 1.082)
Atrial Fibrillation	1.291	<0.001	(1.265, 1.318)
Prior Heart Failure Hospitalization	1.688	<0.001	(1.652, 1.724)
Prior Stroke	1.06	0.007	(1.016, 1.106)
Peripheral Vascular disease	1.159	<0.001	(1.132, 1.187)
Ventricular Tachycardia	1.207	<0.001	(1.182, 1.232)
Prior PTCA	0.654	<0.001	(0.617, 0.693)
Prior CABG	0.925	<0.001	(0.894, 0.957)

Table 4. Multivariable Model for Heart Failure Hospitalization or Death in RBBB

Covariates	Hazard Ratio	P-Value	95% Confidence Interval
Cohort			
CRT-D	1.146	<0.001	(1.099, 1.196)
ICD	Reference		
Demographics			
Gender: Male	0.913	0.002	(0.861, 0.968)
Age			
0-64	1.114	0.017	(1.02, 1.217)
65-69	Reference		
70-74	0.995	0.887	(0.924, 1.071)
75-79	1.12	0.002	(1.043, 1.203)
80-84	1.324	<0.001	(1.229, 1.426)
85+	1.544	<0.001	(1.404, 1.697)
Race			
Black	1.349	<0.001	(1.252, 1.454)
Other	1.01	0.874	(0.897, 1.137)
White	Reference		
Charlson Score			
Charlson Score 0	0.689	0.050	(0.474, 0.999)
Charlson Score 1	Reference		
Charlson Score 2	1.387	<0.001	(1.228, 1.566)
Charlson Score 3	1.61	<0.001	(1.431, 1.812)
Charlson Score 4+	2.2	<0.001	(1.961, 2.468)
Health Conditions			
Diabetes	1.086	<0.001	(1.037, 1.138)
Mitral/Aortic Valve Disorder	1.113	<0.001	(1.062, 1.165)
Hypertension	0.962	0.314	(0.892, 1.038)
Myocardial Infarction	0.964	0.115	(0.92, 1.009)
Ischemic Heart Disease	1.104	<0.001	(1.052, 1.158)
Tricuspid Pulmonary Valve Disorder	1.024	0.409	(0.968, 1.084)
Atrial Fibrillation	1.236	<0.001	(1.183, 1.292)
Prior Heart Failure Hospitalization	1.867	<0.001	(1.782, 1.956)
Prior Stroke	1.025	0.564	(0.943, 1.113)
Peripheral Vascular disease	1.122	<0.001	(1.07, 1.177)
Ventricular Tachycardia	1.088	<0.001	(1.042, 1.136)
Prior PTCA	0.681	<0.001	(0.617, 0.751)
Prior CABG	0.955	0.153	(0.896, 1.017)

Table 5. Multivariable Model for Mortality in LBBB

Covariates	Hazard Ratio	P-Value	95% Confidence Interval
Cohort			
CRT-D	0.946	<0.001	(0.921, 0.972)
ICD	Reference		
Demographics			
Gender: Male	1.271	<0.001	(1.236, 1.306)
Age			
0-64	1.067	0.020	(1.010, 1.126)
65-69	Reference		
70-74	1.107	<0.001	(1.059, 1.157)
75-79	1.354	<0.001	(1.298, 1.412)
80-84	1.645	<0.001	(1.575, 1.717)
85+	2.184	<0.001	(2.074, 2.300)
Race			
Black	1.117	<0.001	(1.067, 1.170)
Other	1.051	0.168	(0.979, 1.128)
White	Reference		
Charlson Score			
Charlson Score 0	0.696	<0.001	(0.573, 0.846)
Charlson Score 1	Reference		
Charlson Score 2	1.268	<0.001	(1.194, 1.346)
Charlson Score 3	1.455	<0.001	(1.372, 1.544)
Charlson Score 4+	2.058	<0.001	(1.943, 2.179)
Health Conditions			
Diabetes	1.101	<0.001	(1.072, 1.131)
Mitral/Aortic Valve Disorder	1.098	<0.001	(1.069, 1.127)
Hypertension	0.858	<0.001	(0.825, 0.892)
Myocardial Infarction	1.011	0.420	(0.985, 1.038)
Ischemic Heart Disease	1.181	<0.001	(1.15, 1.214)
Tricuspid Pulmonary Valve Disorder	1.06	0.001	(1.026, 1.095)
Atrial Fibrillation	1.287	<0.001	(1.255, 1.319)
Prior Heart Failure Hospitalization	1.534	<0.001	(1.494, 1.574)
Prior Stroke	1.097	<0.001	(1.044, 1.154)
Peripheral Vascular disease	1.191	<0.001	(1.158, 1.224)
Ventricular Tachycardia	1.223	<0.001	(1.193, 1.253)
Prior PTCA	0.574	<0.001	(0.533, 0.618)
Prior CABG	0.837	<0.001	(0.802, 0.873)

Table 6. Multivariable Model for Mortality in RBBB

Covariates	Hazard Ratio	P-Value	95% Confidence Interval
Cohort			
CRT-D	1.125	<0.001	(1.07, 1.182)
ICD	Reference		
Demographics			
Gender: Male	1.019	0.593	(0.95, 1.094)
Age			
0-64	0.986	0.811	(0.882, 1.103)
65-69	Reference		
70-74	1.058	0.221	(0.966, 1.159)
75-79	1.284	<0.001	(1.178, 1.4)
80-84	1.539	<0.001	(1.408, 1.682)
85+	2.008	<0.001	(1.802, 2.238)
Race			
Black	1.047	0.338	(0.953, 1.151)
Other	0.922	0.260	(0.8, 1.062)
White	Reference		
Charlson Score			
Charlson Score 0	0.762	0.244	(0.482, 1.204)
Charlson Score 1	Reference		
Charlson Score 2	1.392	<0.001	(1.195, 1.621)
Charlson Score 3	1.712	<0.001	(1.478, 1.983)
Charlson Score 4+	2.558	<0.001	(2.218, 2.951)
Health Conditions			
Diabetes	1.019	0.504	(0.965, 1.076)
Mitral/Aortic Valve Disorder	1.124	<0.001	(1.064, 1.187)
Hypertension	0.906	0.029	(0.829, 0.99)
Myocardial Infarction	0.937	0.017	(0.888, 0.988)
Ischemic Heart Disease	1.071	0.017	(1.012, 1.134)
Tricuspid Pulmonary Valve Disorder	1.003	0.937	(0.938, 1.071)
Atrial Fibrillation	1.24	<0.001	(1.178, 1.306)
Prior Heart Failure Hospitalization	1.653	<0.001	(1.565, 1.745)
Prior Stroke	1.029	0.553	(0.936, 1.131)
Peripheral Vascular disease	1.177	<0.001	(1.115, 1.244)
Ventricular Tachycardia	1.117	<0.001	(1.062, 1.175)
Prior PTCA	0.575	<0.001	(0.509, 0.651)
Prior CABG	0.849	<0.001	(0.786, 0.916)

Table 7A. Prevalence, Relative Risk and Treatment Distribution of Observed Covariates in the Propensity Score Matched LBBB Population

Covariate	Prevalence	Relative Risk	Treatment Distribution
Charlson Score 0	0.01	0.47	0.69
Race: Other	0.03	1.06	1.00
Prior PTCA (Bypass)	0.04	0.92	0.83
Prior Stroke	0.05	1.18	0.90
Age: 85+	0.07	1.31	0.98
Race: Black	0.08	1.09	1.00
Angioplasty	0.10	1.04	0.87
Charlson Score 1	0.11	0.61	0.96
Tricuspid Pulmonary Valve Disorder	0.16	1.12	1.05
Age: 65-69	0.16	0.83	0.98
Charlson Score 2	0.18	0.75	0.96
Age: 80-84	0.18	1.18	1.02
Charlson Score 3	0.20	0.88	1.00
Peripheral Vascular Disease	0.22	1.29	1.00
Age: 70-74	0.23	0.88	0.98
Age: 75-79	0.26	1.01	1.01
Prior Heart Failure Hospitalization	0.28	1.49	1.17
Ventricular Tachycardia	0.38	1.23	0.83
Myocardial Infarction	0.40	1.23	0.91
Atrial Fibrillation	0.45	1.31	1.07
Diabetes	0.46	1.23	1.05
Charlson Score 4+	0.50	1.53	1.04
Mitral/Aortic Valve Disorder	0.58	1.14	1.03
Ischemic Heart Disease	0.60	1.28	0.99
Gender: Male	0.68	1.17	0.98
Hypertension	0.87	1.18	1.00
Race: White	0.89	0.92	1.00

