Impact of QRS Morphology and Duration on Outcomes Following Cardiac Resynchronization Therapy: Results from the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT)

Birnie et al: ECG and CRT Response

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Abstract

Background—The impact of QRS morphology and duration on the effectiveness of cardiac resynchronization therapy (CRT) has usually been assessed separately. The interaction between these two simple ECG parameters and their effect on CRT has not been systematically assessed in a large-scale clinical trial.

Methods and Results—The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) showed that ICD-CRT was associated with a significant reduction in the primary endpoint of all-cause mortality or heart failure hospitalization. For this sub-study we excluded patients in atrial fibrillation and those with a previous pacemaker. All baseline ECGs were reviewed by a panel of three experienced electrocardiographers. A total of 1483 patients were included in this study. Of these 1175 had left bundle branch block (LBBB) and 308 had non-LBBB. In patients with LBBB receiving ICD-CRT there was a reduction in the primary outcome and in each individual component of the primary outcome. Furthermore there was a continuous relationship between QRS duration and extent of benefit. In non-LBBB patients with QRS ≥160ms the HR for the primary outcome was 0.52 (0.29, 0.96) p=0.033); in patients with QRS <160 ms the HR was 1.38 (0.88, 2.14, p=0.155).

Conclusions—In LBBB patients, there was a continuous relationship between broader QRS and greater benefit from ICD-CRT. These data do not support the use of ICD-CRT in patients with non-LBBB, especially when the QRS duration is <160ms. There may be some delayed benefit when the QRS is ≥160 ms, but this needs further investigation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00251251.

Key Words: bundle branch block; electrocardiography, cardiac resynchronization therapy
Cardiac Resynchronization Therapy (CRT) has been shown conclusively to reduce morbidity and mortality in many patients with heart failure and prolonged QRS duration.[1-4] However between 30-50% of patients have limited or no response to this therapy.[5;6] Potential explanations for this include insufficient left ventricular mechanical dyssynchrony[7;8] and excess left ventricular scaring.[9;10] Previous studies have shown that a Left Bundle Branch Block (LBBB) pattern is a strong predictor of outcomes compared to the presence of other ECG morphologies.[11-19] A number of other key clinical questions remain and more data are required to inform these issues.[17;20;21] Patients with narrower QRS durations seem to have a lesser response but is there a QRS duration cut point which can be used to guide patients selection?[17] Is the cut point different for different QRS morphologies?[17] Is there any role for CRT in patients with RBBB[13;22] and non-specific Intra-Ventricular Conduction Delay (NIVCD)? The impact of QRS morphology and duration on the effectiveness of cardiac resynchronization therapy (CRT) has usually been assessed separately.[17] However a few studies have begun to examine these issues together.[19;23;24]

The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized 1798 patients with New York Heart Association class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 msec or more, to receive either an ICD alone or ICD-CRT. The primary outcome was death from any cause or hospitalization for heart failure. The study showed a significant reduction in the primary endpoint with the combination device.[4] The purpose of this sub-study was to examine the interaction between QRS Duration and morphology and outcomes following CRT.
Methods

The RAFT study demonstrated a reduction of all cause mortality and hospitalization for heart failure in patients with ICD-CRT. The details and results of the RAFT trial (NCT#00251251) have previously been published.[4;25] The trial was approved by research ethics committees at each institution and all patients provided written informed consent. For this sub-study the outcomes were the same as in the main trial. That is the primary composite outcome was death from any cause or heart failure leading to hospitalization. Hospitalization for heart failure was defined as admission to a health care facility lasting more than 24 hours with symptoms of congestive heart failure and subsequent treatment for heart failure. The principal secondary outcomes were the components of the primary composite outcome. [4;25] The RAFT study did not show any benefit from CRT in patients with permanent atrial fibrillation and patients with a prior permanent pacemaker.[4;26] These patients were therefore excluded in this analysis of QRS morphology and QRS duration.

At the time of patient enrollment, standard baseline 12-lead electrocardiograms (ECG) were obtained at a paper speed of 25 mm/s. Measurement of QRS duration using manual calipers was performed by KS and AT who were blinded to treatment allocation and outcomes. The lead with the widest QRS duration was used. The duration of 3 consecutive QRS complexes were averaged to obtain the final QRS duration for this analysis (rounded to the nearest 10 ms). Determination of QRS axis was performed by the computer-derived value printed on the ECG. Axis was defined as normal (-30°to +90°) or abnormal (all other values).

