Cardiac Resynchronization Therapy Improves Outcomes in Patients with Intraventricular Conduction Delay but Not Right Bundle Branch Block: A Patient-Level Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Benefit from cardiac resynchronization therapy (CRT) varies by QRS characteristics; individual randomized trials are underpowered to assess benefit for relatively small subgroups.

Methods: The authors analyzed patient-level data from pivotal CRT trials (MIRACLE [Multicenter InSync Randomized Clinical Evaluation], MIRACLE-ICD [Multicenter InSync ICD Randomized Clinical Evaluation], MIRACLE-ICD II [Multicenter InSync ICD Randomized Clinical Evaluation II], REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction], RAFT [Resynchronization-Defibrillation for Ambulatory Heart Failure], BLOCK-HF [Biventricular Versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block], COMPANION [Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure], and MADIT-CRT [Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy]) using Bayesian Hierarchical Weibull survival regression models to assess CRT benefit by QRS morphology (left bundle branch block [LBBB], n=4549; right bundle branch block [RBBB], n=691; and intraventricular conduction delay [IVCD], n=1024) and duration (with 150-ms partition). The continuous relationship between QRS duration and CRT benefit was also examined within subgroups defined by QRS morphology. The primary end point was time to heart failure hospitalization (HFH) or death; a secondary end point was time to all-cause death.

Results: Of 6264 patients included, 25% were women, the median age was 66 [interquartile range, 58 to 73] years, and 61% received CRT (with or without an implantable cardioverter defibrillator). CRT was associated with an overall lower risk of HFH or death (hazard ratio [HR], 0.73 [credible interval (CrI), 0.65 to 0.84]), and in subgroups of patients with QRS ≥150 ms and either LBBB (HR, 0.56 [CrI, 0.48 to 0.66]) or IVCD (HR, 0.59 [CrI, 0.39 to 0.89]), but not RBBB (HR 0.97 [CrI, 0.68 to 1.34]; Pinteraction <0.001). No significant association for CRT with HFH or death was observed when QRS was <150 ms (regardless of QRS morphology) or in the presence of RBBB. Similar relationships were observed for all-cause death.

Conclusions: CRT is associated with reduced HFH or death in patients with QRS ⩾150 ms and LBBB or IVCD, but not for those with RBBB. Aggregating RBBB and IVCD into a single "non-LBBB" category when selecting patients for CRT should be reconsidered.

Registration: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT00271154, NCT00251251, NCT00267098, and NCT00180271.

Clinical Perspective

What Is New?

• In this patient-level data meta-analysis, the authors demonstrate that for patients with intraventricular conduction delay and QRS duration ≥150 ms, cardiac resynchronization therapy (CRT) was associated with lower rates of heart failure hospitalizations and all-cause mortality

• The magnitude of CRT benefits in patients with intraventricular conduction delay ≥150 ms and left bundle branch block ≥150 ms appear similar

• There was no clear CRT benefit for patients with a right bundle branch block of any QRS duration, although potential for benefit at markedly prolonged QRS durations cannot be ruled out

What Are the Clinical Implications?

The practice of combining right bundle branch block and intraventricular conduction delay patients into a single "non–left bundle branch block" category to select patients for CRT is not supported by the data

• Patients with intraventricular conduction delay ≥150 ms should be offered CRT as is done for patients with left bundle branch block ≥150 ms

Nonstandard Abbreviations and Acronyms	
BLOCK HF	Biventricular Versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block
CARE-HF	Cardiac Resynchronization – Heart Failure
COMAPNION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
CRT	cardiac resynchronization therapy
HFH	heart failure hospitalization
ICD	implantable cardioverter-defibrillator
IVCD	intraventricular conduction delay
LBBB	left bundle branch block
LV	left ventricular
LVEF	left ventricular ejection fraction
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MIRACLE ICD	Multicenter InSync ICD Randomized Clinical Evaluation
MIRACLE ICD II	Multicenter InSync ICD Randomized Clinical Evaluation II
NICD-CRT	Cardiac Resynchronization Therapy in Patients With Wide QRS and Non-Specific Intraventricular Conduction Delay
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure
RBBB	right bundle branch block
REVERSE	Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction
SMART-AV	SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is an important treatment for patients with heart failure, reduced left ventricular (LV) ejection fraction (LVEF) and prolonged QRS duration. Although findings from landmark trials[1–8] have led to widespread use of CRT in many patient cohorts, it is widely recognized that a substantial minority of patients (≈30%) might not derive benefit from device implantation. Reasons for a lack of benefit are many and include patient factors, lead placement, and device programming.

Although randomized CRT trials initially enrolled patients based on QRS duration (≥120 ms) rather than morphology, many clinicians subsequently inferred that CRT was only consistently effective for those with a QRS duration ≥150 ms[9,10] and left bundle branch block (LBBB).[10–12] Initially, patients were classified as "non-LBBB," but further analyses suggested possible differences for those with intraventricular conduction delay (IVCD) pattern or right bundle branch block (RBBB).[13,14] Subgroup analyses of individual randomized trials aimed at understanding the relationship between QRS characteristics and the benefit of CRT have been underpowered. Observational studies, although informative, are limited by confounding and lack of a control that helps distinguish effects of treatment from the natural history of disease. Accordingly, we performed a patient-level meta-analysis of randomized CRT trials to assess the relationship between QRS duration and morphology (RBBB, LBBB, or IVCD) and outcomes.

Methods

Data Sources

Data for this study were provided by Medtronic and Boston Scientific via data use agreements that prohibit the coauthors from data sharing. Any requests for data sharing should be directed to either Boston Scientific or Medtronic.

We performed a patient-level meta-analysis of pivotal CRT trials MIRACLE (Multicenter InSync Randomized Clinical Evaluation),[1] MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation),[8] MIRACLE-ICD II (Multicenter InSync ICD Randomized Clinical Evaluation II),[2] REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction),[5] RAFT (ResynchronizationDefibrillation for Ambulatory Heart Failure),[7] COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure),[3] BLOCK-HF (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block),[4] and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy).[6] All trials are high-quality CRT studies that have been published in high-impact journals and have formed the basis for multiple CRT guideline documents. The Duke University Institutional Review Board approved analysis of trial datasets with waiver of informed consent (beyond what was already required for the trial). These studies compared the effects of CRT with either no CRT implantation or CRT device implantation with CRT programming off. For the purpose of this meta-analysis, having CRT programmed off is defined as no CRT. Use of a CRT pacemaker versus CRT with defibrillator varied by study, therefore, concomitant implantable cardioverter defibrillator (ICD) was adjusted for isolation of the association between CRT and outcomes. Because of data privacy restrictions, we were not given access to European patient data which precluded inclusion of CARE-HF (Cardiac Resynchronization – Heart Failure).[15]

Study Population

We included patients with available data on sex, QRS morphology (LBBB, RBBB, or IVCD), and QRS duration, with complete data for the outcomes of heart failure hospitalization (HFH) or death. We

excluded patients in these studies with LVEF >35%, QRS duration < 120 ms, or history of pacemaker or paced QRS morphology on baseline ECG. ECGs were centrally adjudicated for MADIT-CRT, REVERSE, and RAFT. In contrast, only individual site-based ECG interpretations were available for COMPANION, BLOCK-HF, and the MIRACLE studies.