Table 7B. Prevalence, Relative Risk and Treatment Distribution of Observed Covariates in the Propensity Score Matched RBBB Population

Covariate	Prevalence	Relative Risk	Treatment Distribution
Charlson Score 0	0.01	0.32	1.11
Race: Other	0.03	0.96	1.02
Prior PTCA (Bypass)	0.06	0.78	1.01
Prior Stroke	0.06	1.17	1.00
Age: 85+	0.06	1.45	1.04
Charlson Score 1	0.07	0.52	1.04
Race: Black	0.08	1.03	0.99
Angioplasty	0.13	0.99	1.00
Charlson Score 2	0.14	0.74	1.02
Age: 65-69	0.15	0.79	0.99
Tricuspid Pulmonary Valve Disorder	0.17	1.11	1.00
Charlson Score 3	0.19	0.80	0.99
Age: 80-84	0.19	1.25	0.98
Age: 70-74	0.22	0.91	1.00
Age: 75-79	0.26	1.01	1.02
Prior Heart Failure Hospitalization	0.27	1.47	1.04
Peripheral Vascular Disease	0.27	1.34	1.00
Ventricular Tachycardia	0.45	1.19	1.01
Atrial Fibrillation	0.50	1.28	1.01
Diabetes	0.52	1.19	1.00
Myocardial Infarction	0.53	1.11	1.00
Mitral/Aortic Valve Disorder	0.58	1.23	1.01
Charlson Score 4+	0.58	1.58	0.99
Ischemic Heart Disease	0.68	1.11	1.00
Gender: Male	0.85	0.99	1.00
Race: White	0.88	0.99	1.00
Hypertension	0.89	1.16	1.00

Supplemental Figures and Figure Legends

Figure 1. Adjusted hazard ratios for heart failure hospitalization or death (bar height) for an introduced covariate with a total population prevalence of 40% in LBBB, divided by treatment distribution (horizontal axis, range 0.5-2 – illustrates the effect of various distributions of the covariate within both treatment groups) and relative risk of heart failure or death (depth axis, range 1-2 – illustrates the effect of increasing probability of heart failure hospitalization or death due to the covariate). Colors are explained in the legend. Plane indicates no difference between CRT-D and ICD (HR=1).

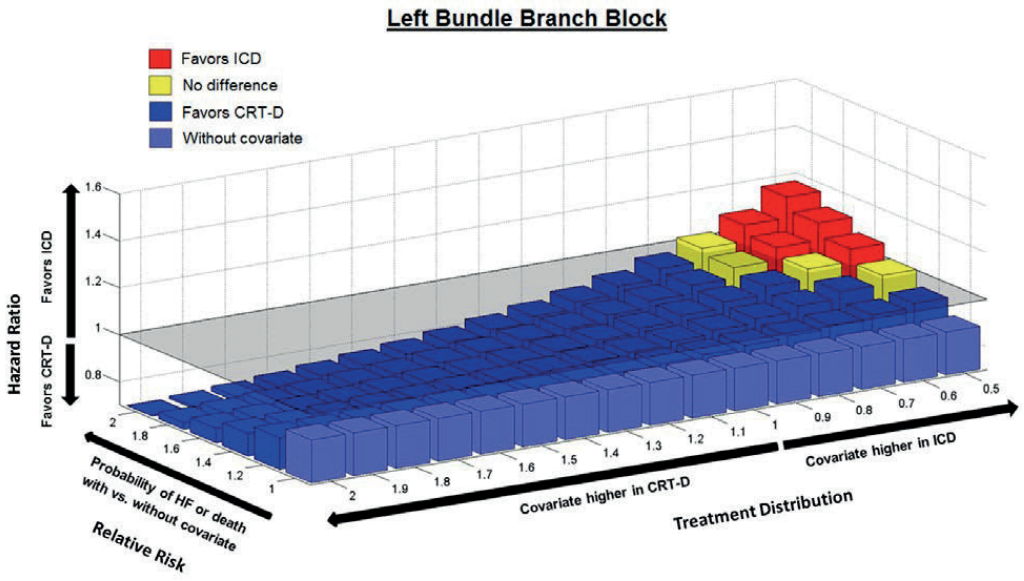


Figure 2. Distribution of hazard ratios and 95% confidence intervals by prevalence, relative risk and treatment distribution of an introduced covariate for propensity score matched left bundle branch block patients with heart failure hospitalization or death as the outcome.

