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

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Background—The impact of QRS morphology and duration on the effectiveness of cardiac resynchronization therapy (CRT) has been usually assessed separately. The interaction between these 2 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 showed that implantable cardioverter defibrillator-CRT was associated with a significant reduction in the primary end point of all-cause mortality or heart failure hospitalization. For this substudy, we excluded patients in atrial fibrillation and those with a previous pacemaker. All baseline ECGs were reviewed by a panel of 3 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 implantable cardioverter defibrillator-CRT, there was a reduction in the primary outcome and in each individual component of the primary outcome. Furthermore, there was continuous relationship between QRS duration and extent of benefit. In patients with non-LBBB and QRS ≥160 ms, the hazard ratio for the primary outcome was 0.52 (0.29–0.96; \( P=0.033 \)); in patients with QRS <160 ms, the hazard ratio was 1.38 (0.88–2.14; \( P=0.155 \)).

Conclusions—In patients with LBBB, there was a continuous relationship between broader QRS and greater benefit from implantable cardioverter defibrillator-CRT. However, our data do not support the use of implantable cardioverter defibrillator-CRT in patients with non-LBBB, especially when the QRS duration is <160 ms. 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 • cardiac resynchronization therapy • electrocardiography

Cardiac resynchronization therapy (CRT) has been conclusively revealed to reduce morbidity and mortality in many patients with heart failure (HF) and prolonged QRS duration. However, between 30% and 50% of patients have limited or no response to this therapy. Potential explanations for this include insufficient left ventricular (LV) mechanical dyssynchrony and excess LV scaring. Previous studies have shown that a left bundle-branch block (LBBB) pattern is a strong predictor of outcomes compared with the presence of other ECG morphologies. Several other key clinical questions remain, and more data are required to inform these issues. 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? Is the cut point different for different QRS morphologies? Is there any role for CRT in patients with right bundle-branch block (RBBB) and nonspecific intraventricular conduction delay (NIVCD)? The impact of QRS morphology and duration on the effectiveness of CRT has been usually assessed separately. However, a few studies have begun to examine these issues together.

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The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized 1798 patients with New York Heart Association class II or III HF, a LV ejection fraction of ≤30%, and an intrinsic QRS duration of ≥120 ms, to receive either an implantable cardioverter defibrillator...
(ICD) alone or an ICD-CRT. The primary outcome was death from any cause or hospitalization for HF. The study showed a significant reduction in the primary end point with the combination device. The purpose of this substudy was to examine the interaction between QRS duration and morphology and outcomes after CRT.

Methods
The RAFT study demonstrated a reduction of all-cause mortality and hospitalization for HF in patients with ICD-CRT. The details and results of the RAFT (NCT#00251251) have been published previously. The trial was approved by research ethics committees at each institution, and all patients provided written informed consent. For this substudy, the outcomes were the same as in the main trial, that is, the primary composite outcome was death from any cause or HF leading to hospitalization. HF hospitalization was defined as admission to a healthcare facility lasting for >24 hours with symptoms of congestive HF and subsequent treatment for HF. The principal secondary outcomes were the components of the primary composite outcome. Therefore, these patients were excluded in this analysis of QRS morphology and QRS duration.