Study Outcomes

The primary study outcome was time to HFH or death. The secondary outcome was time to all-cause death.

Of note, all trials included time to HFH and death as prespecified end points. While the primary endpoint varied by trial, most of the trials were powered to assess for a difference in time to HFH or death (MADIT-CRT, RAFT, COMPANION, and RAFT). BLOCK-HF was powered to detect a difference in HFH, death, or LV reverse remodeling. The MIRACLE studies were powered for differences in functional capacity and heart failure–related quality of life.

Statistical Analysis

Baseline characteristics were compared between participants receiving or not receiving CRT using a t test that allows unequal variances for numeric covariates or using a chi-square test for independence for categorical variables. CRT association with outcomes (vs no CRT) was assessed overall using a Bayesian Hierarchical Weibull survival regression model with a random intercept and a random treatment effect at the trial level. Because of the heterogeneity across trials, our prespecified analysis plan employed parametric Bayesian Weibull models rather than standard Cox models since the former is better able to incorporate several sources of heterogeneity than the later. Both Bayesian Weibull models and Cox models are proportional hazards models and therefore the interpretation is overall similar. Results are presented using hazard ratios (HR) and 95% posterior credible intervals (CrI). We fit an unadjusted model and a model adjusting for baseline characteristics (age, sex, New York Heart Association class, LVEF, QRS duration, QRS morphology, atrial fibrillation, diabetes, hypertension, ischemic cardiomyopathy, use of beta-blockers, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and the presence of an ICD. Age was modeled as a linear spline with a knot at 50 years for the end point of time to HFH or death, and as a linear spline with knots at 50 and 80 years for the end point of time to death. LVEF was modeled as a linear spline with a knot at 20% for the end point of time to death. The association between CRT (vs no CRT) and outcomes was assessed also within 6 QRS subgroups (LBBB ≥150 ms, LBBB <150 ms, RBBB ⩾150 ms, RBBB <150 ms, IVCD ⩾150 ms, IVCD <150 ms), using similar unadjusted and adjusted models but with random treatment effect for each QRS characteristic subgroup at the trial level (interaction between CRT and QRS subgroups). To evaluate if the association of CRT with outcomes differed among QRS subgroups, the posterior probability of no interaction between CRT effect and QRS subgroup was computed.[16,17] All priors are noninformative. For the fixed effects and mean components of the random effect distributions, we used normal distributions as their priors. For the variance components of the random effect distributions, we used half-normal distributions as their priors, and for the shape parameter of the Weibull model a log-normal distribution was used as its prior. The proportional hazard assumption was assessed using the scaled Schoenfeld residuals from a Cox proportional hazard mixed-effects model with random intercept and random treatment effect at the trial level. The adjusted relationship (adjusted HR) between CRT versus no CRT overall and within the 6 QRS subgroups is depicted using forest plots. The heterogeneity of the treatment effect, overall and within QRS subgroups, was measured

as the percentage of variability corresponding to the treatment effect in relation to the sum of the sources of variability arising from the variability of the baseline hazard and of the treatment effect across trials in the corresponding patient population.

The adjusted relationship (adjusted HRs) between CRT versus no CRT overall and within the 6 QRS subgroups is depicted using forest plots. The weights displayed in the forest plots correspond to the percentage of person time contributed by each trial. The association between QRS duration (continuous) and outcomes was assessed similar to the analysis with 6 QRS subgroups. This relationship between QRS duration as a continuous variable and outcomes for CRT versus no CRT is shown in plots depicting the QRS duration on the x axis and the HR for CRT on the y axis, subgrouping by QRS morphology (LBBB, RBBB, and IVCD).

Results

A total of 7168 patients across 8 pivotal CRT trials were initially considered, but after applying exclusion criteria, 6261 patients were included in this analysis. Figure 1 is a consort diagram depicting application of exclusion criteria. The study cohort was older (66 [interquartile range (IQR), 58 to 73] years), predominantly men (75%), predominantly White (87%), had severely reduced LVEF (25% [IQR, 20 to 30]), and had mild or moderate heart failure symptoms (New York Heart Association class II, 52%; New York Heart Association class III, 38%). Common comorbidities included ischemic heart disease (59%), history of hypertension (53%), and diabetes (34%). The most common QRS morphology was LBBB (n=4549 [72.6%]), followed by IVCD (n=1024 [16.3%]) and RBBB (n=691 [11.0%]). Most patients had QRS durations $\geqslant$150 ms (n=4122 [66%]). An ICD was implanted in 77% of patients (n=4813), and 61% of patients were randomized to CRT (n=3822). Table 1 presents the overall analysis population classified by QRS characteristics. Patients with RBBB were more likely to be men and to have ischemic heart disease. The burden of atrial fibrillation, diabetes, and hypertension, and the median ejection fraction, were similar across groups.

The median [IQR] follow-up for the overall cohort was 24 [11 to 42] months. Study-specific Kaplan–Meier event rates are summarized in Tables S1 and S2. Randomization to CRT resulted in reduced risk for HFH or death in an unadjusted analysis (HR, 0.73 [95% CrI, 0.65 to 0.82]). Results were similar in an adjusted analysis accounting for patient characteristics and receipt of an ICD (HR, 0.72 [95% CrI, 0.65 to 0.84]; Figure 2A). Similarly, randomization to CRT resulted in a reduction in all-cause death in unadjusted (HR, 0.77 [95% CrI, 0.66 to 0.92]) and adjusted analyses (HR, 0.78 [95% CrI, 0.67 to 0.94]; Figure 2B). There was a significant interaction between randomization to CRT and QRS characteristics subgroups (defined by morphology and duration) and HFH or death (P<0.001) and all-cause death (P<0.001). Subsequent interaction testing demonstrated a significant interaction between randomization to CRT and QRS duration of $\geqslant$150 ms versus <150 ms for the end points of HFH or death (P<0.001) and all-cause death (P<0.001) with CRT being associated with significant benefit among patients with a QRS duration of $\geqslant$150 ms. In patients with QRS durations $\geqslant$150 ms, there was significant interaction between QRS morphology (LBBB, RBBB, IVCD) and HFH or death (P<0.001), as well as a borderline significant interaction for death (P=0.054)

Unadjusted analyses were performed after stratification of patients into 6 groups defined by QRS morphology (LBBB, RBBB, or IVCD) and duration (<150 ms or $\geqslant$150 ms). In unadjusted analyses, CRT was associated with reduced HFH or eath for patients with QRS $\geqslant$150 ms and either LBBB (HR, 0.55 [95% CrI, 0.48 to 0.65]) or IVCD (HR, 0.66 [95% CrI, 0.42 to 1.00]). CRT was not associated with

reduced HFH or death in any other subgroups (Table 2). When assessing the secondary outcome of all-cause death, results were similar, overall (Table 2).