Prevalence	Relative Risk	Treatment Distribution (the ratio of the proportion of CRT-D patients with covariate to the proportion of ICD patients with covariate)															
		0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.3	1	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)
	1.2	0.93 (0.91-0.96)	0.92 (0.90-0.94)	0.91 (0.89-0.93)	0.90 (0.88-0.92)	0.89 (0.87-0.91)	0.88 (0.86-0.90)	0.88 (0.85-0.90)	0.87 (0.85-0.89)	0.87 (0.85-0.89)	0.86 (0.84-0.88)	0.86 (0.84-0.88)	0.86 (0.83-0.88)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.85 (0.82-0.87)
	1.4	0.98 (0.96-1.00)	0.95 (0.93-0.97)	0.93 (0.91-0.95)	0.91 (0.89-0.93)	0.89 (0.87-0.92)	0.88 (0.86-0.90)	0.87 (0.85-0.89)	0.86 (0.84-0.88)	0.85 (0.83-0.87)	0.85 (0.82-0.87)	0.84 (0.82-0.86)	0.83 (0.81-0.85)	0.83 (0.80-0.85)	0.82 (0.80-0.84)	0.82 (0.80-0.84)	0.81 (0.79-0.83)
	1.6	1.02 (1.00-1.05)	0.98 (0.96-1.00)	0.95 (0.93-0.97)	0.92 (0.90-0.94)	0.90 (0.88-0.92)	0.88 (0.86-0.90)	0.86 (0.84-0.89)	0.85 (0.83-0.87)	0.84 (0.82-0.86)	0.83 (0.81-0.85)	0.82 (0.80-0.84)	0.81 (0.79-0.83)	0.80 (0.78-0.83)	0.80 (0.78-0.82)	0.79 (0.77-0.81)	0.79 (0.76-0.81)
	1.8	1.07 (1.04-1.09)	1.01 (0.99-1.03)	0.97 (0.95-0.99)	0.93 (0.91-0.95)	0.91 (0.88-0.93)	0.88 (0.86-0.90)	0.86 (0.84-0.88)	0.84 (0.82-0.86)	0.83 (0.80-0.85)	0.81 (0.79-0.83)	0.80 (0.78-0.82)	0.79 (0.77-0.81)	0.78 (0.76-0.80)	0.77 (0.75-0.79)	0.77 (0.74-0.79)	0.76 (0.74-0.78)
	2	1.11 (1.09-1.14)	1.04 (1.02-1.07)	0.99 (0.97-1.01)	0.95 (0.92-0.97)	0.91 (0.89-0.93)	0.88 (0.86-0.90)	0.85 (0.83-0.87)	0.83 (0.81-0.85)	0.81 (0.79-0.84)	0.80 (0.78-0.82)	0.78 (0.76-0.81)	0.77 (0.75-0.79)	0.76 (0.74-0.78)	0.75 (0.73-0.77)	0.74 (0.72-0.76)	0.73 (0.71-0.75)
0.4	1	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)
	1.2	0.95 (0.92-0.97)	0.93 (0.91-0.95)	0.91 (0.89-0.94)	0.90 (0.88-0.92)	0.89 (0.87-0.91)	0.88 (0.86-0.90)	0.87 (0.85-0.90)	0.87 (0.85-0.89)	0.86 (0.84-0.88)	0.86 (0.84-0.88)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.84 (0.82-0.87)	0.84 (0.82-0.86)	0.84 (0.82-0.86)	0.84 (0.81-0.86)
	1.4	1.01 (0.99-1.03)	0.97 (0.95-0.99)	0.94 (0.92-0.96)	0.92 (0.90-0.94)	0.90 (0.88-0.92)	0.88 (0.86-0.90)	0.87 (0.85-0.89)	0.86 (0.83-0.88)	0.84 (0.82-0.86)	0.84 (0.81-0.86)	0.83 (0.80-0.85)	0.82 (0.80-0.84)	0.81 (0.79-0.83)	0.81 (0.78-0.83)	0.80 (0.78-0.82)	0.80 (0.77-0.82)
	1.6	1.07 (1.04-1.09)	1.01 (0.99-1.03)	0.97 (0.95-0.99)	0.93 (0.91-0.95)	0.91 (0.88-0.93)	0.88 (0.86-0.90)	0.86 (0.84-0.88)	0.84 (0.82-0.86)	0.83 (0.81-0.85)	0.82 (0.79-0.84)	0.80 (0.78-0.83)	0.79 (0.77-0.81)	0.78 (0.76-0.80)	0.77 (0.75-0.80)	0.77 (0.75-0.79)	0.76 (0.74-0.78)
	1.8	1.12 (1.10-1.14)	1.05 (1.02-1.07)	0.99 (0.97-1.01)	0.95 (0.93-0.97)	0.91 (0.89-0.93)	0.88 (0.86-0.90)	0.85 (0.83-0.88)	0.83 (0.81-0.86)	0.81 (0.79-0.83)	0.80 (0.78-0.82)	0.78 (0.76-0.80)	0.77 (0.75-0.79)	0.76 (0.73-0.78)	0.75 (0.72-0.77)	0.74 (0.71-0.76)	0.73 (0.70-0.75)
	2	1.17 (1.15-1.20)	1.09 (1.06-1.11)	1.02 (0.99-1.04)	0.96 (0.94-0.98)	0.92 (0.89-0.94)	0.88 (0.86-0.90)	0.85 (0.83-0.87)	0.82 (0.80-0.85)	0.80 (0.78-0.82)	0.78 (0.76-0.80)	0.76 (0.74-0.79)	0.75 (0.73-0.77)	0.73 (0.71-0.75)	0.72 (0.70-0.74)	0.71 (0.69-0.73)	0.70 (0.68-0.72)
0.5	1	0.88 (0.86-0.91)	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.91)
	1.2	0.96 (0.94-0.99)	0.94 (0.92-0.96)	0.92 (0.90-0.94)	0.91 (0.88-0.93)	0.89 (0.87-0.91)	0.88 (0.86-0.90)	0.87 (0.85-0.89)	0.86 (0.84-0.89)	0.86 (0.84-0.88)	0.85 (0.83-0.87)	0.85 (0.82-0.87)	0.84 (0.82-0.86)	0.84 (0.82-0.86)	0.83 (0.81-0.86)	0.83 (0.80-0.85)	0.83 (0.80-0.85)