Adjudication of QRS morphology was performed by three experienced cardiologists (AT, LH, AH) who were blinded to treatment allocation and outcomes. Any disagreement was reviewed...
together arriving at a consensus. Categorization of intraventricular conduction was performed according to AHA/ACCF/HRS criteria.[27] Left bundle branch block (LBBB) was defined as a QRS duration of ≥ 120 ms with the following criteria: i) Broad notched or slurred R wave in leads I, aVL, V5 and V6 (an occasional RS pattern in V5 and V6 may occur due to displaced transition of the QRS complex); ii) Absent q waves in leads I, V5, and V6; iii) normal R peak time in leads V1, V2, and V3 (if R waves are present) and > 60 ms leads V5 and V6. [27]Right bundle branch block (RBBB) was defined as a QRS duration of ≥ 120 ms with the following criteria: i) rsr’, rsR’, or rSR’ in leads V1 or V2, with allowance of a wide and notched R wave in V1 and V2; ii) S wave of greater duration than R wave or > 40 ms in leads I and V6; and iii) Normal R peak time in leads V5 and V6 but > 50 ms in lead V1 if a pure dominant R wave (with or without notching) was present in lead V1. [27]Non-specific intraventricular conduction delay was defined as QRS duration of ≥ 120 ms without criteria for LBBB or RBBB. The definition was also be applied to a pattern with LBBB criteria in the precordial leads and RBBB criteria in the limb leads, or vice versa. [27]

**Statistics**

Continuous variables are summarized with mean and standard deviation; categorical variables, with counts and percentages. Comparisons of baseline variables between patients with LBBB, RBBB and NIVCD were done using ANOVA and Fisher exact test. All analyses were conducted according to the intention-to-treat principle. We used survival- analysis techniques to compare study groups with respect to the primary outcome and principal secondary outcomes. Survival was summarized with the use of Kaplan–Meier product-limit estimates (Figure 1). We compared the survival curves using nonparametric log-rank tests. Hazard ratios (HR) and associated 95%
confidence intervals (CI) were calculated with the use of the Cox proportional-hazards model. The ICD-CRT hazard ratio and 95% CI interval was determined for 5 msec subsets of QRS duration from 120 to 200ms and plotted against QRS duration (see Figure 2). The proportional hazards model which generated these values includes an interaction effect for ICD-CRT with QRS duration. In addition, estimates of the effect of ICD-CRT at specific cut points of QRS duration were determined by combining effect estimates using the ratio of hazard ratios above and below the cut point (see Figure 3). For example, if the ratio was 0.6 then this implies that the HR estimate for ICD-CRT compared to ICD for QRS durations above the cut point improved the effect of ICD-CRT by 40% compared to the effect of ICD-CRT for QRS duration below the cut point. Analyses were conducted with the use of SAS software, version 9.2 (SAS Institute).

Results

QRS Morphology

A total of 1483 patients in sinus rhythm met the inclusion criteria for this study after excluding 86 patients with ventricular pacing and 180 patients with permanent atrial fibrillation and 49 with both exclusion criteria. Of these 1175 (79.2%) had LBBB, 141 (12.0%) had RBBB and 167 (14.2%). Patients with NIVCD had significantly shorter QRS duration (138.6±18.4ms, p<0.001) compared to LBBB (161.0±23.5ms) and RBBB (159.9±19.3ms). Table 1 shows the study cohort stratified by QRS morphology. Important differences in the sub-groups include a greater percentage of males with RBBB (86.5%) and NIVCD (89.2%) than those with LBBB (79.9%). Secondly the etiology of heart failure was different with 62.4% of LBBB patients having ischemic etiology compared to 80.1% in the RBBB group and 82.6% in NIVCD group. Thirdly
the left ventricular ejection fraction was slightly lower in patients with LBBB (22.4 ± 5.4% compared to 23.7% ± 4.9 in the RBBB group and 23.4% ± 5 in the NIVCD group).

**Outcomes stratified by QRS morphology**

Table 2 shows outcomes, stratified by QRS morphology. Kaplan-Meir plots of the composite outcome stratified by QRS morphology is shown in Figure 1. In patients with LBBB, there was a reduction in the primary outcome, in all-cause mortality and HF hospitalization, in patients received ICD-CRT. In contrast there was no reduction in outcomes with ICD-CRT in the RBBB or NIVCD sub-groups.