Adjusted models, accounting for patient characteristics and receipt of an ICD, were similar to the unadjusted models (Table 2; Figure 3A). CRT was associated with a reduction in HFH or death among patients with LBBB and QRS ⩾150 ms (HR, 0.56 [95% CrI, 0.48 to 0.66]) and IVCD and ⩾150 ms (HR, 0.59 [95% CrI, 0.39 to 0.89]). While there were no statistically significant relationships within other subgroups, the subgroup with LBBB and QRS <150 ms demonstrated a trend toward reduction in HFH or death that was not statistically significant (HR, 0.85 [95% CrI, 0.68 to 1.07]). Subgroup findings were consistent across trials in adjusted analyses (Figure 3A). Results were similar in adjusted analyses of CRT and all-cause death among QRS subgroups and across trials (Table 2; Figure 3B).

Results were similar in sensitivity analyses using frequentist Cox mixed models (Table S3) and in Bayesian Weibull models removing data from the 3 trials that contribute the fewest events (Table S4).

The continuous relationship between QRS duration and CRT benefit was assessed among the 3 QRS morphology subgroups (Figure 4A). Among patients with LBBB, the 95% CI around the HR for the effect of CRT on the composite of HFH or death was <1.0 when QRS duration exceeded 129 ms; for IVCD patients, this duration was 165 ms and for RBBB patients, the duration was 213 ms, although the CrI was much larger than for LBBB because of the fewer numbers of patients and events. Figure 4B depicts similar overall results for allcause death, although because of the fewer events, Cis are wider with thresholds of 145 ms, 252 ms, and 210 ms for LBBB, IVCD, and RBBB, respectively.

The continuous relationship between QRS duration and CRT benefit was assessed among the 3 QRS morphology subgroups, with additional stratification based on sex (Figure 5). Among patients with LBBB, an association between CRT and reduced HFH or death was observed when the QRS duration exceeded 127 ms in women and 137 ms in men. Among those with IVCD, an association between CRT and reduced HFH or death was observed when the QRS duration exceeded 140 ms in women and 174 ms in men. For RBBB, CRT may reduce the risk of HFH or death when QRS duration exceeded 226 ms for women and 223 ms for men, however, the CrIs were much wider than for LBBB or IVCD.

Discussion

This patient-level meta-analysis assessing association of CRT with HFH or death by QRS characteristics is the largest cohort of CRT trial patients assembled for this purpose and has several clinically relevant findings. First, and consistent with earlier publications, CRT was associated with a markedly lower rate of HFH or death among patients with LBBB ⩾150 ms: CRT appeared beneficial when QRS durations exceeded ≈130 ms in the presence of LBBB. Second, although current guidelines for patients with RBBB and IVCD are combined into a singular non-LBBB cohort, we found that CRT was associated with a lower risk of HFH or death among patients with IVCD and QRS duration ⩾150 ms but not for patients with RBBB or for IVCD when QRS duration was <150 ms. Outcomes were similar for analyses of all-cause death. In exploratory analyses, we observed sex-specific differences; CRT was associated with better outcomes at a shorter QRS duration among women compared to men. These findings have important implications for patient selection for CRT.

Pivotal CRT trials enrolled patients based on QRS duration with the supposition that a prolonged QRS duration (>120 ms) was indicative of electrical dyssynchrony with significant underlying LV activation delay regardless of QRS morphology. However, a substantial proportion of patients have disappointing responses to CRT, which has led to a plethora of research for improved selection of patients for CRT or improved methods of implementation.[18] Early studies suggested LBBB morphology[10–12] and QRS duration >150 ms[9,10] predict greater response to CRT. However, LBBB is often associated with a wide QRS, which may exaggerate benefits in LBBB and, more importantly, may overemphasize a presumed lack of benefit in non-LBBB—although RBBB was described as linked to a lack of CRT response almost from the start. Nevertheless, despite the lack of QRS morphology as an inclusion criterion or as a prespecified subgroup analysis for most trials of CRT, guidelines make strong recommendations based on QRS morphology (dichotomized as LBBB and non-LBBB) and duration (dichotomized as $\geqslant$150 ms and <150 ms) for patient selection.[19,20] Whereas our results support the importance of considering QRS duration when assessing CRT candidacy, they do not support combining RBBB and IVCD into a single group.

Early data demonstrate that some patients with RBBB have activation delays similar to LBBB,[21,22] but it was not until later trials that IVCD patients were studied in more detail. A body surface mapping study of patients with LBBB and IVCD confirmed the presence of LV activation delay among a subset of patients with an IVCD.[23] Although both LV activation delay and QRS duration predicted response to CRT in this cohort, ventricular electrical uncoupling (the difference between mean right ventricular and LV activation times) was the strongest predictor. A secondary analysis of the SMART-AV (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) study demonstrated that QLV (interval from QRS onset to sensed signal on the LV lead), but not QRS morphology, predicted reverse remodeling and improvement in symptoms.[24] These findings helped to confirm the importance of LV activation delay and identify a physiologic rationale for an earlier finding from a MADIT-CRT secondary analysis, which suggested that patients with an “LBBB-like” IVCD derived benefit from CRT.[12] Subsequent studies using the ECG-derived QRS area—a vectorcardiographic measure of electrical dyssynchrony—have demonstrated that electrical dyssynchrony is present in non-LBBB patients and that its presence is associated with more favorable long-term outcomes with CRT.[25,26]

The aforementioned studies have demonstrated the plausibility of CRT benefit in patients with IVCD by documenting the presence of LV activation delay; however, the current study provides the strongest evidence to date that patients with this substrate may benefit from resynchronization. While our study demonstrates that a QRS duration $\geqslant$150 ms may be useful for identifying patients more likely to benefit from CRT, QRS duration is likely to be an unreliable surrogate among IVCD patients (because of concomitant right ventricular activation delay), and even with this caveat, the optimal threshold of QRS duration for patient selection likely varies by sex,[27,28] ethnicity,[29] and body stature.[27,30] The ongoing NICD-CRT (Nonspecific Intraventricular Conduction Delay CRT) trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02454439)31 is a randomized trial of CRT programmed on versus off in patients with IVCD >130 ms and LVEF <35% who were implanted with a CRT pacemaker or CRT with defibrillator. While the NICDCRT trial may help to refine patient selection further; currently, however, the best approach to selection of IVCD patients for CRT may rely on careful examination of the ECG to assess for features in common with LBBB, including a longer QRS duration.