	1.4	1.04 (1.01-1.06)	0.99 (0.97-1.02)	0.96 (0.93-0.98)	0.93 (0.90-0.95)	0.90 (0.88-0.92)	0.88 (0.86-0.90)	0.86 (0.84-0.89)	0.85 (0.83-0.87)	0.84 (0.82-0.86)	0.83 (0.80-0.85)	0.81 (0.79-0.84)	0.81 (0.78-0.83)	0.80 (0.78-0.82)	0.79 (0.77-0.81)	0.78 (0.76-0.81)	0.78 (0.75-0.80)
	1.6	1.11 (1.08-1.13)	1.04 (1.01-1.06)	0.99 (0.96-1.01)	0.94 (0.92-0.97)	0.91 (0.89-0.93)	0.88 (0.86-0.90)	0.86 (0.84-0.88)	0.84 (0.82-0.86)	0.82 (0.80-0.84)	0.80 (0.78-0.82)	0.79 (0.77-0.81)	0.78 (0.76-0.80)	0.76 (0.74-0.79)	0.76 (0.73-0.78)	0.75 (0.72-0.77)	0.74 (0.71-0.76)
	1.8	1.17 (1.14-1.19)	1.08 (1.06-1.10)	1.01 (0.99-1.03)	0.96 (0.94-0.98)	0.92 (0.89-0.94)	0.88 (0.86-0.90)	0.85 (0.83-0.87)	0.82 (0.80-0.85)	0.80 (0.78-0.82)	0.78 (0.76-0.80)	0.77 (0.75-0.79)	0.75 (0.73-0.77)	0.74 (0.72-0.76)	0.73 (0.70-0.75)	0.72 (0.69-0.74)	0.70 (0.68-0.73)
	2	1.22 (1.20-1.25)	1.12 (1.10-1.14)	1.04 (1.02-1.06)	0.97 (0.95-1.00)	0.92 (0.90-0.94)	0.88 (0.86-0.90)	0.84 (0.82-0.87)	0.81 (0.79-0.84)	0.79 (0.76-0.81)	0.77 (0.74-0.79)	0.75 (0.72-0.77)	0.73 (0.70-0.75)	0.71 (0.69-0.73)	0.70 (0.67-0.72)	0.68 (0.66-0.71)	0.67 (0.65-0.70)
0.6	1	0.88 (0.86-0.91)	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.90)	0.88 (0.86-0.91)	0.88 (0.86-0.91)	0.88 (0.86-0.90)	0.88 (0.86-0.91)	0.88 (0.86-0.91)
	1.2	0.98 (0.96-1.00)	0.95 (0.93-0.97)	0.93 (0.91-0.95)	0.91 (0.89-0.93)	0.90 (0.87-0.92)	0.88 (0.86-0.90)	0.87 (0.85-0.89)	0.86 (0.84-0.88)	0.85 (0.83-0.88)	0.85 (0.82-0.87)	0.84 (0.82-0.86)	0.83 (0.81-0.86)	0.83 (0.80-0.85)	0.82 (0.80-0.85)	0.82 (0.80-0.84)	0.82 (0.79-0.84)
	1.4	1.06 (1.04-1.09)	1.01 (0.99-1.03)	0.97 (0.95-0.99)	0.93 (0.91-0.95)	0.91 (0.88-0.93)	0.88 (0.86-0.90)	0.86 (0.84-0.88)	0.84 (0.82-0.87)	0.83 (0.81-0.85)	0.82 (0.79-0.84)	0.81 (0.78-0.83)	0.80 (0.77-0.82)	0.79 (0.76-0.81)	0.78 (0.75-0.80)	0.77 (0.75-0.79)	0.76 (0.74-0.79)
	1.6	1.14 (1.12-1.16)	1.06 (1.04-1.09)	1.00 (0.98-1.02)	0.95 (0.93-0.98)	0.91 (0.89-0.94)	0.88 (0.86-0.90)	0.85 (0.83-0.87)	0.83 (0.81-0.85)	0.81 (0.79-0.83)	0.79 (0.77-0.81)	0.78 (0.75-0.80)	0.76 (0.74-0.78)	0.75 (0.73-0.77)	0.74 (0.71-0.76)	0.73 (0.70-0.75)	0.72 (0.70-0.74)
	1.8	1.21 (1.18-1.23)	1.11 (1.08-1.13)	1.03 (1.01-1.05)	0.97 (0.95-0.99)	0.92 (0.90-0.94)	0.88 (0.86-0.90)	0.85 (0.83-0.87)	0.82 (0.80-0.84)	0.79 (0.77-0.82)	0.77 (0.75-0.79)	0.75 (0.73-0.77)	0.73 (0.71-0.76)	0.72 (0.70-0.74)	0.71 (0.68-0.73)	0.69 (0.67-0.72)	0.68 (0.66-0.71)
	2	1.27 (1.25-1.30)	1.15 (1.12-1.17)	1.06 (1.04-1.08)	0.99 (0.96-1.01)	0.93 (0.91-0.95)	0.88 (0.86-0.90)	0.84 (0.82-0.86)	0.81 (0.78-0.83)	0.78 (0.76-0.80)	0.75 (0.73-0.77)	0.73 (0.71-0.75)	0.71 (0.69-0.73)	0.70 (0.67-0.72)	0.68 (0.65-0.70)	0.66 (0.64-0.69)	0.65 (0.63-0.67)

indicates p-values <0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios less than 1
indicates p-values <0.05 for hazard ratios less than 1
indicates the values of relative risk, prevalence, and treatment distribution (rounded up to the nearest 10th) where some observed covariates fall

Figure 3. Distribution of hazard ratios and 95% confidence intervals by prevalence, relative risk and treatment distribution of an introduced covariate for propensity score matched right bundle branch block patients with heart failure hospitalization or death as the outcome.