**Outcomes stratified by QRS Duration and morphology**

**LBBB**

In Figure 2A the hazard ratio for the primary outcome by QRS duration is displayed. There is a progressive decrease in the rates of the primary outcome in the ICD-CRT group when compared to the ICD only group as the QRS duration increases. In particular, the HR remained less than one at all QRS durations and the upper 95% confidence bound excluded one for all QRS durations >145 msec. The HR ratio analysis (Figure 3) shows a gradual change in the ratio.

**Non-LBBB**

In Figure 2B the hazard ratio for the primary outcome by QRS duration is displayed. There is a progressive decrease in the rate of the primary outcome in the ICD-CRT group when compared to the ICD only group as the QRS duration increases. The HR becomes less than one at 155ms but the upper 95% confidence bound is never less than one. The HR ratio analysis (Figure 3)
found that ratio declined markedly relative to QRS duration at 160ms. In non-LBBB patients with QRS ≥ 160ms the HR for the primary outcome was 0.52 (0.29, 0.96) p=0.033; in patients with QRS < 160 ms the HR was 1.38 (0.88, 2.14, p=0.155). Hence the HR Ratio is 0.52/1.38 = 0.38. This suggests that the HR estimate of death or HF hospitalization (ICD-CRT versus ICD alone) was lower by 62% in patients with QRSd ≥ 160 ms when compared to those with QRSd < 160 ms. Figure 4 shows primary outcome by QRS duration (< and ≥160ms) in non-LBBB patients. The benefit from ICD-CRT began to appear after 2 years of follow-up (see Figure 4B).

**Primary Outcomes stratified by QRS Morphology and Axis**

Table 3 details primary composite outcome as stratified by QRS morphology and QRS Axis. Similar results for each component of primary endpoint (data not shown). These data indicate that QRS axis seem to have no impact on outcomes in the study.

**Discussion**

In this study evaluating the interaction of QRS morphology and QRS duration and outcomes following ICD-CRT, there are two main findings. Firstly in patients with LBBB, there was a progressive relationship between QRS duration and benefit from ICD-CRT, such that patients with wider QRS derived more benefit from ICD-CRT. Furthermore there is likely potential benefit in all LBBB patients regardless of QRS duration, and no cut-point can be clearly indentified to exclude patients who will not respond. Secondly our data do not support the use of ICD-CRT in most patients with non-LBBB, especially when the QRS duration is <160 ms. Indeed there was at trend for harm in this sub-group. There may be some delayed (after 2 years) benefit when the QRS is ≥ 160 ms, but this needs further investigation.
Our finding that LBBB pattern is a strong predictor of better clinical outcomes, compared to the presence of other ECG morphologies is very consistent with previous studies.[11-19] However most studies have reported on QRS duration subsets in the whole study population. Sipahi et al[17] recently published a meta-analysis of these data looking at the impact of QRS duration on clinical event reduction with CRT. They looked at data from 5 randomized trials with a total of 5813 patients. They dichotomized the patients into groups with moderately prolonged QRS duration (>120ms to 143-160ms) and severely prolonged QRS duration (>143-160ms). They found important consistency across all of the clinical trials. The pooled analysis showed a reduction of the composite clinical events with CRT in patients with severe QRS prolongation (risk ratio of 0.60, 95% CI 0.53 to 0.67, p<0.001). In contrast there was no benefit of CRT in patients with moderately prolonged QRS (relative risk of 0.95, 95% CI 0.82, 1.20, p=0.49).[17] They also found that the differential response of the two QRS groups was consistent across all NYHA classes and regardless of whether there was background ICD therapy present. However they did not have access to patient level data so were unable to look at the interaction between QRS morphology and QRS duration.[17]

A few studies have examined the relationship between QRS morphology, duration and outcomes. Dupont et al[23] examined remodeling with CRT in LBBB only patients with QRS duration ≥ and < 150 ms. Both groups had substantial improvements in LV ejection fraction but the improvement was greater for patients with broader QRS (12±12% versus 8 ±10%). In a MADIT-CRT sub-analysis, LBBB patients were also stratified at 150 ms and both subgroups significantly benefited from CRT. The broader QRS group had greater benefit but the confidence intervals were wide and overlapping.[19] The most detailed analysis to date is from the REVERSE
The investigators used linear regression analysis to examine changes in LV volumes in their entire study cohort, and also separately in patients with LBBB. In the LBBB patients they found a continuous relationship between QRS duration and change in volumes. There was an incremental decrease in LVESVi of 5.7 ml/m² for each 10ms increase in QRS.[24] Furthermore they showed that the curve intercepted the axis (i.e. point of no change in volume) at 120ms.[24] Our data add to these observations, also suggesting that in patients with LBBB, the relationship between QRS duration and outcomes from CRT is best treated as a continuous variable.[24] Furthermore there is likely potential benefit in all LBBB patients regardless of QRS duration, and that no cut-point can be clearly identified to exclude patients who will not respond.