At the time of patient enrollment, standard baseline 12-lead ECGs were obtained at a paper speed of 25 mm/s. Measurement of QRS duration using manual calipers was performed by K.S. and A.T. 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 3 experienced cardiologists (A.T., L.H., A.H.) who were blinded to treatment allocation and outcomes. Any disagreement was reviewed together before arriving at a consensus. Categorization of intraventricular conduction was performed according to the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society criteria. LBBB was defined as a QRS duration of ≥120 ms with the following criteria: (1) broad notched or slurred R wave in leads I, aVL, V_{5}, and V_{6} (an occasional RS pattern in V_{5} and V_{6} may occur because of displaced transition of the QRS complex); (2) absent q waves in leads I, V_{1}, and V_{6}; (3) normal R peak time in leads V_{6}, V_{5}, and V_{1} (if R waves are present) and >60 ms leads V_{6} and V_{1}. RBBB was defined as a QRS duration of ≥120 ms with the following criteria: (1) rs' or rsR' in leads V_{1} or V_{6} with allowance of a wide and notched R wave in V_{1} and V_{6}; (2) S wave of greater duration than R wave or >40 ms in leads I and V_{6}; and (3) normal R peak time in leads V_{6} and V_{1} but >50 ms in lead V_{1} if a pure dominant R wave (with or without notching) was present in lead V_{1}. Nonspecific intraventricular conduction delay was defined as QRS duration of ≥120 ms without criteria for LBBB or RBBB. The definition was also applied to a pattern with LBBB criteria in the precordial leads and RBBB criteria in the limb leads or vice versa.

Statistics
Continuous variables are summarized with mean and SD and categorical variables with counts and percentages. Comparisons of baseline variables between patients with LBBB, RBBB, and NIVCD were done using ANOVAs 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 (HRs) and associated 95% confidence intervals (CI) were calculated with the use of the Cox proportional hazards model. HR and 95% CI were determined for 5 ms subsets of QRS duration from 120 to 200 ms and plotted against QRS duration (Figure 2). The proportional hazards model that 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

![Figure 1](http://circheartfailure.ahajournals.org/doi/fig/s1)

**Figure 1.** Death from any cause or heart failure hospitalization by QRS morphology. **A**, Left bundle-branch block (LBBB); **B**, non-LBBB; **C**, right bundle-branch block (RBBB); and **D**, nonspecific intraventricular conduction delay (NIVCD). CI indicates confidence interval; HR, hazard ratio; and ICD-CRT, implantable cardioverter-defibrillator-cardiac resynchronization therapy.
of QRS duration were determined by combining effect estimates using the ratio of HRs above and below the cut point (Figure 3). For example, if the ratio was 0.6 then this implies that the HR estimate for ICD-CRT compared with ICD for QRS durations above the cut point improved the effect of ICD-CRT by 40% compared with 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%) had NIVCD. Patients with NIVCD had significantly shorter QRS duration (138.6±18.4 ms; \( P < 0.001 \)) compared with those with LBBB (161.0±23.5 ms) and RBBB (159.9±19.3 ms). Table 1 shows the study cohort stratified by QRS morphology. Important differences in the subgroups include a greater percentage of men with RBBB (86.5%) and NIVCD (89.2%) than those with LBBB (79.9%). Second, the cause of HF was different, with 62.4% of patients with LBBB having ischemic pathogenesis when compared with 80.1% of patients with RBBB and

![Figure 2.](https://example.com/figure2.png) Hazard ratios for primary composite outcome (death from any cause or heart failure hospitalization) by QRS duration and QRS morphology. A. Left bundle-branch block (LBBB); and (B) non-LBBB.

![Figure 3.](https://example.com/figure3.png) Changes in the magnitude of clinical benefit with cardiac resynchronization therapy-defibrillator compared with implantable cardioverter defibrillator, 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 was derived by dividing the HR of patients with QRSd ≥130 ms from the HR of patients with QRSd <130 ms. In patients with non–left bundle-branch block (LBBB) and QRS ≥160 ms, 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.
82.6% of patients with NIVCD. Third, the LV ejection fraction was slightly lower in patients with LBBB (22.4±5.4%) when compared with patients with RBBB (23.7±4.9%) and patients with NIVCD (23.4±5%).

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 subgroups.