Prevalence	Relative Risk	Treatment Distribution (the ratio of the proportion of CRT-D patients with covariate to the proportion of ICD patients with covariate)															
		0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.3	1	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)
	1.2	1.20 (1.16-1.25)	1.19 (1.15-1.24)	1.18 (1.14-1.22)	1.17 (1.12-1.21)	1.16 (1.11-1.20)	1.15 (1.10-1.19)	1.14 (1.10-1.18)	1.13 (1.09-1.17)	1.13 (1.08-1.17)	1.12 (1.08-1.16)	1.11 (1.07-1.16)	1.11 (1.07-1.15)	1.10 (1.06-1.15)	1.10 (1.06-1.14)	1.10 (1.05-1.14)	1.09 (1.05-1.13)
	1.4	1.27 (1.22-1.31)	1.24 (1.19-1.28)	1.21 (1.17-1.25)	1.19 (1.14-1.23)	1.17 (1.13-1.21)	1.15 (1.11-1.19)	1.13 (1.09-1.18)	1.12 (1.08-1.17)	1.11 (1.06-1.15)	1.10 (1.05-1.14)	1.08 (1.04-1.13)	1.08 (1.03-1.12)	1.07 (1.02-1.11)	1.06 (1.02-1.10)	1.05 (1.01-1.10)	1.04 (1.00-1.09)
	1.6	1.33 (1.29-1.38)	1.28 (1.24-1.32)	1.25 (1.20-1.29)	1.21 (1.17-1.25)	1.18 (1.14-1.22)	1.15 (1.11-1.20)	1.13 (1.09-1.17)	1.11 (1.07-1.16)	1.09 (1.05-1.14)	1.08 (1.03-1.12)	1.06 (1.02-1.10)	1.05 (1.00-1.09)	1.03 (0.99-1.08)	1.02 (0.98-1.07)	1.01 (0.97-1.06)	1.00 (0.96-1.05)
	1.8	1.39 (1.35-1.44)	1.33 (1.29-1.37)	1.28 (1.23-1.32)	1.23 (1.19-1.28)	1.19 (1.15-1.24)	1.16 (1.12-1.20)	1.13 (1.08-1.17)	1.10 (1.06-1.14)	1.08 (1.03-1.12)	1.06 (1.01-1.10)	1.04 (1.00-1.08)	1.03 (0.98-1.07)	1.00 (0.96-1.05)	0.99 (0.95-1.03)	0.98 (0.94-1.02)	0.97 (0.92-1.01)
	2	2.81 (2.77-2.86)	1.39 (1.34-1.43)	1.32 (1.28-1.36)	1.26 (1.22-1.30)	1.21 (1.17-1.25)	1.17 (1.12-1.21)	1.13 (1.08-1.17)	1.10 (1.05-1.14)	1.07 (1.03-1.11)	1.04 (1.00-1.09)	1.01 (0.97-1.06)	1.00 (0.95-1.04)	0.98 (0.94-1.02)	0.96 (0.92-1.00)	0.95 (0.90-0.99)	0.93 (0.88-0.97)
0.4	1	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)
	1.2	1.23 (1.18-1.27)	1.21 (1.16-1.25)	1.19 (1.14-1.23)	1.17 (1.13-1.22)	1.16 (1.12-1.20)	1.15 (1.10-1.19)	1.14 (1.09-1.18)	1.13 (1.08-1.17)	1.12 (1.07-1.16)	1.11 (1.07-1.15)	1.10 (1.06-1.15)	1.10 (1.05-1.14)	1.09 (1.05-1.13)	1.08 (1.04-1.13)	1.08 (1.04-1.12)	1.08 (1.03-1.12)
	1.4	1.30 (1.25-1.34)	1.26 (1.22-1.30)	1.23 (1.19-1.27)	1.20 (1.16-1.24)	1.17 (1.13-1.22)	1.15 (1.11-1.19)	1.13 (1.09-1.17)	1.11 (1.07-1.16)	1.10 (1.05-1.14)	1.08 (1.04-1.12)	1.07 (1.02-1.11)	1.06 (1.01-1.10)	1.04 (1.00-1.09)	1.03 (0.99-1.08)	1.02 (0.98-1.07)	1.01 (0.97-1.06)
	1.6	1.38 (1.34-1.43)	1.32 (1.27-1.36)	1.27 (1.23-1.32)	1.22 (1.18-1.27)	1.19 (1.14-1.23)	1.16 (1.11-1.20)	1.13 (1.08-1.17)	1.10 (1.06-1.14)	1.08 (1.03-1.12)	1.06 (1.01-1.10)	1.04 (1.00-1.08)	1.02 (0.98-1.06)	1.01 (0.96-1.05)	0.99 (0.95-1.03)	0.98 (0.93-1.02)	0.97 (0.92-1.01)
	1.8	1.47 (1.42-1.51)	1.38 (1.33-1.42)	1.31 (1.27-1.36)	1.25 (1.21-1.30)	1.20 (1.16-1.24)	1.16 (1.12-1.20)	1.12 (1.08-1.16)	1.09 (1.04-1.13)	1.06 (1.02-1.10)	1.03 (0.99-1.08)	1.01 (0.97-1.05)	0.99 (0.95-1.03)	0.97 (0.93-1.01)	0.95 (0.91-1.00)	0.94 (0.89-0.98)	0.92 (0.88-0.97)
	2	1.55 (1.50-1.59)	1.44 (1.40-1.49)	1.35 (1.31-1.39)	1.28 (1.24-1.32)	1.22 (1.17-1.26)	1.17 (1.12-1.21)	1.12 (1.08-1.16)	1.08 (1.04-1.12)	1.05 (1.00-1.09)	1.01 (0.97-1.06)	0.99 (0.94-1.03)	0.96 (0.92-1.01)	0.94 (0.90-0.98)	0.92 (0.87-0.96)	0.90 (0.85-0.94)	0.88 (0.84-0.93)
0.5	1	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.14 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)
	1.2	1.24 (1.20-1.29)	1.22 (1.18-1.26)	1.20 (1.15-1.24)	1.18 (1.14-1.22)	1.16 (1.12-1.21)	1.15 (1.11-1.19)	1.14 (1.09-1.18)	1.12 (1.08-1.17)	1.11 (1.07-1.15)	1.10 (1.06-1.14)	1.09 (1.05-1.14)	1.09 (1.04-1.13)	1.08 (1.04-1.12)	1.07 (1.02-1.11)	1.07 (1.02-1.11)	1.06 (1.01-1.10)
	1.4	1.33 (1.29-1.38)	1.29 (1.24-1.33)	1.24 (1.20-1.29)	1.21 (1.16-1.25)	1.18 (1.13-1.22)	1.15 (1.11-1.19)	1.13 (1.08-1.17)	1.10 (1.06-1.15)	1.09 (1.04-1.13)	1.07 (1.02-1.11)	1.05 (1.01-1.10)	1.04 (0.99-1.08)	1.02 (0.98-1.07)	1.01 (0.97-1.06)	1.00 (0.95-1.04)	0.99 (0.94-1.03)
	1.6	1.43 (1.39-1.48)	1.36 (1.32-1.40)	1.29 (1.25-1.33)	1.24 (1.19-1.28)	1.19 (1.15-1.24)	1.16 (1.11-1.20)	1.12 (1.07-1.16)	1.09 (1.05-1.13)	1.06 (1.02-1.10)	1.04 (0.99-1.08)	1.01 (0.97-1.06)	1.00 (0.96-1.04)	0.98 (0.93-1.02)	0.96 (0.92-1.01)	0.95 (0.90-1.00)	0.94 (0.89-0.98)
	1.8	1.52 (1.47-1.57)	1.42 (1.38-1.46)	1.34 (1.29-1.38)	1.27 (1.22-1.31)	1.21 (1.16-1.25)	1.16 (1.11-1.20)	1.11 (1.07-1.16)	1.08 (1.04-1.12)	1.04 (1.00-1.08)	1.02 (0.97-1.06)	0.99 (0.95-1.03)	0.96 (0.92-1.01)	0.94 (0.90-0.99)	0.92 (0.88-0.96)	0.91 (0.86-0.95)	0.88 (0.84-0.93)
	2	1.61 (1.57-1.66)	1.48 (1.44-1.53)	1.38 (1.34-1.42)	1.29 (1.25-1.33)	1.22 (1.18-1.27)	1.16 (1.12-1.21)	1.11 (1.07-1.15)	1.06 (1.02-1.11)	1.02 (0.98-1.07)	0.99 (0.95-1.03)	0.96 (0.92-1.01)	0.93 (0.88-0.97)	0.91 (0.87-0.95)	0.88 (0.84-0.92)	0.86 (0.82-0.91)	0.84 (0.80-0.89)
0.6	1	1.15 (1.10-1.20)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.15 (1.10-1.19)	1.14 (1.10-1.19)	1.15 (1.10-1.19)
	1.2	1.26 (1.21-1.31)	1.23 (1.19-1.28)	1.21 (1.16-1.25)	1.18 (1.14-1.23)	1.16 (1.12-1.21)	1.15 (1.10-1.19)	1.13 (1.09-1.18)	1.12 (1.07-1.16)	1.11 (1.06-1.15)	1.09 (1.05-1.14)	1.09 (1.04-1.13)	1.08 (1.03-1.12)	1.07 (1.02-1.11)	1.06 (1.01-1.10)	1.05 (1.01-1.10)	1.04 (0.99-1.09)
	1.4	1.37 (1.32-1.42)	1.31 (1.27-1.36)	1.26 (1.22-1.31)	1.22 (1.18-1.26)	1.18 (1.14-1.23)	1.15 (1.11-1.19)	1.12 (1.08-1.17)	1.10 (1.05-1.14)	1.07 (1.03-1.12)	1.06 (1.01-1.10)	1.04 (1.00-1.08)	1.02 (0.98-1.06)	1.01 (0.96-1.05)	0.99 (0.95-1.04)	0.98 (0.93-1.02)	0.96 (0.92-1.01)
	1.6	1.48 (1.43-1.52)	1.38 (1.34-1.43)	1.32 (1.27-1.36)	1.25 (1.21-1.29)	1.20 (1.16-1.24)	1.15 (1.11-1.20)	1.11 (1.07-1.16)	1.08 (1.04-1.12)	1.05 (1.01-1.09)	1.02 (0.98-1.06)	1.00 (0.95-1.04)	0.97 (0.93-1.02)	0.96 (0.91-1.00)	0.94 (0.89-0.98)	0.92 (0.87-0.96)	0.90 (0.86-0.95)
	1.8	1.58 (1.53-1.63)	1.45 (1.41-1.50)	1.36 (1.31-1.40)	1.28 (1.24-1.32)	1.21 (1.17-1.26)	1.16 (1.11-1.20)	1.11 (1.07-1.15)	1.06 (1.02-1.11)	1.03 (0.99-1.07)	0.99 (0.95-1.04)	0.97 (0.92-1.01)	0.94 (0.90-0.98)	0.91 (0.87-0.96)	0.90 (0.85-0.94)	0.87 (0.83-0.92)	0.85 (0.81-0.90)
	2	1.68 (1.63-1.72)	1.52 (1.48-1.57)	1.40 (1.36-1.44)	1.31 (1.26-1.35)	1.22 (1.18-1.27)	1.16 (1.11-1.20)	1.11 (1.06-1.15)	1.05 (1.01-1.10)	1.01 (0.97-1.05)	0.97 (0.93-1.01)	0.94 (0.89-0.98)	0.91 (0.86-0.95)	0.88 (0.84-0.93)	0.86 (0.81-0.90)	0.83 (0.79-0.88)	0.81 (0.77-0.86)