We found that patients with non-LBBB and QRS duration ≥ 160 ms appeared to have benefit from ICD-CRT; in contrast in patients with non-LBBB with QRS duration < 160 ms there was a trend for harm from ICD-CRT. There are pathophysiological reasons to expect response to CRT in at least some patients with non-LBBB and cardiomyopathy as it has been shown that they often have conduction delay in both bundles.[14;28] Indeed significant delay in the left ventricular endocardial activation was seen in most patients with RBBB and left axis deviation.[28] However the published clinical data are largely negative to date. Nery et al[16] published a systematic review from randomized clinical trials of CRT on the outcomes of patients with baseline RBBB. There was analyzable data from 5 randomized clinical trials with details of outcomes in 485 patients with RBBB. None of the available data suggested more favorable outcomes (soft or hard) with CRT in these patients. Also Bilchick et al[12] reported on outcomes of 14 946 Medicare registry patients with ICD-CRT (median follow-up, 40 months)
New York Heart Association class IV heart failure and age >80 years were associated with increased mortality after ICD-CRT. RBBB (1-year HR, 1.44; 3-year HR 1.37; P<0.001) and ischemic cardiomyopathy (1-year HR, 1.39; 3-year HR 1.44; P<0.001) were the next strongest adjusted predictors of mortality. Initially it was suggested that the presence of hemi-block may indicate a greater extent of conduction system disease and therefore more likelihood of benefit from CRT. Chapa et al[29] looked at the influence of hemi-block on response to CRT in RBBB patients. Only 4 out of 18 patients with ‘pure’ RBBB compared to 18 out of 26 with co-existent left hemi-block (p=0.005) had an improvement in EF > 5%. In contrast all other studies, including our analysis, found no evidence of benefit in patients with left or right axis deviation (likely representing hemi-block).[13;15;18]

There are fewer data looking at patients with NIVCD undergoing CRT. A number of clinical trials have presented RBBB patients in the same subset as NIVCD and thus these data cannot be assessed separately. Also in other trials there were very few patients with NIVCD for example only ten patients (1%) of the CARE-HF population had NIVCD.[13] MADIT CRT reported on 308 patients with NIVCD. They showed no evidence of benefit from CRT in this patient subset.[19] Indeed there was a trend for an increased risk of the primary end point of heart failure or death in patients undergoing CRT (p=0.102). In the Medicare registry of 14946 patients undergoing CRT there were 2952 (20%) with NIVCD.[10] These patients had intermediate outcomes compared to RBBB and LBBB patients. For example the hazard ratio for mortality at 1 year compared to LBBB patients was 1.18 (1.05 to 1.32).
The benefit from CRT in non-LBBB patients with QRS $\geq 160$ms, developed after 2 years of follow-up and this may in part explain the discrepant finding compared to other studies with shorter follow-up. For example the mean follow-up in MADIT CRT was 28 months compared to 40 months in RAFT.[3;4] Other data are consistent with our observation that there may be a subset of patients with non-LBBB that benefit from CRT. In the Medicare Registry patients were stratified by a QRS duration of 150 ms.[12] For patients with NIVCD there was modestly better outcomes in patients with a QRS duration $\geq 150$ ms compared to patients with duration $<150$ms.[12] Rickard[30] investigated 22 patients with RBBB and 77 patients with NIVCD and found that QRS duration was the only variable significantly associated with a positive remodeling response (odds ratio per 10ms increase 1.23, 95% CI 1.01 to 1.52, $p = 0.048$). Two observational studies have looked at extent of echocardiography measures of LV dyssynchrony in patients with RBBB. They found more reverse remodeling[15;31] and better clinical outcomes[15] in patients with more extensive LV dyssynchrony. Gold evaluated the relationship between outcomes and left ventricular (LV) electrical delay (as measured by the QLV interval i.e. the interval from the onset of the QRS from the surface ECG to the first large peak of the LV electrogram). Importantly they found that LBBB and QRS duration were no longer predictive of CRT response after adjusting for QLV.[32] Another intriguing observation is that of significant reverse remodeling following CRT in some patients with non-LBBB. For example in one study 49% of 89 RBBB patients had a reduction of $\geq 15\%$ reduction in left ventricular end systolic volume at six months following device implantation.[15] In MADIT CRT, 55% of patients with non-LBBB (119 patients) had reverse remodeling by the same criteria, following CRT.[19] By comparison only 6% of non-LBBB patients in the control arm
(ICD only) had this extent of remodeling.[19] Other studies have not reproduced these remodeling findings.[24] [33]