Outcomes Stratified by QRS Duration and Morphology

Left Bundle-Branch Block
In Figure 2A, the HR 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 with that in the ICD-only group as the QRS duration increases. The HR becomes <1 at 155 ms, but the upper 95% confidence bound is never <1. The HR ratio analysis (Figure 3) found that ratio declined markedly relative to QRS duration at 160 ms. In patients with non-LBBB and QRS ≥160 ms, 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 QRS duration ≥160 ms when compared with those with QRS duration <160 ms. Figure 4 shows primary outcome by QRS duration (<160 and ≥160 ms) in patients with non-LBBB. The benefit from ICD-CRT began to appear after 2 years of follow-up (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 were obtained for each component of the primary end point (data not shown). These data indicate that QRS axis seems to have no impact on outcomes in the study.

Discussion
In this study, evaluating the interaction of QRS morphology and QRS duration and outcomes after ICD-CRT, there are 2 main findings. First, 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 patients with LBBB regardless of QRS duration, and no cut point can be identified clearly to exclude patients who will not respond. Second, 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 a trend for harm in this subgroup. 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 with the presence of other ECG morphologies is consistent with previous studies. However, most studies have reported on QRS duration subsets in the whole study population. Sipahi et al\textsuperscript{17} published recently 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 (>120 to 143–160 ms) and severely prolonged QRS duration (>143–160 ms). 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, 0.53–0.67; \( P < 0.001 \)). 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; \( P = 0.49 \)).\textsuperscript{17} They also found that the differential response of the 2 QRS groups was consistent across all New York Heart Association 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.\textsuperscript{17}

A few studies have examined the relationship among QRS morphology, duration, and outcomes. Dupont et al\textsuperscript{23} examined remodeling with CRT in patients with LBBB only with QRS duration ≥150 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 Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) subanalysis, patients with LBBB were also stratified at 150 ms and both subgroups significantly benefited from CRT. The broader QRS group had greater benefit, but the CIs were wide and overlapping.\textsuperscript{19} The most detailed analysis to date is from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial.\textsuperscript{24} 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 patients with LBBB, they found a continuous relationship between QRS duration and outcomes from CRT.\textsuperscript{24} Furthermore, there is likely potential benefit in all patients with LBBB regardless of QRS duration, and that no cut point can be identified clearly to exclude patients who will not respond.

### Table 2. Outcomes Stratified by QRS Morphology

<table>
<thead>
<tr>
<th></th>
<th>ICD-CRT</th>
<th>ICD</th>
<th>HR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LBBB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>594</td>
<td>581</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td><strong>Non-LBBB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>143</td>
<td>165</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>0.702–1.680</td>
<td>0.713</td>
</tr>
<tr>
<td><strong>RBBB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td><strong>NIVCD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>83</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Death, n (%)</td>
<td>19 (22.9)</td>
<td>19 (22.6)</td>
<td>0.930</td>
<td>0.491–1.761</td>
<td>0.825</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, heart failure; ICD-CRT, implantable cardioverter defibrillator-cardiac resynchronization therapy; LBBB, left bundle-branch block; NIVCD, nonspecific intraventricular conduction; and RBBB, right bundle-branch block.
We found that patients with non-LBBB and QRS duration ≥160 ms seem to have benefit from ICD-CRT; in contrast, in patients with non-LBBB and 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. Indeed, significant delay in the LV endocardial activation was seen in most patients with RBBB and left axis deviation. However, the published clinical data are largely negative to date. Nery et al 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 reported on outcomes of 14,946 Medicare Registry patients with ICD-CRT (median follow-up, 40 months). New York Heart Association class IV HF 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 looked at the influence of hemi-block on response to CRT in patients with RBBB. Only 4 of 18 patients with pure RBBB compared with 18 of 26 with coexistent left hemi-block (\( P = 0.005 \)) had an improved outcome.