indicates p-values <0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios less than 1
indicates p-values <0.05 for hazard ratios less than 1
indicates the values of relative risk, prevalence, and treatment distribution (rounded up to the nearest 10th) where some observed covariates fall

Figure 4. Adjusted hazard ratios for all-cause mortality (bar height) for an introduced covariate with a total population prevalence of 40% in LBBB, divided by treatment distribution (horizontal axis, range 0.5-2 – illustrates the effect of various distributions of the covariate within both treatment groups) and relative risk of heart failure or death (depth axis, range 1-2 – illustrates the effect of increasing probability of heart failure hospitalization or death due to the covariate). Colors are explained in the legend. Plane indicates no difference between CRT-D and ICD (HR=1).

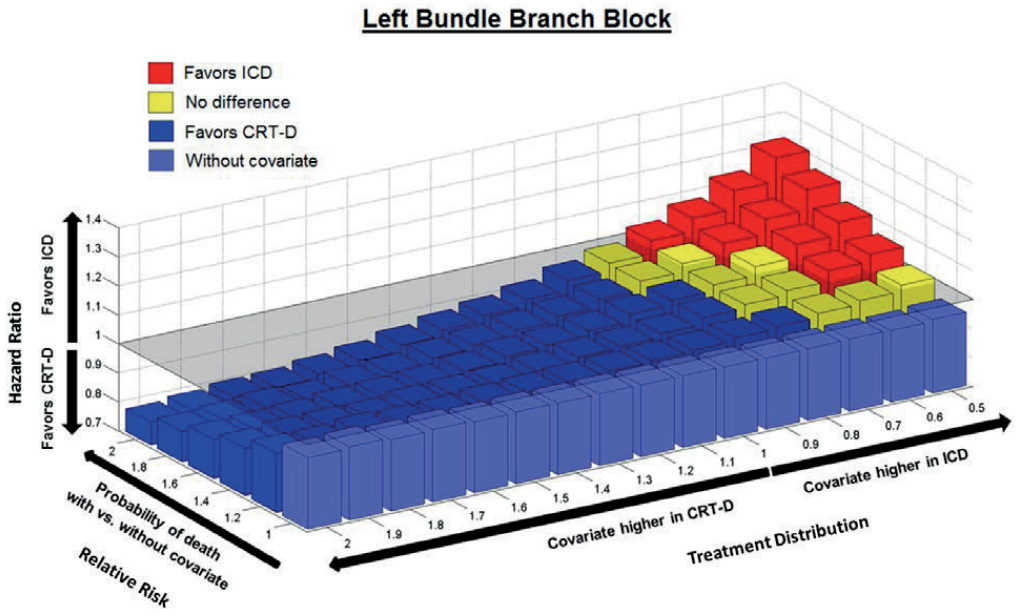


Figure 5. Adjusted hazard ratios for all-cause mortality (bar height) for an introduced covariate with a total population prevalence of 40% in RBBB, divided by treatment distribution (horizontal axis, range 0.5-2 – illustrates the effect of various distributions of the covariate within both treatment groups) and relative risk of heart failure or death (depth axis, range 1-2 – illustrates the effect of increasing probability of heart failure hospitalization or death due to the covariate). Colors are explained in the legend. Plane indicates no difference between CRT-D and ICD (HR=1).

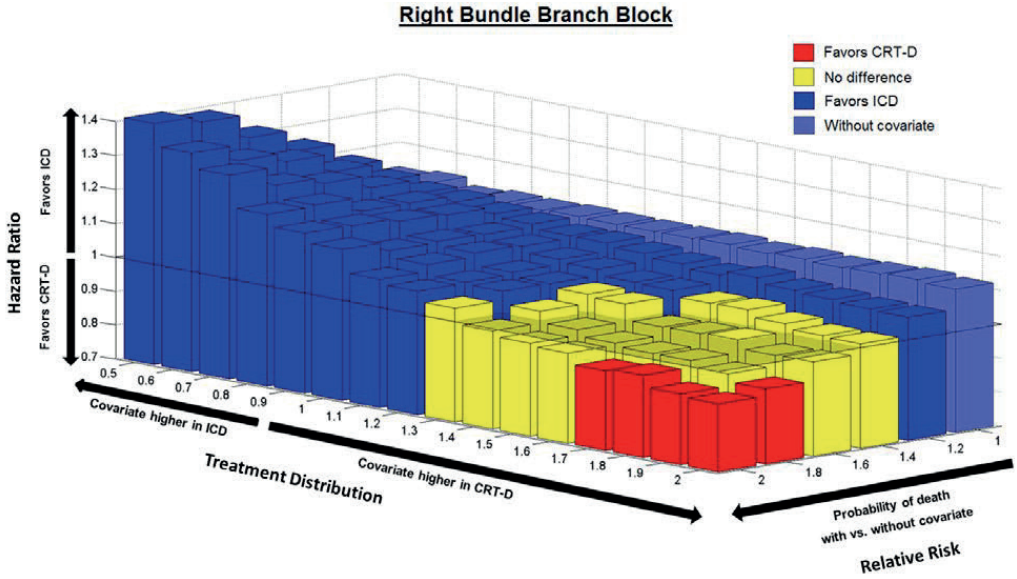


Figure 6. Distribution of hazard ratios and 95% confidence intervals by prevalence, relative risk and treatment distribution of an introduced covariate for propensity score matched left bundle branch block patients with death as the outcome.