Strengths and Limitations

The study has a number of strengths including the large sample size and the use of a blinded committee who reviewed the ECGs and used strict criteria for LBBB, NIVCD and RBBB. The study is limited by the small numbers of patients in the subsets and thus the findings should be interpreted with caution. Hence for example the numbers were too small to subset non-LBBB into RBBB and NIVCD in most analyses. Also the apparent benefit in the non-LBBB subgroup, with QRS duration ≥160 ms, was observed after > 2 years and the numbers of patients with longer follow-up are small. Also patients were not stratified on the basis of QRS morphology or duration and most of the analyses were post-hoc. Another limitation of this study is that there was no routine AV or VV interval optimization performed. However the whole role of the interval optimization in CRT patients is debatable with large studies suggesting no benefit.[33] A final limitation is the use of axis as a surrogate for hemi-block.

Clinical implications

Our study had two main findings. Firstly in patients with LBBB, there was a clear continuous relationship between broader QRS and greater benefit from ICD-CRT. This finding is similar to other recent data indicating that in patients with LBBB the relationship between QRS duration and response to CRT is best treated as a continuous variable. Thus there is likely potential benefit in all LBBB patients regardless of QRS duration, with no cut-point to exclude patients. Secondly our data do not support the use of ICD-CRT in patients with non-LBBB, especially
when the QRS duration is <160 ms. Indeed there was at trend for harm in this sub-group. There may be some delayed (after 2 years) benefit when the QRS is ≥ 160 ms, but this needs further investigation. Resolving the question of non-LBBB patients’ benefit from CRT has implications for large numbers of patients. For example in the US Medicare Registry 11% of patients undergoing CRT had RBBB and 20% had IVCD and furthermore 25% of patients had QRS duration < 140 ms.[12] In a European survey 18% of CRT recipients have QRS duration <130 ms.[34] A patient level meta-analysis of the major clinical trials is required to try to answer these residual questions. A particular focus of that meta-analysis should be on the interaction between QRS morphology, duration and outcomes. In the meantime physicians and patients should be aware of the likely reduced or minimal benefit from CRT in certain patient subsets and this should be factored into the decision making.