Limitations

This meta-analysis of patient-level data from 8 pivotal CRT trials is the largest study of prospectively enrolled patients assessing the relationship between QRS duration and morphology and outcomes. However, a few limitations are noteworthy. Trials applied slightly different inclusion and exclusion criteria and QRS morphology classification definitions. While the study population included more than 6000 patients, some subgroups were small, which may have reduced the power to detect statistically significant differences. While we used advanced Bayesian techniques to account for heterogeneity in study criteria and differences in variable definitions, we cannot rule out the possibility of residual confounding.

Conclusions

In this meta-analysis of patient-level data from 8 pivotal randomized trials, we confirmed CRT benefit among patients with LBBB and identified the novel finding that patients with RBBB and IVCD had different outcomes after CRT. CRT was associated with a lower risk of HFH or death among patients with IVCD and QRS $\geqslant$150 ms, while RBBB patients (with any QRS duration) and IVCD patients with QRS <150 ms did not demonstrate a statistically significant association between CRT and outcomes. These findings challenge the long-standing practice of combining RBBB and IVCD patients into a single non-LBBB subgroup when assessing CRT candidacy.

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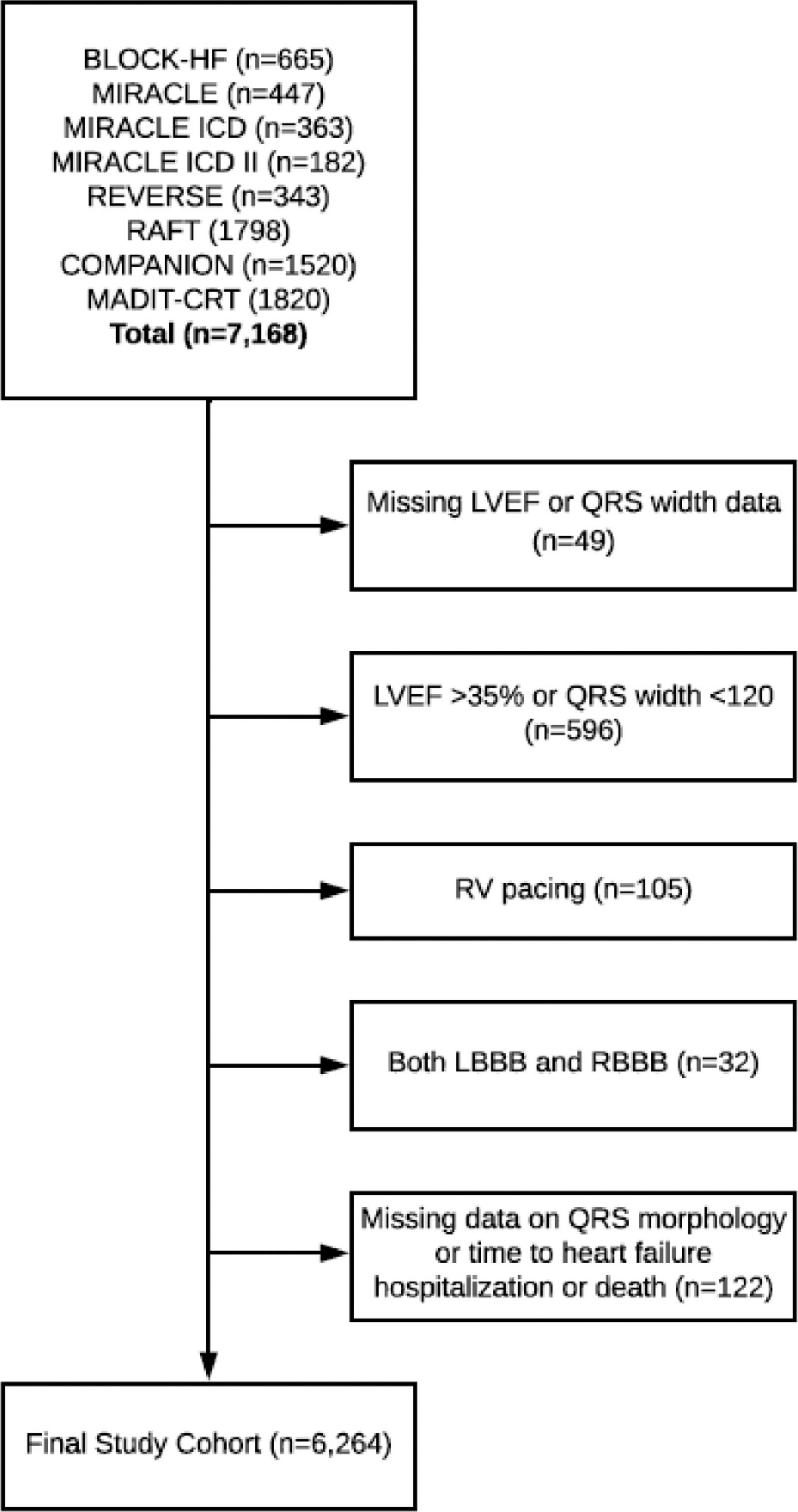
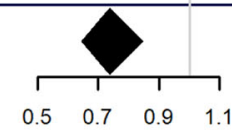

BLOCK-HF (n=665)
MIRACLE (n=447)
MIRACLE ICD (n=363)
MIRACLE ICD II (n=182)
REVERSE (n=343)
RAFT (1798)
COMPANION (n=1520)
MADIT-CRT (1820)
Total (n=7,168)
Missing LVEF or QRS width data (n=49)
LVEF >35% or QRS width <120 (n=596)
RV pacing (n=105)
Both LBBB and RBBB (n=32)
Missing data on QRS morphology or time to heart failure hospitalization or death (n=122)
Final Study Cohort (n=6,264)