Table 3. Hazard Ratios for Primary Composite Outcome Stratified by QRS Morphology and Axis

<table>
<thead>
<tr>
<th>Axis</th>
<th>LBBB Normal</th>
<th>Abnormal</th>
<th>Non-LBBB Normal</th>
<th>Abnormal</th>
<th>RBBB Normal</th>
<th>Abnormal</th>
<th>NIVCD Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>689</td>
<td>485</td>
<td>123</td>
<td>184</td>
<td>32</td>
<td>109</td>
<td>91</td>
<td>75</td>
</tr>
<tr>
<td>HR</td>
<td>0.610</td>
<td>0.678</td>
<td>1.077</td>
<td>0.975</td>
<td>0.407</td>
<td>1.199</td>
<td>1.631</td>
<td>0.822</td>
</tr>
<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>
<td>0.121–1.369</td>
<td>0.673–2.138</td>
<td>0.785–3.388</td>
<td>0.419–1.612</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; LBBB, left bundle-branch block; NIVCD, nonspecific intraventricular conduction; and RBBB, right bundle-branch block.
improvement in ejection fraction >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. Several clinical trials have presented patients with RBBB in the same subset as NIVCD, and thus these data cannot be assessed separately. Also, in other trials, there were few patients with NIVCD, for example, only 10 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 HF or death in patients undergoing CRT (P=0.102). In the Medicare Registry of 14,946 patients undergoing CRT, there were 2952 (20%) patients with NIVCD.10 These patients had intermediate outcomes compared with patients with RBBB and LBBB. For example, the HR for mortality at 1 year compared with patients with LBBB was 1.18 (1.05–1.32).

The benefit from CRT in patients with non-LBBB and QRS ≥160 ms developed after 2 years of follow-up, and this may, in part, explain the discrepant finding compared with other studies with shorter follow-up. For example, the mean follow-up in Madit-CRT was 28 months compared with 40 months in RAFT.34 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 ≥150 ms compared with patients with duration <150 ms.15 Rickard et al30 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 10 ms increase 1.23; 95% CI, 1.01–1.52; P=0.048). Two observational studies have looked at the extent of echocardiography measures of LV dysynchrony in patients with RBBB. They found more reverse remodeling5,14 and better clinical outcomes15 in patients with more extensive LV dysynchrony. Gold et al12 evaluated the relationship between outcomes and LV electric delay (as measured by the QLV interval, ie, 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. Another intriguing observation is that of significant reverse remodeling after CRT in some patients with non-LBBB. For example, in one study, 49% of 89 patients with RBBB had a reduction of ≥15% in LV end-systolic volume at 6 months after device implantation.15 In Madit-CRT, 55% of patients with non-LBBB (119 patients) had reverse remodeling by the same criteria, after CRT.19 By comparison, only 6% of patients with non-LBBB 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 several 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 atrioventricular or interventricular 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 2 main findings. First, 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 patients with LBBB regardless of QRS duration, with no cut point to exclude patients. Second, 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 a trend for harm in this subgroup. There may be some delayed (after 2 years) benefit when the QRS is ≥160 ms, but this needs further investigation. Resolving the question of benefit of patients with non-LBBB 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 NIVCD and, furthermore, 25% of patients had QRS duration <140 ms.24 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 among 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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**CLINICAL PERSPECTIVE**

The impact of QRS morphology and duration on the effectiveness of cardiac resynchronization therapy (CRT) has been usually assessed separately. The interaction between these 2 simple ECG parameters and their effect on CRT has not been assessed systematically in a large-scale clinical trial. The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial showed that implantable cardioverter defibrillator (ICD)-CRT was associated with a significant reduction in the primary end point of all-cause mortality or heart failure hospitalization. For this substudy, we excluded patients in atrial fibrillation and those with a previous pacemaker. We found that in patients with left bundle-branch block receiving ICD-CRT, there was a reduction in the primary outcome and in each individual component of the primary outcome. Also, 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 left bundle-branch block patients regardless of QRS duration, and no cut point could be clearly indentified to exclude patients who will have some expectation of response. In contrast, our results do not support the use of ICD-CRT in patients with non–left bundle-branch block, especially when the QRS duration is ≤160 ms. There may be some delayed benefit when the QRS is ≥160 ms, but this needs further investigation. 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.
Impact of QRS Morphology and Duration on Outcomes After Cardiac Resynchronization Therapy: Results From the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT)

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