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References


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<tr>
<th>Variable</th>
<th>LBBB (n=1175)</th>
<th>RBBB (n=141)</th>
<th>NIVCD (n=167)</th>
<th>ANOVA/Fisher’s Exact</th>
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<td>Gender (Male), N (%)</td>
<td>939 (79.9)</td>
<td>122 (86.5)</td>
<td>149 (89.2)</td>
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<td>Age (mean ± SD)</td>
<td>65.3 ± 9.3</td>
<td>65.3 ± 10.0</td>
<td>64.6 ±10.1</td>
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<td>Weight (kg, mean ± SD)</td>
<td>81.9 ± 17.5</td>
<td>83.3 ± 17.3</td>
<td>85.4 ±19.8</td>
<td>0.21</td>
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<td>733 (62.4)</td>
<td>113 (80.1)</td>
<td>138 (82.6)</td>
<td>&lt;0.0001</td>
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<td>NYHA class II, N (%)</td>
<td>953 (81.1)</td>
<td>124 (87.9)</td>
<td>131 (78.4)</td>
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<td>LVEF (mean ± SD)</td>
<td>22.4 ± 5.4</td>
<td>23.7 ± 4.9</td>
<td>23.4 ± 5.0</td>
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<td>515 (43.8)</td>
<td>60 (42.6)</td>
<td>80 (47.9)</td>
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<td>Diabetes, N (%)</td>
<td>380 (32.3)</td>
<td>61 (43.3)</td>
<td>60 (35.9)</td>
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<td>HF hospitalization prior 12 mo, N (%)</td>
<td>309 (26.3)</td>
<td>30 (21.3)</td>
<td>46 (27.5)</td>
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<td>QRS duration (msec, mean ± SD)</td>
<td>161.0 ±23.5</td>
<td>159.9 ± 19.3</td>
<td>138.6 ±18.4</td>
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<td>1061 (90.3)</td>
<td>120 (85.1)</td>
<td>150 (89.8)</td>
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<td>ACE or ARB, N (%)</td>
<td>1133 (96.4)</td>
<td>138 (97.9)</td>
<td>164 (98.2)</td>
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<td>Spironolactone, N (%)</td>
<td>503 (42.8)</td>
<td>49 (34.8)</td>
<td>71 (42.5)</td>
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<td>Digoxin, N (%)</td>
<td>379 (32.3)</td>
<td>34 (24.1)</td>
<td>45 (26.9)</td>
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<td>Warfarin, N (%)</td>
<td>301 (25.6)</td>
<td>36 (25.5)</td>
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<td>Statin, N (%)</td>
<td>784 (66.7)</td>
<td>107 (75.9)</td>
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<td>Diuretic, N (%)</td>
<td>980 (83.4)</td>
<td>113 (80.1)</td>
<td>141 (84.4)</td>
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<td>Amiodarone, N (%)</td>
<td>175 (14.9)</td>
<td>19 (13.5)</td>
<td>22 (13.2)</td>
<td>0.83</td>
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<td>Six min walk (M, mean± SD)</td>
<td>358.3 ± 111.9</td>
<td>359.9 ± 92.1</td>
<td>357.8 ± 103.1</td>
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<td>Haemaglobin, (g/dl, mean± SD)</td>
<td>137.0 ±15.9</td>
<td>135.1 ± 15.4</td>
<td>138.7 ± 16.7</td>
<td>0.05</td>
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<td>Creatinine (μmol/l, mean± SD)</td>
<td>112.8 ±61.1</td>
<td>120.5 ± 57.3</td>
<td>112.7 ± 34.5</td>
<td>0.28</td>
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Left Bundle Branch Block - LBBB; Right Bundle Branch Block - RBBB; Non-specific Intra-Ventricular Conduction Delay – NIVCD;
New York Heart Association - NYHA; Left Ventricular Ejection Fraction - LVEF; Heart Failure - HF; Angiotensin Converting Inhibitor - ACE; Angiotensin Receptor Blocker - ARB
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<th>ICD-CRT</th>
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<tr>
<td>No. of patients</td>
<td>594</td>
<td>581</td>
<td></td>
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<tr>
<td>Composite N (%)</td>
<td>169 (28.5)</td>
<td>229 (39.4)</td>
<td>0.640</td>
<td>0.524, 0.781</td>
<td>&lt;0.001</td>
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<td>Death N (%)</td>
<td>105 (17.7)</td>
<td>145 (25.0)</td>
<td>0.664</td>
<td>0.516, 0.853</td>
<td>0.0013</td>
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<td>HF Hospitalization N (%)</td>
<td>104 (17.5)</td>
<td>151 (26.0)</td>
<td>0.603</td>
<td>0.469, 0.774</td>
<td>&lt;0.001</td>
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<td><strong>Non-LBBB</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>143</td>
<td>165</td>
<td></td>
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<tr>
<td>Composite N (%)</td>
<td>58 (40.7)</td>
<td>69 (41.2)</td>
<td>0.986</td>
<td>0.695, 1.399</td>
<td>0.937</td>
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<tr>
<td>Death N (%)</td>
<td>29 (20.3)</td>
<td>47 (28.5)</td>
<td>0.705</td>
<td>0.444, 1.121</td>
<td>0.130</td>
</tr>
<tr>
<td>HF Hospitalization N (%)</td>
<td>39 (27.3)</td>
<td>42 (25.5)</td>
<td>1.085</td>
<td>0.702, 1.880</td>
<td>0.713</td>
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<tr>
<td><strong>RBBB</strong></td>
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<td>No. of patients</td>
<td>60</td>
<td>81</td>
<td></td>
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<tr>
<td>Composite N (%)</td>
<td>23 (38.3)</td>
<td>38 (46.9)</td>
<td>0.890</td>
<td>0.530, 1.494</td>
<td>0.659</td>
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<tr>
<td>Death N (%)</td>
<td>10 (16.7)</td>
<td>28 (34.6)</td>
<td>0.544</td>
<td>0.264, 1.121</td>
<td>0.095</td>
</tr>
<tr>
<td>HF Hospitalization N (%)</td>
<td>15 (25.0)</td>
<td>19 (23.5)</td>
<td>1.142</td>
<td>0.580, 2.249</td>
<td>0.705</td>
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<td><strong>NIVCD</strong></td>
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<td>No. of patients</td>
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<td>84</td>
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<tr>
<td>Composite N (%)</td>
<td>35 (42.2)</td>
<td>31 (36.9)</td>
<td>1.116</td>
<td>0.686, 1.815</td>
<td>0.657</td>
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<tr>
<td>Death N (%)</td>
<td>19 (22.9)</td>
<td>19 (22.6)</td>
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<td>0.491, 1.761</td>
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<td>HF Hospitalization N (%)</td>
<td>24 (28.9)</td>
<td>23 (27.4)</td>
<td>1.021</td>
<td>0.574, 1.815</td>
<td>0.944</td>
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</table>