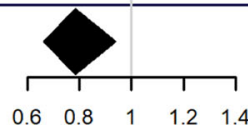
A

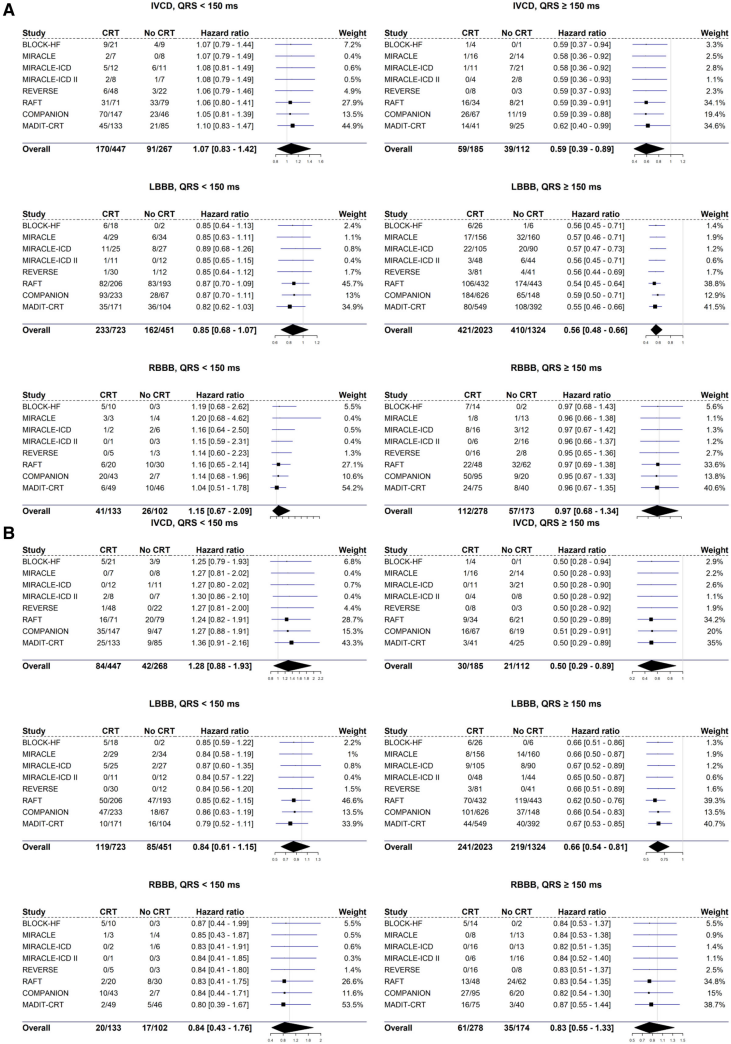
Study	CRT	No CRT	Hazard ratio	Weight
BLOCK-HF	34/93	5/23	0.75 [0.62 - 0.97]	2.8%
MIRACLE	28/219	42/233	0.73 [0.61 - 0.91]	1.5%
MIRACLE-ICD	48/171	46/167	0.77 [0.65 - 1.01]	1.1%
MIRACLE-ICD II	6/78	11/90	0.74 [0.60 - 0.92]	0.6%
REVERSE	10/188	11/89	0.72 [0.55 - 0.86]	2.1%
RAFT	263/811	340/828	0.72 [0.63 - 0.81]	37.9%
COMPANION	443/1211	138/307	0.75 [0.66 - 0.89]	13.2%
MADIT-CRT	204/1018	192/692	0.71 [0.61 - 0.82]	40.8%
Overall	**1036/3789**	**785/2429**	**0.74 [0.65 - 0.84]**	

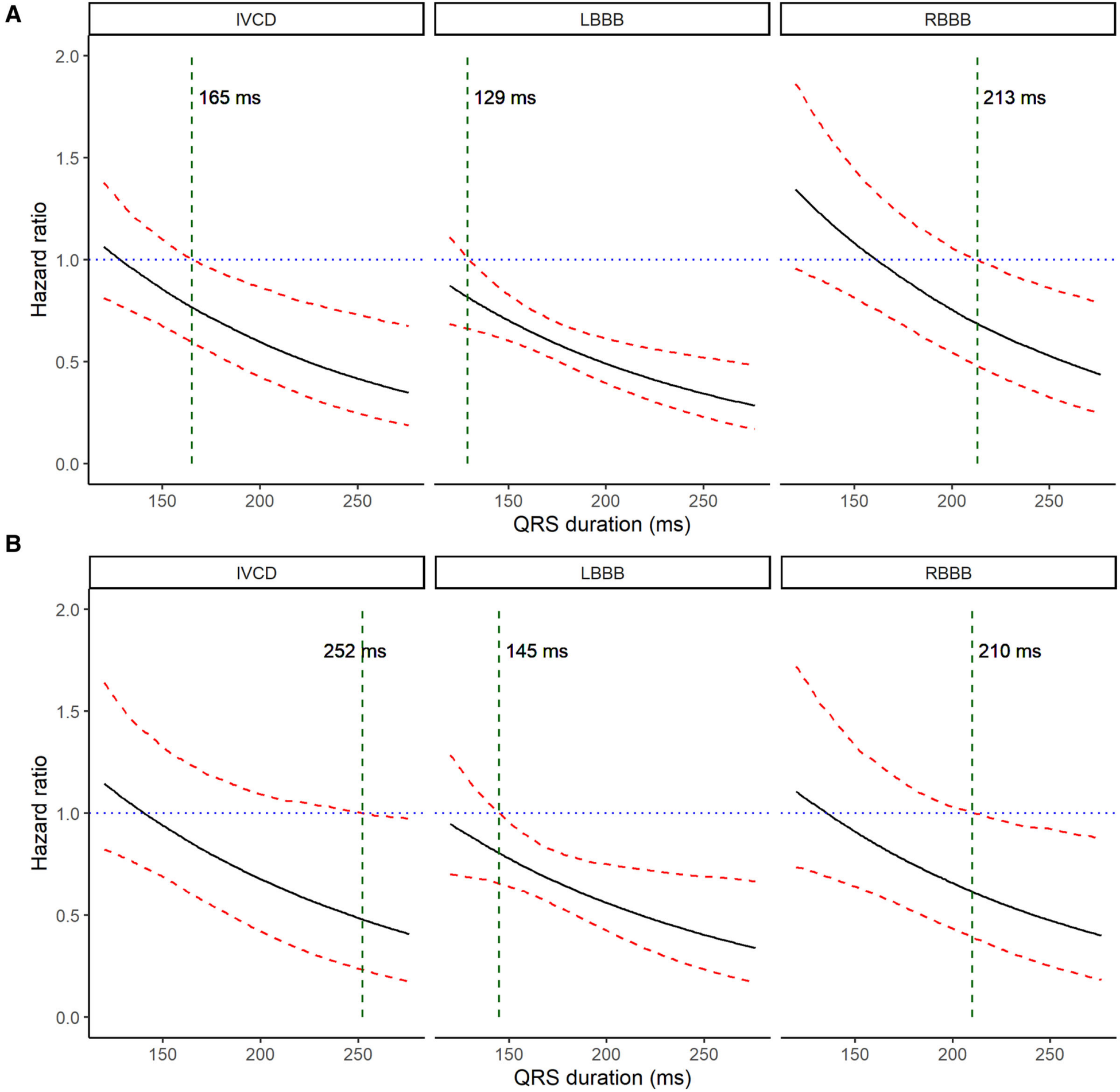


B

Study	CRT	No CRT	Hazard ratio	Weight
BLOCK-HF	27/93	3/23	0.80 [0.65 - 1.08]	2.6%
MIRACLE	12/219	20/233	0.78 [0.62 - 1.00]	1.4%
MIRACLE-ICD	14/171	15/168	0.79 [0.65 - 1.06]	1.1%
MIRACLE-ICD II	2/78	2/90	0.78 [0.62 - 1.03]	0.6%
REVERSE	4/188	0/89	0.77 [0.61 - 1.00]	1.9%
RAFT	160/811	224/828	0.73 [0.60 - 0.85]	38.5%
COMPANION	236/1211	78/308	0.79 [0.67 - 0.98]	14%
MADIT-CRT	100/1018	77/692	0.79 [0.66 - 0.98]	39.8%
Overall	**555/3789**	**419/2431**	**0.78 [0.67 - 0.94]**	