Prevalence	Relative Risk	Treatment Distribution (the ratio of the proportion of CRT-D patients with covariate to the proportion of ICD patients with covariate)															
		0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.3	1	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.94 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)
	1.2	1.00 (0.97-1.02)	0.98 (0.95-1.00)	0.97 (0.94-1.00)	0.96 (0.93-0.99)	0.96 (0.93-0.98)	0.95 (0.92-0.97)	0.94 (0.91-0.97)	0.94 (0.91-0.96)	0.93 (0.90-0.96)	0.93 (0.90-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.94)	0.92 (0.89-0.94)	0.92 (0.89-0.94)	0.91 (0.89-0.94)
	1.4	1.04 (1.01-1.06)	1.01 (0.99-1.04)	0.99 (0.96-1.02)	0.97 (0.94-1.00)	0.96 (0.93-0.99)	0.95 (0.92-0.97)	0.93 (0.91-0.96)	0.93 (0.90-0.95)	0.92 (0.89-0.95)	0.91 (0.88-0.94)	0.90 (0.88-0.93)	0.90 (0.87-0.93)	0.90 (0.87-0.92)	0.89 (0.86-0.92)	0.89 (0.86-0.92)	0.89 (0.86-0.92)
	1.6	1.08 (1.05-1.11)	1.04 (1.02-1.07)	1.01 (0.98-1.03)	0.98 (0.95-1.01)	0.96 (0.93-0.99)	0.94 (0.91-0.97)	0.94 (0.91-0.96)	0.92 (0.89-0.95)	0.90 (0.87-0.93)	0.90 (0.87-0.93)	0.89 (0.86-0.91)	0.88 (0.85-0.91)	0.87 (0.84-0.90)	0.86 (0.83-0.89)	0.87 (0.84-0.90)	0.86 (0.83-0.89)
	1.8	1.12 (1.09-1.15)	1.07 (1.04-1.10)	1.03 (1.01-1.06)	1.00 (0.97-1.02)	0.97 (0.94-1.00)	0.94 (0.91-0.97)	0.93 (0.90-0.96)	0.91 (0.88-0.94)	0.89 (0.86-0.91)	0.89 (0.86-0.92)	0.87 (0.84-0.90)	0.87 (0.84-0.89)	0.85 (0.82-0.88)	0.85 (0.82-0.88)	0.84 (0.81-0.86)	0.83 (0.80-0.85)
	2	1.17 (1.14-1.19)	1.09 (1.07-1.12)	1.04 (1.02-1.07)	1.02 (0.99-1.04)	0.97 (0.94-1.00)	0.95 (0.92-0.97)	0.93 (0.90-0.95)	0.91 (0.88-0.94)	0.88 (0.85-0.91)	0.87 (0.84-0.90)	0.86 (0.83-0.89)	0.84 (0.82-0.87)	0.84 (0.81-0.86)	0.82 (0.80-0.85)	0.81 (0.78-0.83)	0.82 (0.79-0.84)
0.4	1	0.95 (0.93-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.94 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)
	1.2	1.01 (0.99-1.04)	0.99 (0.96-1.02)	0.98 (0.95-1.01)	0.96 (0.94-0.99)	0.96 (0.93-0.98)	0.95 (0.92-0.97)	0.94 (0.91-0.97)	0.94 (0.91-0.96)	0.93 (0.90-0.96)	0.93 (0.90-0.95)	0.92 (0.89-0.95)	0.91 (0.88-0.94)	0.91 (0.88-0.94)	0.91 (0.88-0.94)	0.90 (0.87-0.93)	0.90 (0.87-0.93)
	1.4	1.06 (1.03-1.09)	1.04 (1.01-1.06)	1.00 (0.97-1.03)	0.98 (0.95-1.01)	0.97 (0.94-1.00)	0.94 (0.92-0.97)	0.93 (0.90-0.96)	0.93 (0.90-0.95)	0.91 (0.88-0.94)	0.90 (0.87-0.92)	0.89 (0.86-0.92)	0.89 (0.86-0.91)	0.87 (0.85-0.90)	0.88 (0.85-0.90)	0.87 (0.85-0.90)	0.86 (0.83-0.89)
	1.6	1.11 (1.09-1.14)	1.07 (1.04-1.10)	1.02 (1.00-1.05)	0.99 (0.96-1.02)	0.97 (0.94-1.00)	0.95 (0.93-0.98)	0.93 (0.90-0.95)	0.91 (0.88-0.94)	0.90 (0.87-0.93)	0.88 (0.86-0.91)	0.87 (0.84-0.90)	0.86 (0.83-0.89)	0.85 (0.83-0.88)	0.84 (0.82-0.87)	0.84 (0.81-0.87)	0.83 (0.81-0.86)
	1.8	1.17 (1.14-1.20)	1.10 (1.07-1.13)	1.05 (1.02-1.07)	1.01 (0.98-1.03)	0.98 (0.95-1.01)	0.95 (0.92-0.98)	0.92 (0.89-0.95)	0.90 (0.88-0.93)	0.88 (0.85-0.91)	0.87 (0.84-0.90)	0.85 (0.82-0.88)	0.84 (0.81-0.87)	0.82 (0.79-0.85)	0.82 (0.80-0.85)	0.81 (0.79-0.84)	0.80 (0.78-0.83)
	2	1.22 (1.19-1.25)	1.14 (1.11-1.16)	1.07 (1.05-1.10)	1.03 (1.00-1.06)	0.98 (0.95-1.01)	0.95 (0.93-0.98)	0.92 (0.89-0.95)	0.90 (0.87-0.92)	0.88 (0.85-0.90)	0.86 (0.83-0.88)	0.83 (0.81-0.86)	0.82 (0.79-0.85)	0.80 (0.78-0.83)	0.80 (0.77-0.83)	0.79 (0.76-0.82)	0.78 (0.75-0.81)
0.5	1	0.96 (0.93-0.99)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.94 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.94 (0.91-0.96)
	1.2	1.02 (0.99-1.05)	1.00 (0.97-1.03)	0.99 (0.96-1.01)	0.97 (0.94-1.00)	0.96 (0.93-0.99)	0.95 (0.92-0.97)	0.94 (0.91-0.97)	0.93 (0.90-0.96)	0.93 (0.90-0.95)	0.92 (0.89-0.95)	0.91 (0.88-0.94)	0.91 (0.88-0.94)	0.91 (0.88-0.93)	0.90 (0.87-0.92)	0.89 (0.86-0.92)	0.88 (0.86-0.91)
	1.4	1.10 (1.07-1.13)	1.05 (1.02-1.08)	1.02 (0.99-1.05)	0.99 (0.96-1.02)	0.97 (0.94-0.99)	0.95 (0.92-0.98)	0.93 (0.90-0.96)	0.91 (0.89-0.94)	0.91 (0.88-0.93)	0.90 (0.87-0.92)	0.88 (0.86-0.91)	0.88 (0.85-0.90)	0.87 (0.84-0.90)	0.86 (0.83-0.88)	0.85 (0.82-0.88)	0.85 (0.82-0.87)
	1.6	1.17 (1.14-1.19)	1.09 (1.06-1.11)	1.05 (1.03-1.08)	1.00 (0.98-1.03)	0.98 (0.95-1.00)	0.94 (0.91-0.97)	0.92 (0.89-0.94)	0.91 (0.88-0.94)	0.88 (0.86-0.91)	0.87 (0.84-0.90)	0.86 (0.83-0.88)	0.85 (0.82-0.88)	0.83 (0.81-0.86)	0.83 (0.80-0.86)	0.82 (0.79-0.85)	0.81 (0.78-0.84)
	1.8	1.21 (1.18-1.24)	1.14 (1.11-1.16)	1.07 (1.04-1.10)	1.02 (1.00-1.05)	0.99 (0.96-1.02)	0.95 (0.92-0.97)	0.92 (0.89-0.95)	0.89 (0.87-0.92)	0.88 (0.85-0.90)	0.86 (0.83-0.88)	0.83 (0.81-0.86)	0.82 (0.79-0.85)	0.81 (0.79-0.84)	0.79 (0.76-0.82)	0.79 (0.76-0.82)	0.77 (0.75-0.80)
	2	1.27 (1.24-1.30)	1.17 (1.14-1.20)	1.10 (1.07-1.12)	1.03 (1.00-1.06)	0.99 (0.96-1.02)	0.95 (0.92-0.97)	0.91 (0.88-0.94)	0.89 (0.86-0.92)	0.86 (0.84-0.89)	0.84 (0.81-0.87)	0.82 (0.79-0.84)	0.80 (0.78-0.83)	0.80 (0.77-0.82)	0.78 (0.75-0.81)	0.76 (0.74-0.79)	0.75 (0.72-0.78)
0.6	1	0.94 (0.91-0.97)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.94 (0.92-0.97)	0.95 (0.92-0.98)	0.94 (0.92-0.98)	0.94 (0.92-0.97)	0.94 (0.91-0.97)
	1.2	1.04 (1.01-1.07)	1.01 (0.98-1.04)	0.99 (0.97-1.02)	0.97 (0.95-1.00)	0.96 (0.93-0.98)	0.95 (0.92-0.97)	0.94 (0.91-0.96)	0.93 (0.90-0.95)	0.92 (0.89-0.95)	0.91 (0.88-0.94)	0.90 (0.88-0.93)	0.90 (0.87-0.93)	0.90 (0.87-0.92)	0.89 (0.86-0.92)	0.88 (0.85-0.91)	0.88 (0.86-0.91)
	1.4	1.12 (1.09-1.14)	1.07 (1.04-1.09)	1.03 (1.00-1.06)	0.99 (0.97-1.02)	0.97 (0.94-1.00)	0.95 (0.92-0.97)	0.93 (0.90-0.96)	0.91 (0.88-0.94)	0.90 (0.87-0.92)	0.89 (0.86-0.91)	0.87 (0.84-0.90)	0.86 (0.84-0.89)	0.84 (0.81-0.87)	0.84 (0.81-0.87)	0.83 (0.81-0.86)	0.84 (0.81-0.86)
	1.6	1.19 (1.16-1.22)	1.11 (1.09-1.14)	1.06 (1.03-1.09)	1.01 (0.99-1.04)	0.98 (0.95-1.00)	0.95 (0.92-0.97)	0.92 (0.89-0.95)	0.90 (0.87-0.93)	0.88 (0.85-0.91)	0.86 (0.84-0.89)	0.85 (0.82-0.88)	0.83 (0.80-0.86)	0.81 (0.78-0.84)	0.81 (0.78-0.84)	0.81 (0.78-0.83)	0.80 (0.77-0.82)
	1.8	1.26 (1.23-1.29)	1.16 (1.13-1.19)	1.09 (1.06-1.12)	1.03 (1.00-1.06)	0.99 (0.96-1.01)	0.95 (0.92-0.98)	0.91 (0.88-0.94)	0.89 (0.86-0.92)	0.86 (0.84-0.89)	0.84 (0.81-0.87)	0.83 (0.81-0.86)	0.81 (0.78-0.83)	0.79 (0.76-0.82)	0.78 (0.75-0.81)	0.77 (0.74-0.80)	0.75 (0.73-0.78)
	2	1.30 (1.27-1.33)	1.20 (1.17-1.23)	1.12 (1.09-1.15)	1.04 (1.02-1.07)	1.00 (0.97-1.03)	0.94 (0.92-0.97)	0.91 (0.88-0.94)	0.88 (0.85-0.90)	0.85 (0.82-0.88)	0.83 (0.80-0.85)	0.81 (0.78-0.84)	0.78 (0.75-0.81)	0.77 (0.74-0.79)	0.75 (0.72-0.78)	0.74 (0.71-0.76)	0.73 (0.70-0.76)