ICD-CRT – Implantable Cardioverter Defibrillator – Cardiac Resynchronization Therapy; Confidence Interval - CI; Left Bundle Branch Block - LBBB; Right Bundle Branch Block - RBBB; Non-specific Intra-Ventricular Conduction Delay - NIVCD; HF - Heart Failure
Table 3. Hazard Ratios for Primary Composite Outcome Stratified by QRS Duration and Axis

<table>
<thead>
<tr>
<th>Axis</th>
<th>LBBB</th>
<th>Non LBBB</th>
<th>RBBB</th>
<th>NIVCD</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Abnormal</td>
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<tr>
<td>N</td>
<td>689</td>
<td>485</td>
<td>123</td>
<td>184</td>
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<tr>
<td>HR</td>
<td>0.610</td>
<td>0.678</td>
<td>1.077</td>
<td>0.975</td>
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<tr>
<td>CI</td>
<td>0.468, 0.796</td>
<td>0.501, 0.917</td>
<td>0.587, 1.976</td>
<td>0.632, 1.505</td>
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</tbody>
</table>
**Figure Legends**

**Figure 1.** Death from any cause or heart failure hospitalization by QRS morphology (A LBBB, B non-LBBB, C = RBBB, D= NIVCD)

**Figure 2.** Hazard ratios for primary composite outcome (death from any cause or heart failure hospitalization) by QRS Duration and QRS morphology (A= LBBB, B = non-LBBB)

**Figure 3.** Changes in the magnitude of clinical benefit with CRT-D compared to ICD, at various QRS duration (QRSd) cut points. The HR ratio was calculated by dividing the HR of patients above the QRSd cut-off from those below the cut-off. For example, at a QRSd cut-off of 130 ms, the HR ratio was derived by dividing the HR of patients with QRSd ≥ 130 ms from the HR ratio of patients with QRSd < 130 ms. In non-LBBB patients with QRS ≥ 160ms the HR for the primary outcome was 0.52 (0.29, 0.96) p=0.033); in patients with QRS < 160 ms the HR was 1.38 (0.88, 2.14, p=0.155). Hence the HR Ratio is 0.52/1.38 = 0.38

**Figure 4.** Primary composite outcome (death from any cause or heart failure hospitalization) by QRS duration in patients with non-LBBB (A < 160ms, B ≥160ms)
Non-LBBB

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Hazard Ratio vs. QRS Duration in msec

- Solid line: Hazard Ratio 0.5
- Dashed line: Hazard Ratio 1
- Dotted line: Hazard Ratio 1.5
- Long dashed line: Hazard Ratio 2.5

Range of QRS Duration: 125 to 190 msec
Range of Hazard Ratio: 0 to 3
Ratio of HR above/HR below cutpoint

QRS Duration Cut-Point in msec

LBBB
non-LBBB
Non-LBBB and QRS duration ≥ 160ms

HR 0.528 (95%CI 0.291, 0.959) P = 0.033

Patients at risk

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</table>
Non-LBBB and QRS duration < 160ms

Survival

HR 1.376 (95% CI 0.885, 2.140) p=0.155

Days from Randomization

Patients at risk

<table>
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<th>ICD-CRT</th>
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Impact of QRS Morphology and Duration on Outcomes Following Cardiac Resynchronization Therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT)

David H. Birnie, Andrew Ha, Lyall Higginson, Kiran Sidhu, Martin Green, François Philippon, Bernard Thibault, George Wells and Anthony Tang

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