A
IVCD, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 9/21 4/9 1.07 [0.79 - 1.44] 7.2%
MIRACLE 2/7 0/8 1.07 [0.79 - 1.49] 0.4%
MIRACLE-ICD 5/12 6/11 1.08 [0.81 - 1.49] 0.6%
MIRACLE-ICD II 2/8 1/7 1.08 [0.79 - 1.49] 0.5%
REVERSE 6/48 3/22 1.06 [0.79 - 1.46] 4.9%
RAFT 31/71 33/79 1.06 [0.80 - 1.41] 27.9%
COMPANION 70/147 23/46 1.05 [0.81 - 1.39] 13.5%
MADIT-CRT 45/133 21/85 1.10 [0.83 - 1.47] 44.9%
Overall 170/447 91/267 1.07 [0.83 - 1.42] 100%
IVCD, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 1/4 0/1 0.59 [0.37 - 0.94] 3.3%
MIRACLE 1/16 2/14 0.58 [0.36 - 0.92] 2.5%
MIRACLE-ICD 1/11 7/21 0.58 [0.36 - 0.92] 2.8%
MIRACLE-ICD II 0/4 2/8 0.59 [0.36 - 0.93] 1.1%
REVERSE 0/8 0/3 0.59 [0.37 - 0.93] 2.3%
RAFT 16/34 8/21 0.59 [0.39 - 0.91] 34.1%
COMPANION 26/67 11/19 0.59 [0.39 - 0.88] 19.4%
MADIT-CRT 14/41 9/25 0.62 [0.40 - 0.99] 34.6%
Overall 59/185 39/112 0.59 [0.39 - 0.89] 100%
LBBB, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 6/18 0/2 0.85 [0.64 - 1.13] 2.4%
MIRACLE 4/29 6/34 0.85 [0.63 - 1.11] 1.1%
MIRACLE-ICD 11/25 8/27 0.89 [0.68 - 1.26] 0.8%
MIRACLE-ICD II 1/11 0/12 0.85 [0.65 - 1.15] 0.4%
REVERSE 1/30 1/12 0.85 [0.64 - 1.12] 1.7%
RAFT 82/206 83/193 0.87 [0.70 - 1.09] 45.7%
COMPANION 93/233 28/67 0.87 [0.70 - 1.11] 13%
MADIT-CRT 35/171 36/104 0.82 [0.62 - 1.03] 34.9%
Overall 233/723 162/451 0.85 [0.68 - 1.07] 100%
LBBB, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 6/26 1/6 0.56 [0.45 - 0.71] 1.4%
MIRACLE 17/156 3/60 0.57 [0.46 - 0.71] 1.9%
MIRACLE-ICD 22/105 20/90 0.57 [0.47 - 0.73] 1.2%
MIRACLE-ICD II 3/48 6/44 0.56 [0.45 - 0.71] 0.6%
REVERSE 3/81 4/41 0.56 [0.44 - 0.69] 1.7%
RAFT 106/432 174/443 0.54 [0.45 - 0.64] 38.8%
COMPANION 184/626 65/148 0.59 [0.50 - 0.71] 12.9%
MADIT-CRT 80/549 108/392 0.55 [0.46 - 0.66] 41.5%
Overall 421/2023 410/1324 0.56 [0.48 - 0.66] 100%
RBBB, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 5/10 0/3 1.19 [0.68 - 2.62] 5.5%
MIRACLE 3/3 1/4 1.20 [0.68 - 4.62] 0.4%
MIRACLE-ICD 1/2 2/6 1.16 [0.64 - 2.50] 0.5%
MIRACLE-ICD II 0/1 0/3 1.15 [0.59 - 2.31] 0.4%
REVERSE 0/5 1/3 1.14 [0.60 - 2.23] 1.3%
RAFT 6/20 10/30 1.16 [0.65 - 2.14] 27.1%
COMPANION 20/43 2/7 1.14 [0.68 - 1.96] 10.6%
MADIT-CRT 6/49 10/46 1.04 [0.51 - 1.78] 54.2%
Overall 41/133 26/102 1.15 [0.67 - 2.09] 100%
RBBB, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 7/14 0/2 0.97 [0.68 - 1.43] 5.6%
MIRACLE 1/8 1/13 0.96 [0.66 - 1.38] 1.1%
MIRACLE-ICD 8/16 3/12 0.97 [0.67 - 1.42] 1.3%
MIRACLE-ICD II 0/6 2/16 0.96 [0.66 - 1.37] 1.2%
REVERSE 0/16 2/8 0.95 [0.65 - 1.36] 2.7%
RAFT 22/48 32/62 0.97 [0.69 - 1.38] 33.6%
COMPANION 50/95 9/20 0.95 [0.67 - 1.33] 13.8%
MADIT-CRT 24/75 8/40 0.96 [0.67 - 1.35] 40.6%
Overall 112/278 57/173 0.97 [0.68 - 1.34] 100%
B
IVCD, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 5/21 3/9 1.25 [0.79 - 1.93] 6.8%
MIRACLE 0/7 0/8 1.27 [0.81 - 2.02] 0.4%
MIRACLE-ICD 0/12 1/11 1.27 [0.80 - 2.02] 0.7%
MIRACLE-ICD II 2/8 0/7 1.30 [0.86 - 2.10] 0.4%
REVERSE 1/48 0/22 1.27 [0.81 - 2.00] 4.4%
RAFT 16/71 20/79 1.24 [0.82 - 1.91] 28.7%
COMPANION 35/147 9/47 1.27 [0.88 - 1.91] 15.3%
MADIT-CRT 25/133 9/85 1.36 [0.91 - 2.16] 43.3%
Overall 84/447 42/268 1.28 [0.88 - 1.93] 100%
IVCD, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 1/4 0/1 0.50 [0.28 - 0.94] 2.9%
MIRACLE 1/16 2/14 0.50 [0.28 - 0.93] 2.2%
MIRACLE-ICD 0/11 3/21 0.50 [0.28 - 0.90] 2.6%
MIRACLE-ICD II 0/4 0/8 0.50 [0.28 - 0.92] 1.1%
REVERSE 0/8 0/3 0.50 [0.28 - 0.92] 1.9%
RAFT 9/34 6/21 0.50 [0.29 - 0.89] 34.2%
COMPANION 16/67 6/19 0.51 [0.29 - 0.91] 20%
MADIT-CRT 3/41 4/25 0.50 [0.29 - 0.89] 35%
Overall 30/185 21/112 0.50 [0.29 - 0.89] 100%
LBBB, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 5/18 0/2 0.85 [0.59 - 1.22] 2.2%
MIRACLE 2/29 2/34 0.84 [0.58 - 1.19] 1%
MIRACLE-ICD 5/25 2/27 0.87 [0.60 - 1.35] 0.8%
MIRACLE-ICD II 0/11 0/12 0.84 [0.57 - 1.22] 0.4%
REVERSE 0/30 0/12 0.84 [0.56 - 1.20] 1.5%
RAFT 50/206 47/193 0.85 [0.62 - 1.15] 46.6%
COMPANION 47/233 18/67 0.86 [0.63 - 1.19] 13.5%
MADIT-CRT 10/171 16/104 0.79 [0.52 - 1.11] 33.9%
Overall 119/723 85/451 0.84 [0.61 - 1.15] 100%
LBBB, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 6/26 0/6 0.66 [0.51 - 0.86] 1.3%
MIRACLE 8/156 14/160 0.66 [0.50 - 0.87] 1.9%
MIRACLE-ICD 9/105 8/90 0.67 [0.52 - 0.89] 1.2%
MIRACLE-ICD II 0/48 1/44 0.65 [0.50 - 0.87] 0.6%
REVERSE 3/81 0/41 0.66 [0.51 - 0.89] 1.6%
RAFT 70/432 119/443 0.62 [0.50 - 0.76] 39.3%
COMPANION 101/626 37/148 0.66 [0.54 - 0.83] 13.5%
MADIT-CRT 44/549 40/392 0.67 [0.53 - 0.85] 40.7%
Overall 241/2023 219/1324 0.66 [0.54 - 0.81] 100%
RBBB, QRS < 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 5/10 0/3 0.87 [0.44 - 1.99] 5.5%
MIRACLE 1/3 1/4 0.85 [0.43 - 1.87] 0.5%
MIRACLE-ICD 0/2 1/6 0.83 [0.41 - 1.91] 0.6%
MIRACLE-ICD II 0/1 0/3 0.84 [0.41 - 1.85] 0.3%
REVERSE 0/5 0/3 0.84 [0.41 - 1.80] 1.4%
RAFT 2/20 8/30 0.83 [0.41 - 1.75] 26.6%
COMPANION 10/43 2/7 0.84 [0.44 - 1.71] 11.6%
MADIT-CRT 2/49 5/46 0.80 [0.39 - 1.67] 53.5%
Overall 20/133 17/102 0.84 [0.43 - 1.76] 100%
RBBB, QRS ≥ 150 ms
Study CRT No CRT Hazard ratio Weight
BLOCK-HF 5/14 0/2 0.84 [0.53 - 1.37] 5.5%
MIRACLE 0/8 1/13 0.84 [0.53 - 1.38] 0.9%
MIRACLE-ICD 0/16 0/13 0.82 [0.51 - 1.35] 1.4%
MIRACLE-ICD II 0/6 1/16 0.84 [0.52 - 1.40] 1.1%
REVERSE 0/16 0/8 0.83 [0.51 - 1.37] 2.5%
RAFT 13/48 24/62 0.83 [0.54 - 1.35] 34.8%
COMPANION 27/95 6/20 0.82 [0.54 - 1.30] 15%
MADIT-CRT 16/75 3/40 0.87 [0.55 - 1.44] 38.7%
Overall 61/278 35/174 0.83 [0.55 - 1.33] 100%