indicates p-values <0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios less than 1
indicates p-values <0.05 for hazard ratios less than 1
indicates the values of relative risk, prevalence, and treatment distribution (rounded up to the nearest 10th) where some observed covariates fall

Figure 7. Distribution of hazard ratios and 95% confidence intervals by prevalence, relative risk and treatment distribution of an introduced covariate for propensity score matched right bundle branch block patients with death as the outcome.

Prevalence	Relative Risk	Treatment Distribution (the ratio of the proportion of CRT-D patients with covariate to the proportion of ICD patients with covariate)															
		0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.3	1	1.13 (1.08-1.18)	1.13 (1.08-1.18)	1.13 (1.08-1.18)	1.13 (1.08-1.18)	1.13 (1.08-1.18)	1.13 (1.08-1.17)	1.12 (1.08-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.07-1.18)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.18)
	1.2	1.19 (1.14-1.24)	1.16 (1.11-1.21)	1.16 (1.11-1.21)	1.14 (1.09-1.19)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.11 (1.06-1.16)	1.10 (1.05-1.15)	1.10 (1.05-1.15)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.09 (1.04-1.14)	1.08 (1.03-1.13)
	1.4	1.23 (1.18-1.28)	1.20 (1.15-1.25)	1.18 (1.13-1.23)	1.15 (1.11-1.20)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.12 (1.07-1.16)	1.10 (1.05-1.15)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.03 (0.98-1.08)	1.04 (0.99-1.09)
	1.6	1.29 (1.24-1.34)	1.24 (1.19-1.29)	1.20 (1.15-1.25)	1.17 (1.12-1.22)	1.16 (1.11-1.21)	1.12 (1.08-1.17)	1.11 (1.06-1.16)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.07 (1.01-1.12)	1.05 (1.00-1.10)	1.04 (0.99-1.09)	1.02 (0.97-1.07)	1.01 (0.96-1.06)	1.00 (0.95-1.05)	1.00 (0.95-1.05)
	1.8	1.32 (1.26-1.37)	1.27 (1.22-1.32)	1.23 (1.18-1.28)	1.19 (1.14-1.24)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.11 (1.06-1.16)	1.08 (1.03-1.13)	1.06 (1.01-1.11)	1.04 (0.99-1.09)	1.03 (0.98-1.08)	1.01 (0.96-1.06)	1.01 (0.96-1.06)	0.99 (0.94-1.04)	0.98 (0.93-1.03)	0.98 (0.93-1.03)
	2	1.38 (1.33-1.43)	1.30 (1.25-1.35)	1.26 (1.21-1.31)	1.20 (1.15-1.25)	1.16 (1.11-1.21)	1.13 (1.08-1.18)	1.10 (1.05-1.14)	1.08 (1.03-1.13)	1.05 (1.00-1.10)	1.03 (0.97-1.08)	1.00 (0.95-1.05)	0.98 (0.93-1.03)	0.99 (0.93-1.04)	0.97 (0.92-1.02)	0.96 (0.91-1.01)	0.95 (0.90-1.00)
0.4	1	1.13 (1.08-1.18)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.17)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.13 (1.07-1.18)	1.13 (1.08-1.18)	1.12 (1.07-1.17)
	1.2	1.19 (1.14-1.24)	1.17 (1.12-1.22)	1.15 (1.10-1.20)	1.15 (1.10-1.20)	1.14 (1.09-1.18)	1.13 (1.08-1.18)	1.11 (1.06-1.16)	1.11 (1.06-1.16)	1.10 (1.05-1.15)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.10 (1.04-1.15)	1.08 (1.03-1.13)	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.06 (1.01-1.11)
	1.4	1.26 (1.21-1.31)	1.22 (1.17-1.27)	1.19 (1.14-1.24)	1.17 (1.12-1.22)	1.16 (1.11-1.20)	1.12 (1.07-1.17)	1.11 (1.06-1.15)	1.09 (1.04-1.14)	1.08 (1.03-1.13)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.04 (0.99-1.09)	1.05 (0.99-1.10)	1.03 (0.97-1.08)	1.01 (0.96-1.06)	1.01 (0.96-1.06)
	1.6	1.32 (1.27-1.37)	1.27 (1.22-1.32)	1.23 (1.18-1.28)	1.17 (1.12-1.22)	1.16 (1.11-1.21)	1.12 (1.07-1.17)	1.11 (1.06-1.16)	1.07 (1.02-1.12)	1.06 (1.01-1.11)	1.05 (1.00-1.10)	1.04 (0.99-1.09)	1.00 (0.95-1.05)	1.00 (0.95-1.05)	1.00 (0.95-1.05)	0.98 (0.93-1.03)	0.98 (0.93-1.03)
	1.8	1.39 (1.34-1.44)	1.30 (1.25-1.35)	1.25 (1.20-1.30)	1.21 (1.16-1.26)	1.17 (1.12-1.22)	1.12 (1.07-1.17)	1.10 (1.05-1.15)	1.07 (1.02-1.12)	1.06 (1.01-1.11)	1.02 (0.97-1.07)	0.99 (0.94-1.04)	0.97 (0.92-1.02)	0.96 (0.91-1.01)	0.96 (0.91-1.01)	0.95 (0.89-1.00)	0.92 (0.87-0.97)
	2	1.41 (1.36-1.46)	1.35 (1.29-1.40)	1.30 (1.25-1.35)	1.21 (1.16-1.26)	1.17 (1.12-1.22)	1.15 (1.10-1.19)	1.08 (1.03-1.13)	1.06 (1.02-1.11)	1.04 (0.98-1.09)	0.99 (0.94-1.04)	0.97 (0.92-1.02)	0.97 (0.92-1.02)	0.94 (0.88-0.99)	0.94 (0.89-0.99)	0.91 (0.86-0.96)	0.90 (0.85-0.95)
0.5	1	1.13 (1.08-1.19)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.17)	1.13 (1.08-1.17)	1.13 (1.08-1.18)	1.13 (1.07-1.18)	1.12 (1.07-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.06-1.17)	1.12 (1.06-1.17)	1.12 (1.06-1.17)
	1.2	1.21 (1.16-1.26)	1.19 (1.14-1.24)	1.16 (1.11-1.21)	1.16 (1.11-1.21)	1.13 (1.09-1.18)	1.12 (1.07-1.17)	1.12 (1.07-1.16)	1.11 (1.06-1.16)	1.10 (1.05-1.15)	1.09 (1.04-1.14)	1.09 (1.04-1.14)	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.06 (1.01-1.11)	1.05 (1.00-1.10)
	1.4	1.30 (1.25-1.35)	1.22 (1.17-1.27)	1.20 (1.15-1.25)	1.18 (1.13-1.23)	1.15 (1.11-1.20)	1.13 (1.08-1.17)	1.11 (1.06-1.16)	1.08 (1.04-1.13)	1.07 (1.02-1.12)	1.06 (1.01-1.11)	1.05 (1.00-1.10)	1.03 (0.98-1.08)	1.02 (0.97-1.07)	1.01 (0.96-1.06)	0.99 (0.94-1.04)	0.97 (0.91-1.02)
	1.6	1.34 (1.28-1.39)	1.32 (1.27-1.37)	1.25 (1.20-1.30)	1.20 (1.15-1.25)	1.15 (1.10-1.20)	1.14 (1.09-1.19)	1.10 (1.05-1.15)	1.07 (1.02-1.12)	1.04 (0.99-1.09)	1.03 (0.97-1.08)	1.00 (0.95-1.05)	0.99 (0.94-1.04)	0.98 (0.93-1.03)	0.95 (0.90-1.00)	0.94 (0.89-1.00)	0.95 (0.90-1.00)
	1.8	1.43 (1.38-1.49)	1.33 (1.28-1.38)	1.28 (1.23-1.33)	1.24 (1.19-1.29)	1.17 (1.12-1.22)	1.13 (1.08-1.18)	1.08 (1.03-1.13)	1.06 (1.01-1.11)	1.04 (0.99-1.09)	1.01 (0.96-1.06)	0.98 (0.93-1.03)	0.94 (0.89-0.99)	0.95 (0.90-1.00)	0.94 (0.89-0.99)	0.90 (0.85-0.96)	0.90 (0.84-0.95)
	2	1.49 (1.44-1.54)	1.39 (1.34-1.44)	1.31 (1.26-1.36)	1.24 (1.19-1.29)	1.18 (1.13-1.23)	1.13 (1.08-1.17)	1.09 (1.04-1.14)	1.05 (1.00-1.10)	1.01 (0.96-1.06)	1.00 (0.95-1.05)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.91 (0.86-0.96)	0.91 (0.85-0.96)	0.88 (0.83-0.93)	0.88 (0.83-0.93)
0.6	1	1.13 (1.07-1.18)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.08-1.17)	1.13 (1.08-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.07-1.17)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.12 (1.06-1.17)	1.12 (1.07-1.17)	1.13 (1.08-1.18)	1.12 (1.06-1.17)
	1.2	1.22 (1.17-1.27)	1.22 (1.17-1.28)	1.17 (1.12-1.22)	1.15 (1.10-1.20)	1.14 (1.09-1.19)	1.12 (1.07-1.17)	1.12 (1.07-1.16)	1.11 (1.06-1.16)	1.08 (1.03-1.13)	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.06 (1.01-1.11)	1.06 (1.00-1.11)	1.04 (0.99-1.09)	1.04 (0.99-1.10)	1.03 (0.97-1.08)
	1.4	1.29 (1.24-1.35)	1.26 (1.21-1.31)	1.21 (1.16-1.26)	1.18 (1.13-1.23)	1.16 (1.11-1.20)	1.12 (1.08-1.17)	1.11 (1.06-1.15)	1.08 (1.03-1.13)	1.06 (1.00-1.11)	1.05 (1.00-1.10)	1.04 (0.99-1.09)	1.02 (0.97-1.07)	1.00 (0.94-1.05)	1.00 (0.95-1.05)	0.98 (0.93-1.03)	0.95 (0.89-1.00)
	1.6	1.42 (1.37-1.47)	1.32 (1.27-1.37)	1.25 (1.20-1.30)	1.21 (1.16-1.26)	1.17 (1.12-1.21)	1.13 (1.08-1.18)	1.09 (1.04-1.14)	1.06 (1.01-1.11)	1.03 (0.98-1.08)	1.03 (0.98-1.08)	1.01 (0.96-1.06)	0.99 (0.94-1.04)	0.96 (0.91-1.01)	0.93 (0.87-0.98)	0.94 (0.88-0.99)	0.92 (0.86-0.97)
	1.8	1.47 (1.42-1.52)	1.36 (1.31-1.41)	1.31 (1.25-1.36)	1.23 (1.18-1.28)	1.17 (1.12-1.22)	1.12 (1.07-1.17)	1.09 (1.04-1.13)	1.05 (1.00-1.10)	1.03 (0.98-1.08)	0.98 (0.93-1.03)	0.97 (0.92-1.02)	0.96 (0.91-1.01)	0.92 (0.87-0.97)	0.92 (0.86-0.97)	0.89 (0.84-0.95)	0.90 (0.84-0.95)
	2	1.54 (1.48-1.59)	1.43 (1.38-1.48)	1.32 (1.27-1.37)	1.23 (1.18-1.28)	1.20 (1.15-1.25)	1.13 (1.08-1.18)	1.09 (1.05-1.14)	1.04 (0.99-1.09)	1.01 (0.96-1.06)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.91 (0.86-0.96)	0.89 (0.83-0.94)	0.87 (0.81-0.92)	0.85 (0.80-0.90)	0.86 (0.81-0.91)

indicates p-values <0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios greater than or equal to 1
indicates p-values >=0.05 for hazard ratios less than 1
indicates p-values <0.05 for hazard ratios less than 1
indicates the values of relative risk, prevalence, and treatment distribution (rounded up to the nearest 10th) where some observed covariates fall

Supplemental References

1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40:373-383.