A
IVCD
LBBB
RBBB
165 ms
129 ms
213 ms
Hazard ratio
2.0
1.5
1.0
0.5
0.0
150
200
250
QRS duration (ms)
B
IVCD
LBBB
RBBB
252 ms
145 ms
210 ms
Hazard ratio
2.0
1.5
1.0
0.5
0.0
150
200
250
QRS duration (ms)

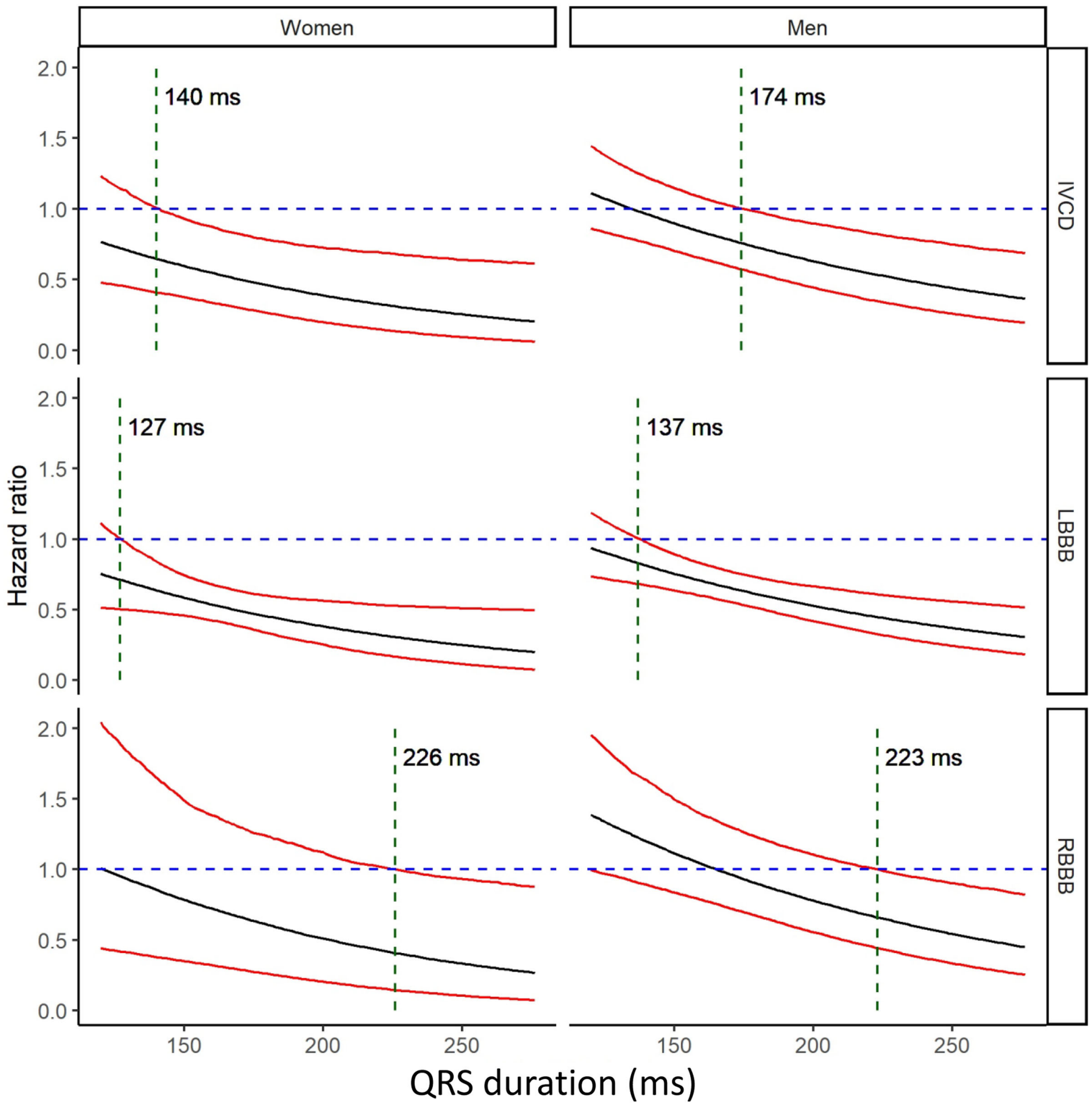

Women
Men
IVCD
LBBB
RBBB
140 ms
174 ms
127 ms
137 ms
226 ms
223 ms
Hazard ratio
QRS duration (ms)
2.0
1.5
1.0
0.5
0.0
150
200
250

Table 1. Characteristics of the Overall Cohort and by Subgroups Defined by QRS Characteristics

Characteristic	Overall (n=6264)	LBBB ≥150 ms (n=3368)	LBBB <150 ms (n=1181)	RBBB ≥150 ms (n=453)	RBBB <150 ms (n=238)	IVCD ≥150ms (n=301)	IVCD <150 ms (n=723)
Age, y*	66 [58–73]	66 [58–73]	67 [58–73]	67 [59–75]	67 [60–75]	66 [58–73]	65 [57–72]
Men	4720 (75%)	2374 (70%)	855 (72%)	419 (92%)	208 (87%)	240 (80%)	624 (86%)
Race or ethnicity†							
Asian	13 (0.5%)	6 (0.4%)	0 (0%)	2 (1.1%)	1 (0.8%)	2 (1.8%)	2 (0.6%)
Black	201 (7.8%)	102 (7.1%)	32 (7.9%)	20 (11%)	9 (7.3%)	7 (6.1%)	31 (9.1%)
White	2260 (87%)	1252 (88%)	358 (88%)	148 (84%)	108 (87%)	99 (87%)	295 (87%)
Hispanic	95 (3.7%)	58 (4.1%)	14 (3.4%)	4 (2.3%)	4 (3.2%)	6 (5.3%)	9 (2.6%)
Native American	12 (0.5%)	3 (0.2%)	2 (0.5%)	3 (1.7%)	2 (1.6%)	0 (0%)	2 (0.6%)
Other	9 (0.3%)	7 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)
NYHA class							
I	324 (5%)	127 (4%)	54 (5%)	32 (7%)	21 (9%)	13 (4%)	77 (11%)
II	3282 (52%)	1775 (53%)	630 (53%)	241 (53%)	141 (59%)	118 (39%)	377 (52%)
III	2354 (38%)	1299 (39%)	447 (38%)	157 (35%)	69 (29%)	148 (49%)	234 (32%)
IV	303 (5%)	166 (5%)	50 (4%)	23 (5%)	7 (3%)	22 (7%)	35 (5%)
Ejection fraction, %*	25 [20–30]	25 [20–29]	26 [20–30]	26.0 [20–30]	28 [24–30]	25 [20–29]	26 [21–30]
Atrial fibrillation	871 (14%)	425 (13%)	155 (13%)	74 (16%)	40 (17%)	49 (16%)	128 (18%)
Diabetes	2158 (34%)	1078 (32%)	425 (36%)	185 (41%)	84 (35%)	103 (34%)	283 (39%)
Hypertension	3343 (53%)	1734 (52%)	629 (53%)	245 (54%)	139 (58%)	171 (57%)	425 (59%)
Ischemia	3697 (59%)	1633 (48%)	747 (63%)	364 (80%)	202 (85%)	219 (73%)	532 (74%)
Antiarrhythmic drug‡	635 (13%)	349 (13%)	116 (13%)	48 (14%)	14 (7%)	47 (22%)	61 (12%)
Beta blocker	5028 (80%)	2732 (81%)	979 (83%)	325 (72%)	183 (77%)	222 (74%)	587 (81%)
ACEi or ARB	5848 (93%)	3153 (94%)	1108 (94%)	422 (93%)	219 (92%)	280 (93%)	666 (92%)
CRT	3822 (61%)	2038 (61%)	729 (62%)	279 (62%)	135 (57%)	187 (62%)	454 (63%)

Table 1. Characteristics of the Overall Cohort and by Subgroups Defined by QRS Characteristics

Characteristic	Overall (n=6264)	LBBB ≥150 ms (n=3368)	LBBB <150 ms (n=1181)	RBBB ≥150 ms (n=453)	RBBB <150 ms (n=238)	IVCD ≥150ms (n=301)	IVCD <150 ms (n=723)
ICD	4813 (77%)	2575 (76%)	917 (78%)	352 (78%)	190 (80%)	213 (71%)	566 (78%)

Data are presented as n (%), except where indicated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; ICVD, intraventricular conduction delay; LBBB, left bundle branch block; NYHA, New York Heart Association; and RBBB, right bundle branch block.

* Data are presented as median [interquartile range].

† Information was available for only 2590 patients.

‡ Information was available for only 4745 patients.

Table 2. Association of CRT With Heart Failure Hospitalization or Death and All-Cause Death by QRS Characteristics

Population	Heart failure hospitalization or death			All-cause death		
	Sample size*	Unadjusted HR (95% CrI)	Adjusted HR (95% CrI)	Sample size*	Unadjusted HR (95% CrI)	Adjusted HR (95% CrI)
Overall	6264 (6218)	0.73 (0.65–0.82)	0.73 (0.65–0.84)	6266 (6220)	0.77 (0.66–0.92)	0.78 (0.67–0.94)
By subgroup						
LBBB ≥150 ms	3368 (3347)	0.55 (0.48–0.65)	0.56 (0.48–0.66)	3368 (3347)	0.65 (0.53–0.80)	0.66 (0.54–0.81)
LBBB <150 ms	1181 (1174)	0.84 (0.67–1.05)	0.85 (0.68–1.07)	1181 (1174)	0.84 (0.62–1.12)	0.84 (0.61–1.15)
RBBB ≥150 ms	453 (451)	1.06 (0.77–1.45)	0.97 (0.68–1.34)	454 (452)	0.96 (0.63–1.47)	0.83 (0.55–1.33)
RBBB <150 ms	238 (235)	1.19 (0.69–2.16)	1.15 (0.67–2.09)	238 (235)	0.88 (0.45–1.68)	0.84 (0.43–1.76)
IVCD ≥150 ms	301 (297)	0.66 (0.42–1.00)	0.59 (0.39–0.89)	301 (297)	0.57 (0.30–1.13)	0.50 (0.29–0.89)
IVCD <150 ms	723 (714)	1.06 (0.82–1.36)	1.07 (0.83–1.42)	724 (715)	1.19 (0.81–1.69)	1.28 (0.88–1.93)

CrI indicates credible interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; ICVD, intraventricular conduction delay; LBBB, left bundle branch block; and RBBB, right bundle branch block.

* Parenthetical values correspond to the number of patients with complete data regarding covariates considered for adjusted models.